Workshop on

Mathematical Trends in Reaction Network Theory

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Book of abstracts

Contents

Invited talks

David F. Anderson (University of Wisconsin, Madison, US).
Stochastic models of biochemical reaction systems and absolute concentration robustness.

Abstract. In a 2010 Science paper Marty Feinberg and Guy Shinar introduced network conditions that guarantee a deterministically modeled biochemical system has a species that satisfies absolute concentration robustness (ACR). I will discuss the results of a recent paper that shows how essentially those same network conditions guarantee that the stochastic model will eventually undergo an extinction event. Such a result can be considered an example of a discrepancy between the limiting behavior of a deterministic system and the limiting behavior of the corresponding stochastic system, with one modeling choice predicting a form of long-term stability and the other predicting long-term instability. However, the extinction event for the stochastic model is typically a rare event on reasonable time frames and information pertaining to the behavior of the ACR species on compact time intervals is needed. I will therefore end the talk by presenting recent results pertaining to stochastically modeled ACR systems on compact time intervals. Specifically, we show via a certain scaling limit that on compact time intervals the distribution of the species satisfying the ACR condition is well approximated by a Poisson random variable whose parameter is determined by the ACR equilibrium of the deterministic model, a property that had been conjectured to hold.

John Baez (UC Riverside, US and Center for Quantum Technologies, Singapore).
Probabilities versus Amplitudes.

Abstract. Some ideas from quantum theory are just beginning to percolate back to classical probability theory. For example, the master equation for a chemical reaction network describes the interactions of molecules in a stochastic rather than quantum way. If we look at it from the perspective of quantum theory, this formalism turns out to involve creation and annihilation operators, coherent states and other well-known ideas — but with a few big differences.

Gheorghe Craciun (University of Wisconsin, Madison, US).
A proof of the Global Attractor Conjecture.

Abstract. In a groundbreaking 1972 paper Fritz Horn and Roy Jackson showed that a complex balanced mass-action system must have a unique locally stable equilibrium within any compatibility class. In 1974 Horn conjectured that this equilibrium is a global attractor, i.e., all solutions in the same compatibility class must converge to this equilibrium. Later, this claim was called the Global Attractor Conjecture, and it was shown that it has remarkable implications for the dynamics of large classes of polynomial and power-law dynamical systems, even if they are not derived from mass-action kinetics. Several special cases of this conjecture have been proved during the last decade. We describe a proof of the conjecture in full generality. In particular, it will follow that all detailed balanced mass action systems and all deficiency zero mass-action systems have the global attractor property. We will also discuss some implications for biochemical mechanisms that implement noise filtering and cellular homeostasis.

David Doty (California Institute of Technology, US).
Computation by (not about) chemistry.

Abstract. The model of chemical reaction networks (CRNs) is extensively used throughout the natural sciences as a descriptive language for existing chemicals. If we instead think of CRNs as a programming language for describing artificially engineered chemicals, what sorts of computations are possible for these chemicals to achieve? The answer depends crucially on several formal choices:

1) Do we treat matter as infinitely divisible (real-valued concentrations) or atomic (integer-valued counts)?

2) How do we represent the input and output of the computation? (e.g., Boolean presence or absence of species, positive numbers directly represented by counts/concentrations, positive and negative numbers represented indirectly by the difference between counts/concentrations of a pair of species)

3) Do we assume mass-action rate laws (reaction rates proportional to reactant counts/ concentrations) or do we insist the system works correctly under a broader class of rate laws?

The talk will survey several recent results and techniques. A primary goal of the talk is to convey the "programming perspective": rather than asking "What does chemistry do?", we want to understand "What could chemistry do?" as well as "What can chemistry probably not do?"

Manoj Gopalkrishnan (Tata Institute of Fundamental Research, India).
Statistical inference with a chemical soup.

Abstract. The goal is to design an "intelligent chemical soup" that can do statistical inference. This may have niche technological applications in medicine and biological research, as well as provide fundamental insight into the workings of biochemical reaction pathways. As a first step towards our goal, we describe a scheme that exploits the remarkable mathematical similarity between log-linear models in statistics and chemical reaction networks. We present a simple scheme that encodes the information in a log-linear model as a chemical reaction network. Observed data is encoded as initial concentrations, and the equilibria of the corresponding mass-action system yield the maximum likelihood estimators. The simplicity of our scheme suggests that molecular environments, especially within cells, may be particularly well suited to performing statistical computations.

Mustafa Khammash (ETH Zürich, Switzerland).
Real-Time Control of Gene Expression.

Abstract. Norbert Wiener's 1948 Cybernetics presented a vision unifying the study of control and communication in the animal and the machine. Predating the discovery of the structure of DNA and the ensuing molecular biology revolution, applications in the life sciences at the time were limited. More than 60 years later, the confluence of modern genetic manipulation techniques, powerful measurement technologies, and advanced analysis methods is enabling a new area of research in which systems and control notions are used for regulating cellular processes at the gene level. We refer to this promising nascent field as Cybergenetics. This presentation describes novel analytical and experimental work that demonstrates how de

novo control systems implemented with stochastic components can be interfaced with living cells and used to control their dynamic behavior.

Michal Komorowski (Institute of Fundamental Technological Research, Polish Academy of Sciences, Poland).
Information flow in signal transduction pathways.

Abstract. All biological organisms need to sense and response to their environment. The molecular reaction networks that coordinate the response of an organism to changing environmental conditions are central for their survival. We must therefore expect these information flow processes to have been optimised over the course of evolutionary history by natural selection. In the talk I will explore analogies between statistical inference and signal transduction to show how the molecular sensing can be performed with high accuracy. Our theoretical analysis reveals three key elements that ensure high fidelity information flow in signalling networks: 1) Inputs and outputs of subsequent signalling components must be matched; 2) Temporal dynamics of signalling enables efficient information coding; 3) Complexity is energetically most favourable mean to increase capacity of signalling networks. Relevance of these principles will be illustrated using experimental analysis of the NF-kB and JAK-STAT signalling pathways as well as nitrogen sensing mechanism in E. coli.

Nicolette Meshkat (North Carolina State University, US).
Algebraic Techniques for the Parameter Identifiability Problem in Systems Biology.

Abstract. The use of algebra to attack problems arising in systems biology has become a popular and effective method to analyze such systems. I will explore some algebraic approaches to investigate the problem of structural identifiability of biological models, i.e. the problem of determining which unknown parameters can be quantified from given input/output data. In particular, I will discuss the use of computational algebraic tools such as Groebner bases and algebraic matroids to determine the identifiability properties of biological models. These tools become particularly helpful when not all of the parameters can be uniquely or finitely determined from data and can be used to help reparameterize the model over identifiable functions of the parameters.

Ovidiu Radulescu (Université de Montpellier 2, France).
Taming the complexity of biochemical networks through model reduction and tropical geometry.

Abstract. Biochemical networks are used as models of cellular physiology with diverse applications in biology and medicine. In the absence of objective criteria to detect essential features and prune secondary details, networks generated from data are too big and therefore out of the applicability of many mathematical tools for studying their dynamics and behavior under perturbations. However, under circumstances that we can generically denote by multi-scaleness, large biochemical networks can be approximated by smaller and simpler networks. Model reduction is a way to find these simpler models that can be more easily analyzed. We discuss several model reduction methods for biochemical networks with polynomial or rational rate functions and propose as their common denominator the notion of tropical equilibration, meaning finite intersection of tropical varieties in algebraic geometry. Using tropical methods, one can strongly reduce the number of variables and parameters of biochemical network. For multi-scale networks, these reductions are computed symbolically on orders of magnitude of parameters and variables, and are valid in wide domains of parameter and phase spaces.

Alan D. Rendall (Johannes Gutenberg Universität Mainz, Germany).
Dynamics of phosphorylation systems.

Abstract. A widespread mechanism for the storage and transfer of information in cell biology is the attachment of phosphate groups to proteins (phosphorylation) and their subsequent detachment (dephosphorylation). These processes are catalysed by enzymes called kinases and phosphatases. In many cases a change in phosphorylation state leads to the activation of the enzymatic activity of a protein so that, for instance, it itself becomes a kinase. Reaction networks built of phosphorylation states of proteins are often modelled by systems of ordinary differential equations. The theme of this talk is what can be said about the qualitative properties of solutions of these ODE, such as bistability, existence of periodic solutions and chaotic behaviour. The emphasis is on specific systems of biological or medical interest. These include the MAP kinase cascade, a signalling network of relevance for innovative cancer therapies, and the KaiABC system, a biological clock in cyanobacteria. It is discussed how the concept of feedback loops can provide insight into the dynamical behaviour and how feedback can result from sequestration: a protein is prevented from taking part in a particular reaction because it is bound to another protein as part of another reaction.

János Tóth (Budapest University of Technology and Economics, Hungary).
On the form of kinetic differential equations.

Abstract. The induced kinetic differential equation of a reaction endowed with mass action kinetics is a subclass of polynomial differential equations. This subclass can be and has been fully characterized: it turned out that a polynomial equation can be considered to be the induced kinetic differential equation of a reaction if and only if it contains no negative cross effect. The sufficiency of this criterion has been proved by a construction: in case the criterion is fulfilled a canonic realization of the differential equation can automatically be given. Here we review old and recent consequences of this characterization.

- Is it possible to find an inducing reaction with given properties such as (weak) reversibility, a minimal number of reaction steps, complexes or deficiency etc. Most of these questions have been affirmatively answered by Szederkényi and his coworkers using (mixed integer) linear programming for the case when the numerical values of the coefficients of the polynomial differential equation without negative cross effect is given. Our appoach to these questions is a bit different: we are going to give symbolic answers, naturally only for simpler questions.

- What are the direct dynamical consequences of the absence of negative cross effect. What can we say about the (linear and quadratic) first integrals of kinetic differential equations? Which one is the minimal oscillatory reaction? Is nonlinearity needed to the formation of a Turing pattern?

- What is the effect of transformations on the absence of negative cross effect? Is it possible to transform kinetic differential equations into homogeneous second degree equations and thus utilize tools from nonassociative algebras? Is it possible to transform the Lorenz equation into a kinetic equation using orthogonal transformations? What is the relationship between the property in question and lumping? How to utilize the special form of kinetic differential equations in estimation, control and sensitivity analysis? How to transform kinetic equations including thermal effects into polynomial form (to investigate blow up)?

To sum up the problem: The absence of negative cross effect seems not to restrict the dynamical richness of polynomial equations. Does this property have dynamic consequences only characteristic for this smaller class of polynomial differential equations?

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Sebastian Walcher (RWTH Aachen, Germany).
Computational aspects of quasi-steady state reduction.

Abstract. Quasi-steady state reduction is a frequently employed heuristical method for parameter-dependent (ordinary) differential equations in (bio-) chemistry and other fields. The common interpretation of this approach in mathematical terms goes via the classical singular perturbation theory due to Tikhonov and Fenichel, but even in this setting nontrivial problems remain for the practical implementation. In the talk, we discuss polynomial or rational parameter-dependent vector fields (which is not a severe restriction for applications in biochemistry). Our first result discusses an explicit, algorithmically accessible reduction formula for a system with a given "small parameter". The reduced equation naturally lives on a certain algebraic variety. Our second result is about the identification of suitable "small parameters" in a given system; it turns out that this problem is also accessible by algorithmic algebra, and leads to semi-algebraic sets in parameter space. Several examples are presented. The talk reports on joint work with Alexandra Goeke.

Contributed talks

Antonio A. Alonso (Bioprocess Engineering Group, IIM-CSIC).
The Structure of feasible equilibria for Mass Action Law (MAL) kinetic systems.

Abstract. Despite their simplicity, systems governed by mass action law kinetics are shown to exhibit a rich variety of dynamic features which comprise multiple equilibria, or bifurcation phenomena leading to oscillatory or even chaotic behaviour. Such systems are typically employed to describe nonlinear dynamics in chemical reaction networks, but over the last years they proved useful in modelling a wide range of nonlinear dynamic systems with applications in biology, process systems, economics or transportation problems. Perhaps because of this, they are at the core of many complex processes in artificial and natural systems. On a biological context for instance, they constitute the hardware-software structure that supports cell function. Understanding the relationship between network structure and parameters will pave the way to analyse complex networks and to design and control chemical systems from reactors to biochemical circuits.

CRNT as its stands nowadays within the field of applied mathematics offers an extraordinary potential for analysis and design of complex dynamic systems. Unfortunately, many of its results remain at a large extent unexploited, when not unnoticed, in the fields of chemical or biochemical engineering. Reasons are diverse but mostly should be found in the heavy machinery that conform methods and proofs.

In trying to fill the gap between theory and potential applications, I will adopt a geometric perspective to examine connections between system parameters, and uniqueness and stability of the resulting equilibria. In particular, a canonical representation of the set of all possible feasible equilibrium solutions is developed. The characterization is made in terms of compartmental matrices which by construction are strictly stable and define the so-called family of solutions.

Feasibility is imposed by a set of constraints, which are linear in the log-transformed space of complexes, and relate to the kernel of the stoichiometric subspace. One such representation can be established in terms of a class of monotonous functions which generalize Wegscheider conditions and turn out to be critical to conclude uniqueness of equilibrium points in a class of deficiency one networks.

One main consequence of such representation is the possibility of a simple constructive proof of the deficiency one theorem. It also allows a precise characterization of the parameter space region of complex balance solutions we refer to as the Horn set. Future directions will be discussed that involve design of networks having multiple equilibria, or the stabilization via complex balance feed-back control of open reaction systems.

Michael Assaf (Hebrew University of Jerusalem).
The Effect of Extrinsic Noise on Gene Regulation.

Abstract. Stochastic gene expression is influenced both by intrinsic noise arising from intracellular variability, and extrinsic noise that arises due to intercellular and environmental variations. While the role of intrinsic noise is well understood, a rigorous understanding of how extrinsic noise influences the function of genetic networks is still lacking. Here we use a semi-classical WKB theory to study the interplay between intrinsic and extrinsic noise in simple network motifs, focusing of how extrinsic noise characteristics affect the overall statistics. Our analytical predictions are compared with Monte-Carlo simulations efficiently accounting for fluctuating reaction rates.

Balázs Boros (Eötvös Loránd University, Budapest).
Two applications of the Deficiency-One Algorithm.

Abstract. The Deficiency-One Algorithm by Martin Feinberg answers for regular deficiency-one reaction networks whether there exist rate coefficients such that the resulting mass action system has multiple positive steady states. The algorithm comprises of deciding the solvability of linear inequality systems, where the number of variables equals to the number of species. The number of inequality systems one needs to consider is at most $2 \cdot 3^{\ell}$, where ell is the number of linkage classes. However, in some cases, this latter number can be reduced significantly, e.g. for networks with two linkage classes, the factor 3^2 reduces to 1.

In this talk, we give a brief overview of the Deficiency-One Algorithm and discuss two applications of the algorithm as described in the sequel. We provide a complete characterisation by multistationarity for reaction networks comprising of two linearly dependent reactions (an example of such a network is $X_1 \rightleftharpoons X_2$ and $X_1 + X_2 \rightleftharpoons 2X_2$). The other application is a generalisation of Badal Joshi's recent work on "one-reaction fully open networks", i.e., the network has only one "real" reaction and all the species take part in flow reactions of the form $X_s \rightleftharpoons 0$. In this talk, we examine the multistationarity of all the subnetworks of such networks (by subnetwork, we mean that only a subset of the flow reactions are present). Characterisation of small multistationary networks might have consequences on multistationarity of bigger networks that contain the small network as an embedded subnetwork.

Daniele Cappelletti (University of Copenhagen).
Complex balanced reaction systems and Product-form Poisson distribution.

Abstract. Stochastic reaction networks are dynamical models of biochemical reaction systems and form a particular class of continuous-time Markov chains on $\mathbb{N}^n$. We provide a fundamental characterisation that connects structural properties of a network to its dynamical features. Specifically, we define the notion of 'stochastically complex balanced systems' in terms of the network's stationary distribution and provide a characterisation of stochastically complex balanced systems, parallel to that established in the 70-80ies for deterministic reaction networks by Horn, Jackson and Feinberg. Additionally, we establish that a network is stochastically complex balanced if and only if an associated deterministic network is complex balanced (in the deterministic sense), thereby proving a strong link between the theory of stochastic and deterministic networks. Further, we prove a stochastic version of the 'deficiency zero theorem' and show that any (not only complex balanced) deficiency zero reaction network has a product-form Poisson-like stationary distribution on all irreducible components. Finally, we provide sufficient conditions for when a product-form Poisson-like distribution on a single (or all) component(s) implies the network is complex balanced, and explore the possibility to characterise complex balanced systems in terms of product-form Poisson-like stationary distributions.

Carsten Conradi (Hochschule für Technik und Wirtschaft, Berlin).
Mathematical analysis of multisite phosphorylation.

Abstract. Multisite phosphorylation plays an important role in intracellular signaling, where many proteins are phosphorylated at $N > 1$ binding sites. It is often assumed that phosphorylation occurs either distributive (i.e. one phosphorylation event per enzyme-substrate binding) or processive (i.e. more than one phosphorylation event per enzyme-substrate binding). This talk focuses on detailed models of the phosphorylation of a protein at N binding sites that are either purely distributive or purely processive. For the distributive system I will give an overview of results concerning multistationarity, bistability and conditions on parameter values guaranteeing these properties. For the processive system I will discuss absence of multistationarity due to uniqueness and stability of steady states.

German Enciso (University of California, Irvine).
Absolutely Robust Networks and Dose Responses.

Abstract. Chemical reaction networks are often under strict regulation to prevent an unintended outcome in the face of noise. An important scientific problem is to discover the mechanisms used by cells to produce a consistent phenotype despite protein variability. I will discuss structural conditions on chemical reaction networks that guarantee absolute robustness with respect to some protein concentrations but not others. Such structural conditions hold under arbitrary parameter values for a given topology. Specifically, I will use absolute robustness in the context of signal transduction, showing how reaction networks can be robust to some inputs while remaining ultrasensitive to other inputs. I will also address in what sense absolute robustness extends to the stochastic case.

Antoni Ferragut (Universitat Jaume I).
Darboux integrability in CRN models.

Abstract. We study the existence of linear and nonlinear conservation laws in chemical reaction networks. It is rather straightforward to identify the linear conservation laws, but the nonlinear conservation laws are much more difficult to study and so far have been rarely considered in the context of the chemical networks. Our aim in this work is to show how to determine nonlinear conservation laws via Darboux theory of integrability. In particular, we show that there are chemical networks which admit both linear and nonlinear conservation laws for any concentration rates as well as networks which do not admit any conserved quantities.

Ankit Gupta (ETH Zürich).
Estimation of parameter sensitivity for stochastic reaction networks.

Abstract. We consider the problem of estimating parameter sensitivity for stochastic models of reaction networks. These sensitivity values help in analyzing a network, understanding its robustness properties and identifying the important reactions for a specific output. Unlike deterministic models, the estimation of parameter sensitivity for stochastic models is a difficult and a computationally challenging problem. In this talk we present an exact formula for parameter sensitivity for the stochastic model and discuss its numerous applications in the context of sensitivity analysis of large reaction networks. These applications include, finding an efficient algorithm for unbiased estimation of parameter sensitivity, showing that sensitivity values are closely preserved under model reduction of reaction networks with multiple time-scales and developing accurate sensitivity estimation methods that work with tau-leaping approximations of the underlying stochastic reaction dynamics.

Jan O. Haerter (Niels Bohr Institute, University of Copenhagen).
Food web assembly rules.

Abstract. In food webs, many interacting species coexist despite the restrictions imposed by the competitive exclusion principle and apparent competition. Using the generalized Lotka-Volterra equations, we show that sustainable coexistence necessitates nonzero determinant of the interaction matrix, a requirement that is equivalent to demanding that each species is part of a non-overlapping pairing. When nonzero determinant cannot be achieved, the matrix rank can be used to quantify the lack of niches, corresponding to unpaired species.

For the species richness at each trophic level, these assembly rules specify sustainable combinations. In neighboring levels, the rules allow the higher level to avert competitive exclusion at the lower, thereby incorporating apparent competition. The constraints predict high species numbers at intermediate levels and thinning at the top and bottom. Using comprehensive food web data, we demonstrate how omnivores or parasites with hosts at multiple trophic levels can loosen the constraints and increase robustness in food webs [1].

For the case of a simple two level system, e.g. the bacteria-phage ecology in the Ocean, we show that a "staircase of coexistence" results, where the species richness of bacteria and phage must be balanced, indeed approximately confirmed by data analysis from Atlantic Ocean samples. For this system, we further describe evolution, and how addition of more and more species must lead to a compression of available parameter space [2].

[1] http://arxiv.org/abs/1501.04497
[2] http://www.nature.com/ismej/journal/v8/n11/full/ismej201480a.html

Mogens H. Jensen (Niels Bohr Institute, University of Copenhagen).
Coupled Oscillators and Arnold Tongues in Cell Dynamics.

Abstract. Oscillating genetic patterns have been observed in networks related to the transcription factors NFkB, p53 and Hes1 [1]. We identify the central feed-back loops and found oscillations when time delays due to saturated degradation are present. By applying an external periodic signal, it is sometimes possible to lock the internal oscillation to the external signal. For the NF-kB systems in single cells we have observed that the two signals lock when the ration between the two frequencies is close to basic rational numbers [2]. The resulting response of the cell can be mapped out as Arnold tongues. When the tongues start to overlap we observe a chaotic dynamics of the concentration in NF-kB [2]. Oscillations in some genetic systems can be triggered by noise, i.e. a linearly stable system might oscillate due to a noise induced instability. By applying an external oscillating signal to such systems we predict that it is possible to distinguish a noise induced linear system from a system which oscillates via a limit cycle. In the first case Arnold tongues will not appear, while in the second subharmonic mode-locking and Arnold tongues are likely [3].

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[2] M.H. Jensen and S. Krishna, Inducing phase-locking and chaos in cellular oscillators by modulating the driving stimuli, FEBS Letters 586, 1664-1668 (2012).

[3] N. Mitarai, U. Alon and M.H. Jensen, Entrainment of linear and non-linear systems under noise, Chaos 23, 023125 (2013).

Badal Joshi (California State University San Marcos).
Identifying Atoms of Multistationarity.

Abstract. We address the question of identifying reaction networks that admit multiple positive steady states, known as multistationary networks. For fully open networks, the 'embedding' relation defines a partial order on the set of multistationary networks – if N is a multistationary, fully open network embedded in the fully open network G, then G is multistationary. The minimal networks with respect to the embedding relation are referred to as *atoms of multistationarity*. We discuss these networks, and the related *embedding minimal multistationary networks*, which exist beyond the context of fully open networks. We identify certain families of atoms of multistationarity and show the existence of an infinite family of atoms when the number of reactions and species is finite, and another infinite family for bounded stoichiometry. This is joint work with Anne Shiu.

Michael Marcondes de Freitas (University of Copenhagen).
Obtaining Persistence from Simplified Models.

Abstract. For many decades, reaction network theory has provided a framework to understand biochemical circuits as systems of ordinary differential equations describing how the concentrations of the involved chemical species evolve over time. Of great interest is the long-term behavior of such systems, in particular, whether or not they exhibit persistence—the property that, as long as there was a positive amount of each chemical species present in the beginning, they cannot go extinct.

It can be very difficult to determine if a system is persistent or not in general. A recent contribution was given by Angeli, De Leenheer and Sontag (2007), who provided checkable graph conditions which are sufficient for persistence in reaction networks.

In our work, we take a model simplification approach to further advance their method. After generalizing their results, we describe a process through which one can extend or simplify a reaction network by adding or removing intermediate complexes and/or catalysts, showing that these operations do not break sufficient conditions for persistence. In fact, for some important classes of reaction networks, such as the class of post-translational modification networks introduced by Thomson and Gunawardena (2009), our conditions are shown to be not only sufficient for, but equivalent to persistence.

To illustrate the scope and reach of our method, consider a two-site phosphorylation process, which can be modeled by the reaction network

$$E + S_0 \rightleftharpoons ES_0 \longrightarrow E + S_1 \rightleftharpoons ES_1 \longrightarrow E + S_2$$

$$F + S_2 \rightleftharpoons FS_2 \longrightarrow F + S_1 \rightleftharpoons FS_1 \longrightarrow F + S_0$$

where S_0, S_1, S_2 represent various forms of a substrate S_0 carrying none, one or two phosphate groups, E and F are enzymes, and the other complexes represent intermediate steps. We show that persistence for the model above is a consequence of persistence for its much simpler underlying substrate model

$$S_0 \rightleftharpoons S_1 \rightleftharpoons S_2.$$

For substrate models such as this one, the aforementioned necessary and sufficient conditions for persistence are much easier to check, thus giving our model simplification approach a computational advantage.

Sergei Maslov (Brookhaven National Laboratory, New York).
Parkinson's Law in bacterial regulation.

Abstract. It has been reported [1] that in prokaryotic genomes the number of transcriptional regulators is proportional to the square of the total number of genes. As a consequence of this trend their fraction among all genes (the so-called "regulatory overhead" of a genome) is less than 0.5% in small (< 500 genes) genomes, while in large genomes ($\sim$10,000 genes) it can be as high as 10%. The situation is reminiscent of the humorous Parkinson's Law describing the rate at which government bureaucracies disproportionately expand over time. We recently proposed [2] a general explanation of the quadratic scaling of regulators in bacterial genomes and illustrated it using a simple model in which metabolic and regulatory networks co-evolve together. In our model organisms acquire new metabolic functions by the virtue of horizontal gene transfer of entire co-regulated metabolic pathways from a shared gene pool (the "universal metabolic network"). Adapting to a new environmental condition (e.g. learning to use a new nutrient source) involves acquiring new enzymes as well as reusing some of the enzymes that are already encoded in the genome. As organism's genome grows larger it is more likely have some of the genes necessary to master a new functional task and thus needs to acquire fewer new genes from the environment. From this argument it follows that the number of functional tasks equal to the number of their transcriptional regulators should always scale faster than linearly with the total number of genes in the genome. The empirically observed quadratic scaling between these two numbers was mathematically derived for a broad range of universal network topologies [3] as well as reconciled [4] with the scaling law describing families of homologous proteins. Evolutionary conserved pathways in our model have a long-tailed power-law distribution of sizes that agrees well with real-life data. This offers a conceptual explanation for the empirically observed broad distribution of regulon sizes defined by out-degrees of transcription factors in regulatory networks.

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Maya Mincheva (Northern Illinois University).
Graph-theoretic condition for multistationarity in conservative networks.

Abstract. Understanding the dynamics of interactions in complex biochemical reaction networks is an important problem in mathematical biology. Mathematical models of biochemical networks often lead to complicated dynamical systems with many unknown parameters. Graphs associated with biochemical networks can be used to predict the existence of multistationarity in a dynamic model without knowing the parameter values. We will present a general graph-theoretic condition for multistationarity applicable to conservative biochemical networks where species concentrations exist for all time.

Namiko Mitarai (Niels Bohr Institute, University of Copenhagen).
Emergence of diversity in a model ecosystem.

Abstract. Ecological systems comprise an astonishing diversity of species that cooperate or compete with each other forming complex mutual dependencies. The minimum requirements to maintain a large species diversity on long time scales are in general unknown. Using lichen communities as an example, we propose a model for the evolution of mutually excluding organisms that compete for space. Competition is controlled by an interaction network with fixed links chosen by a Bernoulli process. New species are introduced in the system at a predefined rate. In contrast to its non-spatial counterpart, our model predicts robust coexistence of a large number of species. In the limit of small introduction rates, the system becomes bistable and can undergo a phase transition from a state of low diversity to high diversity. We suggest that isolated patches of metapopulations formed by the collapse of cyclic relations are essential for the transition to the state of high diversity.

Stefan Müller (Radon Institute for Computational and Applied Mathematics (RICAM)).
Optimal resource allocation in metabolic networks.

Abstract. The promise of metabolic engineering has been in part driven by the availability of a formal framework for reasoning about metabolic fluxes. The most prominent such framework is Flux Balance Analysis (FBA). The main objective of FBA is to optimize yield (biomass achieved per unit of substrate), not rates (e.g. growth rate per unit of substrate). When a cell optimizes rates of specific metabolic reactions, it must appropriately partition enzymes to reactions, since enzyme abundance influences reaction rates. If total enzyme is limited, this becomes a constrained resource allocation problem. Understanding the optimization of rates rather than yield helps in making sense of important adaptive scenarios in which metabolic networks do not behave as predicted by FBA. It is significant both from an evolutionary and a biotechnological perspective.

In our analysis, we go beyond linear methods (such as FBA) based on stoichiometric information. In fact, we explicitly consider kinetic information and arrive at a nonlinear optimization problem with a surprising result: We prove that, for arbitrary kinetics, solutions that optimize rates are elementary flux modes. This is surprising precisely because such flux modes only depend on stoichiometry and yet they show up as optimal states for arbitrary enzyme kinetics, including arbitrary allosteric regulation. Our theoretical result predicts discontinuous metabolic switches and explains the occurrence of low-yield pathways as observed in the Crabtree and Warburg effects. It is of general importance for our understanding of metabolic optimality and will prove useful in numerical approaches concerned with resource allocation in biology and perhaps beyond.

Jeanne Marie Onana Eloundou-Mbebi (Max Planck institute for Molecular Plant Physiology).
From robustness in concentration to robustness of network properties.

Abstract. Characterization of robustness and plasticity (i.e., variability) of biochemical components (e.g., transcripts, proteins, and metabolites) is a first step in understanding evolutionary mechanisms. Recent studies have focused on defining and characterizing the concept of absolute concentration robustness (ACR), whereby the level of a biochemical component, termed species, exhibits the same concentration in the resulting steady states irrespective of the initial conditions. For mass action networks with deficiency one, recent studies have aimed at determining necessary and sufficient conditions that a species shows ACR. Therefore,

the applicability of the resulting characterization is limited to a narrow class of biochemical networks endowed with mass action kinetics.

Here we establish a relation between ACR property of a species and the robustness of the network upon the removal of this species. We demonstrate that species which show ACR do not alter the deficiency of the network upon their removal, irrespective of the biochemical network describing the underlying system of ordinary differential equations. The obtained necessary condition for ACR can be readily applied to large-scale networks due to the purely structural information required for determining the deficiency. Our findings can be extended to study other aspects of robustness, and offer new venues for exploitation of the network deficiency concept.

Irene Otero-Muras (Bioprocess Engineering Group, IIM-CSIC-Spanish Council for Scientific Research).
Chemical Reaction Network Theory (CRNT) insights to improve parameter identifiability in biochemical reaction network models.

Abstract. The process of building useful mathematical models of cellular processes is usually hampered by high levels of uncertainty both structural and parametric. One of the main challenges of systems biology is developing methods and tools helping to overcome this problem, and this includes results connecting structure and dynamic behaviour.

Chemical reaction network theory exploits the particular structure of biochemical networks to derive results linking structural features to long term dynamic properties (most of them are related to the presence or not of multiple steady states, and apply regardless of parametric values). In this way, CRNT results can be used directly for model discrimination (since they allow discarding mechanistic hypothesis with long term dynamics contradicting experimental observations).

Our aim is to develop methods that exploit inherent structural properties of biochemical reaction networks helping to identify the parameters of kinetic models. The approach is based on the so called equilibrium manifold, an algebraic variety derived within the CRNT framework, and makes use of the particular way in which the manifold equations depend on the kinetic parameters.

In case of experimental evidence of bistability, the feasible parameter space can be drastically reduced without the need of quantitative experimental data, by ruling out those regions of the parameter space where the equilibrium manifold does not fulfil a condition for multiplicity of steady states. Moreover, quantitative information about the parameters of the bistable network can be inferred from (quantitative) experimental dose response data.

I will discuss how these results can be extended to design specific experiments that, with a reduced experimental effort, will provide valuable information about the kinetic parameters, both qualitative and quantitative, helping to improve the parametric identifiability not only for bistable switches but also for networks with one single steady state and thus contributing to facilitate the parameter estimation task in combination with standard methods.

Matteo Polettini (University of Luxembourg).
Chemical networks and their topology: a thermodynamic perspective.

Abstract. Large chemical networks subtend complex biochemical processes crucial to life, such as metabolism, respiration, and signal transduction. All such processes operate thermodynamic cycles far from equilibrium that transform environmental resources into valuable products, at the expense of high-entropy waste. While the chemistry of an Avogadro's number

of molecules is well described by macroscopic rate equations, at the cellular level the number of molecules involved might be small, allowing for significant fluctuations that are better described by means of Markovian master equations. It is now well-understood that certain topological properties of the network, such as the deficiency, play a crucial role for chemical dynamics.

In this talk we analyze chemical networks under the light of Stochastic Thermodynamics, a rigorous theory of (possibly fluctuating) nonequilibrium systems. Assuming that closed macroscopic chemical networks "in a box" should abide by elementary laws of physics (the second law of thermodynamics, mass conservation, the mass-action law), we provide a framework to describe open chemical networks subjected to the influx of chemostats, chemical species steadily provided by the environment [1]. We describe the effect of chemostats on the topology of the network, in particular on cycles that support thermodynamic transformations of the free energy differences. We discuss the effect of topology on efficiency and conservation laws. We then consider small numbers of molecules, showing that at steady states the surplus production of entropy due to fluctuations is related to the deficiency of the network [2]. At the mathematical level, these conclusions invoke concepts from graph and hypergraph theory [3].

We finally describe possible future applications of our findings to the analysis and reconstruction of actual metabolic networks. While their enormous complexity requires the application of thermodynamic concepts as guiding principles, owing to the fact that enzymatic reactions have emergent kinematics not obeying the mass-action law, the notion of thermodynamic potentials and their independence on the network topology is delicate and might be affected by the coarse graining of the underlying fundamental reaction pathways.

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Shodhan Rao (Ghent University Global Campus, South Korea).

Complex and detailed balancing of chemical reaction networks revisited.

Abstract. We revisit the classical concepts of complex balancing and detailed balancing in chemical reaction networks from the perspective of algebraic graph theory, in particular the "Laplacian matrix" and "Kirchhoff's Matrix Tree theorem". The notion of complex balanced networks was introduced by Horn and Jackson in the early seventies. They defined complexes of a reaction network as the combination of species in the left hand (substrate) and right hand (product) sides of the various reactions in the network. Further they defined a complex balanced network as one for which there exists a vector of species concentrations at which the combined rate of outgoing reactions from any complex is equal to the combined rate of incoming reactions to the complex. The assumption of a network being complex balanced has powerful consequences for the dynamical behavior, precluding multi-stability and oscillations. In a subsequent paper, Horn derived two necessary and sufficient conditions under which a mass action reaction network is complex balanced.

A detailed balanced network is a complex balanced network for which there exists a vector of species concentrations at which the rate of each of the reactions in the network is

zero. Thermodynamically the assumption of detailed-balancedness is well-justified as it corresponds to microscopic reversibility. In the early 20th century, the conditions for detailed balancing in mass action reaction networks were derived by Wegscheider and these are known as Wegscheider's conditions.

We make use of the matrix tree theorem for weighted directed graphs to derive necessary and sufficient conditions for complex balancing in reaction networks that are governed by mass action kinetics. We show that the use of matrix tree theorem makes this derivation very simple and insightful and one of the two conditions derived using this theorem is more informative than the corresponding Horn's condition for complex balancing.

Next, we make use of the matrix tree theorem to provide a new perspective and results on the Wegscheider's conditions. These results are motivated by a recent work of Dickenstein and Millan in which the notion of formal balancing, which is a weakened version of detailed balancing of reaction networks, is introduced. These authors showed that a mass action reaction network is detailed balanced if and only if it is complex balanced and formally balanced. We show constructively how one can use algebraic graph theory to prove the same result. In addition, we derive equivalent mathematical conditions for formal balancing of reaction networks.

Georg Regensburger (RICAM (Austrian Academy of Sciences)).
Parametrizing complex balancing equilibria of generalized mass-action systems.

Abstract. We use the notion of generalized mass-action systems to study reaction networks where reaction rates can be arbitrary power-laws in the concentrations. In particular, the (real) kinetic orders can differ from the corresponding (integer) stoichiometric coefficients. A fundamental result of chemical reaction network theory concerning existence and uniqueness of complex balancing equilibria for all rate constants and initial conditions can be extended in this framework. The relevant conditions depend only on the network structure and the sign vectors of the stoichiometric and kinetic-order subspaces.

As with mass-action kinetics, complex balancing equilibria are determined by the weighted graph Laplacian and the corresponding tree constants of the underlying network, they can be characterized by binomial equations and parametrized by monomials. In this talk, we discuss efficient methods based on linear algebra to compute explicit parametrizations of complex balancing equilibria in terms of quotients of tree constants. Our approach also allows us to deal algorithmically with indeterminate (symbolic) exponents in the reaction rates. We illustrate our results with examples and an implementation in the computer algebra system Maple.

Meritxell Sáez (University of Copenhagen).
Recovering a reaction network after linear elimination of species.

Abstract. The formalism of chemical reaction network theory (CRNT) puts chemical reaction networks into a mathematical, particularly algebraic, framework. In this framework, the steady states of a chemical reaction network with mass-action kinetics are solutions to a system of polynomial equations. Even for small systems, finding the steady states of the system is a very demanding task and therefore methods that reduce the number of variables are desirable. In [FeWiSIAM] the authors give one such method, in which so-called non-interacting species are eliminated at steady state.

Elimination of certain species in the network is closely linked to the procedure known as the quasi-steady state approximation, which is often employed to simplify the modeling

equations. Under the quasi-steady state approximation, some reactions are assumed to occur at a much faster rate than other reactions, that is, there is a separation of time scales, such that a steady state effectively has been reached for the fast reactions. In this setting, the goal is to study the evolution of the species that have not reached steady state (slow variables), as a new reaction network on their own.

Following the ideas introduced in [FeWiSIAM], we give a graphical method to find the reaction network on the slow variables as well as their production rates. Our method reinterprets the system of equations obtained after substitution of the eliminated variables (fast variables), as a new reaction network with mass-action kinetics, Michaelis-Menten-like kinetics or similar. The procedure is based on the analysis of the species graph and the subgraph corresponding to the eliminated variables and, importantly, allows for computer implementation. Our procedure generalises [FeWiSimp], where the authors consider elimination of intermediate species, like enzyme-substrate complexes, of the original system.

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David Schnoerr (School of Biological Sciences, University of Edinburgh, UK).
Breakdown of the chemical Langevin equation and moment closure approximations for stochastic chemical kinetics.

Abstract. We present results on the chemical Langevin equation (CLE), which is a popular approximation method to describe stochastic effects in biochemical reaction systems, such as gene regulatory networks or enzyme catalyzed reactions. First, we show that the CLE as presented in the literature is mathematically ill-defined for most reaction systems due to the occurrence of negative expressions in square roots in finite time with finite probability. We show that this breakdown is inevitable for these systems if defined in real space, but that it can be overcome by extending the state space to complex variables. We then show that this new CLE predicts real valued moments and gives more accurate predictions than other modified CLEs found in the literature and some other popular approximation methods for two biologically relevant examples.

Next, we investigate a popular moment-closure approximation method (MA) used to approximate the moments of a chemical reaction system. We find that for oscillatory and bistable systems the MAs give meaningful approximations of the moments only for an intermediate range of system sizes. For monostable systems, the latter is only the case for system sizes above a certain critical threshold. Outside of the corresponding range of validity, the MAs can give rise to unphysical oscillations or bistability, or can even lead to divergent time trajectories or to negative values for means and variances, which means they have no physical interpretation anymore.

Kim Sneppen (Niels Bohr Institute, University of Copenhagen).
Promoters kinetics and transcriptional bursts in bacteria.

Abstract. Transcriptional repression may cause transcriptional noise by a competition between repressor and RNA polymerase binding. Although promoter activity is often governed by a single limiting step, we argue that the size of the noise strongly depends on whether this step is the initial equilibrium binding or one of the subsequent steps. The multi-step tran-

scription initiation process allows weak promoters and repressors having fast binding kinetics to have substantial noise.

Gabor Szederkenyi (Faculty of Information Technology and Bionics, Pazmany Peter Catholic University, Budapest).
A computation-oriented representation of kinetic systems with rational reaction rates.

Abstract. In this contribution, kinetic systems having rational functions on the right hand side of the ordinary differential equations (ODEs) are considered. This system class contains majority of the reaction rate functions representable in rational form (like mass-action, Michaelis-Menten, Briggs-Haldane kinetics etc.) occuring in the dynamical modeling of biochemical reaction networks. For mass action dynamics, the factorization of the right hand side as the product of the complex composition matrix, the negative transpose of the weighted Laplacian matrix of the reaction graph (also called the Kirchhoff matrix) and a vector function containing the monomials is often used and (among other purposes) is suitable to conveniently handle several structure-related problems in a computational framework. We extend this type of factorization to rational kinetic systems by introducing a modified Kirchhoff matrix and a so-called rate-weighting matrix containing the denominators of the reaction rates. We give an extension of the algorithm published in [1] for generating the so-called canonical CRN structure for a kinetic dynamics. Similarly to the mass-action case, the reaction graph structure corresponding to a fixed kinetic dynamics is generally non-unique. Using the proposed system representation, we give interesting examples of this phenomenon (called macro-equivalence or dynamical equivalence), and show that several theoretical and computational results obtained previously for mass action systems (see, e.g. [2]) can be directly applied or extended to the studied more general system class.

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Preben Graae Sørensen (University of Copenhagen).
Dynamics of heterogeneous cell populations.

Abstract. The biological function of cell populations depends on the behavior of the entire biochemical network spanned by the cellular reactions and on the exchange of metabolites. In tissues of different cell types, individual variations of the cellular networks are trivial. But also populations of genetically identical cells are heterogeneous in terms of e.g. size and protein expression (e.g. due to stochastic processes in gene expression and the microenvironment) and therefore have individual dynamic properties. Mathematical models describing biological dynamics such as rhythmic behavior, must therefore be robust with respect to relevant levels of cellular heterogeneity. The present contribution presents examples of biochemical models of populations of heterogeneous yeast cells that display robust synchroneous metabolic oscillations, as well as heterogeneous arteriolar models of rythmic contractions.

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Tat Dat Tran (Max Planck Institute for Mathematics in the Sciences, Leipzig, Germany).
A connection between Population Genetics and Chemical Reaction Network.

Abstract. I will consider some chemical reaction networks which can be explained as some mathematical models in population genetics. By this work, many results from these two different fields can be exchanged into each other. In this talk, I give out an explicit formula of the non-stationary solution of a given Moran type network. The stationary distribution in stochastic setting satisfies the large deviation principle with the rate function is the Lyapunov functional in deterministic setting. When there is a unique stable equilibrium, this rate function (Lyapunov functional) is proportional to the Kullback-Leibler divergence.

Andreas Weber (University of Bonn).
Efficient methods to detect saddle-node and Andronov-Hopf bifurcations in chemical reaction networks.

Abstract. We present efficient algorithmic methods to detect saddle-node and Andronov-Hopf bifurcation fixed points in chemical reaction networks with symbolic rate constants. Our methods use the representations of the systems on convex coordinates that arise from stoichiometric network analysis.

One of our methods then reduces the problems of determining the existence of saddle-node bifurcation fixed points as well as of an Andronov-Hopf bifurcation fixed points to certain existentially quantified first-order formulae over the ordered field of the reals involving Jacobian determinants resp. minors of them. These formulae can then be solved using computational logic packages.

The second method uses ideas from tropical geometry to formulate more efficient methods that are incomplete in theory but worked very well for the examples that we have attempted.

The results on the Andronov-Hopf bifurcations have been published (`http://dx.doi.org/0.1016/j.jcp.2015.02.050`), the results on the saddle-node bifurcations are novel. (Results of joint work with Markus Eiswirth, Hassan Errami, Dima Grigoriev, Werner M. Seiler, Thomas Sturm.)

Posters

Bernadett Ács (Pázmány Péter Catholic University).

A new method for computing linearly conjugate weakly reversible structures of kinetic polynomial systems.

Abstract. Chemical reaction networks obeying the mass action law are suitable for modeling complex nonlinear dynamics. In this contribution, by extending a previous result [1], we give a graph-theory and optimization-based algorithm for the determination of linearly conjugate weakly reversible reaction graph structures [2]. It is conjectured that the existence of such structure implies bounded trajectories.

The new contributions of the work are the following: 1. It is proved that dense linearly conjugate realizations, even if a set of linear constraints is required to hold, determine a super-structure, i.e. the reaction graphs of all suitable linearly conjugate realizations are subgraphs of the reaction graph describing the dense realization. 2. We give a new, efficient, polynomial time algorithm for computing dense linearly conjugate realizations. To avoid the application of integer variables we compute the dense realization as the convex combination of a few linearly conjugate realizations computed by solving LP problems. 3. As the main result, we propose a graph-theory-based polynomial time algorithm which computes weakly reversible linearly conjugate realizations of a given kinetic system if the set of complexes is fixed. The idea of this method, as it was published in the case of dynamical equivalence, is that the reaction graph corresponding to a weakly reversible realization can not contain edges linking different strong components. The correctness of the algorithm is proved using result 1. Within the algorithm we compute constrained dense linearly conjugate realizations applying the method developed in contribution 2.

The computational advantage of our method is that instead of solving one big optimization problem with auxiliary variables as it is done in [3], in each step of the algorithm we solve smaller LP problems on a fixed set of variables. Since the number of variables in previously published methods increases rapidly, our algorithm needs less computation time for kinetic systems exceeding a certain size.

It has been proved, too, that if the kinetic system has any weakly reversible realization, then the presented algorithm computes a dense linearly conjugate realization, which determines a super-structure among weakly reversible linearly conjugate realizations.

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Georgios Arampatzis (University of Massachusetts).
Accelerated Sensitivity Analysis in High-Dimensional Stochastic Reaction Networks.

Abstract. Existing sensitivity analysis approaches are not able to handle efficiently stochastic reaction networks with a large number of parameters and species, which are typical in the modeling and simulation of complex biochemical phenomena. In this work, a two-step strategy for parametric sensitivity analysis for such systems is proposed, exploiting advantages and synergies between two recently proposed sensitivity analysis methodologies for stochastic dynamics.

The first method performs sensitivity analysis of the stochastic dynamics by means of the Fisher Information Matrix on the underlying distribution of the trajectories; the second method is a reduced-variance, finite-difference, gradient-type sensitivity approach relying on stochastic coupling techniques for variance reduction. Here we demonstrate that these two methods can be combined and deployed together by means of a new sensitivity bound which incorporates the variance of the quantity of interest as well as the Fisher Information Matrix estimated from the first method.

Results on an epidermal growth factor network with 50 parameters and on a protein homeostasis with 80 parameters demonstrate that the proposed strategy is able to quickly discover and discard the insensitive parameters and in the remaining potentially sensitive parameters it accurately estimates the sensitivities. The new sensitivity strategy can be several times faster than current state-of-the-art approaches that test all parameters.

Sadia Arshad (COMSATS Institute of Information Technology Lahore Pakistan).
Dynamical behaviors of fractional order HIV model.

Abstract. The main goal of this paper is to study the dynamics of fractional order HIV model. Fractional order differential equations are naturally related to systems with memory which exists in most biological systems. Also they are closely related to fractals which are abundant in biological systems. In fact, real world processes generally or most likely are fractional order systems. That is to say, a lot of physical systems show fractional dynamical behavior because of special materials and chemical properties. We investigate the dynamics of the model on cellular level containing interaction between three types of population of cells: non-infected activated or cycling CD4+ T cells which we consider to be target cells, T(t), productively infected T cells, I(t), and HIV virus particles V(t). We present the numerical simulations of the model for different values of fractional order to study the dynamics of virus particles in competition with target cells by varying the infection rate.

Katarina Bodova (IST Austria).
Estimation of quantitative trait evolution.

Abstract. Selection, mutation and random drift affect the dynamics of allele frequencies and consequently of quantitative traits. The system can be formulated as a stochastic process with given transition rates (discrete or continuous time and frequency). While the macroscopic dynamics of quantitative traits can be measured, the underlying allele frequencies are typically unobserved. Our aim is to understand how the macroscopic observables respond to changes in evolutionary forces without following these microscopic processes. The problem has previously been studied by analogy with statistical mechanics: the allele frequency distribution at each time is approximated by the stationary form, which maximises entropy — resulting in a quasi-stationary approximation. Our non-equilibrium maximum entropy approximation extends the current theory, which applied only when mutation is strong 4Nmu>1, to the more realistic

case where mutation is weak 4Nmu<1, so that populations are typically near fixation. This is a joint work with Nick Barton and Gasper Tkacik.

Sana Javed (COMSATS Institute of Information and Technology Lahore Pakistan).
Numerical solutions of fractional order epidemic model.

Abstract. The dynamical study of the carriers play an essential role in the evolution and global transmission of infectious diseases will be discussed in this study. To make this approach novel, we will consider the fractional order model which is generalization of integer order derivative to an arbitrary number. Since the integration involved is non local therefore this property of fractional operator is very useful to study epidemic model for infectious diseases. An extended numerical method (ODE solver) is implemented on the model equations and we will present the simulations of the model for different values of fractional order α to study the effect of carriers on transmission dynamics. Global dynamics of fractional model are established by using the reproduction number.

Badal Joshi (California State University San Marcos).
Detailed balance in reaction networks within deterministic and stochastic models.

Abstract. A detailed balanced reaction network is a reversible reaction network where at equilibrium, each forward reaction occurs at the same rate as the reverse reaction. In the stochastic setting, the Markov chain model can be thought of as another network induced by the reaction network. The nodes of this induced network are populations of each species and edges represent transitions that occur through a single chemical reaction. A Markov chain is detailed balanced, when at stationarity, each forward transition occurs at the same rate as the reverse transition. We address the question of whether the two notions of detailed balance are related. In particular, we show that detailed balance in reaction networks implies that the Markov chain is detailed balanced, but the converse is not true in general.

Richard Kollar (Comenius University Bratislava Slovakia).
Extension and Justification of Quasi-Steady State Approximation for Reversible Bimolecular Binding.

Abstract. The quasi-steady state approximation (QSSA) is commonly applied in chemical kinetics without its rigorous justification. We provide such a justification in the particular case relevant to studies of diffusion in biochemistry: reversible two-step bimolecular binding, in which molecules reversibly form a transient complex that reversibly transforms to a product, in two different regimes. The first one is characterized by the symmetrized Briggs-Haldane criterion $|R_0 - L_0| \ll K_m$. Here R_0 and L_0 are the initial concentrations of reacting receptor and ligand, respectively, and K_m is the Michaelis constant. Furthermore, we validate QSSA under an alternative condition $k_2 + k_{-2} \ll k_1$. Here k_1 is the rate constant of decomposition of the transient complex to the ligand and the receptor and k_2 and k_{-2} are the forward and the reverse rate constants of transformation of the complex to the product, respectively. The derived conditions may be of practical use as they provide weaker requirements for the validity of QSSA compared to the existing results. This is a joint work with Katarina Siskova (University of Ghent).

Luca Laurenti (University of Oxford - Department of Computer Science).
Stochastic Analysis of Chemical Reaction Networks Using Central Limit Approximation.

Abstract. In this poster we present a stochastic temporal logic for analysis of Chemical Reactions Networks (CRNs). The semantics of the logic we present is based on the Central Limit Approximation (CLA) of the Markov Process that is defined by a generic CRN. This makes possible the probabilistic evaluation of proprieties on CRNs, whose stochastic semantics is a Markov Process with finite or infinite state space. Using the mathematical framework of the CLA, we show that it is possible performing model checking on properties built on the linear combination of the species of a CRN, in a way that is absolutely independent from the number of molecules of each specie and from the state space of the Markov Process. This makes our approach scalable and its computational complexity is dominated by the cost of solving the CLA, which requires the solution of a system of differential equations in number quadratic to the specie of the system. We prove the correctness of our approach showing that it is exact when close enough to the thermodynamic limit. Nevertheless, if the assumptions of CLA validity are respected, it can give very good results even for quite small population systems. We use the logic for the model checking of some biological reaction networks taken from the literature, and, where possible, we compare our results to the analysis of the same proprieties performed by Statistical Model Checking (SMC) and by solving the Chemical Master Equation (CME). The results we obtain confirm that the logic and the stochastic semantics we give permit formal analysis of CRNs that are too big to be checked by taking into account the state space of the Markov Process they define. Moreover, the experimental results show that the proposed method speeds up the analysis considerably, compared to SMC or CME, while still providing very good accuracy even for a quite small number of molecules. We expect this new method to make possible the formal analysis of reaction networks up to hundreds of species that are near enough to the thermodynamic limit, where the CLA is accurate. Our approach makes possible the analysis of CRN whose stochastic semantics is a Markov Process, and whose behaviour is still far to the deterministic approximation.

Saeed Masroor (Eindhoven University of Technology).
Analysis of Biochemical Adaptation.

Abstract. Adaptation is the dynamic characteristic of some biochemical networks in which a system after a response to an input signal returns to its prestimulus value even in the continued presence of the signal. Sensory systems in all living organisms and signaling networks are examples of adaptive systems. To quantify the concept of adaptation, two characteristics of an adaptive response are formulated: sensitivity (large peak output response) and precision (the output returns to prestimulation level). We have developed a mathematical technique for estimating sensitivity of adaptive systems. This technique is very useful in identifying mathematical models whose structure allow for perfect adaptation. For several models of adaptive systems found in literature, we prove a bound 1 for their sensitivity, which implies that these systems are not capable of amplifying an input signal. Moreover we use this technique to predict the behavior of a DNA based biochemical reaction network which is currently being implemented in a controlled in vitro setting.

From another standpoint, we are interested in adaptation in general reaction networks. We consider reaction networks that satisfy mass-action and detailed balance. We study the dynamics of the reaction network near equilibrium. A linearization of the reaction rate equation (RRE) helps obtaining expressions for precision and sensitivity. We find a general bound for sensitivity in terms of equilibrium concentrations. Then we prove that non-normality of

the Jacobian of RRE at equilibrium is essential to achieve a sensitivity larger than 1. We have also shown via examples that omitting the condition of detailed balance will result in much higher amplification.

Alvaro Moraes (King Abdullah University of Science and Technology).
A multilevel adaptive reaction-splitting simulation method for stochastic reaction networks.

Abstract. In this work, we present a novel multilevel Monte Carlo method for kinetic simulation of stochastic reaction networks characterized by fast and slow reaction channels.

To produce efficient simulations, we automatically classify the reactions channels into the fast and slow classes. To this end, we first introduce the concept of the level of activity of a reaction channel, which depends on the current state of the system.

Then, we propose a low cost heuristic that allows us to adaptively split the set of reaction channels into two subsets characterized by either a high or low level of activity. Based on a time splitting technique, the increments associated with high activity channels are simulated using the tau-leap method while those associated with low activity channels are simulated using an exact method.

This path simulation technique, which we name mixed method, is amenable for coupled path generation and a corresponding multilevel Monte Carlo algorithm.

To estimate expected values of observables of the system at a prescribed final time, our method bounds the global computational error to be below a prescribed tolerance, TOL, within a given confidence level. This goal is achieved with a computational complexity of order $\mathcal{O}(TOL^{-2})$, the same as with a pathwise exact method, but with a smaller constant.

We also present a novel control variate technique based on the stochastic time change representation by Kurtz, which may dramatically reduce the variance of the coarsest level at a negligible computational cost.

Our numerical examples show substantial gains with respect to the standard Stochastic Simulation Algorithm (SSA).

Amir Niknejad (College of Mount Saint Vincent).
Matrix methods in metabolic networks.

Abstract. A metabolic network can be characterized by a m by n stoichiometric matrix S, where m rows represent the internal metabolites and the n columns represent the internal biochemical reactions. The particular information about metabolic network is embedded in fundamental subspaces of matrix S. For example, the row space of S contains thermodynamic information of the network, while the null space of S reveals information about the steady state of the metabolic network. Recent advances in bioinformatics has given us enormous amount of information about the basic construct of many organism and it is possible now to reconstruct the stoichiometric matrices of various cells and living systems. Systems biologists face a challenge of making sense of this abundant amount of information.

We present a combined and simultaneous analysis of metabolites and biochemical reactions in a metabolic network using matrix factorizations and subspace projection in order to decipher information about metabolic networks.

Yannis Pantazis (University of Crete).
Pathwise Information-theoretic Metrics for Parametric Sensitivity.

Abstract. Analysis of Complex Stochastic Dynamics Stochastic modeling and simulation provide powerful predictive methods for the intrinsic understanding of fundamental mechanisms in complex biochemical networks. Parametric sensitivity analysis is an essential mathematical and computational tool, yielding information regarding the robustness and the identifiability of model parameters. We present a sensitivity analysis methodology suitable for complex stochastic reaction networks with a large number of parameters. The proposed approach is based on information theory metrics and relies on the quantification of information loss due to parameter perturbations between time-series (or path or trajectory) distributions. The pathwise sensitivity analysis employs the rigorously-derived Relative Entropy Rate, which is directly computable from the local dynamics. A key aspect of the method is that an associated pathwise Fisher Information Matrix (pFIM) is defined, which in turn constitutes a gradient-free approach to quantifying parameter sensitivities. The structure of the pFIM turns out to be block-diagonal, revealing hidden parameter dependencies and sensitivities. Finally, we provide connections between the proposed sensitivity analysis method and more standard approaches based on derivative estimation.

Matteo Polettini (University of Luxembourg).
Irreversible thermodynamics of open chemical networks.

Abstract. From a microscopic physical standpoint, elementary reactions are two-body collision processes subjected to conservation laws (mass, charge, angular momentum etc.) whose quantum-mechanical transition amplitudes imply local detailed balance at each step. Under the assumption of molecular chaos, the mass-action law holds and thermodynamic potentials are well defined. These physical assumptions strongly constrain the topology and the kinetics of a chemical network. In particular, a Closed Chemical Network "in a box" relaxes to equilibrium. One way to open up the network is to fix the concentrations of certain chemicals, the chemostats, efficiently provided and withdrawn from the environment. As such external species are identified, the topology of the network changes and an Open Chemical Network ensues, which does not relax to equilibrium and thus requires a consistent thermodynamic description. The topology of the Open Chemical Network is tightly intertwined with its thermodynamics. In particular, only emergent cycles carry thermodynamic affinities, that is, are capable of transducing free energy across the environment and hence are traversed in a preferential direction, prescribed by the second law of thermodynamics. The superposition of cycles describes coupling of thermodynamic processes (e.g. anabolism to catabolism) and it quantified by concepts such as the efficiency. Moreover, introducing chemostats breaks conservation laws. In this poster we describe the topology and thermodynamics of Open Chemical Networks, with special attention to issues that are relevant for the analysis and reconstruction of large metabolic networks.

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Riccardo Rao (University of Luxembourg).
Accuracy in kinetic proofreading: a thermodynamic approach.

Abstract. The high accuracy exhibited by biological information transcription processes is due to kinetic proofreading, i.e., by a mechanism which reduces the error rate of the information-handling process by driving it out of equilibrium.

I plan to present a thermodynamic description of enzyme-assisted assembly processes involving competing substrates [1] (typical examples are the DNA replication and the tRNA charging). The kinetic description of the assembly processes lies on the Schnakenberg Network Theory [2]: the systems are described by chemical reaction networks and their stochastic dynamics by means of Master Equations. The element which complicates the thermodynamic description is the presence of absorbing states.

Within this framework, I introduce a way to evaluate the dissipation rate of the assembly processes, and I discuss how to relate this, and other thermodynamic quantities, to their accuracy. The performance at the steady state of several chemical reaction schemes embedding kinetic proofreading [3, 4] is thus presented and the related time, dissipation and efficiency vs. error trade-offs exhibited for different discrimination regimes. The results obtained are in agreement with other approaches [5].

I finally show, in the same framework, a model which takes into account correlations between consecutive enzyme-assisted assembly steps.

The work I intend to present, highlights the relevance of the distinction between energetic and kinetic discrimination regimes and its relation with the network topology, in enzyme-substrate interactions [1].

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Pedro Vilanova (KAUST).
An Efficient Forward-Reverse Expectation-Maximization Algorithm for Statistical Inference in Stochastic Reaction Networks.

Abstract. In this work, we present an extension to the context of Stochastic Reaction Networks (SRNs) of the forward-reverse representation introduced in "Simulation of forward-reverse stochastic representations for conditional diffusions", a 2014 paper by Bayer and Schoenmakers. We apply this stochastic representation in the computation of efficient approximations of expected values of functionals of SNR bridges, i.e., SRNs conditioned to its values in the extremes of given time-intervals. We then employ this SNR bridge-generation technique to the statistical inference problem of approximating the reaction propensities based on discretely observed data. To this end, we introduce a two-phase iterative inference method in which, during phase I, we solve a set of deterministic optimization problems where the SRNs are replaced by their reaction-rate Ordinary Differential Equations (ODEs) approximation; then, during phase II, we apply the Monte Carlo version of the Expectation-Maximization (EM) algorithm starting from the phase I output. By selecting a set of over dispersed seeds as initial points for phase I, the output of parallel runs from our two-phase method is a cluster of approximate maximum likelihood estimates. Our results are illustrated by numerical examples.

Artur Wachtel (University of Luxembourg).
Connection of Deficiency and Entropy Production in Chemical Reaction Networks.

Abstract. Chemical reaction networks describe the molecular machinery that allows living organisms to metabolize food as well as sense signals and process information.

These biochemical processes typically operate far from equilibrium, dumping high amounts of entropy in the form of waste into the environment.

The organisms themselves are not heavily altered during this process, indicating that cyclic transformations dominate. While some cycles can easily be spotted in the reaction network, others are "hidden". The number of these hidden cycles is known as the *deficiency* of the reaction network. This purely topological concept is known to have a strong influence on the dynamics of reaction networks, both in the deterministic and in the stochastic description.

The theory of Stochastic Thermodynamics defines and formalizes thermodynamic concepts for such stochastic systems out of equilibrium. Its most fundamental quantity is the *entropy production*, which is a bilinear form composed of currents and affinities. In the deterministic case these expressions are well known and comparably easy to determine. In the stochastic case, on the contrary, there are fluctuating corrections to the macroscopic expressions which, in general, are difficult to calculate.

Here we present new findings on the entropy production for reaction networks with mass action kinetics. For generic steady states we show how a recently discovered gauge invariance simplifies the calculation of the stochastic entropy production. Moreover, we point out how the deficiency of a reaction network is connected to the fluctuating corrections of the entropy production. For linear systems these results can be extended from the steady state to all times.