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Abstract: In this paper we show some applications of Advanced and Parallel Computing to the study of mathematical models in Systems Biology and in particular of the network of biochemical reactions occurring inside a cell. Due to their high complexity, the numerical study of these systems must be approached by means of sophisticated Advanced Computing tools. In a deterministic framework, we show two examples of application of Optimal Control techniques to the study of the effects of a drug on enzyme reactions occurring inside a cell, where "ad-hoc" algorithms for the numerical solution of the Hamilton-Jacobi-Bellman equation are used in a parallel environment.

Application of Optimal Control techniques and Advanced Computing to the study of enzyme kinetics

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Abstract

In this paper we show some applications of Advanced and Parallel Computing to the study of mathematical models in Systems Biology and in particular of the network of biochemical reactions occurring inside a cell. Due to their high complexity, the numerical study of these systems must be approached by means of sophisticated Advanced Computing tools. In a deterministic framework, we show two examples of application of Optimal Control techniques to the study of the effects of a drug on enzyme reactions occurring inside a cell, where "ad-hoc" algorithms for the numerical solution of the Hamilton-Jacobi-Bellman equation are used in a parallel environment.

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1 Introduction

Aim of Systems Biology is to integrate biological data as an attempt to understand how biological systems function. Much of Systems Biology is within the realm of molecular biology and physiology, but it demands tools from bioinformatics and experimental data mining, mathematical modelling, proteomics and clinical sciences.
Due to the high complexity of these systems, their numerical treatment implies the usage of efficient numerical algorithms and schemes and high performance hardware and software: in other words, Advanced Computing tools.
In this paper we focus on the mathematical models of the intracellular signal transduction network, i.e., of the complex, interconnected biochemical reaction

systems induced by the cell as a response to external stimuli, like hormones, growth factors, cytokines, heat shocks etc. [4]
In this framework, Advanced Computing tools can be applied, for example, for the implementation of sophisticated algorithms in Reverse Engineering, for the estimation of the unknown kinetic parameters of the network (see, for example, [15]) and, in a stochastic framework, to implement the so called Gillespie Algorithm, or Stochastic Simulation Algorithm (SSA) [9, 10].
On one hand, parameters estimation problems of nonlinear dynamic systems are stated as minimizing a cost function that measures the goodness of the fit of the model with respect to a given experimental data set, subject to the dynamics of the system, thus finding the parameters which calibrate the model so as to reproduce the experimental results in the best possible way. The high computational costs increase very rapidly with the dimension of the problem, i.e., with the number of unknown parameters to estimate.
On the other hand, under some circumstances – for example, when some species are present in small numbers – a discrete and stochastic framework is the most appropriate framework for modeling chemical kinetics. Such a framework is provided by continuous-time, discrete-state Markov processes.
The Stochastic Simulation Algorithm is a very popular method for studying and simulating intrinsic noise.
For a recent review of the evolution of SSA see [13] and references therein.
A prominent transduction mechanism is the phosphorylation by specific enzymes called kinases, and the dephosphorylation by phosphatases [8, 19].
These reactions are organized in complex networks whose behavior is determined by the activity and the interactions of each component.
The model of biochemical reactions was set forth by Michaelis and Menten in 1913 [14], and further developed by Briggs and Haldane in 1925 [6]. This formulation considers a reaction where a substrate S binds an enzyme E reversibly to form a complex C. 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

$$E + S \underset{d}{\overset{a}{\rightleftarrows}} C \xrightarrow{k} E + P, \tag{1}$$

where a, d and k are kinetic parameters (supposed constant) associated with the reaction rates.
The formulation leads to an ODE for each involved complex and substrate. We refer to this as the full system.
From now on we will indicate with the same symbols the names of the enzymes and their concentrations.
Given the initial conditions

$$S(0) = S_T, \quad C(0) = 0, \tag{2}$$

and because of the chemical conservation laws

$$E + C = E_T, \quad S + C + P = S_T \ , \tag{3}$$

for (1) the independent equations are only two:

$$\begin{aligned} \tfrac{dS}{dt} &= -a(E_T - C)S + d\, C, \\ \tfrac{dC}{dt} &= a(E_T - C)S - (d + k)C \ . \end{aligned} \tag{4}$$

The initial conditions give the concentrations of S and C at the beginning of the reaction, and their time development is described by the ODEs, while E and P are linked to S and C through the conservation laws. Here E_T is the total enzyme concentration assumed to be free at time $t = 0$. Also the total substrate concentration, S_T, is free at $t = 0$. This is the so-called Michaelis-Menten (MM) kinetics [14, 5, 17].

Following some theoretical suggestions given in [3], in this paper we study the application of the Optimal Control Theory to the mathematical models of the intracellular signal transduction networks, in order to model the effects of a drug on specific targeted enzymes.

In fact, 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 for example [12]).

This paper is organized as follows.

In Section 2 we will show an example of application of Optimal Control techniques (via Hamilton-Jacobi-Bellman equations) to the study of the effects of a drug on the single Michaelis-Menten reaction, in order to control the degradation of the product P, supposed toxic.

In Section 3 we give another example, related to the phosphorylation-dephosphorylation cycle (or Goldbeter-Koshland switch [11]), where the phosphorylated (activated) substrate concentration must be maintained in a predetermined value range.

In Section 4 we describe the numerical tools, based mainly on the numerical resolution of Hamilton-Jacobi-Bellman equations in high dimension, which we have parallelized and used in a shared memory environment at CASPUR site.

2 Optimal Control and the Hamilton-Jacobi-Bellman equation: Effects of a drug on cellular enzymes degradation.

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.
In the framework of the Dynamic Programming approach we can exhibit a mathematical formulation of the above described problem.
Introducing in (4) a suitable control $\alpha(t)$ we obtain the supplementary equation

$$\frac{dP}{dt} = k\, C(t) - \alpha(t)P(t) \tag{5}$$

where the term $\alpha(t)P(t)$ represents the degradation of P.
We impose that the dynamical system evolves inside a subset Ω of $\mathbb{R}^3$

$$\Omega = \{(S, C, P) \in \mathbb{R}^3 | S \geq 0\ ,\ C \geq 0\ ,\ P \geq 0\} \tag{6}$$

by defining the set of admissible control $\mathcal{K}_{ad}$ as the set of measurable functions $\alpha : [0, T] \to [0, K]$, for some $K > 0$, such that

$$(S(t), C(t), P(t)) \in \Omega \,\text{for each}\, t \in (0, T]. \tag{7}$$

We rewrite system (4), (5) in the vector form

$$\frac{dy}{dt} = g(y(t), \alpha(t)) \tag{8}$$

where

$$y(t) = (S(t), C(t), P(t))^T \in \mathbb{R}^3 \tag{9}$$

$$y(0) = (S_T, 0, 0)^T =: x \in \mathbb{R}^3 \tag{10}$$

and

$$\begin{aligned} g(y(t), \alpha(t)) = (&-a(E_T - C(t))S(t) + d\, C(t)\ , \\ &a(E_T - C(t))S(t) - (d + k)C(t)\ ,\ k\, C(t) - \alpha(t)P(t))^T\ . \end{aligned} \tag{11}$$

For any "admissible control" we define a "cost" functional, depending also on the choice of the initial condition $y(0) = x := y_x(0)$, as

$$J(x, t, \alpha(\cdot)) = \int_0^t l(y_x(s), \alpha(s))e^{-\lambda s}\mathrm{d}s + u_0(y_x(t))e^{-\lambda t} \tag{12}$$

where l is the so called running cost, u_0 the terminal cost and $\lambda \geq 0$ the interest rate.
In our first models we have decided to put $\lambda = 0$ and $u_0 \equiv 0$. Let be

$$u(x, t) = \inf_{\alpha(\cdot) \in \mathcal{K}_{ad}} J(x, t, \alpha(\cdot))\ , \tag{13}$$

then, see for example [1, 2], for each $0 < \tau \leq t$, u satisfies the Dynamic Programming Principle

$$u(x,t) = \inf_{\alpha(\cdot)\in\mathcal{K}_{ad}} \left\{ \int_0^\tau l(y_x(s),\alpha(s))e^{-\lambda s}\mathrm{d}s + u(y_x(\tau,\alpha),t-\tau)e^{-\lambda\tau} \right\} , \quad (14)$$

and, under suitable assumptions, the "value function" $u(x,t)$ is a viscosity solution of

$$u_t + \lambda u + H(x,Du(x)) = 0 \text{ on } \Omega\times(0,T] \quad (15)$$

where $Du = D_x u$ and

$$H(x,Du(x)) = \min_{c\in[0,K]} \{-g(x,c)\cdot Du(x) - l(x,c))\} \ . \quad (16)$$

The uniqueness of u follows from Maximum Principle imposing the initial condition

$$u(x,0) = u_0(x) \text{ on } \Omega\times\{0\} \ . \quad (17)$$

From the solution of (15–17) we can compute an optimal feedback control by

$$\alpha^*(t) = \arg\min_{\alpha} u(y_x(t),t). \quad (18)$$

To force the system to send P to zero we consider l depending on P and on α, because we want to take into account the cost (or the toxicity) of the drug, too. As shown in Figures 1-3, the choice of the function l is fundamental. In fact, a suitable choice of the cost functional l allows us to give optimal strategies to send P to zero. Figure 1 shows that if the cost does not depend on α ($l(x,\alpha) = P^2$), than the optimal strategy is to choose α as large as possible; in our test $\alpha = K = 0.6$. Figure 2 and 3 show that, if $l(x,\alpha) = P^2 + \alpha^2$, it can be more convenient to degrade P only partially.
Let us remark that in this second case the choice of the end time T plays a crucial (and biologically relevant) role for the behavior of the control α and of P. In the case of short end time $T = 10$ (Figure 2), the complete degradation of P should mean high values of α and, consequently, high values of the cost function. The optimal choice consists in a partial degradation of P and small values of α. When $T = 100$ it is less costly for the system to impose initially high values of the control, in order to rapidly degrade P and then letting α tend to 0.

3 Optimal Control and the Hamilton-Jacobi-Bellman equation: Control of the substrate concentration

The second example studies the phosphorylation-dephosphorylation cycle [11, 5, 16]

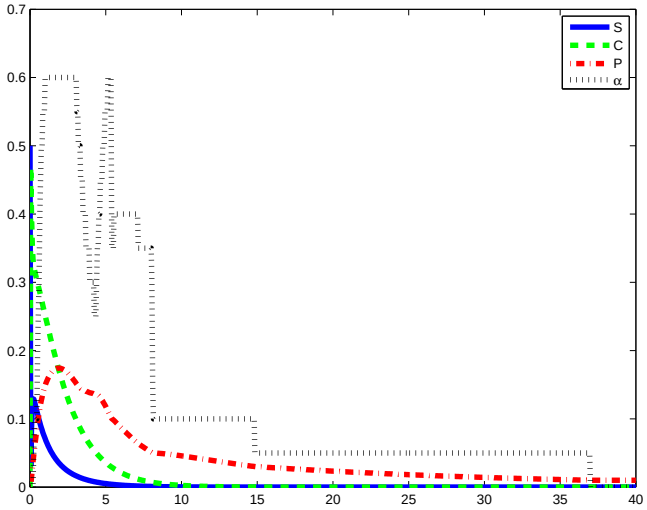

Figure 1: Control of product degradation. $K = 0.6$, $E_T = 0.5$, $S_T = 0.5$, $T = 10$, $l(y_x, \alpha) = P^2$. Since the cost function does not contain α, the control immediately reaches the upper bound, rapidly degrading P.

$$\begin{aligned} S + E_1 &\underset{d_1}{\overset{a_1}{\rightleftarrows}} C_1 \xrightarrow{k_1} E_1 + S^*, \\ S^* + E_2 &\underset{d_2}{\overset{a_2}{\rightleftarrows}} C_2 \xrightarrow{k_2} E_2 + S, \end{aligned} \tag{19}$$

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 for example [18]) that the steady state concentration levels of particular enzymes, as their activation strength or duration, can determine the fate of a cell (proliferation, apoptosis, differentiation etc.).
Consequently it is very important to control in some sense the concentration levels of the different enzymes involved in any reaction.
In this model we want to maintain the concentration level of the phosphorylated substrate above and/or below apriori determined thresholds. Substituting

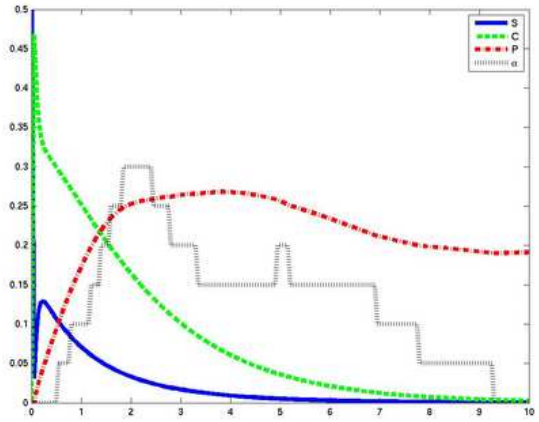

Figure 2: Control of product degradation. $K = 0.6$, $E_T = 0.5$, $S_T = 0.5$, $T = 10$, $l(y_x, \alpha) = P^2 + \alpha^2$. For small values of T it is less costly for the system not to degrade all the product P.

to the kinetic rate k_1 a control $\alpha(t)$, the reaction is governed by the system

$$\begin{cases} \dfrac{dS}{dt} = -a_1(E_{1,T} - C_1)S + d_1C_1 + k_2C_2 \\ \dfrac{dS^*}{dt} = -a_2(E_{2,T} - C_2)S^* + d_2C_2 + \alpha(t) \cdot C_1 \\ \dfrac{dC_1}{dt} = a_1(E_{1,T} - C_1)S - (d_1 + \alpha(t)) \cdot C_1 \\ \dfrac{dC_2}{dt} = a_2(E_{2,T} - C_2)S^* - (d_2 + k_2)C_2 \end{cases} \tag{20}$$

the initial conditions

$$S(0) = S_T \ , \ S^*(0) = 0 \ , \ C_i(0) = 0 \tag{21}$$

and the conservation laws

$$S_T = S + C_1 + C_2 + S^*, \ E_{i,T} = E_i + C_i, \ i = 1, 2. \tag{22}$$

In this case, to keep S^* in a δ-neighborhood of a constant value m, we solve a PDE like (15–17), where the cost functional is

$$l(x, c) = ([S^* - (m + \delta)]^+)^2 + ([-S^* + (m - \delta)]^+)^2. \tag{23}$$

Let us remark that this choice gives quite different results in terms of optimal strategies in Figure 4 and Figure 5. In absence of control ($k_1 = 0.4$), S^* asymptotically tends to a value close to 0.11. The control tends to bring S^* in the

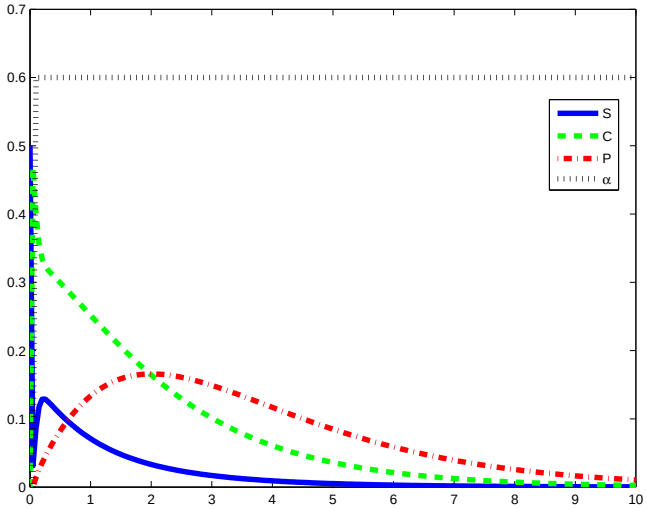

Figure 3: Control of product degradation. $K = 0.6$, $E_T = 0.5$, $S_T = 0.5$, $T = 100$, $l(y_x, \alpha) = P^2 + \alpha^2$. For large values of T it is less costly to allow the control to reach initially high values in order to rapidly degrade P.

range as soon as possible. Consequently when we impose to S^* to belong to a neighborhood of the value 0.12, $\alpha(t)$ initially assumes high values, in order to bring S^* in the range, then its value remains relatively stable. When we impose to S^* to belong to a different δ-neighborhood, the control dramatically jumps from 0.4 to very different values.

4 The Parallel Code

The starting point for numerical simulations was the code developed by Carlini et al. [7] for solving Hamilton-Jacobi equations in high spatial dimensions. This code is able to solve problems in 2 or 3 spatial dimension but suffers of the so–called "curse of dimensionality" implicit in this kind of mathematical formulation.

For this reason we developed 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 implemented using OpenMP, a standard tool designed for shared memory architectures (including new multicore machines) [20].

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 parallel directive. This directive is responsible for creating a group of threads.

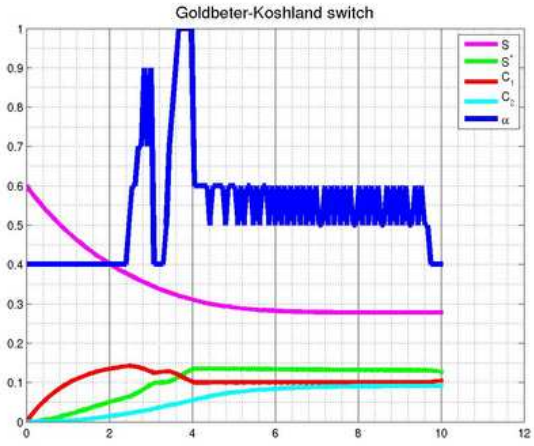

Figure 4: Control of the substrate concentration. $m = 0.12$, $\delta = 0.02$. After a transient phase, the control is relatively stable, because S^* reaches a value close to the asymptotic value obtained in absence of control, putting $k_1 = 0.4$.

The core of the parallel code follows. It should be noted that the OpenMP specific part in the parallel code is very small:

```
!$omp parallel default(shared)&
!$omp do private(jj,nodo,ctrl,in,l,stimaHJ)
                do jj=1,nnodi
                  call Inv_ind(jj,n,In)
                  do l=1,m
                     nodo(l)=x(In(l)+last(l))
                  enddo
                  call STIMAINICTRL(stimaHJ,nodo,ctrl)
                  u(jj)=stimaHJ
                  uctrl(jj)=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.
In Figures 6 and 7 we respectively show the speedup and efficiency of the parallel code, varying the number of processors in the case of the first example.
The speedup shows to be almost linear and very close to the ideal one, while the efficiency values stay above 97%, which is a very good threshold for real applications.
Further optimizations should concern the use of distributed memory techniques and tools (MPI) in order to run efficiently on distributed memory supercom-

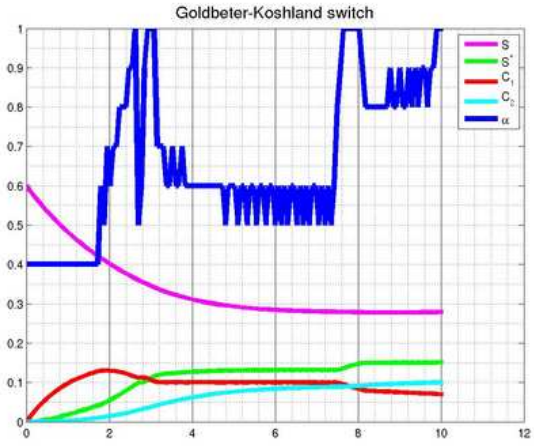

Figure 5: Control of the substrate concentration. $m = 0.18$, $\delta = 0.02$. The control values vary much more than in the previous case, because α must keep S^* in a range which does not contain the asymptotic value obtained in absence of control.

puters using a greater RAM than in a single machine.

References

[1] M. Bardi, I. Capuzzo-Dolcetta, Optimal Control and Viscosity Solutions of Hamilton-Jacobi-Bellman Equations, Birkhäuser, Cambridge, 1997.

[2] G. Barles, Solutions de viscosité des équations de Hamilton-Jacobi, Springer-Verlag, Berlin, 1994.

[3] A. M. Bersani, E. Bersani, L. Mastroeni, Modeling the action of drugs on cellular enzymes by means of optimal control techniques (work in preparation).

[4] U. S. Bhalla, Models of cell signaling pathways, Curr. Opin. Genet. Dev. 14 (2004) 375-381.

[5] H. Bisswanger, Enzyme Kinetics. Principles and Methods, Wiley-VCH, Weinheim, 2002.

[6] G. E. Briggs, J. B. S. Haldane, A note on the kinetics of enzyme action, Biochem. J. 19 (1925) 338-339.

[7] E. Carlini, M. Falcone, R. Ferretti, An efficient algorithm for Hamilton-Jacobi equations in high dimension, Computing and Visualization in Science 7 (2004) 15-29.

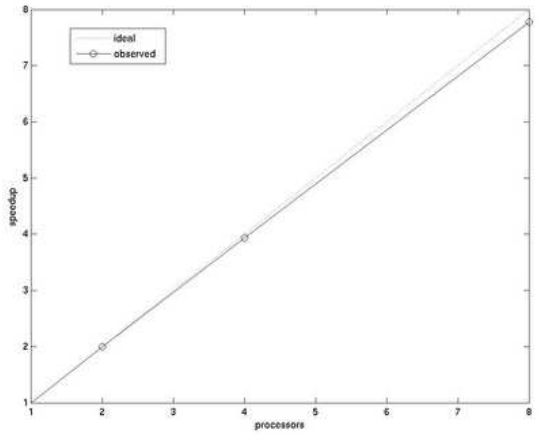

Figure 6: Speedup values in the case of the first example (product degradation).

[8] J. E. Ferrell, Jr., R. R. Bhatt, Mechanistic Studies of the Dual Phosphorylation of Mitogen-activated Protein Kinase, J. Biol. Chem. 272 (1997) 19008-19016.

[9] D. T. Gillespie, Exact Stochastic Simulation of Coupled Chemical Reactions, J. Phys. Chem. 81 (1977) 2340-2361.

[10] D. T. Gillespie, Markov Processes: An Introduction for Physical Scientists, Academic Press, San Diego, 1992.

[11] A. Goldbeter, D. E. Koshland, Jr., An amplified sensitivity arising from covalent modification in biological systems, Proc. Natl. Acad. Sci. 78 (1981) 6840-6844.

[12] N.W.S. Kam, Z. Liu, H. Dai, Carbon Nanotubes as Intracellular Transporters for Proteins and DNA: An Investigation of the Uptake Mechanism and Pathway, Angew. Chem. Int. Ed. 45 (2006) 577-581.

[13] S. MacNamara, A. M. Bersani, K. Burrage, R. B. Sidje, Stochastic chemical kinetics and the *total* quasi-steady-state assumption: application to the stochastic simulation algorithm and chemical master equation (submitted to *J. Chem. Phys.*).

[14] L. Michaelis, M. L. Menten, Die kinetik der invertinwirkung, Biochem. Z. 49 (1913) 333-369.

[15] C. G. Moles, P. Mendes, J.R. Banga, Parameter Estimation in Biochemical Pathways: A Comparison of Global Optimization Methods, Genome Research 13 (2003) 2467-2474.

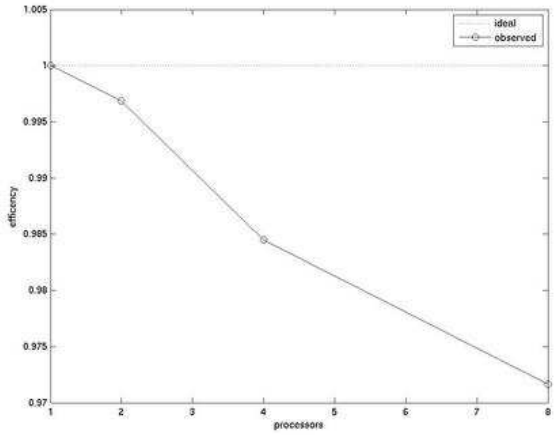

Figure 7: Efficiency values in the case of the first example (product degradation).

[16] M. G. Pedersen, A. M. Bersani, E. Bersani, G. Cortese, The Total Quasi-Steady State Approximation for Complex Enzyme Reactions, Mathematics and Computers in Simulation (in press).

[17] S. Schnell, P. K. Maini, A century of enzyme kinetics. Reliability of the K_M and v_{max} estimates, Comments Theor. Biol. 8 (2003) 169187.

[18] S. Yamada, T. Taketomi, A. Yoshimura, Abstract Model analysis of difference between EGF pathway and FGF pathway, Biochem. Biophys. Res. Commun. 314 (2004) 1113-1120.

[19] Y. Zhao and Z.-Y. Zhang, The Mechanism of Dephosphorylation of Extracellular Signal-regulated Kinase 2 by Mitogen-activated Protein Kinase Phosphatase 3, J. Biol. Chem. 276 (2001) 32382-32391.

[20] The OpenMP API specification for parallel programming, http://openmp.org/wp/