Oscillations and bistability in intracellular signal transduction pathways

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Motivation

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. In the last decade many mathematical models have been formulated to investigate the behavior of complex intracellular biochemical networks. The aim of such modeling (which is an integral part of the 'Systems Biology' large scale project) is roughly twofold: to reproduce and study some particular phenomena observed experimentally (like bistability, oscillations, ultrasensitivity etc.) and to investigate the properties of these networks as information processing and transducing devices. Surprisingly, the mathematical formulation of these highly interconnected enzyme reactions usually lacks a serious criticism of the delicate passage from the kinetics of simple reactions to the kinetics of complex reaction networks. This can be justified when analyzing underlying mechanisms (e.g., the importance of feedback or the creation of oscillations), where the exact kinetic expressions and parameters are less important since one is usually only interested in the qualitative behavior that the system can perform. However, in the light of the Silicon Cell project, which aims at being a both qualitative as well as quantitative precise representation of the living cell, the use of correct parameters, kinetic expressions and initial conditions (i.e., steady-state concentrations of molecular species) becomes crucial.

Methods

One of the principal components of the mathematical approach to Systems Biology is the model of biochemical reactions based on the classical Michelis-Menten kinetics.
This formulation considers a reaction where a substrate binds an enzyme reversibly to form a complex. The complex can then decay irreversibly to a product and the enzyme, which is then free to bind another molecule of the substrate. This scheme is mathematically represented by a system of two nonlinear ordinary differential equations (ODEs), corresponding initial conditions and two conservation laws. Assuming that the complex concentration is approximately constant after a short transient phase leads to the usual Michaelis-Menten (MM) approximation (or standard quasi steady-state assumption or approximation (sQSSA)), which is valid when the enzyme concentration is much lower than either the substrate concentration or the Michaelis constant. This condition is usually fulfilled for in vitro experiments, but often breaks down in vivo. The advantage of a quasi steady-state approximation is that it reduces the dimensionality of the system, passing from two equations (full system) to one (MM approximation or sQSSA) and thus speeds up numerical simulations greatly, especially for large networks as found in vivo. Moreover, the kinetic constants are usually not known, whereas finding the kinetic parameters for the MM approximation is a standard in vitro procedure in biochemistry. However, to simulate physiologically realistic in vivo scenarios, one faces the problem that the MM approximation is no longer valid as mentioned above. 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. Importantly, the tQSSA uses the same parameters as the sQSSA. Hence, the parameters found in vitro from the MM approach can be used by the tQSSA for modeling in vivo scenarios.

Results

Our investigation applies to every biochemical network which includes enzyme reaction cascades. Starting from a single reaction and arriving at the mitogen activated protein kinase (MAPK) cascade, including feedback, 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. However, since the tQSSA, although superior to the sQSSA, also does not always work, we also use the alternative of simulating each step of the reaction by means of the full system of ODEs, which means describing every reaction in terms of two equations, and facing three instead of two parameters for every reaction, as it has been done for example for the MAPK cascade. We also study simple reaction schemes characterized by bistability and concentration oscillations; we compare the solutions of the full system with their standard and total approximations. We show that the parameter ranges giving oscillations or bistability are sometimes slightly different, concluding that in these cases the approximations are absolutely inadequate to represent the behaviour of the network.

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