Nonlinear Stochastic Dynamics of Complex Systems, III: Nonequilibrium Thermodynamics of Self-Replication Kinetics

David B. Saakian\textsuperscript{1,2} and Hong Qian\textsuperscript{3}

\textsuperscript{1}Institute of Physics, Academia Sinica, Nankang, Taipei 11529, Taiwan
\textsuperscript{2}A. I. Alikhanian National Science Laboratory (Yerevan Physics Institute) Foundation
\textsuperscript{2}Alikhanian Brothers Street, Yerevan 375036, Armenia
\textsuperscript{3}Department of Applied Mathematics, University of Washington, Seattle, WA 98195-3925, USA

We briefly review the recently developed, Markov process based isothermal chemical thermodynamics for nonlinear, driven mesoscopic kinetic systems. Both the instantaneous Shannon entropy $S[p_x(t)]$ and relative entropy $F[p_x(t)]$, defined based on probability distribution $\{p_x(t)\}$, play prominent roles. The theory is general; and as a special case when a chemical reaction system is situated in an equilibrium environment, it agrees perfectly with Gibbsian chemical thermodynamics: $k_B S$ and $k_B T F$ become thermodynamic entropy and free energy, respectively. We apply this theory to a fully reversible autocatalytic reaction kinetics, represented by a Delbrück-Gillespie process, in a chemostatic nonequilibrium environment. The open, driven chemical system serves as an archetype for biochemical self-replication. The significance of thermodynamically consistent kinetic coarse-graining is emphasized. In a kinetic system where death of a biological organism is treated as the reversal of its birth, the meaning of mathematically emergent "dissipation", which is not related to the heat measured in terms of $k_B T$, remains to be further investigated.

Index Terms—Biophysics, chemical master equation, chemical potential, detailed balance, entropy, Gillespie algorithm, information.

I. INTRODUCTION

In Part I and Part II of this series,\textsuperscript{1} a chemical reaction kinetic perspective on complex systems in terms of a mesoscopic stochastic nonlinear kinetic approach, e.g., Delbrück-Gillespie processes, as well as a stochastic nonequilibrium thermodynamics (stoc-NET) in phase space, have been presented. Part I provides an overview. Part II, motivated by both Gibbsian statistical mechanics and information theory, focuses on a parametric family of probability distributions $p(x,\beta)$ as a novel theoretical device for exploring a single nonequilibrium steady state probability $P(x)$, $x \in \mathcal{S}$, where $\mathcal{S}$ is a denumerable set of events, and $(\mathcal{S},\mathcal{F},P)$ is the underlying probability space.

The relation between Gibbsian statistical mechanics and information theory has generated endless discussions ranging from “they are completely unrelated except sharing a common term ‘entropy’,” to “they are parts of a single unifying maximum entropy principle”. Throwing a monkey wrench into the midst, we have articulated in\textsuperscript{2} the notion that minus-log-\emph{p}ss can be a very legitimate potential function of an entropic force in a complex dynamics. The origin of this practice was traced back to equilibrium statistical chemical thermodynamics with an exact coarse-graining, and J. G. Kirkwood’s concept of potential of mean force. The seemingly naive question still remains: What is information? Is it a state of a complex system, or a character of its dynamics, or a form of “energy”?\textsuperscript{3,4} In the engineering specific context first discussed by Shannon, information is the mathematical symbols that represent certain messages in communication. Therefore, the theory of information is a theory concerning coding, representations, and communications under uncertainty. On the other hand, in a much broader sense, particularly in the early days of applying information theory to biology, mathematical information theory was used essentially as an applied probability with a singular emphasis on the notion of Shannon entropy\textsuperscript{5}.

Sidestepping these issues, we follow Kolmogorov’s axiomatic theory of probability in which information is simply a very particular function of a random variable $x$ with probability distribution $p_x$:\textsuperscript{3,5} $H_x(x) = -\ln p_x(x)$, $x \in \mathcal{S}$, whose expected value gives Gibbs-Shannon formula.

It is important to remember that in Gibbs’ statistical ensemble theory of equilibrium matters,\textsuperscript{10} the probability of a state $x$ of a matter that is in contact with a temperature bath is

\begin{equation}
\label{eq:1a}
p_x = \frac{e^{-E_x/k_B T}}{\Xi(T)} , \text{ where } \Xi(T) = \sum_{x \in \mathcal{S}} e^{-E_x/k_B T} ,
\end{equation}

in which $E_x$ is the internal energy of the state $x$, $T$ is temperature in Kelvin, $k_B = 1.38064852 \times 10^{-23}$ $m^2 kg s^{-2} K^{-1}$ is Boltzmann’s constant, $\mathcal{S}$ is the set containing all possible states of the matter. The theory of statistical mechanics states that the entropy of the matter is then

\begin{equation}
\label{eq:1b}
S(T) = -k_B \sum_{x \in \mathcal{S}} p_x \ln p_x = \frac{\partial}{\partial T} \left( k_B T \ln \Xi(T) \right).
\end{equation}

In statistical thermodynamics, $F(T) \equiv -k_B T \ln \Xi(T)$ is called free energy, and entropy is $-\partial F/\partial T$. One also has the important equation

\begin{equation}
F = E - TS,
\end{equation}
in which $\overline{E}$ is the mean internal energy

$$\overline{E}(T) = \sum_{x \in \mathcal{S}} E_x p_x. \quad (1d)$$

Viewed from these four widely known mathematical equations, the theoretical device discussed in [2] simply provides an extended exploration of the information content of $P(x)$ and its underlying $(\mathcal{S}, \mathcal{F}, P)$.

There is a growing interest in quantitative relations between the theory of thermodynamics that rules many aspects of the biochemical world and the biological dynamics of organisms, their ecology and evolution. “Every species of living thing can make a copy of itself by exchanging energy and matter with its surroundings.” [11] A living organism has two distinct aspects: One with “genomic information” which is carried in the sequence of polynucleic acids [7], possibly including methylation modifications of base-pairs; and the other is a space-time biochemical dynamics in terms of molecules, which can exhibit chemical, mechanical, and electrical characteristics. The time scales of these two aspects are vastly different: The former cumulates changes generation after generation, which constitutes an evolutionary process. The latter defines “what is living” for each and every individual organism. The relationship between these two has been the subject of many scholarly studies in the field of biology [12], [13], [14], [15], [16].

To a classic physicist or chemist, the cellular biochemical processes are various transformations of energy and matters; to a modern cell biologist, the same processes are usually described as regulation and processing of informations. The physical and chemical processes are interpreted with biological functions [17]. The present paper is an attempt to provide a treatment of this latter aspect in terms of a stochastic kinetic theory. In particular, we analyze rigorously a chemical model that makes the notion of “making a copy of itself by exchanging energy and matter with its surroundings” precise and quantitative. To this end, we revisit a kinetic model for a fully reversible chemical reaction system that consists of an autocatalytic step $A + X \rightarrow 2X$ [18], [19]. This model first appeared in the wonderful book by the late Professor Keizer [20]. This extremely simple model, however, offers us an insight on why a truly meaningful chemical thermodynamic study of biological replication is premature: This is because neither the current cosmological time scale of our universe nor the size of entire biological population on our planet are sufficiently large to provide a meaningful estimation of the probability of “two [daughter cells] somehow spontaneously revert back into one” [11]. Note the “revert back” should not be a fusion of two cells, rather it has to be a process that reverses the entire event-by-event of a cell replication.

It is the non-zero probability of such completely inconceivable processes, in a physicist’s world, that provides an estimation of thermodynamic heat production. When a biologist considers only feasible events to a living organism being birth and death, the quantitative connection to the world of thermal physics has already been lost [1]. This difficulty has been hinted in [21]: “If we assume that the process $I \rightarrow II$ is ‘irreversible’ this implies that the time-reversed dynamics is very unstable so that $\Pr\{II \rightarrow I\}$ is hard to estimate precisely. One uses instead a bigger probability $\Pr\{II \rightarrow I\}$ based on observable processes.” Unfortunately, any remotely reasonable substitution for an authentic de-birth is currently out of reach; death is not an acceptable alternative even for a lower bound estimation.

The paper is structured as follows: In Sec. [I] we give a brief review of the modern theory of stochastic nonequilibrium thermodynamics of Markov systems [22], [23], [24], [25], as presented in Part I [1]. While many of the terminologies and mathematical relations can be found in the review articles [26], [27], [28] and classic text [29], we like to point out that the coherent narrative constructed based on the mathematics, e.g., their interpretations, is unique. We shall show how mathematical logic dictates that entropy in systems with uniform stationary probability should be replaced by a relative entropy, also known as free energy, in systems with non-uniform stationary probability, and how entropy production rate $\epsilon_p$ arises as a distinctly different concept as entropy change $\Delta S$. Then in Sec. [II] we first give the standard chemical thermodynamic treatment of the simple kinetic system with two reversible reactions

$$A + X \xrightleftharpoons[k_{-1}]{k_{+1}} 2X, \quad X \xrightleftharpoons[k_{-2}]{k_{+2}} B. \quad (2)$$

Note, if one neglects the two “backward” reactions, e.g., letting $k_{-1} = k_{-2} = 0$, then the chemical kinetics can be described by the differential equation

$$\frac{dx}{dt} = gx - k_{+2}x, \quad g \equiv k_{+1}a. \quad (3)$$

Eq. (3) describes the “birth and death” of individual $X$ molecules.

The simple chemical model in (2) has a clear self-replication characteristics, it allows a rigorous thermodynamics analysis of the replication/synthesis aspect of a biological organism. Certainly the individual $X$ lacks other fundamentals of a living being: An individual $X$ itself is a dead molecule, not a living organism. Therefore, while it is meaningful to ask the heat dissipation in a self-replication from a complex chemical synthesis standpoint [30], it might not be a sufficient model for the heat dissipation in the self-replication of a living organism since even just being alive, an organism has a continuous heat dissipation as an individual entity, e.g., active metabolism. Simply put: a living organism, which has both metabolism and self-replication, already has a basal level of heat dissipation due to the former even in the absence of the latter. The present analysis, however, makes a conceptual separation between the two processes in an organism. We note that the open chemical systems theory of motor protein chemomechanics serves as a concrete model for the former [31].

1 On the other hand, the upper bound of such an extremely small probability can be estimated from knowing the minimal amount of calories required to reproduce an organism using the very equation (2) in [1].
In Sec. IV a mesoscopic stochastic thermodynamic treatment of the replication kinetics is carried out. Entropy production rate for the kinetic process is studied. Then in Sec. VI we articulate a distinction between thermodynamically consistent and inconsistent kinetic approximations. The paper concludes with a discussion in Sec. VII.

II. A MODERN STOCHASTIC NONEQUILIBRIUM THERMODYNAMICS OF MARKOV SYSTEMS

The very brief summary of Gibbs’ equilibrium statistical thermodynamics, given in Eq. 1, d, illustrates the universality of the entropy function, be it in information theory or in thermal physics. Indeed there is now a more unifying theory of entropy and relative entropy, also known as Kullback-Leibler (KL) divergence in information theory and free energy in statistical thermodynamics, based on the probability theory of Markov processes that describe complex system’s dynamics in phase space [22, 23, 25].

The first basic assumption of this nonequilibrium thermodynamic theory is that a complex mesoscopic dynamical system can be represented by an irreducible continuous time Markov process with appropriate state space \( \mathcal{S} \) and transition probability rates \( q_{\alpha\beta} \), \( \alpha, \beta \in \mathcal{S} \), where \( q_{\alpha\beta} = 0 \) if and only if \( q_{\beta\alpha} = 0 \). Under these assumptions, it can be shown that there exists a unique positive stationary probability \( \pi_\alpha \) for the Markov system in stationarity:

\[
\sum_{\alpha \in \mathcal{S}} \pi_\alpha q_{\alpha\beta} = 0. \tag{4}
\]

For a stationarity process defined by \( \{ \pi_\alpha \} \) and \( q_{\alpha\beta} \), a further distinction between an equilibrium steady state and a nonequilibrium steady state (NESS) can be made (see below): The former has zero entropy production rate, and the latter has a strictly positive entropy production rate. This distinction is determined by the set of transition probability rates \( \{ q_{\alpha\beta} \} \), which necessarily satisfy detailed balance, \( \pi_\alpha q_{\alpha\beta} = \pi_\beta q_{\beta\alpha} \) \( \forall \alpha, \beta \in \mathcal{S} \), if and only if the steady state is an equilibrium. The theory presented below is applicable to both equilibrium and nonequilibrium steady state, as well as a time-dependent non-stationary process.

For a mesoscopic system such as the discrete chemical reactions in 4 with state space \( \mathcal{S} \) being non-negative integers, a second assumption is that it has a macroscopic corresponding continuous dynamics \( x(t), \ x \in \mathbb{R}^n \). Let \( \omega \) be the “size parameter” that connects the mesoscopic system and its macroscopic limit when \( \omega \to \infty \), with \( x \equiv \frac{x}{\omega} \) being number density. Then, for a large class of such Markov systems [24, 25],

\[
\frac{\pi_{\omega x}}{\omega} \simeq e^{-\omega \varphi(x)} \to \delta(x - z), \tag{5}
\]

in which \( \varphi(x) \geq 0 \) and its global minimum is at \( z \). In applied mathematical theory of singular perturbation, Eq. 5 is known as WKB ansatz [34]; in the theory of probability, it is called large deviations principle [32].

Inspired by the similarity between the expression in Eq. 5 and Boltzmann’s law, let us define “the internal energy density of the Markov state \( \alpha \)’’:

\[
E_\alpha = -\frac{\ln \pi_\alpha}{\omega}. \tag{6}
\]

Then the mean energy density at time \( t \):

\[
E(t) = \sum_{\alpha \in \mathcal{S}} p_\alpha(t) E_\alpha = -\omega^{-1} \sum_{\alpha \in \mathcal{S}} p_\alpha(t) \ln \pi_\alpha. \tag{7}
\]

where \( p_\alpha(t) \) is the probability of the system in state \( \alpha \) at time \( t \). Then the free energy, also known as Massieu potential, of the Markov system at time \( t \)

\[
F[p_\alpha(t)] = \omega E - S(t) = \sum_{\alpha \in \mathcal{S}} p_\alpha(t) \ln \left( \frac{p_\alpha(t)}{\pi_\alpha} \right). \tag{8}
\]

Then, concerning these quantities, one has a series of mathematical results:

**A free energy balance equation.** First, an equation that is valid for systems with and without detailed balance, and for processes in stationary and in transient:

\[
\frac{d}{dt} F[p_\alpha(t)] = \omega E_{in}[p_\alpha(t)] - e_p[p_\alpha(t)]. \tag{9a}
\]

in which

\[
E_{in}[p_\alpha] := \frac{1}{\omega} \sum_{\alpha, \beta \in \mathcal{S}} \left( p_\alpha q_{\alpha\beta} - p_\beta q_{\beta\alpha} \right) \ln \left( \frac{\pi_\alpha q_{\alpha\beta}}{\pi_\beta q_{\beta\alpha}} \right) \geq 0, \tag{9b}
\]

\[
e_p[p_\alpha] := \sum_{\alpha, \beta \in \mathcal{S}} \left( p_\alpha q_{\alpha\beta} - p_\beta q_{\beta\alpha} \right) \ln \left( \frac{p_\alpha q_{\alpha\beta}}{p_\beta q_{\beta\alpha}} \right) \geq 0. \tag{9c}
\]

Eq. 9 is interpreted as a free energy balance equation for a Markov system with \( E_{in}[p_\alpha] \) being the instantaneous rate of input energy, a source term, and \( e_p[p_\alpha] \), a sink, as the instantaneous rate of energy lost, or entropy production rate.

**Entropy change, free energy change, and entropy production.** Second, an inequality that is valid for systems with and without detailed balance, and for processes in stationary and in transient:

\[
\frac{d}{dt} F(t) \leq 0. \tag{10}
\]

Combined with (9), this implies \( \omega^{-1} e_p \geq E_{in} \).

One notices that for very particular Markov systems with \( q_{\alpha\beta} = q_{\beta\alpha} \) \( \forall \alpha, \beta \in \mathcal{S} \), they have a uniform \( \pi_\alpha \equiv \text{constant} \). Then \( e_p(t) = \frac{d}{dt} S \). Such systems are analogous to microcanonical ensembles, where the entropy production is the same as entropy increase.

For Markov systems with detailed balance, \( E_{in}(t) \equiv 0 \ \forall t \), and

\[
e_p[p_\alpha] = \frac{d}{dt} S[p_\alpha(t)] - \omega E_{ex}[p_\alpha(t)] \geq 0, \tag{11a}
\]

in which

\[
E_{ex}[p_\alpha] := \sum_{\alpha, \beta \in \mathcal{S}} \left( p_\alpha q_{\alpha\beta} - p_\beta q_{\beta\alpha} \right) \left( E_\beta - E_\alpha \right). \tag{11b}
\]

is interpreted as the instantaneous rate of energy exchange. The inequality in Eq. 11a is analogous to Clausius inequality for spontaneous thermodynamic processes, which gives rise
to the notion of entropy production as a distinctly different concept as $\frac{dS}{dt}$.

**Macroscopic limit.** For a macroscopic system in the limit of $\omega \to \infty$, the probability distribution $p_\omega(t)$ becomes a deterministic dynamics $x(t)$, and Eq. (9) becomes a novel macroscopic equation [24, 33]

$\frac{d\varphi[x(t)]}{dt} = \text{cmf}[x(t)] - \sigma[x(t)]_t$,  \hspace{1cm} (12a)

in which

$\text{cmf}[x] = \sum_{\ell, \text{all reactions}} \left( J_{\ell}^+(x) - J_{\ell}^-(x) \right) \times \ln \left( \frac{J_{\ell}^+(x)}{J_{\ell}^-(x)} \right) e^{-\nu_\ell \cdot \nabla_w \varphi(x)}$, \hspace{1cm} (12b)

$\sigma[x] = \sum_{\ell, \text{all reactions}} \left( J_{\ell}^+(x) - J_{\ell}^-(x) \right) \ln \left( \frac{J_{\ell}^+(x)}{J_{\ell}^-(x)} \right)$, \hspace{1cm} (12c)

$J_{\ell}^+$ and $J_{\ell}^-$ are the forward and backward fluxes of the $\ell$th reversible reaction, integer vector $\nu_\ell$ is its stoichiometry coefficients. cmf is the chemical motive force that satisfies a reaction system out of its equilibrium, and $\sigma$ is the macroscopic rate of entropy production.

If $J_{\ell}^+(x) = J_{\ell}^-(x) e^{\nu_\ell \cdot \nabla_w \varphi(x)} \forall \ell, x$, it is known as detailed balance in chemistry, or G. N. Lewis’ law of entire equilibrium [35]. In such systems, $\text{cmf} = 0$, $\varphi(x)$ is the Gibbs function, $\partial \varphi(x)/\partial x$ is the chemical potential of species $k$, and $\nu_\ell \cdot \nabla_w \varphi(x)$ is the chemical potential difference of the $\ell$th reaction.

**Macroscopic systems with fluctuations.** For a system with very large but finite $\omega$, Eq. (5)provides a “universal”, asymptotic expression for stationary, fluctuating $x$ [32]:

$f_x(x) = \frac{e^{-\omega \varphi(x) + \psi(x)}}{\Xi(\omega)}$, \hspace{1cm} (13)

where

$\Xi(\omega) = \int_{\mathbb{R}^n} e^{-\omega \varphi(x) + \psi(x)} dx$, \hspace{1cm} (14)

in which $\varphi(x)$ is uniquely defined with $\min_x \varphi(x) = 0$.

### III. An Open Chemical System as a Self-Replicating Entity

We now apply the general theory in Sec. III to reaction system (2). There are two reversible reactions with stoichiometric coefficients $\nu_1 = +1$ and $\nu_2 = -1$, respectively. Let $x(t)$ be the concentration of $X$ at time $t$, the kinetics of the reaction system in (4) can be described by

$\frac{dx(t)}{dt} = \sum_{\ell=1,2} \nu_\ell \left( J_{\ell}^+(x) - J_{\ell}^-(x) \right)$

$= k_{+1} a x - k_{-1} x^2 - k_{+2} x^2 + k_{-2} b$, \hspace{1cm} (15)

with $J_{+1}^+(x) = k_{+1} a x$, $J_{-1}^-(x) = k_{-1} x^2$, $J_{+2}^+ = k_{+2} x$, and $J_{-2}^+ = k_{-2} b$. The first of these two reversible reactions in (4) is known as autocatalytic. One can find many examples of this abstract system of reactions in biochemical literature; see [19] for more extensive biochemical motivations. One also notices that in a semi-reversible case when $k_{-2} = 0$ in the system (2), extinction of $X$ is the only long time fate of the kinetics. The differential equation $\frac{dx}{dt} = (g - k_{+2}) x - k_{-1} x^2$, however, predicts a stable population $x^{eq} = (g - k_{+2})/k_{-1}$. This disagreement is known as Keizer’s paradox [18, 36]. We shall use this model as a concrete case of the chemical nature of exchanging of energy and matter in self-replication.

#### A. NESS of an open chemical system

According to (2), an $X$ molecular has transformed the raw material in the form of $A$ into a copy of itself, a second $X$. The canonical mathematical description of this autocatalytic reaction is $\frac{dx}{dt} = gx$ where the constant $g = k_{+1} a$. We shall use $a, x, b$ to denote the concentrations of $A, X, B$, respectively. Clearly, $g$ can be identified as per capita birth rate if one is interested in the population dynamics of $X$. Combining with the second reaction, one has $\frac{dx}{dt} = gx - k_{+2} x$, where $k_{+2}$ can be identified as a per capita death rate. When the $X$ is dead, the material in terms of atoms are in the form of $B$. Therefore, the “birth” and “death” of $X$, or more precisely the synthesis and degradation of $X$, involve an exchange of materials, as source and waste, with its surroundings. One can in fact assume that the concentrations of $A$ and $B$, as the environment of the chemical reaction system in (2), are kept at constant, as a chemostat. This is precisely why living cells have to be “cultured”.

The calorie count one reads from a food label in a supermarket gives the chemical potential difference between $A$ and $B$, introduced below. This is not different from one reads the electrical potential difference on a battery to be used for keeping a radio “alive”.

One might wonder why we assume the reactions in (2) reversible? It turns out, as anyone familiar with chemical thermodynamics knows, one can not discuss energetics in an irreversible reaction system. If the $k_{-2} = 0$, then the chemical energy difference between $X$ and $B$ are infinite; which is clearly unrealistic. In fact, the chemical potential difference between $A$ and $B$, in $k_B T$ unit, is

$\mu_A - \mu_B = (\mu_A - \mu_X) + (\mu_X - \mu_B)$

$= \ln \left( \frac{k_{+1} a}{k_{-1} x} \right) + \ln \left( \frac{k_{+2} x}{k_{-2} b} \right)$

$= -\ln K_{AB}^{eq} + \left( \frac{a}{b} \right)$, \hspace{1cm} (16)

in which the overall equilibrium constant between $A$ and $B$, $K_{AB}^{eq} = k_{-1} k_{-2}/(k_{+1} k_{+2})$. In a chemical or biochemical laboratory, the equilibrium constant is usually determined in an experiment according to

$K_{AB}^{eq} = \text{equi. conc. of A} / \text{equi. conc. of B}$

If $\mu_A > \mu_B$, then there is a continuous material flow from $A$ to $B$, even when the concentration of $X$ is in a steady state: There is a continuous birth and death, synthesis and degradation: metabolism in an “living system”. There is an amount of entropy being produced in the surroundings. An agent has to constantly generating $A$ with high chemical potential from $B$.
with low chemical potential. This entropy production in fact is precisely the \( \mu_A - \mu_B \) \[37\].

The kinetics of \[2\], described by Eq. [15] eventually reach a steady state, with the concentration of \( X \), \( x^{ss} \) as the positive root of the polynomial on the right-hand-side of \( \[15\] 

\[
x^{ss} = \frac{1}{2k-1} \left[ k_{+1}a - k_{-2} + \sqrt{(k_{+1}a - k_{-2})^2 + 4k_{-1}k_{-2}b} \right].
\] (17)

The net flux from \( A \) to \( B \) in the steady state,

\[
J_{ssA\rightarrow B}^f = J_{ss}^f(x^{ss}) - J_{ss}^i(x^{ss}) = J_2^f(x^{ss}) - J_2^i
\]

\[
= \frac{1}{2k-1} \left[ 2\lambda + k_{+2} \sqrt{(k_{+1}a + k_{-2})^2 - 4\lambda} \right]
- \left( a_{k+1}k_{+2} + k_{+2}^2 \right),
\] (18)

where

\[
\lambda = a_{k+1}k_{+2} - bk_{-1}k_{-2} = bk_{-1}k_{-2} \left( \frac{\mu_A - \mu_B}{e^{\frac{\mu_A - \mu_B}{k_BT}} - 1} \right).
\]

And the steady-state entropy production rate according to Eq. [12c] is

\[
\sigma[x^{ss}] = J_{ss}^f(x^{ss}) \times (\mu_A - \mu_B).
\] (19)

We see that the steady state is actually an equilibrium if and only if \( \mu_A = \mu_B \). In this case, \( \sigma[x^{ss}] \) is zero, \( \lambda = 0 \), and one can check that \( J_{ss}^fA\rightarrow B = 0 \): There is no net transformation of \( A \) to \( B \) via \( X \). Otherwise, the \( J_{ss}^fA\rightarrow B \neq 0 \), and it has the same sign as \( \lambda \) and \( (\mu_A - \mu_B) \). Therefore, the macroscopic entropy production rate defined in [19], which is never negative, mathematically quantifies the statistical irreversibility in the self-replication of \( X \).

Generalizing this example is straightforward; hence with this in mind one can claim that \[11\] “[e]very species of living thing can make a copy of itself by exchanging energy and matter with its surroundings”, which can be exactly computed if all the reversible biochemical reactions involved are known.

**B. Time-dependent entropy production rate**

We now turn our attention to the non-stationary transient thermodynamics of system \( 2 \). First, the time-dependent concentration of \( X \), \( x(t) \) is readily solved from \( \[15\] 

\[
x(t) = \frac{\beta C e^{-\beta t}}{1 - C k_{-1} e^{-\beta t}},
\] (20)

in which

\[
\beta = \sqrt{(k_{+1}a - k_{-2})^2 + 4k_{-1}k_{-2}b}, \quad C = \frac{x(0)}{k_{-1}x(0) + \beta}.
\]

Then, the time-dependent entropy production rate \( \sigma[x(t)] \), in \( k_BT \) unit,

\[
\sigma[x(t)] = \left( k_{+1}a x(t) - k_{-1}x^2(t) \right) \ln \left( \frac{k_{+1}a}{k_{-1}x(t)} \right)
+ \left( k_{+2}x(t) - k_{-2}b \right) \ln \left( \frac{k_{+2}x(t)}{k_{-2}b} \right)
\]

\[
= \text{cmf}[x] + \frac{d}{dt} \varphi_{ss}[x(t)].
\] (21)

in which (see Eq. [37] below)

\[
\varphi_{ss}[x] = \int_0^x \ln \left( \frac{k_{-1}x^2 + k_{+2}^2}{k_{+1}a x + k_{-2}b} \right) dx,
\] (23)

and the instantaneous chemical motive force

\[
\text{cmf}[x] = \sum_{\ell=1,2} \left( J_{\ell}^f(x) - J_{\ell}^i(x) \right)
\times \ln \left( \frac{J_{\ell}^f(x)}{J_{\ell}^i(x)} e^{-\beta t \partial \varphi_{ss}(x)/\partial x} \right)
\]

\[
= (k_{+1}ax - k_{-1}x^2) \ln \left( \frac{k_{+1}ax}{k_{-1}x^2 e^{-\partial \varphi_{ss}(x)/\partial x}} \right)
+ (k_{+2}x - k_{-2}b) \ln \left( \frac{k_{+2}x}{k_{-2}b e^{-\partial \varphi_{ss}(x)/\partial x}} \right)
\] (25)

with

\[
\frac{\partial \varphi_{ss}(x)}{\partial x} = \ln \left( \frac{k_{-1}x^2 + k_{+2}x}{k_{+1}ax + k_{-2}b} \right).
\] (26)

That is,

\[
\text{cmf}[x] = (k_{+1}ax - k_{-1}x^2)
\times \left( 1 + \frac{k_{+2}x}{k_{-1}x^2} \right) \left( 1 + \frac{k_{-2}b}{k_{+1}ax} \right)^{-1}
+ (k_{+2}x - k_{-2}b)
\times \ln \left( \frac{k_{+2}x + 1}{k_{+2}x + 1} \right)^{-1}.
\] (27)

This is an example of Eq. [12a] Finally,

\[
\frac{d}{dt} \varphi[x(t)] = \frac{dx(t)}{dt} \ln \left( \frac{k_{-1}x^2 + k_{+2}x}{k_{+1}ax + k_{-2}b} \right)
= (k_{+1}ax - k_{-1}x^2 - k_{+2}x + k_{-2}b)
\times \ln \left( \frac{k_{-1}x^2 + k_{+2}x}{k_{+1}ax + k_{-2}b} \right) \leq 0.
\] (28)

This inequality implies even for a driven chemical reaction system that approaches to a NESS, there exists a meaningful “potential function” \( \varphi[x] \) which never increases.

To connect to the known Gibbsian equilibrium chemical thermodynamics, we notice that chemical detailed balance \( \text{cmf}[x] = 0 \) \( \forall x \) implies

\[
\frac{J_x^+(x)}{J_x^-(x)} = e^{\partial \varphi(x)/\partial x} \ln \left( \frac{J_x^+(x)}{J_x^-(x)} \right),
\] (29)

that is \( k_{+1}k_{+2}/k_{-1}k_{-2} = 1 \). Under this condition, \( \varphi[x] \) in \( \[23\] \) becomes

\[
\varphi[x] = x \ln \left( \frac{k_{+2}x}{k_{+1}a} \right) = x(\mu_Y - \mu_A),
\] (30)

which is the Gibbs function, in unit of \( k_BT \), with state \( A \) as reference.

The function \( \varphi[x] \) in \( \[23\] \) is a nonequilibrium generalization of the Gibbs free energy for open chemical systems that approach to NESS \( \[24\] \), \( \[33\] \), and Eq. \( \[28\] \) is an open-system generalization of the 2nd Law.
IV. STOCHASTIC KINETIC DESCRIPTION BY THE DELBRÜCK-GILLESPIE PROCESS

Chemical reactions at the individual molecule level are stochastic [38], which can be described by the theory of Chemical Master Equation (CME) [39] first appeared in the work of Leontovich [40] and Delbrück [41], whose fluctuating trajectories can be exactly computed using the stochastic simulation method widely known as Gillespie algorithm [42]. These two descriptions are not two different theories, rather they are the two aspects of a same Markov process, just as the Fokker-Planck equation and the Itô integral descriptions of a same Langevin dynamics. More importantly, this probabilistic description and the deterministic mass-action kinetics in Eq. (2) are just two parts of a same dynamic theory: The latter is the limit of the former when fluctuations are sufficiently small, while the volume of the reaction vessel, $\omega$, is large [43].

We now show this theory provides a more complete kinetic characterization of [2] and it is in perfect agreement with the classical chemical kinetics as well as Gibbs’ chemical thermodynamics. Since chemical species in [2] are discrete entities, and the chemical reactions at the level of single-molecules are stochastic, let $p_n(t)$ be the probability of having $n$ number of $X$ in the reaction system at time $t$. Then, $p_n(t)$ follows the CME:

$$\frac{d}{dt}p_n(t) = u_n-1p_{n-1} - (u_n + w_n)p_n + w_{n+1}p_{n+1},$$

(31a)

$$u_n = u_n^{(1)} + u_n^{(2)}, \quad w_n = w_n^{(1)} + w_n^{(2)}, \quad u_n^{(1)} = ak_1n, \quad u_n^{(2)} = k_2\omega b, \quad w_n^{(1)} = \frac{k_1n(n-1)}{\omega}, \quad w_n^{(2)} = k_2n.$$  

(3b)

A. Stationary distribution

The steady state distribution $\pi_n$ that is no longer changing with time, after a certain period of relaxation kinetics. By open system, we mean it has a constant chemical flux between $A$ and $B$, with its direction being determined by which of the $\mu_A$ and $\mu_B$ being greater. The stationary probability distribution for $\pi_n$ is

$$\pi_n = \frac{C}{n!} \left( \frac{k_2\omega b}{k_2+1} \right)^n \left( \frac{\left( 1 - e^{\frac{\mu_A-\mu_B}{k_BT}} \right) + \frac{ak_1\omega b}{k_2+1}}{(1 - e^{\frac{\mu_A-\mu_B}{k_BT}})} \right)^n,$$

(32)
in which $C$ is a normalization constant. We observe that when $\mu_A = \mu_B$, the $p_n^{ss}$ is a Poisson distribution, as predicted by Gibbs’ equilibrium theory of grand canonical ensemble, with the mean number of $X$ being $(k_2\omega b/k_2+1)$, or equivalently the mean concentration $(k_2\omega b/k_2+1)$.

B. Macroscopic limit

With increasing $\omega$, the behavior of the Markov process described by Eq. (31) becomes very close to that described by the mass-action kinetics. In fact, if we let $x = n/\omega$ as the concentration of the species $X$, then

$$\frac{p_n(x,t)}{\omega} \sim e^{-\omega \varphi(x,t)} \rightarrow \delta(x - z(t)),$$

(33)

where

$$\frac{dz(t)}{dt} = J^+(z) - J^-(z),$$

(34)

$$J^+(z) = \lim_{\omega \rightarrow \infty} \left( \frac{u_\omega z}{\omega} \right), \quad J^-(z) = \lim_{\omega \rightarrow \infty} \left( \frac{w_\omega z}{\omega} \right),$$

(35)

and

$$\frac{\partial \varphi(x,t)}{\partial t} = \sum_{\ell=1}^2 J^\ell(x) \left[ 1 - e^{\nu_\ell \varphi_\ell(x,t)} \right] + J^R(x) \left[ 1 - e^{-\nu_R \varphi_R(x,t)} \right].$$

(36)

It turns out that the macroscopic, nonequilibrium chemical energy function appeared in Eq. (28) is the stationary solution to Eq. (36)

$$\varphi^{ss}(x) = - \int_0^x \ln \left( \frac{J^+(z)}{J^-_1(z)} + \frac{J^+(z)}{J^+_2(z)} \right) dz,$$

(37)

and

$$\left( \frac{\partial \varphi^{ss}}{\partial x} \right) = - \ln \left( \frac{J^+_1(x) + J^-_2(x)}{J^+_1(x) + J^+_2(x)} \right)$$

(38)

$$= - \ln \left( \frac{ak_1x + k_2b}{k_1x^2 + k_2x} \right)$$

in which $\mu_A - \mu_B = k_BT \ln \left( \frac{ak_1k_2b}{k_1k_2+1} \right)$. We observe that when the reaction system is not driven chemically, $\mu_B = \mu_A$. Then (38) is $\frac{\mu_A - \mu_B}{k_BT}$, the chemical potential of $X$ in unit of $k_BT$, with state $A$ as reference.

C. The stochastic NESS entropy production rate

According to stochastic thermodynamics, the NESS entropy production rate for the stochastic dynamics in [31], in $k_BT$ unit, is given in Eq. (39):

$$\epsilon_T[\pi_n] = \sum_{n=0}^{\infty} \left( \pi_n u_n^{(1)} - \pi_{n+1} u_{n+1}^{(1)} \right) \ln \left( \frac{\pi_n u_n^{(1)}}{\pi_{n+1} u_{n+1}^{(1)}} \right)$$

$$+ \sum_{n=0}^{\infty} \left( \pi_n u_n^{(2)} - \pi_{n+1} u_{n+1}^{(2)} \right) \ln \left( \frac{\pi_n u_n^{(2)}}{\pi_{n+1} u_{n+1}^{(2)}} \right)$$

$$= \sum_{n=0}^{\infty} \left( \pi_n u_n^{(2)} - \pi_{n+1} u_{n+1}^{(2)} \right) \ln \left( \frac{bk_{-1}k_{-2}}{ak_{1}k_{2}} \right)$$

$$= \omega \ln \left( \frac{ak_1k_2}{bk_{-1}k_{-2}} \right) \left( k_2 \frac{nX}{\omega} - k_2b \right).$$

(39)
This agrees exactly with Eq. 19 which is the entropy production rate per unit volume.

V. COARSE GRAINING: KINETICS AND THERMODYNAMICS

The entropy production given in (19) and (39) can be decomposed into two terms:

\[ \sigma[x^{ss}] = \left\{ J_{\text{net}}^{ss} A \rightarrow X \times (\mu_A - \mu_X) \right\} + \left\{ J_{\text{net}}^{ss} X \rightarrow B \times (\mu_X - \mu_B) \right\} \]

(40)

in which \( J_{\text{net}}^{ss} A \rightarrow X = k_+ a x^{ss} - k_- (x^{ss})^2 \), \( \mu_A - \mu_X = k_B T \ln \left( k_+ / (k_- x^{ss}) \right) \), \( J_{\text{net}}^{ss} X \rightarrow B = k_+ 2 x^{ss} - k_- b \), and \( \mu_X - \mu_B = k_B T \ln \left( k_+ 2 x^{ss} / (k_- b) \right) \). Both terms in \{ \cdots \} are positive. More importantly, if \( k_+ \) and \( k_- \) are very large while \( J_{\text{net}}^{ss} A \rightarrow X \) is kept constant, then \( \mu_A - \mu_X \) will be very small; they are nearly at equilibrium. In this case, we can lump the \( A \) and \( X \) as a single chemical species with rapid internal equilibrium. Such coarse-graining always leads to under-estimating the entropy production [46], [47].

A. Thermodynamically consistent kinetic approximation

We now carry out a more in depth analysis on kinetic coarse-graining. In particular, we try to show the following: There are at least two types of kinetic approximations: those are thermodynamically meaningful and those are not. In mathematical terms: No matter how inaccurate, the former gives a finite approximation of the “true entropy production of the system” while the latter yields a numerical infinity, e.g., the thermodynamics is lost.

According to T. L. Hill [48], the expression in (18) has a unique, thermodynamically meaningful representation \( J_{\text{net}}^{A \rightarrow B} = J_{A \rightarrow B}^A - J_{B \rightarrow A}^B \), in which \( J_{A \rightarrow B}^A = a k_+ k_{+2} / \Sigma \), \( J_{B \rightarrow A}^B = b k_1 k_{-2} / \Sigma \),

\[ \Sigma = \frac{1}{k_{-1}} + \frac{k_{+2}}{2 k_{-1}} \sqrt{\frac{(k_+ a + k_{+2})^2 - 4 \lambda}{\lambda}} \]

(41)

One can show that \( \Sigma \) is strictly positive if all the parameters having finite values. Then, the entropy production rate in (19)

\[ \sigma[x^{ss}] = \left\{ J_{A \rightarrow B}^A - J_{B \rightarrow A}^B \right\} \ln \left( \frac{J_{A \rightarrow B}^A}{J_{B \rightarrow A}^B} \right) \]

(42)

With respect to the expression in Eq. 42 we can reach the following conclusions:

(a) If an approximation leads to \( J_{A \rightarrow B}^A \rightarrow J_+^A \), \( J_{B \rightarrow A}^B \rightarrow J_-^B \) but \( J_+^A / J_-^B \) finite, then there is a meaningful, finite approximated \( \sigma \). This is a sufficient condition but not necessary.

(b) If both \( J_{A \rightarrow B}^A \rightarrow J_+^A \rightarrow \infty \), but \( J_{A \rightarrow B}^A - J_{B \rightarrow A}^B \) is finite, then there is a finite \( \sigma \).

(c) It is possible that \( J_{A \rightarrow B}^A - J_{B \rightarrow A}^B \rightarrow \infty \), \( J_+^A J_-^B / J_{A \rightarrow B}^A \rightarrow 1 \), and \( \sigma \) is finite. For example, \( J_{A \rightarrow B}^A = x + x^2, J_{B \rightarrow A}^B = x^2 \). Then when \( x \rightarrow \infty \) we have \( \sigma = 1 \).

(d) However, if one of the \( J_{A \rightarrow B}^A \) and \( J_{B \rightarrow A}^B \) is finite and another one is not, then \( \sigma = \infty \).

We see that if \( k_{-1}, k_{-2} \rightarrow 0 \) while all other parameters are finite, then it is the scenario (d). In this case, a meaningful thermodynamics no longer exists for the kinetic approximation.

B. Birth-and-death approximation of replication kinetics

For a macroscopic sized system (2) with externally sustained \( a \) and \( b \), the equation for its chemical kinetics is

\[ \frac{dx}{dt} = (k_+ a + k_- b) x - (k_- a + k_{+2}) x. \]

(43)

Let us now consider a particular case in which \( k_+ a \gg k_- b \) and \( x \ll k_2 / k_{-1} \).

(44)

Then it is completely legitimate to approximate the kinetic equation in (43) by an approximated

\[ \frac{dx}{dt} = (g - k_-) x, \quad g \equiv k_+ a. \]

(45)

In fact, the approximation produces accurate kinetic result if the two inequalities in (44) are strong enough.

If system (2) is mesoscopic sized, then the deterministic dynamics in (45) also has a stochastic, Markov counterpart, as a birth-and-death process with master equation for the probability distribution \( p_n(t) = \Pr \{n_X(t) = n \} \), where \( n_X(t) \) is the number of \( X \) in the system at time \( t \):

\[ \frac{dp_n(t)}{dt} = g \left( (n-1) p_{n-1} - np_n \right) - k_{+2} \left( np_n - (n+1) p_{n+1} \right). \]

(46)

For very large \( n \), one can approximate \( n+1 \approx n \approx n-1 \), then this is the equation [9] in ref. [11], if we identify \( k_{+2} \) as \( \delta \).

However, as discussed in Sec. [45] while coarse-graining is a type of mathematical approximation, not all mathematically legitimate kinetic approximations are valid coarse-graining for thermodynamics. The approximated (45) now yields meaningless chemical thermodynamics. To see this, we consider the exact result in Eq. 16

\[ \mu_A - \mu_B = \ln \left( \frac{a k_+ k_{+2}}{b k_{-1} k_{-2}} \right), \]

(47)

and compare it with the mathematical entropy production in the Markov transition of the birth-and-death process (46), from \( n_X = n \) to \( n_X = (n + 1) \):

\[ \text{entropy production of birth-and-death} \]

\[ = \ln \left( \frac{\Pr \{ \text{a birth in } \Delta t \text{ time} \}}{\Pr \{ \text{a death in } \Delta t \text{ time} \}} \right) \]

\[ = \ln \left( \frac{\text{an} k_{+1} p_n}{k_{+2} (n+1) p_{n+1}} \right). \]

(48)

Comparing Eq. 48 and Eq. 47 we see there is no definitive relation, nor definitive inequality between the two quantities: Both \( k_{+1} \) and \( k_{+2} \), which are on the numerator and denominator in [48], are on the numerator in [47].

One also notices that when \( k_{-1} = 0 \), the Markov process described by Eq. 47 is possible to continuously increase without reaching stationarity:

\[ (a k_{+1} n + k_{-2} b a) > k_{+2} n, \forall n. \]

(49)
However, for $k_{-1} \neq 0$, the inequality in (49) can not be valid for all $n$: There must be an $n^*$, when $n > n^*$:

$$nk_{+1} n + k_{-2} \omega < \left( \frac{k_{-1}(n-1)}{\omega} + k_{+2} \right) n. \quad (50)$$

This shows that a chemical kinetics with meaningful thermodynamics is intrinsically stable.

As we have stated earlier, considering microscopic reversibility is a fundamental tenet of stochastic thermodynamics. Any coarse-graining that is thermodynamically meaningful has to respect the nature of microscopic reversibility. On the other hand, the death step represented by $\delta = k_{+2}$ simply is not the reverse step of the birth step represented by $g = k_{+1}$; it cannot provide any meaningful estimation. The reversed step of birth is actually an infant going back to the mother’s womb! In a population dynamics model like (45), while it could be completely accurate in kinetic modeling, nevertheless it cannot provide any meaningful estimation. The reversed step to a living organism being birth and death, the connection to the physical world has already lost in the mathematical thinking.

As pointed out in [11], “it is much more likely that one bacterium should turn into two than that two should somehow spontaneously revert back into one.” Nevertheless, it is the non-zero probability of such completely inconceivable processes, in a physicist’s world, that provides an estimation of thermodynamic heat production. When a biologist considers only feasible events to a living organism being birth and death, the number counting representation of nameless individuals in a population. There are irreversible approximations involved.

Also, with a thermodynamically valid coarse-graining, the computation of entropy production on a coarse level can provide a lower bound for the mechanics based free energy dissipation, as stated in [11]. This result is not new; it has been discussed already in [11] and [11]. In a nutshell, coarse-graining involves “rapid equilibrium” assumption which hides a dissipation in the fast modes of motions. In fact, with a given difference $(J^+ - J^-)$ which fixes the rate of an irreversible process, the entropy production $\ln(J^+ / J^-)$ decreases with increasing one-way fluxes $J^+$ and $J^-$. The physics of living systems is outside classical mechanics. While no living phenomenon and process disobey classical mechanics, the former are phenomena with such a large degree of freedom, heterogeneity, and complexity, their understanding has to be founded on laws and descriptions outside classical mechanics. By classical mechanics, we mean the view of the world in terms of point mass and their movement based on the Newtonian system of equations of motion. In particular, we try to show that the understanding of “heat”, which is so fundamental in the irreversibility of macroscopic mechanical systems, actually has very little to do with irreversibility in living systems! In contrast, chemical thermodynamics and its irreversibility, à la Gibbs, Lewis and Randall, naturally arises from the theory of probability, the mathematics J. W. Gibbs employed in terms of the notion of ensemble, for developing his brand of statistical mechanics. It did not escape our notice that Gibbs was also the originator of the chemical thermodynamics, and the inventor of the notion of chemical potential.

Understanding thermodynamics from Newtonian mechanics was the central thesis of L. Boltzmann’s life work. Indeed, one of the key results of Boltzmann, together with H. von Helmholtz, was to cast the phenomenological First Law of thermodynamics into a mathematical corollary of the Newtonian equation of motion: One knows a Hamiltonian dynamics is restricted on a level set of $H(\{x_i\}, \{v_i\}) = E$, where the $E$ is determined by the initial condition. Recognizing that a thermodynamic state is actually a state of perpetual motion, e.g., an entire level set of $E$ is a mathematical function between the phase-space volume contained by the level-set $\Omega$, $E$, and other parameters in the Hamiltonian function $H(\{x_i\}, \{v_i\}, V, N): \Omega(E, V, N)$. Since the phase-space volume monotonically increases with $E$, one can define

$$E = E(S, V, N), \quad \text{where } S = \ln \Omega(E, V, N). \quad (51)$$

It is then a matter of simple calculus to obtain

$$dE = \left( \frac{\partial E}{\partial S} \right)_{V, N} dS + \left( \frac{\partial E}{\partial V} \right)_{S, N} dV + \left( \frac{\partial E}{\partial N} \right)_{S, V} dN, \quad (52)$$

and define the emergent thermodynamic quantities $T = \frac{\partial E/\partial S}{\partial E/\partial V}$ as temperature, $p = -\left( \frac{\partial E}{\partial V} \right)_{S, N}$ as pressure, and $\mu = \left( \frac{\partial E}{\partial N} \right)_{S, V}$ as chemical potential. Note, from the mechanical standpoint, $T, p, \mu$ are emergent quantities; they characterize how one invariant torus is related to another invariant torus, i.e., one thermodynamic equilibrium state to another thermodynamic equilibrium state.

\(^3\)Note that when dealing with many-body systems, fluid mechanics and quantum mechanics changed their representations from tracking the state of individually labeled particles to counting the numbers: the switching from Lagrangian to Eulerian descriptions in the former and second quantization in the latter.

\(^4\)Here, the importance of ergodicity arises.
It is important to emphasize that, no matter how imperfect, both $T$ and $p$ have well-accepted and widely understood mechanical interpretation, as mean kinetic energy and mean momentum transfer to the wall of a container, respectively. However, $\mu$ has no interpretation in terms of classical motion, whatsoever; rather, it has an interpretation in terms of probability, and in terms of Brownian motion:

$$
\frac{\partial (p(x,t))}{\partial t} = D \frac{\partial^2 (p(x,t))}{\partial x^2} = -\frac{1}{\eta} \frac{\partial (\dot{F})}{\partial x},
$$

where

$$
\dot{F} = -\frac{\partial \mu}{\partial x}, \quad \text{and} \quad \mu = D \eta \ln (p(x,t)) = k_B T \ln (p(x,t)).
$$

$\dot{F}$ is known as entropic force in chemistry, and $\mu$ is its potential function.

A living system is sustained neither by a temperature difference, nor by a pressure difference. It is a phenomenon driven by chemical potential difference. Therefore, we believe any discussion of irreversibility in living systems based on the notion of heat is misguided. Nevertheless, as the physicist in 18th century had recognized in connection to the notion of “heat death of the universe”, a sustained chemical potential difference has to have a consequence in generating heat in a closed, cyclic universe, if one indeed can treat the entire universe as an isolated mechanical system. However, it is equally likely, according to our current, limited understanding of the cosmology and planet formation, that what is being dissipated is simply local inhomogeneity, e.g., low entropy initial condition, in our world, which was formed 13 some billion years ago.

**Information and entropy.** There is a growing interest in the phenomenon of “information to energy conversion” in Maxwell-demon like devices [49]. To quantify information, entropy change has to be distinguished from work. An unambiguous distinction between work and heat is fundamental to thermodynamics: “The difference between heat and work cannot always be uniquely specified. It is assumed that there are cases, involving ideal processes, in which the two can be strictly distinguished from one another” [50]. Unfortunately outside classical mechanics, at least in biochemistry where temperature-dependent heat capacity is a commonplace [51], distinguishing enthalpy change from entropy change becomes increasingly challenging [52, 53, 57]. In a more modern physics setting, heat, probability, and time are intimately related [54]. The success of our present theory on chemical thermodynamics owes to a large extent to a sidestepping the notion of heat, and thus temperature that follows.

**The physical locus of entropy production.** Whether the entropy is produced inside a subsystem, or in the environment outside the system, or just at the boundary [55], is one of the deeper issues in nonequilibrium thermodynamics: To L. Onsager, a transport process driven by a thermodynamic force constitutes dissipation [56]. This is a NESS view of an “insider” of an open subsystem; it can be mathematically justified in terms of the positive chemical motive force (cmf) introduced in Eq. [126] To classical physicists, however, the mechanistic origin of the “thermodynamic force” is outside the subsystem due to spontaneous processes that cause entropy of the total closed system to increase. This view is justified in terms of $\frac{dF}{dt} \leq 0$ for closed systems. We refer the readers to T. L. Hill’s notion of “cycle completion” in stochastic thermodynamics [57] for a much more complete view of the matter. This concept nicely echoes R. Landauer and C. H. Bennett’s principle of computational irreversibility being associated only with memory erasing [58, 59]. It also provides a powerful conceptual framework for further investigating other nagging concepts such as heat dissipation associated with a subsystem in a nonequilibrium steady state (NESS) [37] and endo-reversibility in finite time thermodynamics (FTT) [55, 60].

**ACKNOWLEDGMENT**

D. B. S. and H. Q. acknowledge the MOST grant 104-2811-M-001-102 and the NIH grant R01-GM109964, respectively, for support. H. Q. thanks Ken Dill, Tolya Kolomeisky, and Chao Tang for pointing him to the problem of self-replication, that initiated the present work.

**REFERENCES**

[1] H. Qian, “Nonlinear stochastic dynamics of complex systems, I: A chemical reaction kinetic perspective with mesoscopic nonequilibrium thermodynamics,” arXiv:1605.08070, 2016.

[2] L. F. Thompson and H. Qian, “Nonlinear stochastic dynamics of complex systems, II: Potential of entropic force in Markov systems with nonequilibrium steady state, generalized Gibbs function and criticality,” arXiv:1605.08071, 2016.

[3] C. E. Shannon and W. Weaver, The Mathematical Theory of Communication. Chicago: Univ. Illinois Press, 1963.

[4] S. Toyabe, T. Sagawa, M. Ueda, E. Muneyuki and M. Sano, “Experimental demonstration of information-to-energy conversion and validation of the generalized Jarzynski equality,” Nat. Phys. vol. 6: 988–992, 2010.

[5] D. Mandal and C. Jarzynski, “Work and information processing in a solvable model of Maxwell demons,” Proc. Natl Acad. Sci. U.S.A. vol. 109, 11641–11645, 2012.

[6] H. A. Johnson, “Information theory in biology after 18 years,” Science, vol. 168, pp. 1545–1550, 1970.

[7] T. D. Schneider, “Some lessons for molecular biology from information theory,” In Entropy Measures, Maximum Entropy Principle and Emerging Applications, E. Vargas, M. A. Jiménez-Montaño and J. L. Rius, eds., New York: Springer-Verlag, pp. 229–237, 2003.

[8] A. N. Kolmogorov, “Three approaches to the quantitative definition of information,” Int. J. Comput. Math. vol. 2, 157–168, 1968.

[9] H. Qian, “Mesoscopic nonequilibrium thermodynamics of single macro-molecules and dynamic entropy-energy compensation,” Phys. Rev. E vol. 65, art. 016102, 2002.

[10] R. H. Fowler, Statistical Mechanics: The Theory of the Properties of Matter in Equilibrium. U.K.: Cambridge Univ. Press, 1929.

[11] J. L. England, “Statistical physics of self-replication,” J. Chem. Phys., vol. 139, art. 121923, 2013.

[12] J. Roughgarden, Theory of Population Genetics and Evolutionary Ecology: An Introduction. New York: Macmillan Pub., 1979.

[13] B. M. R. Stadler and P. F. Stadler, “The topology of evolutionary information,” In Modelling in Molecular Biology. G. Ciobanu and G. Rozenberg eds., pp. 267–286, New York: Springer, 2004.

[14] M. W. Kirschner and J. C. Gerhart, The Plausibility of Life: Resolving Darwin’s Dilemma. New Haven: Yale Univ. Press, 2005.

[15] D. Noble, The Music of Life: Biology Beyond Genes. U.K.: Oxford Univ. Press, 2008.

[16] R. A. Weinberg, “Coming full circle — From endless complexity to birth,” Cell, vol. 157, pp. 267–271, 2014.

[17] L. H. Hartwell, J. J. Hopfield, S. Leibler and A. W. Murray, “From molecular to modular cell biology,” Nature, vol. 402, pp. C47–C52, 1999.

[18] M. Vellela and H. Qian, “A quasistationary analysis of a stochastic chemical reaction: Keizers paradox,” Bullet. Math. Biol., vol. 69, pp. 1727–1746, 2007.
