Biophysical Chemistry 4 (1976) 249–251

FREQUENCY SENSITIVE BIOCHEMICAL REACTIONS

L.K. KACZMAREK
Service de Chimie Physique 2, Faculté des Sciences, Université Libre de Bruxelles, Brussels, Belgium

Received 13 January 1976

1. Introduction

A variety of living cells, particularly those involved in certain sensory processes [1–3] have evolved so as to respond to weak mechanical or electrical stimulation at frequencies in the range 0.5–1000 Hz. The purpose of this communication is to demonstrate that a simple biochemical reaction may enjoy a sensitivity to perturbations at specific frequencies in this range.

2. The model

The prerequisite for this type of behaviour is that the reaction scheme should possess multiple steady states with at least one oscillating state. Dynamical patterns of this form have been shown to exist in a number of chemical and biochemical systems [4,5]. The model reaction chosen here is an open first order system far from equilibrium and incorporating a cooperative step,

$$A \rightleftharpoons X \leftrightarrows Y \rightarrow B, \tag{1}$$

where the ringed arrow denotes that molecules of the species Y may interact with each other in such a way as to catalyse the production of Y from X. A detailed model of membrane transport phenomena, based on this principle in which membrane bound complexes interact through a conformational coupling, has been developed by Blumenthal, Changeux and Lefever [6]. The rate of this process may be approximated by representing the free energy of activation as a constant plus a term linearly dependent on the concentration of Y,

$$\Delta F^{\ddagger} = \epsilon - \eta Y, \tag{2}$$

where η is a constant related to the strength of cooperative interaction. The rate constant for the conversion of X to Y therefore becomes $\beta e^{\eta Y}$. Taking the concentration of A to remain constant gives the following kinetic equations for the time evolution of the concentrations of X and Y.

$$dX/dt = k_1 A - k_2 X - \beta e^{\eta Y} X, \tag{3}$$

$$dY/dt = \beta e^{\eta Y} X - k_3 Y. \tag{4}$$

The concentration of Y at steady state (Y_0) is plotted as a function of β in fig. 1, for a set of parameters at which multiple steady states may exist. The stability of these states was obtained by normal mode analysis and unstable states are depicted by a broken line. Computer integration of eqs. (3) and (4) demonstrates that the "upper" unstable steady state in fig. 1 is associated with a stable limit cycle over the range indicated by asterisks.

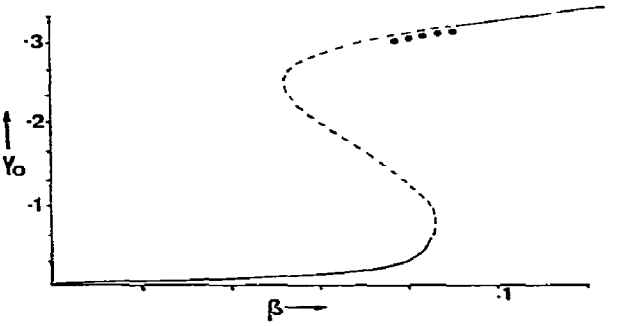

Fig. 1. A plot of the steady state values of Y for eqs. (3) and (4) as a function of β. The parameters are $k_1 A = 1$, $k_2 = 1$, $k_3 = 3$, $\eta = 16$. Stable steady states are represented by a solid line whereas unstable steady states appear on the broken line. The region for which stable limit cycles appear around an unstable focus is marked by asterisks on the upper branch of the curve.

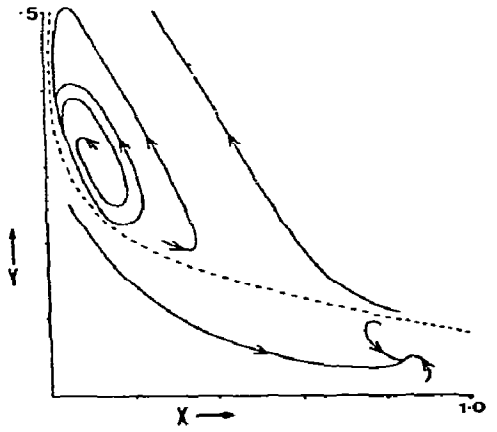

Fig. 2. A representation of the dynamical behaviour of the concentrations X and Y in the phase plane for the parameters $k_1A = 1, k_2 = 1, k_3 = 3, \eta = 16, \beta = 0.077$. The separatrix is depicted by a broken line. Arrows mark the direction of the trajectories towards either the upper stable limit cycle or the lower steady state.

The principal dynamical features in this range include (i) the unstable focus surrounded by a stable limit cycle, (ii) a saddle point, and (iii) a stable focus. The behaviour of the concentrations of X and Y is illustrated in the phase plane diagram of fig. 2. Any set of values for X and Y corresponding to a point above the separatrix of the saddle point, drawn as a broken line, will evolve to the limit cycle at the top left of the diagram. A set of values corresponding to a point below the separatrix will result in stable stationary concentrations of X and Y. It is clear that any external perturbation or internal fluctuation that can momentarily displace the concentrations of X and Y across the separatrix will result in a transition from one stable state to the other. In particular, when the system is in the limit cycle state and a perturbation is applied at some fixed frequency (ω), the likelihood of a transition depends both on the amplitude of the perturbation and on its frequency and phase relative to the limit cycle.

3. Frequency sensitivity

Two physically meaningful ways exist for introducing a weak external perturbation into a chemical reaction scheme. In sensory cells a single reaction step is maximally sensitive to perturbations of the appropriate modality. For a sinusoidal stimulus we may introduce a time dependent rate constant into eqs. (3) and (4). For example,

$$k_1 = k_1' [1 + \mathcal{A} \sin(\omega t + \phi)], \quad (5)$$

or

$$\beta = \beta' [1 + \mathcal{A}' \sin(\omega t + \phi)]. \quad (6)$$

Alternatively, the perturbation may take the form of an external "noise" and may be introduced into eqs. (3) and (4) in a manner analogous to the Langevin force method for the introduction of stochastic noise

$$dX/dt = k_1 A - k_2 X - \beta e^{\eta Y} X + \mathcal{A}'' \sin(\omega t + \phi), \quad (7)$$

$$dY/dt = \beta e^{\eta Y} X - k_3 Y + \mathcal{A}'' \sin(\omega t + \phi). \quad (8)$$

Computer simulations of the nonautonomous systems given by eqs. (5)–(8) were carried out with initial values for X and Y on the limit cycle. A typical result is shown in fig. 3 in which the time taken from the onset of the stimulus to the time when the trajectory attains the "lower" stable steady state (Δt), is plotted against the logarithm of the stimulating frequency, ω. In this case the perturbation was introduced into rate constant k_1 according to eq. (5) with $\mathcal{A} = 0.015$. The minimum

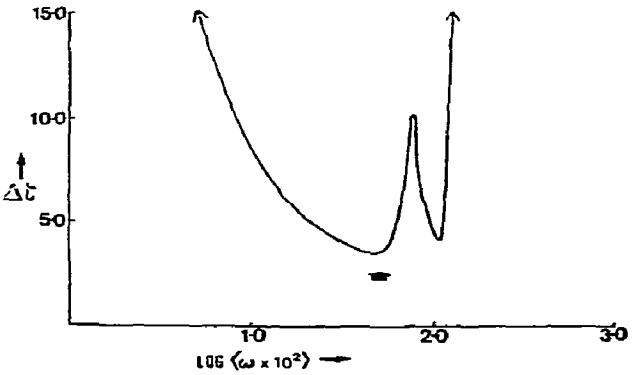

Fig. 3. A plot of the frequency sensitivity of eqs. (3) and (4) with the same parameters as for fig. 2 except that k_1 is perturbed according to eq. (5) ($\mathcal{A} = 0.015$). The initial values for X and Y are an arbitrary point on the limit cycle and the ordinate Δt represents the time taken for the trajectory to reach the lower steady state. The abscissa represents the logarithm of the stimulating frequency ω in eq. (5) and the natural frequency of the unperturbed limit cycle ω_0 is marked by an arrow.

value of Δt, marked by an arrow, corresponds to the frequency of the limit cycle ($\omega_0 = 0.5$). The second minimum in figure 3 occurs at the first harmonic of the limit cycle. Simulations of systems given by eqs. (6)–(8) also gave qualitatively similar results; the exact form of the Δt vs log ω curve depending on both the amplitude ($\mathcal{A}$) and the phase (ϕ) of the stimulus relative to that of the limit cycle. General features, however, included one or more minima and a high frequency "cut-off".

4. Discussion

The possibility of resonance phenomena occurring in chemical reactions has been suggested by the analysis of a linearized system [7]. Close to a point of marginal stability, very weak perturbation of the rate constants can produce marked effects on the concentrations of the reactants. The present analysis shows that sensitivity to specific frequencies may also result from the perturbation of stable limit cycles. This reinforces the idea that weak stimulation may provide meaningful information about the dynamics of nonlinear reactions [7,8].

Examples of biological processes in which frequency sensitive reactions may be important include the sensing of electric fields mediated by receptor cells in certain species of fish [3]. The individual hair cells of the cochlea may also possess a frequency sensing mechanism for those low frequencies at which the basilar membrane is almost uniformly activated [2]. A number of lines of evidence suggest that the binding of calcium ions at neuronal membranes and nerve endings may follow the general scheme (1), incorporating a cooperative step [8–10]. A frequency sensitive component of calcium binding has been detected in chick brain for perturbations with VHF fields modulated at frequencies between 11 and 20 Hz [11]. The construction of more concrete models may expedite the study of these effects.

Acknowledgement

I would like to thank Professors I. Prigogine and G. Nicolis, and Dr. R. Lefever for many stimulating discussions and I am also indebted to the Royal Society for a European Science Exchange Programme Fellowship.

References

[1] G. von Bekesy, Science 123 (1956) 779.
[2] G.A. Miller and W.G. Taylor, J. Acoust. Soc. Amer. 20 (1948) 171.
[3] T.H. Bullock and S. Chichibu, Proc. Nat. Acad. Sci. 54 (1965) 422.
[4] D.S. Cohen, in: Lecture Notes in Mathematics, Vol. 322 (Springer, Berlin, 1973) pp. 16–39.
[5] Y.Y. Sel'kov, Biofizika 15 (1970) 1065.
[6] R. Blumenthal, J.-P. Changeux and R. Lefever, J. Membrane Biol. 2 (1970) 351.
[7] P.J. Ortoleva and J. Ross, J. Chem. Phys. 56 (1972) 293.
[8] W.R. Adey, in: Functional Linkage in Biomolecular Systems, eds. F.O. Schmitt, D.M. Schneider and D.M. Crothers (Raven Press, New York, 1975) p. 325.
[9] F.A. Dodge and R. Rahamimoff, J. Physiol. 193 (1967) 419.
[10] D.E. Downie, J. Theor. Biol. 28 (1970) 297.
[11] S.M. Bawin, L.K. Kaczmarek and W.R. Adey, Ann. N.Y. Acad. Sci. 247 (1975) 74.