Analytical results on systems arising in enzymatic reactions with application to phosphofructokinase model

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***Abstract*—**A reaction-diffusion system based on some biological systems, arising in enzymatic reactions, has been considered. The iterative method by means of a fixed point theorem has been applied in order to solve this system of coupled nonlinear partial differential equations. The existence, uniqueness and positiveness of the solution to system with Robin-type boundary condition have been obtained. A biochemical system has been extended and solved analytically. Quasi-steady states and linear stability analysis have been proved.

***Keywords*—**Mathematical biology, reaction-diffusion system, stability analysis, stationary solution, steady-state.

I. Introduction

A number of numerical studies have been devoted to metabolic pathways, modelized using a system of nonlinear ordinary differential equations. These initial studies were concerned mainly with reactions occurring in a homogeneous milieu (see, for instance, [5]). Several authors have emphasized the dramatic importance of the cell milieu heterogeneity for metabolic pathways dynamics [3], [8]. Therefore, the systems are described by nonlinear PDE's taking into account enzyme reaction, metabolite diffusion, and Robin-type boundary conditions, but now augmented to include an electrical field or a derive term due the possible presence of ions.

These subjects continue to be among the most popular for molecular biologists and students alike, with the availability of a new generation of efficient algorithms for reaction-diffusion problems providing numerical and significant results.

The aim of this paper is: *(i)* to solve some reaction-diffusion systems arising in enzymatic reactions; *(ii)* to take the realistic boundary condition and the derive term into account; *(iii)* to apply the mathematical machinery to phosphofructokinase model.

The development of the iterative method by a means of fixed point theorem makes possible not only the solution of these systems but extensions to more general models with wide classes of nonlinearities and of boundary conditions. Its application to a biological problem may involve extension of the original second member. The basic set up of the original model is discussed in details in [5].

In Section 3, we prove the existence, uniqueness and positiveness of the solution to the resulting reaction-diffusion equations. The associated numerical resolution is briefly recalled in Section 4. Solutions of the governing equations of an extended phosphofructokinase model are reported in Section 5.

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II. Statement of the problem

Let $\Omega =]0, L[$ be a one-dimensional spatial domain, and $I =]0, T[$ a time interval. The concentrations u_i, $i = 1, \ldots, n$ of the metabolites depend on space and time such that $u_i(x,t)$ is the concentration of the i-th species at point x and time t. If we set $\Gamma = \{O, L\}$ the boundary of Ω, $Q = \Omega \times I$, and $\Sigma = \Gamma \times I$, the evolution of the concentrations $u = (u_1, \ldots, u_n)$ is governed by the following nonlinear system:

$$\begin{aligned} \partial_t u - \partial_x (a\, \partial_x u) + b\, \partial_x u + c\, u &= f(x,u) \text{ in } Q \\ a\, \partial_\eta u &= \mu\, (u^{\text{ex}} - u) \quad \text{on } \Sigma \\ u &= u_0 \quad \text{if } t = 0 \end{aligned} \tag{1}$$

where $a = \text{diag}\,(a_1, \ldots, a_n)$, b, c, and μ are diagonal matrices with coefficients defined from Ω into $\mathbb{R}$ or from Γ into $\mathbb{R}^+$. The function $f = (f_1, \ldots, f_n)$ is such that f_i is defined from $\Omega \times \mathbb{R}^n$ into $\mathbb{R}$. The function u^{ex} is defined from Σ into $\left(\mathbb{R}^+\right)^n$, and represents a Robin-type boundary condition, and η designating the external normal unit vector. The initial condition u_0 is defined from Ω into $\left(\mathbb{R}^+\right)^n$.

III. Existence, uniqueness and positiveness of the solution

Let us introduce the following classical notations [4]: *(i)* $H = \left(L^2(\Omega)\right)^n$, where $L^2(\Omega)$ is the Hilbert space of square integrable functions over Ω; *(ii)* $V = \left(H^1(\Omega)\right)^n$, where $H^1(\Omega)$ is the Hilbert space of square integrable functions with first derivative belonging to $L^2(\Omega)$; *(iii)* $L^2(I,V)$ is the space of functions v with norm $\|v\|_V$ belonging to $L^2(I)$; *(iv)* $W(I,V,V')$ is the space of functions v belonging to $L^2(I,V)$ whose derivative dv/dt belongs to $L^2(I,V')$, V' being the topological dual of V.

A. Existence and uniqueness of the solution

Theorem 1: If the following assumptions are satisfied:
(i) The function f is Lipschitz continuous in u independently of x, *i.e.*:
$\exists\, C > 0,\, \forall\, u,\, v \in \mathbb{R}^n,\, |f(u) - f(v)| \leq C\,|u - v|$
and f verifies:
$\forall\, u \in L^2(I,H),\ f(u) \in L^2(I,H)$.
(ii) The functions a_i, b_i, c_i, and μ_i, $i = 1, \ldots, n$, are such that:

$$\begin{array}{rcll} 0 & < & m \leq a_i(x) \leq M & \forall\, x \in \Omega \cup \Gamma \\ 0 & \leq & |b_i(x)| \leq M & \forall\, x \in \Omega \\ 0 & < & m \leq c_i(x) \leq M & \forall\, x \in \Omega \\ 0 & \leq & \mu_i(x) \leq M & \forall\, x \in \Gamma \end{array}$$

(iii) The function $g = \mu\, u^{\text{ex}}$ belongs to $L^2\left(I, H^{-1/2}(\Gamma)\right)$;
(iv) The function u_0 belongs to H;
then system (1) admits a unique solution in $W(I,V,V')$.

Proof: The main steps of the proof are as follows: *(i)* consider a given function $u^{(1)} \in L^2(I,H)$, and prove that system (1) admits a unique solution $u^{(2)}$ when the second member equals to $f\left(u^{(1)}\right)$; *(ii)* define the application $\mathcal{G}$ by $u^{(2)} = \mathcal{G}\left(u^{(1)}\right)$, and prove that $\mathcal{G}$ admits a unique fixed point in an adequate functional space.

The first step of the proof is obtained by introducing a variational equation associated to system (1), say:
$\forall\, v \in V$,

$$\begin{array}{rcl} \left(\partial_t u,\, v\right)_0 + & \left(a\,\partial_x u,\, \partial_x v\right)_0 + \mu_L\, u(L) v(L) & \\ + & \mu_0\, u(0) v(0) + \left(b\,\partial_x u,\, v\right)_0 + \left(c\, u,\, v\right)_0 & \\ & = \left(f,\, v\right)_0 + \mu_L\, u_L^{\text{ex}} v(L) + \mu_0\, u_0^{\text{ex}} v(0) & \\ & u(.,t=0) = u_0(.) \in H & (2) \end{array}$$

where the scalar products $(\,\cdot\,,\,\cdot\,)_0$ are in H.

A bilinear continuous form w defined on $V \times V$ is now introduced:

$$\begin{array}{rcl} w(u,v) & = & \left(a\,\partial_x u,\, \partial_x v\right)_0 + \mu_L\, u(L) v(L) \\ & + & \mu_0\, u(0) v(0) + \left(b\,\partial_x u,\, v\right)_0 + \left(c\, u,\, v\right)_0 \end{array}$$

Following [4], the coercivity of w can be deduced, i.e.:

$$\exists\, \lambda,\, \exists\, \alpha > 0\ :\ w(u,u) + \lambda\, |u|_H^2 \geq \alpha\, |u|_V^2$$

The classical assumptions [4] on parabolic system being verified, the variational equation (2) admits a unique solution in $W(I,V,V')$.

The second step of the proof consists in proving that $\mathcal{G}$ is a contraction mapping on $L^2(I,H)$.
Let us consider $u^{(1)}$ and $\overline{u}^{(1)}$ in $L^2(I,H)$, and $u^{(2)}$ and $\overline{u}^{(2)}$ the related solutions. If we introduce the generic notation $\delta q = q - \overline{q}$, the proof consists in determining the existence of a real number $\nu \in\,]0,1[$ such that:

$$\left|\delta\mathcal{G}\left(u^{(1)}\right)\right|_{L^2(I,H)} \leq \nu\, \left|\delta u^{(1)}\right|_{L^2(I,H)}.$$

The solutions $u^{(2)}$ and $\overline{u}^{(2)}$ to system (1) satisfy the following system:

$$\begin{array}{l} \partial_t\left(\delta u^{(2)}\right) - \partial_x\left(a\,\partial_x\left(\delta u^{(2)}\right)\right) \\ \qquad + b\partial_x\left(\delta u^{(2)}\right) + c\delta u^{(2)} = \delta f\left(u^{(1)}\right) \text{ in } Q, \\ a\partial_\eta\left(\delta u^{(2)}\right) + \mu\delta u^{(2)} = 0 \text{ on } \Sigma, \\ \delta u^{(2)} = 0 \text{ if } t = 0, \end{array}$$

and the associated variational equation:
$\forall\, v \in V$,

$$\begin{array}{l} \left(\partial_t\left(\delta u^{(2)}\right),\, v\right)_0 + \left(a\,\partial_x\left(\delta u^{(2)}\right),\, \partial_x v\right)_0 \\ \quad + \mu_L\, \delta u^{(2)}(L) v(L) + \mu_0\, \delta u^{(2)}(0) v(0) \\ \quad + \left(b\,\partial_x\left(\delta u^{(2)}\right),\, v\right)_0 + \left(c\,\delta u^{(2)},\, v\right)_0 \\ \qquad = \left(\delta f\left(u^{(1)}\right),\, v\right)_0 \end{array} \qquad (3)$$

By considering $v = \delta u^{(2)}$ in (3), and taking the assumptions on functions a, b, c, and μ into account, we get:

$$\frac{d}{dt}\left|\delta u^{(2)}\right|_0^2 \leq \left|\delta f\left(u^{(1)}\right)\right|_0^2 + (2\lambda + 1)\left|\delta u^{(2)}\right|_0^2 \qquad (4)$$

Integrating both sides of (4) between 0 and $s \in I$, and applying the Gronwall lemma [4], we obtain:

$$\left|\delta u^{(2)}\right|_0^2(s) \quad \leq \quad \exp(s) \int_0^s \left|\delta f\left(u^{(1)}\right)\right|_0^2(\tau)\, d\tau$$

and

$$\left|\delta u^{(2)}\right|_0^2(s) \leq \exp(T)\left|\delta f\left(u^{(1)}\right)\right|_{L^2(0,s;H)}^2 \qquad (5)$$

Since the function f is Lipschitz continuous, we have, from inequality (5):
$\forall t \in\,]0,T[$,

$$\left|\delta u^{(2)}\right|_{L^2(0,t;H)}^2 \leq M\, \exp(T) \int_0^t \left|\delta u^{(1)}\right|_{L^2(0,s;H)}^2 ds$$

The proof can now be completed by a recursive calculation, where the m-th iterated value $\mathcal{G}^{(m)}$ of the application $\mathcal{G}$ is contracting with a constant ν such that: $\nu^2 = \frac{(M\exp(T))^m T^m}{(m-1)!} < 1$.
We conclude that $\mathcal{G}^{(m)}$ admits a unique fixed point, and with a Banach fixed point theorem, that $\mathcal{G}$ admits also a fixed point u in $L^2(I,H)$ such that: $u = \mathcal{G}(u)$. □

B. Positiveness of the solution

Let us prove that under suitable conditions, from the biological point of view, the solution to system (1) is nonnegative, i.e. all components are nonnegative.

Theorem 2: If the assumptions of theorem 1 hold, and if, moreover, the functions f, u^{ex} and u_0 are nonnegative, then the solution to system (1) is nonnegative.

Proof: If we perform the following change of variable: $z = \exp(-\lambda t)\, u$, the variational equation (2) may be

written as:

$$\begin{aligned}
&\forall\, v \in V,\\
&(\partial_t z,\, v)_0 + (a\,\partial_x z,\, \partial_x v)_0 + \mu_L\, z(L)v(L)\\
&\quad +\mu_0\, z(0)v(0) + (b\,\partial_x z,\, v)_0 + ((c+\lambda)\, z,\, v)_0\\
&\quad = \exp(-\lambda t)\,(f(x, \exp(\lambda t)\, z),\, v)_0\\
&\quad +\mu_L\, z_L^{\text{ex}} v(L) + \mu_0\, z_0^{\text{ex}} v(0)\\
&\quad \text{with} \qquad z(.,t=0) \;=\; z_0(.) \in H \qquad (6)
\end{aligned}$$

By writing $z = z^+ - z^-$ and considering $v = -z^-$, Eq. (6) becomes:

$$\begin{aligned}
&\tfrac{1}{2}\tfrac{d}{dt}\,|z^-(t)|_0^2 + w_1(z^-, z^-) \;+\mu_L\,(z^-(L))^2\\
&\quad +\mu_0\,(z^-(0))^2 \;=\; -\exp(-\lambda t)\,(f, z^-)_0\\
&\quad -\mu_L\, z_L^{\text{ex}} z^-(L) - \mu_0\, z_0^{\text{ex}} z^-(0)
\end{aligned}$$

with a nonpositive second member and w_1 defined by:

$$\begin{aligned}
w_1(z^-, z^-) = (a\,\partial_x z^-, \partial_x z^-)_0 + (b\,\partial_x z^-, z^-)_0\\
+\,(\,(c+\lambda) z^-, z^-)_0
\end{aligned}$$

Let us now prove that w_1 is nonnegative. By Young inequality, we have:

$$\left|\left(b\,\partial_x z^-, z^-\right)_0\right| \le \frac{\varepsilon}{2}\,\left|b\,\partial_x z^-\right|_0^2 + \frac{1}{2\,\varepsilon}\,\left|z^-\right|_0^2 \qquad \varepsilon > 0$$

so that: $w_1(z^-, z^-) \;\ge\; \left(m - \frac{\varepsilon}{2} M^2\right)\,|\partial_x z^-|_0^2 \;+ \left(m + \lambda - \frac{1}{2\,\varepsilon}\right)\,|z^-|_0^2$.
It is always possible to choose $\varepsilon > 0$ so that: $m - \frac{\varepsilon}{2} M^2 \ge 0$, and then λ so that: $m + \lambda - \frac{1}{2\,\varepsilon} \ge 0$. It follows that w_1 is nonnegative, and we have: $\frac{d}{dt}\,|z^-(t)|_0^2 \le 0$. The function $|z^-|_0^2$ is then a decreasing function of time, and since $z^-(x,0) = 0$, we obtain the theorem. □

IV. Numerical resolution

System(1) can be performed with adequate mathematical machinery. The main difficulty in the resolution is to take into account the derive term $b\,\partial_x u$. See, for details, [3] where a variational formulation relevant to the given problem leads to a rigourous discretization.

A. Variational formulation

The composite variational formulation consists in performing scalar products of the terms of the partial differential equation by some test functions belonging to appropriate spaces. This formulation makes it possible to take the boundary conditions into account, and thus leads to an approximate solution of the initial model.

By introducing an intermediate function $r(x,t)$, the system may be written as:

$$\begin{aligned}
r(x,t) &= -a(x)\,\partial_x u(x,t) \qquad (7)\\
\partial_t u(x,t) &= -\partial_x r(x,t) - b(x)\,\partial_x u(x,t)\\
&\quad -c(x)\,u(x,t) + f(x,u) \qquad (8)
\end{aligned}$$

By performing scalar products of Eqs (7) and (8) by two test functions, respectively ψ belonging to $H^1(\Omega)$ and ϕ belonging to $H(\Omega)$, and by integrating by parts, we get the two following equations:

$$\begin{aligned}
\int_\Omega \frac{r(x,t)}{a(x)}\psi(x)\,dx &= \int_\Omega u(x,t)\partial_x\psi(x)\,dx\\
&- u(L,t)\psi(L) + u(0,t)\psi(0) \qquad (9)\\
\int_\Omega \partial_t u(x,t)\phi(x)\,dx &+ \int_\Omega \partial_x r(x,t)\phi(x)\,dx\\
&+ \int_\Omega b(x)\partial_x u(x,t)\phi(x)\,dx\\
&+ \int_\Omega c(x)u(x,t)\phi(x)\,dx\\
&= \int_\Omega f(x,u(x,t))\phi(x)\,dx \qquad (10)
\end{aligned}$$

B. Discretizations

Eqs (9) and (10) are now discretized, by projection onto different sub-spaces of $H^1(\Omega)$ and $L^2(\Omega)$ respectively. Discretization in space is performed by a classical composite finite element method of order zero, which brings forth an ordinary differential equations system in time. The space domain Ω is divided into N space intervals of the same length h.

We use the θ-method where $\theta \in [0,1]$ is a parameter. This method consists in replacing the equation by a scheme with finite differences in time, either explicit or implicit according to the value of θ. The interval I is divided into NT equal sub-intervals $I_k = \left]t^k, t^{k+1}\right[$ of length τ. Taking $\theta = 0.5$, we obtain the classical Crank-Nicolson method which is unconditionally stable.

System (1) of n coupled partial differential equations is then solved by computing successively the solution of each equation where the source term f is calculated in the i-th equation by considering the values of u_1, …, u_{i-1} obtained from the previous equations. It has been verified [9] in a similar problem that this method of resolution remains precise in comparison with a global and cumbersome resolution, if the time step τ is chosen to be not too large.

V. Application to an enzyme model

The biologically important properties of a biochemical system are the existence of steady states or stationary solutions and the dynamic properties such as oscillations. The reactions considered by [5], [6], [8] as a model applied to phosphofructokinase (PFK) which is an enzyme activited by the end-product lead to the reaction-diffusion system (1) with the following specific form taking the

derive terms and the components into account:

$$\begin{array}{l}\text{in } Q\\ \quad \partial_t\alpha - \partial_x\left(a_1\,\partial_x\alpha\right) + b_1\partial_x\alpha + c_1\alpha = f_1\left(x,\alpha,\beta\right)\\ \quad \partial_t\beta - \partial_x\left(a_2\,\partial_x\beta\right) + b_2\partial_x\beta + c_2\beta = f_2\left(x,\alpha,\beta\right)\\ \text{on } \Sigma\\ \quad a_1\partial_\eta\alpha \;=\; \mu_1\,\left(\alpha^{\text{ex}} - \alpha\right)\\ \quad a_2\partial_\eta\beta \;=\; \mu_2\,\left(\beta^{\text{ex}} - \beta\right)\\ \text{if } t = 0\\ \quad \alpha = \alpha_{_0}\,, \qquad \beta = \beta_{_0}\end{array} \tag{11}$$

where α and β denote the normalized concentrations of the substrate and the product respectively, the exterior concentrations α^{ex}, β^{ex}, and the initial conditions $\alpha_{_0}$, $\beta_{_0}$ are nonnegative. The coefficients c_1 and c_2 are nonnegative; more precisely, in [8], $c_1 \equiv 0$ and $c_2 = k\,\sigma_2$ where $k > 0$ is a real parameter and $\sigma_2 \equiv \sigma_2(x)$ is a function defined on Ω. On the right-hand side, f_1 and f_2 are bounded continuous real functions defined on $\Omega \times \mathbb{R}^+ \times \mathbb{R}^+$ (see below). The boundary coefficients a_1, μ_1, a_2, μ_2 are nonnegative and verify:

$$(a_1, \mu_1) \neq (0,0) \text{ and } (a_2, \mu_2) \neq (0,0).$$

The nonlinear mappings

$$f_1 \text{ and } f_2\colon \Omega \times \left(\mathbb{R}^+\right)^2 \longrightarrow \mathbb{R}$$

are defined by the following expressions:

$$\begin{array}{rcl} f_1(x,\alpha,\beta) &=& k\;\sigma_1(x) - k\;g(x,\alpha,\beta)\\ f_2(x,\alpha,\beta) &=& k\;g(x,\alpha,\beta)\end{array} \tag{12}$$

with the function g defined on $\Omega \times \left(\mathbb{R}^+\right)^2$ by:

$$g\left(x,\alpha,\beta\right) = \frac{\left[2\,E_{_0}\,\varepsilon/(1+\varepsilon)\right]\alpha(1+\alpha/(1+\varepsilon))(1+\beta)^2}{L_\nu(1+c\,\alpha)^2+(1+\beta)^2(1+\alpha/(1+\varepsilon))^2} \tag{13}$$

where $k, \sigma_1, E_{_0}, \varepsilon, L_\nu, c$ are the nonnegative model parameters which may depend on x. For more information on the biological aspects, we refer the interested reader to [5] and references therein.

Goldbeter [6] imposes Dirichlet boundary conditions: $\alpha(0,t) = \alpha(L,t) = \alpha$ and $\beta(0,t) = \beta(L,t) = \beta$, where α and β are the steady-states concentrations. Goldbeter [6] analyzed numerically the behaviour of this model in the presence of diffusion along a single dimension without derive term. This situation is extended to a linear set of cells in the two-dimensional case by Marmillot *et al.* [8]: two phases are associated via permeable cell membrane and computer simulations are discussed.

The rest of this section is divided as follows. In Section V-A, the functions g, f_1 and f_2 are extended and defined on $\Omega \times \mathbb{R}^2$. In Section V-B we present some algebraic results which introduce the explicit expressions of steady-states concentrations and their stability analysis.

A. Extension of the second member

Instead of the original notation (α, β) in [5], we denote here $u = (u_1, u_2)$ for the sake of simplicity. The value of u_i can be *a priori* negative or positive; this leads us to extend the function f_i overall on $\Omega \times \mathbb{R}^2$. In particular, for technical reason, we extend the second member so that f is Lipschitz continuous in u independently of x. For this reason, it is necessary to extend appropriately the function g.

The second member f can be written, for all u with $u_1,\, u_2 \geq 0$, in the form:

$$\begin{array}{rcl} f\big(u\big) &=& k\,\begin{pmatrix} \sigma_1 - g\big(u\big) \\ g\big(u\big)\end{pmatrix}\\ &=& k\,\sigma_1\,\begin{pmatrix} 1 \\ 0\end{pmatrix} + k\,g(u)\,\begin{pmatrix} -1 \\ 1\end{pmatrix}\end{array} \tag{14}$$

with the following hypotheses:

$$k > 0 \qquad \text{is a constant parameter,} \tag{15}$$

$$\sigma_1 \qquad \text{is a bounded nonnegative function defined on } \Omega, \tag{16}$$

and where the function g is defined by (13) with the following hypotheses:

$$E_0, \varepsilon, L_\nu, c \qquad \text{are bounded nonnegative functions defined on } \Omega. \tag{17}$$

Let us note that the function g possesses a denominator which may be equal to zero for some nonpositive values of u_i, in particular when L_ν is equal to zero in a nonempty subset of Ω.

Proposition 3: Under the hypotheses (15)–(16) for the coefficients k, σ_1, and (13)–(17) for the function g and its parameters, the function f, given in (14), admits an extension defined on $\Omega \times \mathbb{R}^2$, again denoted f, such that:

$$|f(u) - f(v)| \leq M\;|u - v|\,, \quad \forall\, u, v \in \mathbb{R}^2, \tag{18}$$

where $M > 0$ is a constant value independent of x, and $|\cdot|$ is the euclidean norm in $\mathbb{R}^2$.

Proof: The function f is defined by (14) where the coefficients k, σ_1 satisfy hypotheses (15)–(16) and the function g is defined by (13) for all $u_1, u_2 \geq 0$ with the coefficients E_0, ε, L_ν, c which verify hypotheses (17). Let us denote g in the form:

$$g(u) = \frac{d_0\,g_1(u_1)\,g_2^2(u_2)}{d_5\,g_3^2(u_1) + g_4^2(u_1)\,g_2^2(u_2)}$$

where the functions g_i are defined from $\mathbb{R}$ to $\mathbb{R}$ by:

$$\begin{array}{rcl} \forall\, z \in \mathbb{R}, \quad g_1(z) &=& z\,(1 + d_1\,z),\\ g_i(z) &=& 1 + d_i\,z\,,\;\; i = 2,3,4\end{array} \tag{19}$$

with the functions d_i defined from Ω with values in $\mathbb{R}$ by: $d_0(x) = \dfrac{2\,E_0(x)\,\varepsilon(x)}{1+\varepsilon(x)}$, $d_1(x) = \dfrac{1}{1+\varepsilon(x)}$, $d_2 \equiv 1$, $d_3(x) = c(x)$, $d_4(x) = \dfrac{1}{1+\varepsilon(x)}$, $d_5(x) = L_\nu(x)$.

Let us extend g on $\Omega \times \mathbb{R}^2$. The functions g_i are firstly extended on $\mathbb{R}$ so that the denominator of g cannot be equal to zero and the extension $\widehat{g}$ is bounded.

If the extension $\widehat{g_i}$ of g_i admits a positive lower bound independently of x, then the denominator of g is always positive independently of x.

Let us introduce the real-valued function θ of a real variable z such that θ is of class $\mathcal{C}^\infty$ and verifies:

$$\begin{cases} \theta(z) = 1 & \text{if } -\eta \leq z \leq R\,, \\ \theta(z) = 0 & \text{if } z \leq -2\,\eta \ \text{ or } \ z \geq 2\,R\,, \\ 0 \leq \theta(z) \leq 1 & \text{if } -2\,\eta \leq z \leq -\eta \ \text{ or } \\ & R \leq z \leq 2\,R\,, \end{cases}$$

where $R > 0$ is a constant sufficiently large versus the physically acceptable value, and η is a positive constant defined by: $\eta = \frac{1}{3 \sup\limits_{\Omega} d_3}$. This constant η is independent of x and exists by means of hypothesis (17).

Let us denote $\widehat{g_3}$ an extension of g_3, defined for all $(x, z) \in \Omega \times \mathbb{R}$ by:

$$\widehat{g_3}(z) = g_3(0) + \int_0^z \theta(y)\, g_3'(y)\, dy \tag{20}$$

where the dependance of x is implicit for the sake of simplicity.

For the completeness of the proof of proposition 3, we need the following technical lemma:

Lemma 4: Under hypothesis (17) about the coefficient c, the function $\widehat{g_3}$, given by (20), admits the following properties: (i) $\widehat{g_3}$ verifies: $\widehat{g_3}(z) \geq m > 0$, $\forall\, z \in \mathbb{R}$, where m is a constant independent of x; (ii) $\widehat{g_3}$ is constant outside of a compact of $\mathbb{R}$; (iii) $\widehat{g_3}$ admits the derivative:

$$\widehat{g_3}'(z) = \theta(z)\, g_3'(z), \quad \forall\, z \in \mathbb{R}. \tag{21}$$

Proof: The function $\widehat{g_3}$ is defined by (20) by means of θ and g_3 whereas g_3 is given by (19) and admits the derivative $g_3'(z) = d_3 \geq 0$, $\forall\, z \in \mathbb{R}$. This leads us to the sign of integral in (20).

Three cases then are possible: *(i)* if $z < -2\eta$, then $\widehat{g_3}(z) = g_3(0) + \int_0^{-2\eta} \theta(y) g_3'(y)\, dy$ since θ equals zero outside of $[\,-2\,\eta, 2\,R\,]$; the integral then verifies: $\int_0^{-2\eta} \theta(y) g_3'(y)\, dy = -\int_{-2\eta}^{0} \theta(y) g_3'(y)\, dy = -d_3 \int_{-2\eta}^{0} \theta(y)\, dy \geq -2\eta d_3$, and by means of η, we obtain: $\int_0^{-2\eta} \theta(y) g_3'(y)\, dy \geq -\frac{2}{3}$, then $\widehat{g_3}$ admits a constant value such that:

$$\widehat{g_3}(z) \geq g_3(0) - 2\,\eta\, d_3 \geq \frac{1}{3}\,, \quad \forall\, z < -2\,\eta\,;$$

(ii) if $-2\,\eta \leq z \leq 2\,R$, then the integral in (20) verifies: $\int_0^z \theta(y) g_3'(y)\, dy \geq \int_0^{-2\eta} \theta(y) g_3'(y)\, dy$, this leads to: $\widehat{g_3}(z) \geq \frac{1}{3}\,, \quad \forall\, z, \ -2\,\eta \leq z \leq 2\,R\,;$

(iii) if $2\,R < z$, then $\widehat{g_3}(z) = g_3(0) + \int_0^{2R} \theta(y) g_3'(y)\, dy$, where the integral is a positive constant; $\widehat{g_3}$ is constant and verifies: $\widehat{g_3}(z) > g_3(0)\,, \quad \forall\, z > 2\,R.$

The integral expression (20) gives us the derivative $\widehat{g_3}'$ in the form: $\widehat{g_3}'(z) = \theta(z) g_3'(z)$, $\forall\, z \in \mathbb{R}$, which is equal to zero outside of $\operatorname{supp}\theta$. □

Let us finish the proof of proposition 3. For each x, an extension $\widehat{g_3}$ of g_3 exists. Let us define on $\Omega \times \mathbb{R}$ the extended functions $\widehat{g_i}$ of g_i by means of a scheme similar to (20).

The extension $\widehat{g}$ of g is then defined for all $(x, u) \in \Omega \times \mathbb{R}^2$ by:

$$\widehat{g}(x, u) \;=\; \frac{d_0\, \widehat{g_1}(u_1)\, \widehat{g_2}^{\,2}(u_2)}{d_5\, \widehat{g_3}^{\,2}(u_1) + \widehat{g_4}^{\,2}(u_1)\, \widehat{g_2}^{\,2}(u_2)}. \tag{22}$$

According to lemma 4 generalized for the functions $\widehat{g_i}$, $i = 2, 3, 4$, the denominator of $\widehat{g}$ admits a strictly positive lower bound independently of x.

Let us consider the extension $\widehat{f}$ of f, defined for all $(x, u) \in \Omega \times \mathbb{R}^2$, by:

$$\widehat{f}(x, u) = k\, \sigma_1(x) \begin{pmatrix} 1 \\ 0 \end{pmatrix} + k\, \widehat{g}(x, u) \begin{pmatrix} -1 \\ 1 \end{pmatrix} \tag{23}$$

This extension $\widehat{f}$ is defined by means of the coefficients k and σ_1 bounded on Ω (see hypothesis (16)), and the function $\widehat{g}$ defined by (22). In order that the function $\widehat{f}$ is Lipschitz continuous in u, independently of x, it is sufficient to prove that $\widehat{g}$ admits the same property. In particular, if $\widehat{g}$ admits bounded continuous partial derivatives, then $\widehat{g}$ is lipschitzian.

According to formula (21) of lemma 4, and defining D by: $D = d_5\, \widehat{g_3}^{\,2}(u_1) + \widehat{g_4}^{\,2}(u_1)\, \widehat{g_2}^{\,2}(u_2)$, we can obtain the partial derivatives of $\widehat{g}$ versus u_1 and u_2.

Since the continuous extended functions $\widehat{g_i}$, $i = 2, 3, 4$, are in the form (20) and their derivatives $\widehat{g_i}'$ in the form (21), the denominators possess a strictly positive lower bound, and the partial derivatives are defined and continuous in $\mathbb{R}^2$.

Moreover, since the coefficients d_0 and d_5 are non-negative and bounded in Ω, and since the functions $\widehat{g_i}$ and their derivatives are bounded in $\mathbb{R}$ independently of x, then the partial derivatives $\frac{\partial \widehat{g}}{\partial u_i}$ are bounded in $\mathbb{R}^2$ independently of x.

We then deduce that $\widehat{g}$ is globally lipschitzian in u, independently of x, and we can conclude that $\widehat{f}$, defined by (23), verifies the Lipschitz property (18) uniformly in G. □

To solve system (11) with the extended second member f by means of a Picard-type fixed point theorem (see Theorem 1), it is necessary to establish the following proposition:

Proposition 5: The function f introduced by (14) and extended by (23), verifies:

$$u \in L^2\,(\,I, H\,) \Longrightarrow f\,(u) \in L^2\,(\,I, H\,)\,. \tag{24}$$

Proof: From (18), it is sufficient to take $v = 0$. We then have: $|f(u) - f(0)| \leq M\,|u|$, $\forall\, u \in \mathbb{R}^n$, and

$|f(u)| \leq M\,|u| + |f(0)|$, $\forall\, u \in \mathbb{R}^n$. By integrating in Q, we obtain (24). □

Lastly, we do precise, for instance:
(i) The extension f is Lipschitz continuous, and f verifies: $u \in L^2(I,H) \Longrightarrow f(u) \in L^2(I,H)$ (see Propositions 3–5);
(ii) We assume that the functions a, b verify:
$\forall\, i = 1,\ldots,n$, $0 < m \leq a_i(x) \leq M$, $\forall\, x \in \Omega \cup \Gamma$, and $0 \leq |b_i(x)| \leq M$, $\forall\, x \in \Omega$. We suppose c_1 sufficiently small positive constant and $c_2 \equiv k\,\sigma_2$ such that: $\forall\, i = 1,\ldots,n$, $\forall\, x \in \Omega$, $0 < m \leq d_i(x) \leq M$ ($k > 0$ is a constant parameter and σ_2 is assumed to be a bounded positive function defined in Ω).
The function μ is such that: $\forall\, i = 1,\ldots,n$, $\forall\, x \in \Gamma$, $0 \leq \mu_i(x) \leq M$. If $\mu_1 > 0$ (respectively $\mu_2 > 0$), then we take $c_1 \equiv 0$ (respectively $c_2 \geq 0$).
(iii) We assume that $g = \mu\, u^{\text{ex}}$ is defined by means of fixed nonnegative constants u_1^{ex} and u_2^{ex}.
(iv) $u_0 = (\alpha_0, \beta_0)$ where α_0 and β_0 are assumed nonnegative real constants.

Since the hypotheses of Theorem 1 are satisfied, there exists a unique solution u to system (11). □

B. Steady states and stability in the first approximation

1) Solution of algebraic equations: Let us establish two lemmas on the existence and the analytical solution of steady-states of the biological reaction-diffusion system (11). For biological reasons, only nonnegative real-valued solutions are considered.

Lemma 6: Let $c_1 = 0$, $c_2 = k\,\sigma_2$ with positive real parameters k and σ_2. Assume f_1 and f_2 defined above (12). The nonlinear system :

$$\{f_1(x,\alpha,\beta) = 0;\ f_2(x,\alpha,\beta) - k\,\sigma_2\,\beta = 0\}$$

admits the following real-valued solutions with the intermediate notations (since the algebraic calculus is hard): $E = \varepsilon E_0$, $\varepsilon_1 = 1+\varepsilon$, $c_1 = 1 - c\varepsilon_1$, $\sigma = \sigma_1\sigma_2^2$, and $\sigma_{12} = \sigma_1 + \sigma_2$,

$$\begin{aligned}\alpha_\pm = \big\{&\varepsilon_1(\sigma c L_\nu \varepsilon_1 - (E-\sigma_1)\,\sigma_{12}^2 \pm \sigma_{12}\left[E^2\sigma_{12}^2\right.\\ &\left.+\sigma L_\nu c_1\,(2E - \sigma_1 c_1)\right]^{1/2})\big\}\\ &/\left\{(2E-\sigma_1)\,\sigma_{12}^2 - \sigma c^2 L_\nu \varepsilon_1^2\right\};\end{aligned}$$

$\beta_\pm = \sigma_1/\sigma_2$.
if and only if: $E^2\sigma_{12}^2 + \sigma L_\nu c_1\,(2E - \sigma_1 c_1) > 0$.

Proof: Considering this problem where: $f_1 \equiv k\,\sigma_1 - k\,g$ and $f_2 \equiv k\,g$, we get the following equations:

$$\begin{aligned}&\sigma_1\left\{L_\nu(1+\alpha c)^2 + (1+\beta)^2\left[1+\alpha/(1+\varepsilon)\right]^2\right\}\\ &\quad = [2E/\varepsilon_1]\,\alpha\,[1+\alpha/\varepsilon_1]\,(1+\beta)^2\ ,\end{aligned}$$

$$\begin{aligned}&[2E/\varepsilon_1]\,\alpha\,[1+\alpha/\varepsilon_1]\,(1+\beta)^2\\ &\quad = \sigma_2\beta\left\{L_\nu(1+\alpha c)^2 + (1+\beta)^2\left[1+\alpha/\varepsilon_1\right]^2\right\}\end{aligned}$$

and we easily find $\beta = \sigma_1/\sigma_2$. It follows from either of these equations that α verifies the following second order polynomial equation: $p\alpha^2 + q\alpha + r = 0$ with
$p = \sigma c^2 L_\nu \varepsilon_1^2 - (2E - \sigma_1)\sigma_{12}^2$,
$q = 2\varepsilon_1\left[\sigma c L_\nu \varepsilon_1 - (E-\sigma_1)\sigma_{12}^2\right]$, and
$r = \sigma_1\varepsilon_1^2\left[\sigma_{12}^2 + \sigma_2^2 L_\nu\right]$.

Hence, an elementary calculation yields:
$q^2 - 4pr = \sigma_{12}^2\left[E^2\sigma_{12}^2 + \sigma L_\nu \underline{c_1}\,(2E - \underline{\sigma_1} c_1)\right]$ and, if $q^2 - 4pr \geq 0$, the expressions $\alpha_\pm$ and $\beta_\pm$ mentioned above are obtained. □

Remark 7: If all parameters are nonnegative and verify: $c\varepsilon_1 \leq 1$ and $(2E - \underline{\sigma_1})(1+\sigma_1/\sigma_2)^2 - c^2\sigma_1 L_\nu > 0$, then nonnegative solution $\alpha_\pm$ exists. For instance [8] and parameters therein, a steady state exists.

In absence of diffusion $a = b \equiv 0$, system (11) admits two steady states. For a large class of parameters, the numerical study of the model [5] shows that these solutions exist in $\mathbb{R}^+$, but the only steady state physically acceptable is $\left(\overline{\alpha}_+, \overline{\beta}_+\right)$. These latter expressions verify precisely Goldbeter-Lefever numerical results [5].

Lemma 8: Let $L_\nu \equiv 0$. Then there exist steady-state solutions: $\alpha_+ = (1+\varepsilon)\sigma_1/(2\varepsilon E_{_0} - \sigma_1)$, $\alpha_- = \underline{-}(1+\varepsilon)$. Moreover, in this case, exists a positive solution α_+ if and only if : $2\varepsilon E_{_0} - \sigma_1 > 0$.
The proof is immediate.

2) Stability analysis: The dynamical evolution of the chemical reactions of system (11) without diffusion nor transport is described by the following ODE:

$$\begin{aligned}\frac{d\alpha}{dt} &= k\sigma_1 - k g(x,\alpha,\beta),\\ \frac{d\beta}{dt} &= k g(x,\alpha,\beta) - k\sigma_2\beta,\end{aligned} \tag{25}$$

with same nonnegative initial conditions $\alpha_{_0}$ and $\beta_{_0}$.

The temporal dynamics in a spacially uniform system are governed by solution of the system (25), where: *(i)* the vecteur (α,β) is the vector of chemical concentrations, and is therefore an element of the nonnegative cone C^+ of a two-dimensional real euclidean vector space; *(ii)* the net rate of production of the i^{th} product depends on g which is a rational function in the α, β's, having no poles in C^+; *(iii)* the real parameters include the kinetic constants but do not change significantly on the time scale of interest.

To be well-posed from the biological standpoint, the solution of (25) should exist and be nonnegative and bounded for $t \in [0, +\infty[$. Nonnegativity is guaranteed by the fact that:

$$\left\{\begin{array}{lcll} f_1(x,0,\beta) = k\sigma_1 & \geq & 0 & \text{for } \beta \geq 0\\ f_2(x,\alpha,0) = k g(x,\alpha,0) & \geq & 0 & \text{for } \alpha \geq 0\end{array}\right.$$

The solution through any initial point in C^+ is unique because the functions f_1 and f_2 are locally Lipschitz continuous in (α,β) throughout C^+.

Around some quasi-steady state $\left(\overline{\alpha},\overline{\beta}\right)$ of the above biological model, stability analysis leads to consider the following derivatives:

$$\overline{\frac{\partial g}{\partial \alpha}} \equiv \frac{\partial g}{\partial \alpha}\left(\overline{\alpha},\overline{\beta}\right) \quad \text{and} \quad \overline{\frac{\partial g}{\partial \beta}} \equiv \frac{\partial g}{\partial \beta}\left(\overline{\alpha},\overline{\beta}\right).$$

Since the calculus is cumbersome, we give only the explicit results by means of intermediate notation $\alpha_1 = 1 + \overline{\alpha} + \varepsilon$:

$$\begin{aligned}\overline{\frac{\partial g}{\partial \alpha}} &= \sigma_1 \frac{\alpha_1 + \overline{\alpha}}{\overline{\alpha}\alpha_1} \\ &- \sigma_1^2 \frac{L_\nu(1+\overline{\alpha}c)c\varepsilon_1^2 + (1+\sigma_1/\sigma_2)^2\alpha_1}{\overline{\alpha}E(1+\sigma_1/\sigma_2)^2\alpha_1}; \\ \overline{\frac{\partial g}{\partial \beta}} &= \frac{\sigma_1\sigma_2}{\sigma_{12}} \cdot \frac{2\overline{\alpha}E - \alpha_1\sigma_1}{\overline{\alpha}E}.\end{aligned}$$

Lemma 9: Some steady-state solution $\left(\overline{\alpha}, \overline{\beta}\right)$ is locally asymptotically stable if and only if:

$$\overline{\frac{\partial g}{\partial \alpha}} - \overline{\frac{\partial g}{\partial \beta}} + \sigma_2 > 0\,.$$

Proof: In absence of diffusion nor transport, let us linearize the system (25) in the neighborhood of steady state $\left(\overline{\alpha}, \overline{\beta}\right)$ and obtain the first approximation system. Hence, the stability of the linearized system is analytically studied by the means of the eigenvalues of the Jacobian matrix, i.e.:

$$\begin{aligned}\lambda_\pm &= -\tfrac{k}{2}\Big[\ \overline{\tfrac{\partial g}{\partial \alpha}} - \overline{\tfrac{\partial g}{\partial \beta}} + \sigma_2 \\ &\mp \left(\ \left(\ \overline{\tfrac{\partial g}{\partial \alpha}} - \overline{\tfrac{\partial g}{\partial \beta}} + \sigma_2\ \right)^2 - 4\sigma_2\overline{\tfrac{\partial g}{\partial \alpha}}\ \right)^{1/2}\Big].\end{aligned}$$

The eigenvalues $\lambda_\pm$ have negative real parts if and only if: $\overline{\frac{\partial g}{\partial \alpha}} - \overline{\frac{\partial g}{\partial \beta}} + \sigma_2 > 0$. The steady state is locally asymptotically stable if and only if this latter condition is true. □

Remark 10: The eigenvalues $\lambda_\pm$ belong to $\mathbb{R}^{*-}$ if and only if the following condition:

$\left(\dfrac{\partial g}{\partial \alpha} - \dfrac{\partial g}{\partial \beta} + \sigma_2\right)^2 \geq 4\sigma_2\dfrac{\partial g}{\partial \alpha}$ is satisfied.

Around some steady state $\left(\overline{\alpha}, \overline{\beta}\right)$, stability analysis gives us an unstable focus if we obtain:

$$\frac{\partial g}{\partial \alpha} - \frac{\partial g}{\partial \beta} + \sigma_2 < 0 \quad \text{and} \quad \frac{\partial g}{\partial \alpha} > 0.$$

Lemma 11: Let us assume $L_\nu \equiv 0$. Then the feasible steady state is always locally asymptotically stable.

Proof: In this case, from Lemma 8, we obtain:

$$\alpha_+ = (1+\varepsilon)\sigma_1/\left(2\varepsilon E_0 - \sigma_1\right) > 0,$$

then it follows:

$$\frac{\partial g}{\partial \alpha} = 1 - \sigma_1/2\,\varepsilon E_0 > 0, \text{ and } \frac{\partial g}{\partial \beta} = 0.$$

The stability condition is always satisfied. □

Remark 12: In a bound-phase ($L_\nu \equiv 0$), the steady state is exponentially stable and the α-stability [1] of the linearized system possesses the degree $d \equiv -\Re\left(\lambda_+\right)$ verifying $d = k\left(1 - \sigma_1/2\,\varepsilon E_0\right)$ or $d = k\,\sigma_2$.

With some parameters values, the system evolves towards a limit cycle in the phase plane as a negative feedback cellular control system, but if we consider bound phase [8] when $L_\nu = 0$, then no sustained oscillations occur in the concentrations as functions of time.

The linearized system in a neighborhood of any steady state has a stable critical point $\left(\overline{\alpha}, \overline{\beta}\right) = (0,0)$ when $\sigma_1 = 0$ (no rate entrance of the substrate) and $\sigma_2 \neq 0$ (with outputflow of the product) in one phase since the Linard and Chipart criterion is always satisfied. For this purpose, we get:

$$\overline{\frac{\partial g}{\partial \alpha}} = \frac{2\,\varepsilon E_0}{(1+\varepsilon)(1+L_\nu)} > 0 \quad \text{and} \quad \overline{\frac{\partial g}{\partial \beta}} = 0.$$

So numerical simulations [5], [8] are confirmed. Note that an important feature of living systems is the stability of their dynamics, in particular their steady states.

VI. Conclusion

Many reaction-diffusion system based on some biological systems, arising in enzymatic reactions, has been studied numerically by means of finite difference method or even finite elements method. Mostly, the existence, uniqueness and positiveness of the solution are implicitly supposed, and steady states and linear stability analysis are studied apart.

Results on the linear stability analysis of the system at the neighborhood of the unique steady state can be derived by both analytical and numerical studies for some values of the parameters of the model (see [9], [10], [3]); these numerical examples used the adequate algorithm presented herein. These analytical and numerical results confirm that the presence of cellular microenvironments can result in a diversity of metabolic dynamics, either homeostatic (asymptotically stable steady state) or oscillatory, depending on the exchanges between the microenvironment and the exterior. There is a constant interest in phosphofructokinase and glycolytic oscillations, see for instance : [2], [11], [12].

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