Parallel Session

Mathematical Methods in Biology VI

PARAMETER ESTIMATION IN MODELS OF BIOLOGICAL OSCILLATORS: DEALING WITH MULTIMODALITY AND OVERFITTING

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Keywords: Parameter estimation, Regularisation, Optimisation, Multimodality, Overfitting.

Biological oscillators play a central role in many key processes, including: the cell cycle, metabolism, signalling, and circadian rhythms. When considering models of biological oscillators described by deterministic non-linear ordinary differential equations (ODEs), the parameter estimation problem can be extremely challenging. Typically, models of biological oscillators are highly non-linear and flexible, exhibiting a wide variety of different dynamics.

These characteristics can cause the exacerbation of two common pitfalls in parameter estimation: multimodality and over-fitting [1]. Multimodality describes the existence of both local and global solutions for the estimation problem. Overfitting is the fitting of the noise in the data, as opposed to the signal. Overfit models explain the data very well but do not have good predictive power. A consequence of multimodality is that standard estimation methods (such as gradient-based local ones) often lead to wrong solutions (underfit local solutions). On the other extreme, global optimisation methods can produce overfit solutions. Overfitting can be a particularly difficult phenomenon to deal with, due to its deceiving nature; overfitting produces extremely high quality fits but with poor predictive power (i.e. the calibrated model does not generalise well). Another issue that adds complexity to the estimation task is the typically large size of the parameter space considered. A lack of prior knowledge results in a huge search space, which considerably increases the complexity of the parameter estimation problem.

While techniques do exist to deal with these problems individually, there are a number of open questions, and such techniques typically require some degree of manual tuning by users. Here, we present a systematic strategy to deal with the aforementioned issues of multimodality, overfitting and large search spaces. This strategy is self-tuning, i.e. it does not require the user to adapt parameters of the algorithm. We make use of efficient global optimisation solvers to avoid convergence to local solutions. Combining these global optimisation solvers with sampling strategies, we systematically reduce the size of the parameter search space

using bounding techniques. We use advanced regularisation techniques to combat overfitting, expanding on the methods discussed in [2]. We avoid the typical regularisation tuning issues by using our sampling strategies to automatically adjust the regularisation parameters. We apply our novel method to a number of challenging biological oscillators, including the well known Goodwin oscillator and the repressilator. We show how our strategy allows for more efficient estimations, avoiding the underfitting and overfitting pitfalls. By using cross-validation, we also show how the use of regularisation allows for calibrated models with greater predictive power.

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SINGLE MOLECULE SWITCHES AND OSCILLATORS

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Keywords: Oscillation, Feedback loops, Bifurcations, Networks.

Switch-like and oscillatory dynamical systems are widely observed in biology. We investigate the simplest biological switch that is composed of a single molecule that can be autocatalytically converted between two opposing activity forms. We test how this simple network can keep its switching behaviour under perturbations in the system. We show that this molecule can work as a robust bistable system, even for alterations in the reactions that drive the switching between various conformations. We propose that this single molecule system could work as a primitive biological sensor and show by steady state analysis of a mathematical model of the system that it could switch between possible states for changes in environmental signals. Particularly, we show that a single molecule phosphorylation-dephosphorylation switch could work as a nucleotide or energy sensor. We also notice that a given set of reductions in the reaction network can lead to the emergence of oscillatory behaviour. We propose that evolution could have converted this switch into a single molecule oscillator, which could have been used as a primitive timekeeper. We discuss how the structure of the simplest known circadian clock regulatory system, found in cyanobacteria, resembles the proposed single molecule oscillator. Besides, we speculate if such minimal systems could have existed in an RNA world.

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GEOMETRIC SINGULAR PERTURBATION ANALYSIS OF SPIKY OSCILLATIONS IN A MINIMAL $NF-\kappa B$ SIGNALING MODEL

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Keywords: Slow-fast systems, $NF-\kappa B$ signaling, Cell biology, Geometric singular perturbation analysis, Oscillations.

Dynamical systems theory provides a powerful framework for understanding models of oscillatory processes arising in cell biology. In this talk I will demonstrate how geometric singular perturbation theory can be used to understand spiky oscillations in a minimal $NF-\kappa B$ signalling pathway model developed in [1].

The four model variables change on different time scales, however, the governing equations are not written in standard form of slow-fast systems. Hence, standard reduction to a globally defined slow manifold is not possible. We use scaling and the blow-up method to identify several limiting subsystems. Based on this geometric decomposition we are able to prove the existence of a limit cycle and explain the pattern of the observed spiky oscillations.

Acknowledgements: This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 661650.

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NOISE CONTROL AND MIXING IN DESIGNING REACTION NETWORKS

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Keywords: Chemical reaction networks, Stochastic dynamics, Molecular computing.

Synthetic biology is an interdisciplinary field of science and engineering that aims to construct biochemical circuits with prescribed behavior. With the advancements in nucleic-acid-based chemistry, arbitrary molecular circuits can be experimentally implemented using solely DNA molecules, interacting via toehold-mediated DNA strand-displacement mechanism [1]. Mathematical and experimental methods for designing abstract biochemical circuits, and then physically realizing them, respectively, have been established for circuits involving molecules in *high-abundance* and operating in well-mixed environments. A proof-of-concept is a recently in-vitro man-made chemical oscillator, called the displacillator [2]. Interfacing the synthetic systems with living organisms and exploiting their potential in nanotechnology is more challenging both experimentally and mathematically, since the synthetic systems involve molecular species in *low-abundance*. In this talk, I will present the much needed mathematical methods for designing synthetic molecular circuits, which perform the desired tasks even when large fluctuations are present. The presented framework is based on the so-called *noise-approximation algorithm* [3], which may be used to control fluctuations in the circuits in a state-dependent manner, while preserving the desired mean-field behavior, and *noise-induced mixing* - a design principle inspired by gene-regulatory networks, which allows different stochastic behaviors to be fused together [4].

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SUCCESS OF OSCILLATIONS IN NEGATIVE FEEDBACK GENE REGULATORY NETWORKS IS DETERMINED BY DEGRADATION RATE UNIFORMITY

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Keywords: Gene Regulatory Networks, Dynamical systems, Oscillations.

Negative feedback biochemical circuits, also called ring oscillators, are capable of sustained oscillations. But what makes a ring oscillator successful? The non-linear interactions, and the particular choice of interactions for each different system impede analytical insight into this question, usually requiring computational exploration [1,2]. In this talk, we will see that, despite the apparent complexity, the stability of the unique steady state undergoing a Hopf bifurcation in a ring oscillator depends only on the degradation rates and a single parameter summarising the rest of the interactions [3]. This allows us to study the role of degradation rates separately from the rest of biological details of the circuit, showing that the parameter region with oscillatory behaviour is maximised when the degradation rates of all the biochemical species are equal. Strikingly, this results holds independently of the regulatory functions used or number of genes. Similarly, the same analysis allows to derive expressions for the oscillation frequency at the bifurcation point and its nature (subcritical or supercritical). Finally, we apply the results to the case in which mRNA is included in the description of a genetic ring oscillator, exploring the role of the natural difference in degradation timescale between mRNA and protein.

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DESIGNING REACTION NETWORKS WITH A GIVEN STATIONARY DISTRIBUTION

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Keywords: Stationary distribution, Reaction network design, Stochastic models for biochemistry.

I will introduce stochastic reaction networks as models for the time evolution of biological system with low chemical species counts. Then, I will talk about some recent investigation on the potentiality of stochastic reaction networks, that my collaboratora and I are carrying on. The possibility of physically implement a given reaction network by means of DNA strands [1] opened new questions and new challenges in the field. Can we design and construct stochastic reaction networks capable of performing a specific task? Is there some limitation? In this talk, I will focus on the design of stochastic reaction networks that in a stationary regime are capable of simulating a given probability distribution. I will show that any probability distribution can be approximated with arbitrary precision by the stationary distribution of an appropriate stochastic reaction. Moreover, the stochastic reaction network can be designed such that the approximation is robust to occasional external inputs.

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