SPT–CRN 2024
Book of Abstracts
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Pula, Sardinia, June 9-15, 2024

Introduction

This is a collection of Abstracts for the presentations (talks and posters) to be given at the workshop SPT–CRN in the SPT (Symmetry and Perturbation Theory) conference series. The focus of this workshop is on (chemical) reaction networks, including both deterministic and stochastic models, and also some mathematical theory that is, or is likely to become, relevant for applications to reaction networks.

The audience in this workshop is rather diverse, and its primary purpose is to present and exchange concepts and ideas. In particular, one special group of introductory and survey talks is dedicated to basic introductions to a field or to special mathematical methods. We thank the speakers in this group for their service to the community.

We hope that this meeting will be enjoyable and fruitful for all participants, and that it will facilitate new contacts and cooperations.

The organizers:

Daniele Cappelletti, Stefan Müller, Sebastian Walcher, Carsten Wiuf

Contents

Chapter 1

Introductory/Survey Talks

The Introductory/Survey Talks may be grouped into three parts:

- Deterministic reaction networks (Balazs Boros, Stefan Müller, Mate Telek)
- Stochastic reaction networks (David Anderson, Daniele Cappelletti, Ankit Gupta)
- Special mathematical methods (Armengol Gasull, Ferdinand Verhulst)

1.1 Boros, Balázs

SPT–CRN 2024

Balázs Boros
Department of Mathematics, University of Vienna, Austria

Deterministic reaction networks, part III - Dynamics

Abstract:
In this talk we focus on the *dynamic* aspects of mass-action systems. We give an overview on the local/global *stability* of equilibria, as well as on the *persistence* and *permanence* of mass-action differential equations. We devote special attention to *bifurcations* of equilibria and closed orbits in reaction networks, including fold, Andronov–Hopf, Bautin, homoclinic, and Bogdanov–Takens bifurcations. Finally, we review recent developments on the *inheritance* of equilibria, closed orbits, and bifurcations from a subnetwork.

1.2 Cappelletti, Daniele

SPT–CRN 2024

David Anderson and Daniele Cappelletti
University of Wisconsin-Madison and Politecnico di Torino

An introduction to the stochastic models of reaction networks

Abstract:
We will present a general introduction to the stochastic models for reaction networks. We plan to introduce multiple ways to understand them, including via the chemical master equation (Kolmogorov's forward equation) and the stochastic equations developed by Tom Kurtz. We will discuss connections between the stochastic models and the continuous ODE models (via the law of large numbers) and also introduce various well-known approximations such as the diffusion approximation and a central limit theorem approximation (typically called the van Kampen or linear noise approximation). Finally, we will explain some modern results related to the stability of such models (in the form of stationary distributions and conditions for exponential ergodicity).

1.3 Gasull, Armengol

SPT–CRN 2024

Armengol Gasull

Dept. de Matemàtiques, Universitat Autònoma de Barcelona and Centre de Recerca Matemàtica, Bellaterra (Barcelona) Spain

Algebraic methods for polynomial differential equations

Abstract:

Given a planar polynomial differential equation we face two questions about its phase portrait that can be studied by using algebraic tools: the knowledge of its exact number of equilibrium points and some information (upper or lower bounds) of the number of limit cycles that it can exhibit.

For the first question we recall and use the beautiful Poincaré-Miranda's theorem (a kind of Bolzano's theorem valid in any dimension). For the second one, and concerning to upper bounds, we will explain the Bendixson-Dulac theorem based on the search of the so called Dulac functions. Somehow, these functions are a generalization of the Lyapunov functions, which recall are usually used to prove non-existence of periodic orbits. Both results will be applied to concrete examples.

The results about critical points are easily extendable to higher dimensions, while the ones on limit cycles are only valid for planar differential equations.

References

[1] A. Gasull, H. Giacomini. Effectiveness of the Bendixon-Dulac theorem. J. Differential Equations, 305, 347–367. 2021.

[2] A. Gasull, V. Mañosa. Periodic orbits of discrete and continuous dynamical systems via Poincaré-Miranda theorem. Discrete Contin. Dyn. Syst. Ser. B, 25(2), 651–670. 2020.

1.4 Gupta, Ankit

SPT–CRN 2024

Ankit Gupta
Department of Biosystems Science and Engineering, ETH Zürich.

Embracing Stochastic Models to Understand Single-Cell Dynamics

Abstract:
Single-cell studies have revealed that even genetically identical cells, cultured under identical conditions, can exhibit significant heterogeneity. One of the primary sources of this variability is the inherent randomness governing the timing of reactions within intracellular networks and pathways. These stochastic effects can profoundly alter the phenotypic traits of cellular populations and give rise to novel biological functions. To effectively capture this intrinsic randomness and assess its impacts, the adoption of stochastic models becomes necessary. The objective of this presentation is to explore this paradigm and discuss certain computational challenges in analysing such models, along with potential solutions. Additionally, I will present some examples from my own research to illustrate how the analysis of stochastic models can yield interesting biological insights.

References

- Ankit Gupta and Mustafa Khammash. *Universal structural requirements for maximal robust perfect adaptation in biomolecular networks.* PNAS, **2022** vol. 119, No. 43.
- Ankit Gupta and Mustafa Khammash. *Frequency spectra and the color of cellular noise.* Nature Communications, **2022**, Vol. 13, No. 4305.
- Stephanie Aoki, Gabriele Lillacci, Ankit Gupta, Armin Baumschlager, David Schweingruber and Mustafa Khammash. *A universal biomolecular integral feedback controller for robust perfect adaptation.* Nature **2019**, Vol. 570, No. 7762.
- Corentin Briat, Ankit Gupta and Mustafa Khammash. *Antithetic Integral Feedback Ensures Robust Perfect Adaptation in Noisy Bimolecular Networks.* Cell Systems, **2016**, Vol. 2(1).

1.5 Müller, Stefan

SPT–CRN 2024

Stefan Müller
Faculty of Mathematics, University of Vienna

**Deterministic reaction networks, part I –
Existence/uniqueness of steady states**

Abstract:
Steady states of (generalized) mass-action systems are given by parametrized systems of polynomial equations (with real exponents). Here, we focus on questions of uniqueness and unique existence of positive steady states, for all rate constants and in all forward invariant sets. These questions correspond to injectivity and bijectivity of (generalized) polynomial maps. In general, injectivity is sufficient to rule out multiple steady states; for complex-balanced equilibria, uniqueness can be characterized. Analogous (but more involved) results hold for bijectivity/unique existence. In most compact form, conditions for existence/uniqueness can be expressed in terms of sign vectors of linear subspaces (oriented matroids).

1.6 Telek, Máté László

SPT–CRN 2024

Máté László Telek

Department of Mathematical Sciences, University of Copenhagen, Denmark

Deterministic reaction networks, part II -
Parameter region of multistationarity

Abstract:
In this presentation, our focus lies on a fundamental property of the ODE system that arises from a deterministic reaction network under the assumption of mass-action kinetics. Specifically, we investigate the number of positive steady states, which depends on the parameters of the reaction network. Using algebraic geometry and real algebraic geometry, several methods have been developed to provide upper bounds on the number of steady states, to identify parameter values (or open regions in the parameter space) leading to a certain number of steady states, or to describe the region where the network exhibits multiple steady states, that is, the network is multistationary. During this talk, we will review these methods, discuss their applicability, and explore potential future improvements.

1.7 Verhulst, Ferdinand

SPT–CRN 2024

Ferdinand Verhulst
Utrecht University

The basics of averaging

Abstract:
After introducing the idea of periodic averaging in systems with a small parameter we will discuss the question of what kind of differential equation admits averaging techniques. Periodic averaging will lead to results with error estimates and the part played by timescales. We will briefly discuss the multiple timescale method and its relation to averaging. Among the many extensions of the theory we will outline more general averaging results where different error estimates arise.

References

1. Ferdinand Verhulst, A Toolbox of Averaging Methods, ordinary and partial differential equations, Surveys and Tutorials in the Applied Mathematical Sciences Vol. 12 , Springer (2023).

2. J.A. Sanders, F. Verhulst and J. Murdock, Averaging Methods in Nonlinear Dynamical Systems, 2ned. Applied Mathematical Sciences Vol. 59, Springer (2007).

Chapter 2

Regular talks and contributed presentations

2.1 Baake, Ellen

SPT–CRN 2024

Ellen Baake
Bielefeld University

Genetic recombination, reaction systems, a partitioning process, and the solution of the differential equation

Abstract:
We consider the system of differential equations describing genetic recombination, which is well known to be equivalent to the law of mass action of a chemical reaction network [1,2]. It is equally well known that this nonlinear system has a dual process backward in time (see [3] for a review). This dual is a (linear) Markov chain in continuous time, which describes how an individual's genes are partitioned across its ancestors when looking back into the past. In the simple case of so-called single-crossover recombination, the semigroup of the Markov chain is known explicitly; this provides a closed solution of the recombination equation. We now go beyond single crossovers and attack the general partitioning process (and hence a more general class of reaction systems).

References
[1] S. Müller, J. Hofbauer, Genetic recombination as a chemical reaction network, Math. Model. Nat. Phenom. 10 (2015), 84–99.
[2] F. Alberti, Genetic recombination as a generalised gradient flow, Monatsh. Math. 196 (2021), 645–663.
[3] E. Baake, M. Baake, Ancestral lines under recombination, in: Probabilistic Structures in Evolution (E. Baake, A. Wakolbinger, eds.), EMS Press, Berlin, 2021, 365–382.

2.2 Bibbona, Enrico

SPT–CRN 2024

Enrico Bibbona
Politecnico di Torino

New deterministic scaling limits of models of nanoparticle growth

Abstract:

We consider the following nanoparticle growth model, where the species M rapresents monomers, and P_i are nanoparticles of size i

$$\begin{cases} mM \overset{\nu N^{1-m}}{\longrightarrow} P_m, \\ M + P_i \overset{\gamma N^{\theta}}{\to} P_{i+1}, i \in \{1, \cdots, N\} \end{cases} \tag{2.1}$$

$M(0) = N$, $P_i(0) = 0$ for all i. We demonstrate that the proportion of particles, at time $N^{\alpha}t$, with a size within the interval $N^{1-\beta}[a, b]$ (for any positive a, b), approaches a deterministic limit for large N. This is subject to the scaling conditions $\theta + \alpha + \beta = 0$ and $1 + \alpha = \beta$. We fully characterize such a scaled size distribution and establish its satisfaction, in terms of Schwartz distributions, of the Lifshitz-Slyozov transport partial differential equation (PDE). We remark that the special case $\beta = 1$ (which implies $\alpha = -1$ and $\theta = 0$) is the so-called classical scaling. In this case the convergence of the stochastoc model to an infinite system of ODEs, named after Becker and Döring, is a classical result, se e.g. [3]. Moreover, after a further coarsening step, the ODE model was shown to be well approximated by the solution of the above mentioned PDE [5,2]. We show in a single step how this PDE solution limit arise directly from the stochastic model, both under the classical scaling and in a wider rande of scalings. To prove the result we use a the framework originally developed for epidemic models in [1]. Preliminary results based on simulations alone are available at [4].
This is joint work with Daniele Cappelletti, Anderson Melchor Hernandez, Gabor Lente, Elena Sabbioni, Paola Siri, and Rebeka Szabo.

References

1. D. Cappelletti and G. A. Rempala, Individual molecules dynamics in reaction network models, SIAM Journal on Applied Dynamical Systems, 22 (2023), pp. 1344– 1382.
2. E. Hingant and R. Yvinec, Deterministic and stochastic Becker-Döring equations: Past and recent mathematical developments, in Stochastic Processes, Multiscale Modeling, and Numerical Methods for Computational Cellular Biology, Springer International Publishing, 2017, pp. 175–204.

3. I. Jeon, Existence of gelling solutions for coagulation-fragmentation equations, Communications in Mathematical Physics, 194 (1998), pp. 541–567.
4. E. Sabbioni, R. Szabó, P. Siri, D. Cappelletti, G. Lente, and E. Bibbona, Final nanoparticle size distribution under unusual parameter regimes. ChemRxiv. 2024.
5. A. Vasseur, F. Poupaud, J.-F. Collet, and T. Goudon, The Becker-Döring system and its Lifshitz–Slyozov limit, SIAM Journal on Applied Mathematics, 62 (2002), pp. 1488– 1500.

2.3 Conradi, Carsten

SPT–CRN 2024

Carsten Conradi
HTW Berlin

On the nice properties of reaction networks that admit a monomial parameterization

Abstract:
Polynomial Ordinary Differential Equations are an important tool in many areas of quantitative biology. Due to high measurement uncertainty, few experimental repetitions and a limited number of measurable components, parameters are subject to high uncertainty and can vary in large intervals. One therefore effectively has to study families of parametrized polynomial ODEs. Multistationarity and Hopf bifurcations have been recognized as important features of these ODEs. As parameter values are confined to large intervals one is generally interested in parameter conditions that guarantee multistationarity or a Hopf bifurcation and further constrain the parameter values. The focus of this talk are mass action ODEs that admit a monomial parameterization of positive steady states. For such systems it is straightforward to derive rate constants where multistationarity or Hopf bifurcations exist. To this class belong, for example, multisite phosphorylation systems, key players in intracellular signaling and regulation.

2.4 Davidovic, Andjela

SPT–CRN 2024

Andjela Davidovic
Institut Pasteur, Paris, France

Parallelized single-cell perturbation experiments: improving parameter inference for stochastic reaction networks using iterative likelihood evaluation

Abstract:

Novel microscopy technologies allow for high temporal precision observation and perturbation of gene expression on a cell-by-cell basis. These technologies have led to the generation of rich data sets and possibilities for more precise parameter inference on biological processes in individual cells.

The biochemical reactions inside single cells are inherently stochastic. They are modelled with stochastic kinetic models governed by the chemical master equation (CME). Learning parameters of these models requires solving CME which is rarely possible, hence we need to deploy methods to approximate its solution. The traditional methods to infer parameters of stochastic kinetic models from single-cell longitudinal data have generally been developed under the assumption that experimental data is sparse. Using them on datasets with many measurement time points for each cell may lead to a large computational cost.

As an alternative, we propose an iterative likelihood evaluation method that approximates likelihoods by factorizing the full likelihoods into transition probabilities between subsequent measurement times. The key idea is to use CME approximations, e.g. the Linear Noise Approximation (LNA) to approximate transition probabilities, and Kalman Filtering (KF) to approximate the full likelihood of each measured cell trajectory.

The iterative methods are particularly suited to the new experimental setups, allowing for frequent, automated measurements that can provide detailed insights into cellular dynamics. We demonstrate that with such data the iterative method yields accurate parameter estimates. Using simulated data, we demonstrate the computational advantage of the iterative method over an open loop use of the LNA.

Finally, we perform single-cell experiments to characterise a light-inducible gene expression system. Thanks to the computational efficiency of our method, we are able to study how much information about model parameters can be gained by exposing different cells in the experiment to different temporal light sequences compared to an experiment in which all cells are exposed to the same light sequence.

Overall, we illustrate how integrating modern microscopy techniques with sophisticated computational approaches can significantly improve our ability to model and understand complex biological systems at the single-cell level.

References

1. Davidović A, Chait R, Batt G, Ruess J. Parameter inference for stochastic biochemical models from perturbation experiments parallelised at the single cell level. PLoS computational biology. 2022 Mar 18;18(3):e1009950.

2.5 De Leenheer, Patrick

SPT–CRN 2024

Patrick De Leenheer
Department of Mathematics, Oregon State University, USA

The many proofs of the reduction phenomenon

Abstract:
In this talk we consider several proofs, old and new, of the reduction phenomenon. Many mathematical models of biological systems that incorporate dispersal and reproduction exhibit the phenomenon that increased dispersal reduces overall growth. Karlin first proved this for basic, parameterized linear discrete-time models in 1975, and many other proofs have been discovered since then. We review some of these proofs, indicate how they are connected and also provide streamlined, novel proofs of this celebrated biological principle.
This is joint work with Lee Altenberg (University of Hawaii) and Jordan McCaslin (Oregon State University).

2.6 Erban, Radek

SPT–CRN 2024

Radek Erban
University of Oxford

Limit cycles, noise control and systematic design of reaction networks

Abstract:

Two types of mathematical models of chemical reaction systems will be considered: (i) deterministic models which are written in terms of reaction rate equations (i.e. ordinary differential equations (ODEs) for concentrations of chemical species involved); and (ii) stochastic models of reaction networks, given in terms of the Gillespie stochastic simulation algorithm, which provides more detailed information about the simulated system than ODEs. I will discuss methods for systematic design of relatively simple reaction systems with exotic dynamical behaviour, including applications to synthetic biology and DNA computing. I will present examples of reaction systems with multiple oscillating solutions or systems whose deterministic models (based on reaction rate equations) undergo specific bifurcations. Since reaction networks in biological applications often involve species at low-copy numbers, a successful network design requires controlling the intrinsic noise in the system. I will discuss reaction networks where stochastic effects are important for understanding the system dynamics, including reaction systems with noise-induced oscillations and multistability.

References

[1] R.Erban and H.W.Kang, Bulletin of Mathematical Biology **85**, 76 (2023)

[2] R.Erban and S.J.Chapman,"Stochastic Modelling of Reaction-Diffusion Processes", Cambridge University Press (2020)

2.7 Fellner, Klemens

SPT–CRN 2024

Klemens Fellner
University of Graz

From Becker-Döring to oscillatory behaviour in prion dynamics.

Abstract:
Prions are able to self-propagate biological information through the transfer of structural information from a misfolded/infectious protein in a prion state to a protein in a non-prion state. Prions cause diseases like Creuzfeldt-Jakob. Prion-like mechanisms are associated to Alzheimer, Parkinson ans Huntington diseases. We present a fundamental bi-monomeric, nonlinear Becker-Döring type model, which aims to explain experiments in the lab of Human Rezaei showing sustained oscillatory behaviour over multiple hours, [1]. Besides two types of monomers, our model suggests a nonlinear depolymerisation process as crucial for the oscillatory behaviour. Since then, experimental evidence seems to confirm this process. We provide details on the mechanism of oscillatory behaviour and show numerical simulations.

References

[1] M. Doumic, K. Fellner, M. Mezache, H. Rezaei, A bi-monomeric nonlinear Becker-Döring type system to capture oscillatory aggregation kinetics in prion dynamics, *Journal of Theoretical Biology*, **480** (2019) 241–261.

2.8 Hofbauer, Josef

SPT–CRN 2024

Josef Hofbauer
University of Vienna

Mass action systems with many limit cycles

Abstract:
How many stable limit cycles can a bimolecular n species mass action systems have?

2.9 Hong, Hyukpyo

SPT–CRN 2024

Hyukpyo Hong
Department of Mathematics, University of Wisconsin–Madison

Network translation allows for revealing long-term dynamics of stochastic reaction networks

Abstract:
Long-term behaviors of biochemical systems are described by steady states in deterministic models and stationary distributions in stochastic models. Their analytic solutions can be obtained for limited cases, such as linear or finite-state systems. Interestingly, analytic solutions can be easily obtained when underlying networks have special topologies, called weak reversibility (WR) and zero deficiency (ZD). However, such desired topological conditions do not hold for the majority of cases. Thus, we propose a method of translating networks to have WR and ZD while preserving the original dynamics was proposed. Additionally, we prove necessary conditions for having WR and ZD after translation. Our method provides a valuable tool for analyzing and understanding the long-term behavior of biochemical systems, and we demonstrate its efficacy with several examples.

References
1. H Hong, J Kim, MA Al-Radhawi, ED Sontag, and JK Kim, *Commun. Biol.* (2021) https://doi.org/10.1038/s42003-021-02117-x
2. H Hong, BS Hernandez, J Kim, and JK Kim, *SIAM J Appl. Math* (2023) https://doi.org/10.1137/22M150469X

2.10 Joshi, Badal

SPT–CRN 2024

Badal Joshi
California State University San Marcos

Chemical mass-action systems as analog computers: implementing arithmetic computations at specified speed

Abstract:
The broad goal of the nascent field of chemistry-based computation is to implement computation in a wet cellular environment using the available materials inside a cell. Recent technological advances, such as DNA-strand displacement, enable implementing arbitrary nonlinear chemical reaction networks in a cell. This allows us to view chemical mass-action systems as a programming language for analog computation. The inputs to the computation are encoded as initial values of certain chemical species and the outputs are the limiting values of other chemical species.

There are numerous works that design reaction networks that carry out basic arithmetic. However, in general, these constructions have not accounted for speed of computation (i.e. the rate of convergence). This often results in computational speed depending on the inputs to the computation, making it unusably slow. In this talk, I will discuss how we designed a full suite of "elementary" chemical systems that carry out arithmetic computations (such as inversion, addition, roots, multiplication, rectified subtraction, absolute difference, etc.) over the real numbers, and that have speeds of computation that are independent of the inputs to the computations. Moreover, we proved that finite sequences of such elementary modules, running in parallel, can carry out composite arithmetic over real numbers, also at a rate that is independent of inputs. I will close with a number of open questions and directions for future work. This is all joint work with David Anderson.

References:

- David F. Anderson, and Badal Joshi. Chemical mass-action systems as analog computers: implementing arithmetic computations at specified speed (preprint on arXiv).
- David F. Anderson, Badal Joshi, and Abhishek Deshpande. On reaction network implementations of neural networks, *Journal of Royal Society Interface*, Vol. 18, Issue 177, (April 2021).

2.11 Kim, Jinsu

SPT–CRN 2024

Jinsu Kim
Department of Mathematics, POSTECH, Korea

Rare events-driven stability of stochastic chemical reaction systems

Abstract:
Continuous-time Markov chains are typically used to model the copy numbers of interacting chemical species in stochastically modeled reaction systems. Their stability is up to the convergence of the probability distribution to a stationary distribution. This convergence is often derived using the existence of strong drift of the Markov chain towards a compact set in the state space, which implies positive recurrence. However, for stochastic reaction systems, the existence of desired drift conditions is often uncertain especially at the boundary of the state space. In this paper, we show that rather than the strong drifts, rare events corresponding to reactions that may not likely fire can yield stability of the Markov chains.

2.12 Kim, Minjoon

SPT–CRN 2024

Minjoon Kim
Postech, Korea

A path method for stochastic reaction systems

Abstract:
We present criteria for non-exponential ergodicity of continuous-time Markov chains on a countable state space. These criteria can be verified by examining the ratio of transition rates over certain paths. We applied this path method to explore the non-exponential convergence of microscopic biochemical interacting systems. Using reaction network descriptions, we identified special architectures of biochemical systems for non-exponential ergodicity. In essence, we found that reactions forming a cycle in the reaction network can induce non-exponential ergodicity when they significantly dominate other reactions across infinitely many regions of the state space. Interestingly, special architectures allowed us to construct many detailed balanced and complex balanced biochemical systems that are non-exponentially ergodic. Some of these models are low-dimensional bimolecular systems with few reactions. Thus this work suggests the possibility of discovering or synthesizing stochastic systems arising in biochemistry that possess either detailed balancing or complex balancing and slowly converges to their stationary distribution.

2.13 Laurence, Lucie

SPT–CRN 2024

Lucie Laurence
INRIA Paris

A Scaling analysis of k-Unary networks

Abstract:
A class of CRNs, defined as k-Unary networks, is investigated. These CRNs have m chemical species and a complexe is either $\emptyset$ or of the form $k_i S_i$, $k_i \geq 1$ for $1 \leq i \leq m$. We analyze a stochastic model of such a CRN via the scaling properties of its associated Markov process $(X_i^N(t))$. For this scaling, input rates are assumed to be large: For $1 \leq i \leq m$, the rate of the reaction $\emptyset \to k_i S_i$ is $\kappa_i N$ for some $\kappa_i \geq 0$, where N is a large parameter.

With a convenient definition of the convergence in distribution, the main result is that, under appropriate conditions, the sequence of processes $(X_i^N(t))$ conveniently rescaled converges to a limiting deterministic dynamical system. The proof of this theorem relies on stochastic calculus, a careful analysis of the hierarchy of the timescales of the CRN, and entropy methods. Several extensions of this result are discussed.

2.14 Liebermeister, Wolfram

SPT–CRN 2024

Wolfram Liebermeister
Université Paris-Saclay, INRAE, MaIAGE, 78350 Jouy-en-Josas, France

Optimal enzyme rhythms in cells

Abstract:
Cells can use periodic enzyme activities to adapt to periodic environments or existing internal rhythms and to establish metabolic cycles that schedule biochemical processes in time. A periodically changing allocation of the protein budget between reactions or pathways may increase the overall metabolic efficiency. To study this hypothesis, I quantify the possible benefits of small-amplitude enzyme rhythms in kinetic models. Starting from an enzyme-optimised steady state, I score the effects of possible enzyme rhythms on a metabolic objective and optimise their amplitudes and phase shifts. Assuming small-amplitude rhythms around an optimal reference state, optimal phases and amplitudes can be computed by solving a quadratic optimality problem. In models without amplitude constraints, general periodic enzyme profiles can be obtained by Fourier synthesis. The theory of optimal enzyme rhythms combines the dynamics and economics of metabolic systems and explains how optimal small-amplitude enzyme profiles are shaped by network structure, kinetics, external rhythms, and the metabolic objective. The formulae show how orchestrated enzyme rhythms can exploit synergy effects to improve metabolic performance and that optimal enzyme profiles are not simply adapted to existing metabolic rhythms, but that they actively shape these rhythms to improve their own (and other enzymes') efficiency. The theory yields optimality conditions for enzyme rhythms in metabolic cycles, with static enzyme adaptation as a special case, and predicts how cells should combine transcriptional and posttranslational regulation to realise enzyme rhythms at different frequencies.

References

Optimal enzyme rhythms in cells, Liebermeister W. (2016/2022), arXiv:1602.05167

2.15 Llibre, Jaume

SPT–CRN 2024

Jaume Llibre
Universitat Autònoma de Barcelona

How to compute analytically the periodic orbits of a differential system

Abstract:
Since the periodic orbits of a differential system are not local objects, they are not easy to compute. Usually they are computed numerically. Here we shall show, under convenient assumptions, how to compute a number of periodic orbits analytically using the averaging theory. We shall present some general results and their applications.

References

[1] A. Buica, J. Llibre, Averaging methods for finding periodic orbits via Brouwer degree, Bulletin des Sciences Mathemàtiques 128 (2004), 7–22.

[2] J. Llibre, D.D. Novaes, M.A. Teixeira, Higher order averaging theory for finding periodic solutions via Brouwer degree, Nonlinearity 27 (2014), 563–583.

[3] J. Llibre, R. Moeckel, C. Simó, Central configurations, periodic orbits and Hamiltonian systems, Advances Courses in Math., CRM Barcelona, Birhauser, 2015.

2.16 Pietri, Mélanie

SPT–CRN 2024

Mélanie Pietri
ENS Paris-Saclay, Université Paris-Saclay

Modeling microalgae growth: translating Monod and logistic ODEs to a BioCRN

Abstract:
Microalgae are highly considered as a promising source for biofuel production. They are photosynthetic microorganisms which convert light into chemical energy while using carbon dioxide. Under stress, they produce significant amount of intracellular lipids, which can be extracted for biofuel. However, optimizing the industrial process is required, particularly controlling growth by adjusting parameters like temperature, CO_2 rate, light intensity, and concentration in nutrients in cell medium.
Many growth models, including mechanistic ones using Ordinary Differential Equations (ODEs), have been extensively investigated for cell cultures. These models describe cell concentration over time under limited resource availability. However, complexity increases with additional parameters to consider multiple resources, making it challenging to interpret their influence on cell growth across different scales (from microscopic scale to macroscopic one).
We propose a multi-resource Bio-Chemical Reaction Network (BioCRN) model for microalgae growth. BioCRN describes the kinetics of bio-chemical species via basic reactions. Our growth model quantifies the impact of two main resources (light and nutrient concentration in cell medium) via reactions between microalgal cells and resources. From the BioCRN we then derive a combined Verhulst-Monod type ODE model by separation of timescale, allowing us to link the ODE parameters to the underlying reactions and shedding light on the structure of multi-resource growth models.

2.17 Plesa, Tomislav

SPT–CRN 2024

Tomislav Plesa
University of Cambridge

Mapping dynamical into chemical systems

Abstract:
In this talk, I will discuss mathematical methods for systematic design of chemical and biological systems with prescribed behaviors [1,2,3,4]. Focus will be placed on chemical reaction networks under mass-action kinetics whose dynamics is described with ordinary-differential equations with polynomial right-hand sides. I will present certain maps, called *chemical maps* [4], that systematically transform general dynamical systems into chemical systems, while preserving desired dynamical features. Using this approach, relatively simple chemical systems will be designed which display exotic dynamical features, such as arbitrary many limit cycles and chaos.

References

[1] Plesa, T., Vejchodský, T., and Erban, R., 2016. Chemical reaction systems with a homoclinic bifurcation: An inverse problem. *Journal of Mathematical Chemistry*, **54**(**10**): 1884–1915.

[2] Plesa, T., Vejchodský, T., and Erban, R, 2017. Test models for statistical inference: Two-dimensional reaction systems displaying limit cycle bifurcations and bistability, 2017. *Stochastic Dynamical Systems, Multiscale Modeling, Asymptotics and Numerical Methods for Computational Cellular Biology.*

[3] Plesa, T., Dack, A., and Ouldridge, T. E., 2023. Integral feedback in synthetic biology: Negative-equilibrium catastrophe. *Journal of Mathematical Chemistry*, **61**: 1980–2018.

[4] Plesa, T., 2024. Mapping dynamical into chemical systems. In preparation.

2.18 Popovic, Lea

SPT–CRN 2024

Lea Popovic
Concordia University, Montreal, Canada

Asymmetric (and spatial) autocatalytic reactions

Abstract:
The study of auto-catalytic reaction networks behaviour requires a stochastic analysis when the overall reactant counts are low. Assuming there is an inflow and an outflow of each species into the system, its dynamics oscillate between patterns of either scarcity or abundance of some of its reactants (Discreteness Induced Transitions, or DIT), which deterministic models based on ODEs fail to capture. We are interested in studying the long-term behaviour of such systems, which due to the inflows and outflows are shown to be ergodic with a unique stationary distribution [BKW20]. For stochastic reaction models with symmetry in autocatalytic parameters ellegant exact formulae of [BKW20] capture the long-term behaviour of this model, showing a phase transition to DIT behaviour when the average overall reactant count is low. We use a connection with a model from population genetic to provide an approximate stationary distribution for the case of asymmetric autocatalytic parameters, and confirm the existance of the same phase transition to DIT behaviour. We explore the implications of using spatial population genetic models to describe the behaviour of spatially heterogeneous systems.

References [BKW20]] J. Kim, E. Bibbona, and C. Wiuf. Stationary distributions of systems with discreteness-induced transitions. *J. R. Soc. Interface*, 17, 2020.

2.19 Renger, Michiel

SPT–CRN 2024

Michiel Renger
Technische Universität München

Hidden Hamiltonian Systems in Chemical Reaction Networks

Abstract:
By Onsager-Machlup theory, if a reaction network is in detailed balance then and only then the reaction rate equation (RRE) is a gradient flow, dissipating entropy while evolving towards the steady state. It turns out that without detailed balance, the RRE can be written as a combination of a gradient flow with a Hamiltonian system. These hidden Hamiltonian systems reveal themselves only after completely shutting down the entropic/gradient flow effects.

We have only been able to identify the Hamiltonian system for a few simple networks, and it is not completely understood why they appear. However, numerics show periodic orbits for *any* network in complex balance, suggesting an underlying Hamiltonian system.

References

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D.R.M. Renger. Macroscopic Fluctuation Theory versus large-deviation-induced GENERIC. arXiv preprint 2402.04092v1, 2024.

2.20 Rink, Bob

SPT–CRN 2024

Bob Rink
Vrije Universiteit Amsterdam

Computing multiple timescale dynamics in nonstandard slow-fast systems and nonplanar coupled oscillator networks

Abstract:
I will present a new asymptotic method for computing invariant manifolds in slow-fast systems and coupled oscillator networks. This method works by calculating an asymptotic expansion for an embedding of a persisting normally hyperbolic manifold as well as the dynamics on it. This allows us to discover hidden timescales in slow-fast systems beyond the standard form. Similarly, we can use the method to find high-order phase reductions for weakly coupled periodic systems that do not consist of simple planar limit cycles. I will illustrate the method by predicting hidden timescales and remote synchronization in a few examples.

This is joint work with Ian Lizarraga, Eddie Nijholt, Soeren von der Gracht, and Martin Wechselberger.

References

Ian Lizarraga, Bob Rink and Martin Wechselberger, *Multiple timescales and the parametrisation method in geometric singular perturbation theory*, Nonlinearity 34, no. 6 (2021), 4163-4201.

Sören von der Gracht, Eddie Nijholt and Bob Rink, *A parametrisation method for high-order phase reduction in coupled oscillator networks*, arXiv 2306.03320.

2.21 Schnell, Santiago

SPT–CRN 2024

Santiago Schnell

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Experimental uncertainty in enzyme kinetics: An ill-posed problems and experimental bias

Abstract:
Enzymes are nature's workhorses, accelerating vital cellular reactions. Understanding their kinetic properties, often quantified by the Michaelis constant (K_M), is fundamental to biochemistry and drug discovery. However, our recent meta-analysis revealed surprisingly high experimental uncertainty in K_M measurements, with an average error reaching up to 10.8-fold. This talk delves into the potential reasons behind this substantial variability. We propose two key culprits: inherent limitations in the underlying mathematical framework (potentially ill-posed for certain enzyme systems) that may be overlooked by experimentalists, and biases introduced during experimental design and data analysis practices. We will explore the challenges posed by these factors and discuss opportunities for mathematical scientists to improve the reliability and robustness of enzyme kinetics studies.

References

J. Eilertsen, S. Schnell, S. Walcher (2023). Natural parameter conditions for singular perturbations of chemical and biochemical reaction networks. *Bulletin of Mathematical Biology* **85**, 48.

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P. Halling, P. Fitzpatrick, F. M. Raushel, J. Rohwer, S. Schnell, U. Wittig, R. Wohlgemuth and C. Kettner (2018). An empirical analysis of enzyme function reporting for experimental reproducibility: missing/incomplete information in published papers. *Biophysical Chemistry* **242**, 22–27.

2.22 Sontag, Eduardo

SPT–CRN 2024

Eduardo D. Sontag
Northeastern University

Flow-dependent Lyapunov functions and contraction analysis

Abstract:
In this talk, we will discuss an approach that we have developed, in joint work with M. Ali Al-Radhawi and David Angeli, to understand the dynamics of biological interaction networks. This approach is based on "flow-dependent Lyapunov functions" which depend on state variables only through flows among variables, and more specifically through reaction rates. They can be equivalently defined as common Lyapunov functions for finite families of linear systems, which leads to an effective computational package. We will illustrate the the power of the approach in establishing stability and ensuring safety constraints in several biological applications, and explore implications to contraction analysis.

References
Please see *http://www.sontaglab.org/publications.html* for preprints of this and related work.

2.23 Stadler, Peter F.

SPT–CRN 2024

Peter F. Stadler
Universität Leipzig

Autocatalysis and Unstable Cores in Parameter-Rich CRNs

Abstract:
Parameter-rich CRNs are built upon kinetic laws that have sufficient flexibility to allow the independent choice of fixed-point coordinates and the absolute numerical values of the non-zero entries of the Jacobian. Although this seems to be a tall order, Michaelis-Menten and generalized mass action kinetics are of this type. In this setting, the existence of choices of parameters that make a given inner fixed point Hurwitz unstable is determined entirely by the stoichiometric matrix. More precisely, the existence of certain quadratic sub-matrices is sufficient. We call these unstable cores. Autocatalytic cores (in the sense of Nghe) turn out to be unstable cores that have the special structure of Metzler matrices. Autocatalysis, therefore can always act as source of instability given suitable choices of parameters, but there are also other causes of dynamic instability, entirely unrelated to autocatalysis.
This is joint work with Nicola Vassena.

References

Vassena N, Stadler PF. Unstable cores are the source of instability in chemical reaction networks. *Proc. Roy. Soc. A.* **480**: 20230694 (2024).

2.24 Tang, Quoc Bao

SPT–CRN 2024

Bao Quoc Tang
University of Graz

Chemical reaction-diffusion systems with boundary equilibria

Abstract:
In this talk, we discuss the large time behaviour of reaction-diffusion systems modelling complex balanced chemical reaction networks possessing boundary equilibria. In the most generality, this involves the Global Attractor Conjecture, which is (allegedly) not fully proved even in the ODE setting. In the PDE setting, the difficult is amplified by the low regularity of renormalised solutions, the seemingly only global solution concept available for higher order chemical reaction-diffusion systems. We approach this problem using the so-called entropy method, which has been well developed for the case without boundary equilibria. Our main idea is to show that if even a trajectory would converge to a boundary equilibrium, this convergence would be so slow that the attraction towards the positive equilibrium becomes dominant, leading eventually to the global convergence towards the latter.

References

1 Laurent Desvillettes, Klemens Fellner, and Bao Quoc Tang. *Trend to equilibrium for reaction-diffusion systems arising from complex balanced chemical reaction networks.* SIAM Journal on Mathematical Analysis 49.4 (2017): 2666-2709.

2 Klemens Fellner, and Bao Quoc Tang. *Convergence to equilibrium of renormalised solutions to nonlinear chemical reaction–diffusion systems.* Zeitschrift für angewandte Mathematik und Physik 69 (2018): 1-30.

2.25 Tonello, Elisa

SPT–CRN 2024

Elisa Tonello
Freie Universität Berlin

Structure and dynamics of discrete interaction networks: some recent trends

Abstract:
Discrete interaction networks, and in particular Boolean networks, offer a qualitative modeling framework that complements continuous approaches. We will first revisit the definitions of the main graph structures central to the analysis of these networks, exploring various interpretations of associated dynamics through illustrative examples. We will then provide an overview of some current research topics, in particular around the characterization of asymptotic behaviour and its relationship to the interaction structure. We will discuss some theoretical results as well as some advancements in applied problems such as network control and marker detection. We will briefly explore how these topics intersect with the popular areas of network reduction and modularity.

2.26 Yu, Polly

SPT–CRN 2024

Polly Yu
Harvard University; University of Illinois Urbana-Champaign

A necessary condition for non-monotonic dose response

Abstract:

Steady state non-monotonic ("biphasic") dose responses are often observed in experimental biology, which raises the question of which network motifs might underlie such behaviours. It is well known that the presence of an incoherent feedforward loop (IFFL) may give rise to a non-monotonic response, and it has been informally conjectured that this condition is also necessary. However, this conjecture has been disproved with an example of a system in which the input and output nodes are the same. We show that a version of the converse implication does hold. Towards this aim, we consider several related notions (infinitesimal homeostasis, biphasic response, and stable biphasic response) and their underlying network motifs. (Joint work with Eduardo Sontag.)