Stochastic Physics, Complex Systems and Biology*

Hong Qian

Department of Applied Mathematics
University of Washington
Seattle, WA 98195, U.S.A.

May 5, 2014

Abstract

In complex systems, the interplay between nonlinear and stochastic dynamics, e.g., J. Monod’s necessity and chance, gives rise to an evolutionary process in Darwinian sense, in terms of discrete jumps among attractors, with punctuated equilibrium, spontaneous random “mutations” and “adaptations”. On an evolutionary time scale it produces sustainable diversity among individuals in a homogeneous population rather than convergence as usually predicted by a deterministic dynamics. The emergent discrete states in such a system, i.e., attractors, have natural robustness against both internal and external perturbations. Phenotypic states of a biological cell, a mesoscopic nonlinear stochastic open biochemical system, could be understood through such a perspective.

Biological systems and processes are complex. One of the hallmarks of complex behavior is uncertainties, either in the causes of an occurred event, or in predicting its future [26, 13]. This “feel” of complexity is intimately related to the following issue [20]: When a system consists of only a few degrees of freedom, say $x_1, x_2$ and $x_3$, a complete description of the “trajectory” of $(x_1, x_2, x_3)(t)$ for all $t$ constitutes a full understanding of the system. However, when a system has a million of degrees of freedom, $x(t) = \{x_i(t)|1 \leq i \leq 10^6\}$, a complete description of the $x(t)$ is not informative at all! One needs to find an particular “angle” to synthesize the large amount of data, or a “pattern” to obtain a summary. In classical physics of inanimate matters with relatively homogeneous individuals, this is

*The 1st Gordon Research Conference on “Stochastic Physics in Biology”, chaired by K.A. Dill, was held on January 23-28, 2011, in Ventura, CA.
accomplished by introducing the concept of *distribution* together with macroscopic thermo-
dynamic quantities, giving rise to the discipline of statistical thermodynamics. In modern
cellular biology, this is known as “data interpretation with respect to biological functions”: Usually a narrative in addition to the data is required [23].

The foregoing brief discussion points to a key departure from the classical physics of
Newton and Laplace [31]: A rational choice of mathematical descriptions of biological
systems and processes requires a probabilistic view of the dynamics, which provides both
individual-based and distribution-based perspectives. Studying system dynamics in terms of
stochastics, either due to intrinsic uncertainties, lack of full knowledge, or due to a need for
organizing large amount of data, is the basis of what we call *stochastic physics*.

**What is Stochastic Physics**

Modern sciences emphasize quantitative representation of experimental observations, widely
known as *mathematical modeling*. Along this line, there are two types of modeling: the *data-
driven* and the *mechanism based* models. In the history of physics, Kepler’s model (laws)
was the most celebrated example of the former, while Newton’s theory of universal gravity,
which “explains” Kepler’s results, is the canonical example of a mechanism. In fact, the very
term *mechanism* was derived from the word *mechanics*. In biology, Mendel’s model (law)
was the former, and Hardy-Weinberg’s theory was the latter. The difference between the
example in physics and the example in biology is that the latter has to take into account of
uncertainties. Data-driven modeling incorporating uncertainties gives rise to the entire field
of statistics - and bioinformatics and financial engineering are two most active branches of
studies in recent years.

This leads straight to the question “where is the mechanism based modeling with uncer-
tainty”? Stochastic physics is precisely the answer to this calling. In sociology and econo-
nomics, this type of modeling is called *agent-based*, and in finance it is called *behavior
finance*.

In applied mathematics, statistics is associated with *data-driven modeling* and stochastic
process is associated with *population distribution based mechanistic modeling*. In physics,
statistical physics has traditionally dealt with more on state of matters in equilibrium rather than dynamics of open, driven systems. Nevertheless, it is a shining example of successful stochastic modeling.

**Nonlinear Physics and Stochastic Physics**

Stochastic physics shares many of the concepts and concerns of the nonlinear physics that has gone before it: They both are focused on dynamics of a system [18]. Technically, for nonlinear systems exhibiting chaotic dynamics, a characterization based on distribution turns out to be more appropriate [25]. Data analyses of chaotic signals also constantly employ methods from statistics [1, 39].

Stochastic dynamics in linear systems and nonlinear systems are fundamentally different [38, 33]. The former can be essentially represented by a Gaussian process, which was extensively studied by eminent physicists like Uhlenbeck, Chandrasekhar, and Onsager [44, 29, 12]. But stochastic dynamics *per se* is not the reason for complex behavior. A Gaussian process has certain unpredictability, nevertheless the ultimate fate of the dynamics is all the same: It fluctuates around its mean value.

However, when one faces a strongly nonlinear system with stochasticity, one has to talk about *evolution*, evolution process in Darwin’s sense with punctuated equilibrium and spontaneous random “mutations” and “adaptations”. This is one of the profound insights derived from the studies of nonlinear stochastic systems: The fluctuations in a nonlinear system with multiple attractors make rare events, something with infinitesimal probability from a Deterministic standpoint, an sure occurrence with probability one in an “evolutionary” time scale [15, 37]. This picture fits J. Monod’s notion of chance and necessity [27, 18]. Furthermore, when encountering external environmental changes, nonlinear multi-stable systems exhibit adaptation by enhanced rate of transition into the “favored attractors”; and ultimately exhibit “rupture” - the nonlinear catastrophe scenario in the presence of stochasticity [9].

Newton-Laplace’s dynamics gives us a sense of convergence. For strongly nonlinear stochastic dynamics, the validity of the converging dynamics is only on a rather limited time scale. In an evolutionary time scale, divergent dynamics emerges. This, we believe, is a
philosophical implication derived from stochastic physics [31].

**Stochastic Physics and Quantitative Biology**

Physics and computer science (CS) are two cornerstones of modern, engineering world. Therefore, it is not surprising that they support the most quantitative aspects of biology. Yet, upon a more careful reflection, one realizes that thinkings in both physics and CS are in odd with that of biologists: Physics considers systems that can be described with a few variables, known as “information poor” according to J.J. Hopfield [20], and CS, while deals with much more complex problems, nevertheless in terms of perfect logics with almost infinite precision. Biological systems are information rich, and biological processes are not about precision or optimal, but rather about functional and survival.

The studies of biological cells, the universal building block of living organisms, also have two foundations that echoed physics and CS: biochemistry and genomics. Biochemistry is founded on the tradition of physics, via the investigations of macromolecular structures and dynamics and biochemical reactions, while genomics heavily utilizes concepts and methods from CS, i.e. coding, information, discrete mathematics, leading to the emergence of bioinformatics in recent years. The heavy influences of physics and CS in biological thinking, in fact in all 21-century modern thinkings, is unmistakable. Nowadays, even the studies of biochemical reaction systems are usually about their information logic flow. Known as signal transduction, it provides a clear link between biochemistry within a cell, to perceived function. However, one often forgets that information is only an abstract term; its physical bases have to be either energy or material. In cell biology, they are represented by the structure and states of macromolecules. The information logic flow aspects of biochemical reaction is our “models” and “interpretations” of a biological organism based on our understanding of its engineering functions! It is a “narrative” cell biologists provide to understand a complex reality [28].

This reveals an important gap in the current dominant thinking of cell biology: the link between the physics of molecules, the chemistry of reactions, and the information logic flow they represents. It is widely recognized that investigations into this link require statistical
physics and molecular thermodynamics in small systems with dynamics [30, 7, 36]. Filling this gap has been called for as the systems biology of cells [45]. Though yet to be proven, it is not difficult to see that the stochastic physics approach as described above has the potential to be a powerful, quantitative language of cellular dynamics and other biological systems [34].

The stochastic physics approach to biology relies more on mechanistic understanding of biological systems and processes than on high-throughput large data sets. It is a powerful tool to generate working hypotheses in a rigorous way. In current biological research, one often states that “we like to know how it works”. However, a scientifically more sound statement should be “we like to know whether it works in this way?”. This goes back to the hypothesis-driven research with strong inference [6]. Taking uncertainties into account, stochastic modeling is based on one’s mechanistic understanding, and relies on mathematical deduction to generate precise hypothesis. It will be an indispensable tool in biological research on par with data-driven bioinformatics.

**Cellular Biology and Theory of Evolution**

Based on the Modern Synthesis of Darwin’s theory of evolution, the current population genetics and genomics [24] attribute the molecular basis of biological variations to different DNA sequences, which is inheritable through Mendelian genetics and Watson-Crick base-pairing mechanism. Biochemistry, however, has been always considered as merely a deterministic mechanics that executes the instructions coded in the DNA [2].

Recent laboratory measurements on stochastic gene expression in single cells with single-molecule sensitivity, however, has broken the genomic monoply of biological variations [10, 8]. Stochasticity has been increasingly recognized as a key aspect of cellular molecular biology. In terms of Darwin’s evolution, Kirschner and Gerhart have maintained that the essential role of cellular and organismal biology is to provide phenotypic variations with plausible molecular mechanisms that bridge genomes and lives [22].

The tenants of stochastic physics fit this perspective. In particular, the mathematical theory of stochastic processes has revealed a rich thermodynamic structure in any stochas-
tic dynamics based on Markov formalism [14]. The thermodynamic theory clearly distinguishes a closed stochastic system which reaches an equilibrium distribution with detailed balance, and an open, driven stochastic system which reaches a nonequilibrium steady state [46, 17, 21, 40]. It has been firmly established that the latter corresponds to precisely cellular biochemical systems upon which continuous chemical driving forces are applied. The conversion of chemical energy into heat in isothermal cellular systems can be characterized by entropy production rate [32, 41].

The external energy supply, as the “environment condition” for an open system, is the thermodynamic necessity for self-organization and complex behavior [32]. Thermodynamics, however, can only tell what is possible and what is not; but it does not tell what is feasible and what is the mechanism. For the latter, detailed “molecular mechanisms” have to be developed. There is clearly a dichotomy between the nature vs. nurture for the function of a biochemical system. A stochastic description of dynamics provides a unique tool to understand the occurrence of sequential events, i.e., kinetics, in terms of the “most probable path” [42, 43, 16].

There is a growing interest in understanding cell differentiation including stem cell differentiation and reprogramming, isogenetic variations, and even cancer carcinogenesis from an evolutionary perspective at the cellular level [19, 5, 43]. The mathematical theory of evolution and population genetics has long been based on stochastic processes [11, 3, 4]. Therefore, the stochastic physics approach to cellular biochemical dynamics provides a natural unifying framework to further this exciting new frontier of biological science.

A stochastic physics based quantitative understanding of cellular biology, in return, will provide a paradigm for studying other complex systems [33, 46, 35].

References

[1] H D I Abarbanel. The analysis of observed chaotic data in physical systems. Rev Mod Phys, 65:1331–1392, 1993.
[2] B Alberts. The cell as a collection of protein machines: Preparing the next generation of molecular biologists. *Cell*, 92:291–294, 1998.

[3] P Ao. Laws in Darwinian evolutionary theory. *Phys Life Rev*, 2:117–156, 2005.

[4] P Ao. Emerging of stochastic dynamical equalities and steady state thermodynamics from Darwinian dynamics. *Comm Theoret Phys*, 49:1073–1090, 2008.

[5] P Ao, D Galas, L Hood, and Zhu X-M. Cancer as robust intrinsic state of endogenous molecular-cellular network shaped by evolution. *Med Hypoth*, 70:678–684, 2007.

[6] D A Beard. Strong inference for systems biology. *PLoS Comp Biol*, 5:e1000459, 2009.

[7] C Bustamante, J Liphardt, and F Ritort. The nonequilibrium thermodynamics of small systems. *Phys Today*, 58(July):43–48, 2005.

[8] L Cai, N Friedman, and X Xie. Stochastic protein expression in individual cells at the single molecule level. *Nature*, 440:358–362, 2006.

[9] Shapiro B E and H Qian. A quantitative analysis of single protein-ligand complex separation with the atomic force microscope. *Biophys Chem*, 67:211–219, 1997.

[10] M B Elowitz, A J Levine, Siggia E D, and P S Swain. Stochastic gene expression in a single cell. *Science*, 297:1183–1186, 2002.

[11] W J Ewens. *Mathematical Population Genetics I. Theoretical Introduction*. Springer, New York, 2004.

[12] R F Fox. Gaussian stochastic processes in physics. *Phys. Rep.*, 48:179–283, 1978.

[13] H Ge, S Pressé, K Ghosh, and K A Dill. Markov processes follow from the principle of maximum caliber. *J Chem Phys*, 136:064108, 2012.

[14] H Ge and H Qian. The physical origins of entropy production, free energy dissipation and their mathematical representations. *Phys Rev E*, 81:051133, 2010.
[15] H Ge and H Qian. Nonequilibrium phase transition in mesoscopic biochemical systems: From stochastic to nonlinear dynamics and beyond. *J R Soc Interf*, 8:107–116, 2011.

[16] H Ge and H Qian. Analytical mechanics in stochastic dynamics: Most probable path, large-deviation rate function and Hamilton-Jacobi equation. *Int J Mod Phys B*, 26:1230012, 2012.

[17] H Ge, M Qian, and H Qian. Stochastic theory of nonequilibrium steady states (Part II): Applications in chemical biophysics. *Phys Rep*, 510:87–118, 2012.

[18] H Haken. *Synergetics, an Introduction: Nonequilibrium Phase Transitions and Self-Organization in Physics, Chemistry, and Biology*. Springer-Verlag, New York, 3rd rev. enl. edition, 1983.

[19] D Hanahan and R A Weinberg. The hallmarks of cancer. *Cell*, 100:57–70, 2000.

[20] J J Hopfield. Physics, computation, and why biology looks so different? *J Theoret Biol*, 171:53–60, 1994.

[21] D-Q Jiang, M Qian, and M-P Qian. *Mathematical Theory of Nonequilibrium Steady States On the frontier of probability and dynamical systems, LNM Vol. 1833*. Springer-Verlag, Berlin, 2004.

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

[23] J Knight. Bridging the culture gap. *Nature*, 419:244–246, 2002.

[24] E V Koonin. Darwinian evolution in the light of genomics. *Nucleic Acids Res*, 37:1011–1034, 2009.

[25] A Lasota and M C Mackey. *Chaos, Fractals and Noise: Stochastic Aspects of Dynamics*. Springer-Verlag, New York, 1994.
[26] M C Mackey. The dynamic origin of increasing entropy. *Rev Mod Phys*, 61:981–1016, 1989.

[27] J Monod. *Chance and Necessity: An Essay on the Natural Philosophy of Modern Biology*. Vintage Books, New York, 1972.

[28] P B Moore. How should we think about the ribosome? *Ann Rev Biophys*, 41:1–19, 2012.

[29] L Onsager and S Machlup. Fluctuations and irreversible processes. *Phys Rev*, 91:1505–1512, 1953.

[30] R Phillips and S R Quake. The biological frontier of physics. *Physics Today*, 59(May):38–43, 2006.

[31] I Prigogine and I Stengers. *Order Out of Chaos: Man’s New Dialogue with Nature*. New Sci. Lib. Shambhala, Boulder, CO, 1984.

[32] H Qian. Phosphorylation energy hypothesis: Open chemical systems and their biological functions. *Ann Rev Phys Chem*, 58:113–142, 2007.

[33] H Qian. Nonlinear stochastic dynamics of mesoscopic homogeneous biochemical reactions systems - an analytical theory. *IoP Nonlinearity*, 24:R19–R49, 2011.

[34] H Qian. Cooperativity in cellular biochemical processes: Noise-enhanced sensitivity, fluctuating enzyme, bistability with nonlinear feedback, and other mechanisms for sigmoidal responses. *Ann Rev Biophys*, 41:179–204, 2012.

[35] H Qian. A decomposition of irreversible diffusion processes without detailed balance. *arXiv.org/abs/1204.6496*, 2012.

[36] H Qian. Hill’s small systems nanothermodynamics: A simple macromolecular partition problem with a statistical perspective. *J Biol Phys*, 38:201–207, 2012.
[37] H Qian and H Ge. Mesoscopic biochemical basis of isogenetic inheritance and canalization: Stochasticity, nonlinearity, and emergent landscape. *MCB: Mol Cellu Biomech*, 9:1–30, 2012.

[38] H Qian, P-Z Shi, and J Xing. Stochastic bifurcation, slow fluctuations, and bistability as an origin of biochemical complexity. *Phys Chem Chem Phys*, 11:4861–4870, 2009.

[39] H Tong. *Non-Linear Time Series: A Dynamical System Approach*. Oxford, UK, 1993.

[40] L von Bertalanffy. The theory of open systems in physics and biology. *Science*, 111:23–29, 1950.

[41] J Wang, L Xu, and E K Wang. Potential landscape and flux framework of nonequilibrium networks: Robustness, dissipation and coherence of biochemical oscillations. *Proc Natl Acad Sci USA*, 105:12271–12276, 2008.

[42] J Wang, K Zhang, and E K Wang. Kinetic paths, time scale, and underlying landscapes: A path integral framework to study global natures of nonequilibrium systems and networks. *J Chem Phys*, 133:125103, 2010.

[43] J Wang, K Zhang, L Xu, and E K Wang. Quantifying the Waddington landscape and biological paths for development and differentiation. *Proc Natl Acad Sci USA*, 108:8257–8262, 2011.

[44] N Wax. *Selected Papers on Noise and Stochastic Processes*. Dover, New York, 1954.

[45] H V Westerhoff and B Ø Palsson. The evolution of molecular biology into systems biology. *Nature Biotech*, 22:1249–1252, 2004.

[46] X-J Zhang, H Qian, and M. Qian. Stochastic theory of nonequilibrium steady states and its applications (Part I). *Phys Rep*, 510:1–86, 2012.