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Chapter 11

Chemical reaction kinetic perspective with mesoscopic nonequilibrium thermodynamics

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We distinguish a *mechanical* representation of the real world in terms of point masses with positions and momenta and the *chemical* representation of the real world in terms of populations of different individuals, each with intrinsic stochasticity, but population wise with statistical rate laws in their syntheses, degradations, spatial diffusion, individual's state transitions, and interactions. Such a formal kinetic system in a small volume V, like a single cell, can be rigorously treated at a mesoscopic scale in terms of a Markov process describing its nonlinear kinetics as well as a nonequilibrium thermodynamics. We introduce notions such as open, driven chemical systems, entropy and its production, free energy and its dissipation, etc. Then in the macroscopic limit when the V tends to infinity, we illustrate how two new "laws", in terms of a generalized free energy of the mesoscopic stochastic dynamics, emerge. Detailed balance and complex balance are two special classes of "simple" nonlinear kinetics. Phase transition is intrinsically related to multi-stability and saddle-node bifurcation phenomenon, in the limits of time $t \to \infty$ as well as system's size $V \to \infty$. Using this approach, we re-articulate the notion of inanimate equilibrium branch of a system and nonequilibrium state of a living, active matter, as originally proposed by Nicolis and Prigogine, and seek a logic consistency between this viewpoint and that of P. W. Anderson and J. J. Hopfield's in which macroscopic law emerges through symmetry breaking.

1. Introduction

This is the Part I of a series on a comprehensive theory of complex systems [1, 2]. Taking living biological cells as an archetype and biochemical kinetic approach as a paradigm, we consider a system *complex* if it contains many interacting subpopulations of individuals that undergo non-deterministic state transitions, and it interacts with its environment through active transports of matters and energy, or information. For examples, tumor is a community of heterogeneous individual cells; economy concerns with individual agents, and ecology deals with various biological organisms.

The above "definition" of a complex system immediately reminds us of

several major areas of studies: nonequilibrium thermodynamics, statistical physics, nonlinear dynamics, stochastic processes, and information theory are some of the widely acknowledged. Ours, however, is not a "new" theory, rather it is a coherent narrative that synthesizes a wide range of methodologies and thoughts contained in the mentioned above. One can easily find in this paper significant influences from the various theories on complexity: the Brussels school of thermodynamics that describes nonequilibrium phenomena in terms of chemical affinity and entropy production [3–6]; the stochastic-process approach to nonequilibrium ensemble theory and entropy production [7–10]; the theory of synergetics which articulates the ideas of nonequilibrium potential and phase transition, as well as slaving principle as an emergent phenomenon near a critical point [11, 12]; the notion of symmetry breaking from the phase transition lore in condensed matter physics [13–16]; catastrophe theory in connection to nonlinear bifurcation [17, 18].

The unique features of our approach are as follows: First, we have two concrete examples of complex chemical systems in mind: A single protein molecule, which consists of a large collection of heterogeneous atoms, in an aqueous solution as a non-driven (closed) chemical system [19], and a single cell, which consists of a large number of different biomolecular species, in a culture medium as a driven open chemical system [20]. While closed and open chemical systems have fundamentally different thermodynamics, some of the key aspects of nonlinear stochastic dynamics are remarkably consistent: 1) Nonlinearity gives rise to discrete states, e.g., conformational states of a protein and epi-genetic states of a cell; 2) stochasticity yields discrete transitions among the states on a much longer time scale. Both systems can be mathematically described in terms of nonlinear stochastic kinetics.

The second feature of our approach is following what the nonlinear, stochastic mathematics tells us [21]. For examples: i) For many of the stochastic models of open chemical systems, one can prove the existence of a unique, ergodic steady state probability distribution, even though its computation is often challenging toward which significant past research has been directed. But the latter should not prevent one to develop a theory based on such a nonequilibrium steady state (NESS) potential function. Indeed, we can show that the mere recognition of its existence provides great logical consistency and theoretical insights in a theory. ii) For Markov stochastic processes under a set of rather weak conditions, one can show a set of mathematical theorems that have remarkable resemblance to the theory of chemical thermodynamics, *à la* Gibbs, and Lewis and Randall [22, 23]. iii) For any stochastic dynamics with a macroscopic bistability as fluctuations tending to zero ($\varepsilon \to 0$), symmetry breaking in the limit of $\varepsilon \to 0$ following time $t \to \infty$

is a necessary consequence of the catastrophe in the nonlinear dynamics, obtained from $\varepsilon \to 0$ precedes $t \to \infty$. While these mathematical results stand on their own, their significance to our understanding of complex systems requires a narrative that is constructed based on all the past theories, thoughts, and discussions.

The nonlinear stochastic dynamic description of complex systems embodies two of the essential ingredients of Darwin's theory of biological evolution: chance, variation, diversity on the one hand and necessity, selection on the other [11, 24–26]. The chemical kinetic theory of living cells based on the Delbrück–Gillespie process description [27–31] allows one to see how various abstract "forces of nature" emerge and play out in a complex system, with individual players as simple, or as complex, as macromolecules.

1.1. *Mechanics and chemistry*

Mechanics and chemistry offer two very different perspectives of a complex system: the former considers the world made of featureless individuals, the *point masses*,[a] with precise positions and velocities; the latter, however, entertains a world made of many types of individuals, each with different internal characteristics. Due to the uniqueness of space and time, each and every point mass is unique. On the other hand, modern studies have shown that individual single molecules in aqueous solution behavior differently: They have *individualities* [32, 33]. More interestingly, when dealing with many-body systems, even fluid mechanics and quantum mechanics turn their representations from tracking the state of individual particles to counting the numbers: the switching from Lagrangian to Eulerian descriptions in the former and second quantization in the latter.

The "chemical kinetic view" of the complex world goes much beyond chemistry: Reaction $S + I \to 2I$ is known as autocatalysis in chemistry, with the S being a reactant and I being its product which also serves as a catalyst for a transformation of an S to an I. The same "kinetic scheme" also describes infection in an epidemiological dynamics, with S and I representing susceptible and infectious individuals, respectively. In fact, we argue that much of the complex systems beyond chemistry contain interacting subpopulations of individuals that undergo non-deterministic state transitions. The chemical view actually offers a reasonable organization of P. W. Anderson's X and Y in the hierarchical structure

[a]A more profound insight is that no matter how complex interactions among a collection of point masses are, its center of mass behaves as a single featureless point mass. However, a system with frictional force no longer has this crucial property.

of science [13]:

X	Y
many-body physics	particle physics
chemistry	many-body physics
molecular biology	chemistry
cell biology	molecular biology
$\vdots$	$\vdots$
psychology	physiology
social sciences	psychology

We note that each X in the left column consists of collections of "individuals" characterized by the Y on the right.

2. Chemical kinetics and chemical thermodynamics

2.1. *A single chemical reaction as an emergent phenomenon*

Is a biochemical macromolecule, a protein, immersed in an aqueous solution simple or complex? The answer to this question depends on one's perspective, and time scale [15]. From the standpoint of molecular physics and in terms of the large number of atoms that are constantly in collisions with each other and with solvent molecules, this is a quite complex system which has its own emergent phenomenon.

The mechanical motions described by a Newtonian molecular dynamics (MD) with solvent molecules being explicitly treated, usually on the time scale of femtosecond (10^{-15} sec.), exhibit great complexity. Yet, the notions of "reaction coordinate" (e.g., order parameter) and "transition state" (e.g., critical state), plus a single rate constant which is on the microsecond to millisecond time scale, fully describe the exponential law for an elementary, unimolecular chemical reaction. This emergent phenomenon has been mathematically described in H. A. Kramers' nonlinear, stochastic theory of energy barrier crossing [34], and the rigorous mathematics of Freidlin–Wentzell theory [35–37].

2.2. *Chemical kinetics and elementary reactions*

Just as point mass is a fundamental concept in mechanics, *elemetary reaction* is a fundamental concept in chemical kinetics: A reaction like

$$\nu_1^+ A_1 + \nu_2^+ A_2 + \cdots \nu_N^+ A_N \longrightarrow \nu_1^- A_1 + \nu_2^- A_2 + \cdots \nu_N^- A_N$$

is said to be elementary if the discrete event of transformation has an exponentially distributed waiting time with rate r, which is a function of numbers of the

reactants, $n_1, n_2, \cdots, n_N$, in a reaction vessel with volume V. If the rate r has the form of

$$r = kV \prod_{=1}^{N} \left(\frac{n\ (n\ -1) \cdots (n\ -\nu^{+} + 1)}{V^{\nu_\ell^{+}}} \right), \tag{1}$$

in which n is the number of molecule A in the vessel, then we said the reaction follows the law of mass action with rate constant k. In a macroscopic sized system, in terms of concentrations $x_1, x_2, \cdots, x_N$, the reaction flux in (1) becomes

$$J = \frac{r}{V} = k \prod^{N} x^{\nu_\ell^{+}}, \tag{2}$$

in which $x\ = n\ /V$ is the concentration of the reactant A. For example, the nonlinear kinetic system

$$S + I \xrightarrow{k_1} 2I, \quad I \xrightarrow{k_2} R, \tag{3}$$

has a macroscopic kinetic equation following the law of mass action

$$\frac{\mathrm{d}x}{\mathrm{d}t} = k_1 xy - k_2 x, \quad \frac{\mathrm{d}y}{\mathrm{d}t} = -k_1 xy, \quad \frac{\mathrm{d}z}{\mathrm{d}t} = k_2 x, \tag{4}$$

where x, y, and z are the concentrations of chemical species I, S, and R, respectively. In the mathematical theory of infectious diseases, however, the same set of equations represent the SIR model [38]. The population dynamics of species in an infectious disease, in ecological dynamics, and chemical species in a rapid stirred reaction vessel, actually share a great deal of commonality: They are all complex nonlinear systems consisting of heterogeneous interacting individuals.

2.3. *Mesoscopic description of chemical kinetics*

The readers are referred to the earlier review articles [39, 40], the Chapter 11 of [41], and the recent texts [31, 42].

3. Nonequilibrium thermodynamics (NET)

The notion of elementary reactions as presented above is fundamentally a stochastic one in which a chemical reaction in an aqueous solution is represented by a rare event in the many-body, heterogeneous atomic system. Each reaction as a single random event is the focus of the Kramers' theory whose prediction is that, when an energy barrier is high, all the complex atomic motions in a unimolecular transition can be represented by a single parameter, the rate constant k. For bimolecular reactions, a diffusion based theory in three-dimensional physical space was first

proposed by M. von Smolochowski (1917), and further developed by Collins and Kimball (1949), A. Szabo and his coworkers [43, 44].

While Kramers' theory connects stochastic molecular state transitions to the motions of the constitutive atoms, a cell consists of a great many macromolecular species and biochemical reactions. The Delbrück–Gillespie process describes the stochastic kinetics of such a system, with two complementary representations: Either in terms of the random, fluctuating number of all molecular species, $n = \left[n_1(t), n_2(t), \cdots, n_N(t)\right]$ that follows Gillespie algorithm [30], or in terms of the probability distribution $p(m_1, \cdots, m_N; t) = \Pr\{n_1(t) = m_1, \cdots, n_N(t) = m_N\}$ that satisfies the Chemical Master Equation (CME) [28, 29]. This theory of mesoscopic stochastic chemical kinetics has rapidly become a mature subject in recent years [31].

We use the term "mesoscopic" in partial agreement with van Kampen [45], Ch. III, p. 57, who stated that "[t]he stochastic description in terms of macroscopic variables ... It comprises both the deterministic laws and the fluctuations about them". There is an important difference, however, between this and our view: What implicitly assumed by van Kampen and physicists of his time was a top-down, macroscopic law known first followed by fluctuations theory; it is a phenomenological approach pioneered by Einstein.

The stochastic chemical kinetic theory is different. With a foundation laid by Kramers' theory, a stochastic chemical kinetic model is *mechanistic*. The deterministic laws then can be mathematically derived, as has been shown by T. G. Kurtz [29]. This conceptual distinction also leads to an essential practical difference: The "noise structure" in the traditional top-down models can only be determined by additional assumptions, e.g., fluctuation-dissipation relation for equilibrium fluctuations. The noise structure in a Delbrück–Gillespie model is completely specified by the chemical kinetics.

The most general setup for a mesoscopic chemical kinetics in a rapidly stirred reaction vessel with volume V considers N chemical species and M elementary chemical reactions:

$$\nu_1^+ X_1 + \nu_2^+ X_2 + \cdots \nu_N^+ X_N \underset{r_{-\ell}}{\overset{r_{+\ell}}{\rightleftharpoons}} \nu_1^- X_1 + \nu_2^- X_2 + \cdots \nu_N^- X_N, \qquad (5)$$

in which both $r_\pm$ are functions of n and V, $1 \leq \quad \leq M$. $\nu_j^\pm$ are stoichiometric coefficients for the forward and the backward reactions $\pm$.

In applied mathematics, compared with what we know abut ordinary differential equations beyond the existence and uniqueness theorems, we currently know very little about the Delbrück–Gillespie process.

3.1. *Gibbs' chemical thermodynamics*

It is widely agreed upon that thermodynamic behavior is an emergent phenomenon of systems with a large number of components. L. Boltzmann's attempt, to provide macroscopic thermodynamics with a Newtonian mechanical foundation, has provided continuous inspiration for understand complexity. Consider a mechanical system, a box of gas with volume V and number of particles N, described by Hamiltonian dynamic equation $\dot{p} = \partial H(p, q/\partial q$ and $\dot{q} = -\partial H(p, q)/\partial p$. According to Boltzmann's fundamental insight [46], a macroscopic thermodynamic state is a state of motion, the entire level set of $H(p, q; V, N) = E$, which is determined by the initial condition of the differential equation. Then entropy $S = k_B \ln \Omega(E, V, N)$ where $\Omega(E, V, N)$ is the phase volume contained by the level set. Thus there exists a definitive function $S = S(E, V, N)$. It then follows from elementary calculus:

$$\mathrm{d}E = \left(\frac{\partial E}{\partial S}\right)_{V,N} \mathrm{d}S + \left(\frac{\partial E}{\partial V}\right)_{S,N} \mathrm{d}V + \left(\frac{\partial E}{\partial N}\right)_{S,V} \mathrm{d}N \tag{6}$$

in which $(\partial E/\partial S)_{V,N} = T$ is identified as temperature, $(\partial E/\partial V)_{S,N} = -p$ is identified as pressure, and $p\mathrm{d}V$ is mechanical work. $(\partial E/\partial N)_{S,V} = \mu$ is called chemical potential.

Consequently thermodynamic quantities such as T, p, and μ are emergent concepts themselves. However, for both T and p clear *mechanical interpretations* have been found: T being mean kinetic energy and p the momentum transfer upon collision of gaseous molecules on the wall of the box. However, one yet to find a clear mechanical interpretation for μ. The chemical potential μ has a μ^o part and a log concentration (or mole fraction) part. The particles in (6) are supposed to be featureless point masses. But if they can be further decomposed into collections of particles, such as molecules in terms of atoms, then the μ can be further interpreted in mechanical terms. The current molecular theory of μ^o is based on such a "mechanical" view, classical or quantum.

The entire living phenomena are mostly driven by $\Delta\mu$, not ΔT or Δp. Chemistry kinetics offers a concrete example of complex systems.

3.2. *The source of complexity*

Biological systems are archetypes of complex system. Why biological and complex systems look so different from those in physics? J. J. Hopfield [14], together with many other condensed matter physicists [6, 12, 47], have all pointed to the information content of a system, and the notion of *symmetry breaking* as the key elements of complex systems [13, 15, 16]. The notion of symmetry breaking,

in a broad sense, is best illustrated in a mesoscopic kinetics with finite volume V: When V is small, the Markov dynamics is ergodic. Multi-stability in this system is represented by multiple peaks of the stationary probability distribution $p^{ss}(n_1, n_2, \cdots, n_N; V)$ [5, 11, 18]. However, when $V \to \infty$, the different peak regions correspond to different basins of attraction according to the systems of ordinary differential equations (ODEs) that follow the law of mass action. The dynamics of the deterministic ODEs has broken ergodicity: Dynamics starts in one basin will never go to another basin. More interestingly, if one takes the limit of $V \to \infty$ after $t \to \infty$ in the mesoscopic kinetic model, it predicts the system has only a single attractor with probability 1. In fact, the stationary probability distribution

$$V^{-1}p^{ss}(x_1V, x_2V, \cdots, x_NV; V) \approx \Xi^{-1}(V)e^{-V\phi(x_1,x_2,\cdots,x_N)}, \tag{7a}$$

$$\Xi(V) = \int_{\mathbb{R}^N} e^{-V\phi(x)}\mathrm{d}x, \tag{7b}$$

in which $\phi(x)$ has a global minimum of 0, at which the entire probability will concentrate when $V \to \infty$ [48]. Phase transition occurs when the global minimum of $\phi(x)$ is not unique.

3.3. *Macroscopic NET of continuous media*

A summary of the standard formalism of macroscopic nonequilibrium thermodynamics (NET) in continuous medium, as introduced in [49], can also be found in [50]. In this theory, (i) the existence of a special macroscopic function $s(x, t)$, the instantaneous entropy density, is hypothesized via the *local equilibrium assumption*, which yields

$$\frac{\partial s(x,t)}{\partial t} = T^{-1}(x,t)\left[\frac{\partial u(x,t)}{\partial t} - \sum_{i=1}^{K}\mu_i(x,t)\frac{\partial c_i(x,t)}{\partial t}\right], \tag{8}$$

in which $u(x, t)$ is internal energy density, $c_i(x, t)$ is the concentration of the ith chemical species, T and μ_i are temperature and chemical potentials. The theory of NET then proceeds as follows:

(ii) Establishing continuity equations for $u(x, t)$ and $c_i(x, t)$: $\partial u_t = -\partial_x J_u(x, t)$, $\partial(c_i)_t = -\partial_x J_i(x, t) + \sum_{j=1}^{M} \nu_{ji} r_j$, where J_u and J_i are energy and particle fluxes in space, and r_j is the rate of the jth reaction with stoichiometric coefficients ν_{ji};

(iii) Substituting the J's and r's into (8);

(iv) Grouping appropriate terms to obtain the density of entropy production rate, $\sigma(x, t)$, as "transport flux $\times$ thermodynamics force", *à la* Onsager. The remaining part is the entropy exchange flux $J_s(x, t)$: $\partial s(x, t)/\partial t = \sigma(x, t) - \partial_x J_s(x, t)$.

3.4. *Mesoscopic NET*

The x in the above macroscopic NET represents the real three-dimensional physical space. One can apply a similar approach to a space of internal degrees of freedom, as initiated by Prigogine and Mazur [53–56], or a dynamics in phase space as in Bergmann and Lebowitz's stochastic Liouville dynamics [9, 10].[b] In these cases, the theory of mesoscopic NET proceeds as follows:

i) Introducing the entropy, or free energy, as a functional of the probability distribution $p_\alpha(t)$, $\alpha \in \mathscr{S}$ for a discrete system, or probability density function $f(\mathbf{x}, t)$; $\mathbf{x} \in \mathbb{R}^n$, for a continuous system. The introduction of entropy function in the mesoscopic theory does not rely on the local equilibrium assumption. Rather,

the $f(\mathbf{x}, t)$ that necessarily satisfies a continuity equation in a phase space:

$$\frac{\partial f(\mathbf{x}, t)}{\partial t} = -\sum_i \frac{\partial}{\partial x_i} J_i(\mathbf{x}, t), \tag{10a}$$

and non-adiabatic entropy production, or free energy dissipation [57]:

$$-\frac{\mathrm{d}}{\mathrm{d}t}\int_{\mathbb{R}^n} f(\mathbf{x}, t) \ln\left(\frac{f(\mathbf{x}, t)}{\pi(\mathbf{x})}\right) \mathrm{d}\mathbf{x} = \int_{\mathbb{R}^n} f(\mathbf{x}, t)\sigma^{(na)}(\mathbf{x}, t)\mathrm{d}\mathbf{x}, \tag{10b}$$

in which the *local density* of non-adiabatic entropy production rate

$$\sigma^{(na)}(\mathbf{x}, t) = -\sum_i J_i(\mathbf{x}, t)\frac{\partial}{\partial x_i} \ln\left(\frac{f(\mathbf{x}, t)}{\pi(\mathbf{x})}\right), \tag{10c}$$

where $\mathbf{J}(x, t)$ is the flux and the $\nabla \ln\left[f(x, t)/\pi(x)\right]$ is the thermodynamic force: the gradient of the local chemical potential function. One also notices that the thermodynamic force $\nabla \ln\left[f(\mathbf{x}, t)/\pi(\mathbf{x})\right]$ can be further decomposed into $\mathbf{X} + \nabla \ln f(\mathbf{x}, t)$ where $\mathbf{X} = -\nabla \ln \pi(\mathbf{x})$ is the thermodynamic variables conjugate to $\mathbf{x}$. Readers with a college chemistry background should recognize this as $\Delta G = \Delta G^o + RT \ln(\text{concentration ratio})$, where $\Delta G^o = RT \ln(\text{equilibrium concentration ratio})$.

Now here comes as the point of departure between the narrative of meso-NET and the narrative of stochastic thermodynamics: The former evokes Onsager's linear force-flux relation

$$J_i(\mathbf{x}, t) = -\sum_j D_{ij}(\mathbf{x})\frac{\partial}{\partial x_j} \ln\left(\frac{f(\mathbf{x}, t)}{\pi(\mathbf{x})}\right). \tag{11}$$

Note this relation is simply a generalized Fick's law. Then it is well-known that combining continuity equation (10a) with Fick's law (11) yields the Fokker–Planck equation.

To "justify" the stochastic descriptions of mesoscopic dynamics is one of the fundamental tasks of statistical physics. Beside this meso-NET approach, there are many others: Bogoliubov–Born–Green–Kirkwood–Yvon (BBGKY) hierarchy, Mori–Zwanzig (MZ) projection, Markov partition and Kolmogorov–Sinai entropy method, etc. Since the meso-NET approach is based on Onsager's linear relation, its validity is limited in the linear irreversible regime.

We note that for a discrete $p_\alpha(t)$:

$$\sigma^{(na)}_{\alpha\beta} = (J_{\alpha\to\beta} - J_{\beta\to\alpha})\,\Delta\mu_{\alpha\beta}, \quad \Delta\mu_{\alpha\beta} = \ln\left(\frac{p_\alpha \pi_\beta}{\pi_\alpha p_\beta}\right). \tag{12}$$

However, the flux J is <u>not</u> linearly related to the thermodynamic potential difference $\Delta\mu$. The same logic will not work for the stochastic dynamics of mesoscopic chemical kinetics.

The linear Fick's law and its alike are phenomenological relations. Derivation of the macroscopic diffusion equation based on this line of arguments naturally leads to more general *nonlinear diffusion equation* [58, 59]. The Fokker–Planck equation in phase space, however, has a much more fundamental origin: It is a mathematical consequence of Chapman–Kolmogorov's integral equation for any Markov process with continuous path in $\mathbb{R}^n$ [60]. In current stochastic thermodynamics, one takes the stochastic, Markov dynamics as given. Nonequilibrium thermodynamics is not used as a justification for stochastic descriptions of fluctuations; rather, one attempts to derive nonequilibrium thermodynamics as a mathematical consequence of stochastic dynamics, in either continuous or discrete state space. As a matter of fact, base on such a *Markov process hypothesis*, one can predict the Onsager's linear force-flux relation, e.g., Fick's law, for stochastic dynamics in continuous space, but it also predicts a non-linear force-flux relation (e.g., Eq. (23) below) for stochastic dynamics with discrete state space, such as mesoscopic chemical kinetics.

3.6. *Stochastic Liouville dynamics*

Bergmann and Lebowitz [9, 10] based their new approach to nonequilibrium processes in the phase space on a Hamiltonian mechanical system that is in contact with one, or multiple heat baths:

$$\frac{\partial p(\mathbf{x},t)}{\partial t} + \Big\{p(\mathbf{x},t), H(\mathbf{x})\Big\}_{\mathbf{x}} = \int \Big[K(\mathbf{x},\mathbf{x}')p(\mathbf{x}',t) - K(\mathbf{x}',\mathbf{x})p(\mathbf{x},t)\Big]\mathrm{d}\mathbf{x}' \tag{13a}$$

in which $\{p, H\}$ is the Poisson bracket, and the rhs represents the stochastic encounter with the heat bath(s). By introducing Helmholtz potental function

$$F\big[p(\mathbf{x})\big] = \int_{\mathbb{R}^n} p(\mathbf{x},t)\Big(H(\mathbf{x}) + \beta^{-1}\ln p(\mathbf{x},t)\Big)\mathrm{d}\mathbf{x}, \tag{13b}$$

they showed non-adiabatic entropy production $\sigma^{(na)} = -\frac{\mathrm{d}F}{\mathrm{d}t} \equiv \frac{\mathrm{d}S}{\mathrm{d}t} - \beta\frac{\mathrm{d}U}{\mathrm{d}t} \geq 0$ if the heat baths have a common temperature β^{-1}. If not, then

$$\sigma^{(na)} = \frac{\mathrm{d}S}{\mathrm{d}t} - \sum_{i=1}^{K}\beta_i\Phi_i, \tag{13c}$$

where Φ_i is the mean rate of energy flow from the ith reservoir to the system: $\frac{\mathrm{d}U}{\mathrm{d}t} = \sum_{i=1}^{K}\Phi_i$. Furthermore, in a nonequilibrium stationary state, $\sigma^{(na)} = \sum_{i,j=1}^{K'}\big(\beta_i - \beta_j\big)\Phi_j$, where $K' < K$ are linearly independent number of energy fluxes.

One notices that the logical development of the mesoscopic NET in phase space is more in line with Boltzmann's mechanical theory of heat than with the

top-down phenomenological approach described by van Kampen, as discussed in the beginning of Sec. 3.

4. Mesoscopic stochastic NET and Hill's cycle kinetics

Most of the mathematical presentations of the mesoscopic, stochastic nonequilibrium thermodynamics (stoch-NET) can be carried out in either discrete or continuous state space. For simplicity, however, we consider a Markov dynamics with a finite discrete state space $\mathscr{S}$:

$$\frac{\mathrm{d}p_\alpha(t)}{\mathrm{d}t} = \sum_{\beta\in\mathscr{S}} \Big(p_\beta(t)q_{\beta\alpha} - p_\alpha(t)q_{\alpha\beta}\Big). \tag{14}$$

We further assume that the Markov process is irreducible and $q_{\alpha\beta} = 0$ if and only if $q_{\beta\alpha} = 0$. With these assumptions, the Markov system has a unique, positive stationary distribution $\{\pi_\alpha\}$ that satisfies

$$\sum_{\beta\in\mathscr{S}} \Big(\pi_\beta q_{\beta\alpha} - \pi_\alpha q_{\alpha\beta}\Big) = 0,\ \forall\alpha\in\mathscr{S},\ \sum_{\alpha\in\mathscr{S}} \pi_\alpha = 1. \tag{15}$$

4.1. *Stationary distribution generates an entropic force*

Since mathematicians can prove the existence of the π_α and its positivity, one can introduce

$$E_\alpha = -\ln\pi_\alpha. \tag{16}$$

This mathematical definition formalizes the notion of an "entropic" (statistical) force that does not cause the motion mechanically, yet it is a *thermodynamic force* precisely as articulated by Onsager. Such a force can do mechanical work, as has been illustrated by the polymer dynamic theory of rubber elasticity. Of course, as any thermodynamic concept, it can have many different mechanistic origin. Still, as we shall show, recognizing this novel "law of force" leads to great insights and consistency. How to measure it, e.g., whether such an entropic force is observable is an entirely different matter. Many researchers have discussed such nonequilibrium steady state potential in the past, see [61–65].

With the energy given in (16), one can introduce generalized entropy and free energy in a Markov System. We use the term "generalized" to emphasize that these quantities exist independent of whether a mesoscopic system is in an equilibrium or not, stationary or not. We assume the Markov dynamics has a unique stationary (invariant) distribution. This means that there is a probability based "force" pushing a system from low probability to high probability.

4.2. *Two mesoscopic laws and three nonnegative quantities*

If the system has a probability distribution p_α, then the mean internal energy and entropy are

$$\overline{E} = \sum_{\alpha \in \mathscr{S}} p_\alpha E_\alpha, \; S = -\sum_{\alpha \in \mathscr{S}} p_\alpha \ln p_\alpha. \tag{17a}$$

Their difference is the Helmholtz free energy

F (
S/T1_ 270.9235 578.7116 19.04106466250006 1 Tf 92626 56006

4.3. *The significance of free energy balance equation*

It is clear that the free energy balance equation (18) is simply an alternative expression of the celebrated entropy balance equation [5, 49] that lies at the foundation of classical NET:

$$\frac{\mathrm{d}}{\mathrm{d}t}S\big[\{p_\alpha(t)\}\big] = e_p\big[\{p_\alpha(t)\}\big] + E_{ex}\big[\{p_\alpha(t)\}\big], \tag{20a}$$

$$E_{ex}\big[\{p_\alpha\}\big] = -E_{in} + \frac{\mathrm{d}\overline{E}}{\mathrm{d}t} \tag{20b}$$

$$= \frac{1}{2}\sum_{\alpha,\beta\in\mathscr{S}}\Big(p_\alpha q_{\alpha\beta} - p_\beta q_{\beta\alpha}\Big)\ln\left(\frac{q_{\beta\alpha}}{q_{\alpha\beta}}\right). \tag{20c}$$

Therefore, for a system with $q_{\alpha\beta} = q_{\beta\alpha}$, such as a microcanonical ensemble, $E_{ex} \equiv 0$ and entropy production is the same as entropy change. In general, however, E_{ex} does not have a definitive sign.

For systems that are in contact with external reservoir(s), it is well known from classical thermodynamics that entropy is not an appropriate thermodynamics potential; free energy is. For stoch-NET, the significant advantage of the free energy balance equation in (18) over the entropy balance equation in (20) is obvious. Since both $E_{in}, e_p \geq 0$, they can be definitively identified as the source and the sink, respectively, for the free energy.

When a Markov system is detail balanced, e.g., $\pi_\alpha q_{\alpha\beta} = \pi_\beta q_{\beta\alpha}\ \forall \alpha, \beta \in \mathscr{S}$, $E_{in} \equiv 0$ and $E_{ex} = \frac{\mathrm{d}\overline{E}}{\mathrm{d}t}$. Such a system is like a closed system which approaches to an equilibrium steady state with $e_p = 0$. The last term on the rhs of the entropy balance equation (20a) can be moved to the lhs, and combined with $\frac{\mathrm{d}S}{\mathrm{d}t}$. This yields precisely the free energy balance equation (18a)!

For systems without detailed balance, a nonequilibrium steady state has $E_{in} = e_p \neq 0$. They correspond to *open, driven systems* with sustained transport, powered by a chemostatic environment.

Chemists have always known that free energy balance is different from mechanical energy conservation: since the former involves an entropic component. People are taught to read the "calorie label" on food products in a supermarket; the validity of this practice testifies the significance of a rigorous *free energy balance equation*.

4.4. *Kinetic cycles and cycle kinetics*

Steady state entropy production rate

$$
\begin{aligned}
e_p^{ss} &= \sum_{i>j\in\mathscr{S}} \left(J_{ij}^{ss} - J_{ji}^{ss}\right) \ln\left(\frac{J_{ij}^{ss}}{J_{ji}^{ss}}\right) \\
&= \sum_{c:\text{ all cycles}} \left(J_c^+ - J_c^-\right)^{ss} \ln\left(\frac{J_c^+}{J_c^-}\right)^{ss} \\
&= \sum_{c:\text{ all cycles}} \left(J_c^+ - J_c^-\right)^{ss} \ln\left(\frac{q_{c_1c_2}q_{c_2c_3}\cdots q_{c_\kappa c_1}}{q_{c_1c_\kappa}q_{c_\kappa c_{\kappa-1}}\cdots q_{c_2c_1}}\right). \qquad (21)
\end{aligned}
$$

In Eq. (21), the kinetic cycle c with κ steps consists of the sequence of states $\{c_1, c_2, \cdots, c_\kappa, c_1\}$. One should wonder what the purpose is to re-express the NESS e_p^{ss} as in (21); it contains great many more terms since the number of possible cycles in a Markov graph is much more than the number of edges (transitions). We note, however, that both $J_{ij}^{ss} = p_i^{ss}q_{ij}$ and $J_{ji}^{ss} = p_j^{ss}q_{ji}$ are functions of the probabilities p_i^{ss} and p_j^{ss}. But $(J_c^+/J_c^-)^{ss}$ is independent of any probability. Entropy production per cycle, also called cycle affinity, is the key to mesoscopic, stochastic nonequilibrium thermodynamics! The $(J_c^+ - J_c^-)^{ss}$ is simply a kinematics term: It counts the numbers of different cycles the system passing through per unit time. Recognizing this, it is immediately clear that one can also introduce a fluctuating entropy production along a stochastic trajectory, counting stochastically completed cycles one at a time [71].

The cycle representation of entropy production in (21) was first proposed and computationally demonstrated by Hill and Chen [71]. Later, Hill's diagram approach was shown to be equivalent to a Markov jump process, for which Eq. (21) can be proven mathematically [72, 73]. A trajectory-based stochastic entropy production was introduced by Qian and Qian for discrete Markov processes as well as continuous diffusion processes in 1985 [74].

4.5. *Nonlinear force-flux relation*

One of the significant results of mesoscopic, stoch-NET is a nonlinear force-flux relationship: The net probability flux between states α and β is $(J_{\alpha\to\beta} - J_{\beta\to\alpha})$, and the chemical potential difference is $\Delta\mu = k_BT\ln(J_{\alpha\to\beta}/J_{\beta\to\alpha})$. Only when $\Delta\mu \ll k_BT$, e.g., $J_{\alpha\to\beta} \approx J_{\beta\to\alpha}$, one has a linear relation

$$
\begin{aligned}
J_{\alpha\to\beta} - J_{\beta\to\alpha} &= J_{\beta\to\alpha}\left(\frac{J_{\alpha\to\beta}}{J_{\beta\to\alpha}} - 1\right) = J_{\beta\to\alpha}\left(e^{\frac{\Delta\mu}{k_BT}} - 1\right) \\
&\approx J_{\beta\to\alpha} \times \left(\frac{\Delta\mu}{k_BT}\right). \qquad (22)
\end{aligned}
$$

In fact, an exact nonlinear force-flux relationship exists:

$$J_{\alpha\to\beta} - J_{\beta\to\alpha} = \left(J_{\alpha\to\beta} + J_{\beta\to\alpha}\right) \tanh\left(\frac{\Delta\mu}{2k_B T}\right). \tag{23}$$

4.6. *Comparison with macroscopic NET*

In comparison with the macroscopic NET [49], the present theory, stoc-NET, is a theory based on free energy, not entropy *per se*. This is expected since the Markov description represents a dynamical system with many degrees of freedom collected under the assumption of "random effects". It is a dynamic counterpart of Gibbs' canonical ensemble rather than microcanonical ensemble.

While the macro-NET uses local equilibrium assumption to introduce the entropy function and secures Gibbs' equation (6), the stoc-NET introduces entropy function following Boltzmann's and Shannon's fundamental insights: It is a functional of the probability distribution in the phase space. This approach allows one to mathematically derive a mesoscopic entropy balance equation, and closely related free energy balance equation. Stoc-NET does not require a local equilibrium assumption, though it assumes a Markov dynamics as an "equation of motion" in a phase space. Recall that Boltzmann's mechanical theory of heat assumes Newton's equation of motion [46].

One of the most significant differences between stoc-NET and macro-NET is that one obtains self-contained mathematical expressions for the entropy flux and entropy production rate in the former. One can further mathematically prove the entropy production rate being nonnegative!

Finally, but not the least, the stoc-NET has an entire theory of fluctuating entropy production along stochastic trajectories, e.g., fluctuation theorems and Jarzynski–Crooks equalities, that provides fundamental characterizations of thermodynamics of small systems [75–77].

5. Further development and applications

5.1. *Nonequilibrium steady state and dissipative structure*

Intracellular biology can be roughly thought as a complex biochemical reaction system carried out by enzymes. The cycle kinetics of enzymes in cellular biochemistry defines equilibrium vs. nonequilibrium steady-state (NESS) as illustrated in Fig. 1.

Essentially all biochemical processes inside a living cells are cycle kinetics. One well-known exception is the creatine phosphate shuttle carried out by creatine kinase. According to stoc-NET, each and every kinetic cycle has to be driven

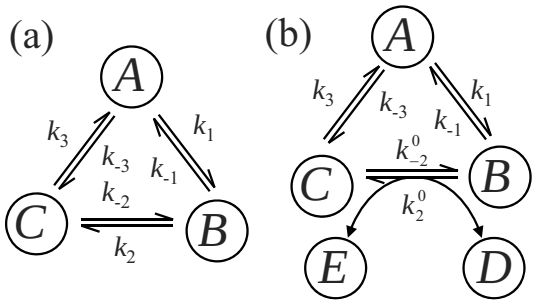


Fig. 1. (a) Unimolecular reactions and (b) pseudo-unimolecular reactions with fixed concentrations c_D and c_E for species D and E. One can map the nonlinear reaction on the right to the left with $k_2^o c_D = k_2$ and $k_{-2}^o c_E = k_{-2}$. They are called pseudo-first-order rate constants. If c_D and c_E are in their chemical equilibrium $c_E/c_D = k_1 k_2^o k_3/(k_{-1} k_{-2}^o k_{-3})$, then $k_1 k_2 k_3 = k_{-1} k_{-2} k_{-3}$. Furthermore, denoting $\gamma = k_1 k_2 k_3/(k_{-1} k_{-2} k_{-3})$, then $k_B T \cdot \gamma = \mu_D - \mu_E$. When $\gamma > 1$, there is a clockwise cycle flux; and when $\gamma < 1$, there is a counter-clockwise cycle flux.

by a non-zero chemical potential difference. Figure 2 are two widely known examples. A stationary state of an open chemical system, sustained by a chemostatic chemical potential difference in its environment and continuously dissipates free energy, epitomizes the notion of dissipative structure [5]. Rigorous mathematical theory of nonequilibrium steady state (NESS) and its applications can be found in [78–80].

5.2. *Macroscopic limit: Gibbs' chemical thermodynamics*

One of the accomplishments of Boltzmann was to obtain the First Law, in the form of Eq. (6), from Newton's equation of motion. But it is not often that one can rely on mathematics to derive a macroscopic law from microscopic dynamic equations, as pointed out by van Kampen [45]:

"Of course, the macroscopic equations cannot actually be derived from the microscopic ones. In practice they are pieced together from general principles and experiences. The stochastic mesoscopic description must be obtained in the same way. This semi-phenomenological approach is remarkably successful ..."

Therefore, it is extremely satisfying when one sees that it is possible to derive Gibbs' macroscopic, isothermal chemical thermodynamics from the mesoscopic chemical kinetic descriptions, e.g., Delbrück–Gillespie process [81, 82].

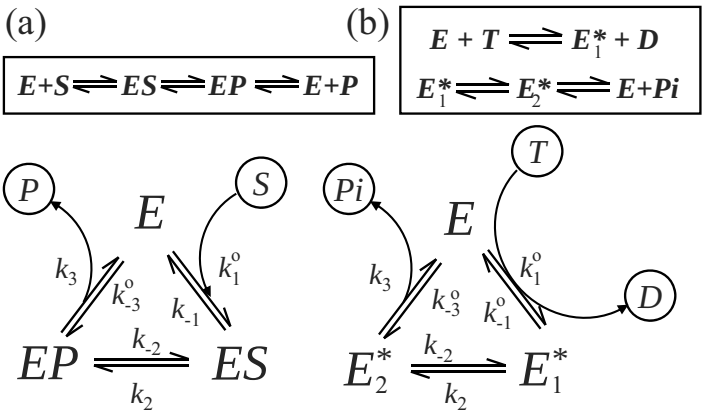


Fig. 2. (a) In cellular metabolism, almost all enzymatic reactions are nearly irreversible. This implies the chemical potential of the substate S is significantly greater than that of the product P. This dictates the enzyme turnover prefers $E \to ES \to EP \to E$ rather than other way around. (b) In cellular signaling pathways, phosphorylation-dephosphorylation cycle is one of the most widely employed biochemical mechanism for regulating cell informations. The cycle is driven by ATP hydrolysis.

5.3. *Applications: biochemical dynamics in single cells*

Both the intracellular genetic regulatory network of self-regulating genes and intracellular signaling networks of phosphorylation-dephosphorylation with substrate-activated kinase or GTPase cycle with substrate-activated GEF (guanine nucleotide exchange factor) are kinetic isomorphic, see Fig. 14 of [80] and Fig. 1 in [83] for illustrations. In fact, they all can be conceptually represented by the following kinetic scheme involving autocatalysis:

$$Y + \chi X \underset{\alpha_2}{\overset{\alpha_1}{\rightleftharpoons}} (\chi + 1)X, \quad X \underset{\beta_2}{\overset{\beta_1}{\rightleftharpoons}} Y. \tag{24}$$

For $\chi = 2$ this system is closely related to the well-known Schlögl model in chemical kinetic literature. The macroscopic kinetics follows the nonlinear differential equation

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -\frac{\mathrm{d}y}{\mathrm{d}t} = \alpha_1 x^{\chi} y - \alpha_2 x^{\chi+1} - \beta_1 x + \beta_2 y, \tag{25}$$

where $x(t)$ and $y(t)$ are the concentrations of X and Y. Given initial values $x(0) = x_0$ and $y(0) = 0$, $y(t) = x_0 - x(t)$. Non-dimensionalization of the ODE yields

$$\frac{\mathrm{d}u}{\mathrm{d}\tau} = \theta u$$

where $\theta = \frac{\alpha_1 x_0^\chi}{\beta_1}$, $\mu = \frac{\beta_2}{\beta_1}$, and $\gamma = \frac{\alpha_1\beta_1}{\alpha_2\beta_2}$. The steady state concentration of X, when $\chi = 0$, is [84]

$$u^{ss} = \frac{\theta + \mu}{\theta + 1 + \mu + \theta/(\mu\gamma)}, \tag{27}$$

which is a monotonically increasing function of θ, the parameter representing biochemical activation. When $\mu \ll 1$ and $\mu\gamma \gg 1$, it is nearly $\frac{\theta}{1+\theta}$, the expected hyperbolic curve [20]. However, when $\gamma = 1$, $u^{ss} = \frac{\mu}{\mu+1}$ is actually independent of θ.

For $\chi = 1$, the steady-state is [83]

$$u^{ss} = \frac{\theta - 1 - \mu + \sqrt{(\theta - 1 - \mu)^2 + 4\mu\theta\left[1 + 1/(\mu\gamma)\right]}}{2\theta\left[1 + 1/(\mu\gamma)\right]}. \tag{28}$$

In the very special case of $\mu = 0$ and $\mu\gamma = \infty$, $u^{ss}(\theta)$ undergoes a transcritical bifurcation at $\theta = 1$. But the transcritical bifurcation is not robust: For $\mu > 0$, the $u^{ss}(\theta)$ in (28) is a smooth, monotonic increasing function of θ.

For $\chi = 2$, the system exhibits nonlinear bistability with saddle-node bifurcation. When $\mu = 0$ and $\mu\gamma = \infty$,

$$u_1^{ss} = 0 \text{ and } u_{2,3}^{ss} = \frac{1 \pm \sqrt{\theta^2 - 4\theta}}{2\theta}, \tag{29}$$

which exhibits saddle-node bifurcation at $\theta^* = 4$. Saddle-node bifurcation is robust.

For biochemical kinetics in a single cell, instead of considering the concentration $x(t)$, one is interested in the number of X molecules at time t, $n_X(t)$, and biochemical reactions occur stochastically one at a time. The Delbrück–Gillespie process theory then is the appropriate mathematical representation of single cell biochemical kinetics and many other complex dynamics, just as differential equation is the appropriate mathematical representation of macroscopic chemical kinetics. The probability $p_k(t) = \Pr\left\{n_X(t) = k\right\}$ satisfies the chemical master equation

$$\frac{\mathrm{d}}{\mathrm{d}t}p_k(t) = v_{k-1}p_{k-1}(t) - \left(v_k + w_k\right)p_k(t) + w_{k+1}p_{k+1}(t), \tag{30a}$$

in which

$$v_k = \frac{\alpha_1 k(k-1)\cdots(k-\chi+1)\left(n_0 - k\right)}{V^\chi} + \beta_2\left(n_0 - k\right), \tag{30b}$$

$$w_k = \frac{\alpha_2 k(k-1)\cdots(k-\chi)}{V^\chi} + \beta_1 k, \tag{30c}$$

where n_0 is the total number of X and Y molecules together. The stationary probability distribution for the n_X is

$$p_k^{ss} = A \prod_{=1}^{k} \left(\frac{v_{\ -1}}{w} \right), \tag{31}$$

in which normalization factor:

$$A = \left[1 + \sum_{k=1}^{n_0} \prod_{=1}^{k} \left(\frac{v_{\ -1}}{w} \right) \right]^{-1}. \tag{32}$$

For $\chi = 2$, it is easy to show that p_k^{ss} has two peaks located precisely at any $\ ^*$ where $v_{\ *-1} = w_{\ *}$. This corresponds to the x^* where $v(x^*) = w(x^*)$, introduced below.

Noting that v and w are both functions of the size of a cell V, their macroscopic limits are

$$v(z) = \lim_{V\to\infty} \frac{v_{zV}}{V}, \quad w(z) = \lim_{V\to\infty} \frac{w_{zV}}{V}. \tag{33}$$

In the macroscopic limit of $V, n_0 \to \infty$, $\frac{n_0}{V} = x_0$, the stochastic process $\frac{n_X(t)}{V}$ becomes a smooth function of time $\hat{x}(t)$, which is the solution to the ODE $\frac{\mathrm{d}}{\mathrm{d}t}x(t) = v(x) - w(x)$. More precisely, the probability distribution $V^{-1}p_{xV}(t)$ approaches to a Dirac-δ function $\delta\big(x - \hat{x}(t)\big)$ when V tends to infinity. Furthermore, this transition from mesoscopic to macroscopic descriptions can be further quantified by a function $\phi(x, t) \geq 0$:

$$-\lim_{V\to\infty} \frac{\ln p_{xV}(t)}{V} = \phi(x, t), \quad \text{or} \quad V^{-1}p_{xV}(t) \simeq e^{-V\phi(x,t)}. \tag{34}$$

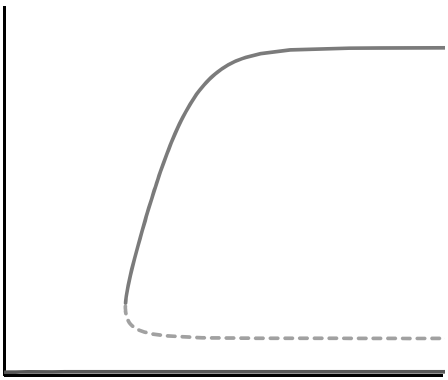
With each fixed t, the global minimum of function $\phi(x, t)$ is when $x = \hat{x}(t)$: $\phi(\hat{x}(t), t) = 0$. Similarly, the steady state probability distribution in (31) has $V^{-1}p_{xV}^{ss} \simeq e^{-V\phi^{ss}(x)}$.

In connection to the deterministic dynamics $\hat{x}(t)$, the emergent function $\phi^{ss}(x)$ has a very important property, which is actually a mathematical consequence of the inequality in Eq. (19): $\frac{\mathrm{d}}{\mathrm{d}t}\phi^{ss}\big(\hat{x}(t)\big) \leq 0$. Therefore, the function $\phi^{ss}(x)$ can be legitimately call a nonequilibrium free energy function, of a landscape.

There is a subtle but fundamental distinction: the landscape for a molecule is given a priori, it is considered as the cause of the dynamics [15]. The "landscape" for a cell is itself a consequence of cellular nonlinear, stochastic dynamics — rigorously defined via the large deviation theory when $V \to \infty$. It is itself an emergent property [85].

5.4. *Complex systems and symmetry breaking*

The u^{ss} given in Eq. (28), which represents the level of X-activity in the nonlinear, driven "biochemical" kinetic system (24), is not only a function of the level of "activation signal" θ, but also a function of the amount of chemical potential difference, $\ln \gamma$, that keeps the system away from chemical equilibrium. As we have already shown, when $\gamma = 1$, the u^{ss} is unresponsive to θ whatsoever: "No dissipation, no signaling transduction" [84]. More quantitatively, Fig. 3 shows multiple u^{ss} as functions of the level of chemical potential driving force, $\ln \gamma$, for $\chi = 2$.



There are many schools of thoughts on complexity. In the writing of condensed matter physicists [13–16], *dynamic symmetry breaking* and *protected properties* or *rigidity*, or break-down of ergodicity,[c] is a key ingredient. In most of physics of equilibrium matter, broken symmetries are few in number; but outside physics, with nonlinear dynamics in an nonequilibrium systems, they are everywhere, as illustrated by the example in Sec. 5.3.

In the case of nonequilibrium systems, the very nature of multi-stability, and the locations of the "attractors" are themselves emergent phenomena, in contrast to inert matter where the multiple attractors are dictated by symmetry in the law of motions. In fact, Hopfield's "dynamic symmetry breaking" can be identified in a NESS with substantial non-zero transport fluxes that break the detailed balance and time reversal symmetry. Indeed, "there is a sharp and accurate analogy between the breaking-up of this [high energy world] ultimate symmetry to give the complex spectrum of interactions and particles we actually know and the more visible complexities" [86]. "At some point, we have to stop talking about decreasing symmetry and start calling it increasing complication" [13], or *complexity*.

One of the important ideas in phase transition is the *order parameter*, first proposed by L. D. Landau. For nonlinear system with bistability, there is necessarily a saddle point[d] and associitiesciitiesd[(86009.37y)-250associ.l50(is)-253()-2essarJ le,

unstable and transitory. Our Fig. 3 indicates that even a low dimensional fixed point, which is much better understood, can and should be considered as a "dissipative structure": On a mesoscopic scale, it has a time irreversible, complex temporal dynamics in its stochastic stationary fluctuations [20, 87].

Fluctuations favor ergodicity or "symmetry", and potential energy or force, on the other hand, prefer special arrangements. One of the profound implications of the notion of an "entropic force" [89] is that detailed, fast dynamics generates probability, which in turn can be formalized as an "emegent force" on a different time scale. Therefore, the entropic force and its potential, or landscape, are themselves emergent properties of a complex dynamics [85]. This is the thermodynamic force of Onsager [88].

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