"Multiscale modeling of spatially distributed biological systems"

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Summary

We have been developing the necessary mathematical and computational framework that can handle the full range of time and length scales required to model complex systems at the stochastic level. Specifically, we have developed a multiresolution framework for efficient stochastic Monte Carlo (MC) simulation to enable spatial and temporal understanding of stochasticity in complex pathways of entire cells. We compared model results with recent microscopy and other biological experiments to validate our models and obtain a better understanding of the mechanisms that drive the behavior of biological systems.

The fundamental role that intrinsic stochasticity plays in cellular functions has been shown via numerous computational and experimental studies. In the face of such evidence, it is important that intracellular networks are simulated with stochastic algorithms that can capture molecular fluctuations. However, separation of time scales and disparity in species population, two common features of intracellular networks, make stochastic simulation of such networks computationally prohibitive. While recent work has addressed each of these challenges separately, a generic algorithm that can *simultaneously* tackle disparity in time *and* population scales in stochastic systems was until now lacking.

This past year, we developed the hybrid, multiscale Monte Carlo (HyMSMC) method that blends stochastic singular perturbation (CSP) concepts, to deal with potential stiffness (developed earlier), with a hybrid of the exact stochastic simulation algorithm (SSA) and the τ-leap algorithm (multiple firings of events), to cope with separation in population sizes. In addition, we introduced CSP as a means of systematically partitioning fast and slow networks and compute relaxation times for convergence, and proposed new statistical criteria of convergence of fast networks to stochastic low-dimensional manifolds. We used several examples, including a gene expression model displaying bistability, to demonstrate the efficiency, accuracy and applicability of the HyMSMC method. An example is shown in Figure 1. Overall, we have found substantial acceleration of the HYMSMC over all previous algorithms.

We have also made major developments on improving accuracy of spatially coarse-grained MC methods. One novel technique

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we developed entails multi-griding along with CSP to carry out reconstruction of the microscopic (unresolved) model.

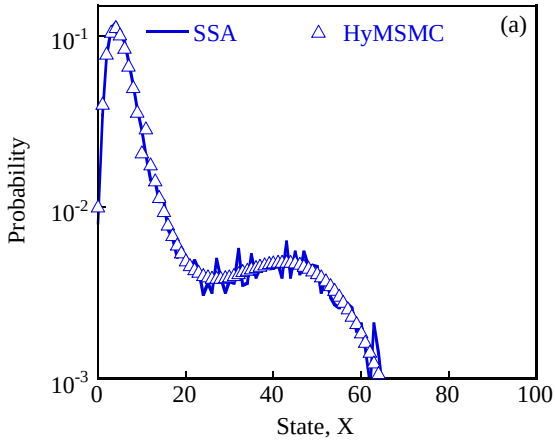

Figure 1: Probability distribution function of species X in a biological network displaying bistability using the SSA and the HyMSMC method.

Yet another powerful method entails error estimates in terms of *a priori* and *a posteriori* error analysis. For the latter method, the proposed algorithms were derived from an initial coarse-grained approximation that is directly computable by MC simulations, and the corresponding numerical error was calculated using the specific relative entropy between the exact and approximate coarse-grained equilibrium measures. Subsequently we carried out a cluster expansion around this first--and often inadequate--approximation and obtained more accurate coarse-graining schemes. The cluster expansions yielded also *sharp* a posteriori error estimates for the coarse-grained approximations that can be used for the construction of adaptive coarse-graining methods. Numerical examples demonstrate that these coarse-graining schemes allow for accurate predictions of critical behavior and hysteresis and improved predictions of earlier coarse-graining schemes.

Finally, we have carried out the first of its kind comparison to single particle tracking experimental data for the homodimerization of the EGF receptor at relatively short times using the multiscale MC toolbox we have been developing (Figure 2). Excellent agreement is seen. Overall, we show that spatial simulation of receptor dynamics can be used to gain mechanistic understanding of receptor activation, which may enable improved cancer treatments in the future.

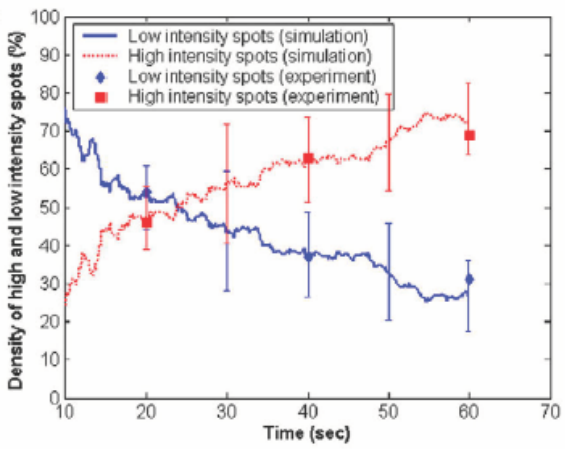

Figure 2: Comparison of intensity vs. time from simulation (lines with error bars) and experiment (points).

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