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Nonlinear oscillations of the Goodwin metabolic pathway with coupling

J.-P. Morillon¹ S. Doubabi

R. Costalat

¹Laboratoire PIMENT - Université de La Réunion

Abstract.

An analytic method has been applied to a biochemical pathway with coupling. The harmonic balancing technique can be used to determine the effects of coupling on the Goodwin metabolic pathway. Its behaviour is modelled by a set of coupled ordinary nonlinear differential equations. This one is transformed to a single feedback loop control with a nonlinear function and a linear filter. It is shown that coupling modifies the linear filter such that the frequency and the amplitude of the oscillations decrease. The results obtained here are derived by both analytical and numerical studies, and compared with previous stability analysis of associated pathways.

Keywords: Metabolic pathways – Pools – Oscillations – Harmonic balance method

1 Introduction

The most commonly encountered form of regulated biochemical pathway, generally referred to as the Yates-Pardee or Goodwin metabolic pathway, consists of a single pathway of enzymatic reactions, where the last product inhibits the first enzyme (single loop negative feedback) [14, 5]. When the length of a Goodwin metabolic pathway is increased, the stability domain of its unique steady state is decreased [12, 14].

From a different point of view, G. Chauvet has suggested that the association of metabolic pathways can result in an increase in their stability domain [2]; this property can be viewed as non-trivial, because an increase in the complexity of artificial systems often results in a decrease of their stability domain.

In our first paper [11], we showed that the parallel association of two Goodwin metabolic pathways, consisting of a set of nonlinear coupled first-order ordinary differential equations, can increase the stability domain of the unique steady state. Moreover, analytical and numerical studies of the stability of this system show that the association of two units can lead to an increase of the domain of stability. From a biological point of view, the results suggest that the exchange of matter between compartments (e.g. cells, organelles, . . .) may be a source of stability for the cell metabolism.

The question arises whether this unusual property can be showed in case of nonlinear oscillations. How coupling with exterior pools of metabolites modifies the behaviour of the oscillations of a Goodwin metabolic system.

Moreover the role of spatial heterogeneity for chemical reactions has been the subject of much research (see, for instance, [8, 1] and references therein). Actually the role of exterior pools with respect to the asymptotic behaviour of such systems has been relatively neglected. On the other hand, the presence of exterior pools appears to be rather natural [1].

In Section 2 the biological model is presented. In Section 3 some definitions and concepts of the harmonic balancing method are given. In Section 4 we apply this technique in order to compare the oscillations of the systems with or without coupling. In Section 5 numerical experiments are given. In last section, some conclusions are submitted, in particular on stability of steady state.

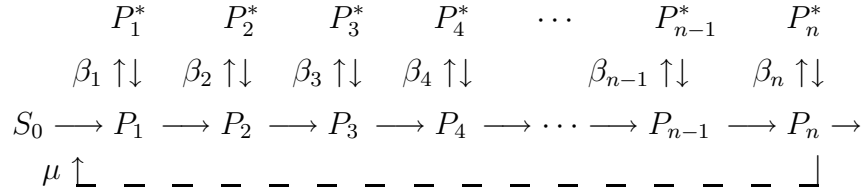


Figure 1: Goodwin biochemical pathway with couplings

2 The model with coupling

We here investigate the oscillations of the Goodwin metabolic pathway [5] by means of the harmonic balancing technique [12], with the addition of some passive diffusion coupling (see Fig. 1). More precisely, we assume that (i) a cell or an organelle u contains a Goodwin metabolic pathway [5]; (ii) the metabolite pool P_i , $i = 1, \dots, n$, can exchange matter with the outside pool P_i^* via passive diffusion, with a non-negative coefficient β_i .

Let us consider one biological unit which contains a Goodwin metabolic pathway, and apply the laws of mass-balance and enzyme kinetics to this system with passive diffusion between interior and exterior compartments.

Implementing the transformation of Walter [14, 12], the system can be modelled by the following set of differential equations that describe the time evolution of metabolic concentrations:

$$\begin{cases} \frac{dP_1}{dt} = & f(P_n) - b_1 P_1 - \beta_1 (P_1 - P_1^*), \\ \frac{dP_k}{dt} = & P_{k-1} - b_k P_k - \beta_k (P_k - P_k^*), \quad k = 2, \dots, n, \\ \frac{dP_k^*}{dt} = & \beta_k (P_k - P_k^*), \quad k = 1, \dots, n, \end{cases} \quad (1)$$

where P_i and P_i^* are the respective time-dependent concentrations of a given metabolite in the unit and the exterior pools. The coefficient b_i characterizes the positive kinetic constant of the reaction $P_i \rightarrow P_{i+1}$ in the unit. The reaction function f is given; in the Goodwin metabolic pathway, f describes the allosteric feedback inhibition of the first reaction by the last product, and can be written as:

$$f(P_n) = \frac{1}{1 + (P_n)^\mu}.$$

where μ is a positive integer. Finally, we assume that association with exterior pools results in passive diffusion, with constant non-negative coefficients β_i . If all the β_i are zero, the unit is said isolated or non-associated.

Existence and uniqueness of the positive steady state are proved in [11]. Results on the linear stability of the system at the neighborhood of the unique steady state can be derived by both analytical¹ and numerical² studies for some values of the parameters of the model (see [11]). Apart the fact that a systematic study of the local properties derived by linearization, may rapidly become cumbersome, the question of discerning whether a system possesses a stable positive steady state or a limit cycle remains to be answered. However, existence of stable oscillations for a Goodwin system without coupling has been proved in [6].

¹Using the criterion of Liénard and Chipart.

²By computing the eigenvalues of jacobian matrix with scientific software such as MATLAB.

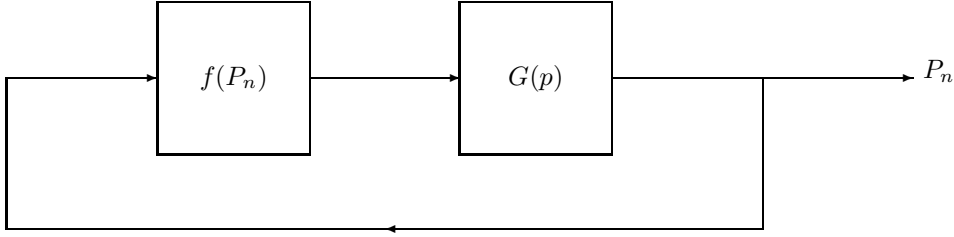


Figure 2: Single feedback loop with a nonlinear function f and a linear filter $G(p)$

3 First order harmonic balancing technique

The harmonic balancing technique for investigating biochemical oscillators can be successfully employed, in particular when the function f of the feedback loop is positive, and monotonically decreasing with his argument.

3.1 Definitions

This mathematical method [9, 4, 7] approximates the output P_n and the nonlinear element $f(P_n)$ by a partial sum of their Fourier series :

$$P_n(t) = \mathcal{R}e \left(\sum_{k=0}^p x_k \exp(ik\omega t) \right),$$

$$f(P_n(t)) = \mathcal{R}e \left(\sum_{k=0}^p y_k \exp(ik\omega t) \right),$$

where the coefficients y_k verify :

$$y_0 = \frac{1}{2\pi} \int_0^{2\pi} f \left(\mathcal{R}e \left(\sum_{k=0}^p x_k \exp(ikt) \right) \right) dt,$$

$$y_k = \frac{1}{\pi} \int_0^{2\pi} f \left(\mathcal{R}e \left(\sum_{l=0}^p x_l \exp(ilt) \right) \right) \exp(-ikt) dt, \quad 1 \leq k \leq p.$$

Using the loop's input-output equation :

$$P_n = G f(P_n)$$

where G is the linear filter so that :

$$G f(P_n) = \mathcal{R}e (G(0) y_0 + G(i\omega) y_1 \exp(i\omega t) + \dots + G(ip\omega) y_p \exp(ip\omega t)),$$

we obtain $p + 1$ balance equations :

$$G(ik\omega) y_k = x_k, \quad 0 \leq k \leq p.$$

Then, an approximation to $P_n(t)$ is obtained by solving these equations. Since the Fourier series of the function f converges rapidly and $G(p)$ is an extreme low pass filter, the first order approximation :

$$P_n(t) = x_0 + x_1 \cos \omega t$$

should be a very good representation of periodic solution for arbitrary dimension n of this system.

Let us define the equivalent gain in the k -th harmonic as $F_k = y_k/x_k$. This function $F_k = y_k/x_k$ is known as the describing function of the nonlinearity f .

This first order approximation leads us to consider the following balance equations :

$$E G(0) = \frac{y_0}{x_0} G(0) = 1, \quad (2)$$

$$F G(i\omega) = \frac{y_1}{x_1} G(i\omega) = 1, \quad (3)$$

where

$$y_0 = \frac{1}{2\pi} \int_0^{2\pi} f(x_0 + x_1 \cos t) dt,$$

$$y_1 = \frac{1}{\pi} \int_0^{2\pi} f(x_0 + x_1 \cos t) \cos t dt.$$

For single loop control system, E is frequency independent and the zero balance equation (2) gives us the mean value x_0 as function of the amplitude x_1 of the oscillation. Then, the first balance equation (3) becomes a function of the amplitude x_1 and the frequency ω , and it is possible to separate this x_1 - ω relation :

$$G(i\omega) = \frac{1}{F(x_1)}.$$

The G - and $1/F$ -curves are studied in the complex plane. If they intersect then the balance conditions are satisfied and a periodic solution exists, otherwise the system cannot oscillate. For f monotonically decreasing, it can be proved that $1/F$ is a continue negative real function, and the set of amplitudes is a connected compact set [12]. An intersection of $G(i\omega)$ - and $1/F(x_1)$ -curves will occur only if:

$$\frac{1}{F_{\text{Max}}} \leq G(i\omega_c) \leq \frac{1}{F_{\text{min}}}$$

where ω_c is the frequency so that the $G(i\omega)$ -curve first intersects the negative real axis. This $G(i\omega)$ -curve is often called the Nyquist contour of the linear element.

3.2 Functions R and R^*

Let us consider the nonlinear system (1) represented by a feedback connection of a linear time-invariant dynamical system and a nonlinear element $f(P_n)$, as shown in Figure 2. We study the behaviour of this autonomous system, and we are interested in investigating the existence of periodic solutions.

Using the simultaneous loop balance conditions, we can construct numerically a function \mathcal{R} of the reaction constants where if $\mathcal{R} > 1$ the system oscillates and if $\mathcal{R} \leq 1$ there is no periodic solution. Comparing the value of \mathcal{R} and the numerical solution by Runge-Kutta method via MATLAB software we find that this technique is very accurate.

In our case (see [12] for technical details), the unique condition for an intersection $G(i\omega_c) \leq 1/F_{\text{min}}$ leads to define \mathcal{R} as functions of the parameters b_i and β_k :

$$\mathcal{R}(b_i, \beta_k) = \frac{|F_{\text{min}}|}{b_1 \cdots b_n} \cdot \left| \frac{G(i\omega_c)}{G(0)} \right| \quad (4)$$

so that $\mathcal{R}(b_i, \beta_k) > 1$ is equivalent to this latter condition.

An algorithm is then possible to determine the existence of limit cycle.

In the sequel, let us denote $R \equiv \mathcal{R}(b_i, 0)$ when the parameters β_k are zero, and R^* otherwise. Let us note that the nonlinear block is the same for these cases. When we compare an isolated system and an associated system with identical parameters, except β_k , we can prove, in special cases, the inequalities $R^* < R$ and $\omega_c^* \leq \omega_c$ where the star $*$ superscript represents an associated system. Then we observe an increasing stability in the sense that the amplitude and frequency decrease.

4 Analysis of oscillations

For the analysis of the non-associated system, i.e. when all $\beta_k = 0$, we introduce the linear filter G :

$$G(p) = \left\{ \prod_{k=1}^n (p + b_k) \right\}^{-1}$$

where p denotes the differentiation operator. After one or several couplings, the harmonic balance method leads us to consider the following filter:

$$G^*(p) = \left[\prod_{k=1}^n \frac{(p + b_k)(p + \beta_k)}{(p + b_k)(p + \beta_k) + p\beta_k} \right] G(p).$$

Proposition.

1. $G(i\omega) = G^*(i\omega)$ if and only if $\omega = 0$ or $\beta_k = 0$, $\forall k = 1, \dots, n$;
2. The arguments of $G(i\omega)$ and $G^*(i\omega)$ verify the following formulae:

$$\text{Arg}G^*(i\omega) = \text{Arg}G(i\omega) - \psi(\omega), \quad \psi(\omega) = \sum_{k=1}^n \psi_k(\omega),$$

with

$$\psi_k(\omega) = \text{Arctan} \frac{(b_k + 2\beta_k)\omega}{b_k\beta_k - \omega^2} - \text{Arctan} \frac{(b_k + \beta_k)\omega}{b_k\beta_k - \omega^2};$$

- (iii) The modulus of $G(i\omega)$ and $G^*(i\omega)$ verify the following estimation:

$$|G^*(i\omega)| \leq |G(i\omega)| \quad \forall \omega > 0.$$

Proof. The expressions for $G(i\omega)$ and $G^*(i\omega)$ are:

$$\begin{aligned} G(i\omega) &= \left(\prod_{k=1}^n \frac{1}{(\omega^2 + b_k^2)^{1/2}} \right) \exp \left(-i \sum_{k=1}^n \phi_k(\omega) \right) \\ G^*(i\omega) &= G(i\omega) \left(\prod_{l=1}^n \frac{(\omega^2 + b_l^2)^{1/2} (\omega^2 + \beta_l^2)^{1/2}}{(\omega^2 + c_l^2)^{1/2} (\omega^2 + d_l^2)^{1/2}} \right) \exp \left(-i \sum_{l=1}^n \psi_l(\omega) \right) \end{aligned}$$

with

$$\phi_k(\omega) = \text{Arctan} \frac{\omega}{b_k},$$

and

$$\psi_l(\omega) = \text{Arctan} \frac{\omega}{c_l} + \text{Arctan} \frac{\omega}{d_l} - \text{Arctan} \frac{\omega}{b_l} - \text{Arctan} \frac{\omega}{\beta_l}, \quad \text{if } \beta_l \neq 0,$$

$$\psi_l(\omega) = \phi_l(\omega) \quad \text{if } \beta_l = 0,$$

$$c_l = \frac{(b_l + 2\beta_l) - \sqrt{b_l^2 + 4\beta_l^2}}{2} > 0,$$

$$d_l = \frac{(b_l + 2\beta_l) + \sqrt{b_l^2 + 4\beta_l^2}}{2} > 0.$$

Let us consider the linear filters G and G^* with a unique coupling, i.e. with $\beta_l = \beta > 0$ and $\beta_j = 0$ for all $j \neq l$. The expressions of $G(i\omega)$ and $G^*(i\omega)$ are deduced of the above, and the equality $G(i\omega) = G^*(i\omega)$ leads to

$$(\omega^2 + b_l^2) (\omega^2 + \beta^2) = (\omega^2 + c_l^2) (\omega^2 + d_l^2), \quad \text{and} \quad \psi_l = 0,$$

equivalent to

$$\omega = 0 \quad \text{or} \quad \beta = 0.$$

Moreover, since we have: $\psi_l(0) = 0$, $\lim_{\beta \rightarrow 0^+} \psi_l(\omega) = 0$, and $b_l \beta = c_l d_l$ when $\omega = 0$ or $\beta = 0$, the converse is obvious.

The arguments of $G(i\omega)$ and $G^*(i\omega)$ verify: $\text{Arg}G^*(i\omega) = \text{Arg}G(i\omega) - \psi_l(i\omega)$ and, by means of Arctan property:

$$\psi_l(\omega) = \text{Arctan} \frac{(b_l + 2\beta)\omega}{b_l \beta - \omega^2} - \text{Arctan} \frac{(b_l + \beta)\omega}{b_l \beta - \omega^2}.$$

The identities: $c_l^2 + d_l^2 = b_l^2 + 4\beta^2 + 2b_l\beta$, and $c_l d_l = b_l \beta$ lead to the inequality: $\forall \omega \in \mathbb{R}$, $|G^*(i\omega)| \leq |G(i\omega)|$.

By successive iterations, we obtain the same results with multiple couplings. **Corollary.** In the complex plane, the $G^*(i\omega)$ -curve, for $\omega > 0$, is nearer the origin than the $G(i\omega)$ -curve. **Proof.** Let us note that we have: $G^*(0) = G(0) \in \mathbb{R}^{*+}$, and $\forall \omega > 0$, $\text{Arg}G(i\omega) = -\sum_{k=1}^n \text{Arctan} \frac{\omega}{b_k} < 0$. If ω is large enough, the Arctan property gives us $\psi_l(\omega) < 0$, then $\text{Arg}G^*(i\omega) > \text{Arg}G(i\omega)$. Moreover, as positive ω increases, the modulus and the argument of $G(i\omega)$ and $G^*(i\omega)$ decrease monotonically:

$$\lim_{\omega \rightarrow +\infty} G(i\omega) = \lim_{\omega \rightarrow +\infty} G^*(i\omega) = 0,$$

$$\lim_{\omega \rightarrow +\infty} \text{Arg}G(i\omega) = \lim_{\omega \rightarrow +\infty} \text{Arg}G^*(i\omega) = -n \frac{\pi}{2}.$$

The curves spiral to origin. Since the $G^*(i\omega)$ -curve does not intersect the $G(i\omega)$ -curve except at $\omega = 0$ or if $\beta_k \equiv 0$, for all k , and since the modulus and the arguments of $G^*(i\omega)$ are smaller than those of $G(i\omega)$ when ω is large enough, we deduce that the $G^*(i\omega)$ -curve is nearer the origin in the complex plane than the $G(i\omega)$ -curve.

The $G(i\omega)$ - and $G^*(i\omega)$ -curves first cross the negative real axis at frequencies ω_c and ω_c^* , if they exist, so that :

$$\sum_{i=1}^n \text{Arctan} \frac{\omega_c}{b_i} = \pi \quad (5)$$

$$\sum_{i=1}^n \left(\text{Arctan} \frac{\omega_c^*}{b_i} + \psi_i(\omega_c^*) \right) = \pi \quad (6)$$

where

$$\psi_i(\omega_c^*) = \text{Arctan} \frac{(b_i + 2\beta_i)\omega_c^*}{b_i \beta_i - (\omega_c^*)^2} - \text{Arctan} \frac{(b_i + \beta_i)\omega_c^*}{b_i \beta_i - (\omega_c^*)^2}.$$

The expression simplifies still further when the following special case is considered. Let us note that a solution $\omega_c > 0$ of Eq. 5 exists if and only if $n \geq 3$. **Proposition.**

1. If $\beta_l b_l > \omega_c^2$ for all l , then $\omega_c^* \leq \omega_c$;
2. If $b_k \equiv b$ and $\beta_k \equiv \beta > 0$, $1 \leq k \leq n$, then
 - (a) $\omega_c^* \leq \omega_c$ if and only if $\beta \geq b \tan^2 \frac{\pi}{n}$.
 - (b) $R^* < R$.

Proof. If $\beta_l b_l > \omega_c^2$, for all $l = 1, \dots, n$, then

$$\psi_l(\omega_c) > 0, \quad \text{and} \quad \sum_{l=1}^n \left(\text{Arctan} \frac{\omega_c}{b_l} + \psi_l(\omega_c) \right) > \pi;$$

so we obtain: $\omega_c^* \leq \omega_c$.

If $b_k \equiv b$ and $\beta_k \equiv \beta > 0$, $1 \leq k \leq n$, we obtain first: $\omega_c = b \tan \frac{\pi}{n}$, and we consider the formula 6:

$$\sum_{l=1}^n \text{Arctan} \frac{\omega_c^*}{b} + \psi_l(\omega_c^*) = \pi.$$

Let us note that $\psi_l(\omega_c) = 0$ according to the case $\beta = 0$.

Let us denote $\psi \equiv n \psi_0$ with

$$\psi_0(\omega) = \text{Arctan} \frac{(b+2\beta)\omega}{b\beta - \omega^2} - \text{Arctan} \frac{(b+\beta)\omega}{b\beta - \omega^2}.$$

We observe that, under this form, $\psi_0(\omega) = 0$ if and only if $\omega = 0$, or $\sqrt{b\beta}$, or $+\infty$ to the limit. In \mathbb{R}^+ , the function ψ_0 is positive in the interval $[0, \sqrt{b\beta}]$.

Let us denote $\omega_0^* = \sqrt{b\beta}$. If $\beta \geq b \tan^2 \frac{\pi}{n}$, then $\forall \omega \in [0, \sqrt{b\beta}]$, $\psi_0 > 0$, and $n \text{Arctan} \frac{\omega_0^*}{b} \geq \pi$, this implies: $\omega_c^* \leq \omega_0^*$.

Since $n \psi_0(\omega_c^*) \geq 0$, we deduce: $n \text{Arctan} \frac{\omega_c^*}{b} < \pi$, this implies: $\omega_c^* \leq \omega_c$.

Conversely, if $\omega_c^* \leq \omega_c$, then $\omega_c^* \leq b \tan^2 \frac{\pi}{n}$, and

$$\sum_{l=1}^n \text{Arctan} \frac{\omega_c^*}{b_l} = n \text{Arctan} \frac{\omega_c^*}{b} \leq \pi,$$

this leads: $\psi(\omega_c^*) \geq 0$, then $\omega_c^* \in [0, \sqrt{b\beta}]$.

Secondly, it is sufficient to prove $|G^*(i\omega_c^*)| < |G(i\omega_c)|$. The representation of G^* leads to:

$$|G^*(i\omega)| < |G(i\omega)| \quad \forall \omega > 0.$$

The functions $|G^*(i\omega)|$ and $|G(i\omega)|$ versus ω are continuous and monotonically decreasing with increasing positive frequency.

Let us denote ω_d so that $|G^*(i\omega_c^*)| = |G(i\omega_d)|$. If $\omega_c < \omega_d$, $|G(i\omega_d)| < |G(i\omega_c)|$, then $|G^*(i\omega_c^*)| < |G(i\omega_c)|$. It remains to prove: $\omega_c < \omega_d$, so $|G^*(i\omega_c^*)| < |G(i\omega_c)|$ is always verified. The equality:

$$\text{Arctan} \frac{\omega_c^*}{b} + \text{Arctan} \frac{(b+2\beta)\omega_c^*}{b\beta - (\omega_c^*)^2} - \text{Arctan} \frac{(b+\beta)\omega_c^*}{b\beta - (\omega_c^*)^2} = \text{Arctan} \frac{\omega_c}{b}$$

leads to:

$$\omega_c = \frac{b\omega_c^{*5} + (b^3 + 2b\beta^2)\omega_c^{*3} + 2b^3\beta^2\omega_c^*}{(b+\beta)\omega_c^{*4} + (b^2\beta + b^3 + b\beta^2)\omega_c^{*2} + b^3\beta^2}.$$

Moreover, $|G(i\omega_d)| = |G^*(i\omega_c^*)|$ implies:

$$\omega_d^2 = \frac{\omega_c^{*4} + (2b\beta + 4\beta^2)\omega_c^{*2}}{\omega_c^{*2} + \beta^2}.$$

So, we obtain:

$$\omega_d^2 - \omega_c^2 = C_1 \omega_c^{*12} + C_2 \omega_c^{*10} + C_3 \omega_c^{*8} + C_4 \omega_c^{*6} + C_5 \omega_c^{*4} + C_6 \omega_c^{*2}$$

with

$$\begin{aligned} C_1 &= \beta^2 + 2b\beta > 0, \quad C_2 = 6b^3\beta + 12b\beta^3 + 6b^2\beta^2 + 4\beta^4 > 0, \\ C_3 &= (4b^3\beta + 2b\beta^3)(2b\beta + 4\beta^2) + 12b^3\beta^3 + 9b^2\beta^4 + 6b^5\beta + 3b^4\beta^2 > 0, \\ C_4 &= 2(b^4\beta^2 + b^3\beta^3)(2b\beta + 4\beta^2) + 2b^3\beta^2(b^2\beta + b\beta^2 + b^3) + 10b^3\beta^5 + 10b^5\beta^3 + 3b^6\beta^2 + 2b^7\beta > 0, \\ C_5 &= 5b^6\beta^4 + 10b^5\beta^5 + 4b^7\beta^3 > 0 \text{ and } C_6 = 2b^7\beta^5. \end{aligned}$$

Lastly, we deduce: $\omega_c < \omega_d$, then $R^* < R$.

Applications

1. According to the condition: $\beta \geq b \tan^2 \frac{\pi}{n}$, when $n \geq 3$, it is possible to find ω_c and ω_c^* solutions of Eqs 5 and 6. This condition leads to $\beta \geq +\infty$ when $n = 2$, $\beta \geq 3b$ when $n = 3$, $\beta \geq b/3$ when $n = 6$. In the case $n = 2$, when $b_k \equiv b$ and $\beta_l \equiv \beta$, the formulae 5 and 6 have no solutions: no oscillations occur. In the cases $n > 2$, couplings with large β give smaller frequencies.

2. The concentrations P_i , $1 \leq i \leq n$, of steady states are not modified by coupling; when steady state is unstable, oscillations appear [11] and coupling decreases the frequency of the oscillations of the system if the diffusion coefficient β is large enough versus kinetic coefficient b . Moreover, if the number of reactants increases, then the stability effect of pools is more effective:

$$n \rightarrow +\infty \implies \beta \geq b \tan^2 \frac{\pi}{n} \rightarrow 0 \implies \omega_c^* \leq \omega_c .$$

Proposition.

If $b_k = \beta_k \equiv b$, for all k , then

1. $n = 4 \implies \omega_c^* = \omega_c$;
2. $n > 4 \implies \omega_c^* \leq \omega_c$.

Proof.

If $b_k = \beta_k \equiv b$, $\forall k$, then we have:

$$\psi_0(\omega) = \text{Arctan} \frac{2\omega}{(3-\sqrt{5})b} + \text{Arctan} \frac{2\omega}{(3+\sqrt{5})b} - 2 \text{Arctan} \frac{\omega}{b} .$$

The expression of $\psi_0(\omega_c)$ gives us:

- if $n = 4$, $\text{Arctan} \frac{2}{3+\sqrt{5}} + \text{Arctan} \frac{2}{3-\sqrt{5}} = \frac{\pi}{2}$, then $\omega_c^* = \omega_c$;
- if $n \geq 4$, then $\psi_0(\omega_c) = \text{Arctan} \frac{3 \tan \pi/n}{1 - \tan^2 \pi/n} - \frac{2\pi}{n} \geq 0$, and the result is obtained:
 $\omega_c^* \leq \omega_c$.

Proposition.

Let us assume that the systems admit both oscillations, i.e. the $G(i\omega)$ - and $1/F(x)$ -curves intersect in the complex plane at point $-x$ of negative real axis (see [12]), and the $G^*(i\omega)$ - and $1/F(x)$ -curves intersect at point $-x^* < 0$ (so, we consider the amplitudes $x, x^* > 0$).

Then: $x^* < x$. **Proof.**

The above results state that, since $|G^*(i\omega)| \leq |G(i\omega)|$, the $G^*(i\omega)$ -curve is nearer the origin in the complex plane than the $G(i\omega)$ -curve. The $G^*(i\omega)$ -curve spirals into the origin in a clockwise direction faster than the $G(i\omega)$ -curve. This is sufficient to prove the above result. Indeed, when we consider the associated system, the balance method gives us the following first harmonic equation: $G^*(i\omega) = 1/F(x)$ where F is a real function of x , the amplitude of the oscillation, and ω , the frequency (coupling does not modify this function F). If the $G(i\omega)$ -, respectively $G^*(i\omega)$ -, and $1/F(x)$ -curves intersect in the complex plane, oscillations occur with amplitude x , respectively x^* , and the amplitude x^* of a periodic solution is smaller when coupling exists (the point $-x^*$ of the negative real axis is nearer the origin than the point $-x$).

5 Numerical experiments

Let us compute the expressions R and R^* . First, we need the expressions of G and G^* , then the approximate solutions ω_c and ω_c^* of Eqs 5 and 6.

Simulations are obtained using the original system:

$$\begin{cases} \frac{dS_1}{d\tau} = \frac{\alpha_0}{1+K S_n^\mu} - \alpha_1 S_1 - g_1(S_1 - S_1^*), \\ \frac{dS_k}{d\tau} = \alpha_{k-1} S_{k-1} - \alpha_k S_k - g_k(S_k - S_k^*), & k = 2, \dots, n, \\ \frac{dS_k^*}{d\tau} = g_k(S_k - S_k^*), & k = 1, \dots, n, \end{cases} \quad (7)$$

Defining new variables $t, P_1, \dots, P_n, P_1^*, \dots, P_n^*$ as:

$$t = \left(\alpha_1 \cdots \alpha_n K^{1/\mu} \alpha_0 \right)^{1/n} \tau ,$$

Table 1: Nonassociated system: $\alpha_j = 1, \quad j = 1, \dots, n-1, \mu = 5$

n	α_0	K	α_n	R	Oscillation
5	50	0.01	0.5	0.8673	No
5	50	1	1	0.9851	No
7	5	0.1	0.5	0.9730	No
7	50	1	5	1.1115	Yes
8	5	0.1	0.5	1.0811	Yes
8	5	0.1	1	0.8653	No

Table 2: Associated system: $\alpha_j = 1, \quad j = 1, \dots, n-1, g_l = 1, \quad l = 1, \dots, n, \quad \mu = 3$

n	α_0	K	α_n	R^*	Oscillation
7	50	0.1	0.5	0.8735	No
8	10	10	1	0.9953	No
9	150	0.1	0.5	1.2199	Yes
10	50	1	0.5	1.3253	Yes
12	1	2	0.5	0.8911	No
15	200	0.01	0.1	1.2414	Yes

$$P_1 = \alpha_0^{-1} \left(\alpha_1 \cdots \alpha_{n-1} K^{1/\mu} \alpha_0 \right)^{1/n} S_1,$$

$$P_k = (\alpha_1 \cdots \alpha_{n-1} \alpha_0)^{-1} \left(\alpha_1 \cdots \alpha_{n-1} K^{1/\mu} \alpha_0 \right)^{k/n} S_k, \quad k = 2, \dots, n,$$

$$P_k^* = (\alpha_1 \cdots \alpha_{n-1} \alpha_0)^{-1} \left(\alpha_1 \cdots \alpha_{n-1} K^{1/\mu} \alpha_0 \right)^{k/n} S_k^*.$$

The resulting equation is equation (1) where:

$$b_k = \alpha_k \left(\alpha_1 \cdots \alpha_{n-1} K^{1/\mu} \alpha_0 \right)^{-1/n}, \quad \beta_k = g_k \left(\alpha_1 \cdots \alpha_{n-1} K^{1/\mu} \alpha_0 \right)^{-1/n}.$$

5.1 Non-associated system

Simulations are obtained, and results are shown in Table 1 using the original system (7).

Direct simulations using MATLAB software confirm this fact.

5.2 Associated system

Some results are shown in Table 2 where the existence of oscillations are pointed out. Comparing the value of R^* and the numerical solution of the set of equations (7), we observe that the values of R^* confirm the existence or not of a periodic solution.

5.3 Comparison between isolated and associated systems

The results in Table 3 exhibit the effects of coupling on the value R^* versus R . When g_k are not zero, the numerical values of R^* are always smaller than those of R . The stability of associated system is increased.

Table 3: Isolated and associated systems: $\alpha_j = 1$, $j = 1, \dots, n-1$, $g_l = 1$, $l = 1, \dots, n$, $\mu = 3$

n	α_0	K	α_n	R	R^*
7	50	0.1	0.5	1.2949	0.8735
8	5	0.1	1	0.8653	0.5992
9	150	1	1	1.6742	1.2231
10	10	2	0.1	0.9513	0.7967
12	100	0.01	5	1.3426	1.0568

Table 4: Frequency comparison: $\alpha_j = a$, $j = 1, \dots, n$, $g_l = g$, $l = 1, \dots, n$, $K = 2$

n	α_0	μ	g	$a \tan^2 \frac{\pi}{n}$	ω_c	ω_c^*
3	50	6	0.065	0.783	0.452	0.556
4	200	7	0.046	0.461	0.461	0.502
4	50	5	0.726	0.363	0.363	0.222
6	5	6	0.210	0.280	0.486	0.516
6	200	2	1.020	0.170	0.294	0.155
8	100	4	1.009	0.086	0.209	0.107

5.4 Frequency comparison

We suppose: $\alpha_j = a$, $j = 1, \dots, n$, and $g_k = g$, $k = 1, \dots, n$. Let us note that the condition $\beta > b \tan^2 \frac{\pi}{n}$ for the nondimensional system (1) is equivalent to the condition $g > a \tan^2 \frac{\pi}{n}$ for the original system (7). We can verify the property $\omega_c^* < \omega_c$ when this condition is satisfied (see, for instance, Table 4 where the opposite cases are shown). In these cases, we have also obtained $R^* < R$. Extensive simulations have conducted us to the special case: if $b_k \equiv b$, $\beta_k \equiv \beta$, for all $k = 1, \dots, n$, so that $b = \beta \tan^2 \frac{\pi}{n}$, then $n = 22$ has given $\omega_c^* = \omega_c$.

6 Discussion

Recently, much attention has been paid to the inhomogeneity and anisotropy of the cell milieu. Although the existence of cellular microenvironments has been demonstrated experimentally in many cases, the physiological significance of cellular organization remains open for speculation. Especially, little is known on the consequences of pools existence on the dynamic behaviour of metabolic pathways, while dynamic properties of metabolic pathways in homogeneous media have been studied for several decades (see, for instance, [12]).

Since the association of metabolic chains can result in an increase in their stability domain (review in [2]), we have studied, in the present work, some effects of pools existence on the oscillations of a Yates-Pardee (or Goodwin) metabolic chain. These effects confirm, in part, Chauvet's hypothesis of increasing stability via association of metabolic units.

Our results show that coupling with exterior pools of metabolites modifies the behaviour of the oscillations of a Goodwin metabolic system in the following way: (i) periodic solutions of the system with coupling have lower amplitudes and frequencies; (ii) coupling can give rise to a steady state, instead of a periodic solution. These observations are consistent with the increase of stability observed when two Goodwin-Yates-Pardee metabolic pathways are

associated [11]. Thus the stability of the Goodwin-Yates-Pardee metabolic pathway, which is the most commonly encountered form of regulated biochemical pathway, is enhanced when matter can be exchanged with the outside.

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