Visualizing Regulation in Rule-based Models

John A.P. Sekar[1], José-Juan Tapia[2], and James R. Faeder[3]

***Short Abstract* — Rule-based models are kinetic models where biochemical structures are modeled explicitly as graphs and kinetic mechanisms are modeled explicitly as reaction rules. The regulatory network of the system, envisioned as a bipartite diagram of sites and processes, is implicit in the overlaps between reaction rules. Visualizing individual mechanisms and identifying pathways and feedback loops would facilitate communicating about the model with other experts. In this work, we have developed an algorithm to automatically infer and organize the network structure of a BioNetGen rule based model. We have provided automated tools for visualizing individual rules as well as the inferred network. These tools are freely available with the latest distribution of BioNetGen software at http://bionetgen.org.**

***Keywords* — rule-based modeling, visualization, BioNetGen, reaction rules, regulatory network**

I. Background

RULE-based frameworks such as BioNetGen [1], Kappa [2] and Simmune [3] use a graph syntax to represent biochemical structures and kinetic mechanisms. Visualizing these models as a regulatory network is necessary to improve communication and usability. The directed bipartite graph showing relations between sites and processes is a classical abstraction used for visualizing regulatory networks. Naïvely automating a bipartite graph for rule-based models encounters combinatorial complexity in overlaps between reaction rules and lack of appeal to expert intuition. Prior to this work, regulatory interactions between reaction rules were inferred manually (Extended Contact Map [4]), automated as a unipartite graph (Rulebender [5]), automated for a subset of overlaps (Simmune Network Viewer [5]), part of the model specification (Rxncon [6]), or inferred by simulation [7]. Here we provide automated inference of the regulatory network by static analysis of a BioNetGen rule-based model and user-guided organization and coarse-graining of the inferred network. The tools described here generate visualizations in Graph Modeling Language (GML) format, which is compatible with dedicated graph layout tools such as yEd (yworks.com/yed) and Cytoscape [8].

II. Results

A. Rule Visualization

BioNetGen structures, called *patterns*, are visualized as site graphs: graphs with nested nodes and edges representing binding interactions. A kinetic mechanism, modeled as a *reaction rule*, is composed of reactant and product patterns. We provide two rule visualizations: (i) *syntactical*, where reactant and product patterns are embedded in a bipartite graph of the rule, and (ii) *compact*, where the action of the rule is shown as a set of graph operations on structures.

B. Regulatory Network Inference

The pattern is coarse-grained from an explicit graph to a set of discrete 'sites' or *atomic patterns*. A reaction rule is then summarized using bipartite relations to atomic patterns: consumption (reactant), production (product) or requirement (context). These are visualized on the bipartite *regulatory graph*. Regulatory graphs of individual rules are aggregated into a regulatory network of the model.

C. Regulatory Network Organization

We have provided flexibility to optimize the visual complexity of the regulatory network. Background sites and constitutive processes that obscure the regulatory structure can be tagged and removed. Rules modeling conditional variants of the same process are automatically identified and grouped together. This grouping can be seeded with equivalence classes for sites, which can be imposed as expert input. Collapsing groups to single nodes leads to compact and coarse-grained network diagrams. Using these tools, we were able to generate regulatory diagrams for large sets of reaction rules, such as the FcεRI interaction library [9] with 162 rules, and the ErbB receptor family pathway model [10] with 544 rules.

III. Conclusion

Rule visualization allows side-by-side display and comparison of kinetic mechanisms. The regulatory graph enables identification of pathways and feedback loops in the system. The user is also able to flexibly organize the network to appeal to expert intuition. Systematic coarse-graining enables compact visualization of large networks.

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[1,2,3] Department of Computational and Systems Biology, University of Pittsburgh. E-mail: {jas237[1], jjtapia[2], faeder[3]}@pitt.edu.

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