# Chemical Reaction Networks

Workshop - Politecnico di Torino - July 1-3 2019

# Book of Abstract

Organizing commitee:
Enrico Bibbona


POLITECNICO
DI TORINO

| | **Monday 01** | **Tuesday 02** | **Wednesday 03** |
|---|---|---|---|
| 09:00 - 09:30 | Registration | Radulescu | Yu |
| 09:30 - 09:45 | Opening | | |
| 09:45 - 10:30 | Rempala | MacLaurin | Kim |
| 10:30 - 10:45 | Coffee break | Coffee break | Coffee break |
| 10:45 - 11:30 | Capelletti | Tóth | Hoessly |
| 11:30 - 12:15 | Mincheva | Nguyen | Deshpande |
| 12:15 - 14:00 | Lunch | Lunch | Lunch |
| 14:00 - 14:45 | Short talks | Renger | Discussion |
| 14:45 - 15:30 | Polettini | Patterson | |
| 15:30 - 16:15 | Penocchio | Agazzi | |
| 16:15 - 16:30 | Coffee break | Coffee break | |
| 16:30 - 17:15 | Forastiere | Andreis | |
| 17:15 - 18:00 | | Vassena | |
| | | | |
| 19:30 | | **Social dinner** | |

# List of speakers

# Main speakers

## SIR Models on Contact Networks

Grzegorz REMPALA
*Ohio State University*

The idea of biochemical reaction networks evolving on a random graph comes from the early work on random walks in random environment. In particular the SIR-type (susceptible-infectious-removed) chemical reaction networks have been extensively studied in such context and several asymptotic results, (e.g., on large graph limits) have been recently established. In this talk, I will discuss some statistical applications of the SIR-like reaction network models evolving on random graphs with given degree distributions and point out to some interesting connections of such models to the general statistical theory of survival analysis.

## Advances on Absolute Concentration Robustness

Daniele CAPPELLETTI
*ETH Zurich*

Absolute concentration robustness is the property of some biochemical system to express a certain chemical species always at the same equilibrium concentration, independently on the initial conditions. A family of such systems has been described by Shinar and Feinberg in 2010 by means of structural properties of the reaction network. I will use tools from Control Theory to prove that a stronger concept of robustness is in place for a family of models that strictly includes the one studied by Shinar and Feinberg: under certain assumptions, both disturbances in the initial conditions and disturbances persistently applied to the system over time can be rejected. I will then show how this result can be used in the context of synthetic biology, and how the property of absolute concentration robustness of a portion of the system can be lifted to the whole chemical system.

## Parametric sensitivity analysis of oscillations in a gene regulation delay model

Maya MINCHEVA
*Northern Illinois University*

Delay-differential equations are often used to model gene expression networks.
A delay model of protein synthesis with sRNA is considered. We carry out sensitivity analysis of the extrema and the period of oscillations at several operating points. Comments on the evolutionary implications of the results will be given.
This is a joint work with B. Ingalls (University of Waterloo, Canada) and M. Roussel (University of Lethbridge, Canada).

## Effective thermodynamics for chemical networks with hidden degrees of freedom

Matteo POLETTINI
*University of Luxembourg*

Thermodynamic modelling of chemical networks often presumes that, at the macroscopic level, the observer has complete information about the flows that circulate in and out of the system: no parasitic current, exact evaluation of the chemical affinities that drive the reactions out of equilibrium. However, most often the observer only measures marginal information, or parts of the network are hidden. Disregarding sources of dissipation might lead to inconsistent claims, such as the violation of the second law. We show that for a class of chemical reaction networks it is nevertheless possible to produce an effective description that does not dispense with the fundamentals of thermodynamics: the 2nd Law, the Fluctuation-Dissipation paradigm, and the more recent and encompassing Fluctuation Theorem. The class of networks is characterized in terms of their deficiency, a topological number roughly describing the number of thermodynamic cycles that are not representable as cycles. We base our theory on the theory of the stochastic thermodynamics of nonequilibrium systems, introducing a class of "marginally time-reversed" Markovian generators that have interesting mathematical and physical properties.

## Thermodynamic efficiency in dissipative chemistry

Emanuele PENOCCHIO
*University of Luxembourg*

Open chemical reaction networks play a central role in chemical biology, and particularly in metabolic processes. They can be seen as thermodynamic machines converting energy far from equilibrium. Recent experiments in dissipative self-assembly also demonstrated that by opening reaction vessels and steering certain concentrations, an ocean of opportunities for artificial synthesis and energy storage emerges. To navigate it, rigorous thermodynamic notions of energy, work and dissipation must be established for these systems. Here, we do so by building upon recent theoretical advances in nonequilibrium statistical physics and mathematical chemical reaction network theory. As a central outcome, we show how to quantify the efficiency of such chemical operations and lay the foundation for performance analysis of any dissipative chemical process.

## Current fluctuations in presence of time-periodic metabolic conditions

Danilo FORASTIERE
*University of Luxembourg*

We address the current response to periodic driving of a crucial biochemical reaction network, namely, substrate inhibition. We focus on the conversion rate of substrate into product under time-varying metabolic conditions, modelled by a periodic modulation of the product concentration. Coarse-graining the original model to a minimal solvable one by means of a projection technique, we study the leading behaviour of the time averaged current and its fluctuations using a path integral approach. We show that there exist different regimes, depending on the kinetic rates, in which positive and negative amplitude resonant effects take place, and we provide interpretations for the role that these non-equilibrium effects can play in the metabolic network.

# Effective computational methods for hybrid stochastic gene networks

Ovidiu RADULESCU
*University of Montpellier*

At the scale of the individual cell, protein production is a stochastic process with multiple scales, combining quick and slow random steps, discontinuous and smooth variation. Hybrid stochastic processes, in particular piecewise-deterministic Markov processes (PDMP), are well adapted for describing such situations. PDMPs are weak limits of the jump Markov processes traditionally used as models for stochastic chemical reaction networks. Although hybrid modelling is now well established in biology, these models remain computationally challenging. We propose several improved methods for computing time dependent multivariate probability distributions (MPD) of PDMP models of gene networks. In these models, the promoter dynamics is described by a finite state, continuous time Markov process, whereas the mRNA and protein levels follow ordinary differential equations (ODEs). The push-forward method computes numerically the probability measure advected by the deterministic ODE flow, through the use of analytic expressions of the corresponding semigroup. Compared to earlier versions of this method, the probability of the promoter states sequence is computed beyond mean field theory. For comparison, we also propose pseudo-spectral methods for solving the partial differential equations satisfied by MPD.

# Phase Reduction and Synchronization in Stochastic Biochemical Oscillators

James MACLAURIN
*New Jersey Institute of Technology*

A common method for analyzing the effects of molecular noise in chemical reaction networks is to approximate the underlying chemical master equation by a Fokker-Planck equation, and to study the statistics of the associated chemical Langevin equation. This so-called diffusion approximation involves performing a perturbation expansion with respect to a small dimensionless parameter $\varepsilon = \Omega - 1$, where $\Omega$ characterizes the system size. For example, $\Omega$ could be the mean number of proteins produced by a gene regulatory network. In the deterministic limit $\Omega \to \infty$, the chemical reaction network evolves according to a system of ordinary differential equations based on classical mass action kinetics.
In this paper we develop a phase reduction method for chemical reaction networks that support a stable limit cycle in the deterministic limit. We present a variational principle for the phase reduction, yielding an exact analytic expression for the resulting phase dynamics. We demonstrate that this decomposition is accurate over timescales that are exponential in the system size $\Omega$. This contrasts with the phase equation obtained under the diffusion approximation, which is only accurate up to times $\mathcal{O}(\Omega)$. In particular, we show that for a constant $C$, the probability that the system leaves an $\mathcal{O}(\zeta)$ neighborhood of the limit cycle before time $T$ scales as $Te^{-C\Omega b\zeta^2}$, where $b$ is the rate of attraction to the limit cycle. An important application of this phase reduction method is to study synchronization due to common extrinsic noise in cellular oscillators. It is common to distinguish between intrinsic noise sources (due to factors such as finite-copy numbers of the reactants, and variability in the microscopic environment), and extrinsic noise sources (environmental factors that perturb the reactions in entire arrays of cells). We construct a model of cellular oscillations perturbed by weakly-correlated extrinsic noise (and, aside from this, completely uncoupled). We demonstrate that the weak extrinsic noise is sufficient to synchronize homogeneous oscillators. We then study the interplay of the common environmental noise with static variations in the properties of the oscillators (sometimes referred to as quenched disorder): the former tends to synchronize the oscillators, and the latter tends to desynchronize them. Finally we apply some of these results to classical bursting genetic oscillators with a delayed inhibition.

## Preliminary report on the realization problem

János TÓTH
*Budapest University of Technology and Economics*

A few months ago in Vienna we (together with colleagues) decided to solve some realization problems of formal reaction kinetics. The general problem (posed and partially solved by several authors) is: Given a system of polynomial differential equations, is it possible to find a reaction network with prescribed properties so that the given ODE is its induced kinetic differential equation. We concentrated on collecting and producing solutions to this problem with special reference to networks which are mass conserving, reversible, weakly reversible, of zero deficiency, complex balanced, detailed balanced, etc. As a by-product, we were able to show the existence of a positive stationary point of three (3D and 6D) repressilator models using a recent result by Boros.
The author and his colleagues started to work on this paper when enjoying the hospitality of the Erwin Schrődinger Institut in Vienna as participants of the meeting Advances in Chemical Reactor Network Theory, 15–19 Oct., 2018. JT thanks the support of the NRDIO, Hungary (SNN 125739).

## Prevalence of deficiency zero reaction networks

Tung NGUYEN
*University of Wisconsin - Madison*

In the mathematical study of reaction networks, the most classical results are those pertaining to models that have a deficiency of zero. In particular, for deterministic models it is well known that weak reversibility and a deficiency zero of the reaction network implies that the model is complex balanced. In the stochastic setting it is known that weak reversibility and a deficiency of zero implies the existence of a stationary distribution that is a product of Poissons.
Given that deficiency zero models play such a significant role in the mathematical study of reaction networks, a natural question is how prevalent are they? In order to answer this question, we consider reaction networks under the Erdos-Renyi random graph framework. In particular, we start with $n$ species, and then let our possible vertices be all zeroth, first, and second order complexes that can be produced from the $n$ species. Edges, or reactions, between two arbitrary complexes then occur independently with probability $p_n$. We establish a function $r(n)$, termed a *threshold function*, such that the probability of the random network being deficiency zero converges to 0 if $p_n \gg r(n)$ and converges to 1 if $p_n \ll r(n)$.
*This is a joint work with David F. Anderson*

## Macroscopic fluctuation theory of Chemical Reaction Networks

Michiel RENGER
*WIAS Berlin*

It is now becoming more widely believed that fluxes hold the key to understanding non-equilibrium thermodynamics. This has lead to the development of macroscopic fluctuation theory (MFT), based on large deviations of fluxes. The major part of MFT deals with microscopic systems with approximately white noise, which corresponds to quadratic large deviation rate functionals. However, typical microscopic models for chemical reactions are driven by Poissonian noise, which yields entropic rather than quadratic functionals. In this talk I will discuss MFT Theory for chemical reaction networks, based on entropic rate functionals.
If time allows I will also discuss connections with gradient flows and GENERIC, and/or the possible occurence of dynamical phase transitions.

## Flux Large Deviations

Robert PATTERSON
*Weierstrass Institute*

I will present an approach to proving a pathwise large deviations principle for pure jump interacting particle models of chemical reactions in the hydrodynamic limit. I will show that working with the reaction fluxes as well as the reactant concentrations leads to an explicit rate function, from which existing results can be recovered and even strengthened by applying the contraction principle. The proof has two main technical components—a stochastic tilting argument (change of measure) and an analytic approximation argument. These two steps are in a general sense standard, but managing their interplay is key to avoiding awkward technical assumptions, which we are able to do with the help of a continuity assumption on the initial condition.
If the chemical reaction network can be brought into detailed balance the large deviations rate function can be used to define a canonical gradient flow for the limiting system and thus give a rigorous derivation of the thermodynamic free energy. However, the proof does not require any form of reversibility and so I will make some comments about ongoing work to extend the result to systems of coagulating particles, where the infinite number of possible sizes for an single particle makes the topological questions and analytic approximation argument more delicate.
*This is a joint work with Michel Renger and Luisa Andreis.*

## Large deviations theory for chemical reaction networks

Andrea AGAZZI
*Duke University*

The microscopic dynamics of well-stirred networks of chemical reactions are modeled as jump Markov processes. At large volume, one may expect in this framework to have a straightforward application of large deviation theory. This is not at all true, for the jump rates are typically neither globally Lipschitz, nor bounded away from zero, with both blowup and absorption as quite possible scenarios. In joint work with Amir Dembo, Jean-Pierre Eckmann and Jonathan Mattingly, we utilize Lyapunov stability theory to bypass this challenges and to characterize a large class of network topologies that satisfy the full Wentzell-Freidlin theory of asymptotic rates of exit from domains of attraction. The extension of such results to the estimation of transitions times between metastable states further requires the positive recurrence of such processes. This property depends critically on dynamics at of the jump Process when the concentration of some of the components are small. Precise statements on the connection between this property and the structure of the underlying network are an active area of research.

## Large-deviation approach to coagulation processes and gelation

Luisa ANDREIS
*WIAS Berlin*

At least since the days of Smoluchowski, there is a desire to understand the behaviour of large particle systems that undergo chemical reactions of coagulation type. One of the phenomena that attracts much attention is the question for the existence of a phase transition of gelation type, i.e., the appearance of a particle of macroscopic size in the system. In this talk, we consider the (non-spatial) coagulating model (sometimes called the Marcus-Lushnikov model), starting with N particles with mass one each, where each two particles coagulate after independent exponentially distributed times that depend on a given coagulation kernel, function of the two masses. We focus on the case in which the corresponding coagulation kernel is multiplicative in the two masses, hence the process is identified as the multiplicative coagulation process.

This case is of particular interest also for its strong relations with the time dependent Erdos-Rényi random graph. We work for fixed time $t > 0$ and derive, for the number N of initial particles going to infinity, a joint large-deviations principle for all relevant quantities in the system (microscopic, mesoscopic and macroscopic particle sizes) with an explicit rate function. We deduce laws of large numbers and in particular derive from the rate function the well-known phase transition at time $t = 1$, the time at which a macroscopic particle (the so-called gel) appears, as well as the Smoluchowski characterisation of the statistics of the finite-sized particles. We discuss also current ongoing work on extending this approach to include systems with more general coagulation kernels and systems where particles are provided with a spatial position.
*This is an ongoing joint work with Wolfgang König (WIAS and TU Berlin), Robert Patterson (WIAS) and Wen Sun (TU Berlin).*

## Good children and bad children

Nicola VASSENA
*Free University of Berlin, Institute of Mathematics*

In this talk we analyse the Jacobian determinant for metabolic networks - with general kinetics. We will show an expansion of the determinant, based on the concept of Child-Selections, i.e., injective maps which associate each (mother) metabolite to an outgoing (child) reaction from itself. This approach provides a clear tool to discriminate between the case where the Jacobian has determined sign and where the sign is undetermined, that is, the sign depends on the specific choice of the reaction rates.
Specifically, we will characterize here ”bad” child selections, possibly responsible for sign changes in the Jacobian of the system and consequent dynamical implications, e.g. change of stability and bifurcations.

## Complex-balanced realization of mass-action systems

Polly YU
*University of Wisconsin - Madison*

A mass-action system with certain structural properties (e.g., weak reversibility, complex balancing) is known to have special dynamical properties (e.g., existence and stability of positive steady states). On one hand, most mass-action systems do not have these structural properties. On the other hand, a mass-action system may be generated by many different reaction networks, some with more complexes than initially thought. We have shown that when searching for complex-balanced realization, it is sufficient and necessary to use only the complexes that show up as exponents in the system of differential equations. Thus, whether a complex-balanced realization exists for a given mass-action system can be determined by a linear feasibility problem. Similar results hold for detailed-balanced, reversible and weakly reversible realizations.
*This is a joint work with Gheorghe Craciun and Jiaxin Jin.*

## Existence of stationary distributions for reaction networks and their approximation

Jinsu KIM
*University of California, Irvine*

One of the most challenging issues facing researchers who study biological systems is the often extraordinarily complicated structure of their interaction networks. Thus, how to characterize network structures that induce emergent phenotype (characteristic behaviors) of the system dynamics is one of the major open questions in systems biology. In the deterministic modeling regime, a number of network structural conditions have been produced, each of which characterizes a different form of stability. Conversely, there are

very few results relating the dynamics of stochastically modeled reaction networks with their associated network structure. In this talk, I will provide network conditions that imply existence of stationary distributions of the associated Markov model for reaction networks. I will also talk about once a stationary distribution exists, how to approximate it based on a model reduction under a certain system scaling and controlling a species so as to induce the existing network to have absolute concentration robustness.

## Stationary distributions and condensation in autocatalytic CRN

Linard HOESSLY
*University of Fribourg*

In this talk I will introduce autocatalytic CRN. I will then give product-form stationary distributions for this class of mostly non-weakly reversible autocatalytic reaction networks of arbitrary deficiency. Then, I provide examples of interest in statistical mechanics (inclusion process), life sciences and robotics (collective decision making in ant and robot swarms). The product-form nature of the stationary distribution then enables the study of condensation in particle systems that are generalizations of the inclusion process.
*This is joint work with Christian Mazza.*

## Endotactic reaction networks and Toric Differential Inclusions

Abhishek DESHPANDE
*University of Wisconsin - Madison*

Toric differential inclusions are known to be a useful tool for proving dynamical properties of reaction networks like persistence,permanence and global attractors. It has been shown that weakly-reversible dynamical systems can be embedded into toric differential inclusions- a key step in the proposed proof of the Global Attractor Conjecture. In this talk, we show that endotactic networks(a larger class of networks than weakly-reversible) can be embedded into toric differential inclusions.
*This is joint work with Gheorghe Craciun.*

# Short talks

Felipe Andres CAMPOS VERGARA,*University of California - San Diego*

Stefano DE PRETEIS,*Fondazione Istituto Italiano di Tecnologia*

Alvaro FLETCHER,*University of California - Irvine*

Mattia FURLAN,*Fondazione Istituto Italiano di Tecnologia*

Franco GALVAGNO,*Politecnico di Torino*

Adam HAYTOUMI,*ENSTA ParisTech*

Hyukpyo HONG,*KAIST*

Angelyn LAO,*De La Salle University*

Jinsil LEE,*University of Georgia*

Nazareno SACCHI,*Politecnico di Torino*

Roberta SIROVICH,*Università di Torino*

Daria STEPANOVA,*Centre de Recerca Matemàtica & Universitat Autònoma de Barcelona*

Chaojie YUAN,*University of Wisconsin - Madison*