DISSIPATIVE STRUCTURES FOR AN ALLOSTERIC MODEL

APPLICATION TO GLYCOLYTIC OSCILLATIONS

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ABSTRACT An allosteric model of an open monosubstrate enzyme reaction is analyzed for the case where the enzyme, containing two protomers, is activated by the product. It is shown that this system can lead to instabilities beyond which a new state organized in time or in space (dissipative structure) can be reached. The conditions for both types of instabilities are presented and the occurrence of a temporal structure, consisting of a limit cycle behavior, is determined numerically as a function of the important parameters involved in the system. Sustained oscillations in the product and substrate concentrations are shown to occur for acceptable values of the allosteric and kinetic constants; moreover, they seem to be favored by substrate activation. The model is applied to phosphofructokinase, which is the enzyme chiefly responsible for glycolytic oscillations and which presents the same pattern of regulation as the allosteric enzyme appearing in the model. A qualitative and quantitative agreement is obtained with the experimental observations concerning glycolytic self-oscillations.

INTRODUCTION

Many studies have recently been devoted to the problem of oscillations in enzymatic systems. Besides circadian rhythms and periodic phenomena due to genetic control (1) these oscillations of shorter period result from the regulation of an enzymatic chain of reactions by its metabolites.

Most models describe the control of an enzyme by end-product inhibition (2, 3), but positive feedback can as well be responsible for periodic behaviors. For example, glycolytic oscillations were attributed to the activation of an enzyme by its reaction product (4–8). Sustained oscillations are known experimentally in the yeast glycolytic system (9) and in the peroxidase reaction (10).

The physiological role of periodic phenomena is still far from being fully understood. It is conceivable that oscillations could serve to regulate the concentration levels of some metabolites within the cell. Furthermore it has been conjectured

that such behavior might contribute to the specification of positional information during embryogenesis (11, 12). The interest in periodic phenomena is thus awakened by the potentiality that they might participate in the appearance of spatially differentiated patterns.

The coupling between spatial and temporal order in systems of chemically reacting and diffusing components has, on the other hand, been investigated (13–18, footnote 1). From a thermodynamic point of view it has been shown that in such systems structures in time or in space can only maintain themselves beyond a minimal level of energy dissipation and require specific nonlinear kinetics. Such organizations were called "dissipative structures" by Prigogine in order to underline their far from equilibrium occurrence (19, 20).

Spatial dissipative structures corresponding to stable time independent concentration patterns have been observed in organic chemistry (21, 22) in the Zhabotinsky reaction, which is also known as a good example of a chemical clock (23). This confirms the theoretically predicted link between both types of phenomena.

Chemical instabilities which can generate macroscopic order have been shown to play a role in some biological systems at the cellular (24–26) and supracellular levels (27). In this work we examine the conditions for the occurrence of dissipative structures in a simple biochemical system described in terms of the well-assessed theory of Monod et al. (28). The model considered represents an allosteric enzyme activated by its product. It can be applied to the description of phosphofructokinase which plays an essential role in glycolytic oscillations and which is known to be an allosteric protein (9, 29).

Positive feedback is introduced in a natural way through the allosteric character of the model without reference to nonmolecular parameters. The role of each effector in terms of parameters which have a clear experimental interpretation is clarified: activation by the product, the influence of the substrate, and cooperativity are related to three independent measurable quantities. Moreover, diffusion of metabolites away from the enzyme is considered. The model therefore presents an extension of the global models presented by Higgins (4–6) and Sel'kov (7, 8) for oscillating glycolysis.

2. MODEL AND KINETIC EQUATIONS

We have considered the simplest model which can explain the experimental facts (see Fig. 1): (*a*) the substrate is supplied at constant rate v_1. (*b*) The enzyme is a dimer which exists under the form R (active) and T (inactive), these forms being interconverted via the transition $R_0 \rightleftharpoons T_0$, where R_0 and T_0 denote the forms bearing no ligand. (*c*) The substrate binds to both forms while the product which is a positive effector of the enzyme binds exclusively to the active form. (*d*) The enzy-

[1] Lefever, R., and G. Nicolis. 1971. *J. Theor. Biol.* 30:267.

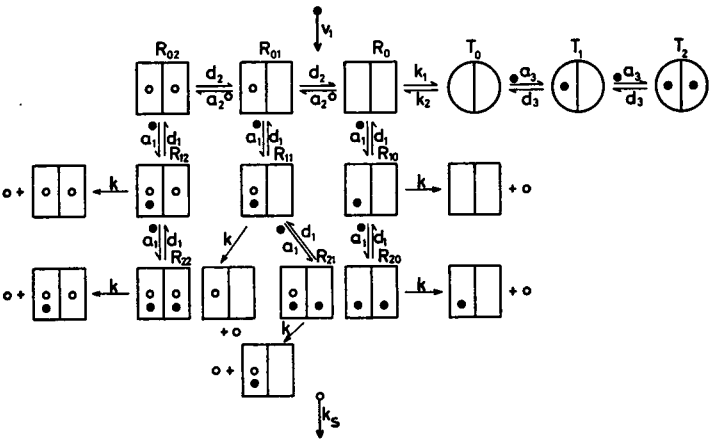

FIGURE 1 Model I (see text). ●, substrate; ○, product.

matic forms R carrying the substrate decompose irreversibly to yield the product. (*e*) The product leaves the system at a rate proportional to its concentration, with a proportionality factor k_s.

The kinetic constants for binding and dissociation for the R forms are represented by a_1, d_1 for the substrate and a_2, d_2 for the product. For the binding and dissociation of the substrate for the T forms, these constants are, respectively, a_3 and d_3. Constants k_1, k_2 are related to the interconversion of R_0 into T_0, while k is the kinetic constant related to the irreversible chemical reaction.

From a thermodynamic point of view one sees that three steps drive the system far from equilibrium: the external constraints (*a*) and (*e*) on the substrate and the product together with the irreversible decomposition of the enzymatic forms. Denoting the concentrations of the product and the substrate, respectively, by A_2 and A_3, one can write a set of kinetic equations of the type (see Fig. 1)

$$\begin{aligned} dA_3/dt = {} & v_1 - 2a_3A_3T_0 + (d_3 - a_3A_3)T_1 + 2d_3T_2 \\ & - 2a_1A_3(R_0 + R_{01} + R_{02}) + (d_1 - a_1A_3)(R_{10} + R_{11} + R_{12}) \\ & + 2d_1(R_{20} + R_{21} + R_{22}), \end{aligned} \tag{1}$$

for the metabolites and similar equations for each enzymatic form together with the conservation relation

$$D_0 = \sum R + \sum T. \tag{2}$$

$\sum R$ is the sum over all the enzymatic forms in the active state while $\sum T$ is the corresponding sum for the inactive state.

Furthermore, in agreement with experimental data (see the Appendix) the following relations hold:

$$\begin{cases} k_1 , k_2 , a_1/A_3 , d_1 , a_2/A_2 , d_2 , a_3/A_3 , d_3 , k \gg 1, \\ A_2/D_0 , A_3/D_0 \gg 1. \end{cases} \tag{3}$$

This permits us to assume fast equilibration of the enzyme with respect to the metabolites, so that the kinetic equations for the enzymatic forms reduce to algebraic relations by a pseudostationary-state hypothesis (30).

Let us now introduce the "normalized" concentrations defined by Monod et al. (28):

$$\alpha = A_3/K_{A_3(R)} , \qquad \gamma = A_2/K_{A_2(R)} , \tag{4}$$

where $K_{A_3(R)} = d_1/a_1$ and $K_{A_2(R)} = d_2/a_2$ are the equilibrium dissociation constants for the R forms of A_3 and A_2, respectively. We make the change of variables

$$\sigma_1 = \nu_1/d_1 , \qquad \sigma_2 = k_3/a_2 , \qquad \epsilon = k/d_1 , \tag{5}$$

and also put for simplicity

$$a_1 = a_2 = a \quad \text{and} \quad d_1 = d_2 = d. \tag{6}$$

Under these conditions, if we also take into account the diffusion of the metabolites while neglecting the diffusion of the enzymatic forms, the system is described by a set of three equations

$$\frac{\partial \alpha}{\partial t} = a\left[\sigma_1 - \frac{[2D_0\epsilon/(\epsilon+1)]\alpha(1+\gamma)^2[1+\alpha/(\epsilon+1)]}{L(1+\alpha c)^2 + (1+\gamma)^2[1+\alpha/(\epsilon+1)]^2}\right] + \mathfrak{D}_\alpha \frac{\partial^2 \alpha}{\partial r^2} , \tag{7a}$$

$$\frac{\partial \gamma}{\partial t} = a\left[\frac{[2D_0\epsilon/(\epsilon+1)]\alpha(1+\gamma)^2[1+\alpha/(\epsilon+1)]}{L(1+\alpha c)^2 + (1+\gamma)^2[1+\alpha/(\epsilon+1)]^2} - \sigma_2\gamma\right] + \mathfrak{D}_\gamma \frac{\partial^2 \gamma}{\partial r^2} , \tag{7b}$$

$$\bar{R} = (1+\gamma)^2[1+\alpha/(\epsilon+1)]^2/\{L(1+\alpha c)^2 + (1+\gamma)^2[1+\alpha/(\epsilon+1)]^2\} , \tag{7c}$$

where $\mathfrak{D}_\alpha$ and $\mathfrak{D}_\gamma$ are the diffusion coefficients of A_3 and A_2, respectively, and $c = K_{A_3(R)}/K_{A_3(T)}$ is the nonexclusive binding coefficient giving the degree of ac-

tivation or inhibition by the substrate. The allosteric constant L, which is equal to the ratio T_0/R_0 in absence of ligands, expresses the degree of cooperativity of the enzyme.

Equations 7 *a* and 7 *b* give the time evolution of metabolites while the function $\bar{R}$ defined as (see reference 28)

$$\bar{R} = \sum R/(\sum R + \sum T),$$

relates the state of the enzyme to the metabolite concentrations.[2]

For simplicity, we have assumed that diffusion takes place in one dimension. The solution of equations 7 *a* and 7 *b* is subject to boundary conditions on the fluxes and concentrations expressing, for example, that the rate of entry of the substrate into the system is given initially and remains time independent. As we only study the linear stability properties around the uniform steady state in this paper, however, we will not need to specify these conditions explicitly (see section 3).

In addition to the entry of the substrate by diffusion, equations 7 *a* and 7 *b* include a source term (σ_1 in equation 7 *a*) and a sink term ($\sigma_2\gamma$ in equation 7 *b*). Thus in the limit of uniform composition (infinitely fast diffusion) the equations reduce to a form which expresses that at every point of the system the substrate enters at a constant rate, produced, for example, by the cycle of reactions to which the system (*I*) belongs, while the product is being removed by a first-order reaction (7). In such a situation the influence of time delay effects due to transport phenomena on the periodic behavior (31) need not be considered.

3. DISSIPATIVE STRUCTURES IN SYSTEM 7

System 7 admits two homogeneous stationary states (α_{01}, γ_0) and (α_{02}, γ_0) where

$$\gamma_0 = \sigma_1/\sigma_2, \tag{8}$$

and

$$\alpha_0 = \frac{\{[D_0\epsilon/(\epsilon+1)]\Gamma^2 - \sigma_1[Lc + \Gamma^2/(\epsilon+1)]\} \pm \Gamma(\delta)^{1/2}}{\{\sigma_1[Lc^2 + \Gamma^2/(\epsilon+1)^2] - 2D_0\epsilon\Gamma^2/(\epsilon+1)^2\}}, \tag{9}$$

where

$$\Gamma = (1 + \sigma_1/\sigma_2),$$

$$\delta = \{2\sigma_1 L[D_0\epsilon/(\epsilon+1)][1/(\epsilon+1) - c] + [D_0\epsilon\Gamma/(\epsilon+1)]^2 - \sigma_1^2 L[1/(\epsilon+1) - c]^2\}. \tag{10}$$

Sign + in expression 9 is related to the root α_{01}.

[2] One verifies easily that for $\epsilon \to 0$ one recovers the expression for $\bar{R}$ previously derived by Monod et al. (28).

In order to study the stability of these states we investigate the response of system 7 to infinitesimal perturbations. As equations 7 *a* and 7 *b* become linear in the perturbations with time and space independent coefficients, they admit solutions of the form

$$\delta X = xe^{\omega t + ir/\lambda}. \tag{11}$$

Inserting this in the evolution equations around the homogeneous steady state (α_0, γ_0), we obtain the dispersion equation

$$\omega^2 + \omega[aC(A - B) + \sigma_2 a + (\mathfrak{D}_\alpha + \mathfrak{D}_\gamma)/\lambda^2]$$
$$+ [a^2\sigma_2 CA + aC(A\mathfrak{D}_\gamma/\lambda^2 - B\mathfrak{D}_\alpha/\lambda^2) + \sigma_2 a\mathfrak{D}_\alpha/\lambda^2 + \mathfrak{D}_\alpha\mathfrak{D}_\gamma/\lambda^4] = 0. \tag{12}$$

We have set

$$A = L(1 + \gamma_0)\{\alpha_0^2 c[2/(\epsilon + 1) - c] + 2\alpha_0/(\epsilon + 1) + 1\}$$
$$+ (1 + \gamma_0)^3[1 + \alpha_0/(\epsilon + 1)]^2,$$
$$B = 2\alpha_0 L[1 + \alpha_0/(\epsilon + 1)](1 + \alpha_0 c)^2,$$
$$C = 2[D_0\epsilon/(\epsilon + 1)](1 + \gamma_0)/\{L(1 + \alpha_0 c)^2 + (1 + \gamma_0)^2[1 + \alpha_0/(\epsilon + 1)]^2\}^2. \tag{13}$$

It should be pointed out that the parameter λ in equation 12 is not arbitrary but has to be consistent with the boundary conditions imposed on system 7.

If we neglect the effect of diffusion, the dispersion equation reduces to the form

$$\omega^2 + \omega[aC(A - B) + \sigma_2 a] + a^2\sigma_2 CA = 0. \tag{14}$$

The system has an unstable focus (32) when

$$C(A - B) + \sigma_2 < 0 \quad \text{and} \quad A > 0. \tag{15}$$

In the phase plane the system evolves towards a limit cycle (see Fig. 2 *a*). One can observe sustained oscillations in the concentrations of the product and the substrate as a function of time (see Fig. 2 *b*). The linear period of these oscillations is given by the expression

$$T = 2\pi/aC[A(B - A)]^{1/2}. \tag{16}$$

Let us now consider the inhomogeneous case. If we write

$$\theta = \mathfrak{D}_\gamma/\mathfrak{D}_\alpha, \tag{17}$$

the condition for the occurrence of a spatial dissipative structure takes the form

$$\theta\mathfrak{D}_\alpha^2/\lambda^4 + a(\mathfrak{D}_\alpha/\lambda^2)[C(\theta A - B) + \sigma_2] + a^2\sigma_2 CA < 0. \tag{18}$$

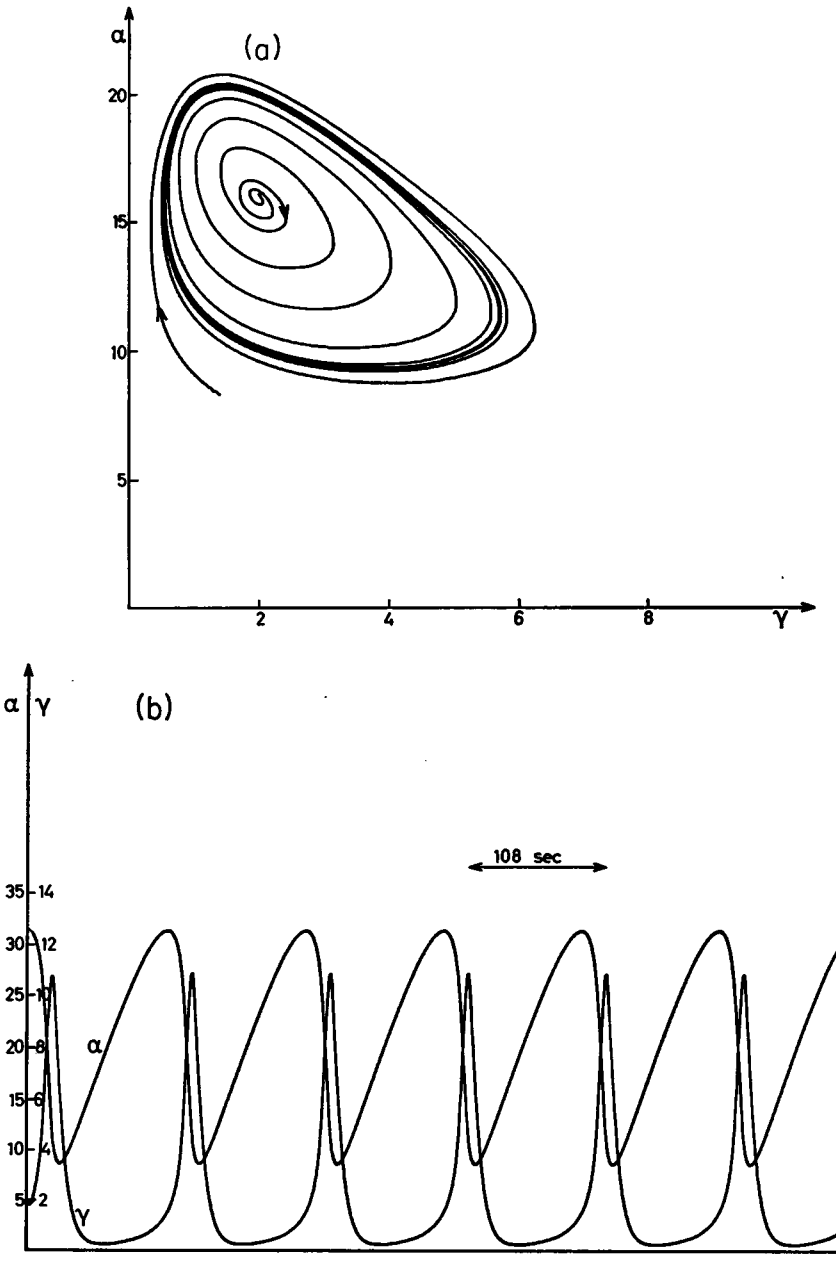

FIGURE 2 Transition of system 7 to a limit cycle (Fig. 2 *a*) in the homogeneous case when the stationary state is an unstable focus; the limit cycle can be reached from the outside. The curve has been obtained at the analogue computer for the following set of values: $\sigma_1 = 2 \cdot 10^{-6}$, $\sigma_2 = 10^{-6}$, $L = 7.5 \cdot 10^{6}$, $c = 10^{-2}$, $D_0 = 5 \cdot 10^{-4}$, $\epsilon = 10^{-1}$, $a = 10^{7}$, $K_{A_3(R)} = K_{A_2(R)} = 5 \cdot 10^{-2}$ (see the Appendix). The stationary state is $\alpha_0 = 16$, $\gamma_0 = 2$. For this case T = 145 sec. Fig. 2 *b* shows the time display of the process for $\sigma_1 = 4 \cdot 10^{-6}$, $\sigma_2 = 2 \cdot 10^{-6}$. Then $\alpha_0 = 24.5$, $\gamma_0 = 2$, and $T = 108$ sec. (For $\sigma_1 = 3 \cdot 10^{-6}$, $\sigma_2 = 1.5 \cdot 10^{-6}$, $T = 120$ sec.)

We see immediately that for positive values of A the condition for homogeneous instability 15 is always verified before condition 18 if we restrict ourselves to the case $\theta \geq 1$, which seems to be justified by the chemical nature of α and γ in the glycolytic example (see section 5). As the numerical study of the model shows that the only steady state physically acceptable is the state (α_{02}, γ_0) and that the quantity A evaluated around it is always positive, a homogeneous instability of the stationary state will occur before an instability with respect to diffusion. The numerical study also shows that this remains true for values of θ down to 0.1. Thus the previous conclusion extends to all cases for which the substrate and the product are molecules which do not differ greatly from one another. Therefore we restrict ourselves hereafter to the problem of temporal structures only.

4. NUMERICAL STUDY

Since we could not obtain an explicit instability condition for the homogeneous case as a function of a critical value of one of the parameters, we have studied numerically stability of the allosteric model (I) as a function of the most important parameters involved: σ_1, ϵ (related, respectively, to the rate of entrance of the substrate and the irreversible decomposition of the enzymatic complexes), c, and L.

In this way a set of stability diagrams $L - c$, $L - \epsilon$, and $L - \sigma_1$ has been constructed, some of which are shown in Figs. 3–5. The choice for the mean values of the different constants is justified in the Appendix. In order to establish those diagrams, expression 15 was evaluated on a digital computer around the steady states (α_{01}, γ_0) and (α_{02}, γ_0).

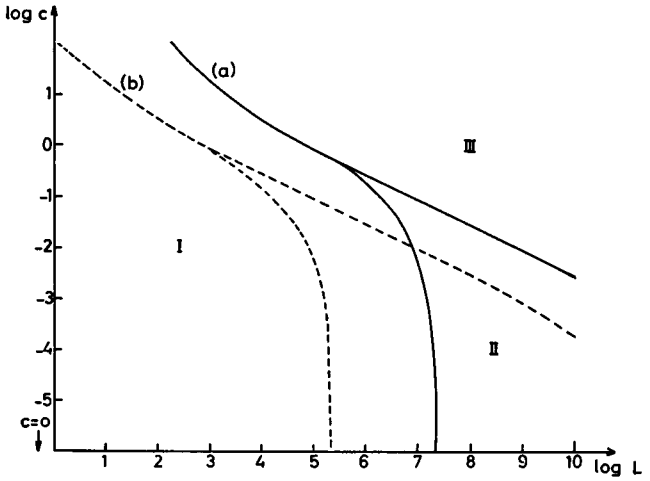

FIGURE 3 Stability diagrams $L - c$. Domains I and III lie, respectively, to the left and to the right of the curves while domain II is the enclosed region. The stationary state remains stable in region I and becomes an unstable focus within region II. Region III does not contain any physically acceptable steady state. Curve (*a*) has been established for $\epsilon = 10^{-3}$ and curve (*b*) for $\epsilon = 10^{-1}$. Other constants are: $\sigma_1 = 10^{-8}$, $\sigma_2 = 5 \cdot 10^{-9}$, $D_0 = 5 \cdot 10^{-4}$.

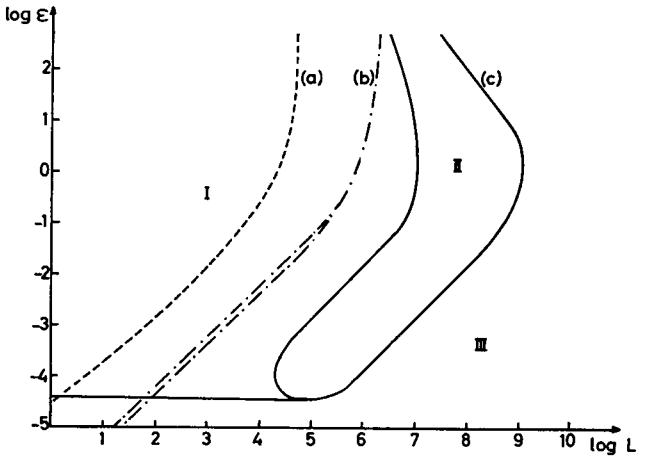

FIGURE 4 Stability diagrams $L - \epsilon$. Curve (*a*) has been established for $c = 10^{-2}$, curve (*b*) for $c = 2$ and curve (*c*) for $c = 5$. Other constants are: $\sigma_1 = 10^{-6}$, $\sigma_2 = 5 \cdot 10^{-9}$, $D_0 = 5 \cdot 10^{-4}$. For curve (*b*), $\sigma_1 = 10^{-9}$, $\sigma_2 = 5 \cdot 10^{-10}$.

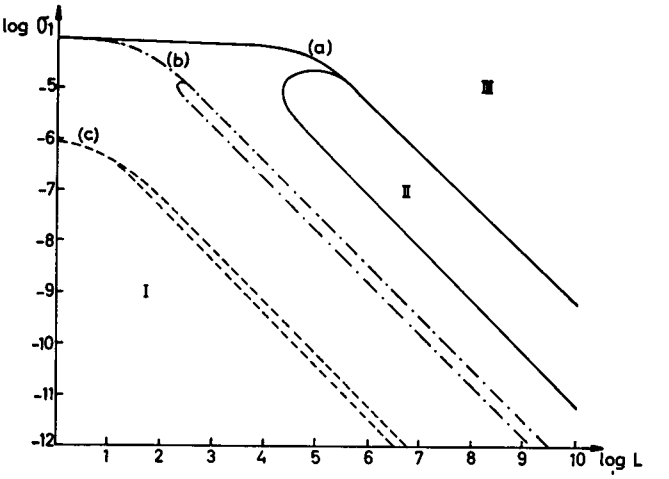

FIGURE 5 Stability diagrams $L - \sigma_1$. Curve (*a*): $c = 10^{-2}$, $\epsilon = 10^{-1}$. Curve (*b*): $c = 0.5$, $\epsilon = 10^{-1}$. Curve (*c*): $c = 1.2$, $\epsilon = 10^{-3}$. Other constants are: $\sigma_2 = \sigma_1/2$, $D_0 = 5 \cdot 10^{-4}$.

The system remains stable within domain I. Limit cycles can be observed in domain II while region III does not contain any physically acceptable steady state.

A survey of the diagrams enables us to deduce the following trends:

(*a*) Instabilities will occur preferentially for large values of the allosteric constant ($L > 10^4$) (see Figs. 3 *a*, 3 *b*, 4 *c*, 5 *a*, 5 *b*), this order of magnitude being in agreement with experimental observations concerning the values of L for allosteric enzymes (see e.g., reference 29).

(*b*) The range of instability increases with the degree of activation by the sub-

strate ($0 \leq c < 1$). The system can still become unstable in presence of substrate inhibition (e.g., $c = 1.2, 2$) but the domain of oscillations is then reduced as compared with the previous case (see diagrams $L - c$ and diagrams $L - \sigma_1$ for different values of c).

By increasing inhibition, oscillations disappear and the diagram divides into two regions. In one of them the system remains stable while in the other there is no physically acceptable steady state. In physical terms this means that the substrate accumulates in such a way that the enzyme cannot follow any longer (see diagram $L - \epsilon$ for $c = 5$).

This is likely to happen when σ_1, c as well as L are too large or when ϵ becomes too small. Indeed, the substrate can accumulate when the rate of its entrance exceeds the possibilities of its consumption by the system, which depend on D_0, ϵ. The same happens when the inactive form of the enzyme increases at the expense of the active one for large values of c and L.

(*c*) The values of σ_1 for which instabilities occur are in an acceptable physiological range (see the Appendix).

(*d*) The same remark holds for ϵ. Moreover in presence of substrate activation, instabilities can occur for a wide range of values of ϵ once the cooperativity exceeds a certain level.

(*e*) Another prediction resulting from the numerical study concerns the range of oscillations of the fraction $\overline{R}$. It has been found that there exists a domain of oscillations in which the enzyme is largely under the form T. For low values of ϵ, the enzyme can also oscillate under the active form.

5. DISCUSSION OF THE APPLICATION TO GLYCOLYTIC OSCILLATIONS

The self-oscillating behavior of some intermediates of the yeast glycolytic system has been studied extensively. The results have first been obtained from experiments on yeast cells (33–35) and later on muscle and yeast extracts (36–38). An account of the present state of the question can be found in the papers of Hess et al. (9, 39).

It is known (4, 39) that the glycolytic enzyme chiefly responsible for these periodicities is phosphofructokinase because of the peculiar way in which it is regulated. In the yeast this allosteric enzyme is indeed activated by its two products, adenosine diphosphate (ADP), via adenosine monophosphate (AMP), and fructose-diphosphate (FDP), while it is inhibited by an excess of adenosine triphosphate (ATP), the first of its substrates, and activated by the second, fructose-6-phosphate (F-6-P) (35, 39). Experimental observations show that the enzyme is regulated under physiological conditions by the couple ATP/ADP (9, 39).

In a recent paper (40) Betz and Sel'kov confirm these results but show that in the presence of all the effectors in concentrations similar to those found in the oscillating cell-free extract, this regulatory scheme is different. Under those conditions,

ATP has no influence on the activity of phosphofructokinase while AMP and F-6-P are effective activators of the enzyme. The effect of AMP can be linked to that of ADP because of the activity of adenylate kinase; moreover both chemicals are always in phase during glycolytic oscillations (39, 40).

Product activation is in fact the essential prerequisite for sustained oscillations. It is on this ground that Higgins (4–6) and Sel'kov (7, 8) have presented global models for the phosphofructokinase reaction. The analytical expressions derived by Sel'kov give a qualitative and, in some regards, quantitative account of self-oscillations in glycolysis.

The allosteric model (I) can be applied to phosphofructokinase since the product ADP is a positive effector of the enzyme. Then substrate α denotes ATP while γ denotes ADP. Experimental studies have shown that in some organisms, like *Escherichia coli* (29), the enzyme could be a tetramer. One can expect, however, that the behavior as described by a dimer remains qualitatively the same.

The evolution of the system has been followed at the analogue computer for various situations. Sustained oscillations obtained with the model (Fig. 2 *b*) agree with experimental observations (see e.g., references 9, 39). The period of oscillations is of the order of some minutes while the order of magnitude of the concentrations A_3, A_2 is 10^{-4}–10^{-3} M if we take $K_{A_3(R)} = K_{A_2(R)} = 5 \cdot 10^{-5}$ M (see the Appendix and reference 29). The ratio A_3/A_2 (= ATP/ADP) can vary within the whole range of experimental data but is usually close to five at the stationary state (38, 40). Moreover, when the system has just entered the region of instability, the period of oscillations corresponds to that given by relation 16.

In order to verify on the model the experiments of Hess et al. (39) we followed the behavior for different values of σ_1. Hess has shown that the glycolytic system remains stable as long as the rate of supply of the substrate is less than 20 mM/hr, which corresponds to $\sigma_1 = 10^{-8}$ mM (see the Appendix). Then by increasing this rate oscillations appear. Further increases promote a change in the nature of oscillations and a shortening of the period. When the rate exceeds 160 mM/hr the system jumps to a higher stationary state.

The trends of this evolution are depicted by diagram $L - \sigma_1$ (Fig. 5 *a*), where the accumulation of the substrate in domain III can stand for the higher steady state. When σ_2 is held constant, it has been shown that as σ_1 increases the amplitude of the oscillations passes through a maximum while the period decreases. This is in agreement with experimental facts (39).

An observation which can possibly bear a physiological significance concerns the mean values of α and γ on a period T. By adding equations 7 *a* and 7 *b* and neglecting diffusion terms we obtain successively

$$\mathrm{d}(\alpha + \gamma)/\mathrm{d}t = \sigma_1 - \sigma_2\gamma, \tag{19}$$

$$(1/T)\int_0^T [\mathrm{d}(\alpha + \gamma)/\mathrm{d}t]\mathrm{d}t = 0 = \sigma_1 - (\sigma_2/T)\int_0^T \gamma \, \mathrm{d}t, \tag{20}$$

hence

$$\langle \gamma \rangle_T = \sigma_1/\sigma_2 = \gamma_0 . \tag{21}$$

So the mean value of γ during a period, denoted here by $\langle \gamma \rangle_T$, is equal to the steady-state value. This is not the case for α. Indeed we see on the graphs obtained at the analogue computer that the mean value $\langle \alpha \rangle_T$ can be less than α_0. Self-oscillations can perhaps contribute to decrease the mean concentration of the substrate with respect to that of the product when the supply of the former becomes too high.

Another prediction resulting from this study is that sustained oscillations seem to be favored by substrate activation. This fact is in agreement with the experimental observations of Betz et al. (40) if we consider the total effect of both substrates, ATP and F-6-P. Clearly, such an effect can only be described unambiguously in an allosteric model in which the role of the substrate is entirely determined by the nonexclusive binding coefficient c.

The problem of spatial organization has not been considered since, as we have discussed it in a previous section, instability with respect to homogeneous perturbations occurs before that with respect to diffusion. It is possible, however, that the system moves first toward a temporal organization; the limit cycle so formed could become subsequently unstable with respect to diffusion, as it seems to happen experimentally in the Zhabotinsky reaction (22). The system could then evolve toward a new dissipative structure which would depend on space. This point is currently under investigation. Preliminary studies[3] show that model systems undergoing nonlinear kinetics may evolve, beyond instability, to a spatiotemporal organization corresponding to a propagating concentration wave.

APPENDIX

Numerical Values of the Parameters Appearing in the Model

Kinetic studies have shown that phosphofructokinase from *E. coli* can be described in terms of a perfect K-system, while our model represents a mixed K-V-system in Monod's terminology (28, 29). In applying model I to the description of oscillations which are observed in the yeast glycolytic system, we have chosen the nearest set of numerical values available, which is that concerning the phosphofructokinase of *E. coli*.

The allosteric constant L was thus given a value around $4 \cdot 10^6$ which was found experimentally for this system by Blangy et al. (29). The same source provides data for the equilibrium dissociation constants of A_3 and A_2. We have taken on this ground

$$K_{A_3(R)} \approx K_{A_2(R)} \approx 5 \cdot 10^{-2} \text{ mM (reference 29).}$$

Constant $a = a_1 = a_2$ was chosen equal to 10^7/mM-sec in order to give the period T an acceptable range (see relation 16). Hence $d = d_1 = d_2 = 5 \cdot 10^5$/sec.

[3] Herschkowitz-Kaufman, M., and G. Nicolis. 1972. *J. Chem. Phys.* **56**:1890.

Relations 5 together with the experimental data cited by Hess et al. (39) yield $\sigma_1 \approx 10^{-8}$ mM. As we have

$$\gamma_0 = \sigma_1/\sigma_2 = A_2^0/K_{A_2(R)} \approx 10^{-1} \text{ mM}/5 \cdot 10^{-2} \text{ mM} = 2,$$

(38, 40) we took σ_2 equal to $5 \cdot 10^{-9}$ mM, which value gives for the rate of sink of ADP the acceptable value

$$k_s A_2 \approx 5 \cdot 10^{-3} \text{ mM/sec.}$$

Constant ϵ was given the value 10^{-3} so that kR_{10}, e.g. is of the order of $5 \cdot 10^{-3}$ mM/sec, if we take $R_{10} \approx 10^{-5}$ mM.

The nonexclusive binding coefficient c related to A_3 was taken equal to 10^{-2}, in order to take into account the total activating effect of the two substrates in the glycolytic example (40). Eventually the total concentration in enzyme D_0 was taken equal to $5 \cdot 10^{-4}$ mM (39).

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