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Mathematical Models of Open and Closed Biochemical Reactions in Living Cells

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Living cells must communicate with the external environment, exchanging information in terms of molecular interactions, starting from suitable plasma membrane receptors and transducing the information by highly complex intracellular networks in which various layers, cascades, subnetworks can be identified. In the last decade many mathematical models have been formulated to investigate the behavior of these networks and their substructures.

This models rely on the assumption that a biochemical reaction can be described in terms of the so-called Michaelis-Menten (MM) kinetics [2], [6], proposed at the very beginning of the last Century, where a substrate S binds reversibly to an enzyme E to form a complex C. The complex can decay irreversibly to a product P and the enzyme, which is then free to bind another substrate molecule. This process is summarized in the scheme

$$E + S \underset{}{\overset{d}{\longleftarrow\!\!\!\longrightarrow}}{}^{a} C \xrightarrow{k} E + P, \tag{0.1}$$

where a, d and k are kinetic parameters (supposed constant) associated with the reaction rates.

Assuming that the complex concentration is approximately constant after a short transient phase leads to the classical *standard quasi steady-state assumption* or *approximation* (standard QSSA, sQSSA)) [2], [7]

$$\frac{dS}{dt} \approx -\frac{V_{max} S}{K_M + S}, \quad S(0) = S_0, \tag{0.2}$$
$$E(0) = E_0, \quad V_{max} = k\, E_0, \quad K_M = \frac{k+d}{a}.$$

Here V_{max} represents the maximal reaction rate and K_M is called the Michaelis constant and reflects the substrate affinity of the enzyme. This approximation is valid whenever [13], [14]

$$\frac{E_0}{K_M + S_0} \ll 1, \tag{0.3}$$

i.e., when the enzyme concentration is much lower than either the substrate concentration or the Michaelis constant K_M.

This approximation 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, and thus speeds up numerical simulations greatly, especially for large networks as found *in vivo*. Moreover, while the kinetic constants in (0.1) are usually not known, finding the kinetic parameters characterizing the sQSSA is a standard procedure in *in vitro* biochemistry [2]. However, to simulate physiologically realistic *in vivo* scenarios, one faces the problem that the sQSSA is no longer valid as mentioned above. Hence, even if the kinetic constants such as K_M were identical *in vivo* and *in vitro*, they should need to be implemented in some other approximation which must be valid for the whole system and initial concentrations under investigation.

In the last decade the *total QSSA* (tQSSA) [3], [17], which is valid for a broader range of parameters covering both high and low enzyme concentrations, has been introduced. It is based on the introduction of the new variable $\overline{S} := S + C$, called *total substrate* and, like in the sQSSA, on the assumption that the complex concentration is approximately constant after a short transient phase. It brings to the equation

$$\frac{d\bar{S}}{dt} \approx -k\, C_-\bar{S}, \quad \bar{S}(0) = S_0, \tag{0.4}$$

where

$$C_-(\bar{S}) = \frac{(E_0 + K_M + \overline{S}) - \sqrt{(E_0 + K_M + \bar{S})^2 - 4E_0\bar{S}}}{2}\,. \tag{0.5}$$

Tzafriri [17] showed that the tQSSA is at least roughly valid for any set of parameters.

Also, the tQSSA has been studied for reversible reactions [18], i.e. reactions of form (0.1), but where enzyme and product can recombine to form the complex.

The new approximation has so far only been found for isolated reactions. Actually, *in vivo* reactions are coupled in complex networks or cascades of intermediate, second messengers with successive reactions, competition between substrates, feedback loops etc. Approximations of such scenarios have been carried out within the sQSSA scheme [2], [5], but often without a thorough investigation of the validity of the approximations. An exception is the case of fully competitive reactions [12], [13], i.e., reactions with competing substrates:

$$S_1 + E \underset{a_1}{\overset{d_1}{\longleftrightarrow}} C_1 \xrightarrow{k_1} E + P_1, \tag{0.6}$$

$$S_2 + E \underset{a_2}{\overset{d_2}{\longleftrightarrow}} C_2 \xrightarrow{k_2} E + P_2\,, \tag{0.7}$$

where S_i, C_i and P_i represent substrate, enzyme-substrate complex and product $i = 1, 2$, respectively.

Since the sQSSA cannot be expected to be valid *in vivo*, employing the tQSSA to these more complex situations would be beneficial.

In [8], [9] we investigated by a theoretical point of view the applicability of the tQSSA to fully competitive reactions.

Moreover, we obtained very promising numerical results for the phosphorylation- dephosphorylation loop and for the double phosphorylation reaction.

In this paper we deepen the theoretical investigation on these last reactions.

The assumption of dynamical equilibrium of the complexes is expected to break down when we deal with more complex reactions, in particular feedback loops. In these cases every QSSA could be inappropriate [1], [10]; thus we need new theoretical frameworks.

Adapting a recently proposed scheme [15], [16], we can represent every layer or substructure of a complex reaction network as a separate (or weakly coupled) biochemical reaction, where the upstream and downstream reactions can be respectively represented by an inflow function $I(t)$ and an outflow function $O(t)$ (on the concentrations of the substrate or of the enzyme catalyzing the reaction) explicitly introduced in the differential equations describing the single reaction. Here we apply the total quasi steady-state approximation on this scheme and show the usefulness of this approach.

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