Effect of self-association on the stability of metabolic units

R. Costalat, J.-P. Morillon and J. Burger

Institut de Biologie Théorique,
10 rue André Boquel,
49100 Angers (France)

Abstract

We study the effect of the association of two formal metabolic units, each of which contains a metabolic chain with one negative feedback loop, on the asymptotic stability of their steady state. Specifically, we assume that: (i) metabolic chains are of the Yates-Pardee or Goodwin type; (ii) when metabolic units are associated, then metabolites can passively diffuse from one unit to the other. We show that (i) the associated system has a unique steady state with positive concentrations; (ii) the association can result in an increase of the asymptotic stability domain in the parameters space. We conclude that association of metabolic units can be a source of stability of metabolic networks.

1. Introduction

One of the most striking properties of biological systems is the increase in their apparent complexity during ontogenesis and phylogenesis. Another important feature of living systems is the stability of their dynamics, as was pointed out by Claude Bernard in the last century, using the concept of homeostasis. Although these notions are difficult to define in a rigorous manner, they can be viewed as very general properties of living systems. On the contrary, an increase in the complexity of an artificial system often results in a decrease in its stability domain. Therefore the question of the link between complexity and stability in living systems, and its possible implications in ontogenesis, phylogenesis, and physiology of organisms, need to be clarified.

The stability of biochemical systems has been the subject of numerous studies, based on kinetic and thermodynamic approaches (see for instance Walter, 1972; Savageau, 1976; Stucki, 1978). One of the most studied biochemical systems consists of a metabolic chain with one allosteric negative feedback loop, and is generally referred to as Yates-Pardee or Goodwin metabolic chain (Walter, 1969(a),(b); Goodwin, 1976; Savageau, 1976; Rapp, 1976; Dibrov *et al.*, 1981(a),(b)). When the length of a Yates-Pardee metabolic chain is increased, then its stability domain is decreased: in some way, we could say that an increase in the complexity of the metabolic chain results in a decrease of its stability.

From a different point of view, G. Chauvet (1987, 1990; 1993, to appear) suggested that the self-association of two formal metabolic units can result in an increase in the stability domain, especially when one unit cannot synthesize one essential metabolite and receives this metabolite from the other unit. Such a property would correspond to an increase both in complexity and stability of a formal biological system. The question arises whether this unusual property can be verified in large classes of formal biological systems on one hand, in real biological systems on the other hand.

In the present work, we study the relation between association and stability in the case of two relatively simple "metabolic units". More precisely, each metabolic unit includes a Yates-Pardee metabolic chain, and association results in diffusion of metabolites between the two metabolic units. The time evolution of the metabolites concentrations is described using an ordinary differential equations (ODEs) system. First some properties of one metabolic unit, i.e., of a Yates-Pardee chain, are recalled. Then the existence and uniqueness of a steady state with non-negative concentrations, and the asymptotic stability of this steady state, are studied in the case of the associated metabolic units.

2. Models of metabolic units

2.1. Model of a metabolic unit

We first consider one metabolic unit including an unbranched metabolic chain with one allosteric negative feedback loop (Figure 1), a system which is similar or identical to those studied by several authors and is known as Yates-Pardee or Goodwin metabolic

chain (Walter, 1969(a),(b); Goodwin, 1976; Savageau, 1976; Rapp, 1976; Dibrov *et al.*, 1981(a),(b)). Every enzyme E_i, whose substrate is P_i, $i = 1$ *to* n, is michaelian, while the first enzyme E_0, whose substrate is S_0, is allosteric.

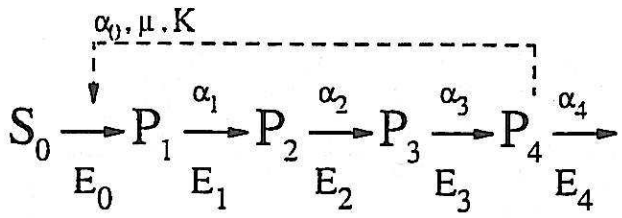

Figure 1. Model of a metabolic chain with one allosteric negative feedback loop (non-associated system), in the case $n = 4$. We assume that this chain is included in a "metabolic unit" u, e.g. a cell.

The following specific assumptions are made, as was proposed by Walter (1969(a)):

(i) the concentration P_i of the corresponding metabolite is far lower than the Michaelis constant $K_{m,i}$ of the enzyme E_i, $i = 1$ *to* n, so that the velocity v_i of the reaction catalyzed by enzyme E_i can be written ($V_{max,i}$ being the maximal velocity):

$$v_i = V_{max,i}\frac{P_i}{K_{m,i}+P_i} \approx \frac{V_{max,i}}{K_{m,i}}P_i = \alpha_i P_i$$

(ii) the velocity of the first reaction $S_0 \rightarrow P_1$ can be written $\alpha_0/(1+K(P_n)^\mu)$, μ, K and α_0 being positive constants. We assume that the concentration of the substrate S_0 is constant.

Then the evolution of the concentrations P_i of the corresponding metabolites can be modeled by the following set of equations:

$$\begin{cases} \dfrac{dP_1}{dt} = -\alpha_1 P_1 + \dfrac{\alpha_0}{1+K(P_n)^\mu} \\ \dfrac{dP_i}{dt} = \alpha_{i-1}P_{i-1} - \alpha_i P_i \qquad i = 2 \text{ to } n \end{cases} \tag{1}$$

2.2. Associated units

Let us consider two associated metabolic units, namely u and u^* (Figure 2). Notations are similar to those used for a single unit, the parameters and metabolites concentrations in unit u^* being written with a star (*) superscript. In Figure 2 solid horizontal arrows represent biochemical reactions, dashed horizontal arrows indicate allosteric feedback, and vertical arrows represent transport of a metabolite P_i from one unit to the other.

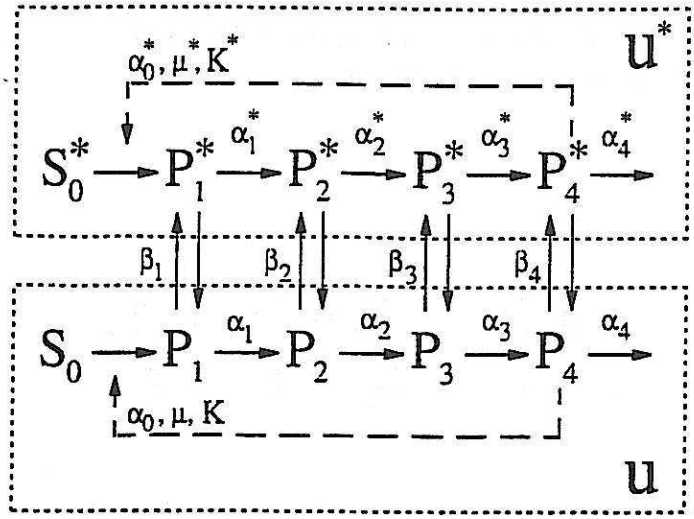

Figure 2. Model of two associated metabolic units, in the case $n = 4$.

In this study, we shall further assume that this transport consists of passive diffusion between two compartments, with a constant coefficient β_i. Then we shall write the following ODEs system for associated metabolic units:

$$\begin{cases} \dfrac{dP_1}{dt} = -\alpha_1 P_1 + \dfrac{\alpha_0}{1+K(P_n)^{\mu}} + \beta_1(P_1^* - P_1) \\ \dfrac{dP_i}{dt} = \alpha_{i-1}P_{i-1} - \alpha_i P_i + \beta_i(P_i^* - P_i) \qquad i = 2 \text{ to } n \\ \dfrac{dP_1^*}{dt} = -\alpha_1^* P_1^* + \dfrac{\alpha_0^*}{1+K^*(P_n^*)^{\mu^*}} + \beta_1(P_1 - P_1^*) \\ \dfrac{dP_i^*}{dt} = \alpha_{i-1}^* P_{i-1}^* - \alpha_i^* P_i^* + \beta_i(P_i - P_i^*) \qquad i = 2 \text{ to } n \end{cases} \tag{2}$$

Systems (1) and (2) will be referred to as non-associated and associated systems respectively. It can be noted that all parameters in these systems are non-negative.

3. Existence and uniqueness of steady state

In order to find the steady states of the non-associated and associated systems, we consider n equations (1) and $2n$ equations (2) respectively, where the left-hand members

are replaced by zero. We shall study only steady states with non-negative concentrations.

The existence and uniqueness of a steady state $(P_1^0, P_2^0, \ldots, P_n^0)$ of the non-associated system (1), with every P_i^0 positive, are easily demonstrated from the scalar equation:

$$\alpha_n K (P_n^0)^{\mu+1} + \alpha_n P_n^0 - \alpha_0 = 0 \tag{3}$$

The case of the associated system is more complex. If we assume that every α_i and every α_i^*, $i = 0$ *to* n, are different from zero, it can be proved, using an adequate change of variables and matrix algebra considerations, that there exists a unique steady state with non-negative concentrations.

Moreover, if there exists one $i \in \{2,3,\ldots,n-1\}$, such that α_i^* is equal to zero (i.e., if there exists one enzymatic block in unit u^*), the same result holds, provided that the corresponding β_i is different from zero.

4. Stability analysis of steady states

4.1. Analytic study of the non-associated system

Let us linearize the system (1) in the neighborhood of the unique steady state and obtain the first approximation system. Hence, the characteristic polynomial is:

$$f_n(\lambda) = \prod_{i=1}^{n} (\lambda + \alpha_i) + \gamma \prod_{i=1}^{n-1} \alpha_i \tag{4}$$

where $\gamma = \alpha_0 \mu K (P_n^0)^{\mu-1} / \left(1 + K (P_n^0)^{\mu}\right)^2$ corresponds to the non-linear term in system (1).

Let us apply the criterion of Liénard and Chipart for asymptotic stability (Gantmakher, 1959), which is more simple than the Routh-Hürwitz criterion. For $n \leq 2$, the steady state is always asymptotically and exponentially stable. For $n = 3$ (respectively $n = 4$), a domain of instability exists, for example with $\mu = 9$ (resp. $\mu = 5$).

4.2. Analytic study of the associated system

The case of the associated system is more complicated but it is possible to follow the same calculations.

For $n = 1$, the roots of the characteristic polynomial (eigenvalues) are real and negative, so that the unique steady state is always asymptotically stable. If the system is symmetrical, i.e. if $\alpha_0 = \alpha_0^*$, $\alpha_1 = \alpha_1^*$, $\mu = \mu^*$, $K = K^*$, then the two eigenvalues will be $\lambda_1 = -(\alpha_1 + \gamma)$ and $\lambda_2 = -(\alpha_1 + \gamma + 2\beta_1)$, so that the α-stability of the system (see Bourlès, 1986) will remain constant.

For $n = 2$, we obtain the characteristic polynomial

$$f_2^*(\lambda) = a_0 \lambda^4 + a_1 \lambda^3 + a_2 \lambda^2 + a_3 \lambda + a_4 \tag{5}$$

where the coefficients a_i, $i = 1$ *to* 4, are positive (their detailed form is given in the

Appendix). The criterion of Liénard and Chipart leads to the necessary and sufficient stability condition:

$$a_1 a_2 a_3 - a_1^2 a_4 - a_0 a_3^2 > 0 \qquad (6)$$

This latter condition is not satisfied when μ is large enough ($\mu \geq 100$). Because μ is the Hill coefficient or so-called "molecularity" of the allosteric reaction, this latter case is not realistic from a biological point of view.

4.3. Numerical study of non-associated and associated systems

Asymptotic stability of non-associated and associated systems was assessed by numerical resolution of systems (1) and (2) respectively, in the case $n = 4$. Parameters were chosen as follows: $K = K^* = 1$, $\mu = \mu^* = 5$, $\alpha_1 = \alpha_2 = 1$, $\alpha_1^* = 1$, $\alpha_2^* = 0$ (we assume that one enzymatic reaction is suppressed or inhibited in one of the two units). $\beta_1 = \beta_2 = \beta_3 = \beta_4 = 0$ in the case of the non-associated system, $\beta_1 = \beta_2 = \beta_3 = \beta_4 = 1$ in the case of the associated system.

The asymptotic stability domain was studied:

(i) in the α_3, α_4-plane (Figure 3), with $\alpha_0 = \alpha_0^* = 50$, $\alpha_3 \equiv \alpha_3^*$, $\alpha_4 \equiv \alpha_4^*$;

(ii) in the α_0, α_4-plane (Figure 4), with $\alpha_3 = 1$, $\alpha_0 \equiv \alpha_0^*$, $\alpha_4 \equiv \alpha_4^*$.

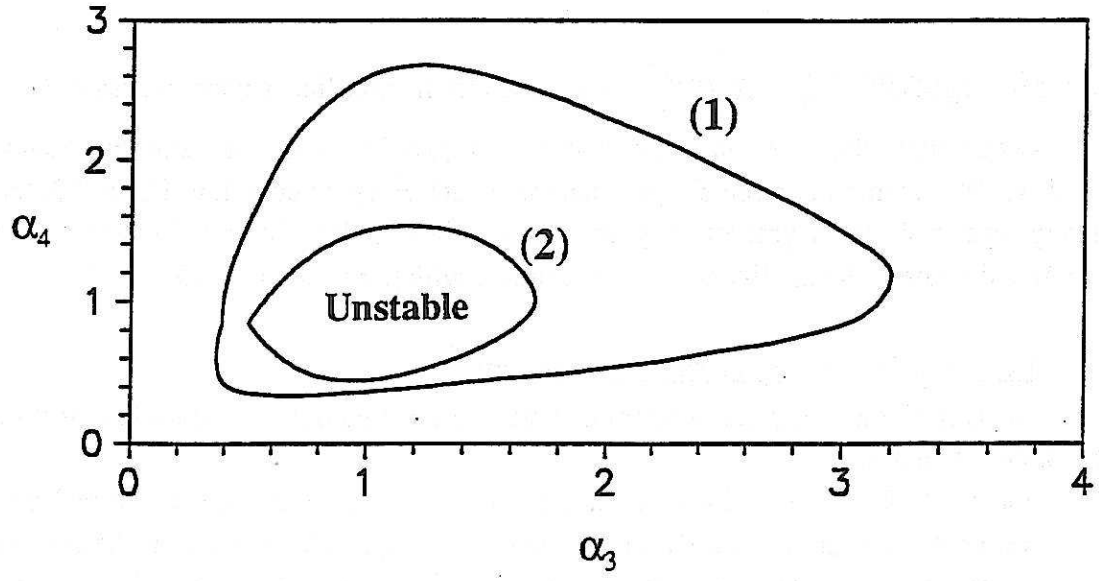

Figure 3. Asymptotic stability domains in the α_3, α_4-plane in the case of (1) the non-associated system, and (2) the associated system. Note that in both cases the stability domain is *outside* the closed line, while instability is observed inside this line. Parameters values are given in the text.

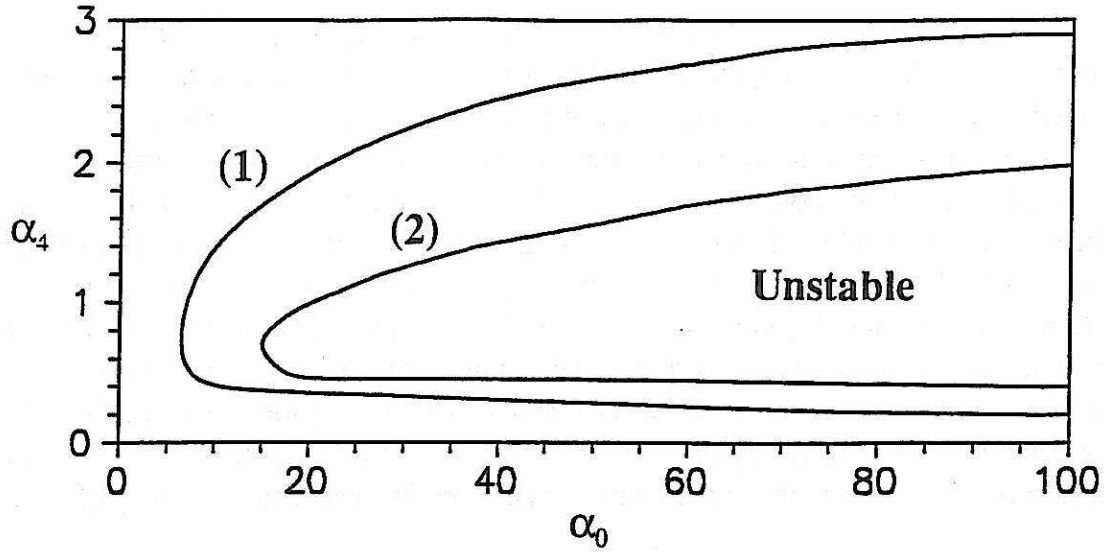

Figure 4. Asymptotic stability domains in the α_0, α_4-plane in the case of (1) the non-associated system, and (2) the associated system. Note that in both cases the instability domain is between the two branches of the corresponding curve. Parameters values are given in the text.

In the case of the non-associated system, an asymptotic stability domain is observed in the α_3, α_4-plane outside a closed line, while instability is observed inside this line (Figure 3). These results were confirmed using the criterion of stability of Liénard and Chipart, as in part (4.1.), and closely match the results obtained by Chauvet and Girou (1983). In the α_0, α_4-plane, the instability domain is between the two branches of curve (1) (Figure 4).

In the case of the associated system, the "instability domain" in the α_3, α_4-plane is still present, but its area is reduced. More precisely, the associated system "instability domain" (bounded by line (2)) is included in the non-associated system "instability domain" (bounded by line (1)). The same result holds in the α_0, α_4-plane.

5. Discussion

In the present work, we compare two different ways by which a metabolic chain with allosteric feedback may become more "complex": (i) an increase in the length of the metabolic chain, i.e. in parameter n; (ii) the association of two metabolic units, resulting in diffusion of metabolites between the two units. The effects of an "increase in complexity" on asymptotic stability differ radically from one case to the other. If the length of the metabolic chain is increased, then the unique steady state solution of the non-associated system becomes "less stable", as was already pointed out by several authors (Walter, 1969(a),(b); Dibrov *et al.*, 1981(a),(b)). For instance, when n equals 1 or 2, the steady-state solution is asymptotically stable whatever the parameters values; if n equals 3, instability can occur when the "molecularity" μ of the allosteric reaction is greater than 8 (which is rarely encountered in real biological systems); if n equals 4, instability can occur when μ is as low as 5.

When two metabolic units are associated, the domain of asymptotic stability may be either (i) decreased, as was shown when n equals 2 in a particular case (which is not very realistic from a biological point of view), or (ii) increased, as was shown when n equals 4 when one enzymatic reaction is suppressed in one of the metabolic units. When n equals 1 and when the system is symmetrical, the α-stability of the system remains constant after association. Therefore, the self-association of the two metabolic units can be a source of stability, if some conditions are fulfilled. This finding can be viewed as non-trivial, because an increase in complexity of artificial systems often results in a decrease of their stability domain. Hence, we think that the approach presented here may be a starting point for further work in understanding why an increase in complexity, due to association of metabolic units, can be a source of stability. Moreover, we believe that this approach should be applied to real biological systems, e.g. to the association of micro-organisms, or to the mitochondria or chloroplasts inside eucaryotic cells.

Appendix

Coefficients of the characteristic polynomial of the associated system ($n = 2$)

$$a_0 = 1 > 0,$$

$$a_1 = \alpha_1 + \alpha_2 + \alpha_1^* + \alpha_2^* + 2(\beta_1 + \beta_2) > 0,$$

$$a_2 = (\alpha_1 + \alpha_2)(\alpha_1^* + \alpha_2^*) + (\alpha_1 + \alpha_2 + \alpha_1^* + \alpha_2^*)(\beta_1 + \beta_2)$$
$$+(\alpha_1 + \beta_1)(\alpha_2 + \beta_2) + (\alpha_1^* + \beta_1)(\alpha_2^* + \beta_2) + 2\beta_1\beta_2 + \alpha_1\gamma + \alpha_1^*\gamma^* > 0,$$

$$a_3 = \alpha_1^*\beta_1(\alpha_2^* + \beta_2) + \alpha_2^*\beta_2(\alpha_1^* + \beta_1) + (\alpha_1 + \alpha_2)(\alpha_1^* + \beta_1)(\alpha_2^* + \beta_2) + (\alpha_1^* + \alpha_2^*)(\alpha_1 + \beta_1)(\alpha_2 + \beta_2)$$
$$+\alpha_1\beta_1(\alpha_2 + \beta_2) + \alpha_2\beta_2(\alpha_1 + \beta_1) + \alpha_1\gamma(\alpha_1^* + \alpha_2^* + \beta_1 + \beta_2) + \alpha_1^*\gamma^*(\alpha_1 + \alpha_2 + \beta_1 + \beta_2) > 0,$$

$$a_4 = \alpha_1\alpha_2\alpha_1^*\alpha_2^* + \alpha_1\alpha_2\alpha_1^*\beta_2 + \alpha_1\alpha_2\alpha_2^*\beta_1 + \alpha_1\alpha_2\beta_1\beta_2 + \alpha_1\alpha_1^*\alpha_2^*\beta_2 + \alpha_1\alpha_2^*\beta_1\beta_2 + \alpha_2\alpha_1^*\alpha_2^*\beta_1 + \alpha_2\alpha_1^*\beta_1\beta_2 + \alpha_1^*\alpha_2^*\beta_1\beta_2$$
$$+\alpha_1(\alpha_1^* + \beta_1)(\alpha_2^* + \beta_2)\gamma + \alpha_1^*(\alpha_1 + \beta_1)(\alpha_2 + \beta_2)\gamma^* + \alpha_1^*\beta_1\beta_2\gamma + \alpha_1\beta_1\beta_2\gamma^* + \alpha_1\alpha_1^*\gamma\gamma^* > 0.$$

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