Modeling Dysregulation of Complex Systems Implicated in Cancer & Diabetes

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***Short Abstract* — Aberrant regulation of large and complex cell signaling cascades often results in disease states such as cancer or diabetes. Computational modeling has proven to be an effective tool for gaining more insight into these systems, however, traditional modeling methods do not generally scale well as the size and complexity of these systems increase, often forcing researchers to make simplifying assumptions that can bias model behavior. To address these problems, we have developed a unique rule-based modeling method, the foundation of which is a formal semantic language called Kappa, that avoids the combinatorial explosion often seen in more traditional reaction-based frameworks.**

***Keywords* — rule-based modeling, stochastic simulation, kappa, EGFR, insulin, HER2**

We have developed a unique rule-based modeling method, the foundation of which is a formal semantic language called Kappa[1,2], that avoids the combinatorial explosion often seen in more traditional reaction-based frameworks. Kappa facilitates easy manipulation of existing models as well as the seamless incorporation of new information, thus allowing for fresh analysis and extension of published models. Using this method, we have successfully built and simulated large and complex systems to explore their underlying dynamic and causal characteristics.

Here we present two examples of the use of our approach to study and extend existing models. First, we have reproduced a model of EGF-induced signaling in gastric cancer, which explores the distribution of activated receptor homo- and hetero-dimers both with and without ligand. It also demonstrates the observed distribution of these dimers in the presence of normal and over-expressed HER2. We are continuing to investigate how ligand and HER2 levels effect key downstream players. Second, we have built a model of insulin signaling based on a highly cited differential equation model. Due to the flexibility of our rule-based modeling framework, we were able to easily expand the model to include additional biological detail. Using both the EGFR and the insulin models, we compare the capabilities of the stochastic and deterministic simulation methods that we have developed and together, these models demonstrate the power of our rule-based modeling approach.

[1] Danos, V., Feret, J., Fontana, W., Harmer, R. & Krivine, J. *Rule-based modelling of cellular signalling*. Lecture Notes in Computer Science 4703, 17-41 (2007).
[2] Danos, V., Feret, J., Fontana, W. & Krivine, J. *Scalable simulation of cellular signalling networks*. Lecture Notes in Computer Science 4807, 139-157 (2007).

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