A Theory of Mesoscopic Phenomena: Time scales, emergent unpredictability, symmetry breaking and dynamics across different levels

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Abstract

By integrating four lines of thoughts: symmetry breaking originally advanced by Anderson, bifurcation from nonlinear dynamical systems, Landau’s phenomenological theory of phase transition, and the mechanism of emergent rare events first studied by Kramers, we propose a mathematical representation for mesoscopic dynamics which links fast motions a level below (microscopic), movements within each discrete state (intra-basin-of-attraction) at a mid-level, and slow, upper-level inter-attractor transitions between neighboring basins with rates exponentially dependent upon the size of the system. The theory represents the fast dynamics by a stochastic process and the mid-level by a nonlinear dynamics. Multiple attractors arise as emergent properties. The interplay between the stochastic element and nonlinearity, the essence of Kramers’ theory, leads to successive jump-like transitions among different basins. We describe each transition as a dynamic symmetry breaking exhibiting Thom-Zeeman catastrophe and phase transition with the breakdown of ergodicity (differentiation). The dynamics of a nonlinear mesoscopic system is not deterministic, rather it is a discrete stochastic jump process. Both the Markov transitions and the very discrete states are emergent phenomena. This emergent inter-attractor stochastic dynamics then serves as the stochastic element for the nonlinear dynamics of a level higher (aggregates) on an even larger spatial and longer time scales (evolution). The mathematical theory captures the hierarchical structure outlined by Anderson and articulates two types of limit of a mesoscopic dynamics: A long-time ensemble thermodynamics in terms of time $t \to \infty$ followed by the size of the system $N \to \infty$, and a short-time trajectory steady state with $N \to \infty$ followed by $t \to \infty$. With these limits, symmetry breaking and cusp catastrophe are two perspectives of a same mesoscopic system on different time scales.
1 Introduction

The notion of symmetry breaking has been considered by many thinkers as a fundamental mechanism for generating complexity [1] [2] [3] [4] [5] [6]. At the core of this idea are two elements: (i) a singular point in the phase space of a nonlinear dynamical system where the future of the dynamics is truly unpredictable [7] and (ii) a noise “too small to be taken into account of by a finite being” [8] with lack of detailed information for physical origin, or too erratic to be fully comprehended by a rational person.

In modern mathematical theory of nonlinear dynamics, (i) is known as a “saddle point”: if a system is located precisely at the point and the dynamics is absolutely deterministic, then it will remain there forever. However, any infinitesimal perturbation will lead the system away towards somewhere else [1]. More importantly, depending upon a particular perturbation, there are in fact many possible outcomes, or fates, which are seemingly chosen by chance. In textbooks illustrations, this is usually drawn as a “double well potential” with an “energy barrier” in between, see Fig. 2A. Chemists have termed the saddle point a “transition state” [9].

What is the fundamental origin of (ii)? In thermal physics, fluctuations are well understood in terms of the dynamics of electrons, atoms and molecules at finite temperature. This leads to a fluctuating dynamic description of individual molecules in aqueous solution [10]: The dynamics is too erratic to be meaningfully represented by deterministic mathematics due to the lack of the detailed information of the motions of the individuals of the system. Therefore, Fourier, Boltzmann, Einstein, Gibbs, Onsager, Eyring, and Kramers, together with many pioneers in the physics of matter, have advanced a probabilistic description of the states and dynamics of a complex, many-body system [2].

The modern theory of matter developed by physicists and chemists explains the macroscopic, deterministic world in terms of the erratic, stochastic dynamics of atoms and molecules. Its fundamental insight lies at the mathematical law of large numbers (LLN): The same law that gives Las Vegas casinos more confidence in their profitability if more people are willing to gamble. However, another lesson from this story has

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1 More precisely, the perturbation has to have a component along unstable manifold. Physically, a perturbation exactly restricted on a stable manifold is nearly impossible.

2 The probability in quantum physics has a fundamentally different origin. Quantum dynamics is conservative while dynamics in thermal physics is dissipative. See [11] [12] [13] for more discussions.
Individual winning event is unpredictable. What is certain is that it will occur with probability 1 on any given machine and the time to the occurrence is an exponentially distributed memoryless random variable [14].

The successes of the LLN in classical statistical mechanics have created an impression that any system consisting of a large number of atoms and/or molecules can be describable by deterministic mathematics: Stochastic behaviors are averaged out. This impression is rather misleading, especially when dealing with nonlinear dynamics of a system consisting of large number of individuals. In fact, as we shall show, stochasticity does not disappear in such systems. They simply manifest themselves as rare events on a longer time scale; larger a system, longer the time. Then on an even longer time scale, numerous rare events constitute another deterministic, continuous dynamics: A single molecule conformational transition is a rare event in H.A. Kramers’ theory, but they are the basis for the deterministic kinetics of a chemical reaction system based on the Law of Mass Action [20, 19, 44].

2 Hierarchical Organization at Different Levels and Different Time Scales

Indeed, P.W. Anderson stated that [11] “[A]t each level of complexity entirely new properties appear, and the understanding of the new behaviors requires research which I think is as fundamental in its nature as any other.” He went on to list a series of different levels of complexity: few-body (elementary particle) physics, many-body physics, chemistry, molecular biology, ..., physiology, psychology, and social sciences. The elementary entities of each level in the hierarchy obey the dynamic laws of a level lower, and at each level an entirely new laws, concepts, and generalizations emerge, and different treatment and theories are necessary. Our theory attempts to provide this hierarchy a mathematical and physical description. This hierarchy shares many features with the organizational hierarchy among protein conformational sub-states advanced by H. Frauenfelder and coworkers [16, 3, 18]: Going downward, a protein consists of secondary structural motifs, which consists of amino acids, which consists of atoms, etc. Going upward, a cell consists

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3 If anything, the logical causality is in the mechanical movements of a slot machine; and why and when a machine is picked due to physiological and psychological processes [2] of an individual gambler.

4 Following this believe, the necessity of employing statistical methods in current engineering, biology, and social sciences has been attributed to our ignorance of a subject or lack of information rather than for any fundamental reasons [7].
of a large number of macromolecules, and a tissue consists of a large population of cells, etc.

The chemical reaction theory, together with protein science, serve a paradigm for stochastic, mesoscopic complexity [3, 17, 19]. Consider a chemical transformation \( A + B \rightarrow C \) in an aqueous solution. A conceptual framework for such a reaction developed by Kramers [20] is now accepted as the theoretical foundation of condensed matter chemistry [21, 22]. In fact, a chemical reaction theory involves three of the levels in Anderson’s hierarchy: (a) few-body physics detailing the collisions of a few water molecules (H\(_2\)O) with a few atoms within reacting molecules; (b) many-body physics concerning molecules \( A, B \) and \( C \) in a sea of solvent molecules; and (c) chemistry whose elementary entities are discrete chemical reactions such as \( A + B \rightarrow C \). In (a) one is concerned with collisions leading to high-frequency vibrations; (b) is primarily interested in the *mechanism* and process of how \( A \) and \( B \) collide, interact and formation of \( C \) occurs in terms of the atoms in the molecules with vibrations and diffusion, while in (c) the actual chemical reaction is focused and only a second-order rate constant for the discrete transition matters. Figs. 1A uses a schematics to illustrate this hierarchy.

Kramers’ theory reveals that these different levels also translate to different time scales [17]: At the time scale of a molecular reaction, the (a) is so rapid that it can be essentially treated as infinitely rapid fluctuating dynamics with certain appropriate statistics. The time scale for (b) is of course determined by the energy and force in the molecular system which Kramers called “a field of force”, and the outcome of the theory is a discrete event of a chemical reaction whose time scale, \( \sim 10^{-7} \) sec., is almost infinite on the time scale of (a), \( \sim 10^{-12} \) sec.

Kramers’ mathematics embodies both “chance” and “necessity” [23, 24, 25].

Now for a cellular biochemist who is interested in a metabolic system with many biochemical species, the individual \( A + B \rightarrow C \) on the sub-\( \mu \)sec scale is just part of fluctuations. He/she is interested in the dynamics of how various concentrations of metabolites change with time. In terms of the Law of Mass Action, steady states of the biochemical reaction system can be predicted. More importantly, recent studies on phenotypic switching point to the stochastic transitions from one biochemical steady state to another in a single cell, on the time scale of \( 10^3 \) sec. Again, to \( 10^{-7}, 10^3 \) is like infinite. Figs. 1B again shows an illustrative schematics.

One of the deepest concepts developed by chemists in connection to chemical reactions is the notion of “transition state” [9]. We see that it is at the very transition state the dynamic of a symmetry breaking
occurs in molecular systems. If a molecular system is infinitely large, then this symmetry breaking is static: the chance of Kramers’ barrier crossing could take the time as long as the age of the universe. This is the symmetry breaking picture of Anderson [1]. However, a macromolecule such as a protein can in fact jump among its different conformational states on the time scale observable in a laboratory [3, 18, 10] and exhibits successive dynamic symmetry breaking [2]. In this latter case, a discrete-state stochastic description of the dynamics in term of a Markov jump process is most appropriate [26, 27]. As differential equation approach to classical dynamics, Markov approach to stochastic dynamics is general. Even certain processes with long memory can be mathematically transformed into a Markovian representation.

A unavoidable mathematical issue is at the heart of any theory of mesoscopic systems. As Anderson pointed out in [1] that “It is only as the nucleus is considered to be a many-body system — in what is often called the $N \rightarrow \infty$ limit — that such [emergent] behavior is rigorous definable.” The thermodynamic limit according to textbooks on equilibrium physics of matters is to take the time $t \rightarrow \infty$ first and then systems size $N \rightarrow \infty$ afterward. In fact, the $t \rightarrow \infty$ never appeared since equilibrium is assumed at the onset. On the other hand, often observed nonlinear dynamic behavior in a macroscopic system is taking the $N \rightarrow \infty$ first for finite $t$. In fact, nonlinear, emergent dynamic behavior of a complex system can only be rigorously defined with $N \rightarrow \infty$, followed with fluctuation analysis with finite $N$. Most of the mathematics in the present paper is concerned with the order of the two limits [29]. In reality, both limits are simple idealizations. Still, each limiting procedure has it validity on an appropriate time scale.

3 Nonlinear bistability, bifurcation, and phase transition

In the mathematical theory of deterministic nonlinear dynamics, symmetry breaking is intimately related to the problem of saddle-node bifurcation [30]. In fact, the theory of saddle-node bifurcation and its topological representation, known as catastrophe theory, is exactly a symmetry breaking problem viewed in a relatively short time scale.

The discussion in this section should be followed closely with Fig. 3 at side. It is essentially a mathematics exercise (an explicit example is given in Supporting Information.) Let us consider an ordinary differential equation (ODE) for 1-d $x(t)$, $dx/dt = b(x; \alpha, \beta)$ with two parameters $\alpha$ and $\beta$. In other words, for each pair of $(\alpha, \beta)$, there is an ODE. Let us further assume that for some values of $(\alpha, \beta)$ the ODE has
only a single stable steady state (fixed point), and for other parameter values there are three steady states, two stable $x^*_1$ and $x^*_2$, and one unstable $x^*_3$ in between: $x^*_1 < x^*_3 < x^*_2$. Note the $x^*$s are functions of $\alpha$ and $\beta$; in fact, all the $x^*$s irrespective of 1, 2, or 3 are roots of $b(x, \alpha, \beta) = 0$. This algebraic equation defines a surface shown in Fig. 2B. When a piece of paper is gently folded, the multiple steady states $x^*$ as functions of $\alpha$ and $\beta$ form a multi-layer surface in 3-d.

In classical van der Waals gas problem, the $x$ is equilibrium volume of a box of gas, $\alpha$ and $\beta$ are temperature and pressure. In a biochemical phosphorylation feedback system, $x$ is the fraction of phosphorylated protein, $\alpha$ and $\beta$ are the kinase activity and ATP phosphorylation potential [31, 32]. The equation $b(x; \alpha, \beta) = 0$ is known as an “equation of state” in van der Waals theory, and an “equation of phosphorylation-dephosphorylation switch” for signaling module [33].

In Fig. 2B, projecting the three layers to the $\alpha\beta$ plane for the two parameters, topologist René Thom had the deep insight that the region has to have a wedged shape with a cusp as shown in Fig. 2B, also in Fig. 3A [34]. Now if you keep $\beta$ constant and vary $\alpha$ across the wedged region starting from far left, as illustrated by the dashed blue line in Fig. 3A, the number of steady states changes from 1, to 2 to 3, and back to 2 and 1. This is shown in Fig. 3B. The black $S$-shaped curve is a “bifurcation diagram” which shows the position of steady state(s) as a smooth function of $\alpha$ (with a given $\beta$).

At the blue vertical lines in Fig. 3B, the phenomena of changing number of steady states are called saddle-node bifurcation. For small and large values of $\alpha$, the system has only a single steady state (fixed point). The blue dashed lines mark the critical $\alpha$ values at which there is a sudden appearance or disappearance of a pair of stable and unstable steady states. The pair “bursts out of blue”; thus acquired the name of blue sky bifurcation [30]. One of the extensively studied examples of this type of behavior in biochemistry is forced molecular dissociation leading to non-covalent bond rupture [35].

So far, we have described how bifurcation arises in nonlinear, deterministic systems with bistability. A deterministic nonlinear approach is usually valid for macroscopic systems. From a mesoscopic perspective, this means all our above discussion starts with a system without fluctuation. More precisely, when one studies a mesoscopic molecular system, the numbers of individuals of various species in a system $\vec{N} = (n_1, n_2 \cdots)$ and the volume $V$ of the system, are usually specified. The ODE perspective is for infinitely large system, i.e., introducing “concentration” $\vec{x}(t) = \vec{N}(t)/V$, and then mathematically taking $\vec{N}, V \to \infty$ to obtain a “macroscopic limiting behavior” in terms of the nonlinear dynamics for $x(t)$. Then in the limit
of \( t \to \infty \), multiple attractors is revealed. Different initial conditions will lead to different steady states. Because of this procedure, the transition between two fixed points, the most important consequence of fluctuations, is not possible in the deterministic analysis. There is a breakdown of ergodicity.

This is not the *thermodynamic limit* which requires a true equilibration among all different attractors. In fact, the most important information missing in the ODE analysis is the relative weights for different attractors. This comes from analysis based on probability and stochastic processes. A finite-size correction naturally introduces stochasticity. Depending upon the chosen representation for a system, a finite-size mesoscopic model can a discrete or continuous stochastic process. For example, the dynamic equation for a stochastic concentration \( x(t) \) can be characterized by

\[
dx(t) = b(x) dt + V^{-\frac{1}{2}} dB_t
\]

where \( V \) represents the size of the dynamical system and \( B_t \) is a Brownian motion. One notices that if \( V \to \infty \), the dynamics is reduced to the above “macroscopic limit”.

To study the true thermodynamic limit, one lets the \( t \to \infty \) first in a stochastic model followed by \( V \to \infty \). This way, an initial value independent (i.e., ergodic) probability distribution across all attractors emerges. The mathematical theory for this type of stochastic differential equation (i.e., nonlinear Langevin equation) shows that the stationary density has the form [36]:

\[
f_{st}^V(x) = C_V e^{-V\phi(x)},
\]

in which \( C_V \) is a normalization factor. Furthermore, \( \phi(x) \) has local minima at \( x_1^* \) and \( x_3^* \) and a maximum at \( x_3^* \). This means the probability distribution \( f_{st}^V(x) \) peaks at \( x_1^* \) and \( x_2^* \). It is the extrema of function \( \phi(x) \) that match the fixed points of \( b(x) \). The behavior of the deterministic dynamics is closely related to the modal values of the finite, mesoscopic system rather than the mean value [37].

The shapes of \( \phi(x) \), the energy landscapes, for different \( \alpha \) and \( \beta \) are shown in Fig. 3A and B. For each \((\alpha, \beta)\) there is a \( \phi(x; \alpha, \beta) \). Along the dashed blue line in Fig. 3A, the corresponding \( \phi(x) \)s are illustrated in orange, as well as the black shapes shown below the curve in 3B. When changing \( \alpha \) horizontally in 3A, the landscape for bistability develops a bias for one of the minima. Outside the wedged region, one of the minima disappears all together.

Note that Eq. 1 is obtained by letting \( t \to \infty \) while keeping \( V \) finite. Now different phenomenon arises if one lets \( V \to \infty \) in 1: The distribution \( f_{st}^V(x) \) will concentrate at the global minimum of \( \phi(x) \) with probability 1! Even though a system can be bistable or multistable, a metastable state, i.e., the non-global local minimum of \( \phi(\vec{x}) \), has zero probability in the limit of \( V \to \infty \), if one allows the system to truly
Therefore as predicted by the LLN, generically there is a unique steady state for a bistable (or multi-stable) system in the true thermodynamic limit, except at a critical $\alpha^*$ when the two minima are precisely equal $\phi(x_1^*, \alpha^*) = \phi(x_2^*, \alpha^*)$, shown in Fig. 2B, and the dashed red curve in Fig. 2A. For each given $\beta$ value, there exists an $\alpha^*(\beta)$.

Therefore, in the limit of $t \to \infty$ followed by $V \to \infty$, i.e., in the true thermodynamic limit, the $S$-shaped curve in Fig. 3B is no more; only a discontinuous jump at $\alpha^*$, marked by the red dashed vertical line. This is reminiscent of the Maxwell construction [38] for the van der Waals theory of non-ideal gas. Similarly, in Fig. 3A the wedge is no longer relevant; only the dashed red curve which should abruptly terminates at the cusp. This is known as a first-order phase transition line.

Now let us focus on the cusp in Fig. 3A. Moving along the red curve inside the wedged region, the landscape changes from symmetric bistable with two equal minima to a monostable single minimum, when passing the cusp. This is magnified in Fig. 3C. It is L.D. Landau’s second-order phase transition [39]. In nonlinear dynamical systems theory, crossing the cusp constitutes a pitchfork bifurcation [30].

Therefore, a kind of symmetry and symmetry breaking emerge in the simple bistable nonlinear system with stochasticity, i.e., a complex mesoscopic system. Table 1 summaries the discussions above: In the left column, $V \to \infty$ with $x = N/V$, followed by $t \to \infty$; in the middle column $t \to \infty$ while holding $V$ finite, and the right column gives the true thermodynamic limit as $t \to \infty$ followed by $V \to \infty$.

How is this mathematical description of bifurcation and phase transition related to the traditional physics of matters? Thermodynamic description of a system neglects all time scales that are too long to be of interests [7] then assumes that all the remaining time scales reach an ergodic stationarity. Deterministic nonlinear dynamic description of a system, on the other hand, considers interesting dynamics in the medium time range: Different initial conditions will lead to different steady states. The true equilibration among different steady states, however, is out of reach in a deterministic description. A mesoscopic system can exhibit rich behavior precisely because both scenarios are accessible and they even interact [38].

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6It is also clear that if the correlation in such a system at $\alpha^*$ were short, then there would be infinite number of “identical, independent subsystems”, which would imply LLN being valid. Thus, the violation of LLN at $\alpha^*$ dictates an infinitely long, non-exponential decay correlation in the system.

7We emphasize this point since strictly speaking there are always slow processes in reality. For example, there is a slow rate of peptide hydrolysis in an aqueous solution for any protein molecule. But this effect is usually neglected, rightly, in the thermodynamic theory of proteins. Also, according to Newton’s third law, there is always a consequence at the origin of a force field that generates a potential field. For example a magnet that induces supercurrent in a type II superconductor decays slowly.

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A mean-field treatment in the classical physics usually entails deriving a relation among “mean values” by neglecting fluctuations. Therefore, it corresponds to $N, V \to \infty$ first. Thus often it is incapable of reaching the ergodic thermodynamic limit. Furthermore, the cusp is precisely the critical point $T_c$ in Landau’s phenomenological phase transition of ferromagnet in terms of free energy $F(x) = (T - T_c)x^2 + bx^4 - Jx$ with $J = 0$. This is the symmetry breaking picture generally discussed in the theory of phase transition. Changing $\alpha$ and $\beta$ correspond to changing $J$ and $T$ in the above $F(x)$. The essence of Landau’s theory is a bistable system with stochasticity (noise).

Yang and Lee have established a more general mathematical origin for phase transition [41, 42]. They have shown the mathematical non-analyticity, a necessary feature of any rigorous phase transition theory, is related to a zero of a partition function moving from complex plane onto real axis in the $V \to \infty$ limit (Recall that the free energy is the logarithm of a partition function.) It has been demonstrated recently that this same mathematical description applies to any bistable system with stochastic elements [31, 32], including mesoscopic biochemical system with bistability. Therefore, the notion of phase transition, together with the concepts such as symmetry breaking and the perspective of “true thermodynamic limit” have a broad applicability to systems exhibiting phenomena as catastrophe, rupture, and hysteresis [35]. It is a complementary description of bistability in the presence of stochasticity.

The notion of symmetry breaking used in [1, 2] is intimately related to bifurcation. While bifurcation of a ground state in solid-state and particle physics is due to a symmetry in a Hamiltonian [3], nonlinear complex systems have symmetries, with canonical forms, at their bifurcation points [30]. However, the existence of multistability and attractors is often an emergent phenomenon itself. Our above discussions illustrate that with stochasticity, bifurcations in the true thermodynamic limit exhibit phase transitions — a probability distribution has certain symmetry; a realization by a particular system breaks the symmetry. In fact a pitchfork bifurcation is a part of catastrophe phenomenon.

4 Emergent discrete stochastic dynamics in nonlinear systems with multiple attractors

The foregoing discussion focused on systems with bistability. For a highly nonlinear, complex system with stochastic elements, there usually will be a large number of attractors. Therefore, on a time scale much longer than the deterministic dynamics that occurs within each basin of attraction, inter-attractor dynamics
can be represented as a Markov jump process among a set of discrete states. This is an insight one learns from macromolecular dynamics like a protein: Kramers’ theory accounts the transition rates between each pair of “conformational states”; but the dynamics of an enzyme is usually represented by chemical kinetics which represents the conformational states in discrete terms. More interestingly, in recent years the Delbrück-Gillespie approach to nonlinear biochemical reaction systems treats each chemical reaction in a mesoscopic volume as a stochastic process, and derives endogenous phenotypic “cellular states” and cellular evolutionary dynamics. Robustness of a cellular state and punctuated equilibrium in state transitions are necessary consequences of this dynamics description.

The time scales, short or long, are defined by the Kramers’ theory for a barrier-crossing process. It is tempting to suggest that complexity at a mesoscopic scale originates from a system with the size at which both the deterministic, converging dynamics on a short-time and the stochastic, diverging dynamics on a long-time are accessible to an observer. We stress that the stochastic fluctuations on the very fast time scale yield the divergent behavior of stochastic jumps out of the basins of attraction on a very long time scale. Conversely, interactions between dynamics at these different time scales lead to slow dynamics modulating the fast motions. A stochastic system in general moves toward states with higher probability, exhibiting a form of contingency, or adaptation. In enzyme kinetics, this is the origin of dynamic disorder. It is also illuminating to point out that an ab initio computation of the emergent stochastic transitions from the detailed dynamics can range from a highly challenging task to practically infeasible: In protein folding, this is only accomplished very recently for a single transition of biochemical significance based on atomic-level molecular dynamics.

Let us reiterate: The insights from the present discussion which departs from the LLN perspective is that stochasticity does not completely disappear in a reasonably large, nonlinear population (mesoscopic) system. Rather, it manifests itself as a stochastic jump process on a much longer time scale among a set of discrete states, as has been shown in Fig. A & B. These discrete states are attractors of an interacting nonlinear dynamical system. These discrete states are determined by the behavior and interactions among individuals within the system; yet their existence, locations, and transition times are completely non-obvious. They are emergent properties. Well-known examples are nonlinearity cooperativity in equilibrium physics and feedbacks in biological networks. In the former, cooperativity leads to crystallization; and in the latter nonequilibrium systems, feedbacks lead to self-organization. The nature of emergent phenomena is a
consequence of nonlinear interactions between individuals \[7,24,57\].

The emergent stochastic dynamics, of course, becomes the stochastic elements for a higher level system in a larger space with longer time. In this fashion, Anderson’s hierarchy moves up level by level with the stochastic, nonlinear dynamics description. This is again illustrated in Fig. [1] Recall the example of a single biological cell as a mesoscopic chemical reaction system where this hierarchy has already been appreciated \[17\]: Boltzmann started the tradition of treating molecular collisions as stochastic elements in a kinetic theory. Kramers has shown that the discrete chemical reaction can be described as Brownian motion in a force field \[20,22\]. Supported by the recent experimental advances in single-molecule chemistry and biophysics \[10\], Delbrück-Gillespie’s theoretical approach to chemical reactions considers each chemical reaction as a stochastic process, and derives “states” and “dynamics” of cell-size biochemical reaction systems \[27,59,48\].

Continuing with this perspective, the question of whether epigenetic phenotypic states at a cellular level is a part of intrinsic biochemical dynamics or an external, environmentally induced phenomenon can be addressed using a mesoscopic dynamic approach \[43,45,47,51,52,37\]. Epigenetic switching might indeed be viewed as a “phase transition” in mesoscopic biochemical systems \[60,61,31,32,19,45,53,54\].

5 Conclusions

The mathematical concept of thermodynamic limit is defined as an infinitely large system reaches its infinitely long-time limit, where the long-time has to be sufficient to overcome all the exponentially small barrier crossing probabilities. Therefore, it is immediately clear that there are two competing limits for time and systems size, and taking which limit first matters. Complex behavior arises when these two limits are not exchangeable due to non-uniform convergence \[62\]. As we have discussed, a real thermodynamic limit, which takes \(t \to \infty\) first, is simple. A mesoscopic system is messy — When Anderson talked about \(N \to \infty\) \[1\], there are in fact two possibilities: finite time dynamics requires taking it before \(t \to \infty\), and thermodynamics requires taking it after \(t \to \infty\): The latter produces a simpler picture of the world, and the former produces a much more complex picture of a world.

The present work focuses on the emergence of discrete transitions between different dynamic basins. While we have not explicitly discussed system with spatial characteristics, we believe a large part of the discussions is applicable to stochastic reaction-diffusion systems \[63\]. Recent work also point to the im-
important phenomena associated with time symmetry breaking in nonequilibrium steady state of mesoscopic systems \[64, 65, 50, 51, 53, 54\]. A deeper understanding toward the relationships among different forms of symmetry breaking in space, time, and dynamics remain to be elucidated \[66, 4\].

In physics, the notion of mesoscopics often refers to dynamics such as conductance fluctuations in small size devices. In the present work we see the scope of “mesoscopic phenomena” to be much more general: It can also cover many other interesting behavior including biochemical cells with self-organizations \[64, 27\]. In fact, it is the description in terms of stochastic nonlinear dynamics, incorporating both chance and necessity \[23\], that gives the middle-level system a unique yet universal characteristics \[24, 27, 67, 59, 50, 53, 54\]. This is one of the most fundamental insights of J.W. Gibbs, and the contribution of chemical science to the theory of complexity \[17\].

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Supplemental Material: A mathematical example

The schematics in Fig. 3 can be mathematically produced through the following example of a cubic system. It is a simple variation of L.D. Laudau’s energy function $F(x) = (T - T_c)x^2 + bx^4 - Jx$.

**A. Ordinary differential equation with bistability.** Ordinary differential equation (ODE)

$$\frac{dx(t)}{dt} = -(x^3 + x^2 - \alpha x + \beta) = b(x)$$

has fixed point(s), or steady state(s), as the roots of cubic polynomial

$$b(x) = -(x^3 + x^2 - \alpha x + \beta) = 0.$$  \hspace{1cm} (3)

Its solutions $x^{ss}(\alpha, \beta)$, as a multi-layer surface with fold, is a function of $\alpha$ and $\beta$. In the $(\alpha, \beta)$ plane, the region in which $x^{ss}(\alpha, \beta)$ takes three values has wedged shape with a cusp (e.g., Fig. 2B). The boundary of the wedged region is given by a parametric equation with $-\infty < \xi < +\infty$:

$$\begin{cases} 
\alpha(\xi) = 3\xi^2 + 2\xi \\
\beta(\xi) = 2\xi^3 + \xi^2 
\end{cases}$$

or, in two-branch form with $\pm$

$$\beta_{\pm}(\alpha) = \frac{2}{9}\left(\alpha + \frac{1}{3}\right)(-1 \pm \sqrt{1 + 3\alpha}) - \frac{\alpha}{9}.$$  \hspace{1cm} (5)

The cups is at $\alpha = -\frac{1}{3}$ and $\beta = \frac{1}{27}$, when $\xi = -\frac{1}{3}$. At the cusp, it is not differentiable: $d\beta/d\alpha = \infty$ according to Eq. 4, but $\xi = -\frac{1}{3}$ according to Eq. 5.

**B. Stochastic differential equation with phase transition.** Stochastic differential equation (SDE)

$$dx(t) = b(x)dt + \sqrt{2A} dB_t$$

has a Fokker-Planck equation

$$\frac{\partial \rho(x, t)}{\partial t} = A \frac{\partial^2 \rho(x, t)}{\partial x^2} - \frac{\partial}{\partial x} \left(b(x)\rho(x, t)\right).$$

Its stationary solution is

$$\rho^{ss}(x) = C \exp \left(\frac{1}{A} \int b(x)dx\right) = C \exp \left[-\frac{1}{A} \left(\frac{x^4}{4} + \frac{x^3}{3} - \frac{\alpha x^2}{2} + \beta x\right)\right],$$

where $C$ is a normalization factor

$$C^{-1} = \int_{-\infty}^{\infty} \exp \left[-\frac{1}{A} \left(\frac{x^4}{4} + \frac{x^3}{3} - \frac{\alpha x^2}{2} + \beta x\right)\right] dx.$$  \hspace{1cm} (9)
Let us denote
\[ \varphi(x) = - \int b(x)dx = \frac{x^4}{4} + \frac{x^3}{3} - \frac{\alpha x^2}{2} + \beta x. \]  
(10)
The \( \varphi(x) \) has two minima separated by a maximum. And the condition for the two minima being equal is a line in \( \alpha \beta \) plane:
\[ \frac{\alpha}{3} + \beta + \frac{2}{27} = 0, \]  
(11)
along which we have
\[ \varphi(x) = \frac{1}{4} \left( x + \frac{1}{3} \right)^4 - \frac{1}{2} \left( \alpha + \frac{1}{3} \right) \left( x + \frac{1}{3} \right)^2 + C', \]  
(12)
where \( C' \) is a constant. Note that the \( \varphi(x) \) in Eq. 12 is an even function of \( \bar{x} = x + \frac{1}{3} \):
\[ \varphi(\bar{x}) = \frac{\bar{x}^4}{4} - \left( \alpha + \frac{1}{3} \right) \frac{\bar{x}^2}{2} + C'. \]  
(13)
This indicates that any cubic system can be transformed into Landau’s canonical energy form. Eq. 13 has two minima with equal value when \( \alpha > -\frac{1}{3} \); It turns into a single minimum at \( \bar{x} = 0 \) when \( \alpha < -\frac{1}{3} \). The \( \varphi(\bar{x}) \) is the canonical form of pitch-fork bifurcation [30]. The line in Eq. 11 is the “phase separation line”, the location for Maxwell-like construction. Its slope \( d\beta/d\alpha = -\frac{1}{3} \) is consistent with Eq. 5.

In the phase-transition theory language, \( \bar{x} \) is called an order parameter. Let \( \tau = 3\alpha + 1 \) and \( J = 27\beta - 1 \). Then we have along the line (11) \( (\bar{x}^*)^3 - 3\tau \bar{x}^* = 0 \), and
\[ \left( \frac{d\ln \bar{x}^*}{d\ln \tau} \right)_{\tau=0} = \frac{1}{2}, \]  
i.e., \( \bar{x}^* \propto \tau^{\hat{\beta}}, \) \( \hat{\beta} = \frac{1}{2} \).
(14)
\( \varphi \) in (13) is called free energy. Near \( \tau = 0 \), substituting \( \bar{x}^* \propto \tau^{\hat{\beta}} \), we have \( \varphi \propto \tau^2 \). Then “heat capacity”
\[ C = \alpha(\partial^2 \varphi/\partial \alpha^2) \propto \tau^{\hat{\alpha}} \]  
with \( \hat{\alpha} = 0 \). Furthermore, from \( \bar{x}(\tau,J) \) given by (5), let \( \chi = \partial \bar{x}/\partial J = \left( 9\tau - 81\bar{x}^2 \right)^{-1} \). Then \( \chi \propto \tau^{-\gamma} \) with \( \gamma = 1 \). Finally, for \( \tau = 0 \), Eq. 3 becomes \( \bar{x}^\beta + J/27 = 0 \). Thus \( J \propto \bar{x}^\delta \) with \( \delta = 3 \). We note that \( \hat{\alpha}, \gamma, \delta \) satisfy \( 2 - \hat{\alpha} = \gamma \frac{\delta+1}{\delta-1} \), and \( \hat{\beta}, \gamma, \delta \) satisfy \( \hat{\beta} = \frac{\gamma}{\delta-1} \).
stochastic dynamics on an individual level
interactions lead to emergent attractors
random jumps in a higher level individual

Figure 1: (a) A schematics showing rapid solvent-macromolecule collisions, as a source of stochasticity and together with a multi-energy-well landscape, gives rise to a kinetic jump process for an individual macromolecule with multiple states (shown within the circle). (b) A level higher, many interacting chemical individuals each with multiple discrete states form mesoscopic nonlinear reaction systems. In the space of copy numbers and concentrations of chemical species, such a system exhibits Monte carlo walk due to each and every stochastic reaction with emergent multiple nonlinear attractors ($C_A, C_B$ represent concentrations of $A$ and $B$). The stochastic transitions within each macromolecule serve as “noise” leading to state switching on the whole reaction system level, shown by $X$, $Y$, and $Z$. (a & b) The same schematics illustrates the Anderson’s hierarchy of complexity: There is a randomness in the dynamics of an “individual”, be it a macromolecule in aqueous solution, a cell in a tissue, a trading company in an economic system, or an animal in an ecological environment. Interactions between individuals in a system form a nonlinear dynamical system with emergent attractors. The fundamental insight of Kramers’ theory is that, while the Law of Large Number is at work, there will be emergent stochastic dynamics, beyond the infinite time of a deterministic nonlinear dynamics, at the systems level in an evolutionary time scale. This randomness, represented by the individual jumps inside the “particle” on the right, then becomes the stochastic element for the nonlinear dynamics of an organism, a level higher, that consists of many such interacting particles.
Figure 2: Double wells with a saddle point and three-layer fold with a cusp. (A) The surface represents an “potential function” and the contours are iso-energy lines. Moving from one well to another, the most likely path with the lowest “barrier” to overcome is through the saddle point, i.e., a mountain pass. (B) The fixed points of an ODE $dx/dt = b(x; \alpha, \beta)$ are the roots of the equation $b(x; \alpha, \beta) = 0$. $x^*$ as a function of $\alpha$ and $\beta$ is a surface in 3-d. Folding a smooth surface into three layers, there is necessarily a cusp in the $\alpha\beta$ plane.
Figure 3: For a mesoscopic model, if one takes its size, i.e., $N, V \to \infty$ first before $t \to \infty$, as usually done in a mean-field treatment, one obtains a nonlinear dynamics with broken ergodicity. The infinite-time limit of such a deterministic system can be described by black curves in (A): there is the well-known cusp catastrophe represented by a wedged region, as the projection in Fig. 2B. Inside (outside) the wedged region, the dynamical system has three (one) fixed points. For a fixed value of $\beta$ while varying $\alpha$, the horizontal blue dashed line crossing the boundary of the wedged region correspond to the two vertical blue dashed lines in (B), where two two saddle-node bifurcations occur. For a true thermodynamic limit, however, one first takes $t \to \infty$ for large but finite $N, V$ and obtains a system’s stationary probability distribution $f_V^{st}(x) = C_V e^{-V \phi(x)}$, where $x = N/V$ and $\phi(x)$ function is the dynamic landscape. $\phi_V(x)$ is shown as the orange and black shapes in (A) and (B). Then one lets $N, V \to \infty$ and obtains $f_V^{st}(x) \to \delta(x - x^*)$ where $x^*$ is the global minimum of the $\phi(x)$. Marking the co-existence of two equal minima, a Maxwell-like construction shown by the vertical red dashed line in (B) is introduced: a discontinuity appears in the $x^*$ as a function of $\alpha$, at $\alpha^*$. In (A), the red dashed line represents the line of $\alpha^*$ for different $\beta$. The cusp of the wedged region matches the critical point in the phase transition theory. In fact, as magnified in (C), along the red phase transition line in (A), there is a pitch-fork bifurcation at the critical cusp. In thermodynamic limit this is known as second-order phase transition.
Table 1: Terminologies and Phenomena in Infinite-time Dynamics

| Deterministic\(^2\) | Stochastic\(^3,4\) |
|----------------------|------------------|
| basin of attraction  | \( V < \infty \)  |
| stable fixed points  | landscape well    |
| (attractors)         | landscape minima |
| unstable fixed point | landscape maxima |
| (repellers)          |                  |
| out-of-blue saddle-  | emergence of a pair of local min & max |
| node bifurcation     |                  |
| bi-stability wedged  | double-well region |
| region               | Maxwell construction for two equal minima |
| n/a                  |                  |
| cusp                 | two equal minima at the boundary of the wedged region |
| pitchfork bifurcation|                  |
|                      | \( V = \infty \)  |
|                      | global landscape minimum, all local minima have zero probability |
|                      | n/a               |
|                      |wedged region collapses into a coexistence line, 1\(^{st}\) order phase transition |
|                      |                  |
|                      | critical point    |
|                      | 2\(^{nd}\) order phase transition |

\(^1\) n/a means a phenomenon has no correspondence, and significance, in this setting.

\(^2\) Deterministic means one takes \( V \to \infty \) first to obtained an ODE for \( x = N/V \), i.e., macroscopic limit, followed by \( t \to \infty \) to obtain steady states (attractors) of the deterministic nonlinear dynamics, starting with different initial values.

\(^3\) Stochastic dynamic with very large but finite size \( (V < \infty) \) has a proper probability density for its stationary process (i.e., \( t \to \infty \) while holding \( V \)): \( f_{st}^{V}(x) = C_{V} e^{-V\phi(x)} \) where \( \phi(x) \) is a landscape.

\(^4\) A true thermodynamic limit takes the results in the middle column, followed by \( V \to \infty \). Because \( f_{st}^{V}(x) \) is normalized, the limit \( f_{st}^{\infty}(x) \) has a singular support, with probability 1 concentrated on the global minimum of \( \phi(x) \).