"Multiscale Simulation Algorithms for Biochemical Systems"

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Summary

Traditional differential equation-based models for simulation of chemically reacting systems fail to capture the randomness inherent in such systems at scales common in intracellular biochemical processes. Discrete stochastic models can more faithfully capture the system behavior, but because they must simulate every reaction event in the system, the computational complexity can become overwhelming for practical biological systems. We have made extensive progress in accelerating these simulations, both by adaptive multiscale algorithms and by fast formulations of the stochastic simulation algorithm. We have developed the theory underlying the new computational methods, as well as a new software tool called StochKit, for multiscale discrete stochastic simulation of biochemical systems.

Biochemical systems are inherently multiscale and stochastic. In microscopic systems formed by living cells, the small numbers of reactant molecules can result in dynamical behavior that is discrete and stochastic rather than continuous and deterministic. An analysis tool that respects these dynamical characteristics is the stochastic simulation algorithm (SSA, Gillespie, 1976[1]), a numerical simulation procedure that is essentially exact for chemical systems that are spatially homogeneous or well stirred. Despite recent improvements, as a procedure that simulates every reaction event, the SSA is necessarily inefficient for most realistic problems. There are two main reasons for this, both arising from the multiscale nature of the underlying problem: (1) stiffness, i.e. the presence of multiple timescales, the fastest of which are stable; and (2) the need to include in the simulation both chemical species that are present in relatively small quantities and should be modeled by a discrete stochastic process, and species that are present in larger quantities and are more efficiently modeled by a deterministic differential equation (or at some scale in between).

This project focuses on the development of adaptive algorithms, and the fundamental theory upon which they must be based, for the multiscale simulation of biochemical systems.

SSA is the workhorse algorithm for stochastic simulation in systems biology, and it will be the core of any multiscale approach. Thus it is important that it is as fast as possible. We developed a formulation of SSA which is both faster and simpler than the previous version[7].

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To speed up the SSA by orders of magnitude, one must give up on the exactness. One possibility for this is tau-leaping, originally developed by Gillespie. Rather than stepping to the next reaction as in SSA, tau-leaping can skip over potentially many reactions at a time. As originally proposed, however, it had no theoretical justification, and many critical practical details remained to be addressed. We developed the underlying theory for tau-leaping[5,8], and led the way to adaptive stepsize selection[3], implicit tau-leaping methods for dealing with stiffness, and a fully-adaptive tau-leaping method which selects between explicit tau-leaping, implicit tau-leaping and SSA during the course of the problem[2].

We developed a very powerful method called slow-scale SSA (ssSSA)[6] for simulation of multiscale discrete stochastic systems, particularly in the situation where there are fast reactions with one or more constituent species are present in small population – where tau-leaping is not appropriate. The ssSSA method can be orders of magnitude faster than SSA for many biochemical simulations.

We developed a software package called StochKit for multiscale discrete stochastic simulation of biochemical systems. StochKit is available at www.engineering.ucsb.edu/~cse.

An introduction to the need for discrete stochastic simulation in biochemical systems, and to our work, can be found in [4].

References:

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