A benchmark for reaction coordinates in the transition path ensemble

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The molecular mechanism of a reaction is embedded in its transition path ensemble, the complete collection of reactive trajectories. Utilizing the information in the transition path ensemble alone, we developed a novel metric, which we termed the emergent potential energy, for distinguishing reaction coordinates from the bath modes. The emergent potential energy can be understood as the average energy cost for making a displacement of a coordinate in the transition path ensemble. Where displacing a bath mode invokes essentially no cost, it costs significantly to move the reaction coordinate. Based on some general assumptions of the behaviors of reaction and bath coordinates in the transition path ensemble, we proved theoretically with statistical mechanics that the emergent potential energy could serve as a benchmark of reaction coordinates and demonstrated its effectiveness by applying it to a prototypical system of biomolecular dynamics. Using the emergent potential energy as guidance, we developed a committor-free and intuition-independent method for identifying reaction coordinates in complex systems. We expect this method to be applicable to a wide range of reaction processes in complex biomolecular systems. © 2016 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4945337>]

I. INTRODUCTION

Many essential processes in biochemistry and biology, such as enzymatic reactions and protein folding, are spontaneous transitions between two stable states separated by an activation barrier. If the energy barrier is high compared to the thermal energy, an activated transition occurs on a time scale orders of magnitude slower than the molecular time scale and is a rare event.¹

Understanding the mechanistic details of rare events presents severe challenges to both simulations and analyses. Brute force molecular dynamics (MD) simulations spend the majority of time sampling stable basins and seldom visit the more interesting transition regions. Due to the numerous degrees of freedom in complex systems, mechanistic interpretation of trajectories from MD simulations is taxing if not impossible. Reaction coordinates, the few coordinates that can determine the progress of a reaction process, are key to reliable mechanistic understanding^{2,3} and provide important clue for efficient methods for enhanced sampling of configuration space. For example, sampling of transition regions can be significantly improved in methods like umbrella sampling,⁴ constrained dynamics,^{5,6} metadynamics,⁷ and orthogonal space sampling,^{8,9} if restraints or constraints are applied to the correct reaction coordinates. On the other hand, knowledge of reaction coordinates allows us to describe the system in a reduced phase space and still capture the essence of the detailed mechanism of the process.

The past decade has witnessed tremendous efforts on identifying reaction coordinates. For some simple systems, reaction coordinates can be solved mathematically¹⁰ or by

exhaustive searching.¹¹ For complex biomolecular processes, however, systematic approach for identifying reaction coordinates remains at its primitive stage. A key concept about the reaction coordinate is the committor,^{12–15} the probability for a given configuration to commit to one stable state before the other. Many methods assume that committor is the “ideal” reaction coordinate and candidates for the reaction coordinate were appraised by their ability to reproduce committor values. In the early works, reaction coordinates were selected manually by intuition. Such “trial-and-error” procedures are labor intensive and thus restricted to simple systems.^{16,17}

Ma and Dinner developed the first automatic method for identifying reaction coordinates out of a large pool of candidates.¹⁸ They combined a genetic algorithm and a neural network (GNN) to find an optimal combination of a pre-determined number of coordinates that can predict the committor most accurately. Subsequently, several approaches based on the committor had been developed.^{19–23} Peters *et al.* proposed the likelihood maximization method^{19–21} to identify reaction coordinates based on one-time committor realizations from transition path sampling with aimless shooting. Antoniou *et al.* identified components of the reaction coordinate first by analysing the variance of coordinates at the separatrix²²—the isocommittor surface where the configurations have equal probability to relax to either of the stable basins, and then by kernel principal component analysis.²³ Methods that do not rely on evaluating committor are available as well.^{24–28} Best and Hummer proposed to examine the distribution of the probability of a trajectory being a transition path, given that the trajectory passes through configurations with a fixed value of a candidate coordinate—the distribution would have the sharpest peak if the candidate is the reaction coordinate.²⁴ This method was later shown to be equivalent to optimizing the separatrix by Peters.²⁹ Recently, Peters *et al.* reported that

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reaction coordinate can be identified from an ensemble of short trajectory swarms²⁵ if dynamics of the system along the reaction coordinate follows a one-dimensional Smoluchowski equation.

However, applications of these methods to complex bimolecular systems are restricted by one or more of the following issues: (1) These methods invokes high computational costs. (2) Their success relies on input from human intuition in that the candidate pool prepared by users has to contain all the essential reaction coordinates. The high computational cost largely originates from evaluating committor or steps equivalent to it. For instance, estimating the committor of a single configuration with the standard shooting procedure³⁰ requires up to 100 short shooting trajectories, each of which is of the average length of reactive trajectories. This computational cost is intimidatingly high for large biomolecular systems even when it can be significantly reduced by a newly developed fitting procedure.³¹

Since the development of transition path sampling (TPS),^{32–34,15} the transition path ensemble (TPE) can be harvested at a relatively low cost similar to that of normal MD simulations without requiring knowledge of reaction coordinate of the system, given that an initial reactive trajectory is available. Since all the dynamic information of a given reaction is contained in its TPE, it should be feasible to extract reaction coordinates from the TPE alone. If we follow the standard picture of a reactive system as consisting of the reaction coordinate interacting with a collection of bath modes,³⁵ it would be natural to assume the existence of some net flow of “activity” along the reaction coordinate, but not along bath modes. To materialize this vague idea of “activity,” we developed a novel measurement, emergent potential energy (EPE), which can be used to benchmark whether a given coordinate is a relevant coordinate, a coordinate that has significant overlap with the reaction coordinate. This benchmark allowed us to select out the relevant coordinates

from a complete set of coordinates that are sufficient to completely specify the configuration space of the system. Then a detailed procedure is developed for obtaining an optimal reaction coordinate as a combination of the relevant coordinates.

In the rest of the paper, Section II introduces the theory that provides the rational of the EPE as an effective benchmark of relevant coordinates, followed by a procedure for optimizing the reaction coordinate as a combination of a few relevant coordinates. Then, the application to a simple biomolecular system will be presented, with the computational details and the results shown in Sections III and IV, respectively. Concluding remarks are given in Section V.

II. THEORY

We first derive a general function of a given coordinate, which can be considered as the cost for making a displacement along the coordinate. Then we consider a special case where the quantity is related to the change of potential energy of the system. Later on, the detailed properties of such an energy cost function are discussed and the reason that it can be used as a benchmark of relevant coordinates is discussed as well.

A. A general cost function for the change of a coordinate

Assume a complete phase space span by $\Gamma \equiv (\xi, q_1, \dots, q_{n-1}, p_\xi, p_1, \dots, p_{n-1})$, with $(\xi, q_1, \dots, q_{n-1})$ being a set of coordinates that uniquely specify the instantaneous configuration of the system and $(p_\xi, p_1, \dots, p_{n-1})$ the conjugate momenta. ξ is an arbitrary coordinate of the complete configuration coordinates. For an arbitrary function $f(\Gamma)$ on Γ , the cost defined by $f(\Gamma)$ for an infinitesimal change of ξ from ξ_o to $\xi_o + \Delta\xi$ in a given ensemble is defined as

$$\langle \Delta f(\Gamma; \xi_o, \Delta\xi) \rangle = \frac{\int d\Gamma \rho(\Gamma) [\Phi(\xi) - \Phi(-\xi)] \delta(\xi - \xi_o) \sum_i \frac{\partial f(\Gamma)}{\partial \gamma_i} \frac{\dot{\gamma}_i}{\xi}}{\int d\Gamma \rho(\Gamma) \delta(\xi - \xi_o)} \Delta\xi \quad (1a)$$

$$= \Delta\xi \langle [\Phi(\xi) - \Phi(-\xi)] \sum_i \frac{\partial f(\Gamma)}{\partial \gamma_i} \frac{\dot{\gamma}_i}{\xi} \rangle_{\xi=\xi_o}, \quad (1b)$$

where γ_i represents an element in $(\gamma_1, \gamma_2, \dots, \gamma_{2n})$, which can be Γ itself or another complete set of phase space descriptors, $\dot{\gamma}_i$ is the time derivative of γ_i . $\delta(x)$ is the Dirac delta function, $\rho(\Gamma)$ is the probability density of states Γ in the ensemble, and $\Phi(x)$ is a Heaviside step function. $\langle \dots \rangle_{\xi_o}$ stands for the ensemble average at $\xi = \xi_o$. $\Delta\xi$ is an infinitesimal change and we assume it to be positive without loss of generality.

In the following, we will explain the rational behind the definition in Eq. (1). Given a trajectory of the system as a sampling of the ensemble, the quantity in Eq. (1) averages over two parts: (a) the change of $f(\Gamma; t)$ in the forward direction

when ξ changes from ξ_o at time t to $\xi_o + \Delta\xi$ at time $t + \Delta t$; (b) the change of $f(\Gamma; t)$ in the backward direction when ξ changes from $\xi_o + \Delta\xi$ at time t to ξ_o at time $t + \Delta t$. We discuss these two parts separately.

(a) First we consider the change of $f(\Gamma; t)$ from ξ_o at time t to $\xi_o + \Delta\xi$ at time $t + \Delta t$, which is a forward step. We sum over all the states with $\xi(t) = \xi_o$ at time t and $\xi(t + \Delta t) = \xi_o + \Delta\xi$ at an successive time $t + \Delta t$. Δt is small and not a fixed value. Assuming $\dot{\xi}(t)$ is unchanged within the infinitesimal change of ξ , we have

$\Delta t = \Delta\xi/|\dot{\xi}(t)|$. At the limit of $\Delta\xi \rightarrow 0$, the summation is over all the states with $\xi(t) = \xi_o$ and $\dot{\xi}(t) > 0$. Thus, the summation of the change of $f(\mathbf{F}; t)$ over these states (S_f) is given by

$$S_f = \int d\mathbf{F} \rho(\mathbf{F}; t) [f(\mathbf{F}; t + \Delta t) - f(\mathbf{F}; t)] \times \delta(\xi(t) - \xi_o) \Phi(\dot{\xi}(t)) \quad (2)$$

here time t is explicitly included to highlight that the integration is over an ensemble consisting of trajectories. Applying Taylor expansion to Eq. (2) and ignoring the second and higher order terms, we obtain

$$S_f = \int d\mathbf{F} \rho(\mathbf{F}; t) \delta(\xi(t) - \xi_o) \Phi(\dot{\xi}(t)) \Delta t \times \sum_i \frac{\partial f(\mathbf{F}; t)}{\partial \gamma_i} \dot{\gamma}_i(t) \quad (3a)$$

$$= \int d\mathbf{F} \rho(\mathbf{F}; t) \delta(\xi(t) - \xi_o) \Phi(\dot{\xi}(t)) \frac{\Delta\xi}{\dot{\xi}(t)} \times \sum_i \frac{\partial f(\mathbf{F}; t)}{\partial \gamma_i} \dot{\gamma}_i(t). \quad (3b)$$

Correspondingly, the total population of such states (N_f) is

$$N_f = \int d\mathbf{F} \rho(\mathbf{F}; t) \delta(\xi(t) - \xi_o) \Phi(\dot{\xi}(t)). \quad (4)$$

- (b) Now, we consider the change of $f(\mathbf{F}; t)$ from $\xi_o + \Delta\xi$ at time t to ξ_o at time $t + \Delta t$, which is a backward step. We average over all the states with $\xi(t) = \xi_o + \Delta\xi$ at time t and $\xi(t + \Delta t) = \xi_o$ at the successive time $t + \Delta t$. Similarly, at the limit of $\Delta\xi \rightarrow 0$, the average is over all the states with $\xi(t + \Delta t) = \xi_o$ and $\dot{\xi}(t + \Delta t) < 0$. Thus, the summation of the change of $f(\mathbf{F}; t)$ over these states (S_b)

is given by

$$S_b = \int d\mathbf{F} \rho(\mathbf{F}; t + \Delta t) \delta(\xi(t + \Delta t) - \xi_o) \times \Phi(-\dot{\xi}(t + \Delta t)) [f(\mathbf{F}; t + \Delta t) - f(\mathbf{F}; t)] \quad (5a)$$

$$= \int d\mathbf{F} \rho(\mathbf{F}; t + \Delta t) \delta(\xi(t + \Delta t) - \xi_o) \Phi(-\dot{\xi}(t + \Delta t)) \times \frac{\Delta\xi}{-\dot{\xi}(t + \Delta t)} \sum_i \frac{\partial f(\mathbf{F}; t + \Delta t)}{\partial \gamma_i} \dot{\gamma}_i(t + \Delta t) \quad (5b)$$

here the Taylor expansion is performed at $t + \Delta t$. The total population of such states (N_b) is

$$N_b = \int d\mathbf{F} \rho(\mathbf{F}; t + \Delta t) \delta(\xi(t + \Delta t) - \xi_o) \times \Phi(-\dot{\xi}(t + \Delta t)). \quad (6)$$

Since $\Delta\xi$ is an infinitesimal change, we can drop time in Eqs. (3)–(6) and rewrite them as

$$S_f = \int d\mathbf{F} \rho(\mathbf{F}) \delta(\xi - \xi_o) \Phi(\dot{\xi}) \frac{\Delta\xi}{\dot{\xi}} \sum_i \frac{\partial f(\mathbf{F})}{\partial \gamma_i} \dot{\gamma}_i, \quad (7a)$$

$$S_b = \int d\mathbf{F} \rho(\mathbf{F}) \delta(\xi - \xi_o) \Phi(-\dot{\xi}) \frac{\Delta\xi}{-\dot{\xi}} \sum_i \frac{\partial f(\mathbf{F})}{\partial \gamma_i} \dot{\gamma}_i, \quad (7b)$$

$$N_f = \int d\mathbf{F} \rho(\mathbf{F}) \delta(\xi - \xi_o) \Phi(\dot{\xi}), \quad (7c)$$

$$N_b = \int d\mathbf{F} \rho(\mathbf{F}) \delta(\xi - \xi_o) \Phi(-\dot{\xi}). \quad (7d)$$

Upon the transition of ξ from the $2n - 1$ dimensional subspace $\xi = \xi_o$ to its nearest neighbour $\xi = \xi_o + \Delta\xi$ in the ensemble, there are forward and backward steps. The sum of the change in $f(\mathbf{F}; t)$ in the forward and backward steps is the net change of $f(\mathbf{F}; t)$. The average net change in $f(\mathbf{F}; t)$ upon the transition of ξ from ξ_o to $\xi_o + \Delta\xi$ is

$$\frac{S_f + S_b}{N_f + N_b} = \frac{\int d\mathbf{F} \rho(\mathbf{F}) \delta(\xi - \xi_o) [\Phi(\dot{\xi}) - \Phi(-\dot{\xi})] \frac{\Delta\xi}{\dot{\xi}} \sum_i \frac{\partial f(\mathbf{F})}{\partial \gamma_i} \dot{\gamma}_i}{\int d\mathbf{F} \rho(\mathbf{F}) \delta(\xi - \xi_o) [\Phi(\dot{\xi}) + \Phi(-\dot{\xi})]} \quad (8a)$$

$$= \frac{\int d\mathbf{F} \rho(\mathbf{F}) \delta(\xi - \xi_o) [\Phi(\dot{\xi}) - \Phi(-\dot{\xi})] \frac{\Delta\xi}{\dot{\xi}} \sum_i \frac{\partial f(\mathbf{F})}{\partial \gamma_i} \dot{\gamma}_i}{\int d\mathbf{F} \rho(\mathbf{F}) \delta(\xi - \xi_o)} = \langle \Delta f(\mathbf{F}; \xi_o, \Delta\xi) \rangle, \quad (8b)$$

which is the quantity defined in Eq. (1).

B. The potential energy cost upon the change of a coordinate

Here we discuss a specific case that $f(\mathbf{F})$ is the potential function $\mathcal{V}(\boldsymbol{\eta})$ of the system, with $\boldsymbol{\eta} \equiv (\eta_1, \dots, \eta_n)$ being an arbitrary complete set of configuration coordinates. Since an infinitesimal change of potential energy can be

decomposed as

$$\Delta\mathcal{V} = \sum_i \frac{\partial \mathcal{V}}{\partial \eta_i} \Delta\eta_i, \quad (9)$$

we define the change of the potential energy on η_i as $\frac{\partial \mathcal{V}}{\partial \eta_i} \Delta\eta_i$. In the following, we discuss the change of potential energy on a coordinate η_i , thus we drop the subscript i from η_i . From Eq. (1), the average net change of the potential energy on η upon the change of a coordinate ξ from ξ_o to $\xi_o + \Delta\xi$ is

$$\langle \Delta\mathcal{V}_\eta(\xi, \mathbf{q}; \xi_o, \Delta\xi) \rangle = \Delta\xi \frac{\int \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \eta} \delta(\xi - \xi_o) \int \rho(\mathbf{F}) [\Phi(\dot{\xi}) - \Phi(-\dot{\xi})] \dot{\eta} / \dot{\xi} d\mathbf{F}_q}{\int d\mathbf{F} \rho(\mathbf{F}) \delta(\xi - \xi_o)} \quad (10a)$$

$$= \Delta\xi \frac{\int \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \eta} \delta(\xi - \xi_o) |\mathbf{M}(\mathbf{F}_q)| \int \rho(\mathbf{F}_q, \mathbf{F}_q) [\Phi(\dot{\xi}) - \Phi(-\dot{\xi})] \dot{\eta} / \dot{\xi} d\mathbf{F}_q d\mathbf{F}_q}{\int d\mathbf{F} \rho(\mathbf{F}) \delta(\xi - \xi_o)}, \quad (10b)$$

where $\Gamma_q \equiv (\xi, \mathbf{q})$ with $\mathbf{q} \equiv (q_1, \dots, q_{n-1})$ and $\Gamma_p \equiv (p_\xi, p_1, \dots, p_{n-1})$. $\Gamma_{\dot{q}}$ is the time derivative of Γ_q . $\mathbf{M}$ is the mass matrix with $\Gamma_p = \mathbf{M}\Gamma_{\dot{q}}$, and $|\mathbf{M}|$, the determinant of $\mathbf{M}$, is the Jacobian for transformation of the unit volume from subspace Γ_p to $\Gamma_{\dot{q}}$. We note that η is considered as a function of $(\xi, \mathbf{q})$. We rename the average net change of the potential energy on η upon the change of a coordinate ξ as the emergent potential energy on η induced by ξ .

In the equilibrium ensemble, it is trivial to prove that the EPE defined in Eq. (10) on any coordinate induced by an arbitrary coordinate vanishes (see supplementary material³⁶). In the following, we will discuss the properties of the EPE on a coordinate in the TPE.

C. The EPE on a coordinate in the TPE

Now we discuss the case in the TPE. Here, we assume that (1) the system can be considered as a reaction coordinate interacting with a collection of bath modes.³⁵ (2) In TPE, the distribution of velocities of the bath modes is independent

of the system configuration and similar to that of the equilibrium ensemble. (3) The distribution of the velocity of the reaction coordinate is biased towards positive values, with the convention that positive velocity guides the system towards the product state. Based on these assumptions, we will demonstrate how to distinguish a reaction coordinate from bath modes with the quantity in Eq. (10). In the main text, we will only briefly explain the case where ξ is the reaction coordinate. For a complete description, see the supplementary material.³⁶ The major conclusions are listed in Table I.

1. When ξ is the reaction coordinate

We consider that ξ is the reaction coordinate and discuss the EPE on an arbitrary coordinate η induced by ξ . Thus for the coordinates in Γ_q , ξ is the reaction coordinate and all the other coordinates $\mathbf{q}$ are bath modes. η can be three kinds of coordinates: (i) η is a bath mode, (ii) η is the reaction coordinate, and (iii) η is a function of the reaction coordinate and a bath mode.

(i) **η is a bath mode:** Without loss of generality, we assume $\eta = q_1$, and we have

$$\langle \Delta \mathcal{V}_\eta(\xi, \mathbf{q}; \xi_o, \Delta \xi) \rangle = \Delta \xi \frac{\int \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial q_1} \delta(\xi - \xi_o) |\mathbf{M}(\Gamma_q)| \int [\Phi(\dot{\xi}) - \Phi(-\dot{\xi})] / \dot{\xi} \int \rho(\Gamma_{\dot{q}}, \Gamma_q) \dot{q}_1 d\dot{q}_1 d\Gamma'_q d\Gamma_q}{\int d\Gamma \rho(\Gamma) \delta(\xi - \xi_o)}, \quad (11)$$

where Γ'_q include all the elements in $\Gamma_{\dot{q}}$ except $\dot{q}_1$. Since q_1 is a bath mode, $\rho(\Gamma)$ is an even function of $\dot{q}_1$ according to our assumptions and the integral of $\rho(\Gamma_{\dot{q}}, \Gamma_q) \dot{q}_1$ over $\dot{q}_1$ vanishes. Thus the EPE on a bath mode induced by the reaction coordinate vanishes in TPE.

(ii) **η is the reaction coordinate:** If η is the reaction coordinate, that is $\eta = \xi$, we have

$$\langle \Delta \mathcal{V}_\eta(\xi, \mathbf{q}; \xi_o, \Delta \xi) \rangle = \Delta \xi \frac{\int \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \xi} \delta(\xi - \xi_o) |\mathbf{M}(\Gamma_q)| \int \rho(\Gamma_{\dot{q}}, \Gamma_q) [\Phi(\dot{\xi}) - \Phi(-\dot{\xi})] d\Gamma_{\dot{q}} d\Gamma_q}{\int d\Gamma \rho(\Gamma) \delta(\xi - \xi_o)}. \quad (12)$$

Since ξ is the reaction coordinate, the distribution of $\dot{\xi}$ is no longer the same as in equilibrium. Because of the net transition from the reactant state to the product state along the reaction coordinate, we expect that $\dot{\xi} > 0$ occurs more frequently than $\dot{\xi} < 0$ in TPE, thus $\langle \Delta \mathcal{V}_\eta(\xi, \mathbf{q}; \xi_o, \Delta \xi) \rangle$ is unlikely to be zero.

(iii) **η is a combination of the reaction coordinate and a bath mode:** If η is a combination of ξ and a bath mode ξ' , and the corresponding bath coordinate orthogonal to η is η' , we assume that η and η' are function of ξ and ξ' only (we use ξ' to represent one of the bath modes in $\mathbf{q}$), without loss of generality. Then, Eq. (10) can be rewritten as,

$$\langle \Delta \mathcal{V}_\eta(\xi, \mathbf{q}; \xi_o, \Delta \xi) \rangle = \Delta \xi \frac{\int \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \eta} \delta(\xi - \xi_o) |\mathbf{M}(\Gamma_q)| \partial \eta / \partial \xi \cdot \int \rho(\Gamma_{\dot{q}}, \Gamma_q) [\Phi(\dot{\xi}) - \Phi(-\dot{\xi})] d\Gamma_{\dot{q}} d\Gamma_q}{\int d\Gamma \rho(\Gamma) \delta(\xi - \xi_o)} \quad (13a)$$

$$= \Delta \xi \frac{\int \frac{\partial \eta}{\partial \xi} \left(\frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \xi} \frac{\partial \xi}{\partial \eta} + \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \xi'} \frac{\partial \xi'}{\partial \eta} \right) \delta(\xi - \xi_o) |\mathbf{M}(\Gamma_q)| \int \rho(\Gamma_{\dot{q}}, \Gamma_q) [\Phi(\dot{\xi}) - \Phi(-\dot{\xi})] d\Gamma_{\dot{q}} d\Gamma_q}{\int d\Gamma \rho(\Gamma) \delta(\xi - \xi_o)}. \quad (13b)$$

Thus, the EPE on a coordinate induced by the reaction coordinate usually does not vanish. Since $\frac{\partial \eta}{\partial \xi} \left(\frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \xi} \frac{\partial \xi}{\partial \eta} + \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \xi'} \frac{\partial \xi'}{\partial \eta} \right)$ can be larger than $\frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \xi}$, the EPE on a coordinate induced by the reaction coordinate can be larger than that on the reaction coordinate itself (compare to Eq. (12)).

D. The EPE of a coordinate in the TPE

From the analyses above, there are several ways to distinguish bath modes from relevant coordinates, which can be either the reaction coordinate or a combination of the reaction coordinate and a bath mode. In the current work,

we first use the EPE on a coordinate ξ induced by itself (the EPE of a coordinate ξ) in TPE with the following criteria:

- The EPE of a bath mode vanishes.
- The EPE of a relevant coordinate does not vanish.

TABLE I. The values of the quantity in Eq. (10) in various cases, where ξ and η can be one of the three kinds of coordinates (a) the reaction coordinate, (b) a function of the reaction coordinate and a bath mode (named as combination coordinate), and (c) a bath mode.

$\xi \setminus \eta$	Reaction coordinate	Combination coordinate	Bath mode
Reaction coordinate	Non-zero	Non-zero	Zero
Combination coordinate	Non-zero	Non-zero	Zero
Bath mode	Non-zero	Non-zero	Zero

1. Why should the EPE of a coordinate work?

The EPE of a coordinate ξ is give by

$$\langle \mathcal{V}_\xi(\xi, \mathbf{q}; \xi_o, \Delta\xi) \rangle = \Delta\xi \frac{\int d\Gamma \rho(\Gamma) \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \xi} \delta(\xi - \xi_o) [\Phi(\xi) - \Phi(-\xi)]}{\int d\Gamma \rho(\Gamma) \delta(\xi - \xi_o)}. \quad (14)$$

Then, we obtain a quantity that is quite similar to an averaged generalized force,

$$C_\xi = \lim_{\Delta\xi \rightarrow 0} \langle \mathcal{V}_\xi(\xi, \mathbf{q}; \xi_o, \Delta\xi) \rangle / \Delta\xi = \langle \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \xi} [\Phi(\xi) - \Phi(-\xi)] \rangle_{\xi=\xi_o}. \quad (15)$$

Note that C_ξ is a function of ξ and is independent of $\Delta\xi$. Now, we consider the following two quantities for the change of the potential energy induced by ξ ,

$$Q_\xi^f = \lim_{\Delta\xi \rightarrow 0} \frac{S_f/N_f}{\Delta\xi} = \frac{\int d\Gamma \rho(\Gamma) \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \xi} \delta(\xi - \xi_o) \Phi(\xi)}{\int d\Gamma \rho(\Gamma) \delta(\xi - \xi_o) \Phi(\xi)} = \langle \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \xi} \rangle_{\xi_o, \xi > 0}, \quad (16a)$$

$$Q_\xi^b = \lim_{\Delta\xi \rightarrow 0} \frac{-S_b/N_b}{\Delta\xi} = \frac{\int d\Gamma \rho(\Gamma) \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \xi} \delta(\xi - \xi_o) \Phi(-\xi)}{\int d\Gamma \rho(\Gamma) \delta(\xi - \xi_o) \Phi(-\xi)} = \langle \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \xi} \rangle_{\xi_o, \xi < 0}, \quad (16b)$$

here $\langle \dots \rangle_{\xi_o, \xi > 0}$ stands for the ensemble average at $\xi = \xi_o$ and $\xi > 0$; $\langle \dots \rangle_{\xi_o, \xi < 0}$ stands for the ensemble average at $\xi = \xi_o$ and $\xi < 0$. These two quantities are the negative of the averaged generalized force in the corresponding ensembles. Q_ξ^f is the average over all the phase points with $\xi > 0$, whereas Q_ξ^b is the average over all the phase points with $\xi < 0$. If the average is over enough samples, both average will converge to the negative of the averaged generalized force in equilibrium ensemble and we generally have

$$Q_\xi^f = Q_\xi^b. \quad (17)$$

In equilibrium ensemble or when the distribution of ξ in TPE is similar to that at equilibrium, we have $N_f = N_b$ and

$$C_\xi = \lim_{\Delta\xi \rightarrow 0} \frac{S_f + S_b}{N_f + N_b} / \Delta\xi \quad (18a)$$

$$= \frac{1}{2} \lim_{\Delta\xi \rightarrow 0} \frac{S_f}{N_f} / \Delta\xi - \lim_{\Delta\xi \rightarrow 0} \frac{1}{2} \frac{S_b}{N_b} / \Delta\xi \quad (18b)$$

$$= \frac{1}{2} Q_\xi^f - \frac{1}{2} Q_\xi^b = 0. \quad (18c)$$

This explains the reason that the EPE of a coordinate in equilibrium ensemble or a bath mode in TPE vanishes.

In TPE, if ξ is not a bath mode (i.e., ξ is a relevant coordinate), then the symmetry between N_f and N_b breaks down and $N_f \neq N_b$ in general, thus either the forward or the backward flow dominates. In other words, the net flow along ξ is non-zero and there is a net force along ξ either forward or backward. Therefore, C_ξ can be considered as the negative of the averaged net force along ξ .

2. Relative importance of different coordinates during the transition process

According to Eq. (13b), the relative importance of a coordinate during the transition process can be quantified by the EPE on this coordinate induced by the reaction coordinate. In case that the reaction coordinate is not known, the relative importance of a coordinate can be approximately quantified by the EPE on it, induced by a relevant coordinate. The more the relevant coordinate overlaps with the reaction coordinate, the better the approximation.

E. The potential of mean force along a coordinate

Since the potential energy of the system does not cover the entropic change in a reaction, the potential of mean force might be a better option to fully quantify the energetic cost, which can be derived from a modified potential energy as shown below.

As given in the previous literatures,³⁷ the potential of mean force along a coordinate ξ in an equilibrium ensemble is given by

$$\frac{d\mathcal{A}(\xi)}{d\xi} \Big|_{\xi=\xi_o} = \langle \frac{\partial \mathcal{H}}{\partial \xi} \rangle_{\xi=\xi_o} = \langle \frac{\partial \mathcal{V}}{\partial \xi} - k_B T \frac{\partial \ln |\mathbf{J}|}{\partial \xi} \rangle_{\xi=\xi_o} \quad (19)$$

where $\mathcal{A}(\xi)$ is the free energy as a function of ξ . $|\mathbf{J}|$ is the determinant of the Jacobian matrix ($\mathbf{J}$) upon changing from Cartesian to generalized coordinates.

For generalized coordinates, one can use a modified potential energy function with

$$\mathcal{U}(\xi, \mathbf{q}) = \mathcal{V}(\xi, \mathbf{q}) + \frac{1}{2} k_B T \ln |\mathbf{G}(\xi, \mathbf{q})| \quad (20)$$

and

$$\frac{d\mathcal{A}(\xi)}{d\xi} \Big|_{\xi=\xi_o} = \langle \frac{\partial \mathcal{U}}{\partial \xi} \rangle_{\xi=\xi_o}. \quad (21)$$

Here, $\mathbf{G}$ is the inverse of $\mathbf{M}$. The second term on the right hand side of Eq. (20) takes into account the energy change due to conformational arrangements. Apparently, the previous conclusions about the potential energy $\mathcal{V}$ can be also applied to $\mathcal{U}$. Therefore, we can use $\mathcal{U}$ as the effective potential energy and use the cost defined by $\mathcal{U}$ to identify the relevant coordinates.

In the equilibrium ensemble, formula that does not require a complete set of coordinates was proposed to estimate the potential of mean force as well.³⁷⁻⁴⁰ For an arbitrary vector field $\mathbf{w}$ such that $\mathbf{w} \cdot \nabla \xi \neq 0$,

$$\frac{d\mathcal{A}}{d\xi}|_{\xi=\xi_0} = \langle \nabla \mathcal{V} \cdot \frac{\mathbf{w}}{\mathbf{w} \cdot \nabla \xi} - k_B T \nabla \cdot \frac{\mathbf{w}}{\mathbf{w} \cdot \nabla \xi} \rangle_{\xi=\xi_0}. \quad (22)$$

When $\mathbf{w} = \nabla \xi$, we have

$$\begin{aligned} \frac{d\mathcal{A}}{d\xi}|_{\xi=\xi_0} &= \langle \frac{1}{|\nabla \xi|^2} (\nabla \mathcal{V} \cdot \nabla \xi - k_B T (\nabla^2 \xi - 2 \frac{\nabla \xi \cdot \mathbf{H}(\xi) \cdot \nabla \xi}{|\nabla \xi|^2})) \rangle_{\xi=\xi_0}. \end{aligned} \quad (23)$$

The equality between terms on the right hand side of Eqs. (21) and (23) holds when the dynamics of ξ is equivalent to that in the equilibrium ensemble, thus such equality does not hold for some coordinates in the TPE.

F. Optimizing the reaction coordinate

Although the theory above provides means to filter out the relevant coordinates, it cannot tell which coordinate is better

if two or more coordinates are identified as being relevant. In the following, we discuss a procedure to optimize the reaction coordinate. Without loss of generality, we assume that two coordinates are identified as being relevant, both of which are functions of the coordinate and bath modes. Optimization is performed over all linear combinations of the two relevant coordinates.

1. An approximate variational condition

According to Eq. (1), the total EPE of the system induced by ξ is given by

$$\begin{aligned} \langle \mathcal{A} \mathcal{V}(\xi, \mathbf{q}; \xi_0, \Delta \xi) \rangle &= \frac{\int d\mathbf{\Gamma} \rho(\mathbf{\Gamma}) \sum_i \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \eta_i} \eta_i \frac{\Delta \xi}{\xi} \delta(\xi - \xi_0) [\Phi(\dot{\xi}) - \Phi(-\dot{\xi})]}{\int d\mathbf{\Gamma} \rho(\mathbf{\Gamma}) \delta(\xi - \xi_0)}. \end{aligned} \quad (24)$$

Then, the accumulated total EPE induced by ξ is given by

$$\mathcal{A} \tilde{\mathcal{V}}_\xi = \int d\xi \lim_{\Delta \xi \rightarrow 0} \langle \mathcal{A} \mathcal{V}(\xi, \mathbf{q}; \xi_0, \Delta \xi) \rangle / \Delta \xi \quad (25a)$$

$$= \int d\xi \lim_{\Delta \xi \rightarrow 0} \frac{\int d\mathbf{\Gamma} \rho(\mathbf{\Gamma}) \delta(\xi - \xi_0) [\Phi(\dot{\xi}) - \Phi(-\dot{\xi})] \frac{d\mathcal{V}(\xi, \mathbf{q}; t)}{dt} \frac{\Delta \xi}{\xi}}{\int d\mathbf{\Gamma} \rho(\mathbf{\Gamma}) \delta(\xi - \xi_0)} \Bigg| \Delta \xi \quad (25b)$$

$$= \int d\xi \lim_{\Delta \xi \rightarrow 0} \frac{\int d\mathbf{\Gamma} \rho(\mathbf{\Gamma}) \delta(\xi - \xi_0) \frac{d\mathcal{V}(\xi, \mathbf{q}; t)}{dt} \Delta t}{\int d\mathbf{\Gamma} \rho(\mathbf{\Gamma}) \delta(\xi - \xi_0)} \Bigg| \Delta \xi, \quad (25c)$$

where $\frac{d\mathcal{V}(\xi, \mathbf{q}; t)}{dt}$ replaces $\sum_i \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \eta_i} \eta_i$. From Eq. (25b) to (25c), $\Delta t = \frac{\Delta \xi}{|\dot{\xi}|}$ and thus $-\Phi(-\dot{\xi})$ becomes $\Phi(-\dot{\xi})$.

For under-damped systems, the committor increases almost monotonically along the transition path³¹ and the distribution of configurations along the committor in TPE is close to the uniform distribution (see Fig. S20³⁶). As demonstrated in the supplementary material,³⁶ under the assumption that the distribution of the configurations in TPE along ξ is uniform, $\mathcal{A} \tilde{\mathcal{V}}_\xi$ can be rewritten as

$$\mathcal{A} \tilde{\mathcal{V}}_\xi \approx \frac{\int dt \frac{d\mathcal{V}(\xi, \mathbf{q}; t)}{dt}}{N \int d\mathbf{\Gamma} \rho(\mathbf{\Gamma}) \delta(\xi - \xi_0)}, \quad (26)$$

where N is the total number of configurations in the TPE. Therefore, the numerator in Eq. (26) is a constant for a given TPE.

In TPE, the reaction coordinate starts from its value in the reactant state and moves along the transition path to its value in the product state, thus the reaction coordinate increases steadily along the transition path, although it moves backward sometimes. One may consider the reaction coordinate as the coordinate along which the system has smallest probability to move backward in TPE. Thus, the denominator in Eq. (26) is much smaller for reaction coordinate than the one for a

bath mode, as the system visits a fixed value of the reaction coordinate almost once in a transition path. Consequently, $\mathcal{A} \tilde{\mathcal{V}}_\xi$ is the largest for the reaction coordinate.

Although the distribution of configuration along a coordinate is largely not a uniform distribution, the deviation from a uniform distribution seems to be caused by the frequent backward movement along the transition path. Such backward movements will induce a further cancellation as indicated by the term $[\Phi(\dot{\xi}) - \Phi(-\dot{\xi})]$ in Eq. (25b), which will reduce the value of its numerator and thus the value of $\mathcal{A} \tilde{\mathcal{V}}_\xi$. On the other hand, as long as $N \int d\mathbf{\Gamma} \rho(\mathbf{\Gamma}) \delta(\xi - \xi_0)$ of a reaction coordinate is lower everywhere than that of other coordinates given that they can be compared by proper unit conversions, $\mathcal{A} \tilde{\mathcal{V}}_\xi$ will be the largest and a uniform distribution is not required.

Based on the above reasoning, we conclude that the optimal reaction coordinate from maximizing $\mathcal{A} \tilde{\mathcal{V}}_\xi$ is a close approximation of the reaction coordinate. Therefore, we name it an approximate variational condition. In addition, the total EPE induced by a coordinate can be used to test if the coordinate is a relevant coordinate as well, and it can be applied in combination with the EPE of the coordinate.

Since the EPE on a bath mode induced by any coordinate vanishes, we can ignore the terms on bath modes in Eq. (24) and obtain

$$\mathcal{A} \tilde{\mathcal{V}}_\xi = \sum_{\eta_i \in (q_s, \dots)} \int d\xi \frac{\int d\mathbf{\Gamma} \rho(\mathbf{\Gamma}) \frac{\partial \mathcal{V}(\xi, \mathbf{q})}{\partial \eta_i} \eta_i \delta(\xi - \xi_0) [\Phi(\dot{\xi}) - \Phi(-\dot{\xi})]}{\int d\mathbf{\Gamma} \rho(\mathbf{\Gamma}) \delta(\xi - \xi_0)}. \quad (27)$$

Here, the summation is over all the relevant coordinates. For large systems, the potential energy on a single coordinate could be still smooth, although the overall potential energy is very noisy. This is the very advantage to decompose the potential energy into single degree of freedom. As the number of relevant coordinates is much smaller than the total number of degrees of freedom of the system, Eq. (27) will greatly reduce the noise of the potential energy and provide fast convergence in numerical estimation of the accumulated total EPE.

2. Auxiliary conditions

Additional conditions can be used in combination with the approximate variational condition to optimize the reaction coordinate. Once an optimized reaction coordinate as a linear combination of two coordinates is determined from the approximate variational condition, a coordinate orthogonal to the optimized coordinate should be a bath mode and it should satisfy the following conditions according to previous reasoning:

- The EPE on the orthogonal coordinate induced by the optimized coordinate should vanish;
- The EPE of the orthogonal coordinate should vanish.

By combining the approximate variational condition with auxiliary conditions, we can optimize the reaction coordinate reliably.

III. COMPUTATIONAL DETAILS

The scheme resulting from analyses above was then applied to identify the reaction coordinate of a prototypical system for biomolecular conformational dynamics, the $C_{7eq} \rightarrow C_{7ax}$ isomerization of alanine dipeptide in vacuum. Since the relevant coordinates of the system are well-known in the

literature,^{18,16} it is an ideal system to validate the proposed approach.

A. MD simulations

All the simulations were carried out with an extended version of the molecular dynamics software suite GROMACS-4.0.7,⁴¹ in which the transition path sampling method was implemented.^{42,43} The AMBER94 force field^{44–46} was used to facilitate the comparison with the previous results.^{18,16} The structure of the alanine dipeptide was optimized using steepest descent algorithm and then equilibrated for 200 ps at 300 K using velocity rescaling with a coupling constant of 0.2 ps.⁴⁷ The time step of integration was 0.5 fs and no constraints were applied.

In transition path sampling, the two stable states were defined with the Ramachandran angles ϕ and ψ (see Table S1 and Fig. S3 for the definition of these dihedral angles³⁶). The reactant state (C_{7eq}) was defined as $-200 < \phi < -55$ (it includes $-180 < \phi < -55$ and $160 < \phi < 180$) and $-90 < \psi < 190$ (it includes $-90 < \psi < 180$ and $-180 < \psi < -170$). The product state (C_{7ax}) was defined as $50 < \phi < 100$ and $-80 < \psi < 0$. 120 000 transition paths for the transition from C_{7eq} to C_{7ax} have been sampled by transition path sampling with equal numbers of shooting, shifting, and reputation moves¹⁵ and were saved every 200 paths, thus 6000 transition paths were harvested. The simulations were performed at constant total energy of 36 kJ/mol, the value that ensures an averaged temperature of about 300 K in the transition path ensemble. The length of each transition path is 2 ps and each transition path contains 4000 configurations. Proper perturbation of the momentum ensures an acceptance ratio of 51% for shooting, the acceptance ratio for shifting is 67%.

The committor of configurations in each transition path was estimated with 1000 shootings with random velocities taken from Boltzmann distribution at temperature of 300 K. The maximum allowed simulation time for each shooting

FIG. 1. A flowchart to illustrate the procedure of identifying the relevant coordinates.

FIG. 2. A flowchart to illustrate the procedure of optimizing the reaction coordinate as a linear combination of the relevant coordinates.

is 2 ps. The trajectory is considered to commit to a stable region if it stays there at least 20 fs. The committor of frames in every 5 fs were estimated and for each transition path there were 400 configurations whose committor was estimated.

B. Decomposition of the potential energy

We used the center of mass, overall rotation around the center of mass, and the internal coordinates as the complete set of coordinates. As shown in a recent paper,⁴⁸ this coordinate set can separate the six external movements from the internal ones. The internal coordinates consist of the bonds, angles, and dihedral angles (the BAT coordinates). As described in Ref. 48, a particular BAT coordinate can be chosen such that the forces on many of such coordinates are independent of the choice of the base of a BKS-tree,⁴⁹ from which the set of BAT coordinates are constructed. Thus the decomposition of potential energy in this coordinates set has the least dependence on the choice of the BKS-tree base. Such sets of coordinates are thought to be of minimum dependence between the potential energy on each coordinate. We choose a set of BAT coordinates that include ϕ, ψ, θ_1 as elements (see Table S1³⁶).

C. Detailed description of the algorithm

As illustrated in Fig. 1, the relevant coordinates can be identified from the TPE alone, which eliminates the need to evaluate the committor.

With the identified relevant coordinates and the chosen sub-ensembles that are close to the barrier region, one can then optimize the reaction coordinate as a linear combination of relevant coordinates following the iterative procedure in Fig. 2. The iterations are performed until the optimized reaction coordinate no longer change.

IV. RESULTS

A. The EPE on a coordinate induced by the reaction coordinate

In general, the committor P_B is considered as close to the “ideal” reaction coordinate. Here, we examined the EPE on a coordinate induced by P_B ; the accumulated EPE on each coordinate is shown in Fig. 3. ϕ and θ_1 are the only two coordinates showing significant EPE. According to the analysis in Section II C 1, ϕ and θ_1 are then the only two coordinates that significantly overlap with the reaction coordinate, a result that is consistent with previous studies.^{18,16} The accumulated EPE measures the energy cost on each coordinate induced by the reaction coordinate, thus it can

FIG. 3. The accumulated EPE on each coordinate induced by the reaction coordinate. Here, the reaction coordinate is approximated by the committor. The accumulated EPE on ϕ , θ_1 , and ψ are shown in black, red, and green, respectively. “tot” is the accumulated total EPE induced by the reaction coordinate. The solid lines are the results using the actual potential energy $\mathcal{V}(\xi, q)$, whereas the dotted lines are the results using $\mathcal{U}(\xi, q)$ as the effective potential energy. The accumulated EPE on other coordinates in both cases is shown in grey lines. Here, $\Delta\xi = 0.02$ and the range of P_B from 0 to 1 is covered (50 intervals).

FIG. 4. The definition of the 6 segments for a transition path. The transition path is represented by a straight line in black, with axis ticks labelling the sub-segments. Two boundaries A and B (black dashed lines) lie on the sides of the transition state region and are defined beforehand. Based on the definition of the boundaries, the transition path is divided into three segments: (I) The transition barrier segment (TBS) starts from its last crossing with the boundary A to its first crossing with the boundary B. (II) The segment before the TBS is the reactant segment (RS). (III) The segment after the TBS is the product segment (PS). The TBS is divided into 8 equal segments (S_B). The RS and PS were divided into 40 equal segments and labelled as S_R and S_P respectively. As the RS and PS are usually much longer than TBS, only part of them are shown. The 6 segments are highlighted and labelled as S1, S2, S3, S4, S5, and S6, respectively. Note, segment 4 is exactly the TBS.

be considered as a measure of its importance during the transition. Consequently, we can rank the relative importance of coordinates and ϕ is the most important coordinate with θ_1 being the second. As expected, the magnitudes of the accumulated net changes of EPE on ϕ and θ_1 reach their maximum around $P_B = 0.5$. In addition, the EPE on ϕ is larger than the one on P_B (compare the black lines and the blue ones in Fig. 3), which is allowed as indicated by Eq. (13). Both the results with the potential energy $\mathcal{V}(\xi, \mathbf{q})$ and the ones using $\mathcal{U}(\xi, \mathbf{q})$ as the effective potential energy support the above statements. The EPE on θ_1 is negative, indicating that θ_1 facilitates the barrier crossing of ϕ .

B. A committor-free procedure for identifying relevant coordinates

Although the procedure above can be used to identify the relevant coordinates, it requires full information of P_B . In the following, we will demonstrate that the EPE of a coordinate can serve as the benchmark of relevant coordinates.

From a preliminary analysis, we noticed that the behavior of θ_1 in the transition region is quite different from that

in the stable basins (see Fig. S8³⁶). Thus, we analysed 6 sub-ensembles of TPE that covered various regions of the TPE. For each transition path, we defined 6 segments as illustrated in Fig. 4, where the two boundaries A and B are defined at $P_B = 0$ and $P_B = 1$, respectively. Then sub-ensemble i ($i = 1, 2, \dots, 6$) corresponds to a collection of segment i of all trajectories in TPE. For each sub-ensemble, the EPE of each coordinate was estimated and then the accumulated EPE of each coordinate from the start of the segment to the barrier top ($P_B = 0.5$) was calculated.

As the accumulated EPE on each transition path varies, we averaged them as the energy cost along a coordinate from the reactant state to the transition state in each sub-ensemble; they are shown in Figs. 5(a) and 5(b). The accumulated EPE of ϕ , θ_1 , and ψ are non-zero, whereas those of other coordinates are vanishingly small. These observations are consistent with our theory and indicate that the three coordinates are the relevant coordinates. As the accumulated EPE of ϕ is of the largest magnitude, ϕ is safely identified as the most important coordinate. We thus estimated the accumulated EPE on each coordinate induced by ϕ (see Fig. 5(c)) and the results reproduced the relative importances of these coordinates

FIG. 5. The accumulated EPE of each coordinate from the reactant state to the transition state in the 6 sub-ensembles. The accumulated EPE of ϕ , θ_1 , and ψ are shown in black, red, and green, respectively. The solid lines are the results using the actual potential energy $\mathcal{V}(\xi, \mathbf{q})$, whereas the dotted lines are the results using $\mathcal{U}(\xi, \mathbf{q})$ as the effective potential energy. The accumulated EPE of other coordinates in both cases are shown in grey lines. (a)—All the results; (b)—the results without the EPE of ϕ . (c)—The accumulated EPE defined by $\mathcal{V}(\xi, \mathbf{q})$ on each coordinate induced by θ_1 in the 6 sub-ensembles.

very well, which is consistent with the results based on the committor. While accumulated EPE of ϕ increases with the length of the segment, the accumulated EPE on θ_1 first increases and then decreases as the length of the segment increases. The energy costs on θ_1 are larger than the ones on ψ in the sub-ensemble 3-6, which correspond to the region near the transition region, while the energy costs on θ_1 are close to the ones on ψ in the sub-ensemble 1-2. Thus, θ_1 is an important reaction coordinate only in the region around the transition barrier, as expected from the analysis based on the committor (see Fig. S8³⁶).

On the other hand, the reaction coordinate should be discussed in the region near the transition state. If we take a larger transition region, e.g., sub-ensemble 1-2, into account, we end up with order parameters instead of the relevant coordinates. Thus, from the results around the transition region, we conclude that ϕ and θ_1 are the two most important relevant coordinates, the same as the previous studies.^{18,16} Furthermore, the accumulated EPE on each coordinate induced by other relevant coordinates that are poor approximations of the reaction coordinate, e.g., θ_1 and ψ , identifies the same relevant coordinates (see Figs. S5B and S5C³⁶), highlighting the robustness of our approach. In addition, results from the total EPE on each coordinate (see Fig. S5D³⁶) produce consistent results. The use of $\mathcal{U}(\xi, \mathbf{q})$ as the effective potential energy gives very similar results (see Fig. 5) as the effective potential energy related to the arrangement of the configurations is negligible in this system.

Taking the results from the sub-ensemble 4 as an example, we examined the validity of our assumptions on the TPE. Fig. 6 shows N_f and N_b at a fixed value of a coordinate; they are almost identical for coordinates that are bath modes. In contrast, N_f and N_b for ϕ , θ_1 , and ψ are quite different from each other. Although N_f and N_b on ψ differ significantly, ψ is not a coordinate that dominates the transition process. A plausible explanation is that ψ is a “slave” coordinate; it is slaved to the movement of ϕ and θ_1 near the transition region.^{50–52} Q_f and Q_b are largely equal for all coordinates, a result

consistent with our theoretical predictions (see Fig. S6³⁶). We have tested the results on Q_f , Q_b , and C_ξ with different bin sizes $\Delta\xi$ and they are consistent (see Figs. S6 and S7³⁶).

As the effective force estimated as $-\frac{\partial \mathcal{U}}{\partial \xi}$ depends on the complete set of coordinates, we estimated $\frac{d\mathcal{A}(\xi)}{d\xi}|_{\xi=\xi_0}$ using Eq. (23) by assuming the dynamics in each coordinate are close to the equilibrium one. We get the same $\frac{d\mathcal{A}(\xi)}{d\xi}|_{\xi=\xi_0}$ for the bath mode coordinates, whereas the $\frac{d\mathcal{A}(\xi)}{d\xi}|_{\xi=\xi_0}$ on the important coordinates are different (see Fig. S12³⁶). Such results further support our assumptions about the TPE. In addition, if we take the integral of $\Delta\xi \langle \frac{1}{|\nabla \xi|^2} (\nabla \mathcal{V} \cdot \nabla \xi - k_B T (\nabla^2 \xi - 2 \frac{\nabla \xi \cdot \mathbf{H}(\xi) \cdot \nabla \xi}{|\nabla \xi|^2})) [\Phi(\xi) - \Phi(-\xi)] \rangle_{\xi=\xi_0}$, an analogue to the term in Eq. (23), along ξ as the accumulated EPE from the reactant state to the transition state, we identified the same coordinates along which the energy cost is non-zero, while the cost on the rest is vanishingly small (see Fig. S5A³⁶). Since there might be a function of the configuration coordinate, whose partial derivative over ξ is $\frac{1}{|\nabla \xi|^2} (\nabla \mathcal{V} \cdot \nabla \xi - k_B T (\nabla^2 \xi - 2 \frac{\nabla \xi \cdot \mathbf{H}(\xi) \cdot \nabla \xi}{|\nabla \xi|^2}))$, such cost function can also be used to distinguish the important coordinates from bath modes according to our theory. However, the exact form of the function is unknown. On the other hand, the potential energy is the energy function used in propagating the dynamics, we thus prefer to use the potential energy function to define the EPE.

Nevertheless, the analyses above used partial information of the committor, i.e., the committor at 0, 0.5, and 1. To completely eliminate the dependence on the information of the committor, two boundaries A and B are defined as the boundary of the reactant state and the boundary of the product state used in TPS, respectively. Similarly, 6 sub-ensemble are defined. Then, for each transition path (only a segment of the sampled transition path) in a sub-ensemble, we set a fixed number of milestones that are equally spaced and the accumulation of the EPE is performed from the start of the transition path to each milestone (including the end of the path). The results are shown in Fig. 7. As expected, the accumulated

FIG. 6. N_f (solid lines) and N_b (dotted lines) of several example coordinates in the case of sub-ensemble 4. See Table S1³⁶ for the name of the coordinates.

FIG. 7. The accumulated EPE of each coordinate in the 6 sub-ensembles. Here, the transition barrier region is defined based on the stable states. The fraction is the normalized location of each milestone.

EPE first increases and then decreases along the milestones in all the sub-ensembles. Consistent with the above results, the energy costs on ϕ , θ_1 , and ψ are non-zero, whereas those of other coordinates are vanishingly small. Similarly, the relative importance of θ_1 compared to ψ decreases as the sub-ensemble includes more regions close to the stable states. In the sub-ensemble around the transition regions, e.g., sub-ensembles 4 and 5, we estimated the accumulated EPE on each coordinate induced by ϕ (see Fig. 8). We found that ϕ and θ_1 are the two major coordinates (compare their values around the barrier top of the EPE of ϕ). Results from other criteria are shown in Fig. S15³⁶ and support the same conclusion. Following this procedure, we can identify the correct relevant coordinates without requiring knowledge of the committor.

To test if the coordinate set we choose is a BAT coordinate set with minimum correlation, we tried another complete set of coordinate (see Table S2³⁶), with the same bonds and angles but different dihedrals. For example, in the branches at the C_α atom (atom 8 in Fig. S3³⁶), three proper dihedrals (ϕ , $dih_4_6_8_10$, and $dih_4_6_8_9$) were chosen, instead of one proper dihedral and two improper dihedrals (ϕ , $dih_10_8_6_14$, and $dih_9_8_6_14$). Similar analyses revealed that ϕ and $dih_4_6_8_10$ are relevant coordinates besides θ_1 . As proved in the supplementary material,³⁶ the sum of changes in potential energy on the dihedrals of a branch remains the same, no matter which dihedrals are chosen. However, the EPE are almost equally distributed onto ϕ and $dih_4_6_8_10$ (see Figs. S13 and S14³⁶), indicating

FIG. 8. The accumulated EPE defined by $\mathcal{V}(\xi, q)$ on each coordinate induced by ϕ . The sub-ensembles are defined based on the stable states and the results of sub-ensemble 4 (a) and 5 (b) are shown. The results of ϕ , θ_1 , and ψ are shown in black, red, and green, respectively. The results of other coordinates in both cases are shown in grey lines. The definition of sub-ensembles is based on the stable states. The fraction is the normalized location of each milestone.

that ϕ and $dih_4_6_8_10$ are highly correlated. A correlation analysis on the potential energy distributed on them reveals their inter-dependences as well (Fig. S11³⁶). Therefore, the coordinate set we chose according to Ref. 48 is of minimum dependence between the potential energy on each coordinate and should be the preferred choice. More detailed explanations are presented in the supplementary material.³⁶

C. Optimizing the reaction coordinate without committor

Given that ϕ and θ_1 are two essential coordinates, it might be useful to identify a single coordinate as a linear combination of ϕ and θ_1 that can provide better approximation of the reaction coordinate. As the reaction coordinate is perpendicular to the separatrix, the isocommittor surface with $P_B = 0.5$, we projected all the configurations with $P_B \in [0.49, 0.51]$ onto the plane of ϕ and θ_1 and the resulting points are narrowly distributed along a line, a result similar to Ref. 16. As the direction perpendicular to the line is the reaction coordinate, we obtained an optimized reaction coordinate $q_s^{\text{ref}} = 0.776\phi + 0.631\theta_1$ (see Fig. S9 and Table S4³⁶). In the following, we will show that the same results can be obtained by the combination of the approximate variational condition and the auxiliary conditions. As the results from $\mathcal{V}(\xi, \mathbf{q})$ and $\mathcal{U}(\xi, \mathbf{q})$ are very close, in the following we will discuss the EPE defined by $\mathcal{V}(\xi, \mathbf{q})$ only.

We consider a coordinate $q_s = \cos(\alpha) * \phi + \sin(\alpha) * \theta_1$ and estimate the accumulated EPE in the 6 sub-ensembles. We first consider the 6 sub-ensembles whose transition barrier segment is defined based on the committor. The accumulated EPE of q_s , the EPE on its orthogonal coordinate induced by q_s , and the accumulated total EPE induced by q_s are shown in Fig. 9. We consider the sub-ensemble 3 and 4, as they

FIG. 9. Solid lines: the accumulated EPE of the coordinate orthogonal to $q_s = \cos(\alpha) * \phi + \sin(\alpha) * \theta$. Dashed lines: The accumulated EPE on the coordinate orthogonal to q_s induced by q_s . Dotted lines: the accumulated total EPE induced by q_s . The corresponding value of α for the optimized coordinate q_s^{ref} is highlighted by the dashed violet line. Here, the total EPE is approximated by the summation of the EPE on ϕ , θ_1 , and ψ . Only the results from sub-ensembles 3 and 4 are shown. The sub-ensembles are defined based on the committor.

included enough transition regions but excluded stable regions sufficiently. Sub-ensembles 5 and 6 are not good options as their transition regions are narrow and the magnitudes of the accumulated EPE are small. Here, the total EPE is well approximated by the sum of the EPEs on ϕ , θ_1 , and ψ . Results from the sum over all the coordinates or other combinations are consistent (see Table S3³⁶). The corresponding value of α for the optimized coordinate q_s^{ref} is highlighted by the dashed violet line. The barrier top from the approximate variational condition (dotted lines) is very close the value of q_s^{ref} , demonstrating the validity of this approximation. There are only two values of α that satisfy the auxiliary conditions, which are around -0.4 and 0.7 , respectively. With the approximate variational condition, one of them (the one close to the barrier top of the accumulated total EPE and is around 0.7) is identified as the value of the optimized q_s , which is also consistent with q_s^{ref} . Note that, the accumulated EPE on the bath mode may not be exactly zero due to numerical errors. In addition, a linear combination may not be the best approximation of the reaction coordinate or the bath mode, thus the accumulation of the net potential energy change on the bath mode could deviate from zero. Given these factors, we simply averaged the results of the three criteria in the sub-ensembles 3 and 4; we obtained an estimation of the reaction coordinate as $q_s^{\text{opt}} = 0.785\phi + 0.619\theta_1$ (see Table S3³⁶), which is consistent with q_s^{ref} .

Now, we consider the case where the transition barrier segment is defined by the stable states. From similar consideration, we examined results in sub-ensembles 4 and 5. Fig. 10 show the accumulated EPE from the start to each milestone of the transition path in sub-ensembles 4. Twenty-one milestones were located in this sub-ensemble and the barrier top of the accumulated EPE is around milestone 10. By applying the three criteria to the results of milestones 9,

FIG. 10. The accumulated EPEs as a function of α for each milestone in the sub-ensemble 4, which is defined based on the stable states. Solid lines: the accumulated EPE of the coordinate orthogonal to $q_s = \cos(\alpha) * \phi + \sin(\alpha) * \theta$. Dashed lines: The accumulated EPE on the coordinate orthogonal to q_s induced by q_s . Dotted lines: the accumulated total EPE induced by q_s . The corresponding value of α for the optimized coordinate q_s^{ref} is highlighted by the dashed violet line. Here, the total EPE is approximated by the summation of the EPE on ϕ , θ_1 , and ψ . The sub-ensemble is divided into 21 milestones. The accumulated total EPE reaches the top around milestone 10. The results of milestones 9, 10, and 11 are highlighted as black, red, and green, respectively. The others are highlighted with light colors.

10, and 11, we obtained the optimized reaction coordinate as $q_s^{\text{opt}} = 0.786\phi + 0.618\theta_1$, which is very close to q_s^{ref} . Results from sub-ensemble 5 support the same conclusions (see Fig. S10 and Table S5³⁶).

V. CONCLUDING REMARKS

We proposed a novel quantity that could be used as a benchmark for relevant coordinates in the TPE. This quantity can be viewed as the energy cost on a coordinate upon an infinitesimal change of the same or another coordinate in TPE. With this cost function, we demonstrated the feasibility of selecting relevant coordinates from a complete set of coordinates and obtaining the reaction coordinate as a linear combination of relevant coordinates, without requiring knowledge of the committor. The algorithm requires only the TPE, which can be harvested with TPS at moderate computational costs even for large systems. Thus the cost for identifying the reaction coordinate is drastically reduced compared to existing methods, e.g., the GNN method. In order to numerically validate the theoretical predictions, we adapted a very large size of TPE. For a moderate size of TPE, the relevant coordinates and the optimized reaction coordinate can be closely reproduced (see Table S6 and Figs. S16–S19³⁶). We expect that the method will be of wide application in the identification of reaction coordinates for complex biomolecular systems.

Although the optimization is performed over a linear combination of two coordinates in our example case, the optimization over several coordinates is straightforward. Similar to TPS, the method requires a proper definition of the stable states with order parameters, which are not required to be relevant coordinates. A very recent algorithm proposed by Tiwary and Berne constructs order parameters as best combination of given candidate collective variables via spectral gap optimization,⁵³ which can be applied to identify better order parameters for TPS. The definition of the transition barrier region seems important in an accurate identification of the reaction coordinate and it can be optimized in an iterative way as discussed in Section III C. In this example, the definition of the transition barrier region is relatively easy and no iteration is required. It could be useful to sample a longer transition path and thus the TPE explores a boarder region than the transition barrier region if the transition barrier region is not well defined in the TPS. The definition of the transition barrier region can be iteratively optimized after we identified the relevant coordinates and one can avoid rerunning TPS.

After selecting the relevant coordinates, the total potential energy can be approximated by the sum of the potential energy on these coordinates. It will greatly reduce the noisiness of the results and could be very useful in data analysis for complex systems, in which the noisiness of the environment could hide the useful information. The selection of a complete set of BAT coordinates with minimum dependence is also very important and can simplify the identification of the reaction coordinate. In addition, the description of the system with BAT coordinates will facilitate the interpretation of

the mechanism of the process as BAT are more “natural” compared to Cartesian coordinates.

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