BIOINFORMATICS APPLICATIONS NOTE Vol. 29 no. 9 2013, pages 1229–1230
doi:10.1093/bioinformatics/btt134

Systems biology

Advance Access publication March 17, 2013

The Simmune Modeler visual interface for creating signaling networks based on bi-molecular interactions

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Associate Editor: Martin Bishop

ABSTRACT

Motivation: Biochemical modeling efforts now frequently take advantage of the possibility to automatically create reaction networks based on the specification of pairwise molecular interactions. Even though a variety of tools exist to visualize the resulting networks, defining the rules for the molecular interactions typically requires writing scripts, which impacts the non-specialist accessibility of those approaches. We introduce the Simmune Modeler that allows users to specify molecular complexes and their interactions as well as the reaction-induced modifications of the molecules through a flexible visual interface. It can take into account the positions of the components of transmembrane complexes relative to the embedding membranes as well as symmetry aspects affecting the reactions of multimeric molecular structures. Models created with this tool can be simulated using the Simmune Simulator or be exported as SBML code or as files describing the reaction networks as systems of ODEs for import into Matlab.

Availability: The Simmune Modeler and the associated simulators as well as extensive additional documentation and tutorials are freely available for Linux, Mac and Windows: http://go.usa.gov/QeH (Note shortened case-sensitive URL!).

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Supplementary information: Supplementary Data are available at *Bioinformatics* online.

Received on December 14, 2012; revised on February 20, 2013; accepted on March 11, 2013

1 INTRODUCTION

Many cellular biochemical signaling processes involve interactions among molecules with multiple binding sites and various biochemical states (such as the phosphorylation states or structural conformations of molecular domains). For example, scaffold proteins with multiple potential binding partners can give rise to very large reaction networks owing to the combinatorial possibilities of multi-molecular complexes containing those proteins (Hlavacek *et al.*, 2003). Conventional modeling approaches rely on creating computational representations of such reaction networks manually, by explicitly listing all multi-molecular complexes and all reactions they can participate in (see Supplementary Text 1 for a comparison of Simmune with other approaches). This can be tedious or impossible, depending on the complexity of the network. To address this problem, a variety of approaches has been developed that can automatically determine all reactions and the resulting complexes based on the user-specified pairwise interactions among molecular binding sites (Feret *et al.*, 2009; Hlavacek *et al.*, 2006; Lok and Brent, 2005; Meier-Schellersheim *et al.*, 2006). Although several tools permit users to simulate or analyze such 'rule-based' networks and models (Colvin *et al.*, 2010; Sneddon *et al.*, 2011; Xu *et al.*, 2011), creating them typically requires writing scripts, which may render the model definition process non-intuitive for researchers with an experimental biological background. A visual interface capturing all relevant aspects of molecular interaction rules using iconographic symbols can considerably lower the threshold for non-theorists to start working with computational models. Moreover, it can offer important advantages over script-based approaches in particular when aspects such as the position of molecular components relative to membranes or symmetry properties of multimeric complexes come into play.

2 SIMMUNE MODELER APPLICATION

The Simmune Modeler represents molecules, their states and binding sites as iconographic symbols that can be manipulated through basic mouse operations for the specification of molecular interactions or enzymatic transformations (see Fig. 1). Molecules can consist of multiple components that can, for trans-membrane molecules, be assigned to the inner or outer leaflet of membranes that embed them. This latter feature makes it straightforward to model the biochemical barrier functionality of cellular membranes in spatially resolved simulations: binding sites on the 'outside' of a membrane will interact only with other 'outside' binding sites. It also provides a natural way to implement the transmembrane signaling behavior of receptors: the ligation of a binding site located on the 'outside' part of the receptor can be linked to a state change affecting availability or reaction rates of 'inside' binding sites.

To visualize the specification of states of molecular components, the Simmune Modeler uses colored tags that can be associated with any user-defined molecular property, such as phosphorylation state or steric accessibility of functional domains. Molecular components can carry any (in principle) number of such tags being displayed as either filled, empty or dotted squares, representing *on*, *off* or *don't care* states, respectively. Similarly, the binding states of molecular binding sites are visualized as filled, empty or dotted circles representing *bound*, *unbound* or *don't care* binding sites. This is useful for specifying reaction rules that depend on particular binding sites being free or occupied. Using combinations of molecular state tags and symbols for binding states, the user can specify the exact

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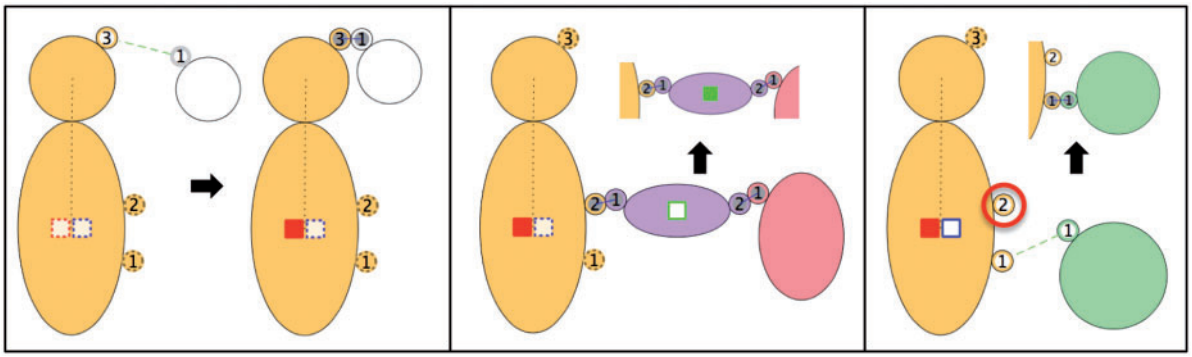

Fig. 1. Visual specification of molecular interactions with the Simmune Modeler. G-protein coupled receptors, once activated by their extracellular ligands, can promote the GDP–GTP exchange by the Gα component of the associated G-protein complexes. Phosphorylation through receptor kinases tags the receptors for internalization as part of their negative regulation. Left panel: Interaction between a ligand (white circle) and the binding site [labeled (3)] of the extracellular domain of the receptor. The association leads to the activation of the cytoplasmic domain of the receptor, as indicated by the red square tag switching from an empty shape with a dotted outline (encoding 'any state' or 'don't care') to a filled shape (encoding 'on'). Note that the engagement of the two binding sites (at receptor and ligand) alters their display mode from empty circles (indicating 'unbound') to filled circles (indicating 'bound'). Center panel: The active receptor induces a GDP–GTP exchange at the associated G-proteins. This switch is indicated as the transformation of the empty green square ('off') on the Gα subunit into a filled green square ('on'). The full complex diagram shows the state before this transformation, the partial diagram in the upper right corner the result state. Note that the transformation requires the receptor to be active (filled red tag), but does not require the ligand to be still bound (dotted outline of the extracellular binding site). Right panel: Interaction between a receptor kinase (green circle) and the cytoplasmic domain of the receptor. This interaction uses a site on the receptor that is different from the site [labeled (2)] recruiting the G-proteins. However, the interaction rule requires that the G-proteins not be bound to the receptor. This is indicated by the empty circle representing a free G-protein recruitment binding site (in this figure emphasized by a red circle around the binding site). The interaction moreover requires the receptor to be active (red filled tag) and the blue tag, representing the receptor's phosphorylation state to be in the off state. After association with the receptor, the receptor kinase can phosphorylate the receptor (switching the blue tag from empty to full, not shown). The full complex diagram shows the state before ligation, the partial diagram in the upper right corner the result state. The model is provided as Supplementary Material

conditions under which a certain biochemical reaction can take place and what the consequences (state modifications) for the interacting molecular complexes are.

In most use cases, the mapping from the molecules before a reaction to the result molecules is uniquely specified through the molecule types of the reaction participants. However, for molecular transformations with multiple instances of a particular molecule type, e.g the autophosphorylation of a multimeric complex consisting of identical subunits, this mapping cannot be inferred automatically. To permit a unique definition of such reactions, the user of the software can specify the mapping explicitly (see Supplementary Text 1 for details).

The Simmune Modeler was designed to support models that include interactions between receptors located on the mebranes of adjacent cells. Molecules such as the important Cadherin-family adhesion receptors can form homophilic bonds whose characteristics depend on whether the molecules are located in the same membrane ('cis' interaction) or in distinct adjacent membranes ('trans' interaction). To take this into account, the Simmune Modeler permits the specification of the binding mode (*cis* or *trans*) for interactions between pairs of membrane-bound molecules (Supplementary Fig. S2). To facilitate model development, model properties can be inspected with the help of a flexible query interface. The models created with the software can be simulated with the Simmune Toolset (Angermann *et al*., 2012) and can be exported as SBML files or mass-action Ordinary Differential Equation (ODE) descriptions that can be imported into Matlab™ or other ODE solver tools (see discussion in Supplementary Text 2). Moreover, the modeler will support the emerging SBML 3 standard for encoding multi-component, multi-state molecular complexes to allow for exchange of models with other rule-based approaches such as BNGL (Hlavacek *et al*., 2006) and Kappa (Feret *et al*., 2009).

ACKNOWLEDGEMENTS

The authors thank all members of the Laboratory of Systems Biology for helpful comments.

Funding: This work was supported by the intramural program of the National Institute of Allergy and Infectious Diseases, NIAID.

Conflict of Interest: none declared.

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