NUMERICAL ANALYSIS OF PROBLEMS ARISING IN BIOCHEMISTRY

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INTRODUCTION:

The purpose of this paper is to show the applications of standard numerical methods to new problems arising in biochemistry.

The source of these problems is a team of biochemists (ERA 338 CNRS, Laboratoire d'Enzymologie Médicale, Université de Technologie de Compiègne) lead by Dr D. THOMAS (1).

They study artificial membranes, made of enzyme linked to inactive protein. Typically such a membrane separates 2 compartments containing some substrate. The substrate diffuses inside the membrane and reacts because of enzyme (which is a catalyst).

We are interested in 2 kinds of problems:-First, what is the state of the system, what are the profiles of concentration of substrate and product, either in transient state, or in steady state, or in quasi steady state ?

-Secondly optimization problems arise, either in identification of kinetic parameters or in optimal control of some quantities such as fluxes of substrate.

In § 1 we describe the 3 kinds of states for which we are asked to give a numerical approximation: transient, steady, and quasi steady states, and the way to obtain this numerical approximation.

In § 2 we give an example of optimization problems: identification of kinetic parameters. This case, as many others, have been studied by JOLY G. (2).

Notations

$s(x,t)$ = concentration of substrate at point x and at time t, $(0 < x < 1)$.

$s(x)$ = concentration of substrate at point x (in steady state).

α(respβ) = concentration of substrate at the boundary $x = 0$ (resp $x = 1$).

σ = (positive) parameter.

h and k are the space and time steps: $Jh = 1$, $Nk = T$.

s_j^n = approximation of $s(jh,nk)$.

$\phi(x) = (\beta - \alpha)\, x + \alpha$

$\Phi_j = \Phi(jh)$

$|\phi| = h \left(\sum_{j=1}^{J-1} \phi_j^2 \right)^{1/2}$, $|\phi| = h \left(\sum_{j=0}^{J-1} \left(\frac{\phi_{j+1} - \phi_j}{h} \right)^2 \right)^{1/2}$

where $\phi = (\phi_0, \phi_1, \ldots, \phi_J)$ with $\phi_0 = \phi_J = 0$. (We shall use $|\phi| \leq [\phi]$)

$F(s) = \sigma s \,/\, (1 + |s|)$

I - STATE OF THE SYSTEM

1.1. - TRANSIENT STATE

For instance at time $t = o$ the membrane is empty of substrate and we are interested by the filling up of the membrane by substrate during a short interval of time $]0,T[$; equations are:

$$(1.1) \quad \begin{cases} \dfrac{\partial s}{\partial t} - \dfrac{\partial^2 s}{\partial x^2} + \sigma \dfrac{s}{1+s} = 0 & 0 < x < 1 \\ s(0,t) = \alpha \qquad\qquad s(1,t) = \beta \\ s(x,0) = 0 \end{cases}$$

It is therefore possible to use the explicit scheme:

$$(1.2) \quad \begin{cases} \dfrac{s_j^{n+1} - s_j^n}{k} - \dfrac{s_{j+1}^n + s_{j-1}^n - 2s_j^n}{h^2} + \sigma \dfrac{s_j^n}{1 + s_j^n} = 0 \\ s_o^n = \alpha \qquad\qquad s_J^n = \beta \\ s_j^o = 0 \end{cases}$$

with

$$(1.3) \quad 0 \leq s_j^{n+1} \leq \max(\alpha,\beta)$$

if

$$(1.4) \qquad k < \frac{1}{\frac{2}{h^2} + \sigma}$$

We can also use the implicit scheme

$$(1.5) \quad \begin{cases} \dfrac{s_j^{n+1} - s_j^n}{k} - \dfrac{s_{j+1}^{n+1} + s_{j-1}^{n+1} - 2s_j^{n+1}}{h^2} + \sigma \dfrac{s_j^{n+1}}{1 + s_j^{n+1}} = 0 \\ s_0^{n+1} = \alpha \qquad s_J^{n+1} = \beta \\ s_j^0 = 0 \end{cases}$$

for which we have the

Theorem 1.1. - Let us call

$$(1.6) \qquad y_j^n = s_j^n - \phi_j$$

Then

$$(1.7) \qquad |y^{n+1}| \leq C \qquad 0 \leq n \leq N-1$$

$$(1.8) \qquad k \sum_{n=0}^{N-1} \left[y^{n+1}\right]^2 \leq C$$

C being a constant independant of h and k.

Proof:

$$(1.9) \quad \begin{cases} \dfrac{y^{n+1} - y_j^n}{k} - \dfrac{y_{j+1}^{n+1} + y_{j-1}^{n+1} - 2y_j^{n+1}}{h^2} = -\sigma \dfrac{\phi_j + y_j^{n+1}}{1 + \phi_j + y_j^{n+1}} \\ y_0^{n+1} = y_J^{n+1} = 0 \qquad y_j^0 = -\phi_j \end{cases}$$

multiplying by $h\,k\,y^{n+1}$ and summing from $j = 1$ to $j = J-1$, one gets:

$$\frac{1}{2}|y^{n+1}|^2 - \frac{1}{2}|y^n|^2 + \frac{1}{2}|y^{n+1} - y^n|^2 + k|y^{n+1}|^2 \leq \sigma k|y^{n+1}| \leq \sigma k|y^{n+1}|$$

$$\leq \frac{1}{2}\sigma^2 k + \frac{1}{2} k|y^{n+1}|^2$$

and at last, summing over n ,

$$(1.10) \qquad |y^{m+1}|^2 + k \sum_{n=0}^{m} |y^{m+1}|^2 < \sigma^2 T + |\Phi|^2 < \sigma^2 T + (\max(\alpha,\beta))^2$$

which gives the result.

To solve (1.5) we can use, to get the s_j^{n+1} from the s_j^n , the following iterative scheme:

$$(1.11) \quad \begin{cases} \dfrac{s_j^{n+1,\ell+1} - s_j^n}{k} - \dfrac{s_{j+1}^{n+1,\ell+1} + s_{j-1}^{n+1,\ell+1} - 2s_j^{n+1,\ell+1}}{h^2} + \sigma \dfrac{s_j^{n+1,\ell+1}}{1 + s_j^{n+1,\ell}} = 0 \\ s_0^{n+1,\ell+1} = \alpha \qquad s_J^{n+1,\ell+1} = \beta \\ s_j^{n+1,0} = s_j^n \end{cases}$$

and we stop the iterations if

$$(1.12) \qquad \frac{\sum_j \left| s_j^{n+1,\ell+1} - s_j^{n+1,\ell} \right|}{\sum_j |s_j^{n+1,\ell+1}|} < \varepsilon$$

(usually $\varepsilon = 10^{-4}$).

We can also use Newton's method and, in (1.11), replace the "reaction term" by

$$(1.13) \qquad F(s_j^\ell) + (s_j^{\ell+1} - s_j^\ell) F'(s_j^\ell)$$

1.2. - STEADY STATE

Steady state equation is:

$$(1.14) \quad \begin{cases} -\dfrac{d^2 s}{dx^2} + \sigma \dfrac{s}{1+s} = 0 \\ s(0) = \alpha \qquad s(1) = \beta \end{cases}$$

The following algorithm

$$(1.15)\quad \begin{cases} -\left(s_{j+1}^{k+1} + s_{j-1}^{k+1} - 2s_j^{k+1}\right) / h^2 + \sigma s_j^{k+1} / (1 + s_j^k) = 0 \\ s_0^{k+1} = \alpha \qquad s_J^{k+1} = \beta \end{cases}$$

with

$$(1.16)\quad s_j^0 = 0 \qquad \text{or} \qquad s_j^0 = \Phi_j = (\beta-\alpha)\, j\, h + \alpha$$

and a stop test of the form

$$(1.17)\quad \frac{\sum_{j=1}^{J-1} \left| s_j^{k+1} - s_j^k \right|}{\sum_{j=0}^{J} \left| s_j^{k+1} \right|} < \varepsilon$$

gives an approximation of its solution in a few iterations.
(5 iterations for $\sigma = 10$, $\alpha = \beta = 1$ and $\varepsilon = 10^{-4}$).

1.3. - STEADY STATE IN THE CASE OF INHIBITION BY EXCESS OF SUBSTRATE

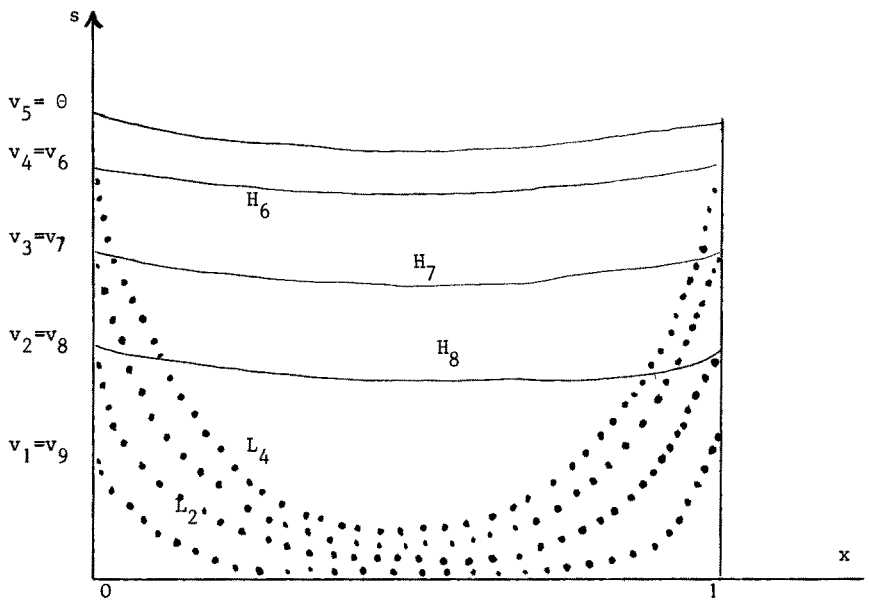
The system is governed by the equations

$$(1.18)\quad \begin{cases} -\dfrac{d^2 s}{dx^2} + G(s) = 0 & 0 < x < 1 \\ s(0) = s(1) = v & v > 0 \end{cases}$$

where

$$(1.19)\quad G(s) = \sigma s / (1 + s + a s^2) \qquad a > 0$$

This system is interesting because it presents some hysteresis for σ large enough:



Let the system be defined by (1.18) with

$$(1.20) \qquad v = v(t) = \begin{cases} t & \text{if } 0 < t < \theta \\ 2\theta - t & \text{if } \theta < t < 2\theta \end{cases}$$

θ being large enough.

In a first phase v increases from 0 to v_5

For $v = v_1, v_2, v_3$ and v_4 we have the dotted profiles.

For $v = v_4$ there is a jump from the "low" profile L_4 to the "high" profile H_6.

Continuing to increase v until v_5, the profile of concentration rises to H_5, remaining in a "high" position.

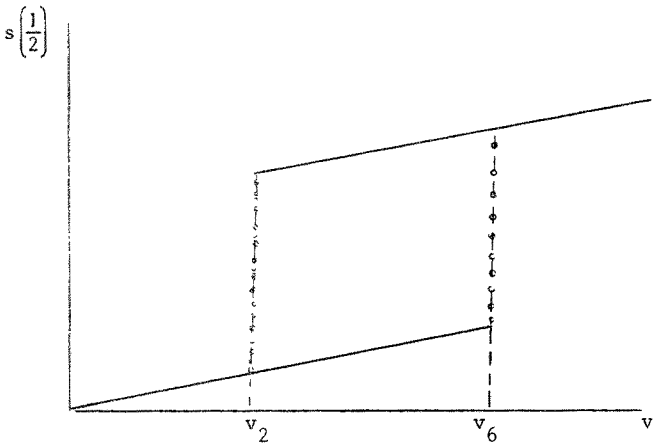
Now after $t = \theta$ v decreases and the profiles superimpose on those found in the ascending phase, at least for $v_6 < v < v_5$.

It is at this moment, when v decreases from v_6 to v_8, that hysteresis appears: the profiles of concentration remain in "high" positions H_6, H_7, H_8.

For $v = v_8$ there is another jump, this time from the high level H_8 to the line L_2.

For $v < v_8$ we find again the same profiles than in the ascending phase.

If we plot $s\left(\frac{1}{2}\right)$ against v we otain:



For v between v_2 and v_6 the system can have 2 stable states, according to its past history.

This is a system with memory.

According to this property we must be prudent when solving (1.18) by a scheme like in § 1.2.

We begin with $s_j^0 = 0$ if we wish to get the "low" profile, and by $s_j^0 = v$ if we desire the "high" one.

1.4. - QUASI STEADY STATE.

In this case $s = s(x,t)$ is governed by

$$(1.21)\quad \begin{cases} -\dfrac{d^2s}{dx^2} + F(s) = 0 \\ \dfrac{\partial s}{\partial t} = \dfrac{\partial s}{\partial x} \quad \text{for} \quad x = 0 \quad , \quad s(0,0) = \alpha_0 \\ \dfrac{\partial s}{\partial t} = -\dfrac{\partial s}{\partial x} \quad \text{for} \quad x = 1, \quad s(1,0) = \beta_0 \end{cases}$$

If we call

$$(1.22)\qquad \begin{aligned} \alpha(t) &= s(0,t) \\ \beta(t) &= s(1,t) \end{aligned}$$

and if we call f and g the functions defined by:

If ξ and η are 2 (positive) numbers and if y is the solution of

$$(1.23)\qquad \begin{cases} -\dfrac{d^2y}{dx^2} + F(y) = 0 \\ y(0) = \xi \quad , \quad y(1) = \eta \end{cases}$$

Then

$$(1.24)\qquad \begin{cases} f(\xi,\eta) = \dfrac{dy}{dx}(0) \\ g(\xi,\eta) = -\dfrac{dy}{dx}(0) \end{cases}$$

The system (1.21) is equivalent to the ordinary differential equations

$$(1.25)\qquad \begin{cases} \dfrac{d\alpha}{dt} = f(\alpha,\beta) \quad , \quad \alpha(0) = \alpha_0 \\ \dfrac{d\beta}{dt} = g(\alpha,\beta) \quad , \quad \beta(0) = \beta_0 \end{cases}$$

to which we apply Runge Kutta method.

1.5. - OTHER SYSTEMS

We conclude this first paragraph by referring to (3) where many other systems are described and numerical and experimental results are compared.

II - OPTIMIZATION PROBLEMS

Examples of optimal control of such biochemical systems have already been given by KERNEVEZ (4), QUADRAT and VIOT (5) and YVON (6).

In this paper we give an example of identification of parameters, which is dependant on the same technique, i.e. we have some cost function to minimize, we use for that a gradient method, and to get the gradient we use an adjoint state.

2.1. - DESCRIPTION OF THE PROBLEM

The (steady) state of the system is defined by

$$(2.1)\qquad \begin{cases} -\dfrac{d^2 s}{dx^2} + v(x)\dfrac{s}{1+s} = 0 & 0 < x < 1 \\ s(0) = \alpha \qquad s(1) = \beta \end{cases}$$

where $v(x)$ is proportional to the concentration of enzyme at point x.

v is an unknown function of x in

$$(2.2)\qquad \mathcal{U}_{ad} = \{ v \mid v \ L^2(0,1) \text{ and } 0 \leqslant v \leqslant M \}$$

M being some positive constant.

Let α_i and β_i $(i = 1,\ldots,N)$ be N choices of the boundary concentrations of substrate.

We shall call $s_i(x;v)$ the solution of (2.1) for the function v and for $\alpha = \alpha_i$, $\beta = \beta_i$.

We observe the fluxes of substrate entering the membrane at $x = 0$ and $x = 1$ for the different values of i $(i = 1,\ldots,N)$:

(2.3) observation = z_{0i} and z_{1i} $(i = 1,2,\ldots,N)$ and we define the cost function

$$(2.4)\qquad J(v) = \frac{1}{2}\sum_{i=1}^{N}\left(\left| -\frac{ds_i(.,v)}{dx}(0) - z_{0i} \right|^2 + \left| \frac{ds_i(.,v)}{dx}(1) - z_{1i} \right|^2 \right)$$

The problem is to find u such that

$$(2.5)\qquad J(u) \leqslant J(v) \qquad \forall v \in \mathcal{U}_{ad}$$

2.2. - LAGRANGIAN, ADJOINT STATE AND GRADIENT.

JOLY G. (2) shows that this problem has at least one solution and gives justification for the following formal indications to find a solution.

First step: define the lagrangian:

$$(2.6)\quad \mathcal{L}(v,s,p) = \frac{1}{2}\sum_{i=1}^{N}\left|-\frac{ds_i}{dx}(0)-z_{0i}\right|^2 + \frac{1}{2}\sum_{i=1}^{N}\left|\frac{ds_i}{dx}(1)-z_{1i}\right|^2 + \sum_{i=1}^{N}\int_0^1 p_i\left(-\frac{d^2s_i}{dx^2} + v(x)\frac{s_i}{1+s_i}\right)dx$$

where $v,s = (s_1,\dots,s_N)$ and $p = (p_1,\dots,p_N)$ are independant and such that

$$(2.7)\quad v \in \mathcal{U}_{ad}$$

$$(2.8)\quad s_i - \Phi \in H_0^1(\Omega)\cap H^2(\Omega) \qquad (\Omega =]0,1[)$$

$$(2.9)\quad p_i \in L^2(\Omega).$$

Second step: for every s define p such that

$$(2.10)\quad \frac{\partial \mathcal{L}}{\partial s} = 0$$

$$(2.11)\quad \left(-\frac{ds_i}{dx}(0)-z_{0i}\right)\left(-\frac{d\psi}{dx}(0)\right) + \left(\frac{ds_i}{dx}(1)-z_{1i}\right)\frac{d\psi}{dx}(1) + \int_0^1 p_i\left(-\frac{d^2\psi}{dx^2} + v(x)\frac{1}{(1+s_i)^2}\psi\right)dx = 0 \qquad \forall \psi \in H_0^1(\Omega)\cap H^2(\Omega)$$

which is equivalent to

$$(2.12)\quad \begin{cases} -\dfrac{d^2p_i}{dx^2} + v(x)\dfrac{1}{(1+s_i)^2}p_i = 0 \\ p_i(0) = -\dfrac{ds_i}{dx}(0)-z_{0i}\ , \quad p_i(1) = \dfrac{ds_i}{dx}(1)-z_{1i} \end{cases}$$

$(i = 1,2,\dots,N)$

Third step: we know that

$$(2.13)\qquad J(v) = \mathcal{L}(v, s(v), p) \qquad \forall\, p$$

$$(2.14)\qquad (J'(v),\phi) = \left(\frac{\partial \mathcal{L}}{\partial v},\phi\right) + \left(\frac{\partial \mathcal{L}}{\partial s} \circ \frac{\partial s}{\partial v},\phi\right) = \left(\frac{\partial \mathcal{L}}{\partial v},\phi\right)$$

if we choose p as indicated in (2.12).

(ϕ is an arbitrary function in $L^2(\Omega)$ an (f,g) denotes $\int_\Omega f(x)\, g(x)\, dx$).

$$(2.15)\qquad (J'(v),\phi) = \sum_{i=1}^{N} \int_0^1 p_i(x)\, \phi(x)\, \frac{s_i}{1+s_i}\, dx$$

2.3. - NUMERICAL METHOD

We work with the discrete lagrangian

$$(2.16)\qquad \widetilde{\mathcal{L}} = \frac{1}{2} \sum_{i=1}^{N} \left| \frac{s_{i,0} - s_{i,1}}{h} - z_{i0} \right|^2 + \frac{1}{2} \sum_{i=1}^{N} \left| \frac{s_{i,J} - s_{i,J-1}}{h} - z_{i1} \right|^2$$

$$+ h \sum_{i=1}^{N} \sum_{j=1}^{J-1} p_{ij} \left(- \frac{s_{i,j+1} + s_{i,j-1} - 2s_{i,j}}{h^2} + v_j \frac{s_{i,j}}{1+s_{i,j}} \right)$$

which corresponds to the discrete state

$$(2.17)\qquad \begin{cases} - \dfrac{s_{i,j+1} + s_{i,j-1} - 2s_{i,j}}{h^2} + v_j \dfrac{s_j}{1+s_j} = 0 \\ s_{i,0} = \alpha \qquad s_{i,J} = \beta \end{cases}$$

to the discrete adjoint state

$$(2.18)\qquad \begin{cases} - \dfrac{p_{i,j+1} + p_{i,j-1} - 2p_{i,j}}{h^2} + v_j \dfrac{1}{(1+s_j)^2}\, p_{i,j} = 0 \\ p_{i,0} = \dfrac{s_{i,0} - s_{i,1}}{h} - z_{i0} \quad , \quad p_{i,J} = \dfrac{s_{i,J} - s_{i,J-1}}{h} - z_{i1} \end{cases}$$

and to the gradient

$$(2.19)\qquad \frac{\partial \widetilde{J}}{\partial v_j} = h \sum_{i=1}^{N} p_{ij}\, \frac{s_{i,j}}{1+s_{i,j}}$$

The algorithm is the steepest descent method:

i/ Start with an initial distribution of enzyme $v = (v_1, v_2, \ldots, v_{J-1})$ such that $h \sum_{j=1}^{J-1} v_j$ = total (given) amount of enzyme inside the membrane.

ii/ Compute the state by (2.17)

iii/ Compute the adjoint state by (2.18)

iv/ Compute the gradient g by (2.19)

v/ find ρ_{opt} such that

$$\tilde{J}(v - \rho_{opt} g) \leq \tilde{J}(v - \rho g) \qquad \forall \rho > 0$$

vi/ if $\left| \frac{J(v - \rho_{opt} g) - J(v)}{J(v)} \right| < \varepsilon$, stop.

else replace v by $v - \rho_{opt} g$ and go to ii/

We have tested the method with

$$v(x) = a \sin \Pi x$$

and $N = 7$ observations, starting with a uniform distribution

$$v_1 = v_2 = \ldots = v_{J-1} = \left(\int_0^1 a \sin \Pi x \, dx \right) / (J-1).$$

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