

ARTICLES

From transition paths to transition states and rate coefficients

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(Received 10 June 2003; accepted 10 October 2003)

Transition states are defined as points in configuration space with the highest probability that trajectories passing through them are reactive (i.e., form transition paths between reactants and products). In the high-friction (diffusive) limit of Langevin dynamics, the resulting ensemble of transition states is shown to coincide with the separatrix formed by points of equal commitment (or splitting) probabilities for reaching the product and reactant regions. Transition states according to the new criterion can be identified directly from equilibrium trajectories, or indirectly by calculating probability densities in the equilibrium and transition-path ensembles using umbrella and transition-path sampling, respectively. An algorithm is proposed to calculate rate coefficients from the transition-path and equilibrium ensembles by estimating the frequency of transitions between reactants and products. © 2004 American Institute of Physics. [DOI: 10.1063/1.1630572]

I. INTRODUCTION

Reactions in condensed phase, such as the folding of a protein or the cooperative binding of oxygen in hemoglobin, occur in a high-dimensional space that includes solvent coordinates in addition to those describing reactants and products.¹ Extracting the factors relevant for such reactions is thus difficult. Simplified descriptions of reduced dimensionality are obtained by introducing “reaction coordinates” and “transition states.” Reaction coordinates are dynamically relevant measures of the progress of a reaction. If the full dynamics is projected onto a well-chosen reaction coordinate, one hopes to recover much of the dynamics relevant for the reaction by using only a simplified representation of noise and memory functions (such as memoryless diffusive Langevin dynamics). Transition states are defined to capture the “bottleneck” of a reaction by condensing reaction paths in phase space into an ensemble of configurations. Dividing surfaces, as distinguished here from transition states, separate reactant and product regions, and should contain the transition states to be kinetically relevant.

Finding “transition states” of reactions is an important step in elucidating reaction mechanisms, identifying the relevant factors controlling the reaction rate, and quantifying the reaction kinetics.^{1–3} For reactions in condensed phase, an ensemble of transition states can be defined as those points in configuration space that have equal probability of reaching the reactant region *A* and the product region *B* in configuration (or phase) space first when propagated forward in time.^{4–9} If the dynamics occurs in phase space, transition states in configuration space are defined by Boltzmann averaging over velocities. Transition-state ensembles that have been “guessed” (e.g., by inspecting the free energy surface

along certain projected coordinates) can then be tested, typically by simulation, by propagating trajectories starting from an equilibrium distribution of points in phase space that satisfy the transition-state criteria.^{5,6} These trajectories are terminated once they reach either the reactant or product region, or when they exceed a maximum time t_{\max} . In a well-chosen transition-state ensemble, the fraction ϕ_A of trajectories reaching the product region first should be identical to the fraction reaching the reactant region first, $\phi_B \approx \phi_A \approx 0.5$, in the limit $t_{\max} \rightarrow \infty$. These “commitment probabilities,”^{4–9} ϕ_A and ϕ_B correspond to the splitting probability introduced by Onsager for ion-pair recombination¹⁰ and the p_{fold} probabilities of protein folding.^{5,11}

Here, I introduce a new definition of transition states as those points in configuration space with the highest probability that equilibrium trajectories passing through them are reactive (i.e., form transition paths between reactant and product regions in phase space). This quantifies the concept that transition-state regions are localities common to most reactive trajectories.¹² I will show that in the high-friction (diffusive) limit of Langevin dynamics, this new definition is equivalent to that using commitment probabilities, with the ensemble of transition states forming a separatrix between reactants and products. For Langevin dynamics (which includes Newtonian dynamics in the limit of zero friction), the transition-state definition can be cast into an expression involving *products* of commitment probabilities for trajectories arriving in and going out from points in phase space.

The paper is outlined as follows: To define transition states, I will first introduce phase space probability densities associated with equilibrium and transition-path ensembles. Explicit expressions for those probabilities will be derived for one-dimensional diffusive Langevin dynamics. I will then establish a relation between transition-path probability densities and commitment (or splitting) probabilities. Following

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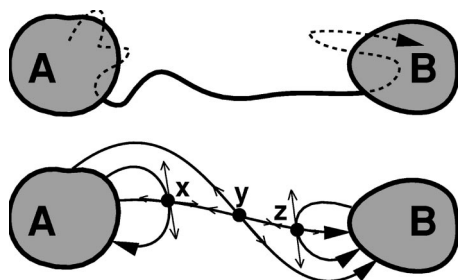


FIG. 1. (Top) schematic illustration of a transition-path segment (thick solid line) of a dynamic trajectory (dashed line) crossing between reactant and product regions A and B. (Bottom) schematic representation of $p(\text{TP}|x)$ = 0.5, 1, and 0.5 for the three points x , y , and z in configuration space. Small arrows pointing in opposite directions indicate that joint trajectories are shot off in the forward and backward directions. Only if these trajectories end in opposite regions A and B, the combined trajectory (with momenta reversed in the backward segments) is considered reactive.

an extension of the theory to dynamics projected onto reaction coordinates, I will illustrate how the relevant probability densities can be calculated from computer simulations. Finally, I will discuss how this approach can be used to calculate reaction rate coefficients from equilibrium free energy and transition-path calculations. I will also describe an algorithm for transition-path sampling by shooting off trajectories from an arbitrary dividing surface. This algorithm produces transition-path ensembles^{12,13} and rate coefficients at the same time and does not require storage of transition paths. It is most efficient if the dividing surface is chosen to contain the transition-state ensemble defined here.

II. THEORY

A. Definition of transition states

Consider a system with a deterministic (e.g., Newtonian) or stochastic (e.g., Langevin) dynamics in phase or configuration space. Two nonoverlapping regions A and B in phase space are identified with reactants and products, respectively. I consider the ensemble of dynamic paths of length t_{max} in this system, with $t_{\text{max}} \rightarrow \infty$. I assume that the dynamics in the full space is Markovian and conserves the equilibrium distribution, $p_{\text{eq}}(x)$. The variable x denotes a position in the full space, i.e., phase space for Newtonian and Langevin dynamics, and configuration space for Langevin dynamics in the high-friction (diffusive) limit. I then identify an ensemble of transition paths as trajectory segments that exit from region A and reach region B without crossing back into A, and vice versa (see Fig. 1). Those paths are of different lengths in time and contain no points in A and B except the beginning and end points. Note that this definition is somewhat more stringent than that used in the transition-path sampling approach^{8,9,13} which requires that the initial point of a path is in A, and either the end-point or an intermediate point is in B for a set of paths of fixed length in time. Note further that the regions A and B are introduced here with the purpose of identifying transition paths between reactants and products, not necessarily to define their equilibrium populations. A and B can thus normally be restricted to regions of high probability in the respective equilibrium distributions.

The transition-path (TP) ensemble defined here determines a conditional phase-space density, $p(x|\text{TP})$. This density can be estimated from histograms of points x that are equally spaced in time along transition-path segments of an equilibrium trajectory, or by binning the paths determined from transition-path sampling.^{9,13}

“Transition states” can now be defined as points with the highest probability that trajectories passing through them are reactive (i.e., form transition paths between reactants and products). The probability for being on a transition path, given that the system is in x is given by

$$p(\text{TP}|x) = \frac{p(x|\text{TP})p(\text{TP})}{p_{\text{eq}}(x)}, \quad (1)$$

where $p(\text{TP})$ is the fraction of time spent in transition paths, averaged over long equilibrium trajectories. The normalizing factor, $p(\text{TP})$, will be used in Sec. II F to calculate kinetic rate coefficients.

Equation (1) combines information from the equilibrium distribution and the ensembles of transition paths. In particular, $p(\text{TP}|x)$ is large when x is rarely populated at equilibrium, but visited frequently along transition paths. $p(\text{TP}|x)$ thus quantifies the “differences between the transition state average and the stable state average”⁸ [$p(x|\text{TP})$ and $p_{\text{eq}}(x)$, respectively] as a measure for the significance of x in transitions between reactants and products. For dynamics in phase space, I will discuss in Sec. II D how the momenta in x can be eliminated through projection onto configurational coordinates to obtain transition states in configuration space.

B. Relation to splitting probabilities for one dimensional Langevin dynamics in the high-friction (diffusive) limit

For one-dimensional diffusive Langevin dynamics (i.e., Langevin dynamics in the limit of high friction) along a configuration-space coordinate x on a potential $V(x)$, explicit expressions for the transition-path probability densities $p(x|\text{TP})$ and $p(\text{TP}|x)$ can be found constructively. Segments of diffusive Langevin dynamics trajectories are transition paths if they start at x_0 and end at x_1 , or vice versa, without leaving the region $x_0 < x(t) < x_1$ at intermediate times. To derive a probability density $p(x|\text{TP})$ of x for the ensemble of transition paths, I consider paths that start at $x_0 + \epsilon$ and then take the limit $\epsilon \rightarrow 0^+$, with $\epsilon > 0$ a small interval on the one-dimensional configurational coordinate along which the diffusive dynamics occurs. I note that in the transition-path ensemble, a path originating from x_0 and ending at x_1 has the same path probability if reversed. Thus, I will not consider the reverse paths explicitly. The probability that a path starting in $x_0 + \epsilon$ will end in x_1 is the splitting probability, $\phi_B(x_0 + \epsilon)$, with $\phi_B(x_0) = 0$, $\phi_B(x_1) = 1$, and $\phi_A(x) = 1 - \phi_B(x)$. The probability that a path originating in $x_0 + \epsilon$ will visit a point x between x_0 and x_1 at time t is given by a Greens function $G(x, t|x_0 + \epsilon, 0)$. The probability that a path continued from a point x will reach x_1 first (i.e., before x_0) is given by $\phi_B(x)$ independent of the preceding trajectory (because of the Markovian dynamics). One then obtains the positional probability density in the transition-path ensemble by taking the limit $\epsilon \rightarrow 0^+$

$$p(x|TP) \propto \lim_{\epsilon \rightarrow 0^+} \frac{\phi_B(x) \int_0^\infty G(x, t|x_0 + \epsilon, 0) dt}{\int_0^\infty G(x_0 + \epsilon, t|x_0 + \epsilon, 0) dt}, \quad (2)$$

where the denominator removes the singularity in the limit $\epsilon \rightarrow 0^+$. The Greens function $G(x, t|x_0 + \epsilon, 0)$ satisfies the Smoluchowski equation

$$\frac{\partial G}{\partial t} = D \frac{\partial}{\partial x} \left\{ e^{-\beta V(x)} \frac{\partial}{\partial x} [e^{\beta V(x)} G] \right\}, \quad (3)$$

with absorbing boundary conditions at x_0 and x_1 [i.e., $G(x_0, t|x_0 + \epsilon, 0) = G(x_1, t|x_0 + \epsilon, 0) = 0$]. D is the diffusion coefficient and $\beta = 1/k_B T$ (where k_B is Boltzmann's constant and T is the temperature). In Eq. (2), $G(x, t|x_0 + \epsilon, 0) dx dt$ is proportional to the probability of a trajectory originating in $x_0 + \epsilon$ at time $t=0$ to visit an interval dx around x during a time interval dt around t , with G normalized to the fraction of trajectories that have not yet crossed the absorbing boundaries.

After integration of Eq. (3) from time $t=0$ to ∞ , the left-hand side reduces to the initial distribution, $-G(x, 0|x_0 + \epsilon, 0) = -\delta(x - x_0 - \epsilon)$, because $G(x, t \rightarrow \infty|x_0 + \epsilon, 0) = 0$. Subsequently integrating both sides twice with respect to x gives

$$D \int_0^\infty G(x, t|x_0 + \epsilon, 0) dt = e^{-\beta V(x)} \begin{cases} c \int_{x_0}^x e^{\beta V(x')} dx' & \text{for } x \leq x_0 + \epsilon \\ (1-c) \int_x^{x_1} e^{\beta V(x')} dx' & \text{for } x > x_0 + \epsilon, \end{cases} \quad (4)$$

where $c = \int_{x_0+\epsilon}^{x_1} e^{\beta V(x)} dx / \int_{x_0}^{x_1} e^{\beta V(x)} dx$. In the limit $\epsilon \rightarrow 0^+$, substitution of Eq. (4) into Eq. (2) gives

$$p(x|TP) \propto \phi_B(x) e^{-\beta V(x)} \int_x^{x_1} e^{\beta V(x')} dx'. \quad (5)$$

The splitting probabilities $\phi_A(x)$ and $\phi_B(x) = 1 - \phi_A(x)$ satisfy the adjoint time-independent Smoluchowski equation¹⁰ and are given by

$$\begin{aligned} \phi_A(x) &= \frac{\int_x^{x_1} e^{\beta V(x')} dx'}{\int_{x_0}^{x_1} e^{\beta V(x')} dx'}, \\ \phi_B(x) &= \frac{\int_{x_0}^x e^{\beta V(x')} dx'}{\int_{x_0}^{x_1} e^{\beta V(x')} dx'}. \end{aligned} \quad (6)$$

Combined with Eqs. (1) and (5), I thus obtain an explicit relation between the splitting probabilities and the transition-path probability $p(TP|x)$

$$p(TP|x) = 2\phi_B(x)[1 - \phi_B(x)] = 2\phi_A(x)\phi_B(x). \quad (7)$$

Note that this is an *equality*, as will be shown below. The maximum of $p(TP|x)$ is at x^\ddagger with $\phi_B(x^\ddagger) = 0.5$. This is illustrated in Fig. 2 for the double-well potential $\beta V(x) = 10(x^2 - 1)^2$. One finds that for diffusive Langevin dynam-

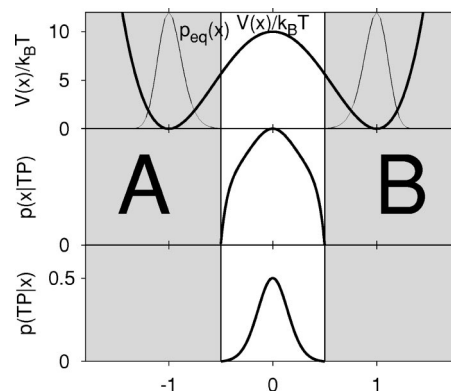


FIG. 2. Double-well potential (top; thick line) with corresponding equilibrium distribution (thin line), $p(x|TP)$ (middle), and $p(TP|x)$ (bottom) for diffusive Langevin dynamics. Reactant and product regions A and B ($x < -x_0$ and $x > x_0$, respectively, with $x_0 = 1/2$) are shown in shaded gray.

ics on that potential with reactant and product regions at $x < -1/2$ and $x > 1/2$, respectively, $p(TP|x)$ is sharply peaked at the barrier $x^\ddagger = 0$.

C. General relation to commitment (or splitting) probabilities

In the following, I will extend the relation between splitting probabilities and the transition-path probability densities $p(TP|x)$ and $p(x|TP)$ to higher dimensions and dynamics in phase space. The conditional probability density $p(TP|x)$, appropriately normalized, is given by the fraction of transition paths created by shooting off joint trajectories forward and backward in time from x . I assume that $x = (p, q)$ is a point in phase space, with coordinate vector q and conjugate momenta p , that evolves under Langevin dynamics (which includes Newtonian and diffusive Langevin dynamics in the limits of low and high friction, respectively). In phase space, Langevin dynamics is Markovian (i.e., memoryless). The joint forward and backward trajectories can then be created by integrating *forward* in time with initial conditions $x(0) = x = (p, q)$ and $x(0) = \bar{x} = (-p, q)$, respectively, and then reversing all momenta of the backward segment. This follows from the acceptance criteria of “shooting moves” for stochastic dynamics.¹⁴ As outlined in detail by Dellago *et al.*⁹ in their review of transition-path sampling, backward paths can be constructed by forward integration because Langevin dynamics conserves the equilibrium Boltzmann distribution and forward and backward propagators are related through detailed balance. Under deterministic Newtonian dynamics, only one realization of forward and backward trajectories can occur, and $p(TP|x)$ is either one or zero. Under stochastic dynamics, different realizations of forward and backward paths can be combined at random. For both deterministic and stochastic dynamics, $p(TP|x)$ is thus given by products of splitting probabilities

$$p(TP|x) = \phi_A(\bar{x})\phi_B(x) + \phi_A(x)\phi_B(\bar{x}), \quad (8)$$

where $\phi_A(x)$ and $\phi_B(x)$ are the fractions of trajectories starting from x that reach A and B first, respectively. Correspond-

ingly, $p(\text{TP}|x)$ is proportional to the sum of products of probabilities that the joint forward and backward paths reach A and B first, respectively, and vice versa.

For diffusive Langevin dynamics, the definition of transition states as points with the highest probability that trajectories passing through them are transition paths is equivalent to that using a “separatrix” or commitment probabilities.^{4–9} This was shown constructively in Sec. IIB for one-dimensional diffusion, and follows for diffusion in arbitrary dimension from Eq. (8) because then $\phi_A(x) = \phi_A(\bar{x})$ and $\phi_B(x) = \phi_B(\bar{x})$. The corresponding maxima of $p(\text{TP}|x)$ are thus degenerate and define a dividing surface between reactant and product regions. In general, the new definition of transition states differs from that based on the “stochastic separatrix”^{4,15,16} formed by points in phase space at which the probability of reaching products first is 1/2 (see, e.g., Ref. 17 for explicit expressions for a parabolic barrier). To define “transition states” in configuration space for Newtonian or Langevin dynamics in phase space, one will need to project onto configurational coordinates, as outlined in the following section. The resulting maxima of the transition-path probability will not normally form a connected dividing surface in configuration space, with a possibility of multiple distinct local maxima, in particular for rough (free) energy surfaces.

D. Projection onto (reaction) coordinates

The definition of transition states as maxima of $p(\text{TP}|x)$, as introduced in Eq. (1), can be extended to low-dimensional projections of phase space, $r = r(x)$. A commonly used projection is to eliminate particle momenta^{7,9} by integration over a Maxwell–Boltzmann velocity distribution. In general, the dynamics in these projections will not be Markovian,¹⁸ even if the dynamics in the complete phase space is. The probability density $p(\text{TP}|r)$ defined in analogy with Eq. (1)

$$p(\text{TP}|r) = \frac{p(r|\text{TP})p(\text{TP})}{p_{\text{eq}}(r)}, \quad (9)$$

can be obtained from a projection of $p(\text{TP}|x)$ weighted by $p_{\text{eq}}(x)$ onto r

$$p(\text{TP}|r) = \frac{\int p(\text{TP}|x) \delta[r - r(x)] p_{\text{eq}}(x) dx}{\int \delta[r - r(x)] p_{\text{eq}}(x) dx}. \quad (10)$$

This follows from Eq. (1) and $p(r|\text{TP}) = \int \delta[r - r(x)] p(x|\text{TP}) dx$.

One may expect that for a suitably chosen coordinate $r = r(x)$, the maximum of $p(\text{TP}|r)$ will give an indication of the location of transition states. A “good” reaction coordinate should give a sharply peaked distribution of $p(\text{TP}|r)$, which can be used to choose among different “candidate” reaction coordinates. A projection was successfully used to find transition states for the kinetics of filling and emptying of nanotubes with one-dimensional chains of water molecules,¹⁹ as “tested” subsequently by calculating commitment probabilities.

E. Computer simulation estimates of $p(\text{TP}|x)$

The probability of being on a transition path, $p(\text{TP}|x)$, can be estimated in simulation calculations by “shooting”

off trajectories from x . For dynamics in phase space, this requires a slight modification of the calculation of commitment probabilities.⁹ Here, conjugate pairs of trajectories are “shot off” into the forward [$x(0) = (p, q)$] and backward [$x(0) = (-p, q)$] direction to calculate the fraction of trajectories passing through $x = (p, q)$ that cross from reactants to products and vice versa, according to Eq. (8). As in transition-path sampling,^{8,9,13,14} one might also want to introduce a maximum allowed duration of transition paths. This is essential for deterministic Newtonian dynamics, where the single trajectory passing through a phase point x is not guaranteed to cross into A or B . As discussed in Ref. 9, the upper cutoff time for transition paths should be larger than typical transition times. It follows from Eq. (9) that to calculate $p(\text{TP}|r)$ for a projected coordinate, initial conditions x in phase space must be drawn from an *equilibrium* ensemble conditioned on $r = r(x)$, i.e., $p(x|r) \propto p_{\text{eq}}(x) \delta[r - r(x)]$.

Alternatively, one can estimate $p(\text{TP}|x)$ from Eq. (1) [or $p(\text{TP}|r)$ from Eq. (9)] by calculating $p_{\text{eq}}(x)$ and $p(x|\text{TP})$ [or $p_{\text{eq}}(r)$ and $p(r|\text{TP})$] by umbrella sampling²⁰ and transition-path sampling,¹³ respectively, or directly from a long equilibrium run with frequent crossings between reactant and product regions. In the transition-path sampling calculations of $p(x|\text{TP})$, an efficient Monte Carlo move is obtained by shooting off trajectories forward and backward from a randomly selected branch point along an existing transition path^{9,13} and propagating them until they reach either the reactant region A or the product region B . If the forward and backward paths end up in opposite regions, the move is accepted. Practical computations should again include a cutoff time for the maximum duration of transition paths, as discussed in Ref. 9. However, unlike in the conventional transition-path sampling with paths of fixed total time,^{9,13} here path lengths are variable, and a newly accepted path enters the transition-path ensemble with a relative weight $1/t_{\text{new}}$, where t_{new} is the length of the new path as measured by its time or number of integration steps. (This additional factor could also be included in a modified acceptance criterion.) The weight change corrects for different path generation probabilities (i.e., picking x as a branch point in the old and new path), and ensures detailed balance in the Monte Carlo scheme.²¹

F. Relation to reaction rates

So far, I have not considered the normalizing factor, $p(\text{TP})$, in Eq. (1). $p(\text{TP})$ is the fraction of time spent in transition paths averaged over long equilibrium trajectories. The number of transitions between reactants and products (and vice versa) per unit time is given by the fraction of time spent in transitions, $p(\text{TP})$, divided by the average duration $\langle t_{\text{TP}} \rangle$ of transition paths. One can thus estimate the frequency of transitions as $p(\text{TP})/\langle t_{\text{TP}} \rangle$. For two-state kinetics



the frequency of transitions between reactant and product regions in phase space can be expressed in terms of the rate coefficients k_1 and k_2 for the conversion between reactants

(A) and products (B). This assumes that transitions are uncorrelated, as is expected for rare transitions with rapid equilibration in reactant and product states.²² Equation (11) leads to a relation among rate coefficients, the transition-path probability, and the average length of a transition path

$$\frac{2}{k_1^{-1} + k_2^{-1}} = 2c_A k_1 = 2c_B k_2 \approx \frac{p(\text{TP})}{\langle t_{\text{TP}} \rangle}, \quad (12)$$

where c_A and c_B denote the equilibrium mole fractions of reactants and products, respectively, with $c_A/c_B = k_2/k_1$ and $c_A + c_B = 1$. By using Eqs. (1) or (9), $p(\text{TP})$ can be calculated from the normalized equilibrium and transition-path probabilities

$$p(\text{TP}) = \frac{p(\text{TP}|x)p_{\text{eq}}(x)}{p(x|\text{TP})} = \frac{p(\text{TP}|r)p_{\text{eq}}(r)}{p(r|\text{TP})}, \quad (13)$$

independent of x and r . In other algorithms, rate coefficients are estimated by calculating the time derivative of the number correlation function² by transition-path sampling methods.^{23–26}

For one-dimensional diffusion, one can calculate the resulting rate of barrier crossing analytically. With $p(\text{TP}|x)$ given by Eqs. (6) and (7), and $p(x|\text{TP})$ from normalizing Eq. (5),

$$p(x|\text{TP}) = \frac{e^{-\beta V(x)} \phi_A(x) \phi_B(x)}{\int_{x_0}^{x_1} e^{-\beta V(x')} \phi_A(x') \phi_B(x') dx}, \quad (14)$$

Eq. (13) becomes

$$p(\text{TP}) = 2 \frac{\int_{x_0}^{x_1} e^{-\beta V(x)} \phi_A(x) \phi_B(x) dx}{\int_{-\infty}^{\infty} e^{-\beta V(x)} dx}. \quad (15)$$

The mean length of transition paths can also be calculated analytically²⁷

$$\langle t_{\text{TP}} \rangle = \frac{\int_{x_0}^{x_1} e^{-\beta V(x)} \phi_A(x) \phi_B(x) dx \int_{x_0}^{x_1} e^{\beta V(x')} dx'}{D}. \quad (16)$$

With Eq. (12), this results in

$$k_1^{-1} + k_2^{-1} \approx D^{-1} \int_{x_0}^{x_1} e^{\beta V(x)} dx \int_{-\infty}^{\infty} e^{-\beta V(x')} dx'. \quad (17)$$

This corresponds to the Kramers formula for one-dimensional diffusion across a high barrier.²⁸

Figure 3 shows the rate of crossing the barrier in the double-well potential of Fig. 2 with $D = 1$. With reactant and product regions defined as $x < -x_0$ and $x > x_0$ for the purpose of identifying transition paths, rate coefficients from Eq. (12) are in excellent agreement with the reciprocal mean first passage times over the range of barrier heights from 3 to $10 k_B T$ for $x_0 = 1/2$. The inset shows that the rate coefficient for crossing a $10 k_B T$ barrier calculated from Eq. (12) approaches the correct value as x_0 increases toward the free energy minimum, $x_0 = 1$.

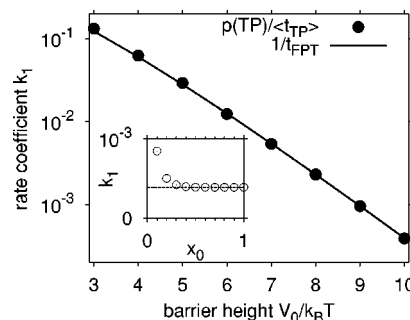


FIG. 3. Rate coefficients $k_1 = k_2$ for diffusively crossing the barrier of the double-well potential $V(x) = (x^2 - 1)^2 V_0$ as a function of the barrier height $V_0/k_B T$. Results are shown on a logarithmic scale. Filled circles show the rate coefficients from Eqs. (12) and (17). For reference, the reciprocal of the mean first passage time is shown as a solid line. The inset shows on a linear scale the rate coefficient (open circles) for a $10 k_B T$ barrier calculated from Eq. (12), for different definitions of reactant and product regions ($x < -x_0$ and $x > x_0$, respectively) used to identify transition paths. The rate coefficient from the decay time of the number correlation function (Ref. 29) is included as a reference (dashed line).

G. Calculation of reaction rates from computer simulations

One possible algorithm to get rate coefficients from Eq. (12) by computer simulations involves a combination of transition-path sampling¹³ and a standard free energy calculation using, e.g., umbrella sampling.²⁰ This is most easily done if a one-dimensional order parameter $r = r(x)$ is introduced that parameterizes the transition region between reactants and products, with $r(x) = r_0$ and $r(x) = r_1$ defining the boundaries of reactant and product regions, respectively. Note that r does not have to be a “good” (i.e., kinetically relevant) reaction coordinate.

One first needs to calculate the free energy $A(r)$ as a function of r to obtain the normalized equilibrium distribution through $p_{\text{eq}}(r) = \exp[-\beta A(r)] / \int_{-\infty}^{\infty} \exp[-\beta A(r)] dr$. This can be accomplished, for instance, by umbrella sampling.²⁰ From conventional transition-path sampling¹³ or from the transition-path sampling algorithm described below, one can then estimate $p(r|\text{TP})$ by accumulating a histogram of r between r_0 and r_1 along transition-path segments, as defined above, and the average length $\langle t_{\text{TP}} \rangle$ of transition paths. Finally, $p(\text{TP}|r)$ is estimated as the fraction of transition paths among trajectories shot off forward and backward from phase points x on the surface $r(x) = r$,

$$p(\text{TP}|r) \approx \frac{\# \text{ accepted shooting moves at } r}{\# \text{ attempted shooting moves at } r} \bigg|_{p(x|r)}, \quad (18)$$

where x is drawn from an equilibrium ensemble, $p(x|r) \propto p_{\text{eq}}(x) \delta[r - r(x)]$. To generate the appropriate equilibrium ensemble according to Eq. (9), one can use configurations from a preceding free energy calculation. One can then estimate the rate coefficients from

$$\frac{2}{k_1^{-1} + k_2^{-1}} \approx \frac{p(\text{TP}|r)p_{\text{eq}}(r)}{p(r|\text{TP})\langle t_{\text{TP}} \rangle}. \quad (19)$$

The right-hand side should be independent of the order parameter r , which can be used as a test of convergence.

Note that $p(\text{TP}|r)$ is not given by the fraction of accepted shooting moves initiated at points on the surface $r = r(x)$ in a transition-path sampling simulation. The reason is that the points on $r = r(x)$ are distributed according to $p(x|\text{TP})$ and not $p_{\text{eq}}(x)$, as required by Eq. (9).

H. Transition-path sampling from single dividing surface

In transition-path sampling calculations, shooting moves have been found to be particularly efficient.^{9,14} The probability of acceptance of a shooting move initiated at a randomly picked phase point x is given by $p(\text{TP}|x)$, which is small almost everywhere except for points x near the transition-state region. As a result, most of the shooting attempts will fail unless importance sampling is used, as in transition-path sampling.¹⁴ In contrast, if shooting moves are initiated where $p(\text{TP}|x)$ is large, then they have a high probability of success. The ensemble of transition states thus determines an optimal set of points to initiate trajectories by shooting moves. To take advantage of this, one can define a dividing surface $r(x) = r^\ddagger$ close to the maxima of $p(\text{TP}|x)$, and exclusively pick points on that surface for shooting moves.

However, the ensemble of trajectories obtained by naively shooting off from points on a single dividing surface $r(x) = r^\ddagger$ is biased, even if the initial points x are drawn from an equilibrium distribution. To generate an unbiased ensemble consistent with long equilibrium trajectories, each trajectory has to be entered into the ensemble with a weight that makes the ensemble of trajectories consistent with the equilibrium density on $r(x) = r^\ddagger$. The resulting relative weight w of a given transition path is

$$w = \left(\sum_{\text{intersections } i} |v_i|^{-1} \right)^{-1}, \quad (20)$$

where the sum is over the points of intersection $x_i = x(t_i)$ of the trajectory with the dividing surface, and v_i is the velocity normal to the dividing surface at the intersection i ,

$$v_i = \left(\frac{\partial r}{\partial x} \cdot \frac{\partial x(t)}{\partial t} \right)_{x(t)=x_i}, \quad (21)$$

where $\partial x(t)/\partial t$ is a function of the phase point x . The weight w can be understood by considering an ensemble of long equilibrium trajectories $x(t)$ that intersect a volume in phase space bound by the dividing surfaces $r(x) = r^\ddagger$ and $r(x) = r^\ddagger + \delta r$. At each of the intersections i , the trajectories spend a time $\delta t_i \approx \delta r / v_i$ inside that volume in the limit of $\delta r \rightarrow 0$. The points of intersection, $x_i = x(t_i)$, weighted by this time δt_i , constitute an equilibrium ensemble of points on $r(x) = r^\ddagger$. Picking points randomly from an equilibrium distribution on $r(x) = r^\ddagger$ and shooting off forward and backward trajectories from those points until they reach either the reactant or product region, is thus equivalent to picking from the ensemble of trajectories associated with the crossing points x_i . If the points x_i are drawn randomly from the equilibrium ensemble, the probability of drawing a particular trajectory segment is proportional to the total amount of time it spends in the $(r^\ddagger, r^\ddagger + \delta r)$ volume. To correct for the resulting over- and underrepresentation of “slow” and “fast” tra-

jectories, respectively, one needs to give a relative weight that is proportional to the inverse of the time spent in the volume. In the limit $\delta r \rightarrow 0$, this results in the relative weight given in Eq. (20).

With the same approach, one can express the probability density $p(r^\ddagger|\text{TP})$ of transition paths at the dividing surface in terms of a path average, without using histograms. The time each path spends in $(r^\ddagger, r^\ddagger + \delta r)$ is proportional to $1/w$ given in Eq. (20). In the limit of $\delta r \rightarrow 0$, one obtains for the probability density

$$p(r^\ddagger|\text{TP}) = \frac{\langle \theta_{\text{TP}} \rangle_{r^\ddagger, p_{\text{eq}}}}{\langle t_{\text{TP}} \rangle \langle \theta_{\text{TP}} (\sum_i |v_i|^{-1})^{-1} \rangle_{r^\ddagger, p_{\text{eq}}}}, \quad (22)$$

where the average in the numerator and the second average in the denominator are over an ensemble of forward and backward trajectories initiated from an equilibrium distribution of phase points on the dividing surface. For each of the trajectory pairs, θ_{TP} is one if they form a transition path (i.e., end in opposite regions) and zero otherwise, such that $\langle \theta_{\text{TP}} \rangle_{r^\ddagger, p_{\text{eq}}} = p(\text{TP}|r^\ddagger)$. Combined with Eqs. (12) and (13), one obtains an expression for the rate coefficients

$$\frac{2}{k_1^{-1} + k_2^{-1}} \approx p_{\text{eq}}(r^\ddagger) \left\langle \theta_{\text{TP}} \left(\sum_i |v_i|^{-1} \right)^{-1} \right\rangle_{r^\ddagger, p_{\text{eq}}}. \quad (23)$$

The average over paths is initiated from an equilibrium ensemble of phase points on the dividing surface $r(x) = r^\ddagger$. Forward and backward trajectories terminate in either the reactant or product region. The sum in Eq. (23) is over the intersections of each path with the dividing surface, where v_i is the velocity normal to the dividing surface at intersection i , as given in Eq. (21). In computer simulations, one should again apply an upper cutoff time for the maximum length of transition paths.

If all trajectories are reactive without recrossing, then one recovers the transition-state theory rate coefficients

$$k_1^{\text{TST}} = \frac{1}{2c_A} p_{\text{eq}}(r^\ddagger) \langle |v| \rangle; \quad (24)$$

$$k_2^{\text{TST}} = \frac{1}{2c_B} p_{\text{eq}}(r^\ddagger) \langle |v| \rangle,$$

as was shown by Chandler for the rate expression from the reactive-flux method.^{2,30} Under the assumptions of transition-state theory, the sum in Eq. (23) contains only one term from the initial (Maxwell–Boltzmann) velocity, and $\theta_{\text{TP}} \equiv 1$, resulting in Eq. (24). However, if trajectories recross, the rate coefficients resulting from Eq. (23) will be smaller because some trajectories are not reactive ($\theta_{\text{TP}} = 0$) and, in addition, multiple recrossings reduce the value of the sum over normal velocities compared to the first term $|v|$ given by the transition-state theory expression.

Two simple algorithms can be devised for shooting off trajectories from a single dividing surface. If only the transition-path ensemble needs to be calculated, a Metropolis Monte Carlo scheme²¹ can be used in which new points on $r(x) = r^\ddagger$ are created according to the equilibrium distribution and accepted if they form transition paths. If in addition to the transition-path ensemble one wants to calculate rate

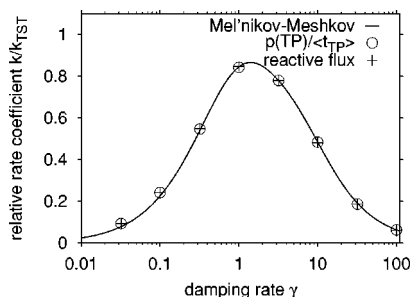


FIG. 4. Rate coefficient for a particle of unit mass to cross the $10 k_B T$ barrier of the symmetric doublewell potential $V(x)/k_B T = 10(x^2 - 1)^2$ with Langevin dynamics as a function of the damping rate γ . The rate coefficient is divided by the transition-state theory value. Circles show the rate coefficients estimated from transition-path sampling by shooting forward and backward trajectories from the top of the barrier. Crosses show rate coefficients calculated from a fit to the plateau region of the derivative of the number correlation function, as estimated by using the reactive-flux formalism (Refs. 2, 30, and 31). Rate coefficients from the theory of Mel'nikov and Meshkov (Ref. 33) are shown as a solid line.

coefficients, then one has to accept the points based on the equilibrium distribution alone, irrespective of whether they result in transition paths. In both algorithms, each of the paths entering the transition-path ensemble [but not the calculation of $p(\text{TP}|r^\ddagger)$] has to be given the relative weight w of Eq. (20). In its computational demands, the second algorithm is comparable to the reactive-flux method^{2,30,31} but produces a transition-path ensemble without additional computational effort.

Formally, the two algorithms work for any dividing surface. However, the transition-path sampling algorithms are most efficient if the dividing surface is chosen such that $p(\text{TP}|x)$ is high for points x on $r(x) = r^\ddagger$ (i.e., the surface contains the “transition states”). Finding an optimal dividing surface with a minimal number of recrossings also forms the key element of variational transition-state theory.³² If transition-state theory is exact, then $p(\text{TP}|x)$ will be one for x on the dividing surface. To choose among different order parameters $r(x)$, as discussed above, and to find a good r^\ddagger , the calculations can be preceded by regular transition-path sampling.^{9,13} Inclusion of additional Monte Carlo moves^{9,13} together with the new algorithm should enhance sampling. Moreover, one can initiate new path sampling simulations from multiple points x on the dividing surface. An appropriate equilibrium ensemble of such “seeding” points for the second algorithm is generated in the umbrella-sampling free energy calculation.

Figure 4 compares rate coefficients for Langevin dynamics calculated from Eq. (23) by using the transition-path shooting algorithm to the theory of Mel'nikov and Meshkov.³³ Rate coefficients have been estimated for a particle moving across a $10 k_B T$ barrier in a double-well potential. To identify transition paths, reactant and product states in phase space are defined by an energy contour line.³⁴ Results for a 5 and $2 k_B T$ contour are indistinguishable. Trajectories are initiated at the barrier top with Maxwell-Boltzmann velocities. As shown in Fig. 4, the rate coefficients determined with the shooting algorithm show the Kramers turnover²⁸ from low to high-friction behavior, and

agree very well with the theoretical curve of Mel'nikov and Meshkov for the rate coefficient as a function of the damping rate γ .³³ Also shown in Fig. 4 are results for the rate coefficients estimated from the derivative of the number correlation function, as calculated by using the reactive-flux expression.^{2,30,31} The agreement between rate coefficients from reactive-flux calculations and transition-path sampling using Eq. (23) is excellent.

III. CONCLUSIONS

I have introduced a definition of transition states as those points in configuration space with the highest relative probability that trajectories passing through them are reactive (i.e., form transition paths between reactants and products). The probability of being on a transition path $p(\text{TP}|x) \propto p(x|\text{TP})/p_{\text{eq}}(x)$ contains information from both the ensemble of reactive trajectory segments (i.e., transition paths) and the equilibrium ensemble, and captures the “difference” between the two. I have shown (constructively in one dimension, and in general by using the shooting algorithm of transition-path sampling^{9,14}) that for Langevin dynamics in the high-friction (diffusive) limit, the definition of transition states introduced here is equivalent to that based on splitting (or commitment) probabilities of 1/2.

In simulation calculations, $p(\text{TP}|x)$ can be estimated by using Eq. (8) as the fraction of transition paths among combined trajectories shot off forward and backward from x . Alternatively, $p(\text{TP}|x)$ can be estimated directly from equilibrium trajectories through Eq. (1) by dividing the probability densities of x in the transition-path and equilibrium ensembles. Moreover, biased sampling methods can be used to determine the two probability densities independently. The numerator, $p(x|\text{TP})$, can be estimated from transition-path sampling,¹³ and the denominator $p_{\text{eq}}(x)$ from umbrella sampling.²⁰ In a recent simulation study of the kinetics of filling and emptying of nanotubes with one-dimensional chains of water molecules,¹⁹ an equilibrium trajectory with less than 20 transitions was sufficient to determine a transition-state ensemble with commitment probabilities sharply peaked around 1/2.

Path-sampling approaches to the calculation of rare-event kinetics^{6–9,12–14,23–26} are appealing because they require no *a priori* knowledge of the reaction mechanism, as captured by transition states forming the bottleneck of the reaction. The definition of transition states used here is naturally suited for the analysis of path-sampling simulations. To identify the kinetic bottlenecks of a reaction, it combines in Eq. (1) the probability density of the path ensemble of reactive trajectories, $p(x|\text{TP})$, with that of the equilibrium ensemble, $p_{\text{eq}}(x)$. This approach can also be useful in finding good reaction coordinates $r = r(x)$, indicated by sharp and high peaks in the projected probability density $p(\text{TP}|r)$. Finally, the formalism developed here directly leads to a new method of calculating rate coefficients from transition-path and equilibrium ensembles.

ACKNOWLEDGMENTS

I want to thank A. Berezhkovskii, R. Zwanzig, and, in particular, A. Szabo for many helpful and stimulating discussions, and C. Dellago for comments on the manuscript.

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