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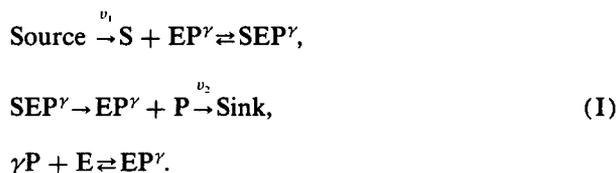
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Thermodynamic analysis of the reversible Selkov model (a simple kinetic model describing glycolytic oscillations) has been done by an entropy production technique of Prigogine and it is shown that only the autocatalytic step can destabilize the steady state in this model. It is derived that at thermodynamic equilibrium, the product $\delta S\, \delta P$ is always a positive quantity which appears to be a Chatelier-like principle for local concentration fluctuation applicable to the autocatalytic step $S \rightleftharpoons P$ of this model.

INTRODUCTION

Oscillations in biochemical systems has become an area of active interest nowadays. The phosphofructokinase reaction is considered as being a possible source of self-oscillation. Selkov[1] proposed a simple kinetic model (I) of enzyme catalysis with product activation of the enzyme, which exhibits limit cycle oscillations. Here, the substrate S (ATP) supplied by a certain source at a constant rate v_1 is irreversibly converted to the product P (ADP). The product P (ADP) is removed by an irreversible sink at the rate v_2. The free enzyme, E (phosphofructokinase) is inactive by itself but becomes active combining with γ product molecules to form the complex EP^γ,

$$\text{Source} \xrightarrow{v_1} S + EP^\gamma \rightleftharpoons SEP^\gamma,$$

$$SEP^\gamma \rightarrow EP^\gamma + P \xrightarrow{v_2} \text{Sink}, \tag{I}$$

$$\gamma P + E \rightleftharpoons EP^\gamma.$$

In 1981, Richter *et al.*[2] proposed the reversible Selkov model (II) given by the following reversible steps:

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S, \tag{1}$$

$$S + 2P \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} 3P, \tag{2}$$

$$P \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} B, \tag{3}$$

where A and B are source and sink concentrations; the substrate S and product P constitute the autocatalytic internal part of the system. The entropy production in such glycolytic oscillatory pathway is related to the issue of energy transduction: the lower the dissipation, the lower the free energy change at constant temperature and pressure, and the higher the energy transduction from reactants to products.

In this paper we have described a linear thermodynamic analysis of this reversible Selkov model by an entropy production technique of Prigogine[3] to identify the steps which favor destabilization. Also, an effort has been made to find

out the mode of local concentration fluctuation of the substrate S and the product P at thermodynamic equilibrium. For our analysis, we assume that the concentrations of A and B are maintained at a constant value by osmotic flow through a semipermeable membrane through which the substrate S and the product P species cannot pass. We further assume that the system is within the range of validity of Onsager reciprocity relations for thermodynamic analysis and is maintained at a constant temperature.

THERMODYNAMIC STABILITY THEORY

That the entropy is a stability function is found in Boltzmann's H Theorem, actually preceded Liapunov's work. Its occurrence in local equilibrium thermodynamics was pointed out by Glansdorf and Prigogine.[3] Their ideas concerned the second differential of local equilibrium entropy $\delta^2 S$. Expanding entropy (S) around equilibrium (S^e) by a Taylor series, one gets

$$S(n_1, n_2, ..., n_k) = S(n_1^e, n_2^e, ..., n_k^e) + \sum_i (\delta S/\delta n_i)^e \alpha_i$$

$$+ (1/2) \sum_{i,j} (\delta^2 S/\delta n_i \delta n_j)^e \alpha_i \alpha_j + \cdots$$

$$= S^e + \delta S + (1/2)\delta^2 S + \cdots \tag{4}$$

here n_i ($i = 1 \rightarrow k$) is an extensive variable; superscript e indicates equilibrium value and $\alpha_i = (n_i - n_i^e)$. Entropy (S) becomes maximum at equilibrium (i.e., $S \leqslant S^e$ for a maximum). Therefore,

$$\delta S = 0 \quad \text{and} \quad \delta^2 S \leqslant 0. \tag{5}$$

From second law of thermodynamics, we have $dS/dt \geqslant 0$. This expression can be written close to equilibrium using Eqs. (4) and (5) as

$$(d\delta^2 S/dt) \geqslant 0. \tag{6}$$

Equation (6) indicates that $\delta^2 S$ is negative and vanishes at equilibrium. Therefore, close to equilibrium $(d\delta^2 S/dt) \geqslant 0$ and $\delta^2 S$ may serve as a Liapunov function. The inequality in Eq. (6) is the stability criterion for steady states close to thermodynamic equilibrium and equality for the thermodynamic equilibrium itself; $(d\delta^2 S/dt)$ is termed as excess entropy production (e.p.).

Now, we need to express stability criterion [Eq. (6)] in a form which includes reaction rates and affinities into the

stability criterion.[3,5,6] Let, N_i equal the number of molecules engaged in reactions ρ with rates J_ρ and stoichiometric coefficients $\nu_{i\rho}$. The rate equations are given by

$$\frac{dN_i}{dt} = \sum_\rho \nu_{i\rho} J_\rho. \tag{7}$$

Let μ_i be the chemical potential of molecular species i and define chemical affinities A_ρ by

$$A\rho = - \sum_i \nu_{i\rho} \mu_i. \tag{8}$$

Let us use Gibbs relation for the total differential of entropy S, as a function of the independent variables E (internal energy), V (volume), and N_i (number of molecules of type i). Therefore, we have[3,6]

$$T\delta S = \delta E + P\delta V - \sum_i \mu_i \delta N_i \tag{9}$$

and

$$\delta^2 S = \delta T^{-1} \delta E + \delta(P/T)\delta V - \sum_i \delta(\mu_i/T)\delta N_i. \tag{10}$$

Equation (10) at constant temperature (T) and pressure (P) takes the form

$$\delta^2 S = - (1/T) \sum_{i,j} (\delta\mu_i/\delta N_j)\delta N_i \delta N_j. \tag{11}$$

Substituting Eqs. (7) and (8), one gets from Eq. (11),

$$(d\delta^2 S/dt) = - (1/T)\sum_{i,j} (d/dt)[(\delta\mu_i/\delta N_j)\delta N_i \delta N_j] \tag{12a}$$

$$= - (1/T) \sum_{i,j} 2(\delta\mu_i/\delta N_j)\delta N_j (d\delta N_i/dt) \tag{12b}$$

$$= - (2/T) \sum_{i,j} \delta\mu_i (d\delta N_i/dt) \tag{12c}$$

$$= - (2/T) \sum_{i,\rho} \delta\mu_i \nu_{i\rho} \delta J_\rho \tag{12d}$$

$$= (2/T) \sum_\rho \delta A_\rho \delta J_\rho. \tag{12e}$$

Equation (12b) is obtained by considering the symmetry of $\delta\mu_i/\delta N_j$ with respect to i and j, and $d(\delta\mu_i/\delta N_j)/dt = 0$; Eq. (12c) by using $\delta\mu_i = \Sigma_j (\delta\mu_i/\delta N_j)\delta N_j$ and Eqs. (12d) and (12e) by using Eqs. (7) and (8), respectively. Therefore, the stability criterion can be expressed using Eqs. (6) and (12e) as

$$(1/2)(d\delta^2 S/dt) = (1/T) \sum_\rho \delta A_\rho \delta J_\rho \geqslant 0. \tag{13}$$

STEADY STATES

The following differential equations represent the kinetics of our model:

$$dS/dt = k_1 A - k_{-1} S - k_2 S P^2 + k_{-2} P^3, \tag{14a}$$

$$dP/dt = k_2 S P^2 - k_{-2} P^3 - k_3 P + k_{-3} B, \tag{14b}$$

where $k_{\pm i}$ is the rate constant of the step $\pm i$. At steady state, $dS/dt = dP/dt = 0$. Therefore, from Eqs. (14a) and (14b) one gets

$$S = (k_1 A + k_{-2} P^3)/(k_{-1} + k_2 P^2)$$
$$= (k_{-2} P^3 + k_3 P - k_{-3} B)/(k_2 P^2). \tag{15}$$

From Eq. (15) one gets after simplification,

$$p^3 + \beta_2 p^2 + \beta_1 p + \beta_0 = 0, \tag{16}$$

where

$$\beta_2 = - (k_1 k_2 A + k_2 k_{-3} B)/(k_{-1} k_{-2} + k_2 k_3), \tag{16a}$$

$$\beta_1 = (k_{-1} k_3)/(k_{-1} k_{-2} + k_2 k_3), \tag{16b}$$

and

$$\beta_0 = - (k_{-1} k_{-3} B)/(k_{-1} k_{-2} + k_2 k_3). \tag{16c}$$

One can solve the cubic equation (16) by a trigonometric substitution.[13] Let $p = P + (\beta_2/3)$, $\rho_1 = \beta_1 - 3(\beta_2/3)^2$, and $\rho_0 = \beta_0 - \beta_1(\beta_2/3) + 2(\beta_2/3)^3$. Then Eqs. (16) take the form

$$[p - (\beta_2/3)]^3 + \beta_2 [p - (\beta_2/3)]^2$$
$$+ \beta_1 [p - (\beta_2/3)] + \beta_0 = 0$$

or

$$p^3 + \rho_1 p + \rho_0 = 0. \tag{17}$$

Suppose $\rho_1\rho_0 \neq 0$, and put $p = m \cos\theta$ in Eq. (17). One therefore gets

$$m^3 \cos^3\theta + \rho_1 m \cos\theta + \rho_0 = 0. \tag{18}$$

Comparing Eq. (18) with the trigonometric identity

$$4 \cos^3\theta - 3 \cos\theta - \cos 3\theta = 0. \tag{19}$$

One gets

$$m^3/4 = \rho_1 m/ - 3 = \rho_0/ - \cos 3\theta. \tag{20}$$

Therefore,

$$m = 2[(-\rho_1/3)]^{1/2} \tag{21}$$

and

$$\cos 3\theta = 3\rho_0/\rho_1 m = \cos 3\alpha. \tag{22}$$

From Eqs. (21) and (22) we have

$$\theta = \alpha = (1/3)\cos^{-1}(3\rho_0/\rho_1 m), \tag{23a}$$

$$\theta_2 = (2\pi/3) + \theta, \tag{23b}$$

$$\theta_3 = (4\pi/3) + \theta. \tag{23c}$$

Therefore, the three roots of Eqs. (16) are explicitly

$$P_1 = p_1 - \beta_2/3 = [2(-\rho_1/3)^{1/2}]\cos\theta - \beta_2/3, \tag{24a}$$

$$P_2 = p_2 - \beta_2/3 = [2(-\rho_1/3)^{1/2}]\cos[\theta + (2/3)\pi]$$
$$- \beta_2/3, \tag{24b}$$

$$P_3 = p_3 - \beta_2/3 = [2(-\rho_1/3)^{1/2}]\cos[\theta + (4/3)\pi]$$
$$- \beta_2/3. \tag{24c}$$

Once the steady state solution of P is known, one can get the steady state solution of S from Eq. (15).

Equilibrium condition: The velocities (J_i) of the three steps ($i = 1,2,3$) in the model system are given by

$$J_1 = k_1 A - k_{-1} S, \tag{25a}$$

$$J_2 = k_2 SP^2 - k_{-2} P^3, \tag{25b}$$

$$J_3 = k_3 P - k_{-3} B. \tag{25c}$$

The affinities (A_i) of the reactions are given[3-6] by the relation

$$A_i = RT \log(K_i/Q), \tag{26}$$

where K_i is the equilibrium constant for the ith reaction and $Q = [\text{product}]/[\text{reactant}]$. Therefore,

$$A_1 = RT \log(K_1 A/S), \tag{27a}$$

$$A_2 = RT \log(K_2 SP^2/P^3), \tag{27b}$$

$$A_3 = RT \log(K_3 P/B). \tag{27c}$$

At thermodynamic equilibrium $A_i = 0$, therefore we have

$$K_1 = k_1/k_{-1} = S_0/A, \tag{28a}$$

$$K_2 = k_2/k_{-2} = P_0/S_0, \tag{28b}$$

$$K_3 = k_3/k_{-3} = B/P_0. \tag{28c}$$

Therefore, the equilibrium condition is given by

$$S_0 = k_1 A/k_{-1}, \quad P_0 = k_1 k_2 A/k_{-1} k_{-2},$$

and

$$k_1 k_2 k_3 A = k_{-1} k_{-2} k_{-3} B, \tag{29}$$

where S_0, P_0 are equilibrium concentrations of the respective species.

DISCUSSION

From Eqs. (25) we have

$$\delta J_1 = k_1 \delta A - k_{-1} \delta S = - k_{-1} \delta S,$$

$$\delta J_2 = (2k_2 SP - 3k_{-2} P^2) \delta P + k_2 P^2 \delta S, \tag{30a}$$

$$\delta J_3 = k_3 \delta P - k_{-3} \delta B = k_3 \delta P.$$

Also from Eqs. (27), we have

$$\delta A_1 = RT \delta(\log K_1 A/S) = - RT \delta S/S,$$

$$\delta A_2 = RT \delta(\log K_2 S/P) = RT(\delta S/S - \delta P/P),$$

$$\delta A_3 = RT \delta(\log k_3 P/B) = RT \delta P/P. \tag{30b}$$

Substituting Eqs. (29) and (30) in Eq. (13), one gets

$$(1/2)(d\delta^2 S/dt) = (1/T) \sum_{i=1}^{3} \delta J_i \delta A_i$$

$$= (I/T)[(-k_{-1} \delta S)(-RT \delta S/S)$$

$$+ \{[(2k_2 SP - 3k_{-2} P^2)\delta P$$

$$+ k_2 P^2 \delta S] RT(\delta S/S - \delta P/P)\}$$

$$+ (k_3 \delta P) RT \delta P/P]$$

$$= R[(k_{-1}/S + k_2 P^2/S)(\delta S)^2$$

$$+ (k_2 P - 3k_{-2} P^2/S)\delta S \delta P$$

$$+ (k_3/P + 3k_{-2} P - 2k_2 S)(\delta P)^2]$$
$$\tag{31}$$

$$= \phi_1(\delta S)^2 + \phi_2 \delta S \delta P + \phi_3(\delta P)^2 \geqslant 0, \tag{32}$$

where

$$\phi_1 = R[(k_{-1} + k_2 P^2)/S], \tag{33a}$$

$$\phi_2 = R(k_2 P - 3k_{-2} P^2/S), \tag{33b}$$

$$\phi_3 = R(k_3/P + 3k_{-2} P - 2k_2 S). \tag{33c}$$

The first term in expression (32) always contributes positive values to the excess e.p.; both k_{-1} and k_2 stabilizing the steady state. In the second term k_2 stabilizes (destabilizes) and k_{-2} destabilizes (stabilizes) the steady state when δS and δP have the same (opposite) sign. In the last term k_3 and k_{-2} stabilizes and k_2 destabilizes the steady state. The stability of the steady states will be threatened if the algebraic sum of all the contributions to the excess e.p. becomes negative, i.e., if

$$\phi_1(\delta S)^2 + \phi_2 \delta S \delta P + \phi_3(\delta P)^2 < 0. \tag{34}$$

It is therefore interesting to note that in the reversible Selkov model[1] only autocatalytic step $S \rightleftharpoons P$ could destabilize the steady state by second and last term in expression (32).

Let us now turn our attention to thermodynamic equilibrium itself which is characterized by zero excess e.p. [vide Eq. (6)] i.e.,

$$(1/2)(d\delta^2 S/dt) = 0. \tag{35}$$

Using expressions (28) and (29) for equilibrium one gets from Eq. (31)

$$(1/2)(d\delta^2 S/dt) = R[(k_{-1}^2/k_1 A + k_1 k_2^3 A/k_{-1} k_{-2}^2)$$

$$\times (\delta S)^2 + (k_1 k_2^2 A/k_{-1} k_{-2}$$

$$- 3k_1 k_2^2 A/k_{-1} k_{-2})\delta S \delta P$$

$$+ (k_3 k_{-1} k_{-2}/k_1 k_2 A - 2k_1 k_2 A/k_{-1}$$

$$+ 3k_1 k_2 A/k_{-1})(\delta P)^2] \tag{36}$$

$$= R[(k_{-1}^2/k_1 A$$

$$+ k_2^2 k_{-3} B/k_{-2} k_3)(\delta S)^2$$

$$- (2k_2 k_{-3} B/k_3)\delta S \delta P$$

$$+ (k_3^2/k_{-3} B + k_1 k_2 A/k_{-1})(\delta P)^2]. \tag{37}$$

Combining Eqs. (35) and (37), one gets

$$(2k_2 k_{-3} B/k_3)\delta S \delta P$$

$$= (k_{-1}^2/k_1 A + k_2^2 k_{-3} B/k_{-2} k_3)$$

$$\times (\delta S)^2 + (k_3^2/k_{-3} B + k_1 k_2 A/k_{-1})(\delta P)^2. \tag{38}$$

Equation (38) holds good for the thermodynamic equilibrium itself of the reversible Selkov model. Equation (38) indicates that the $\delta S \delta P$ term is always positive at thermodynamic equilibrium i.e., the mode of local fluctuation of S and P would be in the same sense (δS and δP having the same sign). This result appears to be a derivation of Le Chatelier-like principle for local concentration fluctuation at thermodynamic equilibrium from Prigogine's idea of entropy production.

FAR FROM EQUILIBRIUM REGION

Once the steady state enters instability domain, it may be further directed in a region far away from equilibrium and beyond the range of validity of Onsager reciprocity relations. The model system described here could be driven in a far

from equilibrium region by introducing irreversibility into the reaction steps. There is, however, a serious problem in extending this method of analysis away from equilibrium. The stumbling block is that the second law of thermodynamics on which this theory is based does not hold good[8-11] for a driven system away from equilibrium. In a far from equilibrium region, $\delta^2 S$ is no longer a Liapunov function and $d\,\delta^2 S/dt$ may be either positive or negative.[12] Richter *et al.*[2] in their thermodynamic analysis of this model obtained both positive and negative values of excess e.p. in the limit cycle region as a function of a, for $b = 0.09$, where

$$a = k_1 A (k_3 N)^{-1}, \quad b = k_{-3} B (k_3 N)^{-1},$$

and

$$N = (k_3/k_2)^{1/2}. \tag{39}$$

CONCLUSION

This linear thermodynamic analysis of the reversible Selkov model has established that only autocatalytic step can destabilize a steady state in this model which is different from the result obtained for the reversible Oregonator model[7] where autocatalytic together with other steps destabilize the steady state. This work also derives that the product of the local concentration fluctuations of the species S and P is always a positive quantity around thermodynamic equilibrium, which appears to be a Chatelier-like principle applicable to the autocatalytic reversible step $S \rightleftharpoons P$.

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