

Scalable Global Views for Biological Rule-Based Modeling

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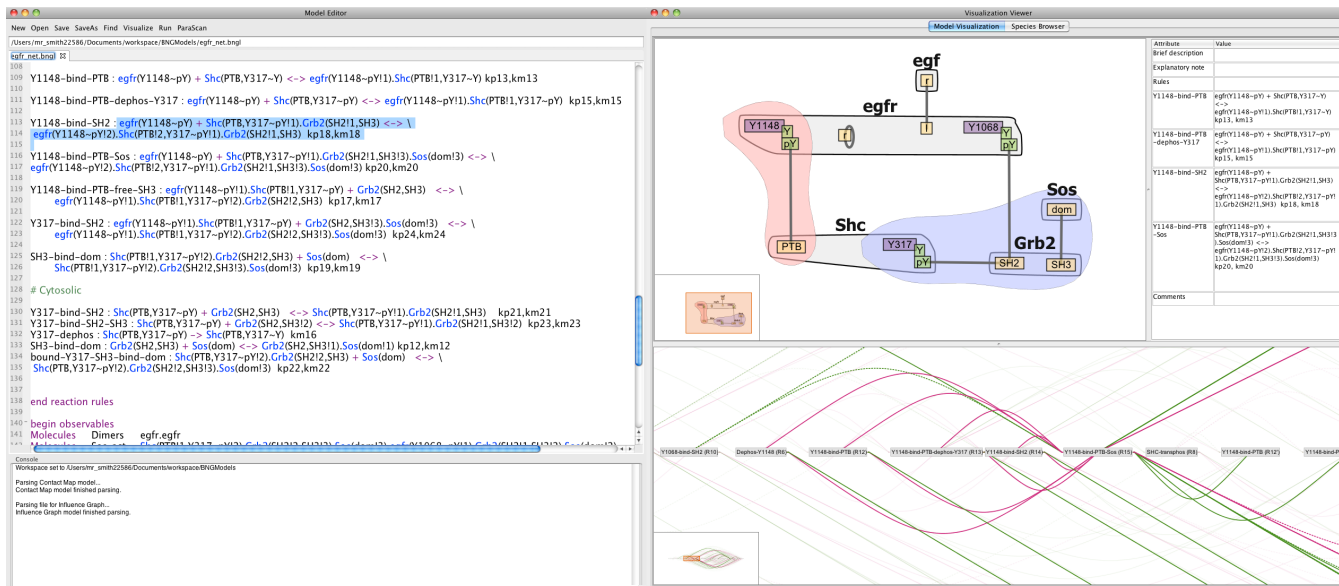


Figure 1: Biological Rule-Based Modeling interface. Shown are the Model Editor pane including console for text output (left) and the Visualization Viewer pane (right). The Visualization Viewer shows two complementary global visual encodings corresponding to the text model in the Editor: the interactive Contact Map (top left), and the Influence Graph (bottom); and also a local view in the Annotation Panel (top right).

ABSTRACT

Rule-based modeling (RBM) is a powerful and increasingly popular approach to modeling cell signaling networks. However, visual tools are needed to make RBM accessible to a broader range of users, to make specification of models less error prone, and to improve workflows. We introduce and evaluate two visual abstractions for scalable global model exploration: interactive contact maps and influence graphs.

Keywords: computational biology, cell signaling, rule-based modeling and simulation, globa/local visualization, bubble sets.

1 INTRODUCTION

Rule-based modeling (RBM) allows for the construction of an executable model that contains a starting set of molecules with possible interaction behaviors [2]. These models are then simulated in order to produce a complete reaction network. If the network matches known cell signaling data, then the model is assumed to be correct and can be used to construct hypotheses about the biological system in question. Thanks to the relative low cost of model alteration and simulation compared to laboratory experimentation, the RBM

approach can be used to gain insight about a reaction network, and can help speed up the discovery of new drugs and therapies.

While the potential benefits of RBM to biology are outstanding, the process of building an RBM from experimental data and detecting and correcting modeling errors (i.e., debugging) can be tedious and frustrating. RBMs are typically defined by the user via a text file. The user defines a set of molecules and proceeds to write rules governing their interaction that are derived from biomed literature knowledge of the system. Although individual rules are easy to write, it is often difficult to fully grasp the implications of a set of rules. The challenge in assimilating the global perspective is particularly acute when trying to understand models written by different researchers. This problem complicates debugging and reduces the accessibility of RBM, especially for biologists with limited programming experience.

The main problem with direct visual representations of complete RBM systems is that such representations are prohibitively large or complex. Motivated by this problem, we propose global visual abstractions for RBMs, and include the implementations in our rule-based modeling IDE called RuleBender. These interactive visual representations help modelers form complex model structures and internal interactions progressively, rather than trying to build and keep track of a complete mental model from the start.

2 METHODS

An RBM definition includes *molecules*, molecule *components*, component *states* (e.g. phosphorylated pY or unphosphorylated pY), *reaction rules*, and chemical and mathematical constants. Each rule is defined by a set of reactants comprised of molecules, components, and states; followed by the post-reaction product

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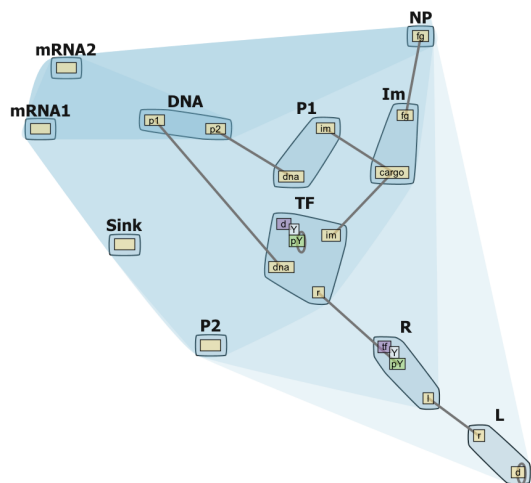


Figure 2: Contact Map with molecule compartment hierarchy. The saturation of the convex hull encompassing a compartment indicates the hierarchical structure of the compartments; the outermost compartment is colored the lightest blue.

which may include new bonds, broken bonds, or changed states of components. In these rules, the molecules, components with states, and bonds that are required for the reaction but are not changed by it are called the *reaction context*. Conversely items that are changed by the reaction are termed the *reaction center*.

To provide a global perspective, we propose two main visual abstractions: the Interactive Contact Map and the Influence Graph. A linked text-based Model Editor and an Annotation view provide complementary local information. The implementation of these visualizations in the tool RuleBender was written in Java using SWT (eclipse.org/swt), JFace (wiki.eclipse.org/index.php/JFace), JFreeChart (jfree.org/jfreechart), and Prefuse (prefuse.org) [3] visualization libraries. It is freely available at rulebender.org.

Contact Map: The Interactive Contact Map (upper right in Fig. 1) is a concise scalable graph representation that provides a global view of *all* of the molecules and *all* of the reaction rules that are defined in the model, and is not associated with any specific state in a simulation. Each molecule in the RBM is rendered a single time. Component states are also displayed as nodes cascading from the components to which they apply. Hierarchical compartments (extracellular, cytoplasmic, etc) are rendered as transparent blue convex hulls around the elements that they contain as shown in Fig. 2.

Following the basic Visual Information Seeking Mantra [4], the Contact Map provides an overview of the model. Pop-up menus provide filtering options. Selecting an edge or a state node brings up a list of reaction rules, and selecting one of these rules brings up a bubble sets overlay [1] that highlights the reaction context in blue and the reaction center in pink.

Influence Graph: While the Contact Map shows in a compact manner the connectivity between the molecules within a model, the relations among the reaction rules may provide further insight into the behavior of a model. Each rule can be thought to consume the molecules in its reactants while creating more of the molecules in its product. When a rule produces something that another rule consumes, we say the first rule *activates* the second. When two rules share molecules in their reactants, the rules *inhibit* each other.

The Influence Graph (lower right of Fig. 1) gives an overall view of the activation/inhibition relations between the reaction rules using graph nodes for the rules, and edges between the nodes to represent the different relationships. The layout of the graph indicates the directionality of the edges: the arcs above the nodes point to the right while the arcs below nodes point to the left. Similar to the

Contact Map, we use colors, filtering, zoom in/out, focus plus context, and details on demand in the Influence Graph. Activation and inhibition filtering operations are also provided. Selecting a rule node displays the rule text and filters the influence arcs related to this node in order to highlight the local information for this rule.

Annotation Panel and Linked Views: The Annotation view contains textual information about any selected visual element (such as the text definition, compartment membership, possible states, associated rules, and links to external databases). To facilitate analysis and debugging, the global views, the annotation panel, and the text model editor are linked through linking and brushing.

3 VALIDATION AND RESULTS

In a pilot study among four expert end-users from the PITT Department of Computational Biology the users were asked to rate the features of RuleBender on a scale of 1 to 5 (not helpful to essential). The visual representations and linked views were rated as useful, while displaying the reaction center/context via bubble sets was rated as very helpful or essential. In particular, we note that adding the bubble sets capability increased the rating of the Contact Map from useful to very useful. We note that in the four weeks following the recent release of RuleBender to the biology community, the system has been downloaded more than 45 times.

RuleBender has been successfully deployed as an educational tool in undergraduate/graduate classrooms at CMU, PITT, Yale, and UNM, as well as in a number of RBM workshops. Feedback revealed that RuleBender had “a nice feel and interface”, and was “incredibly easy [...] to download and use”. The system “could do just about everything we needed for the class assignments.”

4 DISCUSSION AND CONCLUSION

We found that our visual framework creates an efficient RBM workflow by supplementing model creation with global model views. As a measure of success, our users quickly adopted the tool as their main interface to RBM. Much of the appeal of the tool is attributed to its development in a tight feedback loop with domain experts, which provided detailed knowledge of current workflows and allowed for the design of a well organized multi-view interface.

In this paper we have introduced two global visual representations for exploring rule-based models. The Contact Map visual representation helped the users see the model that they had written in a way that clarified its physical structures. Bubble sets made a major difference in how useful the users found this representation. The Influence Graph, in turn, was praised for its ability to identify orphan nodes and subsets of rules, and give insight into the signal firing process. The combined representations thus have complementary strengths. Finally, we found that, although the local and global views of the models and their results are fragmented across multiple views, when combined in linked views and with details on demand, these views allowed the users to overcome several modeling pitfalls.

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