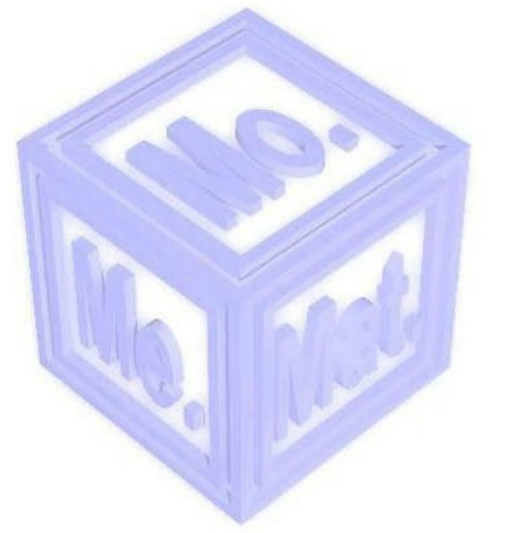
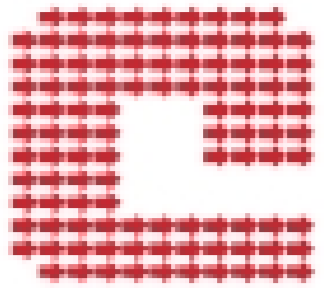


# Application of Optimal Control techniques and

## Advanced Computing to the study of enzyme kinetics



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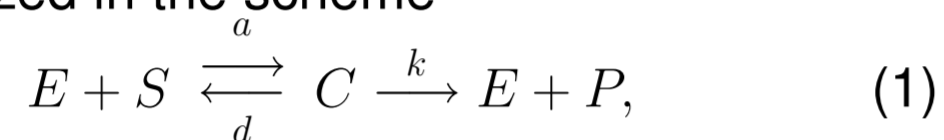
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### 1. Effects of a drug on cellular enzymes

VERY recent medical and pharmaceutical research is focusing on the study of highly specific drugs, which are able to enter a cell and selectively react with targeted enzymes.

The experiments involve nanotechnologies, because, for example, very often the drug molecules are introduced by means of carbon nanotubes, which release them inside the cell (see f.e. [1]).

The model of biochemical reactions considers a reaction where a substrate  $S$  binds an enzyme  $E$  reversibly to form a complex  $C$  [2]. The complex can then decay irreversibly to a product  $P$  and the enzyme, which is then free to bind another molecule of the substrate. This process is summarized in the scheme



where  $a$ ,  $d$  and  $k$  are kinetic parameters (supposed constant) associated with the reaction rates.

We show two examples of application of Optimal Control techniques to the study of the effects of a drug on enzyme reactions.

### 2. Degradation of the product

WHEN we consider reaction (1) we can introduce a term which describes the biochemically relevant phenomenon of degradation, or death, of some enzymes. The degradation can be induced or accelerated by some drugs, that can act directly on a specific enzyme, which can be considered toxic for the cell. Our aim is to send the product  $P$  to zero, by controlling its degradation rate and also taking into account practical limitations, like the toxicity and/or the costs of the drug.

Introducing a suitable control  $\alpha(t)$  we obtain the system

$$\begin{cases} \frac{dS}{dt} = -a(E_T - C)S + dC, \\ \frac{dC}{dt} = a(E_T - C)S - (d+k)C, \\ \frac{dP}{dt} = kC(t) - \alpha(t)P(t), \end{cases} \quad (2)$$

with the initial conditions

$$S(0) = S_T, \quad C(0) = 0, \quad P(0) = 0 \quad (3)$$

and the conservation law

$$E + C = E_T. \quad (4)$$

where the term  $\alpha(t)P(t)$  represents the degradation of  $P$ . Let us denote the dynamics (2) with the initial condition (3) by

$$\begin{cases} \frac{dy}{dt} = g(y(t), \alpha(t)) \\ y(0) = (S_T, 0, 0)^T =: x \end{cases}$$

If we define the cost functional

$$J(x, t, \alpha(\cdot)) = \int_0^t l(y_x(s), \alpha(s)) e^{-\lambda s} ds + u_0(y_x(t)) e^{-\lambda t}$$

then (see f.e. [3]) the value function

$$u(x, t) := \inf_{\alpha(\cdot)} J(x, t, \alpha(\cdot))$$

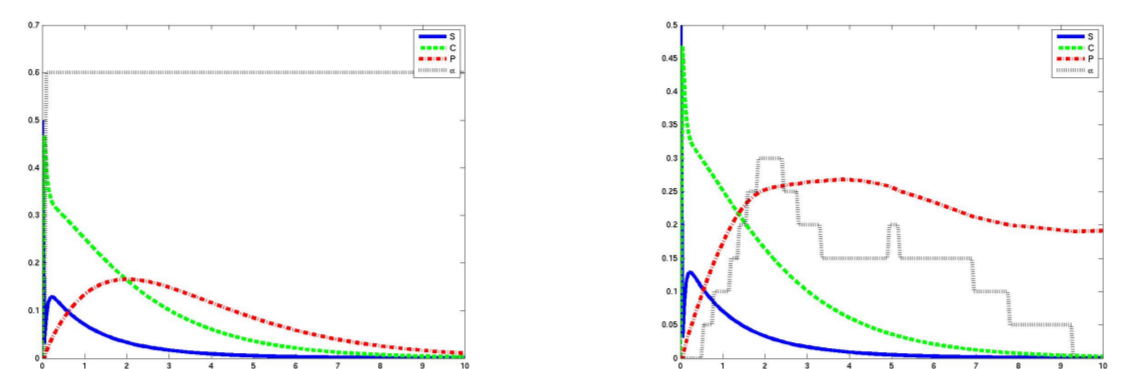
is a viscosity solution of the Hamilton-Jacobi-Bellman equation

$$u_t + \lambda u + \min_{c \in [0, K]} \{-g(x, c) \cdot D_x u(x, t) - l(x, c)\}. \quad (5)$$

From the solution of (5) we can compute an optimal feedback control by

$$\alpha^*(t) = \arg \min_{\alpha} u(y_x(t), t).$$

A suitable choice of the cost functional  $l$  allows us to give optimal strategies to send  $P$  to zero. Figure 1(a) shows that if the cost does not depend on  $\alpha$  ( $l(x, c) = P^2$ ), then the optimal strategy is to choose  $\alpha$  as large as possible; in our test  $\alpha = K = 0.6$ . Figure 1(b) shows that, if  $l(x, c) = P^2 + c^2$ , it is more convenient to degrade  $P$  only partially.

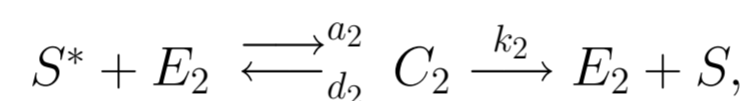
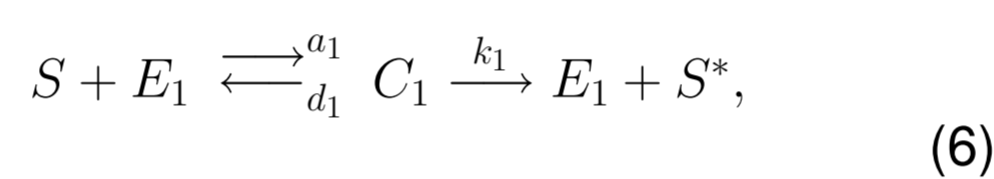


(a)  $l(x, c) = P^2$  (b)  $l(x, c) = P^2 + c^2$

Figure 1: Degradation

### 3. Control of the substrate concentration

THE second example studies the phosphorylation-dephosphorylation cycle [2]



where the substrate  $S$  is respectively phosphorylated (i.e. activated) and dephosphorylated (i.e. inactivated) by means of a kinase  $E_1$  and a phosphatase  $E_2$ .  $S^*$  represents the phosphorylated substrate.

It is well known (see f.e. [4]) that the steady state concentration levels of particular enzymes can determine the fate of a cell (proliferation, apoptosis, differentiation etc.). In this model we want to maintain the concentration level of the phosphorylated substrate above and/or below a priori determined thresholds. Substituting to the kinetic rate  $k_1$  a control  $\alpha(t)$ , the reaction is governed by the system

$$\begin{cases} \frac{dS}{dt} = -a_1(E_{1,T} - C_1)S + d_1C_1 + k_2C_2 \\ \frac{dS^*}{dt} = -a_2(E_{2,T} - C_2)S^* + d_2C_2 + \alpha(t) \cdot C_1 \\ \frac{dC_1}{dt} = a_1(E_{1,T} - C_1)S - (d_1 + \alpha(t)) \cdot C_1 \\ \frac{dC_2}{dt} = a_2(E_{2,T} - C_2)S^* - (d_2 + k_2)C_2 \end{cases} \quad (7)$$

the initial conditions

$$S(0) = S_T, \quad S^*(0) = 0, \quad C_i(0) = 0 \quad (8)$$

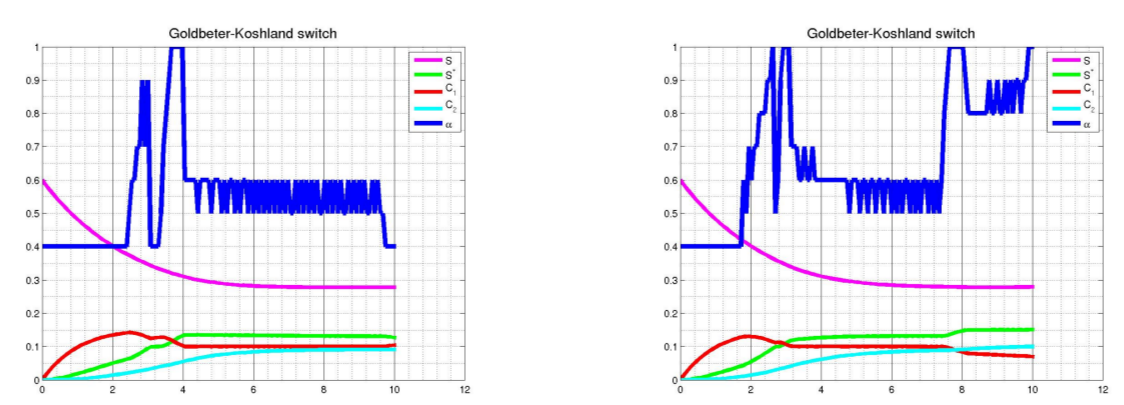
and the conservation laws

$$S_T = S + C_1 + C_2 + S^*, \quad E_{i,T} = E_i + C_i, \quad i = 1, 2. \quad (9)$$

In this case, to keep  $S^*$  in a  $\delta$ -neighborhood of a constant value  $m$ , we solve a PDE like (5), where the cost functional is

$$l(x, c) = ([S^* - (m + \delta)]^+)^2 + ([-S^* + (m - \delta)]^+)^2.$$

Let us remark that this choice gives quite different results in terms of optimal strategies in Figure 2(a) and Figure 2(b). In absence of control ( $k_1 = 0.4$ ),  $S^*$  asymptotically tends to 0.15. When we impose to  $S^*$  to belong to a different  $\delta$ -neighborhood, the control dramatically jumps from 0.4 to very different values.



(a)  $m = 0.12 \delta = 0.2$  (b)  $m = 0.18 \delta = 0.2$

Figure 2: Control of the substrate concentration

### 4. The Parallel Code

THE starting point for numerical simulations was the code developed by Carlini et al. [5] for solving Hamilton-Jacobi equations in high spatial dimensions.

We have implemented a parallel version able, at this moment, to run efficiently up to 4 or 5 spatial dimensions (that is equivalent to say 4 or 5 equations). The preliminary parallelization has been done using OpenMP, a standard tool designed for shared memory architectures (including new multicore machines).

OpenMP is a directive based approach to the parallelization and provides support for concurrency, synchronization, and data handling while obviating the need for explicitly setting up mutexes, condition variables, data scope, and initialization. A typical OpenMP program executes serially until it encounters the first parallel directive. This directive is responsible for creating a group of threads. The core of the parallel code follows. It should be noted that the OpenMP specific part takes only a very small fraction of the code:

```
!$omp parallel default(shared) &
!$omp do private(j,nd,ctrl,in,l,HJ)
do j=1,nnodi
call Inv_ind(j,n,In)
do l=1,m
nd(l)=x(In(l)+last(l))
enddo
call STIMAINICTRL(HJ,nd,ctrl)
u(j)=HJ
uctrl(j)=ctrl(1)
end do
!$omp end parallel
```

The parallel machine used to conduct the numerical tests is a 8 processors IBM System p5 575, working at 1900 MHz clock, with a theoretical peak performance of 60 GFLOPS.

### References

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