

Data driven dynamic modeling of a signalling pathway

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ABSTRACT

Considerable progress has been made identifying the molecular composition of complex signalling networks controlling cell proliferation, differentiation and survival. However, to discover general building principles and quantitatively predict the behavior of signalling networks it is essential to develop data driven dynamic mathematical models describing experimental observations [1]. Pure simulations studies of dynamical models derived from qualitative network cartoons are not sufficient to infer about underlying mechanisms because it can not be decided whether discrepancies between simulated and measured data are caused by ill-chosen parameters or by inadequate models. Therefore, to quantitatively compare competing models, it is essential to estimate parameters from measured data [4].

We report results of data driven dynamic modeling of the core modul of the JAK-STAT signalling pathway based on experimental data. The hormone Erythropoietin (Epo) is the key regulator for the development of red blood cells from erythroid progenitors. Epo binding to its receptor induces a conformational change that transiently activates the receptor-associated tyrosine kinase JAK2. JAK2 phosphorylates tyrosine residues in the Erythropoietin receptor (EpoR) cytoplasmic domain creating docking sites for downstream signalling molecules. Upon EpoR tyrosine phosphorylation, STAT (signal transducer and activator of transcription)-5 binds to the EpoR and is rapidly phosphorylated. After homodimerization of phosphorylated STAT-5 monomers, STAT-5 translocates to the nucleus where it binds to the promotor of target genes and modulates gene expression.

The parameters of the four differential equations describing the systems were estimated from time resolved measurements of receptor activation and tyrosine phosphorylated STAT-5. In contrast to the widely accepted assumption of a linear entity terminated by nuclear export [2], we demonstrate that effective signal transduction requires multiple successive STAT-5 activation-inactivation cycles.

Based on the fitted model we can determine the quantitative behavior of STAT-5 populations not accessible to experimental measurements and reveal that under the conditions used STAT-5 resides in the nucleus for approximately 6 minutes. The dynamic model with parameters fitted from one series of experiments can successfully describe an inde-

pendent experiment. Sensitivity analysis identifies nuclear shuttling as the step most sensitive for perturbations of the system. Blocking the re-entry of STAT-5 into the cytoplasm in the model shows that a pure feed-forward cascade would only have a 40 % effect. It is possible to partially inhibit the nuclear export experimentally by leptomycin B. Fitting parameters under this condition reveals that the blocking-efficiency of leptomycin B is 60 %.

Thus, quantitative data driven dynamic modeling can promote functional understanding of biological systems and allows for identification of targets for medical intervention by realistic *in silico what-happens-if* simulations.

A detailed discussion of the results is given in [3].

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