Rule Refinement in BioNetGen

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***Short Abstract* — Many algorithms that have been developed for the analysis and efficient simulation of reaction networks require further adaptation to be applied to rule-based models. We show here that a process of rule refinement involving systematic addition/modification of reaction context is the key step allowing adaptation.**

***Keywords* — Rule-based modeling, BNGL, Kappa, model reduction, tau leaping, hybrid simulation, rule refinement, reaction network.**

I. Rule-Based Modeling

Rule-based modeling exploits the modularity of molecular interactions to compactly represent, parameterize and simulate chemical reaction networks. In modeling languages such as BioNetGen[1,2] and Kappa[3], molecules and complexes are modeled as structured objects. Substructures of complexes or 'patterns' select molecular species that possess a matching substructure. A 'reaction rule' between patterns thus represents multiple reactions between the selected molecular species. Using reaction rules allows efficient and compact representation of any large, potentially infinite reaction network.

II. Context Specificity In Reaction Rules

The portion of a pattern that is transformed in a reaction rule is called the reaction center and the remaining part is called the reaction context. By manipulating the amount of information in the reaction context, the reaction rule can be made to apply broadly to a wide range of complexes or very narrowly to only a few specific complexes. Thus controlling the context of a reaction rule allows control over the number of reactions that the rule represents.

III. Processing Reaction Networks

Given a finite reaction network, it is often helpful to partition it into sub-networks or process the entire network for theoretical considerations or for simulation efficiency. Two such examples are described here in brief:

a) Model reduction is an endeavor to transform a complex reaction network into a smaller network of ODEs with reduced complexity using 'summed-over' variables. The resulting 'reduced' model is equivalent (either exactly or approximately) to the original reaction network. Model reduction methods include using domain-based macro-states[4], using occurrence levels[5] or layer definitions[6] respectively to reduce a reaction network. The reduced model of a reaction network can be easily constructed in the rule-based framework. However, the converse is not true and an arbitrary rule-based model does not have to correspond to the reduced model of a reaction network.

b) Simulating reaction networks using ODE integration or the network-based Gillespie algorithm[7] quickly becomes unsuitable for combinatorially large networks. Techniques such as tau-leaping[8] require processing the reaction network to sort slowly-changing and quickly-changing populations or rates. In general, hybrid-simulation methods seek to analyze the reaction network and discover regimes to apply higher-level approximations and reduce computing overhead.

There are many other scenarios (detailed balancing, model checking, etc.) where algorithms exist to process and analyze finite reaction networks. However, they are limited by network size, combinatorial complexity and inapplicability to infinite reaction networks.

IV. From Reaction Networks To Rule Sets

It is useful to consider extending network-based approaches to the rule-based framework, since a rule-based model is an exact and compact equivalent of a reaction network. Such extensions would require compatibility restrictions on the rule set. There is no guarantee that an arbitrary set of reaction rules would conform to these restrictions. To ensure compatibility of a rule-based model with a specific network-based approach without completely expanding the network, it is necessary to treat network processing at the level of reaction rules and not at the fundamental reaction level.

This requires a systematic framework to refine reaction rules while maintaining network-equivalence and algorithm-compatibility simultaneously. We present a theoretical framework that takes as input an arbitrary set of reaction rules, systematically alters their context definitions and outputs a refined and expanded rule set compatible with specific network based approaches. We expect that a formal rule-refinement approach would be influential towards new algorithmic advancements in rule-based modeling.

Acknowledgements: We acknowledge & thank Justin S. Hogg and Leonard Harris for useful discussions.

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