Rate constants for diffusive processes by partial path sampling

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We introduce a path sampling method for the computation of rate constants for systems with a highly diffusive character. Based on the recently developed algorithm of transition interface sampling (TIS) this procedure increases the efficiency by sampling only parts of complete transition trajectories confined within a certain region. The algorithm assumes the loss of memory for highly diffusive progressions along the reaction coordinate. We compare the new technique to the TIS method for a simple diatomic system and show that the computation time of the new method scales linearly, instead of quadratically, with the length of the diffusive barrier. The validity of the memory loss assumption is also discussed.

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I. INTRODUCTION

The calculation of rate constants in complex systems by straightforward molecular dynamics (MD) simulation is prohibited by the exponential dependence of the rate on the activation barrier height. The expectation time for a reaction can easily be on the order of milliseconds to seconds, whereas most simulation algorithms are limited to molecular time-steps of femtoseconds. A single occurrence of a rare event in a complex system can thus easily exceed current computer capabilities by orders of magnitude. The standard Bennett-Chandler reactive flux method is able to avoid this timescale problem by calculating the probability to be at the top of the activation free energy barrier in combination with a time dependent transmission coefficient. Although in principle correct, the accuracy of this method is very sensitive to the choice of reaction coordinate. In a complex reaction, an intuitive simple reaction coordinate can lead to extremely low transmission coefficients and, hence, an inaccurate or even immeasurable rate constant. Improving the reaction coordinate, by, for instance, incorporating solvent degrees of freedom (see e.g. Ref. [34]), is usually a very difficult task and requires a lot of a-priori knowledge of the system.

The transition path sampling (TPS) technique of Chandler and co-workers does not need any prior knowledge of the reaction coordinate and harvests a collection of transition paths that connect the reactant with the product states. This ensemble of true dynamical paths allows detailed understanding of the kinetics and mechanism of the reaction. In addition, the rate constant can be computed. Processes as diverse as cluster isomerization, auto dissociation of water, ion pair dissociation, the folding of a polypeptide and reactions in aqueous solution have been studied with TPS (see Ref. [8] for an overview).

As the TPS rate constant calculation is rather computer time consuming, we recently introduced the transition interface sampling (TIS) technique [11], thereby improving the efficiency of the rate constant calculation substantially. By allowing a variable path length, TIS drastically reduces the number of required time-steps for each path. In addition, TIS is less sensitive to recrossings and has a better convergence compare to the TPS rate constant method as it only counts the effective positive terms.

In this paper, we will focus on transitions with a highly diffusive character, or in the regime of high solvent friction. Examples are the folding and unfolding of a protein in water, charge transfer, fragmentation reactions, diffusion of a molecule through a membrane, and nucleation processes. These types of processes have to overcome a relatively flat and wide, but still rough free energy barrier. When applying the TPS (or TIS) shooting algorithm to such a transition, the Lyapunov instability causes the paths to diverge before the basins of attraction have the chance to guide the paths to the proper stable state. Pathways will then become very long and, moreover, the acceptance ratio of shooting will be low. Hence, the shooting algorithm will be very inefficient, resulting in bad sampling. Recently, we showed how to sample long paths efficiently on a diffuse barrier with TPS by introducing a little stochasticity in the trajectories [12].

Here, we will introduce an efficient method to calculate the rate constant for such barriers. To do so, we make use of the TIS effective flux relation and assume that the diffusivity eliminates any memory effects over a distance more than the separation between two interfaces. The rate constant can then be recast in a recursive relation for the hopping transition rates between interfaces. These hopping transition rates can be computed by sampling short trajectories connecting just three successive interfaces. If the assumption of memory loss is valid, this
partial path transition interface sampling (PPTIS) procedure correctly collects the contributions of all possible paths to the rate constant, in principle, even those with infinite lengths.

This paper is organized as follows: In Sec. IIIA we illustrate the PPTIS concept for a simple one dimensional array of well defined metastable states. Although not completely without physical importance, the model in this section can only describe a limited number of physical systems since most diffusive systems do not have well defined metastable regions in the free energy landscape between reactant and product state. In Sec. IIIB we present the TIS technique in a way that facilitates the derivation of the rate expression for general diffusive barriers given in Sec. III C. The implementation of the sampling algorithm and the analysis of the accuracy of the assumptions are discussed in Sec. III D and III E respectively. A comparison between the TIS and PPTIS methods is made in Sec. III F. In Sec. IV we test the method and compare with the TIS results for a isomerization reaction of a diatomic molecule with an intrinsic long and flat barrier immersed in a fluid of repulsive particles. We end with concluding remarks and prospectives in Sec. IV.

II. THEORY

A. Illustration of the PPTIS concept

Before embarking on the general case of diffusive barriers, we will first consider a simple one dimensional system that serves as an illustrative example. This system exhibits a barrier consisting of a series of metastable states as is illustrated in Fig. 1. The overall barrier is high compared to those between metastable states, so that the system shows two state kinetics and an overall rate constant is well defined. We assume that the system can hop from one metastable state to a neighboring one after which it will fully relax. Consequently, the probability to hop to left or right does not depend on the history of the path, and hence the system behaves Markovian. For this type of system, we might write down a master equation and solve for all the population densities in each state on the barrier as a function of time. However, if we assume steady state behavior, and take into account the fact that the population on the barrier is low, the overall rate constant is only determined by the hopping probabilities. We will denote the probabilities to transfer from site $i$ to the right or left metastable state by $t_{i,i+1}$ and $t_{i,i-1}$ respectively, which are related by $t_{i,i+1} + t_{i,i-1} = 1$. For a system with $n - 1$ metastable states: $M_1, M_2, \ldots, M_{n-1}$ and the stable states $M_0 = A$ and $M_n = B$, the reaction rate $k_{AB}$ and its reverse $k_{BA}$ can be expressed as:

$$k_{AB} = k_{0,1} T[1 \rightarrow 0],$$

$$k_{BA} = k_{n,n-1} T[n - 1 \rightarrow 0],$$

with $T[i \rightarrow j]$ the probability to reach via an arbitrary number of hops from metastable state $i$ to metastable state $j$ before visiting metastable state $m$. The computation of the rate constants only requires the determination of the nearest neighbor hopping probabilities $t_{i,i+1}$ and the first hopping rates $k_{0,1}$ and $k_{n,n-1}$. The long distance hopping probabilities $\{T[1 \rightarrow 0], T[j - 1 \rightarrow 0]\}$ can be obtained via following recursive relations (see Appendix V):

$$T[1 \rightarrow 0] = \frac{t_{j-1,j} T[1 \rightarrow j-1]}{t_{j-1,j} + t_{j-1,j-2} T[j - 2 \rightarrow j-1]}$$

$$T[j - 1 \rightarrow 0] = \frac{t_{j-1,j-2} T[j - 2 \rightarrow j-1]}{t_{j-1,j} + t_{j-1,j-2} T[j - 2 \rightarrow j-1]}$$

Starting with $T[1 \rightarrow 0] = T[0 \rightarrow 0] = 1$, we can iteratively solve Eqs. (2) for $j = 2, 3, \ldots$ to $j = n$. In this way we collect analytically the statistics of all possible pathways. This procedure accounts for the straightforward barrier crossings, but also accounts for the contributions to the rate of an infinite number of different pathways that approach from $A$ to $B$ in an infinite number of hops. Although the probability of a single pathway is decreasing with its length, the total contribution of the very long pathways becomes more important when $n$ is increased. In fact, the average path length increases as $\sim n^2$. In case of uniform symmetric hopping ($t_{i,i+1} = t_{i,i-1} = 1/2$ for all $i$) one can show by induction that $k_{AB} = \frac{1}{n} k_{0,1}$, whereas if we would only account the fastest pathway ($M_0 \rightarrow M_1 \rightarrow M_2 \rightarrow \ldots \rightarrow M_n$) it would be much lower, $(\frac{1}{2})^n k_{0,1}$.

At first sight, it seems a bit surprising that the residence time in each metastable state and the absolute intra-barrier rates $k_{i,i\pm1}$ have no influence on the final total rate expression. Only the relative rates are important as they determine the nearest neighbor hopping probabilities by $t_{i,i\pm1} = k_{i,i\pm1} / (k_{i,i+1} + k_{i,i-1})$. Of course, when we start with a system out of equilibrium and calculate the relaxation time from $A$ to $B$ for a system that is initially completely in $A$, the intra-barrier rates $k_{i,i\pm1}$ will be dominant factors.

Our treatment of this model can be related to the solution of Kramer’s equation if one considers a flat high barrier of length $l$. Kramer’s equation then gives for the rate constant $k_{AB} \approx (D/\ell) \exp(-\beta U)$ where $U$ is the barrier height and $D$ the diffusion constant on top of the
barrier. The connection becomes clear when one realizes \( k_{0,1}/k_{1,0} = \exp(-\beta U) \) and \( D/l = k/n \), with \( k \sim k_{1,0} \) the hopping rate, and \( n \) the number of hops on the barrier. Hence, \( k_{AB} = \frac{1}{k_{0,1}} \), just as found above for the symmetric uniform hopping model. A more formal treatment of general diffusive Markov processes can be found in e.g. Ref. \[13\].

The model described above is of limited importance due to its highly symmetric and one-dimensional character. Some processes, however, such as the diffusion of particles through a one-dimensional crystal (e.g. alkanes through zeolites) can be described by this uniform symmetric hopping model. More complex behavior such as diffusion on surfaces, through multi-dimensional crystals, or in (biological) networks usually has to be studied by means of Monte Carlo (MC) algorithms to solve the master equation, often called kinetic MC methods.\[12,15,16\]. Still, the example given here is illustrative for the more complex PPTIS method advocated in this paper. The PPTIS method combines the iterative solution of Eq. \(4\) for the overall rate constant with the TIS algorithm. This approach will enable treatment of a much wider variety of systems with a diffusive character, but not with such a rigid structure as the one dimensional Markov chain.

### B. TIS formalism

Let \( x_t \) denote a point in phase space defined by the position \( r \) and momenta \( p \) of all particles in the system at time \( t \), \( x_t = (r(t), p(t)) \). Although the expressions derived in this paper are also valid for stochastic dynamics, we assume here that the system is deterministic: \( x_t = f(x_{t-1}, t) \). Evaluation of the time propagator function \( f(x, t) \) requires the integration of motion (e.g. by means of MD) starting from configuration \( x \) over a time interval \( t \).

The TIS method is based on the measurement of the flux through dividing surfaces. For this purpose we define a set of \( n \) non-intersecting multidimensional interfaces \( \{0, 1 \ldots n\} \) described by an order parameter \( \lambda(x) \) which is a function of the phase space point \( x \). In this way, interface \( i \) is the \( N-1 \) dimensional surface \( \{x|\lambda(x) = \lambda_i\} \) for a system with \( N \) degrees of freedom. We choose \( \lambda_i \), \( i = 0 \ldots n \) such that \( \lambda_0 < \lambda_1 \), and that the boundaries of state \( A \) and \( B \) are described by \( \lambda_0 \) and \( \lambda_n \), respectively. To derive the TIS rate expression we need to introduce characteristic functions that do not only depend on the instantaneous position, but on the whole trajectory \( x_t \). For each phase point \( x \) and each interface \( i \), we define a backward time \( t^b_i(x) \) and forward time \( t^f_i(x) \):

\[
\begin{align*}
t^b_i(x) &= -\max \{ \{ t|\lambda(x) = \lambda_i \wedge t \leq 0 \} \} \\
t^f_i(x) &= +\min \{ \{ t|\lambda(x) = \lambda_i \wedge t \geq 0 \} \}
\end{align*}
\]

which mark the points of first crossing with interface \( i \) on a forward (backward) trajectory starting in \( x_0 \). Note that \( t^b_i \) and \( t^f_i \) defined in this way always have positive values.

Following Ref. \[11\], we then introduce two-fold characteristic functions that depend on the two interfaces \( i \neq j \):

\[
\begin{align*}
\bar{h}_{i,j}^b(x) &= \begin{cases} 
1 & \text{if } t^b_i(x) < t^b_j(x), \\
0 & \text{otherwise}
\end{cases} \\
\bar{h}_{i,j}^f(x) &= \begin{cases} 
1 & \text{if } t^f_i(x) < t^f_j(x), \\
0 & \text{otherwise}
\end{cases}
\end{align*}
\]

which measure whether the backward (forward) time evolution of \( x \) will reach interface \( i \) before \( j \) or not. However, as the interfaces do not intersect, the time evolution has to be evaluated only for those phase points \( x \) that are in between the two interfaces \( i \) and \( j \). In case \( i < j \), we know in advance that \( t^b_i(x) < t^b_j(x) \) if \( \lambda(x) < \lambda_i \) and \( t^b_i(x) > t^b_j(x) \) if \( \lambda(x) > \lambda_j \). When the system is ergodic, both interfaces \( i \) and \( j \) will be crossed in finite time and thus \( \bar{h}_{i,j}^b(x) + \bar{h}_{j,i}^b(x) = \bar{h}_{i,j}^f(x) + \bar{h}_{j,i}^f(x) = 1 \).

The two backward characteristic functions define the TIS overall states \( A \) and \( B \):

\[
h_A(x) = \bar{h}_{0,n}^b(x), \quad h_B(x) = \bar{h}_{n,0}^b(x).
\]

Together, the overall states cover the entire phase space and, within certain limits, do not sensitively depend on the precise boundaries of stable states \( A \) and \( B \) as long as they are reasonable. That is, the stable states \( A \) and \( B \) should not overlap, each path from \( A \) to \( B \) should be a true reaction for the case of interest, and the chance that a trajectory starting in \( A \) and ending in \( B \) will return to \( A \) should be as unlikely as a complete new event. Within this formalism the rate constant can be written as

\[
k_{AB} = \frac{\langle h_A(x_0) \bar{h}_B(x_0) \rangle}{\langle h_A(x_0) \rangle},
\]

where the dot denotes the time derivative at \( t = 0 \) and the brackets \( \langle \ldots \rangle \) denote the equilibrium ensemble averages. In the above equation, one can replace \( x_0 \) by \( x_t \) for any \( t \) and we will often skip the argument \( x_0 \) when it does not lead to confusion. Eq. \(6\) measures the effective flux through the phase space hyper-surface dividing \( A \) from \( B \). To express this effective flux in terms that can be computed we define the general flux function

\[
\phi_{ij}(x_0) = \bar{h}_{j,i}^b(x_0) \lim_{\Delta t \to 0} \frac{1}{\Delta t} \theta(\Delta t - t^f_i(x_0))
\]

with \( \theta(x) \) the Heaviside step-function. In principle, the flux expressions are defined in the limit \( \Delta t \to 0 \) where it converges to: \( \phi_{ij} = \bar{h}_{j,i}^b \lambda_0 \delta(\lambda(x) - \lambda_j) \). In practice, however, Eq. \(7\) will be more convenient with \( \Delta t \) equal to the MD time step. This function measures the velocity through interface \( i \) at \( t = 0 \) while coming directly from \( j \) without having recessed \( i \).
With this notation we can write Eq. (6) as

\[ k_{AB} = \langle \phi_{i,0} \rangle / \langle h_{A} \rangle = \langle \phi_{i,0} h_{i,0}^f \rangle / \langle h_{A} \rangle \quad (8) \]

for each \( 0 \leq i \leq n \). The ensemble average \( \langle \phi_{i,0} \rangle \) is the effective positive flux from \( A \) through \( i \). This means that we only count those phase points that will cross interface \( i \) in the positive direction in one \( \Delta t \) time step, and come directly from \( A \), or equivalently, \( x \) should be a first crossing point of the corresponding trajectory that starts in \( A \).

For the reverse reaction rate, we can write similar expressions, but then related to the effective negative flux:

\[ k_{BA} = \langle \phi_{0,n} \rangle / \langle h_{B} \rangle = \langle \phi_{n,0} h_{0,n}^- \rangle / \langle h_{B} \rangle . \quad (9) \]

Note that this effective flux formalism has a lot of flexibility. The second equality in Eq. (8) and (9) is true for any interface \( \lambda_i \), independently on its position on the barrier or shape. If transition state theory (TST) is valid and we could choose our order parameter function \( \lambda(x) \) such that \( \{ x \} | \lambda(x) = \lambda_i \} \) is exactly the transition state dividing surface, all points on this surface directing to \( B \) would contribute to the rate. In that case, Eq. (8) would become equivalent to the TST expression. However, for complex systems it is almost impossible to determine the multidimensional dividing surface or it would require a lot of a-priori knowledge. Instead, the strategy of TIS is to relate the effective positive flux through one interface to that through one closer to \( A \).

By introducing the weighted ensemble average \( \langle g(x) \rangle_{\omega} \) for an observable \( g(x) \) and a weight function \( \omega(x) \):

\[ \langle g(x) \rangle_{\omega} = \frac{\langle g(x) \omega(x) \rangle}{\langle \omega(x) \rangle} \quad (10) \]

we can rewrite the rate expression (8) into a product of terms that can be measured as conditional ensemble averages.

\[ k_{AB} = \langle \phi_{1,0} \rangle / \langle h_{A} \rangle \langle h_{i,0}^f \rangle_{\phi_{1,0}} = \langle \phi_{1,0} \rangle / \langle h_{A} \rangle \prod_{i=1}^{n-1} \langle h_{i+1,0}^- \rangle_{\phi_{i,0}} . \quad (11) \]

In the last equality we have used the TIS relation (Eq. (16) in Ref. [11]). The strength of the rate expression (11) is that it rewrites Eq. (6) as a product of conditional probabilities each factor being much higher than the final rate. This recast expression allows a better accessible route for the computational approach, as it drastically reduces the number of necessary MC moves required for an accurate calculation of \( k_{AB} \). The actual algorithm consists of the computation of the effective flux from \( A \) through \( \lambda_1 \), \( \langle \phi_{1,0} \rangle / \langle h_{A} \rangle \), by means of standard MD, followed by the determination of the conditional probabilities \( \langle h_{i+1,0}^- \rangle_{\phi_{i,0}} \) via a path sampling procedure.

The advantage of TIS over the TPS rate constant algorithm is that the path length is variable so that each path can be limited to its strict necessary minimum length. Moreover, the effective positive flux formalism ensures that only positive terms are accounted in the Monte Carlo scheme, which improves the convergence. Still, for diffusive systems path lengths can become exceedingly long, making an accurate calculation problematic, even when using TIS.

C. PPTIS formalism

In previous section, we have reformulated the TIS theory in a way that facilitates the step toward PPTIS. It is important to note that the PPTIS formalism is also based on a relation between effective fluxes, however, not only in the positive, but also in the negative direction. The algorithm allows a more efficient evaluation of the forward rate \( k_{AB} \) and, besides, also gives the reverse rate \( k_{BA} \) with negligible extra costs.

It is convenient to introduce a short notation for the effective flux function

\[ \Phi_{ij}^m(x) \equiv \phi_{ij}(x)h_{i,m}^f(x) \quad (12) \]

In this notation, the ensemble average of \( \Phi_{ij}^{m,0} \) is the effective positive flux from \( A \) through \( \lambda_i \) going to \( B \). Normalizing with \( \langle \phi_{ij} \rangle \) defines the conditional probabilities

\[ P_{m|ij} = \Phi_{ij}^m / \langle \phi_{ij} \rangle . \quad (13) \]

In words, this is the probability for the system to reach interface \( l \) before \( m \) under the condition that it crosses at \( t = 0 \) interface \( i \), while coming directly from interface \( j \) in the past (see Fig. 2). The rate constants can now be written in terms of these probabilities

\[ k_{AB} = \langle \phi_{1,0} \rangle P_{0|1}^n, \quad k_{BA} = \langle \phi_{n,0} \rangle P_{n|0}^n . \quad (14) \]

In addition, we define the one-interface crossing probabilities \( p_i^+, p_i^-, p_i^{\uparrow}, p_i^{\downarrow} \) and \( p_i^{\uparrow} \).

\[ p_i^\pm \equiv P_{i+1|-1}^{(i+1)|i-1}, \quad p_i^{\uparrow} \equiv P_{i+1|-1}^{(i+1)|i+1}, \quad p_i^- \equiv P_{i+1|-1}^{(i+1)|i+1}, \quad (15) \]

which fulfill the following relation:

\[ p_i^{\uparrow} + p_i^- = p_i^+ + p_i^{\downarrow} = 1 . \quad (16) \]

A schematic visualization of \( P_{m|ij} \) and the probabilities \( p_i^{\uparrow}, p_i^-, p_i^+, p_i^{\downarrow} \) is given in Fig. 2. We also define long-distance crossing probabilities \( P_i^{\uparrow} \) and \( P_i^- \) similar to those in Sec. [11A]

\[ P_i^{\uparrow} \equiv P_{0|0}^{(i+1)}, \quad P_i^- \equiv P_{0|0}^{(i-1)}. \quad (17) \]
The main assumption in PPTIS is that trajectories lose their memory, over a short time, and hence over a short “distance”, as measured by $\lambda$. We require that the interfaces are set such that no memory effects are present over more than the distance between two interfaces or, equivalently, that following relation is obeyed:

$$
\langle g(x) \rangle_{\phi_{i-1,i+1}} \approx \langle g(x) \rangle_{\phi_{i,i+1}},
$$

with $q$ an integer larger than one and $g(x)$ any observable corresponding to the actual state $x$ or any future state. With this assumption we can derive recursive relations for the long-distance crossing probabilities using the PPTIS concept introduced in Sec. VI (see Appendix II):

$$
P_{j}^{+} = \frac{p_{j-1}^{+}p_{j-1}^{+}}{p_{j-1}^{+} + p_{j-1}^{-}P_{j-1}^{-}},
$$

$$
P_{j}^{-} = \frac{p_{j-1}^{+}P_{j-1}^{-}}{p_{j-1}^{+} + p_{j-1}^{-}P_{j-1}^{-}}
$$

To solve these recursive expressions we start with $P_{1}^{+} = P_{1}^{-} = 1$, after which we iteratively determine ($P_{j}^{+}, P_{j}^{-}$) for $j = 2, \ldots$ until $j = n$. Substitution of the long distance crossing probabilities into Eq. (13) results in

$$
k_{AB} = \frac{\langle \phi_{1,0} \rangle}{\langle h_{A} \rangle} P_{n}^{+}, \quad k_{BA} = \frac{\langle \phi_{n-1,n} \rangle}{\langle h_{B} \rangle} P_{n}^{-},
$$

We obtain the reverse rate and the equilibrium constant $C = k_{AB}/k_{BA}$ without any significant extra costs, whereas in other path sampling methods the calculation of the reverse rate would require another comparable computational effort.

**D. The Sampling**

The PPTIS method requires the determination of the $p_{i}^{+}, p_{i}^{-}, p_{i}^{x},$ and $p_{i}^{y}$ probabilities. However, $p_{i}^{x}$ and $p_{i}^{y}$ are defined in a different ensemble than $p_{i}^{x}$ and $p_{i}^{y}$. In most cases, it will be convenient to calculate the four probabilities simultaneously. Therefore, we define an ensemble that includes both ensembles via the weight function $\phi_{i\pm}(x)$:

$$
\phi_{i\pm}(x) \equiv \phi_{i,i-1}(x) + \phi_{i,i+1}(x)
$$

In this ensemble, $p_{i}^{+}$ and $p_{i}^{y}$ equal

$$
p_{i}^{+} = \frac{\langle \Phi_{i,i-1}^{+} \rangle_{\phi_{i\pm}}}{\langle \phi_{i,i-1} \rangle_{\phi_{i\pm}}} \quad \text{and} \quad p_{i}^{-} = \frac{\langle \Phi_{i,i+1}^{-} \rangle_{\phi_{i\pm}}}{\langle \phi_{i,i+1} \rangle_{\phi_{i\pm}}}
$$

and $p_{i}^{x}$ and $p_{i}^{y}$ follow from Eq. (19).

For a correct sampling of phase points $x_{0}$ in this ensemble, we generate all possible paths starting from interface $i-1$ or $i+1$ and ending either by crossing $i-1$ or $i+1$ with at least one crossing with $i$. The sampling is performed using the shooting move as explained in Ref. 11 with the difference that there is no need to reject the backward integration as it is allowed to reach either $i-1$ or $i+1$. All paths are confined within $\lambda_{i-1}$ and $\lambda_{i+1}$ and have, even in the case of multiple $\lambda_{i}$ crossings, only one time-slice $x$ along the path for which $\phi_{i\pm}(x) \neq 0$. This defines the phase point $x_{0}$. A big advantage is that the time reversal moves become now very efficient, as they are cheap and will always result in a new phase point $x_{0}$ of the ensemble.

**E. Position of the Interfaces**

Contrary to the TIS technique, where the interfaces should be close to obtain good statistics, the interfaces should be sufficient apart in the PPTIS method to ensure complete loss of memory. A simple test for Eq. (13) would be to measure $\langle g(x) \rangle_{\phi_{i,i-1}}$ for different separations between $\lambda_{i}$ and $\lambda_{i-1}$. The velocity $\lambda$ at the crossing point through $\lambda_{i}$ would be a good candidate for the function $g$. This test is time consuming if it has to be applied for
all possible interface separations. However, one can estimate the memory loss for interface separations smaller than the chosen one during the rate constant calculation. If the interfaces are sufficient apart, one obtains a reasonable validation that the memory is vanished before reaching the next surface. Substituting $\hat{\lambda}(x)$ into Eq. (18) gives

$$\langle \hat{\lambda}(x_0) \rangle_{\phi_{i+1,i}} \approx \langle \hat{\lambda}(x_0) \rangle_{\phi_{i+1,i-1}} \quad (23)$$

This relation can be rewritten in the ensemble of $\phi_{i\pm}$:

$$\frac{\langle \hat{\lambda}(x_F) \hat{h}_{i+1,i-1}^f(x_0) \rangle_{\phi_{i\pm}}}{\langle \hat{h}_{i+1,i-1}^f(x_0) \rangle_{\phi_{i\pm}}} \approx \frac{\langle \hat{\lambda}(x_F) \Psi_{i+1,i-1}^f(x_0) \rangle_{\phi_{i\pm}}}{\langle \Psi_{i+1,i-1}^f(x_0) \rangle_{\phi_{i\pm}}} \quad (24)$$

where $x_F \equiv f(x_0, \min[t_{i-1}^f(x_0), t_{i+1}^f(x_0)])$ is the path endpoint and $\hat{\lambda}(x_F)$ its velocity. A similar expression can be derived for the reverse direction. The endpoint $\hat{\lambda}$ can be calculated in the $\phi_{i\pm}$ ensemble during a PP-TIS simulation. To do this we need an additional MC move when the path has multiple recrossings with the two terms at both sides of the equality in Eq. (24). However, in the ensemble defined by the two most inner sub-interfaces $\phi_{i\pm}$ three points belong to the ensemble (1, 2 and 3). Therefore, an additional MC move is required to measure $\text{MLF}(j\delta\lambda)$ for $j\delta\lambda < \Delta\lambda$.

This works as follows: For each path in the $\phi_{i\pm}$ ensemble, we loop over all sub-interfaces $j$. For each $j$, first collect all the phase points that belong to the ensemble of $\phi_{i\pm,j\delta\lambda}$. Secondly, sample the MLF function for a random point out of the $n$ points $\{x_0(1), x_0(2), \ldots, x_0(n)\}$ for which $\phi_{i\pm,j\delta\lambda}(x_0) \neq 0$. Third, take a uniform random number $\alpha$ between $[0 : 1]$ and repeat the second step if $\alpha > 1/n$. Otherwise, continue the loop over $j$ until $j = n_{\text{sub}}$. Finally, generate a new path, and repeat the whole procedure.

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**F. Comparing TIS with PPTIS**

In order to make a proper efficiency comparison between the two methods, we need to estimate the computational effort for a certain fixed error. We rather calculate the error in the equilibrium constant $C = k_{AB}/k_{BA}$ instead of in the rate $k_{AB}$ itself because the expression of $C$ in terms of the averages, that have to be calculated separately, is much simpler than the recursive expression (13) of $k_{AB}$. Hence, the error propagation from the error in the individual terms is simpler and yields a more transparent comparison with TIS. As $P_j^+ / P_j^- = P_j^+ / P_j^- \cdot P_j^+ / P_j^-$, the equilibrium constant $C$ can be written as:

$$C_{\text{PPTIS}} = \frac{P_{n-1}^+ / P_{n-1}^-}{[\phi_{n-1,n}]} \prod_{i=0}^{n-1} \frac{P_{i}^+ / P_{i}^-}{\phi_{i}} \quad (25)$$

Each term within brackets $[\ldots]$ is calculated separately together with its error. The error propagation of the total $n+1$ terms determines the final overall error. Similarly, in TIS the expression for $C$ can be written as:

$$C_{\text{TIS}} = \frac{[\phi_{i,0}]}{[\phi_{n-1,n}]} \prod_{i=0}^{n-1} \frac{P_{A}(\lambda_i|\lambda_{i-1}) \cdots P_{A}(\lambda_1|\lambda_0)}{P_{B}(\lambda_i|\lambda_{i-1}) \cdots P_{B}(\lambda_{n-2}|\lambda_{n-1})} \quad (26)$$

with $P_A(\lambda_j|\lambda_i) \equiv P_A(\|\lambda_j\|_0)$ and $P_B(\lambda_j|\lambda_i) \equiv P_A(\|\lambda_j\|_0)$. Here, in total $2n$ simulations have to be performed, each
III. NUMERICAL RESULTS

A. The model system

In Refs. [7] and [11], the TPS and TIS methods were tested on a bistable diatomic molecule immersed in a fluid of purely repulsive particles. Here, we use a very similar system to test the PPTIS method, consisting of $N$ two-dimensional particles interacting via the Weeks-Chandler-Andersen (WCA) potential

$$V_{WCA}(r) = \begin{cases} 4\epsilon[(r/\sigma)^{-12} - (r/\sigma)^{-6}] + \epsilon & \text{if } r \leq r_0 \\ 0 & \text{if } r > r_0, \end{cases}$$

(27)

where $r$ is the interatomic distance, and $r_0 = 2^{1/6}\sigma$. In the following we will use reduced units so that the energy and length parameters $\epsilon$ and $\sigma$, the mass of the particles and the unit of time $(m\sigma^2/\epsilon)^{1/2}$ are all equal to unity. In addition, two of the $N$ particles are interacting through a double well potential

$$V_{diff}(r) = \begin{cases} V_{dw}(r) & \text{if } r < r_0 + w \\ h & \text{if } r_0 + w < r < r_0 + w + b \\ V_{dw}(r-b) & \text{if } r > r_0 + w + b \end{cases}$$

(28)

where

$$V_{dw}(r) = h[1 - (r - r_0 - w)^2/w^2]^{1/2}.$$  

(29)

This potential and its first derivative are continuous and the forces are therefore well defined. It has two minima at $r = r_0$, the compact state or state $A$, and at $r = r_0 + 2w + b$, the extended state or state $B$. The minima are separated by a total barrier of length $b + 2w$ and height $h$. For sufficiently large values of $h$, transitions between the states become rare and the rate constants are well defined. For sufficiently large values of $b$, trajectories on the barrier plateau become diffusive. We therefore expect this system to be a good test case for the new PPTIS method.

We simulate the system at constant energy $E = 1.0$ in a square box with periodic boundary conditions. The number density is fixed at 0.7, by adjusting the size of the box. The barrier length should always be less than half the box’s edge, implying the number of particles $N$ to increase accordingly with the value of the barrier length $b$. The remaining barrier parameters are set to $h = 15$ and $w = 0.5$. The total linear momentum is conserved and is set to zero. The equations of motion are integrated using the velocity Verlet algorithm with a time step $\Delta t = 0.002$. The Monte Carlo path sampling is carried out both in PPTIS and TIS by means of the shooting move and the path-reversal move, as explained in Sec. III C and Ref. [11]. The two moves were performed with an equal probability of 50%. The momentum displacement for the shooting move was always gaged such that the acceptance ratio is about 40%, which provides an optimum efficiency of the sampling. The intermolecular distance $r$ is a suitable order parameter to define the interfaces.

In the following two subsections we consider a system with a barrier short enough to gather good statistics in a reasonable computation time. In section III C we study the gain in efficiency of PPTIS over TIS as a function of the diffusive barrier length. In the final section III D we test the memory loss assumption as explained in Sec. III B.

B. System with short barrier

We simulated a system of $N = 100$ WCA particles with a barrier length $b = 2$. The minima of $V_{diff}(r)$ are located at $r \simeq 1.12$ and $r \simeq 4.12$, and the diffusive plateau extends from $r \simeq 1.62$ to $r \simeq 3.62$. State $A$ is defined by interface $\lambda_0$ as $r < 1.22$ and state $B$ by interface $\lambda_{17}$ as $r > 4.02$. In the intermediate regime 16 interfaces were chosen at $r = 1.24, 1.34, 1.40, 1.46, 1.52, 1.62, 2.02, 2.42, 2.82, 3.22, 3.62, 3.72, 3.78, 3.84, 3.90, and 4.00.

First, we ran straightforward MD simulations in state $A$ and $B$ to compute the fluxes that appear in both Eq. (25) and (26) by counting the number of positive crossings through interfaces $\lambda_1$ and $\lambda_{16}$ respectively. We obtained the values $\langle \phi_{1,0} \rangle/\langle h_A \rangle = 0.1160 \pm 0.0008$ and $\langle \phi_{16,17} \rangle/\langle h_B \rangle = 0.117 \pm 0.001$. Subsequently, we calculated the conditional probabilities in Eq. (25). For PPTIS we calculated the one-interface crossing probabilities for all the 16 interfaces on the barrier, while TIS simulations show convergence after 11 windows for both the forward and the backward reaction path. In Fig. 1 we re-

\[
\begin{array}{llll}
\text{Table I: Comparison of PPTIS and TIS. Forward and backward rate constants as well as the equilibrium constant are reported for the system with short energy barrier.}
\end{array}
\]

| Method | $k_{AB}/10^{-10}$ | $k_{BA}/10^{-10}$ | $C$ |
|--------|----------------|----------------|-----|
| PPTIS  | $2.75 \pm 0.07$ | $1.95 \pm 0.04$ | $1.41 \pm 0.05$ |
| TIS    | $2.8 \pm 0.2$   | $2.03 \pm 0.06$ | $1.4 \pm 0.1$  |
and $P$ cause for the first 5 interfaces $i$. The $p^\pm$, $p^\mp$ probabilities follow directly from Eq. (16). Bottom: PPTIS long-distance crossing probabilities $P^\pm_i$, $P^\mp_i$, see Eq. (17). The last points contribute to the rate constants as in Eq. (20). In both graphs the error is within symbol size.

...and the long-distance crossing probability $P^\pm_i$, $P^\mp_i$. The long-distance crossing probabilities appearing in the rate constant $C^\pm_i$, $C^\mp_i$, see Eq. (17). The last points contribute to the rate constants as in Eq. (20). In both graphs the error is within symbol size.

The function $p(r)$ was computed using a biased MD simulation and is plotted in the inset. From the minima of $F(r)$ we derived the free energy difference $\Delta F = F_A - F_B$ and hence the equilibrium constant.

$F(r) = V_{diff}(r) - kT \ln p(r) + \text{constant}$

where in our microcanonical simulations the temperature $T$ is derived from average kinetic energy. A plot of the free energy is shown in Fig. 5. From this curve we derive the free energy difference $\Delta F$ between the two minima, and the equilibrium constant $C = 1.369 \pm 0.001$. All results are consistent with each other within the statistical error.

C. Efficiency Scaling

In both the PPTIS and the TIS method the final equilibrium constant is a product of factors given by Eqs. (25) and (26), respectively. We determined each factor independently by performing $M$ simulation blocks of $m$ Monte Carlo cycles. We adjusted $m$ so that the relative standard deviation of each term in Eqs. (25) and (26) after $M$ block averages was an arbitrary value of 3%. We measured, under the same computational conditions (1.4 GHz AMD Athlon), the CPU-time required and summed up all the times to get the relative efficiency. The final errors on the rate constants given above were obtained by standard propagation rules using all the available blocks of simulations.
We computed the computation times to reach the prefixed 3% error for each factor in Eqs. (25) and (26) and found that for the simple dimer system the efficiency of PPTIS is at least a factor two higher than TIS. In figure 6 we plot the average path-length in each window for the two methods. The direct comparison shows that on the barrier PPTIS keeps the path length constant while the TIS path-length increases. This is expected but it does not directly imply a gain in efficiency as the relative error in the TIS terms is smaller for the longer paths.

In order to compare the efficiency of both PPTIS and TIS quantitatively as a function of barrier length we consider the windows $i = 1 \ldots N_W$. In each window we perform simulations of $m$ Monte Carlo cycles. Let the average path length in each window be $L_i$ and relative error in the observable (e.g. hopping probability) be $\epsilon_i$. If we assume that $m$ is large enough so that all simulations are uncorrelated, then $\epsilon_i$ scales as the inverse square root of $m$. To obtain a fixed error $\epsilon$, one has to rescale the number of paths by $(\epsilon_i/\epsilon)^2$. Moreover, the acceptance ratio is almost independent of the path length for TIS in the kind of systems we have studied here. As a result we found that the required CPU time for $m$ MC cycles scales linearly with its average path length. The total computation time is then proportional to

$$m \sum_{i=1}^{N_W} L_i \left( \frac{\epsilon_i}{\epsilon} \right)^2 \quad (31)$$

If the barrier is very long we can neglect the initial and final windows on the steep side of the barrier and consider only those on the plateau for which we assume a fixed interface separation $\Delta \lambda = b/N_W$. The PPTIS method keeps $L_i$ and $\epsilon_i$ more or less constant (see Fig. 6). The efficiency $\eta$ is the ratio of the TIS to the PPTIS computation time

$$\eta \equiv \frac{\text{CPU}_{\text{TIS}}}{\text{CPU}_{\text{PPTIS}}} \propto \sum_{i=1}^{N_W} L_i \epsilon_i^2 \frac{1}{N_W} \quad (32)$$

where $L_i$ and $\epsilon_i$ are now the TIS path-length and relative error for window $i$. To study the behavior of $L_i$ and $\epsilon_i$ we focus on the TIS calculations for the forward reaction rate constant $k_{AB}$. The observables are the probabilities $P_A(\lambda_{i+1}|\lambda_i)$ (see Eq. (28)). To estimate the TIS effective computation time as function of the barrier length, we first examined the model of Sec. II A with $t_{i,i+1} = \frac{1}{2}$ (uniform symmetric hopping). This simplified system allows us to obtain some analytical results and to perform path sampling on wide barriers with millions of paths. We found that the relative error $\epsilon_j$ in the long distance hopping probabilities $P[1 \rightarrow 0]$ scales as $\sim \frac{1}{\sqrt{j}}$. Moreover, the average length of the corresponding path (the number of hops) scales quadratically with $j$, while the acceptance ratio remained constant.

To test whether this scaling behavior also applies to the dimer model, we considered a system of $N = 256$ particles with a barrier length $b = 6$. The minima of $V_{\text{diff}}(r)$ are located at $r \approx 1.12$ and $r \approx 8.12$. State $A$ is defined by interface $\lambda_0$ as $r < 1.20$. We defined 22 other interfaces, 16 of which on the barrier plateau from $r \approx 1.62$ to $r \approx 7.62$ at intervals $\Delta \lambda = 0.4$. By running several TIS simulations, we computed the crossing probabilities $P_A(\lambda_{i+1}|\lambda_i)$ and their standard deviations for...
The size of the window should be chosen as small as possible, while the second puts a lower bound on it. Similar considerations apply to PPTIS with the addition of the memory loss requirement, which is also a lower bound to the window size. Taking all this into accounts we believe $\Delta \lambda = 0.2$ is an optimal choice. The optimal value of $\Delta \lambda$ is of course dependent on the system and on the choice of order parameter, and has to be estimated by trial and error.

**IV. DISCUSSION AND CONCLUSIONS**

In this paper we have introduced a path sampling algorithm for the efficient calculation of rate constants of two state activated processes with a diffusive barrier. The method is based on the division of phase space by interfaces. We then calculate hopping probabilities from one interface to another, using transition path sampling shooting moves and time reversal moves as our basic instrument to create new paths on each interface ensemble. Using either the iterative scheme given here or for more general hopping networks the method of kinetic Monte Carlo, one can solve the master equation and obtain the final forward and backward rate constants. In deriving this algorithm we assumed complete memory loss between interface, such that the system becomes essentially Markovian, thus validating the use of kinetic Monte Carlo and similar algorithms. We showed that for a relatively simple system, the diatomic molecule, the memory loss assumption (loss of correlation) holds over the entire barrier. We expect that for more complex systems this memory loss requirement will certainly be fulfilled, provided that the dynamics has a stochastic character and the interfaces are placed sufficiently far apart. However, the choice of order parameter requires still some caution, possibly more than in TIS, in order to satisfy the memory loss requirement. For the simple dimer system, we showed that PPTIS is already twice as fast as TIS. More importantly, we argued that the computation time scales linearly with the barrier length, instead of quadratically as for TIS and maybe even with a higher power for TPS. This opens up possibilities for accurate rate constant calculations for complex activated processes.

The method advocated here to tackle diffusive barriers in complex systems is not the first one that has been proposed in the literature. Several techniques have been put forward in the last decade, for instance the diffusive barrier algorithm by Ruiz-Montero et al. and the coarse MD method by Hummer and Kevrekidis. The latter technique uses short trajectories to calculate the average force projected on a order parameter space. They use that force to integrate a stochastic equation of motion and explore the free energy landscape in that way. Rate constants can then in principle be obtained from the dynamics on this coarse grained surface.

The method of Ruiz-Montero et al. is in essence a reactive flux method but enhances the statistics by measur-
ing the flux on many different places on the barrier and weigh those contributions such that the error in the rate constant is as small as possible. The weighing function turns out to be proportional to the inverse of the barrier free energy profile. This means that to get a meaningful result one should have access to the free energy landscape on the barrier, before the rate constant calculation. However, due to complexity, the order parameters chosen as reaction coordinate are not necessarily correct, sometimes resulting in inaccurate barriers and very small transmission coefficients. Moreover, the calculation of a transmission coefficient suffers from the same quadratically dependence of the barrier length.

We stress that there is a large difference between the reactive flux method based on transition state theory and the PPTIS technique. Although we use hyper-surfaces to divide the phase-space we do not rely on a global transmission coefficients. Moreover, the calculation of a landscape on the barrier, before the rate constant calculation is a very bad reaction coordinate.

VI. APPENDIX A

In this appendix we will derive the recursive relations (2) for the chain of metastable states. For the transfer in the positive direction we can write

\[
T[1 \rightarrow j] = T[1 \rightarrow 0]T[j - 1 \rightarrow 0]
\]

and for the reverse direction

\[
T[j - 1 \rightarrow 0] = t_{j-1, j-2}T[j - 2 \rightarrow 0] + T[j - 2 \rightarrow 0]T[j - 1 \rightarrow 0]
\]

Bringing the \(T[1 \rightarrow 0]\) terms of Eq. (35) to the left side gives us:

\[
T[j - 1 \rightarrow 0] = \frac{t_{j-1, j-2}T[j - 2 \rightarrow 0]}{1 - t_{j-1, j-2}(1 - T[j - 2 \rightarrow 0])}
\]  

Using \(1 - t_{j-1, j-2} = t_{j-1, j}\), we see that Eq. (36) is equivalent to the second line in Eq. (2). The first line of Eq. (2) is then obtained by the substitution into Eq. (36).

VI. APPENDIX B

The criterion of Eq. (15) gives for any positive integer \(q > 0\) following approximate relations:

\[
P_{i}^{(\text{t}+q)}(i_{i+1}) \approx P_{i}^{(\text{t}+q)}(i_{i+1})p_{i}^{+}/p_{i}^{-}
\]

With this in mind we can start a derivation similar to Appendix V:

\[
P_{j}^{+} = P_{0}^{(j \rightarrow -1)} = p_{j-1}^{+}P_{0}^{(j \rightarrow -1)}
\]

and for the reverse direction we can write:

\[
P_{j}^{-} = P_{0}^{(j \rightarrow -1)} = p_{j-1}^{-}\frac{P_{0}^{(j \rightarrow -1)}}{p_{j-1}^{-}}
\]

With the help of Eq. (16) we can see that this is equivalent to expression (16). Substitution of this relation into Eq. (38) results in the expression for \(P_{j}^{+}\) in Eq. (19).
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As not only the average velocity should be the same

\[
\langle \dot{\lambda}(x) \rangle_{\phi_{i,i-1}} = \langle \dot{\lambda}(x) \rangle_{\phi_{i,i-1}},
\]

but the whole distribution of velocities at \( \lambda_i \), we used in Sec. III the velocity distribution overlap as measure of the memory loss.

To simplify notation we assume here an equidistant interface separation for all interfaces. One is, however, by no means restricted to do so and one can place each interface at an optimum position concerning efficiency, memory loss and ergodic sampling.

This is contrast with what was found in Ref. [12] using TPS. There, we found a dramatic decrease of acceptance as function of the barrier length. This is caused by increasing rejection probability due to the constraint that the path should not be larger than the fixed length. TIS is less sensitive to this as the path length is variable. Still, for more complex free energy landscapes that may contain many entropic barriers, the TIS acceptance probability might also decrease when the path lengths get longer.