Quasi Steady-State Approximations in Signal Transduction - a Word of Caution

Morten Gram Pedersen, Alberto M. Bersani, Enrico Bersani

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Abstract

The main goal of computational biology, and in particular of Systems Biology, is to define a comprehensive model that can accurately represent the experimental data and serve as a tool to generate and test hypotheses. Consequently, a high accuracy of the model is necessary in order to give a satisfactory prediction, both by a qualitative and quantitative point of view. Enzyme reactions play a pivotal role in intracellular signal transduction. Many enzymes are known to possess Michaelis-Menten (MM) kinetics and the MM approximation is often used when modeling enzyme reactions. However, it is known that the MM approximation is only valid at low enzyme concentrations, a condition not fulfilled in many in vivo situations. Thus, using the MM approximation with its parameter values obtained from in vitro experiments will often lead to false conclusions when simulating in vivo systems. Recently several other mathematical approaches, such as the total quasi steady-state approximation (tQSSA), have been developed for enzymes with MM kinetics. These new approximations are valid not only whenever the MM approximation is, but moreover in a greatly extended parameter range. Starting from a single reaction and arriving at the mitogen activated protein kinase (MAPK) cascade, we give several examples of biologically realistic scenarios where the MM approximation leads to quantitatively as well as qualitatively wrong conclusions, and show that the tQSSA improves the accuracy of the

simulations greatly. Moreover, we discuss the use of approximations in reverse engineering and the biological importance of our findings.