Small Open Chemical Systems Theory: Its Implications to Darwinian Evolution Dynamics, Complex Self-Organization and Beyond*

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Abstract

The study of biological cells in terms of mesoscopic, nonequilibrium, nonlinear, stochastic dynamics of open chemical systems provides a paradigm for other complex, self-organizing systems with ultra-fast stochastic fluctuations, short-time deterministic nonlinear dynamics, and long-time evolutionary behavior with exponentially distributed rare events, discrete jumps among punctuated equilibria, and catastrophe.

1 Introduction

Post-genomic biology can only be fully understood from a combined cellular-molecular and evolutionary perspective. It is an integration of extremely small and extremely large scale dynamics in space and time with significant heterogeneity in the system. These are challenges any researcher concerned with small open systems has to confront: A system being open and nonequilibrium

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means its environmental influences at a large scale, usually through a boundary, are felt to a signif-
icant degree by many of the small components inside the system. On the other hand, the ultra-fast
dynamics on the smallest scale, with large degrees of freedom, appear to be “stochastic”. The
term “mesoscopic” is used in this context in the present work [1][2]. Interestingly, the fundamen-
tal issues in both cellular and evolutionary dynamics are now firmly cast in terms of a common
stochastic mathematics [3][4][5]. While the field of stochastic dynamics has more than 100 years
of history, starting with Einstein’s 1905 study of Brownian motion and Langevin’s 1908 proposal
of a stochastic differential equation, we still know little about it beyond the existence proofs and
formal constructions. In particular, the interplay between nonlinearity and stochasticity giving rise
to emergent phenomena is still not fully understood [6].

Applied stochastic dynamics, as a mathematical tool, is in a rather primitive state compared to
our deeper understanding of the deterministic dynamics that is at the foundation of 300 years of the
Newton-Laplace world view. An applied stochastic dynamic theory with in-depth understanding of
the interaction between deterministic (i.e., drift) and stochastic (i.e., random) elements is urgently
needed for the progress of biology, and for the understanding of other complex, open systems.
In other words, we are particularly interested in how stochastic random motion is “coupled” to
deterministic, often nonlinear, dynamics. When one observes a noisy oscillation, is it a limit cycle
with some noise or a rotational random walk? These questions lead us to study the concept of
entropy in stochastic dynamics. It can be shown that the entire statistical thermodynamic structure,
with its core concepts like entropy, free energy, and the Second Law, is in fact a mathematical one
— molecular thermal physics turns out to be one example. One can equally develop a “thermo”-
dynamic theory for stochastic cellular processes, for evolutionary dynamics, and for the dynamics
of other mesoscopic open systems.

In this article, I shall first give a brief introduction to the current status of the mesoscopic
open-chemical system theory. Then I shall discuss a few topics which, I believe, deserve further
development. For more authoritative reviews of the vast literature, see [7][8][9][10][11].
2 What is the Open Chemical Systems Theory?

When one leaves an aqueous chemical reaction system alone, one observes it goes through a transient process with the concentrations of the chemicals changing with time. This is known as relaxation kinetics. Eventually, it settles into a chemical equilibrium. If the system is sufficiently small, then one can also observe the concentrations continuously fluctuate with time, though all their statistics are time invariant [12, 13]. Chemists call this state a chemical equilibrium steady state.

A living cell as a biochemical system, to a first order approximation, is in a steady state, known as homeostasis [14]. It is not in an equilibrium, however: one has to continuously provide a “nutritious medium” in which the cell “lives”. The medium has to contain “high calorie” chemicals as food for the cell, which in turn returns its “waste product” to the medium. So how should one rigorously define such a chemical state of a system which is open to exchange chemical energy and materials with its surroundings [15]? This is the motivation for developing the open chemical system theory [16, 17, 18]. Such a state of a system is called a nonequilibrium steady state (NESS); it is an example of self-organizing dissipative structure [19]. With the stochastic dynamic perspective, one immediately realizes that a deterministic periodic chemical oscillation is also an NESS [20].

Driven by the environment, chemical fluxes are continuously going through such systems. And because of the presence of nonlinear chemical reactions, these fluxes are coupled to internal (bio)chemical reactions. Therefore, according to Kirchhoff’s law, there will be a myriad of cycle fluxes in an NESS [21]. This is why a living cell contains all kinds of metabolic cycles. A deep mathematical theorem shows that, in a large class of stochastic systems, a cycle flux exists if and only if the rate of entropy production is positive [22, 23]. When some of the cycle fluxes are sufficiently strong, a macroscopic oscillation emerges [24].

The existence of the cycle flux, or circulation, turns out to be a fundamental property of open chemical systems. It is intimately related to the breakdown of detailed balance. It is mathemati-
ally related to a non-self-adjoint generator for Markov processes. The presence of cycle flux also indicates that the stationary probability distribution in one part of the system can be influenced by another part far away. Thus the dynamics are nonlocal. This is not possible for a system with detailed balance, which yields Boltzmann’s Law. Even more important: a strong flux is associated with a deterministic kind of motion (breaking a symmetry). Hence, a severely driven chemical system can exhibit rhythmic dynamics. Chemical energy can suppress fluctuations in small open chemical systems, making them behave like little machines [8, 25, 26].

In the past several years, people have shown that almost every biochemically important cellular function is intimately related to the open chemical system setting, and correlates with the energy expenditure associated with the system. This includes kinetic proofreading [27, 28, 29, 30], cellular signal switching [31], fidelity in DNA replication [32], chemotactic adaptations, and other biochemical computations [33, 34, 35]. Another significant insight is the emergence of chemical multi-stability. In stochastic dynamic terms, this is characterized by a stationary probability density function exhibiting multiple peaks. We say there are multiple stochastic attractors. These attractors are emergent properties of dynamics of an open chemical system. Often, though not always, they are the stochastic counterparts of the deterministic stable attractors [36]. These attractors define an emergent, discrete multi-state stochastic dynamics on an entirely different time scale [1]; a \textit{cellular evolution time scale} emerges [37]. Therefore, the open chemical system model is able to conceptually bridge the detailed biochemical reactions networks and the emergent cellular dynamics that reflect differentiation, apoptosis, and epigenetic switching [38]! Furthermore, it can be shown that there is also an emergent “landscape” [39], akin to the adaptive landscape in evolution theory. This landscape is not locally determined; it is itself an emergent property, and its predictive power is, in some sense, only \textit{retrospective} [40].
3 Nonequilibrium Steady-State, Emergent Landscape and Flux in Open Systems

The concept of a nonequilibrium steady state, also known as a nonequilibrium stationary state, is one of the central concepts in studies of open chemical systems. It deserves a focused and in-depth investigation. Note that for a large class of stochastic dynamics, there is a unique, asymptotically attractive stationary process (invariant measure). That is, the system is always self-organizing. In statistical physics and the mathematical theory of interacting particle systems, related research has been pursued for many years. The emphasis has been on the system’s infinite size limit while assuming the individuals are significant “homogeneous”. Stochastic processes with NESS have not been widely studied. The technical difficulties are mainly in the non-symmetric nature of the process, which makes even the mathematical existence proof impossible. The recent exciting development of the fluctuation theorem is precisely along this line \[8, 41, 7\]. It is an important first step. Still, this result is largely unknown in the field of stochastic processes \[42, 43, 44\].

Using a stochastic differential equation with small noise \((\epsilon)\) as a model system, it will be important to further explore the connection between the NESS invariant density \(f^{\text{ss}}_{\epsilon}(x)\), its \(\epsilon\)-dependence, and its Lyapunov stability in the corresponding deterministic dynamics. Note that while the support of \(f^{\text{ss}}_{\epsilon}(x)\) is highly singular, with Dirac measure in the limit of \(\epsilon\) tending to zero, the quantity

\[
\lim_{\epsilon \to 0} \epsilon \log f^{\text{ss}}_{\epsilon}(x)
\]

is often better behaved, with full support in the space \[37\]. This line of research is intimately related to the theory developed by Freidlin and Wentzell \[45\]. This theory needs to be simplified and delivered to the hands of broader applied mathematicians and scientists.

One should not forget, however, that the landscape \[39\] and the stationary distribution are only half of the characterization of the system. The NESS is also characterized by its flux field \(\mathbf{J}\) which is divergence free; that is \(\nabla \cdot \mathbf{J} = 0\). Our understanding of this aspect of stochastic dynamics is still missing \[46\]. In fact, a cogent stochastic interpretation of the \(\mathbf{J}\) is still elusive. Nevertheless, the \(\mathbf{J}\) gives the “dynamical information” of an open system in its NESS. A connection between
this line of inquiry and the theory of Hodge decomposition and algebraic topology, can be found in [47] [48].

4 The Thermodynamic Structure of Stochastic Dynamical Systems

Historically, thermodynamics has been one of the most important organizational principles for systems with large numbers of atoms and molecules — systems considered to be complex mainly due to their large number of components. When a system has a large number of components, especially when all the components are not homogeneous, the interactions between components can only be characterized in a statistical sense. In fact, only statistical characterization is meaningful. We today recognize that thermodynamics is not merely a physical theory about atoms and molecules. Rather, any stochastic system characterized in terms of Markov dynamics possesses a “thermo”-dynamic structure. Since this theory has nothing to do with the temperature *per se*, we put the “thermo” in quotation marks [49]. In essence, one has resolved what Gian-Carlo Rota considered “a standing between physicists and mathematicians that thermodynamics cannot be axiomatized” [50].

There are two inter-related threads in this general theory: one centers around relative entropy (or Kullback-Leibler divergence), which is intimately related to the free energy in Gibbs’ statistical mechanics $F$ [51] [52]. An important fact about $F$ is $dF/dt = -f_d(t) \leq 0$. The other thread centers around Gibbs-Shannon entropy $S$, which satisfies a conservation law $dS/dt = e_p(t) - h_d(t)$. An important fact here is $e_p(t) \geq 0$. The terms $f_d$, $e_p$, and $h_d$ are called free energy dissipation rate, entropy production rate, and heat dissipation rate, respectively.

For Markov systems with detailed balance, which correspond to closed systems: $f_d(t) = e_p(t)$. Furthermore, in the long time limit, $f_d = e_p = h_d = 0$. This is an equilibrium steady state (with fluctuations).

For Markov systems without detailed balance, which correspond to open systems: $e_p(t) = f_d(t) + Q_{hk}(t)$ where $Q_{hk}(t) \geq 0$. $Q_{hk}$, called house-keeping heat, or adiabatic entropy production...
characterizes the amount of energy expenditure (i.e., a battery) that sustains the system away from equilibrium. In the long time limit, \( f_\alpha = 0 \) but \( e_\alpha = Q_{hk} = h_\alpha > 0 \). The entropy production rate \( e_\alpha \) characterizes total irreversibility. It has two distinctly different origins: the system’s spontaneous relaxation (organization) \( f_\alpha \) and the external environmental drive \( Q_{hk} \).

We have recently suggested to read the above equation \( Q_{hk}(t) - e_\alpha(t) = -f_\alpha(t) = dF/dt \) as a novel balance equation, for free energy \( F \).

This theory has only been presented in an applied mathematics style. Further theoretical mathematical analysis is necessary on the subject, as well as applications using this structure to gain further understanding of stochastic dynamics. In addition, issues such as the “principle of maximal entropy production” and related topics have never been seriously investigated with mathematical rigor until recently \([55, 56, 57]\), even though they are actively discussed in applied fields such as climate science and ecology \([58, 59, 60]\), as well as in high-profile headlines \([61]\).

5 Investigation and Characterization of Complex Systems and Their Dynamics in terms of Nonlinear, Stochastic Models

Sections 3 and 4 set up the fundamental mathematics for studying complex, mesoscopic open-system dynamics. This approach has shown great promise and has provided some powerful novel ideas, as well as a deeper understanding of small open-chemical systems. Whether this approach can be applied to other open systems in biology, economics, and beyond remains to be investigated.

One particular advantage of chemical systems is the existence of the theory of Delbrück-Gillespie processes, together with its chemical master equation. This is the stochastic generalization of the Law of Mass Action from classical, nonlinear chemical kinetics. It is a combination of the stochastic framework above and this particular version of stochastic chemical dynamics that has offered us insights on open, fluctuating biochemical systems through concrete mathematical models.

Applying this approach to other systems is essential to extending our understanding of mesoscopic open systems, and all the topics covered in this special issue. Several other research carried
out under different headings also fit in this general scheme. One of them is the area of *stochastic resonance* (SR). Indeed, SR has offered a great deal to our current understanding of the important issues. But one needs to broaden the scope: as we have pointed out, “oscillations” in an NESS is a necessity. They should not be considered a peculiar type of behavior [2] [62].

## 6 Education: Stochastic Dynamics beyond Brownian Motion

There is no doubt that Brownian motion is one of the most important aspects of stochastic dynamics in continuous space and time. It offers a complete departure from Newton-Laplace’s classic view of a “smooth world”, and has yielded deep insights in connection with geometry and other branches of high mathematics, as recognized by the Fields medals in 2006.

Still, by completely focusing on this aspect of stochastic dynamics, our understanding of a general stochastic dynamical system which contains both stochastic and nonlinear deterministic elements is rather rudimentary. In particular, most mathematics are built around the well-studied *symmetric Markov processes*, which have corresponding self-adjoint linear operators.

As we have discussed, open systems, when represented in terms of Markov processes, are precisely non-symmetric processes. This is one of the lessons we learned from the open-chemical systems theory. The nonsymmetricity can be quantified by *entropy production* [22] [23]. For discrete-state Markov processes, the symmetric processes are equivalent to Kolmogorov’s condition [63]. Concepts such as cycle condition, detailed balance, dissipation and irreversible entropy production have all been independently discovered in chemistry: Wegscheider’s relation in 1901 [64], detailed balance by G.N. Lewis in 1925 [65], Onsager’s dissipation function in 1931 [66], and the formulation of entropy production in the 1940s [67] [68].

Compared to the college education of deterministic mathematics, stochastic mathematics is also embarrassingly behind. Here is an example: while most of my third-year students are familiar with the notion of a random variable $X$ with probability density function $f_X(x)$, most of them have never learned, nor are able to work out, how to compute the distribution of $Y = g(X)$, assuming
is a monotonic function! There is no reason for this: stochastic mathematics is not intrinsically harder if one only deals with discrete events. In particular, with the power of computing, one should be able to teach stochastic thinking to first-year students in science, engineering, economics, and social science. We need to have accessible educational programs. Here I emphasize stochastic thinking as distinctly different from statistical thinking. It is mechanistically motivated mathematical deduction rather than data driven.

Finally, I would like to state that the stochastic dynamical theory is not an alternative to the deterministic one. It is a more complete description of nature, which is capable of representing systems with and without uncertainties.

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