NFsim: Managing Complexity in Stochastic Simulations of Reaction Networks

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***Short Abstract* — We have developed the Network Free Stochastic Simulator (NFsim) to efficiently handle the problem of combinatorial complexity present in many signaling systems. NFsim is a generalized biochemical reaction simulator for rule-based models that utilizes the agent-based stochastic simulation algorithm recently presented in [1,2]. We demonstrate the capabilities of NFsim by constructing an integrated model of the full bacterial chemotaxis system. Although our initial focus is on bacterial chemotaxis, the eventual goal is to utilize NFsim to extend the capabilities of our agent-based platform AgentCell [3] to simulate a wide range of highly multiscale stochastic systems.**

I. Background

Traditional techniques for the simulation of biochemical signaling networks require the enumeration of every possible molecular species and reaction in the system. In many reaction systems the number of molecular species and reactions grows exponentially with the number of molecules making the system difficult to simulate. StochSim is among the only established frameworks able to handle this level of combinatorial complexity [4]. However, the StochSim algorithm is based on fixed-time steps and null events and, consequently, does not produce exact stochastic trajectories and is often prohibitively slow. Bacterial chemotaxis is among the best characterized signal transduction systems in biology [6,7,8,9]. It is also an illustrative example of a relatively simple network that is difficult to model in full because of combinatorial complexity. Therefore, the chemotaxis system presents a clear challenge and a necessary testing ground for novel methods of handling this class of reaction networks.

II. Results and Discussion

NFsim implements the agent-based method of [1,2] to attain performance that scales with the number of events rather than the size of the reaction network. The method treats individual molecules as distinct software objects and defines reactions through the rule-based formalisms of the BioNetGen Language (BNGL) [5]. The reaction system is advanced in time using an event-driven, exact approach. NFsim can take as input an XML-encoded form of BNGL, which greatly facilitates model development. NFsim also extends BNGL by permitting generalized functional forms for reaction kinetics and rapid equilibration of selected components. Initial testing suggests that we have achieved more than an order of magnitude speedup compared to StochSim.

Using our framework, we developed an integrated stochastic model of the full bacterial chemotaxis system that unifies and extends existing models of all the major components of the system [6,7,8,9]. NFsim allows us to explicitly simulate the receptor clustering, tethering, and adaptation reactions that lead to combinatorial complexity. Building on the design of AgentCell [3], we have wrapped our stochastic simulation of chemotaxis in an autonomous cellular agent that can swim in a realistic, time-evolving, 3D environment. As we continue to develop this platform, we plan to apply our methods to study quorum sensing and cell to cell communication in developmental systems.

NFsim represents an important step forward in the design of new tools and methods to capture the complexity of signaling systems. We anticipate our new platform will be able to handle a wide range of multiscale and complex systems.

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