Multiscale Methods and Inverse Problems in Modelling of Intracellular Processes

Radek Erban*

**Mathematical Institute, University of Oxford, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG, United Kingdom*

Summary. Two problems related to minisymposium “Random Dynamical Systems – Recent Advances and New Directions" will be discussed: (i) an inverse problem of constructing chemical reaction networks with given dynamical behaviour, including networks with a specific bifurcation structure or prescribed stochastic (noise-induced) behaviour; and (ii) the development of multiscale methods for spatio-temporal modelling of intracellular processes, which use molecular dynamics simulations in parts of the computational domain and (less-detailed) stochastic reaction-diffusion approaches in the remainder of the domain.

Introduction

In the first part of my talk, I will discuss an inverse problem of constructing mass-action chemical reaction networks with given dynamical behaviour. Such constructions are useful in many application areas. In synthetic biology, such constructed systems may be used as a blueprint for engineering artificial networks. They also add to the set of test problems for numerical methods designed for network inference from data. I will discuss constructions of chemical reaction networks with both (i) prescribed deterministic behaviour (bifurcation structure) and (ii) prescribed stochastic behaviour (including state-dependent fluctuations). This is a joint work with D. Anderson, T. Pleša, T. Vejchodský and K. Zygalakis [1, 2, 3].

In the second part of my talk, I will discuss methods for spatio-temporal modelling in molecular and cell biology, including all-atom and coarse-grained molecular dynamics (MD) and stochastic reaction-diffusion models, with the aim of developing and analysing multiscale methods which use MD simulations in parts of the computational domain and (less-detailed) stochastic reaction-diffusion approaches in the remainder of the domain. The main goal of this multiscale methodology is to use a detailed modelling approach in localized regions of particular interest (in which accuracy and microscopic details are important) and a less detailed model in other regions in which accuracy may be traded for simulation efficiency. This is a joint work with E. Rolls and Y. Togashi [4, 5, 6].

From dynamics to reaction networks

Synthetic biology is a growing interdisciplinary field which aims to design biochemical systems that behave in a desired manner. With the advancement of strand-displacement DNA computing, a large class of abstract biochemical networks may be physically realized using DNA molecules [7]. Methods for systematic design of the abstract systems with prescribed behaviors can be developed at both deterministic and stochastic levels. In the former case, a chemical reaction network is described by a system of ordinary differential equations (ODEs) for concentrations of chemical species, while in the latter case, a stochastic simulation algorithm is used to evolve numbers of molecules of chemical species involved. Stochastic models provide a more detailed understanding of the dynamics of chemical reaction networks. Such a description is often necessary for the modelling of biological systems where small molecular abundances of some chemical species make deterministic models inaccurate or even inapplicable [8].

Considering (less detailed) deterministic models, an inverse problem framework for constructing reaction systems with prescribed properties is presented in [1]. Two examples of constructed chemical reaction networks using the framework are presented in [2]. Both chemical systems are at the deterministic level described by two-dimensional third-degree kinetic ODEs. The first ODE system undergoes a homoclinic bifurcation, with a coexistence of a stable critical point and a stable limit cycle in the phase plane. The second chemical system is described by kinetic ODEs which undergo a multiple limit cycle bifurcation, with a coexistence of two stable limit cycles.

Stochastic effects, neglected at the deterministic level, are increasingly found to play an important role in biochemistry. In such circumstances, methods for controlling the intrinsic noise in the system are necessary for a successful network design at the (more-detailed) stochastic level. To address this problem, the noise-control algorithm for designing biochemical networks is developed in [3]. The algorithm structurally modifies any given reaction network under mass-action kinetics, in such a way that (i) controllable state-dependent noise is introduced into the stochastic dynamics, while (ii) the deterministic dynamics is preserved. The capabilities of the algorithm are demonstrated on a production-decay reaction system, and on an exotic system displaying bistability. For the production-decay system, it is shown that the algorithm may be used to redesign the network to achieve noise-induced multistability. For the exotic system, the algorithm is used to redesign the network to control the stochastic switching, and achieve noise-induced oscillations [3].

From molecular dynamics to whole-cell modelling

MD simulations of molecules in aqueous solutions are limited to modelling processes in relatively small domains containing (only) several thousands of water molecules. Living cells typically consist of 10^{10}–10^{12} water molecules. It

is therefore impossible to use standard all-atom MD models to simulate whole cell dynamics. In particular, biological processes which include transport of molecules between different parts of the cell are usually not described with atomistic-level of detail, even when the molecular structure and function are known for some components of the studied system. A typical approach in the literature is to design macroscopic spatio-temporal models, which can be written, for example, in terms of Brownian dynamics, compartment-based models (reaction-diffusion master equation) or mean-field partial differential equations [8, 9].

In [4], a simple and analytically tractable MD model of the heat bath is considered. A few heavy particles with mass M are coupled with a large number of light point particles with masses $m \ll M$. The collisions of particles are without friction, which means that post collision velocities can be computed using the conservation of momentum and energy. Let us denote the position and velocity of a heavy particle by $\mathbf{X}^\varepsilon = [X_1^\varepsilon, X_2^\varepsilon, X_3^\varepsilon]$ and $\mathbf{V}^\varepsilon = [V_1^\varepsilon, V_2^\varepsilon, V_3^\varepsilon]$, respectively, where $\varepsilon = m/M$. Then it can be shown that $\mathbf{X}^\varepsilon$ and $\mathbf{V}^\varepsilon$ converge in the sense of distribution (weakly) to a suitable Langevin (stochastic) description in the limit $\varepsilon \to 0$, provided that the density of point particles and the distribution of their velocities are appropriately scaled with ε. The limiting Langevin description can be further reduced to a Brownian dynamics model. In [4], these convergence results are used to design and analyse a multiscale approach in domain Ω which can provide MD-level information in a small subdomain $\Omega_{MD} \subset \Omega$ by coupling MD simulations in Ω_{MD} with a coarser Brownian dynamics description in the remainder of the computational domain.

In this talk, I will consider more complicated MD models than the one studied in [4] which include different descriptions of the heat bath (water molecules). I will investigate connections between MD and coarser stochastic models. I will discuss the development of efficient multiscale methods which couple MD and coarser stochastic models in the same dynamic simulation. An example is presented in [5], where a multiscale approach is developed which couples all-atom MD simulations of ions in water with Brownian dynamics. I will also consider multiscale modelling of polymer dynamics, which allows simulations of localized regions of a polymer chain with high spatial and temporal resolution, while using a coarser modelling approach to describe the rest of the polymer chain. This approach is applied to modelling of DNA dynamics in [6].

References

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

[2] T. Pleša, T. Vejchodský and R. Erban (2016). Test models for statistical inference: two-dimensional reaction systems displaying limit cycle bifurcations and bistability, submitted.

[3] T. Pleša, K. Zygalakis, D. Anderson and R. Erban (2017). Noise control for synthetic biology, submitted.

[4] R. Erban (2014). From molecular dynamics to Brownian dynamics. *Proceedings of the Royal Society A* **470**: 20140036.

[5] R. Erban (2016). Coupling all-atom molecular dynamics simulations of ions in water with Brownian dynamics. *Proceedings of the Royal Society A* **472**: 20150556.

[6] E. Rolls, Y. Togashi and R. Erban, Varying the resolution of the Rouse model on temporal and spatial scales: application to multiscale modelling of DNA dynamics, submitted.

[7] D. Soloveichik, G. Seeling, E. Winfree (2010). DNA as a universal substrate for chemical kinetics. *Proceedings of the National Academy of Sciences (PNAS)* **107**: 5393–5398.

[8] R. Erban, S.J. Chapman and P. Maini (2007). A practical guide to stochastic simulations of reaction-diffusion processes. Lecture Notes, available as http://arxiv.org/abs/0704.1908.

[9] R. Erban and S.J. Chapman (2009). Stochastic modelling of reaction-diffusion processes: algorithms for bimolecular reactions. *Physical Biology* **6**: 046001.