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Review article

SDE decomposition and A-type stochastic interpretation in nonequilibrium processes

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An innovative theoretical framework for stochastic dynamics based on the decomposition of a stochastic differential equation (SDE) into a dissipative component, a detailed-balance-breaking component, and a dual-role potential landscape has been developed, which has fruitful applications in physics, engineering, chemistry, and biology. It introduces the A-type stochastic interpretation of the SDE beyond the traditional Ito or Stratonovich interpretation or even the α-type interpretation for multidimensional systems. The potential landscape serves as a Hamiltonian-like function in nonequilibrium processes without detailed balance, which extends this important concept from equilibrium statistical physics to the nonequilibrium region. A question on the uniqueness of the SDE decomposition was recently raised. Our review of both the mathematical and physical aspects shows that uniqueness is guaranteed. The demonstration leads to a better understanding of the robustness of the novel framework. In addition, we discuss related issues including the limitations of an approach to obtaining the potential function from a steady-state distribution.

Keywords nonequilibrium statistical physics, nonequilibrium potential, Lyapunov function, nonlinear stochastic dynamics, systems biology

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The concept of landscape in biology, originally proposed by Wright as the adaptive landscape [1] and by Waddington as the developmental landscape [2], has been developing with relevant applications in biology and beyond [3–6]. The merging of the landscape concept with a fundamental concept from physics, i.e., the potential function or Hamiltonian, further provides a solid mathematical basis for quantitative discussions [7–13]. Specifically, the intuitive picture in which stable states appear as valleys and transition states appear as passes in a potential landscape enables quantitative description of spontaneous transitions between biological phenotypes, including cell fate decisions [4, 6] as well as the genesis and development of complex diseases [14, 15]. In this paper, we review a novel framework for constructing a potential landscape in general nonlinear stochastic dynamics written in the form of a stochastic differential equation (SDE) or Langevin equation with multiplicative noise in physics. The landscape is constructed by decomposing the original SDE (velocity equation) into a force equation with three components: a dissipative force, a transverse force corresponding to the breaking of detailed balance, and a gradient of the potential landscape. The framework is therefore referred to as SDE decomposition.

SDE decomposition leads to the A-type stochastic interpretation, which is distinct from the widely used Ito or Stratonovich interpretation. A unique advantage of the A-type stochastic interpretation is the invariance of the potential landscape under non-small or even large random fluctuations [16], which distinguishes the SDE decomposition framework from those valid for small noise, such as the Wentzel–Kramers-Brillouin method or quasi-potential theory. The invariance is established by the Lyapunov property of the potential function [11] and the Boltzmann–Gibbs-type steady-state distribution separating the potential function and the noise. A series of high-dimensional cancer models, including hepatocellular [17], prostate [18], gastric [19], and acute promyelo-

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cytic leukemia models [20], have been built accordingly on the basis of an endogenous molecular–cellular network hypothesis that cancer corresponds to robust state(s) in a potential landscape emerging from the dynamics of an evolutionarily formed endogenous molecular–cellular network [14, 15]. We show that the potential landscape, which is an important concept originating in equilibrium statistical physics, can be extended to general nonequilibrium scenarios. Confusion in a recent discussion [21] of our framework is also addressed, as a supplement to our Comment [22].

1 Original demonstration

In 2004 [7], SDE decomposition was formulated for a given n-dimensional SDE (which could be considered as a velocity equation in physics),

$$\dot{\boldsymbol{q}} = \frac{\mathrm{d}\boldsymbol{q}}{\mathrm{d}t} = \boldsymbol{f}(\boldsymbol{q}) + N(\boldsymbol{q})\zeta(t), \quad \text{(SDE, Velocity equation)}$$

where $\zeta(t)$ is an l-dimensional vector Gaussian white noise with $\langle\zeta(t)\rangle = 0$ and $\langle\zeta(t)\zeta^\tau(t')\rangle = 2\epsilon\delta(t-t')I$ (I is the $l \times l$ identity matrix, and τ denotes the matrix transpose). $N(\boldsymbol{q})$ is an $n \times l$ matrix that depends on the state variable $\boldsymbol{q}$. The equation $N(\boldsymbol{q})N^\tau(\boldsymbol{q}) = D(\boldsymbol{q})$ defines a fluctuation–dissipation relation (where $D(\boldsymbol{q})$ is the diffusion matrix). Through a transformation to a force equation, decomposition of the SDE into three components would be feasible: a potential function (landscape) $\phi(\boldsymbol{q})$ (a scalar function), a dissipative matrix $S(\boldsymbol{q})$ (symmetric and semi-positive definite), and a transverse matrix $A(\boldsymbol{q})$ (antisymmetric; this part may correspond to the Lorentz force in two or three dimensions):

$$[S(\boldsymbol{q})+A(\boldsymbol{q})]\dot{\boldsymbol{q}} = -\nabla\phi(\boldsymbol{q}) + \hat{N}(\boldsymbol{q})\xi(t), \quad \text{(Force equation)}$$

where $\xi(t)$ is also an l-dimensional vector Gaussian white noise $\langle\xi(t)\rangle = 0$ and $\langle\xi(t)\xi^\tau(t')\rangle = 2\epsilon\delta(t-t')I$, and $\hat{N}(\boldsymbol{q})$ is an $n \times l$ matrix. $\hat{N}(\boldsymbol{q})\hat{N}^\tau(\boldsymbol{q}) = S(\boldsymbol{q})$ defines another fluctuation–dissipation relation. The transformation generates [7, 8] two equations that determine the matrices $S(\boldsymbol{q})$ and $A(\boldsymbol{q})$ by the potential condition in Eq. (1a) and the generalized Einstein relation in Eq. (1b):

$$\nabla \times \{[S(\boldsymbol{q}) + A(\boldsymbol{q})]\,\boldsymbol{f}(\boldsymbol{q})\} = 0, \tag{1a}$$

$$[S(\boldsymbol{q}) + A(\boldsymbol{q})]D(\boldsymbol{q})[S(\boldsymbol{q}) - A(\boldsymbol{q})] = S(\boldsymbol{q}), \tag{1b}$$

where $\boldsymbol{f}(\boldsymbol{q})$ is the deterministic drift velocity, and $D(\boldsymbol{q})$ is the diffusion matrix. Both of them are given by the SDE. The differential operator $\nabla \times \boldsymbol{q} = \partial_i q_j - \partial_j q_i$ is generalized for an arbitrary n-dimensional vector $\boldsymbol{q}$. In principle, the n^2 unknowns in $[S(\boldsymbol{q}) + A(\boldsymbol{q})]$ can be determined by solving the $n(n-1)/2$ partial differential equations in Eq. (1a) under boundary conditions (for the matrices $S(\boldsymbol{q})$ and $A(\boldsymbol{q})$), together with the $n(n+1)/2$ equations given by Eq. (1b) (n^2 unknowns and n^2 equations).

If $S(\boldsymbol{q})+A(\boldsymbol{q})$ is invertible, we can derive the following from Eq. (1b):

$$\begin{aligned} D(\boldsymbol{q}) &= [S(\boldsymbol{q}) + A(\boldsymbol{q})]^{-1}\frac{1}{2}\{[S(\boldsymbol{q}) + A(\boldsymbol{q})] \\ &\quad + [S(\boldsymbol{q}) - A(\boldsymbol{q})]\}[S(\boldsymbol{q}) - A(\boldsymbol{q})]^{-1} \\ &= \frac{1}{2}\left\{[S(\boldsymbol{q}) + A(\boldsymbol{q})]^{-\tau} + [S(\boldsymbol{q}) + A(\boldsymbol{q})]^{-1}\right\}, \end{aligned} \tag{2}$$

which implies that the symmetric part of the inverse matrix of $S(\boldsymbol{q}) + A(\boldsymbol{q})$ is the diffusion matrix $D(\boldsymbol{q})$. Therefore, the relation $[S(\boldsymbol{q}) + A(\boldsymbol{q})]^{-1} = D(\boldsymbol{q}) + Q(\boldsymbol{q})$ is obtained, where $Q(\boldsymbol{q})$ is defined as the antisymmetric part of the inverse matrix. Therefore, the following decomposed velocity equation is obtained:

$$\dot{\boldsymbol{q}} = -[D(\boldsymbol{q}) + Q(\boldsymbol{q})]\nabla\phi(\boldsymbol{q}) + N(\boldsymbol{q})\zeta(t). \quad \text{(Decomposed SDE/velocity equation)}$$

Equation (1) may be transformed into a more standard but equivalent form by rewriting Eqs. (1a) and (1b) as

$$\nabla \times \{[D(\boldsymbol{q}) + Q(\boldsymbol{q})]^{-1}\boldsymbol{f}(\boldsymbol{q})\} = 0, \tag{3}$$

where $n(n-1)/2$ partial differential equations determine the $n(n-1)/2$ unknowns in the antisymmetric matrix Q with the necessary boundary conditions for Q. One class of boundary conditions employed is that near fixed points, every component of Q is independent of the state variables [7, 23]. For general situations, it can be assumed without loss of generality that both D and $\boldsymbol{f}$ are smooth functions of state variables. Boundary conditions are naturally obtained from the actual problem under study. According to the theory of partial differential equations, the existence and uniqueness of the solution could be guaranteed at least locally [24].

From Fig. 1, we can see that Eq. (1b) is a result of taking the zero-mass limit of the $2n$-dimensional Newton's equation with noise on the differential equations for $\boldsymbol{p}$. Meanwhile, the classic Einstein relation corresponds to taking the overdamped limit. Because the zero-mass limit can further keep the transverse matrix A and Q (e.g., the Lorentz force), we call it a generalized Einstein relation. References in the literature to the "generalized Einstein relation" are also ambiguous [21]. On this question of nomenclature, we may refer to a classic textbook by Kubo [25] that is widely acknowledged: There are two fundamental expressions of the fluctuation–dissipation theorem (FDT); the first expression relates the mobility (diffusion) to the correlation function of the velocity [corresponding to our $N(\boldsymbol{q})N^\tau(\boldsymbol{q}) = D(\boldsymbol{q})$], and the second expression connects the resistance (friction) to the correlation function of the random force [corresponding to our

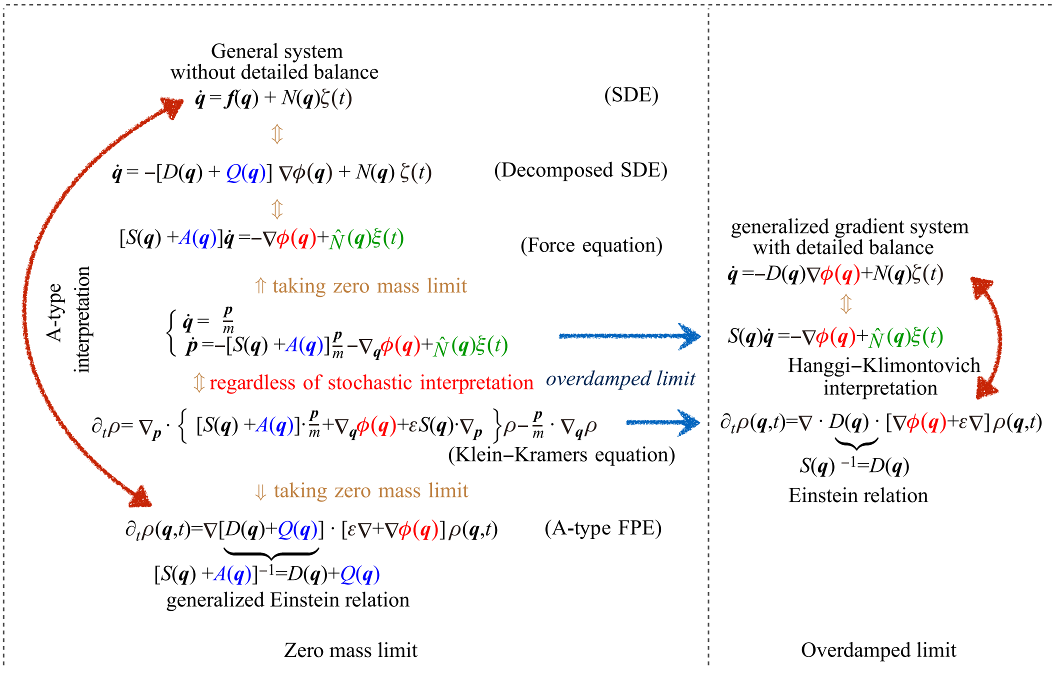

Fig. 1 A-type interpretation can be derived as the zero-mass limit of a $2n$-dimensional Newton's equation with noise and its corresponding Klein–Kramers equation simultaneously. In an abstract state space, the representative point of the system's state can always be considered as a zero-mass particle.

$\hat{N}(\boldsymbol{q})\hat{N}^\tau(\boldsymbol{q}) = S(\boldsymbol{q})]$. The Einstein relation describes the connection between diffusion and friction. These definitions have clear physical meaning and are directly distinguishable. The two FDTs microscopically define the diffusion matrix $D(\boldsymbol{q})$ and the friction matrix $S(\boldsymbol{q})$ and enable us to measure them independently in experiments. Therefore, the generalized Einstein relation in Eq. (1b) can be experimentally tested.

The Hamilton–Jacobi equation for the potential function can be derived directly from the decomposition $\boldsymbol{f}(\boldsymbol{q}) = -[D(\boldsymbol{q}) + Q(\boldsymbol{q})]\nabla\phi(\boldsymbol{q})$, as noted before [8]:

$$\boldsymbol{f}(\boldsymbol{q}) \cdot \nabla\phi(\boldsymbol{q}) + \nabla\phi(\boldsymbol{q}) \cdot D(\boldsymbol{q}) \cdot \nabla\phi(\boldsymbol{q}) = 0. \tag{4}$$

This is the equation employed in Freidlin–Wentzell's quasi-potential theory [9] to solve the potential landscape valid under the weak noise limit, owing to the use of Ito's interpretation. Because our approach is based on the A-type stochastic interpretation (discussed later), it is not limited to small noise, but is valid for arbitrary noise intensities.

The uniqueness of the solution to Eq. (1) has been rigorously proved for linear stochastic processes, including Ornstein–Uhlenbeck processes. If $\boldsymbol{f}(\boldsymbol{q}) = F\boldsymbol{q}$ and any two eigenvalues λ_i and λ_j of the matrix F satisfy $\lambda_i + \lambda_j \neq 0$, the existence and uniqueness of $[S + A]$ in the entire state space are guaranteed by a theorem for the Lyapunov equation [11, 26], where S and A are independent of the state variables provided as a conventional boundary condition for linear processes. Note that the condition $\lambda_i + \lambda_j \neq 0$ is not essential, as has been demonstrated using explicit expressions [23]. There is also a gradient expansion scheme for Eq. (1) with boundary conditions [7, 8] and for linear stochastic processes in which all higher orders vanish.

The uniqueness of the solution of Eq. (1) could also be argued from physical considerations. The two fluctuation–dissipation relations define the diffusion matrix D and friction matrix S, respectively. The transverse matrix A can be related to an effective magnetic field. The physical meanings of S and A are apparent, and they can in principle be measured independently. It is unlikely in a real physical process that two sets of distinct results could be obtained.

1.1 A-type interpretation

Figure 1 presents a summary of the A-type formulation as the generalization of the Hanggi–Klimontovich interpretation [27] to nonequilibrium processes without detailed balance. The starting point is a $2n$-dimensional Newton's equation with noise in the $\boldsymbol{p}$ (momentum) dynamics. It can be shown that for this equation, there is no ambiguity in using stochastic integration; i.e., all stochastic interpretations lead to the same result: a

Klein–Kramers equation for the time evolution of the probability distribution. A derivation using the path integral can be found in Ref. [8]. The A-type interpretation is achieved by taking the zero-mass limit instead of the well-known overdamped limit for the $2n$-dimensional Newton's equation and its corresponding Klein–Kramers equation simultaneously. The distinction is that an antisymmetric matrix $A(\boldsymbol{q})$ or $Q(\boldsymbol{q})$ (corresponding to breaking of the detailed balance) could be preserved. This leads to a natural generalization of the Einstein relation and experimentally testable predictions. The zero-mass-limit justification of SDE decomposition [8, 28] is in fact an explicit realization of a stochastic integration: first, the usual, for example, Ito stochastic integration and then the zero-mass limit. It is not the usual stochastic integration in a standard textbook, as we have already recognized "beyond Ito vs. Stratonovich" [8]. It is possible that a more conventional form could be found.

2 An alternative but nonequivalent demonstration

An alternative but nonequivalent demonstration was recently proposed by Zhou and Li [21]. Their starting point was not the definition of SDE decomposition in Eq. (1) (as mentioned in their paper). They instead used the Hamilton–Jacobi equation to solve the potential function $\phi(\boldsymbol{q})$; this equation explicitly eliminates the antisymmetric matrix $Q(\boldsymbol{q})$. They then tried to use ϕ to reconstruct the dynamical matrix Q and found that there were multiple choices of Q in their Theorem 2. We note that this protocol is not equivalent to the original definition of SDE decomposition, in that the necessary boundary conditions for Q are missing. In fact, a rough estimation of the degrees of freedom found in their Theorem 2 is straightforward. There are $(n-1)n/2$ boundary conditions missing for solving Q in Eq. (3), but $n-1$ boundary conditions are already specified in solving ϕ using the Hamilton–Jacobi equation; thus, the number of undetermined degrees of freedom is $(n-1)n/2-(n-1) = (n-1)(n-2)/2$, which corresponds to their conclusion in Theorem 2.

From a physical viewpoint, the problem of the missing boundary conditions becomes more evident. Let us consider a symmetric problem:

$$[S(\boldsymbol{q})+A(\boldsymbol{q})]\boldsymbol{f}(\boldsymbol{q})=[S'(\boldsymbol{q})+A'(\boldsymbol{q})]\boldsymbol{f}(\boldsymbol{q})=-\nabla\phi(\boldsymbol{q}), \quad (5)$$

$$\begin{aligned} S'(\boldsymbol{q}) &= S(\boldsymbol{q}) + \Delta S(\boldsymbol{q}), \\ A'(\boldsymbol{q}) &= A(\boldsymbol{q}) + \Delta A(\boldsymbol{q}), \\ \Delta S(\boldsymbol{q})\boldsymbol{f}(\boldsymbol{q}) &= -\Delta A(\boldsymbol{q})\boldsymbol{f}(\boldsymbol{q}). \end{aligned} \quad (6)$$

For a given $\phi(\boldsymbol{q})$, there are obviously multiple choices of S and A, such as S' and A', that satisfy Eq. (6). The physical meaning here is straightforward; the frictional force $S(\boldsymbol{q})\boldsymbol{f}(\boldsymbol{q})$, the Lorentz force $A(\boldsymbol{q})\boldsymbol{f}(\boldsymbol{q})$, and the electrostatic potential $\phi(\boldsymbol{q})$ can be tuned independently in an experiment. Given only the electrostatic potential $\phi(\boldsymbol{q})$, one cannot determine the experimental system; there can exist an arbitrary but canceled-out force between the frictional force and the Lorentz force, $\Delta S(\boldsymbol{q})\boldsymbol{f}(\boldsymbol{q}) = -\Delta A(\boldsymbol{q})\boldsymbol{f}(\boldsymbol{q})$, as shown in Fig. 2. To specify the real situation, boundary conditions for the friction and magnetic field should be provided, as for Eq. (1). The case for Q is similar owing to the symmetry between Eqs. (5) and (9) [Eq. (B1) in Ref. [21]].

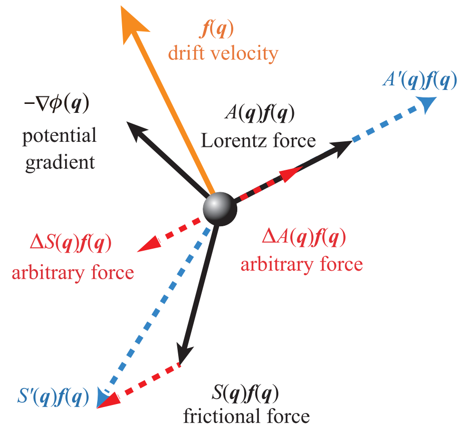

Fig. 2 Without necessary boundary conditions, there are multiple physical realizations of Eq. (5). The extra freedom corresponds to arbitrary canceled-out forces perpendicular to the drift velocity. These realizations may not lead to any physically observable consequence, similar to the reference point (integral constant) for a potential.

Furthermore, regardless of the multiple choices of $Q(\boldsymbol{q})$ resulting from the missing boundary conditions, the steady-state distribution for the A-type Fokker–Planck equation (FPE) is still uniquely determined. If it is normalizable, the A-type FPE

$$\partial_t\rho(\boldsymbol{q},t)=\nabla\cdot[D(\boldsymbol{q})+Q(\boldsymbol{q})]\cdot[\epsilon\nabla+\nabla\phi(\boldsymbol{q})]\rho(\boldsymbol{q},t), \quad (7)$$

has a steady-state solution):

$$\rho_s(\boldsymbol{q}) = \frac{1}{Z(\epsilon)}\exp\left(-\frac{\phi(\boldsymbol{q})}{\epsilon}\right). \quad (8)$$

For the multiple solutions Q and Q' of Eq. (B1) in [21],

$$[D(\boldsymbol{q}) + Q(\boldsymbol{q})]\nabla\phi(\boldsymbol{q}) = [D(\boldsymbol{q}) + Q'(\boldsymbol{q})]\nabla\phi(\boldsymbol{q}) = -\boldsymbol{f}(\boldsymbol{q}), \quad (9)$$

$$Q'(\boldsymbol{q}) = Q(\boldsymbol{q}) + \Delta Q(\boldsymbol{q}), \quad \Delta Q(\boldsymbol{q})\nabla\phi(\boldsymbol{q}) = 0. \quad (10)$$

Because $\nabla\rho_s(\boldsymbol{q}) \propto \nabla\phi(\boldsymbol{q})\cdot\rho_s(\boldsymbol{q})$, Eq. (8) is still a steady-state solution of the A-type FPE, Eq. (7), for arbitrary Q'. Obtaining a steady-state distribution is sufficient in many applications, e.g., calculating the spontaneous transition rates between stable states; therefore, the A-type framework has sufficient robustness to generate the steady-state distribution even if no boundary conditions are specified for the matrices.

3 Examples of constructing nonequilibrium potentials

To illustrate, we first examine a straightforward example, which is a simple planar limit cycle system with constant diffusion:

$$\begin{cases} \dot{q}_1 = -q_2 + q_1(1 - q_1^2 - q_2^2) + \xi_1(t), \\ \dot{q}_2 = q_1 + q_2(1 - q_1^2 - q_2^2) + \xi_2(t). \end{cases} \tag{11}$$

Here $\langle \xi_i(t)\xi_j(t')\rangle = 2\epsilon\delta_{ij}\delta(t-t')$, where δ_{ij} is the Kronecker delta function. The diffusion matrix $D = I$ is an identity matrix. By solving Eq. (3), a Mexican-hat-shaped potential function can be obtained with $\phi(\boldsymbol{q}) = \frac{1}{4}(q_1^2+q_2^2)(q_1^2+q_2^2-2)$. Its corresponding Boltzmann–Gibbs steady-state distribution is

$$\rho_{ss}(\boldsymbol{q}, t\to\infty) = \frac{1}{Z_\epsilon}\exp\left\{-\frac{(q_1^2+q_2^2)(q_1^2+q_2^2-2)}{4\epsilon}\right\}, \tag{12}$$

where $Z_\epsilon = e^{1/(4\epsilon)}\sqrt{\epsilon}\pi^{3/2}\left(1+\mathrm{erf}\left[1/(2\sqrt{\epsilon})\right]\right)$. Further, we obtain

$$\begin{aligned} S(\boldsymbol{q}) &= \frac{(1-q_1^2-q_2^2)^2}{(1-q_1^2-q_2^2)^2+1}\begin{pmatrix}1 & 0\\ 0 & 1\end{pmatrix}, \\ A(\boldsymbol{q}) &= \frac{1-q_1^2-q_2^2}{(1-q_1^2-q_2^2)^2+1}\begin{pmatrix}0 & 1\\ -1 & 0\end{pmatrix}, \\ Q(\boldsymbol{q}) &= \frac{1}{1-q_1^2-q_2^2}\begin{pmatrix}0 & -1\\ 1 & 0\end{pmatrix}. \end{aligned} \tag{13}$$

In this specific case, the steady-state distribution for Ito integration is identical to that of A-type integration [Fig. 3(a) and (b)]. The reason is that $\nabla\cdot Q(\boldsymbol{q})\cdot\nabla\rho_{ss} = 0$; hence, Eq. (12) is also a solution of the Ito FPE [as can be seen by comparison with the A-type FPE, Eq. (7)]. However, for general situations, the distributions are different even when the diffusion matrix is constant. A sufficient condition for the equivalence of Ito and A-type integration is that both D and Q are constant. Two remarks are in order: i) For the limit cycle, $\nabla\cdot f \neq 0$ at the limit cycle; that is, the system is dissipative by the standard definition. However, we have found that the potential function is "flat" at the limit cycle, and the friction matrix is zero. Hence, the motion at the limit cycle is non-dissipative, in contrast to the standard textbook understanding. This may explain why, before our work, many scientists thought that the potential function would not exist for the limit cycle. ii) Because of the antisymmetric matrix Q, there is an uncertainty in relating it to the "current," but it will not affect the steady-state distribution. In this sense, there is a choice of "gauge." This is also similar to the issue of kinetic momentum *vs.* canonical momentum in classical mechanics.

We can also construct the exact nonequilibrium potential for rotationally asymmetric limit cycles with nonuniform velocity along the limit cycle, for which it is argued [29] that no potential function could exist. A typical example resembling the famous van der Pol oscillator is shown in Fig. (3)(c):

$$\begin{cases} \dot{q}_1 = q_2 + \zeta_1(\boldsymbol{q}, t), \\ \dot{q}_2 = -\mu(q_1^2-1)q_2 - q_1 + h(q_1) + \zeta_2(\boldsymbol{q}, t)t, \end{cases} \tag{14}$$

where $h(q_1) = \mu^2 q_1^3/4 - \mu^2 q_1^5/16$. A construction with a chosen diffusion matrix is discussed in detail in Ref. [30]. We show the nonequilibrium potential function here [see also Fig. (3)(d)]:

$$\phi(\boldsymbol{q}) = \frac{1}{4}\left[q_1^2 + \left(q_2 - \mu q_1 + \frac{\mu}{4}q_1^3\right)^2\right]\left[q_1^2 + \left(q_2 - \mu q_1 + \frac{\mu}{4}q_1^3\right)^2 - 8\right], \tag{15}$$

where μ is a parameter. In addition, we have derived exact solutions of the potential function in three examples of the competitive Lotka–Volterra system for the entire state space [31]: (1) the general two-species case, (2) a three-species model, and (3) the May–Leonard model. Further, piecewise linear systems are discussed in Ref. [32] with the exact nonequilibrium potential constructed for the entire parameter space; these systems show Hopf bifurcation and saddle-node infinite period bifurcation. Moreover, we constructed the first nonequilibrium potential in a continuous dissipative chaotic system [33], which exhibits the structure of a chaotic attractor (Fig. 4). Because the construction is nontrivial, we suggest that readers consult the original article, Ref. [33], for details. Note that the constructed nonequilibrium potentials also serve as the Lyapunov function in the deterministic counterpart dynamics. The construction of the Lyapunov function in general nonlinear dynamics is critical for many engineering and mathematical applications and has been considered to require "divine inspiration" even recently [34]. Our framework may provide a direction for obtaining a general solution to this problem.

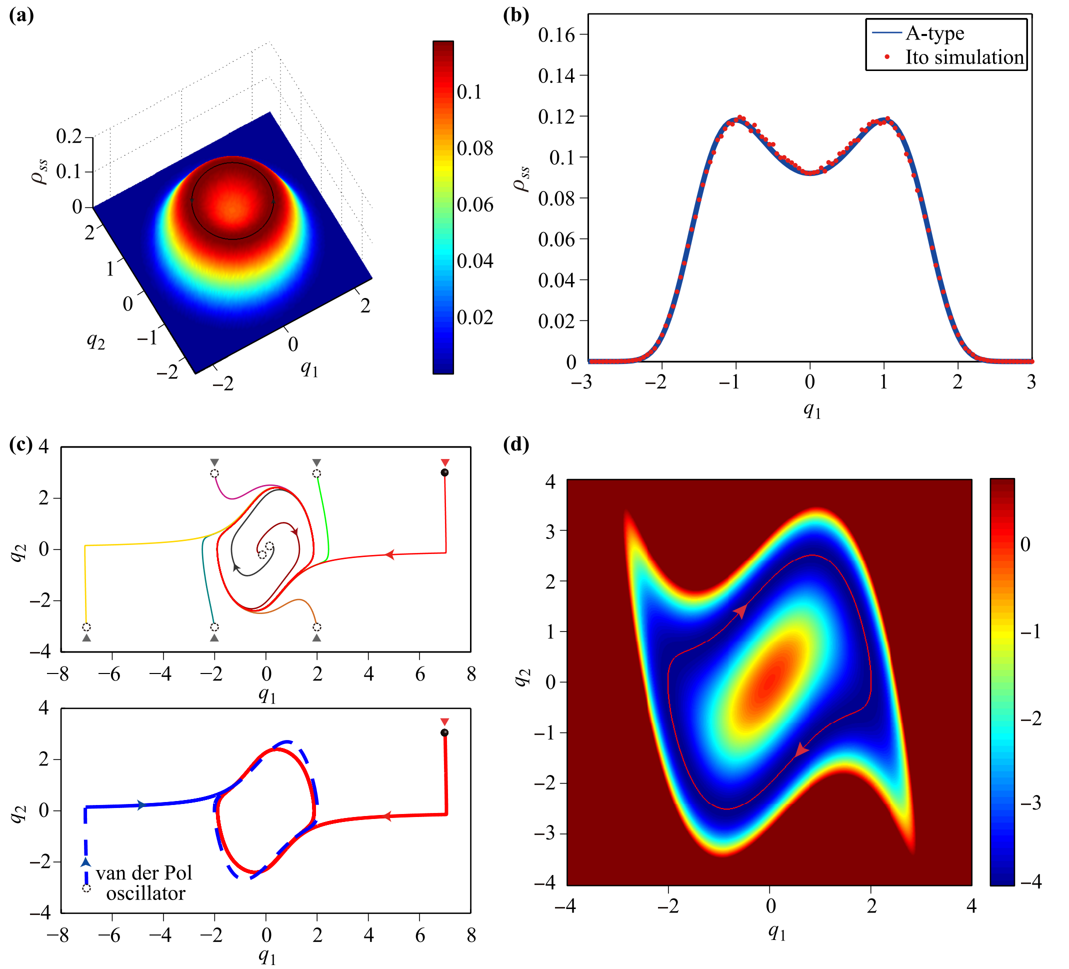

Fig. 3 Construction of nonequilibrium potential function in limit cycle dynamics. **(a)** Steady-state probability distribution function [Eq. (12)] with $\epsilon = 1$; **(b)** comparison with the distribution obtained from Ito simulation at $q_2 = 0$ ($\epsilon = 1$). **(c)** Upper panel: Trajectories (deterministic dynamics) for the system in Eq. (14) with $h(q_1) = \mu^2 q_1^3/4 - \mu^2 q_1^5/16$ ($\mu = 1$). Lower panel: Comparison of two systems. Dashed blue line represents the van der Pol oscillator $h(q_1) = 0$. Red line denotes the system in the upper panel. **(d)** Potential function in Eq. (15). Red line denotes the limit cycle. The graph is drawn below a preset upper bound value 1, and the phase variables are q_1 and q_2. Here the parameter $\mu = 1$. Note that this figure is modified from the original version in Ref. [30].

4 Discussion

We have briefly reviewed the framework of SDE decomposition and the A-type stochastic interpretation. The robustness of the framework was also revealed. In this section, several points are further discussed, clarified, and corrected.

- We first discuss the toy model of a diffusion process on the circle $\mathcal{S}[0, 1]$ in Ref. [21]. We note that it indeed reveals an additional feature that is largely overlooked: There are cases in which the steady-state distribution is not determined by the potential function in the form of the Boltzmann–Gibbs distribution. However, there is no question of having a Hamiltonian or potential function for the dissipative dynamics in such situations [35], and the potential function can even be exactly evaluated [36]. The mathematical reason for this mismatch is that this example brings the multiconnected state space into focus, where the solution to the potential condition, Eq. (1a), is sensitive to this topological constraint [37]. In fact, the potential function can be formulated in different ways while the steady-state distribution stays the same. For the toy model, the decomposition straightforwardly holds with $\phi'(x) = 0$, which leads to $\phi^{AO}(x) = constant$ (with $S = 0$ by the generalized Einstein relation, and $D = 1$, $A \equiv 0$), satisfying the global topological constraint. It can also be demonstrated that the potential func-

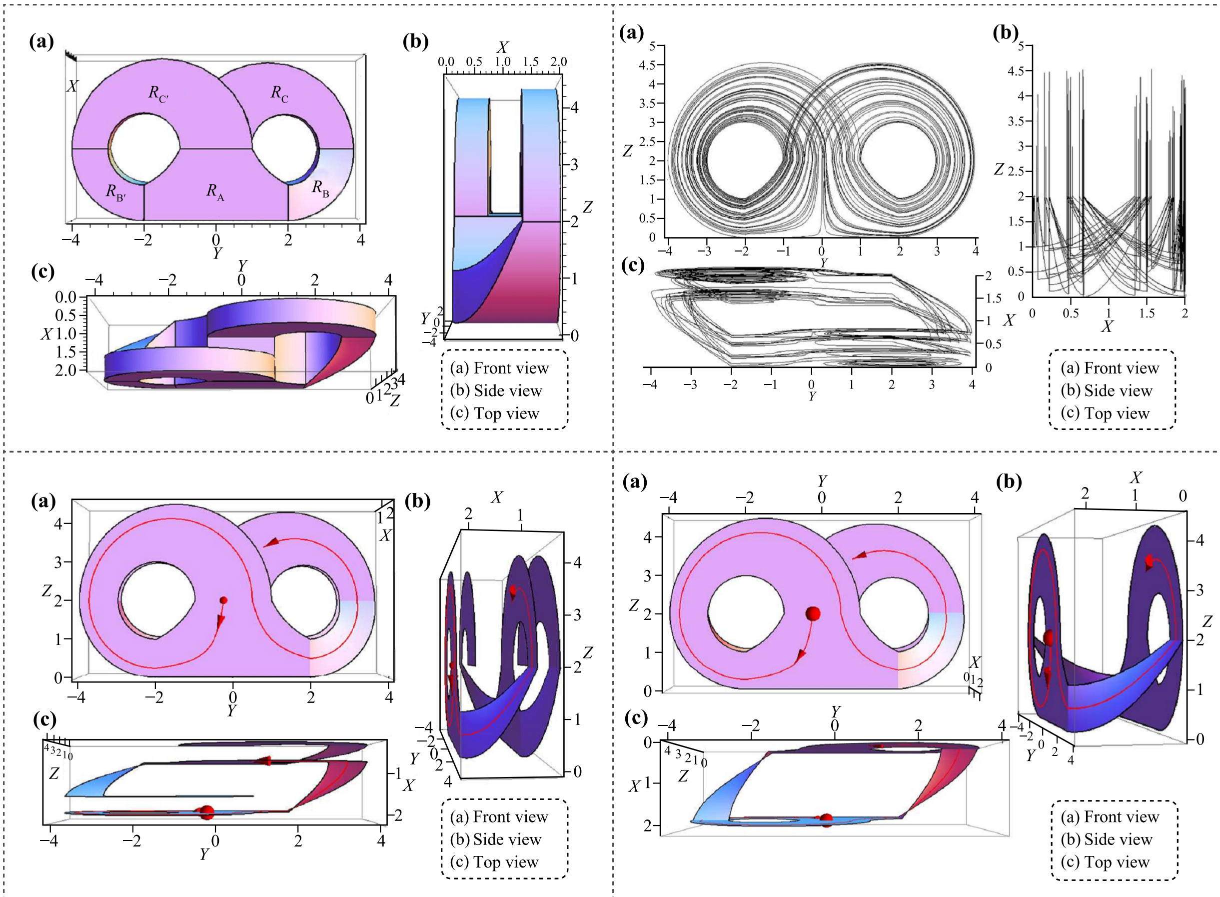

Fig. 4 Potential function for a continuous dissipative chaotic system reveals the structure of a chaotic attractor. Upper left panel: Simplified geometric Lorenz attractor system. We define the system in each region, make it continuous as a whole, and prove that it is chaotic. Upper right panel: Simulated trajectories of the system. Lower left panel: Strange chaotic attractor, where the equipotential surface of the attractor has infinite layers. Lower right panel: Non-strange chaotic attractor, where the equipotential surface of the attractor is just two orientable surfaces folded together. Note that this figure is modified from the original version in Ref. [33].

tion in the winding number representation, a washboard potential $\phi(x) = -x$ (with $S = 1$ by the generalized Einstein relation), is also valid for the dynamics, with thermodynamical information such as the nonequilibrium work when the system is driven by an external control parameter [37]. Note that washboard potentials exist in real physical systems [36], so there is no reason to preclude them. They are solutions of the Hamilton–Jacobi equation. Actually, the two solutions of the Hamilton–Jacobi equation correspond exactly to those of the generalized Einstein relation. This is an explicit example of the consistency between the SDE decomposition framework and the Freidlin–Wentzell formulation.

- The potential function is more generally applicable than the steady-state distribution. When the steady-state distribution does not exist, a potential function may still be obtainable. We have considered this case recently [38]. We observe that this important feature has not been generally appreciated to date in the literature. This feature, together with the above discussion of the toy model, may indicate that there is a serious limitation on the applicability of constructing the potential function from the steady-state distribution.

- The potential function should exist for nonequilibrium processes. It can be obtained by solving the Hamilton–Jacobi equation. This consensus may be important in that, while various constructions of the potential function have been proposed recently [7, 8, 10, 39–43], there has been lingering concern regarding its existence in the mathematical community [34].

- The singularity of the diffusion matrix D does not affect the decomposition framework. We have stressed this feature [8], which is evident from SDE decomposition but not as obvious in other formulations. For example, a naive implementation of the Freidlin–Wentzell formulation involved $1/D$ [21], which apparently requires the non-singularity of D.

- It has been remarked [21] that "the general mathematical expression for OM function in high dimensional cases has been studied in Refs. [39] and [40], which include the result in Ref. [38] as a special case." According to our knowledge, however, Refs. [39] and [40] in Ref. [21] provide just an action function under Stratonovich's interpretation without any explicit action function for the general α-type interpretation, even for the one-dimensional case. In contrast, we find there are multiple consistent explicit action functions under the α-type interpretation, which correspond to different integration rules [44], alleviating the confusion in the field.
- An important question is how to generalize the results obtained for continuous processes to discrete jump processes. We had in fact showed that generalization is possible [45]. Such generalization is a direct extension of SDE decomposition.

In conclusion, we briefly reviewed the SDE decomposition framework and demonstrated that, for a single connected phase space with natural boundary conditions, the SDE decomposition is generally uniquely determined. For a multiply connected phase space, such as a ring, care must be taken with the boundary conditions. The robustness of the A-type FPE with respect to insufficient boundary conditions on the antisymmetric matrix Q was revealed. SDE decomposition has a natural relation to the Hamiltonian dynamics in theoretical physics, which provide a natural candidate for a unifying dynamical framework of nonequilibrium processes.

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References

1. S. Wright, The roles of mutation, inbreeding, crossbreeding, and selection in evolution, in: D. F. Jones (Ed.) Proceedings of the Sixth International Congress of Genetics, Vol. 1, 356–366 (1932)
2. C. H. Waddington, The strategy of the genes: A discussion of some aspects of theoretical biology, New York: MacMillan Company, 1957
3. S. A. Kauffman, The Origins of Order: Self Organization and Selection in Evolution, New York: Oxford University Press, 1993
4. X. M. Zhu, L. Yin, L. Hood, and P. Ao, Calculating biological behaviors of epigenetic states in the phage λ life cycle, *Funct. Integr. Genomics* 4(3), 188 (2004)
5. P. Ao, Global view of bionetwork dynamics: Adaptive landscape, *J. Genet. Genomics* 36(2), 63 (2009)
6. S. Huang, G. Eichler, Y. Bar-Yam, and D. E. Ingber, Cell fates as high-dimensional attractor states of a complex gene regulatory network, *Phys. Rev. Lett.* 94(12), 128701 (2005)
7. P. Ao, Potential in stochastic differential equations: Novel construction, *J. Phys. Math. Gen.* 37(3), L25 (2004)
8. R. Yuan and P. Ao, Beyond itô versus stratonovich, *J. Stat. Mech.* 2012(07), P07010 (2012)
9. M. I. Freidlin and A. D. Wentzell, Random Perturbations of Dynamical Systems, 3rd Ed., Berlin: Springer-Verlag, 2012
10. J. X. Zhou, M. D. S. Aliyu, E. Aurell, and S. Huang, Quasi-potential landscape in complex multi-stable systems, *J. R. Soc. Interface Online* 1–15 (2012)
11. R. Yuan, Y. A. Ma, B. Yuan, and P. Ao, Lyapunov function as potential function: A dynamical equivalence, *Chin. Phys. B* 23(1), 010505 (2014)
12. C. Lv, X. Li, F. Li, and T. Li, Constructing the energy landscape for genetic switching system driven by intrinsic noise, *PLoS One* 9(2), e88167 (2014)
13. D. K. Wells, W. L. Kath, and A. E. Motter, Control of stochastic and induced switching in biophysical networks, *Phys. Rev. X* 5(3), 031036 (2015)
14. P. Ao, D. Galas, L. Hood, and X. M. Zhu, Cancer as robust intrinsic state of endogenous molecular-cellular network shaped by evolution, *Med. Hypotheses* 70(3), 678 (2008)
15. R. Yuan, X. Zhu, G. Wang, S. Li, and P. Ao, Cancer as robust intrinsic state shaped by evolution: A key issues review, *Rep. Prog. Phys.* 80(4), 042701 (2017)
16. Y. Tang, R. Yuan, G. Wang, X. Zhu, and P. Ao, Potential landscape of high dimensional nonlinear stochastic dynamics and rare transitions with large noise, arXiv: 1611.07140 (2016)
17. G. W. Wang, X. M. Zhu, J. R. Gu, and P. Ao, Quantitative implementation of the endogenous molecular-cellular network hypothesis in hepatocellular carcinoma, *Interface Focus* 4(3), 20130064 (2014)
18. X. Zhu, R. Yuan, L. Hood, and P. Ao, Endogenous molecular-cellular hierarchical modeling of prostate carcinogenesis uncovers robust structure, *Prog. Biophys. Mol. Biol.* 117(1), 30 (2015)
19. S. Li, X. Zhu, B. Liu, G. Wang, and P. Ao, Endogenous molecular network reveals two mechanisms of heterogeneity within gastric cancer, *Oncotarget* 6, 13607 (2015)

20. R. Yuan, X. Zhu, J. P. Radich, and P. Ao, From molecular interaction to acute promyelo-cytic leukemia: Calculating leukemogenesis and remission from endogenous molecular-cellular network, *Sci. Rep.* 6(1), 24307 (2016)

21. P. Zhou and T. Li, Construction of the landscape for multi-stable systems: Potential landscape, quasi-potential, a-type integral and beyond, *J. Chem. Phys.* 144(9), 094109 (2016)

22. R. Yuan, Y. Tang, and P. Ao, Comment on "construction of the landscape for multi-stable systems: Potential landscape, quasi-potential, a-type integral and beyond", *J. Chem. Phys.* 145(14), 147104 (2016) [*J. Chem. Phys.* 144, 094109 (2016)]

23. C. Kwon, P. Ao, and D. J. Thouless, Structure of stochastic dynamics near fixed points, *Proc. Natl Acad. Sci. USA* 102, 13029 (2005)

24. A. Pazy, Semigroups of Linear Operators and Applications to Partial Differential Equations, Vol. 44, New York: Springer-Verlag, 2012

25. R. Kubo, M. Toda, and N. Hashitsume, Statistical Physics II: Nonequilibrium Statistical Physics, 2nd Ed., Heidelberg: Springer-Verlag, 1995

26. W. M. Haddad and V. S. Chellaboina, Nonlinear Dynamical Systems and Control: A Lyapunov-based Approach, Princeton: Princeton University Press, 2008

27. P. Ao, Emerging of stochastic dynamical equalities and steady state thermodynamics from Darwinian dynamics, *Commum. Theor. Phys.* 49(5), 1073 (2008)

28. L. Yin and P. Ao, Existence and construction of dynamical potential in nonequilibrium processes without detailed balance, *J. Phys. A: Math. Gen.* 39, 8593 (2006)

29. H. Ge and H. Qian, Landscapes of non-gradient dynamics without detailed balance: Stable limit cycles and multiple attractors, *Chaos* 22(2), 023140 (2012)

30. R. Yuan, X. Wang, Y. Ma, B. Yuan, and P. Ao, Exploring a noisy van der Pol type oscillator with a stochastic approach, *Phys. Rev. E* 87(6), 062109 (2013)

31. Y. Tang, R. Yuan, and Y. Ma, Dynamical behaviors determined by the Lyapunov function in competitive Lotka-Volterra systems, *Phys. Rev. E* 87(1), 012708 (2013)

32. Y. A. Ma, R. Yuan, Y. Li, B. Yuan, and P. Ao, Lyapunov functions in piecewise linear systems: From fixed point to limit cycle, arXiv: 1306.6880 (2013)

33. Y. Ma, Q. Tan, R. Yuan, B. Yuan, and P. Ao, Potential function in a continuous dissipative chaotic system: decomposition scheme and role of strange attractor, *Int. J. Bifurcat. Chaos* 24(02), 1450015 (2014)

34. S. H. Strogatz, Nonlinear Dynamics and Chaos: With Applications to Physics, Biology, Chemistry, and Engineering, 2nd Ed., Boulder: Westview Press, 2015

35. P. Ao and J. Rammer, Influence of an environment on equilibrium properties of a charged quantum bead constrained to a ring, *Superlattices Microstruct.* 11(3), 265 (1992)

36. Y. C. Chen, M. P. A. Fisher, and A. J. Leggett, The return of a hysteretic Josephson junction to the zero-voltage state: I–V characteristic and quantum retrapping, *J. Appl. Phys.* 64(6), 3119 (1988)

37. Y. Tang, R. Yuan, and P. Ao, Anomalous free energy changes induced by topology, *Phys. Rev. E* 92(6), 062129 (2015)

38. S. Xu, S. Jiao, P. Jiang, and P. Ao, Two-time-scale population evolution on a singular land-scape, *Phys. Rev. E* 89(1), 012724 (2014)

39. P. Ao, C. Kwon, and H. Qian, On the existence of potential landscape in the evolution of complex systems, *Complexity* 12(4), 19 (2007)

40. H. Qian, P. Ao, Y. Tu, and J. Wang, A framework towards understanding mesoscopic phenomena: Emergent unpredictability, symmetry breaking and dynamics across scales, *Chem. Phys. Lett.* 665(16), 153 (2016)

41. Y. Cao, H. M. Lu, and J. Liang, Probability landscape of heritable and robust epigenetic state of lysogeny in phage lambda, *Proc. Natl. Acad. Sci. USA* 107(43), 18445 (2010)

42. M. Lu, J. Onuchic, and E. Ben-Jacob, Construction of an effective landscape for multistate genetic switches, *Phys. Rev. Lett.* 113(7), 078102 (2014)

43. H. Qian, The zeroth law of thermodynamics and volume-preserving conservative system in equilibrium with stochastic damping, *Phys. Lett. A* 378(7–8), 609 (2014)

44. Y. Tang, R. Yuan, and P. Ao, Summing over trajectories of stochastic dynamics with multi-plicative noise, *J. Chem. Phys.* 141(4), 044125 (2014)

45. P. Ao, T. Q. Chen, and J. H. Shi, Dynamical decomposition of Markov processes without detailed balance, *Chin. Phys. Lett.* 30(7), 070201 (2013)