Dissipation, Generalized Free Energy, and a Self-consistent Nonequilibrium Thermodynamics of Chemically Driven Open Subsystems

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Nonequilibrium thermodynamics of a system situated in a sustained environment with influx and efflux is usually treated as a subsystem in a larger, closed “universe”. It remains a question what the minimally required description for the surrounding of such an open driven system is, so that its nonequilibrium thermodynamics can be established solely based on the internal stochastic kinetics. We provide a solution to this problem using insights from studies of molecular motors in a chemical nonequilibrium steady state (NESS) with sustained external drive through a regenerating system, or in a quasi-steady state (QSS) with an excess amount of ATP, ADP, and Pi. We introduce the key notion of minimal work that is needed, $W_{\text{min}}$, for the external regenerating system to sustain a NESS (e.g., maintaining constant concentrations of ATP, ADP and Pi for a molecular motor). Using a Markov (master-equation) description of a motor protein, we illustrate that the NESS and QSS have identical kinetics as well as the Second Law in terms of a same positive entropy production rate. The difference between the heat dissipation of a NESS and its corresponding QSS is exactly the $W_{\text{min}}$. This provides a justification for introducing an ideal external regenerating system and yields a free energy balance equation between the net free energy input $F_{\text{in}}$ and total dissipation $F_{\text{dis}}$ in an NESS: $F_{\text{in}}$ consists of chemical input minus mechanical output; $F_{\text{dis}}$ consists of dissipative heat; and the amount of useful energy becoming heat is the NESS entropy production. Furthermore, we show that for non-stationary systems, the $F_{\text{dis}}$ and $F_{\text{in}}$ correspond to the entropy production rate and housekeeping heat in stochastic thermodynamics, and identify a relative entropy $H$ as a generalized free energy. We reach a new formulation of Markovian nonequilibrium thermodynamics based on only the internal kinetic equation without further reference to the intrinsic degree of freedom within each Markov state. It includes an extended free energy balance and a Second Law which are valid for driven stochastic dynamics with an ideal external regenerating system. Our result suggests new ingredients for a generalized thermodynamics of self-organization in driven systems.

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I. INTRODUCTION

Statistical thermodynamics is the mathematical foundation of the material world in terms of classical physics, on which modern chemistry and biology is based. To address the fundamental issues in complex living organisms such as a cell, there are currently two rather different perspectives: A classical physicist maintains a world following the Clausius-Boltzmann’s Second Law of Thermodynamics and considers a living organism as a subsystem in a quasi-stationary state (QSS), due to the slow-changing nature of its environment. According to this view, the thermodynamic origin of a living system resides in the fluctuations of its environment. On the other hand, engineers and cellular biologists consider a complex system in a sustained environment that has to be maintained. How to maintain such environment is not a concern to someone who is only interested in the internal, complex kinetics. In equilibrium statistical physics, these two perspectives have yielded respectively Boltzmann’s microcanonical and Gibbsian canonical ensemble theories of matters.

For isothermal but chemically nonequilibrium systems, this distinction can be best illustrated by two types of laboratory experiments on a single motor protein which converts chemical energy from ATP hydrolysis in an aqueous solution to mechanical work at the sub-cellular level. In the first type of experiments, the amount of ATP, ADP and Pi in the solution are not controlled. However, due to the excess nature of their amount in solution, their concentrations can be considered approximately constant over the entire duration of a single-molecule experiment. Nevertheless, if an experiment is prolonged for a significant period of time, the ATP and ADP+Pi will eventually reach their chemical equilibrium, and the motor protein will cease to execute a directional motion. In the second type of experiments, an ATP-regenerating system is coupled to the motor protein. In this case, the motor protein, as an open, driven chemical system, can reach a nonequilibrium steady state (NESS) with cyclic conformational kinetics while continuously moves along its track, even in the presence of a mechanical load.

In the stochastic, kinetic theories of single motor proteins, both the QSS and NESS are treated math-

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ematically by assuming time-independent, constant concentrations of ATP, ADP and Pi, which leads to identical predictions of the kinetics. The changes in the ATP, ADP, and Pi concentrations in QSS are so miniscule, they can be safely neglected.

From the thermodynamic point of view, the Markovian transition rates for a complete conformational cycle of a single motor protein, say with totally n states, no matter in QSS or NESS, satisfy (see below and also [14])

\[ k_B T \ln \left( \frac{k_{1 \rightarrow 2} k_{2 \rightarrow 3} \cdots k_{n \rightarrow 1}}{k_{1 \rightarrow 1} k_{2 \rightarrow 2} \cdots k_{n \rightarrow n}} \right) = \Delta \mu_{\text{ATP} \rightarrow \text{ADP} + \text{Pi}} - W_{\text{mechanical}} \]

which is precisely the chemical free energy of a single ATP hydrolysis minus the amount of motor mechanical energy output [2, 7, 8, 12], i.e. the net amount of free energy input over the cycle. When this net amount of free energy input is zero, the internal kinetics satisfies detailed balance [13].

A few remarks to (1) are in order. First, we note that for a complete kinetic cycle, the affinity

\[ \gamma = \frac{k_{1 \rightarrow 2} k_{2 \rightarrow 3} \cdots k_{n \rightarrow 1}}{k_{1 \rightarrow 1} k_{2 \rightarrow 2} \cdots k_{n \rightarrow n}} \]

\[ = \frac{c_1(t) k_{1 \rightarrow 2}}{c_2(t) k_{2 \rightarrow 1}} \times \frac{c_2(t) k_{2 \rightarrow 3}}{c_3(t) k_{3 \rightarrow 2}} \times \cdots \times \frac{c_n(t) k_{n \rightarrow 1}}{c_1(t) k_{1 \rightarrow n}} \]

\[ = \frac{c_1^s k_{1 \rightarrow 2}}{c_2^s k_{2 \rightarrow 1}} \times \frac{c_2^s k_{2 \rightarrow 3}}{c_3^s k_{3 \rightarrow 2}} \times \cdots \times \frac{c_n^s k_{n \rightarrow 1}}{c_1^s k_{1 \rightarrow n}} \]

in which \( c_i(t) \) is the concentration of the motor protein in state \( i \) at time \( t \), and \( c_i^s \) is its steady-state concentration, assuming the protein solution is ideal, e.g., single molecular kinetics are statistically identical and independent. In terms of classical chemical thermodynamics in the absence of a mechanical force (\( W_{\text{mechanical}} = 0 \)), the (2a) corresponds to the free energy difference of one ATP hydrolysis, which is independent of the motor protein. Every term in (2b) and (2c) corresponds to the free energy difference of each chemical transformation step including conformational change within this cycle, as the protein is in a transient state or an steady state. But at the level of a complete cycle with the motor protein returning to its beginning state, all the concentration terms drop out and they all become the same. Therefore, as repeated pointed out by T.L. Hill [2, 13, 16], the net amount of free energy dissipation on a cycle level is unambiguous and constitutes the entropy production.

Second, Eq. (2) clearly shows that just as each individual reaction is the fundamental “unit” of a complex chemical equilibrium, each kinetic cycle is the fundamental “unit” of a chemical NESS. This insight has been discussed extensively in [11, 13], which include a mathematical theorem of cycle decomposition at NESS. In a NESS at the cycle level, the free energy input and free energy dissipation are also balanced. The steady state flux distribution among the cycles provides the probability “weight” for the stochastic kinetics.

Third, we see that the internal stochastic kinetics does not differentiate between the amount of chemical energy input and the negative amount of mechanical output; only the net amount of free energy input. This confirms the statement that “one needs to know more than subsystem kinetics to deal with the full First Law” [17, 18]. In fact, the traditional concept of efficiency, which is observed by an “outsider” to the system, can not be determined from the internal kinetics alone. It indicates, however, that if an outside agent can differentiate the chemical input and the mechanical output, then the efficiency of the subsystem at NESS has the appropriate upper-bound:

\[ \frac{\text{mechanical output}}{\text{chemical input}} = 1 - \frac{\text{entropy production}}{\text{chemical input}} \leq 1. \]

Positive entropy production, thus, is the origin of less-than-100% efficiency. All the complications in maintaining the NESS, of course, contribute to a positive entropy production rate, thus a lower efficiency. When a subsystem is in equilibrium with its surrounding, the efficiency is 1, but its actual power is zero. See a discussion of this singular problem in terms of futile cycles [19] and the recent studies on efficiency at maximum power [20, 21].

A complete discussion of energetics requires further detailed thermodynamics beyond the level of free energy, which is decomposed into entropy and enthalpy (or intrinsic energy for system with constant volume). Onto this level, the two setups NESS and QSS become very different [17]: In the QSS, the heat associated with each kinetic cycle is the enthalpy change \( \Delta h \) of ATP hydrolysis. For the NESS, the heat analysis for the ATP-regenerating system is much more complicated.

The objective of the present paper is two-fold: First, in Sec. II a more concrete and detailed energetic comparison, including the First Law and reaction heat, is carried out for the QSS and NESS. With an additional piece of information concerning what exactly the regenerating system does, we show that Eq. (1) is also the minimal amount of heat dissipated possible to sustain the NESS. We shall call a regenerating system with the minimal heat dissipation ideal. Equipped with this novel notion, we show that the entropy production of a Markov process defines the amount of dissipated “heat”, and the equation in (1) is a form of “free energy balance” at NESS, e.g., analogous to the First Law. Our theory shows consistency and contradistinctions in thermodynamics of energy transduction and heat dissipation in the two different perspectives of nonequilibrium systems, QSS and NESS à la Clausius and Kelvin.

Then in Sec. III for non-stationary process, we can further generalize the free energy balance equation and identify a generalized free energy, together with a Second Law. When there is only internal stochastic dynamical information, without any detailed knowledge about the intrinsic degrees of freedom of each Markov discrete
state, as in many applications of Markov models to non-molecular systems, we have to forgo the traditional First Law on energy conservation. Interestingly, if we only focus on the level of free energy, we will get a conservation law of a generalized free energy

$$H \left( \{ c_i \} \| \{ c^s_i \} \right) = k_B T \sum_i c_i \ln \left( c_i / c^s_i \right), \quad (4)$$

for a system approaching NESS, which is suggested recently from the mathematical point of view [15, 22–24]:

$$\frac{d}{dt} H \left( \{ c_i(t) \} \| \{ c^s_i \} \right) = F_{in}(t) - F_{dis}(t); \quad (5a)$$

in which

$$F_{in}(t) = k_B T \sum_{ij} (c_i k_{ij} - c_j k_{ji}) \ln \left( \frac{c^s_i k_{ji}}{c^s_j k_{ij}} \right) \geq 0, \quad (5b)$$

$$F_{dis}(t) = k_B T \sum_{ij} (c_i k_{ij} - c_j k_{ji}) \ln \left( \frac{c_i(t) k_{ji}}{c_j(t) k_{ij}} \right) \geq 0, \quad (5c)$$

and $F_{dis}(t)$ can be further decomposed into

$$F_{dis}(t) = T dS/dt + k_B T \sum_{ij} (c_i k_{ij} - c_j k_{ji}) \ln \left( \frac{k_{ij}}{k_{ji}} \right), \quad (5d)$$

where $S(t) = -k_B \sum_i c_i \ln c_i$ and $k_{ij}$ the transition rate from Markov state $i$ to $j$. However, the novel mathematical results [6], only dependent on the internal kinetics, still beg for a clear thermodynamics interpretations, at least in the simple example of motor protein.

We will show in Sec. III that the nonnegative $F_{in}(t)$, also called housekeeping heat [22, 23, 24, 26], can be regarded as the free energy input to sustain the corresponding NESS, while the entropy production rate $c_\mu(t) = \sum_{ij} F_{dis}(t)$ is just the dissipation at the level of free energy. They are equal to each other in steady state. These two important quantities are all independent of intrinsic degrees of freedom of each chemical/conformational state.

Hence Eq. (5a) is most reasonably interpreted as:

\textit{change in the generalized free energy = source (free energy and work) − sink (dissipation).}

This is a law of balance for the extensive quantity $H$. One can understand how to construct the $H$ as a generalized free energy.

The function $H$ indicates how far the system deviates from the sustained NESS [27]. When a system is very far from its NESS, it has a large $H$, then the non-stationary condition of the system constitutes a source of entropic force which can be utilized; and $H = 0$ when a system is at its NESS.

Based on this newfound NESS perspective, in Sec. III part we shall also show that the new perspective further yields an extended Second Law, which emerges only from driven kinetics with an idealized external regenerating system.

\section{Energetic Comparison and Nonequilibrium Thermodynamics Between QSS and NESS}

The nonequilibrium thermodynamical analysis of the QSS is quite traditional. It follows the original idea of Boltzmann and it is generally applicable: Heat, work, entropy, free energy and other thermodynamic quantities are all well defined. Unfortunately, such an analysis could not be carried out solely based on the internal kinetics of the subsystem; one needs to know nearly every detail of the surroundings e.g. particles in the solution and their interactions [17]. Furthermore, except with extensive studies on temperature dependence, what is heat is never unambiguous [28]. Therefore for the engineers or cellular biologists who are only interested in the internal kinetics of the motor protein, a self-consistent and nearly self-contained thermodynamics is highly desirable. In this part we develop the NESS perspective and try to deduce important thermodynamic relations from internal stochastic kinetics, plus additional information: (A) The identification of the input free energy and output work. Usually for motor the input is chemical free energy and the output is mechanical work. (B) Further decomposition of free energies into their entropic and enthalpic parts.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{The thermodynamics of spontaneous ATP hydrolysis and related ATP regenerating process. The entire cycle would have an $\Delta \mu > 0$ amount of net free energy input and the same amount of energy dissipated. $\Delta \mu$ is just the free energy change of the ATP hydrolysis minus the amount of mechanical energy output. See the main text for details.}
\end{figure}

\subsection{Minimal external work, ideal regenerating system, and an energy balance equation for a subsystem}

Fig. 1 shows a simple biochemical reaction cycle $B \rightarrow C \rightarrow B$ coupled to ATP hydrolysis. The ATP, ADP and Pi concentrations are maintained by an “external” regenerating system:

$$B + ATP \overset{k_1}{\underset{k_{-1}}{\rightleftharpoons}} C + ADP, \quad C \overset{k_2}{\underset{k_{-2}}{\rightarrow}} B + Pi. \quad (6)$$

After completing a reaction cycle (6), the net effect is one ATP being hydrolyzed to ADP+Pi. At the meantime, the regenerating system would convert ADP+Pi
back to ATP externally. This is the essential difference between NESS and QSS which results in one ATP hydrolysis after one cycle. Standard thermodynamics tells us the chemical potentials of each species are defined as

\[ \mu_B = \mu_B^0 + k_BT \ln[B], \quad \mu_C = \mu_C^0 + k_BT \ln[C], \]
\[ \mu_{ATP} = \mu_{ATP}^0 + k_BT \ln[ATP], \]
\[ \mu_{ADP} = \mu_{ADP}^0 + k_BT \ln[ADP], \]
\[ \mu_{Pi} = \mu_{Pi}^0 + k_BT \ln[Pi]. \]

(7)

At chemical equilibrium, \( \mu_B + \mu_{ATP} = \mu_C + \mu_{ADP} \) and \( \mu_B + \mu_{Pi} = \mu_C \), i.e. \( k_1[B]^{0}[ATP]^{0} = k_{-1}[C]^{0}[ADP]^{0} \) and \( k_2[C]^{0} = k_{-2}[B]^{0}[Pi]^{0} \), which also leads to the thermodynamic relations

\[ \mu_B^0 + \mu_{ATP}^0 - \mu_C^0 - \mu_{ADP}^0 = k_BT \ln \left( \frac{k_1}{k_{-1}} \right), \]
\[ \mu_C^0 - \mu_B^0 - \mu_{Pi}^0 = k_BT \ln \left( \frac{k_2}{k_{-2}} \right). \]

(8) (9)

For a complete cycle, one combines Eqs. (7), (8) and (9). The \( \mu_B^0 \)'s and \( \mu_C^0 \)'s in the two reactions in (6) cancel out, and one is left with

\[ \Delta \mu_{ATP \rightarrow ADP+Pi} = \mu_{ATP} - \mu_{ADP} - \mu_{Pi} = k_BT \ln \left( \frac{k_1 k_2 [ATP]}{k_{-1} k_{-2} [ADP] [Pi]} \right). \]

(10)

a special case of the Eq. (11).

Each intrinsic chemical potential can be further decomposed into \( \mu_i = h_i^0 - TS_i^0 \), where \( h_i^0 \) and \( S_i^0 \) are the intrinsic enthalpy and entropy respectively. Then for a single occurrence of the hydrolysis cycle in Fig. 11 the heat dissipation is

\[ Q_d = \left( h_B^0 + h_{ATP}^0 - h_C^0 - h_{ADP}^0 \right) + \left( h_C^0 - h_{Pi}^0 - h_B^0 \right) = h_{ATP}^0 - h_{ADP}^0 - h_{Pi}^0. \]

(11)

Note that the \( Q_d \) can be negative, or even greater than the hydrolysis free energy in (10). This portion of the energy is stored in chemical bond of an ATP molecule.

With the presence of a regenerating system, there is an “external step” converting ADP+Pi back to ATP after each completion of an enzyme cycle. The minimum work (non-PV work) it has to do is the free energy difference between ADP+Pi and ATP, i.e.

\[ W_{min} = \mu_{ATP} - \mu_{ADP} - \mu_{Pi} = \Delta \mu_{ATP \rightarrow ADP+Pi}, \]

(12)

with corresponding enthalpy changes \( -Q_d \). Therefore, the energy dissipation of this external step in the environment, in the form of heat, is

\[ Q_d^{ext} = W_{min} - (h_{ATP}^0 - h_{ADP}^0 - h_{Pi}^0). \]

(13)

We note that \( Q_d^{ext} \) is just the entropy change, off by a temperature factor, for the ATP hydrolysis.

Hence the total heat dissipation of a single forward biochemical cycle in a driven system with regeneration is

\[ Q_{tot} = Q_d + Q_d^{ext} = W_{min} = \Delta \mu_{ATP \rightarrow ADP+Pi} = k_BT \ln \gamma, \]

(14)

where \( \gamma = \frac{k_1 k_2 [ATP]}{k_{-1} k_{-2} [ADP] [Pi]} > 1 \) is the affinity for the reaction cycle.

If, however, the regenerating system is not perfectly efficient, then \( W_{actual} > W_{min} \) and part of it is wasted in the process: \( \delta = W_{actual} - W_{min} \). It follows that \( Q_d^{ext} = W_{actual} - Q_d = W_{min} - Q_d + \delta = k_BT \ln \gamma + \delta \). We call a regenerating system with \( \delta = 0 \) ideal. Therefore, with the assumption of an ideal regenerating system, a balance between chemical free energy and heat can be established, on the level of kinetic cycles.

Now if there is an external, mechanical force exerted on the motor, then the minimum external work to sustain the NESS is still \( W_{min} = \Delta \mu_{ATP \rightarrow ADP+Pi} \), but \( \Delta \mu_{ATP \rightarrow ADP+Pi} \) is no longer equal to \( k_BT \ln \gamma \). Their difference is the mechanical output of the system, i.e. \( F_d \), where \( F \) is the force and \( d \) is the step size of the motor with one ATP hydrolysis. Hence Eq. (11) becomes a form of energy balance. When \( \gamma > 1 \), all the chemical input minus the mechanical output is dissipated while the system remaining steady.

We see the central importance of cycle kinetics from this simple example. Before a completion of a cycle, the regenerating system needs not to do anything to maintain the environment, and all the work done to “the system” is potentially reversible. This has been emphasized by T.L. Hill [16]; a similar argument was put forward by R. Landauer for the thermodynamics of computation [30].

B. Master equation system and thermodynamic constrains

The above results for a single biochemical cycle can be generalized to dynamical models with master equations: Let us consider a motor protein with \( N \) different conformations \( R_1, R_2, \cdots, R_N \). Suppose that the system is kept in a close contact with a large heat bath with constant temperature \( T \) and pressure. For simplicity, the concentration of every substance is assumed to be independent of its position, and there is no external input or output of mechanical energy. Introducing the mechanical part is straightforward as illustrated for the single cycle above.

Let \( k_{ij} \) be the first-order, or pseudo-first-order rate constants for reaction \( R_i \rightarrow R_j \). Assume only one of them is coupled with a chemical free energy source, i.e., ATP and ADP:

\[ ATP + R_i \xrightarrow{k_{i2}} ADP + R_2, \]

where \( k_{i2} \) and \( k_{21} \) are both second-order reaction constants, and \( k_{12} = k_{12}[ATP], k_{21} = k_{21}[ADP] \) are pseudo-first-order rate constants. For simplicity, here we omit the Pi release step, since what we need here is only the reaction \( R_1 \rightarrow R_2 \) having a driving force.

Let \( c_i \) be the concentration of \( R_i \). Then by the law of mass action, such a linear system could be described in
terms of a mathematical model
\[
\frac{dc_i(t)}{dt} = \sum_j (c_j k_{ji} - c_i k_{ij}), \quad (15)
\]

If there is no external mechanism to keep the concentrations of ATP and ADP, then the time evolution of \(c_T = [\text{ATP}]\) and \(c_D = [\text{ADP}]\) is
\[
\frac{dc_T}{dt} = \frac{dc_D}{dt} = -\tilde{k}_{12} c_T c_1 + \tilde{k}_{21} c_D c_2. \quad (16)
\]

Classical equilibrium thermodynamics for closed chemical systems tells us that there is a unique dynamic and chemical equilibrium \(\{c_1^{eq}, c_2^{eq}, \ldots, c_N^{eq}, c_T^{eq}, c_D^{eq}\}\) which satisfies the detailed balance condition \(c_i^{eq} k_{ij} = c_j^{eq} k_{ji}\), where \(k_{12} = \tilde{k}_{12} c_T^{eq}\) and \(k_{21} = \tilde{k}_{21} c_D^{eq}\).

Each species has a chemical potential \(\mu_i(c_i) = \mu_i^0 + k_B T \ln c_i\), where \(\mu_i^0\) is the internal chemical potential of species \(R_i\) and obeys the Boltzmann’s law \(\mu_i = -k_B T \ln c_i^{eq} + \text{const}\). When a system reaches chemical equilibrium, the chemical potentials of different components are the same, i.e. \(\mu_i(c_i^{eq}) = \mu_j(c_j^{eq})\), and \(\mu_i(c_i^{eq}) + \mu_T(c_T^{eq}) = \mu_2(c_2^{eq}) + \mu_D(c_D^{eq})\), where \(\mu_T(c_T) = \mu_T^0 + k_B T \ln c_T\) and \(\mu_D(c_D) = \mu_D^0 + k_B T \ln c_D\) are the chemical potentials of ATP and ADP respectively.

Then it gives the relation between \(\mu_i^0\)'s and \(k_{ij}\)'s of the system, i.e.
\[
\begin{align*}
\mu_i^0 - \mu_j^0 &= k_B T \ln \frac{k_{ji}}{k_{ij}}, \\
\mu_T^0 - \mu_D^0 &= k_B T \ln \frac{c_T^{eq}}{c_T}, \\
\mu_T^0 + \mu_D^0 - \mu_2^0 - \mu_1^0 &= k_B T \ln \frac{k_{12}}{k_{21}}. \quad (17)
\end{align*}
\]

C. Thermodynamics of subsystem QSS within a larger closed system with detailed balance

In this case, the whole system is closed including ATP and ADP; its final dynamical equilibrium is a chemical equilibrium. The total free energy of the system with concentrations \(c_i, c_D,\) and \(c_T\), is
\[
F^{close} = \sum_i c_i \mu_i + c_T \mu_T + c_D \mu_D.
\]

\(F^{close}(t)\) always decreases until it reaches to its minimum at equilibrium:
\[
\frac{dF^{close}(t)}{dt} = -k_B T \sum_{i,j} (c_i k_{ij} - c_j k_{ji}) \ln \left( \frac{c_j k_{ij}}{c_i k_{ji}} \right) \leq 0. \quad (18)
\]
The term \(f_T^{close} = -dF^{close}(t)/dt\) is called free energy dissipation rate [22].

For each chemical/conformational state \(i\) of the motor protein, the internal entropy \(T s_i^0 = h_i^0 - \mu_i^0\). Thus the entropy of the entire system could be defined as \(\tilde{S}^{close} = S^0 + S^{close}\), where \(S^0 = \sum_i s_i^0 c_i + s_T^0 c_T + s_D^0 c_D\) and \(S^{close} = k_B \sum_i [-c_i \ln c_i] - c_T \ln c_T - c_D \ln c_D\). Then the evolution of entropy becomes
\[
\frac{dS^{close}}{dt} = e_p^{close} - \frac{h_d^{close}}{T}, \quad (19)
\]
where
\[
\tilde{h}_d^{close} = \frac{1}{2} \sum_{ij} (c_i k_{ij} - c_j k_{ji}) (h_i^O - h_j^O) + (c_1 k_{12} - c_2 k_{21}) (h_T^O - h_D^O)
\]
is the heat dissipation, and the entropy production rate \(T e_p^{close} = f_T^{close} [1, 2, 11, 24]\). The entropy of the system increases due to entropy generated in spontaneous processes and decreases when heat is expelled into the surrounding. Eq. (19) is an example of the entropy balance equation of Dutch School’s nonequilibrium thermodynamics \(dS/dt = dS_{sys}/dt + dS_{surf}/dt [1, 31]\).

If one only regards the motor protein as the unique target system, and define \(\tilde{S}^{motor} = \sum_i s_i^0 c_i - k_B \sum_i c_i \ln c_i = \tilde{S}^{close} - \tilde{S}_{ATP,ADP}\), then we have
\[
\frac{d\tilde{S}^{motor}}{dt} = e_p^{motor} - \frac{\tilde{h}_d^{motor}}{T}, \quad (20)
\]
where \(e_p^{motor} = e_p^{close}\), and \(\tilde{h}_d^{motor} = \tilde{h}_d^{close} + T d\tilde{S}_{ATP,ADP}\). Here we notice that the definition of entropy and entropy production rate are independent of the mechanical details of the environment, but the traditional definition of heat, i.e., \(h_d^{close}\), is. It involves the entropy change in the solution resulting from the reaction [17]. One needs to overcome such a non-self-containment in order to reach a thermodynamic framework solely based on the internal kinetics of the target system, which is at NESS.

D. Thermodynamics of nonequilibrium driven system

With the presence of an ideal external regenerating mechanism, the concentrations of ATP and ADP would be kept invariant. The system is not at equilibrium in general [32]. The internal chemical kinetics is again described by (15), which approaches to a NESS. Once the concentrations of ATP and ADP are sustained, since the stochastic kinetics of all the motor proteins are statistically identical and independent, we could substitute the concentration with probability in (15), and talk about stochastic thermodynamics with a single-molecule perspective [17].

Recall that each \(\mu_i^0\) could be decomposed into \(h_i^0 - T s_i^0\), hence for each individual occurrence of the transition \(R_i \rightarrow R_j\), the heat dissipation is \(h_i^0 - h_j^0\) which is not coupled with the regenerating system. However, for the real driven reaction \(ATP + R_1 \rightarrow ADP + R_2\), the total heat dissipation should be \((h_1^0 + \mu_T) - (h_2^0 + \mu_D)\) following the above analysis of the simple example in Fig. [1]
Therefore the heat dissipation rate in such a driven open system is
\[
\tilde{h}_d^{open}(t) = \sum_{i>j} (c_i(t)k_{ij} - c_j(t)k_{ji}) (h^o_i - h^o_j) + (c_i(t)k_{12} - c_2(t)k_{21}) (\mu_T - \mu_D)
\]
Furthermore, the heat dissipation in the stationary NESS becomes
\[
\tilde{h}_d^{NESS} = \sum_{i>j} (c^{eq}_i k_{ij} - c^{eq}_j k_{ji}) (\mu^o_i - \mu^o_j) + (c^{eq}_i k_{12} - c^{eq}_2 k_{21}) (\mu_T - \mu_D)
\]
\[
= k_BT \sum_{i>j} (c^{eq}_i k_{ij} - c^{eq}_j k_{ji}) \ln \frac{k_{ij}}{k_{ji}}.
\]
(21)
The rigorous derivation of (21) is based on the fact that in an NESS, its kinetics and thermodynamics can be decomposed into different cycles [1, 2, 11, 24]. As we have stated, the regenerating system would not really do any irreversible work unless there is a completion of a driven cycle. The amount of minimum work, done by the ideal regenerating system, for each internal cycle \(\{i_0 \rightarrow i_1 \rightarrow i_2 \cdots \rightarrow i_n \rightarrow i_0\}\) is
\[
W_{min}^c = k_BT \ln \frac{k_{i_0 i_1} k_{i_1 i_2} \cdots k_{i_n i_0}}{k_{i_0 i_n} k_{i_1 i_0} \cdots k_{i_{n-1} i_1}},
\]
which is also equal to the total heat dissipation \(Q_{tot}^c\) for the same cycle.

For each state \(i\), the internal entropy \(T_s^o_i = h^o_i - \mu^o_i\). Thus the entropy of the open system could be defined as \(S^{open} = S^o + S^{open}\), where \(S^o = \sum_i s^o_i c_i\) and \(S^{open} = -k_B \sum_i c_i \ln c_i\). The evolution of entropy, thus,
\[
\frac{dS^{open}}{dt} = e^p_{\text{open}} - \frac{\tilde{h}_d^{open}}{T},
\]
(22)
where \(e^p_{\text{open}} = k_BT \sum_{i>j} (c_i k_{ij} - c_j k_{ji}) \ln \frac{c_i}{c_j} k_{ij}/k_{ji}\) is the entropy production rate [1, 2, 11, 24]. The “heat term” \(\tilde{h}_d^{open}\) in Eq. (20) now finally becomes real heat and is completely independent of the any details on the regenerating system.

One could easily notice that the entropy \(S^{open} = S^{\text{motor}}\), and more important \(T^{open} = T^{\text{motor}} = T^{close} = f_d^{close}\). It indicates that the entropy production rate is indeed independent of the QSS or NESS perspectives of the subsystem. More importantly, this shows a consistency between the different perspectives of Boltzmann/Gibbs and Prigogine for the traditional Second Law: Boltzmann states entropy never decreases in an isolated system and Gibbs states free energy never increases in a closed isothermal system; while Prigogine states that the entropy production is never negative in an open system, and it can be defined solely from internal kinetics. They are equivalent.

Thus the free energy of the open system
\[
\tilde{F}^{open} = h^o - TS^{open} = \mu^o - TS^{open},
\]
where \(h^o = \sum_i h^o_i c_i\) is the enthalpy, and \(\mu^o = \sum_i \mu^o_i c_i\) is the internal (conditional) free energy of the system. Note that no matter how large the entropic component of \(\mu^o\) is, \(T\delta s^o_i\) enters both \(h^o\) and \(T\delta S^{open}\) and they compensate, leaving \(\tilde{F}^{open}\) invariant [33]. The evolution of such a free energy function would not always decrease any more, which spurred the discovery of relative entropy as a generalized free energy for NESS (see below).

E. Housekeeping heat: the driver of NESS

In the NESS perspective, the heat dissipation for the transition \(i \rightarrow j\) is \(Q_{ij} = k_BT \ln(k_{ij}/k_{ji}) + T(s^o_i - s^o_j)\) no matter coupled with the driving force or not; and meanwhile, the steady-state entropy also could be defined for this single transition [34] as \(\Delta S^{ss}_{ij} = k_B \ln (c_i^{NESS}/c^{NESS}_j) + (s^o_i - s^o_j)\). Therefore, the housekeeping heat \(Q_{hk} = F_{\text{open}}\) in (55) is just ensemble averaged difference between \(T\Delta S^{ss}_{ij}\) and \(Q_{ij}\), which is equal to the entropy production rate at NESS.

Housekeeping heat \(Q_{hk}\) is really the nonequilibrium driver of the system. \(Q_{hk}(t) \equiv 0\) if and only if \(T\Delta S^{ss}_{ij} + Q_{ij} = 0\), which matches the classic definition of equilibrium entropy difference through a reversible process. Hence for master equation with detailed balance which correspond to closed system, \(Q_{hk}(t) \equiv 0\) whenever the system is in the steady or any transient state.

Some might argue that the definition of steady-state entropy contains ensemble information, hence it could not be defined along a stochastic path. We think it is indispensable to distinguish the stationary and instantaneous concentration/distribution of the system. Although the former one still could be regarded as an ensemble property, it is measurable through ergodic internal kinetics, which is only dependent on molecular structures as well as solvent concentrations. Hence, it could somehow still be considered as “intrinsic” property, without a need for an ensemble picture.

F. Efficiency for the chemical to mechanical energy transduction in a NESS

A molecular motor is a mechanical system coupled fully reversibly to a chemical reaction or reactions, with an external force \(F_{\text{mechanical}}\) resisting the mechanical movement driven by the chemical gradient. The external force \(F_{\text{mechanical}}\) does not effect the \(\Delta \mu_{\text{ATP} \rightarrow \text{ADP} + \text{Pi}}\), which is still equal to \(W_{\text{min}}\). Rather, the logarithmic affinity in Eq. (1) now contains a chemical part and a mechanical part. The \(F_{\text{mechanical}}\), therefore, reduces the amount of entropy production as well as the dissipation. However, when the \(F_{\text{mechanical}}\) is greater than the stalling force, the entropy production again increases and the mechanical energy is now being converted into chemical potential, i.e., the chemical flux is against the chemical potential in ATP synthesis. This scenario has been realized in the
reversely run $F_0F_1$ ATPase becoming a ATP synthetase$^{[3,6]}$. On the other hand, the reversal of chemomechanical energy transduction would not occur if the coupling is not fully reversible. A load from a viscous drag force is an example. The direction of the force is always against the stochastic flux that generates movements.

Quantitatively, in the case of chemical to mechanical transduction, the energy conservation is $W_{\min}\times J_{c\rightarrow m} = T\cdot e_p^{open} + P_{\text{mech}}$ where $P_{\text{mech}}$ is a mechanical power, and the efficiency $\eta = \frac{T\cdot e_p^{open} + P_{\text{mech}}}{W_{\min}\times J_{c\rightarrow m}} \leq 1$. In the opposite direction, the above $P_{\text{mech}}$ and $J_{c\rightarrow m} < 0$. Hence, $\eta = \frac{W_{\min}\times J_{c\rightarrow m} + T\cdot e_p^{open}}{W_{\min}\times J_{c\rightarrow m}} \leq 1$. We see that whether the energy transduction is chemical to mechanical or the opposite, the entropy production is always the total dissipation and it is nonnegative, resulting in a less than 100% efficiency. Although such an expression of energy transduction efficiency has been used in many previous works$^{[14,20]}$, its physical meaning becomes more clear now.

### III. Self-consistent nonequilibrium thermodynamics at the level of free energy

In reality, we usually know little about internal degrees of freedom of each Markov state, especially as we study the biological processes. Enlightened by the detailed comparison of QSS and NESS systems as well as the thermodynamic relation$^{[17]}$, we realized that the internal kinetics of the system, e.g. the transition between different conformational states of the motor protein, is essentially related to free energy rather than the intrinsic enthalpy or entropy of each chemical/conformational state. In statistical chemistry, this is the notion of “conditional free energy” for discrete states, or “potential of mean force” for continuous variables$^{[33]}$.

We now propose a self-consistent nonequilibrium thermodynamics of a chemically driven open system with sustained surroundings at the level of free energy, only based on the internal kinetics of the system, which is in a time-dependent transient state toward the corresponding NESS.

#### A. Intrinsic free energy dissipation

At the level of free energy, one can first define the intrinsic free energy dissipation

\[ F_{\text{dis}}^o(t) = \sum_{i>j} (c_i(t)k_{ij} - c_j(t)k_{ji}) \Delta \mu_{ij}^o + (c_1(t)k_{12} - c_2(t)k_{21}) (\mu_T - \mu_D) = k_B T \sum_{i>j} (c_i k_{ij} - c_j k_{ji}) \ln \frac{k_{ij}}{k_{ji}}, \]  

(23)

where $\Delta \mu_{ij}^o = \mu_i^o - \mu_j^o$ is the intrinsic free energy difference between the states $i$ and $j$. At steady state, it is just equal to the heat dissipation $\tilde{h}_{\text{dis}}^{open}$, which implies the thermodynamics at the level of free energy or at more detailed level of intrinsic enthalpy and entropy are the same at NESS. However, the heat dissipation at the transient state is dependent on the decomposition of free energy of each chemical/conformational state into entropy and enthalpy, which is beyond the level of free energy. Hence now we shall use the intrinsic free energy dissipation instead of the heat dissipation.

#### B. Entropy production as the free energy dissipation

In the case of QSS, we already know that $Te_p^{close} = f_{d}^{close}$, which implies the entropy production rate is ultimately related to the free energy dissipation. Still, in the open driven system, we can also interpret the entropy production rate $Te_p^{open}$ as

\[ Te_p^{open}(t) = \sum_{i>j} (c_i(t)k_{ij} - c_j(t)k_{ji}) \Delta \mu_{ij} + (c_1(t)k_{12} - c_2(t)k_{21}) (\mu_T - \mu_D) = k_B T \sum_{i>j} (c_i k_{ij} - c_j k_{ji}) \ln \frac{c_i k_{ij}}{c_j k_{ji}}, \]  

(24)

where $\Delta \mu_{ij} = \mu_i - \mu_j$ is the free energy difference between the states $i$ and $j$. Hence $F_{\text{dis}}(t) = Te_p^{open}(t)$ is the total free energy dissipation.

#### C. Housekeeping heat as the free energy input by the external regenerating system

In the previous sections, we have shown that the housekeeping heat indicates the active driver of a system, e.g., whether an external regenerating system is present. If the corresponding steady-state is an equilibrium, i.e. a system is not externally driven, then the housekeeping heat vanishes for all time even when the system is in a time-dependent transient state.

We also notice that, except $\Delta \mu_{12}^{ss} = \mu_1^{ss} - \mu_2^{ss} + \mu_T - \mu_D$, all other $T\Delta S_{ij}^{ss} - Q_{ij} = \Delta \mu_{ij}^{ss}$, where $\Delta \mu_{ij}^{ss} = \mu_i^{ss} - \mu_j^{ss}$ is actually the NESS free energy difference along the transition from the state $i$ to $j$, which should be always sustained by the external regenerating system. Therefore, the housekeeping heat $Q_{hh}(t)$ could be regarded as the total free energy input $F_{\text{in}}(t)$ to drive such a nonequilibrium system.

In fact, if one knows the entry points for the external free energy input, one can rewrite $F_{\text{in}}$ as

\[ F_{\text{in}} = \frac{d}{dt} \left[ \sum_i \mu_i^{ss} p_i \right] + (\mu_T - \mu_D) (p_1(t)k_{12} - p_2(t)k_{21}). \]
D. Generalized free energy and its time evolution

For a system approaching equilibrium, the free energy input $F_{in} = Q_{hh}$ is zero while the free energy dissipation $T c_p^{close}$ is exactly the derivative of the function $H$ in (5a), which is actually the free energy deviation from the equilibrium (27), and then Eq. (5a) is reduced to (18).

For a system approaching NESS, both the free energy input and dissipation are positive. Interestingly, the net free energy dissipation $F_{dis}^{net} (t) = F_{dis} (t) - F_{in} (t)$ is still the derivative of the function $H$ in (4). Hence at the level of free energy, we can regard $H$ as a generalized free energy at this specific level, whose time evolution is characterized by (5a), i.e.

$$\frac{d}{dt} H \{c_i (t) \} \{c_i^{ss} \} = F_{in} (t) - F_{dis} (t). \quad (25)$$

E. An extended Second Law and evolution of entropy

Not only $F_{in}$ and $F_{dis}$ are both nonnegative, $F_{dis}^{net} (t) = -\frac{dH}{dt} = F_{dis} - F_{in}$ is also nonnegative, which vanishes if and only if the system is at steady-state. Hence $F_{dis}^{net} (t) \geq 0$ could be regarded as an extended Second Law, while the traditional Second Law is just $e_p (t) = \frac{F_{dis} (t)}{T} \geq 0$. They are equivalent only when $F_{in} = Q_{hh} = 0$, which implies the absence of external regenerating system.

The extended Second Law could also be expressed through the evolution of entropy. Define the entropy of the system as $S(t) = -k_B \sum_i c_i (t) \ln c_i (t)$, we can get Eq. (5a), i.e.

$$\frac{dS}{dt} = \frac{F_{dis} - F_{dis}^o}{T} \geq 0,$$

which is one specific form of the fundamental entropy balance equation of nonequilibrium thermodynamics (22, 23, 34). It indicates that the change of entropy is equal to the non-intrinsic free energy dissipation.

Since the nonnegativity of $e_p (t) = \frac{F_{dis}^{net} (t)}{T}$, we then have

$$\frac{dS}{dt} \geq -\frac{F_{dis}^o (t)}{T}.$$

We refer it as the Clausius inequality in the traditional Second Law of thermodynamics, since $F_{dis}^o (t)$ is the same as the heat dissipation, when the system is at NESS.

Furthermore, due to the fact that $F_{dis} (t) = T e_p (t) = F_{in} (t) + F_{dis}^{net} (t)$, we can get

$$\frac{dS}{dt} = \frac{F_{in} + F_{dis}^{net} - F_{dis}^o}{T}.$$

Since $F_{dis}^{net} (t)$ is nonnegative, an extended Second Law emerges as

$$\frac{dS}{dt} \geq \frac{F_{in} - F_{dis}^o}{T} = -\frac{F_{ex}^{dis}}{T}, \quad (28)$$

where $F_{ex}^{dis}$ is the excess intrinsic free energy dissipation.

Similar traditional and extended Second Law also hold beyond the level of free energy. Back to the evolution of entropy (19) and the nonnegativity of entropy production rate, the traditional Second Law here reads

$$\frac{dS^{open}}{dt} \geq -\frac{\tilde{h}^{open}}{T}.$$

One can further rewrite (19) as

$$\frac{dS^{open}}{dt} = (e_p^{open} - \frac{F_{in}}{T} - \frac{\tilde{h}^{open} - F_{in}}{T} = \frac{F_{dis}^{net}}{T} - \frac{Q_{ex}}{T},$$

where the excess heat $Q_{ex}$ is the difference between $\tilde{h}^{open}$ and $F_{in}$ (22). The extended Second Law emerges (22)

$$\frac{dS^{open}}{dt} \geq -\frac{Q_{ex}}{T}.$$

It is different from and stronger than the traditional Second Law, only for really driven system with $F_{in} = Q_{hh} > 0$.

IV. SUMMARY AND DISCUSSION

Is there anything beyond Boltzmann’s notion about the Second Law of Thermodynamics? On this fundamental issue, J.L. Lebowitz (55) and I. Prigogine (1) seem to disagree sharply: The former said “no” while the latter suggested “yes”. Such a debate is focused on the evolution of entropy. If we regard the entropy production $e_p$ as the total entropy increase of an isolated “universe” and $h_d/T$ as the entropy change of the universe, then the fundamental equation in (1) $dS/dt = e_p - h_d/T$ is nothing but a restatement of the entropy increase principle of any isolated system, long realized by Helmholtz and Gibbs. However, one could ask this question differently: Is there anything beyond Boltzmann’s microscopic notion about the Second Law on a mesoscopic scales? One important notion of the NESS perspective (12) is to build a self-consistent thermodynamics in terms solely of a mesoscopic, Markov kinetics of open driven subsystems (11), and to study specially whether $h_d$ is really in the form of heat. This is the motivation of the present article.

With the novel minimum work argument of idealized external regenerating system, we show that the term $h_d$ is the minimum heat dissipation in an idealized NESS: It is also equal to the heat dissipation plus the entropy change of the environment due to the slowly changed external variables at QSS. Furthermore, the total chemical and mechanical free energy input is balanced by the $h_d$. In the light of this new perspective, the concept of efficiency at NESS is well defined in terms of energy if an outsider can separately measure the chemical free energy input and mechanical energy output.

A chemically driven system is referred to a physical or biological system with a sustained source and sink with
chemical potential difference. The concept, in fact, has a broader applicability to population dynamics than traditional chemistry. Fundamental physics considers such a setup only approximate: In an absolutely sense, the source and sink have to be slowly decay toward their own equilibrium (QSS). Therefore, it is generally believed that if one includes these relevant parts of “environment” into an enlarged system with detailed balance, then the Prigogine’s thesis would disappear. However, such a physical argument, which is absolutely valid, begs a resolution on a mathematical level for the following paradox: If one considers (a) NESS and QSS merely two different perspectives of a same system; then it is surprising that they have very different heat dissipation; if (b) one considers them as different systems, then it is even more surprising their kinetics and free energy accounting are identical. We believe this is very much a similar problem faced by Gibbs when he developed his different ensemble theories for the equation of equilibrium state: Whether one considers canonical and isobaric ensembles same or different, the important issue is that they both give same macroscopic thermodynamic relations; but they give different heat capacity: $C_v$ and $C_p$.

The nonequilibrium thermodynamics of NESS and QSS actually exhibit an entropy-enthalpy compensation, a phenomenon long observed in equilibrium statistical thermodynamics of complex biomacromolecular systems \cite{33, 35, 36} : Two very similar systems usually have a similar $\Delta \mu$, but very different $\Delta h$ and $\Delta s$, and they compensate $\Delta h - T \Delta s = \Delta \mu$. This phenomenon was explained as due to the fluctuations of different ensembles \cite{34, 37}. Same phenomenon also arises in stochastic kinetics of single macromolecules \cite{38} and in coarse graining stochastic thermodynamics \cite{33}. All these studies point to the highly malleable, yet powerful and efficient concept of free energy and conditional free energy \cite{39}.

Based on established classical thermodynamics, we have obtained a self-consistent picture for the nonequilibrium driven system. In fact, one can see a distinction between Clausius’ and Kelvin’s historical statements on the 2nd Law: The former is about the spontaneity of a transient process, i.e. the non-negativity of $f_d^{\text{close}}$, while the latter is about a cyclic process with non-negative $e_p^{\text{open}}$ in a NESS.

A new, mesoscopic position on the debate between the two different perspectives is now possible provided by recently developed purely mathematical result on stochastic Markov process \cite{12, 22, 23}. In a nutshell, it has been shown, with some reasonable assumptions and definitions, the entropy production rate $e_p$ consists of two non-negative terms. Such a decomposition can be interpreted as Boltzmann’s thesis and Prigogine’s thesis: The former concerns with a system’s spontaneous relaxation to stationarity; and the latter concerns with a system that is sustained at a nonequilibrium steady (stationary) state. This suggests two origins of irreversibility at a mesoscopic level.

In the present article, we further refine this decomposition in a stochastic transient state towards a NESS with an idealized external regenerating system: The entropy production itself consists of the change of entropy of the system, and total dissipated intrinsic free energy including that from the minimally required amount from the regenerating system. The house-keeping heat, on the other hand, consists of chemical and mechanical free energies, as the net free energy input of the system.

All these are not only consistent with the traditional thermodynamics. They are also self-contained and solely dependent upon only the internal kinetics of the NESS system, which can be directly measured in statistical experiments. They also suggest new ingredients for a generalized nonequilibrium thermodynamics. As we have discussed, free energy is a powerful concept in systems with multiple scales, and scientific theories indeed have a hierarchy structure, with new dynamics emerges at each specific collective level \cite{40}.

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