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# A MODEL OF METABOLIC PROCESSES IN A HETEROGENEOUS MILIEU: FUNCTIONAL AND NUMERICAL SOLUTIONS

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A general system that can be used for the modelization of metabolic pathways dynamics in a heterogeneous milieu is presented. It consists in a set of nonlinear reaction-diffusion equations, involving a convection term originating from the transport of metabolites by an electric field. The functional study is focused on the existence, uniqueness, and positiveness of the solution. A numerical algorithm based on a mixed finite element method is presented, and illustrative examples are also given.

*Keywords:* Enzyme organization; metabolic pathways; reaction-diffusion PDE.

## 1. INTRODUCTION

Metabolic processes generally occur in a heterogeneous milieu: for instance, enzymes can be either bound to charged membranes or cytoskeleton, or confined within an organelle, both features being facets of enzyme organization [16]. Many theoretical studies have been devoted to biochemical pathways in a homogeneous isotropic phase [15] whereas very few models have been worked out to study the dynamics of metabolic pathways in the heterogeneous cell milieu. Ricard *et al.* [9, 14] used a system of two ordinary differential

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equations (ODEs) to model a metabolic cycle occurring at the surface of a charged membrane, whereas Marmillot *et al.* [12] used partial differential equations (PDEs) to model patterns of spatiotemporal organization of phosphofructokinase when it is partitioned between two phases. We used both ODEs [4, 6, 13], and PDEs solved using a finite element method [5], to study the effect of enzyme organization on the stability of Yates-Pardee metabolic pathways. More precisely, Ricard *et al.*, take into account electrostatic effects, but they don't explicitly include diffusion coefficients, so that an essential assumption of their model is that of quasi-equilibrium or of rapid equilibrium within each phase and between different phases. On the other hand, Marmillot *et al.* [12], and we and co-authors explicitly model diffusion, but don't take into account the electrical phenomena.

The purpose of this paper is to study, from both a functional and a numerical point of view, a general system that can be used to model the dynamics of metabolic pathways in a heterogeneous milieu, assuming that the transport of metabolites is the result of the effects of both diffusion and electrical field. This general system is a set of non-linear coupled partial differential equations [5], and it can be regarded as a reaction-diffusion system with an additional term accounting for the migration of charged metabolites in an electrical field.

Illustrative examples are also given, which are based on the Yates-Pardee model of metabolic pathway. These examples show that an electric field can greatly alter the stability of metabolic pathways dynamics, and, more specifically, the amplitude and period of oscillations.

## 2. THE BIOLOGICAL MODEL

Let us consider  $n$  metabolic species undergoing biochemical transformations within a heterogeneous cell milieu, where transport of metabolites is due to both diffusion and migration in an electric field. We assume that in this condition a one-dimensional model is relevant. The evolution of the metabolite concentrations  $u_i$ ,  $i = 1, \dots, n$  can be written as

$$\frac{\partial u_i}{\partial t} = -\frac{\partial J_i}{\partial x} + f_i(x, u_1, \dots, u_n) \quad (1)$$

where  $f_i$ , the reaction term, depends on metabolite concentrations  $u_i$  as well as on the space coordinate  $x$  (for instance due to the heterogeneous diffusion of enzymes in the cell milieu). According to Nernst-Planck theory (for a discussion, see [1] or [7]), we shall assume that the flux  $J_i$  of metabolite  $i$  can be written, as

$$J_i = -D_i \left( \frac{\partial u_i}{\partial x} - z_i \frac{F}{RT} u_i E \right) \quad (2)$$

where  $D_i$  is the diffusion constant and  $z_i$  the charge number of metabolite  $i$ ,  $E$  is the electric field,  $F$  the Faraday's constant,  $R$  the universal gas constant and  $T$  the absolute temperature.

Rearranging Eqs. (1) and (2) we obtain

$$\frac{\partial u_i}{\partial t} - \frac{\partial}{\partial x} \left( D_i \frac{\partial u_i}{\partial x} \right) + z_i \frac{F}{RT} D_i E \frac{\partial u_i}{\partial x} + z_i \frac{F}{RT} \frac{\partial(D_i E)}{\partial x} u_i = f_i(x, u_1, \dots, u_n)$$

that can be rewritten as

$$\frac{\partial u_i}{\partial t} = \frac{\partial}{\partial x} \left( a_i \frac{\partial u_i}{\partial x} \right) - b_i \frac{\partial u_i}{\partial x} - c_i u_i + f_i(x, u_1, \dots, u_n)$$

Boundary conditions for metabolite  $i$  will be written as

$$a_i \frac{\partial u_i}{\partial \eta} = \mu_i (u_i^{\text{ex}} - u_i) \quad (3)$$

where  $\eta$  is the external normal vector to the boundary, and  $\mu_i$  and  $u_i^{\text{ex}}$  given constants. Boundary conditions (3), which are Fourier-type, include specifically (i) Neumann boundary conditions with zero flux (for  $\mu_i = 0$ ), and (ii) Dirichlet boundary conditions.

### 3. MATHEMATICAL STATEMENT OF THE PROBLEM

Let  $\Omega = ]0, L[$  be the one-dimensional spatial domain, and  $I = ]0, T[$  a time interval. The concentrations  $u_i$ ,  $i = 1, \dots, n$  of the metabolites depend on space  $x$  and time  $t$ . If we set  $\Gamma = \{0, L\}$ , the boundary of  $\Omega$ ,  $Q = \Omega \times I$ , and  $\Sigma = \Gamma \times I$ , the evolution of the concentrations

$u = (u_1, \dots, u_n)$  is governed by the following nonlinear system

$$\begin{aligned} \partial_t u - \partial_x(a\partial_x u) + b\partial_x u + cu &= f(x, u) & \text{in } Q \\ a\partial_\eta u &= \mu(u^{\text{ex}} - u) & \text{on } \Sigma \\ u &= u_0 & \text{if } t = 0 \end{aligned} \quad (4)$$

where  $a = \text{diag}(a_1, \dots, a_n)$ ,  $b$ ,  $c$  and  $\mu$  are diagonal matrices with coefficients defined from  $\Omega$  into  $\mathbb{R}$  or from  $\Gamma$  into  $\mathbb{R}^+$ . The function  $f = (f_1, \dots, f_n)$  is such that  $f_i$  is defined from  $\Omega \times \mathbb{R}^n$  into  $\mathbb{R}$ , and the function  $u^{\text{ex}}$  is defined from  $\Sigma$  into  $\mathbb{R}^n$ . The initial condition  $u_0$  is defined from  $\Omega$  into  $\mathbb{R}^n$ .

#### 4. EXISTENCE AND UNIQUENESS OF THE SOLUTION

Let us introduce the following classical notations [2, 8]:

- (i)  $H = (L^2(\Omega))^n$ , where  $L^2(\Omega)$  is the Hilbert space of square integrable functions over  $\Omega$ ;
- (ii)  $V = (H^1(\Omega))^n$ , 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  $v$  such that

$$\int_I \|v(t)\|_V^2 dt < +\infty;$$

- (iv)  $\mathcal{W}(I, V, V')$  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 dual of  $V$ .

The main result can be summarized in the theorem:

**THEOREM 1** *If the following assumptions are satisfied:*

- (i) *The function  $f$  is Lipschitz continuous, i.e.:*

$$\exists C > 0 \quad \text{such that} \quad |f(u) - f(v)| \leq C|u - v| \quad \forall u, v \in \mathbb{R}^n$$

*and  $f$  is such that:*

$$\forall u \in L^2(I, H), \quad f(u) \in L^2(I, H)$$

(ii) The functions  $a, b, c$  and  $\mu$  are such that for  $i=1, \dots, n$ :

$$\begin{aligned} 0 < m \leq a_i(x) < M \quad \forall x \in \bar{\Omega} \\ 0 \leq |b_i(x)| < M \quad \forall x \in \Omega \\ 0 < m \leq c_i(x) < M \quad \forall x \in \Omega \\ 0 \leq \mu_i(x) < M \quad \forall x \in \Gamma \end{aligned}$$

(iii) The function  $u_0^{ex}$  belongs to  $L^2(I, H^{-1/2}(\Gamma))$ ;

(iv) The function  $u_0$  belongs to  $H$ ;

then system (4) admits a unique solution in  $W(I, V, V')$ .

*Proof* The main steps of the proof are as follows:

- (1) Consider a given function  $u^{(1)} \in L^2(I, H)$ , and prove that system (4) admits a unique solution  $u^{(2)}$  when the second member equals  $f(u^{(1)})$ ;
- (2) Define the application  $\mathcal{G}$  by  $u^{(2)} = \mathcal{G}(u^{(1)})$ , 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 (4), say

$$\begin{aligned} (\partial_t u, v)_0 + (a \partial_x u, \partial_x v)_0 + \mu_L u(L) v(L) \\ + \mu_0 u(0) v(0) + (b \partial_x u, v)_0 + (cu, v)_0 \\ = (f, v)_0 + \mu_L u_L^{ex} v(L) + \mu_0 u_0^{ex} v(0) \quad \forall v \in V \\ u(\cdot, t = 0) = u_0(\cdot) \in H \end{aligned} \tag{5}$$

where the scalar products are in  $H$ .

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

$$w(u, v) = (a \partial_x u, \partial_x v)_0 + \mu_L u(L) v(L) + \mu_0 u(0) v(0) + (b \partial_x u, v)_0 + (cu, v)_0$$

Following Dautray–Lions [8] (t.8), the coercivity of  $w$  can be deduced, *i.e.*,

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

The classical assumptions on parabolic systems [8, 2] being verified, the variational equation (5) admits a unique solution in  $W(I, V, V')$ .

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

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

The solutions  $u^{(2)}$  and  $\bar{u}^{(2)}$  to system (4) satisfy the following system:

$$\begin{aligned} \partial_t(\delta u^{(2)}) - \partial_x(a\partial_x(\delta u^{(2)})) + b\partial_x(\delta u^{(2)}) + c\delta u^{(2)} &= \delta f(u^{(1)}) \quad \text{in } \mathcal{Q} \\ a\partial_\eta(\delta u^{(2)}) + \mu\delta u^{(2)} &= 0 \quad \text{on } \Sigma \\ \delta u^{(2)} &= 0 \quad \text{if } t = 0 \end{aligned}$$

and the associated variational equation

$$\begin{aligned} (\partial_t(\delta u^{(2)}), v)_0 + (a\partial_x(\delta u^{(2)}), \partial_x v)_0 + \mu_L \delta u^{(2)}(L)v(L) \\ + \mu_0 \delta u^{(2)}(0)v(0) + (b\partial_x(\delta u^{(2)}), v)_0 + (c\delta u^{(2)}, v)_0 \\ = (\delta f(u^{(1)}), v)_0 \quad \forall v \in V \end{aligned}$$

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

$$\frac{d}{dt} |\delta u^{(2)}|_0^2 \leq |\delta f(u^{(1)})|_0^2 + (2\lambda + 1) |\delta u^{(2)}|_0^2 \quad (6)$$

Integrating both sides of inequality (6) between 0 and  $s \in I$ , and applying the Gronwall lemma [8], we obtain

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

and

$$|\delta u^{(2)}|_0^2(s) \leq \exp(T) |\delta f(u^{(1)})|_{L^2(0, s; H)}^2 \quad (7)$$

Since the function  $f$  is Lipschitz continuous, we have, from inequality (7)

$$|\delta u^{(2)}|_{L^2(0, t; H)}^2 \leq C \exp(T) \int_0^t |\delta u^{(1)}|_{L^2(0, s; H)}^2 ds \quad t \in ]0, T[ \quad (8)$$

The proof can now be completed by a recursive calculation, where the  $m$ -th value of the application  $\mathcal{G}$  is contracting with a constant  $\nu$  such that

$$\nu^2 = \frac{(C \exp(T))^m T^m}{(m-1)!} < 1$$

We conclude that  $\mathcal{G}^{(m)}$  admits a unique fixed point, and with a Banach fixed point theorem [2] p. 83, that  $\mathcal{G}$  admits also a fixed point  $u$  in  $L^2(I, H)$  such that  $u = \mathcal{G}(u)$ .

**5. POSITIVENESS OF THE SOLUTION**

In this section, we prove that under suitable conditions, from the biological point of view, the solution to system (4) is positive. More precisely, we establish the following result.

**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 (4) is nonnegative.*

*Proof* If we perform the following change of variable:  $z = \exp(-\lambda t) u$ , the variational equation (5) may be rewritten as

$$\begin{aligned} &(\partial_t z, v)_0 + (a\partial_x z, \partial_x v)_0 + \mu_L z(L)v(L) + \mu_0 z(0)v(0) \\ &\quad + (b\partial_x z, v)_0 + ((c + \lambda)z, v)_0 \\ &= \exp(-\lambda t)(f(x, \exp(\lambda t)z), v)_0 \\ &\quad + \mu_L z_L^{ex} v(L) + \mu_0 z_0^{ex} v(0) \quad \forall v \in V \\ &z(\cdot, t = 0) = z_0(\cdot) \in H \end{aligned} \tag{9}$$

By writing  $z = z^+ - z^-$  and considering  $v = -z^-$ , Eq. (9) becomes:

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

with a nonpositive second member and  $w_1$  defined by

$$w_1(z^-, z^-) = \int_0^L a(\partial_x z^-)^2 + b(\partial_x z^-)z^- + (c + \lambda)(z^-)^2 dx$$



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

$$|b(\partial_x z^-)z^-| \leq \frac{\varepsilon}{2} b^2 (\partial_x z^-)^2 + \frac{1}{2\varepsilon} (z^-)^2 \quad \varepsilon > 0$$

so that

$$w_1(z^-, z^-) \geq \int_0^L \left( a - \frac{\varepsilon}{2} b^2 \right) (\partial_x z^-)^2 + \left( c + \lambda - \frac{1}{2\varepsilon} \right) (z^-)^2 dx$$

It is always possible to choose  $\varepsilon$  so that  $a - b^2 \varepsilon / 2 \geq 0$  and then  $\lambda$  so that  $c + \lambda - 1/(2\varepsilon) \geq 0$ . It follows that  $w_1$  is nonnegative and we have

$$\frac{d}{dt} |z^-(t)|_0^2 \leq 0$$

The function  $|z^-|_0^2$  is then a decreasing function of time, and since  $z^-(x, 0) = 0$ , the theorem is proved.

It can be noted that when  $n = 1$ , Theorem 2 can directly be applied to a Yates-Pardee metabolic pathway, as described in Section 7, using Eq. (25).

## 6. NUMERICAL RESOLUTION

We indicate in this section, how the numerical calculation of the solution to the system can be performed with adequate mathematical machinery. The procedure for solving the system of coupled equations is based on the calculation of the solution of a single equation. In this section,  $u$  denotes the concentration of one species, that is  $n = 1$ . The main difficulty in the resolution is to take into account the term  $b\partial_x u$ . Further it is shown how a variational formulation relevant to the given problem leads to a rigorous discretization.

### 6.1. Variational Formulation

The mixed variational formulation [10] 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 leads to an approximate solution of the initial model for a wide range of the coefficients of the equations, which is not the case for more conventional methods [11].

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

$$r(x, t) = -a(x) \frac{\partial u}{\partial x}(x, t) \tag{10}$$

$$\frac{\partial u}{\partial t}(x, t) = -\frac{\partial r}{\partial x}(x, t) - b(x) \frac{\partial u}{\partial x}(x, t) - c(x)u(x, t) + f(x, u) \tag{11}$$

By performing scalar products of Eqs. (10) and (11) by two test functions, respectively  $\psi$  belonging to  $H^1(\Omega)$  and  $\varphi$  belonging to  $H(\Omega)$ , and by integrating by parts, we get the two following equations

$$\int_{\Omega} \frac{r(x, t)}{a(x)} \psi(x) dx = \int_{\Omega} u(x, t) \frac{\partial \psi}{\partial x}(x) dx - u(L, t)\psi(L) + u(0, t)\psi(0) \tag{12}$$

$$\begin{aligned} \int_{\Omega} \frac{\partial u}{\partial t}(x, t) \varphi(x) dx + \int_{\Omega} \frac{\partial r}{\partial x}(x, t) \varphi(x) dx + \int_{\Omega} b(x) \frac{\partial u}{\partial x}(x, t) \varphi(x) dx \\ + \int_{\Omega} c(x)u(x, t) \varphi(x) dx = \int_{\Omega} f(x, u(x, t)) \varphi(x) dx \end{aligned} \tag{13}$$

## 6.2. Discretization

Equations (12) and (13) are now discretized, by projection onto different sub-spaces of  $H^1(\Omega)$  and  $L^2(\Omega)$  [10].

### 6.2.1. Discretization in Space

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  $\Omega$  is divided into  $N$  space intervals of the same length  $h$ . We then consider a grid of  $N + 1$  points in  $\bar{\Omega}$ , the closure of  $\Omega$ , made up of the nodes  $x_i = (i - 1)h$ ;  $i = 1, \dots, N + 1$ , and we set

$$\Omega_i = ]x_i, x_{i+1}[, \quad i = 1, \dots, N.$$

The spaces  $L^2(\Omega)$  in which we search for  $u(\cdot, t)$ , and  $H^1(\Omega)$  in which we search for  $r(\cdot, t)$ , are respectively approached by the sub-spaces  $T_h^0$  and  $S_h^0$  defined by:

$$T_h^0 = \{\varphi \in L^2(\Omega) | \varphi|_{\Omega_i} \in P^0(\Omega_i)\}$$

$$S_h^0 = \{\psi \in L^2(\Omega) | \psi|_{\Omega_i} \in P^1(\Omega_i)\}$$

where  $P^m(\Omega_i)$  denotes the set of polynomials, of degree lower or equal to  $m$ , defined in  $\Omega_i$ .

For  $\varphi \in T_h^0$ , we set

$$\varphi(x) = \sum_{j=1}^N \varphi_j T_j(x)$$

where the functions  $T_j$  form a basis of  $T_h^0$  and are defined by

$$T_j(x) = \begin{cases} 1 & x \in \Omega_j \\ 0 & \text{elsewhere} \end{cases}$$

On this basis, we consider in  $T_h^0$  and we set together

$$u(x, t) = \sum_{j=1}^N u_j(t) T_j(x) \tag{14}$$

$$f(x, t) = \sum_{j=1}^N f_j(t) T_j(x) \tag{15}$$

For  $\psi \in S_h^0$ , we set

$$\psi(x) = \sum_{j=1}^{N+1} \psi_j S_j(x) \tag{16}$$

where the functions  $S_j$  form a basis of  $S_h^0$  and are defined by

$$\begin{aligned}
 S_1(x) &= \begin{cases} (x_2 - x)/h & x \in \Omega_1 \\ 0 & \text{elsewhere} \end{cases} \\
 S_j(x) &= \begin{cases} (x - x_{j-1})/h & x \in \Omega_{j-1} \\ (x_{j+1} - x)/h & x \in \Omega_j \\ 0 & \text{elsewhere} \end{cases} \\
 S_{N+1}(x) &= \begin{cases} (x - x_N)/h & x \in \Omega_N \\ 0 & \text{elsewhere} \end{cases}
 \end{aligned}$$

These functions are usually called "hat" functions.

On this basis, we consider in  $S_h^0$  and we set

$$r(x, t) = \sum_{j=1}^{N+1} r_j(t) S_j(x). \tag{17}$$

We now assume that the function  $a(\cdot)$  belongs to the space  $S_h^0$ , and that the functions  $b(\cdot)$  and  $c(\cdot)$  belong to the space  $T_h^0$ .

By putting expressions (14) to (17) into Eq. (13) and by taking successively  $\varphi = T_j, j = 1, \dots, N$ , we obtain

$$\begin{aligned}
 &\frac{\partial}{\partial t} \sum_{i=1}^N \int_{\Omega} u_i(t) T_i(x) T_j(x) dx + \int_{\Omega} \frac{\partial r}{\partial x}(x, t) T_j(x) dx \\
 &+ \int_{\Omega} b(x) \frac{\partial u}{\partial x}(x, t) T_j(x) dx + \sum_{i=1}^N \int_{\Omega} c(x) u_i(t) T_i(x) T_j(x) dx \\
 &= \sum_{i=1}^N \int_{\Omega} f_i(t) T_i(x) T_j(x) dx \quad j = 1, \dots, N
 \end{aligned}$$

We use the method of Lesaint [10] to approach the term

$$\int_{\Omega} b(x) \frac{\partial u}{\partial x}(x, t) \varphi(x) dx$$

in each interval  $\Omega_j$  by  $Q_j$  defined by

$$Q_j(t) = (u_j^+(t) - u_j^-(t)) b(x_j^+) \varphi(x_j^+) \quad j = 1, \dots, N$$

where we denote  $b(x_j^+) = b_j$ , as the value of  $b$  in the interval  $\Omega_j$ . We set, as well,  $c_j$  as the value of  $c$  in the interval  $\Omega_j$ .

By calculating the integrals, we obtain

$$\begin{aligned} \frac{\partial}{\partial t} \sum_{i=1}^N \int_{\Omega} u_i(t) T_i(x) T_j(x) dx &= h \frac{\partial u_j}{\partial t}(t) \\ \int_{\Omega} \frac{\partial r}{\partial x}(x, t) T_j(x) dx &= r_{j+1}(t) - r_j(t) \\ \int_{\Omega} b(x) \frac{\partial u}{\partial x}(x, t) T_j(x) dx &= Q_j(t) \\ Q_j(t) &= b_j(u_j(t) - u_{j-1}(t)); \quad \text{with } u_j^+(t) = u_j(t) \\ &\quad \text{and } u_j^-(t) = u_{j-1}(t) \end{aligned}$$

$$\begin{aligned} \sum_{i=1}^N \int_{\Omega} c(x) u_i(t) T_i(x) T_j(x) dx &= c_j u_j(t) h \\ \sum_{i=1}^N \int_{\Omega} f_i(t) T_i(x) T_j(x) dx &= f_j(t) h \end{aligned}$$

The discrete equation corresponding to Eq. (13) for  $1 \leq j \leq N$  is given by

$$\frac{\partial u_j}{\partial t}(t) + \frac{r_{j+1}(t) - r_j(t)}{h} + b_j \frac{u_j(t) - u_{j-1}(t)}{h} + c_j u_j(t) = f_j(t) \quad (18)$$

In the same way, by taking successively  $\psi = S_j$ ,  $j = 1, \dots, N+1$ , in Eq. (12), we obtain

For  $1 \leq j \leq N+1$

$$\int_{\Omega} \frac{r(x, t)}{a(x)} S_j(x) dx = \int_{\Omega} u(x, t) \frac{\partial S_j}{\partial x}(x) dx - u(L, t) S_j(L) + u(0, t) S_j(0)$$

The integration of the first member of this equation by the method of trapezium leads to the following result

For  $j = 1$

$$\int_{\Omega} \frac{r(x, t)}{a(x)} S_1(x) dx \simeq \frac{h}{2a_1} r_1(t)$$

For  $2 \leq j \leq N$

$$\int_{\Omega} \frac{r(x, t)}{a(x)} S_j(x) dx \simeq \frac{h}{a_j} r_j(t)$$

For  $j = N + 1$

$$\int_{\Omega} \frac{r(x, t)}{a(x)} S_{N+1}(x) dx \simeq \frac{h}{2a_{N+1}} r_{N+1}(t)$$

The second member of the equation gives

For  $j = 1$

$$u(0, t) - u_1(t)$$

For  $2 \leq j \leq N$

$$u_{j-1}(t) - u_j(t)$$

For  $j = N + 1$

$$u_N(t) - u(L, t)$$

Equation (10), which gives  $r(t)$ , becomes

$$r_1(t) = \frac{2a_1\mu_0}{\mu_0h + 2a_1} (u_0^{ex}(t) - u_1(t)) \tag{19}$$

$$r_j(t) = \frac{a_j}{h} (u_{j-1}(t) - u_j(t)) \quad j = 2, \dots, N \tag{20}$$

$$r_{N+1}(t) = \frac{2a_{N+1}\mu_L}{\mu_Lh + 2a_{N+1}} (u_N(t) - u_L^{ex}(t)) \tag{21}$$

Finally, Eq. (18) may be rewritten as a system of ordinary differential equations

$$\dot{\underline{u}}(t) + \mathbf{G}\underline{u}(t) = \underline{F}(t) \tag{22}$$

$$\underline{u}(0) = \underline{u}_0 \tag{23}$$

where

$$\underline{u}(t) = (u_1(t)u_2(t) \cdots u_N(t))^T; \quad \underline{F}(t) = (F_1(t)F_2(t) \cdots F_N(t))^T$$



$$\underline{u}^1 = \underline{u}_0$$

where **I** is the identity matrix of dimension  $N \times N$ .

Taking  $\theta=0.5$ , we obtain the classical Crank-Nicolson method which is unconditionally stable.

Equation (24) is solved, at each step in time, by calculating the solution of a tridiagonal linear system by a LU decomposition method.

The system (4) 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  $u_1, \dots, u_{i-1}$  obtained from the previous equations. It has been verified [3] in a similar problem that, if the time step  $\tau$  is not too large, this method of resolution remains precise in comparison with a global and cumbersome resolution.

### 7. APPLICATION TO A YATES-PARDEE-TYPE PATHWAY

Let us now consider a metabolic pathway where the last metabolite inhibits the enzyme catalyzing the first reaction [5]. The spatial domain  $\Omega$  is divided in three sub-domains. For instance  $(0, x_a)$  corresponds to the inner of an organelle,  $(x_a, x_b)$  to the membrane of the organelle, and  $(x_b, L)$  to the cytosol.

By considering  $n = 4$  metabolites, the concentrations  $u_i$  are governed by the following system, which is a particular case of system (4)

$$\frac{\partial u_1}{\partial t} = \frac{\partial}{\partial x} \left( a_1(x) \frac{\partial u_1}{\partial x} \right) - b_1(x) \frac{\partial u_1}{\partial x} - \frac{V_1(x)u_1}{K_1 + u_1} + \frac{\alpha_0(x)}{1 + Ku_4^p} - c_1(x)u_1 \tag{25}$$

$$\frac{\partial u_i}{\partial t} = \frac{\partial}{\partial x} \left( a_i(x) \frac{\partial u_i}{\partial x} \right) - b_i(x) \frac{\partial u_i}{\partial x} - \frac{V_i(x)u_i}{K_i + u_i} + \frac{V_{i-1}(x)u_{i-1}}{K_{i-1} + u_{i-1}} - c_i(x)u_i \tag{26}$$

The coefficients  $a_i(x)$  describe a classical and passive diffusion process, while the  $b_i(x)$  coefficients are nonzero only for  $x \in (x_a, x_b)$ , *i.e.*, in the



membrane, and also describe the effect of an electric field  $E$  originating from electrical charges distributed on both sides of the membrane. The  $V_i(x)$  and  $K_i$  terms are those of the Henri-Michaelis-Menten law in enzyme catalyzed reactions. An allosteric inhibition of the first reaction by the last product is characterized by the coefficients  $\alpha_0$ ,  $K$  and  $\rho$ .

The reaction terms are rewritten as

$$-\frac{V_i u_i}{K_i + u_i} = -\frac{V_i}{K_i} u_i + \frac{V_i u_i^2 / K_i}{K_i + u_i}$$

so that we can set  $c_i = V_i / K_i$  in the equations. The boundary conditions are set as Neumann conditions, *i.e.*, the flux through the boundary is zero, so that we have  $\mu = 0$  in Eq. (4).

Our purpose is to study the influence of the sign of the product  $z_i E$  in the membrane on the stability of the solution to the system.

The numerical resolution of Eqs. (25) and (26) is performed with the following values of the coefficients:

$$\begin{aligned} L &= 1, \quad x_a = 0.15, \quad x_b = 0.20, \\ a_i(x) &= 100 \quad \text{for } x \in (0, x_a) \cup (x_b, L) \quad i = 1, \dots, 4, \\ a_i(x) &= 1 \quad \text{for } x \in (x_a, x_b), \\ V_1(x) &= V_2(x) = V_3(x) = V_4(x) = 3 \\ &\quad \text{for } x \in (0, x_a), = 0 \text{ elsewhere,} \\ K_i &= 1, \quad i = 1, \dots, 4, \\ \alpha_0(x) &= 3 \quad \text{for } x \in (0, x_a), = 0 \text{ elsewhere,} \\ K &= 1, \quad \rho = 3, \\ b_i(x) &= \pm 50 \quad \text{for } x \in (x_a, x_b) = 0 \text{ elsewhere.} \end{aligned}$$

The boundary conditions are assumed to be of Neumann type, so that  $\mu_i = 0$ .

If the length is expressed in  $\mu\text{m}$ , while time is expressed in units of  $10^{-1}$  s, then  $a_i = D_i = 100$  corresponds to a typical value of  $D_i = 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ , both inside and outside the organelle. Although the membrane width is slightly overestimated, due to the space discretization step, the absolute value of the  $b_i$  coefficients is chosen to ensure a typical ratio of metabolite concentrations at steady state.

Two cases are considered

- (1) When  $b_i(x) = +50$ , a steady state is obtained with the following values ( $i = 1, \dots, 4$ ), which correspond to a Nernst equilibrium:  $u_i(x) = 0.996$  for  $x \in (0, x_a)$ ,  $u_i(x) = 9.2808$  for  $x \in (x_b, L)$ . If this steady state is perturbed, let say if all initial concentrations are multiplied by a factor 1.5, so that  $u_i(x, 0) = 1.495$  for  $x \in (0, x_a)$ ,  $u_i(x, 0) = 13.92$  for  $x \in (x_b, L)$ , damped oscillations with large amplitude and very large period are observed (Fig. 1, where the evolution of  $u_4(x_a/2)$  is plotted *versus* time).
- (2) When  $b_i(x) = -50$ , a steady state is obtained with  $u_i(x) = 1$  for  $x \in (0, x_a)$ ,  $u_i(x) = 0.107$  for  $x \in (x_b, L)$ . If initial conditions are perturbed by a factor 1.5, so that  $u_i(x, 0) = 1.5$  for  $x \in (0, x_a)$ ,  $u_i(x, 0) = 0.161$  for  $x \in (x_b, L)$ , then damped oscillations are still observed, but their pseudo-period is dramatically reduced (Fig. 2).

In both cases, the enzymes are confined to the  $(0, x_a)$  compartment. If we assume that  $(0, x_a)$  is an organelle bounded by a membrane so that internal electric potential is lower than external potential

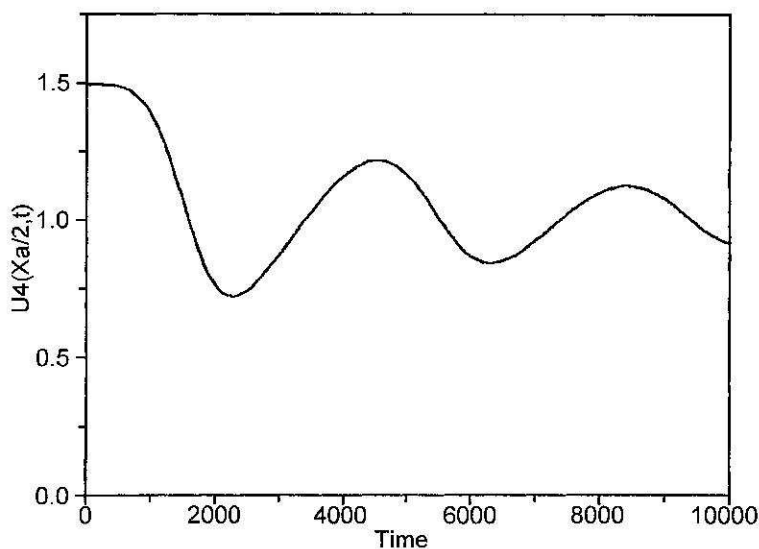


FIGURE 1 Evolution of the 4-th species for  $b_i(x) = +50$ .

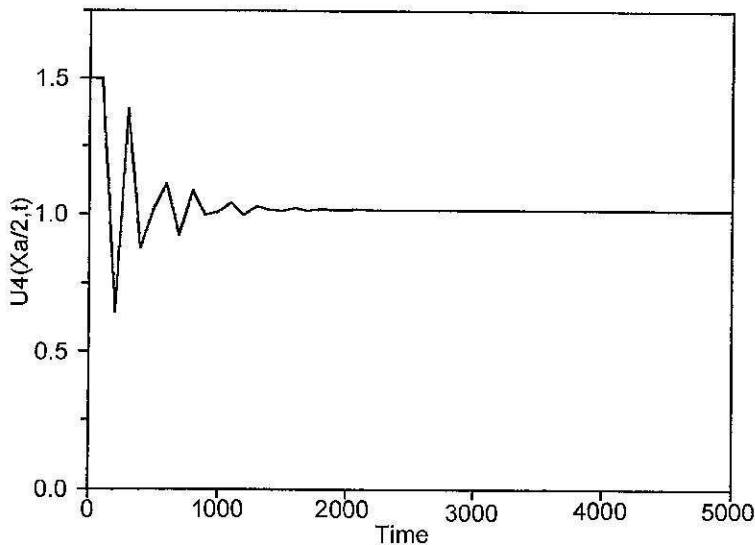


FIGURE 2 Evolution of the 4-th species for  $b_i(x) = -50$ .

(which is the case of mitochondria), then  $E < 0$ , and we have

- In case (1),  $b_i = z_i E > 0$ , so that metabolites are negatively charged;
- In case (2),  $b_i = z_i E < 0$ , and metabolites are positively charged.

Other interpretations could be given: if  $(x_b, L)$  is the interior of the organelle, case (2) corresponds to  $z_i < 0$ .

These examples suggest that the stability of metabolic pathways can be strongly influenced by electric fields effects resulting in migration of metabolites. Our proposed method could be used to study more extensively the possible implications of diffusion-migration upon cellular homeostasis and information transfer.

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