Mathematical problems arising from biochemical reaction networks

organized by
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Workshop Summary

Recent developments have suggested the feasibility of mathematical analysis of biochemical reaction networks arising in systems biology and related disciplines, using methods from computational algebra, algebraic geometry and dynamical systems. Because of the nonlinearity of such systems, previous approaches have largely relied on numerical simulation. Mathematical analysis has provided new biological insights and opened up new avenues for interdisciplinary research. For instance, one class of biochemical reaction networks, based on mass-action kinetics, gives rise to polynomial dynamical systems. Here, among the biologically-relevant dynamical behaviours are steady states, which correspond to the positive real solutions of a system of polynomial equations. Methods from computational algebra and algebraic geometry used to analyse such steady-state behaviour lead to the formulation of several mathematical questions, some of which are detailed below. Important questions also arise regarding the transient dynamics and generalisations to systems which do not satisfy mass-action. A characteristic feature of biologically-relevant networks is that the numerical values of their parameters are often not known, so that it becomes important to understand how dynamical behaviour depends on these values, giving rise to the problem of mapping "the geography of parameter space".

This workshop brought together mathematicians as well as researchers who are closer to the experimental side of systems biology, with the aim of formulating precise open problems in order to pursue their resolution using a variety of mathematical techniques.

Focus Problems

The research focus of the workshop included the following open questions:

(1) *The Global Attractor Conjecture.* This long-standing conjecture about the dynamics of complex-balancing chemical reaction systems has in recent years seen progress by taking a polyhedral geometry point of view as well as by considering which monomials in the differential equations dominate as certain variables go to zero. In the Tuesday working group devoted to this conjecture, Gheorghe Craciun outlined promising new ideas toward a proof of the conjecture.

(2) *Time-scale separation and elimination* A long-standing method for reducing the complexity of molecular systems is time-scale separation. Jeremy Gunawardena's opening talk showed that the main uses of this technique within molecular and systems biology can be interpreted within a purely linear framework and that this could be applied to biochemical networks arising in post-translational modification and in gene regulation. Particular forms of time-scale separation, such as the quasi-steady state approximation (QSSA) in enzyme kinetics, and methods of nonlinear elimination

were also discussed in Gheorghe Craciun's talk on Tuesday. The use of differential algebraic methods for undertaking such eliminations was further explored within a working group. A natural dynamical question in the context of time-scale separation is to ask how well the behaviour of the overall system is approximated, for which the method of singular perturbation and the identification of a "slow manifold" are sometimes able to yield insights, as discussed in David Siegel's talk on Friday.

Additionally, the working group on multisite systems pursued the problem of what can be said when it is unknown which intermediate enzyme-substrate complexes exist in a network. Accordingly, the group proposed a mechanism for the usual enzymatic futile cycle that contains more intermediate complexes than usual, analyzed it dynamical behavior, and asked whether the usual mechanism can be seen as a limit of the proposed larger network.

Anne Shiu's lecture introduced further techniques from computational algebraic geometry that have been used to study chemical reaction networks, but which were largely unknown to the wider group of participants.

(3) *Geography of parameter space.* Alicia Dickenstein's talk on Monday introduced algebraic tools for and outlined challenges inherent in the problem of determining the semi-algebraic decomposition of parameter space according to different dynamical behaviour, such as multistationarity. Also, the pursuit of criteria—such as combinatorial criteria—for establishing or ruling out bifurcations and oscillations was discussed in working groups and in Casian Pantea's talk on Friday.

(4) *Computation and interpretation of steady-state invariants.* Steady-state invariants are polynomial relationships among specified dynamical variables (typically certain species concentrations) at steady state, and they can be used experimentally for discriminating among various mechanisms. Alicia Dickenstein detailed the different "levels" of invariants. One problem posed during the workshop was to make use of techniques in computational algebra in order to yield better and more insightful computations and, additionally, to interpret such invariants biologically. Bernd Sturmfels proposed the question of determining the matroid structure of the subsets of species for which there exist an invariant involving precisely those species, and illustrated the task on a multisite phosphorylation network.

(5) *Extension of mass-action kinetics results.* Working groups on this topic discussed results for more general kinetics than mass-action, such as a criterion on the Jacobian matrix that guarantees that bounded solutions converge to an equilibrium. Also, this working group considered examples in which information about the steady states of certain transformed networks can yield information about the original network.

(6) *Subnetwork analysis.* Consider the question of how information about a small network can be used to gain information about a larger network that "contains" the smaller network in some way. This goal was pursued by Carsten Wiuf in his talk on Thursday, who presented joint results with Elisenda Feliu on how networks that share the same "core" features are related. This topic is related to the problem described above in (2) of what to do when the intermediates are not known.

(7) *Stochastics.* David Anderson posed the following two questions:

- What can be said about the stationary distribution of weakly reversible networks with nonzero deficiency in the stochastic setting?

- What happens to the dynamics of stochastic networks as certain reaction rates go to zero?

Also, Manoj Gopalkrishnan introduced new questions arising from the thermodynamics of information, that may help to resolve the fundamental physical trade-offs involved in information processing and computation:

- Can the usual Lyapunov function for complex-balanced systems (sometimes called the pseudo-Helmholtz free energy function) be seen as the limiting function of an entropy-type function for stochastic systems? Can Lyapunov functions for other models be constructed in an algorithmic manner from knowledge about the stationary distribution of the associated stochastic model?

The above questions were pursued in Manoj's Thursday morning lecture and in a working group.

(8) *Harnessing numerical algebraic geometry techniques.* Dan Bates gave a tutorial on Wednesday that illustrated how the software packages `Bertini` and `Paramatopy` can be used to analyze reaction networks. During a working group on this topic and at other times as well, various participants began collaborating with Dan to determine how these techniques can be used for their work. In particular, Gilles Gnacadja proposed a recurring instance occuring in chemical reaction networks relevant in pharmacology, where this technique could be useful.

(9) *Combinatorial complexity in biology.* One theme of the week, introduced in Jeremy Gunawardena's lecture, was the challenge of dealing with and understanding the combinatorial complexity inherent in biological systems, including post-translational modification systems.

(10) *Computation of functions by reaction networks.* David Doty and David Soloveichik introduced the interpretation of networks as computers. In particular, they were interested in networks for which the steady-state concentrations of certain species depend only on initial concentrations of all species and do not depend on the reaction rates or even the choice of kinetics.

Schedule

Monday	
9 am	Jeremy Gunawardena (Harvard University) *Some remarks on mathematics and biology*
11 am	Alicia Dickenstein (University of Buenos Aires) *Computational algebraic geometry and biochemical reaction networks*
2 pm	"Ask the experts" session

Tuesday	
9 am	Gheorghe Craciun (University of Wisconsin) *Model reduction and parameter identifiability for biochemical reaction networks*
11 am	Gilles Gnacadja (Amgen) *Chemical reaction networks in pharmacology and related mathematical problems*
2 pm	Working groups: *multisite systems, differential algebra/QSSA/elimination, global attractor conjecture*

Wednesday	
9 am	Anne Shiu (University of Chicago) *Tutorial: Using computer algebra software to analyze reaction networks*
11 am	Dan Bates (Colorado State University) *Numerical algebraic geometry for chemical reaction networks or anything else*
2 pm	Working groups: *multistationarity/bifurcations, stochastics, numerical algebraic geometry, beyond mass-action kinetics, computation by networks*

Thursday	
9 am	Carsten Wiuf (University of Copenhagen) *Model choice*
11 am	Manoj Gopalkrishnan (Tata Institute of Fundamental Research, Mumbai) *Thermodynamics of bits and batteries*
2 pm	Working groups: *stochastics/theory of information, spatial aspects, beyond mass-action kinetics*

Friday	
9 am	Casian Pantea (Imperial College, London) *Combinatorial approaches to Hopf bifurcations and oscillations*
11 am	David Siegel (University of Waterloo) *Old results of Vol'pert and new results on slow manifolds*
2 pm	Working groups: *stochastics/theory of information, spatial aspects (tutorial on `VCell` software), beyond mass-action kinetics*