Report from Dagstuhl Seminar 12462

Symbolic Methods for Chemical Reaction Networks

Edited by

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Abstract

During 11–16 November 2012, the Dagstuhl Seminar 12462 "Symbolic Methods for Chemical Reaction Networks" was held in Schloss Dagstuhl – Leibneiz Center for Informatics. The seminar brought together researchers in symbolic computation, chemical engineering, and systems biology. During the seminar, participants presented five-minute talks introducing their research interests, five participants gave longer talks, and all participants had the opportunity to take part in various discussion groups. Abstracts of presentations and summaries of the discussion groups are compiled in this report.

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1 Executive Summary

Anne J. Shiu

Systems of differential equations and hybrid systems more generally are prevalent in chemical engineering and systems biology. The analysis of such systems focuses on resolving their dynamical properties, for instance, determining their equilibria and capacity for multistationarity or Hopf bifurcations. The additional tasks of parameter estimation, model reduction, and model inference are also relevant for these systems. These goals are difficult in general, especially due to the large size of these systems, especially those arising in systems biology. Non-numeric methods are essential in this context, because reaction parameters can vary over a wide range, parameter uncertainty is predominant in systems biology, and even the qualitative behavior of a system typically varies among different regions of the parameter space. Two major lines of research in this area are represented by chemical reaction network

theory and stoichiometric network analysis. Our Dagstuhl seminar brought together researchers from both of these research areas, as well as researchers in symbolic computation and those on the application side (chemical engineering and systems biology). The aim of our seminar was twofold: to introduce practitioners to existing relevant theory and software from symbolic computation, and to allow participants to pose current computational challenges in this area, in order to spur development of symbolic computation methods to resolve these problems. To this end, collaborative working groups on various related topics were held throughout the week.

On Monday during the seminar, most of the participants gave short talks introducing their research interests. On Tuesday, long talks were given by Gheorghe Craciun and Francois Fages. A long talk on Wednesday was given by Stefan Schuster. Markus Eiswirth and Holger Fröhlich gave long talks on Thursday. Discussion groups met throughout the week.

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3 Overview of Short Talks

This section contains abstracts of the short (three-slide, five-minute) talks.

3.1 Differential algebra: theory and applications

Francois Boulier (Université de Lille I, FR)

I talked about differential algebra: theory, applications to engineering, chemistry, biology, and the software I am developing.

3.2 Symbolic computational tools for understanding real polynomial equalities and inequalities

Christopher W. Brown (U.S. Naval Academy – Annapolis, US)

This talk gave a brief overview of the tools symbolic computation provides for understanding objects defined by real polynomial equalities and inequalities. Particular attention was paid to the idea of parametric versions of standard problems, and how solutions are often very different kinds of objects for parameterized problems.

3.3 Qualitative dynamics of biochemical reaction networks

Carsten Conradi (MPI – Magdeburg, DE)

I introduced some research problems currently under investigation in my research team "Qualitative Dynamics of Biochemical Reaction Networks" and briefly introduced two recent results concerning multistationarity and switching in mass action networks.

3.4 Symbolic methods for chemical reaction networks

Alicia Dickenstein (University of Buenos Aires, AR)

I surveyed my recent work on using methods from algebraic geometry for analyzing chemical reaction networks taken with mass-action kinetics. In particular, I discussed the topics of steady state invariants, multistationarity, and absolute concentration robustness.

3.5 A satisfiability-based approach to hybrid systems analysis

Andreas Eggers (Universität Oldenburg, DE)

This talk briefly summarizes the Satisfiability modulo Ordinary Differential Equations (SAT modulo ODE) approach to the analysis of hybrid systems. Starting for example from a hybrid automaton model, we build a predicative encoding of the transition system, which describes the discrete jumps and continuous flows. The conjunction of a predicate describing the system's possible initial states with unwindings of the transition predicate and a target predicate characterizing states whose reachability is of interest yields a SAT modulo ODE formula consisting of Boolean connectives, arithmetic atoms, and ODE constraints. Using our iSAT-ODE solver, we can find candidate solution boxes or prove the absence of solutions to formulae of this kind and thereby provide a tool for bounded model checking (BMC) of hybrid systems. We have also shown that unbounded properties like region stabilization can sometimes be encoded as BMC problems. The iSAT-ODE solver combines techniques from propositional SAT solving with Interval Constraint Propagation and enclosure methods for ODEs using the VNODE-LP solver and a bracketing system approach.

More details can be found in [1].

References

1 A. Eggers, N. Ramdani, N. S. Nedialkov, M. Fränzle. Improving the SAT modulo ODE approach to hybrid systems analysis by combining different enclosure methods. Software and Systems Modeling, Springer, 2012 to appear. DOI: 10.1007/s10270-012-0295-3.

3.6 Computing Hopf bifurcations in chemical reaction networks Using Reaction Coordinates

Hassan Errami (Universität Bonn, DE)

For low-dimensional reaction systems without additional constraints, Hopf bifurcation can be computed by reducing the question of its occurrence to quantifier elimination problems on real closed fields. However deciding its occurrence in high-dimensional systems has proven to be difficult in practice. I discussed a fully algorithmic technique to compute Hopf bifurcation fixed point for reaction systems with linear conservation laws using reaction coordinates instead of concentration coordinates, a technique that extends the range of networks which can be analyzed in practice, considerably.

3.7 The Contraintes project-team

Francois Fages (INRIA Le Chesnay, FR)

Contraintes[1] is a project-team of Inria[2], located in the Paris-Rocquencourt research center[3]. Created in March 2001, Contraintes investigates the theoretical foundations, design, implementation and applications of formal methods from computer science to mastering the complexity of complex systems in two domains: real-life combinatorial optimization problems and cell biology. Our four main scientific themes

- Rule-based Languages
- Constraint Solving Techniques
- Formal Methods for Systems Biology
- Integration of In Silico and In Vivo Approaches

are experimented through the development of the Biochemical Abstract Machine (BIOCHAM) modeling software and applied in collaboration with biologists to the building of computational models of cell signaling, gene expression and cell cycle control.

3.8 Multistationarity and variable elimination in reaction networks

Elisenda Feliu (University of Copenhagen, DK)

In this talk I briefly discussed two mathematical results about the properties of chemical reaction networks. The first result concerns the preclusion of multistationarity in reaction networks for which only qualitative information on the rate functions is known. The second result is a graph-based approach to decide what variables can be linearly eliminated from the steady-state equations of a mass-action system. Finally, applications to the study of different phosphorylation systems were discussed.

3.9 From biological networks to personalized medicine

Holger Fröhlich (Universität Bonn, DE)

This talk covered bioinformatics approaches to deal with biological networks. An overview about projects related to the workshop was presented.

[1] http://www.inria.fr/en/teams/contraintes
[2] http://www.inria.fr/en/
[3] http://www.inria.fr/en/centre/paris-rocquencourt

3.10 Symbolic analysis of finite difference approximations to differential equations describing chemical reaction systems

Vladimir Gerdt (JINR, LIT – Dubna, RU)

To simulate chemical processes one has to solve systems of ODEs (chemical reactions, control of nonlinear chemical processes), systems of DAEs (Rober's problem) or systems of PDEs (diffusion of chemicals on biological cells or membranes, pattern formations in biology, nonlinear chemical oscillators in excitable media). In most cases such systems are polynomially-nonlinear and can not be solved symbolically.

To solve systems of DEs the finite difference method is widely used. It is based upon the application of a local Taylor expansion to replace every differential equation by the difference one defined on the chosen computational grid. The obtained difference equations form a finite difference approximation (FDA) to the given DEs, and together with discrete approximation of initial or/and boundary conditions constitute a finite difference scheme.

An FDA to a system of DEs such that the latter inherits at the discrete level all the properties of the former is s(strongly)-consistent. For a uniform and orthogonal grid s-consistency admits symbolic verification [1]. For numerical solving ODEs or PDEs we suggest to use symbolic methods developed in [1] to select those FDA which are s-consistent.

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1 V.P. Gerdt. Consistency analysis of finite difference approximations to PDE systems. LNCS 7175 (2012) 28–42. arXiv:math.AP/1107.4269

3.11 Functoriality of mass-action kinetics

Manoj Gopalkrishnan (TIFR Mumbai, IN)

Can mass-action kinetics be viewed as a functor from a category of reaction diagrams to a category of differential inclusions, and is this a profitable way to think of mass-action kinetics?

3.12 Finding steady points of mass-action kinetics

Dima Grigoriev (Université de Lille I, FR)

An algorithm is designed which finds steady points with non-zero coordinates of mass-action kinetics whose complexity is better than for existing ones when the number of linearly independent monomials in a system is small enough.

3.13 Symbolic methods for parameter estimation in chemical reaction networks

Daniel Kaschek (Universität Freiburg, DE)

Parameter estimation in chemical reaction networks often focuses on statistical methods which are implemented numerically. The use of symbolical methods simplifies numerical problems, makes the numerical methods more accurate and leads to parameter transformations turning the estimation problem into a better behaving problem. Examples include symbolic expressions for steady states and exploitation of Lie symmetries.

3.14 Is linear integer arithmetic useful?

Marek Kosta (MPI für Informatik – Saarbrücken, DE)

In automated reasoning there are different ways how to combine arithmetic with first-order reasoning. We pose the question: How could we use these combinations with linear integer arithmetic in the field of analysis of chemical reaction networks?

3.15 Computer algebra applied to chemical reaction systems

Francois Lemaire (Université de Lille I, FR)

I am specialized in Computer Algebra, especially the manipulation of algebraic and differential equations. In my short presentation, I explained how the techniques we develop could be applied in modeling in the context of chemical reaction systems. I expressed my motivation in finding new persons to collaborate with concerning the following directions: integrate our techniques in other people's software, help people analyze their chemical reaction systems, develop new algorithms for automating computations made by hand.

3.16 Symbolic methods for chemical reaction networks

Stefan Müller (RICAM – Linz, AT)

As a member of both a mathematics and a biotechnology institute, my research interests concerning "Symbolic Methods for Chemical Reaction Networks" are two-fold: one goal is to generalize CRNT (e.g. the deficiency zero theorem) for power-law kinetics which turns out to be relevant for reactions in intracellular environments, but also in purely chemical

settings; the other aim is to simplify the modeling process (e.g. of a photobioreactor) or the bifurcation analysis (e.g. of a gene regulatory network) by automatizing the computation of (quasi) steady states.

3.17 Metabolic networks from enzyme's domains point of view

Sabine Peres (Université Paris Sud, FR)

In metabolic pathway analyses, the metabolic networks are described in term of biochemical reactions and metabolites. The integration of structural data is required for a comprehensive understanding of the metabolic networks. We represent the metabolic networks with the functional connectivity between the protein functional domains to make more relevant analyses. We used BioPsi, a formal multi-level description based on elementary actions, to assign functions on structural domains and the elementary flux modes theory to check if the already known pathways remain present and to identify new ones. This methodology is applied to the first part of the tricarboxylic acid cycle and the elementary flux modes considering protein domains reveals important aspects in its metabolic pathways.

3.18 Graph-based approaches for the analysis of biochemical regulation networks

Nicole Radde (Universität Stuttgart, DE)

Modeling the dynamics of intracellular regulation networks by systems of ordinary differential equations has become a standard method in systems biology, and it has been shown that the behavior of these networks is often tightly connected to the network topology. We have recently introduced the circuit-breaking algorithm (CBA), a method that uses the network topology to construct a one-dimensional circuit-characteristic of the system. It was shown that this characteristic can be used for an efficient calculation of the system's fixed points. This work was further extended by showing several connections between the circuit-characteristic and the stability of fixed points.

My presentation at the Dagstuhl seminar will focus on graph-based approaches for biological regulation networks, with a focus on the CBA. All statements are illustrated on biological network models.

3.19 Generalized mass action systems: Complex balancing equilibria and sign vectors of the stoichiometric and kinetic-order subspaces

Georg Regensburger (RICAM – Linz, AT)

Mass action systems capture chemical reaction networks in homogeneous and dilute solutions. We suggest a notion of generalized mass action systems that admits arbitrary nonnegative power-law rate functions and serves as a more realistic model for reaction networks in intracellular environments. In addition to the chemical complexes and the related stoichiometric subspace, we introduce corresponding kinetic complexes, which represent the nonnegative exponents in the rate functions and determine the kinetic-order subspace. We show that several results of Chemical Reaction Network Theory carry over to the case of generalized mass action kinetics. Our main result essentially states that, if the sign vectors of the stoichiometric and the kinetic-order subspace coincide, there exists a unique positive complex balancing equilibrium in every stoichiometric compatibility class. However, in contrast to classical mass action systems, multiple complex balancing equilibria in one stoichiometric compatibility class are possible in general.

3.20 PoCaB: A software infrastructure to explore algebraic methods for bio-chemical reaction networks

Satya Swarup Samal (B-it – Bonn, DE)

Given a bio-chemical reaction network, I discussed the different algebraic entities e.g. stoichiometric matrix, polynomial system, deficiency and flux cones which are prerequisite for the application of various algebraic methods to qualitatively analyze them. These entities are computed on the examples obtained from two publicly available bio-databases called Biomodels and KEGG and stored in a publicly available database called PoCaB (http://pocab.cg.cs.uni-bonn.de/).

3.21 SMT solving for hybrid systems

Karsten Scheibler (Universität Freiburg, DE)

Over the past decades embedded systems have become more and more complex. Furthermore, they are now often a combination of digital components and analog parts – making them to embedded hybrid systems. Especially in safety critical environments, a formal correctness proof of such systems is highly desirable. The SMT solver iSAT is suitable to verify safety properties of systems consisting of both, linear and non-linear behaviour. Because of its ability to handle arbitrary boolean combinations of linear and non-linear constraint formulas,

iSAT is also a natural choice for solving such formulas arising in the area of chemical reaction networks.

3.22 Stability and bifurcation analysis of major reaction subnetworks in three-way catalytic monoliths

Igor Schreiber (Institute of Chemical Technology – Prague, CZ)

The three-way catalytic monolithic converter (TWC) used for automobile emission control is the most common reactor. The processes in the TWC include mass transport coupled with simultaneous heterogeneous catalytic oxidation of CO and hydrocarbons, and reduction of NOx in a monolith – a multichannel flow-through reactor. In the first step, we focus on the analysis of complex dynamical modes stemming from the complexity of the chemical and adsorption processes involved. Therefore we take the simplest approximation of the system – an isothermal continuous stirred tank reactor (CSTR). The model exhibits various types of dynamics characteristic of nonlinear systems including multiple steady states, oscillations and chaos. These dynamical features are found via bifurcation diagrams constructed by numerical continuation techniques. Such phenomena are caused by interactions among various reaction and adsorption steps, not by the thermokinetic effect. To account for these dynamical modes, we analyze the reaction mechanism taken from the literature with the use of the stoichiometric network analysis – a tool for decomposition of the reaction network and determination of unstable subnetworks. Such reaction subnetworks may possess positive and negative feedback loops, which may imply periodic oscillations. This analysis is crucial for interpretation of the chemical nature of oscillations observed within certain region of parameters in the oxygen inflow vs. temperature bifurcation diagrams.

3.23 Symbolic computations for control and system theory of biochemical reaction systems

Jan H. van Schuppen (VSCR – Amsterdam, NL)

Biochemical reaction systems are mostly polynomial or rational systems with inputs and outputs as considered in system theory. System identification and system reduction algorithms often require the knowledge of whether a system satisfies particular system theoretic properties and those properties are best determined by symbolic computations. Controllability, observability, and structural identifiability are system properties for which symbolic computations are needed. The lecture contains examples of biochemical reaction systems and a summary of system theory of rational systems. The lecturer hopes to raise the interest of researchers in symbolic computations for the problems of differential algebra of rational systems and of biochemical reaction systems.

3.24 General systems of differential equations

Werner M. Seiler (Universität Kassel, DE)

I briefly review the notion of a "general system" of differential equations. The first part discusses the dichotomy between normal systems and those that are under- or overdetermined and emphasizes the need for a completion to involution. The second part is concerned with implicit systems and introduces several types of singular behavior. In the context of chemical reaction networks, the first topic is related for example to problems arising in a quasi steady state approximation or to the treatment of conservation laws, whereas the second topic provides an alternative point of view of static bifurcations and also leads to phenomena like singularity induced bifurcations.

3.25 Multistationarity and persistence in chemical reaction networks

Anne J. Shiu (University of Chicago, US)

This talk presented two theorems, one concerning multistationarity and the other concerning persistence. The first result (due to joint work with Badal Joshi) states that multistationarity of certain networks can be inferred from the existence of multistationary "embedded" networks, that is, smaller networks obtained from the original network by removing chemical species or reactions. We then posed the challenge of enumerating the multistationary networks that are minimal with respect to this "embedded" network relation. The second result (due to joint work with Manoj Gopalkrishnan and Ezra Miller) states that "strongly endotactic" networks (informally, networks with reactions that point inward) are persistent, that is, trajectories with positive initial condition remain bounded away from zero in all coordinates. This theorem makes progress toward a conjecture of Craciun, Nazarov, and Pantea that asserts that so-called "endotactic" networks are persistent.

3.26 Real quantifier elimination

Thomas Sturm (MPI für Informatik – Saarbrücken, DE)

We explain the notion of real quantifier elimination and discuss by means of an example its sussessful application to the decision of the existence of Hopf bifurcations in a gene regulatory network. We point at the more general and more difficult problem to find necessary and sufficient conditions in the parameters for the existence of such bifurcation and suggest to discuss its relevance.

3.27 Chemical reaction networks: equilibria, Hopf bifurcations, and algorithms

Andreas Weber (Universität Bonn, DE)

For large-scale systems arising from chemical reaction networks, already the parametric computation of equilibria and singularities in the positive orthant is a major challenge—but also of great importance for applications by understanding properties of the reaction networks. We have implemented a newly developed algorithm by Dima Grigoriev, by which we could solve equilibria for most examples from the BIOMOD database and also for the examples showing "absolute concentration robustness" (Shinar and Feinberg, 2010).

As the existence of Hopf bifurcations points yield oscillations we build on previous work with M. El Kahoui and T. Sturm that yield reductions to quantifier elimination over the reals (and computations using REDLOG). In recent joint work with H. Errami, W. Seiler, M. Eiswirth we could compute larger examples fully algorithmically using reaction coordinates.

On the systems side we have built PoCaB – a platform to explore bio-chemical reaction networks by algebraic methods. It not only provides the software framework for automated computations involving different systems, but also contains a database for the algebraic entities computed from the models of chemical reaction networks.

4 Overview of Long Talks

This section contains abstracts of the five long talks.

4.1 Chemical reaction network theory: classical results and recent advances

Gheorghe Craciun (University of Wisconsin Madison, US)

Parameter-free analysis of biochemical reaction network models can often use methods from chemical reaction network theory (CRNT), which was created in the 1970s by Horn, Jackson and Feinberg. We describe some classical results of CRNT and discuss recent extensions of this theory for understanding multistability, persistence, oscillations, and chaotic dynamics in biochemical reaction network models, and in general mathematical models of biological interaction networks. These models lead to polynomial dynamical systems for which functional properties can be analyzed using large-scale symbolic computation.

4.2 Stiochiometric network analysis

Ralf Markus Eiswirth (FHI – MPG Berlin, DE)

By making maximum use of stoichiometric restrictions, Stoichiometric Network Analysis (SNA) allows to solve for the complete set of stationary states of chemical reaction systems and write it down in closed form as a linear combination of extreme subnetworks. Consequently, it is possible to decide whether an instability can occur in a given network anywhere in parameter space. The procedure will be outlined and a classification of chemical instabilities will be given.

4.3 Inferring reaction models from ODEs and model reductions as subgraph epimorphisms

Francois Fages (INRIA Le Chesnay, FR)

Many models in Systems Biology are described as Ordinary Differential Equations (ODEs), which allow for numerical integration, bifurcation analyses, parameter sensitivity analyses, etc. However, before fixing the kinetics and parameter values and going to simulations, various analyses can be performed based only on the structure of the model. This approach has rapidly developed in Systems Biology in the last decade, with for instance, the analyses of structural invariants in Petri net representation [3], model reductions by subgraph epimorphims [1], qualitative attractors in logical dynamics or temporal logic properties by analogy to circuit and program verification. These complementary analysis tools do not rely on kinetic information, but on the structure of the model with reactions.

The Systems Biology Markup Language (SBML) of [2] is now a standard for sharing and publishing reaction models. However, since SBML does not enforce any coherence between the structure and the kinetics of a reaction, an ODE model can be transcribed in SBML without reflecting the real structure of the reactions, hereby invalidating many structural analyses.

In this talk we propose a general compatibility condition between the kinetic expression and the structure of a reaction, describe a symbolic computation algorithm for inferring a reaction model from an ODE system, and report on its use for automatically curating the writing in SBML of the model repository biomodels.net. We illustrate the benefit of this curation by computing faithful hierarchies of models in biomodels.net, related by model reduction relationships defined solely on the structure of the reaction graphs as subgraph epimorphisms.

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4.4 Quantitative and qualitative dynamic modeling of molecular interaction networks

Holger Fröhlich (Universität Bonn, DE)

Molecular interaction networks, such as metabolic networks, signaling pathways and gene regulatory networks, are not static, but have to be understood as dynamical systems. Various computational methods have been established in the literature to model these systems in order to obtain experimentally verifiable hypotheses. Besides quantitative approaches, which are typically formulated in terms of ordinary differential equation systems (ODEs), Boolean Networks have gained a lot of attention for this purpose. This lecture will highlight differences as well as connections between these two modeling schemes and discusses advantages and disadvantages of both from a practical point of view. In this context I will also shed light on the problem of estimating kinetic rate parameters from experimental data via different statistical techniques.

4.5 Unraveling the structure of metabolism by elementary-modes analysis

Stefan Schuster (Friedrich-Schiller-Universität – Jena, DE)

Cellular metabolism has a complex structure due to the large number of reactions involved and the fact that many of these are bi- or trimolecular. To unravel this structure, elementary-mode analysis has become a well-established theoretical tool. It allows one to decompose complex metabolic networks into the smallest functional entities, which can be interpreted as biochemical pathways or, as a special case, substrate cycles. Moreover, it allows the maximization of molar yields, which has important applications in biotechnology. Here, we outline the theoretical basis and the central concepts and algorithms in elementary-mode analysis. Moreover, several illustrative examples of application of that analysis are presented. Current trends and future prospects are discussed.

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5 Working Groups

This section contains summaries of each of the discussion groups.

5.1 Bistability

Carsten Conradi

Recent results concerning reaction networks with generalized mass action kinetics obtained by Mueller and Regensburger were discussed. These results extend the notion of complex balanced equilibrium from networks with 'classical' mass action kinetics to networks allowing a more general form of mass action kinetics. Under certain assumptions on the network structure and the (generalized) kinetics one obtains complex balanced equilibria. In this generalized setting uniqueness of complex balanced equilibria is no longer guaranteed and a sufficient condition for multiple equilibria in terms of sign patterns was discussed.

This discussion group met on Wednesday–Friday, and participants included Carsten Conradi, Markus Eiswirth, Elisenda Feliu, Stefan Müller, Georg Regensburger, Jan van Schuppen, Igor Schreiber, Anne Shiu.

5.2 Preprocessing methods for systems of real constraints

Thomas Sturm

The essential complexity parameter for existential decision problems over the reals is the number of variables n in contrast to the number of constraints k. Dima Grigoriev has published theoretical complexity results for the special case of quadratic constraints, which comprise a satisfiability-preserving transformation for decreasing the number of variables. Essentially, after the transformation there are $2k$ variables instead of n, where k is the number of constraints in the input problem. It turns out that the existing real decision problems arising from chemical reaction systems contain few constraints in comparison to the number of variables; i.e. $k \ll n$. This makes an implementation and its application to chemical reaction systems appear quite appealing. On the other hand most of these examples have high degrees so that it is important to understand to what extent the existing approach could be generalized. Furthermore, although the existing result for the quadratic case is of algorithmic nature it is not straightforward to create corresponding software. Throughout the technical part of our discussions we analyzed the procedure both from a theoretical and from a software engineering point of view.

The discussion group met on both Thursday and Friday, and participants were Christopher Brown, Andreas Eggers, Dima Grigoriev, Marek Kosta, Karsten Scheibler, Thomas Sturm, and Andreas Weber.

5.3 Specialized decision procedures for the existential fragment of the reals

Thomas Sturm

Algebraic decision procedures, which recently have been successfully applied in the analysis of biological and chemical reaction networks, are typically based on quantifier elimination procedures, which in fact solve a more general problem by possibly deciding parametric problems. After translation to real algebra, relevant questions arising from chemical reaction systems often have a special form: They do not involve parameters, and they are purely existential. Furthermore, there are often natural bounds on the possible values of variables, e.g., many variables can be constrained to taking only positive values.

We discussed perspectives for more efficient specialized procedures for these situations. We identified as promising directions recent ideas by de Moura et al. for decision procedures resembling SMT approaches by constructing model assumptions and the use of interval arithmetic in contrast to computation with exact algebraic numbers.

This discussion group met on both Tuesday and Wednesday, and the participants were Christopher Brown, Andreas Eggers, Marek Kosta, Karsten Scheibler, and Thomas Sturm.

5.4 Conservation laws

Francois Lemaire

We discussed about the problem of defining and finding "good" conservation laws of a system of chemical reactions. A basis of conservation laws is easily computed as a kernel of a matrix. However, certain conservation laws are better than others. In particular, conservation laws with positive coefficient and the most zeros are particularly interesting. The outcome of the discussion was that applying techniques for computing elementary flux modes might help. Still, this approach might not be the best one since some combinatorial explosion might happen.

This discussion group met on Tuesday.

5.5 Model reduction by systematic exploitation of scaling symmetries

Daniel Kaschek

Francois Lemaire presented a software package that computes explicit coordinate and parameter transformations originating from scaling invariances of a system of ordinary differential equations (ODEs). Holger Fröhlich, Daniel Kaschek, and Nicole Radde provided typical examples of ODEs from systems biology projects. Possible applications to this class of systems have been discussed. In particular, the concrete structure of a given observation function has been identified to play a crucial role for the utility of the method. A number of new questions have arisen from the discussion, e.g. connections between polynomial conserved quantities and translational symmetries or polynomial symmetries and related coordinate and parameter transformations.

This discussion group met on Tuesday, and the participants were Holger Fröhlich, Daniel Kaschek, Francois Lemaire, and Nicole Radde.

5.6 Parameter estimation

Francois Boulier

Holger Fröhlich recalled the classical numerical approaches for this problem (frequentist and Bayesian approaches). Jan van Schuppen exposed the procedure which is traditional, in control theory, for tackling it. Francois Boulier presented differential algebra techniques related to this question together with a new algorithm which might help transforming differential equations into integral ones and thereby be helpful in the presence of noise. Nicole Radde presented a real problem she is concerned with and Daniel Kaschek started to try to solve it using his methods. Jan van Schuppen exposed computer algebra problems he would like to solve, related to observability, input design and system reduction. Gheorghe Craciun talked about theoretical difficulties which arise when trying to infer chemical reaction systems from the ODE models. However it was poined out that these difficulties might be sometimes turned into advantages. There were various questions by Andreas Weber and Werner Seiler.

This discussion group met on Tuesday and Wednesday.

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