
Stochastic simulation of gene expression: From individual to interacting cells

PhD project in Computational Systems Biology

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Computational Systems Biology

The purpose of systems biology is to understand the biological phenomena that we observe on a cellular, tissue and organism level, through an understanding of the molecular interactions that occur inside individual cells. In contrast to many other biological fields, systems biology has embraced mathematical modeling and simulation as a major tool to achieve those goals. With algorithms and software for computer simulation of the biochemistry of cells and aggregations of them, it is possible to understand and predict their quantitative behavior and to suggest new hypotheses and new experiments. The models need to span multiple scales, from the detailed interactions between molecules on a sub-cellular level to the communication between individual cells, to the interactions of cells in colonies. Those multiscale models should allow for accurate and efficient simulation from molecules to cell populations based on analysis of the models and their numerical properties yielding quantitative measures of the modeling errors.

Project overview. The aim of this project is to *develop and analyze multiscale methods to bridge the gap between stochastic models of cell signaling in individual cells and signaling in collections of large numbers of interacting cells.* An improved understanding of cell-to-cell signaling systems is fundamental in order to understand diverse biological phenomena such as regulation of circadian clocks, differentiation of stem cells, segmentation of the vertebrate embryo and cancer onset, growth and spread. This requires development of new methods in applied and computational mathematics. Specifically, we will

1. Formulate a mathematical and computational model coupling spatial stochastic reaction-diffusion kinetics inside individual cells with cell-to-cell signaling across the boundaries of nearby biological cells.
2. Develop and analyze a method to simulate cell-to-cell communication with a coarse grained algorithm on an outer mesh.

As a specific model system, we will consider Notch-Delta signaling and its role in the oscillatory dynamics of the Hes1 network [10] in collaboration with Prof. Marc Chaplain at Dundee University and Dr. Marc Sturrock at the Molecular Biology Institute (MBI), Ohio.

Background A model of the chemical reactions and the diffusion of molecules in one cell and in colonies of cells and tissues has a many different scales and corresponding models in space and time. Few molecules are involved in the regulation of genes and a stochastic model of them is needed [3]. The number of ATP molecules is large and it is sufficient to solve deterministic PDEs for their concentrations. Some reactions between the molecules may be fast while others are slow. The different levels of modeling can be combined in one simulation model by using multiscale methods. Preferably, the switch between the levels of modeling should be based on computable quantities for good accuracy and efficiency.

The reaction-diffusion system at the mesoscopic level is formulated as a Markov process where diffusion is modeled as discrete jump events on the mesh, where each jump takes a molecule to an adjacent voxel. Reaction events occur between molecules in the same voxel. The time between reaction and diffusion events is exponentially distributed. By the Markov property, the probability density function (PDF) of the system is governed by the forward Kolmogorov equation, which in this setting is referred to as the reaction-diffusion master equation (RDME) [4]. The RDME for the PDF is a scalar difference-differential equation in a very high dimension prohibiting its numerical solution. The macroscopic PDE for the concentrations of the chemical species is the reaction-diffusion equation.

A popular model for a system of interacting and moving biological cells in e.g. tumor tissue and development is the cellular Potts model (CPM). The interaction between cells are described by a Hamiltonian that accounts for e.g. cell adhesion, membrane forces and chemical gradients. The model is simulated by a modified Metropolis algorithm [8]. The CPM does not normally account for the detailed dynamics of intracellular reaction networks of the individual cells. We aim at developing fast stochastic simulations of cell-to-cell signaling, as stochastic effects are essential to describe such systems [10, 9]. In the longer perspective, this can be used to increase the accuracy and fidelity of models such as the CPM or hybrid discrete-continuum models of tumor growth [6].

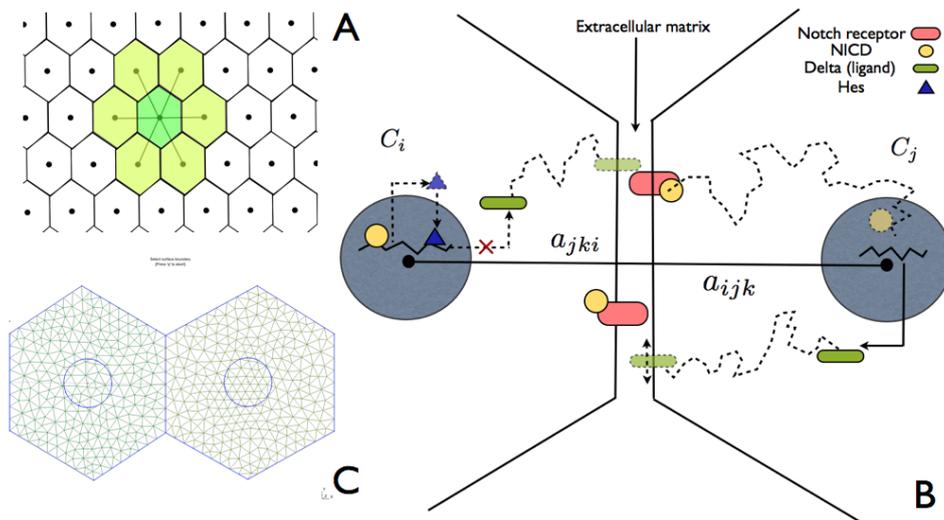


Figure 1: (A) Cells can be modeled as Voronoi cells in an outer mesh. Cell-to-cell signaling can spread e.g. a differentiation decision to neighboring cells in stem cells. (B) Close-up of an edge connecting two cells and a highly simplified schematic of Notch-Delta signaling. The Notch receptor penetrates the cell membrane from the interior of the cell to the extracellular matrix. When a ligand in a neighboring cell binds to Notch, the Notch intracellular domain (NICD) is released, diffuses into the nucleus and effects the expression of the Hes and Hey family genes. (C) At the inner level, a fine mesh is used to simulate the stochastic reaction-diffusion process inside the individual cells.

A multiscale model for stochastic signaling in cell colonies. We will develop multiscale algorithms to simulate signaling in a network of interacting stationary cells. The biological cells in a colony will be modeled geometrically by close-packed Voronoi cells as in Fig. 1A. From a computational point of view, they collectively define a coarse or outer level mesh. Two different forms of signaling between cells will be considered. Short-range signals are transferred between adjacent cells via shared, membrane bound receptors. Long-range signals propagate via small molecules that diffuse in the extracellular matrix of negligible width surrounding all cells in a colony. On the finest scale we consider, each one of the individual cells in the outer mesh will have an internal, fine mesh on which the RDME is used to simulate the intracellular part of the signaling network, see Fig. 1C. The cells exchange information at the vertices of the shared faces of the cells in the outer mesh. The internal biochemical system can either be simulated

using the SSA at a very high computational cost, or by splitting the internal chemistry from the communication on the boundary in an operator split method which will allow for efficient massively parallel simulation. The splitting error can be estimated by extending the analysis in [1].

On the coarse scale, each biological cell in the outer mesh will be considered well-stirred without space dependence. The details of the cell-to-cell signaling in Fig. 1B will be replaced by a stochastic flux across the edges of the outer mesh. The system can now be simulated by SSA based on a RDME defined entirely on the outer mesh with major computational savings. Coarse grained propensity functions a_{ijk} will be derived for the activation or deactivation of a gene S_i in cell k dependent on the state of cell j and of the edge Γ_{jk} . The a_{ijk} will represent the total propensity of several events, each one corresponding to different, sequential steps of the cell-to-cell signaling network. Analytical approximations can be found to the propensities of some of these individual steps, such as the mean time of a newly formed protein to hit a face shared between cells. The rate of absorption to a face depends on the density of free receptors on that face and hence varies with time. Too complicated analytical formulas can be parametrized prior to a simulation on the outer mesh by realizations of the RDME model at the inner level. Such simulations will also be used for verification of the whole coarse grained intracellular signaling model. A few cells in the whole coarse system can be modeled at the finest scale if necessary for the fidelity of the model e.g. in the cell initializing the signaling cascade.

Applications in biology. Together with Chaplain we are investigating spatial stochastic effects in the Hes1 gene regulatory network. Individual mouse embryonic stem cells have been found to exhibit highly variable differentiation responses under the same environmental conditions and experimental evidence suggests that the noisy cyclic expression of Hes1 is responsible for this [5]. Using URDME [2] we have developed a RDME model of the Hes1 network, and in contrast to previous simulations with SSA or PDEs, our model captures both the qualitative and quantitative behavior observed in experiments. Interestingly, the model suggests that intrinsic noise can explain population level heterogeneity in the differentiation response. Our simulations show that the onset of oscillatory dynamics in *individual* cells is very robust to parameter variations, but that the oscillations are always highly stochastic. Cell-to-cell communication via the Notch-Delta pathway in Fig. 1B can reduce this variability in cells during the process of somitogenesis [7], but the mechanism is not well understood. The methodology we plan to develop will be used to study this under various conditions in collaboration with Chaplain and Sturrock.

We will also apply the methods to study embryo development in a collaboration with Carolina Wählby, Uppsala University, and Igor Adameyko (Karolinska institute).

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