Introduction to Rule-Based Modeling with BioNetGen

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***Short Abstract* — Rule-based modeling offers a powerful approach for developing, simulating, and analyzing models of cell regulatory networks. In this tutorial, we will provide an overview of BioNetGen's architecture and capabilities, as well as an interactive tutorial spanning both basic and advanced functionality. Participants should install the software available at http://bionetgen.org.**

***Keywords* — Rule-based modeling, BioNetGen, Signaling pathways.**

I. BACKGROUND

Rule-based modeling offers a powerful approach for developing, simulating, and analyzing models of cell regulatory networks [1]. The molecular components of these systems are modeled as structured objects whose interactions are governed by rules, which specify the conditions under which molecules and complexes can interact as well as their rates of interactions. Rule-based models may be simulated using a wide range of approaches from spatially-resolved stochastic to mass action kinetics and even Boolean. The BioNetGen framework [2] provides many capabilities for rule-based modeling along with a common language that enables a consistent interface among tools.

II. BASIC TUTORIAL

Basic topics that will be covered include model specification, use of global and local functions to specify complex rate laws, parameter scans, and model export. We will present several examples relevant to biological mechanisms, such as Michaelis-Menten kinetics, cooperativity (Hill function), network motifs, and receptor dimerization. Examples will be presented using RuleBender [3], a GUI for BioNetGen that includes capabilities for visualizing simulation results. RuleBender also uses the NFsim [4] framework to execute network-free simulations, which allows simulation of extremely complex models.

III. ADVANCED TOPICS

The BioNetGen framework has recently added novel capabilities including: network visualization [5], translation of standard models into rule-based form [6], performing spatial simulations of rule-based models, and parameter estimation [7]. We will demonstrate how each of these tools can be utilized in support of efforts to develop mechanistic insights into signal transduction and other cellular processes.

A. Visualization

Rule-based modeling allows for the construction of models with increasing complexity for which conventional visualizations are often insufficient. BioNetGen offers several advanced visualization options such as the *compact rule visualization* and *atom-rule graph* [5] to increase the user's ability to analyze and communicate large models.

B. Model Import and Export

BioNetGen enables translation of BNGL models to other widely used file formats such as the Systems Biology Markup Language (SBML) and MATLAB's M-file and MEX-file formats. We will demonstrate these capabilities, along with the use of Atomizer [6], a tool for direct conversion of model components to structured objects.

C. Parameter Estimation

We will demonstrate the use of PTempEst, a tool for calibrating rule-based models to data using parallel tempering [7].

D. Compartmental & Spatial Simulation

We will introduce compartmental BNGL and CellBlender [8] for spatial simulation of rule-based models.

IV. CONCLUSION

The tutorial is intended to be self-contained, requiring minimal background or prior experience with the software. Users with prior experience, however, will also benefit from the advanced topics and potentially from tips and tricks presented along the way.

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