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*Aims and Scope*

The periodical *Dagstuhl Reports* documents the program and the results of Dagstuhl Seminars and Dagstuhl Perspectives Workshops.

In principal, for each Dagstuhl Seminar or Dagstuhl Perspectives Workshop a report is published that contains the following:

- an executive summary of the seminar program and the fundamental results,
- an overview of the talks given during the seminar (summarized as talk abstracts), and
- summaries from working groups (if applicable).

This basic framework can be extended by suitable contributions that are related to the program of the seminar, e. g. summaries from panel discussions or open problem sessions.

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# Optimality and Tight Results in Parameterized Complexity

Edited by

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## Abstract

This report documents the program and the outcomes of Dagstuhl Seminar 14451 “Optimality and tight results in parameterized complexity”. Over the last two decades parameterized complexity has become one of the main tools for handling intractable problems. Recently, tools have been developed not only to classify problems, but also to make statements about how close an algorithm is to being optimal with respect to running time. The focus of this seminar is to highlight and discuss recent, relevant results within this optimality framework and discover fruitful research directions. The report contains the abstracts of the results presented at the seminar, as well as a collection of open problems stated at the seminar.

**Seminar** November 2–7, 2014 – <http://www.dagstuhl.de/14451>

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**Edited in cooperation with** Markus S. Dregi

## 1 Executive Summary

*Stefan Kratsch*

*Daniel Lokshantov*

*Dániel Marx*

*Peter Rossmanith*

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While many seemingly hard computational problems can be solved satisfactorily in practice, classical complexity dictates that they are in fact intractable (NP-hard) in general. This is an unsatisfactory situation since one would desire a more productive interplay between more heuristic practical results and theoretically proven theorems.

Parameterized complexity analyzes the complexity in finer detail by considering additional problem parameters beyond the input size and expresses the efficiency of the algorithms in terms of these parameters. In this framework, many NP-hard problems have been shown to be (fixed-parameter) tractable when certain structural parameters of the inputs are bounded. In the past two decades, there has been tremendous progress in understanding



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which problems are fixed-parameter tractable and which problems are not (under standard complexity assumptions).

In recent years, the field of parameterized complexity seems to have evolved beyond merely classifying problems as fixed-parameter tractable or not. The focus shifted to understanding how close the algorithmic results are to the “best possible” algorithm for the problem. Thanks to significant recent advances on both algorithms (upper bounds) and complexity (lower bounds), we have now a tight understanding of many problems and many algorithmic results can be now proven optimal under reasonable assumptions. Moreover, it turns out that the search for optimality can be formulated with respect to different aspects of parameterized complexity and each such aspect gives a separate challenging but doable research direction. One can consider the optimality of algorithms for parameterized problems (either fixed-parameter tractable or not), the optimality of preprocessing algorithms, and the optimality of algorithms with respect to the generality of the problem being solved. The goal of the seminar was to bring together experts in the area of parameterized complexity and algorithms, highlight these research directions and the relevant recent results, and discuss future research topics.

The scientific program of the seminar consisted of 25 talks. Among these there were five 60 minute tutorials on the core topics of the seminar: Marek Cygan and Michał Pilipczuk (“Exponential Time Hypothesis, Part 1+2”) covered the Exponential Time Hypothesis (ETH), focussing on techniques for proving tight runtime lower bounds under ETH. Daniel Lokshtanov (“The Strong Exponential Time Hypothesis”) introduced Strong ETH as well as related lower bound techniques, and Virginia Vassilevska Williams (“Implications of SETH for polynomial time problems”) gave an overview of tight lower bounds for efficiently solvable problems under Strong ETH. Finally, Dániel Marx (“Every Graph is easy or hard”) covered the topic of dichotomy theorems for graph problems. Throughout, the tutorials were well-received both as a means of introduction to the topics but also as a convenient way of catching up on very recent results pertaining to the seminar. Furthermore, with most tutorials being held on Monday and Tuesday morning this set a productive atmosphere for tackling open problems regarding tight parameterized complexity results. A further 60 minute contributed talk by Saket Saurabh discussed the recent breakthrough result of fixed-parameter tractability of Graph Isomorphism with respect to treewidth. The rest of the talks were 25-minute presentations on recent research of the participants.

The time between lunch and afternoon coffee was left for self-organized collaborations and discussions. An open problem session was organized on Monday evening. Notes on the presented problems can be found in this report.

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## 3 Overview of Talks

### 3.1 On Courcelle's Conjecture

*Hans L. Bodlaender (Utrecht University, NL)*

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**Joint work of** Bodlaender, Hans L.; Heggernes, Pinar; Telle, Jan Arne

Courcelle's theorem tells that every problem that is formulatable in Counting Monadic Second Order Logic can be solved in linear time on graphs of bounded treewidth, with a specific type of algorithm – the form can be captured by the notion of regularity, i.e., the algorithm can be seen as a finite state tree automaton. Courcelle's conjecture states that the reverse also holds, i.e., each regular graph problem can be formulated in CMSOL. In the talk, the status of this conjecture is discussed. Recently, we found a proof for the case of  $k$ -chordal graphs.

### 3.2 The Complexity of Counting $k$ -Matchings Revisited

*Radu Curticapean (Universität des Saarlandes, DE)*

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**Joint work of** Curticapean, Radu; Marx, Dániel

**Main reference** R. Curticapean, D. Marx, "Complexity of Counting Subgraphs: Only the Boundedness of the Vertex-Cover Number Counts," in Proc. of the 55th IEEE Annual Symposium on Foundations of Computer Science (FOCS'14), pp. 130–139, IEEE, 2014; pre-print available as arXiv:1407.2929v1 [cs.CC], 2014.

**URL** <http://dx.doi.org/10.1109/FOCS.2014.22>

**URL** <http://arxiv.org/abs/1407.2929v1>

In this talk, we present a novel #W[1]-hardness proof for the problem of counting matchings of size  $k$ . A hardness proof for this problem was posed as an open problem in the book on parameterized complexity theory by Flum and Grohe, and remained open until recently (C., 2013). However, this first proof relies upon rather complicated algebraic arguments. Furthermore, some steps in this proof can only be verified with the help of a computer, and lastly, the proof can not provide a lower bound under the Exponential Time Hypothesis. In fact, its parameter blowup cannot be easily bounded by any explicit function, similar to a hardness proof for counting  $k$ -cycles by Flum and Grohe that was known before. We present a new proof, published as part of a recent paper (C., Marx, 2014) on the parameterized complexity of counting subgraphs. This new proof is significantly simpler and, in particular, uses only first principles from linear algebra. The reduction is from the problem of counting vertex-colorful copies of a 3-regular graph  $H$  in a vertex-colored graph  $G$ . Given such an instance  $(H, G)$  as input, with  $|V(H)| = k$ , we show how to construct  $3^k$  edge-colored graphs on  $O(k)$  colors such that the following holds: The number of vertex-colorful  $H$ -copies in  $G$  is equal to a linear combination of the numbers of edge-colorful matchings in the constructed graphs. The coefficients in this linear combination are easily computed. Then, the problem of counting edge-colorful matchings of size  $k$  can be reduced to the uncolored version via simple inclusion-exclusion. Since this reduction incurs only linear blowup, it can be used to transfer a lower bound of  $n^{O(k/\log k)}$  for the vertex-colorful subgraph problem under ETH (Marx, 2007) to the problem of counting  $k$ -matchings. Using simple self-contained reductions from counting  $k$ -matchings, we then obtain the same lower bounds for counting directed/undirected paths/cycles of length  $k$ .

### 3.3 Tutorial: Lower Bounds Based on the Exponential Time Hypothesis – Part 1

*Marek Cygan (University of Warsaw, PL)*

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**Joint work of** Cygan, Marek; Fomin, Fedor; Kowalik, Lukasz; Lokshтанov, Daniel; Marx, Dániel; Pilipczuk, Marcin; Pilipczuk; Saurabh, Saket

This talk will be an introduction to lower bounds based on the Exponential Time Hypothesis. We will discuss the Sparsification Lemma and different types of lower bounds that one can obtain based on ETH.

### 3.4 Parameterized Complexity of Bandwidth on Trees

*Markus S. Dregi (University of Bergen, NO)*

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**Joint work of** Dregi, Markus S.; Lokshтанov, Daniel

**Main reference** M. S. Dregi, D. Lokshтанov, “Parameterized Complexity of Bandwidth on Trees,” in Proc. of the 41st Int’l Colloquium on Automata, Languages, and Programming (ICALP’14), LNCS, Vol. 8572, pp. 405–416, Springer, 2014.

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The bandwidth of a  $n$ -vertex graph  $G$  is the smallest integer  $b$  such that there exists a bijective function  $f : V(G) \rightarrow \{1, \dots, n\}$ , called a layout of  $G$ , such that for every edge  $uv \in E(G)$ ,  $|f(u) - f(v)| \leq b$ . In the BANDWIDTH problem we are given as input a graph  $G$  and integer  $b$ , and asked whether the bandwidth of  $G$  is at most  $b$ . We present two results concerning the parameterized complexity of the BANDWIDTH problem on trees. First we show that an algorithm for BANDWIDTH with running time  $f(b)n^{o(b)}$  would violate the Exponential Time Hypothesis, even if the input graphs are restricted to be trees of pathwidth at most two. Our lower bound shows that the classical  $2^{O(b)}n^{b+1}$  time algorithm by Saxe [SIAM Journal on Algebraic and Discrete Methods, 1980] is essentially optimal. Our second result is a polynomial time algorithm that given a tree  $T$  and integer  $b$ , either correctly concludes that the bandwidth of  $T$  is more than  $b$  or finds a layout of  $T$  of bandwidth at most  $b^{O(b)}$ . This is the first parameterized approximation algorithm for the bandwidth of trees.

### 3.5 Kernelization Lower Bounds from Weaker Hardness Assumptions

*Andrew Drucker (University of Edinburgh, GB)*

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**Main reference** A. Drucker, “New Limits to Classical and Quantum Instance Compression,” ECCC TR12-112, Revision #3, December 24, 2014.

**URL** <http://eccc.hpi-web.de/report/2012/112/>

The OR-SAT and AND-SAT problems have played an important role in giving evidence of kernelization hardness for parametrized problems. It is known that these problems don’t have polynomial kernels, unless NP is in co-NP/poly. More recently I have shown this even holds unless NP is in the uniform class co-AM. The newer result’s proof involves some quite different ideas, and might stimulate further research. I will provide a high-level introduction to this work.

### 3.6 FPT Algorithms for the Workflow Satisfiability Problem with User-Independent Constraints: Optimality and Empirical Evaluation

Gregory Z. Gutin (Royal Holloway University of London, GB)

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The WORKFLOW SATISFIABILITY PROBLEM (WSP) asks whether there exists an assignment of authorised users to the steps in a workflow specification, subject to certain constraints on the assignment. The problem is NP-hard and usually parameterized by the number  $k$  of steps (as  $k$  is usually relatively small in practice). The parameterized WSP is W[1]-hard and researchers consider a special family of constraints, user-independent constraints, which are of interest in practice and for which WSP is in FPT. Researchers also consider a subfamily of user-independent constraints, regular constraints. We discuss optimal complexity of FPT algorithms for both families of constraints (they are  $O^*(2^k)$  and  $O^*(2^{k \log k})$ , respectively) and recent experimental results with implementations of fixed-parameter tractable algorithms for WSP with user-independent constraints. For more information, see [1, 2, 3, 4].

#### References

- 1 D. Cohen, J. Crampton, A. Gagarin, G. Gutin and M. Jones, Iterative Plan Construction for the Workflow Satisfiability Problem. *J. Artif. Intel. Res.* 51 (2014), pp. 555–577
- 2 D. Cohen, J. Crampton, A. Gagarin, G. Gutin and M. Jones, Engineering Algorithms for Workflow Satisfiability Problem with User- Independent Constraints. In *FAW 2014*, Lect. Notes Comput. Sci. 8497 (2014), pp. 48–59
- 3 J. Crampton, G. Gutin and A. Yeo, On the Parameterized Complexity and Kernelization of the Workflow Satisfiability Problem. *ACM Trans. Inform. System & Secur.*, 16 (2013), article no. 4
- 4 G. Gutin, S. Kratsch and M. Wahlstrom, Polynomial Kernels and User Reductions for the Workflow Satisfiability Problem. In *IPEC 2014*, Lect. Notes Comput. Sci. 8894 (2014)

### 3.7 Shortest Two Disjoint Paths in Polynomial Time

Thore Husfeldt (IT University of Copenhagen, DK)

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Joint work of Björklund, Andreas; Husfeldt, Thore

Main reference A. Björklund, T. Husfeldt, “Shortest Two Disjoint Paths in Polynomial Time,” in Proc. of the 41st Int’l Colloquium on Automata, Languages, and Programming (ICALP’14), LNCS, Vol. 8572, pp. 211–222, Springer, 2014.

URL [http://dx.doi.org/10.1007/978-3-662-43948-7\\_18](http://dx.doi.org/10.1007/978-3-662-43948-7_18)

Given an undirected graph and two pairs of vertices  $(s_i, t_i)$  for  $i \in \{1, 2\}$  we show that there is a polynomial time Monte Carlo algorithm that finds disjoint paths of smallest total length joining  $s_i$  and  $t_i$  for  $i \in \{1, 2\}$  respectively, or concludes that there most likely are no such paths at all. Our algorithm applies to both the vertex- and edge-disjoint versions of the problem. Our algorithm is algebraic and uses permanents over the quotient ring  $\mathbf{Z}_4[X]/(X^m)$  in combination with Mulmuley, Vazirani and Vazirani’s isolation lemma to detect a solution. We develop a fast algorithm for permanents over said ring by modifying Valiant’s 1979 algorithm for the permanent over  $\mathbf{Z}_2$ .

### 3.8 Uniform Kernelization Complexity of Hitting Forbidden Minors

*Bart Jansen (University of Bergen, NO)*

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**Joint work of** Giannopoulou, Archontia C.; Jansen, Bart M. P.; Lokshтанov, Daniel; Saurabh, Saket  
**Main reference** A. C. Giannopoulou, B. M. P. Jansen, D. Lokshтанov, S. Saurabh, “Uniform Kernelization Complexity of Hitting Forbidden Minors,” arXiv:1502.03965v1 [cs.DS], 2015.  
**URL** <http://arxiv.org/abs/1502.03965v1>

Several results are known concerning the optimality of the sizes of problem kernels. For example, a result of Dell and van Melkebeek shows that  $k$ -VERTEX COVER does not have a kernel with  $O(k^{2-\epsilon})$  bits, for any positive  $\epsilon$ , unless NP is in coNP/poly. For other problems, we are much further from establishing the optimal kernel size. A large family of vertex deletion problems can be captured in the framework of  $\mathcal{F}$ -MINOR-FREE DELETION problems. For a fixed, finite family  $\mathcal{F}$ , the  $\mathcal{F}$ -MINOR-FREE DELETION problem takes as input a graph  $G$  and an integer  $k$ , and asks whether  $k$  vertices can be removed from  $G$  such that the resulting graph does not contain any graph in  $\mathcal{F}$  as a minor. This generalizes  $k$ -VERTEX COVER,  $k$ -FEEDBACK VERTEX SET,  $k$ -VERTEX PLANARIZATION, and other problems. A breakthrough result by Fomin et al. (FOCS 2012) shows that if  $\mathcal{F}$  contains a planar graph (implying that  $\mathcal{F}$ -minor-free graphs have constant treewidth),  $\mathcal{F}$ -MINOR-FREE DELETION has a polynomial kernel. Concretely, there is a function  $g$  (which is not known to be computable) such that  $\mathcal{F}$ -MINOR-FREE DELETION has a kernel with  $O(k^{g(\mathcal{F})})$  vertices. As  $\mathcal{F}$ -MINOR-FREE DELETION captures a large number of classical problems, it would be desirable to find kernels of optimal size. A first question towards finding the optimal kernel size for such problems is whether  $\mathcal{F}$ -MINOR-FREE DELETION has kernels of uniformly polynomial size, i.e., of size  $g(\mathcal{F}) \cdot k^c$  for some constant  $c$  that does not depend on the family  $\mathcal{F}$ . We show that this is not the case: assuming NP is not in coNP/poly,  $\mathcal{F}$ -MINOR-FREE DELETION does not have uniformly polynomial kernels. We can also prove the following contrasting, positive result: there is a function  $g$  such that for every  $t$ , the TREEDPTH- $t$  DELETION problem has a kernel with  $g(k) \cdot k^c$  vertices for a small, absolute constant  $c$ . Since for every fixed  $t$ , TREEDPTH- $t$  DELETION is an instance of  $\mathcal{F}$ -MINOR-FREE DELETION, this shows that when the family of forbidden minors enforce sufficient structure on the solution graphs, uniformly polynomial kernels can be obtained. Our results therefore form the first step into analyzing exactly which aspects of the family of forbidden minors determine the degree of the polynomial in the optimal kernel size.

### 3.9 Parameterized Complexity of Mixed Chinese Postman Problem

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**Joint work of** Gutin, Gregory; Jones, Mark; Wahlstrom, Magnus  
**Main reference** G. Gutin, M. Jones, M. Wahlstrom, “Structural Parameterizations of the Mixed Chinese Postman Problem,” arXiv:1410.5191v3 [cs.CC], 2015.  
**URL** <http://arxiv.org/abs/1410.5191v3>

Given a mixed graph  $G$ , the MIXED CHINESE POSTMAN PROBLEM (MCP) asks us to find a minimum weight closed walk traversing each edge and arc at least once. The MCP parameterized by the number of edges in  $G$  or the number of arcs in  $G$  is fixed-parameter tractable as proved by van Bevern et al. (in press) and Gutin, Jones and Sheng (ESA 2014),

respectively. The parameterized complexity of MCPP with respect to treewidth was an open question of van Bevern et al. Answering this question, we show that somewhat unexpectedly, MCPP is  $W[1]$ -hard with respect to not only treewidth but also pathwidth. On the positive side, we show that MCPP is fixed-parameter tractable (FPT) with respect to treedepth. We are unaware of any natural graph parameters between pathwidth and treedepth and so our results provide a dichotomy of the complexity of MCPP. Furthermore, to the best of our knowledge MCPP is the first natural problem known to be  $W[1]$ -hard with respect to treewidth but FPT with respect to treedepth.

### 3.10 Flip Distance is in FPT time $O(n + k \cdot c^k)$

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**Joint work of** Kanj, Iyad; Xia, Ge

**Main reference** I. Kanj, G. Xia, “Flip Distance is in FPT time  $O(n + k \cdot c^k)$ ,” arXiv:1407.1525v1 [cs.DS], 2014.

**URL** <http://arxiv.org/abs/1407.1525v1>

Let  $\mathcal{T}$  be a triangulation of a set  $\mathcal{P}$  of  $n$  points in the plane, and let  $e$  be an edge shared by two triangles in  $\mathcal{T}$  such that the quadrilateral  $Q$  formed by these two triangles is convex. A *flip* of  $e$  is the operation of replacing  $e$  by the other diagonal of  $Q$  to obtain a new triangulation of  $\mathcal{P}$  from  $\mathcal{T}$ . The *flip distance* between two triangulations of  $\mathcal{P}$  is the minimum number of flips needed to transform one triangulation into the other. The FLIP DISTANCE problem asks if the flip distance between two given triangulations of  $\mathcal{P}$  is  $k$ , for some given  $k \in \mathbb{N}$ . It is a fundamental and a challenging problem whose complexity for the case of triangulations of a convex polygon remains open for over 25 years. In this talk we present an algorithm for FLIP DISTANCE that runs in time  $O(n + k \cdot c^k)$ , for a constant  $c \leq 2 \cdot 14^{11}$ , which implies that the problem is fixed-parameter tractable. The NP-hardness reduction for FLIP DISTANCE given by Lubiw and Pathak can be used to show that, unless the Exponential Time Hypothesis fails, FLIP DISTANCE cannot be solved in time  $O^*(2^{o(k)})$ . Therefore, one cannot expect an asymptotic improvement in the exponent of the running time of our algorithm.

### 3.11 Fast Witness Extraction Using a Decision Oracle

Łukasz Kowalik (University of Warsaw, PL)

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**Joint work of** Björklund, Andreas; Kaski Petteri; Kowalik, Łukasz

**Main reference** A. Björklund, P. Kaski, Ł. Kowalik “Fast Witness Extraction Using a Decision Oracle,” in Proc. of the 22th Annual European Symposium on Algorithms (ESA’14), LNCS, Vol. 8737, pp. 149–160, Springer, 2014.

**URL** [http://dx.doi.org/10.1007/978-3-662-44777-2\\_13](http://dx.doi.org/10.1007/978-3-662-44777-2_13)

The gist of many (NP-)hard combinatorial problems is to decide whether a universe of  $n$  elements contains a witness consisting of  $k$  elements that match some prescribed pattern. For some of these problems there are known advanced algebra-based FPT algorithms which solve the decision problem but do not return the witness. We investigate techniques for turning such a YES/NO-decision oracle into an algorithm for extracting a single witness, with an objective to obtain practical scalability for large values of  $n$ . By relying on techniques

from combinatorial group testing, we demonstrate that a witness may be extracted with  $O(k \log n)$  queries to either a deterministic or a randomized set inclusion oracle with one-sided probability of error. Furthermore, we demonstrate through implementation and experiments that the algebra-based FPT algorithms are practical, in particular in the setting of the  $k$ -PATH problem. Also discussed are engineering issues such as optimizing finite field arithmetic.

### 3.12 Tutorial: Every Graph is Easy or Hard: Dichotomy Theorems for Graph Problems

*Dániel Marx (Hungarian Academy of Sciences – Budapest, HU)*

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Given a family of algorithmic problems, a dichotomy theorem characterizes each member of the family either as “easy” or as “hard.” A classical example is the result of Hell and Nešetřil classifying the complexity of  $H$ -COLORING for every fixed  $H$ : it is polynomial-time solvable if  $H$  is bipartite and NP-hard for *every* nonbipartite graph. Some dichotomy theorems characterize the complexity of a family of problems in a more general setting, where a problem in the family is defined not just by fixing a single graph  $H$ , but by fixing a (potentially infinite) *class* of graphs. For example, a result of Grohe characterizes the complexity of graph homomorphisms when the left-hand side graph is restricted to be a member of a fixed class of graphs. In the talk, we survey classical and recent dichotomy theorems arising in the context of graph problems.

### 3.13 PointLine Cover: The Easy Kernel is Essentially the Best

*Geevarghese Philip (MPI für Informatik – Saarbrücken, DE)*

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**Joint work of** Kratsch, Stefan; Philip, Geevarghese; Ray, Saurabh

**Main reference** S. Kratsch, G. Philip, S. Ray, “Point Line Cover: The Easy Kernel is Essentially Tight,” in Proc. of the 25th Annual ACM-SIAM Symp. on Discrete Algorithms (SODA’14), pp. 1596–1606, SIAM, 2014.

**URL** <http://dx.doi.org/10.1137/1.9781611973402.116>

The input to the NP-hard POINT LINE COVER problem (PLC) consists of a set  $P$  of  $n$  points on the plane and a positive integer  $k$ , and the question is whether there exists a set of at most  $k$  lines which pass through all points in  $P$ . By straightforward reduction rules one can efficiently reduce any input to one with at most  $k^2$  points. We show that this easy reduction is essentially tight under standard assumptions. More precisely, we show that unless the polynomial hierarchy collapses to its third level, for any  $\epsilon > 0$ , there is no polynomial-time algorithm that reduces every instance  $(P, k)$  of PLC to an equivalent instance with  $O(k^{2-\epsilon})$  points. This answers, in the negative, an open problem posed by Lokshtanov (PhD Thesis, 2009). Our proof uses the machinery for deriving lower bounds on the *size* of kernels developed by Dell and van Melkebeek (STOC 2010, JACM 2014). It has two main ingredients: We first show, by a reduction from VERTEX COVER, that unless the polynomial hierarchy collapses, PLC has no kernel of *total size*  $O(k^{2-\epsilon})$  bits. This does not directly imply the claimed lower bound on the *number of points*, since the best known

polynomial-time encoding of a PLC instance with  $n$  points requires  $\omega(n^2)$  bits. To get around this hurdle we build on work of Alon (Mathematika, 1986) and devise an *oracle communication protocol* of cost  $O(n \log n)$  for PLC. This protocol, together with the lower bound on the total size (which also holds for such protocols), yields the stated lower bound on the number of points. While a number of essentially tight polynomial lower bounds on total sizes of kernels are known, our result is to the best of our knowledge, the first to show a nontrivial lower bound for structural/secondary parameters.

### 3.14 Hitting Forbidden Subgraphs in Graphs of Bounded Treewidth

*Marcin Pilipczuk (University of Warwick, GB)*

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**Joint work of** Cygan, Marek; Marx, Dániel; Pilipczuk, Marcin; Pilipczuk, Michał

**Main reference** M. Cygan, D. Marx, M. Pilipczuk, M. Pilipczuk, “Hitting Forbidden Subgraphs in Graphs of Bounded Treewidth,” in Proc. of the 39th Int’l Symp. on Mathematical Foundations of Computer Science 2014 (MFCS’14), LNCS, Vol. 8635, pp. 189–200, Springer, 2014.

**URL** [http://dx.doi.org/10.1007/978-3-662-44465-8\\_17](http://dx.doi.org/10.1007/978-3-662-44465-8_17)

We study the complexity of a generic hitting problem  $H$ -SUBGRAPH HITTING where given a fixed pattern graph  $H$  and an input graph  $G$ , the task is to find a set  $X \subseteq V(G)$  of minimum size that hits all subgraphs of  $G$  isomorphic to  $H$ . In the colorful variant of the problem, each vertex of  $G$  is precolored with some color from  $V(H)$  and we require to hit only  $H$ -subgraphs with matching colors. Standard techniques shows that for every fixed  $H$ , the problem is fixed-parameter tractable parameterized by the treewidth of  $G$ ; however, it is not clear how exactly the running time should depend on treewidth. For the colorful variant, we demonstrate matching upper and lower bounds showing that the dependence of the running time on treewidth of  $G$  is tightly governed by  $\mu(H)$ , the maximum size of a minimal vertex separator in  $H$ . That is, we show for every fixed  $H$  that, on a graph of treewidth  $t$ , the colorful problem can be solved in time  $2^{\mathcal{O}(t^{\mu(H)})} \cdot |V(G)|$ , but cannot be solved in time  $2^{o(t^{\mu(H)})} \cdot |V(G)|^{O(1)}$ , assuming the Exponential Time Hypothesis (ETH). Furthermore, we give some preliminary results showing that, in the absence of colors, the parameterized complexity landscape of  $H$ -SUBGRAPH HITTING is much richer. A preliminary version of this work appeared at MFCS 2014.

### 3.15 Tutorial: Lower Bounds Based on the Exponential Time Hypothesis – Part 2

*Michał Pilipczuk (University of Warsaw, PL)*

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**Joint work of** Cygan, Marek; Fomin, Fedor; Kowalik, Łukasz; Lokshtanov, Daniel; Marx, Dániel; Pilipczuk, Marcin; Pilipczuk; Saurabh, Saket

During the second part of the tutorial on lower bounds based on ETH, we shall see two examples of specific methodologies for proving negative results about the existence of parameterized algorithms with a certain form of the running time. Firstly, we look into problems that are solvable in slightly-superexponential running time, i.e.,  $O^*(2^{O(k \log k)})$ , and then we examine geometric and planar problems for which XP algorithms with running time  $n^{O(\sqrt{k})}$  exist. For both of these families, ETH can be used to pinpoint the optimum form of the running time of a parameterized algorithm solving the problem.

### 3.16 Tree Deletion Set Has a Polynomial Kernel (but no $OPT^{O(1)}$ Approximation)

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**Joint work of** Giannopoulou, Archontia C.; Lokshtanov, Daniel; Saurabh, Saket; Suchý, Ondrej  
**Main reference** A. C. Giannopoulou, D. Lokshtanov, S. Saurabh, O. Suchý, “Tree Deletion Set Has a Polynomial Kernel (but no  $OPT^{O(1)}$  Approximation),” in Proc. of the 34th Int’l Conf. on Foundations of Software Technology and Theoretical Computer Science (FSTTCS’14), LIPIcs, Vol. 29, pp. 85-96, 2014.

**URL** <http://dx.doi.org/10.4230/LIPIcs.FSTTCS.2014.85>

In the TREE DELETION SET problem the input is a graph  $G$  together with an integer  $k$ . The objective is to determine whether there exists a set  $S$  of at most  $k$  vertices such that  $G \setminus S$  is a tree. The problem is NP-complete and even NP-hard to approximate within any factor of  $OPT^c$  for any constant  $c$ . In this talk we give an  $O(k^5)$  size kernel for TREE DELETION SET. An appealing feature of our kernelization algorithm is a new reduction rule, based on system of linear equations, that we use to handle the instances on which TREE DELETION SET is hard to approximate.

### 3.17 Backdoors, Satisfiability, and Problems Beyond NP

Stefan Szeider (TU Wien, AT)

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In this talk I will survey parameterized complexity results for problems related to finding and using backdoors, mainly focusing on the propositional satisfiability problem (SAT). In addition I will discuss recent results on using backdoors to break through complexity barriers between higher levels of the Polynomial Hierarchy.

#### References

- 1 Serge Gaspers and Stefan Szeider. *Backdoors to Satisfaction*. Survey paper. The Multivariate Algorithmic Revolution and Beyond – Essays Dedicated to Michael R. Fellows on the Occasion of His 60th Birthday (Hans L. Bodlaender, Rod Downey, Fedor V. Fomin, Dániel Marx, eds.), volume 7370 of LNCS, pp. 287–317, Springer, 2012.
- 2 Ronald de Haan and Stefan Szeider. *Compendium of Parameterized Problems at Higher Levels of the Polynomial Hierarchy*. Electronic Colloquium on Computational Complexity (ECCC) 21:143 (2014). <http://eccc.hpi-web.de/report/2014/143/>

### 3.18 Tutorial: Implications of Strong ETH for Polynomial Time Solvable Problems

Virginia Vassilevska Williams (Stanford University, US)

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**Joint work of** Vassilevska Williams, Virginia; Roditty, Liam; Abboud, Amir; Weimann, Oren

The Strong Exponential Time Hypothesis (SETH) asserts that there is no  $2^{(1-\epsilon)n} \text{poly}(m)$  time algorithm (for constant  $\epsilon > 0$ ) that solves  $k$ -SAT (for arbitrary  $k$ ) formulas on  $n$

variables and  $m$  clauses. Although unproven, SETH has been a popular conjecture. Recent research has resulted in a variety of conditional lower bounds based on SETH for wide-studied problems within polynomial time. In this talk I will survey some of these. Some examples of results that would refute SETH include:

- a truly subquadratic time 1.499-approximation algorithm for the diameter problem in sparse graphs,
- any fully dynamic algorithm for maintaining the number strongly connected components of a directed graph with nontrivial update time and
- a truly subquadratic time algorithm for local sequence alignment.

### 3.19 Parameterized Complexity of the $k$ -Chinese Postman Problem

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**Joint work of** Gutin, Gregory; Mucciaccia, Gabriele; Yeo, Anders

**Main reference** G. Gutin, G. Mucciaccia, A. Yeo, “Parameterized complexity of  $k$ -Chinese Postman Problem,” *Theoretical Computer Science*, 513(2013):124–128; pre-print available as arXiv:1308.0482v2 [cs.DS], 2013.

**URL** <http://dx.doi.org/10.1016/j.tcs.2013.10.012>

**URL** <http://arxiv.org/abs/1308.0482v2>

We consider the following problem called the  $k$ -CHINESE POSTMAN PROBLEM ( $k$ -CPP): given a connected edge-weighted graph  $G$  and integers  $p$  and  $k$ , decide whether there are at least  $k$  closed walks such that every edge of  $G$  is contained in at least one of them and the total weight of the edges in the walks is at most  $p$ ? The problem  $k$ -CPP is NP-complete, and van Bevern et al. and Sorge asked whether the  $k$ -CPP is fixed-parameter tractable when parameterized by  $k$ . We will prove that the  $k$ -CPP is indeed fixed-parameter tractable. In fact, we prove a stronger result: the problem admits a kernel with  $O(k^2 \log k)$  vertices.

### 3.20 On Graph Motif Problems Parameterized by Dual

*Christian Komusiewicz (TU Berlin, DE)*

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**Joint work of** Komusiewicz, Christian; Fertin, Guillaume

**Main reference** Work in progress

The GRAPH MOTIF problem has as input a vertex-colored graph  $G = (V, E)$  with  $k$  different vertex colors and asks whether there is a connected subgraph on  $k$  vertices containing each color exactly once. We study GRAPH MOTIF parameterized by  $\ell = |V| - k$ . For general graphs we show that, assuming the strong exponential time hypothesis, a previous  $O(2^\ell \cdot |E|)$  time algorithm is optimal. We then provide a faster algorithm for trees. We also consider the LIST-COLORED GRAPH MOTIF problem. In this extension of GRAPH MOTIF each vertex may choose its color from a list of colors. For this variant, we strengthen previous hardness results by showing for example that the problem remains W[1]-hard when the color lists have length at most two.

### 3.21 The Complexity of Geometric Problems in High Dimension

*Christian Knauer (Universität Bayreuth, DE)*

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Many important NP-hard geometric problems in  $\mathbb{R}^d$  are trivially solvable in time  $n^{O(d)}$  (where  $n$  is the size of the input), but such a time dependency quickly becomes intractable for higher-dimensional data, and thus it is interesting to ask whether the dependency on  $d$  can be mildened. We try to address this question by applying techniques from parameterized complexity theory.

More precisely, we describe two different approaches to show parameterized intractability of such problems: A framework that gives fpt-reductions from the  $k$ -clique problem to a large class of geometric problems in  $\mathbb{R}^d$ , and a different approach that gives fpt-reductions from the  $k$ -SUM problem.

While the second approach seems conceptually simpler, the first approach often yields stronger results, in that it further implies that the  $d$ -dimensional problems reduced to cannot be solved in time  $n^{o(d)}$ , unless the Exponential Time Hypothesis (ETH) is false.

### 3.22 Tutorial: Lower Bounds Based on the Strong Exponential Time Hypothesis

*Daniel Lokshтанov (University of Bergen, NO)*

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**Joint work of** Cygan, Marek; Fomin, Fedor; Kowalik, Łukasz; Lokshтанov, Daniel; Marx, Dániel; Pilipczuk, Marcin; Pilipczuk; Saurabh, Saket

This talk will be an introduction to lower bounds based on the Strong Exponential Time Hypothesis (SETH). We will discuss the hypothesis itself, as well as the different kinds of lower bounds that can be obtained assuming the SETH. We also discuss related research directions and open problems.

### 3.23 Fixed-Parameter Tractable Canonization and Isomorphism Test for Graphs of Bounded Treewidth

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**Joint work of** Lokshтанov, Daniel; Pilipczuk, Marcin; Pilipczuk, Michał; Saurabh, Saket  
**Main reference** D. Lokshтанov, M. Pilipczuk, M. Pilipczuk, S. Saurabh, “Fixed-parameter tractable canonization and isomorphism test for graphs of bounded treewidth,” in Proc. of the 55th IEEE Annual Symposium on Foundations of Computer Science (FOCS’14), pp. 186–195, IEEE, 2014.  
**URL** <http://dx.doi.org/10.1109/FOCS.2014.28>

We give a fixed-parameter tractable algorithm that, given a parameter  $k$  and two graphs  $G_1, G_2$ , either concludes that one of these graphs has treewidth at least  $k$ , or determines whether  $G_1$  and  $G_2$  are isomorphic. The running time of the algorithm on an  $n$ -vertex graph is  $2^{O(k^5 \log k)} \cdot n^5$ , and this is the first fixed-parameter algorithm for GRAPH ISOMORPHISM parameterized by treewidth.

Our algorithm in fact solves the more general CANONIZATION problem. We design a procedure working in  $2^{O(k^5 \log k)} \cdot n^5$  time that, for a given graph  $G$  on  $n$  vertices, either concludes that the treewidth of  $G$  is at least  $k$ , or:

- finds in an isomorphic-invariant way a graph  $\tau(G)$  that is isomorphic to  $G$ ;
- finds an isomorphism-invariant *construction term* – an algebraic expression that encodes  $G$  together with a tree decomposition of  $G$  of width  $O(k^4)$ .

Hence, the isomorphism test reduces to verifying whether the computed isomorphic copies or the construction terms for  $G_1$  and  $G_2$  are equal.

### 3.24 Fast Modular Permanents

*Andreas Björklund, (Lund University, SE)*

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Joint work of Björklund, Andreas; Husfeldt, Thore; Lyckberg, Isak

We show that the permanent of an integer  $n \times n$  matrix  $M$  can be computed in  $2^{n - \Omega(n/(d \log d))}$  time in expectation, when you know a bound on the permanent  $|per(M)| \leq d^n$ . This complements results for 0/1-matrices with  $d$  ones per row by Izumi and Wadayama (FOCS, 2012), and by Cygan and Pilipczuk (ICALP, 2013), in a surprisingly straight-forward way. Instead of explicitly using that many entries are zero in the matrix, we use that when the permanent is relatively small (as it is in sparse 0/1 matrices), we can employ Chinese remaindering and modular permanents to get almost the same asymptotic result for every sparse matrix with small non-zero elements, but for many matrices it gives better bounds. In particular, a random  $\{-1, 0, 1\}$ -matrix with  $d$  non-zero elements per row on average, with the non-zero elements sampled uniformly and independently from  $\{-1, 1\}$ , can be solved in  $2^{n - \Omega(n/(\sqrt{d} \log d))}$  expected time.

We use several ideas from Bax and Franklin's result on 0/1 permanent computation to get a fast algorithm for computing a permanent modulo  $p^m$  for prime  $p$ . In particular, we show that the permanent modulo  $2^k$  for  $k > 1$  can be computed in  $kn^{k+1}$  time, improving on Valiant's  $n^{4k-3}$  time algorithm from 1980.

## 4 Open Problems

### 4.1 Solving ILPF in Single Exponential Time in the Number of Variables

Stefan Kratsch (TU Berlin, DE)

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Given a matrix  $A \in \mathbb{Z}^{m \times p}$  and a vector  $b \in \mathbb{Z}^m$ , INTEGER LINEAR PROGRAMMING FEASIBILITY (ILPF) asks you to find a vector  $x \in \mathbb{Z}^p$  such that  $Ax \leq b$ .

#### Question

Is there a  $c^p m^{O(1)}$  time algorithm for some constant  $c$ , that solves ILPF?

#### Remark

The best known algorithm has running time  $p^{O(p)} m^{O(1)}$  [1].

#### References

- 1 Ravi Kannan. Minkowski's convex body theorem and integer programming. *Math. Oper. Res.*, 12(3):415–440, August 1987.

### 4.2 Parameterized Cutwidth

Saket Saurabh (The Institute of Mathematical Sciences, IN)

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Given a graph  $G$  and an integer  $w$  CUTWIDTH asks if there is a linear ordering of the vertices of  $G$  such that any vertical line intersects at most  $w$  edges.

#### Question

- Is there an XP-algorithm for CUTWIDTH parameterized by treewidth?
- Is there an XP-algorithm for CUTWIDTH parameterized by the size of the minimal feedback vertex set?

### 4.3 Batched $k$ -CNF

Virginia Vassilevska Williams (Stanford University, US)

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#### Question

Is there an  $\epsilon > 0$  and an integer  $l \geq 1$  such that for all integers  $k$  and for all  $n$ , for any  $k$ -CNF formula  $F$  over  $n$  variables  $x_1, \dots, x_n$ , the question of whether:

$$\forall x_1, \dots, x_{n/l} \exists x_{n/l+1}, \dots, x_{2n/l} \forall x_{2n/l+1}, \dots, x_{3n/l} \exists \forall \dots \exists x_{n-n/l+1}, \dots, x_n F(x_1, \dots, x_n)$$

is true can be decided in time  $O^*(2^{(1-\epsilon)n})$ ?

## 4.4 Does Bounded Cliquewidth Imply Bounded Linear Cliquewidth?

Daniel Lokshantov (*University of Bergen, NO*)

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The cliquewidth of a graph  $G$  is the minimum number of labels needed to construct  $G$  by applying the following four operations:

- creating of a new vertex  $v$  with label  $i$ ,
- taking the disjoint union of two labeled graphs  $G$  and  $H$ ,
- making every vertex labeled  $i$  adjacent to every vertex labeled  $j$  and
- renaming label  $i$  to label  $j$ .

The linear cliquewidth of a graph  $G$  is defined as a restricted version of cliquewidth where one is only allowed to take the disjoint union of  $G$  and  $H$  if at least one of  $G$  and  $H$  is a graph on a single vertex.

### Question

Let  $\mathcal{F}_k$  be the class of minimal forbidden induced subgraphs in the class of graphs with cliquewidth at most  $k$ . Is there a function  $f: \mathbb{N} \rightarrow \mathbb{N}$  such that the linear cliquewidth of every graph in  $\mathcal{F}_k$  is bounded by  $f(k)$ ?

### Remark

This question is supposed to help on the road to proving that CLIQUEWIDTH is in FPT.

## 4.5 Quadratic Kernel for Planar Steiner Tree

Michał Pilipczuk (*University of Warsaw, PL*)

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Given a planar graph  $G$ , a set of terminals  $T \subseteq V(G)$  and an integer  $k$ , PLANAR STEINER TREE asks for a set of vertices  $X \subseteq V(G)$  of size at most  $k$  such that  $G[V \cup T]$  is connected.

### Question

Does PLANAR STEINER TREE admit a kernel with  $O(k^2)$  many vertices?

### Remark

PLANER STEINER TREE has a kernel of size  $O(k^{142})$  [1].

### References

- 1 M. Pilipczuk, M. Pilipczuk, P. Sankowski, and E.J. Van Leeuwen. Network sparsification for steiner problems on planar and bounded-genus graphs. In *Foundations of Computer Science (FOCS), 2014 IEEE 55th Annual Symposium on*, pages 276–285, Oct 2014.

## 4.6 From Parity Set Cover to Parity SAT

Holger Dell (*Universität des Saarlandes, DE*)

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Given a universe  $U$  of size  $n$ , a set family  $\mathcal{F} \subseteq 2^U$  of size  $m$  and an integer  $t$ ,  $\oplus$ SET COVER asks if the number of subsets  $\mathcal{X} \subseteq \mathcal{F}$  of size at most  $t$  such that  $\bigcup \mathcal{X} = U$  is odd. Similarly,  $\oplus$ SAT asks if the number of satisfying assignments of a SAT-instance is odd.

A serf-reduction is a reduction that preserves sub-exponential running times. Meaning that the resulting instance should be linear in the original instance and not require more than sub-exponential time to compute [2].

### Question

Cygan et al. [1] gave a serf-reduction from  $\oplus$ SAT to  $\oplus$ SET COVER. Is there a serf-reduction from  $\oplus$ SET COVER to  $\oplus$ SAT?

### References

- 1 Marek Cygan, Holger Dell, Daniel Lokshtanov, Dániel Marx, Jesper Nederlof, Yoshio Okamoto, Ramamohan Paturi, Saket Saurabh, and Magnus Wahlström. On problems as hard as CNF-SAT. In *Proceedings of the 27th Conference on Computational Complexity, CCC 2012, Porto, Portugal, June 26–29, 2012*, pages 74–84.
- 2 Russell Impagliazzo, Ramamohan Paturi, and Francis Zane. Which problems have strongly exponential complexity? In *Foundations of Computer Science, 1998. Proceedings. 39th Annual Symposium on*, pages 653–662. IEEE, 1998.

## 4.7 Lower Bounds for Computing Treewidth

Hans L. Bodlaender (*Utrecht University, NL*)

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### Question

Is there a lower bound on the time complexity for computing the treewidth of a graph? For example, is an  $2^{O(k)}n^{O(1)}$  algorithm impossible under ETH?

## 4.8 TSP Below Average on Digraphs

Gregory Z. Gutin (*Royal Holloway University of London, GB*)

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Let  $G$  be a complete digraph with integral weights on the arcs,  $h$  the average weight of a Hamiltonian cycle in  $G$  and  $k$  an integer. Then TSP BELOW AVERAGE asks whether there is a Hamiltonian cycle in  $G$  of weight at most  $h - k$ .

**Question**

Is TSP BELOW AVERAGE in FPT when parameterized by  $k$ ?

**Remark**

It has been proven that TSP BELOW AVERAGE is in FPT when parameterized by  $k$  if  $G$  is a complete, undirected graph [1].

**References**

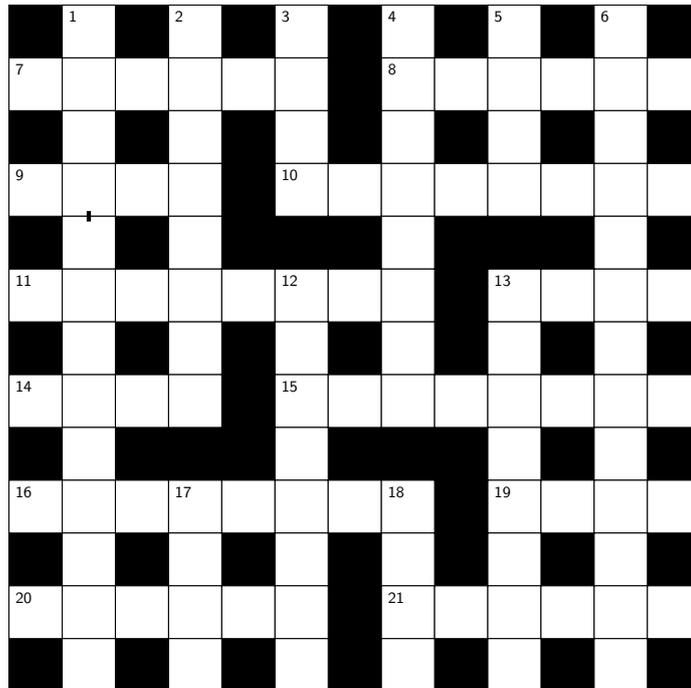
- 1 Gregory Gutin and Viresh Patel. Parameterized TSP: beating the average. *CoRR*, abs/1408.0531, 2014.

## 5 Puzzles

### 5.1 Cryptic Crossword

Thore Husfeldt (IT University of Copenhagen, DK)

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#### Across

- 7** Freethinker Nelson hides a smaller problem. (6)  
**8** Mr No is crazy for graphs like  $K_5$  and  $K_{3,3}$ . (6)  
**9** Remote application for algorithm rejected initially. (4)  
**10** Uppermost parts of perennial Unix command for displaying acyclic graph in PostScript? (8)  
**11** Peer pressured? (8)  
**13** Gadget for viewing booty in the mirror. (4)  
**14** Leaders of Japanese universities lament yearly when ICALP is. (4)  
**15** The German left room before Erik Demaine briefly blushed. (8)  
**16** Holger Dell, perhaps, to date teen in disguise. (8)  
**19** At the start of reduction, apply a trick. (4)  
**20** Rod is covered in soft hair, reportedly. (6)  
**21** Importance of mean and variance, for instance. (6)

#### Down

- 1** Important concept in exponential time complexity is belittling to slave. (4-9)  
**2** A connected, bridgeless cubic graph with chromatic index equal to 4 expresses “I love you” in a sharply critical fasion. (8)  
**3** Leaf lattice contains a set whose closure equals itself. (4)  
**4** Aunt had intercourse, as represented on a surface. (8)  
**5** Sounds like you mend one. (4)  
**6** Unix filesystem in important kernelization. (13)  
**12** Ask wordy drunk when Dagstuhl seminars take place. (8)  
**13** Robertson and Seymour’s results maybe confused me and others. (8)  
**17** Blow nose for very long running times. (4)  
**18** At first, Eppstein liked minimum spanning trees. (4)

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# Algorithmic Cheminformatics

Edited by

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## Abstract

Dagstuhl Seminar 14452 “Algorithmic Cheminformatics” brought together leading researchers from both chemistry and computer science. The meeting successfully aimed at bridging in the apparent gap between the two disciplines. The participants surveyed areas of overlapping interests and identified possible fields of joint future research.

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## 1 Executive Summary

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Dagstuhl Seminar 14452 “Algorithmic Cheminformatics” was organized to intensify the interactions between chemistry and computer science. While the thriving field of bioinformatics/computational biology is a success story of a lively and extensive inter- and trans-disciplinary collaboration between life sciences and computer science, this is much less so in cheminformatics. After a quick raise of a plethora of computational approaches for chemical problems in the 1960–1970s, the field mainly settled down on machine learning approaches in the late 1990s. Over last two decades, computer science plays a comparably marginal role in chemistry research and education.

This is a puzzling state of affairs as chemistry, and in particular the emerging field of systems chemistry, has to offer a wide range of non-trivial computational problems that are very different from those in the well-established areas of quantum chemistry, molecular dynamics, or physical chemistry, for which physics-style models and numeric mathematics have been established as the methods of choice. In particular, complex chemical networks capable of algorithmic self-assembly under far-from-equilibrium conditions, seem to possess a deep connection to the theory of computation, information recoding and compiler theory.



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Dagstuhl Seminar 14452 therefore specifically aimed to establish the connection between theoretical computer science, graph theory and related fields of discrete mathematics, and complexity theory on the one hand and chemistry on the other hand. Several key areas were covered by one or more presentation and extensive discussions among the participants. Topics ranged from formalizing chemical transformations, autocatalytic molecular systems, and the design of chemical experiments, via model checking and key graph algorithms, to chemical information technology and models for the origin of life. Dagstuhl Seminar 14452 successfully brought together wet-lab chemists with theoretical computer scientists and researchers with a focus on bioinformatics and initiated an, as we feel, very fruitful first step towards cross-boundary research.

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### 3 Overview of Talks

#### 3.1 Composition of Transformation Rules

*Jakob Lykke Andersen (University of Southern Denmark – Odense, DK)*

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We use labelled graphs and labelled graph transformation rules to model molecules and reactions patterns. This enables the generation of large chemical spaces from concise descriptions, while still maintaining an explicit model of each atom and bond. Here we present the general concept of composing transformation rules, which we as example use for increasing the practical performance of the algorithms for generating reaction networks. Using rule composition as a fundamental operation we furthermore illustrate how atom-tracing via isotope labelling can be modelled, exemplified by two chemical systems: the enzyme mechanism for beta-lactamase, and the two glycolysis pathways Embden-Meyerhof-Parnas and Entner-Doudoroff.

#### 3.2 Structure formation of peptide foldamers from first principles

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**Joint work of** Schubert, Franziska; Pagel, Kevin; Rossi, Mariana; Warnke, Stefan; Salwiczek, Mario; Kokschi, Beate; von Helden, Gert; Blum, Volker; Baldauf, Carsten; Scheffler, Matthias

**Main reference** F. Schubert, K. Pagel, M. Rossi, S. Warnke, M. Salwiczek, B. Kokschi, G. von Helden, V. Blum, C. Baldauf, M. Scheffler, "Native like helices in a specially designed  $\beta$  peptide in the gas phase," *Physical Chemistry Chemical Physics*, 17:5376–5385, 2015.

**URL** <http://dx.doi.org/10.1039/C4CP05216A>

We study the structure formation and dynamics of peptides and peptide foldamers using first-principles methods,[1] specifically we employ density-functional theory (DFT) corrected for van der Waals interactions. Navigating the conformational space of such flexible (bio-)oligomers is a challenge in itself that we currently tackle with force field based pre-sampling (with basin hopping or replica-exchange molecular dynamics) and then complement with extensive DFT calculations. We compare our results to actual gas-phase experiments, i. e., ion mobility mass spectrometry and vibrational spectroscopy (especially to work by K. Pagel at FU Berlin and G. von Helden at FHI Berlin). I would like to cover three topics in my contribution: With peptides that feature central prolyl-peptide bonds and that model  $\beta$ -turns, we studied the effect of monovalent cations on the structure formation. Cations locally disrupt the hydrogen-bonding network and enforce, by favorable electrostatic interactions, otherwise not observed conformations on the peptide's backbone.[2] Helix formation of peptides Ac-Alan-LysH<sup>+</sup> in the gas phase has been studied for years now.[3] We added a new direction by studying the effect of increased backbone flexibility on the helix forming properties. For that the  $\beta$ -peptide Ac-( $\beta$ 2hAla)<sub>6</sub>-LysH<sup>+</sup> was designed and investigated. We demonstrated for the first time that  $\beta$ -peptides from acyclic monomers can form native-like helices (similar to 3<sub>10</sub>,  $\alpha$ ,  $\pi$ ). At the same time, the stability order of the three helix types seems to be inverted with respect to their natural  $\alpha$ -peptide counterpart. Last I would like to briefly introduce our efforts towards a conformational search and sampling approach that is entirely based on DFT and avoids the use force fields. The performance of the

genetic-algorithm search is assessed by comparison to data for capped amino acids (in house reference data, to be published) and two non-natural  $\alpha/\gamma$  hybrid peptides.[4]

### References

- 1 C. Baldauf, H.-J. Hofmann. Ab initio MO Theory – An Important Tool in Foldamer Research: Prediction of Helices in Oligomers of  $\omega$ -Amino Acids. *Helv. Chim. Acta* 2012 (95), 2348–2383.
- 2 C. Baldauf, K. Pagel, S. Warnke, G. von Helden, B. Koksche, V. Blum, M. Scheffler. How Cations Change Peptide Structure. *Chem. Eur. J.* 2013 (19), 11224-1-1234.
- 3 M.F. Jarrold. Helices and Sheets in vacuo. *Phys. Chem. Chem. Phys.* 2007 (9), 1559–1671.
- 4 R. Kusaka, D. Zhang, P.S. Walsh, J.R. Gord, B.F. Fisher, S.H. Gellman, T.S. Zwier. Role of Ring-Constrained  $\gamma$ -Amino Acid Residues in  $\alpha/\gamma$ -Peptide Folding: Single-Conformation UV and IR Spectroscopy. *J. Phys. Chem. A* 2013 (117), 10847–10862.

### 3.3 Explicit-state model checking

David Dill (Stanford University, US)

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Main reference D. L. Dill, “A Retrospective on Mur $\phi$ ,” in O. Grumberg, H. Veith (eds.). “25 Years of Model Checking - History, Achievements, Perspectives,” LNCS, Vol. 5000, pp. 77–88, Springer, 2008; pre-print available from symposium webpage.

URL [http://dx.doi.org/10.1007/978-3-540-69850-0\\_5](http://dx.doi.org/10.1007/978-3-540-69850-0_5)

URL <https://www7.in.tum.de/um/25/pdf/Dill.pdf>

I did a tutorial on techniques developed in the model-checking/protocol verification community for solving the reachability problem for large implicitly-defined state graphs, with the thought that similar methods might be useful for discovering new synthesis pathways in organic chemistry. I described the basics of explicit state model checking and the optimizations of hash compaction, symmetry reduction, and partial order reduction.

### References

- 1 C. Norris Ip and David L. Dill. Better verification through symmetry. *Formal Methods in System Design*, 9(1–2):41–75, 1996.
- 2 Ulrich Stern and David L. Dill. Parallelizing the Mur $\phi$  verifier. In Orna Grumberg, editor, *9th Int’ Conf. on Computer Aided Verification*, volume 1254 of *Lecture Notes in Computer Science*, pages 256–67. Springer-Verlag, June 1997. Haifa, Isreal, June 22–25.
- 3 Ulrich Stern and David L. Dill. Using magnetic disk instead of main memory in the Mur $\phi$  verifier. In *10th Int’l Conf. on Computer Aided Verification*, pages 172–183, June 1998.

### 3.4 Molecular Codes

Peter Dittrich (Universität Jena, DE)

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Joint work of Görlich, Dennis; Dittrich, Peter

Main reference D. Görlich, P. Dittrich, “Molecular Codes in Biological and Chemical Reaction Networks,” *PLoS ONE*, 8(1):e54694, 2013.

URL <http://dx.doi.org/10.1371/journal.pone.0054694>

A molecular code is a mapping that can be realized by a reaction network and that is contingent, that is, the same reaction network can realize a different mapping using the same set of molecules as a domain and codomain of molecules as the original mapping. With

this definition we can distinguish different chemistries with respect to their ability to realize molecular codes. It seems that chemistries acquired by life can realize much more molecular codes than chemistries found in non-living systems, like the atmosphere photo-chemistry or combustion chemistries. Thus measuring contingency of mappings in a strict sense as demonstrated here might be a useful tool to get a better understanding of the emergence and of evolution of meaningful information and semiotic communication in living systems.

### 3.5 Finding the K Best Synthesis Plans

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Joint work of Fagerberg, Rolf; Flamm, Christoph; Kianian, Rojin; Merkle, Daniel; Stadler, Peter F.

Retrosynthetic synthesis planning works by transforming a target molecule into simpler precursor structures. In one version of this, first a set of bonds in the target molecule is chosen, whose removal then defines the precursor structures. In a next step, a sequence for creating these bonds is chosen, leading to a base synthesis plan. Cost measures, based on e. g. yield/loss of the reactions involved, can be associated with plans. Methods for picking the best plan for a given bond set are known, based e. g. on dynamic programming. Here, we propose to model synthesis plans for a given bond set as hyperpaths in a hypergraph. As a consequence, a polynomial time algorithm to find the K shortest hyperpaths [1] can be adapted to computing the K best synthesis plans for the bond set. Since any modeling and cost measure definition necessarily leaves out many real-world details, finding a (small) set of good plans – as opposed to merely one – allows for a chemist to choose a good plan based on additional chemical knowledge and actual wet-lab feasibility.

#### References

- 1 Lars Relund Nielsen, Kim Allan Andersen, Daniele Pretolani. Finding the K shortest hyperpaths. *Computers & Operations Research*, 32 (2005) 1477–1497

### 3.6 Beyond Numbers: Physical Simulation with Complex States

Harold Fellermann (*Newcastle University, GB*)

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Traditional test tube chemistry typically operates with few purified chemical reagents. This convenience is lost when chemical systems approach the complexity of living systems which are prone to involve a multitude of spatially arranged interacting reagents. Particularly when molecules are able to polymerize and form heteropolymers, the space of potential chemical species becomes infinite. While a plethora of computational techniques exists for finite, small-sized reaction systems, computational tools for combinatorial chemistries over infinite dimensional system spaces are still an area of active development. My talk will introduce the use of formal calculi to infer reactions in complex reaction spaces from a set of axiomatic reaction rules. The first part of the talk will demonstrate how stochastic semantics can infer reaction rates among members of a combinatorial chemical library composed of self-replicating polymers. An example chemistry is formed by self-replicating binary heteropolymers and

I will present how symmetries in the reaction network give rise to a previously unreported selection pressure toward sequences with low information content [1]. The second part of the talk showcases how formal calculi can express a more complex reaction space where reagents are encapsulated in possibly nested nano-compartments such as vesicles. DNA tags on these compartments allow for targeted microfluidic manipulation, and DNA computing operations can be used to either control or report on the outcome of reaction cascades. The overall framework allows for programmable chemistry and has been applied to both chemical production as well as molecular computing [2, 3].

### References

- 1 S. Tanaka, H. Fellermann, S. Rasmussen. *Europhys Lett* 107(2), 28004, 2014
- 2 H. Fellermann and L. Cardelli. *R. Soc. Interface* 11(99), 2014
- 3 H. Fellermann, M. Hadorn, R. Fuchsli and N. Krasnogor. *ACM J. Emerg. Tech. Comp. Sys* 11(3):24, 2014

## 3.7 Artificial Chemical Life

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**Joint work of** Hanczyc, Martin; Ikegami, Takashi

**Main reference** M. M. Hanczyc, T. Ikegami, "Chemical basis for minimal cognition." *Artificial Life*, 16(3):233–243., 2010.

**URL** [http://dx.doi.org/10.1162/artl\\_a\\_00002](http://dx.doi.org/10.1162/artl_a_00002)

We present liquid-liquid droplet systems as physical embodiments of concepts from complex systems, computer science and origin of life research. By creating droplet systems containing chemistry that are far from equilibrium, dynamics are observed governed by fluid mechanics. Dynamic properties presented are self-motion, droplet division and chemotaxis. Developing such dynamics from physical systems approaching equilibrium to something more interesting such as systems capable of decision making and evolution are discussed. Comparisons to dissipative systems as well as the Game of Life are presented.

## 3.8 Algorithms for Autocatalytic Sets

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**Main reference** W. Hordijk, "Autocatalytic sets: From the origin of life to the economy," *BioScience*, 63(11):877–881, 2013.

**URL** <http://dx.doi.org/10.1525/bio.2013.63.11.6>

Life is a functionally closed and self-sustaining chemical reaction network. During the 70s, several formal models of life based on this definition were developed independently, including hypercycles, autopoietic systems, the chemoton model, and autocatalytic sets. The notion of autocatalytic sets has been formalized as RAF theory more recently, and studied in detail in a theoretical and computational way. This has led to more insight into the possible emergence, structure, and further evolution of such sets. These studies were mostly done using a simple model of a chemical reaction system known as the binary polymer model, but the formal

framework has also been applied to real chemical networks such as an experimental system of cooperative RNA molecules and the metabolic network of *E. coli*. In this talk I will give an overview of the formal RAF framework and its main results, with an emphasis on algorithmic aspects of various computational problems related to studying the existence and structure of autocatalytic sets.

### 3.9 A Maximalism Design principle for Chemical Experiments

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**Joint work of** Hanczyc, Marti; Takashi Ikegami

**Main reference** T. Ikegami, M. M. Hanczyc, “The search for a First Cell under the Maximalism Design Principle,” *Technoetic Arts*, 7(2):153–164, 2009.

**URL** <http://dx.doi.org/10.1386/tear.7.2.153/1>

We often assume that evolution proceeds from simple to complex in various levels of description, e. g. morphology and behavioral structures. An example can be found in a suture line pattern of ammonites or the increment of the genomic size from prokaryotes to eukaryotes. In the simulation of artificial life, we tend to simulate how simple creatures develop into complex ones. Increasing complexity corresponds to the direction of evolution (or time so to speak) similar to the second law of thermodynamics. It should be noted that high entropy is not equal to high complexity, as we think living systems absorb the entropy (i. e. neg-entropy) by increasing their structural complexity. Recently, there have been many attempts to make a minimal cell in the nano and micro scales. Here the possible minimal cell would be a liposome that contains a minimal metabolic cycle for self-maintenance and self-replication. However, none of these attempts have succeeded so far (see e. g. [6]). We thus have conducted a chemical experiment: add oleic anhydride oil phase to highly alkaline water phase (pH 12) to see how the hydrolysis of the anhydride proceeds in a glass plate. Immediately the oil begins to react with the water causing the oil phase to break up into smaller spherical droplets, several to hundreds of microns in diameter. These droplets are like gliders in the game of life moving freely in the space and interacting with each other. Different from the game of life, the droplets can change direction spontaneously and coming into contact they never fuse together. In other words, they are far more robust than gliders. Also the droplets have finite life spans of less than 30 minutes and are sensitive to factors in the external environment such as pH. We argue that the mechanism of the movement is caused by the coupling of the hydrolysis reaction at the interface with the fluid dynamics of the droplet. Because of this coupling, chemical reaction lasts much longer than without the coupling. This is a “half living” state as it sustains the non-equilibrium state by its own self-regulation. A key point is that the environmental conditions (such as pH, product concentration, Reynolds number,,) are self-organized by the system itself rather than being prepared by the experimenter. If we try to obtain the same behavior by preparing the oil phase in high pH water along with some product of the reaction, the moving droplets never appear. The moving state, i. e. chemical gliders, appears through radical self-construction of the environment. We state that we cannot rely on the power of self-organization in searching for the origin of life. This is because both self-organization and the rich complex initial state are required. The ratio of the two is determined by the “rareness” of the event. Self-organization tends to simplify the final outcome limiting it to a low degree of complexity, while the low complexity assures the robustness of the outcome. The rich and complex initial state prevents the system from falling into a simple state. Therefore, we call our principle the Maximalism design principle.

## References

- 1 Hanczyc, M.M. and Ikegami, T. Chemical Basis for Minimal Cognition. *Artificial Life*. 16(3):233–243, 2010.
- 2 Hanczyc, M.M., Toyota, T., Ikegami, T., Packard, N. and Sugawara, T. Chemistry at the oil-water interface: Self-propelled oil droplets, *J. Am. Chem. Soc.* (2007); 129(30):9386–9391.
- 3 Ikegami, T and Suzuki, K. From Homeostatic to Homeodynamic Self. *BioSystems*, 91 (2008) 388-400.
- 4 Matsuno, H., Hanczyc, M.M. and Ikegami, T. Self-maintained Movements of Droplets with Convection Flow. *LNAI* 4828, 2007, pp. 179–188.
- 5 Ikegami, T. and Hanczyc, M.M. The search for a First Cell under the Maximalism Design Principle. *Technoetic Arts* 7(2):153–164, 2009.
- 6 Luisi, L. *The Emergence of Life: From Chemical Origins to Synthetic Biology*. Cambridge University Press 2006.

## 3.10 Autocatalysis and evolution in metabolic networks

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**Joint work of** Kun, Ádam; Papp, Balázs; Szathmáry, Eörs

**Main reference** Á. Kun, B. Papp, E. Szathmáry, “Computational identification of obligatorily autocatalytic replicators embedded in metabolic networks,” *Genome Biology*, 9(3):R51, 2008.

**URL** <http://dx.doi.org/10.1186/gb-2008-9-3-r51>

Autocatalysis is central to biology. Life is autocatalytic: given food, a bacterial cell can grow and divide into two more or less identical bacteria. The same argument can be made at different level of biological organization, like genes, enzymes, cells, multicellular organism, eusocial societies, etc. The minimal living entity has 3 subsystems, each of which is autocatalytic: metabolism, membrane (compartmentalization) and information storage. During the evolution of life, living organism were preceded by infrabiological systems that only had two of the above subsystems. In the widely accepted RNA world hypothesis the infrabiological system consisted of the informational and the metabolic subsystem, and compartmentalization occurred later. The compartmentalization of ribozymes (RNA enzymes) lead to the first living system, and thus this is the first major evolutionary transition. Metabolism has obligatory autocatalytic cycles. An obligatory autocatalytic cycle is one whose constituents cannot be produced from the externally available (food) molecules. It turns out that ATP, the universal energy molecule of living systems, is universally obligatory autocatalytic. We have so far analysed 24 Bacterial, 4 Archaeal, and 2 Eukaryotic genome-based metabolic reconstructions. In each of them ATP was found to be obligatory autocatalytic. In certain organisms, other cofactors, such as NAD, CoA, THF, was also found to be obligatory autocatalytic. [2] Plausible metabolic networks can be generated, but then we need to understand how and in what order did reactions in the network get enzymatic catalysis. On one hand, having more reaction catalysed result in higher yield, but more enzymes also require more biomass component to be produced to replicate the whole system. Moreover, side reactions are problematic. We have shown by numerical simulation of an enzyme-catalysed reaction chain that specialist enzymes can appear, but only after the invention of linked genes (chromosome). [1] There is still much to do. The employed reaction network was very simple, not even approaching the complexity of real metabolic network.

Algorithmic, modelling and computational innovation is required to make the transition from toy-models (which are still computationally hard) to more realistic ones.

### References

- 1 Szilágyi A.; Kun Á.; Szathmáry E. Early evolution of efficient enzymes and genome organization. *Biology Direct* 7:38, 2012.
- 2 Kun Á.; Papp B.; Szathmáry E. Computational identification of obligatorily autocatalytic replicators embedded in metabolic networks. *Genome Biology* 9:R51, 2008.

## 3.11 Architectures for Self-reproduction: Abstractions, Realisations and a Research Program

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It is well recognised that von Neumann’s seminal abstraction of machine self-reproduction can be related to the reality of biological self-reproduction – albeit only in very general terms. On the other hand, the most thoroughly studied artificial evolutionary systems, incorporating meaningful self-reproduction, are the coreworld systems such as Tierra, Avida etc.; and these, in general, rely on a purely “self-inspection” mode of reproduction (or, more simply, “replication”). To the extent that the latter has any direct biological analog it would appear to be with molecular level reproduction and evolution in the hypothesised RNA-world. In this presentation I review the details and distinctions between these modes of reproduction. I indicate how the abstract von Neumann architecture can, in fact, be readily realised in coreworld systems; and outline the research program that flows from this. Finally I present some very preliminary results from actually implementing this programme. These validate the overall concept, and the merits (in terms of feasible evolutionary experimentation, with relatively modest computational effort, and in tractable wall clock time); but highlight the rapid onset of a range of difficult challenges in analysing and making sense of the resultant experimental data sets.

### References

- 1 Adami, C. *Artificial Life, An Introduction*. Springer, 1998.
- 2 Adami, C. and Brown, C. T. Evolutionary learning in the 2D artificial life system “Avida”. In Brooks, R. A. and Maes, P., eds., *Proc. Artificial Life IV*, pp. 377–381. MIT Press, 1994.
- 3 Barricelli, N. Symbiogenetic evolution processes realized by artificial methods. *Methodos*, 9(35-36):143–182 1957.
- 4 Barricelli, N. Numerical testing of evolution theories. *Acta Biotheoretica*, 16(3):99–126 1963.
- 5 Burks, A. W., editor *Theory of Self-Reproducing Automata [by] John von Neumann*. University of Illinois Press, Urbana 1966.
- 6 Dewdney, A. K. Computer recreations: A program called mice nibbles its way to victory at the first core wars tournament. *Scientific American*, 256(1):8–11 1987.
- 7 Gilbert, W. Origin of life: The RNA world. DOI: 10.1038/319618a0, 319(6055):618–618, 1986.
- 8 McMullin, B. Architectures for self-reproduction: Abstractions, realisations and a research program. In Adami, C., Bryson, D. M., Ofria, C., and Pennock, T., R., editors, *Artificial Life 13*, pages 83–90. MIT Press 2012.

- 9 Rasmussen, S., Knudsen, C., Feldberg, R., and Hindsholm, M. The coreworld: Emergence and evolution of cooperative structures in a computational chemistry. *Physica*, 42D:111–134 1990
- 10 Ray, T. S. An approach to the synthesis of life. In Langton, C. G., Taylor, C., Farmer, J. D., and Rasmussen, S., editors, *Artificial Life II*, volume X of *Series: Santa Fe Institute Studies in the Sciences of Complexity*, pages 371–408. Addison-Wesley Publishing Company, Inc., Redwood City, California 1992.
- 11 Ray, T. S. An evolutionary approach to synthetic biology: Zen and the art of creating life. *Artificial Life*, 1:179–209 1994.
- 12 von Neumann, J. Theory and organization of complicated automata. In [5], pages 29–87 (Part One). Based on transcripts of lectures delivered at the University of Illinois, in December 1949. Edited for publication by A.W. Burks 1949.
- 13 Watson, J. D. and Crick, F. H. C. Molecular structure of nucleic acids: A structure for deoxyribose nucleic acid. *Nature*, 171:737–738 1953.

### 3.12 Generative Chemistries

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**Joint work of** Andersen, Jakob L.; Flamm, Christoph; Merkle, Daniel; Stadler, Peter F.

**Main reference** J.L. Andersen, C. Flamm, D. Merkle, P.F. Stadler, “Generic strategies for chemical space exploration,” *Int’l J. of Computational Biology and Drug Design*, 7(2–3):225–258, 2014.

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We use undirected labeled graphs and graph rewriting as a natural model for chemical compounds and chemical reactions, respectively. The combinatorial explosion that is often seen in graph grammar based chemical space exploration makes it infeasible to compute the underlying network with a breadth first expansion approach. We alleviate this problem by introducing a strategy framework that is well suited to explore chemical spaces. Within these spaces, which are formally hypergraphs, we find “Chemical Transformation Motifs” like pathways, autocatalytic patterns, or polymerization, based on various optimization techniques. Solutions provide hypothesis on an atomic level that allow, for example, for direct wet-lab verification. The Formose reaction, the Krebs cycle, the Pentose Phosphate Pathway and many more systems are examples where we applied our approaches. The tool implementing our techniques is called “MØD”. The presentation gave a gentle introduction and illustrated the approaches based on several application scenarios.

### 3.13 Systems Chemistry: Self replicators from dynamic molecular networks

*Sijbren Otto (University of Groningen, NL)*

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**Main reference** M. Malakoutikhah, J. J.-P. Peyralans, M. Colomb-Delsuc, H. Fanlo-Virgós, M. C. A. Stuart, S. Otto, “Uncovering the selection criteria for the emergence of multi-building-block replicators from dynamic combinatorial libraries,” *J. of the American Chemical Society*, 135(49):18406–18417, 2013.

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How did life start? Can we make life? These are among the most fundamental questions in contemporary science. In this talk I have shown how, starting from a mixture of relatively simple interconverting organic molecules, a set of self-replicating molecules can emerge

spontaneously. Importantly, the process of self-replication as found to be exponential, which is an important characteristic in the context of Darwinian evolution. Mutation of the replicators were enabled by providing the system with different building blocks. When mixed, these systems gave rise to the emergence of two different replicator quasi-species, of which one is the ancestor of the other. Molecular-level insight into the quasi-speciation process showed that outliers in the mutant distribution of the first quasi-species induced the formation of the second quasi-species. The next step is now to achieve replication far from equilibrium, by allowing concurrent replication and destruction processes to take place. The need and challenges for computational approaches that simulate the complex network of reactions were highlighted. Future progress requires a joined experimental and computations approach.

### 3.14 Systems chemistry and the frontiers of statistical mechanics: fruitful study systems from the Origin of Life

*Eric Smith (Santa Fe Institute, US)*

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The origin of life provides an application domain and a source of questions for cheminformatics. Some questions involve collaboration between computation and laboratory chemistry. Others involve collaboration between computation and statistical physics concepts. All of these have in common a need to extend from a theory of reactions to a theory of reaction systems. Five areas in which chemical experiments and models already exist, which invite a computational analysis, are:

- Radiation chemistry in planetary atmospheres, particularly with respect to oxidation states of carbon, which is important for early organosynthesis.
- Stable isotope chemistry in atmospheres, oceans, and the subsurface, which provides a connection between the rock record and complex atmosphere models.
- Mineral alteration chemistry in hydrothermal systems, which are likely environments for biologically important organosynthesis.
- Organic geochemistry of carbon addition at metal-sulfide surfaces, a class of reactions that may link atmospherically plausible carbon species to prebiotically relevant organic species.
- Organic reactions in solution in the presence of soluble transition metals which form metal-ligand complexes; these are known to create different reaction pathways depending on the metals present.

Another set of conceptual questions is also of interest:

- Can we create a theory of non-equilibrium phase transitions in chemistry, combining the understanding of cooperative and collective dynamics from statistical physics with the rich and heterogeneous state-space structure of chemistry.
- - What are the relations of Ross Ashby's "Law of Requisite Variety" in hierarchical control systems, and data rate theorems for error generation and error correction in chemical and catalytic systems?
- Is there a concept of a standard for chemical problems in the origin of life, in which the problem is well-defined independently of the mechanisms used to approximate a solution? Currently models of geochemical settings tend to be one-off case studies, in which the problem formulated and the particular simulation are closely intertwined, and benchmarking of the quality of solutions is difficult or is performed ad hoc.

### 3.15 Practical Graph Isomorphism

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**Joint work of** McKay, Brendan D.; Piperno, Adolfo

**Main reference** B. D. McKay, A. Piperno, “Practical Graph Isomorphism, II,” *Journal of Symbolic Computation*, 60(Jan. 2014):94–112, 2014.

**URL** <http://dx.doi.org/10.1016/j.jsc.2013.09.003>

I have presented a tutorial reporting the current state of the graph isomorphism problem from the practical point of view. After describing the general principles of the refinement-individualization paradigm and proving its validity, it has been explained how this technique is implemented in several of the key tools in the literature. In particular, the the best known program nauty and an innovative approach called Traces have been described. The presented tools are available at <http://pallini.di.uniroma1.it>

### 3.16 Exercises in Molecular Computing and Robotics

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**Joint work of** Stefanovic, Darko; Stojanovic, Milan; Macdonald, Joanne; Graves, Steven; Lakin, Matthew; Brown, Carl; Olah, Mark

When we say that molecules compute, we mean that they respond to certain inputs, for example, the presence or absence of other molecules, in a precisely defined but potentially complex fashion. The simplest way for a chemist to think about computing molecules is as sensors that can integrate the presence or absence of multiple analytes into a change in a single reporting property. In the talk, I reviewed several forms of molecular computing using concentrations of single-stranded DNA to carry signals. When we began our work, combinatorial approaches to using DNA for computing were used to search for solutions to constraint satisfaction problems. We chose to work instead on logic circuits, building bottom-up from units based on catalytic nucleic acids, focusing on DNA secondary structures in the design of individual circuit elements, and reserving the combinatorial opportunities of DNA for the representation of multiple signals propagating in a large circuit. Such circuit design directly corresponds to the intuition about sensors transforming the detection of analytes into reporting properties. While this approach was unusual at the time, it has been adopted since by other groups working on biomolecular computing with different nucleic acid chemistries. We created logic gates by modularly combining deoxyribozymes as reporting elements with stem-loops as input detection elements. For instance, a deoxyribozyme that normally exhibits an oligonucleotide substrate recognition region is modified such that a stem-loop closes onto the substrate recognition region, making it unavailable for the substrate and thus rendering the deoxyribozyme inactive. But a conformational change can then be induced by an input oligonucleotide, complementary to the loop, to open the stem, allow the substrate to bind, and allow its cleavage to proceed, which is eventually reported via fluorescence. Using multiple modifications, we constructed logic gates, and we constructed large circuits consisting of such logic gates operating in parallel, and orchestrated to carry out arithmetic operations or play simple games of strategy. To enable more complex circuits, with serial connections of gates, we recently developed buffered cascades that use the DNA strand

displacement mechanism to mediate between successive stages in the cascade, and structured substrate molecules to sequester input sequences until needed. We also used deoxyribozymes as the active components of molecular assemblies, called "molecular spiders", that can walk over surfaces and tracks prepared with substrates, cleaving the substrates in the process. I reviewed the coarse-grained models we developed to explain the experimentally observed behaviors of these molecular walkers in the bulk, contrasting their simple, uncoordinated gait with the complex, coordinated gait found in nature's protein molecular motors. Despite this simplicity, our models predict that molecular spiders exhibit a long superdiffusive transient while walking on a track, even in opposition to a force. We hope to be able to use them for cargo transport in engineered nanosystems.

### 3.17 Modeling phototrophic growth: Constraints and optimality in cyanobacterial metabolism

Ralf Steuer (*HU Berlin, DE*)

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Joint work of Steuer, Ralf; Knoop, Henning

Main reference H. Knoop, M. Gründel, Y. Zilliges, R. Lehmann, S. Hoffmann, W. Lockau, R. Steuer, "Flux balance analysis of cyanobacterial metabolism: the metabolic network of *Synechocystis* sp. PCC 6803," *PLoS Computational Biology*, 9(6):e1003081, 2013.

URL <http://dx.doi.org/10.1371/journal.pcbi.1003081>

Cyanobacteria are phototrophic microorganisms of global importance and have recently attracted renewed attention due to their capability to convert atmospheric CO<sub>2</sub> into organic compounds, including carbon-based transportation fuels and bulk chemicals. These ongoing efforts to domesticate cyanobacteria as a human resource would greatly benefit from an in-depths understanding of metabolism. Current approaches to harness the biotechnological potential of cyanobacteria are increasingly supported by integrated experimental and computational approaches to understand the systematic properties of phototrophic growth. From a modelling perspective, cyanobacteria are highly attractive organisms whose computational description spans a large number of challenging questions. In particular, a computational description of phototrophic growth must incorporate a hierarchy of processes, ranging from the biophysics of photosynthesis, the biochemistry of carbon fixation, molecular mechanisms of cellular growth, to global oxygen and carbon cycles. The contribution did outline the construction of computational models of cyanobacteria and the analysis of such models using kinetic and constraint-based methods. Computational modelling is supplemented with highly controlled growth experiments in laboratory-scale photobioreactors that allows us to determine relevant exchange fluxes. Modeling strategies include the high-quality reconstruction of stoichiometric models of cyanobacterial metabolism, their experimental validation, as well as a path towards the incorporation of kinetic properties and their temporal coordination into the description of phototrophic growth.

#### References

- 1 Henning Knoop, Marianne Gründel, Yvonne Zilliges, Robert Lehmann, Sabrina Hoffmann, Wolfgang Lockau, and Ralf Steuer. Flux balance analysis of cyanobacterial metabolism: the metabolic network of *Synechocystis* sp. PCC 6803. *PLoS Comput Biol*, 9(6):e1003081, 2013.

- 2 Henning Knoop, Yvonne Zilliges, Wolfgang Lockau, and Ralf Steuer. The metabolic network of *Synechocystis* sp. PCC 6803: systemic properties of autotrophic growth. *Plant Physiol*, 154(1):410–422, Sep 2010.
- 3 Ralf Steuer, Henning Knoop, and Rainer Machné. Modelling cyanobacteria: from metabolism to integrative models of phototrophic growth. *J Exp Bot*, 63(6):2259–2274, Mar 2012.

### 3.18 Molecular Information Technology

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Matter is animate if and only if it uses information processing to persist. My definition of life places primary importance on the computation any organism is required to continuously perform just to maintain its own complex material organization in a living state. In this real-time struggle against entropy evolution yielded information processing capabilities of formidable efficiency. The success of this molecular level computation is apparent in the marvellous architectures seen throughout biology. With laboratory experiments ranging from self-assembly and semi-biotic robotics to wet artificial neuronal networks based on Belousov Zhabotinsky medium compartmentalized in lipid coated droplets I illustrate how aspects of the molecular information processing inherent to all living systems may eventually be harvested for man-made technology. It is my view that adding molecular information technology to our engineering toolbox will allow us to overcome the complexity limit faced by synthetic chemistry and will lead to technology revolution that rivals the advent of organic chemistry.

#### References

- 1 Philip H. King, Gareth Jones, Hywel Morgan, Maurits R.R. de Planque, and Klaus-Peter Zauner. Interdroplet bilayer arrays in millifluidic droplet traps from 3D-printed moulds. *Lab on a Chip*, 14:722–729, January 2014.
- 2 Chris Lovell, Gareth Jones, Steve Gunn, and Klaus-Peter Zauner. Autonomous experimentation: Active learning for enzyme response characterisation. *JMLR: Workshop and Conference Proceedings*, 16:141–155, April 2011.
- 3 Soichiro Tsuda, Klaus-Peter Zauner, and Yukio-Pegio Gunji. Robot control with biological cells. *BioSystems*, 87:215–223, 2007.
- 4 Klaus-Peter Zauner. Molecular information technology. *Critical Reviews in Solid State and Material Sciences*, 30(1):33–69, March 2005.

## 4 Open Problems

The following list of open problems on the interface between chemistry and computer science have been identified and discussed during the seminar:

1. **General simulation methods for self-assembly systems:** Dynamic combinatorial libraries (DCL) are heavily investigated in the emerging field of Systems Chemistry. Upon physical or chemical perturbation these systems show interesting emergent phenomena such as

- fiber-formation via self-assembly processes. A formal description of these inherently combinatorial systems and efficient simulation techniques to study their dynamic behavior are not developed, as well as algorithmic methods for their rational design.
2. **Reflexive synthesis plans:** Total synthesis, i. e. the construction of a target compound from smaller, readily available building blocks, is at the core of Organic Synthesis. Synthesis plans, which are tree-like data structures, are used to summarize the necessary information for the synthesis of complex molecular structures. To give synthesis plans the property of being fail-safe they would require the presence of alternative reaction sequences to circumvent reaction steps which turn out to fail in the laboratory. A formal framework is needed to describe and computationally design synthesis plans with this “reflexivity property”.
  3. **Covering graphs with tiles (particular sub-graphs):** Terpenes and polyketides are complex, pharmaceutically important, natural products, which are formed in plants via “polymerization” of a small number of distinct building blocks of different metabolic origin. Covering these combinatorial molecular objects with their building blocks (viewed as tiles) would allow for the elucidation from which part of the plants secondary metabolism the various substructures of the natural product originated. This knowledge strongly improves the elucidation of unknown metabolic pathways to these important class of molecules.
  4. **Random graph models of chemical reaction networks:** The detection of statistically significant motives is based on a proper statistical null model. While the theory of random graph models for simple graphs is well developed, almost nothing can be found for hypergraphs, the usual formalization of chemical reaction networks. Chemistry imposes additional semantic structure onto the network, which needs to be preserved during randomization. A proper null model for chemical reaction networks would for instance allow to detect “chemical transformation motifs” in metabolic networks or chemical reaction networks in general.
  5. **Constraint constitutional isomer generator:** An important problem in Mass-Spectroscopy (MS) is the generation of constitutional isomeres from the knowledge of the molecular formula. In many cases additional chemical and physical constrains are known. Efficient algorithms which exploit additional constraints to narrow down the combinatorial space of constitutional isomeres and which are specifically designed for the chemical context are an urgent need.
  6. **MS peak perception and interpretation of small molecules:** High resolution mass-spectroscopy, a recently developed experimental technique, allows to collect information on the structure of small (organic) molecules indirectly via the mass peak of the entire molecule and the pattern of mass peaks after fragmentation of the molecule into smaller pieces. On the algorithmic side the structure elucidation from this type of data is far from complete and current methods do not scale up to the huge amounts of data collected during the measurement of the metabolomes of entire organisms.
  7. **Inverse mechanism problem (from mechanisms to real molecules):** Dynamical systems theory offers an almost complete set of tools to study the dynamics of a chemical reaction system on the level of the differential equations, which are usually derived from the underlying chemical equations. With the advent of Systems Chemistry, however, the inverse problem of specifying a set of molecules, which implement a particular dynamical system gained increasing attention. By assigning molecules to the abstract variables in the reaction equations constraints in the form of sub-graphs propagate through the reaction mechanism mapping the problem into the realm of constraint-optimization problems.

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# High-performance Graph Algorithms and Applications in Computational Science

Edited by

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## Abstract

This report documents the program and the outcomes of Dagstuhl Seminar 14461 “High-performance Graph Algorithms and Applications in Computational Science”. The seminar reflected the recent qualitative change how graph algorithms are used in practice due to (i) the complex structure of graphs in new and emerging applications, (ii) the size of typical inputs, and (iii) the computer systems on which graph problems are solved. This change is having a tremendous impact on the field of graph algorithms in terms of algorithm theory and implementation as well as hardware requirements and application areas.

The seminar covered recent advances in all these aspects with a focus on practical algorithms and their efficient implementation for large-scale problems. The abstracts included in this report contain recent state-of-the-art results, but also point to promising new directions for high-performance graph algorithms and their applications.

**Seminar** November 10–14, 2014 – <http://www.dagstuhl.de/14461>

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**Edited in cooperation with** Christian L. Staudt

## 1 Executive Summary

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Many presentations in this Dagstuhl seminar emphasized recent trends regarding typical inputs and their effect on graph algorithm development for practical purposes. One can divide these presentations into four categories: (i) Traditional graph (or matrix) problems in new scenarios, (ii) graph analytics algorithms of various sorts, (iii) parallel computing aspects



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High-performance Graph Algorithms and Applications in Computational Science, *Dagstuhl Reports*, Vol. 4, Issue 11, pp. 40–58

Editors: Ulrich Carsten Meyer, Henning Meyerhenke, Ali Pinar, and Ilya Safro



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such as tools, computational models, load balancing, and communication; and finally (iv) emerging high-performance application and hardware trends. The following four paragraphs give a brief overview over the talks presented in each of these categories.

Pothen discussed different matching problems and how the emergence of complex networks have changed various matching algorithms recently. Road networks, in turn, are by no means complex and the traditional Dijkstra algorithm solves queries on continental instances in few seconds. Yet, for more challenging scenarios, for example millions of queries per second on web servers or multiple optimization criteria, more elaborate solutions are necessary, as presented by Sanders. Toledo addressed the importance of communication efficiency on large-scale parallel systems for traditional numerical problems such as LU decomposition. A similar numerical topic was the solution of Laplacian linear systems, for which new combinatorial solvers and related techniques from the theory community were presented and discussed by Madry and by Toledo. Furthermore, Boman and Toledo initiated a tangible plan for a scientific competition on solvers for this class of linear systems.

The analytics algorithms part experienced a number of talks on graph clustering and community detection, which means the identification of natural vertex groups in graphs. Several very fast algorithms and their implementation were discussed and compared. Centralities are used for finding important (but in general unrelated) vertices or edges in a graph. Çatalyürek showed how to exploit parallelism in centrality algorithms to speed them up in different hardware settings, including accelerators. Bergamini, in turn, used approximation to obtain a speedup in dynamic graphs. Many other analytics tasks and algorithms were discussed, including anomaly detection presented by Miller and label inference by Chakrabarti, who both focused on techniques for very large graphs. Graph size was also a motivation for sparsification as discussed by Parthasarathy, either to save space or running time (or both) in later stages of an algorithmic pipeline.

Parallelism was the common theme in the third category. Here we summarize algorithmic techniques such as load balancing by graph partitioning, computational models as well as tools and middleware. Several speakers outlined challenges and/or algorithmic solutions in graph partitioning, in particular for complex networks or massively parallel systems. It became also clear that the development of graph algorithms for massive inputs benefits from suitable computational models. An example is the parallel external memory model for which Meyer as well as Veith showed algorithmic solutions. Another prerequisite for efficient graph algorithms in practice is tool support, including building block standards (proposed by Buluc) and communication middleware (presented by Lumsdaine). The pros and cons of different tools were discussed in an animated manner with the co-located Dagstuhl seminar 14462 “Systems and Algorithms for Large-scale Graph Analytics” within a joint session. The organizers are confident that this discussion has led to a better understanding of each other’s community and their contributions. We also hope and think that this exchange will lead to an accelerated dissemination of the respective leading research results across community borders.

Finally, Brugger presented innovative hardware specifically designed to support certain graph algorithms. Talks with a particular focus on innovative applications from outside the core of computer science were presented by several speakers as well. Both Srivastav and Buluc, for example, described algorithms for sequence assembly, a problem in bioinformatics with massive data sets.

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### 3 Overview of Talks

#### 3.1 Community Finding Graph Algorithms on Multicores

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**Joint work of** Ajwani, Deepak; Duriakova, Erika; Hurley, Neil; Sala, Alessandra  
**Main reference** E. Duriakova, N. Hurley, D. Ajwani, A. Sala, “Analysis of the semi-synchronous approach to large-scale parallel community finding,” in Proc. of the 2nd ACM Conf. on Online Social Networks (COSN’14), pp. 51–62, 2014.  
**URL** <http://dx.doi.org/10.1145/2660460.2660474>  
**URL** <http://cosn.acm.org/2014/files/cosn049f-duriakovaAemb.pdf>

Community-finding in graphs is the process of identifying highly cohesive vertex subsets. Many community-finding algorithms are based on the optimisation of an objective through a process of *iterative local update* (ILU), in which vertices are successively moved to the community of one of their neighbours in order to achieve the highest local gain in the quality of the objective. The sequential processing of such iterative algorithms generally benefits from an asynchronous approach, where a vertex update uses the most recent state as generated by the previous update of vertices in its neighbourhood. When vertices are distributed over a parallel machine, the asynchronous approach can encounter race conditions that impact on its performance and destroy the consistency of the results. Alternatively, a semi-synchronous approach ensures that only non-conflicting vertices are updated simultaneously. In this talk, I present our work on the semi-synchronous approach to ILU algorithms for community finding on social networks. Because of the heavy-tailed vertex distribution, the order in which vertex updates are applied in asynchronous ILU can greatly impact on both convergence time and quality of the found communities. We study the impact of ordering on the distributed label propagation and modularity maximisation algorithms implemented on a shared- memory multicore architecture. We demonstrate that the semi-synchronous ILU approach is competitive in time and quality with the asynchronous approach, while allowing the analyst to maintain consistent control over update ordering. Thus, our implementation results in a more robust and predictable performance and provides control over the order in which the node labels are updated, which is crucial to obtaining the correct trade-off between running time and quality of communities on many graph classes.

#### 3.2 Approximating Betweenness Centrality in Large Evolving Networks

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**Joint work of** Bergamini, Elisabetta; Meyerhenke, Henning; Staudt, Christian L.  
**Main reference** E. Bergamini, H. Meyerhenke, C.L. Staudt, “Approximating Betweenness Centrality in Large Evolving Networks,” in Proc. of the 17th Workshop on Algorithm Engineering and Experiments (ALENEX’15), pp. 133–146, SIAM, 2015; pre-print available as arXiv:1409.6241v1 [cs.SI].  
**URL** <http://dx.doi.org/10.1137/1.9781611973754.12>  
**URL** <http://arxiv.org/abs/1409.6241v1>

Betweenness centrality ranks the importance of nodes by their participation in all shortest paths of the network. Therefore computing exact betweenness values is impractical in large networks. For static networks, approximation based on randomly sampled paths has been shown to be significantly faster in practice. However, for dynamic networks, no approximation algorithm for betweenness centrality is known that improves on static recomputation. We

address this deficit by proposing two incremental approximation algorithms (for weighted and unweighted connected graphs) which provide a provable guarantee on the absolute approximation error. Processing batches of edge insertions, our algorithms yield significant speedups up to a factor of 104 compared to restarting the approximation. This is enabled by investing memory to store and efficiently update shortest paths. As a building block, we also propose an asymptotically faster algorithm for updating the SSSP problem in unweighted graphs. Our experimental study shows that our algorithms are the first to make in-memory computation of a betweenness ranking practical for million-edge semi-dynamic networks. Moreover, our results show that the accuracy is even better than the theoretical guarantees in terms of absolute errors and the rank of nodes is well preserved, in particular for those with high betweenness.

### 3.3 2D Partitioning for Scalable Matrix Computations on Scale-Free Graphs

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**Joint work of** Boman, Erik; Devine, Karen; Rajamanickam, Sivasankaran

**Main reference** E. G. Boman, K. D. Devine, S. Rajamanickam, “Scalable Matrix Computations on Scale-Free Graphs Using 2D Graph Partitioning,” in Proc. of the 2013 Int’l Conf. on High Performance Computing, Networking, Storage and Analysis (SC’13), Article No. 50, 12 pages, 2013.

**URL** <http://dx.doi.org/10.1145/2503210.2503293>

Scalable parallel computing is essential for processing large scale-free (power-law) graphs. The data distribution becomes important on distributed-memory computers with thousands of cores. Recently, it has been shown that 2D layouts (edge partitions) have significant advantages over traditional 1D layouts. However, the simple 2D block distribution does not use the structure of the graph, and more advanced 2D partitioning methods are too expensive for large graphs. We propose a new partitioning algorithm that combines graph or hypergraph partitioning with the 2D block distribution. The cost is essentially the same as 1D (hyper-)graph partitioning. We study the performance of sparse matrix-vector multiplication for large scale-free graphs from, e. g., social networks using several partitioners and data layouts, both 1D and 2D. We demonstrate that our new 2D method consistently outperforms the other methods considered, both for SpMV and an eigensolver, on matrices up to 1.6 billion non-zeros and up to 16,384 cores. We leave as future work a comparison to other 2D matrix partitioning methods that are not available in parallel software. (This work was first presented at SC13.)

### 3.4 Beyond the abstract machine model – How looking at real computing systems leads to new algorithmic insights and massive speedups: two case studies

*Christian Brugger (TU Kaiserslautern, DE)*

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Abstract machine models have a simplistic view on computing systems, often assuming all operations having the same cost. While this is useful for asymptotic complexity analysis, they can be misleading when trying to find the best algorithms for finite datasets. In fact

it is not uncommon to have a 3 orders of magnitude difference in the cost of two similar sounding operations. In this talk we will present a more realistic view of today's computing systems. Cover communication costs, operator costs, memory models and data formats. Based on these insights we will look at two case studies. In them we show how it is possible to formulate new algorithms exploiting these differences, resulting in faster implementations.

### 3.5 The Graph BLAS: building blocks for graph algorithms in the language of linear algebra

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**Joint work of** Buluc, Aydin; Bader, David; Gilbert, John; Gonzalez, Joseph; Kepner, Jeremy; Mattson, Timothy  
**Main reference** T. Mattson, D. Bader, J. Berry, A. Buluc, J. Dongarra, C. Faloutsos, J. Feo, J. Gilbert, J. Gonzalez, B. Hendrickson, J. Kepner, C. Leiserson, A. Lumsdaine, D. Padua, S. Poole, S. Reinhardt, M. Stonebraker, S. Wallach, A. Yoo, "Standards for graph algorithm primitives," in Proc. of the 2013 IEEE High Performance Extreme Computing Conference (HPEC'13), pp. 1–2, IEEE, 2013.  
**URL** <http://dx.doi.org/10.1109/HPEC.2013.6670338>

We believe that the state of the art in constructing a large collection of graph algorithms in terms of linear algebraic operations is mature enough to support the emergence of a standard set of primitive building blocks. It is critical to move quickly and define such a standard; thereby freeing up researchers to innovate and diversify at the level of higher level algorithms and graph analytics applications. This effort was inspired by the Basic Linear Algebra Subprograms (BLAS) of dense linear algebra and hence our working name for this standard is "the Graph BLAS". This talk will cover the rationale, minimal requirements, existing tools, best practices, and wish lists.

### 3.6 Fast Graph Centrality Computations

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**Joint work of** Sariyüce, Ahmet E.; Saule, Erik; Kaya, Kamer; Çatalyürek, Ümit V.  
**Main reference** A. E. Sariyüce, E. Saule, K. Kaya, Ü. V. Çatalyürek, "Regularizing Graph Centrality Computations," Journal of Parallel and Distributed Computing, 2014.  
**URL** <http://dx.doi.org/10.1016/j.jpdc.2014.07.006>

Centrality metrics such as betweenness and closeness have been used to identify important nodes in a network. However, it takes days to months on a high-end workstation to compute the centrality of today's networks. The main reasons are the size and the irregular structure of these networks. While today's computing units excel at processing dense and regular data, their performance is questionable when the data is sparse. In this talk, we show how centrality computations can be regularized to reach higher performance.

### 3.7 Joint Inference of Multiple Label Types in Large Networks

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**Joint work of** Chakrabarti, Deepayan; Funiak, Stanislav; Chang, Jonathan; Macskassy, Sofus

**Main reference** D. Chakrabarti, S. Funiak, J. Chang, S. A. Macskassy, “Joint Inference of Multiple Label Types in Large Networks,” in Proc. of the 31th Int’l Conf. on Machine Learning (ICML’14), JMLR Proceedings, Vol. 32, pp. 874–882, 2014.

**URL** <http://jmlr.org/proceedings/papers/v32/chakrabarti14.html>

We tackle the problem of inferring node labels in a partially labeled graph where each node in the graph has multiple label types and each label type has a large number of possible labels. Our primary example, and the focus of this paper, is the joint inference of label types such as hometown, current city, and employers, for users connected by a social network. Standard label propagation fails to consider the properties of the label types and the interactions between them. Our proposed method, called EdgeExplain, explicitly models these, while still enabling scalable inference under a distributed message-passing architecture. On a billion-node subset of the Facebook social network, EdgeExplain significantly outperforms label propagation for several label types, with lifts of up to 120% for recall@1 and 60% for recall@3.

### 3.8 GEMS – a scalable triplestore for unstructured, heterogeneous data sets

*John Feo (Pacific Northwest National Lab. – Richland, US)*

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Data collection and analysis are rapidly changing the way scientific, national security, and business communities operate. Data is no longer “owner generated,” but rather collected from web sources. American economic competitiveness and security depend increasingly on the insightful analysis of unstructured, heterogeneous web-scale data sets. The fixed schemas and tables of relational database do not support unstructured data. NoSQL database do a better job, but are poor at processing joins operations. Neither type of database naturally supports subgraph isomorphism, typed path traversal, and community detection. To perform such complex graph analytics, analysts export a small snapshot of their data into a single system image restricting their global view and paying a steep price in operational requirements. Even so, many analytical capabilities, such as determining behavior from structure, lie out of reach due to the lack of computational power.

In response to these analytic challenges, we are developing GEMS, a scalable triplestore for unstructured, heterogeneous data. The systems has three components: 1) a SPARQL front end to transform SPARQL to data parallel C code; 2) a semantic graph engine with scalable multithreaded algorithms for query processing; and 3) a custom multithreaded runtime layer for scalable performance on conventional cluster systems. Our objectives are twofold: 1) to scale system size as data sizes increase, and 2) to maintain query throughput as system size grows. We are accomplishing these objectives by targeting conventional clusters with large memory nodes, developing an in-memory graph engine, managing a fine-grain multithreaded runtime layer to hide memory latencies, and aggressively aggregating memory requests to maximize system bandwidth.

In this talk, I will discuss the data challenges facing scientists, intelligence analysts, and business leaders. I will describe the GEMS architecture focusing on the graph engine and runtime layer. I will present query patterns in cyber security, fraud, and supply chains, and performance results comparing GEMS to commercial systems.

### 3.9 Multi-Threaded Modularity Based Graph Clustering using the Multilevel Paradigm

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**Joint work of** LaSalle, Dominique; Karypis, George

**Main reference** D. LaSalle, G. Karypis, “Multi-threaded modularity based graph clustering using the multilevel paradigm,” *Journal of Parallel and Distributed Computing*, 2014.

**URL** <http://dx.doi.org/10.1016/j.jpdc.2014.09.012>

Graphs are an important tool for modeling data in many diverse domains. Recent increases in sensor technology and deployment, the adoption of online services, and the scale of VLSI circuits has caused the size of these graphs to skyrocket. Finding clusters of highly connected vertices within these graphs is a critical part of their analysis. In this work we apply the multilevel paradigm to the modularity graph clustering problem. We present fast shared-memory parallel algorithms for modularity maximization that produce clusterings of high quality. The implementation of these algorithms, Nerstrand, runs in a fraction of the time of current methods and exhibits significant speedup with less than one percent degradation of clustering quality of its serial counterpart. Nerstrand works well on large graphs, clustering a graph with over 105 million vertices and 3.3 billion edges in 90 seconds.

### 3.10 PULP: Fast and Simple Complex Network Partitioning

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**Joint work of** Slota, George; Madduri, Kamesh; Rajamanickam, Sivasankaran

**Main reference** G. M. Slota, K. Madduri, S. Rajamanickam, “PuLP: Scalable multi-objective multi-constraint partitioning for small-world networks,” in *Proc. of the 2014 IEEE Int’l Conf. on Big Data (BigData’14)*, pp. 481–490, IEEE, 2014.

**URL** <http://dx.doi.org/10.1109/BigData.2014.7004265>

Complex networks such as web crawls and social networks are known to lack good separators. The common practice in the community is to use well-known graph and hypergraph partitioners as black-box routines and hope that these tools produce good partitions (i. e., low edge cut or communication volume, while maintaining vertex balance). We argue that it is unnecessary to use existing multilevel tools for partitioning complex networks, as these tend to be quite memory- and compute-intensive for graphs with billions of vertices and edges. We design a simple and easy-to-configure parallel graph partitioner called PULP (Partitioning using Label Propagation). As the name suggests, PULP uses a “label propagation”-like initial partitioning strategy. Label propagation is a popular heuristic for the community detection problem. PULP then uses the Fiduccia-Mattheyses heuristic for refining the partitions. PULP simultaneously optimizes for multiple quality measures (total edge cut and max per-partition edge cut), while satisfying user-defined balance constraints on per-partition

edge and vertex counts. It's extremely fast: for instance, on the 1.8 billion edge Slovakian domain web crawl, PULP takes less than a minute on a single compute node, to generate a 128-way vertex partitioning. For partitioning web crawls, we find that the quality of results is comparable to existing tools.

### 3.11 Cuts, Trees, and Electrical Flows

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**Main reference** A. Madry, “Fast Approximation Algorithms for Cut-based Problems in Undirected Graphs,” in Proc. of the 51st Annual IEEE Symp. on Foundations of Computer Science (FOCS'10), pp. 245–254, IEEE CS, 2010; pre-print available as arXiv:1008.1975v4 [cs.DS].

**URL** <http://dx.doi.org/10.1109/FOCS.2010.30>

**URL** <http://arxiv.org/abs/1008.1975v4>

We discuss some of the recent developments in algorithmic graph theory that might be relevant in the context of dealing with massive graphs.

In particular, we present a general framework for obtaining close-to-linear-time approximation algorithms for cut problems in undirected graph. We also discuss the electrical flow paradigm that played key role in some of the recent progress on designing fast algorithms for fundamental flow problems.

### 3.12 Fast generation of dynamic complex networks with underlying hyperbolic geometry

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**Joint work of** von Looz, Moritz; Meyerhenke, Henning; Staudt, Christian L.; Prutkin, Roman

**Main reference** M. von Looz, C.L. Staudt, H. Meyerhenke, R. Prutkin, “Fast generation of dynamic complex networks with underlying hyperbolic geometry,” Karlsruhe Reports in Informatics; 2014,14.

**URL** <http://digbib.ubka.uni-karlsruhe.de/volltexte/1000043881>

The analysis of *complex networks* has become a highly active research area recently since complex networks are increasingly used to represent phenomena as varied as the WWW, social relations, protein interactions, and brain topology. Complex networks are usually *scale-free*, their degree distribution often follows a power law, and the typical distance between two nodes is surprisingly small, regardless of network size and growth. *Generative network models* play a central role in many complex network studies for several reasons: Real data, such as social networks, might contain confidential information, so that it is often desirable to be able to work on similar synthetic networks. Quick testing of algorithms requires small test cases, while projection of future growth and scalability studies need bigger graphs. Moreover, real networks might be impractical to transmit and store, but compression to the parameters of a model is possible.

One generative network model that has been suggested previously as fairly realistic (Krioukov et al. 2010) creates unit-disk graphs in *hyperbolic geometry*. Among the many interesting properties of hyperbolic geometry, most relevant is the *exponential expansion of space*: The area of a hyperbolic circle of radius  $r$  is  $2\pi(\cosh(r) - 1) \simeq e^r$ , allowing a natural embedding of trees and tree-like graphs. In recent years, the link between hyperbolic

geometry and graphs with power-law degree distributions has been studied with respect to routing applications (Boguña et al. 2010). The generative model has a proven high clustering coefficient (Gugelmann et al. 2012), small diameter and a power-law degree distribution with adjustable exponent (Krioukov et al. 2010).

The model distributes nodes randomly on a hyperbolic disk of radius  $R$  and edges are inserted for every node pair whose hyperbolic distance is below a threshold. Calculating the hyperbolic distance between each pair of coordinates has quadratic time complexity. This impedes the creation of massive networks and is likely the reason previously published networks based on hyperbolic geometry have been in the range of at most  $10^4$  nodes. A faster generator is necessary to enable a use of this promising model for networks of interesting scales. Additionally, to judge the realism of these networks, more detailed parameter studies and comparisons from a network analysis point of view are necessary.

As part of our study, we address deficiencies of the *hyperbolic unit-disk graph model* in terms of generation speed and network analysis. First we show how we relate hyperbolic to Euclidean geometry during the generation process. This allows us to employ a new space-partitioning data structure, more precisely a polar quadtree within the Poincaré disk model, to improve the running time of the naive generation process. We proceed by proposing an alternative dynamic model. Instead of deleting and reinserting nodes (Papadopoulos 2010), we let nodes move gradually in the hyperbolic plane. This results in a smoother change of the network, so that we believe it to be more realistic for some applications. We also analyze the time complexity of our static and dynamic generation process, resulting in an expected static running time in  $O((n + m) \log n)$  and an expected dynamic running time in  $O((k + l) \log n)$  when moving  $k$  nodes with  $l$  edges under a reasonable assumption.

Finally, we add to previous studies a comprehensive network analytic evaluation of the generative model based on hyperbolic geometry. The experimental results confirm the theoretical expected running time of  $O((n + m) \log n)$ . In practice, a graph with  $10^7$  nodes and  $10^9$  edges can be generated in less than 5 minutes on our test machine. Network analysis shows a consistently high clustering coefficient and power-law degree distribution over a wide parameter range. The generator will be made available in a future version of NetworKit (Staudt et al. 2013), our open-source framework for large-scale network analysis.

### 3.13 External memory graph algorithms

*Ulrich Carsten Meyer (Goethe-Universität Frankfurt am Main, DE)*

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Large graphs arise naturally in many real world applications. The actual performance of simple RAM model algorithms for traversing these graphs (stored in external memory) deviates significantly from their linear or near-linear predicted performance because of the large number of I/Os they incur. In order to alleviate the I/O bottleneck, many external memory graph traversal algorithms have been designed with provable worst-case guarantees. In the talk I highlight some techniques used in the design and engineering of such algorithms and survey the state-of-the-art in I/O-efficient graph traversal algorithms.

### 3.14 Spectral Anomaly Detection in Very Large Graphs: Models, Noise, and Computational Complexity

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**Joint work of** Miller, Benjamin A.; Arcolano, Nicholas; Wolf, Michael M.; Bliss, Nadya T.

**Main reference** B. A. Miller, N. Arcolano, M. M. Wolf, N. T. Bliss, “Spectral Anomaly Detection in Very Large Graphs: Models, Noise, and Computational Complexity,” arXiv:1412.4411v1 [cs.SI], 2014.

**URL** <http://arxiv.org/abs/1412.4411v1>

Anomaly detection in massive networks has numerous theoretical and computational challenges, especially as the behavior to be detected becomes small in comparison to the larger network. This presentation focuses on recent results in three key technical areas, specifically geared toward spectral methods for detection. We first discuss recent models for network behavior, and how their structure can be exploited for efficient computation of the principal eigenspace of the graph [1]. In addition to the stochasticity of background activity, a graph of interest may be observed through a noisy or imperfect mechanism, which may hinder the detection process. A few simple noise models are discussed, and we demonstrate the ability to fuse multiple corrupted observations and recover detection performance [2]. Finally, we discuss the challenges in scaling the spectral algorithms to large-scale high-performance computing systems, and present preliminary recommendations to achieve good performance with current parallel eigensolvers [3].

#### References

- 1 Benjamin A. Miller, Nicholas Arcolano, and Nadya T. Bliss. Efficient anomaly detection in dynamic, attributed graphs. In *Proc. IEEE Intelligence and Security Informatics*, pages 179–184, 2013.
- 2 B. A. Miller and N. Arcolano. Spectral subgraph detection with corrupt observations. In *Proc. IEEE Int. Conf. Acoust., Speech and Signal Process.*, pages 3449–3453, 2014.
- 3 M. M. Wolf and B. A. Miller. Sparse matrix partitioning for parallel eigenanalysis of large static and dynamic graphs. In *Proc. IEEE High Performance Extreme Computing Conf.*, 2014.

### 3.15 Practical Graph Sparsification

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**Joint work of** Parthasarathy, Srinivasan; Satuluri, Venu; Ruan, Yiye; Fuhry, Dave; Zhang Yang

**Main reference** V. Satuluri, S. Parthasarathy, Y. Ruan, “Local graph sparsification for scalable clustering,” in Proc. of the 2011 ACM SIGMOD Int’l Conf. on Management of Data, pp. 721–732, ACM, 2011.

**URL** <http://dx.doi.org/10.1145/1989323.1989399>

**Main reference** Y. Ruan, D. Fuhry, S. Parthasarathy, “Efficient community detection in large networks using content and links,” in Proc. of the 22nd Int’l World Wide Web Conf. (WWW’13), pp. 1089–1098, 2013.

**URL** <http://dl.acm.org/citation.cfm?id=2488483>

Many real world problems (biological, social, web) can be effectively modeled as networks or graphs where nodes represent entities of interest and edges mimic the interactions or relationships among them. The study of such complex relationship networks, recently referred to as “network science”, can provide insight into their structure, properties and emergent behavior. Of particular interest here are rigorous methods for uncovering and understanding

important network structures and motifs (communities) at multiple topological and temporal scales. Achieving this objective is challenging due to the presence of noise (false or missing interactions), topological(scale-free)) properties and scalability. Given the importance of the graph clustering problem, a number of solutions ranging from hierarchical methods to spectral methods have been designed and developed.

In this talk I will discuss a novel approach to sparsifying or sampling the edges of a graph while retaining the relevant content and structure important to a range of graph processing or graph analytic tasks. Empirical results demonstrate both qualitative as well as quantitative improvements over existing approaches on a wide range of datasets drawn from socio- technological- and biological- domains. Time permitting, I will also illustrate the value of such an approach from the perspective of visually teasing out relevant structure from large scale graphs and networks.

### 3.16 Current challenges for parallel graph partitioning

*Francois Pellegrini (University of Bordeaux, FR)*

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Graph partitioning is a technique used for the solving of many problems in scientific computing, such as the decomposition of a mesh into domains so as to evenly balance the compute load on the processors of a parallel architecture. Because of the ever increasing size of the meshes to handle, partitioning tools themselves had to be parallelized. The parallel versions of these software provide good results for and on several thousands of processors, but the advent of architectures comprising more than a million processing elements raises new problems. Not only do the partitioning results produced by these software have to take into account the heterogeneity of these architectures, but also does the efficient execution of the partitioning software on these architectures require much more sophisticated algorithms. The purpose of this talk is to present the challenges to overcome in order to reach these goals.

### 3.17 Sampling and streaming algorithms for counting small patterns in BIG graphs

*Ali Pinar (Sandia National Laboratories – Livermore, US)*

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Joint work of Pinar, Ali; Seshadhri, C.; Jha, Madhav; Kolda, Tamara

Counting the frequency of small subgraphs is a fundamental technique in network analysis across various domains, most notably in bioinformatics and social networks. Computing these counts can be challenging due to the sizes of the graphs. We have designed sampling algorithms that can provide provably accurate estimates for counting 3- and 4-vertex patterns. These algorithms have error/confidence bounds that depend on the number of samples but independent of the sizes of the graphs. We also designed a sublinear memory streaming algorithm to count triangles. This talk will summarize our results.

### 3.18 Multiscale methods for networks

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**Joint work of** Achi Brandt; Jie Chen; Alexander Gutfraind; William Hager; James Hungerford; Sven Leyffer; Lauren Meyers; Dorit Ron; Ilya Safro; Boris Temkin

**URL** <http://www.cs.clemson.edu/~isafro>

The main objective of a multilevel algorithm is to create a hierarchy of problems, each representing the original problem, but with fewer degrees of freedom. We will discuss several recently developed scalable algorithms for network modeling, fast response to epidemics on networks, the minimum vertex separator, and the minimum logarithmic arrangement problems.

1. We introduce a flexible method for synthesizing realistic ensembles of networks starting from a known network, through a series of mappings that coarsen and later refine the network structure by randomized editing. The method, MUSKETEER, preserves structural properties with minimal bias, including unknown or unspecified features, while introducing realistic variability at multiple scales. Using examples from several domains, we show that MUSKETEER produces the intended stochasticity while achieving greater fidelity across a suite of network properties than do other commonly used network generation algorithms.
2. We present a strategy for designing fast and practical methods of response to cyber attacks and infection spread on complex weighted networks. In these networks, vertices can be interpreted as primitive elements of the system, and weighted edges reflect the strength of interaction among these elements. The proposed strategy belongs to the family of multiscale methods whose goal is to approximate the system at multiple scales of coarseness and to obtain a solution of microscopic scale by combining the information from coarse scales. We consider an optimization problem that is based on the susceptible-infected-susceptible (SIS) epidemiological model. The objective is to detect the network vertices that have to be secured (or immunized) in order to keep a low level of infection in the system.
3. The Vertex Separator Problem for a graph is to find the smallest collection of vertices whose removal breaks the graph into two disconnected subsets that satisfy specified size constraints. This problem can be formulated as a continuous (non-concave/non-convex) bilinear quadratic program. We develop a more general continuous bilinear program which incorporates vertex weights, and which applies to the coarse graphs that are generated in a multilevel compression of the original Vertex Separator Problem. A Mountain Climbing Algorithm is used to find a stationary point of the continuous bilinear quadratic program, while second-order optimality conditions and perturbation techniques are used to escape from either a stationary point or a local maximizer. Computational results and comparisons demonstrate the advantage of the proposed algorithm.
4. We present a fast multiscale approach for the network minimum logarithmic arrangement problem. This type of arrangement plays an important role in the network compression and fast node/link access operations. The algorithm is of linear complexity and exhibits good scalability, which makes it practical and attractive for use in large-scale instances. Its effectiveness is demonstrated on a large set of real-life networks. These networks with corresponding best-known minimization results are suggested as an open benchmark for the research community to evaluate new methods for this problem.

### 3.19 Multicriteria Shortest Paths

*Peter Sanders (KIT – Karlsruher Institut für Technologie, DE)*

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**Joint work of** Sanders, Peter; Erb, Stephan, Mandow, Lawrence; Kobitzsch, Moritz

**Main reference** P. Sanders, L. Mandow, “Parallel Label-Setting Multi-Objective Shortest Path Search,” in Proc. of the 2013 IEEE 27th Int’l Parallel & Distributed Processing Symposium, pp. 215–224, IEEE, 2013.

**URL** <http://dx.doi.org/10.1109/IPDPS.2013.89>

In this talk, we present a parallel algorithm for finding all Pareto optimal paths from a specified source in a graph. The algorithm is label-setting, i. e., it only performs work on distance labels that are optimal. The main result is that the added complexity when going from one to multiple objectives is completely parallelizable. The algorithm is based on a multi-objective generalization of a priority queue. Such a Pareto queue can be efficiently implemented for two dimensions. Surprisingly, the parallel biobjective approach yields an algorithm performing asymptotically less work than the previous sequential algorithms. Using a Pareto queue based on B-trees with parallel bulk updates, this also turns out to be practical. We also discuss generalizations for 3 objective functions and for single target search.

This is a summary of two conference papers [1, 3].

#### References

- 1 Peter Sanders and Lawrence Mandow. Parallel label-setting multi-objective shortest path search. In *IPDPS*, pages 215–224, Washington, 2013. IEEE Computer Society.
- 2 Peter Sanders and Lawrence Mandow. *Parallel Label-Setting Multi-Objective Shortest Path Search*. 27th IEEE Int’l Parallel & Distributed Processing Symp., Boston, USA, 2013.
- 3 Stephan Erb, Moritz Kobitzsch, and Peter Sanders. Parallel bi-objective shortest paths using weight-balanced b-trees with bulk updates. In *Symposium on Experimental Algorithms (SEA)*, Lecture Notes in Computer Science. Springer, 2014.

### 3.20 Parallel Graph Partitioning for Complex Networks

*Christian Schulz (KIT – Karlsruher Institut für Technologie, DE)*

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**Joint work of** Meyerhenke, Henning; Sanders, Peter; Schulz, Christian

**Main reference** H. Meyerhenke, P. Sanders, C. Schulz, “Parallel Graph Partitioning for Complex Networks,” arXiv:1404.4797v3 [cs.DC], 2015.

**URL** <http://arxiv.org/abs/1404.4797v3>

Processing large complex networks like social networks or web graphs has recently attracted considerable interest. To do this in parallel, we need to partition them into pieces of about equal size. Unfortunately, previous parallel graph partitioners originally developed for more regular mesh-like networks do not work well for these networks. This talk addresses this problem by parallelizing and adapting the label propagation technique originally developed for graph clustering. By introducing size constraints, label propagation becomes applicable for both the coarsening and the refinement phase of multilevel graph partitioning. We obtain very high quality by applying a highly parallel evolutionary algorithm to the coarsest graph. The resulting system is both more scalable and achieves higher quality than state-of-the-art systems like ParMetis or PT-Scotch. For large complex networks the performance differences are very big. As an example, our algorithm partitions a web graph with 3.3G edges in 16

seconds using 512 cores of a high-performance cluster while producing a high quality partition – none of the competing systems can handle this graph on our system.

### 3.21 Tools for the Analysis of Large Networks: Algorithms and Software

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**Joint work of** Staudt, Christian; Meyerhenke, Henning; Sazonovs, Aleksejs; Bergamini, Elisabetta; von Looz, Moritz; Lindner, Gerd; Hamann, Michael

**Main reference** C. L. Staudt, A. Sazonovs, H. Meyerhenke, “NetworKit: An Interactive Tool Suite for High-Performance Network Analysis,” arXiv:1403.3005v2 [cs.SI], 2014.

**URL** <http://arxiv.org/abs/1403.3005v2>

Network science can be defined as an interdisciplinary mathematical science studying the statistics, structure and dynamics of complex relational data. While complex network models are applicable to all kinds of domains, the commonality is the observation that the structure of relationships between entities allows important insights into complex systems. In practice, network scientists often need to perform exploratory analysis workflows on massive graph data sets. As computer scientists we can support this emerging field of research by providing appropriate computational tools, which includes both effective and efficient graph algorithms and usable data analysis software. This is what we are trying to do with NetworKit, an open-source tool suite for high-performance network analysis: Our goal is to package current results of our algorithm engineering efforts and put them into the hands of domain experts. NetworKit has a hybrid architecture with a C++/OpenMP backend and a Python frontend. Scaling to massive networks is enabled by methods such as parallel and sampling-based approximation algorithms. The current feature set includes various analytics algorithms, e.g. for community detection, and graph generators. Recent projects extending NetworKit include: 1) A collection of methods for sparsifying complex networks while preserving certain structural properties, a kind of lossy compression for massive networks; 2) A parallel generator for large synthetic networks based on the unit-disk graph model in hyperbolic geometry. In the future we would like to automate many network analysis steps to test for interesting correlations and uncover the significant features of a network. NetworKit is free software, open to a diverse community of algorithm engineers and data analysts.

### 3.22 Communication Efficient LU with Partial Pivoting using a Shape Morphing Data Layout

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**Joint work of** Ballard, Grey; Demmel, James; Lipshitz, Benjamin; Schwartz, Oded; Toledo, Sivan

**Main reference** G. Ballard, J. Demmel, B. Lipshitz, O. Schwartz, S. Toledo, “Communication Efficient Gaussian Elimination with Partial Pivoting using a Shape Morphing Data Layout,” in Proc. of the 25th Annual ACM Symp. on Parallelism in Algorithms and Architectures (SPAA’13), pp. 232–241, ACM, 2013.

**URL** <http://dx.doi.org/10.1145/2486159.2486198>

High performance for numerical linear algebra often comes at the expense of stability. Computing the LU decomposition of a matrix via Gaussian Elimination can be organized so that the computation involves regular and efficient data access. However, maintaining

numerical stability via partial pivoting involves row interchanges that lead to inefficient data access patterns. To optimize communication efficiency throughout the memory hierarchy we confront two seemingly contradictory requirements: partial pivoting is efficient with column-major layout, whereas a block-recursive layout is optimal for the rest of the computation. We resolve this by introducing a shape morphing procedure that dynamically matches the layout to the computation throughout the algorithm, and show that Gaussian Elimination with partial pivoting can be performed in a communication efficient and cache-oblivious way. Our technique extends to QR decomposition, where computing Householder vectors prefers a different data layout than the rest of the computation.

### 3.23 An I/O-efficient Distance Oracle for Evolving Real-World Graphs

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**Joint work of** Ajwani, Deepak; Meyer, Ulrich; Veith, David

**Main reference** D. Ajwani, U. Meyer, D. Veith, “An I/O-efficient Distance Oracle for Evolving Real-World Graphs,” in Proc. of the 7th Workshop on Algorithm Engineering and Experiments (ALENEX’15), pp. 159–172, SIAM, 2015.

**URL** <http://dx.doi.org/10.1137/1.9781611973754.14>

We present an I/O-efficient distance oracle that is able to answer online queries with a constant number of I/O. Furthermore, we developed batched queries that have an amortized I/O-complexity of  $O(\frac{1}{B})$  I/Os per query. Online queries can be processed in milliseconds on SSDs and batched queries within microseconds even on HDDs. All results have been achieved on real world graphs. We explain the experimental results and discuss improvements for the future.

### 3.24 Assigning edge weights in graphs for quantifying vertex closeness

*Panayot S. Vassilevski (LLNL – Livermore, US)*

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**Main reference** Henson, Van Henson; Hysom, David; Sanders, Geoff; Vassilevski, Panayot; Yoo, Andy; “Assigning edge weights in graphs for quantifying vertex closeness,” Lawrence Livermore National Laboratory Technical Report LLNL-JRNL-664198, November 13, 2014.

We propose an algorithm to assign edge-weights in graphs by minimizing a nonlinear functional. The functional is constructed in a way to expose if a vertex is closer to one of its neighbors than to the remaining ones. The functional is well-defined for both undirected and directed graphs, and is efficiently minimized for bipartite graphs. We also outline modifications of the functional applied to embeddings of the original graph into bipartite ones for which the minimization procedures are efficient (and parallelizable).

Based on the computed edge weights we design a recursive (multilevel) pairwise aggregation algorithm for community detection which breaks when a certain “energy” functional reaches a (local) minimum which reflects a balanced set of aggregates, in terms of edge weights. We also explore the use of the computed weights in a state-of-the-art multilevel aggregation-based community detection algorithm such as the Louvain algorithm that maximizes the popular graph modularity measure. The algorithms were applied to several graphs with known (full

or partial) ground-truth communities to verify the applicability of the computed edge weights to such more realistic situations.

The presentation is based on the results reported in [1].

#### References

- 1 V.E. Henson, D. Hysom, G. Sanders, P.S. Vassilevski, and A. Yoo, Assigning edge weights in graphs for quantifying vertex closeness. Lawrence Livermore National Laboratory Technical Report LLNL-JRNL-664198, November 13, 2014.

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# Systems and Algorithms for Large-scale Graph Analytics

Edited by

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## Abstract

This report documents the program and the outcomes of Dagstuhl Seminar 14462 “Systems and Algorithms for Large-scale Graph Analytics”. The seminar was a successful gathering of computer scientists from the domains of systems, algorithms, architecture and databases all of whom are interested in graph processing.

**Seminar** November 9–12, 2014 – <http://www.dagstuhl.de/14462>

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## 1 Executive Summary

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*Eiko Yoneki*

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Graph analytics, the class of data analysis that deals with data forming networks, is emerging as a huge consumer of computational resources due to its complex, data-hungry algorithms. Social networking, personal medicine, bioinformatics, text/graphics content analysis and search engines are a few examples where Tera-, Peta- or even Exa-scale graph processing is required. Graph algorithms are becoming increasingly important for solving multiple problems in diverse fields. As these problems grow in scale, parallel computing resources are required to meet the computational and memory requirements. Notably, the algorithms, software and hardware that have worked well for developing mainstream parallel applications are not usually effective for massive-scale graphs from the real world, which exhibits more complex and irregular structures than traditional data in scientific computing.

Research into large scale graph processing within the computer science community is currently at an early and fragmented stage. This seminar brought together researchers from systems, computer architecture, algorithms and databases to discuss emerging trends and to identify opportunities for future advancement. Prior to the seminar, we had prepared a range of research questions below.

1. What is the correct algorithmic abstraction for systems handling large graphs? Algorithmic complexity researchers use PRAM and I/O complexity models to characterize the algorithmic complexity of graph processing. On the other hand, systems researchers



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- largely build systems that implement scatter-gather and label propagation models of computation. These are different world views rendering theory and practice incompatible with each other. We will begin work towards a formal algorithmic model for existing large scale graph processing systems as part of this seminar with a view to answering this question. This model should accurately describe large-scale graph processing systems built by the systems community as well as be formal enough to enable algorithmic complexity researchers to draw useful conclusions about their scalability with data set size. This will require close co-operation between theoretical computer scientists on the algorithms front to talk to practical systems researchers.
2. What is the taxonomy of applications that graph processing systems should support? Can it be reduced to a set of representative benchmarks that researchers in this area need to care about? We can currently identify two main interest areas. The first is large scale graph traversal, of interest to the high performance computing and web-services community; primarily driven by security applications and from data mining needs. The second is spectral approaches, primarily of interest to the machine learning community, building systems such as Graphlab. The output from this agenda item will be a clear set of well defined applications that the community can agree will serve as objects of study for building high performance graph processing systems.
  3. What is the correct interface to the system that may be assumed when building a graph DSL? DSL researchers are interested in productive and easy ways to specify graph computations. However they have given relatively little thought to interfacing in an efficient way to systems that execute graph computation. The agenda item therefore will be a discussion between programming language researchers and systems, algorithms and database people researchers about the correct level of interface between a DSL and the underlying systems. A good model in this regard is the decoupling of database systems from ways to query them using declarative languages like SQL. The litmus test for success for this agenda item will therefore be a sketch for a DSL that exposes opportunities for optimization, is productive to use and at the same time is oblivious to the underlying system.
  4. What is the design trade-off among different graph processing approaches. For example, (i) the general graph processing system vs. the dedicated approaches specially optimized for specific graph problems, (ii) the running time between pre-processing and graph processing, (iii) performance vs. running expense.

The seminar identified whole graph analytics and point queries on graphs that explore neighborhoods of vertices as distinct application domains, which require separate treatment and systems. All the participants agreed that there was an urgent need to standardize benchmarks and datasets in order to make meaningful progress with graph processing – particularly given the diverse nature of the communities involved. In addition, the seminar identified a number of interesting approaches and trends. There was also considerable participation from industry, which included work in graph databases as well as new systems architectures that will require practitioners to rethink traditional approaches for graph processing.

The seminar consisted of 6 sessions on focused topic presentations and discussions, followed by a joint session with the seminar 14461 on “High-performance Graph Algorithms and applications computational Science”. At the last day of the seminar, the whole morning was dedicated to the discussion on the challenges and future directions of large-scale graph processing (see Section Challenges and Future directions).

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### 3 Overview of Talks

Talks are distributed in the following six sessions. The detail of the seminar schedule can be found at <http://www.dagstuhl.de/schedules/14462.pdf>.

1. Graph/Parallel Processing Systems (3.1–3.7)
2. Storage, I/O, Memory, and Data Format (3.8–3.10)
3. Hardware/Software based Acceleration (GPU, APU) (3.11–3.13)
4. Query/Programming Languages and Applications (3.14–3.17)
5. Distributed and Graph Databases (3.18–3.21)
6. Parallel Processing and Partitioning (3.22–3.24)

#### 3.1 Grappa: A Runtime System for High-Performance Graph Analyses on Commodity Clusters

*Mark Oskin (University of Washington, US, [oskin@cs.washington.edu](mailto:oskin@cs.washington.edu))*

**Note by Editors:** Grappa is a runtime system that provides a distributed shared memory abstraction for a cluster. At Grappa’s core is co-operative multithreading with very low context switch times (in the order of 40–80 ns) and this allows Grappa to provide fine grained access to memory on a different machine while hiding the latency of access behind parallelism. Grappa also uses delegation by moving computation to the data (instead of vice-versa) and aggregates messages to the same machine to amortize per-message overheads on the network. It provides an easy programming model that often looks very much like HPC code. These features make Grappa a great solution for graph processing – it dispenses with the need for good partitioning across machines and manages to beat Powergraph for all possible partitioning strategies that Powergraph can currently use.

#### 3.2 Issues Encountered in Distributed Graph Processing

*Sebastian Schelter (TU Berlin, DE, [sebastian.schelter@tu-berlin.de](mailto:sebastian.schelter@tu-berlin.de))*

**Note by Editors:** This talk focuses on the challenges faced when using distributed graph processing systems in industrial settings. Although the “think like a vertex” programming model has become popular, pre and post-processing steps usually involve relational operators instead. An interesting observation made is that the vertex centric model can be viewed as a join followed by an aggregation, which is the approach used in systems such as GraphX. Further, more complex operations that can be represented as linear algebra operations are not well suited to the vertex-centric model. An example is linerank: a scalable alternative to betweenness centrality to computes the stationary distribution for a random walk on the line graph. Another example is the factorbird work done at Twitter that involved factorizing very large matrices: a parameter server approach was found to work the best. These relational operators or linear algebra operators did not fit in the vertex centric model. LineRank for example can not be computed on top of BSP (Bulk Synchronous Parallel).

### 3.3 Graph Analytics with the Galois System

*Andrew Lenharth (University of Texas Austin, US, lenharth@ices.utexas.edu)*

**Note by Editors:** Galois makes single machine concurrent graph algorithms easier to write by hiding details of synchronization entirely from the user. As input Galois takes a serial program which consists of an algorithm and data structure. It transforms it into a parallel program consisting of operators, a schedule and a parallel data structure. Priority scheduling is at the heart of Galois and enables great performance on algorithms like SSSP or pagerank, something not provided by vertex-centric systems. The ability to use the correct data structure also helps in the case of graphs with large diameter, connected components being an example where standard label propagation algorithms do not work well. Galois provides an order of magnitude improvement over systems such as Powergraph. Priority scheduling allows the use of information from the application layer for the scheduling and processing vertices with a high importance makes the computation faster.

### 3.4 An Evaluation of Pregel-like Graph Processing Systems

*Khuzaima Daudjee (University of Waterloo, CA, kdaudjee@uwaterloo.ca)*

**Note by Editors:** Graph partitioning is an expensive problem and therefore it makes sense to do incremental re-partitioning. We use 1-hop and 2-hop neighbor queries as the workload to optimize for, when re-partitioning, assuming that remote traversals are expensive. The work led to a distributed Neo4j implementation. Another direction of research is to compare and contrast different Pregel-like graph processing systems [1]. Each system features its own optimizations that have been assessed in the evaluation.

#### References

- 1 An Experimental Comparison of Pregel-like Graph Processing Systems. VLDB 2014.

### 3.5 Rethinking Graph Processing with the Machine

*Kimberley Keeton (HP Labs – Palo Alto, US, kimberley.keeton@hp.com)*

**Note by Editors:** The “machine” is a radical new systems architecture currently in development that leverages memristor technology and silicon photonics. The motivator for the machine is that DRAM scaling is hitting a wall, and it is unlikely we can store large amount of data in it. At the same time secondary storage speeds are unlikely to keep up with the needs of analytics applications that need sufficiently low latency access to data. The machine provides vast amounts of persistent low latency storage via memristor technologies with performance much closer to DRAM than NAND flash. Photonics technology is intended to serve as a communication firehose for memristor stores. These provide low cost, compact form factors via vertical cavity emitting lasers and reach speeds on the the order of a terabit a second. The machine will change the way we approach problems such as graph processing. Partitioning graphs across distributed memory in a cluster – a known hard problem – simply disappears since a single machine would have enough capacity to hold the entire graph. Another interesting application is maintaining multiple indexes on the same graph.

### 3.6 Hyperball: In-core Computation of Geometric Centralities

Paolo Boldi (University of Milan, IT, [boldi@di.unimi.it](mailto:boldi@di.unimi.it))

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Given a social network, which of its nodes are more central? This question has been asked many times in sociology, psychology and computer science, and a whole plethora of centrality measures (a.k.a. centrality indices, or rankings) were proposed to account for the importance of the nodes of a network. In this paper, we approach the problem of computing geometric centralities, such as closeness and harmonic centrality, on very large graphs; traditionally this task requires an all-pairs shortest-path computation in the exact case, or a number of breadth-first traversals for approximated computations, but these techniques yield very weak statistical guarantees on highly disconnected graphs. We rather assume that the graph is accessed in a semi-streaming fashion, that is, that adjacency lists are scanned almost sequentially, and that a very small amount of memory (in the order of a dozen bytes) per node is available in core memory. We leverage the newly discovered algorithms based on HyperLogLog counters, making it possible to approximate a number of geometric centralities at a very high speed and with high accuracy. While the application of similar algorithms for the approximation of closeness was attempted in the MapReduce framework, our exploitation of HyperLogLog counters reduces exponentially the memory footprint, paving the way for in-core processing of networks with a hundred billion nodes using just 2TiB of RAM. Moreover, the computations we describe are inherently parallelizable, and scale linearly with the number of available cores.

**Note by Editors:** Hyperball is a new approach to computing the centrality of vertices in large graphs [1]. Normally, this is a computationally intensive approach that is prohibitively expensive to compute for every vertex in a large graph. Hyperball proposes using the notion of geometric centrality of a vertex  $x$  in a graph  $G = (V, E)$ :  $\sum_{y \in V} \frac{1}{\text{dist}(y, x)}$ . Hyperball computes geometric centralities efficiently using HyperLogLog counters and sequential passes over the graph in a manner very similar to HyperANF. Although Hyperball does not admit a tight closed form bound on the error, in practise it returns centrality measures with very low error, while being efficient enough to allow centrality measures to be estimated on graphs with a hundred billion vertices and beyond.

#### References

- 1 <http://arxiv.org/abs/1308.2144>

### 3.7 Naiad

Derek Murray (Google, [derek.murray@gmail.com](mailto:derek.murray@gmail.com))

**Note by Editors:** Naiad is a distributed system for executing data-parallel cyclic dataflow programs. One of its most interesting applications is to combine incremental processing with interactive queries. For example, one might want to build connected components of Twitter users from an incoming stream of messages and then obtain the most popular hashtag in each component. Such applications are easy to write on Naiad, which in turn provides great performance without the user having to worry about the underlying details. At its core Naiad attaches an ordering timestamp to messages flowing through the system. Prioritizing

the processing of messages is key to obtaining good performance from the system. Another key idea is to do any necessary joins incrementally. Naiad also applies batching in order to better apply the priority bases selection of messages to process. Naiad’s timely dataflow API provides a good basis to implement other systems – including graph processing systems.

### 3.8 Traversal of Massive Scale-free Graphs on HPC with NVRAM

*Roger Pearce (Lawrence Livermore National Labs, US, rpearce@llnl.gov)*

**Note by Editors:** Traversing massive graphs with HPC is an important application area as it facilitates processing of massive real-world graphs. The key problem is to tolerate data latencies and the adopted solution is to use parallel asynchronous techniques. An important building block is the visitor abstraction where a visit to a vertex results in traversal of graph edges, which in turn queues further visits to target vertices. Visitor execution scheduler orders visitors to exploit page-level reuse. Another important aspect of the work is partitioning vertices across cluster nodes to queue visitors at. The solution was to split high-degree hub nodes and delegate communication to the copies. The solution also incorporates a message aggregation layer (motivated in much the same way as Grappa) although message aggregation happens both at source and at intermediate software routers. It also motivates a future with NVRAM as MTEPS decreases only by about 10% when moving from DRAM to NVRAM.

### 3.9 Graph Processing from Secondary Storage

*Willy Zwaenepoel (EPFL, CH, willy.zwaenepoel@epfl.ch)*

**Note by Editors:** Graph processing from secondary storage takes an entirely different approach from the traditional one of storing the graph in the main memory of a single machine or many different machines. The aim is to exploit large amounts of secondary storage (including magnetic disks) to process very large graphs using a fraction of the resources normally required. To this end, the talk covers two systems. X-Stream is a system for processing graphs from secondary storage on a single machine. It recasts graph computation to use edge-centric computing and partitions graphs into streaming partitions. This results in purely sequential access to secondary storage. The second system, SlipStream, extends the ideas in X-Stream to work with distributed storage in a cluster. It does so using a combination of flat storage to avoid graph partitioning problems, and work stealing to avoid load imbalance problems.

### 3.10 SSD Prefetching for Large Graph Traversal

*Valentin Dalibard (University of Cambridge, GB, valentin.dalibard@cl.cam.ac.uk)*

**Note by Editors:** Mining large graphs has now become an important aspect of multiple diverse applications and a number of computer systems have been proposed to provide runtime support. Recent interest in this area has led to the construction of single machine graph computation systems that use solid state drives (SSDs) to store the graph. This approach reduces the cost and simplifies the implementation of graph algorithms, making

computations on large graphs available to the average user. However, SSDs are slower than main memory, and making full use of their bandwidth is crucial for executing graph algorithms in a reasonable amount of time. In this paper, we present PrefEdge, a prefetcher for graph algorithms that parallelizes requests to derive maximum throughput from SSDs. PrefEdge combines a judicious distribution of graph state between main memory and SSDs with an innovative read-ahead algorithm to prefetch needed data in parallel. This is in contrast to existing approaches that depend on multi-threading the graph algorithms to saturate available bandwidth. Our experiments on graph algorithms using random access show that PrefEdge not only is capable of maximizing the throughput from SSDs but is also able to almost hide the effect of I/O latency. The improvements in runtime for graph algorithms is up to 14 x when compared to a single threaded baseline. When compared to multi-threaded implementations, PrefEdge performs up to 80% faster without the program complexity and the programmer effort needed for multi-threaded graph algorithms.

### 3.11 In-network processing and NVRAM in Grappa

*Luis Ceze (University of Washington, US, luisceze@cs.washington.edu)*

**Note by Editors:** Systems like Grappa spend a lot of time aggregating messages. However aggregating messages at the sender is limited in view and perhaps a better place to do aggregation is in the network. Moving forward, DRAM capacity per-core is shrinking due to the end of Dennard scaling also affecting DRAM. At the same time, network injection rates are getting better – beginning to rival DRAM. This suggests that it might also be beneficial to do some amount of compute in addition to aggregation in network middle boxes. Another interesting idea is to use Grappa to also tolerate increased latencies to main memory when DRAM is replaced with NVRAM.

### 3.12 Gunrock: High-Performance, High-Level Graph Computation on GPUs

*John Owens (UC Davis, US, jowens@ece.ucdavis.edu)*

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We are building Gunrock, a graph framework for GPUs that delivers high performance on iterative, bulk-synchronous graph primitives with high-level programmability. Gunrock supports efficient traversal, filtering, and computation operators. In my talk I outline challenges facing Gunrock and by extension other GPU graph frameworks: load-balanced, high-performance traversal; scalability beyond the memory footprint of one GPU; addressing higher-level operations beyond graph primitives; and parallel-friendly mutable graph data structures.

**Note by Editors:** Executing graph algorithms on GPUs requires efficient parallel algorithms from the GPU perspective, coding which traditionally requires bridging a “ninja” programming gap. Gunrock aims to bridge this programming skills gap with the right interface, while enabling good use of GPU resources. It uses a bulk synchronous programming model. Traversals maintain an active frontier of active vertices and edges. Each traversal step does

compute and generates a new frontier. Gunrock uses the CSR representation internally as that works best. It also uses careful scheduling of units of work (corresponding to blocks of edges) to GPU units such as cores, threads and warps in order to achieve the best performance. A future area of interest with GPUs and graphs is to look at graphs that change as a result of computation.

### 3.13 Using Integrated GPUs for Accelerated Graph Traversal

*Karthik Nilakant (University of Cambridge, GB, karthik.nilakant@cl.cam.ac.uk)*

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General-purpose GPU computing has been used to improve the performance of a variety of applications. However graph processing is a problem domain that is difficult to adapt to the GPGPU computing model, due to irregularity and poor locality of access. There are aspects of graph processing that can benefit from the additional parallelism provided by the GPU platform, but the need to ship data between system RAM and discrete graphics memory negates the potential performance improvement. Integrated graphics processors (or accelerated processing units) provide a way to avoid this problem, by adopting a unified memory model. In this talk, I show that by adopting a current-generation APU platform.

**Note by Editors:** Systems where CPUs and GPUs are integrated on the same die are becoming commonplace. This represents an opportunity as both see the same shared memory with the same access latency. A graph algorithm can therefore be run more efficiently by partitioning work across the CPU cores and GPUs. However due to their different characteristics, discrimination is needed when assigning work. The key idea is to assign more homogeneous low-degree vertices to GPUs. This leads to substantial speedups over simply assigning all work to CPUs or GPUs.

### 3.14 Graph Languages with Benefits

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There are two types of graph processing workloads – computational analytic and pattern matching. We first discuss the benefit of having a high-level imperative language for computational graph analytic. We give examples of simplicity, performance and portability benefits. Then we discuss (existing) declarative languages for pattern matching workloads. We close the talk by asking how to combine these two languages.

**Note by Editors:** There is a benefit to designing programming languages specifically for graphs. This language should be easy to use both for computational graph analytics like pagerank as well as for declarative queries such as graph pattern matching. Even for computational problems it is useful to raise the level of abstraction above that of “think like a vertex”, a user typically does not want to be aware of or bother with the computational model. At the same time, a higher level of abstraction enables system specific optimization to be brought into play. A good example is ordering vertices by degree to reduce the number

of neighbor list comparisons needed in triangle counting. Oracle now has a proprietary graph processing engine (PGX.dist) that incorporates this philosophy by exposing a DSL which is then compiled down through IR all the way to system level details such as ghost vertices.

### 3.15 Query Languages that Taste like Programming Languages

*Torsten Grust (Universitat Tübingen, DE, torsten.grust@uni-tuebingen.de)*

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We study database query languages whose design mimics those of general-purpose programming languages. In these languages, (1) clauses may be composed freely and nest to arbitrary depth (as long as typing rules are obeyed) and (2) data may be modeled using a rich type system (that admits lists, arrays, dictionaries). This is in contrast to the common design of query languages (see SQL or SPARQL) in which users need to fit their queries into rather rigid templates that query flat data structures.

The compilation of such languages and their execution on common database backends poses a challenge. We borrow insights and adapt techniques invented by the programming language community and the 1990s efforts of implementing nested data parallelism, in particular to let query languages taste more like programming languages.

**Note by Editors:** Combining SQL style query languages with C is a hard problem and often requires bi-lingual developers who communicate using narrow channels from the C heap to the database. The proposed solution is database supported program execution. The program is compiled down to native code and SQL queries that are instantiated automatically on the program heap. This is a direct counterargument to DSLs and suggests that richer language level abstractions are a better way to deal with graphs and other forms of data rather than inventing domain specific languages.

### 3.16 Flattening-Based Query Compilation

*Alexander Ulrich (Universitat Tübingen, DE, alexander.ulrich@uni-tuebingen.de)*

**Note by Editors:** Combining databases and data models such as graphs with programming languages leads to the interesting question of how best to query data in such settings. The proposed solution involves trading iteration for lifted operators and un-nesting comprehensions. A key question is then whether a column backend is better suited for vector operations.

### 3.17 Core Graph Processing Primitives within SAP HANA

*Wolfgang Lehner (TU Dresden, DE, wolfgang.lehner@tu-dresden.de)*

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SAP HANA internally exhibits core primitives for processing graph data stored within the property graph model. In this talk, I will touch the SAP proprietary “Graph Extraction

and Manipulation” language (GEM) and discuss the graph traversal operator as one of the most interesting graph operations. The talk outlines a corresponding plan operator which is embedded into the SAP HANA optimizer and execution runtime and gives insights into two different strategies traversing graphs based on a columnar storage representation.

**Note by Editors:** SAP HANA use cases that involve graphs are traceability track and trace, supply chain planning and optimization, and medical insight for health care. A motivator was that one cannot take data out of the system so why not embed graph analytics into a main memory centric/column store system? HANA allows one to plug in different engines and languages. The stack takes a language, compiles down through an optimizer and plan generator and passes the result to in-memory processing engines including graph engines. The GEM language is used for graph exploration and manipulation. The language allows loading, inserting and deleting objects with possibly irregular structure. The engine can efficiently traverse links between data objects. It uses a threshold that switches between brute force scans of columns to index lookups.

### 3.18 Graph Database, do we need to reinvent the wheel

*Sungpack Hong and Hasan Chafi (Oracle – Belmont, US)*

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Graph is a great data modeling tool that enables powerful data analysis. However, we do not believe that we need a completely new database system only for maintaining graph data. Instead, we propose an system where the graph data is mapped into conventional relational database which provides consistent data management. For the sake of graph analysis, the database is tightly integrated with a fast in-memory/distributed analytic engine. We also open up a discussion about creating graphs directly from relational tables.

**Note by Editors:** Graphs are a relatively new data model that capture arbitrary relationships between entities. They enable newer applications such as collaborative filtering. On the other hand traditional databases provide a great platform for ACID semantics. Combining the two is therefore a good idea. The insight is that one can execute long running analytics on snapshots of the graph in memory. Each snapshot is consistent. This is the new PGX system that is being built at Oracle. It scales out by partitioning the in-memory snapshot and using ghost vertices.

### 3.19 Advancing Graph Query Languages

*Stefan Plantikow (Neo Technology Germany, DE, stefan.plantikow@gmail.com)*

**Note by Editors:** Forrester estimates that over 25% of enterprises will be using graph databases by 2017. Neo4j is a graph database meant for all sources of graph data – cloud, social, mobile and information (wikipedia). Neo4j is an OLTP graph database with use cases in routing, navigation, logistics, network impact analytics, social recommendations, access control, fraud detection and others. It uses a labeled property graph data model with highly connected data. It also employs master-slave replication with query sharding. Cypher is Neo4j’s declarative graph language, addressing the shortcomings of SQL for graph queries.

Cypher handled path sets, functional expressions, and optional matches (outer join). The query model starts from vertices, finds instances of a pattern such that each relationship is uniquely bound and aggregates results.

### 3.20 Efficient Large Scale Data Analytics

*Lei Chen (Hong Kong University of Science and Technology, HK leichen@cse.ust.hk)*

**Note by Editors:** A number of fundamental graph problems such as community detection, centrality computations, frequent subgraph mining needs a scalable and efficient graph analysis toolkit. Most existing toolkits are either designed for HPC or focused on machine learning. An example of a problem not handled well by these toolkits is subgraph detection and listing. Our solution [1] uses a dynamic partitioning algorithm and traversal on an in-memory graph. It uses independence properties on the expansion tree to parallelize subgraph listing.

#### References

- 1 Parallel subgraph listing in a large-scale graph. SIGMOD 2014.

### 3.21 Towards Querying Large Graphs

*Arijit Khan (ETH, CH, arijit.khan@inf.ethz.ch)*

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Given a massive network of interconnected entities such as the Google knowledge graph, how can a user search for an activity at a child-friendly tourist-attraction site inside the New York City that is also close to an Asian restaurant? Freebase that powers Google's knowledge graph alone has over 22 million entities and 350 million relationships in about 5428 domains. Before users can query anything meaningful over this data, they are often overwhelmed by the daunting task of attempting to even digest and understand it. Without knowing the exact structure of the data and the semantics of the entity labels and their relationships, can we still query them and obtain the relevant results? In this talk, I shall give an overview of our user-friendly and scalable techniques for querying of large-scale networks, including heterogeneous networks, uncertain and stream graphs.

**Note by Editors:** Graph queries usually involve a complex combination of structure and content. For example, one might query from a mobile device for good restaurants recommended by friends on the way to the bank. Queries also often involve some amount of fuzz and users might want the best answer rather than an exact answer. One way to solve this problem is to make a vector representing the neighborhood of a vertex and propagate this vector along the edges. A string distance metric can then be used to rank matches. The algorithm starts from low-degree nodes first to avoid explosion in dimensions with high-degree nodes. Compared to existing algorithms, this results in shorter runtimes but can lead to false positives.

### 3.22 Distributed Algorithms for Graph Partitioning and Community Detection

*Sarunas Girdzijauskas (Royal Institute of Technology, SE, sarunas@sics.se)*

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Balanced graph partitioning is a well known NP-complete problem with a wide range of applications. These applications include many large-scale distributed problems including the optimal storage of large sets of graph-structured data over several hosts – a key problem in today’s Cloud infrastructure. However, in very large-scale distributed scenarios, state-of-the-art algorithms are not directly applicable, because they typically involve frequent global operations over the entire graph. In this talk, we introduce a fully distributed algorithm, called JA-BE-JA, that uses local search and simulated annealing techniques for graph partitioning. The algorithm is massively parallel: there is no central coordination, each node is processed independently, and only the direct neighbors of the node, and a small subset of random nodes in the graph need to be known locally. Strict synchronization is not required. These features allow JA-BE-JA to be easily adapted to any distributed graph-processing system from data centers to fully distributed networks. We perform a thorough experimental analysis, which shows that the minimal edge-cut value achieved by JA-BE-JA is comparable to state-of-the-art centralized algorithms such as METIS. In particular, on large social networks JA-BE-JA outperforms METIS, which makes JA-BE-JA, a bottom-up, self-organizing algorithm, a highly competitive practical solution for graph partitioning. We also present a highly parallel solution for cross-document coreference resolution, which can deal with billions of documents that exist in the current web. At the core of our solution lies a novel algorithm for community detection in large scale graphs. We operate on graphs which we construct by representing documents’ keywords as nodes and the co-location of those keywords in a document as edges. We then exploit the particular nature of such graphs where coreferent words are topologically clustered and can be efficiently discovered by our community detection algorithm. The accuracy of our technique is considerably higher than that of the state of the art, while the convergence time is by far shorter. In particular, we increase the accuracy for a baseline dataset by more than 15% compared to the best reported result so far.

**Note by Editors:** JA-BE-JA is a new gossip based algorithm to partition graphs. Each node has access only to its immediate state and that of its neighbors. Nodes communicate only through messages. Each node starts with a random color. Each node attempts to change its color to the most dominant color among its neighbors. An improved version requires nodes to exchange colors for pairwise benefit with simulated annealing. An interesting application of this algorithms was in taking a set of documents, treating the words vertices in a graph and connecting vertices (words) by an edge if they appear in the same document.

### 3.23 Taming Graph Dynamics at Scale

*Felix Cuadrado (Queen Mary University of London, GB, felix.cuadrado@qmul.ac.uk)*

**Note by Editors:** Real world graphs are dynamic. We looked at distributed graph processing systems that offer a Pregel-style interface but support arbitrary changes to the graph. Partition quality is a determinant of graph performance but the quality of the partition can

start to degrade as changes are made to the graph. Therefore we implemented migration based rebalancing. Vertices migrate to where their neighbors are with a migration quota. Oscillation problems are tackled with a stickiness factor. We experimented with a biomedical simulation of heartbeat stem cells – 3TB memory footprint and 64 compute nodes. A key lesson was that BSP greatly aids system optimizations.

### 3.24 An Initial Attempt to Classify Graph Processing Systems and Approaches

*Tamer Özsu (University of Waterloo, CA, tamer.ozsu@uwaterloo.ca)*

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There are many graph processing, graph data management systems. This talk represents our first attempt at understanding the design landscape in this area and identifying design points.

**Note by Editors:** This is an initial attempt to classify graph processing systems and approaches. One dimension for classification is by whether the graphs being tackled are static or dynamic. Included in this dimension is discrimination based on whether the graph access is restricted to streaming. The second dimension is along algorithms: this includes offline, online, streaming and incremental. The third dimension is along whether the workload types being targeted are online queries or analytics over the whole graph. Open questions remain about how to distinguish based on storage (disk/memory), architecture, computing paradigm and the language being used to interface with the system.

## 4 Joint Session

Two talks from Seminar “14461 High-performance Graph Algorithms and Application in Computational Science” are presented:

1. Peter Sanders (KIT – Karlsruher Institute for Technology, DE): Parallel multicriteria shortest paths.
2. Andrew Lumsdaine (Indiana University, US): Distributed control for scalable parallel algorithms.

Three talks from Seminar “14462 Systems and Algorithms for Large-scale Graph Analytics” are presented as follows.

### 4.1 Challenges for Popularizing Graph Applications

*Hasan Chafi (Oracle – Belmont, US, hasan.chafi@oracle.com)*

**Note by Editors:** There is a need to cross the chasm between research and industry in terms of ‘graph solutions’. An important question is, who is going to use graph processing platforms? Startups such as Graphlab have rebranded themselves as machine learning toolkits. It is therefore possible that graph analytics as we see it today is early in the hype cycle. One way to move from hype to practical reality is to talk to industry to find use cases and industry specific graph models.

## 4.2 Graph Analysis Platforms and Evaluations Thereof

*Terence Kelly (HP – Palo Alto, US, [terence.p.kelly@hp.com](mailto:terence.p.kelly@hp.com))*

**Note by Editors:** Graph analysis platforms today suffer from two problems. The first is an overkill on interface. They often make it harder to write graph algorithms that with a simple text editor and compiler. The second is an overkill on implementation. They often incorporate complex solutions to non-problems. For example, the problem of scalability on inputs that actually don't need it (the graphs are too small).

Both these issues stem from the lack of a good baseline to compare these systems against. Simple single threaded baseline implementations of popular graph algorithms are necessary to properly shed light on these problems. The community also suffers from the lack of large enough datasets. An effort to share large graphs or at least their characteristics would be extremely helpful towards moving forward the state of the art.

## 4.3 Graphbench.org

*Luis Ceze (University of Washington, US [luisceze@cs.washington.edu](mailto:luisceze@cs.washington.edu))*

**Note by Editors:** Graphbench is an effort to capture a representative set of graph benchmarks including surrounding systems and environments to enable *standardized* comparisons between systems. Graphbench is an ongoing effort and comments or contributions are most welcome. Some questions and comments were received during the talk itself. An important point was to clearly delineate between different communities when building the benchmark. Should the benchmark be targeted towards the database, systems or HPC community – or all of them? Another important distinction is between graph kernels such as BFS and applications that use those kernels, such as betweenness centrality. Also, should the benchmark be industry focused or mostly aimed at supporting the research community? Finally the dataset itself can have a big impact and therefore decisions such as degree distributions of the input graph will have to be taken as part of the benchmark.

## 5 Challenges, Future Directions

*Eiko Yoneki and Amitabha Roy*

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This section highlights the discussion on the challenges and future directions of large-scale graph processing, where we focused on mainly benchmarking and programming model.

### Benchmark applications

Current research often focuses on fundamental graph processing algorithms such as traversal, shortest paths and centrality measurement. However benchmarking with more complex applications may be more useful for building production-ready systems. This will also help to motivate adoption by industry. An issue is that customers do not have a good grasp of how

to map their data / business logic into graph data and associated analytical processes. As a result, relying on end users to provide examples of important benchmarking applications may not be feasible. Instead, we may look to broad topics of interest among customers in this field and build benchmark applications that fit those topics. Influence analysis and recommendation systems are examples of topics that currently have a lot of interest in the potential user community. The onus is on graph processing researchers to design benchmarks that fit these use cases.

Tracking the convergence of analytical graph processing systems (i.e. graph databases), it is important to build benchmark suites that accommodate both styles of computation. In particular, graph pattern matching is an area that has gained popularity but lacks a standard set of benchmarks. Related to this, there needs to be more of a focus on “fuzzy” pattern matching (even beyond isomorphism / homomorphism), since this is where the real-world applications and customer interest will focus. “Local density” is another important topic (e.g. triangle counting), insofar as such algorithms often exhibit computation patterns that existing systems have difficulty in accommodating.

A promising effort that aligns with these aims is the LDBC (Linked Data Benchmark Council) [5]. This is an EU project with good participation by industry, but possibly needs more academic involvement to discuss issues similar to those outlined here. The LDBC “GraphBench” benchmark suite has two different types of workloads (query-oriented and analysis-oriented). There are also scalable mechanisms of generating data for the benchmark. GraphBench focuses on “chokepoints” or “known bad” query characteristics that are used to stress systems. One of the reasons for SPEC’s success is its stability, which has set clear expectations for developers, and the aim is for LDBC to provide a similarly comprehensive, scalable standard.

## Benchmark datasets

In addition to finding a suite of applications for standardized benchmarking, there is a need to use more varied datasets at the right scale. There has been a tendency in recent graph systems research to test large-scale systems with relatively small-scale data. A major issue is the lack of access to large real-world graph datasets such as social networks. One approach may be to consolidate available datasets into a publicly-accessible repository. A number of repositories are currently available, but need to act as portals (due to a lack of storage). The Milan Laboratory for Web Algorithmic (LAW) [4] is one such portal, the Stanford SNAP database [7] and the Koblenz Network Collection (KONECT) [6] are other examples [1, 3].

With a lack of sufficiently large real-world datasets, an alternative is to synthesize large-scale graph data. However, an issue with graphs is that it is actually a complex problem to synthesize graphs with all the characteristics that have been observed in real networks. There have been efforts (such as the Facebook LinkBench tool) [2] that attempt to at least match some of the characteristics that they have found in smaller datasets into synthesized larger datasets.

Anonymization is a key issue that blocks access to large-scale social data. Social networks are not able to release their data due to legal issues, without some guarantee of privacy. Currently, efforts in this area are largely undertaken by a separate community of security researchers. There needs to be work in this space in order to open up access to large-scale data.

## Programming models

There is a general lack of consensus on the “right” programming model for graph systems, and this is an area that warrants further investigation. It may be that a unified programming model is inappropriate, but there may still be potential for consolidating and validating a class of approaches. A theme that is emerging out of the work by Oracle and SAP is that different programming models may be appropriate at different layers of the system, such as the runtime / scheduler, algorithmic level, and query layer. Another important consideration when building scalable systems is also to consider the base case; designing large-scale systems that impose so much overhead that a sequential standalone program can exhibit better performance seems counterproductive. Conversely, this kind of comparison should form an essential part of the evaluation of any new framework.

## Follow-up plan

There is an opportunity to consolidate the discussion from this into a survey-style paper. Tamer Ozsu’s group at Waterloo is currently composing a taxonomy of existing systems, and this could be augmented with elements of the discussion from this workshop. There is also an opportunity to share the insights on benchmarking with the LDBC committee, particularly highlighting the need for more datasets. The LDBC needs more types of participants in that forum – users as opposed to just industrial developers.

Following on from this, it may be prudent to launch a new workshop based on use cases, benchmarks and workloads in the graph domain. This could be a joint effort with LDBC. Existing workshops such as GRADES at SIGMOD (Workshop on graph data management experiences and systems) provide a platform from paper-publishing, however there appears to be scope for a more discussion-oriented event.

## References

- 1 DIMACS <http://dimacs.rutgers.edu/Challenges/>.
- 2 Facebook LinkBench <http://github.com/facebook/linkbench>.
- 3 Graph500 <http://www.graph500.org/>.
- 4 Laboratory for Web Algorithmics <http://law.di.unimi.it/>.
- 5 LDBC <http://www.ldbc.eu/>.
- 6 Koblenz Network Collection <http://konect.uni-koblenz.de/>.
- 7 Stanford Large Network Dataset Collection <http://snap.stanford.edu/data/index.html>.

**Acknowledgement.** We thank Derek Murray for his great contribution to the organization of the workshop and participation via Skype as he could not travel because of the sudden set down of Microsoft Research Silicon Valley. We also thank Karthik Nilakant and Valentin Dalibard for their help with editing the report.

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Report from Dagstuhl Seminar 14471

# Towards an Affordable Internet Access for Everyone: The Quest for Enabling Universal Service Commitment

Edited by

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## Abstract

This report documents the program and outcomes of the Dagstuhl Seminar 14471 *Towards an Affordable Internet Access for Everyone: The Quest for Enabling Universal Service Commitment*. At the seminar, about 27 invited researchers from academia and industry discussed the challenges and solutions for enabling universal and affordable Internet access. This report gives a general overview of the presentations and outcomes of discussions of the seminar.

**Seminar** November 16–21, 2014 – <http://www.dagstuhl.de/14471>

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## 1 Executive Summary

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Universal Internet Access is considered as one of the fundamental requirements in today's digital age as clean water, roads, schools etc. Enabling universal Internet access is one of the key issues that is being currently addressed at the European level via the Digital Agenda for Europe (DAE) as well as globally. Recognising the importance of broadband Internet, several developed countries have their own national broadband plan, such as the Broadband Development UK (BDUK) in the UK and the National Broadband Plan in the USA.

However a lack of access to the Internet and broadband is a global phenomenon that proportionately and negatively affects the poorest countries in world, where challenges to socio-economic development are most pronounced. It is estimated that only 41% of the world's households are connected to the Internet. Half of them are in less developed countries, where household Internet penetration has reached 28%. This is in stark contrast to the 78% of households in more developed countries.

The disparity in access is even more worrying when one realises that the positive impact of increased Internet and broadband access is greater than any other ICT. In 2009, the World Bank found that in low and middle-income countries a 10% increase in broadband Internet penetration accelerated economic growth by 1.38%. Moreover, the positive effect of Internet and broadband on economic growth and social development are felt more in less



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developed countries, like those in sub-Saharan Africa, than in more developed countries, creating opportunities for levelling up and greater equality.

The main barriers to the economic growth and social benefits identified by the World Bank include the cost of services and a lack of access to terrestrial and wireless networks. Indeed, there is general consensus upon the impact of these challenges, especially that of cost. Brahim Sanou, Director of the Telecommunication Development Bureau (BDT) at the ITU notes *Broadband is still too expensive in developing countries, where it costs on average more than 100 per cent of monthly income, compared with 1.5 per cent in developed countries*. There are indeed several challenges (political, regulatory, socio-economical, technological) to the realization of a Future Internet capability that will offer appropriate access to all parts of society.

The goal of our seminar was to bring together an interdisciplinary group of researchers from academia and research organisations as well as industry to understand the different challenges in enabling universal Internet access and to discuss potential solutions for solving some of the challenges.

This report provides an overview of the talks that were given during the seminar. We also had a dedicated breakout session with two groups specifically focussing on *Socio-Economic Models and Role of Community Networks* and *Internet in a box*. We also had longer informal discussions on specific focussed topics. The discussions and outcomes are summarised in this report.

We would like to thank all presenters, scribes and participants for their contributions and lively discussions. Particular thanks go to the team of Schloss Dagstuhl for their excellent organisation and support.

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## 3 Overview of Talks

### 3.1 The Internet is a series of tubes

*Henning G. Schulzrinne (Columbia University – New York, US)*

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70% to 80% of the cost of deploying fiber networks is civil engineering. Thus, for most high-income countries, the challenge is to reduce the cost of fiber installation, not flying drones. The talk briefly discussed the experience with universal service funding and broadband build-out in the United States, and discussed the limitations of supposedly "cheap" approaches, as well as the wired- wireless trade-offs.

### 3.2 Monetization in the Internet

*Falk Von Bornstaedt (Deutsche Telekom – Bonn, DE)*

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The Internet consists of about 50000 autonomous systems. Interconnections happen via mostly settlement free peerings or via IP-transit. If there are settlements, billing may happen on the basis of average traffic flow, on a flat rate, or in most cases on 95-percentile billing. This means that the buyer of IP transit cannot fulfil his wish of being billed on the average of his monthly basis. The seller would like to bill on the basis of maximum usage, because he has to provide and install this capacity, and even more to be prepared for singular events like big sports events. 95-percentile billing is somehow a compromise; it has strong elements of a peak load pricing.

Prices should lead to an optimal allocation of resources. In the Internet this means an even distribution of traffic over time. 95-percentile pricing for IP-Transit is sometimes giving false signals to the content providers. In 95-percentile billing the top 5% of all measurements are discarded, these are the highest values. As a concrete example, if Apple sends out an iOS upgrade, ISPs have an interest to spread substantial updates like iOS over several days. The current pricing model gives incentives to push all traffic into that period of 5%, so to make the peak even higher instead of levelling out traffic peaks. Any traffic put on top of the peak has a free ride with 95-percentile billing.

One possible consequence could be to move towards higher percentiles like 98-percentile. The option to charge for maximum values is problematic, since maximum values could be generated from denial of service attacks, and the IP transit buyer would not like to pay for, in worst case the IP transit seller might even have the incentive to order an attack.

### 3.3 Comparing Digital Exclusion with the Bottom of Pyramid (BoP): Economic Challenges and Strategies

*Irene Ng (University of Warwick, GB)*

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Bottom of the Pyramid (BoP) was a phrase coined by U.S. President Franklin D. Roosevelt in 1932 when he referred to “the forgotten man at the bottom of the economic pyramid”. In economics, the bottom of the pyramid is the 2.5 billion people who live on less than \$2.50 per day. Bottom of the Pyramid is a phrase used by those interested to develop new business and economic models that deliberately target the poorest regions. When comparing the challenges of the bottom of the pyramid with those marginalised through digital exclusion, there are surprising parallels. Multi-national companies consider targeting BoP with great scepticism when it comes to doing business profitably often due to the perception of corruption, illiteracy, currency fluctuations and inappropriate infrastructures within the BoP. These factors and also the outdated representation of the poor hide the real potential of BoP markets. Similarly, those marginalised by digital exclusion are the vulnerable people, the poor, disabled, or elderly. Increased digital skills are of benefit to consumers (saving £254 a year), to public services, bring improvements in education; bringing older and isolated people to be more effectively engaging in their communities; helping adults back into work and improving health and social services. With digital skills having the greatest impact on the lives of the marginalised in society, it is alarming to see the latest figures from the Office for National Statistics that show that 6.4 million people have never been online. To face this challenge, digital exclusion is currently seen as a challenge for the state. This talk discussed the parallels between BoP challenges and that of digital exclusion and considers the lessons learnt and how new economic and business models could be applied to face the challenges of digital exclusion as a viable option for companies to serve and therefore enable public and private sector collaboration.

### 3.4 Business models for broadband rollout

*Rüdiger Zarnekow (TU Berlin, DE)*

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The talk discussed a medium term deployment plan for fiber broadband rollout. The talk summarised the following key points:

1. FTTH should be deployed once it's capabilities are requested by the customers.
2. There is no market failure as long as the broadband supply meets the customer demand.
3. Business models can foster broadband deployment at various layers of a generic three-layer telecommunication value chain.
4. In rural areas typically only one fixed broadband infrastructure will be deployed.
5. Providers will compete at the Service layer.
6. The use of additional fiber capacities, which are deployed along alternative infrastructures, can decrease deployment costs for rural broadband provisioning.
7. To use these capacities, demand needs to be aggregated along the path of the alternative infrastructure.

### 3.5 Technical reasons for new data transmission charging models

*Adam Wolisz (TU Berlin, DE)*

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Increasing share of Internet traffic is nowadays moving to wireless access. We read more and more about the growth of this traffic. And the operators are complaining that they have to increase massively the capacity of their networks without having a perspective of the proper revenues.

To give a more realistic perspective, it seems to be important to ask a set of basic questions: is the amount of bytes transported between the mobile device and the internet really closely related to the user needs for the content?

The analysis of recent research papers gives evidence of some unpleasant – if not entirely surprising – facts:

1. Many “free” applications generate side traffic (advertisements, analytics) in amounts significantly exceeding this overhead in comparable applications which have to be purchased.
2. Some of the most deployed software ecosystems use for the delivery of the same amount of content almost double the volume of transmitted data.
3. The potential for neither caching nor compression is utilized.

To improve this situation the change of economic model is necessary. The most radical way to go would be widely enforced charging the big content providers for traffic delivery. Charges for content from /to specific services (e.g., education, access to administrative services) could be covered by the local administration or sponsoring. This is only fair, as it can easily be calculated that the local administration saves a lot of money by moving to IT based interaction with the population. This is pretty easy to implement, as operators have very clear interfaces to the providers of large content volumes. In such model only the data from multiple small sources would be covered by a very low basic subscription.

An alternative model less controversial from the point of view of network neutrality purists might be at least a legal obligation to provide for any item of content a strictly standardized, unified label declaring the volume of the intended content and the volume of side content if any. In that case the consumer or the proper process running on his behalf – could make informed decision about selection of the content sources, form etc.

### 3.6 Avoiding building Hell 2.0 in a Paradise Built in Hell 1.0

*Jon Crowcroft (University of Cambridge, GB)*

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As per ghostbusters, when unexpected things happen in society, it isn't obvious who to call. Indeed, BBN's report in to the events in NYC after 9/11 strongly advised against shutting off networks, based on data from emergency services that often, situational awareness was frequently based on data from citizens, as much as from specialists. This is common knowledge (see also Paradise built in hell, by Rebecca Sohit). One thing increasingly exercising interest is the shift from community to government as a social group grows beyond the level where trust via peer-pressure or just personal knowledge works – this is something that needs thought (one example wel documented is the self-help networks that emerge after disasters, and the

very bad things that happen when the first responders arrive and try to take over without understanding the structures that have evolved – this transition applies in many arenas – even the Internet itself which didn't have very much spam or phishing or ddos till it hit a certain size – the emergence of anti-social or even byzantine behaviour is interesting and tools to combat it not well understood – think, also, Wikipedia edit wars, and non-terminating arguments in liquid democracy.

What could we learn and apply from those worlds in ours? Essentially, we require a set of tools to manage what looks at the human, power, and communications network layers, somewhat like a sequence of phase transitions from gas (opportunistic, DTN, dominated by altruism) through liquid (ad hoc, community mesh, peer-to-peer, peer production, mix of altruistic, rational, selfish, and Byzantine behaviours) to a solid (infrastructural, governance, service-oriented, customer-provider relationship managed, through economic/market) basis.

### 3.7 Towards Trustworthy Internet for All

*Georg Carle (TU München, DE)*

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It should be considered a basic human right to have access to trustworthy Internet services, being compliant with personal rights and interests of individuals concerning their data and meta-data. There are a variety of threats against the trustworthiness of Internet services, including the threat of systematic espionage from intelligence agencies.

Network components from commercial vendors with closed-source software may have vulnerabilities due to software weaknesses and the possibility of backdoors. Apart from this, trustworthiness is affected by the country- dependent possibilities of security agencies to obtain legal access to personal data. As a consequence, service users do not know to which extent their data and meta-data is handled in a trustworthy manner by their service provider.

There are several possibilities to improve trustworthiness of Internet services. While it is hard to identify possible software weaknesses in closed-source products, components and services based on open-source software allow the community as a whole to systematically search for software weaknesses, and to assess trustworthiness of components and services in a transparent matter. This means that open-source software has the potential to lead to trustworthy Internet services. In order for this to happen, sufficient coordinated effort towards this goal is required. A promising approach for making such a coordinated effort happen is by fostering an ecosystem similar to the Linux ecosystem in which large and small commercial entities cooperate with a community of volunteers towards realizing trustworthy components and services.

There is also a potential to realize trustworthy Internet services for all by using decentralized authentication and authorisation, based on a Private Key Infrastructure with private X.509 Certificate Authorities associated with the homes of individuals, and using personal trust exchange. Further steps towards increased trustworthiness is realized by the Crossbear PKI notary service (cf. <http://www.crossbear.org>), which allows to detect and to localized TLS Man-in-the-Middle attacks.

As a concluding assessment, it appears impossible to ensure resistance against particular advanced targeted attacks today. At the same time, it appears to be a more realistic goal to raise the cost of large-scale attacks, and to make it difficult to have large-scale data gathering undetected.

### 3.8 Energy considerations for client-side Internet usage in developing regions

*Saleem Bhatti (University of St. Andrews, GB)*

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As more users around the world come online, there is increased use of services and systems. More electricity is used world-wide, and this also increases the carbon emissions due to ICT usage: ICT already produces 2% of worldwide CO<sub>2</sub> emissions, second only (just) to the aviation industry, and those CO<sub>2</sub> emissions are predicted to triple from 2008 to 2020.

In developing regions, there is far lower penetration of users: there are many more users yet to come online, so the potential increase in energy burden on those regions is greater than in developed regions. However, in those regions, the introduction of online services for application such as e-Health, e-Education and e-Government could also have the greatest benefits. For example, use of voice and video has high utility where there are a large number of languages in use and a high level of functional illiteracy. So, governments in such regions, e.g., India, are keen to bring these services to their citizens to improve overall standards of living. However, places like India also have power generation that does not meet normal daily needs, e.g., daily deficits of 6%-15%.

So, as we look at technology for deployment in such regions, to enable applications such as e-Health, we need to look more carefully for the energy usage of systems so that they can be introduced more easily without as a high an energy burden attached to their deployment.

There has been much research in how to improve energy efficiency of hardware components, server systems and datacentres, with applications of such research yielding great benefits in terms of energy usage and associated carbon emissions. However, there has been relatively little work on reducing energy-usage of client-side systems, especially by examining the energy usage of software systems and components.

Our position is that small improvements in energy usage of client systems can have a significant benefit when considering the multiplier of a large population of users [1],[2],[3],[4]. Additionally, improving software energy usage has the benefit of being applicable through software updates to legacy (non-energy efficient) hardware. Software improvements in energy efficiency work in complement to hardware efficiencies.

This talk looked at how changes in protocol usage and video codecs can have a measurable and potentially significant impact on energy usage of client systems, especially when considered for a large population of users.

#### References

- 1 O. Ejembi, S.N. Bhatti. Help Save The Planet: Please Do Adjust Your Picture. ACM MM 2014 – 22nd ACM Int’l Conf. Multimedia. Orlando, FL, USA. Nov 2014. DOI: 10.1145/2647868.2654897
- 2 Y. Yu, S.N. Bhatti. The cost of virtue: Reward as well as feedback are required to reduce user ICT power consumption. ACM e-Energy 2014 – 5th ACM Int’l Conf. Future Energy Systems. Cambridge, UK. Jun 2014. DOI: 10.1145/2602044.2602063
- 3 M. Abu-Tair, S.N. Bhatti. Energy Usage of UDP and DCCP over 802.11n IEEE. AINA 2014 - IEEE 28th Int’l Conf. Advanced Information Networking and Applications. Victoria, Canada. May 2014. DOI: 10.1109/AINA.2014.40
- 4 M. Tauber, S.N. Bhatti, Y. Yu. “Towards Energy-Awareness In Managing Wireless LAN Applications”. IEEE NOMS 2012 – IEEE Network Operations and Management Symp.. Maui, Hawaii, USA. Apr 2012. DOI: 10.1109/NOMS.2012.6211930

### 3.9 The challenge of an Internet for all: can the grid be part of the solution?

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Around 80% of the worldwide population has access to electricity, a number that drops to 35% in the least developed countries. Nevertheless, in many developing countries the infrastructure exists, so the lines are already there. As such, in these countries power line communications (PLC) are arguably the only technology with a deployment cost comparable to wireless. This, we argue, makes it a technological solution worth exploring for Internet access.

Power grids today are being modernized through the introduction of communication networks dedicated to the management of energy transmission and distribution. Although the investment in smart grids today is concentrated in developed countries, smart grids may play an important role in the deployment of new electricity infrastructure in developing countries, by enabling more efficient operation and lower costs. For instance, in sparsely populated areas smart grids could enable a transition from one-off approaches to electrification (battery- or renewable energy-based electrification) to the development of community grids that then connect to the national grid.

Can the grid be part of the solution for the challenge of global access to the Internet? Some opportunities seem to exist. For example, exploring the existing power lines for Internet access using PLC; or leveraging on the distributed, ad hoc nature of community smart grid networks to explore novel low-cost access solutions. But many challenges remain: is the overall cost of these solutions reasonable, when compared to the alternatives? Can the existing infrastructure in these countries really be of some use? With many open questions and several unsolved issues, there's quite a big room for discussion and debate on the topic.

### 3.10 What rights should we have to the Internet?

*Michael P. Fourman (University of Edinburgh, GB)*

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Internet access is increasingly a necessary prerequisite for participation in society. As those who are connected benefit, those who are excluded suffer economic, educational and social exclusion. Market forces do not result in Universal provision. Remote users value the Internet more highly, as it is more difficult for them to find substitutes for the services it enables; but Internet provision is most expensive in remote areas. Network effects mean that we all have an interest in getting more people online, so increasing Internet access brings many positive externalities. These positive externalities justify intervention to address the market failure to deliver universal provision.

However, a purely economic argument, based on such externalities has also failed to deliver anything close to universal provision. Those who remain unconnected, or with inferior service already isolated and/or disadvantaged, and their social exclusion is exacerbated by an increasing digital divide, as those who are well-connected enjoy increasing benefits from the digital economy, and existing non-digital services become uneconomic and are withdrawn.

We must either accept a growing digital divide, or provide stronger arguments for universal provision. In making these arguments we must balance Internet access against many other benefits of modern society, such as freedom, education, and health. Access to these benefits is often prioritised, because they are closely related to fundamental rights. Surely Internet access should be a secondary concern.

Of course the right to health does not entail a right to a hospital; nor does the right to education entail a right to a university. But rights such as these do affect policy. They entail a duty on governments to make best efforts for universal provision, and lead to levels of provision higher than would otherwise be justified. Information is power.

We argue that the changes enabled by modern information and communication technologies have fundamentally changed the balance of power, and that we must revisit established rights to freedom of speech and access to information and education if we are to avoid a fundamental digitally-enabled divide between those who can wield the digitally-enhanced power of information and those who cannot. This leads us to propose fundamental rights to store, process and communicate information. We argue that these are necessary for an inclusive digital society.

### 3.11 Life in the Slow Lane

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Universal Internet access has become critical to modern life leading to many explorations of approaches to increase its availability. One means of addressing the cost of access is to share the WiFi of existing broadband connections utilising their unused capacity [2]. Systems that share home broadband in this way already exist (for e.g., FON), where subscribers' existing broadband connections are shared by making available a wireless network accessible to anyone with a Fon account. These networks are typically provided either as a paid service or incorporated as part of an existing broadband subscription, enabling subscribers to access their network's broadband service via other subscribers' access points while roaming. However, when considering whether to mandate such sharing, there are a number of questions that remain unanswered: (i) is there spare capacity on existing domestic broadband links to do this without impacting service? (ii) how would this capability be used? (iii) would such a service be useful to the target demographic? (iv) are existing subscribers willing to share their capacity?

The talk reports on a limited-scale feasibility study of a Public Access WiFi System (PAWS) [1] that answers these questions. The intent of PAWS is to explore provision of a restricted service that is free at the point of use, targeting demographics that want and need but cannot afford Internet access. As we are interested in the use of such a system in spatial and social context, we apply the "in the wild" method from HCI: lab-based studies fail to show appropriation and use in context; surveys/questionnaires reveal only stated preference rather than actual behaviour; and measurement studies fail to uncover the social challenges that are at least as important as the technical. The intent behind this study is not to make broad statements about the use of a system like PAWS, but to uncover a rich understanding of a small number of users so as to sensitise us to the underlying challenges in deploying such a system. Thus we do not collect the data necessary to comment on broader questions

such as how to incentivise sharers or what the commercial or operational impact would be on ISPs. Instead, we make the following contributions: (i) there are a number of technical challenges, principally signal reach and the variation in both home router availability and ISP configuration, which suggest that the density of deployment required for a system like PAWS to provide free Internet access for the digitally excluded is quite high and probably requires regulation to be effective; (ii) perhaps surprisingly, free access to the Internet is not the instant success one might expect, although some citizens do find even relatively limited access of considerable use; (iii) many existing broadband subscribers appear quite willing to share their bandwidth locally for the common good without requiring significant financial incentive.

The experimental deployment demonstrated the potential utility and viability of a Public Access WiFi Service. Even in the relatively complex form it was presented, users signed up and used it for legitimate, socially beneficial purposes. The primary citizen was clearly sufficiently happy to use the service extensively, and all citizens used it for a wide range of purposes: this suggests that the overall performance of the system was acceptable once past the interactional overheads of signing up and connecting to the VPN. We also observed that several users, not just the primary users, made use of PAWS for the legitimate (foreground) uses it was intended, such as banking and retail. They also brought to light the value of other (background) uses that we did not originally envisage, e. g., software updates.

We believe we can now partially answer the questions we posed: (i) many existing domestic broadband deployments do have sufficient spare capacity that sharing some of it would not be a problem for the owner; (ii) such a capability will be used in a range of ways, some more acceptable than others, suggesting there may be a need to manage the uses to which the shared bandwidth can be put; (iii) the service was useful to at least some of the target demographic; and (iv) given that the compensation we offered failed to sway people who refused to participate, and some sharers did state a willingness to share bandwidth simply for the common good, at least some existing subscribers do appear willing to share their bandwidth without requiring any further incentive. Further research is required to better understand the incentive structure for both the sharers as well as the network operators to enable a service such as PAWS. One plausible incentive structure would be for enabling third party stakeholders such as grassroot user communities or local government who may have a socio-environmental objective rather than purely economical to manage the PAWS service (where sharers could get a small council tax rebate for sharing their connection) while for the network operator they get paid (again) for leasing out the unused capacity (which has already been paid for) [3].

Finally, the ISPs clearly have a role to play in this. Traditionally they have argued against giving free access based on the claim that traffic on their backbone networks costs them money. However, networks are (typically) provisioned for peak use, and citizens using PAWS would not significantly increase peak use (they will not increase the number of access links into ISP networks, and there would be little spare capacity for them to use at peak times anyway). Thus they would increase off-peak but not peak use; any slight increase in peak use could be further mitigated through deployment of less-than-best-effort protocols from the access points into ISP networks, enabling ISPs to further degrade the free service if they found it necessary. We might anticipate regulation would have a part to play in controlling such degradation. There is evidence that some ISPs (e. g., AT&T) are already applying such selective traffic grooming practices for commercial gain; PAWS would encourage them to do so for social benefit.

## References

- 1 A. Sathiseelan, R. Mortier, M. Goulden, C. Greiffenhagen, M. Radenkovic, J. Crowcroft, D. McAuley, A Feasibility Study of an In-the-Wild Experimental Public Access WiFi Network, ACM DEV, San Jose, December 2014.
- 2 A. Sathiseelan, J. Crowcroft, LCD-Net: Lowest Cost Denominator Networking, ACM SIGCOMM Computer Communication Review, April 2013.
- 3 A. Sathiseelan, C. Rotsos, C.S. Sriram, D. Trossen, P. Papadimitriou, J. Crowcroft, Virtual Public Networks, 2nd IEEE European Workshop on Software Defined Networking (EWSDN), Berlin, October 2013.

## 3.12 Community Networks: Access to the Internet or a Different Internet Model?

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Is a different (from the global Internet and Cellular Networks) model for urban communications and networking conceivable? Can Community Networks, now flourishing in many parts of Europe and the world, be the next "big thing" in networking, for once considering the needs of people and urban evolution as a key element, and not as a side effect of technology or business? This talk introduces some of the new trends on people-driven communication efforts, normally community networks, as alternatives to the business-based organization of the networks we use daily.

Let's start from a question: Is the Internet (as we know today, based on commercial services and most of all on "free" services paid by ads and loss of personal data, privacy and freedom) the only communication model possible? The follow up is a discussion of one possible alternative, or better complement, to the Internet and cellular networks: Urban Wireless Community Networks (UWCNs). We stress the urban dimension not because WCNs cannot grow in the countryside or cannot flourish in rural environments, but because we think that inside cities they can grow to have a role which is not only an access network (to the Internet) or an instrument to reduce the digital divide (whatever this means), but they can sustain entirely novel communication paradigms that not only break the Telco and ISPs oligopoly in communications, but also shatter the much more subtler trust of information mediators and aggregators (search engines, centralized social networks, etc.) that are today controlling the way information flows around the world, as the "Snowden Affair" has recently brought to the general public attentions.

Indeed, neither WCNs nor the challenging the Internet model are brand new topics [1],[2], and indeed also community networking go back at least 20 years [3], but today technology makes them more feasible than ever by making the technical design and management easier. However, what makes UWCNs different from the global Internet is their cooperative, bottom-up nature, and it is important to understand why this new model of social networking is emerging.

If we go back to the to the origins of Internet and TCP/IP we find out that the technical approach was distributed, cooperative and social event the web and most of all the "web 2.0" approach was conceptually peer-to-peer. Centralization and concentration are just market-driven economic trends, lead by the fact that the Internet is controlled, in the end, by a small oligopoly of very large players (content mediators and telcos). So, is economic sustainability the true reason for centralization? We claim this is not really true, and a more distributed,

human and social-centric Internet is not only feasible but indeed desirable for the healthy growth of society and economy. What is lacking today is an holistic approach, a novel “science” that let scientists, engineers, economists, sociologists, but most of all politicians and decision makers understand the global context, the consequences of regulations and legal obligations, the far fetching results of apparently local decisions (as for instance implementing a UWCN supporting local services and independent – from the global Internet – communications for a community). Some of these issues have been discussed already [4], but much more remains to be done, specially from a interdisciplinary point of view, trying to make people from as different scientific fields as ICT, sociology, and law, cooperate, find a common language, establish a “new science” that will unleash the potential of UWCNs as means for a new perspective on global communications. We note that this approach will intrinsically reduce the digital divide both in developed countries and in the developing world, as a communal (not communist!) approach is far more sustainable, both economically and socially than a market-based one.

We have recently analyzed some technical challenges, as realizing distributed firewalls adapt for low-energy networking [5], or improving distributed filtering [6], but these are only timid approaches, in our specific field, to tackle a huge problem that requires many more efforts from the community and from society at large to be solved.

#### References

- 1 R. Battiti, R. Lo Cigno, M. Sabel, F. Orava, and B. Pehrson, *Wireless LANs: From WarChalking to Open Access Networks*, Mob. Netw. Appl. SpringerVerlag, June 2005, <http://link.springer.com/article/10.1007Fs11036-005-6422-4>
- 2 R. Lo Cigno, *Untethered Local Communications: From Wireless Access to Social Glue*, In IEEE WONS, Bardonecchia, Italy, Jan. 2011, DOI: 10.1109/WONS.2011.5720198
- 3 D. Schuler. *New Community Networks: Wired For Change*. AddisonWesley Publishing Company Inc., 1996, <http://www.publicsphereproject.org/ncn/>, last visited May 2014.
- 4 R. Lo Cigno, and L. Maccari. *Urban wireless community networks: challenges and solutions for smart city communications*. ACM international Workshop on Wireless and Mobile Technologies for Smart Cities (WiMobCity), Philadelphia, PA, US. 2014, DOI: 10.1145/2633661.2633669
- 5 L. Maccari and R. Lo Cigno, *Waterwall: a cooperative, distributed firewall for wireless mesh networks*, EURASIP Journal on Wireless Communications and Networking, 2013, <http://jwcn.erasipjournals.com/content/2013/1/225>
- 6 L. Maccari and R. Lo Cigno. *Betweenness estimation in OLSR-based multi-hop networks for distributed filtering*. Journal of Computer and System Sciences, 2013, DOI: 10.1016/j.jcss.2013.06.018

### 3.13 Guifi.net experiences – Network infrastructure as a Common-Pool Resource

*Roger Baig Vinas (Guifi.net – Barcelona, ES)*

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Bottom-up initiatives have brought connectivity to places that otherwise would have been left disconnected for a long time. Community Networks, a particular case of Bottom-up, have ported the concepts of the commons and non- speculative access to telecommunication infrastructure, proposing a new model for designing, deploying and operating networks

and have developed the necessary tools to implement an entire economic ecosystem. The emergence of this telecommunication model opens the question how to integrate it in the, so far, unidimensional public-private debate, bringing new challenges in many fields, such as the regulatory framework, the internet governance, the internet management, etc.

Community Networks have proved that they can contribute in great manner in reducing costs of internet expansion, thus to be able to play a significant role in achieving and affordable internet access for everyone.

The underlying principle behind guifi.net is the firm conviction that the optimal way to design, deploy and operate a network is doing it as a common-pool resource (CPR), being the network infrastructure the core resource, which is nurtured by the network segments the participants deploy to reach the network or to improve it, and the fringe unit is the connectivity they get.

In our talk we discussed our fundamental ideas, presented some of the tools the guifi.net community have developed to put our ideas in practice and the results we have achieved. We are confident that most of these ideas and tools can be reused to bring connectivity to other places. All our materials, documents and software included, are publicly available.

The tools presented are:

1. The network license, the Compact for a Free, Open & Neutral Network (<http://guifi.net/en/FONNC>), which precisely defines the rights and the duties of the participants. It is mandatory to accept it to join the network. It is written to be enforceable under the Spanish legislation. Legal certainty is essential to stimulate participation and investment, which in turn, is at the base of any economic activity.
2. The network management and provisioning software tools, a set of software tools to ease the design, deployment, management and operation of the network in a self-provisioning style.
3. The conflicts resolution system, systematic and clear procedure for resolution of conflicts with a scale of graduated sanctions. It consists of three stages, conciliation, mediation and arbitration, all of them driven by a lawyer chosen from a set of volunteers. The cost of the procedures are charged to the responsible party or to both parties in case of a tie.
4. The collaboration agreements, 1) for professional activities and 2) for the rest of entities. Professionals can choose between three degrees of commitment, fully-committed (all the infrastructure deployed is in commons), partially-committed (sometimes they deploy in commons, but others not), or not-committed (they use the infrastructure available in commons, but they never contribute to it).
5. The economic compensations system, has been developed and implemented to compensate imbalances between investment in the commons infrastructure and use the professionals make of it. Expenditures (hardware and manpower) declared by the participants (the professionals but also the volunteers) are periodically cleared according to the network usage of the professionals and their degree of commitment. Fully-committed professionals are charged just to cover the administration costs, partially-committed are charged to meet the investments made by the fully-committed and non-committed are charged to meet the investments made by the fully-committed plus an extra to ensure the CAPEX. At the moment the rates are 10%, 50%, and 100% of the cost of the network usage of each of them. The Foundation centralises and manages the billing system (each professional only makes or receives a single payment). The mechanism is applied at PoP level.

The results:

1. Over 26,500 working nodes
2. More than 50,000 kms of links

3. Multiple technologies used: OF, WiFi, etc.
4. Total estimated guifi.net users: over 80,000
5. Places where 90% of the households have guifi.net access
6. Total estimated OPEX: 6.5M€
7. Total estimated CAPEX: 2.75M€/year
8. CATNIX (Catalan exchange point) member
9. RIPE-NCC member
10. 2 Internet uplinks, 1Gbps each
11. 15 SMEs operating over guifi.net infrastructure
12. Hundreds of volunteers
13. A Foundation + number of local organisations

### 3.14 Experiences and Research in Community Networking: the Community-Lab.net testbed

*Leandro Navarro (Polytechnical University of Catalunya – Barcelona, ES)*

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Experiences, research challenges, lessons learned, from researchers working together with community network activists to understand, model, engineer and experiment on sustainable ways to bootstrap connectivity and digital services at the scale of 7 billion people.

### 3.15 Some Challenges for Rural Broadband: Experience from Scotland

*Mahesh Marina (University of Edinburgh, GB)*

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This talk gives a short overview of our work on the Tegola project that focused on bringing wireless Internet access to some of the remotest parts of Scotland. The talk also briefly presented a recent work on analysing mobile coverage in Scotland. Finally the talk reflects on the experience from these projects and outline some challenges for rural (mobile) broadband.

### 3.16 ICT4D and TVWS

*Marco Zennaro (ICTP – Trieste, IT)*

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TV White Spaces (TVWS) technology and regulation has the potential to make connectivity both technically and economically feasible in Developing Countries where affordable access remains a challenge. The superior propagation characteristics of TVWS technology make it particularly well suited to connecting remote communities. How will this new technology affect ICT4D projects? What are the research challenges in TVWS?

### 3.17 Decentralized, multi-hop networks: Are They really different from the Internet?

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Community networks (CNs) represent a bottom up effort to build independent, community-owned network infrastructures. In light of the recent NSA scandal and the global trend towards centralization of networks and services, they have received large attention, since they represent a completely different approach.

CNs are changing from their initial model. In the past they were created by local hackers in regions where there was no broadband connections with the goal of replacing the last mile. Today, they are blooming in many countries, and in many cases they grow in densely inhabited cities that are already covered by broadband connections. So why do they grow? one reason is that they offer a different model of networking, that embeds social and political motivations that make them different from any other network. People build CNs because they want to own their networking infrastructure, neutral, uncensored, hard to disconnect. The last two years have witnessed the Datagate scandal, a large discussion (both in Europe and USA) about Network Neutrality, and governments that keep disconnecting, censoring and filtering the Internet to repress internal dissent. This produced a high media attention for CNs not because they are a cheap way to achieve Internet access but because they are a community-owned infrastructure that offers some kind of protection from privacy invasion, censorship and disconnection.

But is this effectively true? the talk presents some initial results on the study of some Wireless Community Networks showing that they are indeed more centralized than they seem, both topologically and socially. The topological features of CNs are indeed similar to other networks: a few fraction of the nodes (about 5% in the three CNs that were considered) are vital for the whole network. They are involved in approximately 90% of the shortest paths, and their failure would provoke the fragmentation of the network in many small disconnected islands. Moreover, the analysis of the ownership and of the interactions in the mailing lists in one of the community under analysis show that a few individuals own a large fraction of critical nodes and occupy the discussions in the mailing lists. Thus, in spite of the effort of the communities to maximise resilience, decentralization, and participation CNs are not much different to the Internet.

So the questions this presentation asks are: how can we help the communities to build networks that are truly decentralized? What are the tools they require to fulfil their goals?

### 3.18 Bandwidth for free?

*Michael Welzl (University of Oslo, NO)*

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When we look at what is available in the academic literature as well as already deployed systems to support LBE communication, we can find quite an arsenal of possible mechanisms. These mechanisms differ not only in how they work but also in how they can be applied. For example, some methods involve using the network only in off-peak hours such as 3–5 AM.

Such usage requires scheduling of traffic, which may be fine even for large downloads, but limits usage to schedulable (i. e., non-interactive) applications. This is different with LBE congestion control such as LEDBAT [1], which may operate in parallel with other traffic. In addition to the benefits derived from the congestion control, LBE-marking traffic via DSCP in the IP header could yield more appropriate queuing in routers [2], and traffic engineering could then give such traffic a special treatment too.

LEDBAT is only one out of many congestion control possibilities. Depending on the requirements of the usage scenario, it may sometimes either be too aggressive or not aggressive enough. Alternatives include different LBE congestion controllers [3] and applying priorities in congestion control [4],[5]. Also, it is possible to allow users to transmit or receive traffic with “normal” congestion control whenever it is known that such traffic does not share a bottleneck with “foreground” flows (e. g., a user’s downlink is not necessarily always the bottleneck, e. g., with P2P applications where it is more likely for the sender’s uplink to be the bottleneck). There are methods to detect whether flows share bottlenecks, with one recent mechanism currently being proposed for standardization in the IETF [6]. These methods generally require both ends of a connection to be involved, but they could also be applied at the ends of just the link that is of interest.

LEDBAT-style mechanisms make sense when congestion controls compete. This is often not the case for a user’s uplink, which usually mostly carries TCP acknowledgment (ACK) packets. These packets are small and usually do not reach a number where they begin to congest a link; this means that small data packets could be inserted in between pauses of ACKs, or LBE traffic could even be piggybacked on ACKs (which often do not carry data).

Here, we could only scratch the surface regarding all the LBE possibilities that are already known or can be imagined; it would probably make sense to create a taxonomy of such mechanisms, with their pro’s, con’s and limitations as well as their potential for application in a GAIA context.

## References

- 1 S. Shalunov, G. Hazel, J. Iyengar, M. Kühlewind: “Low Extra Delay Background Transport (LEDBAT)”, RFC 6817 (Experimental), December 2012.
- 2 R. Bless, K. Nichols, K. Wehrle: “A Lower Effort Per-Domain Behavior (PDB) for Differentiated Services”, RFC 3662 (Informational), December 2003.
- 3 David Ros, Michael Welzl: “Less-than-Best-Effort Service: A Survey of End-to-End Approaches”, IEEE Communications Surveys and Tutorials 15(2), pp. 898–908, 2013.
- 4 J. Crowcroft and P. Oechslin. Differentiated end-to-end Internet services using a weighted proportional fair sharing TCP. In ACM SIGCOMM Computer Communication Review archive, volume 28, pages 53–69, July 1998
- 5 Dragana Damjanovic, Michael Welzl: “An Extension of the TCP Steady-State Throughput Equation for Parallel Flows and its Application in MulTFRC”, IEEE/ACM Transactions on Networking 19(6), December 2011.
- 6 David Hayes, Simone Ferlin, Michael Welzl: “Practical Passive Shared Bottleneck Detection Using Shape Summary Statistics”, IEEE LCN 2014, 8–11 September 2014.

### 3.19 Can we fit the Internet in a box?

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What is the Internet? If you ask a network engineer they would explain the many details of TCP/IP. However, the everyday person might likely respond with “Facebook”, “Twitter” or “Netflix”. This talk will explore the feasibility of capturing these applications and services in a single locally usable “Internet Box”. The box will operate independently of the rest of the Internet, allowing those without traditional connectivity to use the “Internet” in an simulated and disconnected manner. If this is proven feasible, many localities that possess no connectivity could hopefully start to use Internet services immediately. The talk will argue why this is a positive first step towards global access for all.

### 3.20 The Liberouter Neighborhood Networking Platform

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Mobile opportunistic networking utilizes device-to-device communication to provide messaging and content sharing mechanisms between mobile users without the need for supporting infrastructure networks. However, enabling opportunistic networking in practice requires a sufficient number of users to download, install, and run the respective routing and application software to provide sufficient node density, and thus connectivity for the network to actually function. We provide a system called liberouter [1], an embedded Linux box based upon the Raspberry Pi platform, that allows bootstrapping mobile devices; serve a wireless access point and storage platform; and can mesh with each other. We explore reaching out to nodes that have not (yet) installed any dedicated software to: (1) allow them to access public content in an opportunistic network to possibly seed their interest and (2) instrument them to assist as (limited) message carriers to improve connectivity [2]. We present three applications to create and interact in temporal (instant) communities.

#### References

- 1 Teemu Karkkainen, Jörg Ott: Liberouter: Towards Autonomous Neighborhood Networking. Proceedings of IEEE/IFIP WONS, March 2014.
- 2 Marcin Nagy, Teemu Karkkainen, Jörg Ott: Enhancing Opportunistic Networks with Legacy Nodes. Proceedings of the ACM MobiCom CHANTS workshop, September 2014.

### 3.21 An interdisciplinary perspective on DIY networking: the case of the Internet Jukebox

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The primary role of a local DIY network can be either the provision of cheap Internet access, as in the case of most community wireless networks, or the support of local applications, as in the case of the liberouter or the piratebox (and a fast growing number of related projects [1]). Depending on the choice of this primary role there is a wide variety of design options at different levels that will determine the successful deployment of such a network [2]. The talk reports on recent efforts to bring together researchers and practitioners from various fields around the (hybrid) design of such local networks: the recent Dagstuhl seminar on “DIY networking: an interdisciplinary perspective” [3], the 3rd EINS summer school “From smart cities to engaged citizens” [4], and the LSE workshop on “The Alternative Internet(s): state of the art and possible futures” [5]. It then focuses on a novel application, the Internet Jukebox, that aims to combine the two possible roles of DIY networking, Internet access and local interactions. More specifically, the Internet Jukebox wishes to experiment with a different way for sharing a very thin Internet connection amongst a local community of users: enable them to decide all together on a single content item to be downloaded in every pre-defined period (according to the capacity of the link) and possibly projected in a public place. So, like in the case of a musical Jukebox the selected content will be the only choice for everyone. However, the selection will not be subject to payments but it will be the outcome of a democratic process, which we call “collaborative Internet consumption”.

#### References

- 1 <http://nethood.org/links.html>
- 2 P. Antoniadis, B. Le Grand, A. Satsiou, L. Tassiulas, R. Aguiar, J.P. Barraca, and S. Sargento, Community building over Neighborhood Wireless Mesh Networks, *IEEE Technology and Society*, 27(1):48–56, 2008.
- 3 <http://www.dagstuhl.de/14042>
- 4 <http://internet-science.eu/summer-school-2014>
- 5 <http://www.iscc.cnrs.fr/spip.php?article1912>

### 3.22 Providing Connectivity or Avoiding Censorship by Mobile Peer-to-Peer Communication? Fiction or Practical Solution?

*Karin Anna Hummel (ETH Zürich, CH)*

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Do-it-yourself delay tolerant networks that utilize user mobility to carry data are still an appealing participatory approach to provide multi-hop peer-to-peer connectivity when there is limited access to the Internet, or the access is unsecure as under repressive political regimes. Examples of limited Internet access are rural African and Indian regions. Another example recently covered in the media is Hongkong, where the basic-democratic movement makes indeed use of an ad-hoc communication technology to circumvent blocking of communication (cf. FireChat app). To serve these application use cases, the talk introduced two possible

system architectures for mobile peer-to-peer networks: with and without stationary data-boxes in addition to mobile carrier devices. The talk raised the question about the practicality of peer-to-peer communication in the envisioned scenarios. First, the talk discussed whether we have already a good understanding of mobility flows and contacts and whether these flows are sufficient to provide reasonable connectivity and network capacity. The talk showed how the cellular network can be utilized as a ubiquitous sensor of human mobility in principle, and exemplifies the approach for a developing country, namely Ivory Coast leveraging mobile phone data provided by Orange Ivory Coast. In the second part, the talk targeted technical obstacles for the deployment of mobile peer-to-peer communication with an emphasis on energy consumption.

### 3.23 Communication Issues and Challenges in the Amazon Region – A special focus at Itaituba, Brazil

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Delivering affordable and effective Internet services in the Amazon has long been a challenge, mostly because of the hostile environment conditions (which imposes difficulties to wireless communications) and high cost of deploying wired infrastructures (such as optical fibers). As a consequence, available services are often overpriced and do not meet the needs of local population (e. g., very low bandwidth), not to mention the intermittent failures and service black-outs that occur very often. This situation is made worse by the apparent inability of existing protocols to perform adequately on narrowly constrained, congested links. In this talk, we provide a glimpse on the current panorama of Internet Services in the Amazon region, focusing on the case of Itaituba (a small town of about 100,000 inhabitants in the midst of the Amazon, Brazil). We also enumerate and discuss some challenges and opportunities for research, based on personal experiences of Internet usage in that region.

### 3.24 Which infrastructure for a better Internet in Africa?

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Reasons for low penetration and low quality of Internet access in Africa are numerous: high Internet access costs inherent to energy instability, transit costs, network operation costs, lack of infrastructure in rural areas, lack of content in Africa, as well as the preference of users for popular Google, Facebook or Youtube content mostly hosted outside Africa which lead to a constant loop (no local content no peering, no peering no local content). We review approaches to tackle this problem. We suggest a better energy provision to the industry (by Africans governments or private companies) which could be boosted by competition in this sector, an orientation of electrification politics towards solar energy storage and furniture, renewable energy, gas and nuclear centrals, as well as the establishment of a climate of fairness and cooperation/partnership by the regulations in the telecoms market. Most importantly, ISPs could increase peering to save on transit costs. They could also implement

traffic engineering and efficient routing to keep local traffic local. Meanwhile, ISPs should invest in terrestrial optical fiber networks deployment or alternative technologies for the middle mile in order to reach more customers. Creation, development of local content and web content hosting should also be encouraged. Considerable efforts are currently being done on the continent to achieve these objectives but they need to be multiplied, as Africa is massive.

## 4 Working Groups

### 4.1 Socio-Economic Models and Role of Community Networks

*Roderick Fanou, Michael P. Fourman, Thomas Huhn, Renato Lo Cigno, Leonardo Maccari, Mahesh K Marina, Henning G. Schulzrinne, and Marco Zennaro*

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We identified four targeted groups when providing universal Internet access and separate issues given their types:

1. Individuals (with differences in availability and use by age, gender, education and to income, where the latter two are strongly correlated);
2. Schools and libraries: installing Internet at schools and libraries lead to the adoption at home;
3. Small businesses: Currently, many small businesses don't have any web or map presence. This reduces their ability to benefit from tourism, for example;
4. Health care facilities: hospitals, clinics, pharmacies, long-term care facilities.

Collectively, schools, libraries, public safety and hospitals are also called community anchor institutions.

We then focused on the following three dimensions:

1. Affordability: lack of income.
2. Availability: The high cost of deployment and maintenance (as well as lower income) typically causes broadband to be less available in rural areas. However, the proportion of served homes that subscribe to Internet access is often higher in rural areas than in urban areas. Availability is not binary, as Internet access may be available, but not reliable, or too expensive.
3. Relevance: Individuals and organizations may not see how Internet access meets their needs or furthers their objectives.

What do people use broadband for?

1. Content consumption
2. Communications: for coordination of personal and commercial affairs; for social connections to relatives and friends, often far away.
3. Applications: Increasingly, Internet access is no longer visible as web browsing. For example, people may use Internet-based mapping applications, but may not be aware that these require Internet access. Mapping applications, in particular, can be very useful for low-income countries.

We then answer to the following three questions:

1. How do you make broadband relevant? We need distinguish two aspects:
  - a. Reasons why people find relevant or not.
  - b. The factors that influence or motivate people to have it. In places where there may not be roads in time of disaster, for instance, talking to your relatives as you talk with your neighbours, communicating with the governments, getting services, participate to the development while your region is isolated due to a disaster, are those benefits that you can get from installing Internet. If we increase relevancy, we may also improve availability, by creating demand.
2. How to reduce the cost?
 

Encouraging and enforcing sharing of critical facilities (from the middle to the last mile/connectivity) may help reduce cost. This could be improved by the regulations.
3. How do you make it widely available?
 

Availability needs to include the notion of affordability.

We discussed ensuring that ducts or dark fiber are installed whenever a new road is built or an older road is resurfaced, or a railroad track is (re)built. Such fiber assets are needed for controlling traffic lights and train signals.

Similarly, all new homes should be equipped with fiber at time of construction, rather than adding it on later at great expense. The availability of fiber and Internet access should be part of the description of a home in real-estate web sites.

There are two models for increasing availability: In the bottom-up model, communities or NGOs build local networks, e. g., within a town or region, and link them later to the Internet. There is no empirical data, however, on how big such networks have to be so that they attract a sufficient number of users and a sustainable business model. In the top-down model, a national organization provides services to member institutions or communities. Examples include the national research and education networks (NRENs) such as Internet2 and JANET. For residential Internet access, the amount of capital needed may exceed the ability of private entities to finance. For example, the cost of running fiber networks to every household in Germany has been estimated at 80 billion Euros. While large, such expenses can be amortized over long time periods.

In many situations, building new networks requires a significant initial capital investment before revenue accrues to the ISP or community network. Thus, loans with reasonable terms can be very helpful. For example, the US Department of Agriculture provides low-interest telecom loans for rural development. It is not clear if larger banks understand telecom well enough to be a patient lender. Such loans may also facilitate the deployment of shared middle-mile infrastructure that allows small (wireless) ISPs to obtain Internet connectivity at reasonable rates.

Regulators can ensure access to backhaul and peering at fair and reasonable terms and rates. In UK, ISPs for instance are not interested in a network with less than a million of customers.

We discussed the use of the franchise business model for providing residential access. While common in other areas such as hospitality and services, we have not seen much of this for providing Internet access. Related models include the credit unions (cooperative banks) in many countries. Franchise models allow sharing of scalable resources, such as routing and security expertise, billing and network operations systems. Many common services, such as billing or network diagnostics, can be provided remotely.

## 4.2 Internet in a Box

*Jon Crowcroft, Gareth Tyson, Jörg Ott, Arjuna Sathiaseelan, Georg Carle, Adam Wolisz, Michael Welzl, Karin Hummel, Panayotis Antoniadis, and Weverton Cordeiro*

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There are many areas of the world that have poor Internet connectivity, and extending high speed access is many years away. This section explores the potential of creating a locally available “Internet Box” that can be placed in a village. The Box will possess storage and computation capacity, alongside local network connectivity. By connecting to the Box, local residents will be able to get an Internet-like experience, accessing all content and services locally present. If a perfect prediction of content consumption can be achieved, the Box would truly be able to emulate a high speed “Internet” connection.

**Initial Concepts.** The Internet in a Box concept could be realised in a number of ways. This subsection details various “tiers” of functionality. Potentially, these tiers could be built iteratively one-by-one. Further, which tier is realised will vary heavily based on the target area of deployment.

**Tier 1:** Curated storage: The simplest model would be to provide a single box that possesses static storage and local network connectivity. The Box will contain a large block of storage that is filled with curated static content. The person selecting what is stored is left undefined. Local WiFi allows users to connect to the Box. Upon connection, users will be able to access a locally available portal that gives access to all content on the Box (e. g., via a web browser). In line with common usage, the most sensible portal might be a search engine interface but more structured access to content categories could be supported, too.

**Tier 2:** Curated and local user generated storage: The next tier would extend the Box to support user uploaded content. This would allow users to create and share their own static media (e. g., webpages, pictures, videos). The uploaded content would then be integrated into the portal to make it locally available to all other users.

**Tier 3:** Curated and local user generated storage and services: The next tier would introduce active services onto the Box. This would move beyond static content provision. Potential services could be online social networks and voice communications. This would be limited to local interactions.

**Tier 4:** Storage and services with one-way connectivity: The next tier would add one-way inbound communications to the Box. This is likely to be periodic and, potentially, unpredictable. This would allow the Box to receive one-way information from external parties. In particular, parts of the curated box contents could be updated on a regular basis.

**Tier 5:** Storage and services with time shifted two-way connectivity: The next tier introduced two-way communications. However, this will not necessarily be synchronous. Request/response intervals could be in the order of hours or days. Further, there may be extended periods without any connectivity whatsoever. This would allow usage data to be uploaded from the Box to a cloud service, which could then later send new content.

**Tier 6:** Storage and services with two-way connectivity: The last tier considered adds two-way synchronous connectivity. Unlike Tier 5, the Box will have on-demand connectivity.

**Challenges.** There are many issues and challenges with building an Internet in a Box. They can be categorised in various dimensions. This subsection explores some of the key problems.

**Networking issues.** There are a number of network issues. At a minimum, the Box must offer local network connectivity. Beyond this, it may be possible to provide some level of backhaul connectivity. This could be used for non-local interactions, as well as exchanging data for refreshing the Box's storage. These issues cut across multiple layers, as the role of network mediation might be performed at a content layer (i. e., selecting what gets sent over the network). Several key questions should be answered in this area:

1. How can the limited backhaul capacity be best utilised?
2. How can local network connectivity be provisioned?
3. How can content be prioritised for managing sequential delivery to the box (via a bottleneck path)?
4. How can content be transformed to address the needs of the network medium and box capacity?

It is envisioned that an "Internet in a box" could have three buttons: green, for schedulable traffic; red, for "direct Internet" (urgent communication); yellow, for lower-priority direct Internet (i. e., network traffic that does not get in the way of a potential "red" user). In an Internet context, where "normal" traffic is handled according to the "Best Effort" service model, lower-priority communication has often been called "Lower than Best Effort" (LBE).

**Repository management and access issues.** On deployment, the Box must be filled with important data in its content repository. An obvious challenge will be devising algorithms to define what content should be placed in the Box's storage. This raises several further research questions. Storage in the Box will likely be separated into curated and auto-selected content. The former is a key social issue that relates to who should have the power to curate what content gets stored. The latter is a greater technical challenge, as it will be necessary to automatically load in interesting content onto the box in a fair manner. This must address highly heterogeneous communications capacity, result in unpredictable intervals between backhaul connectivity. Key research questions to be explored include:

1. How can influence the content on the box?
2. How can they influence the content on the box?
3. How can fair sharing (of content capacity) be measured and ensured?
4. How can variations in communications intervals be managed?
5. What is eligible to be stored on the box?
6. How can the utility of content be measured, e. g., for replacement strategies?
7. How can the content of the box be made accessible for a user interactivity perspective?

**Security and ethical issues.** The introduction of any new technology into an area will create several security and ethical questions. It is particularly important to consider legal and cultural matters: What is acceptable in one region, might be unacceptable in another. Privacy relates closely to this, as it is vital to ensure that people cannot use the Box to monitor others. Important issues include:

1. How can the Box ensure that it adheres to legal constraints of the area?
2. How can the Box ensure privacy for users accessing it?
3. How can the Box reflect cultural aspects of its area?
4. How can the Box offer authenticity of content and services offered locally?

**Deployment practicalities.** A number of extremely challenging deployment issues are apparent when deploying a Box. Each box will need to be robust and sustainable. These factors must then, of course, be traded against price. Relevant requirements include:

1. The Box cheap must be cheap enough for wide-scale deployments.

2. The components used must be readily available on a commodity basis.
3. The Box must have a sustainable power source.
4. The Box must be physically robust relevant to the conditions of its location.
5. The Box must be appropriately and strategically placed to provide coverage to people.
6. The Box's storage and computation must be appropriately dimensioned relevant to price range and service needs.

**Example: Collaborative Internet Consumption and the Internet Jukebox.** The Internet Jukebox is a simple networking device, comprising of a Raspberry Pi connected to the Internet (e.g., through a 3G dongle), a WiFi dongle that leads those connected to a local captive portal, and an external hard disk. The assumption is that the Internet connection is very “thin” and expensive (e.g., a 3G connection with 500MB limit per month). The main difference of the Internet Jukebox, compared to other “Internet-in-a-box”-like technologies is that the content to be downloaded from its thin Internet connection is decided collaboratively between those that will consume it, unlike for example the case of the Outernet (<https://www.outernet.is/en/>).

The selection of the content happens in two separate (but possible parallel) phases: search and download. In the search phase, users search for content in the Internet (through a specific set of supported search engines, e.g., the Youtube API) and choose amongst the results the content that they would like to download, forming a list of desirable content to vote upon. In the download phase, users can place their votes until the “download deadline” (it could be one vote per person or a total “budget” per person in MB that can be distributed in different items). When the deadline arrives, the most popular content is downloaded and possibly projected in place, in the (typical) case when most users do not have a personal device. So, one could imagine for example the “movie of the month” application in a small village where users can only search for youtube videos through the Youtube API and perhaps using only a small provided set of shared devices. Every Sunday the most popular movie is downloaded and projected while previously downloaded movies can be consumed in private by those that do have a device.

## 5 Overall Summary, Conclusions, and Recommendations

This seminar was successful in creating awareness on the different barriers to digital inclusion, understanding the requirements, potential and the limits of solutions that have been proposed to address in this space. While there will continue to be a need for diversity in research approaches, we could identify some areas of synergy.

### 5.1 Infrastructure Deployment

It was clear when hearing about African and South American deployments in detail, that we could make valid comparisons with the experiences of European and North American Internet deployment in the past (going back over twenty to thirty years). There are regulatory barriers, which are highly reminiscent of problems in creating really widespread connectivity in the early 1990s between European countries, between regional networks in the US, and between Europe and the US. The barriers are not the same, but require similar thinking to alter the landscape more favourably. On the other hand, there were new problems to overcome, but also these can be seen as new opportunities to develop technology. In particular, very long

range wireless communications techniques need much more work to deal with the massive distances and somewhat adversarial deployment environments in these areas (e. g., Amazon or Congo rainfall, foliage). At the same time, massive reduction in optical equipment costs, and increases in capacity available affordably on long haul fiber will also help (e. g., coming from some heroic astro-physics groups deployment for VLBI, just for one example). This technology would also address precisely the problems we see in sparsely populated fringes of the EU and North America, however, there are few market-led reasons to see technology developed for people there, whereas in Emerging economic regions such as Brazil, we could see leadership if the political obstacles are reduced.

The main opportunities here are in regulatory/policy work in designing solutions (not something we had more than modest expertise present in the seminar) and application of technical operational experience to fix problems, so that we can move other regions along the s-curve (logistical) faster, if possible (something we had some good examples of during the seminar).

## 5.2 Protocol Work

It is very clear that the Internet is suffering from ossification and obesity in the protocol world. The heterogeneity of available transport protocols and shims is somewhat overwhelming, as well as the prevalence of middle boxes within the net to try to improve performance in the presence of so-called impedance mis-matches between legs of an end-to-end path (e. g., at boundaries between cellular data net and backhaul).

The interactions between new protocol combinations are not well understood. (Number of TCP connections for a web download, adverts from 3rd parties, ECN deployment, SPDY, QUIC, Minion, HTTPS + MPTCP, or video streaming and DCCP or SCTP and some middle box functions, the list goes on and on). Luckily, there are pressures on many companies producing good engineering of protocols to improve things and the IETF has groups (e. g., TAPS, TCPM and others) with strong membership from people actually trying to fix the eco-system.

There is a good academic opportunity for much good empirical work to evaluate the solutions and document best practice.

## 5.3 Socio-Economic Research

It is entirely unclear what the social and economic benefits of Internet access actually are, especially outside of the main deployment areas. It is entirely clear that alternatives have had major successes socially and economically at far lower cost (use of cellular voice and SMS in many places), and that we suggest caution in making naive assumptions that the Internet automatically brings benefits that exceed the costs. Estimates have been made in highly developed regions (oft quoted UK number is 3 Billion pounds per year is saved by the government if the last 15% of the population get access ), but even this figure is not really robust.

Empirical social and economic research is needed to understand the cost/benefit equation in each and every area. We had little expertise in the seminar, but there was consensus on this, that technogeek led heroic deployments of novel solutions often failed to sustain due to (for example) higher operational effort than their value justified. A study of failures would probably make a good academic research topic for groups that work on this (e. g., the Oxford Internet Institute, just for one).

## 5.4 Community Networks

As can be seen in the body of the report, we had very good representation from groups that had highly successful community network deployments. It is clear that these islands are growing, and starting to gain sufficient momentum to hit sustainability. Part of this due to their local, grass roots engagement, but also technologically, they have started to build management tools, and this should certainly help other groups. The main recommendation here is that this is a space to watch! To paraphrase William Gibson, the Street creates its own uses for the tech.

## 5.5 Internet-in-a-box

We also had a very good set of research groups working on these “extreme DTN” solutions to some forms of information access. Crucially, (despite the somewhat misleading name) many of the ideas seemed to offer somewhat different services than a vanilla Internet. Again, the recommendation here is that this is an area to watch. There are, as with community networks, novel technologies, but the bulk of the future work will entail optimising the sustainability of any deployment. Both Community Networks and Internet-in-a-box also require the Protocol Optimisation work that is ongoing in the IETF in any case.

## 6 Appendix

### 6.1 Individual communications tariffs and links to social services as regulated social and economic inclusion measures

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While network and access technologies offer diverse performances and operating costs, the question will always remain of how less favoured users can pay, and for society also how to use communications to embed them back into society with incomes over UN defined poverty line. A key issue has been to render such initiatives sustainable for operators or OTT operators as well, and to have technology-neutral solutions as required by policy makers. Our past and on-going work on mass customized communications tariffs (esp. mobile and Internet), regulated or corporate “good citizenship” driven individual tariff bundles, links between the above and public social measures for less favoured citizens have led to the adoption of social tariffs in some EU countries, with more to follow. A formal methodology has been proposed and adopted by regulators on affordable tariffs. We will also report of live trials of the same in China (agricultural communities), India, South Africa and Laos, and policy initiatives. New research questions arising from these interactions with users, NGOs, operators and regulators, and from the trials or deployments, will also be summarized.

#### References

- 1 L.-F. Pau, Affordability, Social eInclusion, and Addiction in Telecommunications, IEEE Technology and Society Magazine, Vol 31, no 3, Fall 20, 20–26+33
- 2 L.-F. Pau, Telecommunications in South Africa: who is actually regulating?, Journal of Governance and Regulation, Vol 2, no 3, 2013, 128–138 (ISSN: 2220-9352)

- 3 L.-F. Pau, Enabling mobile communications for the needy: affordability methodology, and approaches to requalify universal service measures, *Informatica Economic? Journal*, Vol 13, no 2, 2009, pp. 128–135
- 4 H. Chen, L.-F. Pau, with H. Chen, Mass Customization in Wireless Communication Services: Individual Services and Tariffs, in F.T. Piller & M.M. Tseng (Eds) , *Handbook of research in mass customization and personalization (in 2 Volumes: Volume 1: Strategies and Concepts Volume 2: Applications and Cases)*, World Scientific, 2010
- 5 L.-F. Pau, J. Mottiwalla, J. Motiwalla, India: a case of fragile wireless service and technology adoption? (short version), *Int. J. Mobile Communications*, Vol. 6, No. 3, 2008, 376–389
- 6 H. Chen, L.-F. Pau, Individual telecommunications tariffs in Chinese communities, in: Huang, Wang and Day (Eds), *Global mobile commerce: strategies, implementations and cases*, IGI Global (formerly IDEA Group), September 2007, ISBN 978-1-59904-558-0

## 6.2 Challenges in developing regions

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**Communication Issues and Challenges in the Amazon Region.** In certain places, local communities do have infrastructure for communication (fiber optics for instance), but it is often overpriced and lacks quality. An example is the Brazilian Amazon, a sparsely populated region with low GDP per capita. A fraction of the fiber optic network deployed there was initially meant for monitoring power transmission lines. After some time and political arrangements, that network was leased for commercial and public use.

In the city of Itaituba (PA), a small town (approx. 100,000 inhabitants) in the midst of the Amazon, fiber and satellite are available for data communication. However, the infrastructure in place cannot fully serve the needs of the local community. The current social situation is also not favourable. Approximately 40% of individuals (according to Brazilian IBGE) live below poverty line; they participate on social welfare programs, which improves their monthly income. In spite of financial constraints, in general they have smart phones (which are easier to afford due to instalment buying).

Because of the non-favourable social situation, a large fraction of the community cannot afford (good) connectivity services. For example, a satellite link costs \$95 dollars for 2 Mbps, plus \$380 dollars installation fee. Local providers are cheaper, e. g., \$40 for 512 kbps, and \$46 for 1 Mbps, plus installation fees (these costs may vary depending on the customer's location). The region experiences significant amounts of precipitation (rain) and cloudy weather yearly, and also very high air humidity; this scenario is often hostile for wireless communications there. The city also has four nationwide mobile operators offering data services. The dominant technology is 2G, but two of them also run 3G (deployed more recently); both services are offered with very poor coverage, though. There is no 4G service in the area. The mobile data charges are also expensive. As an example, one of the operators offer a \$0.30 per day pay as you go plan, 10MB allowance, which is a bit expensive for local standards. In addition, voice and data services often black-out. Some mobile operators connect their antennas directly to satellites, possibly to avoid fiber as it fails quite often. Finally, there are public funded connectivity initiatives: Internet for free, for all, through public wireless hotspots. However, they have very low capacity (most of places have just one

off-the-shelf, Access Point deployed) and fail quite often too (because of intense rain or fiber failure).

The local university campus is not an exception to this reality. The Federal Institute of Education, Science, and Technology of Para at Itaituba has two radio links of 4Mbps each. These links connect the campus to a state-run point of presence, and then to the fiber network. Those links could be of higher capacity, and in fact there are some arrangements under way for expansion. However, expansion plans are severely delayed due to financial constraints, and possibly because of lack of a proper political mindset. The radio links frequently disconnect (e. g., during rain, or when the fiber itself fails). The students used to have access to the local network in the past, but because of the high demand and severe resource constraints, they had to be excluded for the sake of professors and staff. In order to improve this situation, the local administration is deploying a backup link to satellite.

In addition to the aforementioned technical problems, the local community also experience political challenges too. For example, there is an ongoing project for building a high speed, optical network interconnecting several public and private institutes in the town. However, the project is now one year delayed because of political affairs. It basically means you now have to increase the OSI layer to 8 (financial) and 9 (political), and the local community as a whole seem to be stuck in 9.

In summary, having the necessary infrastructure for guaranteeing digital inclusion is often not sufficient to guarantee affordable connectivity services to poor communities. The deployment of technology appropriate for the local context, and a political mindset towards ensuring effective digital inclusion, are paramount to deliver good Internet services for the other billion.

We consider the town of Itaituba (Para) in Brazil as an example. It has a population of around 100,000, a Federal Institute for Education, Science and Technology with approximately 600 students. The Institute has an 8Mbps connection to unreliable fiber. Students have no access to the Internet in the campus, as the bandwidth is required for teachers and administrators. A wireless LAN with an “internet on a box” could provide many of the benefits of a campus network, without Internet access and, if designed with this in mind, could be easily connected to the Internet if and when a good fiber connection becomes available. The benefits could include web-based communication between staff and students, social networking tools, and access to content, educational and recreational, selected for its value to this community.

Access to this LAN could also be extended to the local population and businesses, and eventually to neighbouring communities. This would allow the students to become familiar with Internet technologies. We can also view this as a pilot. This same model could also be used in other communities where there is no Internet connection at present. Students from the Institute could be trained to contribute to such future projects.

**Interconnecting Africa: Challenges.** According to the world stats, Africa and Asia have the lowest penetration rates (21% and 32%) with about the half of the world population. More specifically, African countries have some common specificity, as far as Internet access is concerned:

- High cost for customers: due to low income, some people cannot afford access to Internet. For others living in rural areas, Internet is still a luxury, as these areas are not yet reached by technology, ISPs infrastructures or power.
- Poor QoS of Internet.
- Lack of Content: accessing to Internet is for many users, only for browsing, for accessing to Google, Youtube or Facebook. Their blogs or even their mails (private or not) are

hosted outside the continent on Yahoo, Gmail, Hotmail servers mostly for high availability purposes. Besides, people are not used to create local content even though they are knowledgeable: for instance, the lack of will and hardware prevent universities from hosting thesis, works, products or applications developed by their students while similar works are available online.

- Lack of economic incentives for ISPs to peer.
- It is difficult for ISPs to move content closer to people, as alone they do not meet the middleman's requirements.
- Education (from primary school to most universities) do not include familiarisation to computers.
- Most universities are connected to ISPs networks instead of NRENS.

In such context, the key milestones for a better Internet access in Africa can be listed as follows:

- The energy furniture.
- A climate of Fairness and cooperation established by regulators to secure and pave the way for huge investments
- Traffic Engineering, efficient routing by ISPs and Mobile operators, both aiming at keeping local traffic local to the continent. Besides, peering as much as possible and adding services (DNS root servers, cctlds, etc) to IXPs will definitively make ISPs save on transit costs.
- ISPs could then use these saved costs or interests to invest in building the physical infrastructure.
- Developing local content and content hosting to boost local economies. We need to stress that content developed in each country should have to be attractive enough and potential to be exported (education, culture, music, videos, activities specific to the country but well appreciated elsewhere) at least to other countries in its region.

As for the power, the continent is characterised by an abundant solar radiation through the year, abundant wind energy resources along coastal countries, an abundance of coal resources in Southern Africa, over 117 billion of proven oil reserves, overs 14.6 trillion cubic meters of proven gas reserves, etc. However, Energy is still unstable. Since, power is essential for industry and therefore for Internet access, Governments have to do their best to make it stable and sustainable. To this end, they could privilege and focus their efforts from short to long term on solar energy, renewable energy, gas and nuclear centrals.

The African terrestrial optical fiber map looks like the railroad one: very dense in South Africa, less in Eastern Africa and even less in the West. This reflects the level of interconnection among countries in which operate 1,159 ASes as of June 2014.

One way for its improvement is the bottom-up model. It consists for universities and NRENs (Ex: WACREN) to build per country an academic network linking primary schools, universities and hospitals. The existence of such networks would incentivize ISPs and Governments to invest in cross borders connections and Internet provision.

Another way is the up-bottom model which would need the regulations to facilitate fiber deployment, suppress the dominance by incumbents or the discrimination of the new companies as well as ensure price control of essential facilities. That is, regulators must ensure that all ISPs (private and incumbent) have the same rights on telecoms market. Mainly, they must get rid of monopoly (Djibouti, Ethiopia), enable both competition and partnership, encourage infrastructure sharing for the welfare of the citizens, make "crossing borders" easy for the enterprises, make license for ISPs or hosting companies declarative, etc.

Overall, the followings are key points for a better Internet in Africa:

- An affordable (cheap) International connectivity.
- Cross-borders interconnections and regional transit networks.
- Terrestrial optical fiber within regions and cities of countries.
- A Wireless access for the users.
- Content produced by these users (especially students in universities) available online.
- Datacenters connected to IXPs to host servers or government services (content produced locally, caches, CDNs).

Considerable efforts are being done throughout the continent to achieve these objectives. Among others, the AXIS (African Internet Exchange System) set up by the African Union (AU) and conducted by the Internet Society aimed at establishing IXPs per African country after organizing best-practises workshops as well as national and regional capacity building workshops. Liquid Telecom has deployed over the last 5 years its own optical fiber network covering Eastern and Southern Africa. Similarly, the Government of Rwanda has built optical fiber network covering all the 30 districts of its country, even in areas where there are no business reason yet. We can also list the GamersNight project of Liquid Telecom in collaboration with Uganda IX. Such efforts have to be encouraged and multiplied all over Africa to extend the network coverage and empower the digital development of the continent.

### 6.3 Solving the Geographical Challenges: Access Technologies for Rural and Remote Access

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Internet access in rural and remote areas constitutes a significant part of the problem of enabling Internet availability for all, in both developed and developing countries. In the developed world, unavailability of Internet access in rural areas is largely a situation of digital exclusion by default and not by choice, caused by low population densities in rural areas and higher per person cost of deployment of common broadband access technologies (ADSL, cable, fiber) per person. On the other hand, the problem is a lot more complex in developing regions involving socio-economic factors.

Broadly speaking, the nature of the rural access problem in a given region depends on several factors, including population density and distribution, remoteness, nearness to infrastructure that connects into the global Internet, income and education levels, cost and reliability of power infrastructure. Technologies employed for providing rural Internet access vary widely depending on the specific situation. They range all the way from fiber and copper based wired solutions to satellite and wireless technologies. Some of the newer types of wireless technologies (e. g., mesh, long distance WiFi, TV white spaces) are discussed later in this report. Also, in many cases where conventional wired Internet access solutions are not economically viable, the gaps are often filled by network infrastructures involving participation of communities. Therefore, various types of community networks (e. g., Guifi in Spain, Tegola in Scotland, Cybermoor in Cumbria, UK) and their characteristics are also discussed separately in this report.

In many developing countries, significant a percentage of population live in rural areas. For example, two-thirds of people in India live in rural areas. These environments are typically economically deprived and also suffer from poor infrastructure (power and transport).

In Europe and North America, the scale of the rural access problem varies anywhere from 5%–30%. In the UK, a tenth of the population do not have access to basic 2Mbps connections and a third lack access to connections with speeds greater than 30Mbps (what is now being considered superfast broadband). Situation in some parts of the UK is worse. For example, only 9% of the households in rural areas have access to faster connections although studies on data use over broadband connections by Ofcom suggest that rural users would equally benefit from high speed Internet access.

Some lessons and challenges for enabling broadband for all in rural parts of developed countries are outlined here. While these are largely based on the experience from the Tegola rural wireless access project in Scotland, they may hold for other developed country situations as well. Two main policy related challenges for addressing the rural access issue can be identified.

1. Firstly, the models for government interventions to extend broadband reach in rural areas are as important as interventions themselves. In particular, for rural areas, promoting and enabling bottom-up community driven efforts are more likely to succeed as opposed to top-down approach via procurement.
2. Secondly, accessible and affordable backhaul (and middle mile) remains a challenge. Where there is publicly subsidized fiber infrastructure being rolled out, it should be made openly accessible for local ISPs and communities. Also wider use of the public services network infrastructure (e. g., serving schools and hospitals) would be an effective method to intervene in areas where there is no alternative infrastructure.
3. From a technical perspective, more detailed understanding of wireless technologies suitable for addressing the middle mile / backhaul problem (e. g., 24GHz) would be useful for DIY efforts.

Having mobile voice and data access widely available is important in view of growing adoption of smartphones and especially in areas where alternative forms of communication are non-existent or unreliable (e. g., for emergency services). A key challenge in this context is quantifying the gaps and quality of mobile services. While modelling based 2G/3G/4G coverage maps from regulators and operators might suggest that mobile services are ubiquitously available, user experience differs greatly from modelling based coverage estimations. For example, Ofcom's modelling based coverage analysis focusing on outdoors indicates that there is less than 4% of UK premises lacking in 2G/3G coverage whereas consumer experience shows that the actual scale of the problem is much larger around 20%. Therefore it is crucial to assess mobile coverage and quality via measurements, which however is a technically challenging problem. For instance, context needs to be accounted for in user-side measurement of mobile performance. As another example, rural areas may need a combination of network-side management information and user side measurements to identify mobile not-spots. Measurement of mobile performance is also crucial from the perspective of enforcing the coverage obligations associated with spectrum licenses held by mobile operators. Current enforcement mechanisms rely solely on modelling and simulations, which have the same problem, mentioned above. Also in some countries like the UK, newer coverage obligations for 4G require only one operator to provide near universal coverage, which leads to lack of market for mobile services in rural and underserved areas.

In addition to the above, there is a significant value in documenting (or at least highlight the importance of documenting) the current experience and lessons on several important

aspects like sustainability models for community efforts and technology adoption models in developing and underserved areas.

**Role of long distance Wireless.** The long distance Wi-Fi (easily 30 km) are a low cost opportunity for “low bit rate” connectivity of villages (or parts thereof) needing the some connectivity. 802.11 Wi-Fi technology is commonly used for creating wireless networks with a range of about one hundred meters. With careful planning and proper antennas, this same equipment can be used to make point-to-point links of dozens of kilometers.

The two major limitations for using Wi-Fi over long distances are the requirement for line of sight between the endpoints and the vulnerability to interference in the unlicensed band. The first limitation can often be addressed by taking advantage of the terrain elevations, or by using towers to overcome obstacles and provide Fresnel zone clearance. As the distance between sites increases, the curvature of the Earth becomes a serious obstacle, requiring higher elevation at both ends. The second limitation is less pronounced in rural areas, and can be alleviated by migrating to the less crowded 5 GHz band. Low cost equipment supporting TDMA and equipped with high gain directional antennas allow medium to long distance links to be deployed with a very small investment.

**Utilising higher frequencies.** Low cost equipment of higher frequency bands are now becoming available and can be used on unlicensed bands. For example, the 17 GHz frequency is now unlicensed in Europe, with a maximum Equivalent Isotropic Radiated Power (EIRP) of 20 dBm. 24GHz is an unlicensed frequency that can be used for microwave communication for point-to-point wireless backhaul. This is subject to local country regulations. These frequency ranges are subject to rain fade, meaning that atmospheric rain absorbs microwave radio frequency (RF) signal, thus causing a signal loss.

High frequency point-to-point links on these frequency bands may be installed to service locations many kilometers farther than could be served with a single link requiring 99.99% uptime over the course of one year. A secondary lower bandwidth link such as a 5.8 GHz may be installed parallel to the primary link, with routers on both ends controlling automatic failover when the primary link is down due to rain fade. Recent equipment on 24 GHz can deliver wireless throughput of up to 1.4+ Gbps, surpassing conventional wired backhauls, over real-world, 10+ km links.

A lot of effort is devoted to the development of Transmission on 60 GHz. The 802.11ad is only the beginning of the “wave of development”. Using multiple antennas (24+) on a very small surface point-to-point wireless links for distances in the range of 300 Meters can be expected in a few years. With price and reliability comparable to the today’s WLAN access points. This might be a game changing technology as for “connecting WLANs from individual houses” into local structures.

**TV White Space as a solution.** The growing demand for wireless data transmission drives the search for alternatives to the current spectrum management schemes. In the long term, the only viable solution seems to be dynamic spectrum access once the technical details for its implementation are solved. In the short term, the use of currently vacant spectrum allocated to TV broadcast (so-called TV white spaces or TVWS) can alleviate the spectrum crunch while opening the path for dynamic spectrum access. Several measurements campaigns have shown that the TV broadcasting spectrum is mostly unused in sparsely populated areas, especially in developing countries, as there is not enough return on investment for broadcasters to provide many simultaneous TV channels. For the same reasons, these are precisely the areas in which Internet access is frequently lacking.

TV White Spaces technology can take advantage of the improved propagation capabilities

of these frequencies to provide affordable Internet access in rural areas. White spaces are also present in densely populated areas as a consequence of the transition from analog to digital TV, and these can be harnessed for wireless Internet access as well as other wireless communication services. The lower frequencies as compared with the ones used for WiFi (which in some places is becoming too crowded), are less attenuated by walls and offer an interesting alternative also for indoor Internet access, as well as for multimedia distribution. Finally, for machine-to-machine (M2M) applications and the “Internet of Things” paradigm TVWS technology has significant advantages both for developed and developing economies.

A quest towards understanding the potential of TVWS has been initiated by way of experimental measurement campaigns that strive to establish the nature and extent of spectrum usage and the resulting TVWS availability. It is imperative that long term occupancy measurement campaigns and analysis studies be carried out so as to ensure that government bodies, research and development agencies, and other interested parties target the real and evolving spectrum situation.

**Satellite Broadband.** Satellite systems have traditionally used Ku-Band operating at 11-14 GHz, and were often limited to rates less than needed for broadband services. Satellite systems can provide access to large geographical areas and are not constrained by the need to provide backhaul capacity for each location.

A new generation of Ka-Band systems, operating at 20-30 GHz have largely removed the previous constraints, enabling much higher speeds and reducing the size of the antenna needed by a customer. This new generation is now seen as a key enabling technology to deploy broadband access to locations that cannot be cost-effectively reached by other technologies.

Broadband satellite support forward link rates of up to 80 Mbps per forward link with typical user rates offered 2-20 Mbps per terminal and return link rates of 256 kbps – 4 Mbps currently common.

**Powerline Communications.** According to public data (e.g., from the World Bank), there are more electricity lines than telephone lines worldwide. This difference is particularly significant (an order of magnitude at least) in low-income countries. As such, in these countries power line communications (PLC) are arguably the only technology with a deployment cost comparable to wireless. This makes it a technological solution that may be worth exploring for Internet access.

Power grids today are being modernized through the introduction of communication networks dedicated to the management of energy transmission and distribution. Although the investment in smart grids today is concentrated in developed countries, smart grids may play an important role in the deployment of new electricity infrastructure in developing countries, by enabling more efficient operation and lower costs. For instance, in sparsely populated areas smart grids could enable a transition from one-off approaches to electrification (battery- or renewable energy-based electrification) to the development of community grids that then connect to the national grid.

Can the grid be part of the solution for the challenge of global access to the Internet? Some opportunities seem to exist. For example, exploring the existing power lines for Internet access using PLC; or leveraging on the distributed, ad hoc nature of community smart grid networks to explore novel low-cost access solutions. A peer-to-peer network called Gridmates already lets those with excess energy share it with neighbours in need, so one can imagine similar sharing of Internet access using the power line.

But many challenges exist, and indeed the discussion that ensued has led to the conclusion that this solution entails enormous challenges that may or may not preclude its adoption.

These challenges include:

1. problems of noise and interference that are difficult to solve. For example, PLC turns electrical wires into antennas effectively, and this can be problematic. PLC could hamper the reception of broadcast shortwave radio, for instance. More modern protocols, however, seem to include techniques to mitigate this problem;
2. the power infrastructure in low income countries may be really poor, making it extremely difficult (if not impossible) to use the higher frequency bands using the existing power lines;
3. it is important to make realistic calculations of the bandwidth per household, since the last mile is shared, and the backhaul connection can be very limited in these countries;
4. another point worth investigating is the energy cost of providing internet access;
5. also, is the overall monetary cost of this type of solutions reasonable, when compared to the alternatives?

**DTN/Store-carry-forward for developing regions.** In the last decade, opportunistic and delay tolerant networking (DTN) research has resulted in a set of advanced concepts and technologies that are ready to be employed in particular use cases, such as Twimight or WLAN-Opp. Among the most attractive application fields of opportunistic networks are empowering people when disasters strike, circumventing censorship in repressive regimes, and connecting regions where no network infrastructure is available in developing countries. One example of employment of DTN technology is the recent democratic movement in Hongkong, 2014 that made use of a simple DTN-enabled app, namely FireChat.

Although community networks demonstrate that volunteers provide and maintain resources deliberately, it is yet unclear how a solution incorporating mobile carriers will be actually accepted and which capacities one can expect from such networks. A potential system architecture that makes also use of opportunistic store-carry-forward transmission may consist of stationary boxes with storage facilities typically installed at popular places and mobile data carriers. Based on CDR (call detail record) data of cellular network operators, mobility flows, e. g., from city centres to suburban areas can be estimated (e. g., making use of the D4D challenge data of Orange in Ivory Coast) and used to characterize the capacity of a hypothetical DTN network. Although cellular data can provide countrywide mobility flows, these data include only the subset of commuters (those, that are calling) of one operator, which comes at a bias of unclear importance. The capacity formulation considers also the storage on devices, success of transmission, the user's willingness to cooperate, and a scaling factor. An open research issue is how to find good models and configuration ranges of these factors based on social, behaviour, and demographic observation. Questionnaires used to capture the opinion of inhabitants in developing region can provide insights, though the way of asking is important. A general question about whether people would volunteer carrying data of others resulted in a fraction of 8% agreeing if rewarded, 15% agreeing to carry for friends and relatives, and a majority of 77% who would not do it at all. Yet, putting this question into concrete context might result in higher acceptance of the people as they would see concrete application dependent benefits for themselves and their social community.

## 6.4 Community Networks

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Traditionally networking infrastructures and services were provided by the ecosystem of telecom monopolies, mobile and fixed network operators, telecom service providers, complemented with manufacturers of carrier-grade equipment, terminals, etc. However these are driven by business interest and cannot provide networking services everywhere, where there's no market yet, and to everyone in the world, who may not cover the required investment with service fees or generate enough economic profit.

Community networks (CNs) are a bottom up effort to build independent, community-owned network infrastructures. They serve two roles, first they are used to replace the last mile and distribute Internet connectivity, second, they provide services to the local community with a governance model centred on the community and the stakeholders, on an infrastructure owned and managed by the community. They are created starting from principles of neutrality, non-discriminatory access, collective ownership and participated management, and are growing in many places around the world.

Cheaper and simpler to setup network components, combined with open spectrum for WiFi, open knowledge, and open source software, has enabled individuals and small communities to create their own network infrastructures and services without the need of large companies with large investments and complex structures. This model expands the opportunities and empowers citizens to be in the digital society.

This opportunity has enabled new forms of networking service from a local perspective. Individuals, small organisations, and their neighbours can cooperate to create and operate a network infrastructure and services locally. This typically results in creating a local ecosystem open for participation.

Probably for the first time, the design of a communication system can start from the needs of people, from urban evolution and planning, and not be the outcome of technology or business analysis (that failed so many times in the last decades)

Some CNs (one for all: Guifi counts 26000 nodes and about 80,000 users. Originally based in Catalonia is now expanding to all Spain), reached a size that is not anymore governable with only peer-to-peer interaction and independent node management. CNs are actually proposing new models of cooperative, bottom-up organization to face the costs and the challenges of becoming almost a nation-wide network, and are developing the required tools to put them in practice.

CNs should not be considered only as “cheap internet access”. A challenge they take is how to reshape the communications infrastructure in order to be more fair, more decentralized and based on the principles of neutrality and community empowerment. Nevertheless, the networks that are effectively in place do not really reflect this organization, they are topologically fragile [1], with few nodes that can be routing the majority of the traffic, and socially the communities risk to be dominated by few individuals. There is a need for instruments (not only technical but also social, economical and legal) to help the community grow in a sustainable way [2]. Guifi is in the process of creating some of these instruments, that are freely accessible to anyone that want to replicate the approach, among these are: software, licenses, conflict resolution procedures, etc.

Community Networks have developed around the world in very diverse environments to enable local networking infrastructures that allow every citizen to join in and participate in

the digital society. However, while being quite successful in diverse locations in providing local digital network infrastructures and services, there are several challenges, obstacles and lessons learned in its way.

**The Community-Lab testbed.** Community-Lab is an open, distributed experimental infrastructure or testbed with around 200 small computer nodes. It is embedded in several community networks with more than 40,000 routers and users spread in diverse regions of Europe, using mostly wireless but also a growing usage of fibre links. Researchers can deploy experimental services, perform technical and social experiments or access open data traces in Community-Lab. The testbed follows the slice architecture that PlanetLab started and thus allows multiple experiments to share experimental nodes together with production traffic and community network users. Community-Lab is designed and has been used in experiments ranging from the link layer to routing, transport and application layer, or even social experiments.

Community-Lab consists of at least one portal or controller and a set of nodes that are embedded in different community networks. Each node consists of several slivers (Linux containers) which are grouped into slices that represent an experiment or service. The purpose of the Community-Lab controller is to manage and control the testbed, i. e., manage its users, nodes, slices and slivers. Currently there are about 25 research and community organisations involved in the testbed in Europe, Africa and America. Research groups already working with local community networks are encouraged to join Community-Lab <http://community-lab.net>.

**Challenges, Research and Development.** While community networks are widespread, numerous challenges still lie ahead. Some closely resemble “classical” networking, software systems or collective social organisational challenges, while others are very specific to community networks.

The free and open source software development community, working with community networks and the networking and software systems research has developed and enhanced key enabling technologies like the OpenWRT Operating System for embedded devices or the OLSR mesh routing protocol among many others.

Among of the most relevant research results in the last 3 years have been the development of the OLSRv2 mesh routing protocol, the development of hybrid nodes with network attached radio interfaces (DLEP), the optimization of the IPv6-based BMX6 routing protocol with multi-topology extensions, comparative analysis of the topologic properties of diverse community network graphs and its implications.

Collaboration between the FOSS community and community networks has resulted in the development of generic firmware for bootstrapping a community network such as the Quick Mesh Project (qMp) <http://qmp.cat/>, Libre-Mesh <http://libre-mesh.org/> router software distributions (including BMX6) and the NodeDB to manage a set of nodes involved in a community network.

The FOSS software developed for the Community-Lab testbed has been extended to be a resource infrastructure manager for a set of hosts embedded in a community network that can provide distributed resources for experiments or for community services. These nodes include a remote configuration, management and monitoring daemon that, combined with central components, allow managing all of them in unison. Together with the Cloudy distribution developed in the Clommunity project by Guifi.net, and combined with experimental peer-to-peer platform services for video distribution and distributed storage, Community Cloud services have been demonstrated in Guifi.net.

Several open challenges: Scalable and dynamic mechanisms for the interrelated, dynamic and global problem of the allocation of resources such as spectrum; Economic and sustainability models; Collaborative sensing; Local community cloud services and uses to provide digital services to citizens, digital tools for collective awareness, collective action, and social innovation; Socio-economic aspects; Multidisciplinary methods of evaluating community networks as well as their “performance” and sustainability; Self-organising systems; Production of open data sets.

These experiences are being shared in informal and formal interactions in events such as the International Summit for Community Wireless Networks (IS4CWN), the International Workshop on Community Networks and Bottom-up-Broadband (CNBuB), the BattleMesh workshop, or the IRTF Global Access to the Internet for All (GAIA) group.

## References

- 1 L. Maccari and R. Lo Cigno, A week in the life of three large wireless community networks, To appear in Elsevier Ad-Hoc Networks, 2014. Online: <http://www.sciencedirect.com/science/article/pii/S1570870514001474>
- 2 R. Lo Cigno, and L. Maccari. “Urban wireless community networks: challenges and solutions for smart city communications.” ACM international Workshop on Wireless and Mobile Technologies for Smart Cities (WiMobCity), Philadelphia, PA, US. 2014, DOI: 10.1145/2633661.2633669

## 6.5 Key Parameters for Universal Internet Access: Availability, Affordability and Relevance

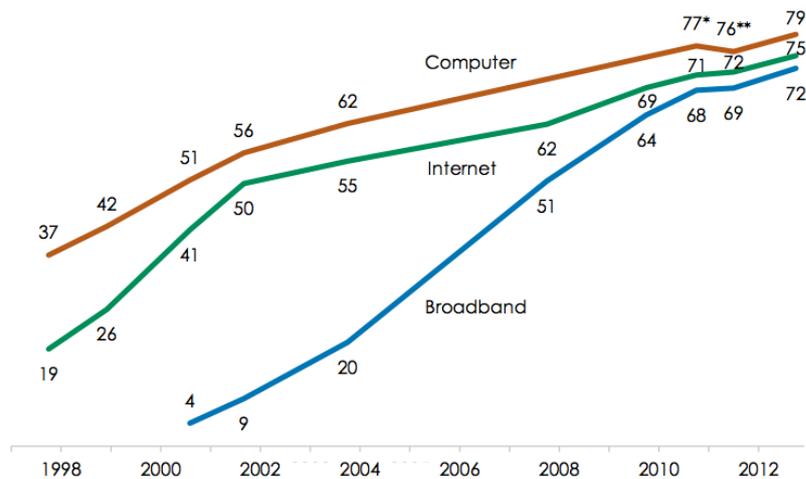
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Internet adoption tends to progress in phases: early rapid adoption in urban areas and by relatively well-educated and higher-income households, then transitioning to a slower pace once between 70% and 85% of households subscribe. For example, in a 2013 survey, the Pew Research Internet Project found that approximately 15% of the adult population does not use the Internet; those least likely to use the Internet include “senior citizens, adults with less than a high-school education and those living in households earning less than \$30,000 per year [1].”

Non-adoption has multiple reasons that vary in each country, and, within each country, by demographics. These reasons are often grouped, somewhat crudely, as availability, affordability and relevance. For the United States, a 2014 NTIA survey<sup>1</sup> (Figure 1) identified 48% as stating “Don’t need. Not interested”, often summarized as “relevance”, as the main reason for not using the Internet at home, followed by “too expensive” (29%), “no computer or computer inadequate” (11%). Only 1% each claimed that there was no Internet access available or that privacy or security concerns dominated. A small percentage (3%) use the Internet somewhere else, e. g., at work, in coffee shops or a library. It is likely that many individuals will have multiple reasons and some non-users increasingly use functions on

<sup>1</sup> [http://www.ntia.doc.gov/files/ntia/publications/exploring\\_the\\_digital\\_nation\\_embracing\\_the\\_mobile\\_internet\\_10162014.pdf](http://www.ntia.doc.gov/files/ntia/publications/exploring_the_digital_nation_embracing_the_mobile_internet_10162014.pdf)



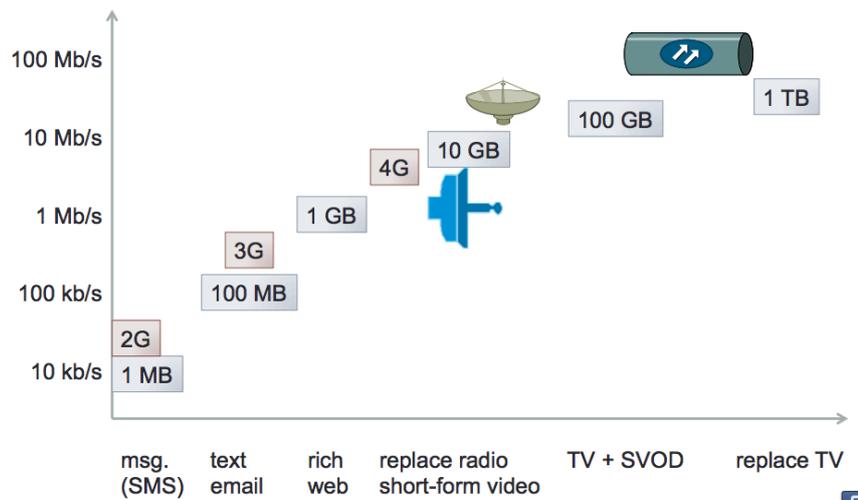
■ **Figure 1** Overview of household adoption rates by technology, Percent of US households, 1997–2012 (Source: NTIA 2014).

smartphones that may require Internet access, e. g., for maps or games, that may not be appear to the user as such.

While the emphasis is often on private use, either at home or mobile, availability, affordability and relevance play a role for use by community anchor institutions such as schools, libraries, health care facilities and local government offices, as well as for small businesses, whether retail, hospitality or small manufacturing. For example, a recent report “finds significant gaps in the availability of high speed broadband among traditionally underserved students and their more affluent, suburban, and White peers” [2].

Availability, affordability and relevance are in turn influenced by a number of external factors, such as industry structure, the regulatory environment, consumer behaviour overall, and available technologies and speed tiers. For example, the level of competition is likely to influence both the price consumers’ pay for access, i. e., affordability, and the investment made in new high-speed access and middle-mile technologies. In turn, the regulatory environment strongly influences industry structure. Consumer behaviour, such as the shift from landline to mobile phones or from linear video to streaming video-on-demand, creates opportunities for existing and new entrants.

**What Kind of Internet?** When we discuss Internet access, it is helpful to distinguish multiple tiers, with very different capabilities (Figure 2). For example, basic messaging, whether via SMS or low-bandwidth IP-based technologies, can already satisfy key information and transaction needs, whether for electronic payments (M-PESA), person-to-person communication or for information retrieval about weather or medical information. Such services may only require access bandwidths of the order of 10 kb/s, such as those enabled by 2G wireless or dial-up, and are likely to consume at most a few MB of data a month. The next step up enables text-heavy web content as well as text email, and is easily achievable through (reliable) 3G coverage or basic ADSL. With bandwidths of a few Mb/s and monthly bandwidth-allowances of around 1 GB, users can access most main-stream web sites, even those not optimized for low-bandwidth devices. At speeds of roughly 10 Mb/s and monthly data usage around 10 GB, the home Internet connection can offer short-form video (e. g., YouTube) and replace FM radio. Between 10 and 100 Mb/s, with data budgets of at least 100 GB, streaming video-on-demand becomes plausible, while, longer term, a full TV replacement



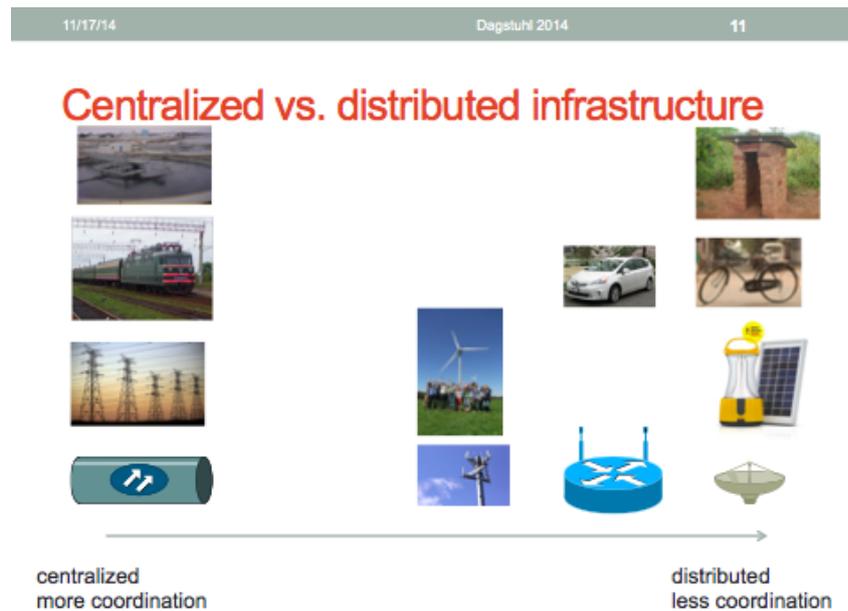
■ **Figure 2** What kind of Internet do we want?

at 4K quality is likely to push the monthly data volume per household to 1 TB and above.

Beyond speed and monthly data volume, there are at least three other dimensions along which one might characterize Internet access: latency, symmetry and uniformity. Latency, typically expressed as round trip time, may vary between 20 ms to the edge of the access provider for fiber and LTE to more than one second for satellite links. Dog-leg routing of traffic through far-away interexchange points may further increase the effective latency. Latency reduces the usability of interactive applications such as phone calls, telemedicine, distance learning and some games, increases the load time of web pages referencing network-based APIs, and may reduce the achievable throughput of bulk data applications. Traditionally, most residential access links, such as ADSL and HFC, have been highly asymmetric, with download speeds ten times higher or more than upload speeds. Creating content requires higher upload speeds, and thus more symmetric networks. Finally, some networks for challenging environments may offer non-uniform access to content<sup>2</sup>, where some content, cached locally, is available immediately and at high bandwidth, while other content may only be available after significant delay measured in minutes or hours, e. g., after fetching it during low-usage overnight hours. Similar ideas are also implemented by modern entertainment systems on commercial aircraft, which host high-bandwidth content locally, supplementing a lower-bandwidth Internet access channel. Some of the “Internet in the box” projects discussed in the workshop report occupy spots on this continuum, with the ideas exploring aspects of related to delay-tolerant and disruption-tolerant networks, or more classical web proxy caching. (For example, the ICOW work [3] places caches on public transit vehicles. Earlier, we had explored local applications, such as bulletin-board systems [4].)

**Centralized vs. Distributed Infrastructures.** All societies above a certain level of development depend on four key infrastructures: potable water and waste water, energy such as electricity and natural gas, transportation and communication (Figure 3). In each case, albeit to differing degrees, these infrastructure services can be provided with various degrees of centralization or local and individual autonomy. Recently, the delivery of electrical energy

<sup>2</sup> The allusion to NUMA concepts in computer architecture is intentional.



■ **Figure 3** Centralised vs. Distributed Infrastructures.

has probably been most visible in exploring these trade-offs, whether through solar powered lanterns and cell towers on one end of the spectrum, or huge wind farms at the other. For communication, a purely local infrastructure seems to have inherently lower value than connecting to the global Internet, even if such purely local infrastructure can clearly be “better than nothing”. Even for communication, there are trade-offs of having infrastructure such as satellite that requires very little coordination among participants and very little on-the-ground investment by local governments vs. a fiber infrastructure that requires the consent and participation of thousands of property owners and local governments, for example.

**What’s Expensive About Networks?** The network engineering and research community has spent most of its efforts on making networking equipment more efficient and cost-effective (Figure 4). However, for most network build-outs, the electronics, optical components and fiber contribute only a small fraction, often less than 30%, of the total cost. For example, a fiber cable with 48 strands might cost \$5,000 per mile, while the finished cost of a middle-mile deployment may range between \$50,000 and \$70,000 per mile. Cables with more fiber strand are proportionally cheaper; for example, a 144-strand cable costs roughly \$10,000 per mile.

The cost of deploying fiber is driven first by the number of homes passed, regardless of how many of those homes subscribe, and then the actual number of subscribers. Depending on how networks are built out, the second cost component is only incurred when the carrier or community has a paying customer. For typical densities in urban and sub-urban environments, the cost seems to be around \$1,000 per home passed for recent deployments. The per-home optical network termination units (ONUs) used to be relatively expensive, at \$300-\$400 per home, but have been dropping to around \$100 to \$200. The costs are generally higher if ducts have to be placed underground, compared to stringing fiber on utility poles, but duct or other underground burial tends to yield a more reliable network. Actual historic FTTH costs range between \$1,000 and \$1,300 per home, for outside plant only.

## Independent 2" Conduit Run for Three User Co-Location

LABOR						
Category	Quantity	Unit	Low Cost/Unit	High Cost/Unit	Low Cost	High Cost
Design	5,280	FT.	\$0.08	\$0.10	\$422	\$528
Engineering and Permits	0	FT.	\$0.25	\$0.25	\$0	\$0
Railroad Crossing	0	LOT	\$5,000.00	\$15,000.00	\$0	\$0
Directional Boring for 2" Conduit	0	FT.	\$8.00	\$20.00	\$0	\$0
Directional Boring for 4" Conduit	0	FT.	\$11.00	\$25.00	\$0	\$0
Trenching for 24" - 36" Depth	5,280	FT.	\$5.00	\$12.00	\$26,400	\$63,360
Place Conduit	15,840	FT.	\$1.00	\$1.75	\$15,840	\$27,720
Place Inner Duct	0	FT.	\$0.50	\$1.50	\$0	\$0
Place Vault	33	EACH	\$500.00	\$750.00	\$16,500	\$24,750
Place Fiber in Conduit	15,840	FT.	\$1.25	\$2.50	\$19,800	\$39,600
Install Splice Enclosure	3	EACH	\$300.00	\$500.00	\$900	\$1,500
Splice Fiber	648	EACH	\$12.00	\$30.00	\$7,776	\$19,440
<b>TOTAL LABOR</b>					<b>\$87,638</b>	<b>\$176,898</b>
MATERIALS						
Category	Quantity	Unit	Low Cost/Unit	High Cost/Unit	Low Cost	High Cost
216 Count Fiber	18,216	FT.	\$1.80	\$2.50	\$32,789	\$45,540
Splice Kit	3	EACH	\$500.00	\$750.00	\$1,500	\$2,250
4" Conduit and Materials	0	FT.	\$2.98	\$3.50	\$0	\$0
2" Conduit and Materials	15,840	FT.	\$0.88	\$1.50	\$13,939	\$23,760
1" Inner Duct	0	FT.	\$0.30	\$45.00	\$0	\$0
Vault	33	EACH	\$450.00	\$600.00	\$14,850	\$19,800
Tax and Freight	1	LOT	\$6,307.80	\$9,135.00	\$6,308	\$9,135
<b>TOTAL MATERIAL</b>					<b>\$69,386</b>	<b>\$100,485</b>

■ **Figure 4** Brief Engineering Assessment: Efficiencies available through simultaneous construction and co-location of communications conduit and fiber, (Source CTC, <http://www.ctcnet.us/>, 2009).

To first approximation, it appears that the cost per home is closely proportional to the distance between homes within one network deployment. Thus, for the same population density, serving homes spaced one-by-one along rural highways may be much more expensive than serving small villages where homes are clustered.

The figure below shows an example calculation of a fiber build-out [5]. Other cost examples include a build-out with 96% aerial and 4% buried construction, in the Northeastern United States, with a cost of \$30,000 per mile. Aerial overlash can be cheaper at \$15,000 per mile, while buried fiber can cost \$89,000 per mile.

It is currently unknown whether combinations of fiber to the neighborhood (FTTN) and VDSL, such as G.Fast, or wireless, whether 5.8 or possibly 60 GHz, can offer a long-term attractive alternative. They may trade-off an initially lower investment with higher operational costs or lower reliability, as well as practical difficulties such as where to place DSLAM and radio components. A more systematic exploration of this trade-off, with real-world cost figures, would be enlightening.

Current field engineering wisdom seems to have converged on a number of recommendations for reducing the cost of building new "greenfield" or overbuilt networks:

- To reduce the cost and difficulty of deployment, active network elements are placed in as few locations as possible. This avoids negotiating for "fiber huts" with local communities or finding in-building space that is accessible for maintenance. Recently, even passive optical networks place the splitter in the head-end and create fiber home runs.
- To reduce the cost of dispatching technicians, all per-home fiber drops and other installa-

Company	Revenue	Capital expenditures	%
Comcast (US), 3Q14	\$11.04B	\$1.644B	14.9
Telekom (DE), 3Q14	€15.6B	€2.58B	16.5
Safarikom (KE), H1FY15	Ksh 79.34B	KSh 12.37	15.5

■ **Figure 5** Expenditures.

- tion is performed at once, e. g., in one Google “fiberhood”.
- To reduce the cost of in-home installation, each home is connected through an all-in-one optical network unit that includes, for example, a high-speed 802.11ac wireless interface that can directly provide network connectivity to the whole home. (Early Verizon FiOS deployments had the ONU in the basement, which is then connected via coaxial cable and MoCa data transmission to the set top box. The set top box is placed near the family TV and also contains a Wi-Fi interface. This requires in-home cabling.)
  - Any active in-network components are reverse-powered through the home, to avoid having to connect to utility power.
  - To the extent possible, homeowners are asked to self-install, as had happened earlier with DSL and cable modems. If ONUs become standardized, it may also be possible for the carrier to ask the consumer to purchase the device, possibly using the Equipment Installation Plan (EIP) model now popular in the United States for smartphones, further reducing capital outlays for the carrier.
  - Communities and other government entities responsible for roads, railways and pipelines should, by default, install at least fiber ducts or dark fiber whenever a road, railroad or pipeline is built or major improvements are made.

Given the large cost differential between the cost of fiber and the total construction cost, there seems to be room for significant improvement on the civil engineering side. One can imagine autonomous underground boring vehicles, possibly leveraging advances in horizontal drilling pioneered by oil shale fracking, that place fiber or ducts with minimal human intervention.

While the capital investment for fiber or other network access technologies is substantial, it is a small fraction of the total cost of operating networks. Below, we show three examples that illustrate that, across three continents, the capital costs are roughly 15% to 16% of the revenue (Figure 5).

These capital expenditures include costs other than for building networks. For example, Figure 6 shows the Q2 2014 capital spending for Comcast, the largest US cable communications company. About half the spending is for customer premises equipment, primarily video set top boxes.

This observation indicates that attempts to reduce the cost of network operations may be more productive than reducing capital expenditures. For example, self-configuring and self-diagnosing networks could reduce the number of field service calls and customer support incidents. Simpler billing models may reduce the need for extensive billing-related expenses. In general, fiber networks have significantly lower maintenance costs than copper or coax

Category	Growth CapEx (\$ mil.)	% of Total (%)	Maintenance CapEx (\$ mil.)	% of Total (%)	Total CapEx* (\$ mil.)	% of Total (%)
Consumer Premises Equipment	668	65	72	16	740	50
Network Infrastructure	107	10	287	64	394	27
Support Capital	48	5	89	20	137	9
Commercial	209	20	0	0	209	14
<b>Total*</b>	<b>1,032</b>	<b>-</b>	<b>448</b>	<b>-</b>	<b>1,480</b>	<b>-</b>

As of Aug. 2014. \* Total excludes \$13 million in discretionary capital. Total including discretionary spending was \$1,493 mil. Source: Comcast. © 2014 SNL Kagan, a division of SNL Financial LLC, estimates. All rights reserved.

■ **Figure 6** Comcast spending trends (Source: SNL Kagan, “Comcast, TWC drive spending as Q2 cable CapEx spikes 27.7% YoY”, August 2014).

networks. One of the gaping holes for engineering solutions that address these problems is the apparent lack of any public data on the cost of operations in real, particularly large-scale, networks. Community networks and networks run by public organizations may offer opportunities to gain insight into real-world operational costs. Without precise cost models, it is impossible to say, for example, whether and where replacing FTTP networks with FTTC plus wireless models is cost effective.

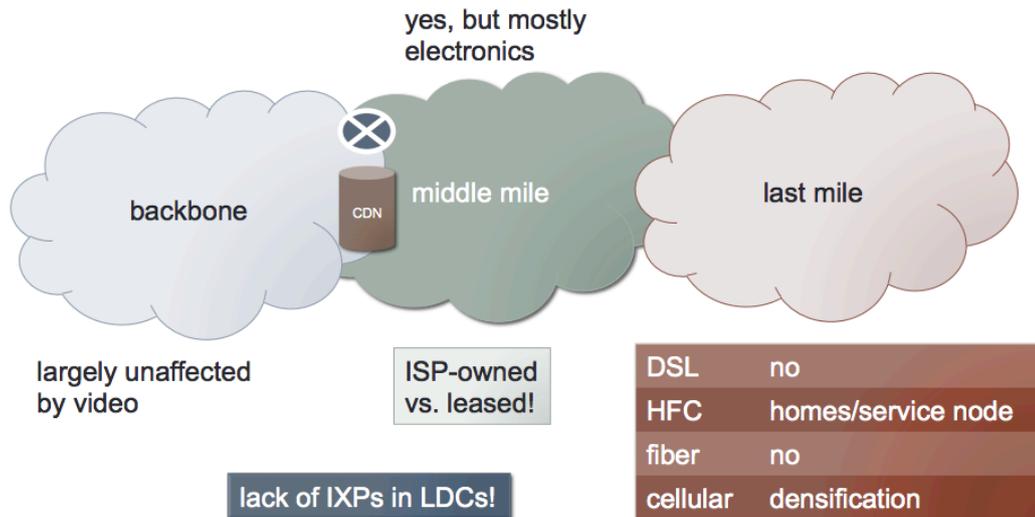
**The Cost of Carrying Bits.** In the figure below (Figure 7), we try to capture, grossly simplified, the three principal components of network costs, namely the Internet backbone, middle mile and last mile, i. e., access. The relative impact of each cost factor depends on the size and geographic scope of the network operator. For example, a small rural network operator may have very limited competitive choices among middle mile providers that can carry its traffic to the nearest interexchange point (IXP). This motivated the United States BTOP program to fund middle mile access, e. g., in Vermont. On the other hand, larger operators with a significant footprint can probably justify either leasing dark fiber or building their own, so that the cost of the middle mile infrastructure is more modest as it can be amortized over large traffic volumes.

As the figure tries to illustrate, the volume-dependent cost also differs significantly among the three components. For example, the middle mile may only require additional electronic components to increase bandwidth, while HFC networks may need nodes to be split. If the last mile is based on fiber, there is essentially no incremental cost of carrying additional bits on that last mile. (This does not necessarily argue for flat pricing; it has been argued that charging based on data consumption reflects the value users place on network connectivity.)

As video has come to dominate Internet traffic, much more of the content can be cached close to the edge, either at the IXP or even at the fiber head end. Thus, additional video volume may only impact the volume-insensitive components of the network.

In many parts of North America and Europe, the cost of Internet transit has decreased steadily, as shown in the figure below (Figure 8)<sup>3</sup>. The cost is shown in dollars per month and Mb/s. (Transit capacity is typically sold at the 95th percentile of 5-minute traffic intervals.) In addition, many large “eye ball” networks, i. e., networks serving consumers,

<sup>3</sup> <http://drpeering.net/white-papers/Internet-Transit-Pricing-Historical-And-Projected.php>



■ **Figure 7** Network costs.

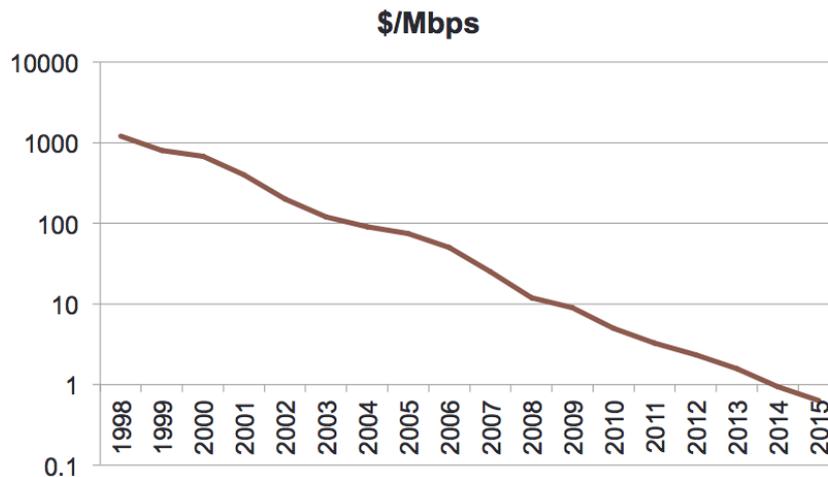
peer settlement-free, i. e., without charge, with other networks, or, in some cases, even charge content distribution networks (CDNs).

Overall, the cost of delivering bits across networks has now, in the United States at least, dropped below the physical cost of delivering bits on disk or DVD. As an example, the postage cost of shipping a Netflix DVD round-trip is approximately \$0.70, translating into \$100 per TB of data. For user-created data, the DVD-R cost itself is about \$0.25, or roughly \$30 per TB. Typical CDN pricing is \$7 to \$20 per TB.<sup>4</sup>

**How to Finance Networks?** As noted earlier, building new network infrastructure requires an initial substantial outlay of capital. Since the take rate is often not known ahead of time, an investor, whether for-profit or community, incurs substantial uncertainty how much revenue they can expect. The uncertainty grows if there is a lower-performance competitor in the same area that might be able to undercut the new entrant on price or upgrade their own facilities. There are a number of approaches that can be tried to provide “patient” capital or reduce the need for up-front investment:

- Wireless mesh networks essentially allow a network to grow with each new user. The only, albeit substantial, investment is middle-mile backhaul. However, such networks may require significant expertise to set up and are probably best suited for DSL-like per-user bandwidths.
- Demand aggregation can take many forms, with Internet cafes, community centers, libraries and schools offering well-known examples. Cooperatives can aggregate both last-mile and middle-mile demand.
- In some countries, governmental and non-governmental organizations provide loans at low interest rates to eligible entities to fund the construction of networks. Similarly, rural electric cooperatives may have longer investment horizons than public companies.
- Vendor financing may be another option, where vendors of equipment and construction

<sup>4</sup> See <http://www.cdnpricing.com> for examples and history.

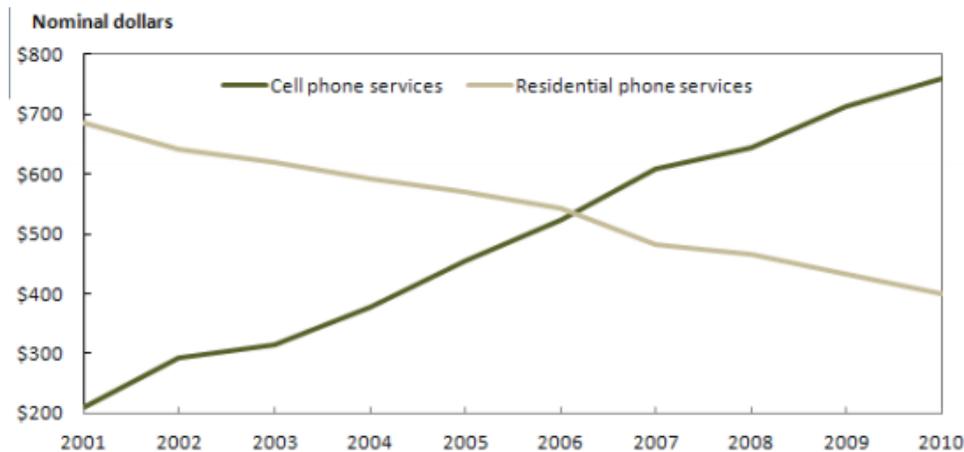


■ **Figure 8** Transit prices

services retain a portion of the revenue. This is attractive if the vendor can obtain better financial terms than the local network operator<sup>5</sup>.

- Franchise models have been successful in areas ranging from take-out food to dog kennels, but appear to be uncommon for providing Internet access. Franchising provides two key benefits: It allows to centralize functions that require significant technical expertise and that enjoy economies of scale, such as, in our case, network management, billing and other OSS functions, as well as bulk purchasing. Franchisees contribute their own capital, labor and knowledge of the local market. However, the investment needed for each local area may well exceed the typical small-business franchise investment of up to, say, \$500,000 in the United States. (At \$1,000 per home passed, this would suffice only for small rural communities. Indeed, the emergence of wireless Internet service providers, without the benefit of franchising, seems to support this scale estimate.)
- Broadband Internet access is unique among residential infrastructure, as it is often added long after a home is built. For gas, water, and electricity, home owners typically finance the last few meters as part of the cost of construction, through a long-term low-interest mortgage. For FTTH, the per-home connection costs are as large as half the total. With standardization of interfaces, it is conceivable that at least new homes and developments make fiber part of the initial construction. Indeed, this idea has been proposed several years ago [6] under the moniker “homes with tails”, but seems to have achieved limited traction in practice.
- In theory, it might be possible to have content providers, whether commercial or not-for-profit, pre-fund the construction of networks, allowing them to reach new consumers or users. However, aggregating diverse content creators and avoiding the free-rider problem appear to be challenging for an infrastructure that is inherently shared. (This is a very old idea – after all, radio and TV stations fund their own transmission systems.)

<sup>5</sup> However, this model can endanger the vendor, as large telecom equipment vendors found out after the 2000 telecom bubble burst in the United States and many competitive local exchange carriers (CLECs) were unable to meet their debt obligations.



■ **Figure 9** Average annual expenditures on cellphone and residential phone service, 2001–2010 (Source: U.S. Bureau of Labor Statistics December 2011 Volume 2, Number 12).

**How to Pay for Networks?** American households have significantly increased their spending on telecommunication services, as shown below (Figure 9)<sup>6</sup> [7]. Given that overall disposable household income (Figure 10), and in particular income not committed to health care, housing and food, has not been increasing for most households in Europe and the United States, there may be limited opportunity for additional growth. In many countries, expenses for cellular and Internet services have displaced paying for landline phone service.

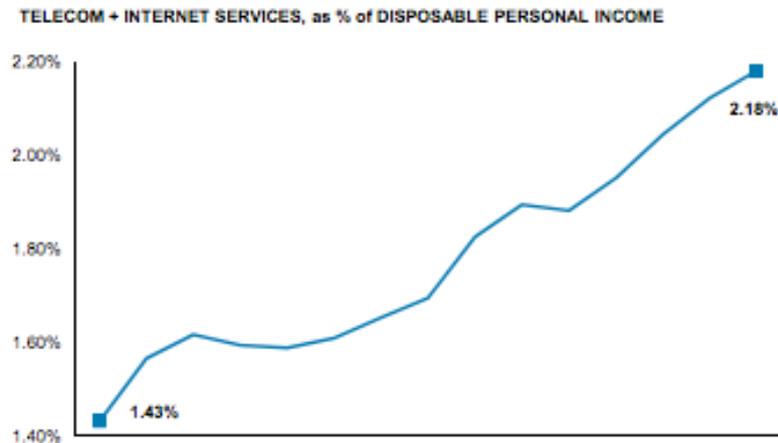
It is well-known that the value of bits to the user differs dramatically, with the lowest-bandwidth applications having the largest value per bit. For example, at 10c per minute, a GSM voice call at 13 kb/s costs roughly \$1,020 per GB, while 4G data is sold at approximately one hundredth of that price, at rough \$10 per GB. Consumers have been willing to pay 10c for each SMS, which translates to \$625,000 per GB, even if the short message fills the 160 byte capacity.

While a detailed analysis is beyond the scope of this review, experience seems to indicate that consumers place significant value on predictable charging models [8]. Even simple usage-based charges generates complaints about discrepancies between volume measured by the end system and by the provider or surprises when better connectivity increases the cost of viewing videos. Application-based charging encourages traffic masking, i. e., converting expensive bits into cheaper ones, which then requires deep packet inspection or other countermeasures<sup>7</sup>. For bandwidth-constrained networks, time-of-day charging appears to have the advantage of being easy to understand, and probably approximating more sophisticated congestion-based charging.

Given the roughly factor-ten difference in bandwidth costs between 4G and landline networks (and arguably the largely zero incremental cost for the user), mobile operating systems have already adapted by automatically delaying high-bandwidth activities such as software updates to times when Wi-Fi is available. (Unfortunately, side-loading of video does not appear to be automated yet. Operating systems, including those for tablets and laptops, could provide significantly better policy support to applications.)

<sup>6</sup> <http://www.bls.gov/opub/btn/archive/consumer-spending-in-2010-pdf.pdf>

<sup>7</sup> For example, Skype masqueraded as web traffic at some point, both to bypass restrictive firewalls and to avoid VoIP limitations.



■ **Figure 10** Internet services as % of disposable income (Source: US Equity Strategy: “Macro Meets Micro: A Five-Year View of the Telecom Services Industry”, Morgan Stanley, July 21, 2014).

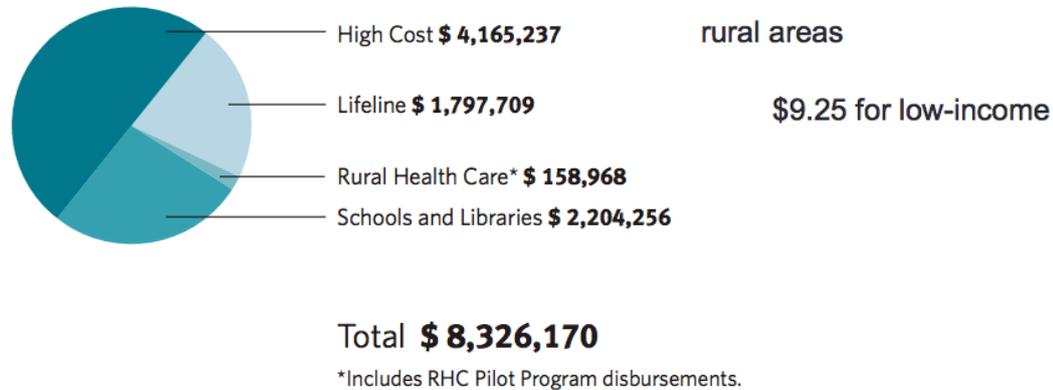
**Zero-rating Content – An Alternative?** The idea of having content providers or advertisers pay for network access, thus reducing the cost burden particularly on low-income consumers, has received a fair amount of discussion. The economics appear to be challenging, however. For example, at a CPM (cost per thousand) for a video pre-roll advertisement of roughly \$10, this translates into 1 cent per video. Since the content creator, e.g., the creator of a YouTube video, receives some compensation and the video distribution service also incurs costs, significantly less than that amount will be available to zero-rate other content. A 720p H.264 video consumes approximately 20 MB per minute, i.e., the typical 30 second video ad itself generates 10 MB. At the incremental rate of \$10/GB, the cost is \$0.01 per MB. Thus, at current rates, the advertising revenue could not even cover the cost of the ad itself, let alone other content that the user might want to watch.

**Universal Service.** The concept of universal service, i.e., providing telecommunications services to all residents regardless of geography or income, has a long tradition, dating back in the United States to at least the 1934 Telecommunication Act. There have been three traditional mechanisms to provide service to low income households and high-cost areas, by cross subsidy, by explicit subsidies by rate payers in general and finally through general tax revenue. Both Europe and the United States have had implicit subsidies within the dominant telecommunication provider, i.e., AT&T and the Bell Operating Companies, as well as explicit subsidies with the United States choosing universal service fees imposed interstate telecommunication charges. Implicit subsidies include obligations to serve all reasonable requests within defined geographic areas, such as “carrier of last resort” obligations in many US states. They also include higher-than-cost long-distance rates, intercarrier compensation for terminating calls in rural areas, higher business line rates and above-cost rates for services such as caller ID.

The United States has a universal service program that consists of four parts, with the most relevant for purposes of this discussion being the Connect America Fund to support high-cost (largely rural) areas and Lifeline, for low-income households. In 2013, the program

### 2013 Approved Disbursements by Program

(Unaudited - in thousands)



■ **Figure 11** 2013 Approved disbursements by program (Source: Universal Service Administrative Company (USAC), Annual Report 2013).

disbursed more than \$8.3 billion, i. e., roughly \$75 per household and year (Figure 11)<sup>8</sup>. High-cost and LifeLine support is paid to carriers, while the rural health care and school and library (e-rate) fund is paid to organizations that then purchase telecommunication services.

A detailed treatise of universal service is well beyond the scope of this summary. The programs have needed significant reforms to address inefficient and fraudulent expenditures. Also, the current contribution mechanism relies on a decreasing portion of consumer and business telecom expenditures, and there is no clear path on whether and how to include Internet access, for example, in the contribution base. Currently, broadband with speeds of 4 Mb/s down and 1 Mb/s up is eligible for support. An increase to 10/1 Mb/s has been proposed.

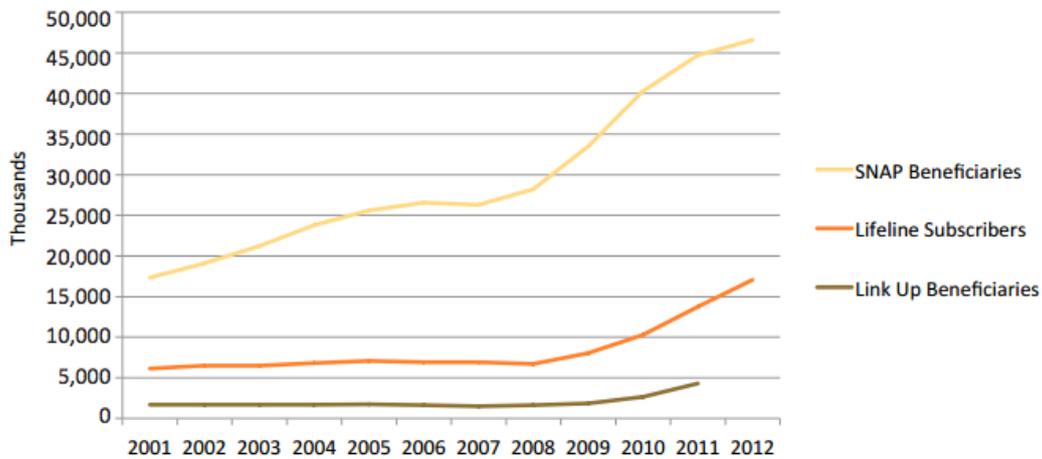
Currently, the FCC is conducting a small-scale (\$100 million) experiment on allocating high-cost support for higher-speed broadband based on a reverse auction, i. e., the entities with the lowest relative cost per subscriber served receive support, thus encouraging an efficient use of funds.

The Lifeline fund [9] largely supports a \$9.25 subsidy for mobile phone service, which is offered competitively by a number of MVNOs (Figure 12)<sup>9</sup>. A typical plan includes 250 minutes of voice calling per month, along with text messaging. There has been discussion, but no action, on extending Lifeline funding to data services. Subscribers have to be on a social service plan such as SNAP (“food stamps”) or be within 135% or 150% of the poverty limit. Each household is eligible for only one phone.

The private EveryoneOn [10] effort offers discounted Internet access, either through some HFC companies (5/1 Mb/s) or via 4G/3G wireless to low-income families with children eligible for free school lunches. For example, 1.2 GB of 4G wireless data is available for a monthly fee of \$10 for families with children that are participating in the free school lunch program. The Comcast Internet Essentials program serves approximately 350,000 households

<sup>8</sup> <http://apps.fcc.gov/ecfs/document/view?id=7521096190>

<sup>9</sup> [http://mercatus.org/sites/default/files/Ellig\\_FCC-phone-subsidy\\_MOP\\_101813.pdf](http://mercatus.org/sites/default/files/Ellig_FCC-phone-subsidy_MOP_101813.pdf)



■ **Figure 12** Lifeline subscribers and beneficiaries (Source: Mercatus.org).

in 2014 . The latter program was instituted as part of a merger condition.

These programs illustrate that there are at least two ways to offer affordable Internet access within the existing industry structure, often in combination. From a provider perspective, the carrier wants to avoid losing price-sensitive customers that currently pay significantly more to low-cost plans. Providers can limit the performance of such plans, or make them otherwise inconvenient, so that they are only attractive to households that cannot afford regular plans. Thus, such plans typically only offer limited speed or data budgets. However, reducing the performance too much will likely limit the take rate or may cause users to abandon a service that is unreliable or not capable of supporting common Internet experiences such as watching video content. Secondly, and probably more effectively, such programs can restrict eligibility by income. Providers may thus primarily reach customers that would otherwise not subscribe at all. Since many families move in and out of poverty, they may also help to attract new customers that stay even after they are no longer eligible for the discounted rate.

In summary, addressing availability, affordability and relevance requires both engineering and economic approaches. To make programs sustainable, they need to offer services that meet modern Internet expectations, if logistically possible. Predictable limitations are likely to be more successful than highly variable quality, but there appears to be little quantitative research on many aspects of universal service, including the cost of building and operating networks.

*One shoe salesman reported back that there was no market because no one wore shoes. His companion reported back that there was a fantastic market because no one wore shoes.*

Edward de Bono, Textbook of Wisdom

## References

- 1 <http://www.pewinternet.org/fact-sheets/broadband-technology-fact-sheet/>
- 2 <http://99in5.org/resources-news/equity/>
- 3 Se Gi Hong, SungHoon Seo, Henning Schulzrinne, and Prabhakar Chitrapu, ICOW: Internet Access in Public Transit Systems, Under review at IEEE Communications Magazine.

- 4 Arezu Moghadam, Suman Srinivasan, Henning Schulzrinne, 7DS – A Modular Platform to Develop Mobile Disruption-tolerant Applications, IEEE NGMAST 2008, Wales, UK, September 2008.
- 5 CTC, 2009, Brief Engineering Assessment: Efficiencies available through simultaneous construction and co-location of communications conduit and fiber.
- 6 [http://www.newamerica.net/publications/policy/homes\\_tails](http://www.newamerica.net/publications/policy/homes_tails), (2008)
- 7 Morgan Stanley, Macro Meets Micro: A Five-Year View of the Telecom Services Industry, July 2014.
- 8 Andrew Odlyzko, Will smart pricing finally take off?, <http://www.dtc.umn.edu/~odlyzko/doc/smart.pricing.pdf>, Oct. 2013.
- 9 <http://www.fcc.gov/guides/lifeline-and-link-affordable-telephone-service-income-eligible-consumers>
- 10 <https://everyoneon.org/>
- 11 <http://corporate.comcast.com/images/MB-10-56-Comcast-Internet-Essentials-Annual-Report-2014-07-31.pdf>

## 6.6 Affordability? Or Willingness-to-pay? The Perspective of Future Markets

*Irene Ng*

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Another perspective of affordability is to look at it not from what the market can afford, but rather what the market is willing to pay. The paradox of understanding a future that has no data is that we can only talk about the future in present terms, using present words, and through the lens (and the data) of the present and formulate some extrapolation based on some assumptions. Yet, if we do so, we run the risk of using the past to predict the future, which, as past innovation have gone on to demonstrate, may not be effective. Affordability is a case in point. We may be able to afford a dictionary, a flashlight or a calculator but when they become freely available on our smartphone, our willingness to pay for the phone increases (though probably not proportionately). That means the current boundaries of products requiring connectivity may not hold and the market is not a zero-sum game where one assumes a market size based on current prices and then analyse how total revenues may be distributed amongst all players within the network. Instead, there may be greater demand for connectivity, quality and speed but this commensurate with an expansion of markets and revenues for new products hereinto not yet known.

To understand a future where markets could expand resulting in greater demand for connectivity and yet generating marginally greater revenues, one would need to know how markets are re-forming in the digital economy and the drivers for such expansions.

**Commodification:** Commodification (a term which dates back to 1975, believed to have originated from Marxist political theory) is used to describe the process by which something with no economic worth is assigned some worth. This is different from commoditisation which is when an offering moves towards undifferentiated competition. The Italian economist Piero Sraffa [1] once said that firms are involved in “the production of commodities by means of commodities”, which means that firms make offerings based on what is offered to firms. This line of thinking of course has led to the commodification of many aspects of life that some

consider excessive. Our dreams, our fears, our stem cells have been commodified to become offerings of status, security and hope. Dallas Smythe, back in 1994 before the proliferation of the Internet, considered TV audiences as commodities. By watching advertisements, the audiences “work” for the media by letting themselves be marketed to and by doing so, media firms mass produce audiences and “sell” them to advertisers [2]. Audiences therefore “labour” for distribution and consumption of things produced. The moral limits of commodification have also been widely discussed [3].

The digital economy has seen a proliferation of commodification practices since many of our value-creating activities have become digitally visible. We click on ads suggested by Google, write information on Wikipedia, update our status on Facebook, tweet about our lives and our opinions, and upload videos on YouTube. With our lives becoming more digitally visible, we produce more data about ourselves even as we consume more digital offerings. We become “prosumers”, a term coined by Alvin Toffler in 1980 to describe a consumer who produces as well as consumes [4]. This thinking has been extended to the digital realm where the digital self becomes “digital labour” through digital value-creating practices [5]. The technical, functional and social capabilities of mobile media mean that there are more varied forms of commodifying our digital labour practices [6]. We contribute “creative”, “intellectual” and “emotional” labour through the way we interact [7],[8]. These digital labour practices are made ever more possible through smartphones. Musicoverly is an app that categorises your music collection on your smartphone and plays music to you according to your mood, in degrees of “dark”, “positive”, “energetic” or “calm” modes. While doing so, your mood becomes part of digital labour. Indeed, our digital labour spawns even more digital labour through the need to maintain our digital identities and social networks. Firms learn about their customers through the collection of their personal data, and repackage them to sell on to other firms. There are many out there who have been campaigning to protect the rights of the increasingly perilous, alienated and exploited, digital “labourer”, arguing that commodification of digital labour dehumanises us.

Commodification of labour or digital labour does not automatically assume that worth is created or that market expands. Rather, it is the step towards which human activity contributes to the firm’s business model and the firm’s capability to create new connected products to compete in digital markets. Commodification is therefore a potential resource acquisition for a market expansion strategy in future markets.

**Digitisation and market expansion:** On the 19th of January 2012, Eastman Kodak US filed for bankruptcy protection. An iconic firm formed in 1889 by George Eastman, Kodak dominated the photographic film business for more than 100 years. During its heyday in 1976, it commanded 90 percent of film sales and 85 percent of camera sales in the U.S [9]. Hundreds of business school students and numerous newspapers, magazines and journals have described and analysed the Kodak failure, with many concluding that Kodak did not move quickly enough into the digital era even though the digital camera was invented by Steven Sasson, a Kodak engineer. Kodak’s dallying for fear of cannibalising its film business resulted in competitor Canon seizing a sizeable market share. The subsequent ubiquity of camera phones created further problems. Urban legend has it that a well-known business consultancy commissioned by Kodak to research into the future of photographs around the turn of the century, when approximately 86 billion analogue photographs were taken per annum, reported that only one in 10 photographs printed were shared. The rest were left gathering dust in photo albums. So it was concluded that the future of photographs would probably not be in the direction of shareability. Imagine the surprise when, within 10 years by 2010, the number of photos shared online is 11 billion and rising, with experts predicting

that the numbers will double by 2015. The number of photographs taken have also soared, with some studies estimating the total number to be around 380 billion. Printing photos at home and in store has dropped to a third at 27 billion. The digital revolution of photography is a case in point on the power of digitisation to change both the message (what photos are taken) as well as the medium (the channels for taking the photos and for communication and sharing). Where we used to take photographs for memories, the ability now to generate (and erase) a photo on demand means that photographs could be taken for many reasons without incurring any further economic costs. Today, photographs are no longer just for keeping memories but for collecting evidence after an accident, or photographing a notice or telephone number when there is no pen or paper. The consultancy engaged by Kodak over 10 years ago didn't get it wrong. It was probably true that only one in 10 photographs were shared before photos were digitised; it's just that the sharing mechanism was through a printed medium. Today, freed from the need to be printed, photographs and other images have become social resources on steroids. The photograph as an offering has completely changed in terms of its benefits, its content, and its channels, from creating it to communicating it, labelled as a digital backwash. Digitisation therefore creates an expansionary effect on markets that would drive changes to the product, its content, the medium and the message.

**Consumption and Experiential Contexts:** The New Focus For Markets. Digital connectivity is also driving the location of markets. Traditionally, market exchanges happened at retail locations. We bought what we needed from shops, whether they were just around the corner or required a shopping trip into town. As Internet access became ubiquitous, online shopping through the World Wide Web became commonplace. Yet, this still meant visiting websites in the same way we visited physical shops. Buying can therefore be viewed as an interruption to our lives (unless you are seeking retail therapy or window shopping). If we wanted something, buying it would be a "cost" in terms of effort, to get what we really want—which is to use or experience it. Google became popular through its ability to match our search needs with websites, reducing such costs. Even so, it still meant that we had to buy in advance of use, whether from a shop or online.

With greater Internet connectivity, exchanges are slowly becoming closer to the contexts of use experience, even allowing us to choose how we wish to be served. We can now do our banking, watch the latest movie on demand and read our newspapers without leaving the house and without waiting too long to do it.

As more digitised offerings become available, we have switched our purchases from single-function items to a "platform" that allows us to buy more digitised offerings to serve us in context. Many widgets in our homes will want to be the platform to serve up more services on demand, as firms begin to realise the strategic advantage of being a potential channel to serve individuals in context and on demand, rather than in traditional market places.

What this means is that the separation between the location of where exchanges happen (i. e., the market space) and the consumption and experiential space is collapsing into a similar time and space. For products that can be fully digitised, such as music, this spatial collapse has had a profound impact on the business and economic model of an entire industry. Digitisation, as Normann [10] puts it, enables individuals to create what he calls "density". Density seeks the mobilisation of the best combination of resources for a particular situation. Ultimately, density means that the customer has the world of specialist knowledge available when and where they like. Creating density is the fundamental driver to the digital economy. Being able to digitally enable resources to be used in context and on demand has an expansionary effect on the market as goods and services that serve contexts also means that firms can tap into a market that is more willing to pay, since the service or product

acquisition is at the point of need. It also helps firms create new business models of both ownership and access. For example, the market for the ownership of luxury cars currently stands at 70 million cars sold in 2012. That is, however, the market for the ownership of these cars. Yet, there may be many out there who do not wish to own, but would like to drive a Porsche on Mondays and a Rolls-Royce on Saturdays. If digital services in cars can help us detect where they are and what condition they are in, there could be a vast appetite for such services. Technology that makes this viable will create an expansionary effect on the entire automotive industry.

The above outline only 3 drivers of market expansion that could increase the total market affordability for greater infrastructural investments in connectivity. There are many more such as lowering coordination costs, reducing overall exchange risks, emerging latent needs and creating increasing returns of scale through both scalability and personalisation, etc [11]. While market expansion could justify greater infrastructural investment, it doesn't however, solve the issue of digital exclusion. However, a more tightly connected ubiquitous market of digital connectivity can create positive externalities that could benefit those who are marginalised by digital exclusion.

Society has benefited greatly from network effects of digital offerings, directly and indirectly. Amongst many other benefits, consumer welfare is increased because of greater choice, lower coordination and reduced search and information costs. Digital connectivity has made us share and collaborate more. This suggests that the digital economy, with lower coordination costs and high scalability and low marginal could reallocate quickly, with the right market incentives to do so. This is especially so when the strategy is that of market expansion.

## References

- 1 Sraffa P (1960) *Production of Commodities by Means of Commodities: Prelude to A Critique Of Economic Theory*. Vora and Co., Publishers PVT Ltd
- 2 Smythe DW (1981) *Dependency Road: Communications, Capitalism, Consciousness And Canada*. Norwood, N.J.: Ablex
- 3 Sandel MJ (2000) What Money Can't Buy: The Moral Limits Of Markets. *Tanner Lectures on Human Values* 21:87–122
- 4 Toffler A (1984). *Future Shock*. Bantam
- 5 Manzerolle V (2010) Mobilizing The Audience Commodity: Digital Labour In A Wireless World. *Ephemera: Theory of Politics in Organization* 10(4):455–469
- 6 Hearn A (2008) Meat, Mask, Burden: Probing The Contours Of The Branded "Self". *Journal of Consumer Culture* 8(2):197–217
- 7 Fuchs C (2009) Class, Knowledge And New Media. *Media, Culture & Society*, 32(1):141–150
- 8 Cohen NS (2008) The Valorization Of Surveillance: Towards A Political Economy Of Facebook. *Democratic Communique* 22(1):5–22.
- 9 Shapiro C & Varian HR (1999) *Information Rules: A Strategic Guide To The Network Economy*. Harvard Business Press
- 10 Normann R (2001) *Reframing Business: When The Map Changes The Landscape*. John Wiley & Sons Inc
- 11 Ng, Irene C L (2014) *Creating New Markets in the Digital Economy: Value and Worth*, Cambridge University Press, UK

## 6.7 Rights on the Internet

*Michael P. Fourman*

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Information is power. We argue that the changes enabled by modern information and communication technologies have fundamentally changed the balance of power, and that we must revisit established rights to freedom of speech and access to information and education if we are to avoid a fundamental digitally-enabled divide between those who can wield the digitally-enhanced power of information and those who cannot.

The per-subscriber cost of providing Internet access depends on both geography and uptake. Uptake depends on a combination of perceived relevance and affordability, while per-subscriber cost of provision depends on terrain and population density. These factors mean that, in most countries, market-driven provision will not be universal. In the UK provision of modern Internet access to the 'final third' of the population was deemed uneconomic.

Increasing Internet access has social value. It enables significant cost reductions and efficiencies in operations and service provision for all sectors of society: public sector, commercial, and third-sector organisations. It provides local businesses with extended visibility and access to global markets. It provides new tools for communication that enhance social cohesion. Network effects make all of these factors increasingly valuable for existing participants once new individuals and organisations come online.

These positive externalities justify intervention to address the market failure to deliver universal provision. However, a purely economic argument, based on such externalities has also failed to deliver anything close to universal provision. Those who remain unconnected, or with inferior service already isolated and/or disadvantaged, and their social exclusion is exacerbated by an increasing digital divide, as those who are well-connected enjoy increasing benefits from the digital economy, and existing non-digital services become uneconomic and are withdrawn.

This social argument has led some to suggest that Internet access should be seen as a human right. Others, with whom we side, disagree. For example, Vint Cerf has said, "There is a high bar for something to be considered a human right. Loosely put, it must be among the things we as humans need in order to lead healthy, meaningful lives, like freedom from torture or freedom of conscience."

Nevertheless, it is easy to argue that Internet access plays a significant role in enabling several established rights, such as the rights to freedom of expression, to work, to access information. As Vint Cerf says, "...technology is an enabler of rights, not a right itself. The Internet has introduced an enormously accessible and egalitarian platform for creating, sharing and obtaining information on a global scale. As a result, we have new ways to allow people to exercise their human and civil rights."

We claim that existing rights are insufficient to ensure that everyone has an equal opportunity to exercise these opportunities. These technologies amplify our human abilities to store, process, and communicate information. The amplification is extreme. Modern machines can have the power of hundreds or thousands of horses. Nuclear explosions can be many thousands (or millions) of times more powerful than the largest conventional detonations. Our information technologies enable the collection, storage, processing and communication of information at a scale that is millions (or trillions) of times that of a naked brain.

Technology is an enabler of rights, not a right itself. We propose fundamental rights to

store, process, and communicate information. Clearly internet access is neither necessary nor sufficient for the exercise of such rights; but it can certainly contribute to enabling them.

The rationale for such rights is that equality of access to the power of information is required to ensure equality of opportunity to choose and pursue a worthwhile life. Vulnerable and marginalized groups in societies tend to be excluded from the opportunities afforded by information technologies.

Rights have value only in their consequences. Our exploration of the consequences of our proposed information rights is an adaptation of an analysis, *The right to health*. Fact sheet No. 323, published by the World Health Organisation.

The right to health means that governments must generate conditions in which everyone can be as healthy as possible. Such conditions include ensuring the availability of

- health services,
- healthy and safe working conditions,
- adequate housing and nutritious food.

The right to health contains four elements: Availability, Accessibility, Acceptability, and Quality. It imposes on States three types of obligation: to respect, protect, and fulfil the right.

Our proposed information rights would have analogous consequences. For example, that governments must generate conditions in which everyone can share in the benefits of an information society. Such conditions include ensuring the availability of

- information infrastructure,
- a safe information environment,
- adequate access to open data and information.

More generally, information rights include four elements:

- Availability: A sufficient quantity of reliable infrastructure, services, tools and data.
- Accessibility: Infrastructure and services accessible to everyone. Accessibility has four overlapping dimensions:
  1. Non-discrimination
  2. Physical accessibility
  3. Economical accessibility (affordability)
  4. Information accessibility.
- Acceptability: All infrastructure, goods and data must be respectful of ethics and culturally appropriate as well as sensitive to gender and life-cycle requirements.
- Quality: Infrastructure, services and data must be sound and adhere to open standards.

Information rights would impose, on States, obligations to respect, protect, and fulfil the rights. Respect: means simply not to interfere with the enjoyment of the right (“do no harm”). Protect: means ensuring that third parties (non-state actors) do not infringe upon the enjoyment of the right (e.g., by regulating non-state actors). Fulfil: means taking positive steps to realize the right (e.g., by adopting appropriate legislation, regulations, policies or budgetary measures).

Recognising such information rights would provide a framework for the development of policy. In particular, such information rights would justify the commitment to universal inclusion that is necessary to avoid a growing digital divide.

The requirement to respect these rights would inform discussions of privacy, surveillance, censorship, and some aspects of net neutrality. The requirement to protect would entail obligations on governments to act against abuses and cybercrime. The requirement to fulfil

would include actions to ensure the availability and accessibility of both infrastructure and education to ensure that all citizens are able to share in the benefits of a digital society.

Another core obligation would be the adoption and implementation of a national strategy and plan of action. This must address the information and communication concerns of the whole population; be devised, and periodically reviewed, on the basis of a participatory and transparent process; contain indicators and benchmarks by which progress can be closely monitored; and give particular attention to all vulnerable or marginalized groups.

Just as for health, each country must move forward in line with a principle of progressive realization. Elsewhere in this document others outline some deliberate, concrete and targeted steps towards universal Internet access that should be taken using the available resources. These resources will include those allocated within a State as well as resources available through international assistance and cooperation.

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# Multiscale Spatial Computational Systems Biology

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## Abstract

This report documents the program and the outcomes of Dagstuhl Seminar 14481 “Multiscale Spatial Computational Systems Biology”. This seminar explored challenges arising from the need to model and analyse complex biological systems at multiple scales (spatial and temporal), which falls within the general remit of Computational Systems Biology. A distinguishing factor of the seminar was the modelling exercise – where teams explored different modelling paradigms, in order to better understand the details of the approaches, their challenges, potential applications, and their pros and cons. This activity was carried out in a collaborative and self-directed manner using the Open Space Technology approach as evidenced by a high degree of communication both within and between the teams. Eight teams were formed, and reports from five of them are included in this document.

**Seminar** November 24–28, 2014 – <http://www.dagstuhl.de/14481>

**1998 ACM Subject Classification** D.2.1 Requirements/Specifications, D.2.2 Design Tools and Techniques, D.2.4 Software/Program Verification, J.3 Biology and genetics

**Keywords and phrases** Multiscale, multidimensional, computational modelling, space, time, systems biology, synthetic biology

**Digital Object Identifier** 10.4230/DagRep.4.11.138

## 1 Executive Summary

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This seminar built on the tradition of two previous Dagstuhl seminars on *Formal Methods in Molecular Biology* in 2009 and 2011 (Seminar 09091, Seminar 11151), but with a special focus on multiscale and spatial modeling and simulation.

Multiscale modelling goes beyond the traditional approach of modelling at just one spatial/temporal scale or organizational level. Until now most models have largely ignored locality within the cell, or cell-cell interactions. However, with the insight that spatial phenomena like localisation and crowding have a considerable influence on reaction processes and many processes cannot be understood with reference to one organisation level only (intra-



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or inter-cellular dynamics), the need for effective and efficient modelling and simulation approaches arises.

The challenges for computer science and mathematics include the development of suitable modelling approaches and associated tools to create coherent descriptions of biological systems by integrating several spatial and/or temporal scales, and methods for the simulation and analysis of the models.

The overall motivation for this seminar was the exploration of the most recent advances in these methods. The seminar brought together researchers working in modelling and analysis of biological systems with diverse professional backgrounds, including informaticians, mathematicians, engineers, biologists, physicians.

A distinguishing factor of the seminar was the modelling exercise – where teams explored different modelling paradigms, in order to better understand the details of the approaches, their challenges, potential applications, and their pros and cons. This activity was carried out in a collaborative and self-directed manner using the Open Space Technology approach as evidenced by a high degree of communication both within and between the teams. Eight teams were formed, and reports from five of them are included in this document (see Section 4).

The teams were formed around the following focii:

- Small GTP-ase pathway.
- Continuous multiscale models for biological tissue.
- Simulating macromolecular crowding with particle and lattice-based methods
- Multiscale modeling of S1P metabolism, secretion and signaling
- DNA structural dynamics.
- Dictyostelium discoideum: Aggregation and Synchronisation of Amoebas in Time and Space.
- Towards a standard exchange format for spatial, multilevel multicellular models.
- Model checking for multiscale spatial biological systems.

The participants decided to take forward the activities in the future outside Dagstuhl, with the goals of carrying out collaborative research, producing scientific papers and applying for larger scale funded international research projects.

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## 3 Overview of Talks

### 3.1 The Smoldyn simulator: overview, applications, and hybrid simulation

*Steven Andrews (Frederic Hutchinson Cancer Center – Seattle, US)*

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**Main reference** S. S. Andrews, N. J. Addy, R. Brent, A. P. Arkin, “Detailed Simulations of Cell Biology with Smoldyn 2.1,” *PLoS Computational Biology*, 6(3):e1000705, 2010.

**URL** <http://dx.doi.org/10.1371/journal.pcbi.1000705>

Smoldyn is a particle-based cell biology simulator which represents proteins or other molecules of interest as individual spheres. These particles diffuse, undergo chemical reactions with each other, and interact with membranes and other surfaces in ways that closely mimic reality. In particular, all interaction rates are quite accurate. Smoldyn is easy to use and supports a wide variety of features. It is typically used either to model cell biology systems (e.g. *E. coli* chemotaxis and neural dendritic spine signaling) or to model simple biophysical problems (e.g. effects of macromolecular crowding and effects of multisite phosphorylation). Martin Robinson and I recently added adjacent-volume hybrid simulation capability to Smoldyn. Here, space is partitioned into adjacent continuum and lattice regions, which are simulated with particle-based and spatial Gillespie type methods, respectively. These enable simulations to represent high levels of detail where required but lower detail (and faster computation) elsewhere.

### 3.2 Some cell biology modeling projects

*Steven Andrews (Frederic Hutchinson Cancer Center – Seattle, US)*

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I work on several cell biology modeling projects. For example, I helped investigate the metabolic control of *E. coli* lipid A biosynthesis. Lipid A is an essential outer membrane lipopolysaccharide that is of particular interest to the medical community. I also wrote the Smoldyn simulator, which is a widely used particle-based biochemical simulator for modeling intracellular spatial organization. My most recent work, which is unpublished, focuses on mechanisms that cell signaling systems apparently use in order to transmit information with high fidelity.

### 3.3 Spatiocyte: a stochastic particle simulator for filament, membrane and cytosolic reaction-diffusion processes

*Satya Arjunan (Osaka University, JP)*

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Spatiocyte is a lattice-based stochastic particle simulator for biochemical reaction and diffusion processes. Simulations can be performed at single molecule and compartment spatial

scales simultaneously. Molecules can diffuse and react in 1D (filament), 2D (membrane) and 3D (cytosol) compartments. The implications of crowded regions in the cell can be investigated because each diffusing molecule has spatial dimensions. By adopting the E-Cell System's multi-algorithm, multi-timescale framework, Spatiocyte can simulate models simultaneously employing deterministic, stochastic and particle reaction-diffusion algorithms. Comparison of light microscopy images to simulation results is supported by Spatiocyte microscopy visualization and molecule tagging features. In both diffusion and reaction problems, Spatiocyte run time is comparable to or better than other well-known particle simulators. Spatiocyte is an open-source software written in C++ and is freely available at <http://spatiocyte.org>. The software package, which currently runs on Linux and Mac OS X systems, comes with example models, Python plotting scripts and an introductory guide to building models.

### 3.4 Approximate analysis of biological systems by hybrid switching jump diffusion

*Marco Beccuti (University of Turin, IT)*

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We consider large state space continuous time Markov chains arising in the field of systems biology. For a class of such models, namely, for density dependent families of Markov chains that represent the interaction of large groups of identical objects, Kurtz has proposed two kinds of approximations. One is based on ordinary differential equations and provides a deterministic approximation, while the other uses a diffusion process with which the resulting approximation is stochastic. The computational cost of the deterministic approximation is significantly lower, but the diffusion approximation retains stochasticity and is able to reproduce relevant random features like variance, bimodality, and tail behavior that cannot be captured by a single deterministic quantity. For particular stochastic Petri net models, we proposed a jump diffusion approximation that aims at being applicable beyond the limits of Kurtz's diffusion approximation in order to cover the case when the process reaches the boundary with non-negligible probability. Now we generalize the method so that it can be applied to any density dependent Markov chains. Other limitations of the diffusion approximation in its original form are that it can provide inaccurate results when the number of objects in some groups is often or constantly low and that it can be applied only to pure density dependent Markov chains. In order to overcome these drawbacks, we propose to apply the jump-diffusion approximation only to those components of the model that are in density dependent form and are associated with high population levels. The remaining components are treated as discrete quantities. The resulting process is a hybrid switching jump diffusion, i. e., a diffusion with hybrid state space and jumps where the discrete state changes can be seen as switches that take the diffusion from a condition to another. We show that the stochastic differential equations that characterize this process can be derived automatically both from the description of the original Markov chains or starting from a higher level description language, like stochastic Petri nets.

### 3.5 Reaction-diffusion & particle-based simulation, and a rule-based language

Arne Bittig (*Universität Rostock, DE*)

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We created a rule-based language for expressing interactions between mobile entities in not well-stirred environments. The language that centres on rules that specify patterns on how the entities' properties change, either over time or as a result of a direct interaction between two entities, here collisions.

While other rule-based languages can express spatial phenomena to a certain extent, e. g. by defining attributes that represent position in space and rules that change these attributes, ours is designed to separate spatial properties like movement and other interaction rules as much as possible.

Applications so far include the growth on actin filaments in cells on differently structured surfaces [1] and mitochondrial health in response to perturbations of fusion and fission processes [2].

We developed a simulator that can treat entities as either individual hard, non-overlapping spheres with continuous coordinates or as dimensionless entities situated in one cell (sub-volume) of a multi-occupancy grid. We then added dynamic nesting, i. e. the possibility of smaller entities to be situated inside larger entities, representing cellular organelles, for example. Our approach culminates in a hybrid simulator where entities at the lowest level are dimensionless members of the multi-occupancy grid (spatial Gillespie) and the larger entities comprise one or more of these grid cells and move along the grid, interacting just like in the purely continuous-space case [3].

#### References

- 1 AT Bittig, C Matschegewski, JB Nebe, S Stählke, AM Uhrmacher. *Membrane related dynamics and the formation of actin in cells growing on micro-topographies: a spatial computational model*. BMC Systems Biology. 2014. **8**:106+.
- 2 AT Bittig, F Reinhardt, S Baltrusch, AM Uhrmacher. *Predictive Modelling of Mitochondrial Spatial Structure and Health*. In: Computational Methods in Systems Biology. vol. 8859 of LNCS. Springer 2014. pp. 252–255.
- 3 AT Bittig, F Haack, C Maus, AM Uhrmacher. *Adapting rule-based model descriptions for simulating in continuous and hybrid space*. In: Computational Methods in Systems Biology. ACM 2011. pp. 161–170.

### 3.6 A Modular Framework for Biomodel Engineering

Mary Ann Blätke (*Universität Magdeburg – IBIO, DE*)

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**Main reference** M.-A. Blätke, A. Dittich, C. Rohr, M. Heiner, F. Schaper, W. Marwan, “JAK/STAT signalling – an executable model assembled from molecule-centred modules demonstrating a module-oriented database concept for systems and synthetic biology,” Mol. BioSyst., 9(6):1290–1307, 2013.

**URL** <http://dx.doi.org/10.1039/C3MB25593J>

In our framework for modular BioModel Engineering, we understand biomolecular instances like genes, mRNAs, proteins and other small molecules as natural building blocks of regulatory

and metabolic processes. Based on this idea, we accordingly define modules in such a way, that each module describes the functionality and interactions of a single biomolecular instance. The relevant mechanisms of a biomolecular instance are unambiguously expressed by Petri nets. Different versions of a module can be obtained due to new insights about the biomolecular instances, different hypothesis or abstractions and assumptions of a molecular mechanism. The modular concept allows to arbitrarily reuse and recombine modules.

The *Biomodelkit Database* (BMKdb) supports our framework and allows to (1) explicitly store the network structure of each module, (2) organise modules, (3) version control modules (4) explicitly link meta information and references of other bio-databases to the network structure of a module. Furthermore, we can use BMKdb to automatically compose models from a chosen set of modules. The network structure of the composed models can be algorithmically mutated according to structural criteria or linked references, which allows the generation of several alternative models, which might be interesting to *in silico* identify models with a specific or desired behaviour.

Extending this framework by the use of coloured Petri nets, we can assign spatial aspects to each module, and thus implement their localisation by compartments or even more by coordinates. This extension allows us to represent different cell geometries, the spatial arrangement of a cell or membrane and their alteration due to e.g. transport processes.

In summary, the approach for modular BioModel Engineering supported by BMKdb and the coloured extension to represent spatial aspects create a versatile and unifying framework for Biomodel Engineering even on a multiscale level.

## References

- 1 Mary-Ann Blätke et al., *JAK/STAT signalling – an executable model assembled from molecule-centred modules demonstrating a module-oriented database concept for systems and synthetic biology*. Mol. BioSyst. 9(6),1290–1307, 2013
- 2 Mary-Ann Blätke et al., *JAK-STAT signalling as example for a database-supported modular modelling concept*. Proceedings of the 10th CMSB Conference, Springer LNCS/LNBI 7605, 362–365, 2012
- 3 Mary-Ann Blätke et al., *Predicting phenotype from genotype through automatically composed Petri nets*. Proceedings of the 10th CMSB Conference, Springer LNCS/LNBI 7605, 362–365, 2012

## 3.7 Logic based analysis of spatio-temporal behaviour

Luca Bortolussi (*Universität des Saarlandes, DE*)

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**Joint work of** Bortolussi, Luca; Nenzi, Laura;

**Main reference** L. Bortolussi, L. Nenzi, “Specifying and Monitoring Properties of Stochastic Spatio-Temporal Systems in Signal Temporal Logic,” in Proc. of the 8th Int’l Conf. on Performance Evaluation Methodologies and Tools (VALUETOOLS’ 14), to appear; pre-print available from author’s webpage.

**URL** <http://bortolussi.dmg.units.it/node/286>

Many biological systems exhibit a behaviour that can be understood only in a spatio-temporal setting, from the development of an organism to tissue dynamics to cell motility.

In order to reason formally on such behaviours, we consider an extension of the linear time, time-bounded, Signal Temporal Logic to describe spatio-temporal properties. Our starting point is a discrete (grid or patch-based) representation of space, with a population

of interacting agents evolving in each location and with agents migrating from one patch to another one. Agents can be cells or molecules in a biological context, but the same logic can be used in other settings (e. g. epidemiology).

We provide both a boolean and a quantitative semantics to this logic, introducing the monitoring algorithms to check the validity of a formula, or to compute its satisfaction (robustness) score, over a spatio-temporal trace. These routines are exploited to do statistical model checking of stochastic models.

This logic has been presented in [1], where it is illustrated on an epidemic example, looking at the diffusion of a cholera infection among communities living along a river.

## References

- 1 Luca Bortolussi and Laura Nenzi. Specifying and Monitoring Properties of Stochastic Spatio-Temporal Systems in Signal Temporal Logic, Proceedings of VALUETOOLS 2014.

## 3.8 Bifurcation analysis of multiscale spatial models

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**Joint work of** de Back, Walter; Zhou, Joseph X.; Brusch, Lutz

**Main reference** W. de Back, J. X. Zhou, L. Brusch, “On the role of lateral stabilization during early patterning in the pancreas,” *Journal of The Royal Society Interface*, 10(79), 2012.

**URL** <http://dx.doi.org/10.1098/rsif.2012.0766>

I propose that multiscale spatial models can be efficiently developed and analysed by means of bifurcation analysis thanks to modularity of interacting subsystems. The generally applicable approach proceeds by (1) defining modules of the multiscale system under consideration, (2) defining the parameters and variables of each module, (3) perform numerical (continuation-based) bifurcation analysis of each module by systematically varying its parameters and recording the steady state or minimum and maximum of space or time-dependent solutions for the module variables, (4) projection of each module’s variable dependencies on its parameters onto the parameter axes of other modules, (5) synthesis of the solution (or solution properties like upper and lower bounds) of the whole multiscale system from the individual projections.

This approach has been applied to and revealed novel biological insights for bursting oscillations during intracellular Calcium signaling [6], protein domains on cellular membranes [5], self-organising cellular compartment identities [4], cell-cell contact driven cell differentiation patterns [3] and cell-cell contact driven cell type reprogramming [2]. In some of these studies, the modelling and simulation framework Morpheus has been used to test and confirm the results of the bifurcation analysis approach [1].

## References

- 1 Starruss, Jörn and de Back, Walter and Brusch, Lutz and Deutsch, Andreas (2014) Morpheus: a user-friendly modeling environment for multiscale and multicellular systems biology. *Bioinformatics* 30 (9), pp. 1331–1332, DOI: 10.1093/bioinformatics/btt772
- 2 de Back, Walter and Zimm, Roland and Brusch, Lutz (2013) Transdifferentiation of pancreatic cells by loss of contact-mediated signaling. *BMC Systems Biology* 7 (1), 77, DOI: 10.1186/1752-0509-7-77
- 3 de Back, Walter and Zhou, Joseph X. and Brusch, Lutz (2012) On the role of lateral stabilization during early patterning in the pancreas. *Journal of The Royal Society Interface* 10, 20120766, DOI: 10.1098/rsif.2012.0766

- 4 del Conte-Zerial, P. and Bruschi, Lutz and Rink, Jochen and Collinet, Claudio and Kalaidzidis, Yannis and Zerial, M. and Deutsch, Andreas (2008) Membrane identity and GTPase cascades regulated by toggle and cut-out switches. *Mol. Syst. Biol.* 4, 206, DOI: 10.1038/msb.2008.45
- 5 Bruschi, Lutz and del Conte-Zerial, P. and Kalaidzidis, Yannis and Rink, Jochen and Habermann, Bianca and Zerial, M. and Deutsch, Andreas (2008) Protein domains of GTPases on membranes: do they rely on Turing's mechanism? in *Mathematical Modeling of Biological Systems* (Eds. Deutsch, Andreas and Bruschi, Lutz and Byrne, H. and de Vries, Gerda and Herzog, Hans-Peter), pages 33–46 (Birkhäuser, Boston), DOI: 10.1007/978-0-8176-4558-8\_4
- 6 Bruschi, Lutz and Lorenz, W. and Or-Guil, Michal and Bär, Markus and Kummer, U. (2002) Fold-Hopf bursting in a model for calcium signal transduction. *Z. Phys. Chem.* 216 (4), pp. 487–497, DOI: 10.1524/zpch.2002.216.4.487

### 3.9 Modulation of biological function by structure and inter-subject variability

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**Joint work of** Bueno-Orovio, Alfonso; Kay, David; Grau, Vicente; Rodriguez, Blanca; Burrage, Kevin  
**Main reference** A. Bueno-Orovio, D. Kay, V. Grau, B. Rodriguez, K. Burrage, “Fractional diffusion models of cardiac electrical propagation: role of structural heterogeneity in dispersion of repolarization,” *Journal of The Royal Society Interface*, 11(97), 2014.

**URL** <http://dx.doi.org/10.1098/rsif.2014.0352>

My research interests focus on investigating the interplay between electrical and structural abnormalities in the human heart, one of the most frequent causes of death in our societies. This is a highly multiscale problem, spanning the cellular (ionic currents across the membrane, and regulation of ionic concentrations inside the cellular domain), tissue (how cells communicate to each other to allow the spreading of electrical impulses), whole-organ (with marked spatial heterogeneity in cellular properties, as well as in the structural composition of the heart) to the whole-body level (propagation of the electrical activity through an heterogeneous torso, routinely recorded in clinical practice as the body-surface electrocardiogram). In fact, it is still pretty much unknown how these different scales communicate with (and affect) the others. On top of that, the large patient-to-patient variability that exists at the population level makes even more challenging to extrapolate results from using a single model representative of an average individual.

In this talk, I will address two of the main methodologies that we have recently proposed to address some of the above mentioned multiscale complexity. In order to better understand the sources of variability underlying the physiological and pathological responses of different individuals, we propose the construction and calibration of populations of models. These populations share the same model equations (i. e., similar biology among different individuals) but different ionic properties (model parameters), and are thoroughly calibrated against experimental data to retain all possible models within physiological range. The resulting experimentally-calibrated populations therefore allow for the investigation of the key ionic determinants of inter-subject variability in multiple properties of the data, as well as to extend model predictions to a new population level.

Secondly, impulse propagation in the heart is known to be modulated by tissue heterogeneity. In cardiac muscle, improved understanding on how this heterogeneity influences electrical spread is key to advancing our interpretation of possible pro-arrhythmic substrates.

We have recently proposed fractional diffusion models as a novel mathematical description of structurally heterogeneous excitable media, as a mean of representing the modulation of the total electric field by the secondary electrical sources associated with tissue inhomogeneities. Our results indicate that structural heterogeneity underlies relevant characteristics of cardiac electrical propagation at the tissue level. The proposed approach may also have important implications in the clinical identification of cardiac structural abnormalities.

### 3.10 Integrative strategy to elucidate the multiple layers of the transcriptional regulation

*Francesca Cordero (University of Turin, IT)*

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The physiology of each individual is the result of a multi-layered organization of biological components starting from intracellular level. High-Throughput (HT) technologies are commonly adopted to acquire new knowledge about gene regulation, epigenomics and genome sequence. The huge amount of heterogeneous data produced by HT technologies has made the data integration a necessary methodology to combine these data in order to gain new insights about all players (DNA sequences, proteins, RNAs, metabolites) involved in regulation of gene expression. We work on the definition of a new approach to integrate HT data. Four steps compose our approach: (i) computation of genome coverage; (ii) selection of regulatory regions; (iii) cistrome organization analysis; (iv) study of gene regulation by hypothesis generation. We applied our methodology to integrate multiple experiments of estrogen receptor genomic occupancy, identifying constitutively occupied estrogen receptor binding sites significantly related to long-range chromatin interactions, enhancer predictions and sites occupied in patients. Interestingly, the high-intensity sites were enriched in enhancer marks even in estrogen deprived cells and mapped closer to gene involved in mammary gland development and cell migration. We are currently working on making our approach able to integrate other sources of information particularly RNA-Seq, proteomic and exome sequencing data whose contribution is pivotal to understand exhaustively complex biological processes and diseases. Finally, we plan to translate the integrative model obtained in a mathematical formalism in order to analyse the temporal behaviours of all players involved in the gene regulation under investigation.

### 3.11 Cellular automaton models for collective cell behaviour

*Andreas Deutsch (TU Dresden, DE)*

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**Main reference** A. Deutsch, S. Dormann, “Cellular Automaton Modeling of Biological Pattern Formation: Characterization, Applications, and Analysis,” Birkhäuser, Boston, 2005 (2nd ed. 2015).

**URL** <http://www.springer.com/birkhauser/biosciences/book/978-0-8176-4281-5>

Cellular automata were invented by J. von Neumann and S. Ulam in the 1950s and have become the basis for various models of natural phenomena. In particular, cellular automata are viewed as paradigm for a simple model of biological complexity. While interaction is formulated by means of a local rule, it is difficult to deal with migration in classical cellular automata. A possible solution are lattice-gas cellular automata which have been introduced in the 1970s and 80s – motivated by fluid dynamical problems – as models of moving and

interacting particle populations. These automata solve the migration challenge through a rule splitting into a deterministic propagation and a stochastic interaction rule. Over the last years we have extended these models to cell populations and analysed collective behaviour in interacting cell populations. We could identify specific mechanisms of collective cell migration, clustering and invasion and show how analysis of the models allows for prediction of emerging properties at the individual cell and the cell population level. These models have applications in biological development and tumor dynamics.

### 3.12 Stochastic and Multiscale Modelling in Molecular, Cell and Population Biology

Radek Erban (University of Oxford, GB)

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I discussed methods for spatio-temporal modelling in molecular, cellular and population biology. Application areas include intracellular calcium dynamics, actin dynamics, gene regulatory networks, and collective behaviour of cells and animals. Three classes of models were considered:

- (i) microscopic (individual-based) models (molecular dynamics [1], Brownian dynamics [2, 3, 4]) which are based on the simulation of trajectories of individual molecules (or individuals) and their localized interactions (for example, reactions);
- (ii) mesoscopic (lattice-based [3, 4]) models which divide the computational domain into a finite number of compartments and simulate the time evolution of the numbers of molecules in each compartment; and
- (iii) macroscopic (deterministic) models which are written in terms of mean-field reaction-diffusion-advection partial differential equations (PDEs) for spatially varying concentrations [4].

I discussed connections between the modelling frameworks (i)–(iii), considering chemical reactions both at a surface [1, 5, 6] and in the bulk [3, 4]. I also presented and analysed hybrid (multiscale) algorithms which use models with a different level of detail in different parts of the computational domain [1, 7, 8]. The main goal of this multiscale methodology is to use a detailed modelling approach in localized regions of particular interest (in which accuracy and microscopic detail is important) and a less detailed model in other regions in which accuracy may be traded for simulation efficiency. I also discussed hybrid modelling of chemotaxis where an individual-based model of cells is coupled with PDEs for extracellular chemical signals [9, 10, 11, 12].

#### References

- 1 Erban, R., 2014. From molecular dynamics to Brownian dynamics. *Proceedings of the Royal Society A*, **470**:20140036.
- 2 Chen, W., Erban, R. and Chapman, J., 2014. From Brownian dynamics to Markov chain: an ion channel example. *SIAM Journal on Applied Mathematics*, **74**(1):208–235.
- 3 Erban, R. and Chapman, J., 2009. Stochastic modelling of reaction-diffusion processes: algorithms for bimolecular reactions. *Physical Biology*, **6**(4):046001.
- 4 Erban, R., Chapman, J. and Maini, P., 2007. A practical guide to stochastic simulations of reaction-diffusion processes. Lecture Notes. Available as: <http://arxiv.org/abs/0704.1908>.
- 5 Erban, R. and Chapman, J., 2007. Reactive boundary conditions for stochastic simulations of reaction-diffusion processes. *Physical Biology*, **4**(1):16–28.

- 6 Erban, R. and Chapman, J., 2007. Time scale of random sequential adsorption. *Physical Review E*, **75**(4):041116.
- 7 Robinson, M., Flegg, M. and Erban, R., 2014. Adaptive two-regime method: application to front propagation. *Journal of Chemical Physics*, **140**(12):124109.
- 8 Franz, B., Flegg, M., Chapman, J. and Erban, R., 2013. Multiscale reaction-diffusion algorithms: PDE-assisted Brownian dynamics. *SIAM Journal on Applied Mathematics*, **73**(3):1224–1247.
- 9 Erban, R. and Othmer, H., 2004. From individual to collective behavior in bacterial chemotaxis. *SIAM Journal on Applied Mathematics*, **65**(2):361–391.
- 10 Erban, R. and Othmer, H., 2005. From signal transduction to spatial pattern formation in E.coli: A paradigm for multi-scale modeling in biology. *Multiscale Modeling and Simulation*, **3**(2):362–394.
- 11 Franz, B. and Erban, R., 2013. Hybrid modelling of individual movement and collective behaviour. *Dispersal, individual movement and spatial ecology: A mathematical perspective* (edited by M. Lewis, P. Maini and S. Petrovskii), Springer, pp. 129–157.
- 12 Franz, B., Xue, C., Painter, K. and Erban, R., 2014. Travelling waves in hybrid chemotaxis models. *Bulletin of Mathematical Biology*, **76**(2):377–400.

### 3.13 Mesoscopic Simulation and Visualization in Systems Biology

Martin Falk (*Linköping University, SE*)

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**Main reference** M. Falk, “Visualization and Mesoscopic Simulation in Systems Biology,” Dissertation, Visualization Research Center, University of Stuttgart, 2013.

**URL** <http://elib.uni-stuttgart.de/opus/volltexte/2013/8474/>

In systems biology, the characteristics and complex interactions of all elements in a particular biological system are investigated using quantitative methods from systems theory. In the presentation, a simplified spatial cell model will be employed to study signal transduction pathways on a microscopic, cellular scale. The model is evaluated on the GPU with a particle-based simulation. Several visualization approaches will be presented, visualizing the simulation results interactively in different ways.

### 3.14 Modeling the cancer stem cell theory and tumor heterogeneity

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**Joint work of** Fornari, Chiara; Beccuti, Marco; Lanzardo, Stefania; Conti, Laura; Balbo, Gianfranco; Cavallo, Federica; Calogero, Raffaele; Cordero, Francesca

**Main reference** C. Fornari, M. Beccuti, S. Lanzardo, L. Conti, G. Balbo, F. Cavallo, R. A. Calogero, F. Cordero, “A Mathematical-Biological Joint Effort to Investigate the Tumor-Initiating Ability of Cancer Stem Cells,” *PLOS One*, 2014

**URL** <http://dx.doi.org/10.1371/journal.pone.0106193>

Tumor heterogeneity is one of the main expressions of tumor complexity, and it plays a crucial role in tumor fate influencing both tumor evolution and treatment responses. Understanding the intrinsically heterogeneous populations of cancer cells, which are their overall dynamics, and how their internal and external stimuli influence the different tumor outcomes are major challenges in the current cancer research.

The Cancer Stem Cell (CSC) hypothesis explains tumor heterogeneity as the result of a hierarchical organization made up of cells with varying proliferation capacities and tumorigenic potentials. CSCs drive tumor growth from the apex of this hierarchy, while their progeny (non-CSCs) have a limited proliferation capacity and constitute the majority of the tumor mass.

Nowadays, multidisciplinary approaches combining mathematical models with experimental assays are becoming relevant for the study of cancer. Therefore, to gain new insights into the composition of breast cancer we developed a compartmental tumor model [1] and then we expanded it with functional parameters encapsulating both the dynamic feedback loops among the heterogeneous cell populations and the microenvironment effects. The model was trained with experimental data to better understand the kinetics of CSCs and non-CSCs both *in vitro* and *in vivo*. Then, combining sensitivity analysis with analytic studies of model parameters [2], we identified those cell phenotypes which mostly influence tumor growth. We found indications that there exists a dynamic equilibrium among different phenotypes and that the dynamic variation of this equilibrium contributes to cancer initiation. Specifically, model results showed that the deregulation of CSC symmetric proliferation is the main responsible of a switching-like behavior which discriminates between tumorigenesis and unsustainable tumor growth.

#### References

- 1 Fornari C., Beccuti M., Lanzardo S., Conti L., Balbo G., Cavallo F., Calogero RA., Cordero F. *A mathematical-biological joint effort to investigate the tumor-initiating ability of CSCs*. PLOS One, 2014
- 2 Fornari C., Balbo G., Halawani SM., Ba-Rukab O., Ahmad AR., Calogero RA., Cordero F., and Beccuti M. *A versatile mathematical pipeline reveals how CSC fate influences tumor progression*. BMC Bioinformatics, [in press]

### 3.15 Computational Platform for Systems Biology

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In this talk, I will talk on computational platform for Systems Biology which consists of two topics. One is on CellDesigner (<http://celldesigner.org>) which is a modeling tool for biochemical and gene-regulatory networks [1]. The main feature of CellDesigner is that it supports standardized technology such as SBML (Systems Biology Markup Language) and SBGN (Systems Biology Graphical Notation), and has a facility to launch several simulators such as ODE based and SSA based solvers. Also it can integrate with existing databases so that users can annotate their model, import a model or kinetic laws, parameters from databases. The current version of CellDesigner is ver. 4.4, which runs on MacOSX, Linux and Windows (both on 32 and 64 bit architectures).

Another topic was on high-performance simulation on GPU. We parallelized ODE, SSA (non-spatial) and PDE solvers with hybrid (both coarse grained and fine-grained) approach. As a result, we achieved X10 speed up on ODE solvers compared with an implementation on CPU [2].

## References

- 1 A. Funahashi, Y. Matsuoka, A. Jouraku, M. Morohashi, N. Kikuchi, Norihiro and H. Kitano, “CellDesigner 3.5: a versatile modeling tool for biochemical networks”. Proceedings of the IEEE, 96:8 (2008).
- 2 K. Nakamura, K. Sumiyoshi, N. Hiroi and A. Funahashi, “Coarse grain parallelization and acceleration of biochemical ODE simulation using GPGPU”. In Proceedings of International Symposium on Nonlinear Theory and its Applications, (2012).

## 3.16 Multiscale modeling of sphingolipids metabolism

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**Joint work of** Anna Gambin; Weronika Wronowska; Agata Charzyńska; Karol Nienaltowski

**Main reference** A. Charzyńska, W. Wronowska, K. Nienaltowski, A. Gambin, “Computational model of sphingolipids metabolism,” arXiv:1411.2441v1 [q-bio.MN], 2014.

**URL** <http://arxiv.org/abs/1411.2441v1>

As suggested by the origin of the word, sphingolipids are mysterious molecules with various roles in antagonistic cellular processes such as autophagy, apoptosis, proliferation and differentiation. Moreover, sphingolipids have recently been recognized as important messengers in cellular signaling pathways. Notably, sphingolipid metabolism disorders have been observed in various pathological conditions such as cancer, neurodegeneration and inflammatory disorders.

The existing formal models of sphingolipid metabolism focus mainly on de novo ceramide synthesis or are limited to biochemical transformations of particular subspecies. Here, we propose the first comprehensive computational model of sphingolipid metabolism in human tissue. Contrary to the previous approaches, we use a model that reflects cell compartmentalization thereby highlighting the differences among individual organelles. In particular our model is applicable to the prediction of changes in the level of synthesis and secretion of chosen sphingolipids species. We model the dynamic of the biochemical network in means of ODE system. This approach can be easily extended to stochastic framework based on Continuous Time Markov Chains.

We focus on the activity of sphingosine-1-phosphate, as it acts on different levels of the organism organization and can be considered as a multiscale messenger. On the one hand it has been reported that S1P intracellularly regulates calcium release, and modulates histone acetylation via HDACs. On the other hand at the organismal level it can regulates organs and tissues activity through binding to the G protein-coupled receptors (S1PRs) that are differentially expressed in different cell types. Activation of S1PRs plays an important role in maintenance of endothelial and epithelial barrier integrity, vascularization and activation and migration of lymphocytes B and T.

Summarizing, the proposed model represents an excellent tool to predict the pleiotropic effect of S1P and other sphingolipids metabolism disregulations.

### 3.17 A Modular Framework for Biomodel Engineering

David Gilbert (Brunel University London, UK)

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**Main reference** Q. Gao, D. Gilbert, M. Heiner, F. Liu, D. Maccagnola, D. Tree, “Multiscale Modeling and Analysis of Planar Cell Polarity in the Drosophila Wing,” *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 10(2):337–351, 2012.

**URL** <http://dx.doi.org/10.1109/TCBB.2012.101>

Our group works on the development of modelling approaches to support both the analysis of multiscale systems, as well as the design of novel biosystems (Synthetic Biology). Modeling across multiple scales is a current challenge in Systems Biology, especially when applied to multicellular organisms. As part of our work, we have developed an approach to model at different spatial scales, using the concept of Hierarchically Colored Petri Nets (HCPN). We have applied HCPN to model a tissue comprising multiple cells hexagonally packed in a honeycomb formation in order to describe the phenomenon of Planar Cell Polarity (PCP) signaling in Drosophila wing. We have constructed a family of related models, permitting different hypotheses to be explored regarding the mechanisms underlying PCP. In addition our models include the effect of well-studied genetic mutations [1].

To explore the complex and high-dimensional solution space over the behaviours generated by such models, we developed a clustering methodology which combines principal component analysis (PCA), distance similarity and density factors through the application of DBScan. To facilitate the interpretation of clustering results and enable further analysis using model checking we applied a pattern mining approach aimed at generating high-level classificatory descriptions of the clusters’ behaviour in temporal logic [2]. Our models support the interpretation of biological observations reported in the literature. This work has been carried out in close collaboration with Monika Heiner and her group from BTU Cottbus – see entries in this document.

We have investigated the use of different geometries for spatial modelling applied to phase variation patterning in bacterial colony growth [4] also developed and implemented a spatio-temporal logic for checking multidimensional models [3]. Work is in progress to extend this to multiscale models – see the entry by Ovidiu Pârvu in this document.

#### References

- 1 Qian Gao, David Gilbert, Monika Heiner, Fei Liu, Daniele Maccagnola, David Tree: *Multiscale Modelling and Analysis of Planar Cell Polarity in the Drosophila Wing*. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 10(2):337–351, 2013
- 2 Daniele Maccagnola, Enza Messina, Qian Gao, David Gilbert: *A machine learning approach for generating temporal logic classifications of complex model behaviours*; Winter Simulation Conference (WSC’12), Berlin, Germany, December 9–12, 2012.
- 3 Ovidiu Pârvu, David Gilbert: *Automatic validation of computational models using pseudo-3D spatio-temporal model checking*; *BMC Systems Biology* 8(2014).
- 4 Ovidiu Pârvu, David Gilbert, Monika Heiner, Fei Liu, Nigel Saunders: *Modelling and Analysis of Phase Variation in Bacterial Colony Growth*. in *Proc. CMSB 2013*, Vienna, Springer, LNCS/LNBI, volume 8130, 78–91, 2013.

### 3.18 Quantitative modeling for Systems Biology.

Simon Hardy (*Université Laval – Québec, CA*)

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In this short talk, I will introduce my research and myself. As a computational biologist, my goal is to build dynamical models in interaction with experimentalists to interpret their data and make testable predictions. In a previous project published in the journal *Science Signaling*, I built a computational model of the cell signaling network activated by the beta-adrenergic G protein coupled receptor and regulating the activity of the transcription factor CREB in podocytes. This model was constrained by several experimental biochemical measurements. It predicted the presence of an unknown regulatory motif. This prediction was confirmed in vitro and validated in vivo. In my current work, my focus is on molecular and cellular neurobiology. My group is working on a modeling methodology to build integrated biophysical models of the CA1 neuron incorporating electrophysiology and cell signaling. We are also working on the regulation of mitochondrial metabolism by the calcium transferred from the endoplasmic reticulum. A third project of our group is the theoretical investigation of the nociception neural circuit in the dorsal horn.

#### References

- 1 Azeloglu, Evren U. and Hardy, Simon V. and Eungdamrong, Narat John and Chen, Yi-bang and Jayaraman, Gomathi and Chuang, Peter Y. and Fang, Wei and Xiong, Huabao and Neves, Susana R. and Jain, Mohit R. and Li, Hong and Ma'ayan, Avi and Gordon, Ronald E. and He, John Cijiang and Iyengar, Ravi: *Interconnected Network Motifs Control Podocyte Morphology and Kidney Function*. *Science signaling*, 2014, 7:311, ra12–ra12, DOI: 10.1126/scisignal.2004621

### 3.19 From Petri Nets to PDEs in 3 Minutes

Monika Heiner (*BTU Cottbus, DE*)

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**Main reference** M. Heiner, D. Gilbert, “BioModel Engineering for Multiscale Systems Biology,” *Progress in Biophysics and Molecular Biology*, 111(2-3):119–128, 2013.  
**URL** <http://dx.doi.org/10.1016/j.pbiomolbio.2012.10.001>

In my group at the Brandenburg Technical University in Cottbus, Germany, we have developed over the last 15 years a unifying Petri net framework comprising a family of related modelling languages – the traditional time-free Petri nets ( $\mathcal{PN}$ ) as well as quantitative, i. e. time-dependent Petri nets, such as

- stochastic Petri nets ( $\mathcal{SPN}$ ),
- continuous Petri nets ( $\mathcal{CPN}$ ), and
- (generalised) hybrid Petri nets ( $\mathcal{HPN}$ ).

These uncoloured Petri nets have been recently complemented by their coloured counterparts, thus comprising

- coloured qualitative Petri nets ( $\mathcal{PN}^c$ ),
- coloured stochastic Petri nets ( $\mathcal{SPN}^c$ ),
- coloured continuous Petri nets ( $\mathcal{CPN}^c$ ), and
- coloured (generalised) hybrid Petri nets ( $\mathcal{HPN}^c$ ).

Coloured Petri nets permit, among others, the convenient and flexible encoding of spatial attributes, and thus the modelling of processes evolving in time and space, which are usually considered as stochastic or deterministic reaction-diffusion systems by help of stochastic or deterministic partial differential equations (PDE). In our approach, the discretisation of space already happens on the modelling level, while traditionally the discretisation is left for the PDE integration method (FEM, FDM, FVM).

Our framework is supported by a related Petri net toolkit consisting basically of *SNOOPY*, *CHARLIE* and *MARCIE*, freely available on our website <http://www-dssz.informatik.tu-cottbus.de>. It has been applied to numerous case studies; those involving spatial aspects include:

- *C. elegans* vulval development composed of six cells [6],
- stochastic membrane systems built from nested active compartments [4],
- $Ca^{2+}$  channels arranged in two-dimensional space [5],
- phase variation in bacterial colony growth (stochastic model explored in two alternatives: cartesian and polar coordinates) [2, 8],
- Brusselator model to explore Turing patterns [7],
- Planar Cell Polarity (PCP) signalling in *Drosophila* wing building on two-level space: a tissue comprising multiple cells hexagonally packed in a honeycomb formation, with logical compartments within each cell [1].

Please see [3] and <http://multiscalepn.brunel.ac.uk/> for a brief introduction and more pointers to related literature, and [7] for a tutorial how to model reaction diffusion systems by help of coloured Petri nets.

#### References

- 1 Q Gao, D Gilbert, M Heiner, F Liu, D Maccagnola and D Tree: *Multiscale Modelling and Analysis of Planar Cell Polarity in the Drosophila Wing*. IEEE/ACM Transactions on Computational Biology and Bioinformatics, 10(2):337–351, 2013
- 2 D Gilbert, M Heiner, F Liu and N Saunders: *Colouring Space – A Coloured Framework for Spatial Modelling in Systems Biology*. In Proc. PETRI NETS 2013, Milano, Springer, LNCS, volume 7927, 230–249, 2013
- 3 M Heiner and D Gilbert: *BioModel Engineering for Multiscale Systems Biology*. Progress in Biophysics and Molecular Biology, 111(2-3):119–128, 2013
- 4 F Liu and M Heiner: *Modeling membrane systems using coloured stochastic Petri nets*. Nat. Computing, 12(4):617–629, 2013
- 5 F Liu and M Heiner: *Multiscale modelling of coupled  $Ca^{2+}$  channels using coloured stochastic Petri nets*. IET Systems Biology, 7(4):106–113, 2013
- 6 F Liu, M Heiner and M Yang: *Modeling and analysing biological systems using coloured hierarchical Petri nets, illustrated by C. elegans vulval development*. WSPC Journal of Biological Systems, 22(3):463–493, 2014
- 7 F Liu, MA Blätke, M Heiner and M Yang: *Modelling and simulating reaction-diffusion systems using coloured Petri nets*. Computers in Biology and Medicine, 53:297–308, 2014
- 8 O Pârvu, D Gilbert, M Heiner, F Liu and N Saunders: *Modelling and Analysis of Phase Variation in Bacterial Colony Growth*. in Proc. CMSB 2013, Vienna, Springer, LNCS/LNBI, volume 8130, 78–91, 2013.

### 3.20 Computational Steering of Multiscale Models

Mostafa Herajy (Port Said University, EG)

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Joint work of Heiner, Monika;

Main reference M. Herajy, M. Heiner, “Hybrid representation and simulation of stiff biochemical networks,” *Nonlinear Analysis: Hybrid Systems*, 6(4):942–959, 2012.

URL <http://dx.doi.org/10.1016/j.nahs.2012.05.004>

URL <http://www-dssz.informatik.tu-cottbus.de/DSSZ/Software/Snoopy#s4>

With the rapid increase of dimensions and sizes of biological models, it becomes imperative to accelerate the simulation process. Moreover, multiscale models come with additional challenges to the execution of model semantics. Thus speeding up the simulation is an essential step towards considering more complex biological phenomena. To achieve this goal, we need to improve the efficiency of the current simulation techniques as well as considering other methods to avoid repeating the same experiment different times such that we can ask “what-if” questions or to amend errors during simulation.

Improving the efficiency of current simulation algorithms can be done via different directions. One of these is to use hybrid simulation. Hybrid simulation of biochemical reaction networks integrates stochastic as well as deterministic approaches to simulate the same model. It can efficiently deal with species of abundant of molecules by assigning a deterministic solver to them, while it accurately simulates species with a few numbers of molecules by assigning a stochastic simulator to them. Using this technique, we have developed a new Petri net class called Generalized Hybrid Petri Nets (*GHPN*) [3] that integrates discrete and continuous places as well as stochastic and continuous transitions. Besides, a *GHPN* model can be simulated using both static and dynamic partitioning.

Nevertheless, going on the direction of improving the efficiency of the simulator cannot alone decrease the time of “dry-lab” experiments. For instance, during the testing of certain hypothesis, we repeat the simulation different times to play with several settings and trying different initial conditions. To this end, we can permit users to change the simulation parameters on the fly while the simulation is progressing. We call this technique computational steering. Thus we have developed and implemented a framework based on the Petri nets approach to allows users examine different paths during the running of the simulation [1]. Moreover, we have presented a Petri net simulation tool called Snoopy Steering and Simulation Server [2], S4 for short, which works as a stand-alone extension of *SNOOPY* [5]. The server permits users to share and interactively steer quantitative Petri net models during a running simulation. Moreover, users can collaborate by controlling the execution of a model remotely from different machines (clients).

#### References

- 1 Herajy, M., Heiner, M.: Petri net-based collaborative simulation and steering of biochemical reaction networks. *Fundamenta Informatica* (129), pp. 49–67 (2014)
- 2 Herajy, M., Heiner, M.: A Steering Server for Collaborative Simulation of Quantitative Petri Nets. In: Ciardo, G., Kindler, E. (eds.) *Proc. PETRI NETS 2014*. LNCS, vol. to appear. Springer (June 2014)
- 3 Herajy, M., Heiner, M.: Hybrid representation and simulation of stiff biochemical networks. *J. Nonlinear Analysis: Hybrid Systems* 6(4), pp. 942–959 (November 2012)
- 4 Herajy, M., Schwarick, M., Heiner, M.: Hybrid Petri Nets for Modelling the Eukaryotic Cell Cycle. *ToPNoC VIII*, LNCS 8100 pp. 123–141 (2013)

- 5 Heiner, M., Herajy, M., Liu, F., Rohr, C., Schwarick, M.: Snoopy – a unifying Petri net tool. In: Haddad, S., Pomello, L. (eds.) Proc. PETRI NETS 2012. LNCS, vol. 7347, pp. 398–407. Springer (2012)

### 3.21 From Networks to Function – Computational Models of Organogenesis

*Dagmar Iber (ETH Zürich – Basel, CH)*

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One of the major challenges in biology concerns the integration of data across length and time scales into a consistent framework: how do macroscopic properties and functionalities arise from the molecular regulatory networks and how do they evolve? Morphogenesis provides an excellent model system to study how simple molecular networks robustly control complex pattern forming processes on the macroscopic scale in spite of molecular noise, and how important functional variants can evolve from small genetic changes. Recent advancements in 3D imaging technologies, computer algorithms, and computer power now allow us to develop and analyse increasingly realistic models of biological control. To incorporate cellular dynamics and cell-cell interactions in our simulations, we have also recently developed a software tool that allows us to solve our regulatory network models on dynamic 2D and 3D tissue domains at cellular resolution. We use data-based modeling to arrive at predictive models of limb and brain development as well as of branching morphogenesis in lungs and kidneys. Moreover, we use modelling to define fundamental mechanism such as those that allow patterns to scale with the size of the embryonic domain and that provide growth control. In the workshop we discussed methods to facilitate parameter estimation for complex spatio-temporal models.

### 3.22 E-Cell system version 4: Development of an integrated platform for particle simulations

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Recently, various techniques for a reaction-diffusion system at the molecular resolution have been proposed in contrast to conventional concentration- and network-based approaches. Meanwhile, demand for the integrated environment including modeling, simulation, visualization and analysis increases.

Here, we present a novel simulation software, E-Cell System version 4, which provides an integrated platform with a fully scriptable, network-free, rule-based modeling environment, spatio-temporal data visualizations and a variety of simulation algorithms: an exact and event-driven particle-based method (the enhanced Greens Function Reaction Dynamics method) [1], the Reaction Brownian Dynamics method[2], a microscopic lattice-based method [3], the spatial Gillespie method, and non-spatial stochastic/deterministic methods. The E-Cell rule-based modeling environment is purely implemented on the Python programming

language, and allows seamless bindings with third-party libraries. Users can easily switch between various techniques with almost no change.

Moreover, for the whole-cell-scale simulation and high performance computers, the parallelization of these particle methods is under development.

### References

- 1 Koichi Takahashi, Sorin Tanase-Nicola, and Pieter Rein ten Wolde. *Spatio-temporal correlations can drastically change the response of a MAPK pathway*. Proc. Natl. Acad. Sci. USA, 2010.
- 2 Marco J. Morelli and Pieter Rein ten Wolde. *Reaction Brownian dynamics and the effect of spatial fluctuations on the gain of a push-pull network*. J. Chem. Phys., 2008.
- 3 Satya N. V. Arjunan and Masaru Tomita. *A new multicompartmental reaction-diffusion modeling method links transient membrane attachment of E. coli MinE to E-ring formation*. Syst. Synth. Biol., 2010.

## 3.23 Information in Biological Reaction Networks

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**Main reference** T. J. Kobayashi, “Implementation of Dynamic Bayesian Decision Making by Intracellular Kinetics,” Physical Review Letters, 104:228104, 2010.

**URL** <http://dx.doi.org/10.1103/PhysRevLett.104.228104>

Biological functions of cells implemented by intracellular reaction networks are inevitably subject to fluctuation and noise due to the intrinsic stochasticity of the reactions. Nonetheless several functions are very robust against such potential disturbance. In addition, cells can adaptively respond to the changing environment even though the state change of the environment is generally highly unpredictable. In order to understand the underlying principle and mechanisms of the robustness to the stochasticity and adaptation to uncertain environment, the notion of information can be a powerful tool to quantify the amount of relevant information on the environment transferred via noisy reaction networks.

In our work, we introduced the mathematical background and simple applications of the information theory [1, 2] with more detailed biological examples such as gradient sensing in chemotaxis. In addition, we also show the linkage between the information obtained and the gain of fitness enjoyed.

**Acknowledgements.** This work was supported by Platform for Dynamic Approaches to Living System from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

### References

- 1 T. J. Kobayashi, “Implementation of Dynamic Bayesian Decision Making by Intracellular Kinetics”. Physical Review Letters, **104**:228104 (2010).
- 2 T. J. Kobayashi, “Connection between Noise-Induced Symmetry Breaking and an Information Decoding Function for Intracellular Networks”. Physical Review Letters, **106**:228101 (2011).

### 3.24 Spatial stochastic reaction kinetics of bistable systems: A challenge for multiscale modeling

Marek Kochaneczyk (*Polish Academy of Sciences – Warsaw, PL*)

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**Joint work of** Kochaneczyk, Marek; Jaruszewicz, Joanna; Lipniacki, Tomasz

**Main reference** M. Kochaneczyk, J. Jaruszewicz, T. Lipniacki, “Stochastic transitions in a bistable reaction system on the membrane,” *Journal Royal Society Interface*, 10(84), 2013.

**URL** <http://dx.doi.org/10.1098/rsif.2013.0151>

In bistable reaction systems, transitions between steady states can involve either stochastic switching (in the whole, well-mixed reactor volume) or, for spatially extended (i. e., not well-mixed) systems, can result from the propagation of a front of the traveling wave. Interestingly, in spatial stochastic bistable systems these two modes of transition can favor distinct steady states [1], and their relative influence on the global system state depends on the diffusion coefficient and volume of the chemical reactor [2]. While the exact method of microscopic kinetic Monte Carlo simulation, which is appropriate for studying such systems numerically, is extremely compute-intensive, reliable stochastic and spatial simulation—capable of capturing subtle behaviors exhibited by bistable systems—poses a real challenge for multiscale modeling.

I will review shortly effects observed in spatial stochastic kinetics of a prototype bistable system of kinases and phosphatases interacting on the plasma membrane [2]. Additionally, an example of the travelling wave propagation in a bottle-shaped reactor of spatially varying noise strength will be presented and discussed in more detail.

#### References

- 1 Zuk PJ, Kochaneczyk M, Jaruszewicz J, Bednorz W, and Lipniacki T. (2012) Dynamics of a stochastic spatially extended system predicted by comparing deterministic and stochastic attractors of the corresponding birth–death process. *Phys Biol* **5**(9):055002.
- 2 Kochaneczyk M, Jaruszewicz J, and Lipniacki T. (2013) Stochastic transitions in a bistable reaction system on the membrane. *J R Soc Interface* **10**(84):20130151.

### 3.25 Colored Petri Nets for Multiscale Systems Biology

Fei Liu (*Harbin Institute of Technology, CN*)

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Due to the ability to produce data of the same phenomenon at different scales, modeling of biological systems shifts from single scales to multiple scales (multiscale systems biology). Traditional methods like Petri nets do not easily scale and thus become difficult to tackle this. In contrast, the multiscale challenges potentially could be tackled by colored Petri nets [1].

In our work, a colored Petri net framework has been developed [1, 2, 3], which can be divided into two levels: uncolored and colored. Each level comprises a family of related Petri net classes, sharing structure, but being specialized by their kinetic information. Specifically, the uncolored level contains qualitative (time-free) Petri nets ( $QPN$ ) as well as quantitative (time-dependent) Petri nets such as stochastic Petri nets ( $SPN$ ), continuous Petri nets ( $CPN$ ), and generalized hybrid Petri nets ( $GHPN$ ). The colored level consists of the colored counterparts of the uncolored level, thus containing colored qualitative Petri nets ( $QPN^c$ ),

colored stochastic Petri nets ( $\mathcal{SPN}^c$ ), colored continuous Petri nets ( $\mathcal{CPN}^c$ ), and colored generalized hybrid Petri nets ( $\mathcal{GHPN}^c$ ).

Colored Petri nets have been applied to investigate a variety of large-scale biological systems, proving its capability to solve many challenges imposed by multiscale systems biology. See some examples in [4, 5, 6]. In a next step, we will continue to explore the extensions of colored Petri nets and their application in multiscale modeling of systems biology, which is now challenging for biologists.

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## References

- 1 F. Liu. Colored Petri Nets for Systems Biology, PhD thesis. Cottbus, Germany: Department of Computer Science, Brandenburg University of Technology Cottbus, 2012.
- 2 M. Heiner, M. Herajy, F. Liu, C. Rohr, and M. Schwarick. Snoopy – a unifying Petri net tool. In Proc. PETRI NETS 2012, LNCS 7347, 2012: 398–407. Springer.
- 3 M. Heiner and D. Gilbert. Biomodel engineering for multiscale systems biology. Progress in Biophysics and Molecular Biology. 2013, 111(2–3): 119–128.
- 4 Q. Gao, D. Gilbert, M. Heiner, F. Liu, D. Maccagnola and D. Tree. Multiscale Modelling and Analysis of Planar Cell Polarity in the Drosophila Wing. IEEE/ACM Transactions on Computational Biology and Bioinformatics. 2013, 10(2):337–351.
- 5 F. Liu and M. Heiner. Multiscale modelling of coupled Ca<sup>2+</sup> channels using coloured stochastic Petri nets. IET Systems Biology, 2013, 7(4):106–113.
- 6 F. Liu and M. Heiner. Modeling membrane systems using colored stochastic Petri nets. Natural. Computing, 2013, 12(4):617–629.

## 3.26 Equivalence and simplification of reaction networks

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**Joint work of** Madelaine, Guillaume; Lhoussaine, Cedric; Niehren Joachim;

**Main reference** G. Madelaine, C. Lhoussaine, J. Niehren, “Attractor Equivalence: An Observational Semantics for Reaction Networks,” in Proc. of the 1st Int’l Conf. on Formal Methods in Macro-Biology, LNCS, Vol. 8738, pp. 82–101, Springer, 2014; pre-print available from author’s webpage.

**URL** [http://dx.doi.org/10.1007/978-3-319-10398-3\\_7](http://dx.doi.org/10.1007/978-3-319-10398-3_7)

**URL** [http://www.lifl.fr/~madelain/doc/2014\\_attractor\\_equivalence.pdf](http://www.lifl.fr/~madelain/doc/2014_attractor_equivalence.pdf)

We study simplification methods for reaction networks in systems biology [1]. Since we ignore all kinetic information, reaction networks can be identified as Petri Nets. Our approach is to follow methods developed in programming languages semantics, and apply them to reaction networks.

We first developed a new observational semantics for reaction networks that we call the attractor equivalence. An attractor is a terminal and strongly connected set of solutions. We consider that two networks are attractor equivalent if, in all possible contexts, they are able to converge to the same attractors, modulo an observation function, and if, when one network can diverge, the other can too. The observation function allow us to represent the fact that we cannot see all informations about molecules, or to neglect some particular molecules. A context, which is also a reaction network, represents a possible behaviour of the environment. Some context restrictions allow us to specify that some molecules are internal to the network, while others can be freely modify by the environment.

We then developed simplification rules, that reduce the size of the network while preserving the attractor equivalence, ie the reduced network will have the same final behaviour than the

initial one, in every context. The simplification is based on a static analyse of the reaction network. We can for instance delete intermediate molecules, merge some reactions (for instance for the Michaelis-Menten reduction), or do simplifications based on symmetries.

We are currently working on a deterministic version of the equivalence and simplification. In this case, the networks have kinetic functions, and the equivalence will preserve the reachability of the steady-states of the network, under some equilibrium conditions and modulo the observation functions.

### References

- 1 Madelaine G., Lhoussaine C., Niehren J. Attractor Equivalence: An Observational Semantics for Reaction Networks. In Proc. First International Conference on Formal Methods in Macro-Biology, 2014, Springer, LNCS, vol 8738, pp. 82–101.

## 3.27 Cancer systems biology at multiple levels

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**Joint work of** Maus, Carsten; Rybacki, Stefan; Uhrmacher, Adelinde M.;

**Main reference** C. Maus, S. Rybacki, A. M. Uhrmacher, “Rule-based multi-level modeling of cell biological systems,” *BMC Systems Biology*, 5:166, 2011.

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For obtaining deep knowledge about the complexity of the development and progression of certain malignant tumor diseases, it is important to study dynamic processes at different organizational levels of life. At the cellular level, for instance, cancer cells may behave differently in response to different stimuli, which can be, for example, quantified with the help of live- cell microscopy and sophisticated image analysis techniques including single-cell tracking. These approaches may reveal important spatial aspects of the system, like cell density, size and velocity of individual cells, or the influence of direct cell- to-cell contact on certain dynamic processes. By using specific fluorescent markers, it is also possible to visualize and quantify the individual progression through different phases of the cell division cycle. Based on these kinds of cellular level data, typically rather abstract phenomenological or statistical models can be developed in order to explain certain observations. By contrast, at the level of molecules, the focus of interest typically lies in quantifying protein expression, their activation, and interaction with each other, that can be measured by quantitative immunoblotting, mass spectrometry, flow cytometry, and fluorescence resonance energy transfer, for example. The typical goal here is to reconstruct regulatory processes like metabolic or signal transduction pathways, for which the development of mechanistic network models plays an important role. However, to explain certain observations, i. e., for a better understanding of the “big picture”, there is also an increasing need for combining different organizational levels within one model, which is often hampered by traditional modeling approaches. Therefore, we have developed ML-Rules [1], an accessible rule-based modeling language aiming at the formal description of multilevel models in a compact and concise manner, with explicit notions of nested hierarchies, states and behavior at any level, as well as upward and downward causation, i. e., interactions between components across different levels of the hierarchy.

### References

- 1 C Maus, S Rybacki, AM Uhrmacher. *Rule-based multi-level modeling of cell biological systems*. *BMC Systems Biology* 2011, 5:166.

### 3.28 Formal validation of multidimensional computational models

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**Joint work of** Pârnu, Ovidiu; Gilbert, David

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**URL** <http://dx.doi.org/10.1186/s12918-014-0124-0>

Systems biology is one of the emerging big data sciences of the 21<sup>st</sup> century whose main aim is to gain a systems level understanding of how biological organisms function. One of the main methods employed for achieving this aim is computational modelling because it enables discovering the mechanisms underpinning various biological functions (via explanatory models), respectively predicting the behaviour of biological systems when they are perturbed (via predictive models).

However any computational model is just an abstraction of a natural biological system and therefore needs to be validated before it is employed for real life applications. One of the most employed in silico computational model validation approaches is called model checking.

Traditionally model checking considers only how numeric properties (e.g. concentrations) change over time and is suitable for small scale systems (e.g. metabolic/signalling pathways). However the development of more complex, potentially multiscale computational models additionally requires capturing how spatial patterns/structures (e.g. microbial populations) and their geometric properties (e.g. area) change over time which are not considered by the traditional model checking approaches.

In order to address this challenge we developed and implemented a spatio-temporal model checking methodology which enables automatically validating (non-)spatial computational models relative to a specification. Models of the real systems are encoded as stochastic spatial discrete-event systems and are simulated to produce timeseries data from which spatial patterns are automatically detected and analysed using parameterised image processing tools. The computational models are validated against a formal specification encoded in the proposed spatio-temporal logic called Bounded Linear Spatial Temporal Logic (BLSTL). Given a computational model and a formal specification as input the model checker Mudi (made freely available at <http://mudi.modelchecking.org>) automatically decides if the model is valid relative to the specification. Our work is a precursor to the development of more complex multiscale computational models.

For more information and relevant references please visit <http://oviduparvu.com>.

### 3.29 A unifying Petri net framework for multi-scale modelling

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Our unifying Petri net framework for multi-scale modelling consists of three tools. First, the generic graph editor *SNOOPY* [2] is responsible for modelling systems in terms of Petri nets. *SNOOPY* includes different kinds of net classes, e.g., qualitative Petri nets, extended Petri nets, continuous Petri nets, stochastic Petri nets and hybrid Petri nets. In addition coloured versions of these net classes are available too. Furthermore, *SNOOPY* has some distinctive features, namely logical nodes and hierarchies via subgraphs. Logical nodes (fusion nodes)

come in two kinds logical places and logical transitions. So it's possible to model in a place oriented or transition oriented manner. Additionally, logical nodes can be used to connect parts of the model without the need of arcs running through the whole model and destroying the layout.

Second, the advanced analysis tool *MARCIE* [1]. It incorporates qualitative analysis of bounded Petri nets using a symbolic state space representation with Interval Decision Diagrams (IDDs), checking standard properties like reversibility, liveness and dead states, computing strongly connected components and CTL model checking. It is possible to make numerical analysis of bounded (generalised) stochastic Petri nets. This is done using an IDD-based “on-the-fly” continuous time Markov chain representation. So it is possible to do transient and steady-state analysis, as well as CS(R)L model checking in a multi-threaded way. Another feature of *MARCIE* is the simulative analysis of unbounded (extended) stochastic Petri nets using stochastic simulation algorithms (SSA). Here, transient and steady-state analysis and PLTLc model checking is available.

Last but not least is *CHARLIE* [3], a tool for static analysis of the net structure including siphon trap property, place/transition invariants and dependent sets. It includes some dynamic analysis too. This is based on an explicit reachability graph representation. Therefore it's useful for small and medium sized state spaces. It features checking of liveness, reversibility and dead states, explicit CTL/LTL model checker, path search, visualisation of the reachability and coverability graph, analysis of time(d) Petri nets and computation of shortest/longest paths.

In summary, our framework is well prepared for the challenges of multi-scale modelling.

## References

- 1 M Heiner, C Rohr and M Schwarick: *MARCIE – Model checking And Reachability analysis done efficiEntly*; In Proc. PETRI NETS 2013, Milano, Springer, LNCS, volume 7927, 389–399, June 2013.
- 2 M Heiner, M Herajy, F Liu, C Rohr and M Schwarick: *Snoopy – a unifying Petri net tool*; In Proc. PETRI NETS 2012, Hamburg, Springer, LNCS, volume 7347, 398–407, June 2012.
- 3 J Wegener, M Schwarick and M Heiner: *A Plugin System for Charlie*; In Proc. International Workshop on Concurrency, Specification, and Programming (CSP 2011), Biaystok University of Technology, ISBN: 978-83-62582-06-8, pages 531–554, September 2011.

## 3.30 Bayesian methodologies in statistical systems biology

*Guido Sanguinetti (University of Edinburgh, GB)*

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Systems biology models often exhibit rich nonlinear dynamics. These are achieved through the use of often large models with many parameters; normally, such parameters are hard to measure experimentally to the required precision. These problems are further exacerbated in multiscale spatial problems, where spatial inhomogeneity issues could effectively turn the parameters in spatially dependent functions.

Bayesian statistics provide a powerful framework for incorporating partial observations in models of biological systems, giving a mathematically consistent formal framework for uncertainty quantification and statistical prediction. In the talk, I will explain with examples taken from my own work how Bayesian ideas can be used effectively in systems biology models.

The basic intuition is formalised around the concept of *hierarchical Bayesian modelling*. In its simplest instantiations, a model constitutes of three layers: a parameter layer, incorporating prior beliefs about parameters; a dynamical layer, incorporating a stochastic model of the system behaviour conditioned on parameter values; and an observation layer, modelling explicitly the observation mechanism and its intrinsic error.

This simple framework can be adapted to spatially distributed systems by using a basis function projection: the spatially distributed process is reduced to a finite dimensional dynamical system by projecting onto a finite set of basis functions, and shifting the stochastic dynamics onto the coefficients of this basis function decomposition.

### 3.31 Cell simulation – towards in silico prediction of phenotype from genotype

*Koichi Takahashi (Osaka University, JP)*

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Can we know, by merely looking at a genome sequence in ATGC, what this organism would look like, how long it would live, what kind of food and environment it would prefer? Direct prediction of phenotypes (biological features) from genotypes (DNA sequence) grown in a specific environment is a holy grail in molecular biology. We would not see the development of this technology in its complete form within a decade or two – however, at the same time, can we imagine life science in the 22nd century without it?

After the establishment of the E-Cell Project in 1996, we developed the first whole genome-scale model of a virtual organism with 127 genes in 1999. Since then we have been developing a set of cell simulation technologies along two axes. The first axis is the completeness of the model measured in terms of the model's coverage of the genome (how many genes are modeled properly). For this, currently we are working on a model of *Escherichia coli*, a popular prokaryotic model organism. The second axis that we defined is the granularity of the model. Many cell simulations suffer from lack of quantitative predictive power, part of which caused by negligence of details; such as molecular localizations in the cell and molecular crowding (extremely high density of intracellular macromolecules). I introduced our high-performance computational technology portfolio, including a microscopic lattice reaction-diffusion method Spatiocyte, and an exact particle method called the enhanced Green's Function Reaction Dynamics. In addition to simulation methods, I additionally introduced our recent developments in the area of simulated fluorescent microscopy, which makes possible direct comparisons between simulations and fluorescent imaging experiments at the level of individual molecules.

### 3.32 Spying “Minorities” in the Cell

*Yuichi Togashi (Hiroshima University, JP)*

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We often model biochemical processes using differential equations of concentrations (reaction rate equations or reaction-diffusion equations). When we use such equations, we implicitly assume that molecules are memoryless (no internal dynamics), tiny (no excluded volume), and many (no finite-size fluctuations). However, in biological cells, these assumptions are

not always fulfilled. We are especially focused on the effects of small numbers of molecules. Each cell has only one to a few copies of DNA, and also many kinds of proteins occur in small numbers [1].

We have shown that for such rare chemicals, not only continuous finite-size fluctuations but also molecular discreteness may matter. We considered two types of discreteness: discreteness in numbers (integerness) [2, 3], and spatial discreteness (finite distances between molecules) [4]. We demonstrated by stochastic simulations that these two kinds of discreteness may lead to novel transitions not seen with the corresponding differential equations of continuous concentrations.

DNA is the ultimate “minority” in the cell. Furthermore, protein machines working on DNA are not always abundant. Suppose that if these machines exist in large numbers, each gene is efficiently searched by the machines and regularly expressed. However, nature preferred interactions between small numbers. The nucleus is crowded and heterogeneous, which may further restrict and modulate the access of molecules. These factors should in general make the behavior stochastic and unstable. Are there any mechanisms to cancel the instability, or any advantages to do so? We are now tackling this question together with experimentalists [5].

### References

- 1 Y. Taniguchi, P. J. Choi, G.-W. Li, H. Chen, M. Babu, J. Hearn, A. Emili, and X. S. Xie, “Quantifying *E. coli* proteome and transcriptome with single-molecule sensitivity in single cells”, *Science* **329**, 533 (2010).
- 2 Y. Togashi and K. Kaneko, “Transitions induced by the discreteness of molecules in a small autocatalytic system”, *Phys. Rev. Lett.* **86**, 2459 (2001).
- 3 Y. Togashi and K. Kaneko, “Switching dynamics in reaction networks induced by molecular discreteness”, *J. Phys. Cond. Matt.* **19**, 065150 (2007).
- 4 Y. Togashi and K. Kaneko, “Molecular discreteness in reaction-diffusion systems yields steady states not seen in the continuum limit”, *Phys. Rev. E* **70**, 020901 (2004).
- 5 <http://www.paradigm-innovation.jp/> (Spying Minority in Biological Phenomena, 23115007) and <http://www.mls.sci.hiroshima-u.ac.jp/chrom/en/> (Platform for Dynamic Approaches to Living System), supported by MEXT, Japan.

### 3.33 Work on spatial modeling and simulation in cell biology at the modeling and simulation group in Rostock

Adelinde M. Uhrmacher (Universität Rostock, DE)

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The focus of my research group is on developing modeling and simulation methods and their application in different areas. Among those applications, cell biology has played a central role for more than a decade. Therefore, our methodological developments focus on supporting multi-level, spatial modeling and simulation. With *Space- $\pi$* , we extended the  $\pi$ -calculus by time and space to support the modeling of concurrent processes in continuous space. Processes are attributed with a position and a movement function, which allow them to move individually in continuous space and to react if the reaction radii of two reactands become sufficiently close [5]. *Attributed- $\pi$* , a colored extension of the stochastic  $\pi$ -calculus, equips processes with attributes and constrains communication between processes based

on these attributes [6]. It allows to model stochastic reaction diffusion systems on a grid as well as dynamic compartments. Inspired by the features supported in attributed- $\pi$ , we developed a rule-based domain-specific language, i. e., *ML-Rules*, which combines dynamically nested species, attributes assigned to species, and reactions being constrained according to these attributes [7]. A more recent refinement allows also to apply functions on solutions, in addition to functions on attributes and rates. Fusion and fission of compartments, endocytosis, and grid-based reaction-diffusion processes can be described in a compact manner. *ML-Space*, the latest addition to our family of spatial modeling and simulation approaches, adapts the syntax of *ML-Rules* and combines it with a spatial hybrid semantics which integrates Brownian Dynamics in continuous space, dynamically nested compartments, and stochastic reaction-diffusion on a grid [1]. Thereby, dynamics with different spatial resolutions and excluded volume effects can be studied. To support a more efficient execution of spatial models, our focus has been on approximate, adaptive algorithms, e. g., [4]. To put the developed methods to test, we aim at answering concrete questions from cell biology, e. g., what signaling mechanisms control the  $\beta$ -catenin dynamics of human neural progenitor cells during early differentiation [8, 3], or why do actin filaments of osteoblasts mimick the structure of the micro-topography they grow on [2].

## References

- 1 A. T. Bittig, F. Haack, C. Maus, and A. M. Uhrmacher. Adapting rule-based model descriptions for simulating in continuous and hybrid space. In *Proceedings of the 9th International Conference on Computational Methods in Systems Biology*, CMSB'11, pages 161–170, New York, NY, USA, 2011. ACM.
- 2 A. T. Bittig, C. Matschegewski, J. B. Nebe, S. Stahlke, and A. M. Uhrmacher. Membrane related dynamics and the formation of actin in cells growing on micro-topographies: A spatial computational model. *BMC Systems Biology*, 8:106, 2014.
- 3 F. Haack, H. Lemcke, R. Ewald, T. Rharass, and A. Uhrmacher. Spatio-temporal model of endogenous ros and raft-dependent wnt/beta-catenin signaling driving cell fate commitment in human neural progenitor cells. *Plos Computations Biology*, 2015 (accepted).
- 4 M. Jeschke, R. Ewald, and A. M. Uhrmacher. Exploring the performance of spatial stochastic simulation algorithms. *Journal of Computational Physics*, 230(7):2562–2574, 2011.
- 5 M. John, R. Ewald, and A. Uhrmacher. A spatial extension to the pi calculus. In *Electronic Notes in Theoretical Computer Science*, volume 194, pages 133–148, Amsterdam, The Netherlands, 2008. Elsevier Science Publishers B. V.
- 6 M. John, C. Lhoussaine, J. Niehren, and A. Uhrmacher. The attributed pi-calculus with priorities. *Transactions on Computational Systems Biology XII*, 5945/2010:13–76, 2010.
- 7 C. Maus, S. Rybacki, and A. M. Uhrmacher. Rule-based multi-level modeling of cell biological systems. *BMC Systems Biology*, 5:166, October 2011.
- 8 O. Mazemondet, M. John, S. Leye, A. Rolfs, and A. M. Uhrmacher. Elucidating the sources of  $\beta$ -catenin dynamics in human neural progenitor cells. *PLOS-One*, 7(8):1–12, 2012.

### 3.34 A short introduction into rule-based spatial multi-level modeling and simulation

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Rule-based modeling has shown to be a powerful approach for modeling intracellular networks, which are characterized by rich molecular diversity [7].  $\kappa$ -calculus [6] and BioNetGen Language (BNGL) [10] are possibly the most widely used rule-based languages for cell biological systems and are supported by a suite of different simulators. They have been and are still joined by many others. The discussion will necessarily be restricted to only a few selected ones, which hopefully still will give an impression on the role of rule-based approaches for multi-level spatial modeling and simulation. Many rule-based approaches, like the  $\kappa$ -calculus, allow describing stochastic reaction diffusion dynamics on a grid. The role of capturing additional compartmental and, possibly, inter-cellular dynamics, is reflected in more recent developments like React(C) [12], ML-Rules [1], Formal Cellular Machinery [4], or Colored Stochastic Multi-Level Multiset Rewriting (CSMMR) [15]. The desire to describe spatial dynamics of discrete molecules in continuous space has led to further developments, like equipping  $\kappa$ -calculus with an alternative Brownian Dynamics [13], using BNGL as input to Brownian Dynamics simulators [1, 8], or adapting the syntax of ML-Rules and combining it with a hybrid simulator which integrates compartmental, stochastic reaction-diffusion, and Brownian Dynamics [2]. Thus, the modeler can select from a portfolio of different rule-based modeling approaches. However, the use of these approaches depends not only on the supported features of the modeling language, but also on the availability and efficiency of simulators (and means for analyzing the model, e. g., for parameter estimation [3]). Developing efficient simulators is anything but trivial [5, 11]. The more expressive the language the more effort is often required in executing those models, cp.[12, p.355], and the more elaborate execution algorithms have to be [9]. This puts more recent approaches that aim at a higher expressiveness at a disadvantage referring to efficiency of execution – which can only be balanced if modeling features are truly needed in applications. The case studies of this Dagstuhl seminar shall help answering this question.

#### References

- 1 S. S. Andrews, N. J. Addy, R. Brent, and A. P. Arkin. Detailed simulations of cell biology with smoldyn 2.1. *PLoS Computational Biology*, 6(3), 2010.
- 2 A. T. Bittig, F. Haack, C. Maus, and A. M. Uhrmacher. Adapting rule-based model descriptions for simulating in continuous and hybrid space. In *Proceedings of the 9th International Conference on Computational Methods in Systems Biology, CMSB'11*, pages 161–170, New York, NY, USA, 2011. ACM.
- 3 L. Calzone, F. Fages, and S. Soliman. Biocham: an environment for modeling biological systems and formalizing experimental knowledge. *Bioinformatics*, 22(14):1805–1807, 2006.
- 4 T. C. Damgaard, E. Højsgaard, and J. Krivine. Formal cellular machinery. *Electr. Notes Theor. Comput. Sci.*, 284:55–74, 2012.
- 5 V. Danos, J. Feret, W. Fontana, and J. Krivine. Scalable simulation of cellular signaling networks, invited paper. In Z. Shao, editor, *Proceedings of the Fifth Asian Symposium on Programming Systems, APLAS '2007, Singapore*, volume 4807 of *Lecture Notes in Computer Science*, pages 139–157, Singapore, 29 November – 1 December 2007. Springer, Berlin, Germany.

- 6 V. Danos and C. Laneve. Formal molecular biology. *Theoretical Computer Science*, 325(1):69–110, 2004. Computational Systems Biology.
- 7 J. R. Faeder. Toward a comprehensive language for biological systems. *BMC Biology*, 9(68), Oct. 2011.
- 8 G. Gruenert, B. Ibrahim, T. Lenser, M. Lohel, T. Hinze, and P. Dittrich. Rule-based spatial modeling with diffusing, geometrically constrained molecules. *BMC Bioinformatics*, 11:307, 2010.
- 9 T. Helms, M. Luboschik, H. Schumann, and A. M. Uhrmacher. An approximate execution of rule-based multi-level models. In *Proceedings of the 11th International Conference on Computational Methods in Systems Biology*, 2013.
- 10 W. Hlavacek, J. Faeder, M. Blinov, R. Posner, M. Hucka, and W. Fontana. Rules for modeling signal-transduction systems. *Science STKE*, 344, 2006.
- 11 J. S. Hogg, L. A. Harris, L. J. Stover, N. S. Nair, and J. R. Faeder. Exact hybrid particle/-population simulation of rule-based models of biochemical systems. *PLoS Computational Biology*, 10(4), 2014.
- 12 M. John, C. Lhoussaine, J. Niehren, and C. Versari. Biochemical reaction rules with constraints. In *European Symposium on Programming Languages*, 2011.
- 13 M. Klann, L. Paulevé, T. Petrov, and H. Koepl. Coarse-grained brownian dynamics simulation of rule-based models. In A. Gupta and T. A. Henzinger, editors, *Computational Methods in Systems Biology – 11th International Conference, CMSB 2013, Klosterneuburg, Austria, September 22-24, 2013. Proceedings*, volume 8130 of *Lecture Notes in Computer Science*, pages 64–77. Springer, 2013.
- 14 C. Maus, S. Rybacki, and A. M. Uhrmacher. Rule-based multi-level modeling of cell biological systems. *BMC Systems Biology*, 5:166, October 2011.
- 15 N. Oury and G. D. Plotkin. Multi-level modelling via stochastic multi-level multiset rewriting. *Mathematical Structures in Computer Science*, 23(2):471–503, 2013.

## 4 Working Groups

### 4.1 Simulating macromolecular crowding with particle and lattice-based methods (Team 3)

*Steven S. Andrews, Satya N. V. Arjunan, Gianfranco Balbo, Arne T. Bittig, Jerome Feret, Kazunari Kaizu, and Fei Liu*

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**Abstract.** Many simulation algorithms have been developed to help model spatial structure in cellular systems, each of which is intended to represent reaction dynamics with high spatial resolution. In this study, we simulated the effects of macromolecular crowding on biochemical reaction rates to investigate which method actually performs best in practice. All 5 simulators investigated showed that diffusion-limited reaction rates decreased monotonically with the fractional crowder occupancy and activation-limited reactions exhibited an initial reaction rate increase with crowder occupancy (due to excluded volume effects). The eGFRD simulations were presumably highly accurate, but were too computationally intensive to be ideal for this problem. The Smoluchowski method as implemented in Smoldyn had simulation parameters that could be connected directly to physical parameters, and did not appear to exhibit simulation artifacts. The Smoluchowski method as implemented in NL-space produced qualitatively similar diffusion-limited results, but did not show a change of dynamics when changing to activation-limited conditions. Spatiocyte used a microscopic lattice, which enabled it to run very fast but introduced lattice artifacts in the results. Finally, we did not collect quantitative results with Kappa, but instead observed that Kappa can be used for this type of problem. Overall, this study showed that the detailed simulation methods substantially affect the results and that each of these simulators can still be improved.

#### 4.1.1 Introduction

Many different biochemical simulation algorithms have been developed that are each intended to represent intracellular reaction dynamics with high spatial resolution and single-molecule precision [1]. These include Green's Function Reaction Dynamics [24], the Smoluchowski method as implemented in Smoldyn [4], the microscopic lattice method as implemented in Spatiocyte [5], and the particle-based method as implemented in NL-space [7, 8]. In addition, the next subvolume method [11] works at a slightly lower level of precision but is also intended to represent spatial detail accurately. It is straightforward to describe the differences between these methods, which we do below. However, the important question is how these algorithms actually perform in practice, which is not obvious from their descriptions. An understanding of this performance is clearly necessary for selecting the algorithm that is most appropriate for a specific modeling task. In this work, we investigated algorithm performance by comparing the abilities of the above-mentioned algorithms to accurately model bimolecular reaction rates in crowded spaces. This is a good test problem because crowded spaces are intrinsically difficult to simulate well.

Crowded spaces are also biologically important. In 1982, Fulton published that actively growing cells are about 17 to 26 percent protein and that red blood cells are about 35 percent protein [14]. These numbers are still commonly accepted. The vast majority of these proteins, and other macromolecular species such as RNAs and ribosomes, typically do not participate directly in any particular reaction that is of interest, but influence it indirectly through

volume exclusion, diffusion inhibition, and other effects. As such, cellular components can be classified as “reactants”, which engage in the reaction of interest, and “crowders”, which comprise everything else. Macromolecular crowding has several effects, including slowing diffusion, stabilizing protein folding, and accelerating bimolecular reactions, all of which have been reviewed extensively [26, 25, 16, 12]. Of these, our focus was on bimolecular reaction rates.

#### 4.1.2 Description of simulation methods

##### Reaction models

The simulation methods that we investigated are based upon a couple of basic reaction models. Consider the generic irreversible chemical reaction  $A + B \rightarrow C$ , which has reaction rate constant  $k$ . We define this reaction rate constant as the mass action reaction rate when the system is at steady-state. That is,  $k$  is defined from the mass action reaction kinetics equation  $d[C]/dt = k[A][B]$ , where square brackets represent chemical concentrations.

In the Smoluchowski model [21], A and B molecules diffuse according to mathematically ideal Brownian motion, meaning that molecules move with infinitely detailed random trajectories. These molecules do not interact with others of the same species, including through excluded volume effects. However, when A and B molecules collide together, where a collision is defined as their centers being separated by a distance equal to the sum of the two molecular radii, they react immediately to form a C molecule. From Smoluchowski’s work [21], the steady-state reaction rate constant is

$$k = 4\pi\sigma D \quad (1)$$

where  $\sigma$  is the sum of the A and B radii and  $D$  is the sum of the A and B diffusion coefficients. This reaction rate is limited solely by diffusion, leading to its being called the diffusion-limited reaction rate.

The Collins and Kimball model [9] extends the Smoluchowski model by treating collisions between A and B molecules with the radiation boundary condition [10] rather than the absorbing boundary condition. In concept, this means that A and B molecules have a small probability of reaction at each collision, so they collide multiple times before they either react or diffuse apart without reacting. The assumption of mathematically ideal diffusion makes the actual model slightly more complicated than this because all dynamics need to be taken in the limit of small diffusive step sizes. In particular, it implies that any single collision between A and B molecules is essentially certain to be followed by an infinite number of collisions and that the reaction probability at each individual collision is infinitesimal. We refer the reader elsewhere for more thorough descriptions [20]. The result of this radiation boundary condition assumption is that the steady-state reaction rate arises from a combination of the diffusion-limited reaction rate, which gives the rate of initial collisions, and also the “intrinsic” reaction rate, which gives the rate of reaction after the first collision. The intrinsic reaction rate is also called the activation-limited reaction rate because it is the observed rate when the chemical reaction is strictly limited by molecules attaining sufficient activation energy to react, and not by the rate of diffusive collisions. In a form introduced by Noyes [18], the Collins and Kimball reaction rate constant is

$$\frac{1}{k} = \frac{1}{4\pi\sigma D} + \frac{1}{k_{int}} \quad (2)$$

where  $k_{int}$  is the intrinsic reaction rate constant.

The reaction-diffusion master equation model is yet a third model. It differs from the Smoluchowski and Collins and Kimball models in that it is based upon a macroscopic description rather than a microscopic description. It combines the assumptions of Fick's law for chemical diffusion [6] and mass action reaction kinetics for chemical reactions. For our particular example, the spatially-dependent concentrations of A, B, and C molecules change over time according to

$$\begin{aligned} [\dot{A}] &= D_A \nabla^2 [A] - k[A][B] \\ [\dot{B}] &= D_B \nabla^2 [B] - k[A][B] \\ [\dot{C}] &= D_C \nabla^2 [C] + k[A][B] \end{aligned} \tag{3}$$

where time and spatial dependencies are implied but not shown for the chemical concentrations.

### Enhanced Green's Function Reaction Dynamics

Enhanced Green's Function Reaction Dynamics (eGFRD) is a particle-based method that simulates the Collins and Kimball reaction model exactly [23]. In it, non-overlapping spherical protective domains are drawn around each particle or pair of particles. Then, random times are drawn from the appropriate probability densities for the possible events that could happen, including particles diffusing to the edges of their domains, single particles reacting through unimolecular reactions, and pairs of particles reacting with each other. The smallest of these times is chosen and that particular event is performed. The system is then updated as necessary, which typically includes the computation of at least some new protective spheres and event times. Then, the next event in the queue is chosen, and so forth. Because the time is stepped from one reaction to the next, this is an event-based algorithm. See Takahashi and ten Wolde [23] for details.

### Smoluchowski dynamics as implemented in Smoldyn

Smoldyn simulations perform a discrete-time version of the Smoluchowski model, using fixed time-steps [4]. At each time-step, Smoldyn displaces each molecule, on each spatial coordinate, by a value chosen from a Gaussian distributed probability density in order to simulate diffusion. It ignores all molecule interactions at this point. Next, Smoldyn performs surface interactions [2]. In the case of inert impermeable surfaces, such as those that we used in this work, it simulates reflection off of the surfaces using ballistic molecular trajectories. These are not based on the assumption that molecules in solution move with long straight-line trajectories, which they do not, but instead on the solution for the probability density of ideally diffusing molecules near planar surfaces, which is simulated exactly using ballistic trajectories [4]. Then, Smoldyn executes reactions for each A-B molecule pair that is separated by a "binding radius" or less. Smoldyn computes this binding radius before the simulation begins from the user's choices of reaction rate constant, the simulation time step, and the A and B diffusion coefficients so that the simulated steady-state reaction rate will be the same as the user's requested reaction rate constant. Although Smoldyn's reaction probability density upon collision is 1, as it is in the Smoluchowski model, Smoldyn actually simulates reaction dynamics in closer agreement with the Collins and Kimball model due to the fact that molecules can diffuse relatively long distances in each time step [4]. The choice of the simulation time step determines where the simulated reaction dynamics are on the continuum between being diffusion-limited and activation-limited.

### Smoluchowski dynamics as implemented in ML-Space

ML-Space simulates reactions in a similar manner as Smoldyn. However, molecules in ML-Space have assigned radii. After ML-Space diffuses a molecule by Gaussian-distributed displacements, as in Smoldyn, it looks for molecule pairs with overlapping radii. If the molecules in the pair are non-reactive, the displacement is reversed and another random displacement is attempted a (customizable) number of times before the last displacement is applied only partially such that the molecule at most touches another. Excluded volume effects are thus covered. If molecules are reactive (as specified in ML-Space's own attributed rule-based language), the respective changes (molecule property changes, replacement, consumption) are applied, the original collision is resolved, if necessary (i. e. if neither is consumed), by moving the colliding molecules apart such that they touch but not overlap, and to-be-produced entities, if present, are placed near the collision site without overlapping any present particles. Such a rule application may fail due to spatial constraints, i. e. non-resolvable collisions or no space for to-be-produced entities. The probability with which a reaction execution shall be attempted on collision can be taken from the ratio of the desired macroscopic rate constant and the theoretical diffusion-limited reaction rate arising from Smoluchowski's equation (1).

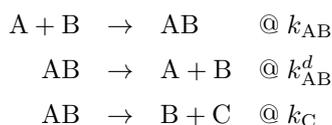
The main goal of ML-Space is to bring together individual-based simulation of larger spatial entities (large molecules or entire biological compartments) and population-, reaction-diffusion-based simulation of small particles as in the Next Subvolume Method [11]. However, we here focus on the purely continuous-space part, not the hybrid simulator.

### Microscopic lattice method as implemented in Kappa

Kappa is a leading language for rule-based modeling (for defining the species and reactions that arise in the formation of multimeric complexes; [13]) and is also software for the same rule-based modeling. Even if spatial extension exists [22], in this work we developed a model in the core of Kappa, thanks to a non-spatial stochastic simulator that runs the Gillespie algorithm [15]. Our goal is to implement the Microscopic lattice method, primarily as an exercise to see whether this could be done.

More precisely, the simulation is done in three steps.

1. The first step is a self-assembling of the lattice of locations. Indeed, space is encoded as a rectangular box of agents, each agent denotes a location being connected to its six neighboring agents through some sites the name of which specifies the direction. So as to avoid border effects, each face of the cube is connected to its opposite one, so that particles can exit from one face and reenter through the opposite one.
2. The second step consists in spawning particles at random in the rectangular box. We assume that each location can contain at most one particle. We consider five kinds of particles: A, B, C, AB, and D. At the beginning, the system contains particles of kinds A, B, and C only.
3. The third step consists in diffusing the particles and letting them react according to the following reactions:



It is worth noticing that the particles of kind D do not react. The first reaction can apply only to adjacent particles. Moreover, the last two reactions require an adjacent location

to be free. Moreover, each particle diffuses to adjacent free locations at respective rates  $d_A$ ,  $d_B$ ,  $d_{AB}$ ,  $d_C$ , and  $d_D$  along each of the six directions.

At each algorithm iteration, the next event (including diffusion of a molecule from one location to its neighboring one and reactions of molecules within adjacent locations) is selected according to its propensity, and the time between two consecutive events is randomly selected according to an exponential law the parameter of which is the overall amount of the propensities of all the potential events. Then, the algorithm repeats. Simulation stops when there are only 10 instances of As left in the system (either free or in AB).

### Microscopic lattice method as implemented in Spatiocyte

Spatiocyte represents space using a fine hexagonal close-packed lattice, in which each lattice site can contain up to one molecule [5]. It performs events using a combination of event-driven and time-driven methods. For diffusion, all molecules that share a diffusion coefficient (e.g. those of the same species) are diffused periodically, at the frequency which produces the correct diffusion coefficient. Molecules cannot share lattice sites, so any non-reactive collisions result in molecules being put back to their starting locations. On the other hand, if two molecules collide and can react, then they react with a pre-determined probability that is calibrated to yield the correct reaction rate; if they don't react, then they are separated like other non-reactive collisions. Unimolecular reactions are performed with event-driven methods, using the Gillespie algorithm [15]. Spatiocyte chooses the event with the earliest time, which may be diffusive or unimolecular reactive, and executes it. Then, Spatiocyte updates the system and repeats.

#### 4.1.3 Theory for crowding effects

Crowding affects irreversible association reactions in two primary ways. First, the crowders occupy volume, which reduces the volume available to the reactants and thus increases their effective concentrations. This increases reaction rates. Also, crowding slows diffusion, which reduces the rate at which reactants collide with each other. This decreases reaction rates. Although these qualitative effects have been well-known for many years, the actual amount by which crowding modifies bimolecular reaction rates is still an open question. Of particular note is recent modeling work by Kim and Yethiraj [17], who showed both the reaction acceleration and deceleration effects. However, their results were not based entirely on physical parameters, but instead were functions of their simulation parameters (their reaction probability upon collision), which limits their value.

The effects of crowding on reaction rates can be estimated some cases. Assume that reactions are irreversible, the crowders are stationary, and the reactants have sufficiently low concentrations that their excluded volume interactions can be ignored. In the activation-limited extreme, in which diffusion timescales are much faster than reaction timescales, the reactants are well-mixed throughout the available volume, meaning that which is not occupied by crowders. This volume is  $V_{avail.} = V_{total}(1 - \phi)$ , where  $V_{total}$  is the total system volume and  $\phi$  is the fractional volume occupancy by crowders. From eq. 2, the reaction rate constant is simply  $k_{int}$ . Within the available volume, the reaction rate is

$$\frac{dn_C}{V_{avail.} dt} = k_{int} \frac{n_A}{V_{avail.}} \frac{n_B}{V_{avail.}}$$

where  $n_A$ ,  $n_B$ , and  $n_C$  represent the numbers of A, B, and C molecules, respectively.

Substituting and simplifying leads to

$$\begin{aligned}\frac{dn_C}{dt} &= \frac{k_{int}n_A n_B}{V_{total}(1-\phi)} \\ \frac{dn_C}{V_{total}dt} &= \frac{k_{int}}{1-\phi} \frac{n_A}{V_{total}} \frac{n_B}{V_{total}} \\ \frac{d[C]}{dt} &= \frac{k_{int}}{1-\phi} [A][B] \\ k_{act.}(\phi) &= \frac{k_{int}}{1-\phi}\end{aligned}\tag{4}$$

Thus, crowding causes activation-limited reactions to accelerate by the factor  $1/(1-\phi)$ .

We are unable to solve for the diffusion-limited extreme, but offer a hypothesis instead. In this case, the available volume is still reduced by the same factor of  $1-\phi$ , so it would make sense for reaction rates to be accelerated exactly as before. In addition, the diffusion coefficient is reduced from  $D$  to some crowding-dependent amount which we denote  $D(\phi)$ . This dependence varies depending on the precise crowding model. Combining these effects, our hypothesis is that the diffusion-limited reaction rate constant changes from eq. 1 to

$$k_{diff.}(\phi) = \frac{4\pi\sigma D(\phi)}{1-\phi}\tag{5}$$

Although intuitively sensible, this derivation is not rigorous. In particular, the Smoluchowski reaction rate equation, eq. 1, is typically derived by computing the radial distribution function of B molecules around the A molecules. The presence of crowders likely changes this radial distribution function, although those effects were not accounted for here.

We are also unable to solve for the general diffusion-influenced reaction rate constant. However, we offer the hypothesis that the diffusion-limited and activation-limited reaction rates, in the presence of crowders, can be combined in the same way as in they are in the Collins and Kimball equation, eq. 2. This yields

$$k(\phi) = \left[ \frac{1-\phi}{4\pi\sigma D(\phi)} + \frac{1-\phi}{k_{int}} \right]^{-1}\tag{6}$$

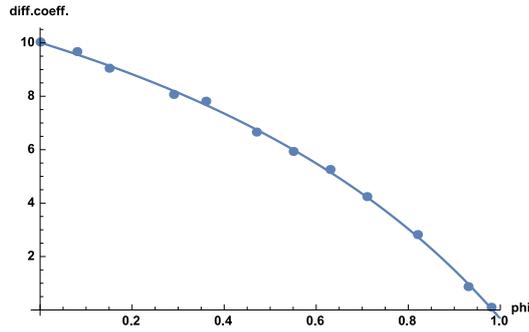
Below, we test these hypotheses with simulations.

#### 4.1.4 Results and Discussion

##### Smoldyn

Smoldyn simulations were performed in a  $50 \times 50 \times 50 \text{ nm}^3$  cube with periodic boundaries. Simulations ran for  $10 \mu\text{s}$  in steps of  $0.001 \mu\text{s}$ , and data were recorded every  $0.01 \mu\text{s}$ . We generated crowders, using the SmolCrowd software, as randomly positioned non-overlapping spheres with  $0.5 \text{ nm}$  radii. These radii were then increased to  $1 \text{ nm}$  (which led to overlaps of up to  $0.5 \text{ nm}$ ) as a simple way of accounting for radii of the A and B molecules that equaled  $0.5 \text{ nm}$ . This increase of the crowder radii enabled us to represent the A and B molecules as simple points, but for them to behave as though they had  $0.5 \text{ nm}$  radii. We computed the crowder volume fraction,  $\phi$ , as the fraction of the simulation volume that was within at least one of these  $1 \text{ nm}$  radii crowder spheres.

Each simulation started with about 1000 randomly placed molecules for each of the three species, A, B, and tracers. All three species diffused with diffusion coefficients of  $D_0 = 10 \text{ nm}^2/\mu\text{s}$  (equal to  $10 \mu\text{m}^2/\text{s}$ , which is a typical, albeit slow, intracellular protein diffusion



■ **Figure 1** Effective diffusion coefficient as a function of crowder volume fraction. Dots represent simulation data for tracer molecules and the line represents a least-squares best fit to the simulation data using a rational function, as described in the main text. These data were from simulations with  $k_0 = 251.3 \text{ nm}^3/\mu\text{s}$ ; the data for other simulations were essentially identical.

coefficient [3]). The tracer molecules did not participate in any reactions or interact with the A or B molecules. Instead, they simply diffused around the system, and we used their mean squared displacements at the end of each simulation to compute their effective diffusion coefficients and, by extension, the effective diffusion coefficients of the A and B molecules.

The A and B molecules reacted with each other with reaction rate constants (for uncrowded systems) of either  $k_0 = 251.3$  or  $k_0 = 25.13 \text{ nm}^3/\mu\text{s}$  (equal to  $1.5 \times 10^8 \text{ M}^{-1}/\text{s}^{-1}$  and  $1.5 \times 10^7 \text{ M}^{-1}/\text{s}^{-1}$ , both of which are extremely fast reaction rates). We chose the former rate constant because its binding radius in the Smoluchowski model, eq. 1, is 1 nm. We used it to investigate nearly diffusion-limited reactions and we used the latter rate constant to investigate more activation-limited reactions. Smoldyn reported that the effective activation-limited reaction rate constants for the two sets of simulations were 1238 and  $33.83 \text{ nm}^3/\mu\text{s}$ , respectively, which were computed from eq. 41 of Andrews and Bray [4]. From these and the  $k_0$  values, the diffusion-limited reaction rate constants were 315.3 and  $97.73 \text{ nm}^3/\mu\text{s}$ , respectively. In contrast to the reactions introduced above, we used the reaction  $A + B \rightarrow B$  here, so that the concentration of B stayed constant throughout the simulation. This simplified the reaction rate constant estimation, as described below. We ran each simulation 10 times and averaged the results for the 10 runs.

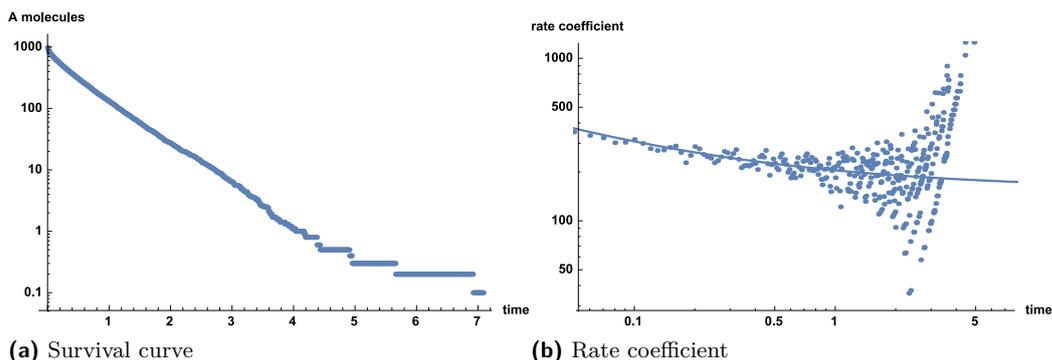
As expected, we found that effective diffusion coefficients decreased monotonically with the crowder occupancy, shown with dots in Figure 1. These data fit well to the rational function

$$D(\phi) = D_0 \frac{1 - a\phi}{1 - b\phi} \quad (7)$$

where  $a$  and  $b$  were fit parameters. The best fit, shown with the line in Figure 1, has  $a = 1.02$  and  $b = 0.48$ . These fit parameters are sufficiently close to 1 and  $1/2$  to be suggestive of a theoretical basis to this fitting function, but we did not pursue it in this work. The percolation threshold, meaning the crowder occupancy where the effective diffusion coefficient becomes zero, is  $\phi_{perc.} = 1/a = 0.98$ .

To compute the steady-state reaction rate constant from simulation data, we first recorded the number of A molecules surviving as a function of time, with a typical example shown in Figure 2A. We then numerically differentiated these data according to the equation

$$k_i = -\frac{n_{A,i+1} - n_{A,i-1}}{(t_{i+1} - t_{i-1})n_{A,i}} \quad (8)$$



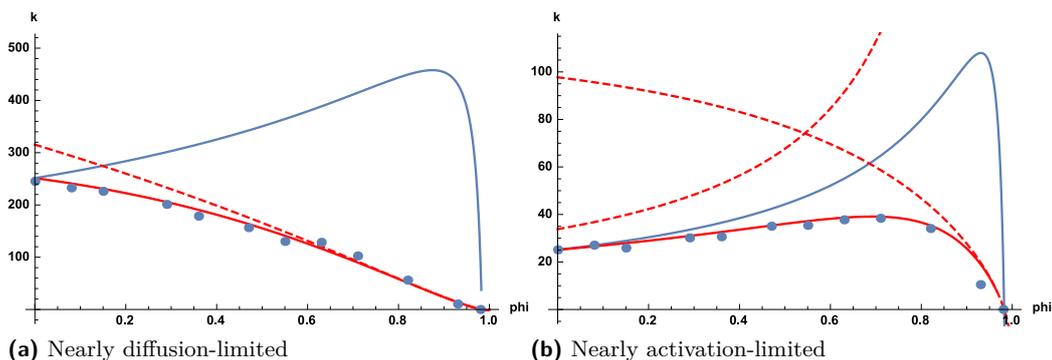
**Figure 2** Data analysis for computing steady-state reaction rate constants. (A) Number of A molecules surviving as a function of time for the average of 10 simulations with  $k_0 = 251.3 \text{ nm}^3/\mu\text{s}$  and  $\phi = 0.47$ ; other data sets were qualitatively similar. (B) Points represent the reaction rate coefficient as a function of time, computed from the data shown in Panel A using eq. 8. The line is a best fit line to the points, using eq. 9

where  $k_i$  is the reaction rate at time point  $i$ ,  $n_{A,i}$  is the number of surviving A molecules at time point  $i$ , and  $t_i$  is the simulation time at time point  $i$ . This numerical derivative produced a very noisy reaction rate coefficient function, as shown in Figure 2B. Adding to the challenge of estimating the reaction rate constant, there is no sharp cut-off between the transient fast reaction rate coefficient at very short times and the steady-state reaction rate constant. Thus, we fit the reaction rate coefficient data with the following function, which has the form of the time-dependent reaction rate coefficient for both the Smoluchowski and Collins and Kimball models,

$$k(t) = c \left( 1 + \frac{d}{\sqrt{t}} \right) \quad (9)$$

where  $c$  and  $d$  are fit parameters;  $c$  is also the steady-state reaction rate constant. This fit skipped the first 19 data points in order to reduce the effect of the short-time transient reaction rate. This fit also used the number of A molecules at each time point as a weighting parameter for the data points in order to give more weight to the less noisy data and less to the noisy data. As seen in Figure 2B, the resulting fits agreed with the data very well. Fitting to this function was possible because we kept the concentration of B molecules constant throughout a simulation.

Figure 3 shows the effect of the crowder volume occupancy on the steady-state reaction rate constant, for primarily diffusion-limited and primarily activation-limited situations. In both cases, the simulated reaction rate at zero crowder density, quantified with the process described above, agreed very closely with the input reaction rate constant (3.5% error for  $k_0 = 251.3 \text{ nm}^3/\mu\text{s}$  and 0.1% error for  $k_0 = 25.13 \text{ nm}^3/\mu\text{s}$ ), which gave us high confidence in our reaction rate quantification method. Both curves qualitatively agree with the predictions given above, in which diffusion-limited reactions are slowed down by crowders due to the slowed diffusion, and activation-limited reactions are accelerated by crowders due to the reduction of accessible volume. However, comparing the data points with the solid blue lines shows that the simulation data do not agree with our hypothesis. We computed these hypothesis curves from eq. 6, while using the empirical fit in eq. 7 for  $D(\phi)$ , the activation-limited reaction rate reported by Smoldyn for  $k_{int}$ , and the diffusion-limited reaction rate constants given above and eq. 1 to compute  $\sigma$ . Note that there are no adjustable parameters in this comparison.



**Figure 3** Simulated reaction rates as functions of crowder volume occupancy. (A) Results for simulations with  $k_0 = 251.3 \text{ nm}^3/\mu\text{s}$ , leading to nearly diffusion-limited reactions. (B) Results for simulations with  $k_0 = 25.13 \text{ nm}^3/\mu\text{s}$ , leading to nearly activation-limited reactions at low crowder densities. In both panels, dots represent simulation data and the solid blue curves represent our hypothesis from eq. 6. The solid red curves represent our modified hypothesis from eq. 10 in which there is one fitting parameter. Dashed lines that tend downwards represent the diffusion-limited reaction rate component of our modified hypothesis, while the dashed line that tends upwards in Panel B represents the activation-limited reaction rate component of our modified hypothesis (the comparable line for Panel A is outside of the displayed plot range).

On the other hand, the solid red lines in Figure 3 show that the data agree well with a modified version of our hypothesis, given as

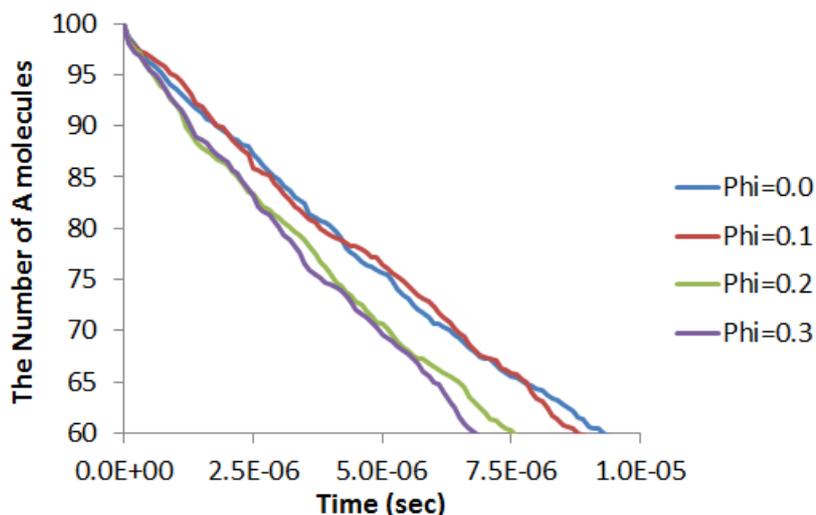
$$k(\phi) = \left[ \frac{(1 - \phi)^\gamma}{4\pi\sigma D(\phi)} + \frac{1 - \phi}{k_{int}} \right]^{-1} \quad (10)$$

where  $\gamma$  is 1 in our hypothesis and is a fit parameter in this modified version. This modification only affects the diffusion-limited portion of the equation, which we were unable to derive rigorously. The nearly diffusion-limited reactions ( $k_0 = 251.3 \text{ nm}^3/\mu\text{s}$ ) fit well when  $\gamma$  was  $-0.3$  and the nearly activation-limited reactions ( $k_0 = 25.13 \text{ nm}^3/\mu\text{s}$ ) fit well when  $\gamma$  was  $0.27$ , both of which we fit by eye. The latter  $\gamma$  value is quite different from our hypothesis value of 1, but agrees with our intuition that the volume exclusion of crowdors should accelerate reaction rates, even when reactions are strongly diffusion influenced. However, the former negative  $\gamma$  value is quite surprising. It shows that when reactions are diffusion-limited, the reaction rate decreases faster than the diffusion coefficient as the crowder density is increased. We do not have an explanation for this result.

Overall, we found that Smoldyn performed very well for simulating the effects of crowding on reaction rates. Simulated diffusion and reaction rate results agreed essentially perfectly with the respective input values when there were no crowdors. Also, reaction rates in the activation-limited case increased in essentially perfect agreement with theory (low  $\phi$  values in Figure 3B). In contrast, those for diffusion-limited situations differed substantially from those in our initial hypothesis. Because Smoldyn has been thoroughly tested in prior work and it agreed with the other results here, this discrepancy strongly suggests that our initial hypothesis was wrong.

### eGFRD

eGFRD simulations were also performed in a  $50 \times 50 \times 50 \text{ nm}^3$  cube with periodic boundaries. 100 A and B molecules were randomly positioned in the cube at the initialization. To keep



■ **Figure 4** Simulation results. Number of A molecules surviving as a function of time for the average of 10 simulations with the volume fraction of 2 nm radii crowders,  $\phi = 0, 0.1, 0.2$  and  $0.3$ .

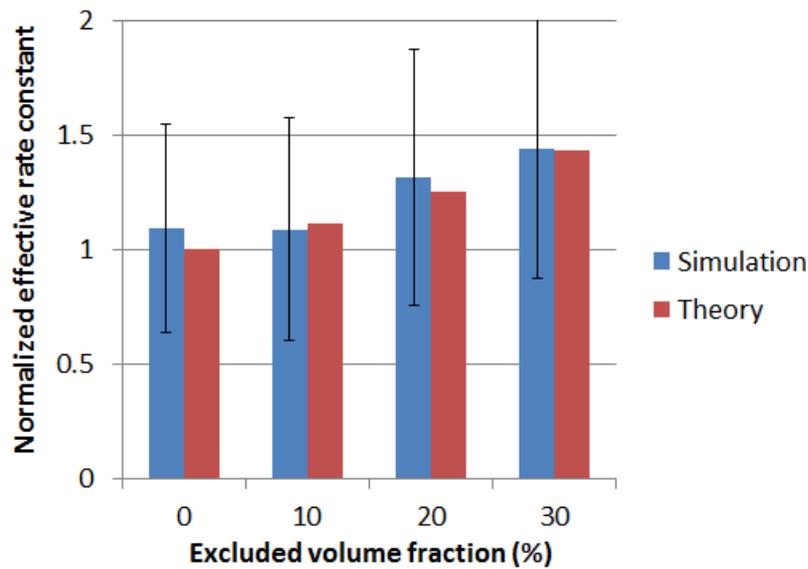
the total excluded volume fraction of molecules during the simulations, A and B molecules react and produce both B and non-reactive C molecules ( $A + B \rightarrow C + B$ ). Therefore, the concentration of B molecules was kept constant during the simulation too. A, B and C molecules were represented as 0.5 nm radii hard-body spheres. Simulations ran until a half of A and B molecules (50 molecules) reacted. With no crowders, it takes about 10  $\mu\text{s}$ . All the exact time of reactions were recorded in the event-driven way. All three species diffused with diffusion coefficients of  $D_0 = 10 \mu\text{m}^2/\text{s}$ .

The reaction rate constant of A and B molecules,  $k_0$ , was  $0.3382 \times k_D$  (corresponding to  $85 \text{ nm}^3/\mu\text{s}$ ), where  $k_D = 4\pi\sigma D$  in eq. 1. This kinetic rate gives nearly diffusion-limited situation. The Collins and Kimball equation, eq. 2, gives the effective reaction rate constant for the intrinsic rate  $k_0$  as  $63.52 \text{ nm}^3/\mu\text{s}$ . The effective rate is four times slower than the perfectly diffusion-limited rate constant,  $k_D = 251.3 \text{ nm}^3/\mu\text{s}$ . We ran each simulation 10 times. The number of A molecules were averaged every 0.1  $\mu\text{s}$  for the 10 runs (figure 4).

First, we generated crowders with 2.1 nm radii (about 4 times larger than other three molecules). 320, 640 and 960 crowders were randomly placed with no overlap for the crowders volume fraction,  $\phi = 0.1, 0.2$  and  $0.3$ , respectively. All crowder molecules were fixed in place throughout the simulations.

The effective reaction rate constants in the crowded media were evaluated by numerically differentiating the time course data of the number of A molecules. (See eq. 8.) To get the steady state rate constant, we ignored the first few data ( $t = 0$  0.3  $\mu\text{s}$ ) and averaged data up to 7  $\mu\text{s}$ . Normalizing with the effective rate constant in non-crowded medium expected by the Collins Kimball equation ( $63.52 \text{ nm}^3/\mu\text{s}$ ) and the constant concentration of B (about 1.3 M), we evaluated the effect of crowders on the rate constants, shown in Figure 5. With these large crowders, the effective rate constant was just affected by the excluded volume (the latter part of eq. 6), but not by the change in the diffusion rate (the former part of eq. 6). Therefore, the effective rate constants were simply given by  $k(\phi) = k/(1 - \phi)$ .

Next, to evaluate the condition with smaller crowders, we randomly placed 47748 molecules with 0.5 nm radii ( $\phi=0.2$ ). We ran the simulations in the same condition for other A and B molecules. However, we could not collect enough data for the analysis because the averaged

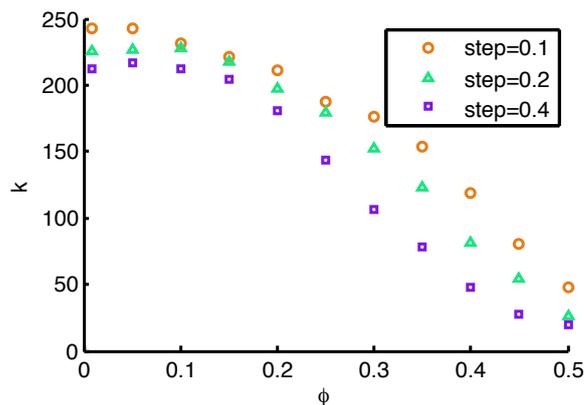


■ **Figure 5** Effect of the excluded volume of 2 nm radii crowders on the effective steady-state rate constants ( $\phi = 0, 0.1, 0.2$  and  $0.3$ ). Theoretical values were given by the equation:  $1/(1 - \phi)$ .

step size in the simulations was too small. The eGFRD method applies the Reaction Brownian Dynamics (RBD) method locally to each domain with more than two molecules, which is called a  $\text{\textcircled{M}}$  domain. To guarantee the exactness and accuracy of a simulation, the step size in the  $\text{\textcircled{M}}$  domain must be smaller than at least  $10^{-5} \times \tau$ , where  $\tau$  is the averaged time to diffuse over the diameter of a molecule,  $\sigma^2/(6D)$ . In our simulations, the step size must be less than  $10^7 \mu\text{s}$ . Thus, by using the larger step size,  $10^{-1} \times \tau$ , we could obtain simulation data for the condition. As a result, the effective rate constant in the crowded medium ( $\phi = 0.2$ ) was about 20% of the rate in non-crowded media. With accounting for the effect on the excluded volume,  $1/(1 - \phi)$ , the slowed diffusion decreased the reaction rate down to 17.2%. Together with the former result, we observed the two contrary effects of molecular crowding on the effective reaction rate by using the eGFRD method. However, as mentioned above, the effective rate constant with small crowders was highly affected by the step size of simulations. To evaluate the theory in the quantitative way, we need much longer and more simulation runs.

### ML-Space

ML-Space simulations were also performed in a  $50 \times 50 \times 50 \text{ nm}^3$  cube, starting with 1000 molecules each of volume  $\pi/6 \text{ nm}^3$  (i. e. spheres of radius 0.5) for species A and B. These already occupy 0.84% of the available space ( $\frac{\pi}{6} \frac{2 \cdot 1000}{50 \cdot 50 \cdot 50}$ ). Crowders of the same size were added in numbers such that the total volume of molecules corresponded to a desired ratio  $\phi$  of the total space. Molecules were placed randomly in continuous space such that there was no pair of overlapping molecules. When this was not possible in a reasonable number of attempts (here generally for  $\phi > 0.3$ ), a regular cubic grid of points with distance  $\geq 1$  was generated and molecules were placed consecutively with each center at a random, so far unoccupied grid point. This way,  $\phi < \frac{\pi}{6} \approx 0.524$  (the density of a cubic lattice sphere packing). The simulation time steps were chosen such that the average traveled distance was 0.1, 0.2 or 0.4 nm. For a fixed diffusion coefficient ( $D_0 = 10 \text{ nm}^2/\mu\text{s}$  here, too), each



■ **Figure 6** Simulated reaction rates as functions of crowder volume occupancy, depending on chosen step size. Results for simulations with reaction probability 1 (in case of collision), leading to a theoretical (diffusion-limited) reaction rate of  $k_0 = 251.3 \text{ nm}^3/\mu\text{s}$ .

doubling of this step size increases the time step by a factor of 4. The reaction  $A + B \rightarrow C$  was used, i. e. the product was not available for further reactions. The effective reaction rate was calculated from the number of reactions in an initial window of  $0.32\mu\text{s}$  and averaged over 5 runs each.

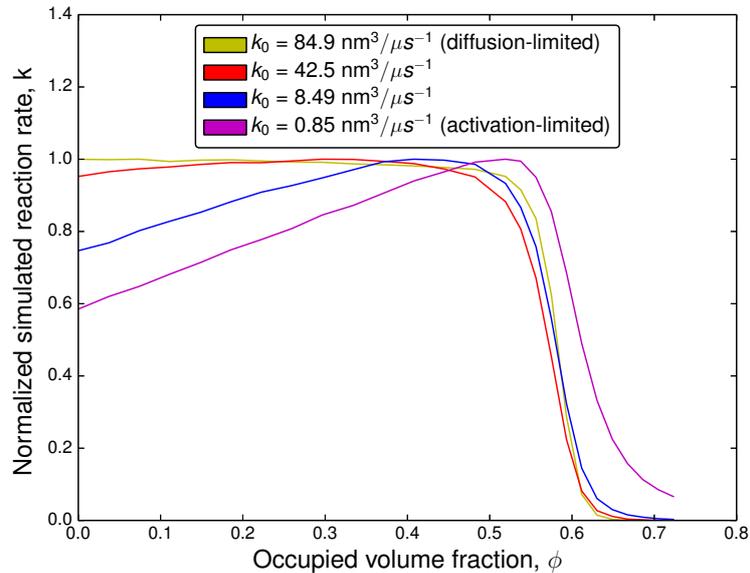
Simulation results for the diffusion-limited case are in general agreement with the predictions. An initially observed increase in the effective reaction rate after the addition of the first few crowders (i. e. small increases in  $\phi$  from its minimum) was not found to be significant. As activation-limited reactions would be incorporated in ML-Space by adjusting the probability of a reaction given an appropriate collision by a factor derived from the desired reaction rate and a calculated collision frequency, simulations of the activation-limited reaction case should only yield a scaled version of the same curve.

The results point to two main insights related to the chosen approach. First, the effective reaction rate decreases with higher crowding, but much faster than expected. We attribute this to several factors:

- When simulating spheres of the same size, the maximum possible crowding coefficient is  $\phi \approx 0.74$ , i. e. much smaller than 1 to begin with.
- With all molecules represented as hard spheres and with ML-Space “resolving” non-reactive collisions by retrying or partially applying the random position update, it should be harder for reactive molecules to get “past” crowders than in approaches that allow temporary partial overlap or treat some particles as points only.
- Our ad-hoc initialization using a cubic lattice may have “trapped” more potentially reactive molecules between crowders than another random initialization approach might have.

Second, we observe that a larger step size leads to a lower effective reaction rate, an effect that is especially pronounced for moderate crowding. Without crowding, the lower rate should arise from collisions not detected when molecules make large( $r$ ) jumps past each other. For moderate crowding, on the other hand, the higher step size may lead to more non-resolvable collisions and thus to a lower effective diffusion, eventually decreasing the chance of reactive molecules colliding.

These considerations indicate that while ML-Space’s continuous-space simulator is in principle capable of simulating crowded environments, representing all entities by hard spheres can impede the realism of the results while at the same time the computational



■ **Figure 7** Normalized simulated reaction rates as a function of crowder volume occupancy with Spatiocyte.

costs rise significantly. It may be worthwhile to implement different methods for the initial placement of non-overlapping spheres in a suitably random manner and to investigate the effect of the collision resolution policy (e. g. number of retries for a move) on the effective diffusion coefficients.

### Spatiocyte

In the case of Spatiocyte, the simulation model is made up of  $50 \times 50 \times 50 \text{ nm}^3$  cube compartment with periodic boundaries. The radius of the lattice voxel is set to  $0.5 \text{ nm}$ . The reaction  $A + B \rightarrow B$  was used to evaluate the changes in the effective reaction rate as a function of crowder volume occupancy. Initially, there were 100 A and 100 B molecules. The diffusion coefficients of A and B were set to  $10 \mu\text{m}^2/\text{s}$ . Non-diffusing crowder species between 0 and 195000 molecules spread in 25 equal intervals were populated randomly in the compartment at initialization. We used four different reaction rates ( $k_0 = 84.9 \text{ nm}^3/\mu\text{s}$ ,  $k_0 = 42.5 \text{ nm}^3/\mu\text{s}$ ,  $k_0 = 8.49 \text{ nm}^3/\mu\text{s}$  and  $k_0 = 0.85 \text{ nm}^3/\mu\text{s}$ ) in the evaluations. Each model was run 100 times to obtain the average number of surviving A molecules. Therefore, in total, we ran  $25 \times 4 \times 100 = 10000$  simulations. We adopted the same approach employed by Smoldyn to calculate the steady-state reaction rate constant from the data. The results of our simulation are provided in Figure 7. Each curve representing the different reaction rates agrees well with our hypothesis.

### Kappa

As written above, the goal of modeling the crowding effect in the core of Kappa was more about checking whether, or not, this kind of systems can be simulated efficiently. Thus, we have gone neither into the parameterisation process, nor into the back-end processing of the

■ **Table 1** Number of rules in the model written in Kappa.

Number of rules per simulation phase	
Self-assembling	18
Spawning of the particles	1
Reactions	18
Diffusion	30
Overall	67

■ **Table 2** Parameterisation of the model written in Kappa.

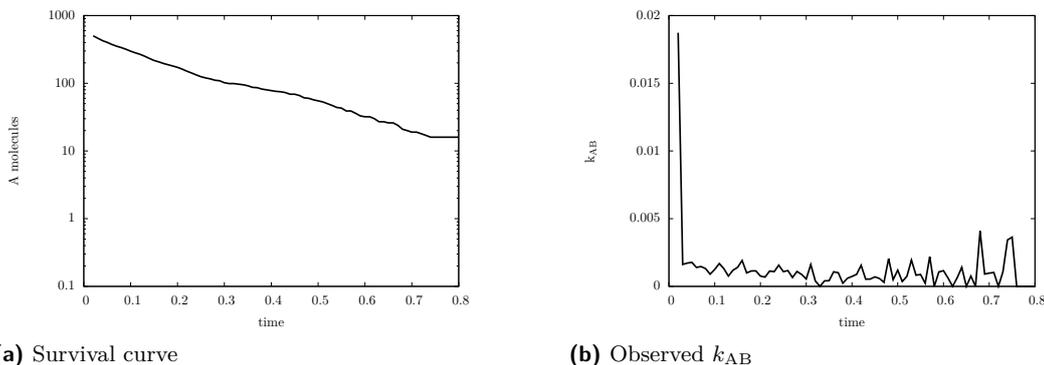
Size		Diffusion rates (cases/seconde)	
length	50 cases	A	1
width	50 cases	B	3
height	50 cases	AB	0.5
Number of particles (initial state)		C	1
A	1000	D	0
B	10000	Reaction rate (events/seconde)	
AB	10000	$A + B \rightarrow AB$	10000
C	0	$AB \rightarrow A + B$	2500
D	0	$AB \rightarrow B + C$	2500

results. Thus we have just performed a single simulation with arbitrary parameters, and we have reported the result of this simulation.

The model is made of 67 rules, which describes the self-assembling of the lattice of locations, the diffusion of particles and the chemical reactions. Table 1 details the number of rules for each phase of the simulation. The number of rules is quite large compared to the relative simplicity of the reaction networks. This is mainly due to the lack of supports for dealing with the symmetries of the lattice of locations. In particular, for the diffusion process, one copy of each diffusion rule had to be given for each of the 6 potential diffusion directions. The same way, 6 rules had to be given for the formation of the complex AB according to the relative position of the two reactants, and 6 rules had to be given for each of the unary reaction depending on which location the second product is spawned. The full model is available at the following url: [http://www.di.ens.fr/dagstuhl\\_14481/crowd\\_3d.ka](http://www.di.ens.fr/dagstuhl_14481/crowd_3d.ka).

We have not computed the values of the parameters from a physical model. In particular, we have not converted continuous diffusion rates into discrete ones. The theory is well-known, but these computations require a careful handling of units and the approximation of 3D ideal Brownian motion into a discrete diffusion process within a finite lattice of locations. These conversions are available, once for all, in many formalisms (including Spatial Kappa [22] for Kappa). Thus, we have not been into these computations, but have used arbitrary parameters instead. See Table 2, for the values that we have assigned to parameters.

The result of the simulation is plotted in Fig. 8. In Fig. 8.(A), we show the survival curve of the particles of kind A, that is to say the sum between the number of instances of particles



■ **Figure 8** Data analysis for computing steady-state reaction rate constants. (A) Number of molecules (either free) or in a complex AB surviving as a function of time on a given simulation. (B) Reaction rate coefficient as a function of time. These data sets have been obtained with the parameters given in Table 2. Observed rates have been sampled over intervals of 0.01s and computed as the effective number of reaction applications, divided by product, for each reactant, of the middle value between the minimum number of instances and the maximum number of instances over the sampling interval.

■ **Table 3** Benchmark for the model written in Kappa. Obtained on Dell LATITUDE E6430s, Proc intel® Core™ i7-3549M CPU @ 3.00 GHz × 4 with 8 Gio RAM, under UBUNTU 14.04 LTS.

Phase	Number of events	CPU time (seconds)	Simulation speed (events/CPU second)
Self-assembling	250148	37.61	6651
Spawning of the particles	21000	11.24	1868
Diffusion and reaction events	137176	55.02	2493
Overall	408324	103.87	3931

A and the number of instances of complexes AB. In Fig. 8.(B), we show the observed rate of association between particles A and particles B. This rate is sampled over 0.01 s intervals of time. During each sampling interval, the minimum and the maximum number of instances of particles A and of particles B are integrated, as well as the number of effective associations between particles of kind A and particles of kind B; the observed rate is then computed as the quotient of the number of associations between As and Bs by the product of the median number of instances of each reactant. This simulation has been obtained with the KASIM simulator [19] version 4.0-refactoring with the random seed 24602700.

In Table 3, we give the computation time for the different phases of the simulation on a personal laptop Dell LATITUDE E6430s, Proc intel® Core™ i7-3549M CPU @ 3.00 GHz × 4 with 8 Gio RAM, under UBUNTU 14.04 LTS.

As a conclusion, we have, through this case study, identified three main kinds of difficulty:

1. The lack of supports to deal with symmetries. For instance, one needs 6 rules to describe the diffusion of the particles of kind A, because one has to provide one rule per potential direction. This is the same for the reactions which have to be duplicated according to the relative position of the reactants and/or where the new product is released. Thus, the lack of supports for dealing with the symmetries of the lattice space is quite cumbersome.

2. The lack of support for computing diffusion rates. Even if it is well known in theory how to convert rate constants from a continuous model of space to a discrete one. It is always quite tricky to make these computations on paper. Thus, having these computations done once for all, at the language level, is highly convenient.
3. Lastly, it is quite uneasy to describe a soup of particles in each spatial unit in the core language. This is why we have followed the microscopic lattice method. Indeed, the consequence of encoding each spatial location as an agent and the topology by the means of bond, is that the fact that a given particle is in a given location has to be encoded by a bond between this particle and the agent that models this location. Then encoding soup of particles per location would require the use of complex data-structures such as hyper-links or double lists (with additional reactions to shuffle the element of these lists arbitrary). An alternative to use of bond to encode the location, is to encode the location of a particle as an internal state. Yet, internal states lack of algebraic structure, thus this alternative would require the duplication of reactions for each location, which is OK for the simulation engine, since the time complexity of an event simulation depends only logarithmically on the overall number of rules.

We notice that the two last points are handled conveniently in Spatial Kappa [22], in which all required conversions are done once for all at the language level; and in which locations are described as the internal state of a specific site for each particle and rules are macro-expanded accordingly. Yet, Spatial Kappa can only deal with regular lattices of locations such as arrays, rectangles, and rectangular boxes, with no periodic interpretation of the coordinates (but this could be implemented quite easily). Conversely, the use of bonds to model locations allows for the description of arbitrary, and even, dynamical topologies of locations.

#### 4.1.5 Conclusions

In this work, we investigated the abilities of several simulators to model the effects of macromolecular crowders on chemical reaction rates. These simulators were an eGFRD simulator, Smoldyn, ML-space, Kappa, and Spatiocyte. Each of these treat space and molecular dynamics in subtly different ways. All of the quantitative data that were directly comparable with each other showed qualitatively similar results. In particular, diffusion-limited reaction rates decreased monotonically with the fractional crowder occupancy, while activation-limited reaction rates exhibited an initial reaction rate increase with crowder occupancy. These results also agreed qualitatively with our hypothesis.

The eGFRD simulations used the most accurate algorithm, so their results are presumably the most accurate. In practice, they agreed well with the theory for activation-limited reactions and reasonably large crowders. However, these simulations proved to be too computationally intensive for further analysis in this work.

The Smoldyn simulation method was better adapted to this investigation because it was still reasonably accurate but it ran much faster. The Smoldyn simulation parameters could be connected directly to physical parameters, which enabled us to verify that the simulated reaction rates closely matched theoretical ones for the cases where we knew the exact theory. This also enabled us to see that our initial hypothesis about the effect of crowding on reaction rates is incorrect. However, a modified hypothesis, which includes one fitting parameter, is able to fit the simulation data very well.

The ML-space results show a monotonic decrease of reaction rates with increasing crowding density. This agrees with the results that Smoldyn found for diffusion-limited reactions,

although the results were quantitatively different. These results had some puzzling aspects, such as the fact that they were time-step dependent, and that they are predicted to arise independent of whether reactions are diffusion-limited or activation-limited.

Spatioocyte was the fastest running simulator of those tested, which enabled it to generate the most result curves, each with the least noisy data. These results show a monotonic decrease of reaction rates with crowder occupancy for diffusion-limited reactions, and an initial reaction rate rise for activation-limited reactions, both of which agree with our hypotheses and with the Smoldyn simulations. Again though, the results are quantitatively different. The differences undoubtedly arise from the differences between continuous-space (Smoldyn) and lattice models (Spatioocyte).

We did not collect quantitative results with Kappa. Instead, we discovered in this investigation that Kappa can be used to successfully simulate reaction rates in crowded volumes, despite being far beyond the initial design goals for Kappa.

Two major conclusions can be drawn from these results. First, the detailed simulation algorithms can have a very large effect on the quantitative results. This includes the exact methods by which simulators treat excluded volume interactions and the use of lattice or continuous space. Second, all of these simulators could be improved upon. The results given here help illustrate the current limitations, and hence suggest areas for improvements.

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## References

- 1 SS Andrews, T Dinh, AP Arkin, and RA Meyers. Stochastic models of biological processes. *Encyclopedia of Complexity and System Science*, 9:8730–8749, 2009.
- 2 Steven S Andrews. Accurate particle-based simulation of adsorption, desorption and partial transmission. *Physical biology*, 6(4):046015, 2009.
- 3 Steven S Andrews. Spatial and stochastic cellular modeling with the smoldyn simulator. In *Bacterial Molecular Networks*, pages 519–542. Springer, 2012.
- 4 Steven S Andrews and Dennis Bray. Stochastic simulation of chemical reactions with spatial resolution and single molecule detail. *Physical biology*, 1(3):137, 2004.
- 5 Satya Nanda Vel Arjunan and Masaru Tomita. A new multicompartmental reaction-diffusion modeling method links transient membrane attachment of e. coli mine to e-ring formation. *Systems and synthetic biology*, 4(1):35–53, 2010.
- 6 Howard C Berg. *Random walks in biology*. Princeton University Press, 1993.
- 7 Arne T. Bittig, Fiete Haack, Carsten Maus, and Adelinde M. Uhrmacher. Adapting rule-based model descriptions for simulating in continuous and hybrid space. In *Proceedings of the 9th International Conference on Computational Methods in Systems Biology, CMSB '11*, pages 161–170, New York, NY, USA, 2011. ACM.
- 8 Arne T. Bittig, Claudia Matschegewski, J. Barbara Nebe, Susanne Stählke, and Adelinde M. Uhrmacher. Membrane related dynamics and the formation of actin in cells growing on micro-topographies: a spatial computational model. *BMC Systems Biology*, 8:106+, 2014.
- 9 Frank C Collins and George E Kimball. Diffusion-controlled reaction rates. *Journal of colloid science*, 4(4):425–437, 1949.
- 10 John Crank. *The Mathematics of Diffusion*. Clarendon Press, Oxford, second edition, 1975.
- 11 Johan Elf and Måns Ehrenberg. Spontaneous separation of bi-stable biochemical systems into spatial domains of opposite phases. *Systems biology*, 1(2):230–236, 2004.
- 12 R John Ellis. Macromolecular crowding: obvious but underappreciated. *Trends in biochemical sciences*, 26(10):597–604, 2001.

- 13 Jérôme Feret, Vincent Danos, Jean Krivine, Russ Harmer, and Walter Fontana. Internal coarse-graining of molecular systems. *Proceedings of the National Academy of Sciences*, 106(16):6453–6458, 2009.
- 14 Alice B Fulton. How crowded is the cytoplasm? *Cell*, 30(2):345–347, 1982.
- 15 Daniel T Gillespie. Exact stochastic simulation of coupled chemical reactions. *The journal of physical chemistry*, 81(25):2340–2361, 1977.
- 16 Damien Hall and Allen P Minton. Macromolecular crowding: qualitative and semiquantitative successes, quantitative challenges. *Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics*, 1649(2):127–139, 2003.
- 17 Jun Soo Kim and Arun Yethiraj. Effect of macromolecular crowding on reaction rates: a computational and theoretical study. *Biophysical journal*, 96(4):1333–1340, 2009.
- 18 Richard M Noyes. Effects of diffusion rates on chemical kinetics. *Prog. React. Kinet*, 1:129–160, 1961.
- 19 Jean Krivine Pierre Boutillier, Jérôme Feret. Kasim, 2010-present. available at <https://github.com/Kappa-Dev/KaSim>.
- 20 Stephen A Rice. *Diffusion-limited reactions*. Elsevier, 1985.
- 21 M von Smoluchowski et al. Versuch einer mathematischen Theorie der Koagulationskinetik kolloider Lösungen. *Z. phys. Chem*, 92(129–168):9, 1917.
- 22 Donal Stewart. Spatial biomodelling. Master's thesis, University of Edinburgh, 2010.
- 23 Koichi Takahashi, Sorin Tănase-Nicola, and Pieter Rein Ten Wolde. Spatio-temporal correlations can drastically change the response of a mapk pathway. *Proceedings of the National Academy of Sciences*, 107(6):2473–2478, 2010.
- 24 Jeroen S van Zon and Pieter Rein Ten Wolde. Simulating biochemical networks at the particle level and in time and space: Green's function reaction dynamics. *Physical review letters*, 94(12):128103, 2005.
- 25 Huan-Xiang Zhou, Germán Rivas, and Allen P Minton. Macromolecular crowding and confinement: biochemical, biophysical, and potential physiological consequences. *Annual review of biophysics*, 37:375, 2008.
- 26 Steven B Zimmerman and Allen P Minton. Macromolecular crowding: biochemical, biophysical, and physiological consequences. *Annual review of biophysics and biomolecular structure*, 22(1):27–65, 1993.

## 4.2 Multiscale modeling of S1P metabolism, secretion and signaling (Team 4)

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### 4.2.1 Background

Sphingolipids (SL) are a class of complex lipids with a sphingoid base (Sph). Modifications of this basic structure that consist in the addition of an amide-linked fatty acid or phosphorylation lead to the formation of bioactive sphingolipids such as ceramide (CER), ceramide-1-phosphate (C1P), sphingosine-1-phosphate (S1P) or sphingomyelin (SM). For a long time, sphingolipids were believed to serve mainly structural purposes and have only been recognized as important messengers in cellular signaling pathways in the last two decades. A

notable body of work has been devoted to studying the influence of sphingolipid metabolism on cellular fate: motility, proliferation, differentiation and apoptosis. Importantly, individual sphingolipid species appear to have an antagonistic effect on cell growth and survival. Indeed, sphingolipids are known to have critical implications for the pathogenesis and treatment of diverse conditions such as cancer, inflammation and neurodegenerative disorders. Particularly sphingosine-1-phosphate has been widely discussed as a critical signaling molecules, important in immunity and inflammation. Sphingosine-1-phosphate acts on different levels of the organism organization, it can be considered as a multiscale messenger. On the one hand it has been reported that S1P intracellularly regulates calcium release, and genes expression via modulation of histone acetylation. On the other hand at the organismal level it can regulate organs and tissues activity through binding to the G protein- coupled receptors (S1PRs) that are differentially expressed in different cell types. Activation of S1PRs plays an important role in maintenance of endothelial and epithelial barrier integrity, vascularization and activation and migration of lymphocytes B and T.

#### 4.2.2 Challenges

Our goal was to develop the multiscale model of inflammation process [1]. We focused on the role of sphingosine-1-phosphate (S1P) as it is signaling molecule crucial for the immunity and the inflammation. S1P is produced by endothelial cells and then transported into the blood and lymph. The gradient of S1P within lymphoid organ is chemotactic signal for lymphocytes. Lymphocytes activated by S1P egress lymph nodes and enter blood stream.

Our multiscale approach spans through different levels of signaling: the detailed kinetic model of sphingolipids metabolism is embedded into human genome scale metabolic network Recon2) [10] and then the chemotaxis process is modeled using grid-based model of diffusion based on coloured Petri nets [3]. In parallel, studies aimed to add the regulatory parts to the given metabolic network have been started. Finally the issue of the sphingolipids metabolic network simplification has been investigated.

#### 4.2.3 Approaches considered

The computational model of sphingolipid metabolism is based on the system of Ordinary Differential Equations (ODEs) describing the evolution of species concentration. Kinetics of the model is mostly based on the Mass Action Law (MAL) for the molecular transportation reactions and the Michaelis-Menten (MM) approach for enzymatically catalysed reactions. The modeled kinetics also covers the inhibition within competing species. Reactions parameters were estimated basing on publicly available literature data and some default assumptions based on experience with Biochemical Systems Theory (BST), while the initial concentrations of particular sphingolipid species in each organelle were taken from the LIPID MAPS database.

The sphingolipids metabolism was modeled in the context of genome scale metabolic network. First the kinetic model has been used to calculate steady state flux distribution in sphingolipid synthesis pathways. Steady state fluxes were then used as constraints for Flux Balance Analysis (FBA) [9] of human genome scale metabolic network (Recon 2) [10]. The FBA provided insights into global set of metabolic reactions that need to operate to sustain steady state flux predicted by the kinetic model.

In order to add the multi-scale or multi-level aspects into our project, we wanted to integrate a reaction-diffusion part and chemotaxis driven movement of cells.

Moreover we studied the possibility to integrate the regulatory network with our metabolic

model. The regulation of enzymes involved in the modeled process was described by means of Quasi Steady State Petri Net [2].

#### 4.2.4 Major results

In this hybrid simulation we have a variable for each of 2169 human metabolic genes. We are able to perform qualitative simulation to determine which of these genes are mechanistically (rather than statistically) associated with lymphocyte egress.

Steady state fluxes in kinetic model were calculated in Copasi [4] considering all biochemical reactions stored in Recon2. Since our kinetic model of sphingolipids metabolism reports a detailed description of all enzymatic reactions related to the synthesis, transportation, transformation and degradation of sphingolipids, we firstly update the reactions related to the sphingolipids metabolism stored in Recon2 according to our model. We map the fluxes between our model and Recon2 searching each enzyme and transporter in the database. When the enzyme or transporter was found we verify that the kinetics aspects described by Recon2 are the same reported in our model. A large number of enzymes are not reported in Recon2 or they are associated to an incomplete kinetics, in these cases we update the database following our knowledge. Finally, the fluxes' mapping performed have enriched Recon2 with a more detailed and complete description of sphingolipid mechanisms.

The sphingosine-1-phosphate (S1P) level in lymphoid tissues forms a gradient as shown in [6]. The T-cells are attracted by this gradient and move from thymus into the blood along this gradient. Such a gradient could be modelled as a coloured Petri net as demonstrated in [5]. It is represented by an explicit space modelling technique, i. e., there is a 2- dimensional discrete grid with the size X,Y. The number of tokens on such a grid- place describes the amount of the substance, S1P in our case, at that position. Transitions between grid-places are used to let the substance diffuse in space by consuming and producing tokens. One is able to use this model in different paradigms, either as continuous Petri net (set of ordinary differential equations) or as stochastic Petri net. Now we can incorporate the gradient Petri net directly in our model and can use S1P as source for the gradient. In the next step we want to add the T-cells and let them move along the gradient. In contrast to the reaction-diffusion part, where we used an explicit space representation, we use an implicit space representation now. For simplicity, the T-cells are modelled just as single places, describing their internal state. Additionally their position is stored in two places X and Y. The amount of tokens on these places is used as coordinates. The actual movement is done by 8 transitions, each one is responsible for a certain direction, e. g., moving one step in x-direction is done by increasing the number of tokens on place X. In order to make the T-cells move along the gradient the amount of S1P has to taken into account. Finally this model would be integrated in the quasi steady state Petri net of molecular interaction networks describing gene regulation, signalling and whole-cell metabolism in human cells [2].

We used the generic graph editor *SNOOPY* [3] for modelling and simulating Petri nets. *SNOOPY* includes different kinds of net classes, e. g., qualitative Petri nets, extended Petri nets, continuous Petri nets, stochastic Petri nets and hybrid Petri nets. In addition coloured versions of these net classes are available too. Furthermore, *SNOOPY* has some distinctive features, namely logical nodes and hierarchies via subgraphs and has animation as well as simulation capabilities.

Moreover, we studied small regulation subsystem. We defined a negative feedback loop for the regulation of sphk1 gene expression. Sphk1 encodes an enzyme catalyzing synthesis of S1P via phosphorylation of sphingosine (Sph). In our qualitative model of gene regulation, the following interactions have been included: (I) synthesis of S1P catalyzed by SPHK1, than

S1P activates Nf-kB which in sequel activates transcription factor TP73. TP73 is responsible for up- regulation of PPAP2A synthesis. Finally PPaP2A, which belongs to the phosphatases, catalyzes degradation of S1P. Different formalisms (ODE, FBA, time-free, qualitative Petri Net and Coloured Petri Net) were used to define the model of gene expression regulation, and to integrate it with genome scale metabolic network. Addition of the regulatory parts to the given metabolic network (in this case sphingolipids metabolism pathway) might be also used for the prediction of metabolites overproduction. The difficulty then is that the precise kinetic functions of the regulatory reactions are not known, so that one has to reason with networks with partial kinetic information. We believe that required predictions can be based on abstract interpretation as developed in [8], but the verification of this conjecture, which requires quite some modeling and reasoning efforts, must be left to future work.

In parallel, we studied the simplification of the sphingolipids metabolic network, while preserving steady-states. Small models are easier to understand, analyze and simulate. The idea here is to use simplification of [7], but refined such that the kinetics are preserved. The initial model was the network of 69 biochemical reactions, 39 variables that of species concentrations and 129 parameters of inhibition and reaction rates in the stationary state. By removing some 'intermediary species' (e.g. those that were used only one time as reactant and one time as product) we reduced the size of the network, deleting 10 species, 5 reactions and 5 parameters, while preserving the steady-state.

Summarizing, our approach is definitely multiscale (intercellular metabolic network and modeling on the tissue level) and includes space context (cellular organelles and diffusion of S1P in blood). We applied multiple formalisms, like: ODE, FBA, time-free, qualitative Petri Net, Coloured Petri Net and multi-coarse graining, i.e. concentration in sphingolipid pathway, fluxes in genome scale metabolism, discrete states in gene regulation, grid-based model of diffusion and chemotaxis.

## References

- 1 JG Cyster, SR Schwab: Sphingosine-1-phosphate and lymphocyte egress from lymphoid organs. *Annu Rev Immunol.* 2012; 30:69–94.
- 2 CP Fisher, NJ Plant, JB Moore, AM Kierzek: QSSPN: dynamic simulation of molecular interaction networks describing gene regulation, signalling and whole-cell metabolism in human cells; *Bioinformatics* (2013) 29 (24): 3181–3190 September 23, 2013.
- 3 M Heiner, M Herajy, F Liu, C Rohr and M Schwarick: Snoopy – a unifying Petri net tool; In Proc. PETRI NETS 2012, Hamburg, Springer, LNCS, volume 7347, 398–407, June 2012.
- 4 S Hoops, S Sahle, R Gauges, C Lee, J Pahle, N Simus, M Singhal, L Xu, P Mendes, U Kummer (2006). COPASI: a COmplex PATHway SIMulator. *Bioinformatics* 22, 3067–74.
- 5 F Liu, MA Blätke, M Heiner and M Yang: Modelling and simulating reaction-diffusion systems using coloured Petri nets; *Computers in Biology and Medicine*, 53:297–308, October 2014.
- 6 M Maceyka, S Spiegel: Sphingolipid metabolites in inflammatory disease; *Nature.* 2014 Jun 5;510(7503):58–67. DOI: 10.1038/nature13475
- 7 G Madelaine, C Lhoussaine, J Niehren: Attractor Equivalence: An Observational Semantics for Reaction Networks In Proc. First International Conference on Formal Methods in Macro-Biology, 2014, Springer, LNCS, vol 8738
- 8 J Niehren, J Mathias, C Versari, F Coutte, J Philippe: A Modeling Language for Reaction Networks with Partial Kinetic Information, Technical Report, University of Lille, 2015.
- 9 JD Orth, I Thiele, BOPalsson: What is flux balance analysis? *Nat Biotechnol.* 2010 Mar; 28(3):245-8.
- 10 Thiele I, Swainston N, Fleming RM, Hoppe A, Sahoo S, Aurich MK, Haraldsdottir H, Mo ML, Rolfsson O, Stobbe MD, Thorleifsson SG, Agren R, Bölling C, Bordel S, Chavali AK,

Dobson P, Dunn WB, Endler L, Hala D, Hucka M, Hull D, Jameson D, Jamshidi N, Jonsson JJ, Juty N, Keating S, Nookaew I, Le Novre N, Malys N, Mazein A, Papin JA, Price ND, Selkov E Sr, Sigurdsson MI, Simeonidis E, Sonnenschein N, Smallbone K, Sorokin A, van Beek JH, Weichart D, Goryanin I, Nielsen J, Westerhoff HV, Kell DB, Mendes P, Palsson BØ. A community-driven global reconstruction of human metabolism. *Nat Biotechnol.* 2013 May; 31(5):419–25.

### 4.3 DNA Structural Dynamics (Team 5)

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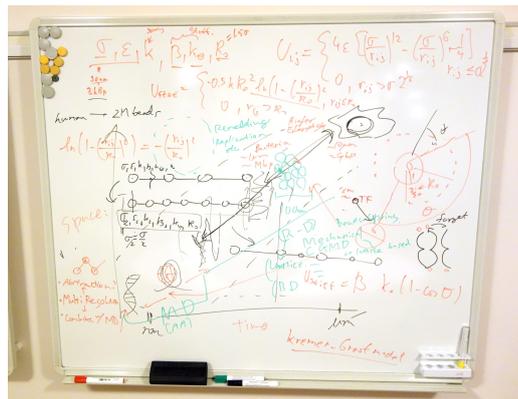
#### 4.3.1 Background

In each human cell, approximately 2-m long ( $3 \times 10^9$  basepairs  $\times$  2 sets) DNA chains are packed into the nucleus, which is typically only 10  $\mu$ m in diameter. DNA forms a complex with proteins to allow proper folding, collectively called the chromatin structure. The basic units of this structure are the nucleosomes, approximately 10-nm, barrel-shaped beads comprising the DNA wrapped around histone proteins. These beads are stacked to form a fiber and further hierarchical structures. During cell division (mitosis), the structure is further compacted into X-shaped mitotic chromosomes.

Because the chromatin structure is complex, modeling the system inevitably poses a *multiscale challenge*, especially because the structure is hierarchical, from single basepairs to the whole nucleus, which cannot be captured in totality by a monolithic model. Although a large amount of information on DNA sequences has been accrued to date, details regarding the formation of the 3-dimensional structures and their relevance to functions such as replication, transcription, and repair remain unclear. DNA structure is, to some extent, shaped by the physical properties of the DNA and proteins, without the involvement of specialized mechanisms. Both, *direct modeling* (based on the physical properties of the microscopic elements) and *inverse modeling* (based on experimentally observed constraints to structure) schemes have been used for theoretical and computational studies on this topic.

The nucleus contains a variety of molecular machines that act on DNA; these machines function by binding to the target DNA sequence. Because the DNA molecule is essentially a 1-dimensional sequence folded into a 3-dimensional structure, the target searching process is a part of information processing and is influenced by the structure of the DNA. As the nuclear environment is crowded, for example, structural fluctuations may enhance accessibility [1]. Additionally, the operation of molecular machinery may affect the DNA structure; for example, many transcription factors distort the DNA conformation to modulate transcriptional activity. Even the overall DNA structure sometimes changes drastically, not only repositioning itself but also moving dynamically, e. g., oscillatory horsetail movement in fission yeast [2]. Therefore, the interplay between spatial structures of DNA, and the searching, binding, and operation of molecular machinery acting on DNA should be considered for devising a model. This rules out simple mean-field approximations, and represents a *spatial challenge*.

During the case study session, we introduced published work on theoretical and computational studies [3, 4, 5] (also see reviews in [6]). These reports have adopted the direct



■ **Figure 9** A snapshot of the group discussion.

modeling approach, which depends on polymer models. For example, Jun and Mulder [3] simulated replicating bacterial chromosomes, and suggested that the sister chromosomes can be spontaneously segregated by maximization of the conformational entropy in a rod-shaped cell without any special driving mechanisms. Rosa and Everaers [4] showed that the mixing of large polymer chains, such as the human chromosomes, is slow enough for the initially condensed chromosomes to be focused in specific regions (chromosome territories) within the nucleus after cell division. With regards to the inverse modeling approach, chromosome conformation capture techniques [7], such as 3C, 4C, 5C, and Hi-C, have been recently adopted. These techniques help identify parts of DNA that are in close proximity of each other and use that information as distance constraints to reconstruct the 3-dimensional DNA structure.

#### 4.3.2 Approaches and Results

To better understand the complete system involving DNA, it is important to combine DNA structural dynamics and reaction-diffusion processes of other molecules acting on the DNA [8]. Molecular dynamics simulations, using either all-atom models, structure-based coarse-grained models, or polymer chain (beads-spring) models, have been considered, in addition to reaction-diffusion simulations, either lattice-based or Brownian dynamics. Further abstraction, such as reaction-diffusion-like models or phase-field models for phenomena at the whole nucleus level, may be possible.

In this group study, however, a fundamental challenge was pointed out (Fig. 10). In typical systems, small-scale dynamics are rapid enough to be averaged to make a description at a coarse-grained level, and the changes cannot propagate over a long distance within a short time. Therefore, multiscale modeling by iterative coarse-graining of both spatial and temporal scales is possible. In this case, we need to consider only small-scale rapid changes, and long-term changes only at coarse-grained levels. However, some events at the nucleosomal level (e. g., operation of chromatin remodeling factors) are rapid, but may occur after long intervals (from hours to days). This means that small-scale structures may retain memory (state) over a long time. Additionally, the rate or timing of such events may depend on the DNA structure, either small- or large-scale. Therefore, the global structure can interfere with rare (after long intervals), microscopic events. This represents a loop in the modeling procedure and results in the breakdown of the multiscale modeling strategy.

To address this issue directly, the small-scale structural states should be retained for long periods. We considered polymer-like models, which can be explicitly connected to simulations

of molecular dynamics or reaction-diffusion at the microscopic scale, and to reaction-diffusion-like phenomenological models at the macroscopic scale, if necessary. However, because the gap of scales is very large, it is unfeasible to simulate microscopic models for a long time, e. g., during a complete cell cycle. To mitigate this challenge, we only considered the timing of rare events at the microscopic scale. The general concept is to consider details only when necessary; in the current case, to simulate microscopic structures only when such events are likely to occur. For instance, during the searching processes by DNA-binding molecules such as transcription factors, simulation with fine grains is conducted when the molecule approaches DNA, and with a more coarse-grained model at other times. Although this is not exactly a multiscale model but rather a *multi-resolution* model, we tried to construct such a simulation with variable resolution, based on a polymer chain (bead-spring) model.

We started with the model previously described in [4] and considered parameter conversion, or renormalization of the polymer chain. Using the conversion rule, we constructed a mixed-resolution model and a conceptual simulation (Fig. 11), with different coarse-graining levels of beads and springs. To generate a variable (on demand) resolution model (Fig. 12), methods to coarse- or fine-grain the elements and the criteria to do so (e. g., the distance to the DNA-binding molecule) must be defined. In particular, reconstruction of finer grain structure, keeping consistency of the microscopic structural states, is crucial and still ongoing.

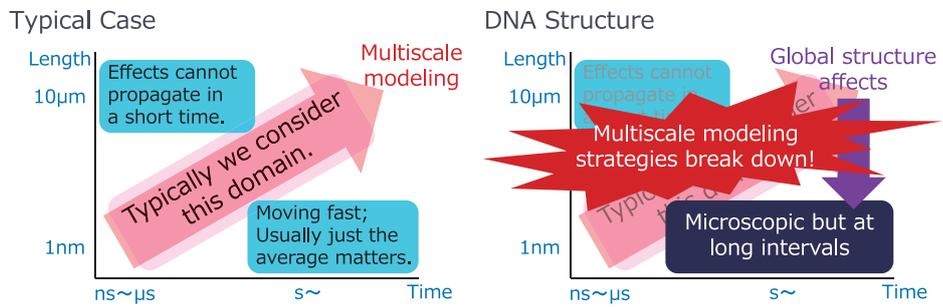
### 4.3.3 Discussion and Future Direction

Spatiotemporal organization of the cell nucleus is currently drawing attention, and an international consortium for *nucleome* studies will be created [9, 10]. Whole-nucleus modeling will be a requirement in the near future, and while the fundamental challenge of multiscale modeling of DNA structures discussed here persists, there is a need to devise a solution.

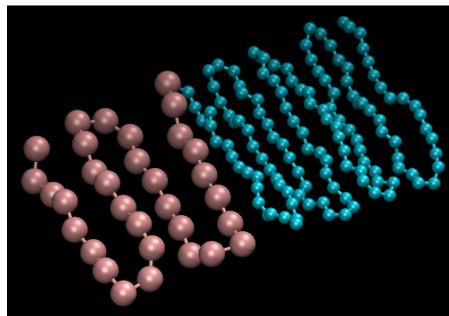
As mentioned earlier, polymer-like models are simple and can be combined with molecular dynamics or reaction-diffusion simulations at the microscopic scale, and phenomenological models at the macroscopic scale. Multi-resolution approaches, as considered here, may be useful to overcome the hurdle of scales to proceed toward multiscale modeling and application.

### References

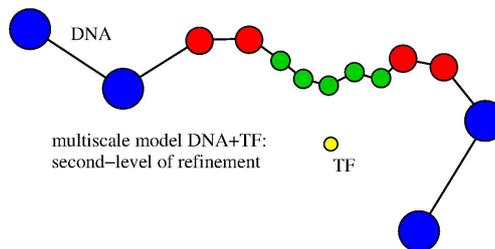
- 1 S. Hihara et al., “Local Nucleosome Dynamics Facilitate Chromatin Accessibility in Living Mammalian Cells”, *Cell Rep.* 2, 1645 (2012).
- 2 Y. Chikashige et al., “Telomere-Led Premeiotic Chromosome Movement in Fission Yeast”, *Science* 264, 270 (1994).
- 3 S. Jun and B. Mulder, “Entropy-driven Spatial Organization of Highly Confined Polymers: Lessons for the Bacterial Chromosome”, *Proc. Natl. Acad. Sci. USA* 103, 12388 (2006).
- 4 A. Rosa and R. Everaers, “Structure and Dynamics of Interphase Chromosomes”, *PLoS Comput. Biol.* 4, e1000153 (2008).
- 5 H. Wong et al., “A Predictive Computational Model of the Dynamic 3D Interphase Yeast Nucleus”, *Curr. Biol.* 22, 1881 (2012).
- 6 R. Hancock and K. W. Jeon eds., *New Models of the Cell Nucleus: Crowding, Entropic Forces, Phase Separation, and Fractals*, *Intl. Rev. Cell Mol. Biol.*, Vol. 307 (2014).
- 7 J. Dekker, K. Rippe, M. Dekker and N. Kleckner, “Capturing Chromosome Conformation”, *Science* 295, 1306 (2002).
- 8 R. Erban, “From Molecular Dynamics to Brownian Dynamics”, *Proc. Roy. Soc. A* 470, 20140036 (2014).
- 9 The 4D Nucleome program, National Institutes of Health, U.S. <http://commonfund.nih.gov/4Dnucleome/index>
- 10 Platform for Dynamic Approaches to Living System, MEXT, Japan. <http://www.mls.sci.hiroshima-u.ac.jp/chrom/en/>



■ **Figure 10** Challenges for multiscale modeling of DNA structure.



■ **Figure 11** A conceptual model with mixed resolution (simulation snapshot).



■ **Figure 12** Schematic representation of the variable resolution model. Fine-grained structures are simulated only when the DNA-binding molecule (TF) approaches.

## 4.4 Dictyostelium discoideum: Aggregation and Synchronisation of Amoebas in Time and Space (Team 6)

Marco Beccuti, Mary Ann Blätke, Martin Falk, Simon Hardy, Monika Heiner, Carsten Maus, Carsten Nähring, and Christian Rohr

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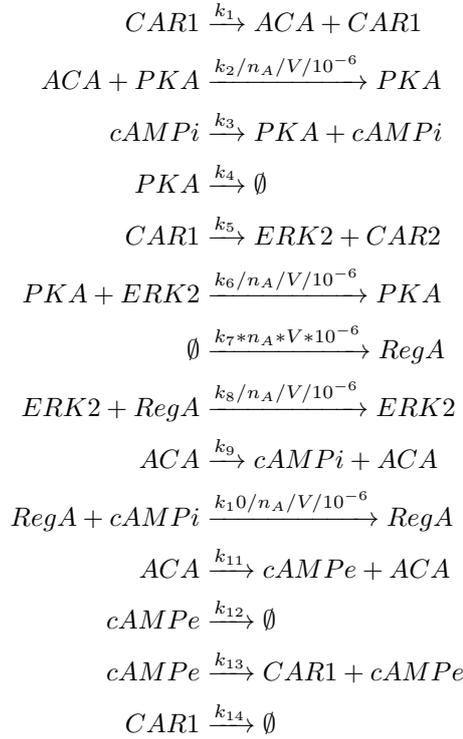
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Modelling the *Dictyostelium discoideum* amoeba aggregation process during their unique asexual life cycle is a multiscale challenge involving their movement, which is a result of the oscillating *cAMP* reaction diffusion system. The *cAMP* reaction diffusion system is controlled by an intracellular signalling mechanism of sensing and processing the *cAMP* signal and secreting produced *cAMP*. So far there exist (1) physical models, describing the details of movement of amoebas during their aggregation, but abstracting the signalling mechanism by an abstract mathematical function, and (2) biochemical models of the signalling mechanism neglecting the movement. The goal of our project is to integrate both aspects, the movement and the signalling mechanism in a single coherent model. To achieve this goal, we applied four complementing modelling approaches: (1) low-level Petri nets with hierarchical simulation, (2) coloured Petri nets with standard simulation techniques, (3) ML-Rules, and (4) cellular automata combining ODEs, PDEs and a cellular Potts Model. All approaches are able to qualitatively represent the model of amoeba movement coupled with the signalling mechanism. But in any case, the computation of the model behaviour is the challenging crux. Thus, the modelling formalism is less an issue than the applied simulation technique. As already known, parallel or hierarchical simulation techniques have a better overall performance and are thus more appropriate for multiscale models of chemotactical processes like the aggregation process of *D. discoideum* amoebas.

### 4.4.1 Background

*Dictyostelium discoideum* amoebas are single soil-living eukaryotic cells with a unique asexual life cycle consisting of four stages: vegetative growth, aggregation, migration and culmination. The involved processes transform the unicellular amoebas first into a multicellular slug and then into a fruiting body within its lifetime. The aggregation is crucial for the life cycle and is the result of starvation of *D. discoideum* amoebas, which initiates a regulatory process based on *cAMP*. *cAMP* acts as a hormone-like signal among the amoebas. The amoebas sense and process the *cAMP* signal and secrete newly produced *cAMP* to their environment. The secreted *cAMP* forms a reaction-diffusion system, which is able to oscillate. The amoebas adjust their movement according to the resulting temporal *cAMP* gradient, thereby the amoebas stream along different branches towards the center and form a multicellular aggregate.

Modelling the aggregation process of *D. discoideum* amoebas is a challenging multiscale problem, which has already been addressed by several studies, which can be divided into two model types: (1) physical models of the aggregation process describe the movement and interaction among amoebas in great detail and abstract the internal signalling process by an abstract function or pre-compute the behaviour of amoebas as a function of the *cAMP* gradient in their direct environment [4]; and (2) biochemical models describing the sensing of the *cAMP* signal, the internal signalling process and the secretion of newly produced *cAMP*, but neglecting the physical part of the aggregation process [14].



■ **Figure 13** Chemical Reaction Equation of the internal signalling mechanism of *D. discoideum* amoebas.

The aim of our project is to create a coherent model which integrates both aspects, the internal signalling process and the aggregation process of single amoeba cells based on the *cAMP* reaction diffusion system. For this purpose, we apply four complementing modelling approaches: (1) low-level Petri nets modelled in GreatSPN [1] with a hierarchical simulation performed by a C++ standalone application, (2) coloured Petri nets with standard simulation techniques in Snoopy [12], (3) ML-Rules with a stochastic simulation algorithm [17], and (4) cellular automata approach combining ODEs, PDEs and a cellular Potts Model in Morpheus [22].

The model design of all approaches is based on two publications from *Kim et al.* [14] and *Cavoli et al.* [4]. From the paper *Kim et al.* [14], we extracted the chemical reaction equation of the intracellular signalling network of *D. discoideum* amoebas, see Fig.13. All parameter and constant values used in the reaction equations shown in Fig.13 are also given in [14], as well as the initial number of molecules for each species. The paper from *Cavoli et al.* [4] describes the physical model of *D. discoideum* amoeba movement.

All approaches were able to qualitatively represent the model of *D. discoideum* amoeba movement coupled with the signalling mechanism. The challenging crux is the computation of the dynamic behaviour of the amoeba population in space. Thus the modelling formalism is less an issue than the applied simulation technique. As already known, parallel or hierarchical simulation techniques have a better overall performance and are thus more appropriate for multiscale models of chemotactical processes like the aggregation process of *D. discoideum* amoebas.

In Section 4.4.2, we will discuss the multiscale challenges involved in aggregation of *D. discoideum* amoebas in detail. Section 4.4.3 gives an detailed overview of each approach used in this project, as well as the results that have been achieved so far in modelling and simulating the model of *D. discoideum* aggregation. Finally, we briefly compare and summarise the overall results of the applied modelling approaches.

#### 4.4.2 Multiscale Challenges

The modelling of *D. discoideum* amoeba aggregation implicates several multiscale modelling challenges in time and space. The aggregation process implies the spatial arrangement and movement of single amoebas in space, as well as the diffusion of *cAMP*. Both, *D. discoideum* amoebas and *cAMP*, form temporal patterns and are thus subjected to a spatial arrangement. The amoebas use *cAMP* as a hormone-like signal to communicate with each other and to adjust their movements to form the aggregate. Since we do consider a specific signalling mechanism that processes the *cAMP* signal, we also imply a hierarchical organisation of the amoebas. Last but not least, the *cAMP* diffusion, the intracellular signalling and the movement of single amoebas happen on different time scales.

#### 4.4.3 Approaches

In order to create and simulate the model of *D. discoideum* amoeba aggregation, which involves the movement of single amoebas, the internal signalling process and the *cAMP* reaction-diffusion system, we apply four complementing modelling approaches: (1) low-level Petri nets in GreatSPN [1] with hierarchical simulation performed with a C++ standalone application, (2) coloured Petri nets with standard simulation techniques in Snoopy [12], (3) ML-Rules with a stochastic simulation algorithm [28] and (4) cellular automata approach combining ODEs, PDEs and a cellular Potts Model in Morpheus [22].

#### 4.4.4 Hierarchical Simulation Based on a Petri Net Model

##### Petri Nets in a Nutshell

Petri Nets [19] are a formal modelling language based on a graphical notation with a precise mathematical definition, which includes a formal syntax and formal semantics. A Petri net is a bipartite directed graph with two types of nodes: *places* and *transitions*. The places, graphically represented as circles, correspond to the state variables of the system (e.g., chemical compounds, specific enzymes), while the transitions, graphically represented as rectangles, correspond to the events (e.g., chemical reactions) that can induce system state changes. Places and transitions are connected by directed arcs expressing the relations between states and event occurrences. Tokens, graphically represented as black dots, are used to represent the value of the system state variables, so that the state of a Petri net model, called marking, is represented by the number of tokens in each place. The evolution of a Petri net is given by the occurrence of enabled transitions, where a transition is enabled if and only if each input place contains a number of tokens greater or equal than a given threshold defined by the multiplicity of the corresponding input arc. A transition occurrence, called firing, removes a fixed number of tokens from its input places and adds a fixed number of tokens to its output places (according to the multiplicity of its input/output arcs). Based on the definition of standard Petri nets, several specialised Petri net classes have been derived. Their specialisation might be due to the extension of the syntax, e.g. the introduction of additional arc types (e.g., inhibitor arcs, reset arcs) or transitions (e.g., immediate transitions), or

based on the use of a different semantics (e. g. time semantics). For instance, the semantic of Stochastic Petri nets (SPN) [18] is defined by a continuous-time Markov chain (CTMC) [23], where the semantics of continuous Petri nets refers to a structured description of an ordinary differential equation system. The combination of both semantics yields hybrid Petri nets, which can be represented as Piecewise Deterministic Markov Processes (PDMP) [6].

Several functional properties of the model, like boundedness, the occurrence of structural deadlocks and traps, can directly be derived by exploiting the Petri net graph representation independently of its initial marking, while the temporal analysis of the model requires analytical or numerical simulation approaches.

Due to the generalised syntax and different semantics a Petri net can feature besides the principle locality and the ability to express concurrency, Petri nets are ideally suited to describe biological systems. This has already been proven in several case studies for example covering the internal signalling of the *D. discoideum* amoebas during their aggregation process. There exist several powerful Petri net tools to design and analyse Petri nets in various ways. The most popular tools for this task are (in alphabetical order) Charlie [8], GreatSPN [1], LOLA [21], Marcie [13], PEP-Tool [11], Snoopy [12], and TINA [3].

### Standard diffusion processes in a Nutshell

A continuous time stochastic process with (almost surely)<sup>1</sup> continuous sample paths fulfilling the Markov property is called a *diffusion* process. The simplest and most fundamental diffusion process is the Brownian motion  $B(t)$ , also known as Wiener process  $W(t)$ .

► **Definition 1.**  $B(t)$  is a Brownian motion if it is a diffusion process satisfying:

- $B(0) = 0$ ,
- $E[B(t)] = 0$  and  $Var[B(t)] = \sigma^2 t$ ,
- $B(t)$  has a stationary, independent increment.

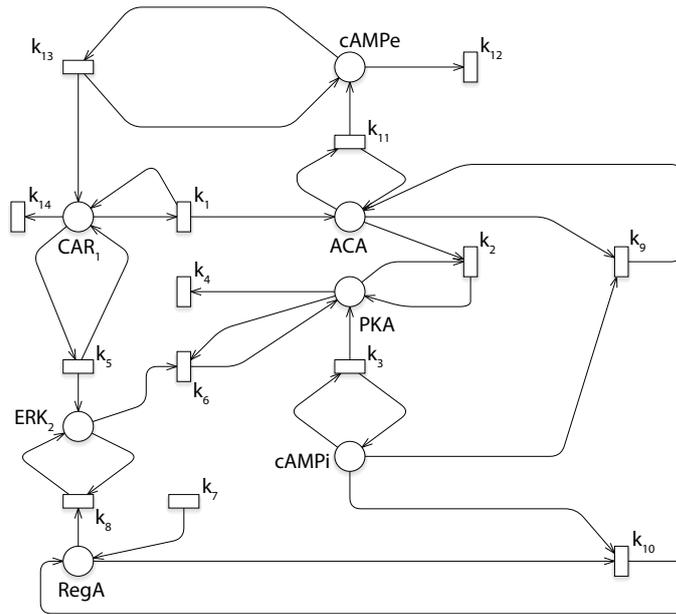
Several physical processes, which are continuous (in space and time) and satisfying the Markovian properties, can be modelled as a Brownian motion, for instance: molecular motion, stock market fluctuations, communications systems, neurophysiological processes. Moreover, discrete processes (e. g. population growth models, disease models, queuing models for large systems) can be well approximated by this diffusion in its limit when the discretisation becomes smooth. In our proposed approach we model the diffusion of the *D. discoideum* amoeba through a Stochastic Differential Equation (SDE) system depending on the concentration of *cAMP* in the system's environment. The Brownian motion is introduced to capture the stochastic nature of the process. An example of this diffusion is provided in the next subsection.

### Model of *D. discoideum* Aggregation

In this section we describe a new multi-level approach to model and analyse the aggregation process of *D. discoideum* amoebas during their unique asexual life-cycle. In particular, we consider a 2-level model, in which the first level, modelled using the SPN formalism, describes the internal signalling of the *D. discoideum* amoebas. The second level models instead the movement of the *D. discoideum* amoebas through an SDE system representing the diffusion process. The interactions between the two levels are defined in terms of the *cAMP* concentration.

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<sup>1</sup> “almost surely” means “with probability 1”



■ **Figure 14** SPN model describing the internal signalling of a single *D. discoideum* amoeba.

**Internal signalling of the *D. discoideum* amoeba.** To model the internal signalling of the *D. discoideum* amoebas we focus on the SPN formalism, so that the temporal behaviour of the quantities of the chemical compounds is modelled by a random process governed by the so-called Chapman-Kolmogorov differential equation [7] corresponding to the behaviour of a biological system described by the chemical Master Equation [9]. However, due to time constraints, fluid approximation [15] are exploited to speed-up the solving process. With these approximations the temporal behaviour of the compounds contained in different places becomes a completely predictable process. The fluid approximation translates the system reactions into ODEs with one equation per place according to the law of Generalised Mass Action (GMA) [24]. Hence, the ODE system describing the model by means of GMA is of the form:

$$\frac{dX_i(t)}{dt} = \sum_{j=1}^{N_i} k_{ij} \prod_{h=1}^E X_h(t)^{g_{ijh}} \quad (i = 1, \dots, E)$$

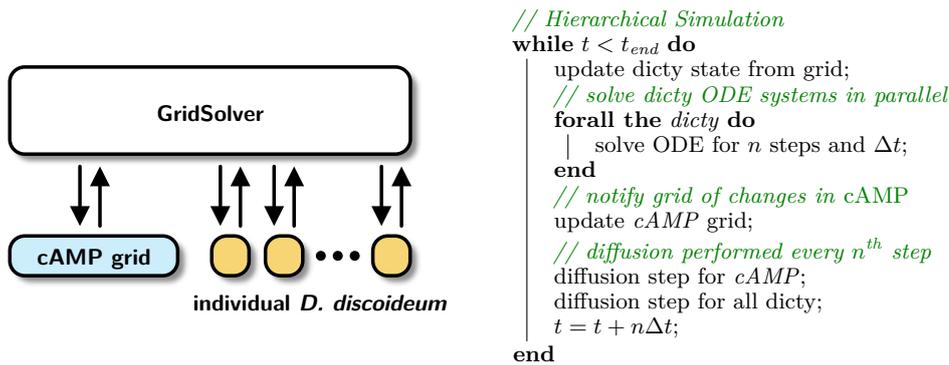
where  $E$  is the number of interacting compounds and  $X_i(t)$  the amount of the  $i^{\text{th}}$  compound at time  $t$ . Moreover,  $N_i$  is the number of reactions in which the  $i^{\text{th}}$  compound is involved, the parameters  $k_{ij}$  are rate constants describing the speeds of these reaction and the parameters  $g_{ijh}$  are the kinetics orders which depend on the stoichiometry mechanism of the reactions.

Fig. 14 shows the SPN model describing the internal signalling of a single *D. discoideum* amoeba according to the fourteen chemical reactions given in Fig. 13. Then, this SPN model is replicated for each *D. discoideum* amoeba in the system.

**Movement of the *D. discoideum* amoebas.** The diffusion process of each *D. discoideum* amoebas is of the form:

$$\frac{dX_i(t)}{dt} = D \cdot f(X_i(t), \nabla cAMP(t)) dt + \sqrt{D \cdot f(X_i(t), \nabla cAMP(t))} dB_i(t)$$

where  $D$  is the diffusion coefficient,  $f$  is a function returning the *D. discoideum* amoeba movement direction according to its current position (i. e.,  $X_i(t)$ ) and  $cAMP$  gradient (i. e.,



■ **Figure 15** The GridSolver is responsible for the communication between *cAMP* grid and individual *D. discoideum* amoeba (left). The key component of the GridSolver is the algorithm for the hierarchical simulation (right).

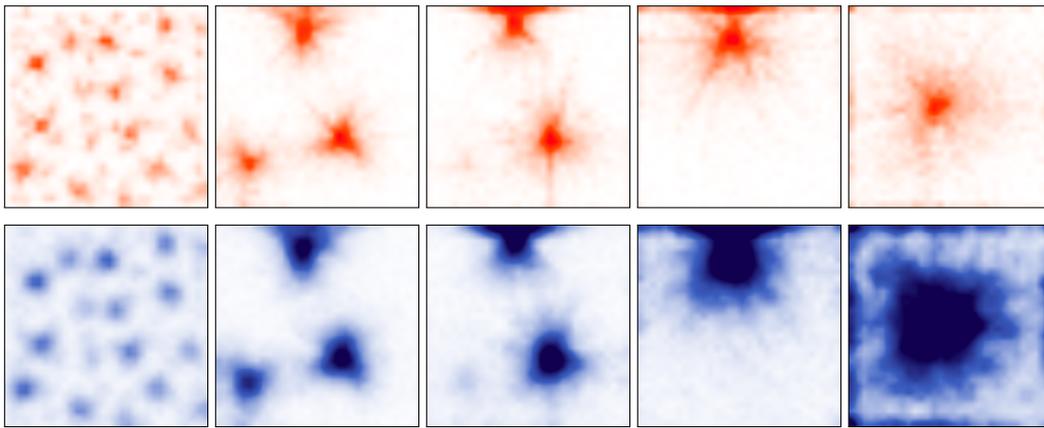
$\nabla cAMP(t)$ ). The initial position of the  $i^{\text{th}}$  *D. discoideum* amoeba  $X_i(0)$  and the *cAMP* gradient are randomly initialised. Moreover, the *cAMP* gradient is updated after every movement step according to the first level model.

### Experimental Setup

In this approach, we use GreatSPN to derive a structured ODE system from the Petri net model describing the internal signalling of the *D. discoideum* amoebas (see [2] for more details on this new GreatSPN feature). The ODE system is converted into a single C++ class file including a numerical solver utilising either the Euler method or a stochastic approach relying on SDEs. The use of this class allows us to set up and simulate a single amoeba independent of the others. The structure of the hierarchical model is also reflected in our prototypical implementation. Fig. 15 depicts the software architecture as well as the algorithm used for the hierarchical simulation. Since the internal simulation of the individual amoeba is handled independently of the environment, we use a superordinate coordinator called *GridSolver*. This GridSolver is responsible for synchronising the amoeba with their local environment. In the current set-up, the environment is modelled as a two-dimensional uniform grid and consists only of *cAMP* molecules following a Brownian motion. These molecules can, however, feature local variation in density caused by *D. discoideum* amoeba. The individual *D. discoideum* instances feature a unique ID and a 2D position, within the simulation domain defined by the *cAMP* grid.

To simulate the entire system, the algorithm (cf. Fig. 15, right) is executed by the GridSolver. First, the internal states of all amoeba are updated according to the local *cAMP* concentrations. After this update step, the ODE system of each amoeba is solved individually by calling the aforementioned solver generated by GreatSPN. Since the ODE solvers have no interdependency, we can easily parallelise their computations in multiple threads. For now, we are using the functionality provided by OpenMP<sup>2</sup> to enable parallelisation on a single compute node. Each solver performs  $n$  steps with a step width of  $\Delta t$ . As the amoeba can consume and produce *cAMP*, these changes in the *cAMP* concentration have to be propagated to the *cAMP* grid to be in sync. Then, we perform a diffusion step for all *cAMP*

<sup>2</sup> <http://www.openmp.org>



■ **Figure 16** Results of our hierarchical simulation approach for 10 000 *D. discoideum* amoeba and 100 000 *cAMP* molecules. The *D. discoideum* amoeba (orange) are randomly distributed at  $t = 0$  min, but clearly tend to accumulate after some time. The corresponding *cAMP* concentration is depicted in blue.

molecules and update the *cAMP* grid. As a final step, the *D. discoideum* move with respect to a Brownian motion, which is, however, influenced by the local *cAMP* concentration gradient.

By adjusting the number of steps  $n$  of the ODE solvers, we can fine-tune the interval between local and global interactions. For low  $n$ , the diffusion process will be in lock-step with the simulation of the internal state of the *D. discoideum*. This will, however, annihilate the gains obtained by the parallelisation. On the other hand, increasing  $n$  will lead to a higher CPU utilisation due to less communication and synchronisation via the GridSolver.

We implemented the proposed hierarchical algorithm in a C++ test application and run some experiments. The simulation domain corresponded to a physical size of  $1 \text{ mm} \times 1 \text{ mm}$  and was divided into  $32 \times 32$  uniform grid cells. Both, *D. discoideum* amoeba and *cAMP* molecules are randomly distributed on the grid. At  $t = 0$ , the scene contained 10 000 amoeba and 100 000 *cAMP* molecules. For diffusion coefficients we used the values reported by Calovi et al. [4], i. e.  $D_{\text{Dicty}} = 0.024 \text{ mm}^2 \text{ min}^{-1}$  and  $D_{\text{cAMP}} = 0.024 \text{ mm}^2 \text{ min}^{-1}$ . We perform  $n = 833$  steps with  $\Delta t = 18 \mu\text{s}$  to solve the ODEs before the diffusion process takes place. Altogether, 1600 diffusion steps were computed yielding a total simulated time of 400 minutes. The computations were run on a Intel Xeon CPU, 2 GHz, with 6 cores and hyperthreading enabled. The calculations were completed after 13 minutes. The results are depicted in Fig. 16. Although being randomly distributed in the beginning, the *D. discoideum* amoeba aggregate and move around as a single unit. However, despite the visible aggregation we have not seen any pattern emerging from the movements so far. Further investigations will be performed with respect to parameters and modelling.

## Discussion

In this section we have proposed a new promising approach to study the aggregation process of *D. discoideum* amoebas during their unique asexual life-cycle, in which the system is defined through a **multiscale model** and analysed using a **hierarchical simulation method** based on a fluid approximation of the system behaviour. We have shown how the description of this system in terms of a **multiscale** model has allowed us to easily find a solution of the internal signalling of the *D. discoideum* amoebas. Then, this aspect together with fluid approximation has provided an important speed-up of the solution process allowing us to

easily analyse more complex models (in terms of *D. discoideum* amoeba population and space size). Moreover, the proposed SDE diffusion is able to capture the stochasticity of the original system, so that a better approximation is obtained.

Two future directions will be investigated: 1) how to exploit the system symmetries (e. g., in terms of internal signalling of the *D. discoideum* amoebas) to further speed-up the solution process; 2) how to model the internal behaviour of each *D. discoideum* amoeba through an SDE system to obtain a better approximation.

#### 4.4.5 Coloured Petri Nets for Multiscale Systems

##### Coloured Petri Nets in a Nutshell

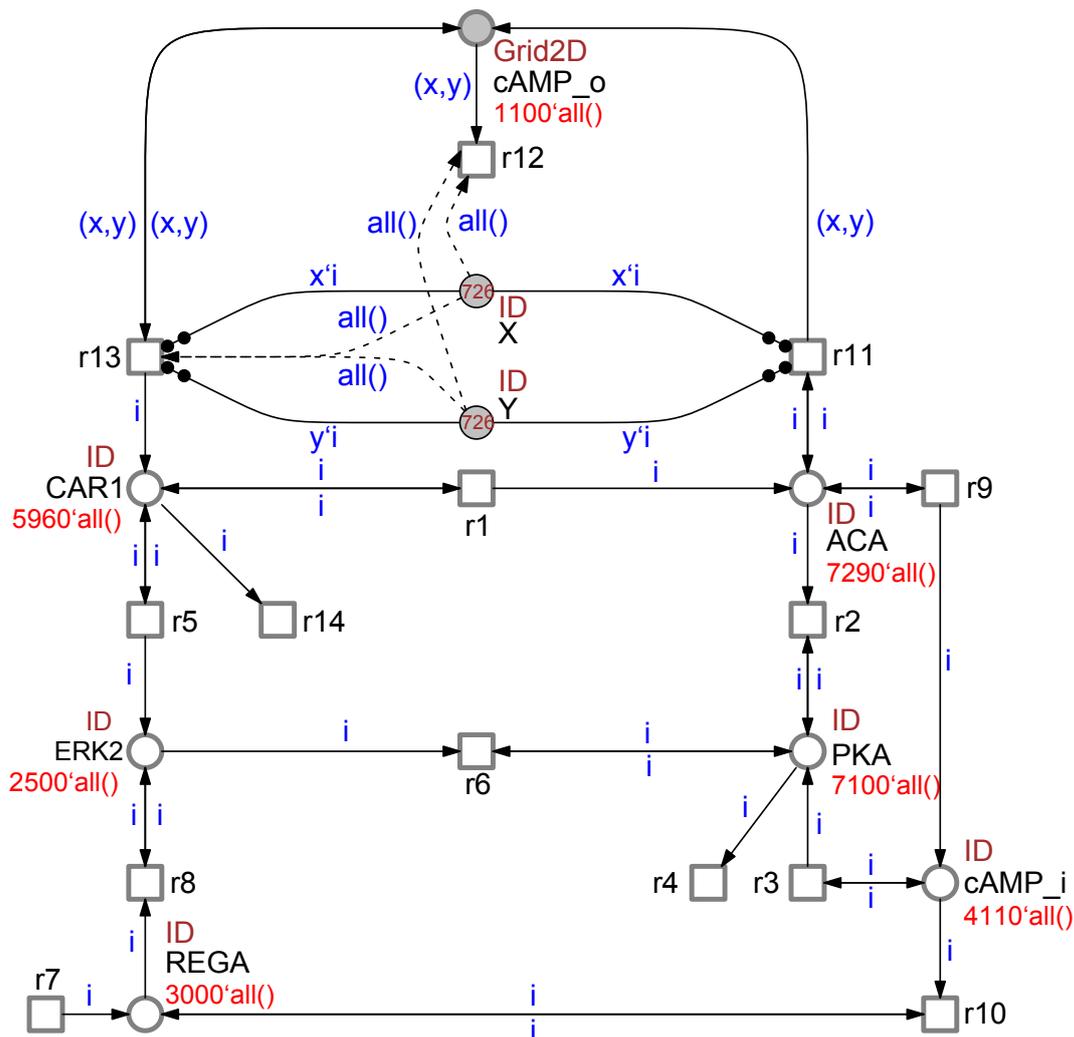
The general concepts of Petri nets has already been explained in Section 4.4.4. The coloured Petri net formalism is an high level formalism, which extends the Petri net formalism with “colour”. Its main feature is the possibility of having distinguished tokens, which can be graphically represented as dots of different colours: the colour attached to a token carries some kind of information. This formalism provides two advantages: a more compact and readable representation of the system, and the possibility of using efficient solution techniques. The definition of data types (e. g. integer, string, Boolean, etc.) and operations based on these data types in coloured Petri nets allows us to annotate nodes and arcs of the Petri net graph. *Colour sets* are associated with places and are defined by a data type and a set of corresponding entities, which refer to the number of existing place instances. *Variables* of the defined colour sets permit to access the currently available colours and are used in arc expressions to allow the flow of tokens of their bound colours along an arc. Variables can also be used to define *predicates* and *guards*, both are Boolean expressions, which impose restrictions to the colour set by permitting only a subset of colours. Predicates are used in arc expressions (only a subset of colours may flow a long the arc), to define the marking (place instances can have different markings) and firing rates (transition instances can have different firing rates depending on the colour). Guards are used for transitions to restrict the number of existing transition instances. Coloured Petri net allow also to define *constants* of different data types, which can also be used to define colour sets, predicates and guards. The annotations used in a coloured Petri net can be unwound to obtain a corresponding unfolded Petri net. Vice versa, each Petri net can be folded into a coloured Petri net using annotations.

Popular tools for coloured Petri nets are CPNTools [20], GreatSPN [1], and Snoopy [12].

The extension of low-level Petri nets to coloured Petri nets does not only allow the representation of simple biological systems like metabolic signalling or gene regulatory networks, but also the expression of complex multiscale systems. The use of coloured Petri nets allows to easily model multiscale systems with:

- repetition of identical or varying components,
- spatial or hierarchical organisation of components,
- communication processes among components,
- movement of components,
- replication, deletion or differentiation of components,
- pattern formation of components in time and space (1D, 2D, 3D).

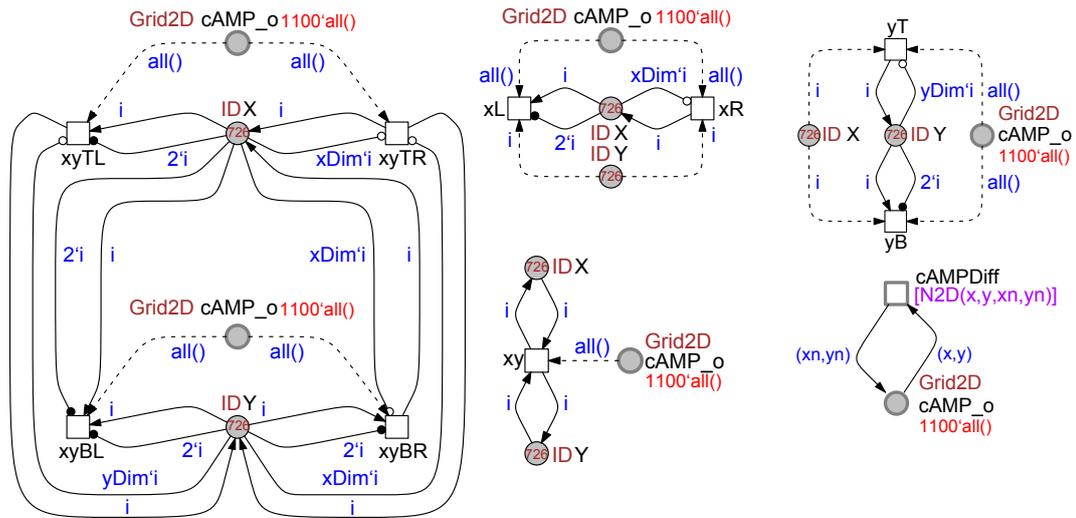
In this sense, a component can be a gene, a molecule, a cellular component, a cell, a multicellular complex, a tissue, an organ, an organism, or a population etc. Thus coloured Petri nets can express the internal signal network and aggregating movement of *D. discoideum* amoebas, as well as the *cAMP* reaction-diffusion system.



■ **Figure 17** Intracellular signal network of *D. discoideum*.

### Model of *D. discoideum* Aggregation

We built a coloured Petri net model of *D. discoideum* aggregation in combination with its intracellular signal network. The intracellular signal network was modelled based on [14]. It could be rebuild very well, and acted in accordance with the settings. The use of coloured Petri nets allows us to create many instances of the signalling network very easily. Therefore we made an integer colour set, called ID, and one colour of ID stands for one amoeba. The colour set was assigned to each place of the signal network, except external *cAMP*. This was used to connect all instances. At this stage, all instances of the amoeba are fixed at the same position. In order to enable movement of *D. discoideum* amoebas, we added two places X and Y defining the position of it. The number of tokens on X and Y is treated as x- and y-coordinates. This technique models space implicitly, whereas we used the explicit space modelling for external *cAMP*. To achieve this, we assigned a product colour set, called Grid2D to external *cAMP*. So this unfolds to one *cAMP* place for each grid position. Fig. 17 shows the intracellular signal network including external *cAMP*.



■ **Figure 18** Movement subgraphs of *D. discoideum*: (a) diagonal movement, (b) horizontal movement, (c) vertical movement, (d) no movement, and (e) diffusion of external *cAMP*.

■ **Table 4** Size of the unfolded Petri net.

$ Dicty $	Grid Size	$ Places $	$ Trans $	$ Arcs $
25	$5 \times 5$	225	1919	46 163
125	$11 \times 11$	1089	32 663	3 859 523

Additionally, the movement of the amoeba is modelled as coloured Petri net, too. Fig. 18 (a-d) show the subnets responsible for the movement. There is one transition moving an amoeba in the desired direction. This leads to eight movement transitions and one transition for staying at the current position. Fig. 18 (d) shows the diffusion of external *cAMP*.

We started with a coloured stochastic Petri net and used the kinetic rates given in [4]. But we recognised that we couldn't get results in reasonable time, even for a small number of *D. discoideum* (25 amoeba) and a grid size of  $5 \times 5$ . We decided to switch to coloured hybrid Petri nets. In contrast to the stochastic case, some parts of the net are now treated in a continuous way. So, all places and transitions related to the movement of the amoeba remain discrete; and the intracellular signal network, as well as the external *cAMP* diffusion became continuous. We got a significant performance boost using this approach and were able to simulate 121 amoeba and a grid of  $11 \times 11$ .

The size of the unfolded Petri nets are given in Table 4. The large number of arcs is conspicuous and indicates strong dependencies in the net.

## Discussion

This kind of system can be modelled in an intuitive way using coloured Petri nets. It's quite easy to model large populations of amoeba like *D. discoideum* and large grid sizes, too. But afterwards we have to deal with two problems. First, the coloured Petri nets have to be unfolded, which is a non-trivial problem, but is handled well in tools like Snoopy or CPNTools. Second, multiscale models tend to have large discrepancies in the kinetic

rates, which is the most challenging part, when it comes to analysing and simulating such models. Pure stochastic approaches are not able to handle this case in reasonable time, even approximative algorithms like  $\tau$ -leaping are overburdened. On the other hand, pure continuous approaches can not simulate discrete events. So the hybrid approach is the most promising so far. Despite that, there is great potential for parallel computing which is not exploited so far.

#### 4.4.6 Rule-based Multilevel Modelling with ML-Rules

##### ML-Rules in a Nutshell

ML-Rules is a rule-based language for modelling biological systems and their dynamics at different levels of a nested hierarchy [28, 16]. Its semantics is discrete population-based and translates basically to continuous-time Markov chains (CTMCs). Consequently, and since this is often required for describing cell biological systems at multiple levels, stochasticity is an essential feature of ML-Rules.

The basic model entities in ML-Rules are called *species*, which may represent any object of interest, e. g., a cell or a protein. Each species consists of a name and a fixed tuple of attributes (similar to Petri nets with colours). Attributes are written within parenthesis behind the species name, e. g.,  $A(\text{"on"}, 5)$  describes a species with name “A” and two attributes “on” and “5”. In addition, ML-Rules supports the concept of *nested species* to build hierarchical model structures, i. e., species can be enclosed by other species and can enclose other species themselves. That means, species are not only characterised by their names and attributes, but also by their context (the species they are enclosed by) and content (the set of species they contain, called *solution*). Nested species are specified with the help of square brackets. Note that species at any level within such a hierarchy may have assigned attributes, e. g.,  $A[B(1)[C(\text{"off"})]+C(\text{"on"})]$ , where the attribute-less root species A encloses two attributed species (B(1) and C("on")), of which B also encloses another C.

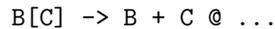
Since ML-Rules belongs to the reaction-centric family of rule-based formalisms, the dynamics of a model are described by so called *rule schemata*, each of which may encode for possibly infinitely many concrete rule instantiations, helping to effectively reduce redundancy and thereby facilitating compact model descriptions [5]. A rule schema consists of three parts: a set of reactant species, a set of product species, and a firing rate. The general notation for specifying a rule schema is as follows:

$$\text{reactants} \rightarrow \text{products} @ \text{rate}$$

A rule schema can be instantiated at any (sub-)solution of the current model state to which the set of reactants would match, i. e., the rule schema  $C \rightarrow D+E$ , which produces both species D and E from one C (the rate is omitted), would lead to two instances of the rule at two different levels of the hierarchy when applying it to solution  $A[B[C]+C]$ .

The firing rate  $r \in \mathbb{R}_0^+$  of a rule determines the frequency with which a rule is being executed. To let the rate depend on the amount of matched reactants, so called *species identifiers* can be defined through which the according species population size can be dynamically accessed. For example, the above rule could look like  $C:c \rightarrow D+E @ \#c$ , in case its rate shall be proportional to the amount of species C within a given solution. Rate kinetics in ML-Rules are not restricted to the law of mass-action, which is an important feature for multilevel modelling in general [16]. Complex mathematical expressions and conditional constraints are allowed to manipulate the reaction rate of a rule schema, e. g., to specify thresholds that control a rule to only fire if a certain amount of reactants is available.

To model upward and downward causation between different hierarchical levels, ML-Rules supports the specification of rule schemata that involve nested reactant and product species. In the same way, changing the model structure dynamically becomes possible by specifying nested reactants and products of a rule, which is another important feature for specifying biological multilevel models, since many biological processes, e. g., endocytosis, cell division, and death, are changing the hierarchical composition of the system. Similarly as has been described above, nested reactants and products are specified by using square brackets. For example, the following rule describes the release of a species C from a species B that encloses C:



Additionally, to bind the *remainder-solution* of B, a special variable of type <name>? can be introduced:



In this case, the special variable `sol?` binds all species contained by the matched species B, except the one (C) explicitly specified. Without this variable, all enclosed species would get lost after firing, because the semantics assumes product species being substitutes and not modifications of the reactants.

### Model of *D. discoideum* Aggregation

To describe the model of *D. discoideum* amoeba aggregation in ML-Rules, first all constant parameters and species types need to be defined (Fig. 19, lines 1-5). An integer number within parenthesis behind the species name defines the number of attributes for each species, i. e., in this example most species do not have assigned attributes, while both external *cAMP* (`cAMPe`) as well as the *D. discoideum* amoebas (`CELL`) have two attributes, one for each coordinate in a 2-dimensional space. Species `nc` is an artefact needed to describe a certain reaction, which will be discussed later.

The next step is to define the initial model state (initial solution), which is realised with the help of two nested for-loops in order to place one *D. discoideum* amoeba and a certain amount of external *cAMP* (`init_cAMPe cAMPe(x,y)`) to each position in space (Fig. 19, lines 9-12). The spatial environment is thus only implicitly defined by the two parameters `xmax` and `ymax` describing upper boundaries of the x and y coordinates. In addition, each instance of the `CELL` species contains a couple of different species (lines 13-18) to also model intra-cellular proteins.

Modelling the intra-cellular biochemical reactions (Fig. 20, lines 2-12) does typically not require to write down the enclosing cell compartment, due to the initial set-up and dynamic instantiation of reaction rules. However, for the zero-order reaction of RegA production a context needs to be explicitly specified (line 8). Of course this holds also true for the release of *cAMP* to extra-cellular space (line 15) and the intra-cellular production of CAR1 in dependence on external *cAMP*, where both levels of the model's hierarchy play a role. For the latter reaction, we need to introduce an additional species `nc` that is used to keep track of the total amount of *D. discoideum* amoebas at a certain position in space. Otherwise it would be impossible to specify the correct reaction rate.

Finally, rule schemata are also used to describe the spatial dynamics of the model, i. e., the movement and diffusion of cells and external *cAMP* respectively (Fig. 21). For cell movement, the amount of external *cAMP* at two adjacent grid positions constrains cell movement to the position with higher *cAMP* concentration (lines 2-4). The diffusion of external *cAMP* is

```

1 //Constant parameters
2 init_cAMPe:1100; k1:2; xmax:...
3
4 //Species definitions
5 ACA(0); PKA(0); ERK2(0); RegA(0); CAR1(0); cAMPi(0); cAMPe(2); CELL(2); nc(2);
6
7 //Initial solution
8 >>INIT[
9   for y:1 while (y <= ymax) with (y + 1) [
10     for x:1 while (x <= xmax) with (x + 1) [
11       init_cAMPe cAMPe(x,y) +
12       nc(x,y) + CELL(x,y)[
13         init_cAMPi cAMPi +
14         init_ACA ACA +
15         init_PKA PKA +
16         init_ERK2 ERK2 +
17         init_RegA RegA +
18         init_CAR1 CAR1
19       ]
20     ]
21 ]
22 ];

```

■ **Figure 19** Definiton of parameters, species, and the initial solution of the ML-Rules model.

modelled by eight rules, one for each direction in space (lines 7-14). Constraints checking for upper and lower bounds ensure that the spatial environment does not get increased during simulation.

## Discussion

We found it pretty easy and straightforward to encode the model of *D. discoideum* amoeba aggregation in ML-Rules. The model description is concise and can express all desired dynamic processes within an arbitrarily large spatial setting by a small and constant number of rules. An artefact of the model description could be avoided by a currently developed extension of ML-Rules supporting functions on solutions. This would allow to dynamically count the number of cells at each position without the need for an additional “helper” species and thus would also increase the readability of respective rules (see also [16]).

However, *modelling* is an essential but not the only important issue. To make *in-silico* experiments one must also being able to analyse or *simulate* the model. Since so far there are only stochastic simulation algorithms available for ML-Rules and due to the expressiveness of the language, execution is rather slow and hampers the simulation of larger grids and cell numbers. To speed up the simulation we scaled all initial molecule numbers and second-order reaction rate coefficients by a factor of 50, still resulting in the characteristic oscillating behaviour of intra-cellular protein amounts (Fig. 22). In addition, the application of tau-leaping [10] dramatically increases the performance of simulation runs. However, simulating larger grid sizes and numbers of *D. discoideum* amoeba seems still to be impractical with the currently available completely stochastic simulators, clearly raising the need for faster simulation algorithms or a hybrid execution semantics.

```

1 //Intra-cellular dynamics
2 CAR1:c -> ACA + CAR1 @ k1*#c;
3 ACA:a + PKA:p -> PKA @ k2*#a*#p;
4 cAMPi:a -> PKA + cAMPi @ k3*#a;
5 PKA:p -> @ k4*#p;
6 CAR1:c -> ERK2 + CAR1 @ k5*#c;
7 PKA:p + ERK2:e -> PKA @ k6*#p*#e;
8 CELL(x,y)[s?]:c -> CELL(x,y)[RegA + s?] @ k7*#c;
9 ERK2:e + RegA:r -> ERK2 @ k8*#e*#r;
10 ACA:a -> cAMPi + ACA @ k9*#a;
11 RegA:r + cAMPi:a -> RegA @ k10*#r*#a;
12 CAR1:c -> @ k14*#c;
13
14 //Release and degradation of external cAMP
15 CELL(x,y)[ACA:a + s?]:c -> cAMPe(x,y) + CELL(x,y)[ACA + s?] @ k11*#a*#c;
16 cAMPe(x,y):a -> @ k12*#a;
17
18 //CAR1 production
19 cAMPe(x,y):a + CELL(x,y)[s?]:c + nc(x,y):b ->
20     CELL(x,y)[CAR1 + s?] + nc(x,y) + cAMPe(x,y) @ k13*(#a/#b)*#c;

```

■ **Figure 20** Biochemical reaction rules in ML-Rules.

#### 4.4.7 Multiscale and Multicellular Modelling with Morpheus

##### Morpheus in a Nutshell

The modelling environment Morpheus is a simulation software that was recently published [22]. It integrates dynamical, spatial and cell-based modelling into a single multiscale and multicellular modelling framework. Unfamiliar with this tool at the beginning of the Dagstuhl workshop, our team decided to explore the features of Morpheus to build a model of the wave generation and the collective behaviour of *D. discoideum*. In our initial assessment, Morpheus seemed well-suited to model in a unified manner the intracellular *cAMP* signalling dynamics of individual amoebas with ODEs, the reaction-diffusion system of extracellular *cAMP* with PDEs and the cell motility of the amoeba collective along a *cAMP* gradient with a cellular Potts model (CPM). Such a model combining the three core formalisms of Morpheus was not available yet as an example use case on the tool Web site.

Ordinary and partial differential equations are well known mathematical formalisms and are widely used. Cellular Potts models are used to simulate the collective behaviour of cellular structures using a lattice-based approach. Each pixel of the lattice is updated following an effective energy function, also known as the Hamiltonian. This allows cells to interact through fusion, signalling, volume and surface control, chemotaxis and proliferation.

##### Model of the *D. discoideum* *cAMP* dynamics

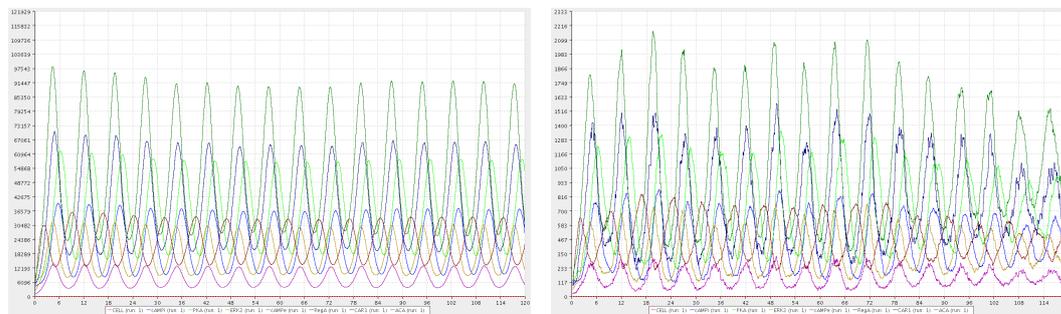
To have a basis for comparison and validation for the simulation results for the collective behaviour of the *D. discoideum* population model built with Morpheus, we used the initial conditions of the Calovi model [4] for two different contexts. In the model for the first context, the amoebas are evenly distributed on a 2D grid, 26 microns apart from one another and immobile. Each amoeba has the ODE intracellular signalling model from *Kim et al.* [14] (see Fig. 13). A reaction-diffusion system was defined for the extracellular *cAMP* (*cAMPe*).

```

1 //Cell movement to adjacent position depending on external cAMP
2 CELL(x1,y1)[s?]:c + nc(x1,y1) + cAMPe(x1,y1):a1 + cAMPe(x2,y2):a2
3   -> CELL(x2,y2)[s?] + nc(x2,y2) + cAMPe(x1,y1) + cAMPe(x2,y2)
4   @ if (#a2>#a1) && (abs(x1-x2)<1) && (abs(y1-y2)<1)
5     then kd_dicty*(#a2/#a1)*#c else 0;
6
7 //Diffusion of external cAMP
8 cAMPe(x,y):a -> cAMPe(x,y+1) @ if (y<ymax) then kd_camp*#a else 0;
9 cAMPe(x,y):a -> cAMPe(x+1,y+1) @ if (x<xmax) && (y<ymax) then kd_camp*#a else 0;
10 cAMPe(x,y):a -> cAMPe(x+1,y) @ if (x<xmax) then kd_camp*#a else 0;
11 cAMPe(x,y):a -> cAMPe(x+1,y-1) @ if (x<xmax) && (y>1) then kd_camp*#a else 0;
12 cAMPe(x,y):a -> cAMPe(x,y-1) @ if (y>1) then kd_camp*#a else 0;
13 cAMPe(x,y):a -> cAMPe(x-1,y-1) @ if (x>1) && (y>1) then kd_camp*#a else 0;
14 cAMPe(x,y):a -> cAMPe(x-1,y) @ if (x>1) then kd_camp*#a else 0;
15 cAMPe(x,y):a -> cAMPe(x-1,y+1) @ if (x>1) && (y<ymax) then kd_camp*#a else 0;

```

■ **Figure 21** Spatial dynamics rule schemata in ML-Rules.

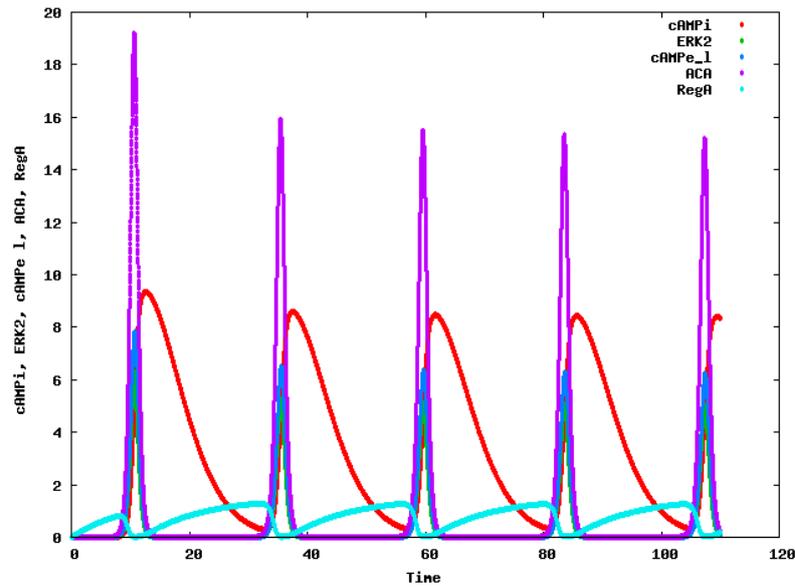


■ **Figure 22** Intra-cellular dynamics with the original (left) and scaled (right) parameters of molecule numbers and second-order reaction rate coefficients. Scaling factor  $s = 50$ .

In the PDE layer, each cell secretes *cAMP* in its surrounding according to its own cyclase activity level (variable *ACA* in the ODE model). The external *cAMP* can diffuse in space with the diffusion constant  $D$  and is also degraded linearly using the equation:

$$\frac{dcAMPe(t)}{dt} = k_{11} \cdot ACA(t) - k_{12} \cdot cAMPe(t) + D \cdot \nabla^2 cAMPe(t)$$

A PDE reporter is defined for each individual cell. The reporter averages the local *cAMP* concentration and determines the value of the variable *cAMPe* for the ODE model. In this model, the receptors of the amoebas are activated by the *cAMP* concentration level in their surrounding, in turn this activates internal signalling that leads to the production of *cAMP*, some of which is secreted. A first simulation of the intracellular dynamics shows results similar to the published data (see Fig. 23). Next, we simulated a population of 324 immobile cells and monitored the *cAMP* concentration in the media. The extracellular *cAMP* was set to 0 everywhere except in the lower left corner, where it was set to  $0.5 \mu\text{M}$ . Results show a gradual activation of the cells as a wave of *cAMP* propagates from the lower left corner (see Fig. 24). This wave does not correspond to the published data. This will be discussed in the lessons learned subsection.



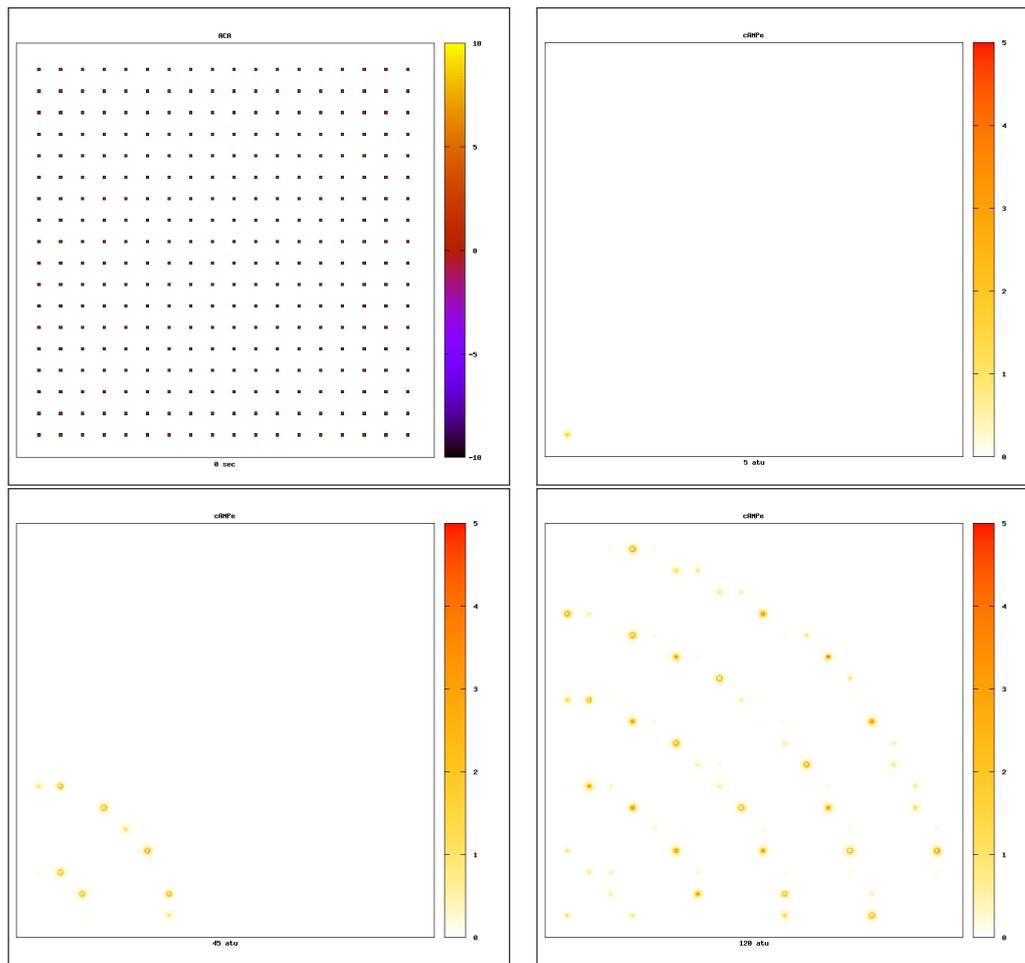
■ **Figure 23** Intracellular dynamics of the ordinary differential equations model.

### Model of the *D. discoideum* chemotaxis

Without a swirling wave, the movement of the *D. discoideum* cells can not become coordinated. Without this essential feature and failing to reproduce it for now, we nonetheless implemented a chemotaxis model with Morpheus. In this model, the intracellular *cAMP* signalling is again incorporated in each cell as ODEs. The production of internal *cAMP* and the initiation of kinase activity is regulated through the binding of the external *cAMP* to the CAR receptor. Contrary to the previous model, the cells do not secrete *cAMP* to the external pool this time. Instead, a constant gradient is maintained. *D. discoideum* cells are no longer immobile; a chemotaxis term sensitive to external *cAMP* is added to the Hamiltonian of the CPM. For an initial spatial distribution similar to the previous model and a *cAMP* gradient constant over time with maximums in the upper and lower right corners, simulation results show the expected chemotaxis behaviour of the *D. discoideum* as they accumulate in the two regions with the highest *cAMP* concentration (see Fig. 25).

### Discussion

The use of Morpheus is mostly intuitive and we were satisfied with the user interface. A lot of information is available to assist the modeller during the construction of the dynamical model. Our confidence in the tool was strengthened when the ODE numerical results obtained with Morpheus were found to be identical to the simulation results of the same equations with the software environment for statistical computing R. We liked the archive feature where every simulation results are saved along with the xml file of the model definition. This facilitates the retrieval of previous versions of the model and this feature should be appreciated by any well-seasoned modeller. We struggled with the definition of the intersection points between the ODE, PDE and CPM formalisms like the PDE reporter for the ODE or the CPM parameters defined in the CellTypes interface. Without the help from a developer of the Morpheus tool, we would not have been able to complete the two models we presented in this paper. More contextual documentation in the user interface of Morpheus should

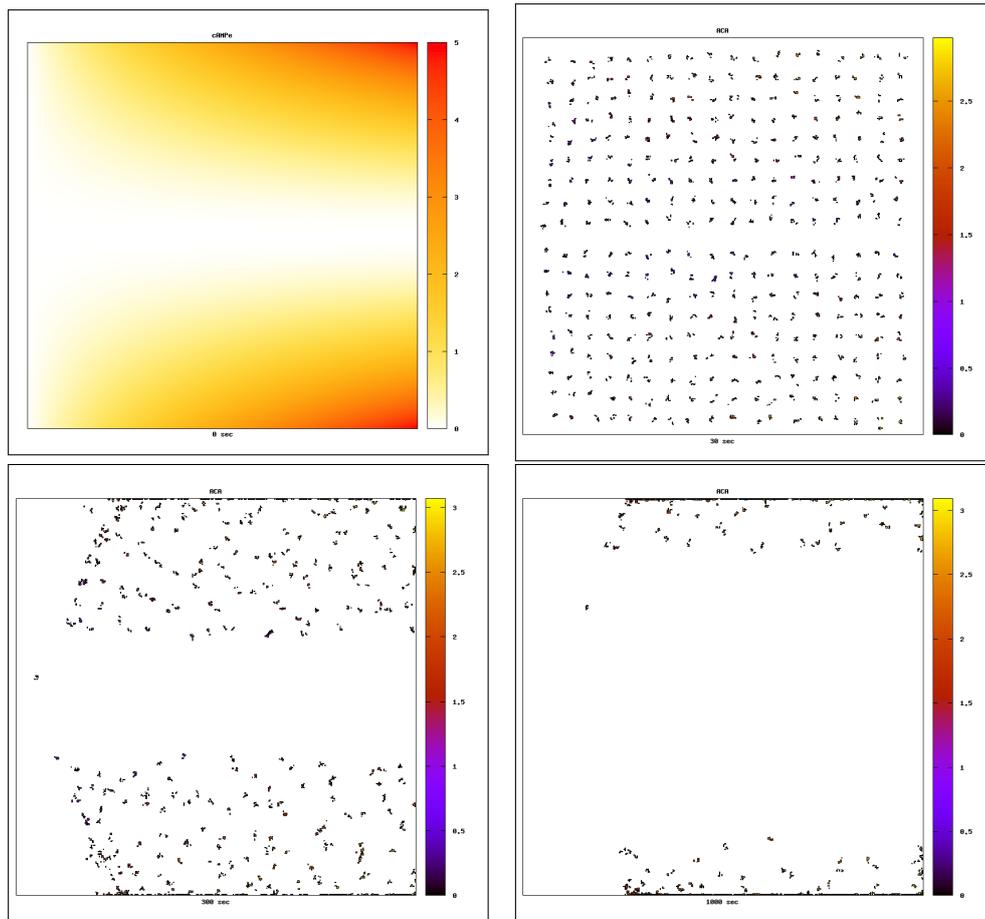


■ **Figure 24** Spatial dynamics of *cAMP* with immobile *D. discoideum*. In (a), the distribution of the cells. In (b), (c) and (d), the concentration of extracellular *cAMP* as a signalling wave propagates at 5, 45 and 120 minutes respectively.

alleviate the difficulties we experienced. A more explicit interpretation of the units for the different parameters would also be a good addition to increase Morpheus usability.

The signalling model from *Kim et al.* has an oscillatory behaviour. For future work, we need to modify this model, maybe by adding receptor desensitisation, to have an excitable behaviour. This last behaviour is necessary to relay a *cAMP* signal and to generate waves, and eventually a single, large spiralling wave.

We weren't able to generate the appropriate waves for this reason. Consequently, there is no structured *cAMP* gradient to cause a collective aggregation behaviour of the amoebas at the moment. Nonetheless, we completed our technical proof of concept by presenting two different Morpheus multiscale and multicellular models. The first model combines the signalling dynamics of 324 *D. discoideum* amoebas (ODEs) sensing and producing a *cAMP* spatial distribution (PDE). In the second model, we generated an artificial gradient (PDE) and the 324 *D. discoideum* amoebas experienced chemotaxis (CPM).



■ **Figure 25** Chemotaxis of *D. discoideum* in response to a *cAMP* gradient. In (a), the *cAMP* gradient constant throughout the simulation. In (b), (c) and (d), the spatial distribution of the cells as they move at 30, 300 and 1000 seconds, respectively.

#### 4.4.8 Discussion and Future Directions

We modelled the mechanism of *D. discoideum* amoeba aggregation by applying four different, but complementing modelling approaches: (1) low-level Petri nets in GreatSPN [1] with a hierarchical simulation performed with a C++ standalone application, (2) coloured Petri nets with standard simulation techniques in Snoopy [12], (3) ML-Rules with a stochastic simulation algorithm [1], and (4) cellular automata approach combining ODEs, PDEs and a cellular Potts Model in Morpheus [22]. Each of the four resulting models integrates the movement of amoebas, which depends on the temporal and local *cAMP* gradient and the *cAMP* reaction-diffusion system, which is given by a mechanistic description of the internal signalling process.

For all approaches it was intuitive and straightforward to encode the multiscale model of *D. discoideum* amoeba aggregation in a coherent and concise way. The expression of a large spatial setting and a large population of *D. discoideum* amoebas is easily possible for each applied approach. Thus, all approaches were able to qualitatively represent the model of *D. discoideum* amoeba movement coupled with the discrete description of the *cAMP* signalling mechanism and the *cAMP* reaction-diffusion system.

However, the performance of *in-silico* experiments to analyse and simulate the model behaviour of *D. discoideum* amoeba aggregation was the challenging part, due to the large model size and discrepancies in the kinetic rates, both are general issues for multiscale models. As the coloured Petri net and the ML Rules approach have shown, pure stochastic approaches are (currently) not suitable to handle the simulation of larger model settings in a reasonable time, which clearly raises the need for faster simulation algorithms. Here, hybrid approaches, combining stochastic and deterministic frameworks, are most promising so far. Despite that the parallelisation of simulation does also have great potential to speed up the computation time. The parallelisation of the internal signalling in *D. discoideum* amoebas has been accomplished in the approach using low-level Petri nets and a hierarchical simulation method based on a fluid approximation. Both, the parallelisation and the integration of a fluid approximation substantially decreased the simulation time, which allows the analysis of larger spatial settings and larger populations of *D. discoideum* amoebas. A speed-up of the simulation process for this approach can in the future be realised by exploiting the symmetries of the internal signalling of *D. discoideum* amoebas. Furthermore, considering the internal signalling as an SDE system could result into a better approximation.

Our experiences show that modelling of multiscale systems is less an issue than the efficient execution of *in-silico* experiments to analyse and simulate the model behaviour. There are several suitable modelling formalisms to represent complex multiscale systems in a coherent and concise way. The application of hierarchical and parallel simulation techniques have great potential to dramatically decrease the simulation time and are, thus, the key to investigate the dynamic behaviour of complex multiscale systems, like the aggregation process of *D. discoideum* amoebas and several other chemotactical mechanisms.

## References

- 1 Baair, S., Beccuti, M., Cerotti, D., De Pierro, M., Donatelli, S., Franceschinis, G.: The GreatSPN tool: Recent enhancements. SIGMETRICS Perform. Eval. Rev. 36(4), 4–9 (2009)
- 2 Beccuti, M., Bibbona, E., Horváth, A., Sirovich, R., Angius, A., Balbo, G.: Analysis of Petri net models through stochastic differential equations. In: Application and Theory of Petri Nets and Concurrency – International Conference on PETRI NETS 2014, 273–293 (2014)
- 3 Berthomieu, B., Vernadat, F.: Time Petri nets analysis with Tina. In: International Conference on Quantitative Evaluation of Systems, 123–124 (2006)
- 4 Calovi, D.S., Brunnet, L.G., de Almeida, R.M.C.: cAMP diffusion in *Dictyostelium discoideum*: A Green’s function method. Phys. Rev. E 82, 011909 (2010)
- 5 Danos, V., Feret, J., Fontana, W., Harmer, R., Krivine, J.: Rule-based modelling and model perturbation. In: Transactions on Computational Systems Biology XI, vol. 5750, 116–137. Springer Berlin Heidelberg (2009)
- 6 Davis, M.H.A.: Piecewise-deterministic markov processes: A general class of non-diffusion stochastic models. Journal of the Royal Statistical Society. Series B (Methodological) 46(3), 353–388 (1984)
- 7 Feller, W.: An Introduction to probability theory and its applications, Vol. 1. John Wiley (1968)
- 8 Franzke, A.: Charlie 2.0 – a multi-threaded Petri net analyzer . Diploma thesis, BTU Cottbus, Dep. of CS (2009)
- 9 Gillespie, D.: A rigorous derivation of the master chemical equation. Physica 188, 404–425 (1992)
- 10 Gillespie, Daniel T: Approximate accelerated stochastic simulation of chemically reacting systems. The Journal of Chemical Physics 115(4), 1716–1711 (2001)

- 11 Grahlmann, B.: The PEP tool. In: Computer Aided Verification, 440–443. Springer (1997)
- 12 Heiner, M., Herajy, M., Liu, F., Rohr, C., Schwarick, M.: Snoopy – A unifying Petri net tool. In: Application and Theory of Petri Nets and Concurrency – International Conference on PETRI NETS 2012, vol. 7347, 398–407 (2012)
- 13 Heiner, M., Rohr, C., Schwarick, M.: MARCIE – Model checking And Reachability analysis done effiCIEntly. In: Application and Theory of Petri Nets and Concurrency – International Conference on PETRI NETS 2013, vol. 7927, 389–399 (2013)
- 14 Kim, J., Heslop-Harrison, P., Postlethwaite, I., Bates, D.G.: Stochastic noise and synchronisation during *Dictyostelium* aggregation make cAMP oscillations robust. PLoS Computational Biology 3(11), e218 (2007)
- 15 Kurtz, T.G.: The relationship between stochastic and deterministic models for chemical reactions. J Chem Phys 57(7), 2976–2978 (1972)
- 16 Maus, C.: Toward accessible multilevel modeling in systems biology: A rule-based language concept. Logos, Berlin (2013), PhD thesis (University of Rostock, Germany)
- 17 Maus, C., Rybacki, S., Uhrmacher, A.M.: Rule-based multi-level modeling of cell biological systems. BMC Systems Biology 5(166) (2011)
- 18 Molloy, M.K.: Performance analysis using stochastic Petri nets. IEEE Transactions on Computers 31(9), 913–917 (1982)
- 19 Petri, C.: Kommunikation mit Automaten. Ph.D. thesis, Department for Instrumental Mathematics, University Bonn (1962)
- 20 Ratzer, A.V., Wells, L., Lassen, H.M., Laursen, M., Qvortrup, J.F., Stissing, M.S., Westergaard, M., Christensen, S., Jensen, K.: CPN tools for editing, simulating, and analysing coloured Petri nets. In: Application and Theory of Petri Nets and Concurrency – International Conference on PETRI NETS 2003, 450–462 (2003)
- 21 Schmidt, K.: Lola a low level analyser. In: Application and Theory of Petri Nets and Concurrency – International Conference on PETRI NETS 2000, 465–474 (2000)
- 22 Starruß, J., de Back, W., Brusch, L., Deutsch, A.: Morpheus: A user-friendly modeling environment for multiscale and multicellular systems biology. Bioinformatics 30(9), 1331–1332 (2014)
- 23 Stewart, W.J.: Probability, Markov chains, queues, and simulation: The mathematical basis of performance modeling. Princeton University Press (2009), chapter 15
- 24 Voit, E.O.: Computational analysis of biochemical systems. Cambridge University Press (2000)

#### 4.5 Towards a standard exchange format for spatial, multilevel multicellular models (Team 7)

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Standardization of model descriptions has boosted the field of systems biology over the last decade. Standard formats such as SBML and CellML have allowed the exchange of models of biochemical reaction networks between users and simulation software, enhanced reproducibility of models and enables the creation of public model repositories. However, the recent shift in systems biology towards spatial multilevel models requires new modeling formalisms and simulation software for which existing exchange formats are not suitable. Here, we discuss the major challenges in defining a standard exchange format for computational

models of multilevel and multicellular systems and formulate some suggestions for the establishment of a standard exchange format for such simulation models.

#### 4.5.1 Background

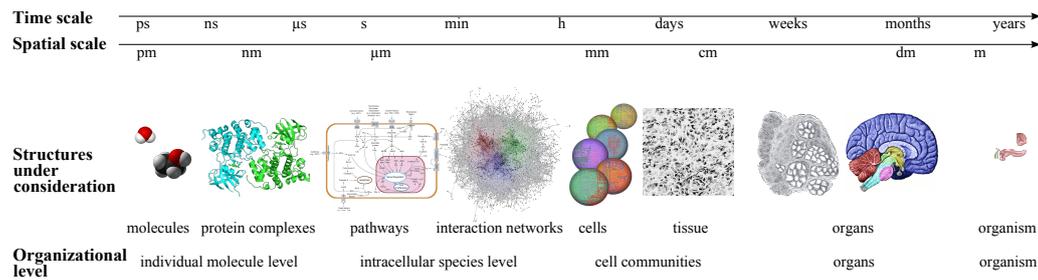
Efficient exchange and storage of information relies on common agreements for communication and representation. For instance, data representation and communication through the internet depends on a number of standard formats including HTML (hypertext markup language) and HTTP (hypertext transfer protocol). With the rise of large data sets and computational models in bioinformatics and systems biology, the life sciences have become strongly dependent on such information technology which has led to the establishment of various standard exchange formats [5, 23, 12]. In systems biology, standards such as CellML [26] and SBML (systems biology markup language) [19] have been established to describe, store and exchange complex biochemical network models.

This has greatly facilitated the exchange of these models between researchers and has allowed their simulation on a large number of different simulation software platforms. By abstracting computational models from the specific implementation of particular simulation software, standard formats have improved the transparency and reproducibility of computational modeling in systems biology. Moreover, the model markup language has allowed the establishment of public online repositories such as BioModels Database [24], which stores annotated, published and curated models that can be downloaded, used, and extended by other researchers. Standard exchange formats have therefore not only enhanced scientific scrutiny, but also promoted the open knowledge transfer within systems biology.

However, research interests in systems biology are shifting and now extend well beyond the computational modeling of biochemical networks, for which the aforementioned standard exchange formats have been created. Now, whole cells, tissues, organs and body models are increasingly addressed. In more detail, examples are the dynamics at cell behavioral level, e. g. growth, division and differentiation of cells, and cell-cell interaction, and in how far they are influenced by processes on the molecular level. Space often plays a crucial role in these dynamics. Therefore, multi-level modeling and simulation in space becomes increasingly important. It is therefore unsurprising that an increasing number of methods and software tools have been developed that aim at simulating these kind of spatial dynamics. The input to these tools are typically software-specific formats, which does not facilitate a reuse of models between tools. Neither do the intricate spatial dynamics and the underlying assumptions allow an easy reuse of models. Here, we discuss some of the key challenges in defining a standard exchange format for spatial multilevel multi-cellular models in which biological systems are modeled from the biochemical up to the tissue level at cellular resolution.

#### 4.5.2 Multi-level multicellular systems biology

In recent years, systems biology has expanded its scope to include regulatory mechanisms not only within cells but within tissues and even whole organs [10]. On the one hand, this is driven by the desire to predict effects of intracellular (dys)function on the tissue level that is more accessible to clinical investigation (e. g. histopathology). On the other hand, it is caused by the growing awareness that dynamics at higher levels can have important effects on lower a level's dynamics, a principle called 'downward causation' [8, 37]. Thus, dynamics at tissue level might influence dynamics at cellular level, and dynamics at cellular levels might influence the dynamics of biochemical reaction networks.



■ **Figure 26** Relation between scales and levels in systems biology, taken from [3], inspired by [25].

■ **Table 5** Cell-based modeling methods.

Cell-based modeling method	Cell shape	Reference
Cellular automata	Lattice site	[11]
Center-based model	(Deformed) Sphere	[13]
Cellular Potts model	Lattice domain	[16]
Vertex model	Polygon	[15]
ML-Space	Rigid sphere	[2]
Subcellular element model	Multiple volume elements	[35]

### Computational models of multilevel multicellular systems

The investigation of effects of interactions and feedback between the molecular, cellular and tissue level requires computational models that represent spatio-temporal dynamics encompassing multiple scales (fig. 26). Although a wide range of methods for spatial multilevel modeling exists [9, 22], an increasingly popular approach are hybrid models combining discrete cell-based models with continuous simulations for molecules [43].

In this modeling paradigm approach, cells are represented as individual agents that specifically capture aspects of the biophysical properties of biological cells and their interaction. A fundamental advantage of this approach is that tissue inhomogeneities such as cell-to-cell variability and complex spatial architectures can be readily captured. A number of different computational methods have been proposed to represent cells. These differ in their spatial resolution and the way how their dynamics is computed (table 5). These methods, collectively called cell-based models, allow for the representation of cell movement, cell-cell adhesion, and cell division and therefore present a suitable framework to study how tissue-level phenomena may emerge as a result of cellular behaviors and interactions. These models are usually classified into lattice and lattice-free (also: off-lattice) models. The former (cellular automaton, Cellular Potts model) define a minimal length scale at which cells can move. In the latter the position is a real-valued variable hence space is continuous. An important advantage of simulations in continuum space is that cell position can change gradually, without any minimum length scale.

The parameters specifying cellular properties (e.g. cell division propensity, or cell-cell interaction) can be coupled to subcellular models representing biochemical regulatory networks, solved for each cell individually. Moreover, cell-based models can be coupled to reaction-diffusion models typically representing the release, distribution and activity of extracellular signaling molecules, or of metabolites or nutrients through the tissue. These

■ **Table 6** Software platforms for multilevel multicellular modeling.

Software platform	Institute	Reference
BioCellion	ISB Seattle	[20]
CellSys	Uni. Leipzig & INRIA, Paris	[17]
Chaste	Uni. Oxford	[30]
CompuCell3D	Indiana Uni.	[40]
Morpheus	TU Dresden	[38]
EPISIM	Uni. Heidelberg	[39]
VirtualLeaf	CWI Amsterdam	[29]

approaches combine different modeling formalisms, i. e., they support modeling cellular dynamics as discrete agents, intra-cellular dynamics by reaction species networks, and extra-cellular dynamics as reaction-diffusion systems.

In contrast to these multi-formalism approaches, others aim at supporting different types of spatial dynamics within one formalism, e. g., the language ML-Space allows to express and combine cellular dynamics, mesh-based reaction diffusion systems for intra- and extra-cellular dynamics and individual cells moving as individual spheres in continuous space exploiting a rule-based approach [2, 4], many concepts ML-Space adopts from ML-Rules which supports compartmental dynamics, as well as stochastic reaction species and reaction-diffusion on a regular grid [28]. Both, as other spatial simulations exploit a declarative rule-based description of models, e. g., [21], to aim at a comprehensive and compact description of spatial multi-level, multi-scale models within one language [14].

However, requirements for developing models (as is the goal of the above approaches) and requirements for providing a standard for exchanging models between tools and for storing and retrieving models by tools are different, and with this respect multi-formalism approaches appear more promising. The combination of different methods, allows a divide and conquer strategy, i. e., to reuse existing standards, model specifications, and to combine those. Thus, existing systems biological models may be “plugged” in spatial and multilevel systems and their behavior can be explored within a multicellular context. A key advantage of this approach is its modularity.

Parameters can initially be set phenomenologically and subsequently replaced with explicit mechanistic sub-models, depending on the available knowledge and data of the underlying process. This renders it a prime example of the middle-out modeling strategy [36], which, in contrast to top-down or bottom-up approaches, starts by modeling one particular level and progressively connecting this to higher and lower levels of biological organization.

However, integration of disparate spatial dynamics as the discrete dynamics of cells, the continuous, deterministic or stochastic intra-cellular dynamics or the deterministic or stochastic reaction-diffusion extra-cellular dynamics in one model and implementing it is a challenging effort and requires considerable computational expertise. Therefore, dedicated software is needed that implements these methods and their combination such that novel model developments can build upon existing models without the need to re-implement model parts that have already been implemented in a proprietary or in-house tool.

### Software platforms

A small but growing number of publicly available and mostly open source software platforms for simulation of multilevel multicellular systems have been published to date (table 6), with new platforms appearing every few months. Each of these provides reusable implementations for one or several cell-based models that can be integrated with models for intracellular and extracellular dynamics. They allow for flexible customization by the user, albeit in wide diverse ways. Whereas some are libraries with high-level application programming interfaces (API), others are frameworks with specialized scripting languages and visual interfaces, and a few come as graphical applications aimed at ease-of-use.

Developers of these software platforms are aware of the importance and benefits of standardization. This is apparent, for instance, in the fact that several platforms support the use of SBML for the specification of intracellular models. However, no standard exchange format currently exists for the representation of the type of multilevel multicellular models that these software platforms provide. Therefore, models developed in one platform cannot be simulated in another platform, unless it is re-coded completely. This hampers cross-validation of simulation results as well as obstructs their reproducibility (and testing the correctness of the software). A modeler needs to choose the model type, and then deal with the tool specific way to first translate his hypotheses into the chosen model type, and then turn it into an executable code. In most cases the functionality of the code is insufficient to express the hypotheses and additional model components have to be formulated, and implemented in the chosen software. A desired procedure would start to formalize the hypothesized biological/biophysical/biochemical mechanisms and processes in a standard way that could be read automated by software tools acting as engine to execute the model. Prospectively, this could make complex multi-level modeling addressing multi-cellular tissues accessible to biologists and physicians.

#### 4.5.3 Challenges and recommendations

Before turning to the challenges of the standardization of multilevel multicellular models, let us first describe more carefully what we mean with a standard exchange format. The primary task of an exchange format is to facilitate the exchange of models between different simulation software platforms as well as users. Therefore, the description of the model should be clearly separated from its simulation and its implementation. This implies that the description of the model should be focusing on the biological processes it aims to describe. It is therefore decoupled from details of execution, analysis and visualization.

The separation of model from implementation requires a declarative language that describes the logic of a process rather than its algorithmic control, as in imperative or procedural languages. In other words, a declarative format describes *what* process is modeled instead of *how* this should be simulated. Declarative model descriptions have the additional benefits of being sharable as well as easily integrated into larger models. Most declarative exchange formats in systems biology are based on the extensible markup language (XML), which provides a hierarchically structured means to store data and allows domain-specific terminology. The domain-specificity of exchange formats offers expressive power focused on a particular problem domain by the use of appropriate notations and abstractions [41].

The exchange standard should facilitate and distinguish the description of the properties of its components, description of the topology and the (multilevel) relations within the system, and the description of the dynamics of the system.

**Challenge 1: From procedural programs to declarative model description**

Most of the aforementioned software platforms provide users the ability to configure and customize computational models in a flexible fashion using either programming languages (e.g. C++, Fortran) or scripting languages (e.g. Python). It is therefore common practice to implement computational models of multi-scale multicellular system directly in imperative or procedural code. Thus, no distinction is made between a model (the set of biological mechanisms that is being represented) and its implementation (the set of computer instructions that simulates these mechanisms).

This is most evident in those software platforms that are provided as libraries, such as Chaste [30]. Chaste provides high-level interfaces for the configuration and initialization of various cell-based models and sub-models and makes the numerical details of its simulation transparent. Yet, both the logic and the control flow of simulation models are entirely specified in C++.

Some platforms provide users with the ability to describe models declaratively, e.g., in a rule-based language (as mentioned above), and support importing SBML models and exporting SBML models (partially, based on heuristics), e.g., [33]. Some use directly XML formats to store their models.

Several platforms do provide declarative XML-based formats, but these are typically limited to parameterize simulation models. CompuCell3D [40], for instance, provides a XML model specification format (CC3DML) that allows users to specify models in terms of cellular behaviors, initial conditions and parameterization. However, model descriptions in CC3DML are static in the sense that the parameters and cellular behaviors cannot be changed during simulation. For the construction of complex biological models in which parameters may change dynamically as a function of other model components, CompuCell3D users must revert to scripting or programming to specify these dependencies in a procedural fashion.

Of the available software platforms, only two use XML-based languages to fully describe simulation models, EPISIM [39] and Morpheus [38]. Both provides graphical interfaces that enables the user to construct models in terms of their logic and the relations between model components, which is stored in a declarative fashion in XML-based formats. These declarative model descriptions contain the full model description and are subsequently used to configure the simulation, albeit in different ways.

EPISIM automatically translates the XML file into executable Java code using a XSLT (extensible stylesheet language transformations) processor based on a set of transformation rules [39]. Morpheus, in contrast, does not translate the models in its declarative language MorpheusML into executable code, but rather includes an interpreter that reads a declarative model description and configures its simulation accordingly. In MorpheusML, the logic of a simulation model is specified in terms of definitions of symbolic identifiers and relations between these symbolic identifiers that are as mathematical expressions. By resolving the tree of interdependencies between the symbolic identifiers, the simulation is automatically scheduled ensuring that the order of initialization and execution is such that up-to-date data is used in all computations and the time intervals are adjusted to ensure correctness and avoid redundant computations [38]. The use of symbolic identifiers and mathematical expressions in this model description language is similar to SBML, as is reflected in the fact that SBML can be automatically converted into MorpheusML.

In the later approaches instead of internal domain specific languages, e.g., which provide classes but still allow to implement in a general purpose host language, the modeling languages offered above are realized as external domain specific languages. The benefit lies in being able to design a true custom syntax for the problem at hand. The drawback is a specific full

parser to process models in this language has to be implemented. Thus, the later approach is less flexible, and models cannot be extended easily by new features on demand. In any case a clear separation of concern: clearly distinguishing between model, execution of a model, analyzing the trajectory of a model, etc. appears as a pre-requisite for contributing to and exploiting standardized exchange formats, and other tools, like workflow systems.

### **Challenge 2: Unifying syntax and semantics of cell-based models**

One of the most challenging issues in standardization of multicellular models (the multilevel aspect is discussed below) is the formulation of a uniform description of cell-based models. Since most software platforms specialize on different cell-based modeling formalisms, an exchange format should account for a range of cell-based models. Yet, each cell-based model requires the specification of model-specific parameter sets.

On the one hand, the biophysical constraints ensure that there is considerable overlap between the biological interpretation of parameters. For instance, many cell-based models require the specification of cell size in terms of area (2D) or volume (3D) and the specification of adhesive properties. However, the exact computational interpretation of these parameters can differ substantially. For instance, in subcellular elements models, cell volume determines the number of volume elements of each cell, in the cellular Potts model it determines a target value for the number of lattice nodes cells, in the vertex model it determines the area within the polygonal representation of cells, while in cellular automata models, cell volume is a meaningless concept. Still, whether or not a parameter can be meaningfully interpreted within the context of a specific simulator can be left to the responsibility of the software reading the exchange format. On the other hand, there are also model-specific parameters that are required by a particular cell-based model, but only have meaning within one or a small subset of model formalism. For instance, the specification of a “temperature” parameter is required for cellular Potts models and some vertex models, but is only relevant for cell-based models that depend on energy-minimization using the Metropolis algorithm.

In fact, in biochemical network modeling, an analogous problem is encountered. Reaction networks formulated in SBML format can be simulated as ordinary differential equations as well as discrete stochastic simulation using Gillespie’s algorithm. However, these simulation techniques require different information (e.g. molecular concentrations versus amounts of molecules in a volume) or interpret information differently (e.g. kinetics rate are interpreted as substance per time or events per time). To facilitate these ways of simulation, SBML provides attributes to fully specify both simulation types (e.g. Compartment/Volume, hasOnlySubstanceUnits attributes). However, SBML also allows the specification of attributes that are meaningless in certain simulations. For instance, the reversible flag for reactions is only meaningful for deterministic simulation, and for stochastic simulations the reaction should be converted into two irreversible ones. In SBML, it is left to simulators such as COPASI [18] to implement conversion rules for these cases.

Along these lines, we argue that an exchange standard for multicellular simulations should provide parameters to fully specify all supported cell-based models. Yet, whether or not parameters are meaningfully interpreted or converted or even ignored, is the responsibility of the simulation software and falls beyond the specification of the exchange format.

Nevertheless, it remains of utmost importance to be able to convert parameterizations between specific cell-based models because the lack of convertibility directly impedes the task of the exchange format as facilitating the exchange between different software platforms. This will require challenging mathematical analyses and rigorous comparison of the structures of the various cell-based modeling frameworks. Apart from a number of comparative case

studies [7, 32], only a handful of rigorous mathematical analyses have been conducted to date [42]. As a notable exception, in a recent paper, Maree and coworkers that shown that cell behavior and tissue packing can be predicted by analytically deriving forces and tensions from energy-based models (Magno et al., to appear). This demonstrates the equivalence of the vertex and cellular Potts models with respect to their behavior as models for cell surface mechanics and provides rules for automated conversion between their parameterizations. Future work on similar analyses for force-based models and analytic comparison of force-based and energy-based models will provide crucial information to be able to convert model descriptions between cell-based modeling formalisms.

### Challenge 3: Putting everything together

The particular type of multilevel models that we focus on here encompasses various levels of biological organization: intracellular molecular biochemistry, intercellular biophysical interactions and extracellular signaling. These are typically represented in terms of species/reaction systems, cell-based models and reaction-diffusion systems. Thus, in addition to representing processes at multiple spatiotemporal scales, these simulations integrate multiple model formalisms, including deterministic and stochastic models, well-mixed and spatial models, and continuous and discrete models.

Integration of these model formalisms implies accounting for interactions and feedbacks between the various submodels. These can be trivial, such as the unidirectional dependency of cell division on a subcellular model of the cell cycle, but these may also involve indirect feedback loops, such as when the cell cycle model itself depends on the local concentration of a cell-produced (autocrine) diffusive signaling molecule. In fact, a network of interdependencies between the various submodels may need to be represented, since exploring the interplay between levels of biological organization is exactly the reason for multilevel multicellular modeling.

Fortunately, from the perspective of defining an exchange format, these multilevel and multimodel aspects provide both a natural division and between different submodels (modularity) as well as a defined tree structure in which these submodels can interact (hierarchy). Therefore, we can take advantage of existing markup languages for various submodels as well as current effort in defining modular and hierarchical compositions.

Various exchange formats for spatial multilevel models have been proposed. FieldML facilitates the encoding of geometric models in mathematical form with respect to biological and medical phenomena with spatial-temporal variation, such as the simulation of vector fields and gradients [6]. The physiological hierarchy markup language (PHML) is a successor of insilicoML (ISML) and is used by PhysioDesigner software to define biological or biophysical elements as modules, which can be encapsulated and hierarchically linked [1]. While these standardization efforts provide extensive support for complex spatial modeling and provide means for hierarchically structuring submodels, there are several drawbacks in adopting these formats. Both focus on describing physiological phenomena, such as the electrophysiology of the heart, and do not explicitly address the cellular scale. Moreover, they are used by limited number of software platforms and are therefore supported by a relatively small community.

While SBML itself does currently not providing spatial or multilevel modeling, it is supported by a large community and has several promising (proposed) extensions to facilitate more complex modeling approaches. Moreover, because various software platforms for multilevel multicellular modeling already support SBML, this may provide the best-suited format and community to establish the exchange format for multilevel multicellular models. The SBML core package handles the description of nonspatial processes that can be simulated

■ **Table 7** Proposed benchmark problems with increasing model complexity. This include recurring model tasks as well as different combinations of submodels.

Problem	Cellular	Intracellular	Extracellular
Population growth	•		
Cell sorting	•		
Cell cycle model	•	•	
Chemotaxis	•		•
Autocrine chemotaxis	•		•
Cell cycle model + autocrine chemotaxis	•	•	•

in terms of ordinary differential differentiation or stochastic simulation algorithms and is used as a format for the representation of intracellular biochemical networks by a number of the software platforms given in table 6. Moreover, the proposed SBML-spatial package<sup>3</sup> provides the specification of spatial processes and geometries that can be used to describe the distribution of extracellular signaling molecules. This package is already used by VirtualCell [31] as well as a new library for spatial reaction-diffusion models [27]. Therefore, exchange standards for two of the three aforementioned main submodels (the exception being the description of multicellular models) have already been developed and can be readily integrated.

In addition to the encoding of the various submodels, a format is required to combine these submodels into a modular and hierarchical structure. For this task, the recently released SBML package for hierarchical model composition (SBML-comp<sup>4</sup>) is relevant. This package allows the coupling of multiple SBML models that may be structured in a hierachical fashion. It applies a white-box (as opposed to black-box) approach in which information-hiding interfaces are absent and all elements of a modeling component are available as potential coupling points with other components [34]. This allows for a high degree of flexibility and customization in interconnecting SBML models.

SBML package for dynamic structures (SBML-dyn<sup>5</sup>) is an extension to encode multicellular systems displaying dynamic cellular events (e. g., proliferation, differentiation, endocytosis, exocytosis, and cell death). This extension is designed to work with already existing SBML packages such as SBML-spatial and SBML-comp.

#### 4.5.4 Discussion

An increasing number of software platforms is available to model biological systems from the biochemical to the tissue level with cellular resolution. However, the lack of a standardized way to describe these computational models is currently hampering their reproducibility and exchange among simulation software as well as among users. In this report, we have outlined some of the key challenges that need to be overcome in order to establish such a standard exchange format for multilevel multicellular models. Long-term investments and coordination among users, software developers and standardization committees will be required to surmount

<sup>3</sup> [http://sbml.org/Documents/Specifications/SBML\\_Level\\_3/Packages/spatial](http://sbml.org/Documents/Specifications/SBML_Level_3/Packages/spatial)

<sup>4</sup> [http://sbml.org/Documents/Specifications/SBML\\_Level\\_3/Packages/comp](http://sbml.org/Documents/Specifications/SBML_Level_3/Packages/comp)

<sup>5</sup> [http://sbml.org/Documents/Specifications/SBML\\_Level\\_3/Packages/Dynamic\\_Structures\\_%28dyn%29](http://sbml.org/Documents/Specifications/SBML_Level_3/Packages/Dynamic_Structures_%28dyn%29)

these problems. However, as exemplified by the success of standardization in biochemical modeling in systems biology, free and open exchange of multilevel multicellular models as well as the establishment of public model repositories will act to consolidate the field and disclose it to a wider audience in biological and biomedical research.

One immediate challenge to be confronted by developers of the various software platforms is the separation of model from numerical implementation in terms of the adoption of declarative model descriptions. Even without the existence of a standardized model description, the adoption of a standard exchange format will be greatly simplified if the various simulation platforms have already generalized and abstracted their procedural implementations into software-specific declarative languages. Moreover, this process will aid the establishment of an exchange format by exploring the similarities between the different software-specific declarative languages. This should be accompanied by the automatic conversion between parameter sets. Recent studies demonstrate that such conversion is possible for a limited set of cell-based models. However, there is an urgent need for analytic work that compares cell-based models in order to reveal the relationships between their parameters.

Major differences exist in how cells and their interactions are described in the different cell-based modeling formalisms. As a consequence, each requires a specific set of parameters, rendering it unlikely that a useful standardized model descriptions will be possible that completely separates the biological model from the computational models.

In contrast to attempts to generalize (biological or simulated) cellular behavior from the top-down, we envision a bottom-up approach that starts from the available software platforms and commonly used modeling formalisms and generalizes their descriptions up to a point that models implemented for the various platforms can be reliably exchanged.

This process should ideally be guided by practical application at every step. It is therefore worthwhile to formulate a set of benchmark problems that include recurring modeling tasks in cell-based modeling as well as their integration to intracellular and extracellular models, such as those presented in Table 7.

## References

- 1 Yoshiyuki Asai, Takeshi Abe, Masao Okita, Tomohiro Okuyama, Nobukazu Yoshioka, Shigetoshi Yokoyama, Masaru Nagaku, Kenichi Hagihara, and Hiroaki Kitano. Multilevel modeling of physiological systems and simulation platform: Physiodesigner, flint and flint k3 service. In *Applications and the Internet (SAINT), 2012 IEEE/IPSJ 12th International Symposium on*, pages 215–219. IEEE, 2012.
- 2 Arne T. Bittig, Fiete Haack, Carsten Maus, and Adeline M Uhrmacher. Adapting rule-based model descriptions for simulating in continuous and hybrid space. In *Proceedings of the 9th International Conference on Computational Methods in Systems Biology, CMSB'11*. ACM, 2011.
- 3 Arne T. Bittig, Matthias Jeschke, and Adeline M. Uhrmacher. Towards modelling and simulation of crowded environments in cell biology. In Theodore E. Simos, George Psihoyios, and Ch. Tsitouras, editors, *AIP Conference Proceedings*, volume 1281, pages 1326–1329. AIP, 2010.
- 4 Arne T Bittig, Claudia Matschegewski, J Barbara Nebe, Susanne Stählke, and Adeline M Uhrmacher. Membrane related dynamics and the formation of actin in cells growing on micro-topographies: A spatial computational model. *BMC Systems Biology*, 8:106, 2014.
- 5 Alvis Brazma, Maria Krestyaninova, and Ugis Sarkans. Standards for systems biology. *Nature Reviews Genetics*, 7(8):593–605, 2006.
- 6 Randall D Britten, G Richard Christie, Caton Little, Andrew K Miller, Chris Bradley, Alan Wu, Tommy Yu, Peter Hunter, and Poul Nielsen. Fieldml, a proposed open standard for the

- physiome project for mathematical model representation. *Medical & biological engineering & computing*, 51(11):1191–1207, 2013.
- 7 Helen Byrne and Dirk Drasdo. Individual-based and continuum models of growing cell populations: a comparison. *Journal of mathematical biology*, 58(4-5):657–687, 2009.
  - 8 D. T. Campbell. ‘downward causation’ in hierarchically organised biological systems. In F. J. Ayala and T. Dobzhansky, editors, *Studies in the philosophy of biology: Reduction and related problems*, pages 179–186. Macmillan Press, 1974.
  - 9 Joseph O Dada and Pedro Mendes. Multi-scale modelling and simulation in systems biology. *Integrative Biology*, 3(2):86–96, 2011.
  - 10 LA D’Alessandro, S Hoehme, A Henney, D Drasdo, and U Klingmüller. Unraveling liver complexity from molecular to organ level: Challenges and perspectives. *Progress in biophysics and molecular biology*, 2014.
  - 11 Andreas Deutsch and Sabine Dormann. *Cellular automaton modeling of biological pattern formation*. FASEB, 2005.
  - 12 Andreas Dräger and Bernhard Ø Palsson. Improving collaboration by standardization efforts in systems biology. *Frontiers in bioengineering and biotechnology*, 2, 2014.
  - 13 Dirk Drasdo. Center-based single-cell models: An approach to multi-cellular organization based on a conceptual analogy to colloidal particles. In *Single-Cell-Based Models in Biology and Medicine*, pages 171–196. Springer, 2007.
  - 14 James R Faeder. Toward a comprehensive language for biological systems. *BMC Biology*, 9(68), Oct. 2011.
  - 15 Alexander G Fletcher, Miriam Osterfield, Ruth E Baker, and Stanislav Y Shvartsman. Vertex models of epithelial morphogenesis. *Biophysical Journal*, 106(11):2291–2304, 2014.
  - 16 François Graner and James A Glazier. Simulation of biological cell sorting using a two-dimensional extended potts model. *Physical review letters*, 69(13):2013, 1992.
  - 17 Stefan Hoehme and Dirk Drasdo. A cell-based simulation software for multi-cellular systems. *Bioinformatics*, 26(20):2641–2642, 2010.
  - 18 Stefan Hoops, Sven Sahle, Ralph Gauges, Christine Lee, Jürgen Pahle, Natalia Simus, Mudita Singhal, Liang Xu, Pedro Mendes, and Ursula Kummer. Copasi-a complex pathway simulator. *Bioinformatics*, 22(24):3067–3074, 2006.
  - 19 Michael Hucka, Andrew Finney, Herbert M Sauro, Hamid Bolouri, John C Doyle, Hiroaki Kitano, Adam P Arkin, Benjamin J Bornstein, Dennis Bray, Athel Cornish-Bowden, et al. The systems biology markup language (sbml): a medium for representation and exchange of biochemical network models. *Bioinformatics*, 19(4):524–531, 2003.
  - 20 Seunghwa Kang, Simon Kahan, Jason McDermott, Nicholas Flann, and Ilya Shmulevich. Biocellion: accelerating computer simulation of multicellular biological system models. *Bioinformatics*, 30(21):3101–3108, Nov 2014.
  - 21 M. Klann, L. Pauleve, T. Petrov, and H. Koepl. Coarse-grained brownian dynamics simulation of rule-based models. In *Computational Methods in Systems Biology*, 2013.
  - 22 Michael Klann and Heinz Koepl. Spatial simulations in systems biology: From molecules to cells. *Int J Mol Sci*, 13(6):7798–7827, 2012.
  - 23 Edda Klipp, Wolfram Liebermeister, Anselm Helbig, Axel Kowald, and Jörg Schaber. Systems biology standards – the community speaks. *Nature biotechnology*, 25(4):390–391, 2007.
  - 24 Nicolas Le Novere, Benjamin Bornstein, Alexander Broicher, Melanie Courtot, Marco Donizelli, Harish Dharuri, Lu Li, Herbert Sauro, Maria Schilstra, Bruce Shapiro, et al. Biomod-els database: a free, centralized database of curated, published, quantitative kinetic models of biochemical and cellular systems. *Nucleic acids research*, 34(suppl 1):D689–D691, 2006.
  - 25 J. Li, W. Ge, J. Zhang, and M. Kwauk. Multi-scale compromise and multi-level correlation in complex systems. *Chemical Engineering Research and Design*, 83(6):574–582, June 2005.

- 26 Catherine M Lloyd, Matt DB Halstead, and Poul F Nielsen. Cellml: its future, present and past. *Progress in biophysics and molecular biology*, 85(2):433–450, 2004.
- 27 T. Matsui, N. Hiroi, and A. Funahashi. Implementation of spatial model simulator and its sbml support. In *International Workshop on Quantitative Biology*, page 29, 2012.
- 28 Carsten Maus, Stefan Rybacki, and Adelinde Uhrmacher. Rule-based multi-level modeling of cell biological systems. *BMC Syst Biol*, 5(1):166+, 2011.
- 29 Roeland M H. Merks, Michael Guravage, Dirk Inzé, and Gerrit T S. Beemster. Virtualleaf: an open-source framework for cell-based modeling of plant tissue growth and development. *Plant Physiol*, 155(2):656–666, Feb 2011.
- 30 Gary R. Mirams, Christopher J. Arthurs, Miguel O. Bernabeu, Rafel Bordas, Jonathan Cooper, Alberto Corrias, Yohan Davit, Sara-Jane Dunn, Alexander G. Fletcher, Daniel G. Harvey, Megan E. Marsh, James M. Osborne, Pras Pathmanathan, Joe Pitt-Francis, James Southern, Nejib Zemzemi, and David J. Gavaghan. Chaste: an open source C++ library for computational physiology and biology. *PLoS Comput Biol*, 9(3):e1002970, 2013.
- 31 Ion I Moraru, James C Schaff, Boris M Slepchenko, ML Blinov, Frank Morgan, Anuradha Lakshminarayana, Fei Gao, Ye Li, and Leslie M Loew. Virtual cell modelling and simulation software environment. *IET systems biology*, 2(5):29, 2008.
- 32 Philip J Murray, Alex Walter, Alexander G Fletcher, Carina M Edwards, Marcus J Tindall, and Philip K Maini. Comparing a discrete and continuum model of the intestinal crypt. *Physical biology*, 8(2):026011, 2011.
- 33 Sebastian Nähring, Carsten Maus, Roland Ewald, and Adelinde M Uhrmacher. From standardized modeling formats to modeling languages and back – an exploration based on sbml and ml-rules. In R. Pasupathy, S.-H. Kim, A. Tolk, R. Hill, and M. E. Kuhl, editors, *Proceedings of the 2013 Winter Simulation Conference*. Institute of Electrical and Electronics Engineers, Inc., 2013.
- 34 Maxwell L Neal, Michael T Cooling, Lucian P Smith, Christopher T Thompson, Herbert M Sauro, Brian E Carlson, Daniel L Cook, and John H Gennari. A reappraisal of how to build modular, reusable models of biological systems. *PLoS computational biology*, 10(10):e1003849, 2014.
- 35 Timothy J Newman. Modeling multicellular structures using the subcellular element model. In *Single-Cell-Based Models in Biology and Medicine*, pages 221–239. Springer, 2007.
- 36 Denis Noble. Modeling the heart—from genes to cells to the whole organ. *Science*, 295(5560):1678–1682, 2002.
- 37 Denis Noble. A theory of biological relativity: no privileged level of causation. *Interface Focus*, page rsfs20110067, 2011.
- 38 Jörn Starruß, Walter de Back, Lutz Brusch, and Andreas Deutsch. Morpheus: a user-friendly modeling environment for multiscale and multicellular systems biology. *Bioinformatics*, 30(9):1331–1332, 2014.
- 39 Thomas Sütterlin, Christoph Kolb, Hartmut Dickhaus, Dirk Jäger, and Niels Grabe. Bridging the scales: semantic integration of quantitative sbml in graphical multi-cellular models and simulations with episim and copasi. *Bioinformatics*, 29(2):223–229, 2013.
- 40 Maciej H Swat, Gilberto L Thomas, Julio M Belmonte, Abbas Shirinifard, Dimitrij Hmeljak, and James A Glazier. Multi-scale modeling of tissues using compucell3d. *Methods in cell biology*, 110:325, 2012.
- 41 Arie Van Deursen, Paul Klint, and Joost Visser. Domain-specific languages: An annotated bibliography. *Sigplan Notices*, 35(6):26–36, 2000.
- 42 Anja Voss-Böhme. Multi-scale modeling in morphogenesis: a critical analysis of the cellular potts model. *PloS one*, 7(9):e42852, 2012.
- 43 Dawn C Walker and Jennifer Southgate. The virtual cell—a candidate co-ordinator for ‘middle-out’ modelling of biological systems. *Briefings in Bioinformatics*, page bbp010, 2009.

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# Automated Planning and Model Checking

Edited by

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## Abstract

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This report documents the program and the outcomes of Dagstuhl Seminar 14482 “Automated Planning and Model Checking”. There has been a lot of work on the exchanges between the areas of automated planning and model checking, based on the observation that a model-checking problem can be cast as a planning problem and vice-versa. The motivation for this seminar was to increase the synergy between the two research communities, and explore recent progress in the two areas in terms of techniques, tools and formalisms for describing planning and verification problems. The main outcomes were a greater common understanding of planning and model-checking issues and challenges, and greater appreciation of the crossover between the modelling languages and methods. Different application domains were also explored, where planning and model-checking can be effectively integrated.

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## 1 Executive Summary

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In the area of formal methods, model checking deals with the problem of fully-automated property validation and correctness verification. Given a formal model of a system and a property specification, the task is to explore the state space and verify whether or not the property is satisfied by the model. In artificial intelligence, automated planning deals with the automatic generation of plans for achieving a goal. Given the description of the initial state, the goal state, and the set of possible actions, a planner uses heuristic search to look for a sequence of actions that transforms the initial state into the goal state.



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There has been a lot of work on the exchanges between the two areas (automated planning and model checking), based on the observation that a model-checking problem can be cast as a planning problem, where the goal state is a state violating the property to be verified in the model-checking problem. Thus, if a plan is found by the planner, it corresponds to error trace that a model checker would return (this paradigm is called directed model checking). The link can also be exploited in the other way around, using a model checker to search the planning state space, stopping the search when a goal state is found (this paradigm is called planning via model checking).

The general aim of this Dagstuhl Seminar was to increase the synergy between the two research communities. This involved sharing views, thoughts and contributions across the following streams:

**Techniques and Tools:** During the seminar we considered the most recent advances in automated planning and model checking and explored the possibility of using recent planning tools (heuristic search, sampling-based motion-planning algorithms, symbolic search algorithms, ...) for system falsification (particularly in challenging domains such as hybrid systems) and for boosting the use of model checking systems for finding plans.

**Modelling Languages:** One of the goals of the seminar was to consider the family of PDDL languages and the formalisms for describing verification problems and discuss how to make the communication between the two areas easier, exploring the possibility of common languages or translation between existing formalisms.

There were a number of talks on “X” Modulo Theories, where “X” ranged from SAT and Search to Planning. These talks explored the relationship between generic solution methods and different proof systems, leading to discussions about the relative benefits of viewing problems from the perspectives of the different generic methods. This fostered an improved understanding of each other’s perspectives and modelling approaches.

Discussions also focused on relationships between hybrid planning and hybrid model-checking. There were tutorials on the modelling languages used in the two paradigms, and their semantics, and the discrepancies between these led to lively discussion. In hybrid planning using PDDL, a key semantic issue is the use of epsilon time to separate inter-dependent actions, in order to prevent the planner from relying on synchronised activity. For example, if an action, A, achieves the precondition of another action, B, the validity of the plan depends on A being ordered strictly before B, by at least epsilon time. This is because the state following the co-occurrence of these two actions is indeterminate. The model-checking community does not require this epsilon. In hybrid model-checking a partial order on events is maintained, and there was an extended discussion about why planning forces an ordering using epsilon separation when this is not necessary in model-checking. From this discussion the following distinction emerged: model-checking simply requires there to be a single ordering of events that is consistent with the constraints, as this provides the required counter-example to the correctness of the model. In planning, by contrast, *all* orderings of events must be consistent with the constraints, requiring exponential work to check the validity of a partially ordered plan. Once this point was understood there was a greater common understanding between the planning and model-checking proponents, and greater appreciation of the crossover between modelling languages and methods.

Other topics covered by the contributed talks include:

- directed model checking and falsification
- plan validation
- heap and other data structures

- GPU-based state space exploration
- hybrid systems
- heuristic search
- planning and verification on real-world scenarios

The program featured the following components:

- On Monday we started with 7 tutorial-type introductory talks about plans validation, planning in hybrid systems through model checking, guided search for hybrid systems, falsification of hybrid systems through motion planning, planning via symbolic model checking, directed model checking of timed systems, heap implementations. The purpose of these tutorials was to familiarise members of the different communities with the basics of the other fields and with the existing synergies between the fields.
- From Tuesday, each day featured one or two long talks plus a number of short talks, with enough time for discussion after each talk.
- On Tuesday and Thursday afternoon we had two open discussion sessions.
- Wednesday afternoon featured a hike.

A feature of this seminar was the very high level of engagement and interaction between the participants, leading to a lively and productive week. The decision not to formalise discussions into panels or break-out sessions proved to be a good one, allowing more flexible response to topics as they arose. Similarly, the decision to leave some of the talk slots open allowed spontaneous pursuit of ideas that came out of discussions. The mixture of long and short talks also encouraged this. The workshop ended on a high note, with many new ideas for collaboration having been identified.

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### 3 Overview of Talks

#### 3.1 Guided Search for Hybrid Systems

*Sergiy Bogomolov (Universität Freiburg, DE)*

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Hybrid systems represent an important and powerful formalism for modeling real-world applications such as embedded systems. A verification tool like SpaceEx is based on the exploration of a symbolic search space (the region space). As a verification tool, it is typically optimized towards proving the absence of errors. In some settings, e. g., when the verification tool is employed in a feedback-directed design cycle, one would like to have the option to call a version that is optimized towards finding an error path in the region space. A recent approach in this direction is based on guided search. Guided search relies on a cost function that indicates which states are promising to be explored, and preferably explores more promising states first. In this talk, we present two approaches to define and compute efficient cost functions. We develop our approaches on the top of the symbolic hybrid model checker SpaceEx which uses regions as its basic data structures.

In the first part of the talk, we introduce a box-based distance measure which is based on the distance between regions in the concrete state space. In the second part of the talk, we discuss an abstraction-based cost function based on pattern databases for guiding the reachability analysis. For this purpose, a suitable abstraction technique that exploits the flexible granularity of modern reachability analysis algorithms is introduced. We illustrate the practical potential of our approaches in several case studies.

#### 3.2 Transitive Reduction for Inference of Biological Networks on GPUs

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**Joint work of** Bošnački, Dragan; Odenbret, Maximilian R; Wijs, Anton; Ligtenberg, Willem; Hilbers, Peter;  
**Main reference** D. Bošnački, M. R. Odenbrett, A. Wijs, W. Ligtenberg, P. Hilbers, “Efficient reconstruction of biological networks via transitive reduction on general purpose graphics processors,” *BMC Bioinformatics*, 13:281, 2012.

**URL** <http://dx.doi.org/10.1186/1471-2105-13-281>

Transitive reduction [1] is a graph transformation which is inverse of transitive closure. A transitive reduction of a graph is a minimal graph (in the number of edges) that comprises the same nodes as the original graph while preserving the same connectivity of the original graph, i. e., there is a path between two nodes  $a$  and  $b$  in the original graph  $G$  if and only if there is a path between  $a$  and  $b$  in its transitive reduction  $G'$ . In bioinformatics transitive reduction arises in the problem of reconstruction of biological networks from so called perturbation experiments. The goal is to distinguish direct from indirect interactions, i. e., to remove each direct connection between two network nodes that can be explained as a chain of indirect interactions (path in the weighted graph). In this context we introduce transitive reduction for weighted graphs along the lines of [2]. The transitive reduction algorithm for weighted graphs is isomorphic with the Floyd-Warshall shortest path algorithm and as such it lends itself to parallelization. We present some efficient implementations of this algorithm and its variations on general purpose graphics processing units (GPUs). We also discuss how

transitive reduction can be possibly used in planning and model checking, e. g., in the context of computing canonical representations of zones in timed automata.

### References

- 1 A. V. Aho, M. R. Garey, J. D. Ullman, *The transitive reduction of a directed graph*, SIAM J Comput 1972, 1(2):131–137, <http://epubs.siam.org/doi/abs/10.1137/0201008>
- 2 D. Bošnački, M. R. Odenbrett, A. Wijs, W. Ligtenberg, P. Hilbers, Efficient reconstruction of biological networks via transitive reduction on general purpose graphics processors, BMC Bioinformatics 2012, 13:281, <http://dx.doi.org/10.1186/1471-2105-13-281>

## 3.3 All You Want to Know About Heaps

Stefan Edelkamp (Universität Bremen, DE)

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**Joint work of** Edelkamp, Stefan; Chen, Jingsen Elmasry, Amr; Katajainen; Jyrki; Larsson Träff, Jesper; Weiß, Armin

**Main reference** H. Kaplan, R. E. Tarjan, U. Zwick, “Fibonacci heaps revisited,” arXiv:1407.5750v1 [cs.DS], 2014.  
**URL** <http://arxiv.org/abs/1407.5750v1>

The talk surveys theoretical and practical results for state-of-the-art heap implementations.

Starting with introducing binary, strong, and weak heaps, we cover

- constant-factor-optimal sequential sorting with WEAKHEAPSORT, QUICKHEAPSORT and QUICKXSORT; the latter taking at most  $n \lg n - 1.3999n + o(n)$  element comparisons on average,
- constant-factor-optimal adaptive heap sorting requiring at most  $n \lg(Inv/n) + O(n)$  element comparisons and exploiting Cartesian trees as well as buffered heaps.

We observe (and prove) that – in contrast to a heap – repeated insertion in a weak heap requires at most  $3.5n + o(n)$  element comparisons. There are other algorithm engineering aspects for heap construction (e. g. depth-first or bottom-up sift-downs) that reduce the number cache misses and branch mispredictions.

By modifying the heap construction algorithms of Gonnet and Munro and of McDiarmid and Reed, both requiring  $O(n)$  extra space, via transforming weak heaps (or a navigation piles) into heaps, we contribute two *in-place* heap construction algorithms, where the extra space is limited to most  $O(1)$  words. The algorithms match the best-known worst-case and average-case bounds, namely  $\sim 1.625n$  and  $\sim 1.52n$  element comparisons, respectively.

Strong heaps are used as a building block for *optimal in-place heaps*, which offer a constant-factor-optimal *delete-min* operation with at most  $\lg n + O(1)$  element comparisons in the worst-case, while keeping the *insert* operation worst-case constant time. The history of this problem shows that it remained unresolved for more than 30 years. Strong heaps offer two *sift-down* operations: one rotates subtrees, the other stretches the heap. Allowing a limited number of heap violating nodes and by strengthening the heap condition in bottom trees this construction bypasses a well-known bound for heaps. The deamortization construction of such strengthened lazy heaps is tricky: in-case the insertion buffer becomes full, the approach relabels the insertion buffer into an area for *submersion*.

Next, we turn to algorithmic engineering aspects of *single-source shortest-paths* graph search (such as node labels, a joint graph and heap node representation and the proper use of C++-templates). We study the sequence of  $m$  *decrease-key*,  $n$  *insert*, and  $n$  *delete-min* operations known to be applied in Dijkstra’s algorithm and A\* equipped with a consistent heuristic. Rank-relaxed weak heaps (allowing a logarithmic number of heap-violating nodes)

are presented and shown to be state-of-the-art in theory calling for at most  $2m + 1.5n \lg n$  element comparisons, while the best implementation of Fibonacci heaps requires about  $2m + 2.88n \lg n + O(n)$  element comparisons. It is conjectured that for handling this sequence at most  $2m + n \lg n + O(n)$  element comparisons are needed.

Last but not least, we will look at the latest developments of Fibonacci heaps, comparing *enhanced lazy Fibonacci heaps* that apply naive linkage in the consolidation with a 2014 proposal of *simple Fibonacci heaps* in terms of numbers of element comparisons, pointer assignments and running times for different sequences of operations. Variants with *cascading cuts* are experimentally compared with variants that apply *cascading rank decreases*, and put in to context with an implementation of 4-ary heaps.

All algorithms have been implemented for the CPHSTL library, which compares positively with LEDA.

## References

- 1 A. Bruun, S. Edelkamp, J. Katajainen, and J. Rasmussen. *Policy-based benchmarking of weak heaps and their relatives*. In Int. Symp. on Exp. Algorithms (SEA), volume 6049 of Lecture Notes Comput. Sci., pages 459–435. Springer, 2010.
- 2 D. Cantone and G. Cinotti. *QuickHeapsort, an efficient mix of classical sorting algorithms*. Theoretical Computer Science, 285(1):25–42, 2002.
- 3 J. Chen, S. Edelkamp, A. Elmasry, and J. Katajainen. *In-place heap construction with optimized comparisons, moves, and cache misses*. In Symposium Mathematical Foundations of Computer Science (MFCS), volume 7464 of Lecture Notes Comput. Sci., pages 259–270. Springer, 2012.
- 4 T. H. Cormen, C. E. Leiserson, R. L. Rivest, and C. Stein. *Introduction to Algorithms*. The MIT Press, 3rd edition, 2009.
- 5 V. Diekert and A. Weiss. *QuickHeapsort: Modifications and improved analysis*. In International Symposium on Computer Science in Russia (CSR), pages 24–35, 2013.
- 6 R. D. Dutton. *Weak-heap sort*. BIT, 33(3):372–381, 1993.
- 7 S. Edelkamp and I. Wegener. *On the performance of weak-heapsort*. In STACS, pages 254–266. Springer, 2000.
- 8 S. Edelkamp and P. Stiegeler. *Implementing Heapsort with  $n \log n - 0.9n$  and Quicksort with  $n \log n + 0.2n$  comparisons*. ACM Journal of Experimental Algorithmics, 7:5, 2002, 7: Article 5, 2002.
- 9 S. Edelkamp, A. Elmasry, and J. Katajainen. *Two constant-factor-optimal realizations of adaptive heapsort*. In Int. Workshop on Combinatorial Algorithms (IWOCA), volume 7056 of Lecture Notes in Computer Science, pages 195–208. Springer, 2011.
- 10 S. Edelkamp, A. Elmasry, and J. Katajainen. *A catalogue of algorithms for building weak heaps*. In Int. Workshop on Combinatorial Algorithms, pages 249–262, 2012.
- 11 S. Edelkamp, A. Elmasry, and J. Katajainen. *The weak-heap data structure: Variants and applications*. J. Discrete Algorithms, 16:187–205, 2012.
- 12 S. Edelkamp, A. Elmasry, and J. Katajainen. *The weak-heap family of priority queues in theory and praxis*. In Computing: the Australasian Theory Symposium (CATS), pages 103–112, 2012.
- 13 S. Edelkamp, A. Elmasry, and J. Katajainen. *Weak-heaps engineered*. J. Discrete Algorithms, 23:83–97, 2013.
- 14 S. Edelkamp and A. Weiss. *QuickXsort: Efficient sorting with  $n \log n - 1.399n + o(n)$  comparisons on average*. CSR, 2014.
- 15 S. Edelkamp, A. Elmasry, and J. Katajainen. *An In-Place Priority Queue with  $O(1)$  Time for Push and  $\lg n + O(1)$  Comparisons for Pop*. CSR, Lake Balkal, 2015.
- 16 J. Katajainen. *The ultimate heapsort*. In Computing: CATS, pages 87–96, 1998.

- 17 D. E. Knuth. *Sorting and Searching*, volume 3 of The Art of Computer Programming. Addison Wesley Longman, 2nd edition, 1998.
- 18 C. J. H. McDiarmid and B. A. Reed. *Building heaps fast*. Journal of Algorithms, pages 352–365, 1989.
- 19 J. Vuillemin. *A data structure for manipulating priority queues*. Commun. ACM, 21(4):309–315, 1978.
- 20 I. Wegener. *The worst case complexity of McDiarmid and Reed’s variant of bottom-up-heap sort is less than  $n \log n + 1.1n$* . STACS, pages 137–147, 1991.
- 21 J. W. J. Williams. *Algorithm 232: Heapsort*. Commun. ACM, 7(6):347–348, 1964.

### 3.4 Specification guided testing and verification for Cyber-Physical Systems

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**URL** <https://sites.google.com/a/asu.edu/s-taliro/>

Every year the software which controls Cyber-Physical Systems (CPS) increases in complexity. Due to the increased complexity, numerous design and implementation errors are discovered while CPS are operational in the field. Such errors can have catastrophic effects to human life and to the economy. In this talk, we present how the error detection process in CPS can be accelerated using Model-Based Development (MBD) and formal specifications. Temporal logic is a formal specification language that can capture both state- space and real-time system requirements. For example, temporal logics can mathematically state requirements like “whenever the system switches to first gear, then it should not switch back to second gear within 2.5sec”. Our approach in tackling this challenging problem is to convert the verification problem into an optimization problem through a notion of robustness for temporal logics. Through this transformation, any stochastic optimization algorithm can be used for automatic test case generation. In addition, we show how the basic underlying theory can be extended to provide a solution to the conformance problem and to the on-line monitoring problem. We have implemented our testing and verification framework into a Matlab (TM) toolbox called S-TaLiRo (System’s TemporAl LogIc Robustness). Finally, in this talk, we demonstrate that S-TaLiRo can provide answers to challenge problems from the automotive and medical device industries.

### 3.5 VAL: The Plan Validator for PDDL+

*Maria Fox (King’s College London, GB)*

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**Joint work of** Fox, Maria; Long, Derek; Howey, Richard;  
**Main reference** M. Fox, R. Howey, D. Long, “Validating Plans in the Context of Processes and Exogenous Events,” in Proc. of the 20th National Conf. on Artificial Intelligence (AAAI’05), pp. 1151–1156, AAAI Press, 2005.  
**URL** <http://www.aaai.org/Library/AAAI/2005/aaai05-182.php>

In recent years a significant part of the planning community has moved towards the application of planners to realistic problems. In the third International Planning Competition (held in 2002) planners addressed domains featuring temporal constraints and numeric resources. The modelling language PDDL2.1 was introduced for this competition, building on the previously

well established, but propositional, PDDL. A critical element in the use of PDDL2.1 has been the common understanding of the semantics of the language. The VAL system, described in this talk, was introduced as a reference semantics for PDDL2.1, enabling plan validity to be checked against domain and problem specifications. VAL has played this role since 2002, remaining a vital tool for many researchers. However, the competition did not explore the continuous modelling features of PDDL2.1, such as duration-dependent effects and continuously increasing and decreasing numeric values. Further modelling support for these features was provided in PDDL+, and VAL was extended to handle them but, with few exceptions, these features have not been much explored in planning since their introduction. The validation of plans using actions with continuous effects presents significant challenges. In this talk we review the need for continuous effects in planning, their semantics and the problems that arise in validation of plans that include them. We consider a motivating example and explain the exact methods exploited by VAL.

### 3.6 Heuristics for Classical Planning: We’re More Rigorous Than You Thought!

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Joint work of Domshlak, Carmel; Helmert, Malte; Pommerening, Florian; Röger, Gabriele; Seipp, Jendrik

The talk discusses the problem of optimal classical planning and its solution by heuristic search. There are two main technical parts. The first part presents the four major concepts under which heuristic approaches until around 2009 have been subsumed: *delete relaxation*, *abstraction*, *critical paths* and *landmarks*. It then explores some formal connections between these approaches within the framework of polynomial heuristic compilation. The second part covers some more recent ideas in this area: the *state equation* heuristic, *negative cost partitioning* and *potential heuristics*. It turns out that these ideas are closely connected and help us better understand previous heuristics based on abstraction.

### 3.7 Scenario-based Online Planning under Uncertainty

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Joint work of Ye, Nan; Somani, Adhiraj; Hsu, David; Lee, Wee Sun

Main reference A. Somani, N. Ye, D. Hsu, W. S. Lee, “DESPOT: Online POMDP planning with regularization,” in Proc. of the 27th Annual Conf. on Neural Information Processing Systems (NIPS’13), pp. 1772–1780, 2013.

URL <http://papers.nips.cc/paper/5189-despot-online-pomdp-planning-with-regularization>

URL <http://bigbird.comp.nus.edu.sg/pmwiki/farm/appl/>

Partially observable Markov decision process (POMDPs) provide a principled framework for planning under uncertainty, but are computationally intractable, due to the “curse of dimensionality” and the “curse of history”. To overcome these difficulties, our new online POMDP algorithm samples a small set of randomly sampled “scenarios”. It captures the execution of all policies on these scenarios in a compact structure called a Determinized Sparse Partially Observable Tree (DESPOT) and focuses the search for an optimal policy

over the sampled scenarios. We show that while the DESPOT algorithm optimizes over the sampled scenarios only, it computes a near-optimal optimal policy, provided that an optimal policy admits a compact representation. It also compares favorably with the state-of-the-art online POMDP algorithm on a set of benchmark tests, but provides stronger theoretical guarantee. I will also present experimental results showing the DESPOT algorithm running online in real time on an autonomous robot vehicle navigating among many pedestrians. Source code is available for download at <http://bigbird.comp.nus.edu.sg/pmwiki/farm/appl/>.

### 3.8 SAT Modulo Monotonic Theories

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**Joint work of** Bayless, Sam; Bayless, Noah; Hoos, Holger; Hu, Alan;

**Main reference** S. Bayless, N. Bayless, H. H. Hoos, A. Hu, “SAT Modulo Monotonic Theories,” AAAI 2015, to appear; pre-print available from author’s webpage.

**URL** <http://www.cs.ubc.ca/labs/isd/Projects/MonoSAT/>

I will present the concept of a “monotonic theory” and show how to build efficient SMT (SAT Modulo Theory) solvers, including efficient theory propagation and clause learning, for such theories. Examples of monotonic theories include graph properties such as reachability, shortest path, connected components, minimum spanning tree, and max-flow/min-cut, as well as geometric properties like convex hulls, visibility, etc. We demonstrate our framework by building SMT solvers for each of these theories. We apply these solvers to procedural content generation problems, demonstrating major speed-ups over state-of-the-art approaches based on SAT or Answer Set Programming, and easily solving several instances that were previously impractical to solve. Because this method provides an easy way to extend SMT solving efficiently to “physical world” theories, I believe that this holds promise for planning problems as well (although we don’t have any experimental results for planning yet).

### 3.9 Adapting a Policy On-line when the POMDP Model Changes

*Hanna Kurniawati (The University of Queensland, AU)*

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**Joint work of** Kurniawati, Hanna; Klimenko, Dimitri; Song, Joshua; Yadav, Vinay

**Main reference** H. Kurniawati, V. Yadav, “An Online POMDP Solver for Uncertainty Planning in Dynamic Environment,” in Proc. of the 16th Int’l Symp. on Robotics Research (ISRR’13), 2013; pre-print available from author’s webpage.

**URL** [http://robotics.itee.uq.edu.au/~hannakur/dokuwiki/papers/isrr13\\_abt.pdf](http://robotics.itee.uq.edu.au/~hannakur/dokuwiki/papers/isrr13_abt.pdf)

Over the past several years, POMDP-based planning has advanced tremendously. In 10 years, it has moved from planners that can only solve up to 12 states in days to planners that can solve problems with more than 5 dimensional continuous state space in seconds, making POMDP framework to start being practical for robotics problems. However, one issue remains: The POMDP model should not change. When a POMDP model may change during run-time, we either model all possible changes as part of the POMDP model, creating an unnecessarily large POMDP problem, or resort to replanning, which throws away all prior computation and plan from scratch. In this talk I will present my recent work that tries to mediate these two extreme approaches.

A software toolkit that implements the above algorithm can be downloaded from <http://robotics.itee.uq.edu.au/~tapir>. The algorithm and software can also be used as an on-line POMDP solver when there's no changes in the model.

### 3.10 PMT: Planning Modulo Theories

*Derek Long (King's College London, GB)*

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Planning has traditionally focussed on states described by a finite set of propositional variables, or, equivalently, finite domain variables (SAS+). Over the past decade, there has also been interest in extending the more successful approaches to include treatment of states with number-valued state variables. In recent years, the SAT community has turned its attention to problems in which predicates, functions and constants can be “interpreted”, modulo one or more theories (such as arithmetic, linear arithmetic constraints, arrays and so on) leading to SAT Modulo Theories (SMT). We explore the extension of Planning inspired by the ideas in SMT, to Planning Modulo Theories (PMT). PMT offers state variables with values drawn from new types, such as sets, arrays and so on. We show that the successful planning relaxations, based on reachability analysis and relaxed plan extraction, can be extended to PMT using abstract interpretations of the symbols in the corresponding theories. These abstractions must obey certain conditions that can be expressed in terms of semi-lattices. The talk illustrates these ideas and briefly outlines the behaviour of a PMT planner.

#### References

- 1 Peter Gregory, Derek Long, Maria Fox, J. Christopher Beck, *Planning Modulo Theories: Extending the Planning Paradigm*. In Proceedings of Twenty-Second International Conference on Automated Planning and Scheduling, ICAPS 2012.

### 3.11 Planning in Hybrid Domains through Model Checking

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The talk presents two approaches for planning in hybrid domains, both based on model checking. The first approach is based on the *Discretise and Validate* method [1], where first the continuous model is discretised, then the discretised model is solved using explicit model checking, and finally the discretised solution is validated against the continuous model. If the solution is not valid, then the discretisation is refined and the process iterates. This approach has been implemented in the UPMurphi tool [3]. An application of the approach to the problem of efficient multiple battery load management is presented [2].

The second approach uses symbolic model checking, and is based on a translation from PDDL+ to the semantics of standard automata [4],[5]. This translation represents a first bridge between planning in hybrid domains and hybrid system model checking, as it allows

the use of existing tools in hybrid system verification for planning in hybrid domains. A case study based on SpaceEx is presented.

### References

- 1 Giuseppe Della Penna, Daniele Magazzeni, Fabio Mercorio, *A universal planning system for hybrid domains*. In *Applied Intelligence*, 36(4), 932–959, 2012.
- 2 Maria Fox, Derek Long, Daniele Magazzeni, *Plan-based Policies for Efficient Multiple Battery Load Management*. In *Journal of Artificial Intelligence Research (JAIR)* 44:335–382. June 2012.
- 3 Giuseppe Della Penna, Benedetto Intrigila Daniele Magazzeni, Fabio Mercorio, *UPMurphi: a Tool for Universal Planning on PDDL+ Problems*. In *Proceedings of the Nineteen International Conference on Automated Planning and Scheduling, ICAPS 2009*.
- 4 Sergiy Bogomolov, Daniele Magazzeni, Andreas Podelski, Martin Wehrle, *Planning as Model Checking in Hybrid Domains*. In *Proceedings of the Twenty-Eighth AAAI Conference on Artificial Intelligence*, 2014.
- 5 Sergiy Bogomolov, Daniele Magazzeni, Stefano Minopoli, Martin Wehrle, *Foundations of Must Semantics for PDDL+*. In *Proceedings of the Twenty-Fifth International Conference on Automated Planning and Scheduling, ICAPS 2015*.

## 3.12 LTL, Regular Expressions (Golog) & Automata: 101 things you can do with non-classical planning

*Sheila McIlraith (University of Toronto, CA)*

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The field of Artificial Intelligence Automated Planning has seen significant advances in the last 15 years, largely as a result of innovations in planning-specific heuristic search and SAT techniques. Much of the focus has been on so-called classical planning systems which assume complete information about the initial state of a system at the outset of planning, deterministic actions, and a final state goal. Unfortunately, many interesting real-world problems violate classical planning assumptions. In this talk, I will discuss planning with temporally extended goals, constraints, and preferences, specified in Linear Temporal Logic (LTL) and via programs specified in an Algol-like language called Golog, which together capture the expressivity of finite state automata. A main focus of this talk will be on how to leverage these expressive languages to help guide heuristic search. We have explored these techniques in a diversity of problem settings from web service composition to verification and concurrent test generation. This talk should be of some interest to anyone who is concerned with reachability in dynamical systems. This is joint work with Jorge Baier, Christian Fritz, Meghyn Bienvenu, and Shirin Sohrabi.

### 3.13 Falsification of Safety Properties in Hybrid Systems through Motion Planning

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Hybrid systems often arise in embedded controllers used in the automotive industry, manufacturing, robotics, environmental- and health-monitoring devices whenever physical aspects of the system are modelled by combining discrete logic with continuous dynamics. This talk summarizes our research efforts in developing motion-planning approaches that can be used for the falsification of safety properties in hybrid systems. When the system is unsafe, these motion-planning approaches construct witness trajectories by expanding a search tree to explore the state space of the hybrid system. To improve the computational efficiency, these motion-planning approaches use discrete abstractions and discrete search to guide the expansion of the motion tree.

#### References

- 1 Erion Plaku and Lydia Kavraki and Moshe Vardi. *Falsification of LTL Safety Properties in Hybrid Systems*. In International Journal on Software Tools and Technology Transfer, 15(4):305–320, 2013.
- 2 James McMahan and Erion Plaku. *Sampling-based tree search with discrete abstractions for motion planning with dynamics and temporal logic*. In Proceedings of IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS), 2014.
- 3 Erion Plaku. *Robot Motion Planning with Dynamics as Hybrid Search*. In Proceedings of AAAI Conference on Artificial Intelligence (AAAI), 2013.

### 3.14 Planning for Energy Systems

Sylvie Thiébaux (Australian National University, AU)

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Public awareness of climate change, the rising costs of maintaining an ageing infrastructure, energy market volatility, and countries dependence on energy imports have motivated the development of new renewable and distributed technologies for generating, storing and managing energy. In turn, using these technologies to their full potential requires a fundamental paradigm shift in the way power systems are planned and operated. The talk describes a range of interesting planning problems that arise in the energy systems space, along with the challenges they raise for AI planners. Whilst these problems are currently solved using optimisation technologies, integrating ideas from AI planning has the potential to lead to improvement in scalability and solution quality. The talk illustrates in detail some of these challenges and potential benefits by comparing two approaches to the problem of power supply restoration in power distribution systems: one based on optimisation [15] and one based on an extension of AI planning [9].

#### References

- 1 Keith Bell, Amanda Jane Coles, Andrew Coles, Maria Fox, and Derek Long. The role of AI planning as a decision support tool in power substation management. *AI Commun.*, 22(1):37–57, 2009.

- 2 Joshua Champion, Chris Dent, Maria Fox, Derek Long, and Daniele Magazzeni. Challenge: Modelling unit commitment as a planning problem. In *Proc. 23rd International Conference on Automated Planning and Scheduling (ICAPS'13)*, June 2013.
- 3 Carleton Coffrin and Pascal Van Hentenryck. A linear-programming approximation of AC power flows. *INFORMS Journal on Computing*, 26(4):718–734, 2014.
- 4 Carleton Coffrin, Pascal Van Hentenryck, and Russell Bent. Last-mile restoration for multiple interdependent infrastructures. In *Proc. 26th AAAI Conference on Artificial Intelligence*, July 2012.
- 5 Giuseppe Della Penna, Daniele Magazzeni, Fabio Mercorio, and Benedetto Intrigila. Up-murphi: A tool for universal planning on PDDL+ problems. In *Proc. 19th International Conference on Automated Planning and Scheduling (ICAPS'09)*, September 2009.
- 6 Peter Gregory, Derek Long, Maria Fox, and J. Christopher Beck. Planning modulo theories: Extending the planning paradigm. In *Proc. 22nd International Conference on Automated Planning and Scheduling (ICAPS'12)*, June 2012.
- 7 C. Hijazi, C. Coffrin, and P. Van Hentenryck. Convex quadratic relaxations of nonlinear programs in power systems. *Optimization On-Line*, aug. 2013.
- 8 Hassan Hijazi and Sylvie Thiébaux. Optimal ac distribution systems reconfiguration. In *18th Power Systems Computation Conference (PSCC'14)*, Wroclaw, Poland, August 2014. IEEE.
- 9 Franc Ivankovic, Patrik Haslum, Sylvie Thiébaux, Vikas Shivashankar, and Dana Nau. Optimal planning with global numerical state constraints. In *24th International Conference on Automated Planning and Scheduling (ICAPS'12)*, pages 167–175, Portsmouth, USA, June 2014.
- 10 Boon Ping Lim, Menkes van den Briel, Sylvie Thiébaux, Scott Backhaus, and Russell Bent. Hvac-aware occupancy scheduling. In *Proc. 29th AAAI Conference on Artificial Intelligence (AAAI'15)*, January 2015.
- 11 Terrence Mak, Hassan Hijazi, and Pascal Van Hentenryck. Power system restoration with transient stability. In *Proc. 29th AAAI Conference on Artificial Intelligence (AAAI-15)*, January 2015.
- 12 Masahiro Ono, Wesley Graybill, and Brian C. Williams. Risk-sensitive plan execution for connected sustainable home. In *Proc. 4th ACM Workshop on Embedded Sensing Systems for Energy-Efficiency in Buildings (BuildSys'12)*, pages 45–52, November 2012.
- 13 Chiara Piacentini, Varvara Alimisis, Maria Fox, and Derek Long. Combining a temporal planner with an external solver for the power balancing problem in an electricity network. In *Proc. 23rd International Conference on Automated Planning and Scheduling (ICAPS-13)*, June 2013.
- 14 Paul Scott, Sylvie Thiébaux, Menkes van den Briel, and Pascal Van Hentenryck. Residential demand response under uncertainty. In *International Conference on Principles and Practice of Constraint Programming (CP'13)*, September 2013.
- 15 Sylvie Thiébaux, Carleton Coffrin, Hassan Hijazi, and John Slaney. Planning with mip for supply restoration in power distribution systems. In *International Joint Conference on Artificial Intelligence (IJCAI'13)*, pages 2900–2907, August 2013.
- 16 Eric Timmons and Brian C. Williams. Enumerating preferred solutions to conditional simple temporal networks quickly using bounding conflicts. In *AAAI-15 Workshop on Planning, Search and Optimisation (PlanSOpt'15)*, January 2015.

### 3.15 Directed model checking for timed systems

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Joint work of Wehrle, Martin; Kupferschmid, Sebastian

This talk provides an introduction to directed model checking for timed systems. Directed model checking is an established approach for detecting error states in concurrent systems. A popular variant to find shortest error traces is to apply the A\* search algorithm with distance heuristics that never overestimate the real error distance. An important class of such distance heuristics is the class of pattern database heuristics, which are based on abstractions of the system under consideration. In this context, we propose downward pattern refinement, a systematic approach for the automatic construction of pattern database heuristics for timed automata. Our experiments show the practical potential of the resulting pattern database heuristic.

#### References

- 1 Sebastian Kupferschmid and Martin Wehrle. *Abstractions and Pattern Databases: The Quest for Succinctness and Accuracy*. In Proceedings of the 17th International Conference on Tools and Algorithms for the Construction and Analysis of Systems (TACAS 2011), 2011.
- 2 Martin Wehrle and Sebastian Kupferschmid. *Downward Pattern Refinement for Timed Automata*. In International Journal on Software Tools for Technology Transfer (STTT), DOI: 10.1007/s10009-014-0346-x.

### 3.16 GPUexplore: Many-core On-the-fly State Space Exploration Using GPUs

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Joint work of Wijs, Anton; Bosnacki, Dragan

Main reference A. Wijs, D. Bošnački, “GPUexplore: Many-Core On-The-Fly State Space Exploration Using GPUs,” in Proc. of the 20th Int’l Conf. on Tools and Algorithms for the Construction and Analysis of Systems (TACAS’14), LNCS, Vol. 8413, pp. 233–247, Springer, 2014.

URL [http://dx.doi.org/10.1007/978-3-642-54862-8\\_16](http://dx.doi.org/10.1007/978-3-642-54862-8_16)

In recent years, General Purpose Graphics Processors (GPUs) have been successfully applied in multiple application domains to drastically speed up computations. Model checking is an automatic method to formally verify the correctness of a system specification. Such specifications can be viewed as implicit descriptions of a large directed graph or state space, and for most model checking operations, this graph must be analysed. Constructing it, or on-the-fly exploring it, however, is computationally intensive, so it makes sense to try to implement this for GPUs. In this talk, I explain the limitations involved, and how to overcome these. I discuss the possible approaches involving related work, and propose an alternative, using a new hash table approach for GPUs. Experimental results with our prototype implementations show significant speed-ups compared to the established sequential counterparts.

### 3.17 Optimal Temporal Plan Execution with Bounded Risk

Brian C. Williams (MIT – Cambridge, US)

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Automated task planning and execution is key to creating robotic systems that perform tasks robustly based on intuitive goal descriptions. Automated activity planning and plan execution are both key elements. Plan executives must often map simple discrete activities specified in the plan to continuous control trajectories or motions. This involves automated planning, but within a continuous domain.

In addition, planners must ensure correctness despite uncertainty in the environment, for example, due to temporal delays, actuator disturbances and sensor noise. To adapt, plan executives should dynamically adjust the timing of activities and control trajectories that implement these activities, and activity plan descriptions should offer flexibility in temporal and state constraints, needed to perform these adaptations.

Finally, when uncertainty is unbounded, successful plan execution cannot be guaranteed, there is always some risk of failure. In this event, activity plans should include specifications of what level of risk of failure is acceptable, and plan executives should ensure that they operate within this risk bound.

The first half of this tutorial presents algorithms for dynamically executing temporal plans by scheduling activities and by mapping these activities to continuous control trajectories. The second half of this tutorial introduces temporal plan descriptions that specify risk bounds in the form of chance constraints, and then presents stochastic methods for scheduling and generating control trajectories that are guaranteed to operate within these risk bounds.

### 3.18 Statistical Model Checking for Markov Decision Processes

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**Joint work of** Henriques, David; Martins, Joao; Zuliani, Paolo; Platzer, Andre; Clarke, Edmund;  
**Main reference** D. Henriques, J. Martins, P. Zuliani, A. Platzer, E. M. Clarke, “Statistical model checking for Markov decision processes,” in Proc. of the 9th Int’l Conf. on Quantitative Evaluation of Systems (QEST’12), pp. 84–93, IEEE, 2012.  
**URL** <http://dx.doi.org/10.1109/QEST.2012.19>

We present a statistical model checking approach for verifying temporal logic properties of Markov Decision Processes.

Statistical Model Checking (SMC) is a simulation-based verification technique for stochastic systems. It combines randomised sampling with statistical analysis. Basically, execution traces of the underlying (stochastic) model are first sampled and then checked against a linear-time bounded temporal property. The results of these checks are used to compute appropriate *statistical* guarantees on whether the given property is true or not. A disadvantage of SMC is that it might return wrong answers, albeit the probability of such occurrences can be made arbitrarily low. An advantage of SMC is that it usually scales much better than traditional model checking techniques, since it does not perform an exhaustive state space search. As such, SMC can be useful for verifying extremely large systems.

Systems that combine probabilism and nondeterminism, *e. g.*, Markov Decision Processes (MDP), represent a hurdle for SMC. In particular, for MDPs it is not clear how the simulator

should resolve nondeterministic choices in order to generate sample executions of the model. Different resolutions of nondeterminism (*i. e.*, schedulers) may result in widely different system behaviours. In general, a finite-state MDP satisfies a given temporal property with a maximum and a minimum probability.

In this talk we give an overview of our recently proposed SMC-based approach for MDPs. In particular, our approach aims at finding a scheduler that maximises the probability that a given property is true. It does so by iteratively sampling over the model space and by building probabilistic candidate schedulers which cannot decrease the probability that the property is true. In particular, we use reinforcement learning to build schedulers which give more probability to those actions likely to lead to property satisfaction. We apply our approach to a number of case studies and compare the results with the leading probabilistic model checker, PRISM. The results show that our approach can scale to MDPs that cannot be handled with traditional techniques. We conclude by discussing possible extensions of our technique for schedulers with memory and for properties with unbounded temporal operators.

### References

- 1 D. Henriques, J. Martins, P. Zuliani, A. Platzer, E. M. Clarke. *Statistical Model Checking for Markov Decision Processes*. In QEST 2012: IEEE, pages 84–93.
- 2 H. L. S. Younes and Reid G. Simmons. *Probabilistic Verification of Discrete Event Systems Using Acceptance Sampling*. In CAV 2002: LNCS vol. 2404, pages 223–235.
- 3 M. Kwiatkowska, G. Norman, D. Parker. *PRISM 4.0: Verification of Probabilistic Real-time Systems*. In CAV 2011: LNCS vol. 6806, pages 585–591.
- 4 H. L. S. Younes, E. M. Clarke, P. Zuliani. *Statistical Verification of Probabilistic Properties with Unbounded Until*. In SBMF 2010: LNCS vol. 6527, pages 144–160.

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