MULTISCALE MODELING OF SPATIALLY DISTRIBUTED BIOLOGICAL SYSTEMS

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ABSTRACT

Most biological systems exhibit a vast disparity of length and time scales and are inherently stochastic in nature. Currently, stochastic Monte Carlo (MC) simulation is plagued by the multiscale nature of these systems. The overall objective of our work is to develop the necessary mathematical and computational framework that can handle the full range of time and length scales required to model complex biological systems, with emphasis on spatially distributed systems, and apply this framework to an important biological system, namely the epidermal growth factor receptor (EGFR), whose signal disregulation is implicated in a number of cancers. The intrinsic fluctuations present in intracellular networks, especially at the genetic level, cannot be captured using deterministic models. The potential impact of fluctuations on cell physiology necessitates use of stochastic algorithms. These algorithms lead to tremendous computational load due to (i) the execution of one event at a time, (ii) the presence of some large populations, and (iii) stiffness.

We have recently devised the binomial tau-leap method for the first two challenges. Drawing analogies from singular perturbation and low dimensional manifold methods in deterministic systems, we have also developed a multiscale MC algorithm to handle stiffness. Its essence lies in the relaxation of the fast network to a stable quasi-equilibrium manifold in a short relaxation time compared to the time scales of the slow network. Unlike deterministic models, this stochastic manifold is represented by a time-invariant distribution of the fast states that controls the rates of slow variables. Novel relaxation criteria, invoking hypothesis testing principles and computational singular perturbation concepts, have been developed. We have finally developed a hybrid algorithm that seamlessly integrates the above methods to handle simultaneous separation in time scales and populations of species. We have devised a new algorithm whereby the tau-leap method is extended to microscopic lattices with good speedup and accuracy.

In previous work, we have successfully developed coarse-grained MC (CGMC) methods applicable to simple systems. We have recently developed CGMC methods for multicomponent species and/or site types. Numerical examples are presented to demonstrate the method. Furthermore, we introduce the concept of homogenization at the stochastic level over all site types of a spatially coarse grained cell. Homogenization provides a novel coarsening of the number of processes, an important aspect for complex problems plagued by numerous microscopic processes (combinatorial complexity). As expected, the homogenized CGMC method outperforms the traditional KMC method on computational cost while retaining good accuracy.

Using the CGMC method, spatial modeling of ligand-mediated membrane receptor dimerization reaction dynamics was performed. Parameterization of GCMC simulations is done from coarse-grained molecular dynamics (CGMD) simulations. The simulations demonstrate the importance of spatial heterogeneity in membrane receptor localization. Comparison to experimental data will be shown.