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# States with identical steady dissipation rate in reaction networks: A non-equilibrium thermodynamic insight in enzyme efficiency

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A non-equilibrium steady state is characterized by a non-zero steady dissipation rate. Chemical reaction systems under suitable conditions may generate such states. We propose here a method that is able to distinguish states with identical values of the steady dissipation rate. This necessitates a study of the variation of the entropy production rate with the experimentally observable reaction rate in regions close to the steady states. As an exactly-solvable test case, we choose the problem of enzyme catalysis. Link of the total entropy production with the enzyme efficiency is also established, offering a desirable connection with the inherent irreversibility of the process. The chief outcomes are finally noted in a more general reaction network with numerical demonstrations.

## 1. Introduction

A major shift in the field of thermodynamics in the last century was from idealized equilibrium processes to natural irreversible processes [1–4]. Chemical reactions continue to play a pivotal role in this development and provide significant motivation in studying the non-equilibrium thermodynamic properties of systems *in vitro* as well as *in vivo* [5–10]. Since a closed system always tends to thermodynamic equilibrium (TE), a natural generalization in the theory of irreversible thermodynamics has been achieved via the concept of a steady state [1,11]. In this regard, the quantity of primary importance is the entropy production rate (EPR) [12–14]. The EPR vanishes for a closed system in the long-time limit that reaches a true TE. On the other hand, EPR is positive definite for a steady state that can emerge in an *open* system. The easiest way to model such a system in the context of chemical reactions is to assume that concentrations of some of the reacting species are held fixed [15,16]. Under this condition, aptly known as the chemiostatic condition [17], EPR tends to a non-zero constant, reflecting a steady dissipation rate (SDR) to sustain the system away from equilibrium [18]. The corresponding steady state is denoted as the non-equilibrium steady state (NESS) [19–22]. This concept has been extensively used in analyzing single-molecule kinetic experiments [16,17,23]. The NESS also includes the TE as a special case when detailed balance (DB) is obeyed [24], thus providing a very general framework.

Recently, an important progress was made in the theory and characterization of NESS, considering a master equation formalism [25–27]. These studies have established that the classification of NESS requires *not only* the steady distribution (as in TE) but *also* the stationary fluxes or probability currents. This approach enables one to identify *all possible* combinations of transition rates that ultimately lead the system to the *same* NESS. However, these NESSs in general have different values of the EPR, and hence the SDR.

This proposition prompts one to check (i) how states with the same EPR at NESS can be generated and (ii) whether there exist ways to distinguish these states. Here, we shall address both the issues by considering an enzyme-catalyzed reaction under chemiostatic condition. Expressing the EPR as a function of experimentally measurable reaction rate, we emphasize also that, the quantity that identifies the various NESSs having the same EPR is linked with the enzyme efficiency, a useful measure that is expressible in terms of enzyme kinetic constants.

## 2. The system

The basic scheme of enzyme catalysis within the Michaelis–Menten (MM) framework with reversible product formation step is shown in Fig. 1. Under chemiostatic condition, [S] and [P] are kept constant by continuous injection and withdrawal, respectively. This is the simplest model to mimic an open reaction system. Unlike the usual case of full enzyme recovery with total conversion of substrate into product in a closed system, here both the concentrations of free enzyme E and the enzyme-substrate complex ES reach a steady value. Also, instead of the rate of

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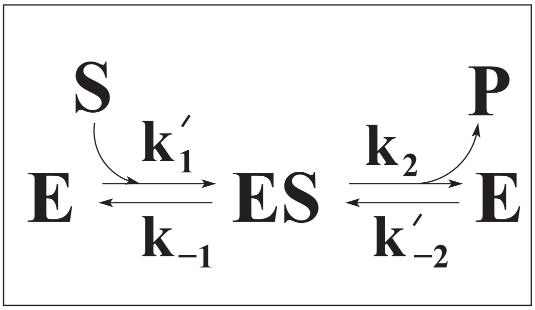

**Fig. 1.** Schematic diagram of MM kinetics of enzyme catalysis with reversible product formation step under chemiostatic condition.

product formation, the progress of reaction is characterized by the rate of evolution of [E] (or [ES]).

### 2.1. Kinetics

We define the pseudo-first-order rate constants as $k_1 = k'_1[\mathrm{S}]$ and $k_{-2} = k'_{-2}[\mathrm{P}]$. Concentration of E is denoted by $c_1(t)$ and that of ES is given by $c_2(t)$. We have then

$$c_1(t) + c_2(t) = z. \tag{1}$$

Here $z$ is a constant that stands for the total enzyme concentration. Then the rate of the reaction, $v(t)$, is written as

$$v(t) = \dot{c_1} = -Kc_1(t) + (k_{-1} + k_2)z, \tag{2}$$

where $K = (k_1 + k_{-1} + k_2 + k_{-2})$. With the initial condition, $c_1(0) = z$, the time-dependent solution is given as

$$c_1(t) = \frac{z}{K}\left((k_{-1} + k_2) + (k_1 + k_{-2})e^{-Kt}\right). \tag{3}$$

The steady state enzyme concentration corresponds to the long-time limit of Eq. (3):

$$c_1^s = ((k_{-1} + k_2)z)/K. \tag{4}$$

At any steady state, we thus note

$$v(t) = \dot{c_1} = 0 = \dot{c_2}. \tag{5}$$

### 2.2. Non-equilibrium thermodynamics

The fluxes of the reaction system are defined pairwise as [2,13,14]

$$J_1(t) = k_1c_1(t) - k_{-1}c_2(t), \tag{6}$$

$$J_2(t) = k_2c_2(t) - k_{-2}c_1(t). \tag{7}$$

From Eqs. (1), (2), (6) and (7), one gets

$$\dot{c_1} = J_2(t) - J_1(t). \tag{8}$$

At the steady state, Eq. (8) leads to

$$J_1^s = J_2^s = J^s. \tag{9}$$

An NESS is characterized by a non-zero flux, $J^s \neq 0$. At TE, the fluxes vanish for both the reactions. One may note, then the system satisfies DB.

The conjugate forces of the fluxes given in Eqs. (6) and (7) are defined as [2]

$$X_1(t) = \mu_E + \mu_S - \mu_{ES} = T\ln\frac{k_1c_1(t)}{k_{-1}c_2(t)}, \tag{10}$$

$$X_2(t) = \mu_{ES} - \mu_E - \mu_P = T\ln\frac{k_2c_2(t)}{k_{-2}c_1(t)}. \tag{11}$$

Corresponding to the scheme depicted in Fig. 1, the EPR is then given by [1,2]

$$\sigma(t) = \frac{1}{T}\sum_{i=1}^{2} J_i(t)X_i(t). \tag{12}$$

We set here (and henceforth) the Boltzmann constant $k_B = 1$. In the present case, the steady value of EPR becomes

$$\sigma^s = \frac{1}{T}J^s(\mu_S - \mu_P). \tag{13}$$

Therefore, unless the substrate and the product take part in equilibrium, the reaction system reaches an NESS with a SDR equal to $\sigma^s$.

## 3. EPR close to NESS

The problem is now transparent. If the rate constants become different, the steady concentrations will also differ. But, one can adjust them in such a way that $\sigma^s$ remains the same. In these situations, one needs an additional parameter to distinguish these states. To proceed, we define a small deviation in $c_1(t)$ around NESS as

$$\delta = c_1(t) - c_1^s. \tag{14}$$

It then follows from Eq. (1) that

$$c_2(t) = c_2^s - \delta. \tag{15}$$

From Eqs. (2) and (14), the reaction rate becomes

$$v(t) = -K\delta. \tag{16}$$

Now, putting Eqs. (6)–(11) and (14)–(16) in Eq. (12) and taking only the first terms of the logarithmic parts, we obtain the EPR close to NESS as

$$\sigma(t) = \mathrm{A}_0 + \mathrm{A}_1 v(t) + \mathrm{A}_2 v^2(t). \tag{17}$$

Here

$$\mathrm{A}_0 = J^s \ln\frac{k_1k_2}{k_{-1}k_{-2}}, \tag{18}$$

$$\mathrm{A}_1 = -\frac{1}{K}\left((k_1 + k_{-1})\ln\frac{k_1c_1^s}{k_{-1}c_2^s} + (k_2 + k_{-2})\ln\frac{k_{-2}c_1^s}{k_2c_2^s}\right), \tag{19}$$

$$\mathrm{A}_2 = \frac{1}{K}\left(\frac{1}{c_1^s} + \frac{1}{c_2^s}\right). \tag{20}$$

As $v(t)$ vanishes at any steady state, the SDR at NESS is given by

$$\sigma^s = \mathrm{A}_0 > 0. \tag{21}$$

However, at TE,

$$\sigma^s = \mathrm{A}_0 = 0; \tag{22}$$

one may check that here DB holds:

$$\frac{k_1k_2}{k_{-1}k_{-2}} = 1. \tag{23}$$

Inspection of Eq. (17) reveals that, near NESS, $\sigma(t)$ varies *linearly* with $v(t)$ with a slope $\mathrm{A}_1$. Thus, while $\mathrm{A}_0$ distinguishes an NESS from a true TE, $\mathrm{A}_1$ plays the same role in identifying systems with the *same* SDR but having *different* time profiles.

## 4. Results and discussion

In this section, we consider various situations where the reaction system reaches NESS with the same SDR. Focusing on Eq. (18), the different cases that keep $\mathrm{A}_0$ invariant are discussed next.