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# Reaction Affinity and Entropy Production in a Model Glycolytic Oscillation

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The thermodynamics of nonequilibrium states in the reversible Selkov model is reported. The reaction velocity and entropy production as a function of reaction affinity are computed.

The thermodynamics of nonequilibrium states in physicochemical systems has become a subject of great interest in recent years.[1−6] Living organisms are open systems exchanging energy and matter with the surrounding. According to the second law we must have $\Delta S_{\mathrm{Sys}} + \Delta S_{\mathrm{surr}} \geq 0$ for an organism. Let $\Delta_i S > 0$ be the system's entropy change due to the irreversible processes in the glycolytic pathway, which occurs inside the system and $\Delta_e S$ be the system's entropy change due to the exchange of energy and matter between the system and surroundings. Therefore, $\Delta S_{\mathrm{sys}} = \Delta_i S + \Delta_e S$. The $\Delta_e S$ term must be negative to compensate for the positive $\Delta_i S$. The organism discards matter with a greater entropy content than the matter it takes in, thereby losing entropy to the environment to compensate for the entropy produced in internal irreversible processes.

For such systems the classical level of thermodynamic description is in terms of the rate of chemical entropy production with the associated generalized flux and thermodynamic force. This entropy production (e.p.) formalism is essentially built on the validity of the local equilibrium hypothesis with respect to temperature even at nonequilibrium situations. Garcia-Collin et al.[7−9] discussed the possibility of extending this classical formalism so that the kinetic mass action law may be implemented in terms of the extended irreversible thermodynamics, for which the local equilibrium hypothesis may not apply. However, it is established that for most chemical reactions, the thermodynamic variables change on the same time scale as the progress variable and therefore, there is no need[10] for extended thermodynamics.

Ross et al. proposed a simple mathematical model of a glycolytic system, which is based on the model of Selkov,[11] which exhibits periodic oscillations. This model is known as the reversible Selkov model,[12] which is represented by the following three reversible steps, (1) to (3):

$$\mathrm{A} \rightleftharpoons \mathrm{S} \tag{1}$$

$$\mathrm{S} + 2\mathrm{P} \rightleftharpoons 3\mathrm{P} \tag{2}$$

$$\mathrm{P} \rightleftharpoons \mathrm{B} \tag{3}$$

where A and B are the controllable source and sink concentrations. The source is the input of chemicals such as glucose or fructose, and the sink is the products of phosphofructokinase 1 (PFK1) reaction through pyruvate kinase coupled to the adenosine nucleotide systems. The substrate S (ATP) and the product P (ADP) constitute the autocatalytic internal part of the system; $k_i$ ($k_{-i}$) represents the forward (reverse) rate constant of the *i*th step of the present model. The present communication reports on the numerical simulation of the reaction affinity and entropy production in this model for non-equilibrium stationary states.

Writing the time evolution equations for the species A, B, S, and P according to the kinetic mass action law and applying the scaling defined in eqs 4c, the following ordinary differential equations are obtained:

$$\mathrm{d}s/\mathrm{d}\tau = a - \kappa s - sp^2 + K_2 p^3 \tag{4a}$$

$$\mathrm{d}p/\mathrm{d}\tau = -p + b + sp^2 - K_2 p^3 \tag{4b}$$

where

$$k_3 t = \tau;\ S/N = s;\ P/N = p;\ N = (k_3/k_2)^{1/2};$$
$$a = (k_1 A)\cdot(k_3 N)^{-1};\ b = k_{-3}B(k_3 N)^{-1};\ \kappa = k_{-1}/k_3;$$
$$K_2 = k_{-2}/k_2 \tag{4c}$$

It is assumed that the system is open and the scaled concentrations *a* and *b* are maintained at constant values by appropriate external fluxes; *s* and *p* are the scaled concentrations of the species S (ATP) and P (ADP), respectively.

For the thermodynamic description, the rate equations for steps (1), (2), and (3) are given by

$$J_1 = k_1\mathrm{A} - k_{-1}\mathrm{S}$$
$$J_2 = k_2\mathrm{SP}^2 - k_{-2}\mathrm{P}^3$$
$$J_3 = k_3\mathrm{P} - k_{-3}\mathrm{B} \tag{5}$$

where $J_i$ represents the reaction velocity of the *i*th step. Using eq 5 and the scaling defined in eqs 4c one is ready to be led to the following results:

$$J_1 = k_3 N(a - \kappa s)$$
$$J_2 = k_3 N(sp^2 - K_2 p^3)$$
$$J_3 = k_3 \mathrm{N}(p - b) \tag{6}$$

Since the concentrations of ATP and ADP are very low (of the order of less than 1 mM), the ideal solution approximation for

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the mixture of reactant and product molecules is applicable. Also, using the scaling defined in eqs 4c, one obtains the affinities[13] of the individual steps ($A_i$) and the overall reaction ($A$) given by the relations:

$$A_1 = RT \ln (a/\kappa s)$$

$$A_2 = RT \ln (s/K_2 p)$$

$$A_3 = RT \ln (p/b)$$

$$A = A_1 + A_2 + A_3 = RT \ln (a/\kappa K_2 b) \tag{7}$$

The time-independent steady states are described by the following two equations:

$$\kappa s_o = (a + b) - p_o$$

$$(1 + \kappa K_2)p_o^{\,3} - (a + b)p_o^{\,2} + \kappa(p_o - b) = 0 \tag{8}$$

Therefore, one can obtain the steady-state values ($s_o$, $p_o$) numerically from eq 8 for the known values of the parameters $\kappa$, K$_2$, $a$, and $b$. The entropy production per unit volume ($d_iS/dt$) due to nonequilibrium steady state is given by

$$d_iS/dt = (1/T) \sum_i J_i A_i \geq 0 \tag{9a}$$

where $J_i$ and $A_i$ are, respectively, the velocity and affinity of the $i$th reaction. Substituting the values of $J_i$ and $A_i$ from eqs 6 and 7 and using eq 4c to scale time $t$ to $\tau$, one obtains

$$d_iS/d\tau = NR((a - \kappa s) \ln (a/\kappa s) + (sp^2 - K_2 p^3)$$

$$\ln (s/K_2 p) + (p - b) \ln (p/b)) \tag{9b}$$

Once the values of $a$, $b$, $\kappa$, $K_2$, and the steady-state values of $s$ and $p$ (i.e., $s_o$ and $p_o$) are known, one can calculate $d_is/d\tau$ from eq 9b for nonequilibrium states including the state of thermodynamic equilibrium represented by eq 10 below. The nonlinear oscillatory region was explored in the past by Richter et al.[12]

The following relations[12,14] hold good at the state of thermodynamic equilibrium of the reaction scheme, eqs 1– 3; subscript "e" stands for the equilibrium state:

$$s_e = a/\kappa;\ p_e = s_e/K_2 = a/\kappa \mathrm{K}_2;\ p_e = b;\ b = a/\kappa K_2 \tag{10}$$

It is worthwhile to mention that the time-independent steady state coincides with the state of thermodynamic equilibrium if the boundary conditions are compatible with the equilibrium condition, i.e., if the flow rate of the open system is made zero (closed system).

A direct relation between the affinity ($A$) and the heat of reaction ($Q$) is given[13] as

$$A = -(\partial Q/\partial \xi)_{P,T} + T(\partial S/\partial \xi)_{P,T} \tag{11}$$

where the extent of the reaction ($\xi$) is related to its velocity ($J$) by the relation

$$J = d\xi/dt \tag{12}$$

and the subscripts $P$ and $T$ indicate the constancy of pressure and temperature, respectively. According to the textbooks on classical thermodynamics, it is sometimes possible to neglect the entropy ($S$) variation term in eq 11 because of its minor contribution. In such cases, the entropy production due to a chemical change becomes simply proportional to the heat of reaction as given below:

$$d_iS/dt = AJ/T = -(1/T)\ (\partial Q/\partial t)_{\mathrm{P,T}} \tag{13}$$

In this approximation, the entropy production of a living organism can be measured by its metabolism, as recorded by calorimetry.

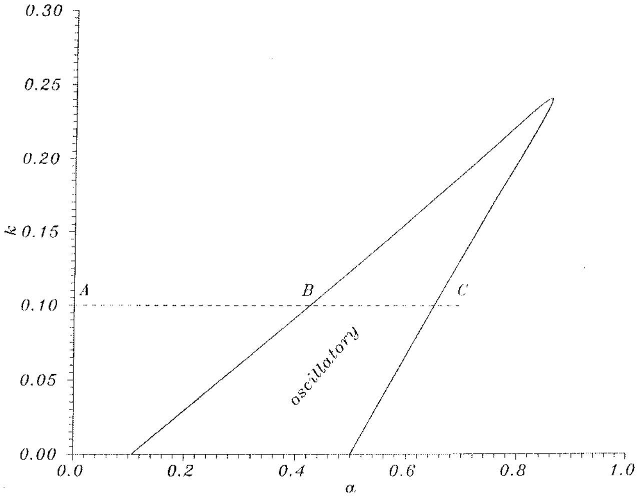

**Figure 1.** Phase diagram of the reversible Selkov model in ($a$-$\kappa$) phase plane; $b$, 0.09; $K_2$, 1.

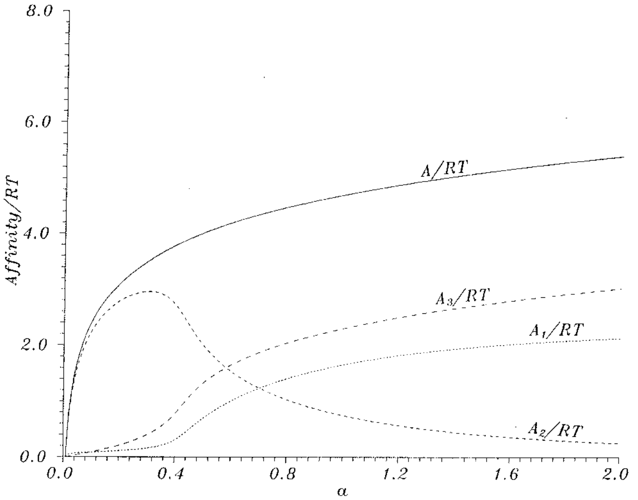

**Figure 2.** The affinity as a function of $a$ in the reversible Selkov model; $A_i$, the affinity of the $i$th step and $A$, the overall affinity; $\kappa$, 0.1; $K_2$, 1; $b$, 0.09.

Figure 1 shows the computed phase diagram of the model in (a$-\kappa$) phase plane, which presents Hopf bifurcation lines separating the oscillatory and the nonoscillatory regions. The horizontal line ABC cuts the phase diagram at two Hopf bifurcation points, B and C. Figure 2 shows the affinity as a function of the parameter $a$ for the individual steps as well as the overall reaction for appropriate values of $b$, $\kappa$, and $K_2$, which yield the most convenient results (see eq 7). For low values of the parameter $a$, the chemical potential changes due to the autocatalytic step (2) are much greater than those of the other two steps, which exhibit very little change of chemical potential. The affinity of steps (1) and (3) of this model[11,12] increases slowly with the increase of $a$; but in the case of the autocatalytic step (2), the curve, first shows a maximum with the increase of $a$ and decreases thereafter with further increase of $a$. The affinity curve for the overall reaction shows an exponential increase

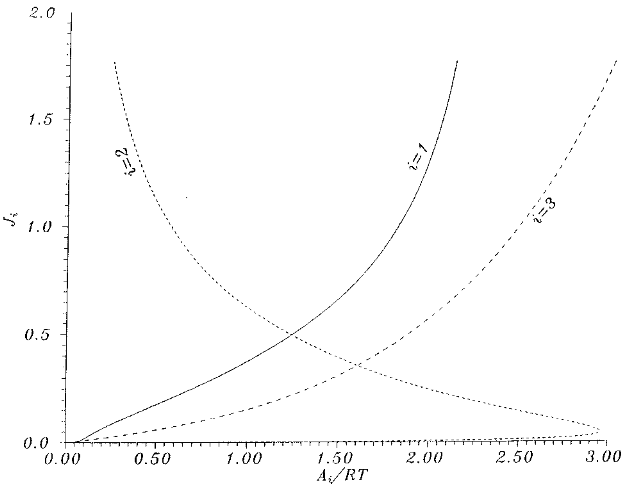

**Figure 3.** The velocity ($J_i$) as a function of the affinity ($A_i$) of the three individual steps ($i = 1,2,3$, respectively) in the reversible Selkov model; the parameters are the same as Figure 2.

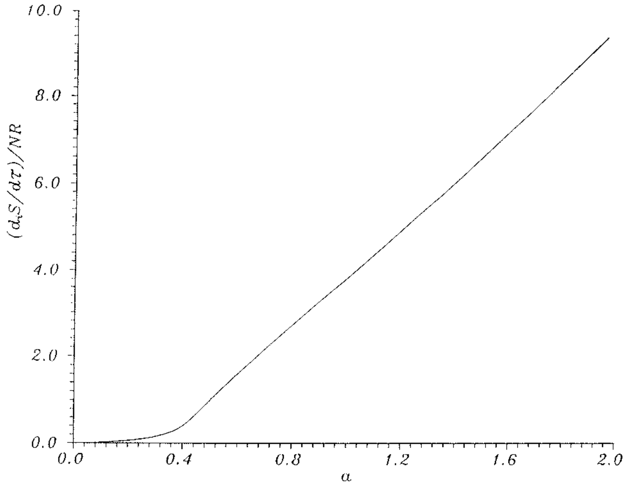

**Figure 4.** The entropy production as a function of *a* in the reversible Selkov model; the parameters are the same as Figure 2.

with the increase of *a*, indicating that *a* is a measure of the distance from the state of thermodynamic equilibrium (see eq 10). Figure 3 is the variation of velocities ($J_i$) of the three individual steps of the model with their corresponding affinities ($A_i$). The affinities of steps (1) and (3) increase exponentially with the increase of the velocities of the corresponding steps, whereas for the autocatalytic step (2), the reaction velocity remains very, very low until the corresponding affinity overcomes a barrier of 2.95*RT*, beyond which the velocity of step (2) increases exponentially accompanied with a decrease of its affinity. Interestingly, the $J_2$ vs $A_2$ plot in Figure 3 displays a beautiful allosteric regulatory mechanism of the autocatalytic step (2). The total velocity *J* increases exponentially with the total affinity *A*, was reported in the past (see Figure 3 of ref 12). Figures 4 and 5 present the entropy production as a function of the parameter *a* and the overall affinity (*A*), respectively, for the most convenient values of $\kappa$, $K_2$, and *b*. This gives a numerical estimate of the entropy production in this model at different distances from the state of thermodynamic equilibrium. Figure 4 agrees well with the total entropy production calculation carried out in the past (see Figure 4 of ref 12), in which the entropy production of steps (1), (2), and (3) were also calculated separately.

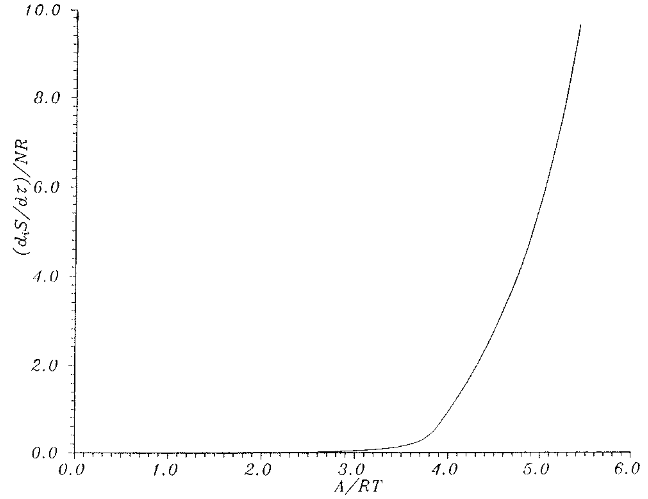

**Figure 5.** The entropy production as a function of the overall affinity (*A*) in the reversible Selkov model; the parameters are the same as Figure 2.

This communication has reported the nonequilibrium thermodynamics of the reversible Selkov model,[12] a generic model of glycolytic oscillations. An application of the calculation of entropy production in glycolytic pathway is: the less the dissipation (*T* times entropy production for this isothermal process), the less is the Gibbs free energy change ($\Delta G$ at constant *T* and *P*) and the more is the energy transduction from reactants to products to ensure higher efficiency of the biochemical engines. Figures 2 and 5 demonstrate that the low values of *a* (the scaled concentration of the input substrates such as glucose or fructose) in the range $0 < a < 0.3$, which correspond to the overall affinity (*A*) in the range $0 < A < 3.5RT$, produce very low entropy production (dissipation). This low entropy production region may be considered useful to ensure high energy transduction in a stationary glycolytic pathway.

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