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# Stochastic bifurcation, slow fluctuations, and bistability as an origin of biochemical complexity

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We present a simple, unifying theory for stochastic biochemical systems with multiple time-scale dynamics that exhibit noise-induced bistability in an open-chemical environment, while the corresponding macroscopic reaction is unistable. Nonlinear stochastic biochemical systems like these are fundamentally different from classical systems in equilibrium or near-equilibrium steady state whose fluctuations are unimodal following Einstein–Onsager–Lax–Keizer theory. We show that noise-induced bistability in general arises from slow fluctuations, and a pitchfork bifurcation occurs as the rate of fluctuations decreases. Since an equilibrium distribution, due to detailed balance, has to be independent of changes in time-scale, the bifurcation is necessarily a driven phenomenon. As examples, we analyze three biochemical networks of currently interest: self-regulating gene, stochastic binary decision, and phosphorylation-dephosphorylation cycle with fluctuating kinase. The implications of bistability to biochemical complexity are discussed.

## 1. Introduction

Molecular motor is a chemical system derived from biological organisms with fundamental importance to our understanding of living matter.[1,2] See ref. 3 for an entire volume of review articles dedicated to this subject. The theory of molecular motor has taught us how to think about open, driven mesoscopic systems as a theoretical chemistry problem, and the importance of free energy dissipation in their biological functions.[4,5] One of the origins of the ratchet model for molecular motor is the phenomenon of *noise-induced transition*.[6] In recent years, related phenomena have also appeared in other biochemical systems, such as transcription regulation and cellular signaling.[7,8] In this paper, we shall discuss several recent problems using the concepts, models, and techniques developed from studying molecular motors.

Biochemical reactions in aqueous solution or condensed phase are stochastic due to thermal agitations. This is a firmly demonstrated fact from a wide range of experimental measurements: from single membrane channel conductance to fluorescence correlation spectroscopy, from single-molecule enzymology to single motor protein movements.[9–12] When the number of molecules involved in a biochemical reaction system is very large, however, the stochasticity disappears and a deterministic, macroscopic behavior emerges. This is the Law of Large Numbers; the same law allows Las Vagas casinos to be confident in their profitability only if a large number of people gamble. Biochemical reactions inside a living cell have long been considered only with deterministic chemical kinetics. In fact, a cell has always been thought as a "chemical machine" that performs biological functions as the macroscopic machines we know of in daily life. But while the number of molecules of intermediate metabolites is very large (*i.e.*, 100 μM in a 10 fl (femtolitre) volume is about $6 \times 10^5$ of molecules), there is only a single copy of DNA! In recent years, there has been a great interest in the stochasticity in transcriptional and translational processes, both theoretically and experimentally. There are now well documented experimental measurements on the stochasticity of biological macromolecules at the level of single cells with behavioral significance and evolutionary implications.[13,14]

For any chemical reaction system which is well-stirred, its kinetics can be described by a stochastic model using the chemical master equation (CME), which is an equivalent mathematical representation of the widely known Gillespie algorithm.[15] A Gillespie algorithm, or more precisely the minimal process sampling,[16] to a CME is the same as a stochastic differential equation to a Fokker-Planck equation, *i.e.*, stochastic trajectory *versus* probability distribution. If the system is very large in the copy number of each type of molecule, then the CME is equivalent to the corresponding ordinary differential equations (ODE) based on the Law of Mass Action.[15] Since a biochemical reaction network, usually shown as in Fig. 2–4, does not specify the size of the reaction system, one can either develop a CME model or an ODE model. The latter is the deterministic, macroscopic counterpart of the former. Experimentally, one should think of the former as a biochemical reaction network inside a cell, and the latter as a cellular extract from tens or handreds of thousands of ground cells.

Since there is only a single copy of DNA, the chemical kinetics of gene regulations inside a living cell has to be based on the CME; this is very different from the traditional biochemical studies of gene regulations *in vitro*. One of the recent advances in cell biology is the realization that the kinetics of these two systems, though consisting of identical biochemical networks of interest, can have very different

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behavior simply because the size difference in the experimental setups.[17]

Stochastic bifurcation with noise-induced bistability is one of such interesting phenomena. A theory of noise-induced bistability was systematically studied in the classic text[6] as an abstract mathematical model for a nonequilibrium phenomenon. In recent years, there is a growing literature on its possible role in cellular regulation.[7,8,18] See ref. 19 for an excellent presentation of the general mathematical modeling approach to stochastic gene regulation.

In this paper, we present a simple unifying theory for stochastic bifurcation and noise-induced bistability based on the concept of slow fluctuations from the theory of rate processes.[20] We study three biochemical network models that exhibit stochastic bifurcation:

(i) Self-regulating gene;[7,19]

(ii) Binary stochastic decision;[18]

(iii) Phosphorylation–dephosphorylation cycle with fluctuating kinase.[8,21,22]

We show that stochastic bistability can be understood as a unimodal system with a slowly fluctuating parameter that dictates the location of the peak of the distribution. If the range of fluctuation is large, then bistability can arise. Such bistability disappears with increasing the rate of the fluctuation. Therefore there is a pitchfork bifurcation with the fluctuation rate as the parameter. Here we shall point out that bistability is always a driven, nonequilibrium system behavior. Within the framework of the CME, it has been shown that for any closed chemical system, its stationary, *i.e.*, equilibrium, distribution is necessarily unimodal.[23,24]†

This paper is organized as follows: In section 2 we present a brief discussion of our theory; section 3 contains our analyses for three examples of current biochemical networks. In section 4 we discuss the implication of bistability to emergent properties and biochemical complexity. The section 5 contains more details of the mathematical methods for analyzing the models.

## 2. Slow fluctuations and stochastic bistability

The previous work in ref. 7, 8, 18, 19 and 22 has clearly shown stochastic bistability in various biochemical regulatory network models. We refer the readers to these original papers for the motivation and relevance of the models and their behaviors. What has not been completely made clear in the past, however, is that the rate of the fluctuations in all these cases has to be slow. This we shall demonstrate in this section *via* a simple toy model.

We shall emphasize that noise-induced bistability discussed in this paper is a different phenomenon from the bistability in the context of deterministic nonlinear dynamics. In the latter, with the present of molecular fluctuations, a system can transit between the two stable states.[24,25] Systems with noise-induced bistability has a single unique stable state in its macroscopic, deterministic counterpart. The difference between stochastic and deterministic kinetics, *i.e.*, between small and large systems, also disappears when the fluctuations become sufficiently rapid.

Nonlinear chemical bistability has been extensively studied in the past in the chemical literature, both theoretically[26] and experimentally.[27] See an earlier text by Epstein and Pojman[28] and a recent one by Ross,[29] as well as many cited references in ref. 24.

### 2.1 Stochastic dynamics and its deterministic counterpart

Naively, one would expect that the CME theory only provides variances to the mean values obtained from the ODE theory. While this statement has ample truth in it, recent research has shown many interesting cases in which stochasticity leads to behavior completely unexpected from the ODE. It is these latter cases that generated a growing awareness in stochastic thinking in cell biology.

The naive view is in fact based on our general understanding from statistical physics: If a system is sufficiently large, the statement is true. More interestingly, for a closed chemical reaction system, even if it is small, it can be shown that its stationary concentration distribution is unimodal, with the peak being the equilibrium concentration predicted by the ODE model.[23]‡ The concentration distribution provides the fluctuation (*i.e.* variance) in the equilibrium concentration. In fact, one type of fluctuation theory, developed by Einstein, Onsager, Lax, and Keizer,[31,32] follows precisely this line. One of the key ingredients of the Einstein–Onsager–Lax–Keizer fluctuation theory is that one can obtain the flucutations from the *same, linear* dynamics equations for the mean values. Following this approach, the stochasticity only adds a correction to the mean; it does not add complexity. In fact, the mean dynamics of a small system is similar to the deterministic dynamics in the limit of large system size.

One place where the naive view clearly should not work is when a distribution is bimodal. If a distribution has two peaks with equal size, then the mean is located at the value that is the least probable. In this case, the mean dynamics of a small system and the deterministic dynamics from ODE can be significantly different.

### 2.2 A toy model

To put the idea of slow and rapid fluctuations leading to bistability and bifurcation on a firm ground, we shall here introduce a simple mathematical model, a model of models, that can be solved easily to a sufficient extent. While the model is rather abstract, we believe it is the canonical form of this type of problem.

We consider a simple stochastic dynamics $\boldsymbol{X}(t)$

$$\mathrm{d}\boldsymbol{X} = -(\boldsymbol{X} - \mu)\mathrm{d}t + \sqrt{2}\mathrm{d}\boldsymbol{B}_t, \qquad (1)$$

where $\boldsymbol{B}_t$ is the standard Brownian motion. The stationary distribution for $\boldsymbol{X}(t)$ is a Gaussian distribution centered at $\mu$

† In the framework of the CME, equilibrium coexistence of two phases still have a non-zero rate of fluctuation between the two pure phases. Thus the CME considers the equilibrium composition to be 50–50 in a much longer time scale. This time scale might not be realistic in a macroscopic system, but can be estimated for mesoscopic systems by nucleation theory.

‡ It is instructive to point out that for an equilibrium distribution, because of the principle of detailed balance, the rate of a reversible reaction does not change the distribution. Thus, changing the time scale of a pair of forward and backward rate constants will not lead to a bifurcation as observed in noise-induced bistability. Stochastic bistability is necessarily an open-chemical system phenomenon.[30]

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with variance 1.[6,23] Now consider that the $\mu$ in fact is a fluctuating $\mu(t)$ taking two equally probable values $\pm\lambda$, with the rate of fluctuation being $q$. Then the Fokker–Planck equation for the system with fluctuating $\mu$ is a coupled diffusion on $(-\infty,\infty)$:

$$\frac{\partial u_1}{\partial t} = \frac{\partial^2 u_1}{\partial x^2} + \frac{\partial}{\partial x}(x+\lambda)u_1 - qu_1 + qu_2,$$

$$\frac{\partial u_2}{\partial t} = \frac{\partial^2 u_2}{\partial x^2} + \frac{\partial}{\partial x}(x-\lambda)u_2 + qu_1 - qu_2, \qquad (2)$$

with no flux boundary conditions at $x = \pm\infty$. $u_1(x,t)$ and $u_2(x,t)$ are the probability density functions for $\boldsymbol{X}(t)$ with $\mu = -\lambda$ and $\mu = +\lambda$, respectively.

We are interested in the stationary distribution. But first, it is easy to show that if $q \gg 1$, then there is a rapid equilibration $u_1(x) = u_2(x)$. Therefore, if one sums the two equations in (2), one has:[33]

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2} + \frac{\partial}{\partial x}(xu), \qquad (3)$$

where $u(x,t) = u_1(x,t) + u_2(x,t)$. The stationary distribution for this equation is a Gaussian centered at $x = 0$ with variance 1. On the other limit, if $q \ll 1$, then the stationary distribution is simply:[33]

$$u^{ss}(x) = \frac{1}{2\sqrt{2\pi}}(e^{-(x-\lambda)^2/2} + e^{-(x+\lambda)^2/2}). \qquad (4)$$

Hence, if $\lambda > 1$, then $u^{ss}(x)$ has two maxima near $\pm\lambda$. For $\lambda \leq 1$, the maxima of the two Gaussian distributions in eqn (4) are too close to be separated.

Therefore when $\lambda$ is large, the steady state distribution has a single peak at $x = 0$ for $q \gg 1$ but two peaks near $x = \pm\lambda$ for $q \ll 1$. There must be a bifurcation from large $q$ to small $q$. A complete analysis of the bifurcation of this model is outside the scope of the present paper. However, we shall consider the case of $\lambda \gg 1$, *i.e.*, the fluctuation in the mean of the Guassian is much greater than its variance.

We introduce $u(x) = u_1^{ss}(x) + u_2^{ss}(x)$ and $v(x) = u_1^{ss}(x) - u_2^{ss}(x)$. Then from eqn (2) we have

$$\frac{\mathrm{d}^2 u(x)}{\mathrm{d}x^2} + \frac{\mathrm{d}}{\mathrm{d}x}(xu + \lambda v) = 0, \qquad (5)$$

$$\frac{\mathrm{d}^2 v(x)}{\mathrm{d}x^2} + \frac{\mathrm{d}}{\mathrm{d}x}(xv + \lambda u) - 2qv(x) = 0. \qquad (6)$$

Eqn (5) can be integrated and noting that $\left[\frac{\mathrm{d}u}{\mathrm{d}x} + xu + \lambda v\right]_{x=\pm\infty} = 0$, we have

$$\lambda v(x) = -\frac{\mathrm{d}u(x)}{\mathrm{d}x} - xu(x). \qquad (7)$$

Substituting this into eqn (6), it becomes

$$\frac{\mathrm{d}^3 u(x)}{\mathrm{d}x^3} + 2x\frac{\mathrm{d}^2 u(x)}{\mathrm{d}x^2} + (x^2 - \lambda^2 - 2q + 3)\frac{\mathrm{d}u(x)}{\mathrm{d}x} + 2(1-q)xu(x) = 0. \qquad (8)$$

We are interested in the behavior of $u(x)$ around $x = 0$: $u'(0) = 0$ since the solution to eqn (8) is an even function. Furthermore, if $u''(x) > 0$, $u(x)$ is concave and bistable since $u(x) \geq 0$ and $u(\pm\infty) = 0$. If $u''(x) < 0$, $u(x)$ is convex with a peak at $x = 0$. Since $\lambda \gg 1$, much larger than other coefficients around $x = 0$, the dominant term of the eqn (8) is

$$-\lambda^2 \frac{\mathrm{d}u(x)}{\mathrm{d}x} = 0$$

which gives a constant solution $u(x) = c_0$. As a result, in terms of the small parameter $\lambda^{-2}$, the solution of eqn (8) has the form

$$u(x) = c_0 + \frac{\eta(x)}{\lambda^2}, \quad c_0 > 0$$

then the equation for $\eta(x)$ becomes

$$\frac{1}{\lambda^2}\left(\frac{\mathrm{d}^3\eta}{\mathrm{d}x^3} + 2x\frac{\mathrm{d}^2\eta}{\mathrm{d}x^2} + (x^2 - 2q + 3)\frac{\mathrm{d}\eta}{\mathrm{d}x} + 2(1-q)x\eta\right) - \frac{\mathrm{d}\eta}{\mathrm{d}x} + 2c_0(1-q)x = 0. \qquad (9)$$

Since $\lambda \gg 1$, we discard the small terms and obtain

$$-\frac{\mathrm{d}\eta(x)}{\mathrm{d}x} + 2c_0(1-q)x = 0$$

so

$$\eta(x) = c_0(1-q)x^2, \; u(x) = c_0\left(1 + \frac{(1-q)}{\lambda^2}x^2\right). \qquad (10)$$

Therefore, when $q < 1$, $\eta(x)$ is concave at $x = 0$, implying the existence of two peaks on both sides; when $q > 1$, $\eta(x)$ is convex at $x = 0$, *i.e.*, a maximum.

Numerical computation shown in Fig. 1 verifies the above analytical result. With increasing $q$ from 0 to 1, the two peaks of $u(x)$ move toward the center $x = 0$, and merge into one at some critical value $q_c$. The critical point of bifurcation is $q_c \approx 1$ for large $\lambda$, as predicted in eqn (10). The position of the local maximum undergoes a pitchfork bifurcation as $q$ is decreased.

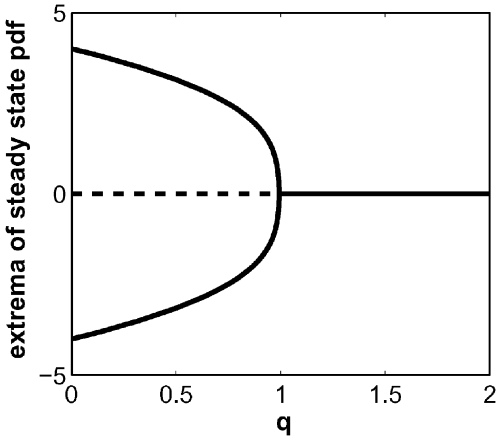


**Fig. 1** Bifurcation diagram of local extrema of $u(x)$, the sum of steady state probability density functions (pdf) $u_1^{ss}(x)$ and $u_2^{ss}(x)$ according to the toy model in eqn (2), where $q$ is the rate of fluctuation between the two states. The solid and dashed lines represent the maximum and the minimum, respectively. Parameter $\lambda = 4$ in this calculation.

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The toy model shows how stochastic bistability arises from a unimodal stationary distribution. This is the advantage of studying this model. In general for more complex models, only the limiting cases of very large and very small $q$, *i.e.*, rate of fluctuations, can be solved analytically. This is the approach we shall use in section 3.

### 2.3 Dichotomous fluctuation, colored and white noise

There are in general two different ways to introduce dynamic disorder, or fluctuations, into a reaction system: discrete dynamic disorder and continuous dynamic disorder.[20] They are sometimes known respectively as *dichotomous noise* and Ornstein-Uhlenbeck *colored noise* (due to the finite relaxation time) in the theory of noise-induced transitions.[6]

Consider the fluctuating $\mu(t)$ in eqn (1) as an example. A discrete fluctuation has $\mu = \pm\lambda$ following a two-state Markov dynamics:

$$\frac{\mathrm{d}P_{+\lambda}(t)}{\mathrm{d}t} = -qP_{+\lambda} + qP_{-\lambda},$$

$$\frac{\mathrm{d}P_{-\lambda}(t)}{\mathrm{d}t} = qP_{+\lambda} - qP_{-\lambda}, \qquad (11)$$

where $P_{+\lambda}(t)$ and $P_{-\lambda}(t)$ are the probability of $\mu = +\lambda$ and $-\lambda$ at time $t$, respectively. This is what we have done in section 2.2. In a continuous fluctuation, on the other hand, $\mu$ satisfies an Ornstein-Uhlenbeck (OU) dynamics

$$\mathrm{d}\boldsymbol{\mu} = -q(\boldsymbol{\mu} - \mu_0)\mathrm{d}t + \sigma\mathrm{d}\boldsymbol{B}_t. \qquad (12)$$

The OU process leads to a stationary Gaussian distribution with mean $\mu_0$ and variance $\sigma^2/(2q)$. In the theory of motion narrowing and dynamic disorder which deals with time-dependent phenomena,[20] these two types of fluctuation often yield similar conclusions. However, for stochastic bistability and bifurcation, the shape of the fluctuation distribution matters. It is not difficult to show that if one uses fluctuating $\mu(t)$ in eqn (1) in terms of an OU process, there will be no stochastic bifurcation.

There are other important differences between the recent work on stochastic bifurcation and the earlier work on dynamic disorder:[20] In the past, the fluctuations, or noise, were often introduced into a system as external in an *ad hoc* manner. To investigate the effect of fluctuations, choosing dichotomous or OU noise is often a matter of convenience. The CME for biochemical reaction network, however, provides a rigorous procedure which naturally introduces the fluctuations as internal noise. In the past, the noise is "added" to deterministic dynamics; the CME is itself a stochastic dynamics. This distinction means that there is little free choice for what type of "noise" to use in a biochemical model; it comes with the problem. For gene regulation, it has to be a two-state process. For a molecule with fluctuating copy number but large mean, an OU might be a reasonable approximation. But this is only an approximation since molecular number has to be non-negative integers. Wu *et al.* have developed a model which combines network regulation with kinase dynamic disorder.[22]

In some models the fluctuations are modeled by white noise. For example, in the model for PdPC with zeroth-order enzyme kinetics and fluctuating kinase,[8] assumed that the kinase activity follows $E(t) = E_0 + \boldsymbol{W}(t)$ with $\boldsymbol{W}(t)$ being white noise ($=\sigma\mathrm{d}\boldsymbol{B}_t/\mathrm{d}t$). White noise is usually understood as a very rapidly fluctuating stochastic process. In fact, it is so rapid that for any two times $t_1 \neq t_2$: $\langle \boldsymbol{W}(t_1)\boldsymbol{W}(t_2)\rangle = 0$. Still, Samoilov *et al.* reported stochastic bistability with kinase activity fluctuating as white noise.[8] We shall now explain this result in light of our theory.

Recall that for both dichotomous and OU fluctuations, there is a rate and an amplitude. These two quantities are best represented by the correlation function of a stationary fluctuating process: $Ae^{-qt}$. We have so far focused on the rate $q$. The implicit assumption is that we have kept the amplitude of the fluctautions, $A$, constant. For the toy model in eqn (1), $A = \lambda^2$, and if $\lambda < 1$, then no matter how small the $q$, there will be no bistability. On the other hand, if $\lambda \geq 4$, then the bifurcation occurs always at $q_c \approx 1$.

The above discussion indicates that for some systems, fluctuations with larger $q$, *i.e.*, very rapid, can still have bistability if $A$ is sufficiently large. In some other systems, however, a large $A$ can not compensate for a large $q$. The book[6] contains a careful discussion of this issue (chapter 8) and showed an example in which stochastic bistability occurs when $2A/(q + 1)$ is greater than a critical value. White noise has both its fluctuating rate and amplitude $q$, $A \to \infty$ in such a way that $A/q = \sigma^2$. Therefore, white noise can lead to stochastic bistability in some systems but not in others. A system that exhibits stochastic bistability with white noise will do the same with colored noise, but the converse is not true.

### 2.4 Random modulation, dynamics disorder, and stochastic bifurcation

In the theory of spectral line shapes, also known as Anderson–Kubo theory of random modulation, two Lorentzian (or Gaussian) spectra in the frequence domain can merge into a single one due to rapid chemical exchange:[34] The spectra are determined by the chemical structure of a molecule, and the structural fluctuation, also called chemical exchange, leads to spectral narrowing. Similarly, if one is interested in rate processes and expresses the distribution of relaxation rate in the Laplace space, then the distribution can undergo "peak splitting" due to slow chemical exchange. All these phenomena are intimately related due to a simple mathematical structure, as pointed out by Szabo, Xie and their colleagues:[35,36]

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} u_1 \\ u_2 \end{pmatrix} = \left[\begin{pmatrix} \boldsymbol{L}_1 & 0 \\ 0 & \boldsymbol{L}_2 \end{pmatrix} + q\begin{pmatrix} -a & b \\ a & -b \end{pmatrix}\right]\begin{pmatrix} u_1 \\ u_2 \end{pmatrix}. \qquad (13)$$

For the theory of spectral line shapes, the $\boldsymbol{L}$'s are imaginary constants; for the theory of rate processes in closed chemical systems, the $\boldsymbol{L}$'s are real, negative constants. For the stochastic bifurcation, the $\boldsymbol{L}$'s are elliptic differential operators. See eqn (2). The mathematics of all these problems is the perturbation of an eigenvalue problem, as we shall briefly explain below.

Very fast fluctuation means the $q$ parameter in the eqn (13) is very large. If one multiplies a $1/q$ throughout the equation, we see that the first matrix on the right-hand-side is a

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perturbation to the second matrix, which has an eigenvalue zero. Then, according to the perturbation theory of eigenvalue problem, the perturbed eigenvalue, as the leading order, is

$$\frac{b\boldsymbol{L}_1 + a\boldsymbol{L}_2}{a+b}. \qquad (14)$$

On the other hand, very slow flucutation means the $q$ is very small. Then the second matrix is a perturbation to the first. If the eigenvalues of $\boldsymbol{L}$'s are not zero, then the leading order behavior is simply that of $q = 0$.

The theories of random modulation and dynamic disorder are both interested in the perturbed eigenvalue, while the stochastic bifurcation is interested in the perturbed eigenvector.§

## 3. Three examples of stochastic bistability and bifurcation

The above toy model has clearly demonstrated the role of slow fluctuations and how the rate modulates the noise-induced bistability. The traditional chemical reaction rates in aqueous solutions are usually very fast, thus slow fluctuations might not be a common place. However, in biochemistry that involves macromolecules like proteins, slow conformational dynamics is in fact widely present in enzyme kinetics.[37] Furthermore, many temporal dynamics inside a living cell are not dictated by the intrinsic chemical reaction rates but by the network regulations that serve certain biological functions.

The terms "fast" and "slow", *i.e.*, multiple time-scale, in stochastic processes share the same features as that in deterministic dynamical systems: on a short-time scale, one treats the slow process as essentially static, while on a long time scale, one treats the fast process as in its stationary probability distribution instantaneously. This last feature will be amply illustrated by the following biochemical examples.

### 3.1 Self-regulating gene

A single cell has only one copy of DNA. Therefore, to construct the deterministic counterpart for the biochemical reaction systems shown in Fig. 2, one needs to consider an *in vitro* biochemical experiment with a large number of cells. In this case, the biochemical reactions in the system are

$$\alpha + R \underset{f}{\overset{\hat{h}}{\rightleftharpoons}} \beta, \quad \beta \xrightarrow{g(c_\alpha, c_\beta)} R + \alpha, \quad R \xrightarrow{k} \varnothing. \qquad (15)$$

Let $\alpha_0$ be the total DNA concentration. We shall also denote

$x$: concentration of free repressor $R$,

$c_\alpha$: concentration of $\alpha$, the DNA in the "on" state without binding of the repressor,

$c_\beta$: concentration of $\beta$, the DNA in the "off" state.

Then $c_\alpha + c_\beta = \alpha_0$, and the traditional differential equations for the dynamics of the regulatory network in terms of $\alpha(t)$ and $x(t)$:

$$\frac{\mathrm{d}c_\alpha}{\mathrm{d}t} = f(\alpha_0 - c_\alpha) - \hat{h}xc_\alpha, \quad \frac{\mathrm{d}x}{\mathrm{d}t} = g(c_\alpha, c_\beta) - kx. \qquad (16)$$

§ In fact, the Anderson localization in a random medium is another example of such problems.

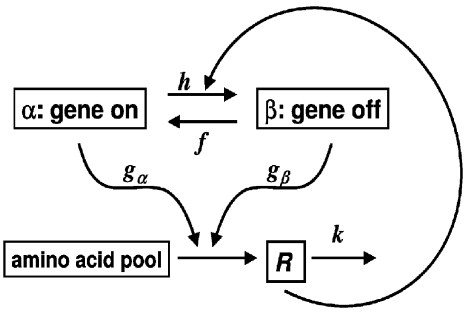


**Fig. 2** Biochemical network of a self-regulating gene. $\alpha$ and $\beta$ represent the "on" and "off" states of a gene. $R$ represents the gene product which is the repressor of the gene activation. The repressor synthesis rate differs depending upon whether the gene is on or off, $g_\alpha$ and $g_\beta$, respectively. The repressor also has a degradation rate of $k$. All the rate constants in the diagram are number based. To convert to concentration-based rate constants, the first-order rate constants $f$ and $k$ are unaltered, but the second-order rate constant $\hat{h} = hV$ where $V$ is the volume of the reaction system. Also see eqn (15).

The term $g(c_\alpha,c_\beta) = c_\alpha g_\alpha + c_\beta g_\beta$ represents the synthesis rate for the repressor with the presence of $c_\alpha$ and $c_\beta$ amount of $\alpha$- and $\beta$-DNA.

The system in eqn (16) has only a single steady state (see section 5.1).

The stochastic model in terms of the CME was given in ref. 7 and 19. The mathematical model shares a great deal of similarity to that of the "ratchet model" for molecular motor and conformational diffusive Michaelis–Menten theory for fluctuating enzymes:[1,38,39]

$$\frac{\mathrm{d}p_\alpha(n)}{\mathrm{d}t} = g_\alpha p_\alpha(n-1) - (g_\alpha + kn)p_\alpha(n) + k(n+1)p_\alpha(n+1) - hnp_\alpha(n) + fp_\beta(n) \qquad (17a)$$

$$\frac{\mathrm{d}p_\beta(n)}{\mathrm{d}t} = g_\beta p_\beta(n-1) - (g_\beta + k(n-1))p_\beta(n) + knp_\beta(n+1) + hnp_\alpha(n) - fp_\beta(n) \qquad (17b)$$

with boundary conditions $p_\beta(0) = 0$ and $p_\alpha(-1) = 0$. See section 5.1 for more discussion on the CME. Note our equation is somewhat different from that of Hornos *et al.* We have assumed, as in eqn (15), that only the free repressor can be degraded.

As for the toy model, there are two limiting cases for which the steady state distribution eqn (17) can be solved easily: (i) rapid gene on-and-off and (ii) slow gene on-and-off[33] (see section 5.1). It is shown that (i) has a stationary distribution for the number of repressors which is unimodal, with its maximum located at the deterministic steady state value. In the other limit, however, (ii) has a stationary distribution which is bimodal, with its maxima located at $g_\alpha/k$ and $g_\beta/k$. These results show that slow fluctuations lead to stochastic, or noise-induced bistability, which has no deterministic counterpart. The result on slow fluctuations, though obtained by a different mathematical method in ref. 7 and 19, has never

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been explicitly articulated as the key. See ref. 7 and 19 for the more detailed treatment.

### 3.2 Stochastic binary decision

We now turn to a model for stochastic decision bistability derived from T-cell activation by Artyomov *et al.*[18] The basic biochemical network is shown in Fig. 3, in which one mainly is interested in the competition for signaling molecule $A$ between $A^*$ and $A^{\#}$, the protected and the inactivated states. While the network in Fig. 3 is more realistic, its essential behavior can be understood from a much simpler kinetic system:

$$A^* \xleftarrow{\alpha} A \xleftarrow{\beta} A^{\#}. \tag{18}$$

Kinetics like this have been studied in prokaryotic transcription termination[40] and kinetic check point for DNA replication fidelity.[41] What is different in the present work is that the pseudo-first-order rate constants $\alpha$ and $\beta$ are fluctuating due to the concentration (or activity) fluctuations in enzymes $E$ and $S$ in Fig. 3: $\alpha = k_3[E]$ and $\beta = k_5[S]$.

The kinetic equations for the reactions in eqn (18) are:

$$\frac{d[A]}{dt} = -(\alpha(t) + \beta(t))[A],\ \frac{d[A^*]}{dt} = \alpha(t)[A],\ \frac{d[A^{\#}]}{dt} = \beta(t)[A]. \tag{19}$$

We are interested in the fraction of protected $A^*$ in the steady state

$$\theta = \frac{[A^*]}{[A^*] + [A^{\#}]} = \frac{\alpha}{\alpha + \beta}. \tag{20}$$

The ratio $\frac{[A^*]}{[A^{\#}]}$ has been called branching ratio in the prokaryotic transcription termination literature.[40,42]

If the fluctuating $\alpha(t)$ and $\beta(t)$ are very fast, then one can replace $\alpha(t)$ and $\beta(t)$ in eqn (19) by their time averages $\bar{\alpha}$ and $\bar{\beta}$. Then $\theta$ is always equal to $\bar{\alpha}/(\bar{\alpha} + \bar{\beta})$. To consider $\alpha$ and $\beta$ fluctuating slowly, let us assume they are independent and each follows a log-normal distribution:

$$\alpha = a_1 e^{-b_1},\ \ \beta = a_2 e^{-b_2},\ \ f_{b_i}(x) = \frac{1}{\sqrt{2\pi}\sigma_i} e^{-\frac{x^2}{2\sigma_i^2}},\ \ (i = 1, 2). \tag{21}$$

These represent the fluctuations in the enzymatic activities of $E$ and $S$ in Fig. 3. One is then interested in the probability distribution for the fraction of protected $A^*$.

A surprising result (see section 5.2), which was implicated in ref. 18, is that if the fluctuation rate of $b_1$ and $b_2$ are much slower than $a_1$ and $a_2$, *i.e.*, and if the variance $\sigma_1^2 + \sigma_2^2$ is sufficiently large, then the distribution of $\theta$ is bimodal!

The model of stochastic binary decision is, therefore, again a good example for our general theory of bistability caused by slow fluctuations. Furthermore, we shall note that if the fluctuations in $\alpha$ and $\beta$ are sufficiently small, than there will be no bistability: This is the case when the $E$ and $S$ in Fig. 3 are present in macroscopic quantity. The deterministic counterpart of the model is uni-stable.

### 3.3 Phosphorylation–dephosphorylation cycle with fluctuating kinase

Our third example is the most widely appeared biochemical module in cell biology: the phosphorylation-dephosphorylation cycle (PdPC) shown in Fig. 4.¶ A large body of literature on the deterministic dynamics of such systems exists.[15] Stochastic models have also been developed in recent years.[8,21,43–47]

There are two different starting points for introduing the fluctuating kinase activity (or dynamic disorder): one can either start with the macroscopic deterministic dynamics, usually a system of ordinary differential equations, or one can start with a mesoscopic stochastic model for the *distribution* of the phosphorylated substrate.

Mechanistically, there are two fundamentally different types of "fluctuations" in the kinase (and/or phosphatase) activity: that of enzyme dynamic disorder due to conformational fluctuations of proteins, and that of kinase concentration fluctuation. For the PdPC, both types of fluctuations contribute to fluctuations in the enzyme activity. We shall, therefore, make no distinction between them in the following analysis.

**Introducing fluctuating kinase into deterministic dynamics.** In the simplest model for PdPC, one has a kinase catalysis rate $\alpha$ and a phosphatase catalysis rate $\beta$ between two states of a substrate enzyme: unphosphorylated $E$ and phosphorylated $E^*$:[15]

$$E \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} E^*. \tag{22}$$

Now with fluctuating $\alpha$, we note that if the fluctuation is much slower than the rates in the PdPC, then the fraction of phosphorylated substrate is $\theta = s/(1 + s)$ where $s = \alpha/\beta$. This is exactly the same expression as in eqns (20) and (34)!

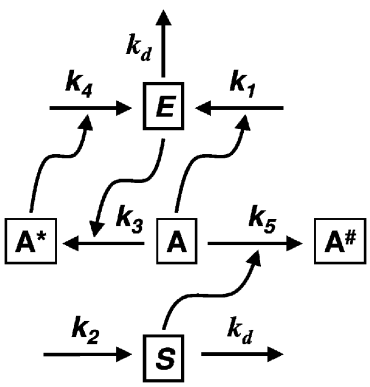


**Fig. 3** Biochemical network of binary decision kinetics. In the model of ref. 18 for T-cell activation, an agonist ($A$) can be either protected ($A^*$) or inactive ($A^{\#}$). The two competing processes are catalyzed by an activator $E$ and an inhibitor $S$, respectively. The reactions with rate constants $k_1$, $k_2$ and $k_4$ all have constant sources. Note that the model for decision making has a steady state which is not dynamic; rather $A^*$ and $A^{\#}$ are absorbing states.

¶ An identical kinetic scheme is obtained for biochemical network of GTPase if one identifies $E \rightarrow$ GDP-bound GTPase, $E^* \rightarrow$ GTP-bound GTPase, kinase $\rightarrow$ guanine exchange factor, and phosphatase $\rightarrow$ GTPase activating protein.

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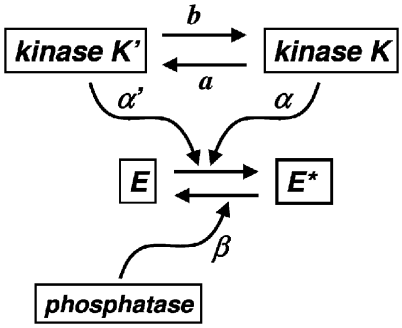


**Fig. 4** Biochemical network of phosphorylation–dephosphorylation cycle (PdPC) with fluctuating kinase activity. The substrate enzyme $E$ can be phosphorylated to become $E^*$, catalyzed by a kinase with two fluctuating conformations $K$ or $K'$. The dephosphorylation is catalyzed by a phosphatase $P$. If the number of substrate molecules are sufficiently greater than that of the kinase and the phosphatase, then the PdPC has a zeroth-order kinetics (see the text).

Therefore, though the biochemical contexts are very different, the stochastic binary decision and bistability in PdPC with fluctuating kinase share the same mathematical model (see section 5.3, $K = 1/s$). Samoilov *et al.* have studied a more realistic PdPC with zeroth-order kinetics.[8]

**Stochastic approach to zeroth order PdPC.** For PdPC with the zeroth order kinetics, the probability distribution for the number of substrate molecules in the $E^*$ state follows a truncated geometric distribution:[8,43–46]

$$p_{E^*}(n) = \frac{1-s}{1-s^{N+1}} s^n. \qquad (23)$$

where $s = \alpha/\beta$. Here we assume that the total number of substrate molecule is $N$.

Eqn (23) indicates that if $s < 1$, the peak of the distribution $p_{E^*}(n)$ is at $n = 0$ and if $s > 1$ then it is at $n = N$. Therefore, if the activity of the kinase is slowly fluctuating between $\alpha$ and $\alpha'$ such that $s' = \alpha/\beta > 1$ and $s'' = \alpha'/\beta < 1$, as in Fig. 4, then the distribution of the number of active $E^*$ will be bimodal:[22]

$$p_{E^*}(n) = \left(\frac{a}{a+b}\right)\frac{1-s''}{1-s''^{N+1}} s''^n + \left(\frac{b}{a+b}\right)\frac{1-s'}{1-s'^{N+1}} s'^n. \qquad (24)$$

On the other hand, if the fluctuation rates $a$ and $b$ are rapid, then we have again eqn (23), now with the averaged $s = (as'' + bs')/(a + b)$. Finally, the deterministic counterpart for the biochemical reaction system in Fig. 4 has a single steady state at the peak position: $[E^*] = 0$ if $s < 1$ and $[E^*] = E_T$ if $s > 1$, *i.e.*, ultrasensitivity.[15]

In summary, the model of PdPC with fluctuating kinase activity is another example of our general theory that bistability can arise from systems with slow fluctuations. However, if the fluctuations are rapid, then the bistability disappears, and the corresponding deterministic equations always have unistability. This is stochastic bifurcation.

## 4. Discussion

It has been suggested that one of the sources of complex cellular dynamics is the complex biochemical reaction networks leading to stochastic behavior at system level. But stochastic dynamics *per se* is not the reason for complex behavior. In fact, the traditional fluctuation theory in equilibrium physics assumes the fluctuation to be Gaussian distributed. Although a stochastic Gaussian process has some uncertainties, the ultimate fate of the dynamics is simple: it will be near the center of the distribution. Stochastic fluctuations with a bimodal distribution are an entirely different matter. From a Newtonian–Laplacian deterministic standpoint, the fate of a bimodal system is truly uncertain.

There is no disagreement that biological systems are complex. But how do we understand complexity; what is its origin? This is a deep question to which no complete answer exists. However, we would like to offer some insights from our recent studies[24,48–50] including the present one.

Deterministic dynamics in terms of periodic and quasi-periodic motions are considered simple. In deterministic dynamics, complex behavior is associated with the so-called chaotic motion. Note that one of the hallmarks of a chaotic system is the existence of a large number of unstable states. A dynamical system exhibiting stochastic motions seems complex. But a more careful analysis can show otherwise. A stationary Gaussian process is really nothing more than a single deterministic steady-state with some uncertainty given by the variance: it is the stochastic counterpart of a linear deterministic system.[51] Therefore, to assess the complexity of mesoscopic stochastic motion, one should investigate its deterministic counterpart.‖ This suggestion is somewhat counter-intuitive: If the biochemical system one studies is mesoscopic and there is no experimental reality to carry out a corresponding macroscopic experiment, usually one does not investigate the large-system size limit of the mathematical model: that is considered to be irrelevant. But for complex behavior, some of the more interesting information is in the deterministic counterpart, even though there is no possibility of observing the dynamics directly. We suggest this is one of the ways to define emergent properties of complex mesoscopic systems.[52]

Following the above argument, we immediately see that the dynamics of systems in thermodynamic equilibrium are not complex. Indeed, closed (*i.e.*, equilibrium) or linear biochemical systems can not have bistability. Complex behavior arises only from both nonlinear and nonequilibrium systems.[49]

Any realistic mathematical model for biochemical systems has to have bounded long-time behavior simply because of the conservation of atoms in biochemical reactions. Bistability is in fact the simplest system which contains an unstable state while at the same time its long-time dynamics is bounded. The unstable states being the essence of the complexity has a rather long philosophical background. J. C. Maxwell has said "It is manifested that the existence of unstable conditions renders impossible the prediction of future events, if our knowledge of the present state is only approximate, and not accurate." (ref. 53 p. 440).

‖ For simple stochastic dynamics, obtaining the distribution, *i.e.*, histogram, and time correlation function might be sufficient. But if the dynamic process is time dependent, the standard statistical method will no longer apply. See the discussion on stochastic motion *versus* dynamic complexity in ref. 48.

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Prigogine and Stengers[54] have discussed extensively the work of Maxwell. In particular, they have emphasized the philosophical concept of the "singular point(s)" in Maxwell's writing, who also said: "At these (unstable) points, influences whose physical magnitude is too small to be taken account of by a finite being, may produce results of the greatest importance. All great results produced by human endeavour depend on taking advantage of these singular states when they occur." (ref. 53, p. 443). This is an insight which could have profound consequence in our understanding of the biology of cancer,[55] which might be an alternative *functional cellular attractor* in a multi-stable biochemical system.[24]

This line of thinking was also cogently articulated in the writing of Hopfield[56] who considered the complexity in biological systems due to "the large amount of dynamically broken symmetry". The symmetry breakings *via* singular points lead to the "immense amount of information necessary to specify the significant state of biological matter".**

Chemical systems have long been considered a model for understanding complex dynamics.[57] In terms of nonlinear chemical reactions in a finite-size continuous-stirred tank and the Law of Mass Action, a closed chemical reaction system is alway uni-stable.[23,24] This indicates that closed systems exhibit no complex behavior; complex behavior is truely an driven phenonenon in an open system; It is the consequence of interactions between a *system* and its *environment*. Instability is not possible in a closed chemical system, as dictated by the Second Law of Thermodynamics.[5,50]

## 5. Mathematical models and methods

### 5.1 Self-regulating gene

The biochemical kinetics in Fig. 2 can be modeled either in the deterministic ordinary differential eqns (16) or in the stochastic chemical master eqn (17). To obtain the latter, one first draws the master equation graph shown in Fig. 5. Translating this diagrapm into a set of master equations is straightforward.[15] This yields eqn (17).

**Deterministic model.** For the two differential equations in eqn (16), the nullclines in the $c_\alpha$, $x$ plane are:

$$x = \frac{f(\alpha_0 - c_\alpha)}{\hat{h}c_\alpha} \text{ and } x = \frac{\alpha_0 g_\beta + (g_\alpha - g_\beta)c_\alpha}{k}. \tag{25}$$

Since $g_\alpha > g_\beta$, the first nullcline is monotonic decreasing and the second nullcline is monotonic increasing. Hence there is a unique steady state. The steady-state $x^*$ satisfies:

$$\frac{f\alpha_0}{\hat{h}x^* + f} = \frac{kx^* - \alpha_0 g_\beta}{g_\alpha - g_\beta}. \tag{26}$$

Solving the quadratic equation we can obtain $x^*$, which yields $c^*_\alpha$.

**Stochastic model with rapid gene on-and-off.** In this case, $h$, $f \gg g_\alpha, g_\beta$ and $k$ in eqn (17). We then have a rapid equilibrium $p_\beta(n)/p_\alpha(n) = hn/f$ for all $n \geq 0$. Adding the two equations in eqn (17) we obtain a single equation for the total probability $p(n) = p_\alpha(n) + p_\beta(n)$:

$$\frac{\mathrm{d}p(n)}{\mathrm{d}t} = g(n-1)p(n-1) - \{g(n) + \kappa(n)\}p(n) + \kappa(n+1)p(n+1), \tag{27}$$

where the rates of protein synthesis and degradation are

$$g(n) = \frac{fg_\alpha + hng_\beta}{f + hn},\ \kappa(n) = \frac{kn[f + h(n-1)]}{f + hn}. \tag{28}$$

the stationary distribution to eqn (27) is

$$p^{ss}(n) = C\prod_{\ell=1}^{n}\frac{g(\ell-1)}{\kappa(\ell)}, \tag{29}$$

where $C$ is a normalization factor. Since $g_\alpha > g_\beta$, $g(n)$ is a decreasing function of $n$; since $h \gg k$, $\kappa(n)$ is an increasing function of $n$. Thus, the distribution has a single peak, which is located at $\ell^*$ that satisfies

$$g(\ell^* - 1) = \kappa(\ell^*) \Rightarrow \frac{fg_\alpha + h\ell^* g_\beta}{f + h\ell^*} \approx k\ell^*. \tag{30}$$

Here we approximated $\ell^* - 1 \approx \ell^*$ and identified $\alpha_0 = 1/V$. This is the same equation as in eqn (26).

**Stochastic model with slow gene on-and-off.** In this limit, $h$, $f \ll g_\alpha, g_\beta$ and $k$. In this case, we have two Poisson distributions if $h = f = 0$:

$$p_\alpha(n) = \frac{(g_\alpha/k)^n}{n!}e^{-g_\alpha/k},\ p_\beta(n) = \frac{(g_\beta/k)^{n-1}}{(n-1)!}e^{-g_\beta/k}. \tag{31}$$

Substituting these two into eqn (17), one can obtain, for small $h$ and $f$, the total probabilities in $\alpha$ and $\beta$, $P_\alpha$ and $P_\beta$:

$$\frac{hg_\alpha}{k}P_\alpha = fP_\beta,\ P_\alpha + P_\beta = 1. \tag{32}$$

Therefore we have

$$p_{\alpha\cup\beta}(n) = \frac{fg_\alpha^n e^{-g_\alpha/k} + nhg_\alpha g_\beta^{n-1}e^{-g_\beta/k}}{n!k^{n-1}(kf + hg_\alpha)}, \tag{33}$$

which is bimodal.

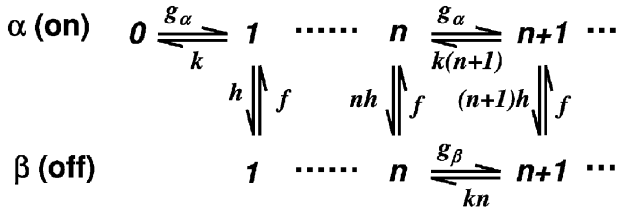


**Fig. 5** The detailed master equation graph[15] for the stochastic model of self-regualting gene shown in Fig. 2. $n$ is the total number of repressor molecules including the one bound to the gene. However only the free repressors can be degradated. The diagram helps to write the chemical master equation (CME) in eqn (17).

### 5.2 Stochastic decision bistability

The mathematics used in this section is elementary probability. The conclusion, however, is illustrated in Fig. 6. When the

** It is worth mentioning that the singular state is an unstable fixed point with a positive eigenvalue, *i.e.*, Lyapunov exponent. Positive Lyapunov exponent is a hallmark of chaotic dynamics which is the standard example for complexity.

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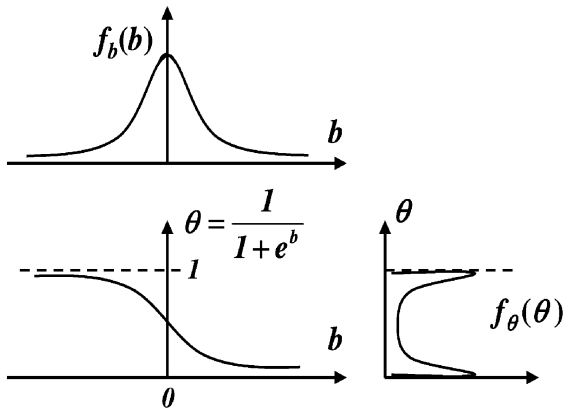


**Fig. 6** The key result of this figure is that if $b$ is Gaussian distributed, then $\theta$ can be bimodal, provided that the variance of the $b$, $\sigma^2 > 2$. The implication for the two-state transition $A \rightleftharpoons B$, with equilibrium constant $K = e^{-\Delta G^\circ/k_B T}$ and fluctuating $\Delta G^\circ$ is discussed in the main text.

fluctuations are slow, we have the steady state $\theta$ given in eqn (20),

$$\theta(b_1, b_2) = \frac{\alpha}{\alpha + \beta} = \frac{1}{1 + ae^{b_1 - b_2}}, \qquad (34)$$

where $a = a_2/a_1$. Since $b_1$ and $b_2$ are independently distributed Gaussian random variables, $b = b_1 - b_2$ is also Gaussian with mean zero and variance $\sigma^2 = \sigma_1^2 + \sigma_2^2$. Therefore, the distribution of $\theta$ is (see Fig. 6):

$$f_\theta(\theta) = \frac{1}{\sqrt{2\pi}\sigma} \exp\left[-\frac{1}{2\sigma^2}\left(\ln\frac{1-\theta}{a\theta}\right)^2\right]\left(\frac{1}{\theta} + \frac{1}{1-\theta}\right). \qquad (35)$$

The distribution $f_\theta(\theta)$ is bimodal if the $\sigma^2$ is sufficiently large. For example, if $a = 1$ we have

$$f_\theta(\theta) = \frac{2}{\sqrt{\pi}\sigma}\left[1 + 4\left(1 - \frac{1}{\sigma^2}\right)\left(\theta - \frac{1}{2}\right)^2 + O\left(\theta - \frac{1}{2}\right)^4\right]. \qquad (36)$$

This means $f_\theta(\theta)$ has a positive curvature at $\theta = \frac{1}{2}$ if $\sigma^2 > 1$. In other words, the distribution is bimodal, as shown in Fig. 6.

### 5.3 Fluctuating "equilibrium constant" $K$ and fluctuating free energy $\Delta G^\circ$

Eqn (34) can also be interpreted as the fraction of molecules in state $A$ for a two-state transition $A \rightleftharpoons B$, with equilibrium constant $K = e^{-\Delta G^\circ/k_B T}$ and fluctuating $\Delta G^\circ$. In the past, fluctuating "equilibrium constant" has been studied[58] but no bistability was reported. This is because in order to exhibit bimodality in $\theta = 1/(1 + K)$, the fluctuation distribution for $K$ has to satisfy certain stringent conditions. For example, for distribution $f_K(K) \propto (\eta + K)^{-\nu}$: one requires $1 < \nu < 2$ and $\eta < \nu/2$. For distribution $f_K(K) \propto K^\nu e^{-\lambda K}$, there is no bimodal behavior for any $\theta$. We use the quotation marks for "equilibrium constant" because a system with fluctuating $\Delta G^\circ$ must be driven; it does not reach a true equilibrium but rather a nonequilibrium steady state.

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