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Chung-Yuan Mou and Chung-Hsien Liang



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Nonequilibrium thermodynamic analysis of Michaelis–Menten kinetics

Chung-Yuan Mou^{a)} and Chung-Hsien Liang^{b)}

Department of Chemistry, National Taiwan University, Taipei, Taiwan, Republic of China

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We developed a method of analysis of nonequilibrium steady states of chemical reaction system. The analysis is applied to systems of Michaelis–Menten type reactions. We focus our attention on the consequence of the quasi-steady-state approximation to the rate of entropy production. Under separation of time scale, the description of the complete kinetic system can be contracted to slow variables. We find that the resulting rate of entropy production can be written in a new and revealing way consisting of steady-state contribution, intermediate species-specific affinity production, and channel-mixing entropy terms. The species-specific term in entropy production is in the canonical form so that a thermodynamiclike description of far-from-equilibrium steady state becomes possible. Under the quasi-steady-state approximation, we find the rate of entropy production is first order. This applies also to more complicated models. Finally, we discuss the implications in stochastic fluctuations of the free energy of the system. The Michaelis–Menten type of reactions considered in this paper do not show the possibility in gains of power from fluctuating external environment.

I. INTRODUCTION

The thermodynamics of the dissipative steady state far from equilibrium has received certain attention in the last two decades.^{1–5} Much of the recent work emphasizes the frequent analogies between equilibrium thermodynamics and nonequilibrium steady states, e.g., fluctuations,³ extended thermodynamic relations,^{4,5} and susceptibility.⁶ The purpose has been towards the establishment of the macroscopic thermodynamics description of nonequilibrium steady states. Among these, steady states in the chemical reaction (well-stirred) system seem to be particularly attractive owing to the fact that its rate equations can often be easily written down according to mass-action law and its fluctuations can be investigated with stochastic master equations.⁷

The beauty in thermodynamic description lies in its vast contraction of variables. Classical thermodynamics of equilibrium states involves a description of matter in terms of a few extensive thermodynamics functions only, volume, entropy, internal energy, etc. Two systems with the same values of all the relevant extensive thermodynamics quantities are said to be identical, for all purpose, although they could have very different microscopic states. Within thermodynamics, one could have many choices of extensive variables depending on the degree of contraction in description. For example, in treating the chemical system, one could choose a description on the level of detailed chemical equilibrium of all the elementary reactions, or one could investigate only the total equilibrium.

For the nonequilibrium system, the usual level of thermodynamics description is in terms of the rate of entropy production dS/dt ^{1,2} (internal), generalized flux $\{J_i\}$, and generalized thermodynamic force $\{X_i\}$. They are related by

$$dS/dt = \sum_i J_i X_i. \quad (1)$$

Phenomenological rate laws are expressed in the relations between J_i and X_i . For the linear relationship between them, one has the principle of minimum entropy production.² For a chemical reaction system, the description is in terms of rate J_i and affinity A_i of each reaction.²

$$TdS/dt = \sum_i J_i A_i, \quad (2)$$

where infinity A_i is the difference in free energy for the i th reaction.

Consider a set of N coupled chemical reactions involving S species, with the stoichiometry of the i th reaction given by

$$\sum_j \nu_{ij} Y_j = 0. \quad (3)$$

The stoichiometric coefficient ν_{ij} is negative if species Y_j is a reactant in the reaction and positive if it is a product. With the introduction of the extent of reaction variable ξ_{ij} ,

$$dn_j = \sum_i \nu_{ji} d\xi_i. \quad (4)$$

The reaction affinity is given by

$$A_j = - \sum_i \nu_{ji} \mu_i. \quad (5)$$

The rate of entropy production of the reaction system is

$$dS/dt = - \sum_j (A_j/T) (d\xi_j/dt). \quad (6)$$

Now the i th reaction rate can be written as

$$d\xi_i/dt = t_i^+ - t_i^-, \quad (7)$$

where t_i^+ and t_i^- are the rates for the forward and backward reactions (i th step). For reactions at constant temperature and pressure, the rate of entropy production (dS/dt) is given by the canonical form

$$(1/R) (dS/dt) = - \sum_i (t_i^+ - t_i^-) \ln (t_i^+/t_i^-), \quad (8)$$

where R is the gas constant and T is the absolute temperature.

For a complex reaction system consisting of a set of elementary reactions such as Eq. (3), often one would like to use a reduced set of variables to describe its kinetics based on some steady state, or equilibrium approximations. This is

^{a)} To whom all correspondence should be addressed.

^{b)} Present Address: Institute of Nuclear Energy Research, Atomic Energy Council, P.O. Box 3-6, Lung Tang, Taiwan, Republic of China.

possible in most cases because of the existence of large difference in the relevant time scale in the kinetic system. The use of adiabatic elimination⁸ of the fast variables leads to a simplified description of the kinetic system in terms of a slow manifold in reduced (slow) variables. Fraser⁹ presented an iterative scheme to investigate the geometrical structure of steady-state approximations for simple chemical reaction systems. The steady-state approximation is a limiting case of the more general slow manifold description. When fast variables are eliminated by steady-state approximation, some intermediate variables are no longer present in the final steady-state rate. We would like to analyze the thermodynamic description of entropy production in reduced variables. Under the steady-state approximation, individual steps in the kinetic system are not in local equilibrium and fluctuations around the steady state are not in the equilibrium Poissonian form^{2,6} (the term local comes from this method). One would like to find out how the entropy production can be described. When is the canonical form (8) still valid?

Recently, Ross, Hunt, and Hunt¹⁰ have presented a thermodynamic analysis of global validity for effectively one-variable, irreversible chemical systems with multiple steady states. In order to find the total dissipation, they focused their attention on a hybrid free energy function of a hypothetical reaction chamber, maintained by the “two-piston” apparatus at steady state, to bring out the important species-specific affinity. This quantity is useful in descriptions of entropy production for deviations from the steady-state.

In this paper, we choose to investigate the chemical reaction system under batch condition. That is, steady states are not maintained by external constraints, but the time scale of the system would allow for the quasisteady state in its evolution. We will perform an analysis of entropy production on the well-known reaction Michaelis–Menten^{11,12} kinetics and its modifications. This reaction scheme is important in the biochemical enzyme system and from our point of view it provides the simplest case of the quasisteady state system. At the quasisteady state of the simple Michaelis–Menten type, the system can be described without explicitly including the intermediate and it is not in local equilibrium (no detailed balancing). We would like to develop its nonequilibrium thermodynamic description for such contractions using the steady-state approximation. The result of our analysis is partitioning of total entropy production into hierarchy levels of a different time of scale instead of the usual level of reaction steps [Eqs. (4)–(8)]. The slowest level is the quasisteady state description, while the species-specific affinity¹⁰ description appears naturally in the next level. The rest of the total entropy production can be interpreted in a very interesting way as the production of entropy of mixing of reaction channel.

The arrangement of the paper is as follows: We will give a complete analysis of nonequilibrium thermodynamics of the Michaelis–Menten reaction in Sec. II. We will show that the entropy production rate can be written in a new form so that it is centered around the quasisteady state. One can identify the steady-state contribution, intermediate species-specific term, and other contributions. The result will be use-

ful towards building nonequilibrium thermodynamics of steady states. Then, in Sec. III, we extend the conclusion obtained to more complicated Michaelis–Menten reaction systems and calculate the rate of free energy for the quasisteady states. Over a large range of time, total free energy shows a simple first-order decay. This is characteristic of the quasisteady state situation. In Sec. IV, we consider the effect of internal fluctuations by using our previous theory of entropy production of fluctuations.⁶ It was shown that for this type of reaction, there is no extra entropy production due to fluctuation.

II. NONEQUILIBRIUM THERMODYNAMICS OF MICHAELIS–MENTEN KINETICS

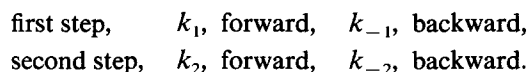
Since the pioneering work of Michaelis and Menten¹² enzyme kinetics, approximations by assuming rapid attainment of steady states among enzyme species has been commonly used to simplify the rate equations into algebraic equations. In fact, the Michaelis constant is ubiquitously employed to characterize the kinetic property of the system.^{11,12} Later, there exist many varieties of modified Michaelis–Menten kinetic schemes.^{12,13}

The simplest case is that of an enzyme-catalyzed reaction where there is a single substrate S ; an example is the hydrolysis of an ester. The rate varies linearly with the substrate concentration (first-order kinetics) and becomes saturated at high substrate concentration (zero-order kinetics). The kinetics can be expressed as

scheme A,



rate constants,



Here, E and S are the enzyme and substrate, P is the product, and ES is an addition complex. If $k_{-2} \ll k_2$, k_1 and the initial concentration of S is large, the system attains a quasisteady state shortly after the start of the reaction and remains so until almost to the end. During this period, the concentration of enzymes and intermediate ES remains almost constant. The net reaction rate is given by

$$v_{\text{net}} = k_2 [ES] - k_{-2} [E][P]. \quad (10)$$

At the quasisteady state, we have

$$[ES]_{\text{ss}} = (k_1 [S][E] + K_{-2} [P][E]) / (k_2 + k_{-1}). \quad (11)$$

Then the net reaction rate can be written as

$$v_{\text{net}} = (k_1 k_2 [E][S] - k_{-1} k_{-2} [E][P]) / (k_2 + k_{-1}). \quad (12)$$

For the case of $k_2 \ll k_{-1}$, the net rate is

$$v_{\text{net}} = \{(k_1/k_{-1})k_2 [E][S] - k_{-2} [E][P]\}. \quad (13)$$

This is the case of local equilibrium since the first term on the right-hand side is simply the result of local equilibration between ES and E .

Now we would like to investigate the rate of entropy production. According to Eq. (8), the total rate is given by

$$\begin{aligned}
 (1/R)(dS/dt) &= (k_1[E][S] - k_{-1}[ES]) \\
 &\quad \times \ln(k_1[E][S]/k_{-1}[ES]) \\
 &\quad + (k_2[ES] - k_{-2}[E][P]) \\
 &\quad \times \ln(k_2[ES]/k_{-2}[E][P]). \quad (14)
 \end{aligned}$$

We will divide the total rate of entropy production into two parts $(dS/dt)_{ss}$ denoting steady state contribution and $(dS/dt)_x$ the rest which is related to the intermediates. Then the steady-state entropy production is given by the product of the steady-state rate and the total affinity

$$\begin{aligned}
 (1/R)(dS/dt)_{ss} &= \{(k_1 k_2 [E][S] \\
 &\quad - k_{-1} k_{-2} [E][P]) / (k_2 + k_{-1})\} \\
 &\quad \times \ln(k_1 k_2 [S] / k_{-1} k_{-2} [P]). \quad (15)
 \end{aligned}$$

We observe that this is in the canonical form of Eq. (8). At the quasisteady state, the system can be thought of as an effective elementary reaction $E + S \rightleftharpoons E + P$ with the forward and backward rates being $k_1 k_2 [E][S] / (k_2 + k_{-1})$ and $(k_{-1} k_{-2} [E][P]) / (k_2 + k_{-1})$, respectively. Notice also that $(dS/dt)_{ss}$ is not explicitly $[ES]$ dependent.

Let the deviation of $[ES]$ from its steady-state value be x , e.g., $x = [ES] - [ES]_{ss}$, then it is given by

$$\begin{aligned}
 x = [ES] - \{(k_1[E][S] + k_{-2}[E][P]) / \\
 (k_2 + k_{-1})\} &= \{(k_2 + k_{-1})[ES] - (k_1[E][S] \\
 &\quad + k_{-2}[E][P])\} / (k_2 + k_{-1}). \quad (16)
 \end{aligned}$$

We define the reaction flux for each step as

$$\begin{aligned}
 j_+^1 &= k_1[E][S], \quad j_+^2 = k_{-2}[E][P], \\
 j_-^1 &= k_{-1}[ES], \quad j_-^2 = k_2[ES] \quad (17)
 \end{aligned}$$

and the total flux with respect to the change of $[ES]$ is given by

$$j_+ = j_+^1 + j_+^2, \quad j_- = j_-^1 + j_-^2. \quad (18)$$

Equation (16) can be written as

$$x = (j_- - j_+) / (k_2 + k_{-1}). \quad (19)$$

The rate of entropy production can now be written as

$$\begin{aligned}
 (1/R)(dS/dt) &= (1/R)(dS/dt)_{ss} - x k_{-1} \ln(k_1[E][S] / \\
 &\quad k_{-1}[ES]) + x k_2 \ln(k_2[ES] / k_{-2}[E][P]). \quad (20)
 \end{aligned}$$

The intermediate ES can either go to reactant or product with the ratio

$$r = k_{-1} / (k_2 + k_{-1}), \quad 1 - r = k_2 / (k_2 + k_{-1}). \quad (21)$$

In terms of the reaction flux, Eq. (20) can be cast in the following form:

$$\begin{aligned}
 (1/R)(dS/dt) &= (1/R)(dS/dt)_{ss} + (j_- - j_+) \ln \\
 &\quad \times \{(j_-^1)(j_-^2)^{1-r} / (j_+^1)(j_+^2)^{1-r}\}. \quad (22)
 \end{aligned}$$

The second term in the above equation represents the excess entropy production over the steady-state value. Now we

would like to write the equation in the form that the term specific to ES would appear in the canonical form

$$\begin{aligned}
 (1/R)(dS/dt) &= (1/R)(dS/dt)_{ss} + (j_- - j_+) \ln(j_- / j_+) \\
 &\quad + (j_- - j_+) \ln\{(j_-^1)(j_-^2)^{1-r} / (j_+^1)(j_+^2)^{1-r}\} \\
 &\quad + (j_- - j_+) \ln\{(j_+^1)(j_+^2)^{1-r} / (j_-^1)(j_-^2)^{1-r}\}. \quad (23)
 \end{aligned}$$

The first and second terms on the right-hand side of Eq. (23) are positive definite, but the final two terms are not, although the total entropy production rate must be positive definite. The second term on the right-hand side of Eq. (23) is the species-specific affinity found by Ross, Hunt, and Hunt.¹⁰ It is in the canonical form of Eq. (8), describing an equilibriumlike state maintained by the two fluxes j_- and j_+ , but, actually the ratio of j_- and j_+ does not correspond to an equilibrium constant of any elementary reaction. The third and fourth terms in Eq. (23) represent the contribution of unsteady flux through $[ES]$; they will also vanish at the steady state.

Equation (23) is in the same form as Eqs. (6.5) and (6.6) of the paper by Ross, Hunt, and Hunt.^{10(a)} We have derived them by a straightforward method. In Ref. 10(a), it is obtained through a special hybrid free energy function and some gedanken experiments involving semipermeable subsystems.

The species-specific term in entropy production is important in several aspects. First, it is in the canonical form so that a thermodynamiclike description of the far-from-equilibrium steady state becomes possible. Details of this approach will be presented in another paper. Second, Ross, Hunt, and Hunt^{10(a)} had already shown that the integral of the species-specific affinity globally provides a valid Liapunov function for the evolution of the intermediate. These results are independent of the number of steady states and they hold both near and far from equilibrium. Thirdly, for a large class of mechanisms with a single intermediate (ES here), the result (23) is parallel; one just replaces the corresponding terms in j_i according to the mechanism. Finally, and most importantly, the integral of the species-specific affinity appears in the time-dependent transition probability of the single-variable master equation in the description of the fluctuation of the steady state.^{10(a)} It gives the coexistence condition of the multiple steady state.^{7,10(a),14}

According to Eq. (11), we can write the species-specific affinity as

$$RT \ln(j_- / j_+) = RT \ln([ES] / [ES]_{ss}) = \mu - \mu_{ss}, \quad (24)$$

e.g., the difference in the chemical potential with respect to the steady state as a reference state. The function $(\mu - \mu_{ss})$ meets the requirements of a chemical driving force for the attainment of the steady state, but it differs from local equilibrium thermodynamics in that the left-hand side of Eq. (24) does not conform to the law of mass action, i.e., j_- and j_+ do not represent the rates of any single elementary step. This implies that when one generalizes the free energy function for the nonequilibrium steady state, it should include dependence on flux, or put another way, one has to include

flux as a thermodynamic variable. This is the program of extended thermodynamics developed by Eu⁴ and others.⁵ As pointed out by Ross, Hunt, and Hunt,¹⁰ this also arises in the description of momentum relaxation in a dilute gas via the Boltzmann equation and Boltzmann *H* theorem.¹⁵

We now define the following ratios of reaction rates:

$$R_-^1 = j_-^1 / j_-, \quad R_-^2 = j_-^2 / j_-, \\ R_+^1 = j_+^1 / j_+, \quad R_+^2 = j_+^2 / j_+.$$

They express the fraction of reaction channels for the depletion and production of the intermediate *ES*. Multiplying Eq. (23) by temperature, then one can write the dissipation function as

$$T(dS/dt) = T(dS/dt)_{ss} + (j_- - j_+) \{ \mu - \mu_{ss} \} \\ + RT [r \ln(R_-^1) + (1-r) \ln(R_-^2) \\ + r \ln(R_+^1) + (1-r) \ln(R_+^2)]. \quad (25)$$

Equation (25) is the main result of this paper; it represents the rate of loss of the system's capacity to do work. It is interesting to observe that the final terms in Eq. (25) can now be interpreted as owing to some analog of "entropy of mixing" of reaction channels for the production and depletion of the intermediate species *ES*. Therefore, the free energy production rate can be written in a well-organized way. The steady-state contribution, intermediate species chemical potential change term (second term), and the ideal free energy of mixing of entrance and exit channel terms (the final two terms). The final part is not in canonical form and not positive definite.

According to Eq. (15), at the quasisteady state, the dissipation function (rate of free energy production) can now be written in the general form

$$d(\Delta G)/dt = J\Delta G, \quad (26)$$

where *J* is the steady-state net flux for the total reaction and ΔG is the free energy of reaction of the system. From Eq. (12), it is obvious that the relation between *J* and driving force ΔG can not be linear in general. Instead, practically the rate flux *J* is approximately constant over a large range of concentration under the steady-state approximation. Then one would have an exponential decay of the available work of the system at the quasisteady state

$$\Delta G = \Delta G_0 \exp(-Jt), \quad (27)$$

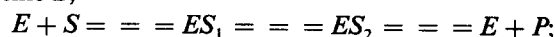
where ΔG_0 is the value of ΔG at initial time. This relation would be further demonstrated for more complex enzyme kinetic systems in the next section. Of course, for true steady states maintained at constant external driving force, dissipation is also constant. Equation (27) is interesting in that it gives one a first order decay of free energy. In physical chemistry, when one encounters first order decay of substance or heat, one usually has a simple underlining random (Poissonian) process for the quantity. What does this mean for the free energy change of the reaction? It means that at the steady state the fluctuation of the exchange of work of the system with environment is a random process. A theory for the fluctuation of free energy of a steady-state system far from equilibrium would be interesting to develop. At present, we know little about this aspect. We speculate that the

pseudo-first order decay of available work is quite general in many of the biological complex reaction systems. In the next section, we will demonstrate similar behavior to that of Eq. (27) with numerical calculations of two more complex Michaelis-Menten type reactions. The total free energy of the system decays in a fashion that can be approximated by a simple exponential over a large range of time.

III. MULTIPLE ENZYME-CATALYZED SYSTEMS

A more realistic sequence than scheme A involves two central complexes *ES*₁ and *ES*₂ as shown in scheme B. The quasisteady state then gives approximately constant values of *ES*₁ and *ES*₂. We will investigate this model in this section. We will examine the rate of free energy production for this model here:

scheme B,



rate constants,

$$\begin{array}{llll} \text{first step,} & k_1, \text{ forward,} & k_{-1}, \text{ backward,} \\ \text{second step,} & k_2, \text{ forward,} & k_{-2}, \text{ backward,} \\ \text{third step,} & k_3, \text{ forward,} & k_{-3}, \text{ backward.} \end{array}$$

Figure 1 shows the result of a calculation of the rate of entropy production for scheme B. One sees that it is approximately exponential over a large range of the time. In this range this quasisteady state approximation of the intermediates *ES*₁ and *ES*₂ is valid. Then Eq. (27) is nearly obeyed and the rate of free energy production is proportional to the total free energy of the system. In this region, one expects

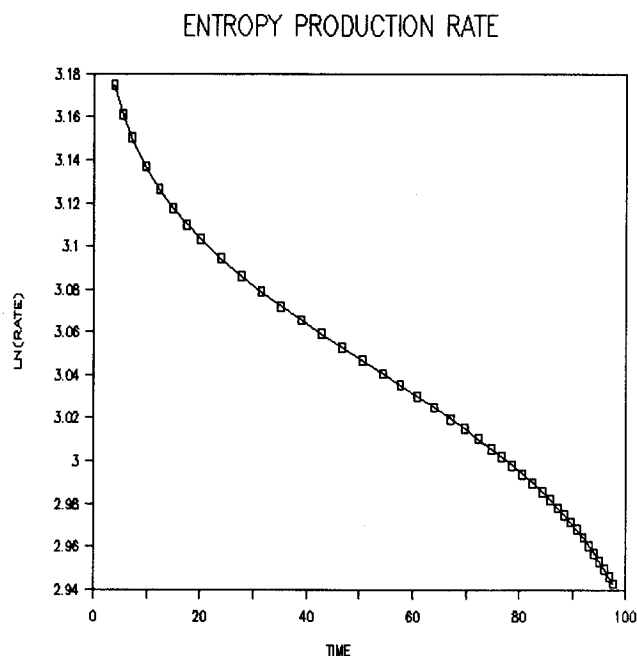


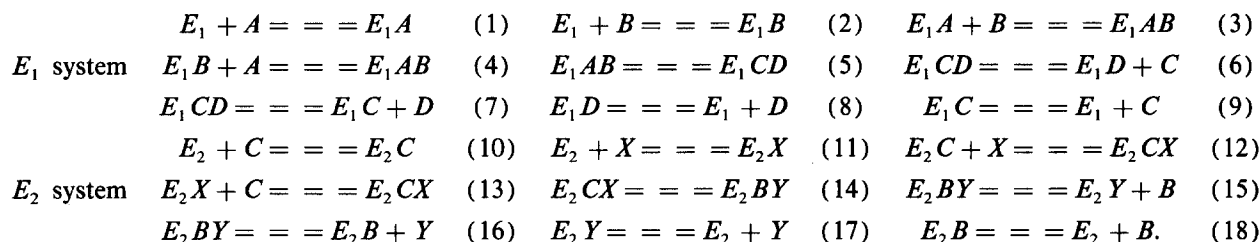
FIG. 1. Model B, \ln (entropy production rate) vs time. In the range $t = 20$ – 80 , where the quasisteady state approximation applies, the curve shows approximately exponential behavior. Parameters: $k_1 = 5 \times 10^5$; $k_{-1} = 5$; $k_2 = 1000$; $k_{-2} = 100$; $k_3 = 1$; $k_{-3} = 0.0001$. Initial conditions $S = 100$, $E = 1$.

that intermediates do not enter explicitly into the affinity of the entropy production.

This quasisteady state behavior is quite characteristic of the Michaelis-Menten type reactions even for many more complex systems. We give another more complex coupled reaction system involving Michaelis-Menten reactions. Scheme C provides a model for the enzyme cycling¹⁶ in which the reaction proceeds with excess starting A and X to

accumulative amount of Y and D . The time course of a typical reaction is shown in Fig. 2. The system attains a behavior following a slow manifold immediately after the start of the reaction, and remaining so until almost to the end. During this period, the concentration of enzymes and common intermediate B , and C remains roughly constant. The concentration of D and Y follows an identical time course, increasing linearly with time:

scheme C, coupled cyclic Michaelis-Menten kinetic scheme



Using a (typical) set of rate constants (Table I), we solve the kinetic equations and calculate the decay of reaction affinity, the result is shown in Fig. 2. We also plot the concentration of the intermediates E_1 and E_2 . They are not quite constant over the time range plotted, but the log (A/RT) vs time plot is quite linear. So the exponential behavior of Eq. (27) is obeyed over most of the range of time. We expect that this behavior, the evolution of free energy along slow manifold being simple exponential decay, is more prevalent than the quasisteady state approximation for every intermediate species.

Both schemes B and C do show the exponential behavior of free energy of a pseudo-first order decay. This is in accord with the simple Michaelis-Menten model (scheme A). We would leave complete thermodynamic analysis for these complex systems to future general theory, but it seems to us the conclusions of Sec. II would still be valid, e.g., a first order of decay of free energy and its simple underlining random (Poissonian) process for the quantity. It means that at these quasisteady states, the fluctuation of the exchange of work of the system with environment is a random process. In the next section, we will discuss this aspect from the point of view of stochastic thermodynamics⁶ if one considers the contribution of fluctuations to the rate of free energy production.

TABLE I. Rate constants for scheme C in the calculation.

$k_1 = 10^6$	$k_{-5} = 3$	$k_{10} = 5 \times 10^5$	$k_{-14} = 30$
$k_{-1} = 250$	$k_6 = 50$	$k_{-10} = 25$	$k_{15} = 50$
$k_2 = 5 \times 10^5$	$k_{-6} = 100$	$k_{11} = 3.5 \times 10^5$	$k_{-15} = 100$
$k_{-2} = 30$	$k_7 = 30$	$k_{-11} = 30$	$k_{16} = 30$
$k_3 = 2 \times 10^6$	$k_{-7} = 100$	$k_{12} = 10^6$	$k_{-16} = 10$
$k_{-3} = 10$	$k_8 = 10$	$k_{-12} = 10$	$k_{17} = 10$
$k_4 = 2.5 \times 10^6$	$k_{-8} = 500$	$k_{13} = 2.5 \times 10^6$	$k_{-17} = 5$
$k_{-4} = 15$	$k_9 = 20$	$k_{-13} = 15$	$k_{18} = 20$
$k_5 = 10$	$k_{-9} = 200$	$k_{14} = 5$	$k_{-18} = 2$

IV. ENTROPY PRODUCTION OF FLUCTUATIONS

Mou, Luo, and Nicolis⁶ presented a stochastic theory, based on chemical master equation, of entropy production for steady states in chemical reaction system. It was shown that in addition to the usual Gibbsian form of entropy production we discussed above, there is an extra entropy production due to internal fluctuation $(diS/dt)_f$. This comes from the non-Poisson character of the probability distribution in a nonequilibrium steady state. It was further shown that this entropy production of fluctuation $(diS/dt)_f$ is proportional to the net power gain factor for the system under

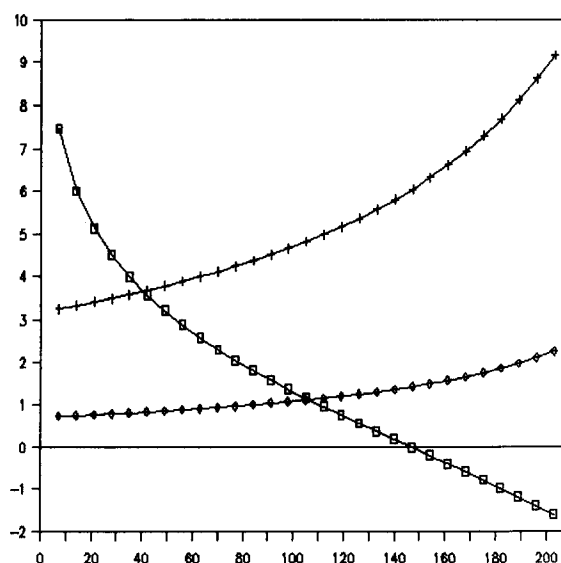


FIG. 2. Model C, squares are $\ln(A/RT)$ vs time from $t = 30$ to 200, the decay of affinity A/RT is almost exponential. Crosses are $[E_1]$ and \circ are $[E_2]$. Kinetic rate constants are listed in Table I.

external fluctuation. We will discuss, in this section, the entropy production of fluctuation for the quasisteady states considered in the enzymatic system of this paper.

First, let us summarize the theory of Mou, Luo, and Nicolis⁶ briefly. It was shown that in addition to the usual Gibbsian form of entropy production, there is an entropy production due to fluctuations which is of the order $O(V^0)$. This comes from the non-Poisson character of the probability distribution in a nonequilibrium system. It was derived from chemical master equation that $(diS/dt)_f$ is related to the second derivatives of fluxes of the reactions as in Eq. (27) of Ref. 6

$$\left(\frac{diS}{dt}\right)_f = \frac{1}{2} \sum_p A_p(\{X\}) \times \left\{ \sum_{ij} (\sigma_{ij} - \delta_{ij} X_i) \frac{\partial^2}{\partial X_i \partial X_j} J_p(\{X\}) \right\}. \quad (28)$$

Here, X_i represents the concentration of species i and σ_{ij} is the covariance of fluctuations of concentrations. One can see that in the Michaelis–Menten schemes considered in this work J 's are always linear in the intermediate species considered, the entropy production due to fluctuation always vanishes. This means that one cannot gain work from a fluctuating environment from these schemes, or put in another way, the fluctuation of available work (free energy) production is always random. This is a consequence of the Poissonian character of the concentration fluctuation for the linear system. It is also in accord with our conclusion in Sec. II discussing the first order decay of free energy. In order to have nonzero work gain from the fluctuating environment, the reaction flux must be nonlinear in the relevant intermediate species as the Schlögl model discussed in Ref. 6.

V. CONCLUDING REMARKS

In summary, we have performed an analysis of the nonequilibrium thermodynamics of Michaelis–Menten reactions. It is based on the separation of time scale, and entropy production is analyzed into a hierarchy of contributions to match the time scale involved. Using the quasisteady as reference state, the entropy production can be exactly separated into the form that involves steady-state contribution, intermediate species-specific chemical potentials, and entropy production due to reaction channel mixing [see Eq. (25)]. The analysis parallels those of Hunt, Hunt, and Ross,¹⁰ but it is for a closed system so the complete evolution of entropy production can be rationalized this way. Our approach is straightforward in following the logic of time scale separation. This analysis can be easily extended to a more complex reaction system involving more than one intermediate species. In fact, we are able to rederive all the results in Ref. 10 without using the auxiliary hybrid free energy function (to be presented in a separate paper).

At present, our separation of time scale is based on simple steady-state approximations. For more rigorous analysis, one needs a better method of eliminating fast variables. It

was shown by Fraser and Nguyen⁹ that for a correct description of the complex chemical reaction system, one needs to compute the slow manifold and the quasisteady state may not be an accurate description of the intermediate species. We have developed our analysis based on quasisteady state approximations, but in numerical examples of more complex system, one can still see an exponential decay of the total entropy production function for extended time domain. It implies that a similar analysis of hierarchy of entropy production in terms of the slow manifold would be possible and the result would be very interesting.

We also show that in the regime where the quasisteady state approximation is valid. The evolution of free energy of the system is simple exponential. This raises the general question of the natural path in the kinetic system.^{17–19} Garfinkle¹⁷ first proposed that a closed stoichiometric chemical reaction system traverse a unique natural path from initiation to equilibrium. Along such a path, the time rate of evolution of free energy can be analytically described independently of phenomenological or mechanistic consideration. This is unlikely to be true in general. Subsequently, it was shown¹⁸ that this claim not to be correct due to false suppression of the data trend in plotting. The proposed natural path is only valid under local equilibrium assumption.¹⁹ For the models considered in this paper, our result shows that the decay of free energy is indeed mechanism dependent in the far from equilibrium situation, but the simple exponential decay seems to be prevalent even when quasisteady state is not the slow manifold for the evolution of the system. The rate is mechanically dependent, but the form of exponential decay of free energy seems to be quite “natural.” It is worth further studying. In this work, this simple decay behavior is shown to be a consequence of the steady-state approximation for the Michaelis–Menten reaction and it allows a reduced thermodynamics description.

Finally, the significance of the simple exponential decay is interpreted in terms of a theory of fluctuation of the free energy of the system. The entropy production due to fluctuation for this kind of quasisteady state system always vanishes. This means that one cannot gain work from a fluctuating environment for these schemes. The stochastic thermodynamic description of the nonequilibrium kinetic system needs an analysis parallel to the present approach.

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