# Construction of the landscape for multi-stable systems: Potential landscape, quasi-potential, A-type integral and beyond

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Motivated by the famous Waddington's epigenetic landscape metaphor in developmental biology, biophysicists and applied mathematicians made different proposals to construct the landscape for multi-stable complex systems. We aim to summarize and elucidate the relationships among these theories from a mathematical point of view. We systematically investigate and compare three different but closely related realizations in the recent literature: the Wang's potential landscape theory from steady state distribution of stochastic differential equations (SDEs), the Freidlin-Wentzell quasi-potential from the large deviation theory, and the construction through SDE decomposition and A-type integral. We revisit that the quasi-potential is the zero noise limit of the potential landscape, and the potential function in the third proposal coincides with the quasi-potential. We compare the difference between local and global quasi-potential through the viewpoint of exchange of limit order for time and noise amplitude. We argue that local quasi-potentials are responsible for getting transition rates between neighboring stable states, while the global quasi-potential mainly characterizes the residence time of the states as the system reaches stationarity. The difference between these two is prominent when the transitivity property is broken. The most probable transition path by minimizing the Onsager-Machlup or Freidlin-Wentzell action functional is also discussed. As a consequence of the established connections among different proposals, we arrive at the novel result which guarantees the existence of SDE decomposition while denies its uniqueness in general cases. It is, therefore, clarified that the A-type integral is more appropriate to be applied to the decomposed SDEs rather than its primitive form as believed by previous researchers. Our results contribute to a deeper understanding of landscape theories for biological systems. © *2016 AIP Publishing LLC.* [http://dx.doi.org/10.1063/1.4943096]

## I. INTRODUCTION: LANDSCAPE THEORIES FOR MULTI-STABLE SYSTEMS

Published in 1957, the Waddington's epigenetic landscape metaphor[1] provides a vivid pictorial description as well as an insightful qualitative tool to understand the mechanism of gene regulation in evolutionary and developmental biology.[2–4] In recent years, we witness the growing interests and efforts to quantitatively realize this metaphor in a rationalized way and construct a scalar "energy landscape function" $\phi(x)$ defined in the state space in complex physical, chemical, and biological systems with multiple attractors.

The motivations and historical backgrounds of introducing the energy landscape function and energy landscape theory into complex systems have been overviewed and discussed by many previous researchers.[4–7] To understand a highly complex stochastic multi-stable system, there exists the necessity to compare the relative stability of different attractors,[6,8] to account for the transition rates between neighboring stable states induced by noise,[9,10] and to form an intuitive picture that reveals the essential mechanism underlying the complex system.[11,12] In the gradient and equilibrium systems, the potential function fulfils these needs, respectively, by supplying the relative height of different stable states, by appearing in the famous Kramers' transition rate formula[13] and by offering a potential field view to comprehend the "driving force" underneath the complex systems. From this point of view, the energy landscape function constructed for non-gradient and non-equilibrium systems aims to play a similar role and can be regarded as the generalizations or substitutions of the potential function in such systems. In physics, the energy landscape function also has close relationships with the framework of non-equilibrium thermodynamics.[14] In chemistry, the energy landscape function provides useful illustrations for the protein folding problems.[15] In biology, the landscape theory has been applied extensively not only to explore the fundamental problems in evolution[4] but also to study the robustness, adaptivity, and efficiency of real biological networks, with some recent progress in Refs. 16–18.

Since it might be difficult to achieve all the above goals at one stroke, the existing landscape functions are proposed from various perspectives to satisfy certain needs and criteria. These efforts include utilizing the information of steady state distribution to explore the relative stabilities of different attractors,[6,19] analyzing the transition path and transition rate among stable points,[20–22] and decomposing the "driving force" of the particles in the system.[19,23] Of course, there are overlapping and connections between

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these proposals and perspectives; hence, inspecting these proposals from a unified point of view is urgent for future developments.

In this paper, we will focus on three representative and closely related works among the landscape theories: (i) The Wang's potential landscape theory from the steady state distribution of stochastic differential equations (SDEs); (ii) the Freidlin-Wentzell quasi-potential (FW quasi-potential) from the large deviation theory (LDT); and (iii) Ao's construction through SDE decomposition and A-type integral (it will be called *SDE decomposition theory* below for short). To clarify the connection and difference among them is the main concern of this paper.

The considered three theories were proposed from different motivations and backgrounds. Enlightened by the Boltzmann distribution law in equilibrium statistical mechanics, Wang *et al.*[19] constructed the potential landscape from the steady-state distribution of non-equilibrium biological systems and adopted it in the analysis of many real biological models including budding yeast cell cycle,[11] stem cell differentiation,[22] and calcium oscillation.[24] Arising in the study of Freidlin and Wentzell on LDT for diffusion processes,[20] the quasi-potential was proposed and has been applied by the authors in genetic switching models[16,25] and cell cycle dynamics.[12] Motivated by the fluctuation-dissipation theorem, Ao and his co-workers performed the SDE decomposition to obtain the underlying potential function[23,26] and proposed the so-called A-type integral interpretation of the SDEs.[27]

Compared with the fruitful applications of energy landscape theories in chemical and biological research, to the authors' knowledge, only limited work has been done to elucidate their relationships and connections, which is supposed to serve as the theoretical foundation to judiciously choose and appropriately apply these proposals in studying real systems. The coincidence of Wang's potential landscape function with FW quasi-potential as noise tends to zero has been recognized in previous studies.[5,6,21] In Ref. 6, an overview related to these theories was presented for systems with state-independent noise, which showed the equivalence between FW quasi-potential and Ao's potential and their difference with Wang's potential landscape under the state-independent noise assumption.

In this paper, we will continue the discussion of Ref. 6 in a more general setup by considering the diffusion process of the form

$$dX_t = b(X_t)dt + \sigma(X_t)dW_t, \quad \sigma(x)\sigma(x)^t = 2\varepsilon D(x), \tag{1}$$

where the subscript $t$ means the time dependence instead of time derivative, $X_t$ is a stochastic process in $R^n$, $W_t$ is the standard Brownian motion, and $\varepsilon$ represents the strength of noise. Here we employ the notation $dW_t$ as in probability theory since $\dot{W}_t$ is not an ordinary function mathematically.[28] Unless otherwise stated, the stochastic integral is understood in Ito sense. SDEs (1) are an abstraction of general chemical reaction kinetic models in biological systems.[29] The state-dependent diffusion matrix $D(x)$ enables us to investigate both intrinsic and extrinsic noise.[30] Since Waddington's metaphor describes the cell development as the motion of marbles among valleys, it is also helpful to interpret $b(x)$ as the "force" and $D(x)$ as the "diffusion coefficient" in (1).

The main contribution of this paper is twofold. First, by revealing or revisiting the relationships among the three landscape theories for biological systems modeled by SDEs (1), some easily confounded concepts will be stressed and clarified while some new understandings will be provided. For instance, when re-deriving the relationship between Wang's potential landscape and FW quasi-potential, the distinctions between local and global FW quasi-potential will be accentuated and understood from the exchange of limit orders for time and noise. We will also prove that the FW quasi-potential exactly coincides with the potential function in SDE decomposition theory under certain conditions. Second, as a by-product of the established connections, we get new insights on the existing landscape theories. Specifically we will provide a mathematically rigorous existence result for SDE decomposition theory and show that under the current framework of the proposal,[23] the decomposition is generally not unique when the dimension of SDEs (1) is bigger than or equal to 3. As a corollary, we clarify that the A-type integral interpretation for SDEs (1) might be ill-defined and thus only be applied to a known decomposed form. This novel result clarifies the misunderstandings held by some previous researchers.

The paper is organised as follows. We will study the potential landscape theory, quasi-potential theory, and the SDE decomposition theory in Sections II–IV, respectively. In each section, we introduce the definition, investigate the connection with other proposals, and especially make discussion on transition paths. In Section V, an example of constructing energy landscape for the diffusion on the circle $\mathbb{S}[0,1]$ through different theories is provided as further explanation. Finally we discuss the implications of our results and some future topics in Section VI.

## II. WANG'S POTENTIAL LANDSCAPE THEORY

The potential landscape function proposed by Wang *et al.* is defined through the steady state distribution, which is a generalization of Boltzmann's distribution law in equilibrium statistical mechanics. The constructed landscape has also been analyzed from transition path and force decomposition perspectives.[19,22] In this framework, the force can be decomposed into a potential term plus a flux term, which is the origin of the notion of "potential landscape."[19]

### A. Starting point: Steady state distribution

The starting point of constructing Wang's potential landscape is the steady state distribution of SDEs (1). We have the Fokker-Planck equation of SDEs (1),

$$\partial_t P(x,t) + \nabla \cdot J(x,t) = 0, \tag{2}$$

where $P(x,t)$ is the probability density function (PDF) of the process $X_t$ at time $t$, and the probability flux

$$J(x,t) = b(x)P(x,t) - \varepsilon\nabla \cdot (D(x)P(x,t)).$$

The steady state distribution $P_{ss}(x)$ and steady state probability flux $J_{ss}(x)$ can be obtained by solving

$$\nabla \cdot J_{ss}(x) = \nabla \cdot [b(x)P_{ss}(x) - \varepsilon \nabla \cdot (D(x)P_{ss}(x))] = 0. \quad (3)$$

Then the potential landscape function $\phi^{PL}(x)$ is defined as

$$\phi^{PL}(x) = -\ln P_{ss}(x). \quad (4)$$

The relationship $P_{ss}(x) = \exp(-\phi^{PL}(x))$ is reminiscent of the Boltzmann-Gibbs distribution in equilibrium statistical mechanics.

The rationale of the potential landscape can be shown explicitly if we consider a gradient system with

$$b(x) = -\nabla V(x),\ D(x) = I.$$

We have

$$P_{ss}(x) = \frac{1}{Z}\exp\Big(-\frac{1}{\varepsilon}V(x)\Big), \quad J_{ss}(x) = 0,$$

thus

$$\phi^{PL}(x) = \frac{1}{\varepsilon}V(x) + \ln Z. \quad (5)$$

In this case, the potential landscape $\phi^{PL}(x)$ is equivalent to the original driving potential $V(x)$ up to a rescaling and a shift. But of course, this observation does not hold for general $b(x)$ or $D(x) \neq I$, in which case one gets a generalized potential.

In practice, there are mainly two approaches to numerically compute $P_{ss}(x)$ and therefore $\phi^{PL}(x)$. The most direct approach is to solve Fokker-Planck equation (2) by applying deterministic numerical methods with appropriate boundary condition. However, the computational cost of such strategy increases exponentially and quickly becomes unaffordable even when the dimension $n \geq 4$. Hence in high dimensional cases, $P_{ss}(x)$ is either obtained by exploring the special feature of the considered dynamics, e.g., the mean field approximation[11] or obtained by direct Monte Carlo simulation of SDEs (1) until steady state distribution. However, this approach also encounters the difficulty of slow convergence when the noise strength $\varepsilon$ is very small, in which case the metastability and ergodicity turn to be key issues.[31] Moreover, both the representation and storage of the high dimensional potential landscape need to be studied at first. We confront with the curse of dimensionality.

### B. Force decomposition: Non-equilibrium steady states (NESS)

Wang's potential landscape theory can also be studied from force decomposition perspective. From the relationship between flux and probability $J_{ss}(x) = b(x)P_{ss}(x) - \varepsilon\nabla \cdot (D(x)P_{ss}(x))$, we can represent the drift term $b(x)$ in the decomposition form

$$\begin{aligned} b(x) &= \frac{\varepsilon}{P_{ss}(x)}\nabla \cdot (D(x)P_{ss}(x)) + \frac{J_{ss}(x)}{P_{ss}(x)} \\ &= -\varepsilon D(x)\nabla\phi^{PL}(x) + \varepsilon\nabla \cdot D(x) + \frac{J_{ss}(x)}{P_{ss}(x)}. \end{aligned} \quad (6)$$

To gain more intuitions from (6), let us specifically take $D(x) = I$ and $\varepsilon = 1$. Then

$$b(x) = -\nabla\phi^{PL}(x) + \frac{J_{ss}(x)}{P_{ss}(x)}.$$

We will discuss two cases for different values of $J_{ss}(x)$ and their biological meaning.

The first case is $J_{ss}(x) = 0$. Such condition is called the *detailed balance* in probability theory, while in statistical mechanics, systems with zero flux correspond to equilibrium states. Under such circumstances, we have $b(x) = -\nabla\phi^{PL}(x)$. Hence the detailed balance condition implies the equilibrium states where the biological system is simply driven by the gradient of potential landscape and the steady state distribution is of the Boltzmann-Gibbs form $P_{ss}(x) = \exp(-\phi^{PL}(x))$.

The second case is $J_{ss}(x) \neq 0$, which is more common in biological systems. Under such circumstances, when the system reaches steady state, the probability flux does not vanish, leading to the NESS. The force $b(x)$ is now decomposed into the gradient term $-\nabla\phi^{PL}(x)$ and an additional non-gradient term $J_{ss}(x)/P_{ss}(x)$, which is also called "curl flux" term in previous literature because $\nabla \cdot J_{ss}(x) = 0$ (but the term itself is not divergence-free). One typical example of NESS in biological models is the oscillatory dynamics, because the limit cycle cannot exist in gradient systems and must be driven by the curl term. Many concepts in non-equilibrium statistical mechanics such as entropy production can be analyzed within NESS framework and one may consult Ref. 32 for a systematic survey.

A simple illustrative example to show the construction of the $\phi^{PL}(x)$ and the non-equilibrium nature of NESS will be presented in Section V.

### C. Transition path: Path integral and challenges

Following Feynman's path integral approach to quantum mechanics,[33] we can also solve Fokker-Planck equation (2) formally by integrating the individual paths $\psi(t)$ according to their weight[34]

$$\begin{aligned} P(x_f,T|x_i,0) &= \int \mathcal{D}\psi\, P(\psi|\psi(0) = x_i, \psi(T) = x_f) \\ &= \frac{1}{Z}\int \mathcal{D}\psi \exp(-S_T[\psi]), \end{aligned} \quad (7)$$

where $x_f$ denotes the final state, $x_i$ denotes the initial state, and $Z$ is the partition function in path space. The weight of each path $P(\psi|\psi(0) = x_i, \psi(T) = x_f)$ is assigned according to its action functional $S[\psi]$. For diffusion process, the action functional can be expressed as the time integral of Onsager-Machlup Lagrangian function[35]

$$S_T[\psi] = \int_0^T L^{OM}(\psi, \dot{\psi})ds, \quad (8)$$

whose concrete form will be discussed later. If SDEs (1) are ergodic and suppose the system starts from $x_0$, then $P_{ss}(x) = \lim_{T\to\infty} P(x,T|x_0,0)$, yielding the *formal* relationship

TABLE I. Summary for the potential landscape $\phi^{PL}(x)$.

| Realization of Waddington's metaphor candidate I: Potential landscape | |
|---|---|
| Definition | $\phi^{PL}(x) = -\ln P_{ss}(x)$ (steady state distribution) |
| Numerical strategy | Deterministic numerical method (e.g., difference method) for Fokker-Planck equation (in low dimensional system)<br>Monte Carlo simulation for stochastic differential equation (in high dimensional system, inefficient when noise strength $\varepsilon$ is small) |
| Force decomposition | $b(x) = -\varepsilon D(x)\nabla\phi^{PL}(x) + \varepsilon\nabla\cdot D(x) + J_{ss}(x)/P_{ss}(x)$, where $J_{ss}(x)/P_{ss}(x)$ reflects the NESS nature of the system |
| Transition path perspective | $\phi^{PL}(x) = -\lim_{T\to\infty}\ln\frac{1}{Z}\int\mathcal{D}\psi\exp(-\int_0^T L^{OM}(\psi,\dot\psi)ds)$, where the integral is over all the paths $\psi$ satisfying $\psi(T) = x$ |

between potential landscape and transition path

$$\phi^{PL}(x) = -\ln P_{ss}(x) = -\lim_{T\to+\infty}[\ln\int\mathcal{D}\psi\exp\left(-\int_0^T L^{OM}(\psi,\dot\psi)ds\right) - \ln Z]. \tag{9}$$

Several problems will be encountered in this formal treatment of potential landscape theory from transition path perspective.

First, if we want to compute the potential landscape at point $x$ from transition path perspective, one may have to sum up the weights over all transition paths starting from one given point $x_0$ and reaching $x$ as time goes to infinity. Numerically constructing potential landscape from such tactics turns out to be a challenging task. To avoid such inconvenience, another version of landscape function is constructed from the "effective action" of the "dominant path."[34] To briefly state, the landscape function at point $x$ equals to the minimum action $S_T[\psi]$ in Eq. (8) of all the paths $\psi$ connecting $x$ to the reference point $x_0$ (usually the attractor of the system). The minimum action path is dominant especially when $\varepsilon$ is small because it corresponds to the path with maximum weight in Eq. (7). However, such proposed landscape function might not be well-defined. For instance, let us consider a specific gradient system with

$$b(x) = -\nabla V(x),\ D(x) = I,\ \varepsilon = 1,\ V(x) = \frac{1}{2}x^2.$$

Take $x_0 = 0$, then the action functional has the concrete form by Eq. (10),

$$S_T[\psi] = \int_0^T L^{OM}(\psi,\dot\psi)ds = \int_0^T\frac{1}{4}(\dot\psi+\psi)^2ds - \frac{1}{2}T,$$
$$\psi(0) = x,\ \psi(T) = 0.$$

Hence the minimum action path $\hat\psi$ satisfies $d\hat\psi/dt = -\hat\psi, \hat\psi(0) = x, \hat\psi(+\infty) = 0$, also indicating that $S_T(\hat\psi) = -\infty$. In this case, we have that the landscape function proposed in Ref. 34 is minus infinity at every point $x \neq 0$, which is not a desirable result. We remark that this phenomenon results from the divergence term $\frac{1}{2}\nabla\cdot b(x)$ in the OM function (cf. Eq. (10)).

Moreover, the choice of concrete OM function form $L^{OM}(\psi,\dot\psi)$ for the general diffusion process is a rather subtle and controversial issue. It is shown in Ref. 36 that if the diffusion matrix $D(x)$ is constant and $n = 1$, the most probable path (i.e., the path with largest weight) corresponds to the minimizer of action functional with Lagrangian

$$L^{OM}(\psi,\dot\psi) = \frac{1}{4\varepsilon}[\dot\psi - b(\psi)]^t D^{-1}(\psi)[\dot\psi - b(\psi)] + \frac{1}{2}\nabla\cdot b(\psi). \tag{10}$$

For the state-dependent diffusion matrix $D(x)$, it is argued in Ref. 37 that the term $\frac{1}{2}\nabla\cdot b(\psi)$ in (10) should be replaced by $\sum_{i,j,k}\frac{1}{2}D_{ij}\partial_{x_j}(D^{-1}_{ik}b_k)$. While in Ref. 38, it is claimed that an additional term involving second order derivative of $\sigma(x)$ (only the one dimensional case is considered in Ref. 38) should be added. We remark 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.

The above difficulties can be all resolved in small noise limit. If $\varepsilon$ is sufficiently small, then only the term $\frac{1}{4\varepsilon}[\dot\psi - b(\psi)]^t D^{-1}(\psi)[\dot\psi - b(\psi)]$ will count in OM function (10), which corresponds to the Friedlin-Wentzell (FW) function (12). Moreover, the weight of the most probable path will dominate in (9) according to Laplace's integral asymptotics (see Appendix A). This observation leads to the introduction of quasi-potential below, whose theory has been well established within the rigorous mathematical framework of the LDT of Freidlin and Wentzell for diffusion processes.[20]

A summary for the discussions above on the potential landscape theory is provided in Table I.

## III. FREIDLIN-WENTZELL QUASI-POTENTIAL THEORY

The quasi-potential theory first proposed by Freidlin and Wentzell aims to quantify the landscape for multi-stable system whose noise amplitude $\varepsilon$ is small enough, which is a reasonable assumption when the number of molecules in the considered system is large. Although the theory was well-established based on the LDT,[20] we will continue adopting the path integral formulation here to present the essential ingredients of the theory instead of rigorous treatments. The relationship between Freidlin-Wentzell quasi-potential and Wang's potential landscape has been explored in previous literature under different circumstances,[5,6,12] while we will

address the distinctions and connections between the *local* FW quasi-potential, which is computed from the transition path connecting the stable points pairs, and the *global* FW quasi-potential, which is relevant to the steady state distribution of the system and therefore Wang's potential landscape. We will also discuss the transitivity issue introduced in Ref. 6.

### A. Starting point: Local quasi-potential and transition path

Let $X_t^\varepsilon$ denote the trajectory of SDE (1). The Freidlin-Wentzell theory roughly tells that for a given regular connecting path $\psi(t)$ and $\varepsilon$, $\delta$ small enough, we have

$$\mathbb{P}(\sup_{0\le t\le T}|X_t^\varepsilon-\psi(t)|\le\delta)\approx\exp(-\varepsilon^{-1}S_T[\psi]). \quad (11)$$

The action functional $S_T[\psi]$ is also called the *rate functional* in LDT with the expression

$$S_T[\psi]=\int_0^T L^{FW}(\psi,\dot\psi)dt,$$

where

$$L^{FW}(\psi,\dot\psi)=\frac{1}{4}[\dot\psi(s)-b(\psi(s))]^tD^{-1}(\psi(s))[\dot\psi(s)-b(\psi(s))] \quad (12)$$

is the dominate $O(\varepsilon^{-1})$ term in the OM functional. We also call $S_T[\psi]$ the FW functional in the later text. Approximation (11) is indeed derived by applying Laplace asymptotics to the path integral formulation. Borrowing the idea from classical mechanics, we call $L^{FW}(\psi,\dot\psi)$ the Lagrangian of action $S_T$, and correspondingly define the Hamiltonian of the system by taking the Legendre dual of the Lagrangian[41]

$$H(\psi,p)=b(\psi)^tp+p^tD(\psi)p. \quad (13)$$

Assume $x_0$ is a stable fixed point of the deterministic dynamical system $dx/dt=b(x)$, representing a meta-stable biological state. Then the *local* quasi-potential at state $x$ with respect to $x_0$ is defined as

$$\phi_{loc}^{QP}(x;x_0)=\inf_{T>0}\inf_{\psi(0)=x_0,\psi(T)=x}\int_0^T L^{FW}(\psi,\dot\psi)dt. \quad (14)$$

The heuristic explanation of this definition is that the energy difference between state $x$ and $x_0$ can be evaluated by the least action cost of moving the system from $x_0$ to $x$, because only the minimum action path dominates in Eq. (9) in the limit $\varepsilon\to0$. The larger $\phi_{loc}^{QP}(x;x_0)$ is, the harder it is for the system to transit from $x_0$ to $x$. In fact, the transition rate from $x_0$ to $x$ is proportional to $\exp(-\phi_{loc}^{QP}(x;x_0)/\varepsilon)$ for sufficiently small $\varepsilon$.[20]

To understand the intuition behind the quasi-potential, let us consider a gradient dynamics with a single-well potential $V(x)$, i.e.,

$$b(x)=-\nabla V(x),\ D(x)=I.$$

We assume that $V(x)\ge0$ and $V(x_0)=0$ is the unique minimum of $V(x)$. It is shown in the supplementary material[42] that the path with minimum action $\hat\psi$ satisfies $\dot{\hat\psi}=\nabla V(\hat\psi)$ and $\hat\psi(T)=x$ (this $T$ equals $\infty$ indeed), and its action is $V(x)$. By definition, we have $\phi_{loc}^{QP}(x;x_0)=V(x)$ in this single-well gradient case. The quasi-potential generalizes the potential concept in general situation.

LDT result (11) also implies that the minimizer of variational problem (14) gives the minimum action or most probable path connecting two metastable states in zero noise limit. To compute the local quasi-potential and minimum action path numerically, one possible strategy is to derive and solve the Euler-Lagrange equation of variational problem (14). However, one will encounter a singular boundary value problem because the system does not reach $x$ in finite time. This difficulty can be overcome by applying the geometric minimum action method (gMAM) to solve variational problem (14) directly through Maupertuis principle in the space of curves.[12,16,43]

### B. Distinctions between the local and global quasi-potential

The local FW quasi-potential is defined with respect to the given reference stable state $x_0$. It is already known that the function $\phi_{loc}^{QP}(x;x_0)$ only reflects the relative barrier heights and difficulty of transitions within single attractor or between neighboring pairs of stable points.[6,20] Under such circumstances, the concept of *global* FW quasi-potential $\phi_{glob}^{QP}(x)$ in Freidlin-Wentzell theory, which is defined pointwisely in the whole space and irrelevant to the specific reference state $x_0$, will be essential for the study of multi-stable systems to quantify and compare the relative stability of different stable points. Compared with the local version which is computed from transition path, the global FW quasi-potential has close relation with the steady state distribution of the system.

The intuition and working procedure to construct the quasi-potential function for multi-stable systems from the perspective of steady distribution is presented in the book[20] in great detail, although the term "global quasi-potential" has not been explicitly articulated there. The authors of Ref. 5 name this version of quasi-potential as the "global landscape" and view its disagreement with the "local landscape" as the origin of non-equilibrium steady states. In our derivation below, we will call this "global landscape" as the FW global quasi-potential $\phi_{glob}^{QP}(x)$. Our analysis will contribute to show that the relation between the local and global version of quasi-potential can be understood from the exchange of limit order for noise strength $\varepsilon$ and time $t$, and both are solutions of a specific steady Hamilton-Jacobi equation to be shown in Section III E. This exploration will also naturally lead to the well-known connection between Wang's potential landscape and FW quasi-potential.

From steady state distribution point of view, the desired limit under small noise assumption is

$$\lim_{\varepsilon\to0}-\varepsilon\ln P_{ss}(x)=-\lim_{\varepsilon\to0}\lim_{t\to+\infty}\varepsilon\ln P^\varepsilon(x,t|x_0,0), \quad (15)$$

where $P^\varepsilon(x,t|x_0,0)$ denotes the transition PDF from one stable fixed point $x_0$ at $t=0$ to state $x$ at time $t$. On the other hand, incorporating path integral formulation (7) and Laplace's

method in path space, we get

$$\begin{aligned} &-\lim_{\varepsilon\to 0}\varepsilon \ln P^{\varepsilon}(x,t|x_0,0) \\ &\quad = -\lim_{\varepsilon\to 0}\varepsilon\Big[\ln\int \mathcal{D}\psi\,\exp(-\varepsilon^{-1}S_t[\psi]) - \ln Z\Big] \\ &\quad = \inf_{\psi(0)=x_0,\psi(t)=x} S_t[\psi], \end{aligned} \tag{16}$$

where $S_t[\psi]$ corresponds to the FW functional since the higher order terms disappear in the zero noise limit. Correspondingly we obtain

$$\begin{aligned} -\lim_{t\to+\infty}\lim_{\varepsilon\to 0}\varepsilon \ln P^{\varepsilon}(x,t|x_0,0) &= \lim_{t\to+\infty}\inf_{\psi(0)=x_0,\psi(t)=x} S_t[\psi] \\ &= \phi^{QP}_{loc}(x;x_0). \end{aligned} \tag{17}$$

Although the above equations are formally established through path integral approach, whose rigorous treatment needs to be further explored, we can gain some heuristic findings from the results. We observe that the difference between the left hand side of Eq. (17) and the right hand side of Eq. (15) is just the exchange of limit order for $t$ and $\varepsilon$. In FW theory, the limit of Eq. (15) corresponds to the global quasi-potential $\phi^{QP}_{glob}(x)$ mentioned above, i.e.,

$$\lim_{\varepsilon\to 0} -\varepsilon \ln P_{ss}(x) = -\lim_{\varepsilon\to 0}\lim_{t\to+\infty}\varepsilon \ln P^{\varepsilon}(x,t|x_0,0) = \phi^{QP}_{glob}(x). \tag{18}$$

The distinction between the limits in (17) and (18) can be understood from the separation of time scales.[5] For a dynamical system with multiple attractors perturbed by small noise, the system will fluctuate around one specific attractor in a short time scale $\tau_S$, while transit among different attractors in a longer time scale $\tau_L$. According to LDT or Kramers' theory, the time scale separation is of order $\tau_L/\tau_S = \exp(\Delta V/\varepsilon)$, where $\Delta V$ represents the characteristic barrier height between different attractors. In the limit order in (17), the time $t$ is fixed first, and $\varepsilon$ can be chosen sufficiently small such that $t \sim O(\tau_S)$. Hence the limit $\phi^{QP}_{loc}(x;x_0)$ only reflects the local information about $x_0$ because the system mainly fluctuates around the stable point and could not see the outside region in this regime. In comparison, when the limit order in (15) is considered, the small noise $\varepsilon$ is fixed first, and we can wait sufficiently long time $t \sim O(\tau_L)$. Therefore the limit corresponding to $\phi^{QP}_{glob}(x)$ can tell about the global behavior of the system because transitions among different states are common under such circumstance.

When we study the long time behavior in biological systems (e.g., cell differentiation), it is more appropriate to view the noise amplitude as fixed *a priori* while the time as dependent on the observation. In this sense, the limit order in Eq. (15) is more relevant and thus the global quasi-potential is a more advisable candidate to quantify the Waddington's metaphor rather than the local version.

### C. Constructing global quasi-potential from local ones

Unexpectedly, the global quasi-potential can be constructed from local ones with an interesting pruning-and-sticking procedure.[20] Let us illustrate this point with a simple example.

Consider a one dimensional Brownian dynamics with double-well potential $V(x)$,

$$dX_t = -\nabla V(X_t)dt + \sqrt{2\varepsilon}dW_t, \tag{19}$$

where we assume $V(x)$ has two local minimum points $x_1$, $x_2$ with $V(x_1) < V(x_2)$, and one local maximum point $x_3$ in between. A schematics of $V(x)$ is depicted in Fig. 1(a). In the deterministic version, we have two stable states $x_1, x_2$ and one unstable state $x_3$.

The local quasi-potential with respect to $x_1$ and $x_2$ can be obtained by solving the variational problem directly, with details presented in the supplementary material.[42] We have

$$\phi^{QP}_{loc}(x;x_1) = \begin{cases} V(x) - V(x_1), & x < x_3, \\ V(x_3) - V(x_1), & x_3 \le x \le x_2, \\ V(x) + V(x_3) - V(x_1) - V(x_2), & x > x_2, \end{cases}$$

and similarly

$$\phi^{QP}_{loc}(x;x_2) = \begin{cases} V(x) + V(x_3) - V(x_1) - V(x_2), & x < x_1, \\ V(x_3) - V(x_2), & x_1 \le x \le x_3, \\ V(x) - V(x_2), & x > x_3. \end{cases}$$

The general methodology and theoretical results for sticking local quasi-potentials into a global one appear in the book.[20] However in this simple one dimensional example with only two stable points, the strategy is quite straightforward:

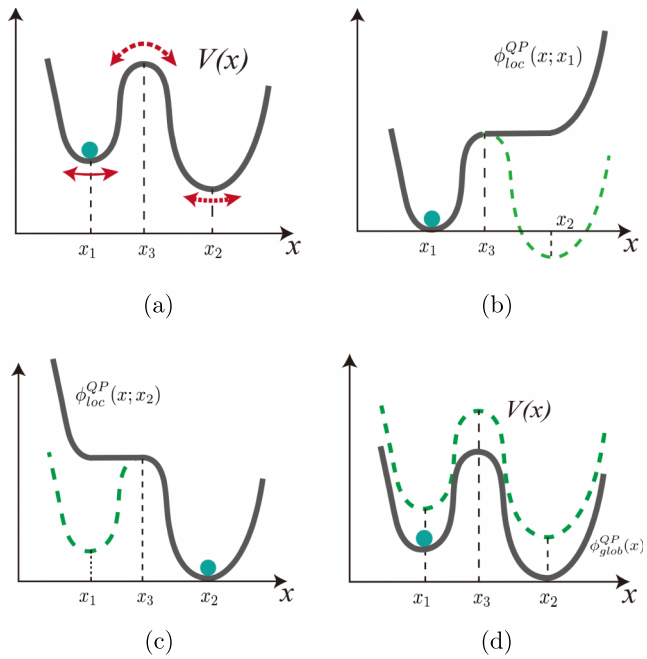



FIG. 1. The original potential field and construction of local and global quasi-potential for a bi-stable gradient system. Panel (a) shows the original potential field $V(x)$. Panels (b) and (c) show the constructed local quasi-potential starting from metastable states $x_1$ and $x_2$, respectively. In panel (d), the green dashed line is the original potential $V(x)$ and the gray solid line is the global quasi-potential $\phi^{QP}_{glob}(x)$. (a) The schematics of double-well potential $V(x)$. (b) Local quasi-potential constructed from $x_1$. (c) Local quasi-potential constructed from $x_2$. (d) The constructed global quasi-potential is a shift of $V(x)$ in the gradient case.

- Step 1. Cut out the parts of the local potential outside of the attraction basin of the starting stable point $x_1$ or $x_2$.
- Step 2. Paste the processed local potentials together through the unstable point $x_3$.
- Step 3. Shift the obtained potential such that the minimum of the global quasi-potential is 0.

Step 3 is not necessary, in general, since only the difference of potential matters for a dynamical system. Expressing the above procedure in a mathematical way, we have

$$\phi^{QP}_{glob}(x) = \min\left\{\phi^{QP}_{loc}(x;x_1) + V_{2,1}, \phi^{QP}_{loc}(x;x_2) + V_{1,2}\right\} - \min\{V_{1,2}, V_{2,1}\}, \quad (20)$$

where $V_{1,2}$ and $V_{2,1}$ denote the barrier height from stable point $x_1$ to $x_2$ and from $x_2$ to $x_1$, respectively. The construction procedure of the global quasi-potential is schematically shown in Fig. 1.

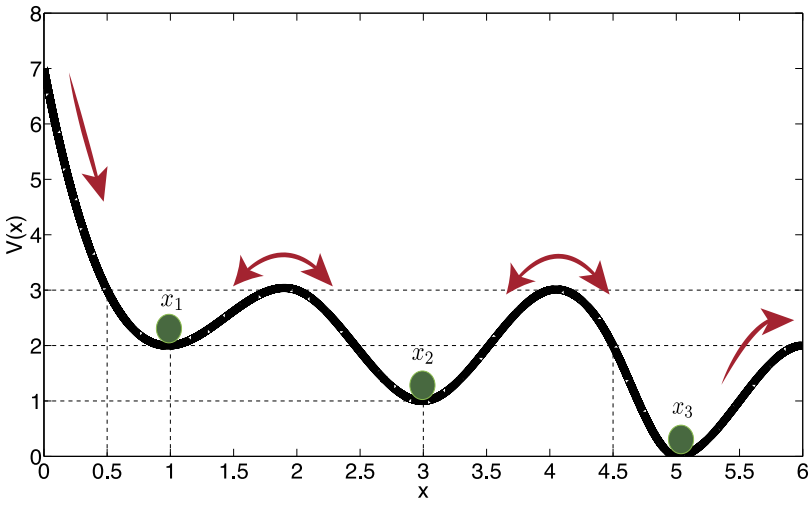
### D. Further remarks and connection with Wang's proposal

Below we will provide further remarks on the function and limit of local and global quasi-potential via a concrete example. Specially we will focus on the connections among transition rates, quasi-potentials, and transitivity issue.

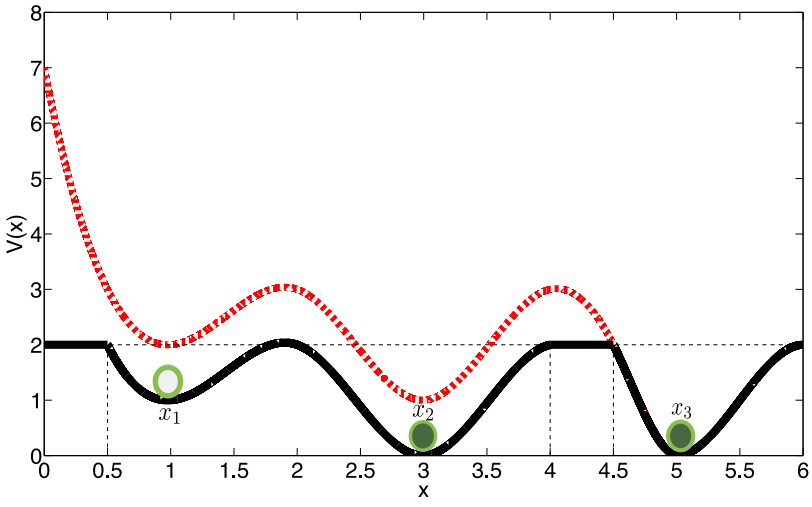
Let us consider a gradient system defined on the circle whose perimeter is $L = 6$,

$$dX_t = -\nabla V(X_t)dt + \sqrt{2\varepsilon}d\tilde{W}_t, \quad X_t \in \mathbb{S}[0, L], \quad (21)$$

where $\tilde{W}_t$ is the Brownian motion on the circle and $-\nabla V(x)$ is the periodical driving force with period $L = 6$. The shape of the potential function $V(x)$ in one period is sketched in Fig. 2(a). Note that $x = 0$ and $x = 6$ should be considered as the same point in the manifold, and $x_1 = 1, x_2 = 3, x_3 = 5$ are the three stable fixed points of the system. We also assume that $V(0.5) = 3, V(4.5) = 2$. Such type of dynamics on manifolds can be easily realized by embedding an essentially low-dimensional dynamics in a high dimensional space with




(a)




(b)

FIG. 2. The original potential field and global quasi-potential landscape for the gradient system on the circle. Panel (a) shows the original potential field $V(x)$ in one period with arrows denoting the direction of most probable transition path among attractors. Panel (b) shows the constructed global quasi-potential (solid black line) and original potential field (dashed red line). From the steady state distribution perspective, $x_2$ and $x_3$ are more stable than $x_1$. In the long run, the system will stay at $x_2$ and $x_3$ with equal probability while seldom visit state $x_1$ if the noise is sufficient small. (a) The schematics of periodical $V(x)$ in one period. (b) The constructed global quasi-potential is pieced together with $V(x)$.

high barrier in ambient environment. Similar systems have been observed during the study of cell cycle models.[12]

To simplify the notations, we denote local quasi-potential of $x_j$ with respect to $x_i$, $\phi^{QP}_{loc}(x_j; x_i)$ as $V_{i,j}$, then by minimizing the actions we obtain

$$V_{1,2} = 1, V_{2,3} = 2, V_{3,1} = 2,$$
$$V_{2,1} = 2, V_{3,2} = 3, V_{1,3} = 3.$$

With the existence of a large barrier in $0 \le x \le 1$, the most probable transition path from $x_1$ to $x_3$ must cross $x_2$.

At first we claim that the transitivity property does not hold for this system. In order to compare the relative stability of multiple attractors, the transitivity is defined in Ref. 6 that if $P_{a\to b} > P_{b\to a}$, $P_{b\to c} > P_{c\to b}$, then $P_{a\to c} > P_{c\to a}$ for any three points $a$, $b$, and $c$, where $P_{a\to b}$ is the transition rate from $a$ to $b$, and the others are similarly defined. In this example, from $V_{1,2} < V_{2,1}$ and $V_{2,3} < V_{3,2}$ we have $P_{x_1\to x_2} > P_{x_1\to x_2}$ and $P_{x_2\to x_3} > P_{x_3\to x_2}$, implying that $x_2$ is more stable than $x_1$ and $x_3$ is more stable than $x_2$, since the "less stable" state is more likely to transit into the "more stable" state. Then it seems natural to conclude that $x_3$ is more stable than $x_1$ if the transitivity property holds for the comparison of stability. However, this contradicts with the fact that $V_{3,1} < V_{1,3}$ which implies it is easier to transit from $x_3$ to $x_1$ other than $x_1$ to $x_3$. This tells us that the transitivity does not hold for local quasi-potentials in general.

According to Freidlin and Wentzell, the key quantity $W(x)$ relevant to the asymptotic invariant measure of the emergent Markov Chain is obtained by

$$W(x_1) = \min\{V_{3,2} + V_{2,1}, V_{2,3} + V_{3,1}, V_{2,1} + V_{3,1}\} = 4,$$
$$W(x_2) = \min\{V_{3,1} + V_{1,2}, V_{2,3} + V_{3,2}, V_{1,2} + V_{3,2}\} = 3,$$
$$W(x_3) = \min\{V_{2,1} + V_{1,3}, V_{2,3} + V_{3,1}, V_{2,1} + V_{3,1}\} = 3.$$

The global quasi-potential can then be calculated as

$$\begin{aligned}\phi^{QP}_{glob}(x) &= \min\{W(x_1) + \phi^{QP}_{loc}(x; x_1),\\ &\quad W(x_2) + \phi^{QP}_{loc}(x; x_2), W(x_3) + \phi^{QP}_{loc}(x; x_3)\}\\ &\quad - \min\{W(x_1), W(x_2), W(x_3)\}\\ &= \begin{cases} 1 + \phi^{QP}_{loc}(x; x_1), & 0.5 \le x < 2\\ \phi^{QP}_{loc}(x; x_2), & 2 \le x < 4.5\\ \phi^{QP}_{loc}(x; x_3), & 0 \le x < 0.5 \quad \text{or} \quad 4.5 \le x < 6 \end{cases}\\ &= \begin{cases} 2, & 0 \le x < 0.5\\ V(x) - 1, & 0.5 \le x < 4\\ 2, & 4 \le x < 4.5\\ V(x), & 4.5 \le x < 6 \end{cases}.\end{aligned}$$

One may also consult Refs. 5 and 20 for more details on constructing the global quasi-potential. The global quasi-potential for system (21) is depicted in Fig. 2(b).

We notice that compared with the potential function $V(x)$, the global quasi-potential function itself can be stuck together at $x = 0$ and $x = 6$ since $\phi^{QP}_{glob}(0) = \phi^{QP}_{glob}(6) = 2$. For this gradient system defined on the circle, the global quasi-potential landscape $\phi^{QP}_{glob}(x)$ no longer coincides with the potential field $V(x)$.

From the steady state distribution perspective, the invariant probability $P_{ss}(x)$ will be approximately proportional to $\exp(-\phi^{QP}_{glob}(x)/\varepsilon)$ for small $\varepsilon$, indicating that in the long run, the system with small random perturbation will stay at $x_2$ and $x_3$ with equal probability while rarely appear in state $x_1$. In this sense, the global quasi-potential reveals that $x_2$ and $x_3$ possess the same stability and they are more stable than attractor $x_1$. However, one needs to notice that the global quasi-potential does *not* correctly quantify the transition rate between attractors. From the global quasi-potential landscape, the "energy barrier" from $x_2$ to $x_3$ and from $x_3$ to $x_2$ is the same, while from local quasi-potential landscape, we know the transition from $x_2$ to $x_3$ is more frequent than from $x_3$ to $x_2$.

This example informs us that the two scalar functions, the local quasi-potential and the global quasi-potential, actually exhibit different information about the multi-stable system. If one pays more attention to the difficulty of local transitions (or transition rates) between attractors, then constructing a local quasi-potential landscape by minimizing action function is more appropriate. On the other hand, if the long time behavior of the system is of greater interest, then it is more advisable to construct a global quasi-potential landscape obtained by piecing the local quasi-potential together, and one needs to be careful with the conclusions about the transition rate drawn from this landscape.

Moreover, it should be addressed here that as revealed by steady state distribution analysis, it is the global quasi-potential, rather than the local one, that corresponds to the limit of Wang's potential landscape function when $\varepsilon \to 0$. In order to establish connections with other proposals, we will simply call the global quasi-potential $\phi^{QP}_{glob}(x)$ as quasi-potential $\phi^{QP}(x)$ in the later text. From the definition in Eq. (18), we reach the relationship between Wang's potential landscape and quasi-potential as explored in Refs. 5, 6, and 12,

$$\lim_{\varepsilon\to 0} \varepsilon\phi^{PL}(x) = \phi^{QP}(x). \tag{22}$$

This fact can be also observed from (5) as a special case.

### E. Force decomposition: HJE and orthogonality

As in Section II B, we will investigate the decomposition of the force $b(x)$ in terms of the global quasi-potential. We will obtain an $\varepsilon$-independent decomposition of $b(x)$, which can be viewed as the limit of Eq. (6). This decomposition is particularly useful for describing the optimal transition path between meta-stable states.

Substituting the well-known WKB ansatz[44]

$$P_{ss}(x) = \exp\left(-\frac{\phi(x)}{\varepsilon} + \phi_0(x) + \varepsilon\phi_1(x) + \cdots\right)$$

into steady Fokker-Planck equation (3) and collecting leading order terms, we arrive at a steady Hamilton-Jacobi equation for $\phi(x)$ as

$$H(x, \nabla\phi) = 0, \tag{23}$$

where $H(x,p)$ is exactly the Hamiltonian defined in (13). Relation (22) tells us the fact $\phi(x) = \phi^{QP}(x)$; thus $\phi^{QP}(x)$ satisfies the same Hamilton-Jacobi equation (23). This point

TABLE II. Summary for the quasi-potential $\phi^{QP}(x)$.

| Realization of Waddington's metaphor candidate II: Quasi-potential | |
|---|---|
| Definition | $\phi^{QP}_{loc}(x;x_0) = \inf_{T>0}\inf_{\psi(0)=x_0,\psi(T)=x}\int_0^T L^{FW}(\psi,\dot{\psi})dt$ (transition path)<br>$\phi^{QP}_{glob}(x) = -\lim_{\varepsilon\to 0}\varepsilon \ln P_{ss}(x)$ (steady state distribution) |
| Numerical strategy | Geometric minimum action method (gMAM) or solve Hamilton-Jacobi equation<br>Stick the local quasi-potentials together into the global quasi-potential |
| Force decomposition | $b(x) = -D(x)\nabla\phi^{QP}(x) + \ell(x)$ and the orthogonality between gradient and non-gradient term $\langle \ell(x), \nabla\phi^{QP}(x)\rangle = 0$, where $\ell(x)$ reflects the NESS nature of the system |
| Connection with potential landscape | $\lim_{\varepsilon\to 0}\varepsilon\phi^{PL}(x) = \phi^{QP}(x)$. The quasi-potential is a good approximation to the potential landscape when noise is small, where the numerical simulation for $\phi^{PL}(x)$ is inefficient<br>$\lim_{\varepsilon\to 0} J_{ss}(x)/P_{ss}(x) = \ell(x)$. The force decomposition based on quasi-potential is the limit version of force decomposition based on potential landscape |

can be also obtained from the Hamilton-Jacobi theory for variational problem (14) in classical mechanics.[41]

Now we can have the decomposition

$$b(x) = -D(x)\nabla\phi^{QP}(x) + \ell(x), \tag{24}$$

and the orthogonality condition

$$\ell(x)\cdot\nabla\phi^{QP}(x) = 0 \tag{25}$$

holds by (23). We note here that decomposition (24) is the zero noise limit of (6) because

$$\varepsilon\phi^{PL}(x) \to \phi^{QP}(x), \quad \varepsilon\nabla\cdot D(x) \to 0$$

and $J_{ss}(x)/P_{ss}(x) \to \ell(x)$ by the decomposition equality of $b(x)$. When the system is at equilibrium, i.e., $J_{ss}(x) = 0$, we have $\ell(x) = 0$ and thus $b(x) = -D(x)\nabla\phi^{QP}(x)$. In general $\ell(x)$ is not zero and the non-equilibrium effect exists. We comment that the normal decomposition proposed in Ref. 6 is a special case of Eq. (24) by taking $D(x) = I$.

We take the oscillatory biological dynamics to illustrate the use of force decomposition in the framework of quasi-potential theory. Following the arguments in Ref. 5, $\phi^{QP}(x)$ is constant along a limit cycle $\Gamma$. Hence from force decomposition (24), we have $b(x) = \ell(x)$ on $\Gamma$, suggesting that the oscillatory biological system is completely driven by the non-gradient force $\ell(x)$ on the limit cycle. However, the potential landscape $\phi^{PL}(x)$ is generally not constant along the limit cycle due to the finite size effect. This phenomenon is explicitly exhibited during the landscape study for budding yeast cell cycle.[12]

Decomposition (24) is also useful to characterize the optimal transition path between meta-stable states in the small noise case. Consider two neighboring meta-stable states $x_0$ and $x_1$ separated by the basin boundary $\Gamma$ with unique saddle $x^*$. We aim to find the optimal transition path $\psi(t)$ from $x_0$ to $x_1$. It can be shown that the optimal transition path is composed of two segments (see the supplementary material[42] for details),

$$\text{Uphill path:} \quad \begin{cases} \dot{\psi} = D(\psi)\nabla\phi^{QP}(\psi) + \ell(\psi), \\ \psi(-\infty) = x_0,\ \psi(\infty) = x^*, \end{cases}$$

$$\text{Downhill path:} \quad \begin{cases} \dot{\psi} = -D(\psi)\nabla\phi^{QP}(\psi) + \ell(\psi) = b(\psi), \\ \psi(-\infty) = x^*,\ \psi(\infty) = x_1, \end{cases}$$

where we have two bi-infinite boundary value problems because $x_1$, $x_2$, and $x^*$ are all stationary points of the corresponding dynamics.

The basic concepts and properties related to quasi-potential theory are summarized in Table II.

## IV. SDE DECOMPOSITION AND A-TYPE INTEGRAL

Motivated by the fluctuation-dissipation theorem,[26] Ao and his co-workers performed the SDE decomposition to obtain the underlying potential function $\phi^{AO}(x)$[23] and proposed the so-called A-type integral interpretation of the SDEs.[27] Though formally it is quite relevant to the concepts considered previously, there are seldom mathematical studies on these results. In this section, we will show that the potential function $\phi^{AO}(x)$ in the decomposed SDE is nothing but the quasi-potential $\phi^{QP}(x)$ under reasonable conditions. Furthermore, some ambiguities in the SDE decomposition theory such as the existence and uniqueness of the decomposition will also be clarified via the connection with the quasi-potential theory.

### A. SDE decomposition and the potential

In Ref. 23, it is claimed that SDEs (1) can be transformed into an equivalent decomposed form

$$\begin{aligned} [S(X_t) + A(X_t)]dX_t &= -\nabla\phi^{AO}(X_t)dt + \tilde{\sigma}(X_t)dW_t, \\ \tilde{\sigma}(x)\tilde{\sigma}(x)^t &= 2\varepsilon S(x), \end{aligned} \tag{26}$$

where $S(x)$ is a positive semi-definite matrix, $A(x)$ is an anti-symmetric matrix, and $\phi^{AO}(x)$ is the desired potential function.

In terms of physical interpretation, the stochastic process of decomposition form (26) can be related to the following physical process with frictional and Lorentz forces:

$$\begin{cases} dX_t = V_t dt \\ mdV_t = -[S(X_t) + A(X_t)]V_t dt - \nabla\phi^{AO}(X_t)dt \\ \qquad + \tilde{\sigma}(X_t)dW_t,\ \tilde{\sigma}(x)\tilde{\sigma}(x)^t = 2\varepsilon S(x) \end{cases} \tag{27}$$

as the mass of the particle $m$ tends to zero. In high dimensional case ($n > 3$), $-S(x)V_t$ is the generalization of frictional force, $-A(x)V_t$ is the generalization of Lorentz force, and

$\tilde{\sigma}(x)\tilde{\sigma}(x)^t = 2\varepsilon S(x)$ is the generalization of Einstein relation in Langevin dynamics.[27]

To mathematically execute the transformation from (1) to (26) in practice, some conditions are imposed on $S(x)$ and $A(x)$. By solving these conditions either analytically or numerically, the SDE decomposition as well as potential function $\phi^{AO}(x)$ is thought to be available.[23] In this construction, Eqs. (1) and (26) are related by the relationship $[S(x) + A(x)]b(x) = -\nabla\phi^{AO}(x)$ and $[S(x) + A(x)]\sigma(x) = \tilde{\sigma}(x)$. Inserting these expressions into $\nabla \times [-\nabla\phi^{AO}(x)] = 0$ and $\tilde{\sigma}(x)\tilde{\sigma}(x)^t = 2\varepsilon S(x)$ will yield the following constraints on $S(x)$ and $A(x)$:

$$\nabla \times [(S(x) + A(x))b(x)] = 0, \tag{28a}$$

$$[S(x) + A(x)]D(x)[S(x) - A(x)] = S(x), \tag{28b}$$

in which $\nabla \times f$ is defined as the $n \times n$ anti-symmetric matrix $(\nabla \times f)_{ij} = \partial_i f_j - \partial_j f_i$ for $f \in \mathbb{R}^n$. Hence Eqs. (28a) and (28b) form a nonlinear partial differential equation (PDE) system with $(n^2 - n)/2$ and $(n^2 + n)/2$ equations, respectively.

It is claimed in Ref. 23 that for given $b(x)$ and $D(x)$, the above $n^2$ conditions can determine $n^2$ unknown functions in $S(x)$ which is symmetric with $(n^2 + n)/2$ unknowns, and $A(x)$ which is anti-symmetric with $(n^2 - n)/2$ unknowns. Having solved $S(x)$ and $A(x)$, the potential function $\phi^{AO}(x)$ in (26) is then given by

$$\nabla\phi^{AO}(x) = -[S(x) + A(x)]b(x) \tag{29}$$

as the consequence. However, this assertion needs further mathematical justification since solving nonlinear PDE systems (28a) and (28b) is not trivial.

### B. Steady state distribution: A-type integral interpretation

One of the key parts of the proposal[23] is that the stochastic integral in decomposed SDE (26) should be interpreted as the so-called A-type integral beyond Ito or Stratonovich framework,[27] which is defined as follows.

Assume that $[S(x) + A(x)]$ is invertible in Eq. (26) and denote $G(x) = [S(x) + A(x)]^{-1}$. From (28b), we have $G(x) + G^t(x) = 2D(x)$ or $G(x) = D(x) + Q(x)$, where $Q(x)$ is an anti-symmetric matrix. The A-type Fokker-Planck equation for decomposed process (26) can be derived from zero-mass limit of extended system (27) as shown in Ref. 45,

$$\partial_t \rho = \nabla \cdot G(\varepsilon\nabla + \nabla\phi^{AO})\rho = -\nabla \cdot (b\rho) + \varepsilon\nabla \cdot (D + Q)\nabla\rho. \tag{30}$$

In one dimensional case ($n = 1$), this Fokker-Planck equation also corresponds to the right-most endpoint stochastic integral interpretation of original process Eq. (1), but there is no explicit stochastic integral interpretation of it in higher dimensions. Moreover, different from the intuitive claims in Ref. 27 that the A-type integral interpretation can be *equivalently* applied to original process (1) in general, the results in Section IV D below will suggest that the A-type Fokker-Planck equation for (1) might not be well-determined if the dimension $n \geq 3$.

One feature about the Fokker-Planck equation of A-type integral is that its steady state distribution is of Boltzmann form,

$$P_{ss}(x) = \frac{1}{Z_\varepsilon} \exp\Big(-\frac{\phi^{AO}(x)}{\varepsilon}\Big)$$

with the potential function $\phi^{AO}(x)$ appearing in the decomposition. Hence, in this case, we obtain

$$\phi^{AO}(x) = -\varepsilon \ln P_{ss}^{\text{A-type}}(x) - \varepsilon \ln Z_\varepsilon. \tag{31}$$

The first looking on (31) is reminiscent of potential landscape $\phi^{PL}(x)$. But a careful comparison tells us that the steady state distribution $P_{ss}^{\text{A-type}}(x)$ is totally different from the $P_{ss}(x)$ in (4) because of different interpretations of SDEs. This often brings confusions in the literature. Furthermore, we will show that $\phi^{AO}(x)$ is nothing but the quasi-potential $\phi^{QP}(x)$.

### C. Connection with quasi-potential

Recall that if we denote $G(x) = [S(x) + A(x)]^{-1}$, then relation (28b) yields $G(x) = D(x) + Q(x)$ where $Q(x)$ is an anti-symmetric matrix. Now we can decompose the force $b(x)$ with the form

$$\begin{aligned} b(x) &= -G(x)\nabla\phi^{AO}(x) = -[D(x) + Q(x)]\nabla\phi^{AO}(x) \\ &= -D(x)\nabla\phi^{AO}(x) + \ell(x), \end{aligned}$$

where $\ell(x) = -Q(x)\nabla\phi^{AO}(x)$. Since $Q(x)$ is anti-symmetric, we have

$$\ell(x) \cdot \nabla\phi^{AO}(x) = -(\nabla\phi^{AO})^t Q \nabla\phi^{AO} = 0.$$

Therefore just as the quasi-potential $\phi^{QP}(x)$, the potential function $\phi^{AO}(x)$ also satisfies the Hamilton-Jacobi equation

$$[b(x) + D(x)\nabla\phi^{AO}(x)] \cdot \nabla\phi^{AO}(x) = 0. \tag{32}$$

The fact that $\phi^{AO}(x)$ and $\phi^{QP}(x)$ share same partial differential equation (32) tells us that they are indeed the same function, at least when $b(x)$ has only one stationary stable state and no other attractors since there are multiple solutions of the HJE in general. Meanwhile, we do not know how to regularize to select the reasonable solution of (32) based on the original definition of $\phi^{AO}(x)$. But we will accept the choice that $\phi^{AO}(x)$ is the noise vanishing limit of (32) as the quasi-potential $\phi^{QP}(x)$ in this paper.

Result (32) also implies that the construction of $\phi^{AO}(x)$ can be achieved by the same strategy as discussed for the quasi-potential $\phi^{QP}(x)$, while the naive method by utilizing Definition (29) directly is not a feasible approach because the solution of $S(x)$ and $A(x)$ may be an even harder problem. On the contrary, we will instead study the decomposition and determine the corresponding $S^{QP}(x)$ and $A^{QP}(x)$ through the obtained quasi-potential $\phi^{QP}(x)$, i.e., $\phi^{AO}(x)$. With this perspective, we define

$$\begin{aligned} [S^{QP}(X_t) + A^{QP}(X_t)]dX_t &= -\nabla\phi^{QP}(X_t)dt + \tilde{\sigma}(X_t)dW_t, \\ \tilde{\sigma}(x)\tilde{\sigma}(x)^t &= 2\varepsilon S^{QP}(x), \end{aligned} \tag{33}$$

which we called the *reconstruction* of SDE decomposition starting from quasi-potential. Through this reconstruction, the quasi-potential $\phi^{QP}(x)$ can be reinterpreted as $\phi^{AO}(x)$, which also indicates that $\exp(-\phi^{QP}(x)/\varepsilon)$ can serve as the steady-state distribution under the A-type stochastic integral interpretation of Eq. (33).

TABLE III. Summary for the potential function $\phi^{AO}(x)$ constructed in SDE decomposition theory.

| Realization of Waddington's metaphor candidate III: SDE decomposition | |
|---|---|
| Definition | Decompose the original SDE into $[S(X_t)+A(X_t)]dX_t = -\nabla\phi^{AO}(X_t)+\tilde{\sigma}(X_t)dW_t$, with the restriction $\tilde{\sigma}(x)\tilde{\sigma}(x)^t = 2\varepsilon S(x)$<br>The potential function is defined by $\nabla\phi^{AO}(x) = -[S(x)+A(x)]b(x)$ (force decomposition) |
| Numerical strategy | Solve $n^2$ non-linear PDEs (not practical in general) |
| Steady state distribution | Interpreted under A-type integral framework, $\nabla\phi^{AO}(x) = -\varepsilon\nabla \ln P_{ss}^{\text{A-type}}(x)$ |
| Force decomposition | $b(x) = -D(x)\nabla\phi^{AO}(x)+\ell(x)$ plus the orthogonality between gradient and non-gradient term $\langle \ell(x), \nabla\phi^{AO}(x)\rangle = 0$, where $\ell(x) = Q(x)\phi^{AO}(x)$ and $Q(x)$ is an anti-symmetric matrix |
| Connection with quasi-potential | $\phi^{AO}(x)$ coincides with $\phi^{QP}(x)$ in broad situations. Although the two functions are interpreted under different frameworks, as the landscape function they are the same |
| Connection with potential landscape | $\lim_{\varepsilon\to 0}\varepsilon\nabla\phi^{PL}(x) = \nabla\phi^{AO}(x)$ |
| Existence and uniqueness of decomposition | The existence of Ao's SDE decomposition for general diffusion process can be guaranteed under the reasonable conditions stated in Theorem 1 while in high dimensional case ($n \geq 3$) the decomposition $(S, A, Q)$ is not unique in general |

Our theoretical results on the reconstruction deal with arbitrary solution $\phi(x)$ of Hamilton-Jacobi equation, which is not limited to the quasi-potential $\phi^{QP}(x)$. The existence of reconstruction (33) starting from $\phi(x)$ is guaranteed by the following theorem:

**Theorem 1.** *Suppose $D(x)$ is not singular and $\phi(x)$ is the solution of Hamilton-Jacobi equation (32). If $b(x)$ and $\nabla\phi(x)$ have the same zeros, then there exist a positive definite matrix $S(x)$ and an anti-symmetric matrix $A(x)$ such that $[S(x) + A(x)]b(x) = -\nabla\phi(x)$ and $[S(x) + A(x)]D(x)[S(x) - A(x)] = S(x)$.*

We also discovered that, in general, the constructed $S(x)$ and $A(x)$ are not unique in high dimensions ($n \geq 3$). Moreover, this under-determination of $S$ and $A$ can be also quantitatively characterized:

**Theorem 2.** *Suppose $D(x)$ is not singular and $\phi(x)$ is the solution of Hamilton-Jacobi equation (32). If $\phi(x)$ is also nonsingular (i.e., $\nabla\phi(x) \neq 0$) for fixed $x \in \mathbb{R}^n$, then $S(x)$ and $A(x)$ in Theorem 1 have the degrees of freedom $(n-1)(n-2)/2$.*

The detailed proof is presented in Appendix B. Here let us remark on the two conditions imposed in Theorem 1: the non-singularity of diffusion matrix $D(x)$ and the common-zero assumption of $b(x)$ and $\nabla\phi(x)$. It can be found in the proof that the non-singularity of $D(x)$ is just a technical condition which is not always necessary in practice. For the common-zero assumption, a related example will be provided in Section V to show that the violation of such assumption may lead to the ambiguity of A-type integral Fokker-Planck equation.

### D. Existence and uniqueness issue of SDE decomposition

Our theoretical results on the SDE decomposition lead to the discussion about rigorous mathematical aspects of the proposal.[23]

One fundamental theoretical issue is the existence and uniqueness of the SDE decomposition. Starting from SDE (1), the quasi-potential function $\phi^{QP}(x)$ can be constructed. As long as $\phi^{QP}(x)$ satisfies the common-zero assumption (which can be viewed as an inherent property of the SDE), the existence of the decomposition can be established as the corollary of Theorem 1. However, Theorem 2 suggests that when $n \geq 3$, the original SDE might be decomposed into a family of different SDEs in form (26) satisfying the restrictions in (28) (these SDEs share the same potential function $\phi^{QP}(x)$), indicating that the imposed conditions in the theory do not uniquely determine the decomposition.

These results clarify that it is more appropriate to apply the A-type stochastic integral interpretation to decomposed SDEs (26) rather than original SDE (1), since there might be a family of different $G(x)$ corresponding to the same original SDEs, which renders the Fokker-Planck equation undetermined (cf. the examples in the supplementary material[42]).

Therefore, we conclude that the potential function $\phi^{AO}(x)$ and the decomposition matrix $S(x)$, $A(x)$, and $G(x)$ should be analyzed separately in the SDE decomposition theory. In the A-type integral framework, $\phi^{AO}(x)$ (which is shown to be consistent with $\phi^{QP}$ in many situations) determines the steady state distribution, while $S(x), A(x)$, and $G(x)$ (which are not uniquely determined in general) reveal the relaxation behavior of probability evolution in Fokker-Planck equation. It is interesting to note that for a given SDE (1), there may exist various relaxation processes leading to the same invariant distribution under A-type integral interpretation, which suggests that the potential function $\phi(x)$ serves as a more characteristic quantity for SDE (1) rather than $S(x)$ and $A(x)$.

We summarize our explorations and findings on the SDE decomposition theory in Table III.

## V. COMPARATIVE STUDY THROUGH A TOY EXAMPLE

In this section, a simple yet illuminating example will be provided to help us gain better understanding of the landscape construction proposals discussed in Secs. I–IV. We consider the following diffusion process defined on the circle $\mathbb{S}[0, 1]$:

$$dX_t = dt + \sqrt{2\varepsilon}d\tilde{W}_t, \quad X_t \in \mathbb{S}[0, 1], \tag{34}$$

where $\tilde{W}_t$ is the Brownian motion on the circle. Physically, it describes a particle doing uniform circular motion under random perturbations.

In potential landscape theory, let $p(x,t)$ denote the probability density of particle appearing at point $x \in [0,1]$ on the circle at time $t$. The Fokker-Planck equation is

$$\partial_t p + \partial_x(p - \varepsilon\partial_x p) = 0, \quad p(x,t) = p(x+1,t).$$

We can obtain the steady state distribution $P_{ss}(x) = 1$, $x \in [0,1]$ and steady state flux $J_{ss}(x) = 1$. Therefore the potential landscape satisfies $\phi^{QP}(x) = \ln P_{ss}(x) = 0$ on the circle. From force decomposition perspective, the particle is completely driven by the curl term $J_{ss}/P_{ss} = 1$, reflecting the non-equilibrium nature of the system. In fact, the uni-direction feature of this system has close relation with the concept of entropy production in non-equilibrium statistics.[46] The rotation number of this system is 1, and the entropy production rate is $\varepsilon^{-1}$.

In the framework of quasi-potential, the landscape can be either computed from Hamilton-Jacobi equation or minimum action approach. The Hamilton-Jacobi equation is

$$(1 + \phi'(x))\phi'(x) = 0$$

with boundary condition $\phi(x) = \phi(x+1)$, yielding the solution $\phi^{QP}(x) = \text{Constant}$. From the minimum action approach, the least action path $\psi(t)$ connecting any points $x_1$ and $x_2$ on the circle satisfies the deterministic counterpart $\dot{\psi}(t) = 1$ and the action on the path is zero, also indicating that the quasi-potential on the circle should be constant. Interestingly, if we choose the transition path in the opposite direction, then action will increase along the path, which also reflects the system's non-equilibrium property (the time irreversibility). The driving force on the particle is solely the non-gradient term $\ell(x)$ along the circle. This phenomenon is depicted in Fig. 3.

Because the quasi-potential $\phi'(x) = 0$ on the circle while $b(x) = 1$, we cannot apply our results on the connection between the quasi-potential and $\phi^{AO}$ directly as stated in Theorem 1. We will construct the SDE decomposition directly from definition. Assume the SDE decomposition has the form

$$[s(X_t) + a(X_t)]dX_t = -\phi'(X_t) + \tilde{\sigma}(X_t)d\tilde{W}_t,$$
$$X_t \in \mathbb{S}[0,1], \quad \tilde{\sigma}^2(x) = 2\varepsilon s(x).$$

Since $n = 1$, we have $a(x) = 0$ and $\phi'(x) = s(x)$ in (28). Moreover, condition (28) yields $s^2(x) = s(x)$, implying that $s(x) = 0$ or $s(x) = 1$ by the smoothness of $s(x)$. On the other hand, the boundary condition $\phi(x+1) = \phi(x)$ requires that $\phi'(x) = s(x) = 0$. With these facts, we know that decomposed equation (26) is not well defined because both sides are zero. A-type integral Fokker-Planck equation (30) does not apply in this case.

The comparison of different proposals to realize Waddington's metaphor for the system modeled by Eq. (34) is presented in Table IV.

Although the considered example is just a toy model, it has already been discovered in the study of a cell cycle model[12] that similar phenomenon can happen in biological networks where the gradient of quasi-potential vanishes on a manifold. This example informs us that in some non-equilibrium systems, the landscape itself cannot describe the whole picture, thus must be combined with other tools to obtain a more comprehensive understanding of the system.

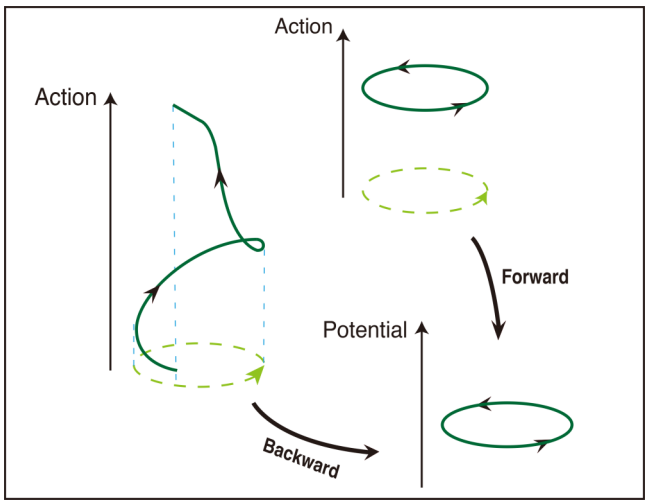



FIG. 3. Constructing the quasi-potential for the diffusion process on the circle modeled by Eq. (34). If the path is in the opposite direction of the force term, the action will increase along it. The least action path satisfies the deterministic counterpart of the stochastic process where the action as well as the quasi-potential remains to be zero. This reflects the time irreversibility of the system.

TABLE IV. Different realizations of Waddington's metaphor for the simple diffusion process on the circle.

| Proposals | Landscape function | Special features |
|---|---|---|
| Potential landscape | $\phi^{PL}(x) = 0$ | The system (rotation number 1, entropy production rate $\varepsilon^{-1}$) is completely driven by non-gradient force |
| Quasi-potential | $\phi^{QP}(x) = 0$ | The action remains constant along the clockwise path while increases along the anti-clockwise path |
| SDE decomposition | $\phi^{AO}(x) = ?$ | The both sides of the decomposed SDE are 0 and the corresponding A-type integral Fokker-Planck equation is ill-defined |

## VI. DISCUSSIONS AND CONCLUSION

In this paper, we have adopted different perspectives (steady state distribution, transition path, and force decomposition) to investigate three existing landscape theories. To summarize our findings, we conclude that the quasi-potential $\phi^{QP}(x)$ is the limit of potential landscape $\phi^{PL}(x)$ as the noise strength goes to zero, and the potential $\phi^{AO}(x)$ in SDE decomposition theory coincides with $\phi^{QP}(x)$ in many situations. We also discover that condition (28) does not uniquely determine the decomposition. To avoid ambiguity, it will be more reasonable to define the A-type integral to decomposed form (26) rather than its primitive form. Next we provide some discussions based on our results in this paper.

From a numerical point of view, the Monte Carlo simulation is more efficient than the deterministic methods

in high dimensions to obtain potential landscape $\phi^{PL}(x)$, while when the noise amplitude is small, even Monte Carlo simulation becomes costly due to the metastability issue.[31] In such circumstance, it is advisable to approximate potential landscape $\phi^{PL}$ by quasi-potential $\phi^{QP}$, which can be computed by gMAM or other numerical methods. The path integral formulation adopted by us might imply other MCMC algorithms to compute the potential landscape, especially when the noise amplitude $\varepsilon$ is in the intermediate regime, where it is too large to adopt quasi-potential approximation while too small to effectively conduct Monte Carlo simulation. In such cases, the idea of importance sampling might help to get the estimation of $\phi^{PL}(x)$ effectively.

Our results on the existence and uniqueness of decomposition (26) provide a negative answer to the open problem raised in Ref. 47: whether conditions (28) are sufficient to determine the decomposition uniquely? In cases when $n \geq 3$, we find that there is a class of processes of form (26) which correspond to same SDE (1) and their A-type Fokker-Planck equations are different. The non-uniqueness of SDE decomposition also appears in the construction of Lyapunov functions for dynamical systems.[48] However, the non-uniqueness there arises from the arbitrariness of choosing diffusion matrix $D(x)$, while our results suggest that even if $D(x)$ is fixed, the decomposition is also not unique. Our results on the non-uniqueness of SDE decomposition raise a meaningful question both experimentally and theoretically: given the system described by (1), how would nature choose one particular process with decomposition form (26) from all the candidates? Could there exist any other restrictions on $S$ and $A$ besides condition (28) which helps determine the decomposed process uniquely?

After studying the construction of landscapes for diffusive dynamics, it is natural to consider how to generalize these concepts to discrete jump processes. For the potential landscape theory, one needs to compute on the discrete lattices, and the cost may be significant when the number of molecules is large. The quasi-potential theory relies on the unified LDT framework and can be easily applied to the models with large system size,[16] but there will be difficulty to handle the hybrid system with low copy number of species. It looks that the SDE decomposition theory is difficult to be generalized to the discrete cases and thus the discussion in the current paper does not apply.

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## APPENDIX A: LAPLACE'S METHOD AND LAPLACE PRINCIPLE

Laplace's method is used for approximating integrals of exponential type, stating that

$$\int_a^b e^{g(x)/\varepsilon} dx \sim \sqrt{\frac{2\pi\varepsilon}{|g''(x_0)|}} e^{g(x_0)/\varepsilon}, \quad \text{as } \varepsilon \to 0+, \tag{A1}$$

where $x_0$ is assumed to be the unique maximum of $g(x)$.

In large deviation theory, the logarithmic form of Eq. (A1) is commonly used, known as the Laplace principle. Suppose $A$ is a regular subset (Borel set in mathematics) and $\varphi$ is a measurable function, then

$$\lim_{\varepsilon \to 0} \varepsilon \ln \int_A e^{-\varphi(x)/\varepsilon} dx = -\inf_{x \in A} \varphi(x).$$

In the main text, we also formally adopt the Laplace principle in the infinite dimensional path space.

## APPENDIX B: PROOF OF THE THEOREMS ON SDE DECOMPOSITION THEORY

We will prove Theorem 1 of the main article by reconstructing the desired $S$ and $A$ in the theorem, and the results in Theorem 2 of the main article will be revealed during the reconstruction process.

The main idea of the reconstruction procedure consists of three steps:

- Step 1. Finding a solution $\phi(x)$ of Hamilton-Jacobi equation (32) with appropriate boundary conditions.
- Step 2. Constructing a matrix function $G(x)$ such that $G(x)\nabla\phi(x) = -b(x)$ and $G(x) + G^T(x) = 2D(x)$. We can show that the desired $G(x)$ can be constructed by solving certain linear systems, whose solvability is guaranteed by the conditions in the theorem. The degrees of freedom of $G(x)$ can be also obtained.
- Step 3. Setting $S(x) = [G^{-1}(x) + G^{-T}(x)]/2$ and $A(x) = [G^{-1}(x) - G^{-T}(x)]/2$, thus obtaining the decomposed form in Eq. (26). The invertibility of $G(x)$ is implied by the non-singularity of $D(x)$.

If the described procedure works, then Theorem 1 will be verified. In theoretical aspects, one needs to ensure the following:

- The existence of solutions for the linear system arises in step 2, which guarantees the existence of $G(x)$.
- The invertibility of the constructed $G(x)$, which guarantees the existence of $S(x)$ and $A(x)$ in step 3.
- The verification of condition (28) in the main article for $S(x)$ and $A(x)$ obtained in step 3, which guarantees the constructed $S, A$ and $\phi(x)$ are the desired quantities in Eq. (26).

We will show that under the assumptions stated in Theorem 1, all the requirements above can be satisfied. Theorems 1 and 2 can then be proved as the result.

### 1. The existence of $G(x)$

From $G(x) + G^T(x) = 2D(x)$, we can write $G(x) = D(x) + Q(x)$, where $Q(x)$ is an anti-symmetric matrix. Hence the existence of $Q(x)$ such that

$$Q(x)\nabla\phi(x) = -b(x) - D(x)\nabla\phi(x) \tag{B1}$$

will imply the existence of $G(x)$ in step 2 of the reconstruction procedure. We use the vector $q(x) = (q_1(x), q_2(x), \ldots, q_{n(n-1)/2}(x))^T$ to represent $Q(x)$ by

$$Q(x) = \begin{pmatrix} 0 & q_1 & q_2 & \cdots & q_{n-2} & q_{n-1} \\ -q_1 & 0 & q_n & \cdots & q_{2n-4} & q_{2n-3} \\ -q_2 & -q_n & 0 & \cdots & q_{3n-7} & q_{3n-6} \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ -q_{n-2} & -q_{2n-4} & -q_{3n-7} & \cdots & 0 & q_{n(n-1)/2} \\ -q_{n-1} & -q_{2n-3} & -q_{3n-6} & \cdots & -q_{n(n-1)/2} & 0 \end{pmatrix}.$$

We can transform Eq. (B1) into the following linear system for vector $q(x)$:

$$\Psi(x)q(x) = -b(x) - D(x)\nabla\phi(x). \tag{B2}$$

The coefficient matrix $\Psi(x)$ has the form

$$\Psi(x) = (\Psi_1(x), \Psi_2(x), \ldots, \Psi_{n-1}(x)),$$

where the $i$th block $\Psi_i(x)$ is an $n \times (n-i)$ matrix with the structure

$$\Psi_i(x) = \begin{pmatrix} O \\ \tilde{\Psi}_i(x) \end{pmatrix},$$

in which $O$ represents the $(i-1) \times (n-i)$ zero matrix and the structure of $\tilde{\Psi}_i(x)$ is

$$\tilde{\Psi}_i(x) = \begin{pmatrix} \phi_{x_{i+1}} & \phi_{x_{i+2}} & \phi_{x_{i+3}} & \cdots & \phi_{x_{n-1}} & \phi_{x_n} \\ -\phi_{x_i} & 0 & 0 & \cdots & 0 & 0 \\ 0 & -\phi_{x_i} & 0 & \cdots & 0 & 0 \\ 0 & 0 & -\phi_{x_i} & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & -\phi_{x_i} & 0 \\ 0 & 0 & 0 & \cdots & 0 & -\phi_{x_i} \end{pmatrix} \in \mathbb{R}^{(n-i+1)\times(n-i)},$$

where $\phi_{x_i}$ denotes $\partial_{x_i}\phi(x)$. The concrete expression of $\Psi$ for dimension $n = 4$ takes the following form:

$$\Psi = \begin{pmatrix} \phi_{x_2} & \phi_{x_3} & \phi_{x_4} & 0 & 0 & 0 \\ -\phi_{x_1} & 0 & 0 & \phi_{x_3} & \phi_{x_4} & 0 \\ 0 & -\phi_{x_1} & 0 & -\phi_{x_2} & 0 & \phi_{x_4} \\ 0 & 0 & -\phi_{x_1} & 0 & -\phi_{x_2} & -\phi_{x_3} \end{pmatrix}. \tag{B3}$$

Based on the above manipulations, the existence of $G(x)$ is converted to the solvability of linear system (B2). This can be ensured by studying the following two cases.

- Case 1: $\nabla\phi(x) \neq 0$.

  Notice that all column vectors of matrix $\Psi$ are orthogonal to $\nabla\phi$ and from Hamilton-Jacobi equation we know the right hand side $-b(x) - D\nabla\phi(x)$ is also orthogonal to $\nabla\phi$. Thus the column space of augmented matrix $A = (\Psi, -b - D\nabla\phi)$ is orthogonal to the non-zero vector $\nabla\phi$. This indicates that the column space cannot be the whole space $\mathbb{R}^n$ (otherwise $\nabla\phi = 0$), so we have $\text{rank}(A) \leq n-1$. On the other hand, from $\nabla\phi \neq 0$ we may assume $\phi_{x_{i_0}} \neq 0$. Then there exists an $(n-1) \times (n-1)$ nonsingular diagonal sub-matrix of $\Psi$ with diagonal elements $\pm\phi_{x_{i_0}}$. Hence $n-1 \leq \text{rank}(\Psi) \leq \text{rank}(A) \leq n-1$, which yields $\text{rank}(A) = \text{rank}(\Psi) = n-1$ and therefore guarantees the existence of solution $q(x)$.
- Case 2: $\nabla\phi(x) = 0$.

  From the assumption that $b$ and $\nabla\phi$ have the same zeros, we must have $b(x) = 0$. Then in Eq. (B2), the $\Psi$ on the left hand side is a zero matrix and the right hand side is a zero vector; therefore, any $q(x) \in \mathbb{R}^n$ solves the linear system.

Hence we conclude that under the assumptions stated in Theorem 1, the solution $q(x)$ of linear system (B2) always exists. This ensures the existence of $Q(x)$ and $G(x)$ in step 2 of the reconstruction procedure.

### 2. The invertibility of $G(x)$

To show that the matrix $G(x)$ constructed is invertible for any given $x$, we need to utilize the relation $G(x) = D(x) + Q(x)$ and the fact that $D(x)$ is positive definite. Assume that $y \in \mathbb{R}^n$ is the solution of linear system $G(x)y = 0$. We then have

$$0 = y^t G(x)y = y^t[D(x) + Q(x)]y = y^t D(x)y.$$

From the positive definiteness of $D(x)$, we conclude that $y = 0$. This ensures the invertibility of $G(x)$.

### 3. Verification of conditions for $S(x)$ and $A(x)$

With the constructed $G(x)$, we define

$$S(x) = \frac{1}{2}[G^{-1}(x) + G^{-T}(x)] \quad \text{and}$$
$$A(x) = \frac{1}{2}[G^{-1}(x) - G^{-T}(x)].$$

Direct calculation shows that

$$\begin{aligned} [S(x) + A(x)]b(x) &= G^{-1}(x)b(x) = -\nabla\phi(x), \\ [S(x) + A(x)]D(x)[S(x) - A(x)] &= G^{-1}(x)\frac{1}{2}[G(x) + G^T(x)]G^{-T}(x) \\ &= \frac{1}{2}[G^{-T}(x) + G^{-1}(x)] = S(x), \end{aligned}$$

which concludes the proof of Theorem 1. The results also indicate that the constructed $S(x)$ and $A(x)$ from the procedure satisfies condition (28) in the main article and thus $S, A, \phi$ are the desired quantities in transformed stochastic process (26) in the main article.

Moreover, the argument in case 1 of Appendix B 1 also implies that the degrees of freedom for solutions of linear system (B2) are $n(n-1)/2-(n-1)=(n-1)(n-2)/2$ provided that $\nabla\phi(x)\neq 0$. Since $G(x)$ has the structure

$$G(x)=G^*(x)+\sum_{k=1}^{(n-1)(n-2)/2}\lambda_k(x)Q_k(x),$$

where $G^*(x)$ is a special solution and $Q_k(x)$ a set of linearly independent fundamental solutions, then $G^{-1}(x)$ and the constructed $S(x)$ and $A(x)$ also possess the degrees of freedom $(n-1)(n-2)/2$, which leads to the conclusion of Theorem 2.

## 4. Some remarks

Finally, let us remark on the two conditions imposed in Theorem 1: the non-singularity of diffusion matrix $D(x)$ and the common-zero assumption of $b(x)$ and $\nabla\phi(x)$. It can be found in the proof that the non-singularity of $D(x)$ is just a technical condition to ensure the invertibility of the constructed $G(x)$ in the second step. In practice, as long as the solved $G(x)$ is invertible, this assumption on $D(x)$ can be removed. For the common-zero assumption, in the first place one can show that if $b(x_0)=0$, then $\nabla\phi(x_0)=0$ provided that $\det D(x_0)\neq 0$. The violation of common-zero assumption mostly happens in the case $b(x_0)\neq 0$ and $\nabla\phi(x_0)=0$. From $[S(x_0)+A(x_0)]b(x_0)=-\nabla\phi(x_0)$, we know $S(x_0)+A(x_0)$ is degenerate, implying that the A-type integral Fokker-Planck equation is not well-defined at $x_0$ as presented in Section V of the main article.


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