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Poster presentation

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

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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 the generation of reliable qualitative insight into how to develop the most effective therapeutic and deliver it to the right patient.

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 different 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. The application of sensitivity analysis allows us to gain quantitative insights into important issues including network topology and the importance of cellular heterogeneity with respect to protein expression. We show how these insights find application in drug targeting and biomarker identification.