06161 Abstracts Collection
Simulation and Verification of Dynamic Systems
— Dagstuhl Seminar —

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Abstract. From 17.04.06 to 22.04.06, the Dagstuhl Seminar 06161 "Simulation and Verification of Dynamic Systems" was held in the International Conference and Research Center (IBFI), Schloss Dagstuhl. During the seminar, several participants presented their current research, and ongoing work and open problems were discussed. Abstracts of the presentations given during the seminar as well as abstracts of seminar results and ideas are put together in this paper. The first section describes the seminar topics and goals in general. Links to extended abstracts or full papers are provided, if available.

Keywords. Modeling, Simulation, Verification, Dynamic Systems, Systemsbiology

06161 Executive Summary – Simulation and Verification of Dynamic Systems

Simulation is widely used for modeling engineering artifacts and natural phenomena to gain insight into the operation of those systems. Formal verification is concerned with proving or disproving the correctness of a system with respect to a certain property. Despite of these different objectives, the fields of simulation and verification address similar research challenges. Particularly, in the application area systems biology simulation and verification are moving together. The Dagstuhl Seminar was dedicated to intensifying this dialogue, and stimulating the exchange of ideas. Three working groups discussed questions: Why are biological systems difficult to model?, What role does refinement and abstraction play in combining simulation and verification?, What is the role of communication and composition in simulating and analysing dynamic systems? The results of the working groups can be found in the working groups' report.

Dagstuhl Seminar Proceedings 06161
Simulation and Verification of Dynamic Systems
http://drops.dagstuhl.de/opus/volltexte/2006/710

Keywords: Modelling, Simulation, Verification, Systemsbiology

Joint work of: Riis-Nielson, Hanne; Nicol, David M.; Priami, Corrado; Uhrmacher, Adelinde M.

Extended Abstract: http://drops.dagstuhl.de/opus/volltexte/2006/702

06161 Working Groups' Report:The Challenge of Combinig Simulation and Verification

Simulation has found widespread use for experimentation and exploration of the possible impacts of a variety of conditions on a system. In contrast, formal verification is concerned with proving or disproving the correctness of a system with respect to a certain property, using mathematical and logical methods.

Keywords: Modelling, Simulation, Verification, Systemsbiology

Joint work of: Batt, Gregory; Bradley, Jeremy; Ewald, Roland; Fages, François; Hermans, Holger; Hilston, Jane; Kemper, Peter; Martens, Alke; Mosterman; Pieter; Nielson, Flemminsg; Sokolsky, Oleg; Uhrmacher, Adelinde M.; and all other participants of the Dastuhl seminar

Extended Abstract: http://drops.dagstuhl.de/opus/volltexte/2006/724

Formal verification of hybrid models of genetic regulatory networks

Gregory Batt (Boston University, USA)

The functioning and development of living organisms is controlled on the molecular level by genetic regulatory networks. The switch-like character of genetic regulations has motivated the development of hybrid models of genetic networks. These models describe the dynamics of the networks as a combination of continuous evolutions and discrete events.

In this talk, I will present two classes of hybrid systems that are particularly well adapted to modeling genetic networks, based on piecewise affine or piecewise multiaffine differential equations.

Methods have been recently developed for the formal verification of the dynamical properties of these systems. They rely on the use of discrete abstraction and model checking, and have been designed to cope with large uncertainties on the values of the parameters that one often encounters when analyzing these systems. These techniques make it possible to assess the validity of a model, by checking the consistency between predictions and experimental data, or to design networks whose behaviors satisfy given temporal specifications.

Work done in collaboration with:
Hidde de Jong (INRIA), Johannes Geiselmann (UJF, Grenoble), Jean-Luc Gouzé (INRIA), Radu Mateescu (INRIA), Michel Page (UPMF, Grenoble), Delphine Ropers (INRIA), Tewfik Sari (UHA, Mulhouse), Dominique Schneider (UJF, Grenoble),
and with:
Calin Belta (Boston Univ.), Boyan Yordanov (Boston Univ.), Ron Weiss (Princeton Univ.).

Abstract Interpretation of Graph Transformation

Jörg Bauer (Universität des Saarlandes, D)

The semantics of many dynamic systems can be described by evolving graphs. Graph transformation systems (GTS) are a natural, intuitive, and formally defined method to specify systems of evolving graphs, whereas verification techniques for GTS are scarce.

We present an abstract interpretation based approach for GTS verification. Single graphs are abstracted in two steps. First similar nodes within a connected component, then similar abstracted connected components are summarized. Transformation rules are applied directly to abstract graphs yielding a bounded set of abstract graphs of bounded size that over-approximates the concrete GTS and can be used for further verification. Since our abstraction is homomorphic, existential positive properties are preserved under abstraction. Furthermore, we identify automatically checkable completeness criteria for the abstraction.

The technique is implemented and successfully tested on the platoon case study.

Keywords: Abstract Interpretation, Graph Transformation

Joint work of: Bauer, Jörg, Wilhelm, Reinhard

Extended Abstract: http://drops.dagstuhl.de/opus/volltexte/2006/703

From π-calculus to differential equations and return

Luca Bortolussi (Universitá di Udine, I)

Studying and understanding the relations between discrete and continuous modeling techniques is considered one of the most important problems in computational system biology. This will be the focus of our presentation, which is more of a work in progress than a statement of results.

In particular, we concentrate on the relations between process algebra paradigm (mainly stochastic π-calculus), and a class of ordinary differential equations (DE) called S-Systems. The aim of this study, in the long run, is to devise an

hybrid modeling approach, connecting together the simplicity of internal description of systems (a feature of process algebras) and the quantitative power of external modeling (in terms od DE). A more concrete goal is to analyze the relationships between these two techniques in terms of parameters and their determination. In particular, we are working at identifying methodologies to estimate stochastic rates for π-processes, given the differential equations, and viceversa.

As a side step in this direction, we defined an "extension" of π-calculus, by integrating into it the computational power of Constraints. In particular, we defined a stochastic version of Concurrent Constraint Programming (sCCP) with both synchronous and asynchronous communication. The first motivations for the use of this process algebra are its flexibility and the fact that it is easy to program. But, even more important, it leads to a "clever" definition of parameters, i.e. the programmer has complete freedom in setting (non-constant) rates for transitions.

In our aim to clarify how information may flow from stochastic process algebras to DE, we started by taking a closer look into Gillespie algorithm. In fact, Gillespie approach can be seen as a simulation of a Continuous Time Markov Chain (CTMC), where the state space is the set of tuples of integers counting the different molecules present in the system, and where the rate of transitions are determined by summing up the basic rates of all possible reactions. This clearly shows why Gillespie Algorithm works when applied to process algebras (it simulates exactly the CTMC induced by the reduction semantic), enabling an easy implementation of a simulator for CCP (metainterpreter in Prolog, 500 lines). Moreover, this point of view gives a way to formalize the concept of observables in the realm of stochastic simulations (in π-calculus) of biological systems. In fact, what we observe are changes in concentration, or better the changes in the number of instances of some processes. Once we have a formal description of traces in this space of observables, we can compute a set of traces and use this information to train parameters for a set of differential equations (S-Systems) representing the same system. In this way, we may be able to identify the underlying mathematical law governing the phenomenon under consideration. This method is feasible to be extended by adding to the set of π-calculus traces also experimental data (modulo rescaling).

The work done up to this point not only extends expressive power of the computational machinery over π-calculus, but it also allows a natural passage from differential equations to process algebras. In fact, if we have the possibility of defining arbitrary rate functions, we can use the information contained in S-Systems by writing simple sCCP processes whose rates are controlled by the expressions appearing in the differential equations. As a simple case study, we considered repressilator. But a more interesting question emerges here: in this last passage, we calculated rates for processes with a fixed structure. It would be much more interesting to be able to define also the logical control structure of processes, starting from a DE description. This essentially means to find the

best set of agents whose collective behaviour best approximates the DE's one. A path towards this goal may pass through symbolic dynamical systems.

Keywords: Process algebras, constraints, differential equations

Joint work of: Bortolussi, Luca; Policriti, Alberto

Stochastic process algebra models of a Circadian clock

Jeremy Bradley (Imperial College London, GB)

We present stochastic process algebra models of a Circadian clock mechanism used in many biological organisms to regulate time-based behaviour. We compare modelling techniques from different modelling paradigms, PEPA and stochastic π-calculus.

Keywords: Stochastic process algebras, ODEs, Circadian clock

Joint work of: Bradley, Jeremy; Thorne, Thomas

Extended Abstract: http://drops.dagstuhl.de/opus/volltexte/2006/705

Artificial Biochemistry

Luca Cardelli (Microsoft Research UK, GB)

I have been investigating the mass behavior of stochastic interacting automata. A "law of mass action" governs stochastic interactions; it is inspired by chemistry and incorporated in stochastic pi calculus in the form of the Gillespie simulation algorithm. The dynamics of even just finite state automata is very puzzling. This work is largely explorative: it is almost all simulation, with a tiny bit of process algebra, and no verification. But I think it points to the need for new (or renewed) verification efforts.

Modeling (and Simulating) Biological Processes with Stochastic Multiset Rewriting

Matteo Cavaliere (Microsoft Research - University of Trento, I)

Membrane systems were originally introduced as models of computation inspired by the structure and the functioning of living cells. More recently, membrane systems have been shown to be suitable also to model cellular processes.

Inspired by brane calculi, a new model of membrane system with peripheral proteins has been recently introduced. Such model has compartments (enclosed by membranes), floating objects, and objects attached to the internal and external surfaces of the membranes. The objects can be processed/transported inside/across the compartments and the transport is regulated by opportune objects attached to the membranes surfaces. We present a stochastic simulator of this model, with a style of syntax based on chemical reactions. We show that the simulator can be particularly useful in modelling biological processes that involve compartments, surface and integral membrane proteins, transport and processing of chemical substances. As examples we present the simulation of circadian clock and the G-protein cycle in yeast.

Keywords: Systems biology, membrane systems, formal language, simulation

Extended Abstract: http://drops.dagstuhl.de/opus/volltexte/2006/706

Biological Validation as Model Checking

François Fages (INRIA Rocquencourt, F)

We illustrate the Thesis that, to a large extend: - biochemical systems can be identified to transition systems (of different kinds, with discrete or continuous dynamics), - the biological properties known from experiments can be formalized in Temporal Logic (propositional or with numerical constraints) - and biological validation amounts to model checking in this setting.

Through models on the cell cycle control we examplify this approach together with its reverse-engineering counter-part implemented in the Biochemical Abstract Machine environment BIOCHAM, for searching parameter values and learning reaction rules from temporal logic properties.

Keywords: Systems Biology, Temporal Logic, Model Checking, Constraints, Cell Cycle

Full Paper:
http://contraintes.inria.fr/~fages/Papers/CCFS05tcsb.pdf

Guiding Simulation by Model Checking

Holger Hermanns (Universität des Saarlandes, D)

This talk discusses how verification techniques, in particular *model checking* can be used to guide *discrete event simulation*. We believe that this combination is very promising, and rich in potential applications.

The mathematical workhorse for this approach is a nondeterministic *and* stochastic model, in particular the model of a stochatic timed automata. These models are rich in modelling power, which makes them well-suited for many

diverse application areas. However, discrete-event-simulation can only be used in a meaningful way, if nondeterminism is resolved by some means. This is where model-checking comes into play, to provide examples (or counterexamples) of interesting behaviour sequences to be studied via simulation.

A concrete example will be used to illustrate this general approach. In the example, we use real-time model checking with UPPAAL to synthesize feasible production schedules for a laquer production plant. Then we study the effect of machine breakdowns and repairs for the synthesized schedules using the discrete-event simulator of the Möbius toolset. The entire toolflow is supported by the modelling language MODEST, and its accompanying tool MOTOR.

Keywords: Model checking, discrete event simulation, real time, stochastics, scheduling, nondeterminism

Joint work of: Hermanns, Holger; Mader, Angelika; Bohnenkamp, Henrik; Usenko, Yaroslav; Klaren, Rick

Full Paper:
http://csdl.computer.org/comp/proceedings/qest/2004/2185/00/21850028abs.htm

See also: Henrik C. Bohnenkamp, Holger Hermanns, Ric Klaren, Angelika Mader, Yaroslav S. Usenko: Synthesis and Stochastic Assessment of Schedules for Lacquer Production. in: Proc. of the 1st International Conference on Quantitative Evaluation of Systems, QEST 2004, 28–37, IEEE CS Press, 2004.

Population models from PEPA descriptions

Jane Hillston (University of Edinburgh, GB)

Stochastic process algebras emerged about 15 years ago as system description techniques for performance modelling. Originally they were focussed on the generation of continuous time Markov chains facilitating steady state and transient analysis numerically. As with all state-based modelling techniques they suffer from problems of state space explosion.

Recently we have been exploring techniques to capture a representation of the system at the population level from the PEPA description, rather than capturing individual behaviours as happens in the CTMC semantics. In this talk I wil explain the mapping to the population model, a set of non-linear ordinary differential equations, and illustrate it with a case study of an Internet worm infection.

Keywords: Stochastic Process Algebra, Fluid Approximation, Discrete vs Continuous models

Population models from PEPA descriptions

Jane Hillston (University of Edinburgh, GB)

Stochastic process algebras such as PEPA have enjoyed considerable success as CTMC-based system description languages for performance evaluation of computer and communication systems. However they have not been able to escape the problem of state space explosion, and this problem is exacerbated when other domains such as systems biology are considered. Therefore we have been investigating alternative semantics for PEPA models which give rise to a population view of the system, in terms of a set of nonlinear ordinary differential equations. This extended abstract gives an overview of this mapping.

Keywords: Stochastic Process Algebra, Fluid Approximation, Discrete vs Continuous models

Extended Abstract: http://drops.dagstuhl.de/opus/volltexte/2006/707

Model Checking Dynamic, Communicating Systems

Hardi Hungar (OFFIS - Oldenburg, D)

The talk presents experiences in automatically verifying or exploring dynamic, asynchrnously communicating systems specified in operational UML. The BDD-based methods which have been successful for hardware and static, synchronous systems turn out to work badly in the presence of asynchronous, buffered communication and dynamic object creation and deletion. Explicitly distinguishing discrete state components shows greater promise, as demonstrated via two different approaches. Extending such techniques with an efficient handling of arithmetical data remains a challenge, but constitutes a prerequisite for verifying data-intensive dynamic systems.

Keywords: Model checking, VIS, SPIN, UML, Rhapsody, communication, dynamic creation

Joint work of: Hungar, Hardi; Lettrari, Marc; Rakow, Jan-Hendrik; Robbe, Oliver; Schinz, Ingo; Toben, Tobe; Westphal, Bernd

Verification of Simulation Models - Experiences and Challenges

Peter Kemper (Universität Dortmund, D)

Verification and Simulation share many issues, one is that simulation models require validation and verification. Both are treated in the literature at a rather high level and seem to be more an art than engineering.

This talk considers discrete event simulation of stochastic models that are formulated in a process-oriented language.

The ProC/B paradigm is used as a particular example of a class of simulation languages which follow the common process interaciton approach and show common concepts used in performance modeling, namely a) layered systems of virtual machines that contain resources and provide services and b) concurrent processes that interact by message passing and shared memory. The talk identifies typical faults in simulation models that were developed to model logistic systems, it shows ways to support a user in verifying a simulation model, and it indicates challenges for further research.

A Petri Net Approach to Verify and Debug Simulation Models

Peter Kemper (Universität Dortmund, D)

Verification and Simulation share many issues, one is that simulation models require validation and verification. In the context of simulation, verification is understood as the task to ensure that an executable simulation model matches its conceptual counterpart while validation is the task to ensure that a simulation model represents the system under study well enough with respect to the goals of the simulation study.

Both, validation and verification, are treated in the literature at a rather high level and seem to be more an art than engineering. This paper considers discrete event simulation of stochastic models that are formulated in a process-oriented language.

The ProC/B paradigm is used as a particular example of a class of simulation languages which follow the common process interaction approach and show common concepts used in performance modeling, namely a) layered systems of virtual machines that contain resources and provide services and b) concurrent processes that interact by message passing and shared memory.

We describe how Petri net analysis techniques help to verify and debug a large and detailed simulation model of airport logistics. We automatically derive a Petri net that models the control flow of a ProC/B model and we make use of invariant analysis and modelchecking to shed light on the allocation of resources, constraints among entities and causes for deadlocks.

Keywords: Discrete event simulation, verification, debugging, process interaction, Petri net analysis

Joint work of: Kemper, Peter; Tepper, Carsten

Full Paper: http://drops.dagstuhl.de/opus/volltexte/2006/708

Bacterial gene expression in (yet) a(nother) π-calculus

Céline Kuttler (Interdisciplinary Research Institute - Lille, F)

Stochastic simulation of genetic networks based on models in the stochastic π-calculus is a promising recent approach. This talk presents an extensible model of the central mechanisms of gene expression i.e. transcription and translation, for the prototypical case of bacteria. We reach extensibility through an object-oriented programming style in the π-calculus, and a module system. We use multi-profile objects with inheritance, that are compiled into the stochastic π-calculus extended by pattern guarded choices.

We illustrate the coverage of our model in a simulation case study that demonstrates translational bursting in bacterial gene expression.

Keywords: Simulation, π-calculus, systems biology, concurrent programming, gene expression

Advanced Technologies to Accelerate Mixed Signal Simulation

Pieter J. Mosterman (The MathWorks Inc. - Natick, USA)

Verification is an important aspect of chip design with about half of total engineering time spent on it. In particular, the design and maintenance of the test benches that are required for verification make this an expensive step in the overall chip design. The expense is further compounded by the observation that the test bench is not part of the functional design that forms the eventual product. System-level simulation can be employed to mitigate these expenses, as the designed component is tested by embedding it into a system model. Because of the different tools typically used for the system design and logic emulation, at present, a co-simulation approach to facilitate the system-level verification appears to be the only feasible solution.

Co-simulation has to address an important difference in simulation technologies that are typically used in the respective tools. Where system-level design tools often employ a time-driven simulation approach, logic-emulation tools tend to be based on event-driven simulation methods. This presentation discusses the combination of event-driven and time-driven simulation and identifies the issues that arise in such a hybrid approach.

Keywords: Hybrid systems, chip design, design automation, system on chip, co-simulation

Network Simulation Performance Optimizations, and the Need for Validation

David M. Nicol (Univ. of Illinois - Urbana, USA)

The simulation of very large networks requires modeling approaches that are more abstract than the packet-oriented one standard among most commonly used simulators. Examples include use of flow models to describe traffic, and on-demand computation of BGP routes through Autonomous Systems. This talk describes some of these optimizations, the work we've done to validate modeled network behavior using them, and open problems.

Context Dependent Analysis of BioAmbients

Henrik Pilegaard (Technical University of Denmark, DK)

BioAmbients is a derivative of mobile ambients that has shown promise of describing interesting features of the behaviour of biological systems. The technical contribu- tion of this paper is to extend the Flow Logic approach to static analysis with a couple of new techniques in order to give precise information about the behaviour of systems written in BioAmbients. Applying the development to a simple model of a cell releasing nutrients from food compunds we illustrate how the proposed analysis does indeed improve on previous efforts.

Keywords: Static analysis, abstract interpretation, BioAmbients

Full Paper: http://drops.dagstuhl.de/opus/volltexte/2006/709

See also: Pilegaard, H., F. Nielson, H. Riis Nielson, 'Context Dependent Analysis of BioAmbients', Proceedings of EAAI 2006 (1st International Workshop on Emerging Applications of Abstract Interpretation), to appear

Static Analysis of a Model of the LDL Degradation Pathway

Henrik Pilegaard (Technical University of Denmark, DK)

BioAmbients is a derivative of mobile ambients that has shown promise of describing interesting features of the behaviour of biological systems. As for other ambient calculi static program analysis can be used to compute safe approximations of the behaviour of system models. We use these tools to model and analyse the production of cholesterol in living cells and show that we are able to pinpoint the difference in behaviour between models of healthy systems and models of mutated systems giving rise to known diseases.

Keywords: Static analysis, Systems Biology, BioAmbients, LDL Degradation Pathway

Full Paper: http://drops.dagstuhl.de/opus/volltexte/2006/723

Safety Verification of Hybrid Systems by Constraint Propagation Based Abstraction Refinement and Integrated Falsification

Stefan Ratschan (MPI für Informatik - Saarbrücken, D)

The talk will describe the algorithms behind the tool HSolver (http://hsolver.sourceforge.net) that allows the safety verification of hybrid systems. Furthermore, it will discuss some first ideas to extending it with falsification capabilities. These should exploit information generated by the verification engine for guiding the search for counter-examples (i.e., for trajectories from an initial to an unsafe state).

Keywords: Verification, hybrid systems

Joint work of: Ratschan, Stefan; She, Zhikun; Smaus, Jan-Georg

Formal Analysis of Network Simulations

Oleg Sokolsky (University of Pennsylvania, USA)

We discuss using formal run-time verification techniques in conjunction with very detailed simulations of ad hoc routing protocols in the NS network simulator. Our analysis has found violations of significant high-level protocol properties. We also discuss debugging strategies that utilize the interplay between the simulation and verification engines.

Full Paper:
http://repository.upenn.edu/cis_papers/85/

Verifying Spatially-Explicit Simulation of Virulence Evolution Via Analytical Models

Boleslaw Szymanski (Rensselaer Polytechnic, USA)

We developed a simulation of the detailed model of virulence evolution that indicates that spatial structure constrains disease virulence. The mean-field approximation predicts evolution to criticality; any small increase in virulence capable of dynamical persistence is favored.

However, pair approximation of the detailed model agrees with the simulation spatial structure constraining disease virulence. Increased spatial clustering reduces the maximal virulence capable of single-strain persistence and, more importantly, reduces the convergent-stable virulence level under strain competition. The spatially detailed model predicts that increasing the probability of superinfection, for given difference in virulence, increases the likelihood of between-strain coexistence. When strains differing in virulence can coexist ecologically, our results may suggest policies for managing diseases with localized transmission. Comparing equilibrium densities from the pair approximation, we find that introducing a more virulent strain into a host population infected by a less virulent strain can sometimes reduce total host mortality and increase global host density.

Keywords: Epidemics, virulence, superinfection, simulation, mean-field approximation, pair-wise approximation

Joint work of: Szymanski, Boleslaw; Maniatty, William; Caraco, Thomas

See also: "Spatially structured superinfection and the evolution of disease virulence" Thomas Caraco, Stephan Glavanakov, Shengua Li, William Maniatty, and Boleslaw K. Szymanski, to appear in: Theoretical Population Biology, 2006.

Component-based Modeling and Simulation - An Exploration based on James II

Adelinde M. Uhrmacher (Universität Rostock, D)

Many biological systems but also software systems (e.g. so called multi-agent systems) are characterized by their complexity in terms of number and heterogeneity of involved components and interaction patterns. To support an efficient and effective analysis of these systems a flexible simulation system is needed. Thereby flexibility refers to the modeling and simulation layer alike. The modeling and simulation system James II exploits reusable components for that purpose. We will present results achieved and discuss some of the open questions.

Model Checking of Hybrid Systems: From Reachability towards Stability

Silke Wagner (MPI für Informatik - Saarbrücken, D)

We call a hybrid system stable if every trajectory inevitably ends up in a given region. In this talk, I present a model checking algorithm for stability. The idea of the algorithm is to reduce the stability proof for the whole system to a set of (smaller) proofs for several one-mode systems.

Joint work of: Wagner, Silke; Podelski, Andreas