Potential landscape of high dimensional nonlinear stochastic dynamics and rare transitions with large noise

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Quantifying stochastic processes is essential to understand many natural phenomena, particularly in biology, including cell-fate decision in developmental processes as well as genesis and progression of cancers. While various attempts have been made to construct potential landscape in high dimensional systems and to estimate rare transitions, they are practically limited to cases where either noise is small or detailed balance condition holds. A general and practical approach to investigate nonequilibrium systems typically subject to finite or large multiplicative noise and breakdown of detailed balance remains elusive. Here, we formulate a computational framework to address this important problem. The current approach is based on a least “action” principle to efficiently calculate potential landscapes of systems under arbitrary noise strength and without detailed balance. With the deterministic stability structure preserving A-type stochastic integration, the potential barrier between different (local) stable stables is directly computable. The prevailing methods such as those based on WKB or Freidlin-Wentzell quasi-potential theory can be classified into the case of the present framework under small noise limit. We demonstrate our approach in a numerically accurate manner through explicitly solvable examples. We further apply the method to investigate the role of noise on tumor heterogeneity in a 38 dimensional network model for prostate cancer, and provide a new strategy on controlling cell populations by manipulating noise strength.

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I. INTRODUCTION

Studying stochastic dynamics is a central task to understand various natural and experimental phenomena in physics [1, 2], chemistry [3], and biology [4–6]. Specifically, stochastic transitions induce current switching in semiconductor [7], reveal population stabilization [8] or extinction [9], and provide an integrated picture for genesis and progression of complex diseases such as cancers [10]. Potential landscape [11–13] can be constructed for the underlying dynamical systems, and used as a powerful tool to quantify multi-stability and estimate rare transitions. However, a general approach to achieve this task in practice remains elusive. The first challenge is that real-world systems are intrinsically high dimensional, e.g., gene regulatory network [4, 14], which makes the brute force simulation computationally unfeasible. In addition, systems may also subject to significant random fluctuations [15–18] that have functional roles such as driving cell fate decision [5, 19–21]. To investigate such noisy effects with robust efficiency in high dimensional systems is another major difficulty.

Previous attempts of simulating the steady state distribution to calculate the potential landscape suffer from exponentially increasing computational cost, and thus direct simulation encounters the curse of dimensionality. The sampling efficiency can be improved when detailed balance condition is employed [22], however, this condition breaks down for nonequilibrium systems. Except simulations, the methods based on WKB approximation [23] or Freidlin-Wentzell quasi-potential theory [24–27] are proposed, but their applications are restricted by the zero noise limit. The reason is that they use fixed points of the deterministic model as most probable states for the stochastic process. Nevertheless, such determined fixed point positions can be altered by their implicitly used stochastic integration, typically Ito’s or Stratonovich’s [28], known as “noise effects” [29–32]. The deviation appears even when noise is additive (illustrated in FIG. 1), and becomes dramatic when noise is intensive, which is widely observed in real-world systems [15–18]. Therefore, on one hand, the high dimensionality defies the use of expensive stochastic simulation; on the other hand, stochastic simulation seems inevitable except when noise is small. This conundrum avoids quantifying stability and rare transitions in high dimensional systems with large noise and breakdown of detailed balance.

Towards resolving this problem, we develop a computational framework based on path integral, least “action” principle and A-type interpretation [33] of the stochastic differential equation (SDE). We obtain a potential function exactly corresponding to the steady state distribution for SDE and the Lyapunov function [34] for the deterministic counterpart, an ordinary differential equation (ODE), as exemplified in FIG. 1(d-f). We further classify two independent causes for the deviation between

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ODE and SDE when using the prevailing stochastic integrations: 1) the existence of a non-detailed balance part; 2) a variable-dependent diffusion matrix (multiplicative noise). The present method is applicable to both cases, and has two advantages: 1) the computational cost to calculate potential difference is scalable; 2) it is robust under arbitrary noise strength through a general consistency between ODE and SDE, and thus break the small noise restriction.

The present approach can be applied to a wide range of high dimensional stochastic dynamics, and enables us to investigate the role of large noise. It provides an efficient way to calculate probability ratios and transition rates between stable states. We demonstrate the method in a numerically accurate manner through an example with various noise intensities, and apply it to a 38 dimensional network model for prostate cancer [35]. In particular, the tumor heterogeneity [6, 36, 37] is observed controllable by noise intensity. The result may uncover a mechanistic basis for hyperthermia.

In Sect. II, we introduce the framework to generally establish a consistency between SDE and its ODE counterpart. We demonstrate the present efficient numerical approach to calculate potential differences between stable states in Sect. III, and then apply this method to the biological example in Sect. IV. We discuss the relationship with previous works and summarize in Sect. V. In Appendix A, we analyze the deviation between ODE and SDE when using prevailing simulations, and classify the effects of non-detailed balance and multiplicative noise.
through explicitly solved examples. “Action” functions for various stochastic integrations, numerical implementation, analysis on pre-factor of rate formula and differences with Freidlin-Wentzell’s framework [24] are also in Appendixes.

II. FORMULATION

A. Deviation between ODE and SDE

ODE and SDE can model a wide range of dynamics [28, 34], for example, chemical reactions [2], population stabilization [8], neural network [38], and carcinogenesis [35]. ODEs have been successfully used to quantitatively model average behaviors of the stochastic process [14, 39–41], for example, stable states correspond to biological phenotypes [10]; SDEs, by further adding a vanishing-mean noise term to capture the source of stochasticity offer a convenient way of examining stability and spontaneous transitions in nonlinear systems [5, 19, 42, 43]. A major advantage of SDE modeling is the extractable dynamical information from the ODE counterpart, which may greatly reduce the computational cost of stochastic modeling. However, unexpected “noise effects” emerge in using SDEs and are reported widely [29–32]. We also demonstrate here that even for a two dimensional example with additive white noise, the dynamical structure can be dramatically altered by noise, e.g., from multi-stable to uni-stable, when applying prevailing simulation methods like Ito’s or Stratonovich’s [28], as shown in FIG. 1(a-c).

To study multi-stability and stochastic transitions, the concept of landscape originally proposed by Wright [11] and Waddington [12] has been developed as a quantitative tool [13, 24, 25, 44] and are widely used [5, 23, 26, 27]. Valleys in the landscape correspond to the locally most probable states in the steady state distribution of the stochastic process, and can be recognized as different biological phenotypes [45, 46], for instance. The height of the potential barrier from a valley to another along the landscape corresponds to the transition rate. For a given SDE model, as the unexpected “noise effects” when using prevailing stochastic integrations generally deviate valleys from stable states of the ODE counterpart and alter the dynamical structure, one cannot use information obtained by ODE, and has to simulate the steady state distribution to identify the valleys’ positions and figure out potential barrier in the landscape, introducing intricacies in applications.

There are two independent causes for the deviation between ODE and SDE with using the prevailing stochastic simulations: 1) the existence of a non-detailed balance part; 2) multiplicative noise. Both causes are related to the freedom of choosing a stochastic interpretation for SDE. With the presence of multiplicative noise, it is known that conventional stochastic integrations like Ito’s and Stratonovich’s lead to distinct modeling results [28]. However, the deviation by non-detailed balance has not been noticed before, and it can occur even for systems with additive noise, where Ito’s and Stratonovich’s show no difference. Therefore, the prevailing stochastic simulations could not achieve the consistency for systems without detailed balance. More details are given in Appendix A.

Regarding the issues raised above, one may ask the following question: Is there a possibility to eliminate such unexpected “noise effects” and establish a general consistency between ODE and SDE modeling even under large fluctuations? If possible, dynamical information from the ODE counterpart can be inherited by the SDE modeling, such that the valleys’ positions in the landscape of SDE is obtainable by calculating stable states of ODE. The consistency is particularly necessary in a scenario where an ODE model is properly constructed and quantitatively correspond to experimental data on average, but are invalidated by the usual way of simulating SDE in reconstituting the original stochastic process and vice versa.

B. Bridging ODE and SDE

We provide a background on the framework that bridges ODE and SDE:

\[
\dot{x} = f(x), \quad (1)
\]

\[
\dot{x} = f(x) + G(x)\zeta(t), \quad (2)
\]

where the \( N \)-dimensional vector \( x \) denotes state variables, and \( \dot{x} \) represents its time evolution. The deterministic part is \( f(x) \), and the \( M \)-dimensional Gaussian white noise \( \zeta(t) \) has \( \langle \zeta(t) \rangle = 0 \), \( \langle \zeta(t)\zeta(t') \rangle = 2\epsilon\delta(t-t') \), where \( \epsilon \) is the noise strength playing the role of temperature, the superscript \( \tau \) denotes transpose, \( \delta(t-t') \) is the Dirac delta function, and \( \langle \cdot \cdot \cdot \rangle \) represents noise average. Here, \( G(x)G^\tau(x) = D(x) \) defines the symmetric positive definite diffusion matrix \( D(x) \). The multiplicative noise \( G(x)\zeta(t) \) models that system state can in turn regulate noise by feedback, or inhomogeneity of the noisy environment. The results in Sect. III are valid for multiplicative noise. The stochastic integration [28] for Eq. (2) is to be specified below.

It is challenging to generally construct Lyapunov function [34] for ODEs, because \( f \) is typically nonlinear and cannot be written directly as the gradient of a potential function \( U(x) \): \( f \neq -\nabla U \). Even so, a decomposed dynamics equivalent to Eq. (2) was discovered [13], and Eqs. (1) and (2) can be coherently decomposed as:

\[
f(x) = -[D(x) + Q(x)]\nabla L(x), \quad (3)
\]

\[
\dot{x} = -[D(x) + Q(x)]\nabla \phi(x) + G(x)\ast\zeta(t), \quad (4)
\]

where the matrix \( Q(x) \) is anti-symmetric with \( \nabla \phi^\ast Q \nabla \phi = 0 \), and the asterisk means A-type stochastic integration [33]. A Lyapunov function \( L(x) \) and a
potential function \( \phi(x) \) are constructed, and \( L(x) \) satisfies \( dL/dt \leq 0 \) for any trajectory of Eq. (1) \([47–49]\). For Eq. (4), by solving the corresponding Fokker-Planck equation (FPE):

\[
\frac{\partial \rho(x, t)}{\partial t} = \nabla_x^\top [D(x) + Q(x)] \nabla_x \phi(x) + \epsilon \nabla_x \rho(x, t),
\]

(5)

which is obtained from the zero-mass limit on a 2N-dimensional Klein-Kramers equation \([50]\), the steady state obeys Boltzmann-Gibbs distribution \( \rho_{ss}(x) = \exp[-\phi(x)/\epsilon] \). As the steady state is invariant under transformation \( \phi \to \phi + C \) for any constant \( C \), we have chosen \( C \) such that the distribution is normalized.

**A-type integration** is defined as the connection between SDE (2) and FPE (5), and realized by two explicit limiting procedures: first the usual integration limit and then the zero mass limit \([50]\). Even for systems with additive noise, it is different from the conventional \( \alpha \)-type stochastic integration \([33]\) (\( \alpha = 0 \) is Ito’s, \( \alpha = 1/2 \) is Stratonovich’s), except that when detailed balance condition holds \( (Q = 0) \) it corresponds to \( \alpha = 1 \). An exact transformation from A-type integration to Ito’s has been achieved \([33]\). **A-type simulation** can thus be implemented as follows: Eq. (4) is transformed to be an equivalent SDE under Ito’s interpretation:

\[
x = f(x) + \epsilon \Delta f(x) + G(x) \cdot \zeta(t),
\]

(6)

where \( \Delta f(x) = \sum_j \partial_{x_j} [D_{ij}(x) + Q_{ij}(x)] \), and the dot denotes Ito’s integration. Thus, one can simulate Eq. (6) with Ito’s scheme to realize A-type simulation for Eq. (2).

An advantage led by the A-type simulation is that for arbitrary noise strength the sampled steady state distribution of Eq. (2) corresponds to the Lyapunov function and potential function:

\[
L(x) = \phi(x) = -\epsilon \ln \rho_{ss}(x)|_A,
\]

(7)

where the subscript A denotes A-type simulation. Then, the deterministic part of Eq. (2) has the same decomposition as Eq. (1), and positions of fixed points from Eq. (1) are not changed after added noise. For Ito’s or Stratonovich’s integrations one cannot recognize fixed points of ODEs from the simulated distribution even for additive noise, as shown in FIG. 1(a–c). A-type simulation also reserves topology of the landscape for arbitrary noise strength \([33, 48]\).

To implement A-type simulation, the matrix \( Q(x) \) needs to be solved. The computational cost by the gradient expansion method \([13]\) is proportional to the square of systems’ dimension. In the following, we provide a new numerical approach to calculate the potential function in Eq. (7). The computational cost to get the energy barrier is linearly proportional to dimension, rather than square of dimension by gradient expansion method and exponential increasing by stochastic simulation (see analysis in Sect. III C), as listed in the table of FIG. 1.

### III. RESULT

**A. Efficient calculation on potential difference**

The essential information for multi-stable systems is the relative stability between stable states, which can be extracted from the potential difference \([1, 2]\). Based on the property that fixed points for ODE and locally most probable states for SDE are identical in our framework, we have the following protocol for a typical situation, where two stable fixed points \( x_1^* \) and \( x_2^* \) are connected by a saddle point \( s^* \) (Protocol I):

1. Identify positions of the three fixed points from ODE, including two stable fixed points and a connecting saddle point.

2. Calculate the potential difference between each stable fixed point and the saddle point \( \Delta \phi(x)|_{x_1^*} \), \( \Delta \phi(x)|_{x_2^*} \), by the least “action” method given by Eq. (13) below. The potential difference between \( x_1^* \) and \( x_2^* \) is \( \Delta \phi(x)|_{x_1^*} - \Delta \phi(x)|_{x_2^*} \).

The path integral formulation for Eq. (2) is applied here to calculate the potential difference. The formulation needs to be consistent with the stochastic integration used \([51]\). For A-type integration, \( P(s^*, T_2|x^*, T_1) = \int_{x_1^*}^{x_2^*} D_{A} \exp\{-S_T[x]|_A/\epsilon\} \), where the “action” \( S_T[x]|_A \) is a function of paths \( x[t] \) with \( x^* \) and \( s^* \) as start point at time \( T_1 \) and end point at \( T_2 \) separately. As we have transformed Eq. (2) to Eq. (6), it is more convenient to use the equivalent path integral formulation:

\[
P(s^*, T_2|x^*, T_1) = \int_{x_1^*}^{x_2^*} D_{I} \exp\{-S_T[x]|_I/\epsilon\},
\]

(8)

where the subscript I means Ito’s integration. The measure on paths is defined as:

\[
\int_{x_1^*}^{x_2^*} D_I x = \lim_{K \to \infty} \prod_{k=1}^{K-1} \int dx^k/\sqrt{\det[2\pi\epsilon dt D(x^k-1)]},
\]

where functions of \( x \) take pre-points in each interval. The time is discretized into \( K \) segments with \( T_1 = t_1 < \cdots < t_k < \cdots < t_K = T_2 \), each interval being \( dt \) and \( x^k = x(t_k) \).

The “action” function:

\[
S_T[x]|_I = \frac{1}{4} \int_{T_1}^{T_2} \left[ dt [\dot{x} - f(x) - \epsilon \Delta f(x)]^\top D^{-1}(x) \cdot [\dot{x} - f(x) - \epsilon \Delta f(x)] \right],
\]

(9)

where the integration obeys Ito’s rule \([28]\). Note that the present “action” function is different from that of Freidlin-Wentzell’s framework \([24]\) except when \( \epsilon \to 0 \). Even for SDE with additive noise, the difference still exists, because \( \Delta f(x) = \sum_j \partial_{x_j} Q_{ij}(x) \) can be nonzero for systems without detailed balance.
By using the decomposition in Eq. (4), we have:

$$S_T[x]_A = \frac{1}{4} \int_{T_1}^{T_2} \int_I dt \tilde{x} - D \nabla \phi + Q \nabla \phi - \epsilon \Delta f \nabla f^{-1} \nabla^T f \nabla f^{-1} \nabla f^{-1} \nabla f^{-1}$$

$$\times (\nabla \phi + Q \nabla \phi - \epsilon \Delta f) + \int_{T_1}^{T_2} \int_I dt \tilde{x} \nabla \phi$$

$$\geq \Delta \phi [x]_{x^*} - \epsilon \int_{T_1}^{T_2} dt \nabla^2 f \nabla f^{-1} \nabla f^{-1} \nabla f^{-1}$$

where we have used $\nabla \phi \nabla \phi = 0$, and Ito's formula [28]: $\int_{T_1}^{T_2} \int_I dt \tilde{x} \nabla \phi = \Delta \phi [x]_{x^*} - \epsilon \int_{T_1}^{T_2} dt \nabla^2 f \nabla f^{-1} \nabla f^{-1} \nabla f^{-1}$

For clarity, we ignore the symbol $(x)$ for functions of $x$ in the derivation. The inequality in Eq. (10) becomes equality for the least “action” path:

$$\dot{x} = D(x) \nabla \phi(x) - Q(x) \nabla \phi(x) + \epsilon \Delta f(x),$$

In the limit of $\epsilon \to 0$,

$$S_T[x]_A \geq \Delta \phi [x]_{x^*}.$$ 

Thus, Eq. (9) counts the accumulation of noise, whose minimization equals to the “uphill” energy $\Delta \phi [x]_{x^*}$. When the trajectory passes the saddle point, it goes “downhill” obeying $\dot{x} = -D(x) \nabla \phi(x) - Q(x) \nabla \phi(x) + \epsilon \Delta f(x)$, where minimization of Eq. (9) is zero.

From Eq. (12), minimization of the “action” function $S(s^* | x^*)_A = \inf_{s \in T} \inf_{x \in X, x(T) = s} S_T[x]_A$ in the limit of $\epsilon \to 0$ equals to potential difference between $s^*$ and $x^*$, and with Eq. (7) we reach a formula to calculate potential barrier:

$$\lim_{\epsilon \to 0} S(s^* | x^*)_A = \Delta \phi [x]_{x^*} = -\epsilon \ln \rho_{ss}(s^* | x^*)_A.$$ 

We emphasize that the first equality holds only when $\epsilon \to 0$, but the second equality is for arbitrary noise strength, which is different from that of Freidlin-Wentzell’s framework valid for $\epsilon \to 0$ [24]. The significance of Eq. (13) is that it enables to obtain potential difference by minimizing the “action” when $\epsilon \to 0$, and the result exactly corresponds to that of Lyapunov function for ODE and by A-type simulation of SDE with arbitrary noise strength.

**B. Probability ratio and transition rate**

As the steady state obeys the Boltzmann-Gibbs distribution, the probability ratio between stable states is:

$$\frac{\rho(x_2)}{\rho(x_1)} = \exp \left[ -\frac{1}{\epsilon} \Delta \phi(x)_{x^*_1} - \Delta \phi(x)_{x^*_2} \right].$$

where $\Delta \phi(x)_{x^*_1} = \Delta \phi(x)_{x^*_1} - \Delta \phi(x)_{x^*_2}$. Equation (14) is valid under arbitrary noise strength, and thus can show variation of the ratio with different noise intensities. It provides the probability ratios of quantities such as the number of different cell types. Specifically, we apply it to analyze tumor heterogeneity by large noise in Sect. IV.

When $\epsilon$ is small compared to the height of the potential barrier $\Delta \phi(x)_{x^*_1}$, the asymptotic transition rate formula [1, 2] from the stable fixed point $x^*_1$ to $x^*_2$ is:

$$R(x_2 | x^*_1) \propto \exp \left[ -\frac{1}{\epsilon} \Delta \phi(x)_{x^*_1} \right].$$

Different from [52], in our framework the non-detailed balance part does not provide correction terms that explicitly appear in the pre-factor of the rate formula as analyzed in Appendix E.

**C. Comparison on computational cost**

Computational costs of methods mentioned above for systems with respect to dimension $N$ are analyzed here. For stochastic simulation of Eq. (4), we mesh each dimension into $n$ points, and the computational cost is exponentially proportional to dimension, $cost \sim O(n^N)$. This method also has the problem of slow convergence when noise strength is small. For the gradient expansion [13], as in each step a matrix needs to be evaluated, the computational cost is approximately $cost \sim O(N^2)$. The least “action” method here needs a one dimensional path connecting two points, and thus its cost is linearly proportional to dimension, $cost \sim O(N)$. Therefore, the least “action” method is efficient in high dimensional systems. We list the results in the table of FIG. 1.

**D. Protocol to obtain a global landscape**

Protocol I can be extended to obtain a global landscape for systems with multiple stable states (Protocol II):

1. Identify positions of all fixed points under consideration from ODE.

2. Choose a saddle point as reference. Starting from points in small neighborhood of the saddle point, find all stable fixed points reached by simulating ODE. Calculate potential difference between the saddle point and the stable fixed points by Eq. (13).

3. Repeat step 2 for all saddle points. Fix relative potential difference between the saddle points if they reach common stable fixed points by step 2.

4. For any other points in state space, find the fixed point that it reaches by simulating ODE. Obtain their potential difference by Eq. (13).

The consistency between ODE and SDE enables to utilize information of fixed points and basins of attraction from
ODE, which greatly improves the efficiency of our algorithm. As each point in state space reaches a single fixed point, its potential value is uniquely determined, which leads to a global landscape without ambiguity. Specifically, the probability ratio between a fixed and a point within the potential well is calculated by Eq. (14), which corresponds to cell-to-cell variability inside the attractor. For dynamical systems with complex attractors such as limit cycle [34, 48, 53], the point on the stable limit cycle can be treated similarly as the stable fixed point, and thus our method can be generalized.

E. Steps of applying the present method

As the computational cost to obtain potential differences between states is scalable, our method is applicable to high dimensional systems. The steps to use our method is:

1. Identify positions of the fixed points from ODE, and classify them into the set of stable and unstable (saddle) points.

2. Calculate the potential difference between fixed points by Protocol I. Extract probability ratios and transition rates by Eqs. (14) and (15) separately.

3. Use Protocol II to get a global landscape if needed.

We study the biological examples in Sect. IV and Appendix G according to these steps.

IV. APPLICATION

Heterogeneity of cell populations is widely observed in biological systems such as cancer [54], where different cell phenotypes emerge in tumor tissues [37, 55, 56]. It is proposed that an underlying regulation network and quantification on the network dynamics by SDE models can describe various cell types and transitions between them [6, 10, 44, 45]. Starting from the SDE model, the calculated potential landscape provides an integrated picture to study heterogeneity. Specifically, valleys in the landscape correspond to different cell types, and the potential barrier separating them quantifies the transition rates. This approach of landscape is helpful to understand systematically the effect of perturbations on cell type interconversions.

Here, we investigate whether the variation of noise strength leads to changes of cell types, as noise plays a crucial role in biological processes, for example, it drives the cell fate decision [20, 21]. The previous methods [23–27] can not be applied to study the function of large noise, because identification on valleys of landscape and calculation on potential barrier by these methods are restricted to the zero noise limit. Now, we are able to quantify the role of large noise on heterogeneity in high dimensional network dynamics, because the present calculation on landscape is robust under arbitrary noise strength. From our method, the ratios of cell types can be controlled by manipulating noise strength, which allows the cell-to-cell variability under the same gene regulation network.

As an illustrative example, we demonstrate the effectiveness of our approach by applying it to a network model for prostate cancer [35]. The network dynamics is modeled by a 38 dimensional SDE [35]. The ODE counterpart and the parameters are given in the Supplemental Material [57]. From analysis on the ODE, we know the system has 10 stable fixed points and 16 saddle points. To exemplify the method, we consider four stable fixed points corresponding to various cell types shown in FIG. 2: differentiated (D), proliferating (P), cancer (C), inflammation (I) with their positions given in [35]. For clarity, we consider additive noise case and choose $D(x)$ as identity matrix in this example. It should be emphasized that the deviation between ODE and SDE appears even with additive noise, because this system does not obey detailed balance condition. As a result, considering additive noise is sufficient to demonstrate the advantage of our method based on A-type integration compared with the prevailing methods based on other stochastic integrations.

We use the least “action” method to calculate heights of the potential barriers between stable states, as shown in FIG. 2. According to Eq. (14), the probability ratios of different cell types can be calculated under various noise strengths. We list the ratios between the states of D, P, C, I in FIG. 3, which shows qualitative different results with changing noise. When noise is small, e.g., $\epsilon = 0.01$, most of the cells belong to the cancer and the inflammation states, whereas little are in states of differentiated and proliferating. When noise becomes large such as $\epsilon = 1$, various cell types are almost equal in number. This demonstrates the emergence of tumor heterogeneity with respect to increasing noise strength.

We elucidate more on the application of controlling the ratios of cell types through varying noise intensity, which can be implemented by tuning temperature. First, it was demonstrated that an therapy with combination of hyperthermia and other treatments, such as immunotherapy and radiotherapy, can improve the efficiency of cancer cure [58]. In those cases, temperature plays the role of enhancer to switch on and off the effectiveness of other therapies. Specifically, drug cytotoxicity triggered by temperature variation leads to death of tumor cells, and therefore combination of hyperthermia and chemotherapy is regarded as an effective treatment of cancer [59]. Second, as different levels of heating were found to bring distinct modulatory effect on tumor targets, our method valid for arbitrary noise strength may be applied to study sensitivity of thermal treatment regulated by temperature, which will provide new designs on clinical trials [60]. Third, the regional hyperthermia to radiotherapy [61] shows an improvement on survival rates of cancer patients, because hyperthermia can guide the action of...
FIG. 2. (Color online) Left panel: The chosen four cell types in the prostate cancer model [35]: differentiated (D), proliferating (P), cancer (C), inflammation (I). They are stable fixed points obtained from ODE of the 38 dimensional system. The states D-P, D-I, C-I, P-C are saddle points, and the red fixed point in the middle is unstable. Right panel: the heights of potential barriers between stable fixed points connected by saddles. The lengths of arrows are proportional to barrier heights listed in the table below. Table: potential barriers between stable fixed points are calculated by the least “action” method. We set $K = 100$, $T = 20$, and have checked that larger $K$ and $T$ values lead to convergent results. The parameters of the system chosen here are for typical cancer patients [35], where cancer and inflammation states are more stable.

$$\begin{array}{|c|c|c|c|c|c|c|}
\hline
\text{Initial states} & \text{D} & \text{P} & \text{C} & \text{I} \\
\hline
\text{Final states} & \text{P} & \text{I} & \text{D} & \text{C} & \text{P} & \text{I} & \text{D} & \text{C} \\
\hline
\text{Potential barrier} & 0.0275 & 0.0510 & 0.0210 & 0.0511 & 0.1042 & 0.0257 & 0.1043 & 0.0324 \\
\hline
\end{array}$$

FIG. 3. The probability ratios between D, P, C, I states of the prostate cancer model. The ratios are calculated by Eq. (14) with heights of potential barriers listed in the table of FIG. 2, where the values are normalized by the I state. We consider noise intensities: $\epsilon = 0.01, 0.02, 0.05, 0.1, 1$. The tumor heterogeneity emerges when noise strength becomes large where the four types of cells are almost equally distributed.

V. DISCUSSION

For a physical system with clearly separated sources for the deterministic force and the stochastic force, stochastic interpretation for SDE (Langevin equation) is chosen by nature. Experiments [62, 63] have shown that a class of systems chooses the anti-Ito’s integration [33, 64], corresponding to A-type in one dimension. For effective models without a clear-cut distinction between deterministic and stochastic components, each stochastic interpretation has its own advantage. For example, Stratonovich’s interpretation enables the use of ordinary calculus. The correspondence between ODE and SDE modeling under arbitrary noise strength is a unique property for A-type integration.

In biological problems, noise has a variety of sources [65], such as locations of molecules, micro-environmental fluctuations, gene expression noise, and cellular processes like cell growth. Beside, noise may propagate through regulation networks [66]. For complex systems like cancer, noise may come from different sources. SDE model reconstitutes the random fluctuations into a single noise term, which reflects the various sources of noise [19, 66, 67]. Therefore, several experimental operations can implement the change of the noise strength discussed here in real biological systems.

Our method can be applied to systems that are modeled by master equation (ME) with discrete dynamical variable [28]. First, ME can be transformed to be

chemistry to specific heated tumor region. This can be modeled by multiplicative noise, as exemplified in Appendix A. Therefore, the present approach could form the theoretical basis for hyperthermia that employs effect of temperature in tumor treatment.

With the obtained potential barrier, transition rates of cell type interconversions is given by Eq. (15), which provides a quantitative understanding on cancer genesis. Under the given parameters and noise strength, the result provides a set of predictions: 1) cancer and inflammation states are more stable than proliferating and differentiated states; 2) transitions from cancer state to proliferating state and from inflammation state to differentiated state are difficult than the other way around; 3) transition to cancer state from inflammation state is more frequent than from proliferating state. These suggest that the model describe a cancer patient, and new strategies for medical treatments should be designed to rise the potential energy of cancer and inflammation states.
the chemical Langevin equation with continuous variable [42], which can be cast into the form of Eq. (2). Then, our method is applicable to improve efficiency. The approximation is tolerably accurate when the copy number of variables are large, and it also requires that the dynamical process has a time scale during which multiple reactions occur and the reaction rate does not change dramatically [42]. These conditions are expected to hold for the present high dimensional cancer dynamics [14, 35], where the proteins usually has high copy numbers. Second, ME may also be expanded to a FPE and further corresponds to Eq. (4) with consistent modeling predictions, as demonstrated through an explicit procedure in Appendix B. Third, for systems with low copy numbers, SDE can still provide an appropriate description on the effect of noises [19]. Fourth, for stochastic processes on the level of single molecules, such as gene burst process [68], ME is a more proper approximation to capture the discrete nature of species [9, 69]. Nevertheless, this kind of noise will diminish by accumulation of proteins with long lifetime [70].

Mathematically, SDE and ME are two independent modeling methodologies, and are on an equal footing to describe the stochastic dynamics. Both ME and SDE are models with intrinsic discrepancy to the real dynamical process. From computational side, a whole set of ME to describe the stochastic dynamics in detail is typically high dimensional, and the Gillespie algorithm [71] to simulate ME is time consuming. Thus, the present method handling SDE valid for arbitrary noise strength is practically useful to investigate high dimensional systems with large fluctuations, particularly when the ODE counterpart is properly constructed and quantitatively correspond to the average experimental data.

Several other remarks are in order. First, our calculation on potential difference is applicable to systems both with and without detailed balance condition [13], i.e. \( Q = 0 \) or not. Breakdown of detailed balance inducing a curl flux in the state space affects the least “action” path, and generally leads to \( S(\mathbf{x}_i|\mathbf{x}_j) \neq S(\mathbf{x}_j|\mathbf{x}_i) \). For such cases, the least “action” path also differ from the deterministic saddle-node trajectories [24, 72]. Second, there are many efficient numerical methods to calculate fixed points of ODEs in high dimension [73], such as Newton iteration method. Third, the word “action” is in quotation mark because the present “action” function has the dimension of energy, and the conventional action in classical physics has the dimension of energy multiplied by time.

We next compare our framework with the previous works. First, authors in [23] used a WKB method and reached a Hamiltonian-Jacobi equation \( \nabla \phi(\mathbf{x})^* D(\mathbf{x}) \nabla \phi(\mathbf{x}) + \nabla \phi(\mathbf{x})^* f(\mathbf{x}) = 0 \) in the lowest order of \( \epsilon \to 0 \). However, computational cost of solving this partial differential equation increases exponentially. This Hamiltonian-Jacobi equation is valid for arbitrary orders of \( \epsilon \) in our framework [50]. Second, our method is different from the previous path integral approach [44], where their “action” function gives an effective potential rather than the exact potential \( \phi(\mathbf{x}) \) constructed consistently in Eq. (3) and Eq. (4). Third, the unexpected “noise effects” in using SDEs have been widely reported [29–31], and whether the phenomena are produced by the physical effect of the zero-mean noise or by the intricacy of using various stochastic integrations [32, 74] (also see the example in Appendix B) is a question without a definite answer. These effects in general defy the use of dynamical information from the ODE counterpart, and our method provide a possibility to reserve useful results by ODE analysis for SDE with arbitrary noise strength.

We analyze the difference between our framework and Freidlin-Wentzell’s [24], based on which the “quasi-potential” has been calculated in many systems recently [25–27]. First, the consistency between “action” function’s form and stochastic integration (classified in Table II) has not been considered in Freidlin-Wentzell’s action. Only the present “action” function of Ito’s form is the same as the usual Freidlin-Wentzell’s action [24]. Second, our decomposition \( f(\mathbf{x}) = -[D(\mathbf{x}) + Q(\mathbf{x})] \nabla \phi(\mathbf{x}) \) with \( \nabla \phi(\mathbf{x}) Q(\mathbf{x}) \nabla \phi(\mathbf{x}) = 0 \) is generally different form the usual Freidlin-Wentzell form \( f(\mathbf{x}) = -\nabla U(\mathbf{x}) + l(\mathbf{x}) \) with \( \nabla U(\mathbf{x}) \cdot l(\mathbf{x}) = 0 \), except when diffusion matrix \( D(\mathbf{x}) \) is proportional to identity. For general \( D(\mathbf{x}) \), the minimization of “action” function Eq.(D1) does not directly equal to the function \( U(\mathbf{x}) \) even in the limit of \( \epsilon \to 0 \). For example, when \( D(\mathbf{x}) \) is a diagonal matrix with distinct constant elements, the “action” \( S_T[\mathbf{x}] \geq \sum_i \int_{T_1}^{T_2} dt (\dot{x}_i - f_i)^2 / 2 \neq \Delta U(\mathbf{x})|_{\mathbf{x}^*} \). On the other hand, if we apply the “action” without the diffusion matrix as in [25], \( S_T[\mathbf{x}] = \sum_i \int_{T_1}^{T_2} dt (\dot{x}_i - f_i)^2 / 2 \), it does not include the effect of \( D(\mathbf{x}) \). A more detailed comparison is given in Appendix F.

To conclude, we have provided a new approach to study multi-stability and stochastic transitions between stable states for SDE modeling. The potential function can be efficiently calculated corresponding to the Lyapunov function of ODE and the landscape by A-type simulation of SDE with arbitrary noise strength. Our method generates consistent predictions on stochastic processes from both ODE modeling on the average behavior as well as SDE modeling including the effect of noise. It gives probability ratios between stable states subject to large noise, such that expensive stochastic simulations can be avoided. The results reveals a new mechanism to control the ratios of cell types by manipulating noise intensity. Our approach should also be practically useful to study role of noise in dynamical modeling for other high dimensional stochastic processes.
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Appendix A: Analysis on the deviation caused by prevailing stochastic simulations

1. Deviation caused by the breaking of the detailed balance condition

a. An example with double-well potential

We demonstrate here an exact result on the deviation by Ito’s simulation on the valley’s position. We also use the least “action” method to calculate the potential values of points along the line $x_1 = 1$, as shown in FIG. 1(f). The potential differences by the least “action” method and A-type simulation are quantitatively consistent with the analytical formula, whereas Ito’s simulation causes deviation on positions of fixed points and barrier height.

We further consider this system with multiplicative noise. For clarity, we choose:

$$D = d + d_1x_1^2, \quad Q = ax_1(x_2 - 3)$$

where the two parameters $d_1$ and $d_2$ are nonzero. We obtain potential differences between the saddle point and the two stable fixed points for different $d_1$, $d_2$. The potential values as listed in Table I are also quantitatively consistent with the analytical formula. Systems with more general diffusion matrix $D(x)$ can be studied similarly.

b. Exact result for the deviation by Ito’s simulation on the valley’s position

We demonstrate here an exact result on the deviation of fixed points’ position by Ito’s simulation. This example given by [33]:

$$\begin{aligned}
\dot{x}_1 &= -dH[-(x_1 - 1) + (x_1 - 1)^3] \\
&\quad - ax_1(x_2 - 3)H(x_2 - 1) + \sqrt{d} \cdot \zeta_{x_1}(t), \\
\dot{x}_2 &= ax_1(x_2 - 3)H[-(x_1 - 1) + (x_1 - 1)^3] \\
&\quad - dH(x_2 - 1) - \epsilon a(x_2 - 3) + \sqrt{d} \cdot \zeta_{x_2}(t).
\end{aligned}$$

Then, the potential function is obtained by simulating the steady state distribution with A-type integration $\phi = \epsilon \ln \rho | A$, and it is quantitatively consistent with the analytical formula, as shown in Fig. 1(d-e). Note that the matrix $Q(x)$ leads to different simulation results between Ito’s and A-type.

We also use the least “action” method to calculate the potential values of points along the line $x_1 = 1$, as shown in FIG. 1(f). The potential differences by the least “action” method and A-type simulation are quantitatively consistent with the analytical formula, whereas Ito’s simulation causes deviation on positions of fixed points and barrier height.

We further consider this system with multiplicative noise. For clarity, we choose:

$$D = \begin{pmatrix} d + d_1 x_1^2 & 0 \\ 0 & d + d_2 x_2^2 \end{pmatrix},$$

where the two parameters $d_1$ and $d_2$ are nonzero. We obtain potential differences between the saddle point and the two stable fixed points for different $d_1$, $d_2$. The potential values as listed in Table I are also quantitatively consistent with the analytical formula. Systems with more general diffusion matrix $D(x)$ can be studied similarly.

Table I. Potential difference between the saddle point and the two stable fixed points for the example Eq. (A1) with multiplicative noise. The values are obtained by least “action” method, where we set $K = 500$, and do minimization for $T \in [0.5, 10]$ with 0.5 as step length. We choose the saddle point as the zero potential reference. The other parameters are $d = a = H = 1$.

| Fixed points | (0,1)     | (1,1)     | (2,1)     |
|--------------|-----------|-----------|-----------|
| $d_1 = 0$, $d_2 = 0$ | $-0.2495$ | $0.2418$  |
| $d_1 = 1$, $d_2 = 10$ | $-0.2502$ | $0.2485$  |
| $d_1 = 10$, $d_2 = 10$ | $-0.2514$ | $0.2432$  |
When applying Ito’s simulation to this SDE, we find that it corresponds to an A-type SDE with

\[ \dot{Q} = \begin{pmatrix} 0 & A(x_1, x_2) \\ -A(x_1, x_2) & 0 \end{pmatrix}, \]

and a potential function \( \tilde{\phi} \). As these two processes should be identical, we have the following conditions:

\[
-bI + \begin{pmatrix} 0 & kx_2 \\ -kx_2 & 0 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = -bI + \begin{pmatrix} 0 & A \\ -A & 0 \end{pmatrix} \begin{pmatrix} \partial_{x_1} \tilde{\phi} \\ \partial_{x_2} \tilde{\phi} \end{pmatrix} + \epsilon \left( \frac{\partial x_2 A}{\partial x_1} - \frac{\partial x_1 A}{\partial x_2} \right). \tag{A5}
\]

To consider the deviation of fixed points’ positions, we use \( \nabla \tilde{\phi} = 0 \), and get

\[
-bI + \begin{pmatrix} 0 & kx_2 \\ -kx_2 & 0 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \epsilon \left( \frac{\partial x_2 A}{\partial x_1} - \frac{\partial x_1 A}{\partial x_2} \right). \tag{A6}
\]

If we further choose \( \tilde{Q} = Q \), we get equations:

\[
\begin{pmatrix} b & kx_2 \\ -kx_2 & b \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = - \begin{pmatrix} \epsilon k/b \\ 0 \end{pmatrix}, \tag{A7}
\]

which gives a solution:

\[ x_1 = -\epsilon k/b, \quad x_2 = 0. \tag{A8}\]

This solution indicates the deviation of fixed points’ position when using Ito’s simulation is linearly proportional to \( k \), which agrees with the simulation results [33].

### 2. Deviation caused by multiplicative noise

#### a. An exact example

It is widely known that in the presence of multiplicative noise different stochastic integrations of Eq. (2) lead to distinct results. Typically, Ito’s or Stratonovich’s integration was used [28]. However, recent works have demonstrated applications of stochastic integrations beyond Ito-Stratonovich both theoretically [33, 64] and experimentally [62, 63]. Here, we show analytically that Ito’s integration causes deviation compared with dynamics of deterministic counterpart, but A-type gives consistent results.

We consider a set of SDE with multiplicative noise:

\[
\begin{align*}
\dot{x}_1 &= 2x_1 - x_1 \left( x_1^2 + x_2^2 \right) + \sqrt{x_1^2 + x_2^2} \zeta_1(t) \\
\dot{x}_2 &= 2x_2 - x_2 \left( x_1^2 + x_2^2 \right) + \sqrt{x_1^2 + x_2^2} \zeta_2(t)
\end{align*}\tag{A9}
\]

where \( \epsilon = 1 \), the diffusion matrix \( D(x_1, x_2) = (x_1^2 + x_2^2) I \), and the stochastic integration has not been specified. Under A-type integration, the steady state distribution of this system is \( \rho_{ss}(x)|_I = \exp[-\phi(x)/\epsilon]/Z_I \) with the normalization constant \( Z_I \) and

\[ \phi(x) = -\ln \left( x_1^2 + x_2^2 \right) + \frac{x_1^2 + x_2^2}{2}. \tag{A10}\]

The distribution of Ito’s simulation for Eq. (A9) is identical to the A-type’s simulation for the system:

\[
\begin{align*}
\dot{x}_1 &= -x_1 \left( x_1^2 + x_2^2 \right) + \sqrt{x_1^2 + x_2^2} \zeta_1(t) \\
\dot{x}_2 &= -x_2 \left( x_1^2 + x_2^2 \right) + \sqrt{x_1^2 + x_2^2} \zeta_2(t)
\end{align*}\tag{A11}
\]

whose expression can be similarly calculated as \( \rho_{ss}(x)|_I = \exp[-\psi(x)/\epsilon]/Z_I \) with the normalization constant \( Z_I \) and

\[ \psi(x) = \frac{1}{2} \left( x_1^2 + x_2^2 \right). \tag{A12}\]

The two distributions \( \rho_{ss}(x)|_I \) and \( \rho_{ss}(x)|_I \) have obvious differences, for instance, \( \rho_{ss}(0,0)|_A = 0 \) but the origin \((0,0)\) is the most probable state for \( \rho_{ss}(x)|_I \).

### Appendix B: “Noise-induced transitions” induced by stochastic integration

We demonstrate here that occurrence of the noise-induced transitions observed in SDE [29–31, 75] depends on choosing the stochastic integration for SDE interpretation, and the present A-type integration leads to a consistent result between SDE and its ODE counterpart [76]. We take the system in [75] as an example. We start from the Fokker-Planck equation (FPE) obtained there:

\[
\partial_t \rho(x_1, x_2, t) = \left[ -\partial_{x_1} A_1 - \partial_{x_2} A_2 \right. \\
\left. + \frac{1}{2N} \sum_{i,j=1}^{2} \partial_{x_i} \partial_{x_j} B_{ij} \right] \rho(x_1, x_2, t), \tag{B1}
\]

where \( A_1 = -A_2 = z(x_2 - x_1) \) and \( B_{ij} = (2x_1 x_2 + z(x_1 + x_2))/(1)^{i+j} \). After doing the coordinate transformation:

\[
\begin{align*}
w &= x_1 + x_2, \\
z &= x_1 - x_2
\end{align*}\tag{B2}
\]

with the Jacobian \( J = 1/2 \) and \( \tilde{J} = 2 \), the transformed Fokker-Planck equation is one-dimensional:

\[
\partial_t \tilde{\rho}(w, z, t) = \left[ -\partial_z (-2z) \right. \\
\left. + \frac{1}{2N} \partial^2_r [r(w^2 - z^2) + 2zw] \right] \tilde{\rho}(w, z, t). \tag{B3}
\]

Thus, the diffusion coefficient is:

\[ D(w, z) = \frac{1}{2N} [r(w^2 - z^2) + 2zw], \tag{B4}\]

with \( \partial_z D(w, z) = -rz/N \).

For a given FPE, one can derive a class of corresponding SDEs with using various stochastic integrations. If A-type integration is used, we get a SDE whose ODE part is consistent with the underlying FPE dynamics. In detail, with A-type integration rule [33], we obtain the stochastic differential equation:

\[ \dot{z} = -2\epsilon z + \frac{1}{N} rz + \sqrt{D(w, z)} * \zeta(t). \tag{B5}\]
where the asterisk denotes the A-type integration, \( \zeta(t) \) is Gaussian white noise with \( \langle \zeta(t) \rangle = 0 \), \( \langle \zeta(t) \zeta(t') \rangle = 2\delta(t - t') \). Here the superscript \( \tau \) denotes transpose, \( \delta(t - t') \) is the Dirac delta function, and \( \langle \cdots \rangle \) represents noise average.

According to [75], we set \( r = 1 \) without loss of generality, because we can rescale \( \epsilon \) to absorb \( r \). As the total number of ants \( N \) is conserved, we have \( w = 1 \). Thus, \( D(w, z) = [(1 - z^2) + 2\epsilon]/2N \), and Eq. (B5) becomes:

\[
\dot{z} = \left( \frac{1}{N} - 2\epsilon \right) z + \sqrt{\frac{1}{2N}[(1 - z^2) + 2\epsilon]} \ast \zeta(t), \tag{B6}
\]

With using the Ito’s integration rule [28], the corresponding stochastic differential equation is:

\[
\dot{z} = -2\epsilon z + \sqrt{\frac{1}{2N}[(1 - z^2) + 2\epsilon]} \cdot \zeta(t), \tag{B7}
\]

where the dot denotes the Ito’s integration.

Note that the drift terms for the above two SDEs are different. The variable \( z = x_1 - x_2 \) ranges over the interval \([-1, 1]\). Then, the deterministic force in Eq. (B6) can both push the system away from the state \( z^* = 0 \) when \( 1 > 2\epsilon N \), and attract the system back to \( z^* = 0 \) when \( 1 < 2\epsilon N \). Therefore, ODE part in Eq. (B6) is consistent with the underlying FPE dynamics.

1. Potential function and steady state distribution

The potential function satisfying Eq. (B6) is:

\[
\phi(z) = (1 - 2N\epsilon) \ln(1 + 2\epsilon z^2), \tag{B8}
\]

and steady state obeys Boltzmann-Gibbs distribution:

\[
\rho(z) = \frac{1}{Z} \exp[-\phi(z)] = \frac{1}{Z(1 + 2\epsilon z^2)(1 - 2N\epsilon)}, \tag{B9}
\]

where \( Z \) is normalization constant. When \( 1 > 2N\epsilon \), the distribution has a U shape, and the system is bistable. When \( 1 < 2N\epsilon \), the distribution has an inverted U shape, and the distribution is centered at \( z^* = 0 \). Thus, the deterministic force in Eq. (B6) shows consistent behaviors as the steady state distribution.

Appendix C: “Action” function’s forms with different stochastic integrations

The difference of “action” functions and least “action” paths under various stochastic integrations, e.g. A-type, Ito’s and Stratonovich’s, can be neglected in the limit of \( \epsilon \rightarrow 0 \), which can be proved similarly as the above procedure in Eq. (9). Take the “action” function Stratonovich’s integration as an example,

\[
S_T[\mathbf{x}]|_S = \frac{1}{4} \int_{T_1}^{T_2} dt \langle \mathbf{x} - \mathbf{f} \rangle^\tau D^{-1}(\mathbf{x}) \mathbf{x} + \frac{1}{2} \epsilon J_S
\]

\[
= \frac{1}{4} \int_{T_1}^{T_2} \int_I dt \langle \mathbf{x} - D\nabla \phi + Q\nabla \phi \rangle^\tau D^{-1} \times \langle \mathbf{x} - D\nabla \phi + Q\nabla \phi \rangle + \int_{T_1}^{T_2} dt \langle \mathbf{x} - D\nabla \phi + Q\nabla \phi \rangle^\tau D^{-1} \epsilon J_S
\]

\[
\geq \Delta + \frac{1}{2} \epsilon J_S, \tag{C1}
\]

where \( J_S \) is the time integral of the Jacobian term. In the limit of \( \epsilon \rightarrow 0 \), \( S_T[\mathbf{x}]|_S \geq \Delta \phi(\mathbf{x})^2 \). The typical forms of “action” function and their transformed form with Ito’s interpretation [51] are listed in table II. The discretized “action” function and their transformed form with Ito’s interpretation, for example, pre-point scheme is needed for Ito’s interpretation. Because the difference among stochastic integrations is negligible in the limit of \( \epsilon \rightarrow 0 \), we can choose convenient schemes as needed.

1. Euler-Lagrangian equation for the least “action” path

Euler-Lagrangian equation from the “action” Eq. (D1) is calculate as follows. For convenience, we rewrite the Lagrangian to be:

\[
L = \frac{1}{4} \langle \dot{x}_i - f_i \rangle D^{-1}(\dot{x}_i - f_j), \tag{C2}
\]

where we have used the notion of Einstein summation in this paper. Then, the Euler-Lagrangian equation is an ordinary differential equation:

\[
0 = \frac{d}{dt} \frac{\partial L}{\partial \dot{x}_i} - \frac{\partial L}{\partial x_i}
= \frac{1}{2} \frac{\partial D^{-1}}{\partial x_i} \dot{x}_i (x_j - f_j) + D^{-1}(\dot{x}_j - \frac{\partial f_j}{\partial x_i} \dot{x}_i)
+ \frac{1}{2} \frac{\partial D^{-1}}{\partial x_i} (\dot{x}_j - f_j) - \frac{1}{4} (\dot{x}_i - f_i) \frac{\partial D^{-1}}{\partial x_i} (\dot{x}_j - f_j), \tag{C3}
\]

which gives the solution of the least “action” path.

Appendix D: Numerical implementation

We have demonstrated in Appendix C that differences of “action” functions for Eq. (2) with various stochastic integrations can be neglected when \( \epsilon \rightarrow 0 \). Therefore, we can choose “action” with specific stochastic integration for the convenience of numerical calculations. Here, we adopt the “action” with Ito’s integration [51]:

\[
S_T[\mathbf{x}]|_I = \frac{1}{4} \int_{T_1}^{T_2} \int_I dt \langle \mathbf{x} - \mathbf{f} \rangle^\tau D^{-1}(\mathbf{x}) \mathbf{x} - \mathbf{f}(\mathbf{x}). \tag{D1}
\]
TABLE II. “Action” functions for different stochastic integrations (A-type, Ito’s and Stratonovich’s) and their transformed forms with Ito’s interpretation. The usual Freidlin-Wentzell’s action [24] is the same as the Ito’s form here. The order for the time integral of the Jacobian term \( J_A \) is O(1). The difference of “action” functions among these stochastic integrations can be neglected in the limit of \( \epsilon \to 0 \).

| Stochastic integration | The present “Action” function \( S_T[x] \) | \( S_T[x] \) transformed to Ito’s interpretation |
|------------------------|---------------------------------|---------------------------------|
| A-type                 | \( \frac{1}{2} \int_{T_1}^{T_2} |\dot{x}(t) - f(x(t))|^2 D^{-1}(\dot{x}(t) - f(x(t))) dt + \epsilon J_A \) | \( \frac{1}{2} \int_{T_1}^{T_2} |\dot{x}(t) - f(x(t))|^2 D^{-1}(\dot{x}(t) - f(x(t))) dt \) |
| Ito’s (Freidlin-Wentzell) | \( \frac{1}{2} \int_{T_1}^{T_2} |\dot{x}(t) - f(x(t))|^2 D^{-1}(\dot{x}(t) - f(x(t))) dt \) | \( \frac{1}{2} \int_{T_1}^{T_2} |\dot{x}(t) - f(x(t))|^2 D^{-1}(\dot{x}(t) - f(x(t))) dt \) |
| Stratonovich’s | \( \frac{1}{2} \int_{T_1}^{T_2} |\dot{x}(t) - f(x(t))|^2 D^{-1}(\dot{x}(t) - f(x(t))) dt + \frac{1}{2} \epsilon J_S \) | \( \frac{1}{2} \int_{T_1}^{T_2} |\dot{x}(t) - f(x(t))|^2 D^{-1}(\dot{x}(t) - f(x(t))) dt \) |

When \( \epsilon \to 0 \), its minimization equals to the potential difference \( \lim_{\epsilon \to 0} S(s^*[x^*]_{\vert t} = \lim_{\epsilon \to 0} S(s^*[x^*])_{\vert A} = \Delta \phi(x)_{\vert \tau} \), with the least “action” path satisfying \( \dot{x} = \mathcal{D} \nabla \phi - Q \nabla \phi \), and deviation between the least “action” path and that by \( \dot{x} = -\mathcal{D} \nabla \phi - Q \nabla \phi + \epsilon \Delta f \) for Eq. (9) disappears as well.

Numerically, we use discretized form of Eq. (D1) as the object function to minimize. The discretized scheme adopted corresponds to the stochastic integration [51], such as pre-point scheme is needed for Ito’s interpretation. Thus, we minimize the discretized “action”:

\[
S_T[x]_{\vert t} = \frac{1}{4} \sum_{k=1}^{K} \Delta t_k \left[ \frac{x^k - x^{k-1}}{\Delta t_k} - f(x^{k-1}) \right]^T D^{-1}(x^{k-1}) \cdot \left[ \frac{x^k - x^{k-1}}{\Delta t_k} - f(x^{k-1}) \right],
\]

where we divide the time intervals to be \( T_1 = t_1 < \cdots < t_k < \cdots < t_K = T_2 \) with \( \Delta t_k = t_k - t_{k-1} \). The trajectory \( x(t) \) is divided into \( K \) pieces with \( x^k = x(t_k) \). Besides, Eq. (D1) is explicitly independent of \( \epsilon \), and thus its numerical minimization has implicitly taken the limit \( \epsilon \to 0 \). We choose straight line connecting the two points as initial path, and use the fmincon function in the toolbox of MATLAB to do minimization, where set \( T = -T_1 = T_2 \).

For Eq. (2), when \( Q(x) \nabla \phi(x) \) is dominate compared to \( D(x) \nabla \phi(x) \), the least “action” path rotates and is relatively long in length. Then, the number of points \( K \) is required to be large enough such that the minimization procedure can find out the long least “action” path [77]. Besides, we find in the numerical experiment that if \( T \) is too large, the least “action” path may pass an additional saddle point (limit cycle) with higher potential energy before going through the expected saddle point. Special care is needed to choose suitable \( K \) and \( T \) in these cases.

There are numerical methods to improve the efficiency of finding the least “action” path, such as the geometric minimum action method [78] and the adaptive minimum action method [79]. They can be applied to optimize our current numerical code.

Appendix E: Pre-factor of the rate formula due to non-detailed balance part

The FPE corresponding to Eq. (4) is [33]:

\[
\partial_t \rho(x, t) = \nabla_x^T \left[ D(x) + Q(x) \right] \left[ \nabla_x \phi(x) + \nabla_x^T \rho(x, t) \right],
\]

(E1)

where the steady state obeys Boltzmann-Gibbs distribution \( \rho(x, t \to \infty) = \exp[-\phi(x)/\epsilon] \).

Inserting WKB ansatz with pre-factor:

\[
\rho_{ss}(x) = C(x) \exp \left( -\frac{\phi(x)}{\epsilon} \right)
\]

(E2)

into our FPE at steady state:

\[
0 = \epsilon \nabla_x^T \left[ D(x) + Q(x) \right] \left[ \nabla_x \phi(x) + \nabla_x^T \rho(x, t) \right] 
\]

\[
\cdot \left[ \nabla_x \nabla_x \phi(x) \right] - \left[ \nabla_x \phi(x) \right] \left[ D(x) + Q(x) \right] \left[ \nabla_x \phi(x) \right],
\]

(E3)

we get for the order of \( O(1) \):

\[
0 = \left[ \nabla_x \phi(x) \right] \left[ D(x) + Q(x) \right] \left[ \nabla_x \phi(x) \right],
\]

(E4)

which implies that \( C(x) = \text{constant} \). Note that we does not have the order of \( O(1/\epsilon) \) here, for which the Hamilton-Jacobi equation

\[
\nabla_x^T \phi(x) D(x) \nabla_x \phi(x) + \nabla_x \phi(x) f(x) = 0
\]

(E5)

is obtained by the decomposition [50].

We also insert the WKB ansatz to the FPE corresponding to Eq. (6):

\[
0 = -\left[ \nabla_x^T [f(x) + \epsilon \Delta f(x)] \right] C(x) + \epsilon \left[ \nabla_x^T \nabla_x D(x) \right] C(x)
\]

\[
- \left[ \nabla_x C(x) - \frac{1}{\epsilon} C(x) \nabla_x \phi(x) \right] f(x) + \epsilon \Delta f(x)
\]

\[
+ 2 \epsilon \nabla_x^T D(x) \left[ \nabla_x C(x) - \frac{1}{\epsilon} C(x) \nabla_x \phi(x) \right]
\]

\[
+ \epsilon D(x) \left[ \nabla_x^T \nabla_x C(x) - \frac{2}{\epsilon} \nabla_x \phi(x) \nabla_x C(x) \right]
\]

\[
- \frac{1}{\epsilon} C(x) \nabla_x^T \nabla_x \phi(x) - \frac{1}{\epsilon^2} C(x) \nabla_x \phi(x) \nabla_x \phi(x),
\]

(E6)
where $\Delta f_i(x) = \partial_{x_i}[D_{ij}(x) + Q_{ij}(x)]$. Then, we get Eq. (E5) for the order of $O(1/\epsilon)$, and for the order of $O(1)$:

$$0 = -\nabla_x \phi(x)[D(x) + Q(x)]\nabla_x C(x),$$

(E7)

which again implies that $C(x)$ is a constant. The order of $O(\epsilon)$ is also zero. As a result, the non-detailed balance part does not provide correction terms that explicitly appear in the pre-factor of the rate formula.

In general, the pre-factor in the rate formula depends on other coefficients such as the friction coefficient $[1, 2]$, and from Kramers equation its dependence on the friction coefficient is significantly different for large friction and small friction limit.

### Appendix F: Comparison with Freidlin-Wentzell decomposition

Our decomposition on the drift force $f(x) = -[D(x) + Q(x)]\nabla \phi(x)$ with $\nabla \phi(x)Q\nabla \phi(x) = 0$ is generally different form the usual Freidlin-Wentzell form $f(x) = -\nabla U(x) + l(x)$ with $\nabla U(x) \cdot l(x) = 0$ [24], based on which landscape has been calculated in various systems recently [25–27]. They are mathematically identical when the diffusion matrix $D(x)$ is identity. For general diffusion matrix $D(x)$, the “action” function Eq. (11) in the main text does not directly equal to the potential function $U(x)$ in Freidlin-Wentzell decomposition. We demonstrate it more clearly by a simplified case as follows.

We show that when diffusion matrix is a diagonal matrix with distinct constant elements, the Freidlin-Wentzell action does not give the exact potential difference even with $\epsilon \to 0$. If we have $f(x) = -\nabla U(x) + l(x)$ with $\nabla U(x) \cdot l(x) = 0$, then

$$S_T[x]|_I = \sum_i \int_{T_1}^{T_2} dt \frac{1}{4D_{ii}} (\dot{x}_i - f_i)^2$$

$$= \sum_i \int_{T_1}^{T_2} dt \frac{1}{4D_{ii}} (\dot{x}_i + \partial_{x_i} U - l_i)^2$$

$$\geq \sum_i \int_{T_1}^{T_2} dt \frac{1}{4D_{ii}} \dot{x}_i \partial_{x_i} U - \sum_i \int_{T_1}^{T_2} dt \frac{\partial_{x_i} U}{D_{ii}} l_i$$

(F1)

where the last term cannot be eliminated when $\epsilon \to 0$.

On the other hand, if we apply the “action” without the element of diffusion matrix [25],

$$S_T[x] = \sum_i \int_{T_1}^{T_2} dt \frac{1}{4} (\dot{x}_i - f_i)^2,$$  

(F2)

it does not count the effect of diffusion matrix explicitly.

### 1. When diffusion matrix is identity

When diffusion matrix is identity, our decomposition is the same as the usual Freidlin-Wentzell form, and both “action” functions give the potential function. Besides, various stochastic interpretations give the same result when $\epsilon$ is small. The drift force in the stochastic differential equation (SDE) of the main text has a decomposition $f(x) = -\nabla U(x) + l(x)$ with $\nabla U(x) \cdot l(x) = 0$. For convenience, we use the equivalent “action” function under Ito’s interpretation:

$$S_T[x]|_I = \sum_i \int_{T_1}^{T_2} dt \frac{1}{4} (\dot{x}_i - f_i)^2$$

$$= \sum_i \int_{T_1}^{T_2} dt \frac{1}{4} (\dot{x}_i + \partial_{x_i} U - l_i)^2$$

$$\geq \Delta U - \epsilon \sum_i \int_{T_1}^{T_2} dt \partial_{x_i}^2 U,$$  

(F3)

where the subscript $I$ means Ito’s interpretation. If we can get a special trajectory satisfying $\dot{x} = \nabla U(x) + l(x)$, the equality holds. The equality relies on the crucial condition $\nabla U(x) \cdot l(x) = 0$. The minimized “action” gives $\Delta U$ when $\epsilon \to 0$.

### 2. An example that can be decomposed in our and Freidlin-Wentzell way

We construct an example that can be decomposed as both our ways and Freidlin-Wentzell way. It is given by a SDE under A-type integration:

$$\begin{align*}
\dot{x}_1 &= -(1 + x_1^2)x_1 - [1 - x_1x_2 - (x_2^2 - x_1^2)]x_2 + \zeta_1(t), \\
\dot{x}_2 &= [-1 - x_1x_2 + (x_2^2 - x_1^2)]x_1 - (1 + x_2^2)x_2 + \zeta_2(t),
\end{align*}$$

(F4)

where $\langle \zeta(t) \rangle = 0$, $\langle \zeta(t)\zeta^*(t') \rangle = 2\epsilon \delta(t - t')$. We have:

$$D = \begin{pmatrix}
1 + x_1^2 & 1 - x_1x_2 \\
1 - x_1x_2 & 1 + x_2^2
\end{pmatrix} \geq 0,$$

$$Q = \begin{pmatrix}
0 & -(x_2^2 - x_1^2) \\
(x_2^2 - x_1^2) & 0
\end{pmatrix}, \quad \phi = (x_1^2 + x_2^2)/2.$$

(F5)

Note that $D(x)$ and $Q(x)$ are singular along the line $x_2 = -x_1$. This singularity leads to nonzero finite potential values at the fixed points along $x_2 = -x_1$ for Eq. (F4) without noise.

The system can also be decomposed as:

$$\begin{align*}
\dot{x}_1 &= -(x_1 + x_2) - (x_1^3 + x_1^2x_2 - x_1x_2^2 - x_2^3) + \zeta_1(t), \\
\dot{x}_2 &= -(x_1 + x_2) - (x_1^3 - x_2^3 + x_1x_2^2 + x_1^2x_2 + x_2^3) + \zeta_2(t).
\end{align*}$$

(F6)

Thus, we get $f(x) = -\nabla U(x) + l(x)$ with

$$U = (x_1^2 + x_2^2)/2 + x_1x_2, \quad l = \begin{pmatrix}
-(x_1 + x_2)(x_2^2 - x_1^2) \\
x_1(x_2^2 - x_1^2)
\end{pmatrix},$$

(F7)
and $\nabla'U(\mathbf{x}) \cdot I(\mathbf{x}) = 0$. Note that minimum of $U(\mathbf{x})$ corresponds to the fixed points of Eq. (F4) without noise.

From the above derivation, we see that for the corresponding deterministic system the potential function constructed in our framework is not unique without given a diffusion matrix $D(\mathbf{x})$.

**Appendix G: Two more biological examples**

1. **Toggle switch**

We first consider the dynamical system describing the genetic toggle switch [40] with additive noise. The deterministic part of the dynamical model is:

$$
\begin{align*}
\dot{x}_1 &= \frac{\alpha_1}{1 + x_2^\gamma} - x_1, \\
\dot{x}_2 &= \frac{\alpha_2}{1 + x_1^\gamma} - x_2.
\end{align*}
$$

where $x_1$ and $x_2$ are the concentration of the Repressor 1 and 2 separately, and $\alpha_1$, $\alpha_2$, $\beta$, $\gamma$ are parameters with specific biological meaning. The noise is Gaussian and white. The diffusion matrix is set as $D(x_1, x_2) = dI$ with identity matrix $I$. By analyzing the structure of nullclines ($dx/dt = 0$ and $dy/dt = 0$), bistability happens when $\beta, \gamma > 1$ [40].

We use Ito’s simulation to get the steady state distribution, and show that Ito’s simulation of Eq. (G1) leads to deviation on the position of the potential minimum. When noise strength is large, Ito’s simulation show that one stable state is destroyed in the bistable parameter region of ODE, as shown in FIG. 4. Note that Stratonovich’s and Ito’s integrations generate identical results for Eq. (G1) with additive noise.

Two fixed points calculated from ODE are $x_1^* = (0.4027, 1.9995)$, $x_2^* = (1.9981, 0.0309)$. We list in table III the potential values obtained by the least “action” method for a set of parameters. The potential difference from Repressor 1 to Repressor 2 is greater than that from the other way around, which demonstrates that the genetic switch prefers the state with higher concentration of Repressor 1 under the given parameters. Therefore, our results on potential barrier height tells the relative stability and transition rates between two states of the genetic switch. The system with other parameters can be calculated in a similar way.

2. **A model for cell fate decision**

We apply our method to a 4 dimensional model which was used to study cell fate determination in pluripotent stem or progenitor cells [80]. This model consists of two coupled modules: the pluripotency module and the differentiation module. The pluripotency module is represented by the mutual activation of Oct4 and Sox2, whereas the differentiation module is modeled by mutually inhibiting mesendodermal and ectodermal genes. Inhibitions or activations among these nodes were given in [80]. A quantitative description of the model consists of a set of coupled stochastic differential equations with additive noise. The deterministic part is given by Eq. (G2) with the Gaussian white noise as that in Eq. (2) of the main text. The diffusion matrix is set as $D(x_1, x_2, x_3, x_4) = dI$. The variables $x_1$, $x_2$, $x_3$, $x_4$ denote concentration of Oct4, Sox2, mesendodermal, ectodermals separately.

![FIG. 4. (Color online) Steady state distribution by Ito’s simulation of Eq. (G1), which leads to deviation on the positions of the locally most probable states. When noise strength is large, Ito’s simulation show that one of the stable states is destroyed in the bistable parameter region of ODE. The noise strengths are $\epsilon = 0.1, 1, 5, 10$.](image)

| Initial state | Repressor 1 | Repressor 2 |
|---------------|------------|------------|
| End state     | Repressor 2 | Repressor 1 |
| Potential barrier | 0.1353 | 0.2819 |
TABLE IV. Potential barrier between the three stable fixed points calculated by the least “action” method for the example Eq. (G2). The mesendodermal state, the ectodermal state, and the pluripotency state, representing high concentration of the corresponding genes, are given by the three stable fixed points $x_1^* = (0.0218, 0.0218, 1, 0.0545)$, $x_2^* = (0.0218, 0.0218, 0.0545, 1)$, $x_3^* = (1.3309, 1.3309, 0.4423, 0.4423)$. We set $K = 100$, $T = 50$. We have checked that larger $K$ and $T$ values lead to convergent results with relative error smaller than 0.005. The parameters of the system are the same as those in [80].

| Initial states | mesendodermal | ectodermal | pluripotency |
|---------------|---------------|------------|-------------|
| End states    | ectodermal    | pluripotency | mesendodermal | pluripotency | mesendodermal | ectodermal |
| Potential barrier | 0.0736 | 0.0697 | 0.0736 | 0.0699 | 0.0318 | 0.0332 |

\[
\begin{align*}
\dot{x}_1 &= d_0 \left[ C_0 + I_0 \frac{K_{p, in}^{n_{p, in}}}{K_{p, in}^{n_{p, in}} + x_3^{n_{p, in}}} \frac{K_{p, in}^{n_{p, in}}}{K_{p, in}^{n_{p, in}} + x_4^{n_{p, in}}} \\
&\quad \cdot \left( KM + \frac{(Oct4 \cdot Sox2)^{n_{p, act}}}{K_{p, act}^{n_{p, act}} + (Oct4 \cdot Sox2)^{n_{p, act}}} - x_1 \right) \right], \\
\dot{x}_2 &= d_s \left[ C_s + I_s \frac{K_{p, in}^{n_{p, in}}}{K_{p, in}^{n_{p, in}} + x_3^{n_{p, in}}} \frac{K_{p, in}^{n_{p, in}}}{K_{p, in}^{n_{p, in}} + x_4^{n_{p, in}}} \\
&\quad \cdot \left( KM + \frac{(Oct4 \cdot Sox2)^{n_{p, act}}}{K_{p, act}^{n_{p, act}} + (Oct4 \cdot Sox2)^{n_{p, act}}} - x_2 \right) \right], \\
\dot{x}_3 &= d_M \left[ C_M + I_M w \frac{x_1^{n_a}}{K_{a, in}^{n_a} + x_1^{n_a}} + I_M \frac{K_{p, in}^{n_i}}{K_{i, in}^{n_i} + x_3^{n_i}} \frac{K_{p, in}^{n_i}}{K_{i, in}^{n_i} + x_4^{n_i}} - x_3 \right], \\
\dot{x}_4 &= d_E \left[ C_E + I_E w \frac{x_2^{n_a}}{K_{a, in}^{n_a} + x_2^{n_a}} + I_M \frac{K_{p, in}^{n_i}}{K_{i, in}^{n_i} + x_3^{n_i}} \frac{K_{p, in}^{n_i}}{K_{i, in}^{n_i} + x_4^{n_i}} - x_4 \right]. 
\end{align*}
\]

(G2)

We calculate from ODE the three stable fixed points $x_1^* = (0.0218, 0.0218, 1, 0.0545)$, $x_2^* = (0.0218, 0.0218, 0.0545, 1)$, $x_3^* = (1.3309, 1.3309, 0.4423, 0.4423)$ with the parameters given in [80], which represent three cell types correspondingly: the mesendodermal state, the ectodermal state, and the pluripotency state. We list in table IV the height of potential barriers from one stable fixed point to another by the least “action” method. The result shows that the differentiated mesendodermal and ectodermal states are more stable than the meta-stable state of pluripotent stem cell. This provides a understanding on why stem cells have a higher probability to transit toward more differentiated cells than the other way around. The result also allows us to predict the rate and timescale of transitions between cell types, which may lead to clinical methodologies to shepherd cells from one state into another.

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