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A Data-Driven Computational Model of the ErbB Receptor Signaling Network

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Signal transduction networks are often described by qualitative models that incorporate experimental findings from different cell types. However, a large body of evidence suggests that cell signaling differs substantially from one cell type to the next. Even in cases in which the topology of signaling networks is conserved, different cell types respond differently under the same experimental conditions. In this work we address the problem of developing quantitative and cell-type specific models of cells signaling that incorporate experimental data obtained from protein arrays and mathematical modeling. As a biological system we examine signaling mediated ErbB receptor family as the current literature is very controversial.

The EGF receptor system is a complicated network comprising at least 12 growth factor ligands and four receptors, ErbB1 (EGFR), ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4). ErbB1 and ErbB4 are fully active receptors, ErbB3 is lacking a tyrosine kinase domain, ErbB2 lacks the ability to bind ligands and mainly acts as a coreceptor. Due to the combinatorics and the fact that only receptor dimers signal, a large body of different signaling dimers are formed, generating a variety of cellular signals that include ERK and AKT activation. The specificity and potency of intracellular signals is determined by the nature of the ligand, by the expression level of the different ErbB family members as well as by the differences within the signaling cascades triggered by the different homo- and heterodimers. The cascades that regulate ERK and AKT do not function independently from each other but are characterized by crosstalk on several levels as indicated in Figure 1.

In the following graph the regulatory network of the EGF receptor family is depicted. Boxes indicate various membrane bound and cytosolic proteins, black arrows indicate activation/ phosphorylation of a protein and a red "T" indicates inhibition.

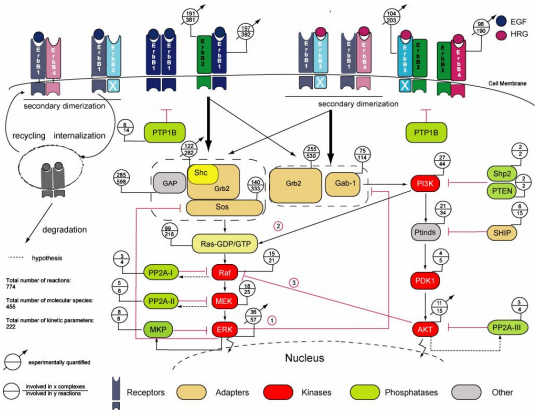

Figure 1. Regulatory network of the ErbB family signal transduction network triggering ERK and AKT activation including the crosstalk between the two pathways.

In recent years computer models of signal transduction pathways have gained acceptance. We have developed a computational model of the ErbB receptor family signal transduction for two ligands, EGF and HRG, based on our previously developed EGF receptor model (Schoeberl:2002) and a large body of experimental data. The system analysis of the four receptors and resulting dimers in association with two different ligands sheds light on the signaling network from a functional perspective. Our model accommodates differences in the expression levels of ErbB receptors. These differences

have been identified as important factors in contributing to various types of cancer, especially breast cancer.

The mathematical model is based on Ordinary Differential Equations (ODEs). Due to the very large number of possible combinations of dimers the model reaches a size of about 520 ODEs, and 220 kinetic parameters.

For the parameter estimation (=training of the model) various biochemical data formats such as time courses and protein quantification is needed. These biochemical data were collected with the help of protein arrays (Nielsen:2003), which allowed us to measure several time courses of protein phosphorylation in parallel on one array. Likewise we are able to quantitatively compare the phosphorylation level in the different cell lines simultaneously.

In assessing the crosstalk between the ERK and AKT pathway, we find that the topology of the signal transduction network is a critical feature for correctly predicting actual data. In contrast, kinetic parameters such as the 220 play a secondary role. We show this by analyzing the crosstalk on different levels with different strength within the signaling cascade. Furthermore, we show that a model that has been developed for A431 cells, human squamous carcinoma cells, can be used to make *insilico* predictions about the efficacy of small molecule inhibitors against the ErbB1 or ErbB2 receptor on the receptor level but also on the level of AKT and ERK phosphorylation in this cell line.

Computational models like the one developed here are very useful if they are applicable to other cell lines. Using A431, SK-BR3 and BT474 cells we show that simply by characterizing the protein expression levels in these cell types as accurately as possible, we can predict the extent of ERK and AKT phosphorylation. We verified the *insilico* findings with our own experimental data in these cell lines mentioned above. Beyond this, the model has allowed us to explain controversial experimental findings described in the literature.

The good correlation between the experimental findings and the *insilico* predictions lead us to the conclusion that experimental results from different cell lines which seem contradictory at the first glance do not result from differences in the network topology but from differences in the protein expression levels. More work needs to be done however, to explore whether this also holds true in cells with a different tissue of origin.

We will discuss how these mechanistic data-driven models can be very valuable within the drug development process and with respect to biomarker identification (Nielsen and Schoeberl 2005).
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References

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