One-Dimensional Birth-Death Process
and Delbrück-Gillespie Theory of Mesoscopic Nonlinear
Chemical Reactions

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As a mathematical theory for the stochastic, nonlinear dynamics of individuals within a population, Delbrück-Gillespie process (DGP) \( n(t) \in \mathbb{Z}^N \) is a birth–death system with state-dependent rates which contain the system size \( V \) as a natural parameter. For large \( V \), it is intimately related to an autonomous, nonlinear ODE as well as a diffusion process. For nonlinear dynamical systems with multiple attractors, the quasi-stationary and stationary behavior of such a birth–death process can be understood in terms of a separation of time scales by a \( T^* \sim e^{\alpha V} \) (\( \alpha > 0 \)): a relatively fast, intra-basin diffusion for \( t \ll T^* \) and a much slower inter-basin Markov jump process for \( t \gg T^* \). In this paper for one-dimensional systems, we study both stationary behavior (\( t = \infty \)) in terms of invariant distribution \( p^{ss}_n(V) \), and finite time dynamics in terms of the mean first passage time (MFPT) \( T_{n_1 \to n_2}(V) \). We obtain an asymptotic expression of MFPT in terms of the “stochastic potential” \( \Phi(x, V) = -(1/V) \ln p^{ss}_x(V) \). We show in general no continuous diffusion process can provide asymptotically accurate representations for both the MFPT and the \( p^{ss}_n(V) \) for a DGP. When \( n_1 \) and \( n_2 \) belong to two different basins of attraction, the MFPT yields the \( T^*(V) \) in terms of \( \Phi(x, V) \approx \phi_0(x) + (1/V)\phi_1(x) \). For systems with saddle-node bifurcations and catastrophe, discontinuous “phase transition” emerges, which can be characterized by \( \Phi(x, V) \) in the limit of \( V \to \infty \). In terms of timescale separation, the relation between deterministic local nonlinear bifurcations, and stochastic global phase transition is discussed. The one-dimensional theory is a pedagogic first step toward a general theory of DGP.

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1. Introduction

Nonlinear ordinary differential equations (ODEs) and diffusion processes are two important mathematical models, respectively, for dynamics of deterministic and stochastic systems. To understand the mathematical properties of these dynamical models, it is obligatory to first have a thorough analysis of one-dimensional (1-D) systems. In the case of a nonlinear ODE, this is

$$\frac{dx(t)}{dt} = b(x),$$

where $x(t)$ is the state of a system at time $t$, and in the case of diffusion processes, it is

$$\frac{\partial u(x,t)}{\partial t} = \frac{\partial}{\partial x} \left( D(x) \frac{\partial u(x,t)}{\partial x} - b(x)u(x,t) \right),$$

in which $u(x,t)$ is the probability density for a system being in state $x$ at time $t$. A wealth of mathematics has been created by thorough investigations of these simple systems. They are now textbook materials with great pedagogic values [1, 2, 3, 4]. When $D(x) = 0$, Equation (1b) is reduced to Equation (1a) via the method of characteristics; (1b) is known as the Liouville equation of (1a) in phase space. The solution to Equation (1b) with vanishing $D(x)$ can be considered as a viscosity solution to the first-order, hyperbolic partial differential equation.

In recent years, in connection to mesoscopic size cellular biochemical dynamics, a new type of mathematical models has emerged: the multi-dimensional birth–death process. An $N$-dimensional birth–death process is a Markov jump process with discrete state $\vec{\ell} \in \mathbb{Z}^N$ and continuous time $t$ [5]. When applied to nonlinear biochemical reaction systems [6], its time-dependent probability mass distribution, $p_{\vec{\ell}}(t)$ satisfies the Chemical Master Equation (CME), first studied by M. Delbrück, while its stochastic trajectories can be sampled according to the Gillespie algorithm [7, 8, 9, 10, 11].

The new theory for the Markov dynamics of population systems deserves more attentions from applied mathematicians [12]. In addition to its own importance in applications, it also provides a unique opportunity for studying the relationship between dynamics at mesoscopic and macroscopic levels, which in the past has been studied mainly in terms of diffusion processes with Brownian noise. It is a widely hold belief that birth–death processes can be approximated by diffusions. This turns out not to be the case for nonlinear systems with multiple attractors, as we show.

With this backdrop in mind, it is again obligatory to first carry out an comprehensive analysis for a 1-D CME system. Doering et al. have conducted an extensive investigation for the asymptotic expressions of the mean first passage time (MFPT) [13, 14]. The aim of this work is not on this per se, but to
illustrate the overall mathematical structure of stochastic nonlinear population
dynamics in terms of the 1-D system.

The CME for a 1-D birth–death process takes the form
\[
\frac{d}{dt} p_n(t) = u_{n-1} p_{n-1}(t) - (w_n + u_n) p_n(t) + w_{n+1} p_{n+1}(t), \quad (n \geq 0) \tag{1c}
\]
in which state-dependent birth and death rates \( u_n(V) \) and \( w_n(V) \) are in general
functions of \( n \) as well as a crucial parameter \( V \), the spatial size or any other
extensive quantity of the reaction system. For chemical systems consisting of
only first-order, linear reactions, both \( u_n \) and \( w_n \) are independent of \( V \) [15,
16, 17]. Linear systems have found wide applications in modeling stochastic
dynamics of single biological macromolecules [9], such as in single-molecule
enzymology and molecular-motor chemomechanics [18, 19, 20, 21].

The dependence on \( V \) gives rise to a very special feature of the theory
of Delbrück-Gillespie processes (DGP) and its corresponding CME: One can
study the important relation between a stochastic dynamical model with a
small \( V \) and a nonlinear deterministic dynamical system with infinitely large \( V \)
[22, 23]. T.G. Kurtz’s theorem precisely establishes such a convergence from
the stochastic trajectories of a DGP to the solution of a nonlinear ODE like
Equation (1a). In the 1-D DGP, each of (1a), (1b), and (1c) has a role. There
is also a substantial difference between the stochastic system (1b) in which
the stochasticity \( D(x) \) and deterministic \( b(x) \) are not related \textit{per se}, while
the stochasticity is intrinsic in the dynamics of (1c). Therefore models based
on diffusion processes are often phenomenological, while the discrete model
provides a more faithful representation of a system’s emerging dynamics based
on individual’s stochastic behavior.

One might be surprised by that there are still significant unresolved
mathematical questions for a 1-D birth–death process. We simply point out
that for large \( V \), the problem under investigation is intimately related to the
Equation (1b) with a singularly perturbed coefficient \( D(x) \propto (1/V) \). This is
still an active area of research on its own [24]. In addition, even though
straightforward, many explicit formulae in connection to the 1-D Equation (1c),
also known as hopping models in statistical physics, had not been obtained
until a need arose from applications. A case in point was the 1983 paper of B.
Derrida [25]. See also [13, 14] for recent work on the asymptotic analysis of the
MFPT problem. Finally, the newly introduced van’t Hoff-Arrhenius analysis
[26] and the analysis for limit cycles [27] both require consistent asymptotic
expansions for large \( V \) beyond the usual leading order.

One of the questions we study in this work can be succinctly described in
terms of the diagram in Figure 1. It is well established that in the limit of large \( V \),
the stationary solution to the 1-D (1c) has a WKB (Wentzel-Kramers-Brillouin)
type asymptotic expansion \( p_n(V) \sim \exp(-V\phi_0(x) - \phi_1(x)) \) where \( x = n/V \)
[4, 28, 29]. In chemical terms, \( n \) is the copy number of a chemical species
Figure 1. Logical schematics showing, for a 1-D DGP, the mathematical relations between infinite-time stationary distribution $p^st_n$, MFPT for finite-time dynamics, and their $V \to \infty$ asymptotics. MFPT for 1-D DGP can be exactly expressed in terms of $p^st_n$ as given in the lower-left box (Equation 24); $p^st_n$ also has an asymptotic form shown in the upper-right box.

For 1-D continuous diffusion, its stationary density function is related to MFPT as shown by the two boxes on the right (Equation 6). The two MFPTs are “analogous” if we identify $w_m$ with $D(z)$ and replace summations with integrals. A remaining question: What is the asymptotic expression for the MFPT in terms of the asymptotic stochastic potential $\phi_1(x)$.

and $x$ is its concentration. Furthermore, it is straightforward to compute the MFPTs for both discrete birth–death processes and continuous diffusion [30, 31]. However it is unclear, as indicated by the question mark in Figure 1, whether and how the MFPT of the birth–death processes in the limit of large $V$ is related to the “stochastic potential function” $\phi_0(x) + (1/V)\phi_1(x)$ obtained from the WKB expansion [28, 29]. This is answered in Equations (25) and (34).

For the stationary solution of Kolmogorov Forward Equation (1c), we now have a good understanding: For nonlinear dynamical systems with two attractors, there is an exponentially large time, $e^{\alpha V}$ ($\alpha > 0$) that separates the intra-basin dynamics in terms of Gaussian processes [11] from the inter-basin dynamics of a Markov jump process between two discrete states. The “boundary layer” in the singularly perturbed problem is precisely where different basins of attraction join [2, 24]. $-e^{-\alpha V}$ is in fact the second largest eigenvalue of the linear system (1c), with zero being the largest one. When $V = \infty$, there is a breakdown of ergodicity [32, 33, 34].

Recognizing this exponentially large time is the key to resolve the so-called Keizer’s paradox [33, 35, 36] which illustrates the two completely different pictures for the “steady states” of a deterministic system and its CME counterpart. It is also the key to understand the difficulty of approximating a CME like (1c) with a diffusion equation like (1b) for systems with multistability [11, 32, 34]. See more discussions later.

The MFPT is the solution to the time-independent backward equation with an inhomogeneous term $-1$ [30, 31]. An ambiguity arises in the asymptotics of MFPT as a WKB solution to the backward Equation [14]. This is reminiscent
of the WKB approach to the stationary forward equation in terms of the nonlinear Hamilton-Jacobi Equation [37]. One of the results in this work, however, is the asymptotic MFPT in relation to the asymptotic stationary solution to the corresponding forward equation.

2. Background on diffusion processes

Because of the intimate relationship between Equations (1c) and (1b), we give a brief summary of the relevant results for 1-D continuous diffusion in Section 2.1. Even though it contains no new mathematical result, the presentation is novel. Then in Section 2.2, we discuss Keizer’s paradox from a novel perspective by considering a second-order correction to the Kramers-Moyal expansion [30, 31].

2.1. Continuous diffusion

For a continuous diffusion process with $\epsilon$-small diffusion coefficient:

$$\frac{\partial f(x, t)}{\partial t} = \frac{\partial}{\partial x} \left( \epsilon D(x) \frac{\partial f}{\partial x} - b(x) f \right), \quad (D(x) > 0) \quad (2)$$

the stochastic potential function

$$\Psi(x) = -\int_0^x \frac{b(z)}{D(z)} \, dz \quad (3)$$

plays a central role in its dynamics. In terms of the $\Psi(x)$, one has the stationary distribution

$$f^{ss}(x) = Ae^{-\frac{1}{\epsilon} \Psi(x)}, \quad (4)$$

where $A$ is a normalization factor. $\Psi(x)$ is also a Lyapunov function of the ODE dynamics $\frac{dx}{dt} = b(x)$ since

$$\frac{d}{dt} \Psi(x(t)) = \frac{d\Psi(x)}{dx} b(x) = -\frac{b^2(x)}{D(x)} \leq 0. \quad (5)$$

Furthermore, the MFPT arriving at $x_2$ starting at $x_1$ with a reflecting boundary at $x_0$ ($x_0 < x_1 < x_2$) is [30, 31]

$$T_{x_1 \to x_2} = \int_{x_1}^{x_2} e^{\Psi(y)/\epsilon} \frac{dz}{D(z)} \int_{y}^{x} e^{-\Psi(z)/\epsilon} \, dy. \quad (6)$$

On the other hand, solving the stationary flux $J$ passing through $x_2$ with Dirichlet boundary value $f(x_2) = 0$, leaving the boundary value at $x_1$ unspecified, but
enforcing a normalization condition $\int_{x_0}^{x_2} f^{ss}(x) dx = 1,$

$$J^{-1} = \int_{x_1}^{x_2} e^{-\Psi(y)/\epsilon} dy \int_{y}^{x_2} e^{\Psi(z)/\epsilon} \frac{dz}{D(z)}. \tag{7}$$

Note that Equations (6) and (7) are exactly the same if $x_0 = x_1$ in (6). To understand the origin of this intriguing observation, consider the following Gedanken experiment: Let a diffusing particle start at $x_1 = x_0$, which is also a reflecting boundary. The particle can only move rightward, and as soon as it hits $x_2 (> x_1)$, one immediately takes it back to $x_1$. Repeating this procedure forms a renewal process. Then the mean renewal time is $T_{x_1 \rightarrow x_2}$ in Equation (6). Now imagine that one connects $x_2$ with $x_1$ to form a circle, and installs a one-way permeable membrane at the $x_2$–$x_1$ junction: a particle that hits from the $x_2$ side goes through the membrane and starts at $x_1$ instantaneously; but a particle that hits from the $x_1$ side is reflected. The stationary distribution for the diffusion particle then satisfies $f^{ss}(x_2) = 0$, $\int_{x_1}^{x_2} f^{ss}(x) dx = 1$, and a constant flux $J(x_1) = J(x_2)$ is the $J$ in Equation (7).

According to the elementary renewal theorem [5], $T_{x_1 \rightarrow x_2} = J^{-1}$.

Another problem which is widely employed in studies of molecular motor uses periodic boundary conditions at $x_1$ and $x_2$. Since there is no one-way permeable membrane, the boundary condition is $f^{ss}(x_1) = f^{ss}(x_2) \neq 0$. The cycle flux (i.e., mean velocity for a single motor) then is

$$J_{\text{cycle}} = \frac{e^{-\Psi(x_2)/\epsilon} - e^{-\Psi(x_1)/\epsilon}}{T_{x_1 \rightarrow x_2} e^{-\Psi(x_2)/\epsilon} + T_{x_2 \rightarrow x_1} e^{-\Psi(x_1)/\epsilon}}.$$  

The renewal process is then replaced by a semi-Markov process which can go both clockwise and counter-clockwise on a circle [38]. Birth–death processes on a circle will be the subject of a forthcoming paper.

2.2. Higher-order Kramers-Moyal expansion and Keizer’s paradox

Keizer’s paradox was originally introduced to understand a discrepancy between the infinite time behavior of a CME and its deterministic counterpart in terms of nonlinear ODE [33, 36]. The resolution is in the vast separation of timescales: the infinitely long time in the ODE is still a very short time in the stochastic dynamics of the CME which involves “uphill climbing” and “barrier crossing.” The same result also explains the discrepancy between the stationary distribution of a CME and the stationary distribution of the corresponding diffusion approximation via a Fokker-Planck Equation [32, 34]. This is now a well-understood subject, intimately related to the finite-time condition required in Kurtz’s convergence theorem [22]: The convergence when $V \rightarrow \infty$ is not uniform with respect to $t$.

We now offer a different, more explicit approach to illustrate the diffusion approximation problem. The diffusion approximation of a CME in terms of a
Fokker-Planck equation is actually a truncated Kramers-Moyal expansion up to $V^{-1}$ [30, 31]. Naturally one can investigate the consequence of keeping the $V^{-2}$ term in the expansion:

$$\frac{d}{dx} \left[ \epsilon^2 a(x) \frac{d^2 u}{dx^2} + \epsilon D(x) \frac{du}{dx} - b(x) u \right] = 0,$$

(8)

where $\epsilon = 1/V$. Applying no-flux boundary condition at $x = \infty$, we have

$$\epsilon^2 a(x) \frac{d^2 u}{dx^2} + \epsilon D(x) \frac{du}{dx} - b(x) u = 0.$$

(9)

We apply the WKB method [2, 39] by assuming the solution to Equation (9) of the form

$$u(x) = \exp \left[ -\frac{1}{\epsilon} \phi_0(x) + \phi_1(x) + \epsilon \phi_2(x) + \cdots \right].$$

(10)

We then substitute the $u(x)$ into Equation (9) and collect terms with the leading order $\epsilon^0$ to yield

$$a(x)(\phi'_0(x))^2 - D(x)\phi'_0(x) - b(x) = 0.$$

(11)

We note that if $a(x) \equiv 0$, then $\phi_0(x) = -\int_0^x (b(z)/D(z))dz$, as given in Equation (3). In this case, a root of $b(x) = 0$, $x^*$, has $\phi'_0(x^*) = 0$ and $\phi''_0(x^*) = -b'(x^*)/D(x^*)$. Hence, a stable fixed point of the ODE $dx/dt = b(x)$ corresponds to a local minimum of $\phi_0(x)$ and a peak in the distribution $e^{-\phi_0(x)/\epsilon}$.

When $a(x) \neq 0$, Equation (11) still indicates that at $x^*$, the root of $b(x) = 0$, $\phi'_0(x^*) = 0$. Furthermore, differentiating Equation (11) with respect to $x$ once, we obtain $\phi''_0(x^*) = -b'(x^*)/D(x)$. Therefore, the local behavior of $\phi_0(x)$ near a fixed point $x^*$ is independent of the higher order terms! However, if $a(x) \neq 0$, then the global behavior of the solution to Equation (11) will have a nonnegligible difference from $-\int_0^x (b(z)/D(z))dz$. This difference contributes to the difference $|\phi_0(x'_+^*) - \phi_0(x'_-^*)|$.

Equation (11) is in fact a third-order truncated version of the exact equation for $\phi'_0(x)$ given by G. Hu [29]:

$$\mu_0(x)(e^{\phi'_0(x)} - 1) + \lambda_0(x)(e^{-\phi'_0(x)} - 1) = 0,$$

(12)

with $b(x) = \mu_0(x) - \lambda_0(x)$, $D(x) = (\mu_0(x) + \lambda_0(x))/2$, and $a(x) = (\lambda_0(x) - \mu_0(x))/6$. The exact, nontrivial, solution to Equation (12) is $\phi'_0(x) = \ln(\lambda_0(x)/\mu_0(x))$, which is given in Equation (16a) below.
3. One-dimensional birth–death processes: stationary distribution and mean first passage time

We now be interested in the Kolmogorov Forward Equation (1c) for the 1-D DGP. To be consistent with the macroscopic Law of Mass Action, we further assume both birth and death rates have asymptotic expansions in the limit of $V, n \to \infty, n/V \to z$:

$$V^{-1}u_x(V) = \mu_0(z) + \frac{\mu_1(z)}{V} + \frac{\mu_2(z)}{V^2} + O(V^{-3}), \quad (13)$$

$$V^{-1}w_x(V) = \lambda_0(z) + \frac{\lambda_1(z)}{V} + \frac{\lambda_2(z)}{V^2} + O(V^{-3}). \quad (14)$$

3.1. Stationary distribution and local behavior near a fixed point

In terms of the birth and death rates $u_n(V)$ and $w_n(V)$, the stationary distribution to Equation (1c) is

$$p_{st}^n = p_{st}^0 \prod_{\ell=0}^{n-1} \frac{u_\ell(V)}{w_{\ell+1}(V)}. \quad (15)$$

With large $V$, applying the lemma in section 7.1 of [40], an extended version of this paper, the asymptotic expansion for $p_{st}^V(V)$ is

$$\ln p_{st}^V(V) \approx \ln f_{st}^V(x) = V \int_0^x \ln \left( \frac{\mu_0(z)}{\lambda_0(z)} \right) dz - \int_0^x \left( \frac{\lambda_1(z)}{\lambda_0(z)} - \frac{\mu_1(z)}{\mu_0(z)} \right) dz - \frac{\ln(\mu_0(x)\lambda_0(x))}{2} + O(V^{-1}), \quad (16)$$

in which we have neglected an $x$–independent term $\ln p_{st}^0(V)$.

We point out that if one applies a diffusion approximation to the master Equation (1c), we obtain the diffusion Equation (1b) with

$$D(x) = \frac{\mu_0(x) + \lambda_0(x)}{2V} + \frac{\lambda_1 + \mu_1 + \lambda_0' - \mu_0'}{2V^2}, \quad \text{and} \quad (17a)$$

$$b(x) = \mu_0(x) - \lambda_0(x) + \frac{1}{V} \left( \mu_1 - \lambda_1 - \frac{1}{2}(\lambda_0' + \mu_0') \right). \quad (17b)$$

Then the stationary distribution to the approximated diffusion process is

$$\ln \tilde{f}(x) = 2V \int_0^x \frac{\mu_0(z) - \lambda_0(z)}{\mu_0(z) + \lambda_0(z)} dz + \int_0^x \frac{\lambda_0(4\mu_1 + \lambda_0' - 3\mu_0') - \mu_0(4\lambda_1 + 3\lambda_0' + 3\mu_0')}{(\mu_0 + \lambda_0)^2} dz + O(V^{-1}), \quad (18)$$

which is different from Equation (16), even in the leading order.
However, it is easy to verify that the leading-order terms in the indefinite integrals in (16) and (18), as functions of \( x \), have matched locations for their extrema as well as their curvatures at each extrema. This is because both

\[
\frac{d \ln f^s(x)}{dx} = V \ln \frac{\mu_0(x)}{\lambda_0(x)} \quad \text{and} \quad \frac{d \ln \tilde{f}(x)}{dx} = 2V \frac{\mu_0(x) - \lambda_0(x)}{\mu_0(x) + \lambda_0(x)}
\]  

are zero at the root of \( b(x) = \mu_0(x) - \lambda_0(x) \). One can further check that both have identical slopes at their corresponding zeros.

Therefore, near a stable fixed point \( x^* \) of \( \frac{dx}{dt} = \mu_0(x) - \lambda_0(x) \):

\[
\mu_0(x^*) = \lambda_0(x^*) \quad \text{and} \quad \mu'(x^*) = \lambda'(x^*)
\]

both approaches yield a same Gaussian process with diffusion equation

\[
\frac{\partial f(\xi, t)}{\partial t} = \lambda_0(x^*) V \frac{\partial^2 f(\xi, t)}{\partial \xi^2} - \frac{\partial}{\partial \xi} ((\mu'(x^*) - \lambda'(x^*))\xi f(\xi, t)),
\]  

(20)

where \( \xi = x - x^* \) is widely called fluctuations in statistical physics. This is Onsager-Machlup’s Gaussian fluctuation theory in the linear regime [11, 41, 42, 43].

### 3.2. Mean first passage time and diffusion approximation

Corresponding to the Kolmogorov forward equation in Equation (1c), the Kolmogorov backward equation for the birth–death process is

\[
\frac{dg_n}{dt} = w_n g_{n-1} - (u_n + w_n) g_n + u_n g_{n+1}.
\]  

(21)

Then, \( T_n (0 \leq n \leq n_2) \), the MFPT arriving at \( n_2 \), starting at \( n \) with a reflecting boundary at 0, satisfies the inhomogeneous equation

\[
w_n T_{n-1} - \left(u_n + w_n\right) T_n + u_n T_{n+1} = -1,
\]  

(22)

with the boundary conditions

\[
T_0 = T_{-1} \quad \text{and} \quad T_{n_2} = 0.
\]  

(23)

The solution can be found in many places, for example, chapter XII in [30] and equation 31 in [13]. The result is most compact when expressed in terms of the stationary distribution \( p^{st}_n(V) \) in Equation (15):

\[
T_{n \to n_2} = \sum_{m=n+1}^{n_2} \sum_{\ell=0}^{m-1} \frac{p^{st}_\ell(V)}{w_m(V) p^{st}_m(V)}.
\]  

(24)

In the limit of large \( V \), one has the asymptotic expression for \( T_{n_1 \to n_2} \) (see again section 7.2 of [40]):

\[
V \int_{x_1}^{x_2} \ln \left[ \frac{\lambda_0(z)}{\mu_0(z)} - 1 \right] \mu_0(z) dz \int_{z}^{\infty} \ln \left[ \frac{\mu_0(y)}{\lambda_0(y)} - 1 \right] \lambda_0(y) e^{V \Phi(y, V)} dy,
\]  

(25)
in which \( x = n/V, \ x_2 = n_2/V, \) and
\[
\Phi(x, V) = -\frac{1}{V} \ln P_{x,V}^{st}(V) = \phi_0(x) + \frac{1}{V} \phi_1(x) + O(V^{-2}), \tag{26}
\]
given in Equation (16).
Comparing Equations (25) and (6), we see that the effective “potential function”
\[
\tilde{\Psi}(x, V) = \Phi(x, V) + \frac{1}{V} \ln \frac{\mu_0(x)/\lambda_0(x) - 1}{\ln \mu_0(x) - \ln \lambda_0(x)}, \tag{27}
\]
and effective diffusion coefficient
\[
\tilde{D}(x) = \frac{1}{\mu_0(x)} \left( \frac{\mu_0(x) - \lambda_0(x)}{\ln \mu_0(x) - \ln \lambda_0(x)} \right)^2. \tag{28}
\]
We note that near \( \mu_0(x) = \lambda_0(x), \)
\[
\tilde{D}(x) \approx \lambda_0(x) \left[ 1 + \frac{(\lambda_0 - \mu_0)^2}{12 \lambda_0^2} \right]. \tag{29}
\]
Following Equation (3), Equations (27) and (28) imply that
\[
\tilde{b}(x) = \left( \frac{1 - \lambda_0(x)/\mu_0(x)}{\ln \mu_0(x) - \ln \lambda_0(x)} \right) (\mu_0(x) - \lambda_0(x)). \tag{30}
\]
As we show, even though the general formula for the MFPT given in Equation (25) has a complex expression for the effective diffusion coefficient \( \tilde{D}(x) \) and effective drift \( \tilde{b}(x), \) the Kramers-like formula for barrier crossing, Equation (34) which only involves \( D(x) \) at the peak of the potential function, is simple and recognizable.
Noting the disagreement between the correct asymptotic Equation (16) and the stationary distribution (18) from the diffusion approximation with \( D(x) \) and \( b(x) \) given in Equation (17), Hänggi et al. proposed an alternative diffusion equation with
\[
D_{hgtt}(x) = \frac{\mu_0(x) - \lambda_0(x)}{\ln \mu_0(x) - \ln \lambda_0(x)}, \quad b(x) = \mu_0(x) - \lambda_0(x), \tag{31}
\]
as a more appropriate approximation for the 1-D Equation (1c) [32]. While the Hänggi-Grabert-Talkner-Thomas diffusion yields the correct leading order stationary distribution (16), we note that the \( D_{hgtt}(x) \) is different from the \( \tilde{D}(x) \) in Eq. (28). In fact,
\[
\frac{D_{hgtt}(x)}{\tilde{D}(x)} = \frac{\ln \mu_0 - \ln \lambda_0(x)}{1 - \lambda_0/\mu_0} < 1 \text{ when } \frac{\lambda_0}{\mu_0} > 1; \quad > 1 \text{ when } \frac{\lambda_0}{\mu_0} < 1, \tag{32}
\]
and near $\mu_0(x) = \lambda_0(x)$,

$$
D_h^{htt}(x) = \lambda_0 \left[ 1 + \frac{\mu_0 - \lambda_0}{2\lambda_0} - \frac{(\lambda_0 - \mu_0)^2}{12\lambda_0^2} \right].
$$

(33)

The Hänggi-Grabert-Talkner-Thomas diffusion process with diffusion and drift given in Equation (31) is the only diffusion process that yields the correct deterministic limit $b(x)$ and asymptotically correct stationary distribution (16). However, the discrepancy between $D_h^{htt}(x)$ and $\tilde{D}(x)$ (Equations 29 and 33) indicates that it will not, in general, give the asymptotically correct MFPT. Therefore, diffusion processes have difficulties in approximating both the correct stationary distribution and the correct MFPT of a birth–death process in the asymptotic limit of large $V$. This conclusion has been dubbed diffusion’s dilemma [11, 44].

3.3. Kramers’ formula and MFPT for barrier crossing

With a correct potential function $\phi_0(x)$, the difference between the discrete DGP with asymptotic large $V$ and continuous approximation disappears in the computations of MFPT for Kramers problem, that is, barrier crossing. This is because, as we have demonstrated, all different approximations can preserve local curvatures at the stable and unstable fixed points. At a fixed point $x^*$ of $b(x)$: $b(x^*) = 0$, and the $D(x^*) = \lambda_0(x^*) = \mu_0(x^*)$ in both Equations (29) and (33). And with a correct “barrier height” and local curvatures at the extrema, the Kramers formula is completely determined.

In fact, applying Laplace’s method and considering an energy barrier between $x_1^* = n_1^*/V$ and $x_2^* = n_2^*/V$, located at $x^\dagger$, Equation (25) can be simplified into (see again section 7.4 of [40] for details)

$$
T^* = T_{n_1 \rightarrow n_2} = \frac{2\pi}{\lambda_0(x^\dagger)\sqrt{\phi_0(x_1^*)(\phi_0'(x^\dagger))}} e^{V\{(\Phi(x_1^*, V) - \Phi(x_1^*, V)) \} \left\{ 1 + O \left( \frac{1}{V} \right) \right\}},
$$

(34)

in which $\Phi(x, V) = \phi_0(x) + (1/V)\phi_1(x)$. Note that Equation (34) contains a $(1/V)\phi_1(x)$ term in the exponent. This is a key result of the present paper, a new feature for the DGP.

Note also that the ambiguity discovered in [14] is associated with MFPT with both starting and end points within a same basin of attraction. It does not appear in Kramers’ formula for inter-basin transition.

The $T^*$ given in Equation (34) plays an all-important role in the dynamics with multiple attractors. It divides the local, intra-basin dynamics from the stochastic, inter-basin jump process. The barrier

$$
V \left( \Phi(x^\dagger, V) - \Phi(x_1^*, V) \right) = V \left\{ \phi_0(x^\dagger) - \phi_0(x_1^*) \right\} + \left\{ \phi_1(x^\dagger) - \phi_1(x_1^*) \right\},
$$

(35)
thus the time $T^*$, can be increasing or decreasing with $V$, depending on $\phi_0(x^{\uparrow}) - \phi_0(x^*_1) > 0$ or $< 0$. This distinction leads to the concept of *nonlinear bistability* versus *stochastic bistability* [10, 26, 45].

4. Nonlinear bifurcation and stochastic phase transition: a potential function perspective

*Bifurcation* is one of the most important characteristics of nonlinear dynamical systems [1, 46]. Therefore, a nonlinear stochastic dynamic theory cannot be complete without a discussion of its stochastic counterpart. Stochastic bifurcation is still a developing area in random dynamical systems [47] and stochastic processes [4]. In fact, the very notion of stochastic bifurcation has at least two definitions: the P- (phenomenological) and D- (dynamic) bifurcations [47]. We shall not discuss the fundamental issues here; rather we provide some observations based on applied mathematical intuition. This discussion is more consistent with the P-bifurcation advocated by E.C. Zeeman [48].

The canonical bifurcations in 1-D nonlinear dynamical systems are *transcritical*, *saddle-node*, and *pitchfork* bifurcations [1]. The saddle-node bifurcation and its corresponding stochastic model have been extensively studied in terms of the Maxwell construction [49]. The key is to realize the separation of timescales, and the different orders in taking limits $V \to \infty$ and $t \to \infty$. The steady states of deterministic nonlinear ODEs are initial value dependent; but the steady state distribution of the stochastic counterpart, in the limit of $V \to \infty$, is unique and independent of the initial value. An ODE finds a “local minimum” of $\Psi(x)$ in the infinite time while its stochastic counterpart finds the “global minimum” at its infinite time.

In this section, We mainly discuss the transcritical bifurcation which has not attracted much attention in the past. We show that in certain cases, it is in fact intimately related to the extinction phenomenon and Keizer’s paradox.

4.1. Transcritical bifurcation

The normal form of transcritical bifurcation is [1]

$$\dot{x} = b(x) \approx \mu(x - x^*) - (x - x^*)^2 \text{ near } x = x^* > 0, \quad (36)$$

in which the locus of bifurcation is at $x = x^*$; It occurs when $\mu = 0$. Transcritical bifurcation is a local phenomenon and the far right-hand side of (36) is the Taylor expansion of $b(x)$ in the neighborhood of $x = x^*$. Let us assume that the system’s lower bound is 0; for an ODE to be meaningful to population dynamics, the $b(0)$ has to be nonnegative. This implies $b(x)$ has another, stable fixed point $x_1^*$, $0 \leq x_1^* < x^*$ when $|\mu|$ is sufficiently small.
Figure 2. Transcritical bifurcation occurs between $\mu_2$ and $\mu_3$ at $x = x^*$, as shown by the solid and dashed black lines in (A), and corresponding stochastic potential $\Phi(x)$ shown in (B). Phase transition(s) can occur between $\mu_1$ and $\mu_2$, and between $\mu_3$ and $\mu_4$, when the global minimum of the potential function $\Psi(x, \mu)$ switches between at $x_1^*$ (blue) and near $x^*$ (solid black). The global minimum is represented by the red curve. The phase transition, therefore, is not really associated with the transcritical bifurcation. A very minor “imperfection” can lead the two black lines, solid and dashed, to become the two green lines. While the transcritical bifurcation disappeared, the phase transitions are still present. The latter phenomenon is structurally stable while the former is not [48]. The bifurcation is local while the phase transitions are global.

At the critical value of $\mu = 0$, the steady state at $x = x^*$ has the form of $\dot{x} = -(x - x^*)^2$. Hence the corresponding potential function, near $x = x^*$, will be

$$
\Psi(x; \mu = 0) = -\int_{x^*}^{x} \frac{b(z)}{D(z)} dz = \frac{(x - x^*)^3}{3D(0)} + O((x - x^*)^4). \quad (37)
$$

Since $D(x) > 0$, the $\Psi(x)$ is neither a minimum nor a maximum at $x = x^*$. There is a minimum of $\Psi(x)$ at $x_1^*$. Now for sufficiently small $\mu \neq 0$, a pair of minimum and maximum develop in the neighborhood of $x^*$, approximately at $x^*$ and $x^* + \mu$. Then by continuity, the newly developed minimum of $\Psi(x, \mu)$ must not be lower than $\Psi(x_1^*, \mu)$. In other words, the stationary distribution of the stochastic dynamics, in the limit of $V \to \infty$, will not be in the neighborhood of the location of a transcritical bifurcation.

However, as in the case of saddle-node bifurcation, phase transition might occurs for larger $|\mu|$. Note that the local minimum associated with the transcritical bifurcation could become the global minimum of $\Phi(x, \mu)$. Then that occurs, there is a phase transition. This is illustrated in Figure 2. Note however, the phase transitions are not associated with the transcritical bifurcation per se: It is really the competition between two stable fixed points, the solid green line and the blue line, $x_1^*$.

If the $x = x^*$ happens at the boundary of the domain of $x$, we have a more interesting scenario. Consider the birth–death system with $u_n(V) = k_1n$ and $w_n(V) = k_{-1}n(n - 1)/V + k_2n$. Then the corresponding $\mu_0(x) = k_1x$, \ldots
\[ \lambda_0(x) = k_{-1}x^2 + k_2x, \text{ and} \]
\[ b(x) = \mu_0(x) - \lambda_0(x) = (k_1 - k_2)x - k_{-1}x^2, \quad x \geq 0. \] (38)

The ODE \( \dot{x} = b(x) \) has a transcritical bifurcation at \( x = 0 \) when \( k_1 - k_2 = 0 \).
When \( k_1 < k_2 \), the system has only a stable fixed point at \( x = 0 \); when \( k_1 > k_2 \), it has a stable fixed point at \( x = \frac{k_1 - k_2}{k_{-1}} \), and \( x = 0 \) is a unstable fixed point.

However, the stochastic stationary distribution has a probability 1 at \( n = 0 \), that is, extinction, for any value of \( k_1 - k_2 \). This is Keizer’s paradox [33].

Therefore, when a transcritical bifurcation occurs at the boundary of a domain, the stochastic steady state exhibit no discontinuous “phase transition.” Rather, the boundary is an absorbing state. On the other hand, when a transcritical bifurcation occurs in the interior of the domain, there might not be phase transition associated with it. Transcritical bifurcation and phase transition are two different phenomena.

4.2. Saddle-node bifurcation

The normal form of saddle-node bifurcation is [1]
\[ \dot{x} = b(x) \approx \mu - x^2 \quad \text{near} \quad x = 0, \] (39)
in which the locale of bifurcation is again at \( x = 0 \) and it occurs when \( \mu = 0 \). Again, it is clear that the stochastic phase transition is not associated with a single saddle-node bifurcation event per se. However, it is necessitated by the two saddle-node bifurcation events in a catastrophe phenomenon, which has a deeper topological root. This is illustrated in Figure 3.

5. Summary

Multidimensional DGP have been widely employed in recent years as a dynamic theory for single-cell biochemistry. It is applicable to population systems with individual, “agent-based” stochastic nonlinear dynamics, and long-time discontinuous stochastic evolution [10, 11]. The dynamics of such a process is intimately related to both nonlinear ODEs and multidimensional diffusion processes. In this paper, we have systematically studied the simplest, 1-D system. Steijaert et al. [50] have also presented a summary for the CME with a single variable.

One of the special features of a DGP is a parameter \( V \), the system size. When \( V \to \infty \), the trajectory of a DGP becomes the solution to an ODE. Near a fixed point of the ODE, a continuous Gaussian diffusion process captures the asymptotic large \( V \) stochastic behavior. However, for a system with multiple stable fixed points, no continuous diffusion can be a faithful asymptotic that correctly represents both global multimodal stationary distribution as well as
Figure 3. (A) Two saddle-node bifurcations together give the catastrophe phenomenon. At the four different parameter $\mu$ values, the stochastic potential has a single minimum ($\mu_1$), then passing through saddle-node bifurcation to have two minima, with the lower one being the global minimum ($\mu_2$). Then at $\mu_3$, the global minimum is the upper one. And finally at $\mu_4$, saddle-node bifurcation leads again to a single steady state. The stochastic phase transition occurs between $\mu_2$ and $\mu_3$, denoted by the red dashed line known as the Maxwell construction [49]. The stochastic potential $\Psi(x)$ corresponding to the four $\mu$’s are illustrated below the bifurcation diagram. (B) Two saddle-node bifurcations occur at $\mu_1$ and $\mu_2$. In this case, however, there is no phase transition, as illustrated by the given $\Psi(x)$ below the bifurcation diagram. The two minima do not switch their positions as in (A).

local Gaussian dynamics. In fact, it is known that the two limits $V \to \infty$ and $t \to \infty$ can not exchange: For system with multiple stable fixed points undergoing cusp catastrophe, the limit of $t \to \infty$ followed with $V \to \infty$ yields a discontinuous phase transition, defined as the switching of global minimum in stochastic potential $\Phi(x, \mu)$ (Figure 3A). This paper also studied transcritical bifurcation, and shows it might or might not yield a phase transition in terms of the $\Phi(x, \mu)$ (Figure 2B). In fact, transcritical bifurcation is not a structurally stable phenomenon but phase transition is. 1-D nonlinear bifurcations are local while a phase transition is global.

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References

1. L. Perko, *Differential Equations and Dynamical Systems*, Vol. 7 (3rd ed.), Springer, New York, 2001.
2. R. E. O'Malley, *Singular Perturbation Methods for Ordinary Differential Equations*, Vol. 89: Applied Mathematical Science, Springer-Verlag, New York, 1991.
3. R. M. Mazo, *Brownian Motion: Fluctuations, Dynamics, and Applications*, Vol. 112: International Series of Monographs on Physics, Oxford University Press, U.K., 2002.
4. Z. Schuss, *Theory and Applications of Stochastic Processes: An Analytical Approach*, Vol. 170: Applied Mathematical Science, Springer, New York, 2010.
5. H. Taylor and S. Karlin, *An Introduction to Stochastic Modeling*, 3rd ed., Academic Press, New York, 1998.
6. I. R. Epstein and J. A. Poiman, *An Introduction to Nonlinear Chemical Dynamics: Oscillations, Waves, Patterns, and Chaos*, Oxford University Press, U.K., 1998.
7. D. A. McQuarrie, Stochastic approach to chemical kinetics, *J. Appl. Prob.* 4:413–478 (1967).
8. D. T. Gillespie, Stochastic simulation of chemical kinetics, *Ann. Rev. Phys. Chem.* 58:35–55 (2007).
9. H. Qian and L. M. Bishop, The chemical master equation approach to nonequilibrium steady-state of open biochemical systems, *Int. J. Mol. Sci.* 11:3472–3500 (2010).
10. H. Qian, Cellular biology in terms of stochastic nonlinear biochemical dynamics, *J. Stat. Phys.* 141:990–1013 (2010).
11. H. Qian, Nonlinear stochastic dynamics of mesoscopic homogeneous biochemical reactions systems - An analytical theory, *Nonlinearity* 24:R19–R49 (2011).
12. T. G. Kurtz, *Approximation of Population Processes*, SIAM Publication, Philadelphia, PA, 1987.
13. C. R. Doering, K. V. Sargsyan, and L. M. Sander, Extinction times for birth-death processes: Exact results, continuum asymptotics, and the failure of the Fokker-Planck approximation, *Multiscale Modeling Simul.* 3:282–299 (2005).
14. C. R. Doering, K. V. Sargsyan, L. M. Sander, and E. Vanden-Eijnden, Asymptotics of rare events in birth-death processes bypassing the exact solutions, *J. Phys. Cond. Matt.* 19:065145 (2007).
15. C. Gadgil, C. H. Lee, and H. G. Othmer, A stochastic analysis of first-order reaction networks, *Bull. Math. Biol.* 67:901–946 (2005).
16. W. J. Heuett and H. Qian, Grand canonical Markov model: A stochastic theory for open nonequilibrium biochemical networks, *J. Chem. Phys.*, 124:044110 (2006).
17. T. Jahnke and W. Huisinga, Solving the chemical master equation for monomolecular reaction systems analytically, *J. Math. Biol.* 54:1–26 (2007).
18. H. Qian and E. L. Elson, Single-molecule enzymology: Stochastic Michaelis-Menten kinetics. *Biophys. Chem.* 101:565–576 (2002).
19. H. Qian, Cooperativity and specificity in enzyme kinetics: A single-molecule time-based perspective. *Biophys. J.* 95:10–17 (2008).
20. Y. Zhang and M. E. Fisher, Dynamics of the tug-of-war model for cellular transport, *Phys. Rev. E.* 82:011923 (2010).
21. Y. Zhang and M. E. Fisher, Measuring the limping of processive motor proteins, *J. Stat. Phys.* 142:1218–1251 (2011).
22. T. G. Kurtz, Limit theorems for sequences of jump Markov processes approximating ordinary differential processes, *J. Appl. Prob.* 8:344–356 (1971).
23. J. Keizer, The McKeans model, Kac's factorization theorem, and a simple proof of Kurtz's limit theorem, in *Probability, Statistical Mechanics, and Number Theory: A Volume Dedicated to Mark Kac*, (G.-C. Rota Ed.), pp. 1–23, Academic Press, New York, 1986.
24. R. E. O’MALLEY, Singularity perturbed linear two-point boundary value problems, *SIAM Rev.* 50:459–482 (2008).
25. B. DERRIDA, Velocity and diffusion constant of a periodic one-dimensional hopping model, *J. Stat. Phys.* 31:433–450 (1983).
26. Y. ZHANG, H. GE, and H. QIAN, van’t Hoff-Arrhenius analysis of transition rate dependence upon system’s size: Stochastic vs. nonlinear bistabilities in population dynamics, Available at: http://arXiv.org/abs/1011.2554 (2010).
27. H. GE and H. QIAN, Landscapes of non-gradient dynamics without detailed balance: Stable limit cycles and multiple attractors, *Chaos*, 22:023140 (2012).
28. G. NICOLIS and J. W. TURNER, Stochastic analysis of a nonequilibrium phase transition: Some exact results, *Physica A* 89:326–338 (1977).
29. G. HU, Lyapounov function and stationary probability distributions. *Zeit. Phys. B* 65:103–106 (1986).
30. N. G. Van KAMPEN, *Stochastic Processes in Physics and Chemistry*, Rev. and enl. ed., Elsevier Science, North-Holland, 1992.
31. C. W. GARDINER, *Handbook of Stochastic Methods for Physics, Chemistry, and the Natural Sciences*, 2nd ed., p. 263, Springer, New York, 1985.
32. P. HÄNGGI, H. GRABERT, P. TALKNER, and H. THOMAS, Bistable systems: Master equation versus Fokker-Planck modeling, *Phys. Rev. A*. 29:371–378 (1984).
33. M. VELLELA and H. QIAN, A quasistationary analysis of a stochastic chemical reaction: Keizer’s paradox, *Bull. Math. Biol.* 69:1727–1746 (2007).
34. M. VELLELA and H. QIAN, Stochastic dynamics and nonequilibrium thermodynamics of a bistable chemical system: The Schlögl model revisited, *J. R. Soc. Interf.* 6:925–940 (2009).
35. J. NEWBY and J. P. KEENER, An asymptotic analysis of the spatially-inhomogeneous velocity-jump process, *Multiscale Modeling Simul.* 9:735–765 (2011).
36. P. CHILDS and J. P. KEENER, Slow manifold reduction of a stochastic chemical reaction: Exploring Keizer’s paradox, *Disc. Continu. Dyn. Sys. B* 42:1775–1794 (2012).
37. 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).
38. H. QIAN and X. S. XIE, Generalized Haldane equation and fluctuation theorem in the steady state cycle kinetics of single enzymes, *Phys. Rev. E*. 74:010902(R) (2006).
39. J. D. MURRAY, *Asymptotic Analysis*, Vol. 48: Applied Mathematical Science, Springer-Verlag, New York, 1984.
40. Y. ZHANG, H. GE, and H. QIAN, One-dimensional death-birth process and Delbrück-Gillespie theory of mesoscopic nonlinear chemical reactions, Available at: http://arXiv.org/abs/1207.4214 (2012).
41. L. ONSAGER and S. MACHLUP, Fluctuations and irreversible processes, *Phys. Rev.* 91:1505–1512 (1953).
42. J. KEIZER, On the macroscopic equivalence of descriptions of fluctuations for chemical reactions, *J. Math. Phys.* 18:1316–1321 (1977).
43. H. QIAN, Mathematical formalism for isothermal linear irreversibility. *Proc. R. Soc. A Math. Phys. Engr. Sci.* 457:1645–1655 (2001).
44. D. ZHOU and H. QIAN, Fixation, transient landscape and diffusion’s dilemma in stochastic evolutionary game dynamics, *Phys. Rev. E* 84:031907 (2011).
45. L. M. BISHOP and H. QIAN, Stochastic bistability and bifurcation in a mesoscopic signaling system with autocatalytic kinase, *Biophys. J.* 98:1–11 (2010).
46. Y. KUZNETSOV, *Elements of Applied Bifurcation Theory*, Vol. 112: Applied Mathematical Science (3rd ed.), Springer, New York, 2004.
47. L. Arnold, Random Dynamical Systems, Springer, New York, 1998.
48. E. C. Zeeman, Stability of dynamical systems, Nonlinearity 1:115–155 (1988).
49. 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).
50. M. N. Steijaert, A. M. L. Liekens, D. Bošnački, P. A. J. Hilbers, and H. M. M. Ten Hikelder, Single-variable reaction systems: Deterministic and stochastic models, Math. Biosci. 227:105–116 (2010).

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