Towards Understanding Cellular Proliferation and Death Signal Processing in Cancer

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***Short Abstract* — New targeted cancer therapies induce dramatic responses in specific cancer types. However, tumor drug resistance almost inevitably follows. Understanding the underlying mechanism(s) leading to a particular drug resistance is complicated by the complexity of the protein interaction network in a cell. We are developing computational models to link proliferation and apoptosis related signaling in ErbB-dependent cancer cells to phenotypic cell fates, and creating new tools to efficiently calibrate and analyze these models.**

***Keywords* — ordinary differential equation models, erbb signaling, multi-objective optimization, sensitivity analysis**

I. Background

THE four receptors in the ErbB receptor family bind many ligands and transmit signals involved in proliferation, growth, and survival. Dysregulation of ErbB signaling occurs frequently in cancer and is commonly pharmaceutically targeted [1]. The large array of drugs targeting proteins in the ErbB signaling network make computationally predicting network response to multiple perturbations an attractive prospect. Two system outputs, proliferation and apoptosis, are particularly important when characterizing system response to single or combination cancer therapies. ErbB-related signaling has been extensively modeled within the mass action kinetics formulism [2-4], providing a foundation for this work.

II. Present Work

We are currently developing tools in three distinct areas in order to better understand cellular proliferation and death signaling in cancer. First, we are building ODE models that encode the intersection of proliferation and apoptotic signaling networks in ErbB-signaling dependent cancers. Secondly, we are developing new multi-objective calibration methods to make calibrating these models to large experimental datasets efficient and feasible. Lastly, we are exploring methods to characterize the parameter sensitivity and dynamic modes of these models to enable more effective model analysis.

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A. Model building

We are expanding previous models of ErbB-dependent MAPK-Ras and PI3K-Akt signaling [4] to include proliferation markers and connections to previous models of apoptotic signaling [5]. Our models are encoded using PySB [5], which allows efficient model creation and testing of multiple model variants. Experimental data for model variation is collected by collaborators at multiple time points in several ErbB-dependent breast cancer and lung cancer cell lines; absolute protein values for use in model calibration are then determined using mass spectrometry methods [6].

B. Calibration Methods

We are developing new algorithms to efficiently sample the joint probability distributions of model parameters [7] using multi-objective criteria to generate an approximation of the Pareto front. Our algorithms are designed to be highly parallelizable in order to increase calibration efficiency.

C. Model analysis

We have implemented a variance-based sensitivity analysis method to determine model output sensitivities to parameters and combinations of parameters using fewer model evaluations [8]. We are also utilizing tropical geometry to reduce models and characterize model modes [9].

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