TOPOLOGICAL ANALYSIS OF CHAOS IN A THREE-VARIABLE BIOCHEMICAL MODEL

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ABSTRACT

A three-variable biochemical prototype involving two enzymes with autocatalytic regulation proposed by Decroly and Goldbeter (1987) is analyzed using a topological approach. A two-branched manifold, a so-called template, is thus identified. For certain control parameter values, this template is a horseshoe template with a global torsion of two half-turns. This implies that the bifurcation diagram can be described using the usual sequences associated with a unimodal map with a differentiable maximum as well as exemplified by the logistic map. Moreover, a type-I intermittency associated with a saddle-node bifurcation is exhibited. The dynamics from a single time series are also investigated to determine whether it is possible to investigate the dynamics of this biochemical model from the measure of a single concentration.

1. INTRODUCTION

Glycolytic oscillations are the prototype for periodic phenomena in biochemistry. First observations of such self-oscillations were made by Duysens and Amesz (1957). A review of experimental observations on glycolytic oscillations may be found in Goldbeter (1996). The source of oscillations within the glycolytic system was first identified by Ghosh and Chance (1964). Glycolysis represents a chain of enzyme reactions which in yeast transforms a sugar such as glucose or fructose into ethanol and CO_2. When a hexose such as glucose 6-phosphate or fructose 6-phosphate is taken as the glycolytic substrate, periodic behavior is observed. This observation indicates that the source of oscillations is beyond the first two enzymes of the chain, hexokinase and glucose-phosphate isomerase. However, when the phosphofructokinase step is bypassed by injecting fructose 1,6-bisphosphate as glycolytic substrate, the oscillations disappear. Periodic behavior therefore originates at the enzymic step catalysed by phosphofructokinase. Indeed, a simple model for the phosphofructokinase reaction generating self-oscillations was proposed by Sel'kov (1968). An allosteric model for glycolytic oscillations was later proposed by Goldbeter and Lefever (1972).

These models can be reduced into two-variable models and, according to the Poincaré-Bendixson theorem, only fixed point or limit cycle may be observed. In other terms, only periodic self-oscillations characterized by a single frequency can be generated by such models. Since chaotic behaviors are now observed in biochemical

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systems as exemplified by the glycolysis (Nielsen *et al.*, 1997), it is required to use a model involving at least three variables, three being the smallest dimension of the phase space in which a chaotic behavior may be embedded. Such a model may be built when two instability mechanisms coupled in series are considered (Decroly and Goldbeter, 1982). Such a model generates a large set of dynamical behaviors such as chaotic attractors or burstings. The aim of this paper is to characterize the topology of the typical behavior generated by the three-variable model introduced by Decroly and Goldbeter, (1982). The model is introduced in Section 2. Hereafter, the attractor is described in terms of first-return maps, population of periodic orbits and templates (Section 3). Particular behaviors called intermittencies are identified (Section 4). Section 5 is devoted to the important question: Is it possible to investigate the dynamics from the time evolution of a single concentration? Section 6 gives a conclusion.

2. THE THREE-VARIABLE BIOCHEMICAL MODEL

The coupling in series of two enzymes with autocatalytic regulation permits the construction of a three-variable biochemical prototype containing two instability-generating mechanisms (Decroly and Goldbeter, 1982). The substrate S is introduced at a constant rate into the system; this substrate is transformed by enzyme E_1 into product P_1, which serves as substrate for a second enzyme E_2 that transforms P_1 into P_2. The two allosteric enzymes are both activated by their reaction product; P_1 and P_2 are thus positive effectors for enzymes E_1 and E_2, respectively. The system is considered as spatially homogeneous as in the case of experiments on glycolytic oscillations. The set of three ordinary differential equations thus reads as:

$$\begin{aligned} \dot{x} &= V - \sigma_1 \phi_1(x, y) \\ \dot{y} &= q_1 \sigma_1 \phi_1(x, y) - \sigma_2 \phi_2(y, z) \\ \dot{z} &= q_2 \sigma_2 \phi_2(y, z) - K_s z \end{aligned} \tag{1}$$

where x, y, and z are (dimensionless) normalized concentrations of substrate S and of the reaction product P_1 and P_2, respectively. The normalized maximum rates of the enzyme E_1 and E_2 are σ_1 and σ_2. The ratios of the dissociation constants are quantified by q_1 and q_2. When $q_1 > 1$ ($q_1 < 1$), the product P_1 varies faster (slower) than the substrate S. A similar feature between the dissociation constants of both reaction products is quantified by q_2. V denotes the substrate injection rate and K_s the apparent first-order rate constant for the removal of the final product in a reaction catalyzed by a Michaelian enzyme far from saturation by its substrate. The rate functions ϕ_1 and ϕ_2 of the allosteric enzymes E_1 and E_2 are given by

$$\phi_1(x, y) = \frac{x(1+x)(1+y)^2}{L_1 + (1+x)^2(1+y)^2}$$

$$\phi_2(y, z) = \frac{y(1+z)^2}{L_2 + (1+z)^2}$$

For simplicity, the rate of enzyme E_2 depends in a linear manner on the concentration y of its substrate, i.e. the enzyme is never saturated by it. The control parameters are fixed to:

$$\sigma_1 = 10.0s^{-1} \qquad q_1 = 50.0 \qquad L_1 = 5.0 \times 10^8$$
$$\sigma_2 = 10.0s^{-1} \qquad q_2 = 0.02 \qquad L_2 = 100.0$$

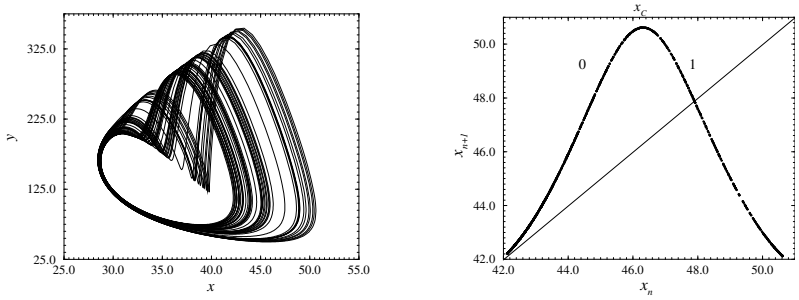
It has been shown that this model goes through a period-doubling cascade when the control parameter K_s is increased (Goldbeter, 1996). Beyond the accumulation point, the asymptotic behavior settles down onto a chaotic attractor. This is the behavior which will be characterized here.

3. TOPOLOGICAL CHARACTERIZATION OF A CHAOTIC REGIME

An (x,y)-plane projection of a typical chaotic attractor is shown in Figure 1a for $V = 0.45$ s^{-1} and $K_s = 2.00$. The first step of a topological characterization is to compute a first-return map to a Poincaré section. In the case of this three-variable model, the Poincaré section may be defined as the set

$$P = \{(x_n, y_n) \in \mathbf{R}^2 \mid y_n = 100.0,\ \dot{y}_n < 0.0\}$$

The first-return map (Figure 1b) is constituted by two monotonic branches separated by a critical point located at $x_c = 46.31$. This critical point defines a partition of the attractor which allows one to encode the trajectories by strings of symbols. Most of the time, these symbols are chosen among integers. For instance, the increasing branch is encoded by symbol '0' and the decreasing branch by symbol '1'. Thus, a trajectory is encoded in a string of '0' and '1'. Obviously, the periodic orbits are encoded by finite strings which are repeated. The population of periodic orbits embedded within the attractor displayed in Figure 1a is reported in Table 1. For instance, the period-4 orbit encoded by (1011) crosses the Poincaré section three times in branch 1 and once in branch 0.



(a) Chaotic attractor (b) First-return map

Figure 1. Chaotic attractor solution of the three-variable biochemical model with $V = 0.45$ s^{-1} and $K_s = 2.00$. The first-return map to the Poincaré section P is unimodal, i.e. constituted by two monotonic branches separated by a critical point. This critical point is located at a differentiable maximum.

Since the first-return map is unimodal, i.e. has a unique critical point and has a differentiable maximum, it belongs to the class of maps associated with the class exhibited by Feigenbaum (1978) and, independently, by Coullet and Tresser (1978).

As a consequence, the order of creation of periodic orbits when a control parameter is increased can be predicted by the so-called *unimodal order* (Collet and Eckman, 1980). This order is also introduced with the topological characterization procedure by Letellier *et al.* (1995). All the periodic orbits are thus created by saddle-node bifurcations or period-doubling bifurcations. In the case of the three-variable biochemical model investigated here, the order of creation of periodic orbits can be predicted until the first-return map presents a third monotonic branch, that is until the control parameter K_s is less than or equal to 2.00. The topological structure of the attractor is now investigated for this particular value of K_s.

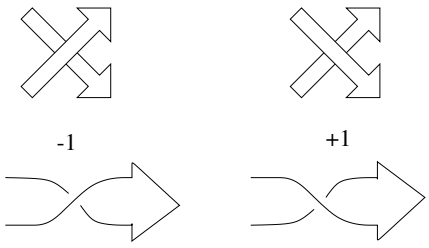
Table 1. Population of periodic orbits embedded within the chaotic attractor. Only orbits with period less than 8 are reported. The symbolic sequences are ordered according to the unimodal order observed when the K_s-control parameter is increased. The beginning of the period-doubling cascade may be recognized with the three orbits, (1), (10) and (1011), respectively.

(S)	(S)	(S)	(S)
(0)	(1011011)	(1001)	(10000)
(1)	(101)	(1000)	(1000011)
(10)	(100)	(1000101)	(100001)
(1011)	(100101)	(100010)	(100000)
(101111)	(1001011)	(100011)	(1000001)
(10111)	(10010)	(1000110)	(1000000)
(10110)	(1001101)	(10001)	

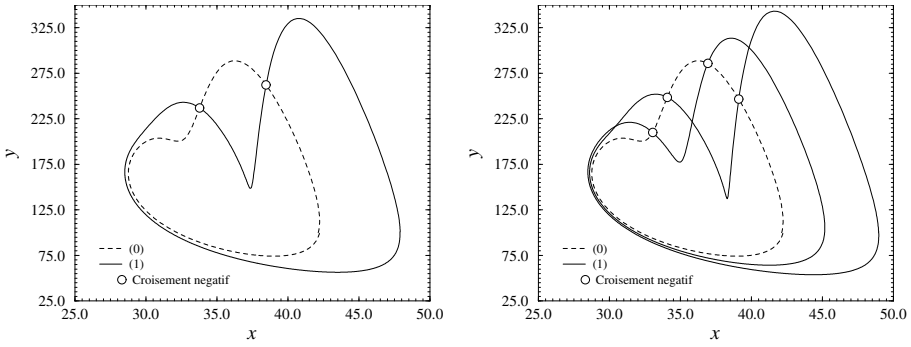
Table 2. Linking numbers between couple of periodic orbits counted in a plane projection. All these linking numbers can be predicted from the template shown in Figure 3.

	(0)	(1)	(10)	(101)
(1)	-1			
(10)	-2	-3		
(101)	-3	-4	-8	
(100)	-3	-4	-8	-12

By topological structure, we mean the relative organization of the periodic orbits in the phase space $\mathbf{R}^3(x,y,z)$. Such a relative structure is quantified by using linking numbers associated with couples of periodic orbits. For instance, when the two periodic orbits encoded by (0) and (10) are considered, the linking number $lk(10,0)$ between them is equal to the half sum of the oriented crossings counted in a regular plane projection. In the present case, four negative crossings are counted (Figure 2) according to the following convention:



The crossings are therefore signed using the third coordinate. The linking number $lk(10,0)$ is equal to -2 (Figure 2a). It means that orbit (10) turns twice around orbit (0) in the negative sense or, equivalently, that orbit (0) turns twice around orbit (10) in the negative sense. Linking numbers are computed for a large set of couples of orbits. A few of them are reported in Table 2.



(a) $lk(1,0) = -1$ (b) $lk(10,0) = -2$

Figure 2. Couple of periodic orbits projected in the plane (x,y). Four negative crossings are found. The linking number $lk(10,0)$ is therefore equal to -2.

The idea is then to find a branched manifold on which the relative organisation of periodic orbits can be reproduced. All the linking numbers must be predicted by using this branched manifold which is called a template. A review of the topological characterization procedure and how to find a template of an attractor is given by Gilmore (1998). In the case of the three-variable biochemical model, the topological structure is described by the template displayed in Figure 3.

A Horseshoe template is always constituted by one odd branch and one even branch, i.e. it has one branch with an odd number of half-turns and one branch with an even number of half-turns. These numbers of half-turns associated with each branch are defined as the local torsions (Figure 3). The global torsion designates the number of crossings between the two branches (Figure 3). In fact, the even branch is associated with the increasing branch of the first-return map encoded by 0 and the odd branch corresponds to the decreasing branch encoded by 1.

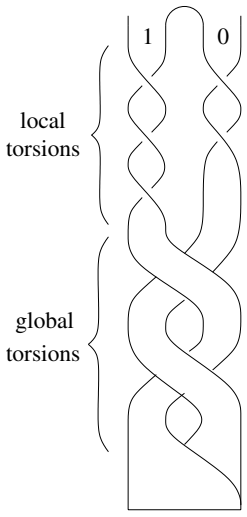
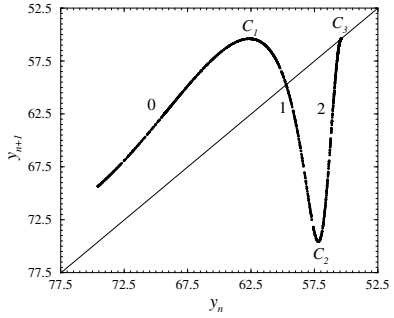


Figure 3. Template associated with the attractor generated by the three-variable biochemical model. This is a Horseshoe template with a global torsion of two half-turns.

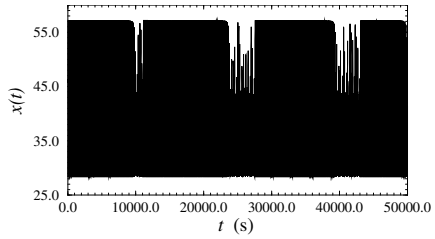
The template, which is associated with the attractor generated by the three-variable biochemical model, corresponds to a Horseshoe template with a global torsion of two negative half-turns (Figure 3). The even branch is associated with two half-turns and the odd branch with three half-turns.

4. INTERMITTENCIES

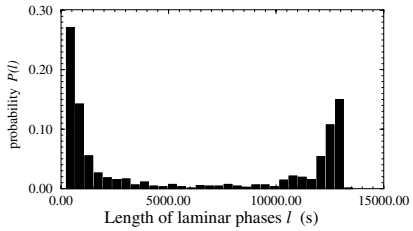
When a behavior is characterized by a unidimensional map, we are ensured of observing type-I intermittencies associated with each saddle-node bifurcation inducing a periodic window. Indeed, in a bifurcation diagram associated with such a map, many periodic windows are observed. Each of them appears through a tangent bifurcation, which is also a saddle-node bifurcation. One stable periodic orbit and one unstable periodic orbit are therefore simultaneously created. The smaller the periods of the orbits, the more observable the periodic windows are. For instance, from the population of periodic orbits reported in Table 1, the orbits (100) and (101) are created through a saddle-node bifurcation and a period-3 window is easily observed in the bifurcation diagram. With these periodic windows, an intermittent behavior is necessarily associated. In the case of the biochemical model, the most observable periodic window is associated with a period-1 orbit appearing for K_s slightly greater than 2.015807. At this K_s-value, the first-return map is tangent to the bissecting line (Figure 4a). Two period-1 orbits are therefore created. The periodic window is associated with the stable orbit created by this saddle-node bifurcation appearing when the first-return map reaches the bissecting line at the third critical point (Figure 4a).



(a) First-return map



(b) Intermittent time series



(c) Distribution of the laminar length l

Figure 4. An intermittent behavior is observed for $K_s = 2.015807$, corresponding to a tangent bifurcation. Laminar phases during which the behavior is almost periodic are interrupted by chaotic bursts. The distribution of the laminar length l is characteristic of a type-I intermittency.

When the concentration of substrate (or any reaction product) is measured slightly before the bifurcation, an intermittent behavior is observed (Figure 4b). This particular feature results from the fact that the trajectory visits the thin canal between the bissecting line and the first-return map. The trajectory thus stays very close to the stable periodic orbit bifurcation for a long time. It will be created by the saddle-node. This is the so-called laminar phase. From time to time, the trajectory escapes from this thin canal and evolves on the chaotic attractor. A chaotic burst is thus observed (Figure 4b). Consequently, the intermittent behavior is almost periodic for a finite time, interrupted by chaotic bursts before being reinjected into the thin canal. Such a scenario has been theoretically predicted by Pomeau and Manneville (1980).

At least three types of intermittency exist, each of them being associated with a specific reinjection mechanism. They are distinguished by a distribution $P(l)$ of the laminar length l which is characteristic of the reinjection mechanism. Such a distribution computed for the intermittency just before the period-1 window is displayed in Figure 4c. It exhibits two characteristic lengths, one around 860 s which is associated with the short laminar phases while the other is around 12500 s and is associated with the long phases. The histogram of the distribution of the laminar lengths is characteristic of a type-I intermittency as expected when a saddle-node bifurcation is involved (Figure 4c).

5. ANALYSIS OF THE THREE-VARIABLE BIOCHEMICAL MODEL THROUGH A SINGLE VARIABLE

When investigating a glycolytic reaction, an important question must be faced: *Shall all the concentrations be measured to investigate the global dynamics?* Indeed, one of the most interesting results from the theory of nonlinear dynamical systems is that the description in the phase space of the dynamics does not necessarily require the knowledge of all the dynamical variables involved in the full description of a state of the system. According to the information redundancy principle, a time series corresponding to the time evolution of a single reaction product or substrate may be sufficient to provide the relevant information to investigate such a chain of enzyme reactions. Thus, according to the Takens' theorem (1981), the phase portrait may be reconstructed from a single scalar time series, e.g. the time evolution of a single species, by using time delay or derivative coordinates. The reconstructed phase portrait is thus expected to be diffeomorphically equivalent to the original one which is usually not measurable, i.e. all the dynamical variables spanning the phase space cannot be simultaneously recorded. For instance, one may easily imagine that it could be quite difficult to simultaneously measure the concentrations of the two reaction products for investigating this biochemical oscillating reaction.

When one uses a single time series, one may be ensured of having the best quality for the reconstructed phase portrait when a diffeomorphism between the reconstructed phase portrait and the original one is found. Such a quality may be obtained when the embedding dimension d_E is sufficiently large. According to Takens' theorem, it must be greater or equal to $2D_H + 1$ where D_H ideally refers to the Haussdorff dimension which could be conveniently approximated by the correlation dimension estimated with the algorithm proposed by Grassberger and Procaccia (1983). Theoretically, i.e. with an infinite amount of data without any noise, all the dynamical variables may be

used. Unfortunately, when one is facing data from the real world, time series are necessarily corrupted by noise and discretized in time, such equivalence is not always observed and we may find that some variables are better than others (Letellier *et al*., 1998a). Such an annoyance may be amplified by the non-availability of data with sufficient quality as often observed in studying biological systems. It is therefore rather important to state whether the biochemical model may be equivalently investigated from any time series of one concentration of a product or substrate involved in the reactions.

Here we will say that two dynamical variables are equivalent when they will induce reconstructed phase portrait characterized by the same template. In order to do so, a reconstructed phase portrait must be built starting from a single scalar time series $\{U_i\}$ which may be constituted by the time evolution of one of three dynamical variables of the biochemical model, i.e. x, y or z. The reconstructed phase portrait is then spanned by using delay coordinates

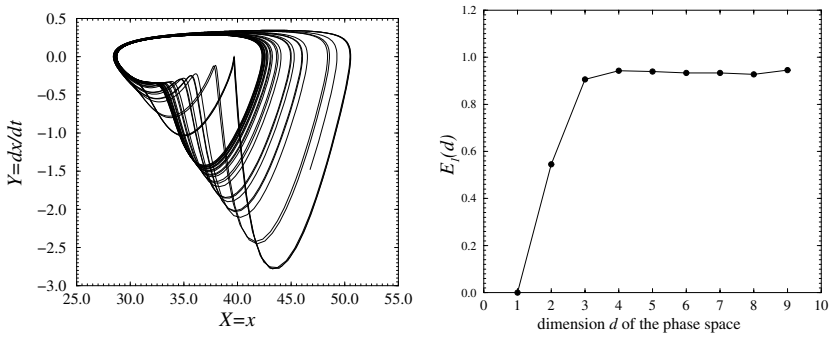
$$\{U(t), U(t+\tau), U(t+2\tau), ..., U(t+(d_E-1)\tau)\}$$

or the derivative coordinates

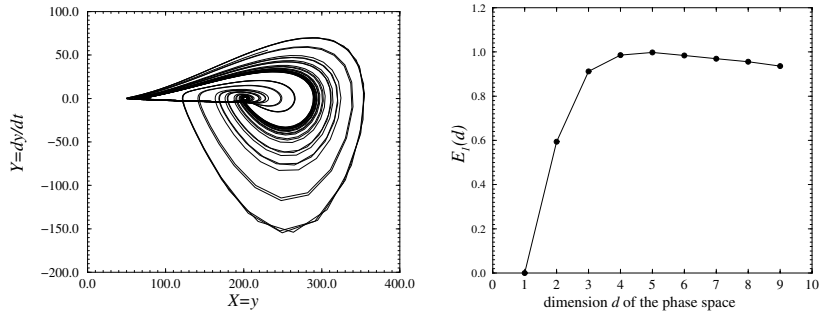
$$\{U(t), \dot{U}(t), \ddot{U}(t), ..., \frac{d^{d_E-1}U(t)}{dt^{d_E-1}}\}$$

Gibson *et al*. (1992) showed that both coordinate sets are equivalent. Indeed, a map being a rotation and a rescaling may always be found between a phase portrait reconstructed with the delay coordinates and the derivative coordinates. Let us choose the derivative coordinates. In order to know how many coordinates are required to properly reconstruct the phase portrait, the so-called embedding dimension has to be estimated. Such a dimension corresponds to the minimum number of coordinates required to reconstruct a phase portrait for which the trajectory does not present any self-crossing. Such self-crossing are forbidden by the deterministic character of the dynamics investigated since a self-crossing necessarily induces two different future states for a single present state. The embedding dimension may be computed by using the false nearest neighbors' method (Abarbanel *et al*., 1993) for which an improved algorithm has recently been proposed by Cao (1997). The latter is used here. For the three variables of the biochemical model, the embedding dimension is equal to 3 (Figure 5). Note that using the correlation dimension for such a system is typically between 2.0 and 3.0 and, consequently, the dimension suggested by the Takens' criterion would be at least 5. Such a high dimensional space would be required to be ensured that a diffeomorphism exists between the original unknown phase portrait and the reconstructed one. Nevertheless, it often appears that a less dimensional space is sufficient and most of time a phase portrait may be properly reconstructed in a space which has a dimension equal to the dimension of the original phase space. Indeed, the Takens' criterion should be considered as the upper limit for which a diffeomorphism can be identified between the original phase portrait and the reconstructed phase portrait. In the present case, 3 is the smallest dimension for reconstructing the phase portrait since no chaotic behavior would not be identified with a smaller dimension. The reconstructed phase space may be therefore spanned by the three variables reading as:

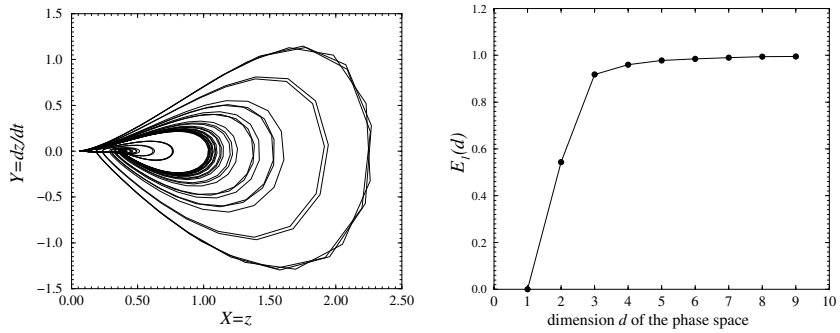
$$U = x,\ y \text{ or } z; \quad V = \dot{U}; \quad W = \ddot{U}$$



(a) x-induced attractor



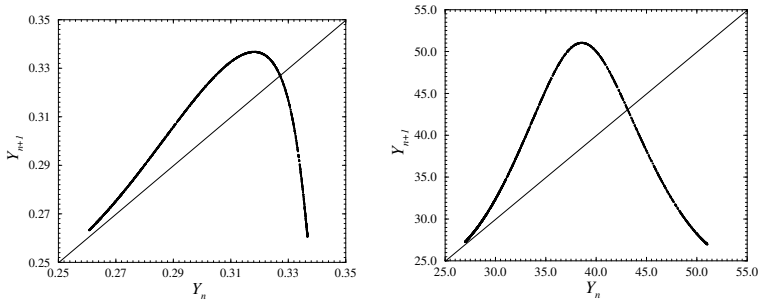
(b) y-induced attractor



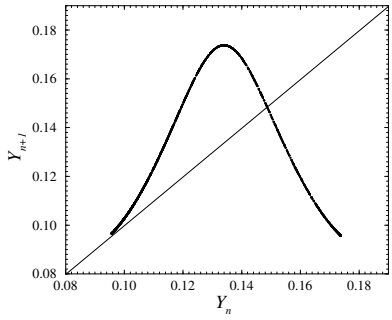
(c) z-induced attractor

Figure 5. Plane projections of the three phase portraits induced by the three variables of the biochemical model. The embedding dimension has been computed from each time series using the Cao's algorithm. In the three cases it is found that the reconstructed phase portrait can be embedded in a 3D phase space. The index $E_1(d)$ measures the relative change in the average distance between two neighbour points in $\mathbf{R}^d$ and their respective images in $\mathbf{R}^{d+1}$ when the dimension of the reconstructed phase space is increased from d to $d + 1$.

Plane projections of the three induced phase portraits are displayed in Figure 5. Nevertheless, all the induced phase portraits do not have the same shape. For instance, the phase portrait induced by the x-variable, i.e. the concentration of the substrate, does not present any region where different trajectories are difficult to distinguish. Such a nice property guarantees an easy topological characterization. Indeed, when such regions where different trajectories are not well distinguished, it becomes rather difficult to count the linking numbers and, consequently, it is much more difficult to extract a template. Nevertheless, it is possible to show that these three induced attractors are characterized by the same template as the original phase portrait as well as exemplified by their first-return map (Figure 6) which is very similar to the one computed from the original phase portrait (Figure 1b).



(a) x-induced attractor (b) y-induced attractor

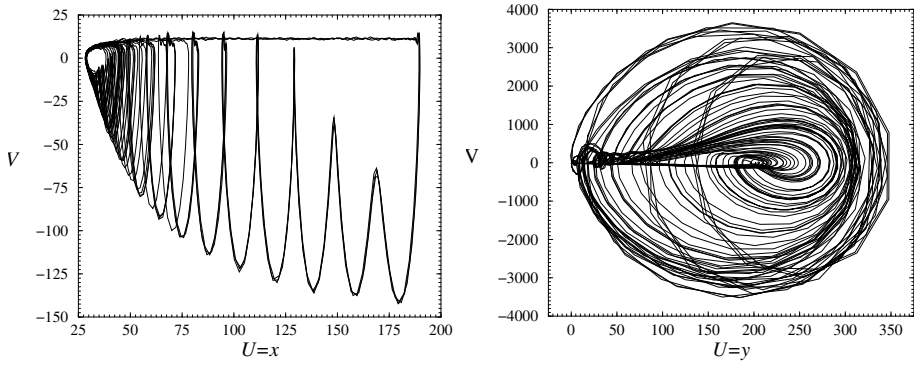


(c) z-induced attractor

Figure 6. First-return maps of the three phase portraits induced by the three variables of the biochemical model. All of these maps are similar to the one computed for the original phase portrait, i.e. is a unimodal map with a differentiable maximum.

In order to show that the observability of the dynamics is smaller from the y-variable than from the x-variable, a stochastic perturbation of a small amplitude (around 0.01) is added during the integration process to simulate a real time series. This is the so-called multiplicative noise. A time series is thus recorded at a sampling rate equal to 50 Hz. As done when real data are investigated, a slight smoothing is applied using a window of 8 points. The derivatives are thus computed by analytically deriving a polynomial fitted using a Singular Value Decomposition (SVD)

(Broomhead and King, 1986) as already used for experimental data by Letellier *et al.* (1998b). Two time series, recorded and processed in the same conditions, are investigated. In any case, the multiplicative noise has developed the chaotic regime as currently observed. In addition to such a feature, the phase portrait may be affected during the reconstruction procedure. From the phase portrait reconstructions shown in Figures 7, it is easily seen that the x-variable which induces a portrait is not affected by the noise too much (at least it preserves its global shape) while the y variable presents an induced phase portrait quite significantly affected by the noise. Moreover, since the phase portrait did not present a clear hole in the middle of the y-induced attractor, the portrait reconstructed from the noisy y time series becomes very difficult to investigate. Indeed, in that case, it is almost impossible to safely compute a Poincaré section. Consequently, the experimentalist will take advantage of measuring the concentration of the substrate rather than those of the reaction products to investigate a reaction involving two enzymes with autocatalytic regulation.



(a) x-induced attractor (b) y-induced attractor

Figure 7. Phase portraits reconstructed from the x and the y variables when a multiplicative noise is superimposed on the dynamics. The time series processings are similar for both time series, i.e. a sampling rate equal to 50 Hz and a window for smoothing the data equals 8 points.

6. CONCLUSION

A three variable biochemical model describing the coupling in series of two enzymes with autocatalytic regulation has been analyzed by using a topological approach. The chaotic attractor generated by this system is thus described in terms of a template which corresponds to a Horseshoe template with a global torsion of two negative half-turns. Such a template defines a class of dynamics which could be related to the class introduced by Thomas (1999) and described in terms of feedback circuits deduced from the jacobian matrix of the system. This very important link will be carefully investigated elsewhere.

The three-variable biochemical model has been characterized by a unidimensional map and, consequently, saddle-node bifurcations and intermittencies are associated with periodic windows in the bifurcation diagram. Such a feature suggests that glycolytic oscillations may present a seemingly periodic behavior which will be interrupted by chaotic bursts. The lengths of the periodic phases are not constant. Two

main lengths are identified, one short and one long, as theoretically predicted for a type-I intermittency.

Finally, it has been shown that the dynamics of this biochemical reaction may be investigated from the time evolution of a single concentration. Although a higher dimensional description could be required in that case, it has been shown that the three induced attractors are topologically equivalent to the original phase portrait. Nevertheless, the dynamics are easier to investigate when the substrate concentration is recorded rather than the concentration of one of the two reaction products.

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