The Silicon Cell Initiative: a modular approach to building the Silicon Yeast Cell

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One of the biggest challenges for System Biologists lies in building kinetic models on a cellular level. Attempts on modelling at this scale have mostly been limited to structural models of metabolism (e.g.[1]). Powerful as such structural models have proven to be, they are limited by the absence of kinetic information. Thus, although structural models can be used to estimate e.g. maximal obtainable product yields, they cannot predict whether such yields will be obtained, as the actual fluxes are dependent on the kinetics of the individual reactions. In contrast to structural information, kinetic information (rate equations and parameter values) cannot be derived from the gene sequence and must be experimentally determined. With each cell containing several thousands of enzymes each having at least three kinetic parameters, setting up kinetic models at a cellular level seems impossible. We here propose a modular approach to building such kinetic models. Metabolism is divided in separate modules for which models are constructed and validated independently. The models are collected in a model database and can be grouped together to ultimately lead to a model of the whole cell. In studies where one aims at describing system behaviour as a function of the enzyme characteristics it is important that the kinetic parameters are measured and not fitted on systems behaviour. This type of models we termed Silicon Cell models and the approach is explained in more detail at (http://www.siliconcell.net). We illustrate the approach using yeast as an example. We have started a database of kinetic models (http://jjj.biochem.sun.ac.za; [2]) that can be accessed over the internet and the models can be run interactively. We have started grouping different yeast models together leading to an overall improvement of predicting experimental steady state values. Our initiative is part of the Yeast Systems Biology Network (http://www.ysbn.org) an international workgroup that has agreed to use our database of models as a computational web site. We propose to use this work group as a vehicle to connect experimental and modelling labs together and divide yeast modules over the different labs.

[1] Price, N.D., Papin, J.A., Schilling, C.H. and Palsson, B.O. (2003) Genome scale microbial in silico models: the constraint based method, Trends in Biotechnology, 21: 162–169.

[2] Olivier, B.G. and Snoep, J.L. (2004) Web-based kinetic modelling using JWS Online, Bioinformatics, 20: 2143–2144.