Applications of sensitivity analysis for drug discovery and development in the ErbB network

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***Short Abstract* — Merrimack Pharmaceuticals is using quantitative biochemical network models to guide the development of oncology therapeutics. Here, using a validated ErbB receptor network model that includes ligand-receptor binding, receptor trafficking, and intracellular signal transduction, we present the use of global and local sensitivity analysis as *in silico* tools applied to drug targeting and biomarker identification. We find that sensitivity analysis gives quantitative insights into issues including network topology and the importance of cellular heterogeneity with respect to protein expression.**

***Keywords* — ErbB network, sensitivity analysis, drug discovery, biomarkers**

I. Introduction

Receptor-mediated signaling networks are very attractive targets for the development of oncology therapeutics. However, the complexity of these networks, characterized by redundancy, cross-talk, and non-linearity, hinders reliable qualitative insight into developing more effective therapeutics that can be delivered to the right patients.

We are using quantitative biochemical network models of receptor signaling to yield significant improvements in drug design and decision-making throughout the development of our therapeutics. As an example, we have developed a model of the ErbB receptor network that includes ErbB1-4, ligand-receptor binding of ErbB ligands, receptor trafficking, and intracellular signal transfer leading to ERK and Akt phosphorylation. The model is first trained using quantitative experimental data and then our *in silico* predictions are verified by an independent set of experiments.

Using this validated biochemical network model, we present methodologies for using local and global sensitivity analyses as *in silico* drug discovery tools. Sensitivity analysis has many applications in model-based drug discovery, including identification of optimal network intervention points for therapeutics and assessing kinetic and thermodynamic parameters for inhibitor action. Here, we use sensitivity analysis to gain quantitative insights into issues including network topology and the importance of cellular heterogeneity with respect to protein expression. We show how these insights can be applied to drug targeting and biomarker identification.

II. Experimental Design

We have explored the role of EGFR overexpression on the sensitivities of ERK and AKT signaling to intracellular protein levels. Simulations were performed using EGF stimulation on two ErbB receptor expression profiles with 10-fold difference in EGFR levels. For each ligand/receptor combination, global sensitivity analysis was performed in the MATLAB environment by carrying out 2000 local sensitivity calculations with the initial conditions for intracellular proteins randomly sampled using the Latin hypercube method [1]. Sampling was done using a log-uniform distribution ranging from 0.01-100 times the nominal expression level for each protein.

III. Conclusions

Global sensitivity analysis provides valuable information that is distinct from the more commonly used local sensitivity analysis. However, the computational cost of the global calculations is quite substantial.

Our results show that the optimal choice of drug targets should reflect the molecular heterogeneity inherent to human tumors. For maximum therapeutic index, it is important to identify network intervention points which are broadly effective in a population of cancer cells with heterogeneous protein expression. Conversely, therapies should be avoided that inhibit a locally but not globally sensitive target.

References

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