Current Synthetic and Systems Biology

Ricard, Curr Synthetic Sys Biol 2015, 3:3
http://dx.doi.org/10.4172/2332-0737.1000125

Review Article Open Access

Systems of Connected and Aggregated Enzyme Reactions

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Abstract

It is well known that in the living cell many enzymes display numerous interactions. It is logical to think that these interactions affect the behaviour of these enzymes. The change may be enormous and can lead to quasi-novel reactions. The system thus generated is controlled by a number of "local flows" that generate some specific properties such as the emergence of information in the system.

Keywords: Enzyme; Metaprocess; Thermodynamic; Substrate

Introduction

It is often explicitly, or implicitly, considered that an enzyme reaction occurring under steady state conditions is a system that collects connected states of the enzyme that appear during the reaction. Moreover, there is little doubt that many enzymes *in vivo* are aggregated as multienzyme complexes in such a way that one can wonder whether the corresponding enzyme reactions are not aggregated to form a functional structure that connects and associates the elementary reactions as to form a coherent whole.

The isolated enzyme reaction as a coherent system

Let us consider an isolated enzyme reaction shown in Figure 1. This reaction is assumed to be simple. It involves two substrates, A and B, that bind to the enzyme following a compulsory order.

We assume for simplicity that catalysis and product release occur in one step. The corresponding steady state equation can be written as

$$\frac{v}{[E]_O} = \frac{kk_1[A]k_2[B]}{k_{-1}k_{-2} + k_{-1}k + (k_{-2}+k)k_1[A] + kk_2[B] + k_1[A]k_2[B]} \quad (1)$$

In this expression, where $[E]_0$ is the total enzyme concentration, one can write

$$k_1 = k_{-1}K_1$$

$$k_2 = k_{-2}K_2 \quad (2)$$

Where K_1 and K_2 are equilibrium binding constants of substrates A and B to the enzyme. Equation (1) can then be rewritten as

$$\frac{v}{[E]_O} = \frac{kk_{-1}k_{-2}K_1K_2[A][B]}{k_{-1}k_{-2} + k_{-1}k + (k_{-2}+k)k_{-1}K_1[A] + kk_{-2}K_2[B] + k_{-1}k_{-2}K_1K_2[A][B]} \quad (3)$$

Dividing numerator and denominator by $k_{-1}k_{-2}$ yields

$$\frac{v}{[E]_O} = \frac{kK_1K_2[A][B]}{1 + \frac{k(k_{-1}+k_2[B])}{k_{-1}k_{-2}} + \frac{k_1[A](k_{-2}+k)}{k_{-1}k_{-2}} + K_1K_2[A][B]} \quad (4)$$

Setting

$$\frac{k[A](k_{-2}+k)}{k_{-1}k_{-2}} = K_1[A] + \frac{k_1[A]k}{k_{-1}k_{-2}} = K_1[A] + u'_{EA} \quad (5)$$

and $\frac{k(k_{-1}+k_2[B])}{k_{-1}k_{-2}} = u'_E$ (6)

Equation (12) becomes

$$\frac{v}{[E]_O} = \frac{kK_1K_2[A][B]}{1 + K_1[A] + K_1K_2[A][B] + u'_E + u'_{EA}} \quad (7)$$

One can notice that u'_E and u'_{EA} can be viewed as local flows that lead to the free enzyme *E* and to the *EA* complex, respectively. Both of these local flows are expressed relative to a local flow of substrate desorption ($k_{-1}k_{-2}$). The flows u'_E and u'_{EA} allow the system to be in a steady state i.e. to display constant concentrations of *E, EA* and *EAB* under non-equilibrium conditions [1]. It is worth noticing that such a situation implies the self-organization of the system due to the local flows u'_E and u'_{EA} [2].

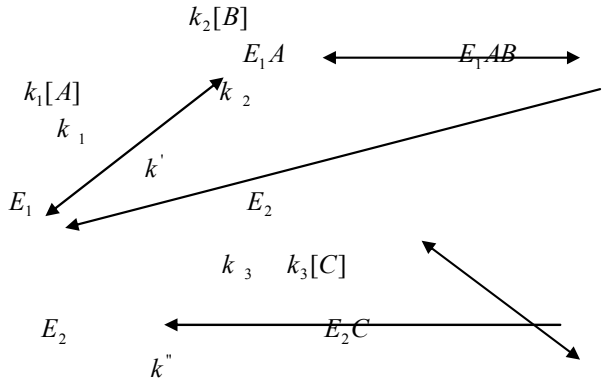

Figure 1: Two simple enzyme reactions involving either the sequential binding of two substrates, or of one substrate only, to the enzyme.
The double arrows indicate that the binding process is reversible. The simple arrow means that the catalytic process is not.

Now let us consider another simple reaction catalyzed by enzyme E_2, for instance the hydrolysis of substance *C*. One has the situation described in Figure 1. If the processes shown in Figures 1 and 2 take place in a complex made up of two enzymes E_1 and E_2 in interaction the resulting "global process" can be described as shown in Figure 2.

The rate equation of the two-enzyme global model

The rate equation of the global system of Figure 3 becomes more

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Received June 29, 2015; **Accepted** August 27, 2015; **Published** August 29, 2015

Citation: Ricard J (2015) Systems of Connected and Aggregated Enzyme Reactions. Curr Synthetic Sys Biol 3: 125. doi:10.4172/2332-0737.1000125

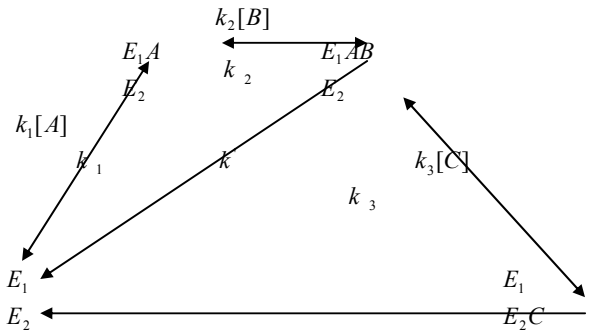

Figure 2: If the two enzymes E_1 and E_2 are bound together their activity gives rise to an atypical process with two catalytic constants.

complex than the individual equations of the enzymes E_1 and E_2 in isolation. However, one can notice that the global system is dependent upon antagonistic effects exerted by system 1. A first effect is a tendency to drift towards thermodynamic equilibrium. This tendency is exerted through the rate constants of substrate binding and release. A second effect is a tendency of the system to drift from the equilibrium and is exerted through a subtle combination of catalytic and substrate binding constants [3]. The situation is thus of the same type, but more complex, than the one already described. A global steady state of the system its organization, is the result of these interactions.

Let us consider the concentrations of the four states $\begin{bmatrix}E_1\\E_2\end{bmatrix}, \begin{bmatrix}E_1A\\E_2\end{bmatrix}, \begin{bmatrix}E_1AB\\E_2\end{bmatrix}$ and $\begin{bmatrix}E_1\\E_2C\end{bmatrix}$. One has

$$\begin{bmatrix}E_1\\E_2\end{bmatrix} = k_{-1}k_{-2}k_{-3} + u_E$$
$$\begin{bmatrix}E_1A\\E_2\end{bmatrix} = k_1[A]k_{-2}k_{-3} + u_{EA}$$
$$\begin{bmatrix}E_1AB\\E_2\end{bmatrix} = k_1[A]k_2[B] + u_{EAB} \quad (8)$$
$$\begin{bmatrix}E_1\\E_2C\end{bmatrix} = k_1[A]k_2[B]k_3[C]$$

One can notice that

$$k_1[A] = k_{-1}K_1[A]$$
$$k_2[B] = k_{-2}K_2[B] \quad (9)$$
$$k_3[C] = k_{-3}K_3[C]$$

The relations (8) can be rewritten as

$$\begin{bmatrix}E_1\\E_2\end{bmatrix} = k_{-1}k_{-2}k_{-3} + u_E$$
$$\begin{bmatrix}E_1A\\E_2\end{bmatrix} = K_1[A]k_{-1}k_{-2}k_{-3} + u_{EA}$$
$$\begin{bmatrix}E_1AB\\E_2\end{bmatrix} = K_1[A]K_2[B]k_{-1}k_{-2}k_{-3} + u_{EAB} \quad (10)$$
$$\begin{bmatrix}E_1\\E_2C\end{bmatrix} = K_1[A]K_2[B]K_3[C]$$

As previously, k and K are the rate and the equilibrium constants. u_E, u_{EA} and u_{EAB} are local functions that tend to increase the steady state concentrations of $\begin{bmatrix}E_1\\E_2\end{bmatrix}, \begin{bmatrix}E_1A\\E_2\end{bmatrix}$ and $\begin{bmatrix}E_1AB\\E_2\end{bmatrix}$. Dividing the concentrations of $\begin{bmatrix}E_1\\E_2\end{bmatrix}, \begin{bmatrix}E_1A\\E_2\end{bmatrix}$ and $\begin{bmatrix}E_1AB\\E_2\end{bmatrix}$ by $k_{-1}k_{-2}k_{-3}$ yields

$$\begin{bmatrix}E_1\\E_2\end{bmatrix}_r = 1 + \frac{u_E}{k_{-1}k_{-2}k_{-3}} = 1 + u_E^{'}$$
$$\begin{bmatrix}E_1A\\E_2\end{bmatrix}_r = K_1[A] + \frac{u_{EA}}{k_{-1}k_{-2}k_{-3}} = K_1[A] + u_{EA}^{'} \quad (11)$$
$$\begin{bmatrix}E_1AB\\E_2\end{bmatrix}_r = K_1K_2[A][B] + \frac{u_{EAB}}{k_{-1}k_{-2}k_{-3}} = K_1K_2[A][B] + u_{EAB}^{'}$$
$$\begin{bmatrix}E_1\\E_2C\end{bmatrix}_r = K_1K_2K_3[A][B][C] = \begin{bmatrix}E_1\\E_2C\end{bmatrix}_r$$

One can see that, depending on the complexity of the model, the *u,s* and *u',s* describe local flows leading to states *E, EA* and *EAB* of the system. These functions *u',s* are the corresponding local flows divided by the same "flow" of substrate release i.e. $k_{-1}k_{-2}k_{-3}$.

The u's functions are responsible for the spontaneous organization of the system

A *u*, or a *u'* function can be viewed as a function that tends to create and maintain some kind of a stability in a dynamic system [4]. The *u* can be viewed as graphs leading to nodes *E,* EA or *EAB*. The *u'* are the same graphs leading to the same nodes divided by the "flow" of substrate release i.e. $k_{-1}k_{-2}k_{-3}$. Hence, the numerators of these ratios collect all the possible pathways leading to the same node and including substrate binding, release, or catalysis. The denominators of these ratios correspond to substrate release processes leading to the same nodes [5]. Hence any individual *u'* is the ratio between two local flows, one involving catalysis as well as substrate binding, substrate release and catalysis. The local flows are all identical and expressed by $k_{-1}k_{-2}k_{-3}$. In Figure 3 are shown the networks pertaining to Figure 2.

One can see from the data of Figure 3 that u_E collects four pathways leading to $\begin{bmatrix}E_1\\E_2\end{bmatrix}$. Similarly, u_{EA} collects three pathways leading to node $\begin{bmatrix}E_1A\\E_2\end{bmatrix}$ and u_{EAB} one pathway only. It follows that the expressions of $u_E^{'}$ $u_{EA}^{'}$ and u_{EA} are

$$u_E^{'} = \frac{k_{-1}k_{-2}k^{"}}{k_{-1}k_{-2}k_{-3}} + \frac{k_2[B]k^{'}k^{"}}{k_{-1}k_{-2}k_{-3}} + \frac{k_{-1}k^{'}k^{"}}{k_{-1}k_{-2}k_{-3}} + \frac{k_2[B]k_3[C]k^{"}}{k_{-1}k_{-2}k_{-3}}$$
$$u_{EA}^{'} = \frac{k_1[A]k^{'}k^{"}}{k_{-1}k_{-2}k_{-3}} + \frac{k_1[A]k_3[C]k^{"}}{k_{-1}k_{-2}k_{-3}} + \frac{k_1[A]k_{-2}k^{"}}{k_{-1}k_{-2}k_{-3}} \quad (12)$$
$$u_{EAB}^{'} = \frac{k_1[A]k_2[B]k^{"}}{k_{-1}k_{-2}k_{-3}}$$

These expressions can be rewritten as

$$u_E^{'} = \frac{k^{"}}{k_{-3}}\left(1 + \frac{k^{'}}{k_{-2}}\right) + K_2[B]\frac{k^{"}}{k_{-1}}\left(K_3[C] + \frac{k^{'}}{k_{-3}}\right)$$
$$u_{EA}^{'} = K_1[A]\frac{k^{"}}{k_{-3}}\left(\frac{k^{'}}{k_{-2}} + 1\right) + K_1[A]K_3[C]\frac{k^{"}}{k_{-2}} \quad (13)$$

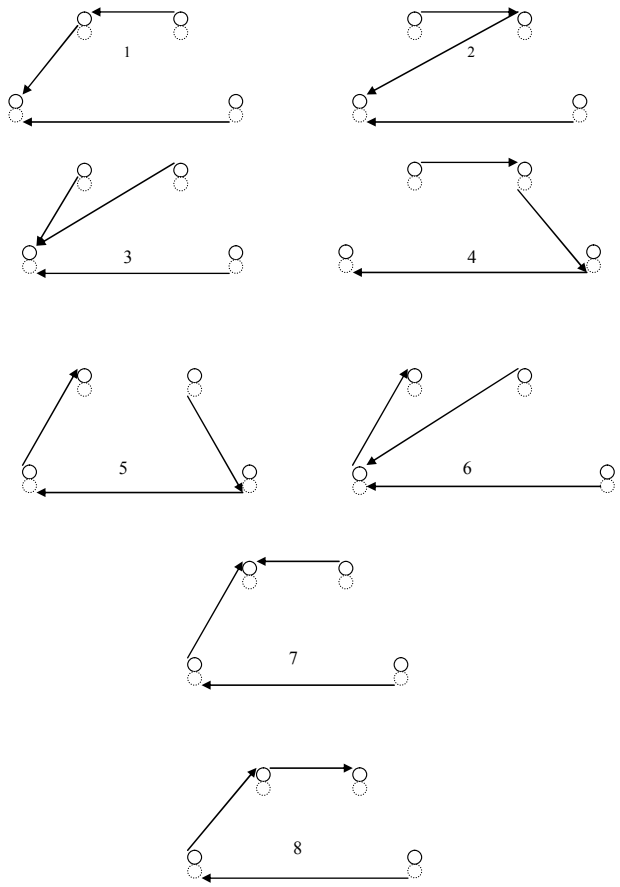

Figure 3: The various types of catalytic flows. 1-4 represent the four flows that lead to the free enzyme. 5-7 show the three flows leading to the EA complex. 8 shows the flow leading to the EAB complex.

$$u'_{EAB} = K_1K_2[A][B]$$

It is worth noting that all these expressions vanish if substrate desorption constants are much larger than the corresponding catalytic constants K' and K''.

The interactions between the enzyme reaction

The steady state of the system can be derived from equations (11). The expression of the steady state rate can be derived from the following equation

$$\frac{v}{[E]_0} = \frac{k'\begin{bmatrix}E_1AB\\E_2\end{bmatrix} + k''\begin{bmatrix}E_1\\E_2C\end{bmatrix}}{\begin{bmatrix}E_1\\E_2\end{bmatrix} + \begin{bmatrix}E_1A\\E_2\end{bmatrix} + \begin{bmatrix}E_1AB\\E_2\end{bmatrix} + \begin{bmatrix}E_1\\E_2C\end{bmatrix}} \tag{14}$$

Taking advantage of equations (11) and (12) leads to

$$\frac{v}{[E]_0} = \frac{k'K_1K_2[A][B] + k''K_1K_2K_3[A][B][C] + u'_{EAB}}{1 + K_1[A] + K_1K_2[A][B] + K_1K_2K_3[A][B][C] + u'_E + u'_{EA} + u'_{EAB}} \tag{15}$$

If we take account of expressions (13), the numerator N and the denominator D become

$$N = \left(k' + \frac{k''}{k_{-3}}\right)K_1K_2[A][B] + k''K_1K_2K_3[A][B][C] \tag{16}$$

and

$$D = 1 + K_1[A]\left(1 + \frac{k''}{k_{-3}} + \frac{k'k''}{k_{-2}k_{-3}}\right) + \frac{k'k''}{k_{-1}k_{-3}}K_2[B] + K_1K_2[A][B]\left(1 + \frac{k''}{k_{-3}}\right)$$

$$+K_1K_3[A][C]\left(\frac{k''}{k_{-2}} + \frac{k''}{k_{-1}}\right) + \frac{k''}{k_{-3}}\left(1 + \frac{k'}{k_{-2}}\right) + K_1K_2K_3[A][B][C]. \tag{17}$$

It follows that

$$\frac{v}{[E]_0} = \frac{\left(k' + \frac{k''}{k_{-3}}\right)K_1K_2[A][B] + k''K_1K_2K_3[A][B][C]}{1 + K_1[A]\left(1 + \frac{k''}{k_{-3}} + \frac{k'k''}{k_{-2}k_{-3}}\right) + \frac{k'k''}{k_{-1}k_{-3}}K_2[B] + K_1K_2[A][B]\left(1 + \frac{k''}{k_{-3}}\right)} \tag{18}$$
$$+K_1K_3[A][C]\left(\frac{k''}{k_{-2}} + \frac{k''}{k_{-1}}\right) + \frac{k''}{k_{-3}}\left(1 + \frac{k'}{k_{-2}}\right) + K_1K_2K_3[A][B][C]$$

The local flows and their significance

The system made up of two enzymes and three substrates is far more complex than an enzyme reaction involving three substrates [6]. This implies that some kind of interactions between the two enzymes should take place. In fact, the local flows u's should play an important role in defining such information. If we consider the ratio $u'_{EAB}/(u'_E + u'_B + u'_{EAB})$ $u'_{EAB}/(u'_E + u'_{EA} + u'_{EAB})$ it can be viewed as the probability of occurrence of B, $p(B)$, generated by the local flows. Similarly, $u'_{EAB}/(u'_E + u'_B)$ $u'_{EAB}/(u'_E + u'_{EA})$ can be viewed as the

conditional probability $p(B/A)$. One has

$$p(B)=\frac{k_1[A]k_2[B]}{k_{-1}\left(k_{-2}+k^{'}\right)+k_2[B]\left(k^{'}+k_3[C]\right)+k_1[A]\left(k_{-2}+k^{'}\right)+k_1[A]\left(k_{-2}+k^{'}\right)} \quad (19)$$

$+k_1[A]k_2[B]+k_1[A]k_3[C]$ and

$$p(B/A)=\frac{k_1[A]k_2[B]}{k_1[A](k^{'}+k_{-2})+k_1[A]k_2[B]+k_1[A]k_3[C]} \quad (20)$$

It is then clear that $p(B/A)>p(B)$ and it is well known that the information generated by the system is

$$I(B:A)=\log\frac{p(B/A)}{p(B)} \quad (21)$$

Hence one can conclude that some information is generated in the system owing to the activity of the local flows u'. This amount of information is directly related to the expression

$$\frac{p(B/A)}{p(B)}=1+\frac{k_1[A](k^{'}+k_{-2})+k_3[B](k^{'}+k_3[C])}{k_1[A](k^{'}+k_{-2})+k_1[A]k_2[B]+k_1[A]k_3[C]} \quad (22)$$

This expression is, of necessity, larger than one which means that information has been generated in the system [7].

Discussion

It is well known that, in the living cell, many enzymes are not in a free state but are bound to other enzymes and form complexes. Moreover, within such a complex, it is quite possible that an enzyme changes its conformation upon the binding of a ligand to another enzyme. Hence its properties will be altered. The idea developed in the present paper is that the physical association possesses a biological meaning, namely that two, or more than two, associated enzymes are able to catalyse a unique "*metaprocess*" involving the interaction of two, or more than two, catalytic processes [8]. Then one can expect that the global system emerging from the interactions between different enzymes can be considered as some kind of novel entity.

One of the basic ideas of the present paper is to express reaction rates in terms of equations involving *equilibrium constants* for systems that are *away from equilibrium*. Such an apparent paradoxical situation can be explained only if the local concentrations of free enzyme, as well as that of the enzyme-substrate complexes, are maintained at fixed values by *local* flows. For the system considered in this paper, there is, in fact, three local flows, one leading to free enzyme and two others leading to enzyme-substrate(s) complexes. It is the dynamics of the system that maintains constant for a while the concentrations of free and bound enzyme. It is the dynamics of the system that contributes to define its organization that can be complex. Moreover the local flows generate an information that can be used to contribute to the organization of the system. Such systems are able to self-organize [9]. It is then apparent that, for simple physical reasons, the system can maintain, or alter, the probability of occurrence of its nodes. In other words, this physical model can display elementary self-organization.

References

1. Nicolis G, Prigogine I (1977) Self-Organization and Nonequilibrium Systems. John Wiley and Sons, USA.
2. Rickey Welch G (1985) Organized Multienzyme Systems. Catalytic Properties. Academic Press, USA.
3. Laidler KJ (1958) The Chemical Kinetics of Enzyme Action. Clarendon Press, Oxford, UK.
4. Laidler KJ, Bunting P (1973) The Chemical Kinetics of Enzyme Action. Clarendon Press, Oxford, UK.
5. Ricard J, Cornish-Bowden A (1984) Dynamics of Biochemical Systems. Plenum Press, UK.
6. Dixon M, Webb EC (1979) Enzymes. Longman (3rdedn), UK.
7. Schultz R (1994) Enzyme Kinetics. Cambridge University Press, UK.
8. Ricard J (1999) Biological Complexity and the Dynamics of Life Processes. Elsevier, USA.
9. Westerhoff HV, Van Dam K (1987) Thermodynamics and Control of Biological Free- energy Transduction. Elsevier, UK.

Citation: Ricard J (2015) Systems of Connected and Aggregated Enzyme Reactions. Curr Synthetic Sys Biol 3: 125. doi:10.4172/2332-0737.1000125