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Optimizing transition interface sampling simulations

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We demonstrate that a recently proposed adaptive optimization algorithm for forward flux sampling simulations [E. E. Borrero and F. A. Escobedo, J. Chem. Phys. 129, 024115 (2008)] can be easily applied within the framework of transition interface sampling. This optimization algorithm systematically identifies the kinetic bottlenecks along the order parameter used to partition phase space via interfaces and improves the statistical accuracy of the reaction rate constant estimate. In different versions of the algorithm, the number or the placement of the interfaces (or both) are varied in order to allocate the numerical effort in a balanced way. The algorithm is demonstrated for a simple two-dimensional model and for the dipole flip transition of icelike structures inside carbon nanotubes. For these test systems, the optimization yielded an efficiency increase by a factor of 2-15.


I. INTRODUCTION

Transition path sampling (TPS) simulations have been used extensively to study the mechanism and kinetics of processes dominated by rare transitions between long-lived stable states. Examples range from chemical reactions to protein unfolding,1–3 one variant of TPS, transition interface sampling (TIS),4–6 permits a particularly efficient calculation of transition rate constants. In a TIS simulation, one considers pathways of variable length that cross a series of non-intersecting interfaces, usually defined through an order parameter, spanning the space between the initial and final state. Transition probabilities calculated in separate path sampling simulations for each interface are then combined to obtain the transition rate constant.

Although TIS is less sensitive to the choice of order parameter than other interface-based path sampling methods (e.g., forward flux sampling),2 the efficiency of the simulation, determined primarily by how the path space is partitioned and sampled, can be improved by a smart placement of the interfaces. Recently, Borrero and Escobedo7 proposed an adaptive optimization algorithm for forward flux sampling simulations designed to identify suitable strategic positions of the interfaces. In this staging scheme, named adaptive λ-staging, the kinetic bottlenecks of a path sampling simulation are identified by tracking the conditional probabilities to reach consecutive interfaces. Feeding back information gathered from a preliminary path sampling simulation for an initial set of interfaces, the computational effort is reallocated by concentrating the interfaces, and hence the major part of the sampling effort, in the bottleneck regions, typically occurring between the initial state and the transition state region. Note that this approach does not require any a priori knowledge of the transition states in order to identify the bottlenecks of the TIS simulations. Borrero and Escobedo7 verified the validity of their optimization algorithm for the case of forward flux sampling (FFS) simulations and showed that it leads to a considerable efficiency increase in the calculation of reaction rate constants.

In this work, we demonstrate that this optimization approach can be easily extended to TIS simulations. The remainder of this paper is organized as follows. First, in Sec. II A, a brief overview is given of the TIS algorithm for sampling the transition path ensemble and for calculating transition rate constants. In Sec. II B, we introduce the adaptive λ-staging optimization algorithm in the framework of TIS simulations. Finally, in Sec. III, we demonstrate the applicability of this optimization algorithm to TIS simulations using a simple test bed system and the dipole flip transition of ordered water chains inside carbon nanotubes as illustrative examples.

II. METHODS

A. TIS algorithm

Transition interface sampling4–6 is a TPS technique2,8,9 developed for the efficient calculation of reaction rate constants of rare transitions between two known stable states, A and B, defined as regions in configuration space. In this method, the configuration space between the two stable states is partitioned by introducing a series of n non-intersecting interfaces, defined as the iso-surfaces of a suitable order parameter λ(r), i.e., interface i is characterized by \( \lambda(r) = \lambda_i \). Here, \( r \) represents a point in configuration space specifying the positions of all particles of the system. As one moves from region A to region B crossing consecutive interfaces, the values of the order parameters increase monotonically, \( \lambda_i < \lambda_{i+1} \). The interfaces are defined such that the boundaries of A and B correspond to \( \lambda(r) = \lambda_0 = \lambda_A \) and \( \lambda(r) = \lambda_n+1 = \lambda_B \), respectively. While the boundaries of A and B are assumed to be given, the \( n \) interfaces between them can be optimized to increase the efficiency of the rate calculation.
For each interface, one defines a distinct path ensemble consisting of all trajectories that originate in region $A$ from initial conditions distributed according the appropriate equilibrium distribution, cross interface $i$ and then either cross interface $i+1$ or return to region $A$. Trajectories distributed according to these ensembles are harvested using efficient TPS-techniques such as shooting\textsuperscript{8} and path swapping.\textsuperscript{10} These pathways have variable length since the generation of a new pathway is terminated as soon as the trajectory reaches either region $A$ or interface $i+1$, contributing to the efficiency of the TIS-algorithm with respect to earlier TPS methods for the calculation of reaction rate constants.\textsuperscript{11,12}

Since the sequence of path ensembles sampled in the TIS-method corresponds to a transformation in small steps from an ensemble of unconstrained pathways starting in $A$ to an ensemble of reactive trajectories connecting $A$ and $B$, reaction rate constants can be readily computed in the TIS-framework. The forward reaction rate constant $k_{AB}$ can be expressed as an effective positive flux,$\textsuperscript{4,5}$

$$k_{AB} = \Phi_{A,1} P(\lambda_B | \lambda_1). \tag{1}$$

This equation states that the reaction rate constant $k_{AB}$ is the product of the effective positive flux $\Phi_{A,1}$ through interface 1 and the conditional probability $P(\lambda_B | \lambda_1)$ that a trajectory crossing interface 1 coming from $A$ will reach $B$ before returning to $A$. Consequently, the rate calculation in the TIS-formalism consists of two steps. First, the flux $\Phi_{A,1} = N_1 / \Gamma$ is estimated by counting the number $N_1$ of effective positive crossing events of the first interface at $\lambda_1$ from a simulation of total length $\Gamma$ in the initial basin $A$. Such an effective positive crossing occurs when the system crosses interface 1 for the first time after leaving region $A$. The second step consists in calculating the crossing probability $P(\lambda_B | \lambda_1)$, which is written as a product of conditional probabilities,

$$P(\lambda_B | \lambda_1) = \prod_{i=1}^{n} P(\lambda_{i+1} | \lambda_i). \tag{2}$$

Here, $P(\lambda_{i+1} | \lambda_i)$ is the conditional probability that a trajectory coming from $A$ and crossing interface $i$ reaches interface $i+1$ rather than returning to $A$ first.

For a suitable spacing of the interfaces, the conditional probabilities $P(\lambda_{i+1} | \lambda_i)$ can be determined for $i = 1$ to $n$ in separate TPS-type simulations. To compute the conditional probability $P(\lambda_{i+1} | \lambda_i)$, one samples the ensemble of trajectories that start in $A$, cross interface $i$ and then either return to $A$ or cross interface $i+1$. The conditional probability $P(\lambda_{i+1} | \lambda_i)$ is then estimated as

$$P(\lambda_{i+1} | \lambda_i) = \frac{N_{A \to A^{-i} \to i+1}}{N_{A \to A^{-i}}}, \tag{3}$$

where $N_{A \to A^{-i} \to i+1}$ is the number of harvested paths that connect $A$ with interface $i+1$, given that interface $i$ was crossed (i.e., trajectories of the form of $\lambda_A \to \lambda_i \to \lambda_{i+1}$) and $N_{A \to A^{-i}}$ is the total number of paths sampled in the respective path ensemble. Forming the product of the conditional probabilities according to Eq. (2) then yields the conditional probability $P(\lambda_B | \lambda_1)$ and, in combination with the effective positive flux through interface 1, the reaction rate constant $k_{AB}$. For a more detailed discussion of the TIS method we refer the reader to the original literature.$\textsuperscript{4–6}$

### B. Adaptive $\lambda$-staging optimization algorithm

The numerical efficiency of the TIS-approach for the calculation of reaction rate constants crucially depends on the number and the placement of the interfaces between the initial and the final region. In this section, we first analyze the efficiency of the method and then propose a procedure to identify optimum interfaces along the same lines as done in Ref. 13 for forward flux sampling. Following Allen et al.$\textsuperscript{13}$ we define the computational efficiency $\varepsilon$ of a TPS simulation as

$$\varepsilon = \frac{1}{C \nu}. \tag{4}$$

Here, $C$ denotes the computational cost, for instance, expressed as the number of central processing unit (CPU) hours required to carry out a particular simulation and $\nu$ is the statistical error in the estimated value of the rate constant $k_{AB}$ quantified by the relative variance of the reaction rate constant determined in repeated simulations,

$$\nu = \frac{\text{var}[k_{AB}]}{k_{AB}^2}. \tag{5}$$

With this particular choice, the computational efficiency $\varepsilon$ is independent of the total length of the simulation used to determine the reaction rate constant. Assuming that the flux $\Phi_{A,1}$ can be calculated with high precision and the main source of statistical error in the reaction rate constant is the conditional probability $P(\lambda_B | \lambda_1)$, the statistical error $\nu$ is proportional to the variance of $P(\lambda_B | \lambda_1)$,$\textsuperscript{13}$

$$\nu \propto \text{var}[P(\lambda_B | \lambda_1)]. \tag{6}$$

Hence, the maximization of the efficiency of a TIS simulation with fixed computational cost $C$ requires the minimization of the variance in the estimate of $P(\lambda_B | \lambda_1)$.

Now, considering that in a TIS-simulation the conditional probability $P(\lambda_B | \lambda_1)$ is determined as the product of the conditional probabilities $P(\lambda_{i+1} | \lambda_i)$, the rules of error propagation yield,$\textsuperscript{13}$

$$\text{var}[P(\lambda_B | \lambda_1)] = P(\lambda_B | \lambda_1)^2 \sum_{i=1}^{n} \frac{\text{var}[P(\lambda_{i+1} | \lambda_i)]}{P(\lambda_{i+1} | \lambda_i)^2}, \tag{7}$$

Assuming that the events being counted for the estimation of the conditional probabilities $P(\lambda_{i+1} | \lambda_i)$ of Eq. (3) are outcomes of $N^{(A^{-i})}$ discrete shooting trials and, hence, follow a binomial distribution, Eq. (7) can be further simplified to\textsuperscript{13}

$$\text{var}[P(\lambda_B | \lambda_1)] = P(\lambda_B | \lambda_1)^2 \sum_{i=1}^{n} \frac{1 - P(\lambda_{i+1} | \lambda_i)}{N^{(A^{-i})} P(\lambda_{i+1} | \lambda_i)}. \tag{8}$$

Note that in Eq. (8) we have used the fact that the total number of sampled trajectories $N^{(A^{-i})}$ of Eq. (3) is a constant in all the TIS simulations for the different interfaces, such that $\text{var}[P(\lambda_{i+1} | \lambda_i)] \propto \text{var}[N^{(A^{-i})}]$. Moreover, in the derivation of Eq. (8) we have assumed, for simplicity, that paths harvested in a TIS-simulation are statistically independent from each other. While not strictly true, this assumption is justified.
as paths generated in a TPS simulation are effectively decorrelated after a small number of shooting moves.

Because the probabilities \( P(\lambda_{i+1} | \lambda_i) \) are directly determined by the positions \( \lambda_i \) of the interfaces, one can minimize the variance \( \text{var}[P(\lambda_B | \lambda_1)] \) in Eq. (8), and hence the statistical uncertainty in the computed transition rate constant, by repositioning the interfaces in an appropriate way. To achieve this goal in the context of forward flux sampling and to increase the efficiency of the simulation, Borrero and Escobedo\(^7\) proposed two distinct but related strategies. In the first approach, valid for fixed numbers \( N^{(A \rightarrow i)} \) of sampled trajectories, the interfaces are placed with higher density in the bottleneck regions of configuration space such that the computational effort of the path simulation is concentrated on pathways crossing these regions. In the second approach, valid for fixed interface positions \( \lambda_i \) and total computational cost, the numbers \( N^{(A \rightarrow i)} \) of trajectories sampled at each interface \( \lambda_i \) are varied such that a larger number of pathways is harvested for those ensembles with small \( P(\lambda_{i+1} | \lambda_i) \) values. In this paper we will proceed analogously.

The statistical error in the reaction rate constant, quantified by the variance of the estimated crossing probability \( P(\lambda_B | \lambda_1) \) as expressed in Eq. (8), can be minimized by varying the positions of the interfaces for fixed numbers \( N^{(A \rightarrow i)} \) of trajectories sampled at each stage. Borrero and Escobedo\(^7\) showed that minimization of Eq. (8) with respect to the conditional probabilities \( P(\lambda_{i+1} | \lambda_i) \) subject to the constraint that \( P(\lambda_B | \lambda_1) = \prod_{i=1}^{n} P(\lambda_{i+1} | \lambda_i) \) is constant yields the condition

\[
N^{(A \rightarrow i)} P(\lambda_{i+1} | \lambda_i) = N^{(A \rightarrow i-1 + 1)} = N_S. \tag{9}
\]

This equation implies that the same number \( N_S \) of pathways of type \( \lambda_A \rightarrow \lambda_i \rightarrow \lambda_{i+1} \) need to be harvested at each interface, leading to equal statistical errors in the estimates of the conditional probabilities \( P(\lambda_{i+1} | \lambda_i) \) for all interfaces. If the total number \( N^{(A \rightarrow i)} \) of sampled pathways is the same at each interface, the constant flux condition of Eq. (9) is equivalent to the requirement that all conditional probabilities \( P(\lambda_{i+1} | \lambda_i) \) are equal. Note, however, that the minimization of the variance \( \text{var}[P(\lambda_B | \lambda_1)] \) is not strictly equivalent to the optimization of the computational efficiency \( \varepsilon \), because also the computational cost depends on where the interfaces are placed. To take into account this dependence in the optimization of the efficiency, one would have to express analytically the computational cost of the simulation in terms of the \( \lambda_i \). In the case of FFS-simulations such analytical expressions for the computational cost have been derived by Allen et al.\(^{13}\) Accordingly, Borrero and Escobedo\(^7\) have obtained expressions for calculating the set \( \{N^{(A \rightarrow i)}\} \) that optimizes the sampling of FFS-type simulations for any given staging. Hence, once the phase staging is optimized to position interfaces at the bottleneck regions [via Eq. (9)], the \( \{N^{(A \rightarrow i)}\} \) set is then optimized to improve the sampling in all regions for a fixed computational cost. Since such an expression is not available for the computational cost of a TIS-simulation, we make the simplifying assumption that the cost of the entire simulation is independent of the particular interface positions for a preset number of interfaces, which is indeed approximately true as we will see later.

To find an optimum set of interfaces satisfying Eq. (9) one proceeds in an iterative fashion. Starting from a given, non-optimum set of interfaces \( \{\lambda_i\} \) the goal is to determine a new set of interfaces \( \{\lambda_i'\} \) that satisfy the condition of Eq. (9). As suggested by Borrero and Escobedo,\(^7\) this repositioning of the interfaces can be achieved by first defining an interpolation function \( f(\lambda) \) expressed in terms of the conditional probabilities \( P(\lambda_{i+1} | \lambda_i) \). There is no unique choice of this function, but it should be monotonic in order to provide a one-to-one correspondence between \( f \) and \( \lambda \), and it should not depend on the position and the number of the interfaces. A practical choice for \( f(\lambda) \) is\(^7\)

\[
f(\lambda_i) = \frac{\sum_{j=1}^{i} \ln P(\lambda_{j+1} | \lambda_j)}{\sum_{j=1}^{n} \ln P(\lambda_{j+1} | \lambda_j)}, \quad i = 1, \ldots, n. \tag{10}
\]

This function is strictly defined only for the discrete values \( \lambda_i \), but it can be easily extended to all values of \( \lambda \) in the interval \([\lambda_1, \lambda_n]\) by interpolation. Based on the function \( f(\lambda) \), the procedure to find an optimum set of interfaces consists of the following steps. First, a TIS simulation is carried out with an arbitrary, non-optimum set of interfaces \( \lambda_i \). The conditional probabilities \( P(\lambda_{i+1} | \lambda_i) \) computed in this first TIS simulation are then used to determine the function \( f(\lambda_i) \) at the positions \( \lambda_i \) according to Eq. (10). Note that the initial staging should be able to produce an estimate for \( P(\lambda_B | \lambda_1) \) (i.e., \( P(\lambda_{i+1} | \lambda_i) > 0 \) for all \( \lambda_i \)) such that the monotonic \( f(\lambda) \) function can be constructed. The new and optimized values \( \lambda_i' \) are computed by first determining the values of \( f \) corresponding to the desired values of \( P(\lambda_{i+1} | \lambda_i) \) as determined from Eq. (9), and then inverting the interpolated function at these values. This procedure can be iterated if necessary.

The optimality condition of Eq. (9) can be satisfied by varying the conditional probabilities \( P(\lambda_{i+1} | \lambda_i) \) or the number of trajectories \( N^{(A \rightarrow i)} \) sampled at each interface, or both of these quantities simultaneously. Hence, three schemes for the \( \lambda \) staging optimization are possible:

1. For a fixed number \( n \) of interfaces (interfaces 0 and \( n + 1 \), which correspond to the boundaries of regions \( A \) and \( B \), as well as interface 1 are fixed such that only \( n - 1 \) interfaces can be moved) and constant number \( N^{(A \rightarrow i)} \) of sampled trajectories one can reposition the interfaces such that uniform conditional probabilities \( P(\lambda_{i+1} | \lambda_i) \) with

\[
P(\lambda_{i+1} | \lambda_i) = P(\lambda_B | \lambda_1) \tag{11}
\]

are achieved.

2. For a given constant value of \( P(\lambda_{i+1} | \lambda_i) = p \) and constant \( N^{(A \rightarrow i)} \), one can determine the optimum number of interfaces, \( n = \ln[P(\lambda_B | \lambda_1)] / \ln p \), and their locations.

3. For a fixed number of interfaces \( n \) and a given set of conditional probabilities \( P(\lambda_{i+1} | \lambda_i) \), one can also attain an optimum sampling by choosing the numbers \( N^{(A \rightarrow i)} \) satisfying condition Eq. (9); i.e., \( N^{(A \rightarrow i)} = N_S / P(\lambda_{i+1} | \lambda_i) \). Thus, in this approach one distributes the numerical effort in an optimum way for fixed interfaces rather than moving the positions of the interfaces.

In this work, we use schemes 1 and 2 for optimizing the \( \lambda \)-staging.
III. APPLICATIONS

In this section, we demonstrate the interface optimization using the transition between two minima on a two-dimensional potential energy surface and the dipole flip of icelike water inside a narrow pore as illustrative examples.

A. Two-dimensional potential energy surface

We first test the optimization procedure for the transition of a single particle between two minima on the 2D potential energy surface given by

\[ V(x, y) = \frac{1}{6} \left[ 4(1 - x^2 - y^2)^2 + 2(x^2 - 2)^2 \right. \]

\[ \left. + [(x + y)^2 - 1]^2 + [(x - y)^2 - 1]^2 - 2 \right]. \]  

(12)

Here, \( x \) and \( y \) denote the Cartesian coordinates of the particle. The particle is confined to the interval \([-1, 1]\) in \( x \)- and \( y \)-direction and the particle is reflected back into this square region when it attempts to cross its boundary. Reduced units are used throughout. A contour plot of this potential energy surface, which has been used previously to test the adaptive optimization \( \lambda \)-staging algorithm for forward flux sampling simulations, is shown in the Fig. 1(a). This energy landscape has two minima centered at \((-1,0)\) and \((1,0)\), respectively, separated by a barrier located at \( x = 0 \) with saddle points at \((0,-1)\) and \((0,1)\), respectively. In going from \( A \) to \( B \) through one of the saddle points the particle has to cross an energy barrier of \( \Delta E = 1 \). The motion of the particle on the potential energy surface is governed by the Langevin equation with particle mass \( m = 1 \) and friction coefficient \( \gamma = 2.5 \), integrated with a time step \( \Delta t = 0.01 \).

At low temperatures, the particle spends most of the time fluctuating about the potential energy minima and transitions between the minima are rare. Accordingly, the initial region is defined by \( \lambda_A = x \leq -0.8 \) and the final region by \( \lambda_B = x \geq 0.8 \). The \( x \)-coordinate serves as the order parameter, \( \lambda(x, y) = x \), used to define the interfaces, which are orthogonal to the \( x \)-axis. TIS runs were carried out as a series of \( M = 10 \) blocks, each consisting of \( N(\Delta t) = 10,000 \) sampled trajectories, at a reciprocal temperature \( \beta = 1/k_B T = 10 \), where \( T \) is the temperature and \( k_B \) is the Boltzmann constant. The maximum momentum displacement at the shooting point was \( \delta p = 0.2 \). After each block of the TIS simulation, the adaptive optimization \( \lambda \)-staging algorithm described in Sec. II B was employed to reposition the interfaces using the current \( P(\lambda_{i+1}|\lambda_i) \) versus \( \lambda \) data. The initial positions of the 9 interfaces, orthogonal to the \( x \) axis, are listed in Table I and are shown in Fig. 1(a) as dashed blue lines.

For this particular system, the interface positions \( \{\lambda_i\} \) converge to their optimum values already after the first block such that further optimization steps do not yield any additional efficiency increase. The optimum interfaces \( \{\lambda_i\}_1 \), obtained via scheme 1 of Sec. II B for \( n = 9 \) interfaces and \( N(\Delta(t)=10,000 \) trajectories, are listed in Table I and are shown as solid red lines in Fig. 1(a). Note that only \( n - 1 \) interfaces are moved during the optimization procedure because the boundaries of region \( A \) (interface 0) and region \( B \) (interface \( n \)) as well as the location of \( \lambda_i \) are fixed. Here and in the following the subscripts 1 and 2 next to the set of optimum interfaces \( \{\lambda_i\}_1 \) and \( \{\lambda_i\}_2 \) refer to optimization approach 1 and 2 of Sec. II B, respectively. From TIS simulations using the unoptimized interfaces \( \{\lambda_i\} \) and the optimized interfaces \( \{\lambda_i\}_1 \) listed in Table I, we estimated a reaction rate constant of \( k_{AB} = 3.2 \pm 0.1 \times 10^{-6} \) and \( k_{AB} = 3.4 \pm 0.2 \times 10^{-6} \), respectively.

It is interesting to note that in their optimum arrangement the interfaces are concentrated in the region preceding the transition states and the conditional probabilities have a value of \( P(\lambda_{i+1} | \lambda_i) \approx 0.45 \). In particular, interface \( n \), the last interface before region \( B \), is located at \( x = 0 \), the \( x \)-position of the saddle points. Under certain conditions, discussed in
TABLE I. Optimized interface positions \( \{ \lambda \}_1 \) obtained via scheme 1 of Sec. II B and \( \{ \lambda \}_2 \) obtained via scheme 2 of Sec. II B, and conditional probabilities \( P(\lambda_{i+1} | \lambda_i) \) for the 2D energy surface shown in Fig. 1(a). The optimized sets reported here were obtained after ten iterations of the adaptive \( \lambda \)-optimization algorithm. However, note that our derived condition for optimum staging in Eq. (9) does not fully specify the \( P(\lambda_{i+1} | \lambda_i) \) values since we could simultaneously change the \( P(\lambda_{i+1} | \lambda_i) \) and \( N^{(A \rightarrow B)} \) values to satisfy it. The average shooting acceptance ratio for all TIS simulations using the initial, and optimized \( \{ \lambda \}_1 \) and \( \{ \lambda \}_2 \) sets was \( \geq 0.3 \). We found that one single optimization iteration is sufficient to reach the optimized interface set for the simple toy system studied here.

| \( i \) | Initial \( \{ \lambda \}_i \) staging \( \{ \lambda \}_i \) \( P(\lambda_{i+1} | \lambda_i) \) | Optimized \( \{ \lambda \}_1 \) staging \( \{ \lambda \}_1 \) \( P(\lambda_{i+1} | \lambda_i) \) | Optimized \( \{ \lambda \}_2 \) staging \( \{ \lambda \}_2 \) \( P(\lambda_{i+1} | \lambda_i) \) |
|---|---|---|---|---|
| 0 | \(-0.80(=\lambda_A)\) | ... | \(-0.80(=\lambda_A)\) | ... |
| 1 | \(-0.70\) | 0.17 | ... | ... |
| 2 | \(-0.65\) | 0.15 | ... | ... |
| 3 | \(-0.54\) | 0.20 | ... | ... |
| 4 | \(-0.36\) | 0.27 | ... | ... |
| 5 | \(-0.18\) | 0.46 | ... | ... |
| 6 | 0.20 | 0.86 | ... | ... |
| 7 | 0.38 | 0.89 | ... | ... |
| 8 | 0.56 | 1.00 | ... | ... |
| 9 | 0.74 | 1.00 | ... | ... |
| 10 | \(0.80(=\lambda_B)\) | ... | \(0.80(=\lambda_B)\) | ... |
| 11 | ... | ... | ... | ... |
| 12 | ... | ... | ... | ... |

The following, this interface is indeed expected to coincide with the transition state surface. Consider a situation where the number of interfaces has been selected such that the conditional probabilities have a value of \( P(\lambda_{i+1} | \lambda_i) \approx 0.5 \) for all \( i \). If the order parameter \( \lambda(r) \) is a good reaction coordinate, all configurations of the surface defined by \( \lambda(r) = \lambda_i \) have the same probability \( p_B \), called committor,\textsuperscript{14-16} to reach region \( B \) before reaching region \( A \). In this case, and provided that the dynamics is diffusive, the conditional probability for the last interface before region \( B \) equals the committor \( p_B \) for configurations on that surface, \( P(\lambda_{n+1} | \lambda_n) = P(\lambda_B | \lambda_n) = p_B \). In particular, a conditional probability \( P(\lambda_B | \lambda_n) \) close to 1/2 implies that configurations on the \( \lambda_i \) interface have equal probability to evolve towards the initial region \( A \) or the final region \( B \). In other words, the committor of these configurations is \( p_B \approx 0.5 \) such that interface \( n \) is close to the transition state surface. Thus, in an interface optimization with \( P(\lambda_{i+1} | \lambda_i) \approx 0.5 \) the last mobile interface is automatically positioned in the transition state region.

Statistical analysis of the TIS simulation for the 2D model system indicates that the efficiency of the rate constant calculation is improved considerably by the optimization of the interface locations. The statistical errors \( \nu \) in the estimated rate constant \( k_{AB} \), as quantified by the variance of the crossing probability \( P(\lambda_B | \lambda_1) \), obtained for the initial and the optimized interface positions, are shown in Fig. 2 as a function of the CPU time required to carry out the simulation. All simulations were performed on the same machine. In these simulation, each block consisting of \( N^{(A \rightarrow B)} = 10000 \) sampled trajectories produces an estimate of the crossing probability \( P(\lambda_B | \lambda_1) \) such that the variance \( \left| P(\lambda_B | \lambda_1) \right|^2 - P(\lambda_B | \lambda_1)^2 \) can be determined. Here, the overbar denotes an average over the \( M \) blocks. As can be inferred from Fig. 2, the optimization procedure leads to a considerable increase of the computational efficiency of the TIS simulation by a decrease of the statistical error for the same CPU time, see Eq. (4). Compared to the initial interface positions, the optimized interfaces lead to a reduction of the statistical error by a factor of \( \nu_{\text{optimized}} / \nu_{\text{unoptimized}} \approx 7 \), implying that to reach a given target accuracy in the rate constant, the optimized simulation requires only about 15% of the numerical effort of the unoptimized simulations. The computational cost of the optimized \( \{ \lambda \}_1 \) simulation is decreased by about 10%, because the optimized interfaces are placed with higher density in the bottleneck regions between the initial state and the transition state region, leading to shorter, and therefore computationally less costly trajectories. Hence, the overall

FIG. 2. Statistical error \( \nu \) in the estimated rate constant \( k_{AB} \) versus CPU time for TIS simulations of the transition on the 2D potential energy surface. Solid line with circles: initial staging; dashed line: optimized staging \( \{ \lambda \}_1 \) obtained via scheme 1 of Sec. II B; solid line: optimized staging \( \{ \lambda \}_2 \) obtained via scheme 2 of Sec. II B.
efficiency for the optimized TIS simulation increases by a factor of \(\approx 8\).

The optimized set of interfaces \(\{\lambda_i\}_1\) shown in Fig. 1(a) was obtained by repositioning the interfaces to satisfy the condition that the conditional probabilities \(P(\lambda_{i+1}|\lambda_i)\) are the same for all interfaces [see Eq. (11)]. In this approach the number of interfaces \(n\) is fixed in advance. As we mentioned in Sec. II B, however, one can obtain another set of optimized interfaces \(\{\lambda'_i\}_2\) by first specifying the value of the conditional probability \(P(\lambda_{i+1}|\lambda_i)\) and then determining the number \(n\) of interfaces and their optimum positions. We thus performed a second series of TIS optimization simulations for \(P(\lambda_{i+1}|\lambda_i) = [P(\lambda_B|\lambda_i)]^{1/\nu} = 0.5\), starting from the initial set of \(n = 9\) interface listed in Table I. The number of interfaces, \(n = \ln[P(\lambda_B|\lambda_1)]/\ln p\), was determined using the crossing probability \(P(\lambda_B|\lambda_i) = 5.06 \times 10^{-4}\) computed in the unoptimized TIS simulation. The optimized interface positions \(\{\lambda'_i\}_2\) obtained after approximately \(M = 10\) iterations with \(n = 11\) for \(P(\lambda_{i+1}|\lambda_i) = 0.5\) are shown in Table I along with the corresponding conditional probabilities \(P(\lambda_{i+1}|\lambda_i)\). The statistical error in the estimated value of \(k_{AB}\) calculated in a TIS simulation with this optimized set of interfaces is \(\nu \approx 0.35\). Hence, in this case the statistical error is reduced by a factor of \(\frac{\nu_{\text{unoptimized}}}{\nu_{\text{optimized}}} \approx 16\) with respect to the TIS simulation with the unoptimized set of interfaces, while the computational cost was approximately the same \(\frac{C_{\text{unoptimized}}}{C_{\text{optimized}}} \approx 0.95\). Compared to the unoptimized TIS simulation the computational cost of the optimized \(\{\lambda'_i\}_2\) simulation is increased by about \(10\%\) due to the additional interfaces introduced during the optimization. Hence, the overall efficiency for the optimized TIS simulation increases by a factor of \(\approx 15\).

Note that the optimized sets of interface positions \(\{\lambda_i\}_1\) and \(\{\lambda'_i\}_2\), listed in Table I, satisfy the condition for optimum staging of Eq. (9) by repositioning the interfaces for a preset number of interfaces, \(n = 9\), and fixed \(P(\lambda_{i+1}|\lambda_i) = 0.5\) (such that the last interface is positioned at the transition state), respectively. For both optimized stagings, we observed a significant improvement of the overall efficiency. However, we cannot conclude that a constant conditional probability of 0.45 or 0.5 between two adjacent interfaces should be most efficient. To determine the optimum \(P(\lambda_{i+1}|\lambda_i) = p\) value that maximizes the overall efficiency \(e\) in Eq (4) one would need to determine the CPU time for a series of TIS-simulations, such that the maximum of the \(e\) versus \(P(\lambda_{i+1}|\lambda_i) = p\) curve can be obtained. For instance, for the optimization of TIS simulations, van Erp and Bolhuis\(^5\) assumed that the total computational time \(t_{\text{CPU}} \sim \sum_i n(n-1)/2\) of a TIS-simulation can be estimated as a sum of individual contributions for each ensemble, where the average path length for each ensemble, \(L_i \sim i(\lambda_i - \lambda_0)/n\), is proportional to the separation of the order parameter between the two stable states. Using this analytical expression for the total computational cost, they found the general condition that a \(P(\lambda_{i+1}|\lambda_i) \approx 0.2\) value for all \(i\) leads to optimum TIS efficiency.\(^4\) However, as they also argued, an assumption for the computational cost independent of the particular interface positions, location of the shooting points, and the crossing probabilities may not be valid for all systems (e.g., diffusive barrier crossing systems).\(^4\) Moreover, note that our derived condition for optimum staging in Eq. (9) does not fully specify the \(P(\lambda_{i+1}|\lambda_i)\) values, because we could simultaneously change the \(P(\lambda_{i+1}|\lambda_i)\) and \(N^{(A \to B)}\) values to satisfy it.

The sampling efficiency of a TIS simulation can be further increased if, in addition to an optimum placement of the interfaces, a biased selection of shooting points is used, as suggested by Jurasek and Bolhuis.\(^7\) In this approach, shooting points are selected with higher probability near the respective interface at \(\lambda\) according to the distribution

\[
p(\tau) = \frac{\exp[-(\lambda(\tau) - \lambda_i)/\sigma^2]}{\sum_{\tau'=0}^{\tau-M} \exp[-(\lambda(\tau') - \lambda_i)/\sigma^2]},
\]

Here, \(\tau\) numbers the time slice along the current pathway of length \(L\) and \(\lambda(\tau)\) is the value of the order parameter \(\lambda\) at time slice \(x_\tau\). The parameter \(\sigma\) controls how strongly the shooting point is biased to lie close to interface \(i\). Selecting shooting points in this way increases the number of trajectories of the form \(\lambda_A \to \lambda_i \to \lambda_B\) or \(\lambda_A \to \lambda_i \to \lambda_{i+1}\), thus improving the acceptance rate and the efficiency of the TIS simulation. Shooting points near region \(A\), which often lead to rejected trajectories, are avoided by the bias. In TIS simulations carried out for the transition in the 2D model with a bias width of \(\sigma = 0.2\), the biased selection of shooting points reduces the statistical error in the rate constant \(k_{AB}\) by a factor of about 3 both for the optimum interfaces \(\{\lambda_i\}_1\) and \(\{\lambda'_i\}_2\).

### B. Ordered water chains inside carbon nanotubes

To investigate the efficiency increase obtained by optimizing the interfaces in a TIS simulation of a higher dimensional system, we studied the flip of the total dipole of water inside a narrow pore of diameter in the nanometer regime. Under such confinement, which can be realized in single-walled carbon nanotubes (CNT), water forms icelike structures consisting of stacked rings of water molecules.\(^18\) \(^20\) Within and between rings, water molecules are held together by hydrogen bonds. An example of such an icelike structure inside a (9,8) carbon nanotube is show in Fig. 3. For this particular pore width, the rings consist of 5 water molecules, each of which donates and receives one intra-ring hydrogen bond and one inter-ring hydrogen bond. In the direction of the pore axis, water molecules form ordered chains (see Fig. 3), in

![FIG. 3. Schematic representation of the stacked 5-ring water structure inside a carbon nanotube. (Top) Side view; (bottom) view along the pore axis. At the left-hand side end of the CNT (x = 0), the 5-ring structure is well established. On the right-hand side edge, however, a missing water molecule causes large fluctuations disturbing the formation of perfect 5-membered rings. The configuration shown here has a positive total dipole moment, because three ordered chains of hydrogen bonded water molecules are oriented in positive axis-direction while only two chains point into the negative direction.](image)
which hydrogen bonds are oriented in the same direction. Due to dipole-dipole interactions between the water molecules, neighboring chains tend to point in opposite directions, such that for a system of rings consisting of an even number of water chains, half of the chains point into one direction and half in the other direction forming a anti-ferroelectrically ordered structure. As a result, such structures do not carry a net dipole moment. In contrast, for an icelike structure consisting of rings with an odd number of water chains, the perfect anti-ferroelectric order is frustrated such that the dipole moment of the ordered chains cannot compensate each other and a net dipole moment arises. Due to symmetry, this net dipole moment has two possible orientations, parallel or anti-parallel to the pore axis. In this section, we study the kinetics of the transitions between these two orientations with opposite dipole moment for the pentagonal stacked ring structure in a (9,8) carbon nanotube.

The system considered here, shown schematically in Fig. 3, consists of \( N_w = 124 \) water molecules described by the TIP3P model with a Lennard-Jones-cutoff of 15 Å and confined to the interior of a (9,8) carbon nanotube with a length of 7.25 nm. The nanotube is not modelled with atomistic resolution, but rather replaced by a cylindrically symmetric effective potential obtained in earlier work\(^{21} \) from the radial density profile of a single water molecules in a (6,6) carbon nanotube. In this type of carbon nanotube, which has a diameter of 8.1 Å, water forms single file chains and the pore potential is given by

\[
V_{sf}(r) = a_2 r^2 + a_4 r^4 + a_6 r^6 + a_8 r^8, \quad (14)
\]

where \( r \) is the oxygen-axis distance and the potential parameters are \( a_2 = -0.2281 \) kcal mol\(^{-1} \) Å\(^{-2} \), \( a_4 = 1.09 \) kcal mol\(^{-1} \) Å\(^{-4} \), \( a_6 = 0.2341 \) kcal mol\(^{-1} \) Å\(^{-6} \), and \( a_8 = 0.3254 \) kcal mol\(^{-1} \) Å\(^{-8} \). For wider carbon nanotubes, the pore potential is given by

\[
V_{sf}(r) = \begin{cases} 
0 & \text{for } r \leq r_0, \\
V_{sf}(r - r_0) & \text{for } r > r_0,
\end{cases} \quad (15)
\]

such that the pore walls are felt by the oxygen atoms only beyond \( r_0 \). The (9,8) carbon nanotube considered here has a pore diameter of 11.7 Å corresponding to \( r_0 = 1.8 \) Å. The water molecules are prevented from diffusing away in axial directions by flat soft walls orthogonal to the pore axis. The confining potential felt by the oxygen atoms is given by

\[
V_{wall}(x) = \begin{cases} 
0.4x^2 - 0.3x^3 & \text{for } x < 0, \\
0 & \text{for } 0 \leq x \leq L, \\
0.4(L-x)^2 - 0.3(L-x)^3 & \text{for } x > L
\end{cases} \quad (16)
\]

where \( x \) is the oxygen position along the CNT axis and \( L = 7.25 \) nm is the carbon nanotube length.

The system evolves at constant energy at a total energy corresponding to a temperature of roughly 250 K. The equations of motion were integrated using the velocity Verlet algorithm\(^{23} \) with a time step of 1.65 fs and the rigid bonds of the water molecules were handled with the RATTLE algorithm.\(^{24} \)

For this system we carried out a TIS simulation to study the transition from the stable state with positive dipole moment, state \( A \), to the state with negative dipole moment, state \( B \). In state \( A \), three of the five ordered, hydrogen bonded chains of water molecules point in the positive axis direction, while only two of them are oriented in the opposite direction resulting in a positive net dipole moment. For \( N_w = 124 \) water molecules, four of the chains have 25 molecules while one is formed by 24 molecules. Due to the missing molecule a well-defined 5-membered ring structure only occurs at the left end of the ice-structure while at its right end a four-ring of water molecules is formed (see Fig. 3). This perturbation to the perfect ring structure causes the dipole flipping event to occur preferentially through an L-defect propagating along one single chain from the left (\( x = 0 \)) to right edge of the pore.\(^{25} \) An L-defect, named in analogy to the L-defects observed in bulk hexagonal ice, occurs where the perfect orientational order of a hydrogen bonded water chain is interrupted by a molecule that donates two hydrogen bonds without accepting any from neighboring water molecules.\(^{21, 26} \) In our TIS simulations, we used the dipole moment per water molecule along the pore axis, \( \lambda_w \), as order parameter to define the interfaces. The momentum displacement at the shooting point had a fixed magnitude of \( \delta p = 5 \).

In Table II, we list the initial positions of the \( n = 8 \) interfaces used to partition configuration space for the dipole flip of the pentagonal ice carbon nanotube. The initial and final regions, \( A \) and \( B \), were defined by \( \lambda_A = \delta_w \geq 0.16 \) and \( \lambda_B = \delta_w \leq -0.12 \), respectively. Note that despite the symmetry of the CNT, we defined the upper limit of region \( B \) as \( \delta_w = -0.12 \). We found that once the system reaches \( \delta_w = -0.12 \) it exhibits a water structure inside CNT, where three ordered chains of hydrogen bonded water molecules are oriented in negative axis-direction while only two chains point into the positive direction. TIS runs were then carried out as a series of \( M=10 \) blocks, each consisting of \( N^{(A \rightarrow B)} = 300 \) trajectories. Between blocks, the adaptive optimization \( \lambda \)-staging algorithm was employed to recalculate the number of interfaces and reposition them such that \( P(\lambda_{i+1} | \lambda_i) \approx 0.5 \) for all interfaces. The shooting probability defined in Eq. (13) was used to draw shooting points near the respective interfaces.

Table II includes the optimized interface parameters \( \lambda_i \) obtained after 10 iterations and the corresponding conditional probabilities \( P(\lambda_{i+1} | \lambda_i) \). Note that Table II also lists the average length of the trajectories and the shooting acceptance ratio for both the initial and optimized \( \lambda_i \) sets. The optimization has essentially converged after two iterations, as can be seen in Fig. 4(a) showing the function \( f(\lambda) \) of Eq. (10) used to redistribute the interfaces. Different initial sets for the interface positions were also tested, where one or two iterations were sufficient to obtain suitable convergence of the optimized staging (data not shown). Fig. 4(b) shows the interface positions \( \lambda_i \) as function of \( i \) at different stages of the optimization. From the TIS simulations with the optimized interfaces we obtained a rate constant of \( k_{AB} = 0.459 \pm 0.005 \) ns\(^{-1} \) for the dipole flip transition.

To determine how the optimum interface placement increases the efficiency of the TIS simulation, we performed a second series of \( M=10 \) blocks of \( N^{(A \rightarrow B)} = 300 \) trajectories each. In this TIS simulation, we used the initial set of
TABLE II. Initial interfaces \(\{\lambda_i\}\) (left) and optimized interfaces \(\{\lambda'_i\}\) (right) alongside with the corresponding conditional probabilities \(P(\lambda_{i+1}|\lambda_i)\) for the icelike structure of stacked 5-membered rings in a (9,8) carbon nanotube. \(L_i\) is the average length of the trajectories in picoseconds over the whole \(\lambda_i\) ensemble and \(\alpha_i\) denotes the shooting acceptance ratio for \(\lambda_i\) ensemble. Dipole moments per molecule, \(\lambda = \delta_n\), are given in units of Å. During the optimization, both the number \(n\) of the interfaces as well as their positions were varied to obtain a desired constant \(P(\delta_{i+1}|\delta_i) = |P(\delta_B|\delta_1)|^{1/n} \approx 0.5\). The optimized interfaces \(\{\lambda'_i\}\) reported here were obtained after \(M = 10\) iterations. However, two single iterations are sufficient to reach the optimized values \(\{\lambda'_i\}\) (see Fig. 4).

<table>
<thead>
<tr>
<th>(i)</th>
<th>({\lambda_i}) staging</th>
<th>({\lambda'_i}) staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0)</td>
<td>0.160 ((=\lambda_A))</td>
<td>0.160 ((=\lambda_A))</td>
</tr>
<tr>
<td>(1)</td>
<td>0.120</td>
<td>0.120</td>
</tr>
<tr>
<td>(2)</td>
<td>0.105</td>
<td>0.105</td>
</tr>
<tr>
<td>(3)</td>
<td>0.095</td>
<td>0.099</td>
</tr>
<tr>
<td>(4)</td>
<td>0.080</td>
<td>0.091</td>
</tr>
<tr>
<td>(5)</td>
<td>0.065</td>
<td>0.082</td>
</tr>
<tr>
<td>(6)</td>
<td>0.040</td>
<td>0.072</td>
</tr>
<tr>
<td>(7)</td>
<td>0.000</td>
<td>0.060</td>
</tr>
<tr>
<td>(8)</td>
<td>(-0.040)</td>
<td>0.045</td>
</tr>
<tr>
<td>(9)</td>
<td>(-0.120) ((=\lambda_B))</td>
<td>0.015</td>
</tr>
<tr>
<td>(10)</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

The interfaces listed in Table II without optimization between the blocks, i.e., both the number as well as the positions of the interfaces remained fixed throughout the simulation. This set of simulations yielded a rate constant value of \(k_{AB} = 0.437 \pm 0.02\) ns\(^{-1}\).

Compared to the unoptimized TIS simulation the computational cost of the optimized simulation is increased by about 10% due to the additional interface introduced during the optimization. The statistical error \(\nu\) in the rate constant calculation of the optimized simulation, however, is reduced by about 60% leading to an overall efficiency increase by a factor of \(\approx 2\).

IV. FINAL REMARKS

In this work, we extended the adaptive \(\lambda\)-optimization algorithm, proposed by Borrero and Escobedo,\(^7\) for optimizing the interface placement in TIS simulations. The optimization algorithm seeks to reallocate the computational effort in order to reduce the statistical error in the estimate of the rate constant. We demonstrated the optimization procedure for the transition between two energy minima on a simple 2D potential energy surface and for the dipole flip transition of an icelike water structure encapsulated in the cavity of a narrow carbon nanotube. For these systems, the optimization yielded an efficiency increase ranging from a factor of 2 for the dipole transition to a factor of 8-15 for the 2D potential energy surface. Moreover, we showed for the CNT example that two iterations were sufficient to obtain suitable convergence of the optimum phase staging. Hence, for complex systems where path sampling simulations are computationally costly, one or two iterations should be enough to optimize the sampling and staging. Thus, the optimization procedure suggested here can lead to a considerable efficiency increase and will be useful.
to carry out well-balanced parallel TIS simulations. Finally, we foresee that the proposed optimization algorithm can be easily extended to other interface-based path sampling methods, such as partial path transition interface sampling which is most suitable to treat diffusive crossing barrier systems.

TIS simulations carried out for the optimized placement of interfaces can also be combined with the likelihood maximization method to extract useful information on the mechanistic details of complex transitions. In particular, a strategic \( \lambda \)-staging can be used in conjunction with the biased selection of shooting points to obtain committor data from which the reaction coordinate can be estimated. This type of analysis will be the subject of future studies.

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