ANALYTICAL MECHANICS IN STOCHASTIC DYNAMICS: MOST PROBABLE PATH, LARGE-DEVIATION RATE FUNCTION AND HAMILTON–JACOBI EQUATION

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Analytical (rational) mechanics is the mathematical structure of Newtonian deterministic dynamics developed by D’Alembert, Lagrange, Hamilton, Jacobi, and many other luminaries of applied mathematics. Diffusion as a stochastic process of an overdamped individual particle immersed in a fluid, initiated by Einstein, Smoluchowski, Langevin and Wiener, has no momentum since its path is nowhere differentiable. In this exposition, we illustrate how analytical mechanics arises in stochastic dynamics from a randomly perturbed ordinary differential equation $dX_t = b(X_t)dt + \epsilon dW_t$, where $W_t$ is a Brownian motion. In the limit of vanishingly small $\epsilon$, the solution to the stochastic differential equation other than $\dot{x} = b(x)$ are all rare events. However, conditioned on an occurrence of such an event, the most probable trajectory of the stochastic motion is the solution to Lagrangian mechanics with $L = \|\dot{q} - b(q)\|^2/4$ and Hamiltonian equations with $H(p, q) = \|p\|^2 + b(q) \cdot p$. Hamiltonian conservation law implies that the most probable trajectory for a “rare” event has a uniform “excess kinetic energy” along its path. Rare events can also be characterized by the principle of large deviations which expresses the probability density function for $X_t$ as $f(x, t) = e^{-u(x, t)/\epsilon}$, where $u(x, t)$ is called a large-deviation rate function which satisfies the corresponding Hamilton–Jacobi equation. An irreversible diffusion process with $\nabla \times b \neq 0$ corresponds to a Newtonian system with a Lorentz force $\ddot{q} = (\nabla \times b) \times \dot{q} + (1/2)\nabla\|b\|^2$. The connection between stochastic motion and analytical mechanics can be explored in terms of various techniques of applied mathematics, for example, singular perturbations, viscosity solutions and integrable systems.

Keywords: Excess kinetic energy; exponentially small asymptotics; Freidlin–Wentzell theory; landscape; large deviations; Hamilton–Jacobi equation; most probable path; stochastic dynamics.
Stochastic theory of nonequilibrium steady states and its applications. Part I

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\textbf{ABSTRACT}

The concepts of equilibrium and nonequilibrium steady states are introduced in the present review as mathematical concepts associated with stationary Markov processes. For both discrete stochastic systems with master equations and continuous diffusion processes with Fokker–Planck equations, the nonequilibrium steady state (NESS) is characterized in terms of several key notions which are originated from nonequilibrium physics: time irreversibility, breakdown of detailed balance, free energy dissipation, and positive entropy production rate. After presenting this NESS theory in pedagogically accessible mathematical terms that require only a minimal amount of prerequisites in nonlinear differential equations and the theory of probability, it is applied, in Part I, to two widely studied problems: the stochastic resonance (also known as coherent resonance) and molecular motors (also known as Brownian ratchet). Although both areas have advanced rapidly on their own with a vast amount of literature, the theory of NESS provides them with a unifying mathematical foundation. Part II of this review contains applications of the NESS theory to processes from cellular biochemistry, ranging from enzyme catalyzed reactions, kinetic proofreading, to zeroth-order ultrasensitivity.

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Stochastic theory of nonequilibrium steady states. Part II: Applications in chemical biophysics

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\textbf{A B S T R A C T}

The mathematical theory of nonequilibrium steady state (NESS) has a natural application in open biochemical systems which have sustained source(s) and sink(s) in terms of a difference in their chemical potentials. After a brief introduction in Section 1, in Part II of this review, we present the widely studied biochemical enzyme kinetics, the workhorse of biochemical dynamic modeling, in terms of the theory of NESS (Section 2.1). We then show that several phenomena in enzyme kinetics, including a newly discovered activation–inhibition switching (Section 2.2) and the well-known non-Michaelis–Menten-cooperativity (Section 2.3) and kinetic proofreading (Section 2.4), are all consequences of the NESS of driven biochemical systems with associated cycle fluxes. Section 3 is focused on nonlinear and nonequilibrium systems of biochemical reactions. We use the phosphorylation–dephosphorylation cycle (PdPC), one of the most important biochemical signaling networks, as an example (Section 3.1). It starts with a brief introduction of the Delbrück–Gillespie process approach to mesoscopic biochemical kinetics (Sections 3.2 and 3.3). We shall discuss the zeroth-order ultrasensitivity of PdPC in terms of a new concept — the temporal cooperativity (Sections 3.4 and 3.5), as well as PdPC with feedback which leads to biochemical nonlinear bistability (Section 3.6). Also, both are nonequilibrium phenomena. PdPC with a nonlinear feedback is kinetically isomorphic to a self-regulating gene expression network, hence the theory of NESS discussed here could have wide applications to many other biochemical systems.

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Cooperativity in Cellular Biochemical Processes: Noise-Enhanced Sensitivity, Fluctuating Enzyme, Bistability with Nonlinear Feedback, and Other Mechanisms for Sigmoidal Responses

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Keywords
hysteretic enzyme, kinetic proofreading, nonequilibrium, open chemical systems, signal transduction

Abstract
Cooperativity in classical biophysics originates from molecular interactions; nonlinear feedbacks in biochemical networks regulate dynamics inside cells. Using stochastic reaction kinetic theory, we discuss cooperative transitions in cellular biochemical processes at both the macromolecular and the cellular levels. We show that fluctuation-enhanced sensitivity (stochastic focusing) shares an essential feature with the transition in a bistable system. The same theory explains zeroth-order ultrasensitivity with temporal cooperativity. Dynamic cooperativity in fluctuating enzyme (i.e., dynamic disorder), stochastic focusing, and the recently proposed stochastic binary decision all have a shared mechanism: They are generalizations of the hyperbolic response of Michaelis-Menten kinetics $x/(K + x)$, with fluctuating $K$ or stochastic $x$. Sigmoidal dependence on substrate concentration necessarily yields affinity amplification for competing ligands; both sigmoidal response and affinity amplification exhibit a square law. We suggest two important characteristics in a noise: its multimodal distribution structure and its temporal irreversibility. The former gives rise to self-organized complexity, and the latter contains useful, albeit hidden, free energy that can be utilized for biological functions. There could be structures and energy in biochemical fluctuations.
INTRODUCTION

Ever since the work of Adair, Monod et al. (59), and Koshland et al. (48) on oxygen binding by hemoglobin and of Schellman (85) and Zimm & Bragg (110) on α-helix formation of polypeptides, the concept of cooperativity has become one of the most important cornerstones of molecular biophysics (33). This concept is now widely used in biology, beyond macromolecular interactions; a special issue of *Nature Chemical Biology* was dedicated to the subject in 2008 (16).

Phenomenologically, cooperativity is intimately related to various mathematical expressions known as sigmoidal. It deviates from hyperbolic $ax/(b+x)$, also known as Michaelis-Menten (MM) kinetics and Hill’s function. The reason for the central role of $ax/(b+x)$ as noncooperativity lies in the notion of identical, independent subsystems, each having two states, within a system. This is known as Bernoulli trials. For a sequence of $N$ independent, identical, but unfair coins, each with probabilities $p$ and $q = 1 - p$ for heads and tails, respectively, the expected number of heads is $Np/(p+q) = Nz/(1+z)$, where $z = p/q \in [0, \infty)$. Note $ax/(b+x)$ can also be written as $az/(1+z)$ with $z = x/b$.

In chemistry, $z/(1+z)$ is known as the Langmuir-Hill equation. It relates the binding of molecules on a solid surface (macromolecule) to concentration of a medium (ligand) above the surface (macromolecule) at a fixed temperature. A statistical mechanical treatment of this problem based on a binomial distribution follows exactly the probabilistic theory of Jacob Bernoulli, the Swiss who discovered the mathematical constant $e$ in 1683.
INVITED ARTICLE

Nonlinear stochastic dynamics of mesoscopic homogeneous biochemical reaction systems—an analytical theory

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Abstract

The nonlinear dynamics of biochemical reactions in a small-sized system on the order of a cell are stochastic. Assuming spatial homogeneity, the populations of $n$ molecular species follow a multi-dimensional birth-and-death process on $\mathbb{Z}^n$. We introduce the Delbrück–Gillespie process, a continuous-time Markov jump process, whose Kolmogorov forward equation has been known as the chemical master equation, and whose stochastic trajectories can be computed via the Gillespie algorithm. Using simple models, we illustrate that a system of nonlinear ordinary differential equations on $\mathbb{R}^n$ emerges in the infinite system size limit. For finite system size, transitions among multiple attractors of the nonlinear dynamical system are rare events with exponentially long transit times. There is a separation of time scales between the deterministic ODEs and the stochastic Markov jumps between attractors. No diffusion process can provide a global representation that is accurate on both short and long time scales for the nonlinear, stochastic population dynamics. On the short time scale and near deterministic stable fixed points, Ornstein–Uhlenbeck Gaussian processes give linear stochastic dynamics that exhibit time-reversible circular motion for open, driven chemical systems. Extending this individual stochastic behaviour-based nonlinear population theory of molecular species to other biological systems is discussed.

Mathematics Subject Classification: 82C31, 37N25, 92C40

(Some figures in this article are in colour only in the electronic version)
Cooperativity and Specificity in Enzyme Kinetics: A Single-Molecule Time-Based Perspective

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ABSTRACT An alternative theoretical approach to enzyme kinetics that is particularly applicable to single-molecule enzymology is presented. The theory, originated by Van Slyke and Cullen in 1914, develops enzyme kinetics from a "time perspective" rather than the traditional "rate perspective" and emphasizes the nonequilibrium steady-state nature of enzymatic reactions and the significance of small copy numbers of enzyme molecules in living cells. Sigmoidal cooperative substrate binding to slowly fluctuating, monomeric enzymes is shown to arise from association pathways with very small probability but extremely long passage time, which would be disregarded in the traditional rate perspective: A single enzyme stochastically takes alternative pathways in serial order rather than different pathways in parallel. The theory unifies dynamic cooperativity and Hopfield-Ninio’s kinetic proofreading mechanism for specificity amplification.

There is a resurgence of interest in the theory of enzyme kinetics due to several recent developments in biochemical research: Foremost is the systems approach to cell biology which demands quantitative characterizations of cellular enzymatic reactions in terms of Michaelis-Menten (MM)-like kinetics (1–3). Second, recent advances in single molecule enzymology have generated exquisite information on protein dynamics in connection to enzyme catalysis (4). And third, the theoretical advance of our understanding of biochemical reaction networks in terms of the thermodynamics of open-system, nonequilibrium steady state (often nowadays abbreviated as NESS) (5–7). Single-molecule enzymology and enzymatic reactions inside cells have shown the necessity of modeling enzyme reactions in terms of stochastic mathematics (8–13).

The above-mentioned developments have led us to re-examine the concept(s) of cooperativity in the context of enzyme kinetics. Protein conformational changes, especially those induced by ligand bindings and/or covalent modifications, are one of the cornerstones of molecular biology that connect macromolecular physics with cellular biological functions. Beside allosterism, cooperativity has been studied in monomeric enzymes with only a single substrate binding site; this has led to the important concepts of hysteretic behavior and mnemonic enzymes (reviewed in (14–17)). It is understood that such cooperativity is a NESS phenomenon. Therefore, it is fitting to call it dynamic cooperativity (18) in contrast to equilibrium allosterism. Kinetic cooperative is another term used in the literature. This work, however, focuses on nonequilibrium cooperative behavior in steady states rather than on transient kinetics. A nonequilibrium steady state (NESS) has constant chemical fluxes in the system, while an equilibrium state has zero flux in each and every reaction (19).

The early experimental evidence for fluctuating protein dynamics was provided by Linderstrøm-Lang and his amide proton hydrogen-deuterium exchange method (20). Dynamic cooperativity can occurs in enzymes with slow fluctuating conformational substates within the unbound (E) form. Such slow fluctuations, also called dynamic disorder, are precisely what has been firmly established in recent single-molecule experiments (4,11,13).

On the theory side, an alternative to the MM approach that is particularly applicable to single-molecule enzyme kinetics has also emerged. This theory, originated by Van Slyke and Cullen in 1914 (21), develops enzyme kinetics from a time perspective rather than the traditional rate perspective. As we shall show, the time approach, while it is equivalent in principle to that of MM, provides a much more intuitive understanding of the nature of dynamic cooperativity.

This article is organized as follows. We first establish a single-molecule perspective for enzyme kinetics in terms of state probabilities, cycle fluxes, and most importantly, mean first passage times: This is a new kinetic language that differs from the traditional one. Using this distinct approach, we present some of the results well-known in textbooks, specifically the double reciprocal relation for irreversible enzymes and the Briggs-Haldane result on reversible enzymes. Stochastic enzyme kinetics with more than one, but still a small number of copies of an enzyme, is studied in the section Single Enzyme to Small Copy Numbers Inside Cells. This is a realistic situation for many regulatory reactions inside cells. Small biochemical reaction systems are now routinely modeled by the chemical master equation (22). We present a novel relationship between the theory of single molecules and the quasi-steady-state analysis of the chemical master equation of enzyme kinetics recently developed by Rao and Arkin (23). The section Fluctuating Enzymes and Dynamic Cooperativity introduces dynamic cooperativity, which appears as sigmoidal behavior, as it emerges in monomeric, single-site enzymes with conformational fluctuations in the unbound state. Two necessary conditions for such behavior are established, namely,
Phosphorylation Energy Hypothesis: Open Chemical Systems and Their Biological Functions

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Key Words
chemical kinetics, kinetic proofreading, nonequilibrium steady state, signal transduction, thermodynamics

Abstract
Biochemical systems and processes in living cells generally operate far from equilibrium. This review presents an overview of a statistical thermodynamic treatment for such systems, with examples from several key components in cellular signal transduction. Open-system nonequilibrium steady-state (NESS) models are introduced. The models account quantitatively for the energetics and thermodynamics in phosphorylation-dephosphorylation switches, GTPase timers, and specificity amplification through kinetic proofreading. The chemical energy derived from ATP and GTP hydrolysis establishes the NESS of a cell and makes the cell—a mesoscopic–biochemical reaction system that consists of a collection of thermally driven fluctuating macromolecules—a genetically programmed chemical machine.
FEATURE ARTICLE

Open-System Nonequilibrium Steady State: Statistical Thermodynamics, Fluctuations, and Chemical Oscillations

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Gibbsian equilibrium statistical thermodynamics is the theoretical foundation for isothermal, closed chemical, and biochemical reaction systems. This theory, however, is not applicable to most biochemical reactions in living cells, which exhibit a range of interesting phenomena such as free energy transduction, temporal and spatial complexity, and kinetic proofreading. In this article, a nonequilibrium statistical thermodynamic theory based on stochastic kinetics is introduced, mainly through a series of examples: single-molecule enzyme kinetics, nonlinear chemical oscillation, molecular motor, biochemical switch, and specificity amplification. The case studies illustrate an emerging theory for the isothermal nonequilibrium steady state of open systems.

1. Introduction

To traditional chemists, a biological cell is a chemical reaction system as complex as one can imagine. Still, no matter how complex a chemical system is, if it is left alone in a test tube, it gradually approaches a chemical equilibrium. In biology, an equilibrium state is dead; in physics, it is the least organized state of a system, irrespective of how complex the system is.

All the above statements are embodied in the fundamental theory of equilibrium statistical thermodynamics. The subject is introduced to every chemistry undergraduate in a physical chemistry class. But to think about the physical chemistry of a living cell, one realizes that we are dealing with a scenario that is completely different from all that was said above. In fact, the most important thing to a biochemist studying living cells is to maintain a “cell culture”. That is, he or she has to regularly change the medium in which cells grow.

If not complexity, then what is the difference between a set of reactions in a test tube and in a living cell? The answer is that the former is in a closed system with chemical isolation, while the latter is open to exchange with its environment, both in chemical energy and in materials. If the exchange with its surroundings is sustained, then an open system usually approaches a steady state that is not an equilibrium. The most distinguished characteristics of a nonequilibrium steady-state (NESS) is that it has nonzero fluxes and nonzero chemical potential gradients in the system. It converts chemical energy into heat. Chemical reaction systems in NESS can process information and generate spatial patterns; they are the chemical basis of cellular signal transduction and biological morphogenesis.

The focus of this article is to present an introductory theory of NESS with fluctuations. A more comprehensive review is forthcoming. We believe that the pedagogically most effective exposition starts with several simple examples, which we shall present in Section 2. In Section 3, we establish the statistical thermodynamics in terms of the Smoluchowski equation that characterizes stochastic dynamics of molecular systems. According to Kramers’ theory, the Smoluchowski equation characterizes the chemical kinetics of a single-molecule reaction system. In Section 4, we review the general theory of chemical reactions in a closed system and show several key results that are pertinent to our discussion. In Section 5, a recently developed application of NESS theory to complex networks of chemical reactions in terms of their stoichiometry is presented. In particular, we establish the analogue of Kirchhoff’s current and loop laws for chemical reaction networks. In Section 6, we illustrate three key applications of the theory of NESS to current biology: the kinetic proofreading mechanism for specificity amplification, biochemical switches and their energy expenditure, and motor proteins and their chemomechanics. Section 7 concludes the paper with a discussion.

2. Three Examples

In this section, we give three simple examples of biochemical reaction systems in NESS with increasing complexity. We provide kinetic as well as thermodynamic analyses. While the former is routinely carried out, the latter is not. Through elementary mathematics, these examples illustrate a novel nonequilibrium statistical thermodynamic theory and show how it is applied.
Cycle kinetics, steady state thermodynamics and motors—a paradigm for living matter physics

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Abstract
An integration of the stochastic mathematical models for motor proteins with Hill’s steady state thermodynamics yields a rather comprehensive theory for molecular motors as open systems in the nonequilibrium steady state. This theory, a natural extension of Gibbs’ approach to isothermal molecular systems in equilibrium, is compared with other existing theories with dissipative structures and dynamics. The theory of molecular motors might be considered as an archetype for studying more complex open biological systems such as biochemical reaction networks inside living cells.

1. Introduction
One of the origins of modern molecular biology is physical chemistry, which provides a host of quantitative techniques for studying biochemical reactions and biological macromolecules, as well as the theoretical guiding principles in terms of statistical thermodynamics for designing experiments in and analysing laboratory measurements from aqueous solutions [1–4]. The standard theory of statistical thermodynamics [5], be it on equilibrium or kinetics, however, only applies to closed systems. In cell biology, it is important to study biochemistry in open systems with constant energy inputs and dissipations [6, 7].

While there are several nonequilibrium theories for open systems, Hill’s [8] was directly motivated by concrete biological problems and is most applicable to open biochemical systems. One of his motivations was studying muscle contraction. Hill’s work on muscle theory is a landmark after the pioneering work of Huxley [9], with sufficient statistical thermodynamic rigour [10, 11]. The general theory, which sets up a new theoretical framework for open systems with chemical energy input but without explicit material exchange, is summarized in two books [8, 12]. Two important concepts in the new theory of open systems are the cycle kinetics and nonequilibrium steady state (NESS) thermodynamics.

Hill’s work was developed before the discovery of in vitro motility assay of single motor proteins [13, 14]. In the 1990s, several mathematical models emerged which were applicable...
Review

Thermodynamics of stoichiometric biochemical networks in living systems far from equilibrium

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Abstract

The principles of thermodynamics apply to both equilibrium and nonequilibrium biochemical systems. The mathematical machinery of the classic thermodynamics, however, mainly applies to systems in equilibrium. We introduce a thermodynamic formalism for the study of metabolic biochemical reaction (open, nonlinear) networks in both time-dependent and time-independent nonequilibrium states. Classical concepts in equilibrium thermodynamics—enthalpy, entropy, and Gibbs free energy of biochemical reaction systems—are generalized to nonequilibrium settings. Chemical motive force, heat dissipation rate, and entropy production (creation) rate, key concepts in nonequilibrium systems, are introduced. Dynamic equations for the thermodynamic quantities are presented in terms of the key observables of a biochemical network: stoichiometric matrix $Q$, reaction fluxes $J$, and chemical potentials of species $l$ without evoking empirical rate laws. Energy conservation and the Second Law are established for steady-state and dynamic biochemical networks. The theory provides the physiochemical basis for analyzing large-scale metabolic networks in living organisms.

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Keywords: Biological networks; Cycle kinetics; Mathematical modeling; Metabolism; Systems biology

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1. Introduction

Thermodynamics is one of the branches of physics most directly applied to biochemistry. Concepts such as entropy, enthalpy, and free energy are the cornerstones of understanding various biological processes such as protein folding, protein–DNA interaction, and DNA supercoiling. Yet, a majority of thermodynamic analyses and/or kinetic studies focus only on “non-living” systems. By a non-living system, we mean that if one waits a sufficiently long time compared with its relaxation time, the system approaches a