Modeling Complex Biochemical Systems in Time and Space Using BioNetGen and MCell

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THE consequences of protein-protein interactions are difficult to specify and track with conventional modeling approaches based on reaction rate equations – simulated using either ODE's or stochastic chemical kinetics – because of the combinatorially large number of protein phosphoforms and protein complexes that these interactions potentially generate. Rule-based modeling languages such as BioNetGen and Kappa have been developed to address this problem and to allow development of cell regulatory networks based on concise descriptions of biochemical interactions that take the form of rules. In a rule-based model, molecules are represented as structured objects and rules define biochemical interactions through transformations of these objects to represent such processes as post-translation modification, binding, and transport. The approach allows systematic incorporation of site-specific details about protein-protein interactions into a model for the dynamics of cell regulatory networks, including processes involving cell signaling, gene regulation, and metabolism.

Reaction rules differ from reactions used in conventional reaction network models in that they represent only the *local* requirements that reactants must fulfill in order to undergo biochemical transformation at a particular point, e.g., binding site or post-translational modification site. A single rule may therefore encode a large number of potential reactions in a system involving many different chemical species. A key advantage of rules, in addition to their compactness, is modularity – which allows models describing different aspects of a protein's function to be combined in a straightforward manner. Rules also provide an exact way to represent existing knowledge or hypotheses about biochemical mechanisms, making models easier to understand and visualize.

In this tutorial I will demonstrate how a rule-based model is specified in the BioNetGen language (BNGL) using the RuleBender interface and demonstrate how such models can be visualized, simulated, and analyzed using a variety of simulation approaches including ordinary differential equations, stochastic chemical kinetics (aka, the Gillespie algorithm), and spatially-resolved stochastic chemical kinetics. I will show how models developed in BNGL can be exported to SBML for simulation by other tools, and demonstrate a pipeline we have recently developed for simulating spatially-resolved rule-based models using the particle-based Monte Carlo simulator MCell.