MINISYMPOSIUM

MULTI-SCALE MODELING AND SIMULATIONS OF STOCHASTIC SYSTEMS IN BIOLOGY

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Biological systems consist of a large number of species with reactions which occur in multiple spatio-temporal scales. Because performing stochastic simulations of such systems are computationally expensive and prohibitive, various strategies to reduce the computational cost have been investigated, e.g. quasi-state-state approximation of chemical master equation or hybrid methods. Also it is of interest how the interaction between different scales, e.g. between cellular and tissue scales, affects noise at the single cell level. In this mini-symposium, the focus will be on recent research reporting on advances in this area. In the first talk, a general description of the multi-scale properties of biochemical reaction networks will be presented as well as to how to use the quasi-steady state approximation to simplify the stochastic system. In the second talk, an adaptive hybrid simulation method will be presented, which greatly accelerates the stochastic simulations of multi-scale chemical reaction networks. In the third talk, a mesoscopic-microscpoic hybrid method will be described, which allows the efficient simulation of stochastic spatio-temporal dynamics of chemical reactions. In the fourth talk, a multi-level Monte Carlo algorithm will be presented, which allows for estimating summary statistics to characterise biochemical reaction networks. In the final talk, new research will be presented linking noise dynamics at two different spatial scales, in particular showing how the tissue level noise affects noise at the single cell level.

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REDUCTION OF MULTISCALE STOCHASTIC BIOCHEMICAL REACTION NETWORKS

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Keywords: Multiscale stochsatic system, Biochemical reaction network, Quasi-steady-state approximation, Feedforward network, Complex balanced network.

Biochemical reaction networks (BRNs) in a cell frequently consist of reactions with disparate timescales. The stochastic simulations of such multiscale BRNs are prohibitively slow due to high computational cost for the simulations of fast reactions. One way to resolve this problem uses the fact that fast species regulated by fast reactions quickly equilibrate to their stationary distribution while slow species are unlikely to be changed. Thus, on a slow timescale, fast species can be replaced by their quasi-steady state (QSS): their stationary conditional expectation values for given slow species. As the QSS are determined solely by the state of slow species, such replacement leads to a reduced model, where fast species are eliminated. However, it is challenging to derive the QSS in the presence of nonlinear reactions. In this talk, I will describe under which condition such stochastic QSS can be accurately approximated by a deterministically derived QSS (e.g. Michaeils-Menten equation), which allows to use the non-elementary functions for the propensity functions of the Gillespie algorithm. Furthermore, I will also present two classes of multiscale BRNs which can be reduced by deriving an exact stochastic QSS rather than approximations: a feedforward network or a complex balanced network.

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ADAPTIVE HYBRID SIMULATION AND SENSITIVITY ESTIMATION FOR MULTISCALE STOCHASTIC REACTION NETWORKS

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Keywords: Multiscale networks, Model reductions, Piecewise deterministic Markov processes, Sensitivity analysis.

Stochastic reaction networks are commonly used to understand the role of intracellular noise in Systems Biology. For these models, the probability distribution of the state-vector evolves according to the Chemical Master Equation (CME), whose solutions are often required to be estimated by Monte Carlo methods such as Gillespie's Stochastic Simulation Algorithm (SSA). Such simulations become impractical for multiscale networks that are characterised by wide variations in reaction timescales as well as copy-number scales of various species. To deal with this problem, hybrid simulation approaches have been developed that approximate the dynamics with a suitably constructed Piecewise Deterministic Markov process (PDMP) which is computationally easier to simulate and analyze. In my talk, I will describe how this PDMP construction can be automated and how we can adapt this construction during the simulation-run to improve the computational performance and the accuracy of the estimated CME solution (see [1]). I will also discuss how these PDMP approximations can be exploited for the purpose of estimating the parameter sensitivities for multiscale stochastic reaction networks.

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MESOSCOPIC-MICROSCOPIC SPATIAL STOCHASTIC SIMULATION WITH AUTOMATIC SYSTEM PARTITIONING

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Keywords: Stochastic, Reaction diffusion.

The reaction-diffusion master equation (RDME) is an on-lattice mesoscopic model that allows for efficient simulation of spatially resolved stochastic chemical kinetics. It can be orders of magnitude faster than off-lattice, hard-sphere microscale simulations, if the lattice spacing can be chosen coarse enough. This is not always the case though, and some systems demand a high spatial resolution for acceptable resolution of the dynamics of the system, even on long time scales. However, different reactions in the same model often require different degrees of mesh resolution, and a model may need to be simulated on a very fine mesh because of only a few reactions demanding a high spatial resolution. This can make the RDME inefficient for systems with multiscale properties. Mesoscopic-microscopic hybrid methods address this problem by resolving the most challenging reactions with a microscale, off-lattice simulation, while simulating most of the system with a much coarser mesoscale, on-lattice simulation. Previously such methods have required the modeler to have *a priori* knowledge of how to partition the system. In this talk I will present a method for automatically partitioning a class of models into microscopic and mesoscopic subsets, based on indirect error estimates.

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ROBUSTLY SIMULATING BIOCHEMICAL REACTION KINETICS USING MULTI-LEVEL MONTE CARLO APPROACHES

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Keywords: Markov chains, Stochastic simulation, Variance reduction.

In this work, we consider the problem of estimating summary statistics to characterise biochemical reaction networks of interest. Such networks are often described using the framework of the Chemical Master Equation (CME). For physically-realistic models, the CME is widely considered to be analytically intractable. A variety of Monte Carlo algorithms have therefore been developed to explore the dynamics of such networks empirically. Amongst them is the multi-level method, which uses estimates from multiple ensembles of sample paths of different accuracies to estimate a summary statistic of interest [2]. In this work, we develop the multi-level method in two directions: (1) to increase the robustness, reliability and performance of the multi-level method, we suggest an improved variance reduction method for generating the sample paths of each ensemble; and (2) to improve computational performance, we provide a different mechanism for choosing which ensembles should be included in the multi-level algorithm.

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THE EFFECT OF CELL-CELL COUPLING ON SINGLE-CELL NOISE

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Keywords: Chemical master equation, Stochastic simulation, Multiscale.

Noisy gene expression is known to be of fundamental importance to single cells, and is therefore widely studied and modelled in single-celled organisms. Extending these studies to multicellular organisms is challenging since their cells are generally not isolated, but rather individuals in a tissue, in contact and communication with several neighbour cells. Cell-cell coupling via signalling, active transport or pure diffusion, ensures that tissue-bound cells are neither fully independent of each other, nor an entirely homogeneous population. In this talk, we show that increasing the strength of coupling between cells can either increase or decrease the single-cell variability (and therefore the heterogeneity of the tissue), depending on the statistical properties of the underlying genetic network. We confirm these predictions using spatial stochastic simulations of simple gene regulatory networks, and experimental tissue data from rat pituitary tissue, a leaf of Arabidopsis thaliana, and a population of mouse broblast cells. The results suggest that cell-cell coupling may be one of several noise-control strategies employed by multicellular organisms, and highlight the need for a deeper understanding of multi-scale stochastic systems.

References

[1] Benjamin Hepp, Ankit Gupta, and Mustafa Khammash. Adaptive hybrid simulations for multiscale stochastic reaction networks. *The Journal of chemical physics*, 142(3):034118, 2015.

[2] M.B. Giles. (2008). *Multilevel Monte Carlo Path Simulation*, Operations Research 56(3): 607-617.