Due to the time scale problem, rare events are not accessible by straight forward molecular dynamics. The presence of multiple reaction channels complicates the problem even further. The feasibility of the standard free energy based methods relies strongly on the success in finding a proper reaction coordinate. This can be very difficult task in high-dimensional complex systems and even more if several distinct reaction channels exist. Moreover, even if a proper reaction coordinate can be found, ergodic sampling will be a challenge. In this article, we discuss the recent advancements of path sampling methods to tackle this problem. We argue why the path sampling methods, via the transition interface sampling technique, is less sensitive to the choice of reaction coordinate. Moreover, we review a new algorithm, parallel path swapping, that can dramatically improve the ergodic sampling of trajectories for the multiple reaction channel systems.

PACS numbers:

I. INTRODUCTION

Path sampling has shown to be efficient tool to study rare events that are not accessible by straight forward molecular dynamics (MD). The principal idea behind the method \[1\] is to reduce the superfluent exploration of the stable states and to generate trajectories that have a high chance to become reactive. Via the transition interface sampling (TIS) method \[2, 3, 4, 5\], sets of trajectories can be generated that progressively climb across the barrier towards the product state. Besides the rate of the reaction, the TIS path ensembles allow to analyze the mechanism. Each TIS simulation in the series give a correct distribution of pathways that reach a certain level towards reactivity. Some of them will fail to reach a next level and some of them will successfully make a step further. Therefore, these path ensembles yield a treasure of information for analyzing complex reaction mechanisms in a very intuitive way. The main TIS equation relates the reaction rate with a flux through a surface closely to the reactive state time the overall crossing probability

\[
k_{AB} = f_A P_A(\lambda_B | \lambda_A). \tag{1}
\]

The flux \(f_A\) is simply the number of crossings with surface \(\lambda_A\) per unit time. \(P_A(\lambda_B | \lambda_A)\) is the probability that whenever the surface \(\lambda_A\) is crossed, the system will go all the way over the barrier to cross the surface \(\lambda_B\) at the other side. The surfaces are generally defined by a parameterization using a single parameter called reaction coordinate (RC) or order parameter. The RC can be any non-linear function of all particle positions and velocities in the system \[30\]. The surface (or interface) \(\lambda\) is then simply defined as the collection of phase points for which this function is exactly \(\lambda\). Typical examples of RCs are distances of bonds that have to broken or formed, the size of the largest solid cluster in nucleation studies, or the number of native bonds for protein folding. By convention, we assume that \(\lambda_A < \lambda_B\). It is important to realize that the reaction rate \(k\) does not depend on the choice of the function RC or on the values \(\lambda_A\) and \(\lambda_B\) as long as they obey some very basic principles. That is, each trajectory from \(\lambda_A\) to \(\lambda_B\) should be a true reactive event of the reaction of interest. In addition, the chance, that the system quickly returns to \(\lambda_A\) after \(\lambda_B\) is crossed, should be of the same order as that of an independent reverse reaction.

\(f_A\) can be computed by straight-forward MD. \(P_A(\lambda_B | \lambda_A)\) is very small and therefore difficult to compute. However, if we define a set of interfaces in between with \(\lambda_0 = \lambda_A, \lambda_n = \lambda_B, \) and \(\lambda_i < \lambda_{i-1}\), we can invoke following exact factorization:

\[
P_A(\lambda_B | \lambda_A) = \prod_{i=0}^{n-1} P_A(\lambda_{i+1} | \lambda_i). \tag{2}
\]

Here, \(P_A(\lambda_{i+1} | \lambda_i)\) is a history dependent conditional crossing probability that is much higher than \(P_A(\lambda_B | \lambda_A)\) and, therefore, much easier to compute. It equals the probability that, given the system is about to cross \(\lambda_i\) for the first time since its last crossing with \(\lambda_A\), it will cross \(\lambda_{i+1}\) as well before \(\lambda_A\). Computing this factor can be done by generating a representative set of trajectories that start at \(\lambda_A\), cross \(\lambda_i\), and end at either \(\lambda_A\) or \(\lambda_{i+1}\). The fraction that ends at \(\lambda_{i+1}\) equals \(P_A(\lambda_{i+1} | \lambda_i)\). Recent TIS simulations employ a somewhat different ensemble. They consider all possible pathways that start at \(\lambda_A\), end at either \(\lambda_A\) or \(\lambda_B\), and have at least one crossing with \(\lambda_i\). \(P_A(\lambda_{i+1} | \lambda_i)\) is then the fraction that crosses \(\lambda_{i+1}\). Generating this set is only slightly more expensive as most trajectories will end at \(\lambda_A\) anyway. However, this approach makes it much easier to initialize the TIS parameters, such as the interface positions, while running one path simulation after the other in the simulation series. Moreover, the implementation of the new path swapping technique is much more straightforward when these ensembles are used. Of course, the crucial point is how to generate these trajectories. In principal we could simply run a MD trajectory and cut out the pieces of interest, but then our efficiency would be as bad as MD. Luckily, Dellago et al. developed efficient
Monte Carlo moves to generate these trajectories within the context of transition path sampling (TPS) [6]. The algorithm only requires to provide a single trajectory that satisfies the conditions. The principal MC move, called shooting, picks a random timeslice of the old trajectory, changes the velocities by a small amount, and integrates the equations of motion backward and forward in time to obtain a new trajectory. This trajectory can be accepted if it also satisfies the opposed conditions. The MC move in TIS is a slight adaptation of this shooting move to allow flexible path lengths (for a graphical illustration of the TIS shooting algorithm see [7]). This flexible path length is a strong improvement upon the original TPS algorithm. The trajectories in TIS will on average be shorter than in TPS. In addition, TIS does not introduce any systematic error as the small fraction of long trajectories is also taken into account. These will usually lie outside the range of path lengths one would consider in TPS. Other improvements are that the TIS formulation of the reaction rate is less sensitive to recrossings and that TPS shifting moves have become redundant in the TIS algorithm.

The TIS algorithm has been successfully applied to several systems ranging from protein folding [8], nucleation [9], micelle fusion and fission [10], and DNA denaturation [11]. Moreover, the TIS theory has initiated the development of several new path sampling methods such as the partial path TIS (PPTIS) [12] and forward flux sampling (FFS) [13]. PPTIS was especially designed for diffusive barrier crossings. It uses a history-loss assumption to reduce the path length even further. FFS is exact, like TIS, but uses another type of MC move in which one integrates the equations of motion only forward in time. The advantages of FFS is that it works for both equilibrium and out of equilibrium systems and that the dynamics do not necessarily have to be reversible. The disadvantage is that FFS introduces much stronger correlations between data points. This has a negative effect on the efficiency of the method, which can become extreme if the dynamics bear a strong deterministic character or when the RC is not well chosen [14]. Both PPTIS and FFS are based on Eqs. (1) and (2).

In this article we will discuss the computational challenging problem of multiple reaction channels. This problem is quite generic for any transition that involves many important degrees of freedom and it poses several difficulties. First of all it is extremely difficult to derive good RCs (like committor surfaces [15, 16]) for such a system that can be efficiently be used in a free energy based approach. Therefore, one would either need a systematic approach to obtain feasible RCs or a method that is much less sensitive to the choice of RC than the standard methods. Second, in order to explore one channel after the other, one needs a MC sampling that is highly nonlocal. Finally, the method should be very flexible and able to let the nonlocal MC moves coincide with a high rate of acceptance. We will show that TIS encompasses both the required insensitivity to the RC and the nonlocal character of shooting moves. Moreover, using the additional new technique of parallel path swapping (PPS), we can also fulfill the last requirement up to a very satisfactorily level. This results in a very efficient approach to treat multiple reaction channel systems. This article is organized as follows. In Sec. II we discuss the issue of RC sensitivity for TIS and related methods. In Sec. III we introduce the new PPS technique and review recent results, based on this method, for the DNA denaturation [11]. We end with conclusions in Sec. IV.

II. REACTION COORDINATE DEPENDENCE

The problem of finding suitable RCs in high-dimensional complex systems has been an outstanding problem for several decades. The free energy based approaches, pioneered by Wigner [17], Eyring [18], and Keck [19] and further developed by Bennett [20], Chandler [21], rely on a two-step approach. First the free energy as function of the proposed RC needs to be calculated using umbrella sampling (US) [22] or thermodynamic integration (TI) [23] techniques. From this, the free energy barrier can be derived and the transition state theory (TST) approximation for the rate. For complex systems, the TST approximation needs to be corrected for fast recrossing events by a dynamical factor $\kappa$ (with $0 < \kappa \leq 1$), called the transmission coefficient. If $\kappa$ is not too low, it can be accurately determined by releasing dynamical trajectories forward and backward in time from the top of the free energy barrier. $\kappa$ is then related to the fraction of trajectories that connect reactant state $A$ with product state $B$. In this way, one can determine $k$ exactly, independently to the choice of RC, and one obtains a set of reactive trajectories that can be subject of further investigations. However, if the RC fails to capture the actual mechanism, the vast majority of trajectories are either of the type $A \rightarrow A$ or $B \rightarrow B$ and $\kappa$ becomes immeasurably small. Illustrative for this effect are chemical reactions in solution which require considerable solvent rearrangements. The top of the free energy barrier, defined by a RC that does not include the solvent degrees of freedom, will either correspond to the situation where the solvent can easily incorporate the reactant or the product species. As result, both forward and backward dynamics will rapidly collapse to the same state. In addition, the evaluation of the free energy barrier itself becomes problematic. Considerable hysteresis will occur in US or TI when the system is dragged over the barrier from reactant to product state and back.

This RC problem was the main driving force to develop alternative methods like TPS [1]. Although it is quite evident that TPS can generate reactive trajectories quite efficiently using a simple type of RC, it is not so clear if the same is true for the actual reaction rate evaluation. Only recently, Ref. [14] really proved, by analytical results of a simple 2D model, that the TIS efficiency of the reaction rate calculation is much less sensitive to
an improper choice of the RC than free energy based methods. There are two reasons for this. First of all, as paths are global identities (the weight of a path does not depend on a single point), the sampling of paths instead of phase points can eliminate hysteresis effects [14]. Secondly, whereas free energy based methods apply important sampling approaches to configuration space only, hoping that the dynamical factor will be not too small, path sampling applies importance sampling techniques on the dynamical factor directly. The RC insensitivity is not generic for any type of path sampling method. It is valid for the original TPS method as well, but not for e.g. PPTIS or FFS [14]. We can also give a third reason which was not important for the 2D example studied in [14]. As the TIS/TPS shooting move is nonlocal, it should be able to circumvent barriers that are orthogonal to the RC. Indeed, a TPS water trimer study [24] revealed that the shooting algorithm was capable of finding two reaction mechanisms across different saddle points separated by a barrier higher than the total energy of the NVE simulation. An approach to enhance this effect is explained in the next section.

The different dependence on the RC of TIS and FFS, although based on the same equations, can be explained by the argument that Eq. (2) has two possible interpretations. The conditional crossing probabilities can be viewed as a kind of physical (non-Markovian) hopping probabilities to go from one interface to the other like climbing up a ladder. This interpretation is very close to the FFS implementation of Eq. (2). The alternative interpretation is that Eq. (2) simply corresponds to a multiplication of ratios between the number of paths contained by different sets: \( \mathcal{P}_A(\lambda_B | \lambda_A) = \frac{\# \text{paths} \in [n^+]}{\# \text{paths} \in [0]} \times \frac{\# \text{paths} \in [1]}{\# \text{paths} \in [2^+]} \times \frac{\# \text{paths} \in [3^+]}{\# \text{paths} \in [4]} \times \ldots \times \frac{\# \text{paths} \in [(n-1)^+]}{\# \text{paths} \in [n]} \), where \([i^+]\) defines the collection of paths that start at \( \lambda_A \) and have at least one crossing with \( \lambda_i \) before revisiting \( \lambda_A \) or ending at \( \lambda_B \). From this, it is directly clear that if we replace e.g. \([3^+]\) in this factorization by an arbitrary different set of trajectories, this still does not change the validity of the equation. This has an important implication. The final trajectory set \([n^+]\) can be fundamentally different than \([3^+]\). They do not necessarily have to resemble up to \( \lambda_3 \).

In Fig. 11 we give two simple examples for seven interfaces \( \{0_0, \ldots, 6_6\} \). Shown here are path survival diagrams. In Fig. 11 (top), we assume that only 1 out of the \( 10^6 \) trajectories that initially start at \( \lambda_A \) will reach \( \lambda_B \) and at each interface only 10% survives reaching the next one. Hence, if we would simply run straightforward MD trajectories, we would need at least \( 10^6 \) trajectories to hope for a single reactive event. Now, if we only run 100 trajectories per TIS (or FFS) ensemble, we expect that each time 10 trajectories will reach the next level. Our final result \( \mathcal{P}_A(\lambda_B | \lambda_A) = \prod_{i=1}^n \mathcal{P}_A(\lambda_i | | \lambda_{i-1}) = (10/100)^6 = 1 \cdot 10^{-6} \) is exactly identical to a perfect brute force calculation but using only 600 trajectories instead of \( 10^6 \) and having 10 fully reactive trajectories instead of only 1 in the end. This directly shows the orders of magnitude improvement of the path sampling simulations compared to MD. In a bit more elaborate calculation, one can show that the effective computational cost scales exponentially with the barrier height in brute force MD and only quadratically in TIS. This is similar to US using rectangular bias windows [14]. In Fig. 11 (bottom), we show a bit more complicated example with two channels. One is initially favorable but turns into a dead end. The paths gathered by TIS for the \([2^+]\) ensemble do not contain a single green path. Still, the product of the obtained crossing probabilities gives the right result.
Inside the reactant well, or to generate the bridging trajectory that is high in energy and thus likely rejected. Trajectories of non-locality of the shooting move and its ability to avoid being rejected. Alternatively, in order to make use of the standard shooting move is applied for a multiple reaction channel system. The trajectories of such a trajectory is very high in energy and will likely be rejected and we remain in the same channel. On the other hand, if we consider the trajectories of the [3+] ensemble, these are much higher in energy and can easily move from one channel to the other. It would be very useful if we could somehow make advantage of the high energy paths of the [3+] ensemble and the non-local shooting moves from inside the reactant well.

A very successful method in standard MC is the parallel tempering or replica exchange method [22]. In this method one performs several simulations in parallel at different temperatures. Then, with a certain frequency and acceptance probability the configurations at one temperature simulation is being swapped with a lower temperature simulation. The high temperatures will easily explore the rough free energy surface as they have a much lower probability to get trapped. The low temperature simulations will benefit from the exchange of information as they will be able to hop from one potential basin to another without having to cross the intermediate barriers physically. The combination of path sampling and parallel tempering has been used before [26], but the main disadvantage of this approach is that one needs to perform expensive additional simulations whose information is useless if one is interested in the reaction rate at one temperature alone. In addition, parallel tempering will not help to circumvent entropic barriers using the non-locality of the shooting move. However, if one realizes that the TIS method already consists of a series of simulations, it makes sense to introduce a swapping move between these [11].

In order to create the maximum flexibility of swapping moves at all levels, it is convenient to replace the initial MD simulation for the flux calculation by another type of path ensemble \( \{0^-\} \). These consists of all the paths that start at \( \lambda_A \), then go initially towards the negative direction, and finally end again at \( \lambda_A \). The initial flux can than be obtained from the average path lengths in the \( \{0^-\} \) and \( \{0^+\} \) ensemble:

\[
f_A = \left( \langle t_{0^{-}_{\text{path}}} \rangle + \langle t_{0^{+}_{\text{path}}} \rangle \right)^{-1},
\]

where \( \langle t_{0^{-}_{\text{path}}} \rangle, \langle t_{0^{+}_{\text{path}}} \rangle \) are the average path lengths in these ensembles. In this series of path ensembles, \( \{0^-\}, \{0^+\}, \{1^+\}, \ldots, \{(n-1)^+\} \}, \) the swapping move becomes extremely effective. Note that the swapping moves do not require any force calculations except for the swapping between \( \{0^-\} \) and \( \{0^+\} \) (see Fig. 3). Here, the last timestep of the old path in the \( \{0^-\} \) ensemble is used as initial point to generate a new trajectory in \( \{0^+\} \) by integrating the equation of motion forward in time. Conversely, the initial point of the old path in \( \{0^+\} \) is followed backward in time to generate a path in \( \{0^-\} \). The TIS

**III. PARALLEL PATH SWAPPING**

In Fig. 2 we depict the problems that can occur when the standard shooting move is applied for a multiple reaction channel system. The trajectories a and c of the \( \{1^+\} \) ensemble are situated in different channels of the potential energy barrier. It is not very likely that the shooting move will be able to connect these trajectories. It would require to generate a bridging trajectory b, but such a trajectory is very high in energy and will likely be rejected. Alternatively, in order to make use of the non-locality of the shooting move and its ability to avoid transversal barriers, we might want to shoot from inside the reactant well. However, such a point is not part of the paths of this ensemble that start at \( \lambda_A \). We might shift the \( \lambda_A \) interface more into the reactant well with the expense that all trajectories become longer and thus more expensive. However, even then we must be very lucky because if we fail to cross \( \lambda_1 \), this trajectory must be rejected and we remain in the same channel. On the other hand, if we consider the trajectories of the [3+] ensemble, these are much higher in energy and can easily move from one channel to the other. The flexibility of the TIS method. FFS which propagates other.

![Contour plot illustrating the multiple channel barrier](image)

**FIG. 2:** (color online) Illustration of the multiple channel barrier. Contour plot is shown below. Trajectories a and c are two possible trajectories in the \( \{1^+\} \) ensemble situated in two different channels. In order to find trajectory c from trajectory a, we would either need to shoot (with some luck) from inside the reactant well, or to generate the bridging trajectory b that is high in energy and thus likely rejected. Trajectories d and e are trajectories in the \( \{3^+\} \) ensemble. They are much higher in energy and can easily move from one channel to the other.

is a very important point to realize as it shows once more the flexibility of the TIS method. FFS which propagates trajectories only forward in time will not be able to recapture the green trajectories once they are lost. Hence FFS requires to sample much more trajectories at the initial interface ensembles or to devise a RC where this problem will not occur. Of course, in order to recapture the successful green pathway it is of eminent importance that the TIS shooting move will be able to make this transition. In the next section we show how PPS can be a very effective tool to enhance these transitions.
The effectiveness of this algorithm was illustrated in Ref. [11] for the denaturation transition of DNA using the mesoscopic Peyrard-Bishop-Dauxois (PBD) model [27]. In this model, the DNA molecule is represented by a sequence of one-dimensional particles representing the relative base-pair separations from the groundstate positions. Each particle is positioned in an external Morse potential describing the interaction of base-pairs of opposite strands. In addition, a first-neighbor anharmonic spring potential is used for the stacking interaction between bases of the same strand. The width and depth of the Morse potential are adapted to describe the weak AT or the strong GC interaction. Due to thermal fluctuations the hydrogen bonds between base-pairs of opposite strand can break, which corresponds to a particle moving on the plateau of the Morse potential. However, if the neighboring particles are still in the closed state, this particle will be rapidly pulled back into the stack. The fully denaturated state is achieved when all base-pairs move on Morse plateau after which the two DNA strands have no interaction anymore and can move to infinite distances. This event is very rare for the larger molecules and has a very complex dynamics as it can proceed via different path ways. The DNA molecule might initially open up at one end and propagate the opening through the molecule. Alternatively, a bubble in the middle might appear that continues to grow in both directions. Henceforth, the denaturation process is a typical example of a multiple reaction channel system and an accurate evaluation of the rate is quite a challenge for the larger molecules.

In Ref. [11] the dynamics of a 20 base-pair DNA molecule of AT bases was investigated by TIS with and without swapping. As RC, the base-pair separation of the base-pair with the smallest distance was used. In total eight interfaces \( \{ \lambda_0, \ldots, \lambda_7 \} \) were defined (for more details see Ref. [11]). The calculated rates rates were in good agreement 0.0492 ± 0.0062 and 0.0524 ± 0.0025 ns\(^{-1} \) for standard TIS and TIS with path swapping respectively. The latter has a significant lower error despite a much shorter simulation. A very accurate integration method [28] for quasi one-dimensional systems confirmed the path swapping result within a 0.6 % uncertainty.

A very instructive approach to quantify the efficiency of the individual simulations and the simulation in total is given in [14] by the introduction of so-called efficiency times \( \tau_{\text{eff}} \). These are defined as the number of force calculations required to obtain a statistical error equal to 1 in a given simulation. For the TIS simulations \([0^*], [1^*], \ldots\) these can be expressed as [14]:

\[
\tau_{\text{eff}}^{[i^*]} = \frac{1}{p_i} \xi_i L_i \mathcal{N}_i.
\]

Here, \( p_i = p_A(\lambda_{i+1}|\lambda_i) \) and \( L_i = (t_{\text{path}}^{[i^*]})/\Delta t \) with \( \Delta t \) the MD timestep. These are in principle independent to the simulation method. \( \xi_i \) is the ratio between the average cost of the simulation cycle and \( L_i \). \( \mathcal{N}_i \) is the effective correlation between trajectories.

Fig. 4 shows the five parameters in Eq. (4) for the seven TIS path ensembles using standard TIS and path swapping. The results for \( \xi_i \) and \( L_i \) are the same as expected. The values for \( \xi_i \) show that the average cost per cycle is reduced by a factor 1.5 for the \([0^*]\) and by a factor 2 for the \([i^*], i > 0\), simulations. This is due to the swapping moves that do not require any force calculations except for \([0^*] \leftrightarrow [0^*]\). However, more importantly is the dramatic reduction of \( \mathcal{N}_i \). The large values of \( \mathcal{N}_i \) in the standard TIS simulations are directly related to the problems of ergodic sampling when the system gets stuck for a long time in one specific reaction channel. Most spectacular is the reduction in the \([0^*]\) ensemble by more than two orders of magnitude. The reduction in both \( \xi_i \) and \( \mathcal{N}_i \) is reflected in \( \tau_{\text{eff}}^{[i^*]} \). The computational cost is reduced at all levels by at least a factor of two, but much more for ensembles \([0^*], \ldots, [4^*]\) that consists of shorter paths with lower energy. When all results are taken together, it can be concluded that the path swapping technique resulted in a gain of efficiency by more than a factor 20.

### IV. CONCLUSIONS

We have discussed the ability of path sampling to study transitions that proceed via multiple reaction channels. This is a common phenomenon for any complex reaction mechanism that involves many degrees of freedom. The analysis of these processes are a huge challenge from a...
computational point of view. Besides all the difficulties of rare event simulations, many additional issues come into play. The development of a feasible RC, that can be used in a standard free energy based method, is notoriously difficult for high dimensional complex systems. Finding a RC that can well describe several reaction mechanisms simultaneously is even more difficult than that.

Alternatively, one could rely on a method for which the correct RC does not play such a crucial role. We have given several justifications why this is the case for the TIS and TPS path sampling methods. For a 2D model system of a slanted barrier, the advantageous scaling of TIS compared to standard methods was proven rigorously when the effective computational cost as function of the ‘qual-

ity of the RC’ was calculated analytically [14]. In sec. [11] we gave some additional arguments based on a fictitious two channel problem displayed by the path-survival diagram of Fig. [1]. The difficulty of this example is that one channel is initially favorable but finally turns into a dead end. If we assume a perfect ergodic sampling, the TIS simulations are still able to return the right result using a minimal amount of trajectories. FFS, in which trajectories are propagated only forward in time, would not be able to achieve the same. It can not change the history of the paths and will therefore get stuck in the unfavorable channel. Apart from this, to be able to sample between several distinct reaction mechanisms, one needs to combine nonlocal MC moves with a high rate of acceptance. The shooting move has shown to have the required nonlocal characteristics [24], but in order to sample efficiently, transitions between the different channels need to occur at a much higher frequency than in the standard shooting algorithm.

Sec. [11] shows a very promising approach to accomplish this based on the ideas of parallel tempering [25]. Instead of performing several path sampling simulations at different temperatures [26], the swapping occurs between the different interface ensembles. The initial MD simulation to compute the flux is replaced by an ‘internal’ path ensemble which allows to swap trajectories at all levels in the system. Compared to standard parallel tempering, this gives the advantage that there is no need to extend the number of TIS simulations. It also provides a way to overcome entropic barriers for which parallel tempering would not help. We reviewed the results of Ref. [11] where this method was applied on the DNA denaturation transition using the mesoscopic PBD model. These results showed that the PPS technique improved the TIS efficiency by more than a factor 20.

Still, there are many issues that need to be studied and more improvements might be possible. An exact estimate of the total error becomes more complicated as the standard error propagation rules assume that the different simulations are independent. We think that the presence of covariant terms will not have a huge effect, but this will be investigated explicitly in the near future. In [14] we derived relations for how to divide a total fixed simulation time over a simulation series to obtain the lowest possible overall statistical error. The optimum was found when each simulation was given a simulation time proportional to $\propto \sqrt{\tau_{\text{eff}}}$

This result is generic for any type of method for which the final quantity is obtained by a product outcomes from a series of independent simulations. Finding the optimal way to divide the total simulation time in a PPS algorithm is much more complicated. The simulations are no longer independent and each simulation has a double function. Besides the evaluation of the intrinsic property, their function is also to assist the ergodic sampling of the other simulations. So far, the PPS simulations were performed using the same number of trajectories for each ensemble. We are now developing an improved PPS-TIS method that iteratively
adapts the number of trajectories per ensemble to the optimal ratios [29]. We think that TIS in combination with PPS can become an important standard method for the sampling of rare events in complex systems and multiple reaction channels in particular.

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[30] Normally, configuration space will be sufficient. However, to ensure the stability of states A and B, the surfaces $\lambda_A$ and $\lambda_B$ might require explicit kinetic energy dependence (see e.g. [2]).
[31] It is a bit more complicated than this. In addition, one needs to avoid the overcounting of successful trajectories that cross the top of the barrier multiple times and each trajectory needs to be weighted with its initial velocity at the top along the direction of the RC [2].