Measuring and Modeling Cell Decision Processes

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***Short Abstract* —Life-death decisions in mammalian cells are controlled by extracellular ligands and the receptors to which they bind. I will discuss a combined model-measure approach to dissecting the biochemistry of pro-death and pro-survival pathways downstream of mitogenic and death receptors and to deriving new mechanistic insight. Our differential-equation based models are topologically complex and invariably non-identifiable given available data. I will describe approaches for managing uncertainty in topology and parameterization and discuss an approach to probabilistic reasoning about cellular biochemistry that represents a significant advance on the anecdotal descriptions that currently predominate in molecular and cellular biology.**

***Keywords* — Signal transduction, apoptosis, mitogenesis, kinetic modeling, model calibration, model identifiability,**

I. Introduction

Our goal in representing complex biochemical processes as formal mathematical models is to enable more rigorous and extensible approaches to inferring mechanism, elucidating the origins of variability among genetically identical and non-identical cells, and understanding the coordinated activities of multiple proteins in determining cellular phenotype. Creation of suitable models invariably involves the judicious selection of prior knowledge (typically from the literature), choosing an appropriately detailed set of equations to describe the prior knowledge and then comparing models to experimental data. Only then can the processes of hypothesis generation and testing begin. Each of the steps in model creation, calibration and validation is fraught with uncertainty that must be managed appropriately if valid conclusions are to emerge. I will describe a multi-faceted environment for computational analysis of mammalian signal transduction and discuss our experience in using it to analyze prototypical mammalian signal transduction pathways, one involving pro-survival ErbB receptors and the other pro-death TRAIL/Fas receptors.

II. Results

Because the pathways we study are comprised of relatively abundant molecules (typically thousands of copies per cell), we rely primarily (although not exclusively) on models that involve compartmentalized networks of ODEs. The process of determining which aspects of prior knowledge should be included in a model is managed using a Semantic Biology Wiki (*SBWiki*) that imports and exports SBML and MIRIAM annotation. Actual models are assembled from BNG rules using PySB, whose Python-based programmatic representation of protein networks is sufficiently abstract to be intelligible even to inexperienced users but sufficiently precise to allow unambiguous instantiation in equations. Diverse experimental data on the dynamics of particular species (much of it based on single-cell microscopy) is then used in a Bayesian parameter estimation scheme to sample fully parameter space based on convergent MCMC procedures. Finally, model-based predictions are generated and evaluated in light of parametric uncertainty and uncertainty in model topology.

These procedures set the stage for model analysis using a variety of approaches that examine bifurcations, reaction fluxes and alternative mechanistic hypotheses.

III. Conclusions

We have begun to apply an approach to reasoning across biochemical mechanism that has the flexibility and intuitive appeal of the "word models" that predominate in molecular biology but that involve a more rigorous approach to reasoning across prior knowledge and quantitative data. I will describe applications to understanding cell-to-cell variability in responses to TRAIL, the nature of the biochemical "switches" that make apoptosis and all-or-none process and the mechanisms of action of therapeutic drugs that target ErbB receptors. All of the software and algorithms I will discuss are freely available.

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