THiMED: Time in Hierarchical Model Extraction and Design

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Abstract. We describe our approach to modeling timing of cell signaling systems in which existing information about the system spans from detailed mechanistic knowledge to much coarser observations about cause and effect. The results for several models emphasize the fact that the selection of timing implementation can have both qualitative and quantitative effects on the model's transient behavior and its steady state.

Keywords: timing, cell signaling, stochastic model, delay

1 Introduction

Time of occurrence and duration of events often play an important role in decision making in cell signaling networks [1]. Although timing of events can be modeled using reaction rates, exact element regulations are not always well understood, and even more, rates of reactions are not known. Still, to better understand how the overall system works, it is important to capture in the model much of the available knowledge about the system. When experimental observations provide insights into indirect cause-effect relationships only, and do not explain many of the detailed interaction mechanisms [2], our modeling approach accounts for (*i*) thresholds in element activity, thus discretizing model variables [3], (*ii*) relative delays between events and in element responses to regulation changes, thus capturing critical event timing.

2 Approach

We model system elements using multi-valued variables, and by using this approach we are able to capture multiple layers of cell signaling: interactions between receptors and external stimuli, intracellular signaling, gene regulation, cell's response to stimuli, and feedback to cell receptors [1][2]. Such an approach has been shown valuable in providing critical insights into system's transient behavior, when models are coarse-grained in parts or in whole due to available knowledge. To increase accuracy of the model, in our approach we allow for implementation of timing details that

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capture relative delays between events. Once the delays are described formally (e.g., using delay truth tables [3]), our tool translates them into variable update rules. We identified three different methods to model delays that occur between a change in given element regulation (i.e., change in combination of regulator values and current element value), and a corresponding change in the element's value.

In the first delay implementation, all regulator value combinations that satisfy the same transition requirement in terms of previous and next element value and delay interval (i.e., all delay truth table entries with same output value) are lumped into a single function. Such implementation assumes that measuring delay (lapsed time) is not reset even when the actual conditions change, as long as the outcome is same. This approach allows for minimizing element update functions, since multiple table entries can be lumped into a single function. In contrast to the first approach, if the conditions change before the required delay interval has lapsed, even when the new output is same for the new conditions, measuring of delay interval is reset. This delay modeling approach requires different "memory" implementation compared to the first approach. The third approach implements delays as "buffers" that add steps to the pathway, thus delaying propagation of any value of a regulator (for any combination with other regulators) to some or all of its downstream elements. This approach can be used when modeling pathway sections without crosstalk or when only indirect causal relationships are known, while the overall timing of the pathway still needs to match the timing of other pathways in the network.

We have also worked on simulation approaches to accurately account for these different delay modeling methods. Depending on the simulator setup, delay values in cell signaling models can be assumed exactly as defined, or can represent upper bounds or mean delay values.

2.1 Results

We applied the described timing modeling approaches in development and analysis of two models, T cell differentiation model [1] and immune crosstalk in malaria infection in mosquitoes [2]. We have shown that, depending on the delay implementation method, different delay values can affect results both qualitatively and quantitatively, and can change both transient behavior and steady state of individual elements, as well as of the system as a whole.

3 References

1. N. Miskov-Zivanov, et al., "The duration of T cell stimulation is a critical determinant of cell fate and plasticity," in Science Signaling, 6, ra97, November 2013
2. Y. Vodovotz, et al., Modeling Host-Vector-Pathogen Immuno-inflammatory Interactions in Malaria, in Complex Systems and Computational Biology Approaches to Acute Inflammation, pp. 265-279, Springer New York, 2013.
3. N. Miskov-Zivanov, et al., "Dynamic behavior of cell signaling networks: model design and analysis automation." in Proc. of Design Automation Conference (DAC), Article 8, 6 p., June 2013.