Markov state modeling and dynamical coarse-graining via discrete relaxation path sampling

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A method is derived to coarse-grain the dynamics of complex molecular systems to a Markov jump process (MJP) describing how the system jumps between cells that fully partition its state space. The main inputs are relaxation times for each pair of cells, which are shown to be robust with respect to positioning of the cell boundaries. These relaxation times can be calculated via molecular dynamics simulations performed in each cell separately and are used in an efficient estimator for the rate matrix of the MJP. The method is illustrated through applications to Sinai billiards and a cluster of Lennard-Jones discs. © 2015 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4926940>]

I. INTRODUCTION

A key question in computational chemistry is how to coarse-grain the dynamics of complex molecular systems, that is, retain the most salient features of their evolution in a simplified way that permits better analysis and interpretation. This issue has been made even more relevant recently by the advent of massive parallel computing that produces time-series data whose size and complexity defy straightforward analysis. We can nowadays simulate the evolution of proteins using fully resolved atomic computations on cumulative time spans that were completely out of reach just a few years ago,^{1,2} but making sense of the output of these simulations remains a challenge. How to organize these data or generate them in the most efficient and informative way is an active subject of research.³

In this context, much effort has recently been devoted to the development and analysis of Markov State Models (MSMs).^{4–7,80,81} For recent reviews on MSMs that address many issues about them, including how to assess their accuracy, we refer the reader to Refs. 82 and 83. In fact, the analysis of complex first order rate equations via a master equation (ME)⁸ formulation has been widely used in other areas of molecular science for many decades.^{9–12} Much of the recent work is based upon molecular dynamics (MD) simulations, whereas the ME framework was previously exploited using kinetic transition networks^{13–16} based on geometry optimization and unimolecular rate theory.^{9–11} In a nutshell, MSMs aim at coarse-graining the dynamics of the system via mapping it onto a continuous-time Markov jump process (MJP), that is, a process whose evolution involves memoryless jumps between discretized states representing various typical conformations of the original system. That such a reduction is possible rests on the observation that most molecular systems display metastability: they do indeed stay trapped in specific regions of their conformational space for

long enough periods of time that they forget the memory of how they got there, then make a transition to another such region, etc. This feature offers the possibility that if we somehow identify the states of the MSMs with these metastable regions, we should indeed be able to construct an MSM that is both accurate (i.e., such that the dynamics remains Markovian after projection on these states, which is not the case in general) and informative about the original dynamics. Previous ME applications to clusters, solids, and biomolecules exploited a natural coarse-graining in terms of local minima of the potential energy surface,^{9–11,17–19} or suitably lumped sets of minima and transition states.^{20–23}

In practice, however, implementing this coarse-graining approach faces several difficulties. Even if we roughly know where the metastable states are, any reconstruction procedure based on processing a MD trajectory directly, such as a maximum likelihood estimator (MLE) for the rate matrix of the MJP using as input the time series projected on these states, will be affected by the precise location of the boundaries between them. In particular, these estimators can produce inaccurate results for the rate matrix because they will include spurious recrossings at these boundaries. This issue is not very different from the one that affects transition state theory (TST),^{24–28} where the predicted reaction rate is always an overestimate of the true rate due to these recrossings.^{29–31} Some methods for simulation of rare events based on TST reduce the effect of recrossing by either assigning only a portion of configuration space to states (see the illustration in Fig. 1)^{31–38} or by computationally expensive adjustments of the dividing surface.^{39–41} In the context of MSM building, two approaches have been proposed to solve the recrossing problem. The first, which is the one that is most widely used, is to process the time series at a finite time lag.⁷ In other words, describe the process as a discrete-time Markov chain whose transition probability describes its evolution at these lags. While this procedure does indeed eliminate somewhat the impact of the spurious recrossings, it has the disadvantage that it requires specifying what the lag should be, which is by

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FIG. 1. Schematic representation of possible ways to define the cells. Left: definition used in transition path sampling (TPS)³³ and related reactive flux methods. The trajectory is assigned to cell A or B (and colored in red or blue, respectively) when it is within one of these cells, and unassigned when it is outside. Center: definition using target sets in which the trajectory is assigned to the last cell it hit. Right: definition used in the original TST and in the present work. The cells fully partition the state space and the trajectory is assigned to the cell it is currently in.

no means trivial since the slow evolution of the system that the MSM is supposed to capture can itself span a wide range of different time scales. It is also nontrivial to deduce the rate matrix of a MJP from the transition probability at discrete time: this is the so-called embedding problem of Markov chains.^{42,43}

Another approach that has been proposed to solve the recrossing problem is to use target sets (see Fig. 1). Instead of partitioning the conformation space into a collection of states whose union is the full space itself and assign the trajectory to the state it is currently in, the idea is to introduce well-separated target sets within the metastable regions and assign the trajectory to the last one of these sets it hit. Since the trajectory will take time to go from one such target set to another, recrossings will be much less frequent and the MLE more accurate. Such a procedure was first discussed by Buchete and Hummer⁴⁴ and formalized in the context of milestoning^{6,45–50} via transition path theory.^{19,51,52} One drawback of such an approach is that defining target sets may turn out to be nontrivial: they must be small enough to eliminate spurious recrossings, but at the same time large enough (or positioned well enough) to be sampled properly. This trade-off may be hard to achieve in practice.

The main purpose of this paper is to revisit the standard approach for methods that employ explicit dynamics based on fully partitioning the state space, but abandoning the MLE procedure for the reconstruction. That is, instead of using the trajectory directly, we collect some statistical information about it to estimate the rate matrix of the MJP. In the jargon of statistics, this procedure amounts to abandoning the standard Bayesian approach, and rather using what is called a method of moments. The “moments” we will use here are time integrals of the instantaneous probability distribution to find the system in any one of the cells. Clearly, if we knew this distribution, we could use its time evolution to deduce the rate matrix of the MJP since this evolution is governed by a simple linear ME (see (10) below). As we will see, such a direct approach turns out to be ineffective in practice, but it can be factorised in a way that makes it efficient. Specifically, a MJP on many states can always be artificially modified to only describe the relaxation of the system onto two specific states that are adjacent in the chain. The rates of hopping back and forth between these two states in the original chain can then be easily deduced from the evolution of the probability distribution on these two states in the modified chain. The main achievement of this paper is

to propose a way to implement this artificial modification of the dynamics at the molecular level. As we will show, this approach offers a way to deduce the rate matrix of the MJP that is both efficient (it only involves parallel MD simulations restricted to the states) and accurate (that is, rather insensitive to the precise location of the boundary of these states).

The remainder of this paper is organized as follows. In Sec. II we introduce the assumptions of our modification of the dynamics and derive an analytical expression for the relaxation time in a pair of cells in terms of quantities characteristic for individual cells. Then in Sec. III we give a numerical recipe for efficient sampling of these quantities. We provide a step-by-step application of the approach using a simple model system (Sinai billiards⁵³) in Sec. IV. We show how this estimator can be used to simulate rare events in Sec. V in a method that we call the discrete relaxation path sampling (DRPS). DRPS is robust with respect to the placement of cell boundaries and can be used for a wide range of friction regimes.

II. THEORETICAL ASPECTS

A. Setup

We consider a system of n point particles whose instantaneous positions in configuration space $\Omega \subset \mathbb{R}^{3n}$ and velocity at time t are denoted by $(\mathbf{x}(t), \mathbf{v}(t)) \in \Omega \times \mathbb{R}^{3n}$ and whose evolution is governed by the Langevin equation,

$$\begin{aligned} \dot{\mathbf{x}}(t) &= \mathbf{v}(t), \\ \mathbf{M}\dot{\mathbf{v}}(t) &= -\nabla\mathcal{V}(\mathbf{x}(t)) - \gamma\mathbf{v}(t) + \sqrt{2k_B T}\boldsymbol{\gamma}^{1/2}\boldsymbol{\eta}(t), \end{aligned} \quad (1)$$

where $\mathbf{M}$ is the mass matrix, $\mathcal{V}(\mathbf{x})$ the potential energy, k_B the Boltzmann constant, T the temperature, γ the friction tensor, and $\boldsymbol{\eta}(t)$ a white-noise process satisfying $\langle \boldsymbol{\eta}(t) \rangle = 0$ and $\langle \boldsymbol{\eta}(t)\boldsymbol{\eta}^T(s) \rangle = \mathbf{I}\delta(t-s)$. For simplicity, we will assume that γ is position independent in the derivations below, but the final procedure can also be used when $\gamma \equiv \gamma(\mathbf{x})$. The instantaneous probability density function (PDF) $\varrho(\mathbf{x}, \mathbf{v}, t)$ of the system whose evolution is governed by (1) satisfies the inertial Fokker-Planck equation (FPE),

$$\begin{aligned} \partial_t \varrho &= -\mathbf{v} \cdot \partial_{\mathbf{x}} \varrho + \mathbf{M}^{-1} \nabla \mathcal{V}(\mathbf{x}) \cdot \partial_{\mathbf{v}} \varrho \\ &\quad + \partial_{\mathbf{v}} \cdot (\mathbf{M}^{-1} \gamma \mathbf{v} \varrho + k_B T \mathbf{M}^{-2} \gamma \partial_{\mathbf{v}} \varrho). \end{aligned} \quad (2)$$

The stationary solution to this equation is the Boltzmann-Gibbs equilibrium density,

$$\varrho^e(\mathbf{x}, \mathbf{v}) = Z^{-1} e^{-\beta \mathcal{H}(\mathbf{x}, \mathbf{v})}, \quad (3)$$

where $\mathcal{H}(\mathbf{x}, \mathbf{v}) = \frac{1}{2} \mathbf{v}^T \mathbf{M} \mathbf{v} + \mathcal{V}(\mathbf{x})$ is the Hamiltonian, $\beta = 1/(k_B T)$, and Z is the partition function,

$$Z = \int_{\Omega \times \mathbb{R}^{3n}} e^{-\beta \mathcal{H}(\mathbf{x}, \mathbf{v})} d\mathbf{x} d\mathbf{v}. \quad (4)$$

We will also be interested in two specific limiting cases. The underdamped situation when $\gamma \rightarrow 0$ and (1) reduces to Hamilton’s equations,

$$\dot{\mathbf{x}}(t) = \mathbf{v}(t) \quad \mathbf{M}\dot{\mathbf{v}}(t) = -\nabla\mathcal{V}(\mathbf{x}(t)) \quad (5)$$

and the overdamped limit when $\gamma \rightarrow \infty$ and (1) reduces to

$$\dot{\mathbf{x}}(t) = -\beta \mathbf{D} \nabla \mathcal{V}(\mathbf{x}(t)) + \sqrt{2\mathbf{D}}^{1/2} \boldsymbol{\eta}(t), \quad (6)$$

where the diffusion tensor $\mathbf{D}$ is related to γ via Einstein's relation $\gamma = k_B T \mathbf{D}^{-1}$. In the underdamped situation we will also consider the case when the equilibrium density for (5) is the microcanonical density

$$\varrho_m^e(\mathbf{x}, \mathbf{v}) = Z_m^{-1} \delta(E - \mathcal{H}(\mathbf{x}, \mathbf{v})), \quad (7)$$

where $Z_m = \int_{\Omega \times \mathbb{R}^{3n}} \delta(E - \mathcal{H}(\mathbf{x}, \mathbf{v})) \, d\mathbf{x} \, d\mathbf{v}$ and E is the total energy. (7) holds for (5) if we start from a given initial condition with energy E rather than an ensemble distributed according to (3).

B. State definition and Markov assumption

Our aim is to construct a Markov chain in a finite state space that captures the essential features of the dynamics of the molecular system. This coarse-graining involves a mapping from the phase space of the original system to a discrete set of states. The mapping will be performed at the level of the positions, and involves decomposing Ω into N non-overlapping connected cells (or sets) $B_1, \dots, B_N$, whose union is Ω ,

$$\bigcup_{i=1}^N B_i = \Omega, \quad B_i \cap B_j = \emptyset \text{ for all } i, j \text{ with } i \neq j. \quad (8)$$

The instantaneous probability $p_i(t)$ to find the system in cell B_i at time t is given in terms of the PDF $\varrho(\mathbf{x}, \mathbf{v}, t)$ as

$$p_i(t) = \int_{B_i \times \mathbb{R}^{3n}} \varrho(\mathbf{x}, \mathbf{v}, t) \, d\mathbf{x} \, d\mathbf{v}, \quad i = 1, \dots, N. \quad (9)$$

Our aim will be to derive an equation for $p_i(t)$. If one assumes that the dynamics between the sets B_i are Markovian, then $p_i(t)$, $i = 1 \dots, N$ satisfy the ME,

$$\dot{p}_i(t) = \sum_{\substack{j=1 \\ j \neq i}}^N p_j(t) k_{j,i} - \sum_{\substack{j=1 \\ j \neq i}}^N p_i(t) k_{i,j}, \quad (10)$$

where $k_{i,j}$, $i, j = 1, \dots, N$, $i \neq j$, are the entries of the rate matrix. To leading order in Δt , $k_{i,j} \Delta t$ gives the probability that the system jumps to state $j \neq i$ in $[t, t + \Delta t)$ given that it was in i at time t .

Clearly, since (9) involves some projection (or coarse-graining), the dynamics between the sets B_i described by $p_i(t)$ will no longer be Markovian in general, even if the original dynamics are. Even if we assume Markovianity, the estimation of the rate constants $k_{i,j}$ from a time series is nontrivial: in particular, procedures that seem reasonable may produce an inaccurate set of rate constants. We will explain below why this is the case, and how to get around this difficulty. Note that since the original dynamics satisfies detailed balance, so must the dynamics specified by (10). Hence, we have

$$p_i^e k_{i,j} = p_j^e k_{j,i}, \quad i, j = 1, \dots, N, \quad (11)$$

where p_i^e is the probability to find the system in state i at equilibrium,

$$p_i^e = \int_{B_i \times \mathbb{R}^{3n}} \varrho^e(\mathbf{x}, \mathbf{v}) \, d\mathbf{x} \, d\mathbf{v}, \quad i = 1, \dots, N. \quad (12)$$

C. Estimation via pairwise relaxation between cells

Suppose that we single out a pair of states, (i, j) with $i \neq j$ and $k_{i,j} \neq 0 \neq k_{j,i}$, and artificially eliminate all transitions except those between these two states. At the level of the MJP, this elimination can be done by setting $k_{l,m} = k_{m,l} = 0$ for all $(m, l) \neq (i, j)$, and it reduces (10) to a single pair of equations describing how the probabilities relax to equilibrium between i and j if these two states were artificially isolated from the rest of the chain,

$$\begin{aligned} \dot{p}_i^*(t) &= -p_i^*(t) k_{i,j} + p_j^*(t) k_{j,i}, \\ \dot{p}_j^*(t) &= -p_j^*(t) k_{j,i} + p_i^*(t) k_{i,j}, \end{aligned} \quad (13)$$

where $p_i^*(t)$ and $p_j^*(t)$ denote the probabilities to find the system in states i and j , respectively, in the modified chain. Since $p_j^*(t) = 1 - p_i^*(t)$, (13) can be reduced to a single equation for $p_i^*(t)$ whose solution for the initial condition $p_i^*(0) = 1$ is

$$p_i^*(t) = p_i^{*,e} + p_j^{*,e} e^{-(k_{i,j} + k_{j,i})t}, \quad (14)$$

where

$$p_i^{*,e} = k_{j,i} / (k_{i,j} + k_{j,i}), \quad p_j^{*,e} = k_{i,j} / (k_{i,j} + k_{j,i}) \quad (15)$$

are the equilibrium populations of two states in the modified chain, i.e., $p_i^*(t) \rightarrow p_i^{*,e}$ and $p_j^*(t) \rightarrow p_j^{*,e}$ as $t \rightarrow \infty$. They are related to the equilibrium probabilities for the original chain defined in (12) via

$$p_i^{*,e} = \frac{p_i^e}{p_i^e + p_j^e}, \quad p_j^{*,e} = \frac{p_j^e}{p_i^e + p_j^e}. \quad (16)$$

We will calculate $k_{i,j}$ via estimation of these quantities along with the relaxation time $\tau_{i,j}^{\text{rxn}} = \tau_{j,i}^{\text{rxn}}$ defined by integrating $p_i^*(t) - p_i^{*,e}$ on $t \in [0, \infty)$,

$$\tau_{i,j}^{\text{rxn}} = \frac{1}{p_j^{*,e}} \int_0^\infty (p_i^*(t) - p_i^{*,e}) \, dt = \frac{1}{k_{i,j} + k_{j,i}}. \quad (17)$$

Solving (15) and (17) in $k_{i,j}$ and $k_{j,i}$ gives the estimates

$$k_{i,j} = \frac{p_j^{*,e}}{\tau_{i,j}^{\text{rxn}}}, \quad k_{j,i} = \frac{p_i^{*,e}}{\tau_{j,i}^{\text{rxn}}}. \quad (18)$$

Note, since $\tau_{i,j}^{\text{rxn}} = \tau_{j,i}^{\text{rxn}}$, we have

$$p_i^{*,e} k_{i,j} = p_j^{*,e} k_{j,i}, \quad (19)$$

so detailed balance is satisfied.

D. Pairwise relaxation at MD level

Let us now discuss how to implement the artificial modification of the chain leading to (13) at the level of the original dynamics. This change is non-trivial, since it amounts to letting the system relax freely between B_i and B_j while at the same time prohibiting transitions from these two cells to any other cell. The question we address next is how to enforce this constraint since the original dynamics permits such transitions. Note that the answer involves calculations that are somewhat technical and may be skipped at first reading: the main result we will arrive at is the estimator in (42) for the rates $k_{i,j}$.

We will base our discussion on deriving equations for the instantaneous probability fluxes from B_i to B_j and from B_j to

B_i , denoted as $f_{i,j}^*(t)$ and $f_{j,i}^*(t)$, respectively. In terms of these quantities, the equation for $p_i^*(t)$ can be written as

$$\dot{p}_i^*(t) = f_{j,i}^*(t) - f_{i,j}^*(t). \quad (20)$$

We will also need to consider the instantaneous fluxes to the cells adjacent to B_i and B_j that the system would experience if we did not artificially prohibit transitions toward such cells. Denoting by $m \sim i$ and $m \sim j$ the indices of all the cells adjacent to B_i and B_j , respectively, these fluxes will be denoted by $f_{i,m}^*(t)$ for $m \sim i$ with $m \neq j$ and $f_{j,m}^*(t)$ for $m \sim j$ with $m \neq i$.

1. Flux balance equations

To derive closed equations we need to introduce two additional quantities. The first is $f_{i,j}^e(t)$, defined as

$f_{i,j}^e(t)$ = probability density that a trajectory initiated at equilibrium in B_i exits this cell to B_j at time t .

Here, initiated at equilibrium means starting from an initial condition drawn from $\varrho^e(\mathbf{x}, \mathbf{v}) \chi_{B_i}(\mathbf{x}) / p_i^e$ in B_i , where $\chi_{B_i}(\mathbf{x}) = 1$ if $\mathbf{x} \in B_i$ and $\chi_{B_i}(\mathbf{x}) = 0$ otherwise. Thus,

$$p_{i,j}^e = \int_0^\infty f_{i,j}^e(t) dt \quad (21)$$

gives the probability that a trajectory initiated at equilibrium in B_i exits this cell to B_j (and $\sum_{j \sim i} p_{i,j}^e = 1$), whereas

$$\tau_{i,j}^e = \frac{1}{p_{i,j}^e} \int_0^\infty t f_{i,j}^e(t) dt \quad (22)$$

gives the mean time this trajectory takes to exit B_i conditional on exiting to B_j . The second quantity we will need is $L_{j,m}^i(t)$, defined as

$L_{j,m}^i(t)$ = probability density that an equilibrium trajectory entering cell B_i from B_j at time s exits it to B_m at time $s + t$.

Thus,

$$p_{j,m}^i = \int_0^\infty L_{j,m}^i(t) dt \quad (23)$$

gives the probability that a trajectory entering B_i from B_j exits this cell to B_m (and $\sum_{m \sim i} p_{j,m}^i = 1$ for every $j \sim i$), whereas

$$\tau_{j,m}^i = \frac{1}{p_{j,m}^i} \int_0^\infty t L_{j,m}^i(t) dt \quad (24)$$

gives the mean time a trajectory spends in B_i if it enters this cell from B_j and exits towards B_m . These quantities are well-defined for systems with finite or zero friction—the case of the overdamped equation when $\gamma \rightarrow \infty$ needs to be treated separately (Appendix A). In Sec. III, we show how the quantities above can be estimated from MD simulations performed independently in each cell B_i , which ensures that the procedure we propose allows for a significant speed-up compared to brute-force MD simulations for the entire system. Note that, because of detailed balance, we have

$$p_j^i L_{j,m}^i(t) = p_m^i L_{m,j}^i(t), \quad (25)$$

where p_j^i is the probability that an equilibrium trajectory enters B_i from B_j (so that $\sum_{j \sim i} p_j^i = 1$). Integration of (25) over t also leads to

$$p_j^i p_{j,m}^i = p_m^i p_{m,j}^i, \quad \tau_{j,m}^i = \tau_{m,j}^i. \quad (26)$$

Next we use the quantities above to derive closed equations for the fluxes. To do so, we will work under the following assumptions: each time the trajectory goes out of B_i toward B_m with $m \sim i$ and $m \neq j$, or out of B_j toward B_m with $m \sim j$ and $m \neq i$, we imagine that we switch to another trajectory, pruned from a long equilibrium trajectory, which enters B_i from B_m with $m \sim i$ and $m \neq j$, or B_j from B_m with $m \sim j$ and $m \neq i$, respectively. This reinjection guarantees that there is no net flux out of $B_i \cup B_j$ (thereby realizing the artificial modification of the chain discussed in Sec. II C), while at the same time enforcing some loss of memory at the boundaries. Similarly, each time the trajectory goes out of B_i to B_j , or out of B_j to B_i , we imagine that we switch to another trajectory, again pruned from a long equilibrium trajectory, that enters B_j from B_i , or B_i toward B_j , respectively. This initiation guarantees conservation of the fluxes between B_i and B_j , while at the same time enforcing some loss of memory at the boundary between these cells. This loss of memory rule is the main approximation we make, and it does not influence the results if the dynamics over the cells can indeed be accurately described via a Markov chain.

Because of the loss of memory rule we can write the following flux balance equations that mimic the chain modification introduced in Sec. II C at the MD level:

$$\begin{aligned} f_{i,m}^*(t) &= p_i^*(0) f_{i,m}^e(t) + \sum_{\substack{l \sim i \\ l \neq j}} \int_0^t f_{i,l}^*(t-s) L_{l,m}^i(s) ds \\ &\quad + \int_0^t f_{j,i}^*(t-s) L_{j,m}^i(s) ds, \quad (m \sim i), \\ f_{j,m}^*(t) &= p_j^*(0) f_{j,m}^e(t) + \sum_{\substack{l \sim j \\ l \neq i}} \int_0^t f_{j,l}^*(t-s) L_{l,m}^j(s) ds \\ &\quad + \int_0^t f_{i,j}^*(t-s) L_{i,m}^j(s) ds, \quad (m \sim j). \end{aligned} \quad (27)$$

In (27), the first terms on the right hand sides correspond to first passage of particles through the boundaries. The second terms correspond to reinjection of particles at boundaries between the relaxing cells and their neighbours, and the third terms correspond to the flux through the boundary between the relaxing cells B_i and B_j . These flux-balance equations are one of the main results of this paper. They are valid for any initial probabilities in the cell, $p_i^*(0)$ and $p_j^*(0) = 1 - p_i^*(0)$. The equations in (27) can be solved via Laplace transform. However, as we show next in Secs. II D 2 and II D 3, a full solution of these equations is not necessary to derive the rates $k_{i,j}$.

2. Equilibrium balances

As $t \rightarrow \infty$, the fluxes tend to asymptotic values, i.e., $f_{i,j}^*(t) \rightarrow f_{i,j}^{*,e}$, etc. These asymptotic fluxes are also those observed at all times if the initial distributions in B_i and B_j

correspond to equilibrium, i.e., we have

$$f_{i,m}^{*,e} = p_i^{*,e} f_{i,m}^e(t) + \sum_{l \sim i} f_{i,l}^{*,e} \int_0^t L_{l,m}^i(s) ds \quad (m \sim i), \quad (28)$$

where we used the property that $f_{i,j}^{*,e} = f_{j,i}^{*,e}$. A similar equation holds for $f_{j,m}^{*,e}$ with $m \sim j$. As $t \rightarrow \infty$, since $f_{i,m}^e(t) \rightarrow 0$, using (23) we see that (28) reduces to

$$f_{i,m}^{*,e} = \sum_{l \sim i} f_{i,l}^{*,e} p_{l,m}^i \quad (m \sim i). \quad (29)$$

This is a homogeneous system of equations, which admits nontrivial solutions, since summing (29) over $m \sim i$ and using $\sum_{m \sim i} p_{l,m}^i = 1$ gives the identity

$$\sum_{m \sim i} f_{i,m}^{*,e} = \sum_{m,l \sim i} f_{i,l}^{*,e} p_{l,m}^i = \sum_{l \sim i} f_{i,l}^{*,e}. \quad (30)$$

In fact, it is easy to see that the solutions to (29) are of the form

$$f_{i,m}^{*,e} = f_i^{*,e} p_m^i \quad (m \sim i), \quad (31)$$

where p_m^i is the probability to enter B_i from B_m (see (25)) and $f_i^{*,e}$ is the total equilibrium flux through all boundaries of B_i .

To proceed further, we can subtract (29) from (28) and use (31) to deduce that

$$\begin{aligned} p_i^{*,e} f_{i,m}^e(t) &= \sum_{l \sim i} f_{i,l}^{*,e} \int_0^t L_{l,m}^i(s) ds \\ &= f_i^{*,e} \sum_{l \sim i} \int_0^t p_l^i L_{l,m}^i(s) ds \quad (m \sim i). \end{aligned} \quad (32)$$

Integrating this equation on $t \in [0, \infty)$ then gives

$$\begin{aligned} p_i^{*,e} p_{i,m}^e &= f_i^{*,e} \sum_{l \sim i} p_l^i p_{l,m}^i \tau_{l,m}^i \\ &= f_i^{*,e} p_m^i \sum_{l \sim i} p_{m,l}^i \tau_{m,l}^i \quad (m \sim i), \end{aligned} \quad (33)$$

i.e., we have

$$f_i^{*,e} p_m^i = \frac{p_i^{*,e} p_{i,m}^e}{\sum_{l \sim i} p_{m,l}^i \tau_{m,l}^i} \quad (m \sim i). \quad (34)$$

This equation can be used to determine the equilibrium distribution $p_i^{*,e}$ by setting $m = j$ in (34), using the equation similar to (34) for $f_j^{*,e} p_i^j$, and combining both equations using $f_i^{*,e} p_j^j = f_{i,j}^{*,e} = f_{j,i}^{*,e} = f_j^{*,e} p_i^j$. This gives

$$\frac{p_i^{*,e} p_{i,j}^e}{\sum_{l \sim i} p_{j,l}^i \tau_{j,l}^i} = \frac{p_j^{*,e} p_{j,i}^e}{\sum_{l \sim j} p_{i,l}^j \tau_{i,l}^j} \quad (35)$$

and since $p_j^{*,e} = 1 - p_i^{*,e}$, we deduce that

$$p_i^{*,e} = \frac{p_{j,i}^e \sum_{l \sim i} p_{j,l}^i \tau_{j,l}^i}{p_{i,j}^e \sum_{l \sim i} p_{i,l}^j \tau_{i,l}^j + p_{j,i}^e \sum_{l \sim i} p_{j,l}^i \tau_{j,l}^i}. \quad (36)$$

3. Fluxes and rates

We now determine the rates $k_{i,j}$ from the flux balance equations (27). We start by subtracting every equation in (27) from the corresponding one in (28), integrating over $t \in [0, \infty)$, and defining

$$\begin{aligned} p_{i,m}^* &= \int_0^\infty (f_{i,m}^*(t) - f_{i,m}^{*,e}) dt, \quad (m \sim i), \\ p_{j,m}^* &= \int_0^\infty (f_{j,m}^*(t) - f_{j,m}^{*,e}) dt, \quad (m \sim j). \end{aligned} \quad (37)$$

Assuming that $p_i^*(0) = 1$ and $p_j^*(0) = 0$, this leads to

$$\begin{aligned} p_{i,m}^* &= p_j^{*,e} p_{i,m}^e + \sum_{\substack{l \sim i \\ l \neq j}} p_{i,l}^* p_{l,m}^i + p_{j,i}^* p_{j,m}^j, \quad (m \sim i), \\ p_{j,m}^* &= -p_j^{*,e} p_{j,m}^e + \sum_{\substack{l \sim j \\ l \neq i}} p_{j,l}^* p_{l,m}^j + p_{i,j}^* p_{i,m}^i, \quad (m \sim j). \end{aligned} \quad (38)$$

Similarly, let us define

$$\begin{aligned} \tau_{i,m}^* &= \int_0^\infty t (f_{i,m}^*(t) - f_{i,m}^{*,e}) dt, \quad (m \sim i), \\ \tau_{j,m}^* &= \int_0^\infty t (f_{j,m}^*(t) - f_{j,m}^{*,e}) dt, \quad (m \sim j). \end{aligned} \quad (39)$$

Using (27) and (28), we deduce that these quantities satisfy

$$\begin{aligned} \tau_{i,m}^* &= p_j^{*,e} (p_{i,m}^e \tau_{i,m}^e + p_{j,m}^i \tau_{j,m}^i) + \sum_{l \sim i} p_{i,l}^* p_{l,m}^i \tau_{l,m}^i \\ &\quad + \sum_{\substack{l \sim i \\ l \neq j}} \tau_{i,l}^* p_{l,m}^i + \tau_{j,i}^* p_{j,m}^j, \quad (m \sim i), \\ \tau_{j,m}^* &= -p_j^{*,e} (p_{j,m}^e \tau_{j,m}^e + p_{i,m}^j \tau_{i,m}^j) + \sum_{l \sim j} p_{j,l}^* p_{l,m}^j \tau_{l,m}^j \\ &\quad + \sum_{\substack{l \sim j \\ l \neq i}} \tau_{j,l}^* p_{l,m}^j + \tau_{i,j}^* p_{i,m}^i, \quad (m \sim j). \end{aligned} \quad (40)$$

Since we already know $p_j^{*,e} = 1 - p_i^{*,e}$, (38) and (40) form a closed set of linear algebraic equations for $(p_{i,m}^*, p_{j,l}^*)$ and $(\tau_{i,m}^*, \tau_{j,l}^*)$ with $m \sim i$ and $l \sim j$. The solution to these equations permits us to derive the rate $k_{i,j}$ since

$$\begin{aligned} \tau_{i,j}^{\text{rxn}} &= \frac{1}{p_j^{*,e}} \int_0^t \int_s^\infty (f_{j,i}^*(u) - f_{i,j}^*(u)) du ds \\ &= \frac{1}{p_j^{*,e}} \int_0^\infty s (f_{j,i}^*(s) - f_{i,j}^*(s)) ds \\ &= \frac{\tau_{j,i}^* - \tau_{i,j}^*}{p_j^{*,e}}. \end{aligned} \quad (41)$$

Inserting this expression in (18) gives the desired estimate for $k_{i,j}$,

$$k_{i,j} = \frac{(p_j^{*,e})^2}{\tau_{j,i}^* - \tau_{i,j}^*}. \quad (42)$$

Thus, it simply remains to solve (38) and (40). It is easy to see that one equation in (38) is redundant (indeed, if we sum all these equations we arrive at the trivial identity $0 = 0$). Thus, we can remove one equation from (38), solve the resulting inhomogeneous system with, say, $p_{i,j}^* = 0$, and add to this

solution any multiple of the solution of the homogeneous system solved with $p_{i,j}^* = 1$. Using the notation $\mathbf{p}^*$ for the vector with entries $p_{i,m}^*$ and $p_{j,l}^*$ with $m \sim j$ and $l \sim j$, and denoting these solutions by $\mathbf{p}^{*,\text{inhom}}$ and $\mathbf{p}^{*,\text{hom}}$, respectively, the general solution to (38) is then

$$\mathbf{p}^* = \mathbf{p}^{*,\text{inhom}} + C\mathbf{p}^{*,\text{hom}}. \quad (43)$$

The constant C in this expression can be determined from the solvability condition for (40), namely, that the source term in the equation belongs to the range of the linear operator acting on $\boldsymbol{\tau}^* = (\tau_{i,m}^*, \tau_{j,l}^*)$ with $m \sim j$ and $l \sim j$. When this is the case, we can solve (40) similarly to (38): remove one equation from (40), solve the resulting inhomogeneous system with, say, $\tau_{i,j}^* = 0$, and add to this solution any multiple of the solution of the homogeneous system solved with $\tau_{i,j}^* = 1$. Denoting these solutions by $\boldsymbol{\tau}^{*,\text{inhom}}$ and $\boldsymbol{\tau}^{*,\text{hom}}$, respectively, the general solution to (40) is then

$$\boldsymbol{\tau}^* = \boldsymbol{\tau}^{*,\text{inhom}} + C'\boldsymbol{\tau}^{*,\text{hom}}, \quad (44)$$

where C' is another constant, whose value does not affect the estimate for the rate. Indeed, it can be checked that $p_{i,j}^{*,\text{hom}} - p_{j,i}^{*,\text{hom}} = \tau_{i,j}^{*,\text{hom}} - \tau_{j,i}^{*,\text{hom}} = 0$, i.e., the homogeneous part of the solution for $\boldsymbol{\tau}^*$ does not influence the estimate for the rate in (42).

III. SIMULATION PROTOCOL

Imagine that we had at our disposal a long equilibrium trajectory of the original system. We could then prune out of this trajectory the pieces during which it travels through a given cell B_i . Below we will discuss how to bypass this brute-force procedure, and efficiently generate these pieces directly via MD simulations restricted to cell B_i , but for time being let us just assume that we have these pieces at hand. The question we address here is how to estimate the quantities defined in Sec. II D 1 from these pieces.

Denote by $N_{j,m}$ the number of trajectory pieces in cell B_i that travel from $\partial B_j \cap \partial B_i$ to $\partial B_m \cap \partial B_i$, and let $t_{j,m}^n$ with $n = 1, \dots, N_{j,m}$ be the duration of each of these pieces. Because of detailed balance, we can read these trajectories in reverse, meaning that we can symmetrise both $N_{j,m} = N_{m,j}$ and $t_{j,m}^n = t_{m,j}^n$. Define also

$$N_j = \sum_{m \sim i} N_{j,m} = \sum_{m \sim i} N_{m,j}, \quad N = \sum_{j \sim i} N_j. \quad (45)$$

In terms of these quantities, we have the following estimator for $L_{j,m}^i(t)$:

$$\tilde{L}_{j,m}^i(t) = \frac{1}{N_j} \sum_{n=1}^{N_{j,m}} \delta(t - t_{j,m}^n), \quad (46)$$

and the following estimators for $p_{j,k}^i$ and $\tau_{j,k}^i$:

$$\tilde{p}_{j,m}^i = \frac{N_{j,m}}{N_j}, \quad \tilde{\tau}_{j,m}^i = \frac{1}{N_{j,m}} \sum_{n=1}^{N_{j,m}} t_{j,m}^n. \quad (47)$$

Every point along a piece of trajectory is also a sample of Boltzmann-Gibbs density (3) conditioned on the system being

in cell B_i . Thus, we can use them to estimate $f_{i,m}^e(t)$,

$$\tilde{f}_{i,m}^e(t) = \frac{\sum_{j \sim i} \sum_{n=1}^{N_{j,m}} \Theta(t) \Theta(t_{j,m}^n - t)}{\sum_{j,m \sim i} \sum_{n=1}^{N_{j,m}} t_{j,m}^n}, \quad (48)$$

where $\Theta(t)$ denotes the Heaviside step function. (48) implies the following estimators for $p_{i,m}^e$ and $\tau_{i,m}^e$:

$$\begin{aligned} \tilde{p}_{i,m}^e &= \frac{\sum_{j \sim i} \sum_{n=1}^{N_{j,m}} t_{j,m}^n}{\sum_{j,m \sim i} \sum_{n=1}^{N_{j,m}} t_{j,m}^n}, \\ \tilde{\tau}_{i,m}^e &= \frac{1}{2} \frac{\sum_{j \sim i} \sum_{n=1}^{N_{j,m}} (t_{j,m}^n)^2}{\sum_{j \sim i} \sum_{n=1}^{N_{j,m}} t_{j,m}^n}. \end{aligned} \quad (49)$$

A. Sampling via velocity reversal at the cell boundaries

One efficient way to generate the trajectory pieces in B_i that bypasses the need to prune them from a long equilibrium trajectory is to use the procedure originally proposed in Ref. 49. This procedure amounts to reflecting the velocity each time the trajectory hits the boundary of cell B_i so as to keep it in this cell. Specifically, if $(\mathbf{x}^*, \mathbf{v}^*)$ denotes the update of $(\mathbf{x}(t), \mathbf{v}(t))$ after one-time step Δt by a standard MD integrator for (1), we set

$$(\mathbf{x}(t + \Delta t), \mathbf{v}(t + \Delta t)) = \begin{cases} (\mathbf{x}^*, \mathbf{v}^*), & \text{if } \mathbf{x}^* \in B_i, \\ (\mathbf{x}(t), -\mathbf{v}(t)), & \text{if } \mathbf{x}^* \notin B_i. \end{cases} \quad (50)$$

Such calculations can be performed independently in each cell and, up to time-discretisation error, they produce a trajectory that samples exactly the Boltzmann-Gibbs density (3) conditional on the system being in cell B_i . The pieces of this trajectory when it travels between boundaries of B_i can be used directly to calculate the quantities $N_{j,m}$ and $t_{j,m}^n$ used in the estimators above.

B. Sampling from equilibrium initial data in the cell (DRPS)

The procedure described in Sec. III A works when the friction is finite, $\gamma > 0$, but its efficiency deteriorates as $\gamma \rightarrow 0$. This is because, upon collision with a boundary, the trajectory follows itself in reverse for a while, and only decorrelates due to the heat bath: as γ decreases, the time scale for this decorrelation to occur will become longer and longer. In particular, it will never happen for Hamiltonian systems where $\gamma = 0$. In such situations, it is necessary to first generate initial data according to the Boltzmann-Gibbs density conditional in B_i , e.g., by using the procedure described in Sec. III A using a friction coefficient whose value has been artificially increased. Ergodic sampling should be ensured,

while dynamical information is irrelevant in this initialization step, so a straightforward Metropolis Monte Carlo (MC)⁵⁴ or an enhanced method for thermodynamic sampling^{55–59} can be used.

Second, from each of these initial data, we can generate pieces of trajectory with the actual dynamics by running them both forward and backward in time until they reach a boundary of B_i . Using again $N_{j,m}^N$ and $t_{j,m}^n$ to denote the number and length of these trajectories, we can then use them to estimate $L_{j,m}^i(t)$ and $f_{i,m}^e(t)$. However, we need to reweight the estimators given in the beginning of Sec. III by the duration of each trajectory piece since there are more initial conditions along a long trajectory than a short one. This gives the following estimator for $L_{j,m}^i(t)$:

$$\tilde{L}_{j,m}^i(t) = \frac{\sum_{n=1}^{N_{j,m}} \frac{\delta(t - t_{j,m}^n)}{t_{j,m}^n}}{\sum_{m \sim i} \sum_{n=1}^{N_{j,m}} \frac{1}{t_{j,m}^n}}, \quad (51)$$

and the following estimators for $p_{j,m}^i$ and $\tau_{j,m}^i$:

$$\begin{aligned} \tilde{p}_{j,m}^i &= \frac{\sum_{n=1}^{N_{j,m}} \frac{1}{t_{j,m}^n}}{\sum_{m \sim i} \sum_{n=1}^{N_{j,m}} \frac{1}{t_{j,m}^n}}, \\ \tilde{\tau}_{j,m}^i &= \frac{N_{j,m}}{\sum_{n=1}^{N_{j,m}} \frac{1}{t_{j,m}^n}}. \end{aligned} \quad (52)$$

It also gives the following estimator for $f_{i,m}^e(t)$:

$$\tilde{f}_{i,m}^e(t) = \frac{1}{N} \sum_{j \sim i} \sum_{n=1}^{N_{j,m}} \frac{\Theta(t) \Theta(t_{j,m}^n - t)}{t_{j,m}^n}, \quad (53)$$

which implies the following estimators for $p_{i,m}^e$ and $\tau_{i,m}^e$:

$$\tilde{p}_{i,m}^e = \frac{N_j}{N}, \quad \tilde{\tau}_{i,m}^e = \frac{1}{N_j} \sum_{j \sim i} \sum_{n=1}^{N_{j,m}} t_{j,m}^n. \quad (54)$$

These estimators can be used both for systems with finite and zero friction.

IV. APPLICATION TO DYNAMICAL BILLIARDS

Here we illustrate the simulation protocol proposed in Sec. III B and demonstrate the correctness of the estimator using a two-dimensional Sinai billiard.⁵³ Specifically, we consider a rectangular billiard table with sides of lengths $2 + 2h$ and $2 + 2\delta$, with $0 < \delta < h$, and with a hard disk of diameter 2 placed in its center (Fig. 2). A single mass point moves at constant speed of magnitude $v_* = 1$ between the disk and the rectangle and collides elastically with their boundaries. This dynamic is ergodic and the equilibrium density of the

FIG. 2. The billiard example. Cell B_1 is shaded red, while cell B_2 is green. The boundary ($y = -l$) is denoted by a red dotted line, and the optimal boundary ($y = 0$) is the black horizontal dotted line.

system is constant everywhere,

$$\varrho^e(\mathbf{x}, \mathbf{v}) = \frac{1}{2\pi S}, \quad (55)$$

where S is the area of the billiard,

$$S = 4(1 + h)(1 + \delta) - \pi. \quad (56)$$

If the diameter of the disk is similar to the width of the smaller edge of the billiard table, i.e., if $\delta \ll 1$ the transitions between the top and the bottom halves of the billiard are rare events, which can be modelled by a two-state MJP. Since there are no spurious recrossings in this system, the rate of these transitions (i.e., the rates of the MJP) can be estimated via TST if we use the dividing surface of smallest length between the top and bottom halves. By definition, the TST rate is the ratio of the equilibrium flux and the equilibrium population

$$k_{1,2}^{\text{TST}} = 2 \frac{1 + \delta - \sqrt{1 - l^2}}{\pi S_1}, \quad (57)$$

which for $l = 0$ gives

$$k_{1,2}^{\text{TST}}(l = 0) = k_{2,1}^{\text{TST}}(l = 0) = \frac{\delta}{\pi S},$$

where the factor of π in the denominator comes from integration over all possible velocities. Next, we checked the accuracy of various estimators for this rate by dividing the system into two cells B_1 and B_2 that do not cut the billiard exactly in half. Specifically, for B_1 and B_2 we used the regions in the billiard that lie above and below the line $y = l$, where $|l| < 1$. The equilibrium population in B_1 is then

$$p_1^e = \int_{B_1} \varrho^e(\mathbf{x}, \mathbf{v}) d\mathbf{x} d\mathbf{v} = \frac{S_1}{S}, \quad (58)$$

where S_1 is the area of cell B_1 . The equilibrium population in cell B_2 is $p_2^e = 1 - p_1^e$. For the special case of $l = 0$, $p_1^e = p_2^e = 0.5$.

TABLE I. Rate constants for Sinai billiards multiplied by 10^3 in three pairs of columns corresponding to different positions of the dividing surface, $l \in \{0, -0.2, -0.4\}$. The columns marked by $\pm$ contain the statistical errors.

l	0	$\pm$	-0.2	$\pm$	-0.4	$\pm$
$k_{1,2}^{\text{TST}}$	12.11	0	16.18	0	31.58	0
$k_{1,2}^*$	10.6	0.11	10.58	0.05	10.63	0.08
$k_{1,2}^\ddagger$	5.61	0.018	6.44	0.022	7.96	0.04

To estimate the rates in the MJP via DRPS, we used (42) with $\tau_{i,j}^*$ and $\tau_{j,i}^*$ obtained by solving (38) and (40). The quantities needed in these equations were estimated via (52) and (54) using 10^5 trajectories of length no more than 10^4 . These trajectories were generated using event-driven simulations in which one propagates the system exactly from one collision with a wall to the next, and update exactly the orientation of the velocity at each collision. The results of these simulations when $h = 1$, and $\delta = 0.05$ are summarised in Table I. All values are multiplied by 10^3 for convenience of comparison, so the units of the rate constants represent the reciprocal of time required to travel a distance of 1000 circle radii. Each calculation was performed 15 times to calculate a statistical error in terms of the standard deviation of the results. As can be seen, DRPS describes the relaxation properly for each value of l and the rate constant $k_{1,2}^*$ it predicts is rather insensitive to the position of the dividing surface.

For comparison, we also tested various other estimators and checked their robustness with respect to the position of the dividing surface. First we checked the TST rates obtained using different dividing surfaces analytically using (57) and numerically, initiating velocities for 10^5 particles according to Knudsen's cosine law.⁶⁰ Not surprisingly, the TST rate constant varies dramatically with the position of this surface and rapidly ceases to be accurate when it is no longer the one of smallest length (see the TST estimates in the second and third columns of Table I).

An alternative estimate for the rate constant can be obtained from the first passage times,^{61–63}

$$k_{1,2}^\ddagger = \frac{p_2^e}{\tau_{1,2}^e p_2^e + \tau_{2,1}^e p_1^e}, \quad (59)$$

where $\tau_{1,2}^e$ is the mean first passage time obtained from the simulation in cell B_1 as

$$\tau_{1,2}^e = \frac{\sum_i^n \tau_{i,1/2}}{n}. \quad (60)$$

Here, $\tau_{i,1/2}$ are the lengths of trajectories starting from a randomly selected point in B_i and ending at the boundary between the cells. We see in Table I that this estimate is never very accurate, for the reasons explained in Appendix D. We did not test other methods such as boxed MD,^{64–66} temperature-accelerated MD,^{67,68} and hyperdynamics^{69–71} for this example. Unlike DRPS the accuracy of these methods will depend on the position of the dividing surface and will only give reliable results when the trajectory commits to the other cell after hitting the dividing surface (i.e., if the distributions of first exit times of these cells are exponential).

FIG. 3. The process studied in Sec. V. Structural transition from the global minimum to the second lowest minimum of $\text{LJ}_7^{2\text{D}}$ is a rare event at low temperature.

V. REARRANGEMENT OF A LENNARD-JONES CLUSTER

To illustrate the applicability of the method to a system with more degrees of freedom, we studied a structural transition for a cluster of seven Lennard-Jones discs ($\text{LJ}_7^{2\text{D}}$) (Fig. 3). This system was previously used for testing methods for sampling the dynamics of rare events.^{17,33,72,73} All discs have the same mass, μ_0 , so the parameters of the Lennard-Jones potential (well depth ϵ_0 and the disc radius σ_0) define the unit of time $\tau_0 = \sigma_0 \sqrt{\mu_0 / \epsilon_0}$. Here, we apply our method to a transition from the second-lowest energy minimum to the global minimum. The collective coordinate ξ represents the total squared distance from the second-lowest minimum calculated after alignment with respect to overall rotation and translation.^{74,75} Optimisation of permutation isomers was not part of the structure alignment procedure during MD propagation. The energy landscape is smooth with a relatively steep potential energy gradient along the coordinate.

A. MD and MC simulations

The cells represent slices along the coordinate ξ , so each cell borders two other cells. Three different cell sizes, $\Delta\xi$, were used to partition the coordinate between $\xi = 0.10\sigma_0$ and $\xi = 1.00\sigma_0$ into 9, 18, and 45 cells to test the sensitivity of the method to this parameter.

First, at least one starting structure per state is needed. Starting structures for MC were obtained by pulling a parabolic potential along the coordinate at a rate of $5 \times 10^{-3} \sigma_0 / \tau_0$ at $k_B T = 0.05 \epsilon_0$ using a force constant of $10 \epsilon_0 / \sigma_0^2$. Permutational isomers were considered during the structure alignment in this step only.⁷⁶

In the second step, an independent MC simulation constrained to each cell was used to reproduce the canonical distribution. MC simulations were performed at conditions consistent with the following MD simulation, at a temperature of $k_B T = 0.05 \epsilon_0$ using the Metropolis MC algorithm⁵⁴ rejecting any conformation outside the cell. Each simulation consisted of 10^6 steps with an acceptance ratio around 0.3.

Finally, 100 representative structures from the MC simulation were used as the starting structures for the MD simulation in each cell. MD simulations were propagated using a Nosé-Hoover propagator⁷⁷ and one bead with artificial mass equal to 1.0 and temperature of $k_B T = 0.05 \epsilon_0$ using time step $\Delta t = 0.01 \tau_0$. To prevent accumulation of numerical errors, each velocity initiation was followed by five steps during which the time step was gradually changed from $10^{-6} \tau_0$ to $\Delta t = 0.01 \tau_0$. The total number of 10^6 MD steps in each cell provided roughly 4000 trajectories in each cell.

FIG. 4. Free energy profile along reaction coordinate ξ defined in terms of the distance from minimum two. The DRPS free energy curves for all cell sizes (2, 5, 10 represent $\Delta\xi$ of 0.02, 0.05, and 0.10 σ_0 , respectively) are all very close to the exact curve, which demonstrates how robust the method is with respect to cell definition.

B. Results

The reaction pathway for the transition studied in this work has a single free energy maximum (Fig. 4). It is natural to define state A as all the cells between minimum 2 and the barrier top. State B then consists of all the cells between the barrier top and the global minimum. The rates calculated from the DRPS transition matrix by the new graph transformation (NGT)⁷⁸ method are in the column denoted “division” in Table II. The statistical error was analysed by performing the whole simulation 15 times and calculating the standard deviation of the computed rate constants.

The results can be compared to those obtained using discrete path sampling (DPS)¹⁷ in which states are defined in terms of basins of attraction of the minima. There is a difference between these two state definitions. DRPS is more expensive but also more accurate, since it properly describes anharmonicity and spatial diffusion. In the case of DRPS, the statistical error in the calculation of the difference in free energy is within 1%, which corresponds to an error in $\ln(k\tau_0)$ of 0.3. The error in DPS is mostly caused by using harmonic density of states.⁷⁹

The original transition path sampling (TPS) study³⁴ of this system defined states as small spheres in configuration space near to the energy minima. The results obtained with TPS can be compared to the DRPS results with states defined by values of $\xi < 0.1\sigma_0$ (for the state representing minimum 2) and $\xi > 1.0\sigma_0$. The phenomenological rate constants from matrix renormalisation are in the table in the column “close to

TABLE II. Rate constants for the structural transition of the LJ cluster described above. The first two columns are the rate constants between cells defined by partitioning of space (DRPS) at ξ corresponding to free energy maxima and using the harmonic superposition approximation within DPS, respectively. The third and fourth columns define states by $\xi < 0.1\sigma_0$ and $\xi > 1.0\sigma_0$ (DRPS) and by the maximum distance from minima (TPS).

	Division	DPS	Close to minima	TPS
$\ln(k_{12} \times \tau_0)$	-28.8 ± 0.2	-26.9	-29.6 ± 0.2	-28.7
$\ln(k_{21} \times \tau_0)$	-9.3 ± 0.1	-9.2	-9.5 ± 0.1	-7.2

minima.” These rate constants are slightly lower than the ones defined by full partitioning of the space, since the cells closer to the barrier top are not included in the states. Error estimates for TPS are not yet available.

VI. CONCLUDING REMARKS

In this work we have derived an estimator for the rate matrix of a master equation and developed a corresponding method for simulation of rare events. Since the estimator is robust with respect to the position of the dividing surface, we can separate the system into arbitrary cells. Even though the quality of description in terms of a master equation depends on the Markovianity of the transition from one cell to another, tests of the new estimator clearly demonstrate that it is robust with respect to Markovianity of cell-to-cell transitions. The main advantage over other common methods for simulation of rare events is the complete partitioning of space, which is one of the requirements for the correct limiting behaviour. The sampling of trajectories is straightforward to implement, as it only requires MD simulations that can be performed in each cell separately and subsequently processed using a protocol also developed here.

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NOMENCLATURE

B_i	cell defining state i , $B_i \subset \Omega \subset \mathbb{R}^{3n}$
$\mathbf{D}$	diffusion tensor
DRPS	discrete relaxation path sampling
$f_{i,j}^*(t)$	flux from B_i to boundary $\partial B_i \cap \partial B_j$
$f_i^{*,e}$	the total equilibrium flux through boundaries ∂B_i
$f_{i,j}(t)$	distribution of first passage times from equilibrium distribution in B_i to boundary $\partial B_i \cap \partial B_j$
$\mathcal{H}(\mathbf{x}, \mathbf{v})$	the total energy (Hamiltonian)
h	length parameter of billiard table
k_B	the Boltzmann constant
k_f	force constant
$k_{i,j}$	rate constant for $i \rightarrow j$ transition
$k_{i,j}^{\text{TST}}$	rate constant calculated using the TST ²⁵
$k_{i,j}^{\text{MLE}}$	rate constant calculated using the MLE
$k_{i,j}^{\text{A5}}$	rate constant calculated using (A5)
$L_{j,m}^i(t)$	distribution of lengths of trajectories in B_i with endpoints at $\partial B_i \cap \partial B_j$ and $\partial B_i \cap \partial B_m$
l	position of the dividing surface on the billiard table
LJ	Lennard-Jones
LJ_7^{2D}	cluster of seven LJ discs
$\mathbf{M}$	matrix of particle masses

MC	Monte Carlo
MD	molecular dynamics
ME	master equation
MJP	Markov jump process
MLE	maximum likelihood estimator
MSM	Markov state model
NGT	new graph transformation ⁷⁸
$\hat{n}_{i,j}(\mathbf{x})$	unit vector normal to $\partial(B_i \cup B_j)$ pointing towards $B_i \cup B_j$
PDF	probability density function
$p_i(t)$	population in B_i at time t in the original chain
$p_i^*(t)$	population in B_i at time t in the modified chain
p_i^e	equilibrium population in B_i
p_j^i	probability that an equilibrium trajectory enters B_i from B_j
p_i^*	equilibrium population in B_i in the modified chain
$p_{i,j}^e$	probability of exit from equilibrium in B_i to $\partial B_i \cap \partial B_j$
$p_{j,m}^i$	probability for a trajectory entering B_i through $\partial B_i \cap \partial B_j$ to exit B_i through $\partial B_i \cap \partial B_j$
$p_{i,m}^*$	the total population that exited from B_i through $\partial B_i \cap \partial B_j$ during relaxation compared to the equilibrium population
S	surface area of both cells on Sinai billiard
S_i	surface area of the i th cell on Sinai billiard
T	temperature
TPS	transition path sampling
TPT	transition path theory
TST	transition state theory
t	time
$t_{j,m}^n$	length (duration) of a trajectory
$\mathcal{V}$	the potential energy
$\mathbf{v}$	velocity vector
$\mathbf{x}$	position vector
Z	partition function
β	reciprocal temperature
γ	friction tensor in the Langevin equation; friction constant in 1D
$\delta(t)$	the Dirac delta function
δ	the minimum width of the gap between the rectangle and the circle on Sinai billiard
∂B_i	boundary of cell B_i
$\partial_x Y$	partial derivative of Y with respect to x
ϵ_0	well depth of the Lennard-Jones potential
$\eta(t)$	white noise
$\Theta(t)$	the Heaviside step function
ξ	collective coordinate for the LJ cluster transition
$\varrho(\mathbf{x}, \mathbf{v}, t)$	instantaneous population density in a system with momenta
$\varrho^e(\mathbf{x}, \mathbf{v})$	canonical equilibrium population density
$\varrho_m^e(\mathbf{x}, \mathbf{v})$	microcanonical equilibrium population density
$\varrho_e(\mathbf{x}, \mathbf{v})$	canonical equilibrium population density normalised to a cell pair

σ_0	particle radius in the LJ potential
$d\sigma(\mathbf{x})$	an element of surface
τ_0	characteristic unit of time for the Lennard-Jones potential
$\tau_{i,j}^{\text{rxn}}$	relaxation time in a modified chain
$\tau_{i,j}^{\text{ex}}(\mathbf{x})$	mean time of exit from point $\mathbf{x} \in B_i$ to $\partial B_i \cap \partial B_j$
$\tau_{i,j}^e$	mean time of exit from equilibrium in B_i to $\partial B_i \cap \partial B_j$
$\tau_{j,m}^i$	mean length of trajectories entering B_i through $\partial B_i \cap \partial B_j$ and exiting B_i through $\partial B_i \cap \partial B_j$
$\tau_{i,m}^*$	defined by (39), has units of time
Ω	configuration space, $\Omega \subset \mathbb{R}^{3N}$

APPENDIX A: NO-FLUX BOUNDARY CONDITIONS FOR OVERDAMPED AND INERTIAL LANGEVIN DYNAMICS

Here we discuss another way to realize the artificial modification of the chain that led to (13). The procedure discussed here applies for Langevin equation (1) with finite friction and overdamped Langevin equation (6). In the overdamped case, the pairwise relaxation between the two cells B_i and B_j described in Sec. II C can be realized by imposing no-flux boundary conditions at the boundaries of the union of these two cells. At the level of the FPE, this amounts to studying

$$\partial_t \rho^*(\mathbf{x}, t) = \nabla \cdot \left(\mathbf{D} \rho_{i,j}^e(\mathbf{x}) \nabla \left(\frac{\rho^*(\mathbf{x}, t)}{\rho_{i,j}^e(\mathbf{x})} \right) \right) \quad (\text{A1})$$

solved for $\mathbf{x} \in B_i \cup B_j$ with a no-flux boundary condition on $\partial(B_i \cup B_j)$, i.e.,

$$\hat{n}_{i,j}(\mathbf{x}) \cdot \mathbf{D} \nabla \left(\frac{\rho^*(\mathbf{x}, t)}{\rho_{i,j}^e(\mathbf{x})} \right) = 0 \quad (\text{A2})$$

for $\mathbf{x} \in \partial(B_i \cup B_j)$. Here $\hat{n}_{i,j}(\mathbf{x})$ denotes the outward pointing unit normal to $\partial(B_i \cup B_j)$ at $\mathbf{x}$ and $\rho_{i,j}^e(\mathbf{x}) = \exp(-\beta(V(\mathbf{x}))/Q_{i,j})$, $Q_{i,j} = \int_{B_i \cup B_j} \rho_{i,j}^e(\mathbf{x}) d\mathbf{x}$ is the Boltzmann density conditional on the system being in $B_i \cup B_j$ (i.e., such that $\int_{B_i \cup B_j} \rho_{i,j}^e(\mathbf{x}) d\mathbf{x} = 1$). An initial condition consistent with the relaxation from B_i to B_j described in Sec. II C is

$$\rho_i^*(\mathbf{x}, 0) = \begin{cases} \rho_{i,j}^e(\mathbf{x})/p_i^{*,e}, & \text{if } \mathbf{x} \in B_i \\ 0, & \text{otherwise} \end{cases}, \quad (\text{A3})$$

where $p_i^{*,e} = \int_{B_i} \rho_{i,j}^e(\mathbf{y}) d\mathbf{y}$ and $\rho_j^*(\mathbf{x}, 0) = 0$.

The relaxation time can be obtained from $\rho^*(\mathbf{x}, t)$ as

$$\tau_{i,j}^{\text{rxn}} = \frac{1}{p_j^e} \int_0^\infty \left(\int_{B_i} \rho_i^*(\mathbf{x}, t) d\mathbf{x} - p_i^e \right) dt \quad (\text{A4})$$

and $k_{i,j} = p_j^{*,e}/\tau_{i,j}^{\text{rxn}}$. As we will show below in Appendix B, these rate constants can be expressed in terms of mean first exit times from B_i to B_j , $\tau_{i,j}^e$, and B_j to B_i , $\tau_{j,i}^e$, as

$$k_{i,j} = \frac{p_j^{*,e}}{\tau_{i,j}^e p_j^{*,e} + \tau_{j,i}^e p_i^{*,e}}. \quad (\text{A5})$$

The mean exit times $\tau_{i,j}^e$ can be calculated from $\rho^*(\mathbf{x}, t)$ as

$$\tau_{i,j}^e = \int_0^\infty \int_{B_i} \rho_i^*(\mathbf{x}, t) d\mathbf{x} dt, \quad (\text{A6})$$

and a similar formula holds for $\tau_{i,j}^e$ if we revert the roles of B_i and B_j .

Formula (A5) also holds in the case of frictional Langevin equation (1) if instead of $\rho^*(\mathbf{x}, t)$ we use the solution to (2), solved in $(\mathbf{x}, \mathbf{v}) \in (B_i \cup B_j) \times \mathbb{R}^{3n}$ with the following boundary condition on $\partial(B_i \cup B_j)$:

$$\varrho^*(\mathbf{x}, \mathbf{v}, t) = \varrho^*(\mathbf{x}, -\mathbf{v}, t). \quad (\text{A7})$$

If the assumptions of TST hold exactly, i.e., if all distributions of first passage times are exponential, expression (A5) gives rate constants equal to one half the rate constants predicted by the TST. This factor of 2 is caused by loss of direction at the boundary, causing half of the particles to instantaneously recross the boundary.

APPENDIX B: DERIVATION OF FORMULA (A5)

Eq. (A5) was originally proposed by Northrup and Hynes⁶¹ and Schulten *et al.*⁶² A derivation of this formula in one dimension was given by Bicout and Szabó.⁶³ Here, we derive the equation for arbitrary dimensionality. To this end, it is convenient to subtract the asymptotic value $\lim_{t \rightarrow \infty} \rho_i^*(\mathbf{x}, t) = \rho_{i,j}^e(\mathbf{x})$ from $\rho_i^*(\mathbf{x}, t)$ and consider the evolution of $\tilde{\rho}_i^*(\mathbf{x}, t) = \rho_i^*(\mathbf{x}, t) - \rho_{i,j}^e(\mathbf{x})$. This quantity is governed by

$$\partial_t \tilde{\rho}_i^*(\mathbf{x}, t) = \nabla \cdot \left(D \rho_{i,j}^e(\mathbf{x}) \nabla \left(\frac{\tilde{\rho}_i^*(\mathbf{x}, t)}{\rho_{i,j}^e(\mathbf{x})} \right) \right), \quad (\text{B1})$$

to be solved for $\mathbf{x} \in B_i \cup B_j$ with the boundary condition

$$\hat{\mathbf{n}}_{i,j}(\mathbf{x}) \cdot D \nabla \left(\frac{\tilde{\rho}_i^*(\mathbf{x}, t)}{\rho_{i,j}^e(\mathbf{x})} \right) = 0, \quad \text{for } \mathbf{x} \in \partial(B_i \cup B_j), \quad (\text{B2})$$

and the initial condition

$$\tilde{\rho}_i^*(\mathbf{x}, 0) = \begin{cases} \rho_{i,j}^e(\mathbf{x}) p_j^{*,e} / p_i^{*,e}, & \text{if } \mathbf{x} \in B_i, \\ -\rho_{i,j}^e(\mathbf{x}), & \text{if } \mathbf{x} \in B_j. \end{cases} \quad (\text{B3})$$

If we integrate (B1) on $t \in [0, \infty)$ and define

$$f_i^*(\mathbf{x}) = \int_0^\infty \tilde{\rho}_i^*(\mathbf{x}, t) dt \quad (\text{B4})$$

we arrive at the following equation for $f_i^*(\mathbf{x})$:

$$-\tilde{\rho}_i^*(\mathbf{x}, 0) = \nabla \cdot \left(D \rho_{i,j}^e(\mathbf{x}) \nabla \left(\frac{f_i^*(\mathbf{x})}{\rho_{i,j}^e(\mathbf{x})} \right) \right), \quad (\text{B5})$$

to be solved for $\mathbf{x} \in B_i \cup B_j$ with the boundary condition

$$\hat{\mathbf{n}}_{i,j}(\mathbf{x}) \cdot D \nabla \left(\frac{f_i^*(\mathbf{x})}{\rho_{i,j}^e(\mathbf{x})} \right) = 0, \quad \text{for } \mathbf{x} \in \partial(B_i \cup B_j). \quad (\text{B6})$$

Even though the operator acting on $f_i^*(\mathbf{x})$ at the right hand side of (B5) is not invertible (its null-space is spanned by multiples of $\rho_{i,j}^e(\mathbf{x})$), this equation has a solution because its left hand side belongs to the range of this operator. This result can be obtained by integrating both sides over $B_i \cup B_j$ and noticing

that they both vanish. The solution is unique if we impose the constraint that

$$\int_{B_i \cup B_j} f_i^*(\mathbf{x}) d\mathbf{x} = 0, \quad (\text{B7})$$

which follows from the fact that $\int_{B_i \cup B_j} \tilde{\rho}_i^*(\mathbf{x}, t) d\mathbf{x} = 0$. Notice also that since the source term at the left hand side of (B5) is discontinuous on $\partial B_i \cap \partial B_j$, we also need to impose some condition at this boundary. Specifically, we must require that $f_i^*(\mathbf{x})$ be continuous at $\partial B_i \cap \partial B_j$, and that

$$\begin{aligned} & \int_{\partial B_i \cap \partial B_j} \rho_{i,j}^e(\mathbf{x}) \hat{\mathbf{n}}_{i,j}(\mathbf{x}) \cdot D \left[\nabla \left(\frac{f_i^*(\mathbf{x})}{\rho_{i,j}^e(\mathbf{x})} \right) \right]_{B_i \text{ side}} d\sigma(\mathbf{x}) \\ &= \int_{\partial B_i \cap \partial B_j} \rho_{i,j}^e(\mathbf{x}) \hat{\mathbf{n}}_i \cdot D \left[\nabla \left(\frac{f_i^*(\mathbf{x})}{\rho_{i,j}^e(\mathbf{x})} \right) \right]_{B_j \text{ side}} d\sigma(\mathbf{x}), \end{aligned} \quad (\text{B8})$$

where $d\sigma(\mathbf{x})$ is the surface element on $\partial B_i \cap \partial B_j$, and the brackets indicate on which side of $\partial B_i \cap \partial B_j$ the gradient is evaluated. Thus, the gradient of $f_i^*(\mathbf{x})$ may be discontinuous on $\partial B_i \cap \partial B_j$, but (B7) requires that the flux across $\partial B_i \cap \partial B_j$ be zero. This condition is inherited from (B1), in which probability must be conserved across $\partial B_i \cap \partial B_j$, i.e., the current out of B_i is the same as that into B_j and vice versa.

We can express the solution to (B5) in terms of $\rho_{i,j}^e(\mathbf{x})$ and two mean first exit times, $\tau_{i,j}^{\text{ex}}(\mathbf{x})$ and $\tau_{j,i}^{\text{ex}}(\mathbf{x})$. Specifically, let $\tau_{i,j}^{\text{ex}}(\mathbf{x})$ be the mean time that a trajectory starting from $\mathbf{x} \in B_i$ and bouncing off the boundaries $\partial B_i \cap \cup_{k \neq j} \partial B_k$ takes to reach $\partial B_i \cap \partial B_j$ for the first time, and define $\tau_{j,i}^{\text{ex}}(\mathbf{x})$ similarly for the exit out of B_j through $\partial B_i \cap \partial B_j$. The mean first exit time $\tau_{i,j}^{\text{ex}}(\mathbf{x})$ satisfies

$$-\rho_{i,j}^e(\mathbf{x}) = \nabla \cdot \left(\rho_{i,j}^e(\mathbf{x}) D \nabla \tau_{i,j}^{\text{ex}}(\mathbf{x}) \right) \quad (\text{B9})$$

to be solved for $\mathbf{x} \in B_i$ with the mixed boundary conditions

$$\begin{cases} \hat{\mathbf{n}}_{i,j}(\mathbf{x}) \cdot D \nabla \tau_{i,j}^{\text{ex}}(\mathbf{x}) = 0 & \text{for } \mathbf{x} \in \partial B_i \cap \cup_{k \neq j} \partial B_k, \\ \tau_{i,j}^{\text{ex}}(\mathbf{x}) = 0 & \text{for } \mathbf{x} \in \partial B_i \cap \partial B_j, \end{cases} \quad (\text{B10})$$

and similarly for $\tau_{j,i}^{\text{ex}}(\mathbf{x})$. It can then be checked by direct substitution that the solution to (B5) with the boundary conditions in (B6) and (B8) can be expressed as

$$f_i^*(\mathbf{x}) = \begin{cases} \rho_{i,j}^e(\mathbf{x}) (C_i + \tau_{i,j}^{\text{ex}}(\mathbf{x}) p_j^{*,e} / p_i^{*,e}), & \text{if } \mathbf{x} \in B_i, \\ \rho_{i,j}^e(\mathbf{x}) (C_i - \tau_{j,i}^{\text{ex}}(\mathbf{x})), & \text{if } \mathbf{x} \in B_j, \end{cases} \quad (\text{B11})$$

where the constant C_i is determined by the constraint (B7). This form gives $C_i = [\tau_{i,j}^e(\mathbf{x}) - \tau_{i,j}^{\text{ex}}(\mathbf{x})] p_j^{*,e}$, where the equilibrium average in B_i of $\tau_{i,j}^{\text{ex}}(\mathbf{x})$ is

$$\tau_{i,j}^e = \frac{1}{p_i^{*,e}} \int_{B_i} \tau_{i,j}^{\text{ex}}(\mathbf{x}) \rho_{i,j}^e(\mathbf{x}) d\mathbf{x}. \quad (\text{B12})$$

Comparing (17) with (B4) we can see that the relaxation time $\tau_{i,j}^{\text{rxn}}$ can be expressed in terms of $f_i^*(\mathbf{x})$ as

$$\tau_{i,j}^{\text{rxn}} = \frac{1}{p_j^{*,e}} \int_{B_i} f_i^*(\mathbf{x}) d\mathbf{x}. \quad (\text{B13})$$

Using result (B11) in (B13) we get

$$\begin{aligned}\tau_{i,j}^{\text{rxn}} &= \frac{1}{p_j^{*,e}} \left(p_i^e p_j^e \tau_{j,i}^e - p_i^{*,e} p_j^{*,e} \tau_{i,j}^e + p_j^{*,e} \tau_{i,j}^e \right) \\ &= p_i^{*,e} \tau_{j,i}^e + p_j^{*,e} \tau_{i,j}^e,\end{aligned}\quad (\text{B14})$$

which is the connection between the relaxation times and first passage times. Using this expression in (18) gives (A5).

APPENDIX C: MLE

Here, we briefly discuss the difficulties related to using maximum likelihood estimation of the rate matrix. In this setup, given the sets $B_i, i = 1, \dots, N$, and the long piece of the configurational part of the trajectory, $\mathbf{x}(t)$ for $t \in [0, T_{\text{max}})$, one starts by mapping $\mathbf{x}(t)$ onto a piecewise constant function that retains only the information about the index of the set $\mathbf{x}(t)$ is currently in, i.e., define

$$\alpha(t) = i \quad \text{if } \mathbf{x}(t) \in B_i. \quad (\text{C1})$$

The function $\alpha(t)$ takes values in the index set $\{1, 2, \dots, N\}$ and jumps from one value to another each time $\mathbf{x}(t)$ moves from one set to another (for example, $\alpha(t)$ jumps from i to j when $\mathbf{x}(t)$ moves from B_i to B_j). Given $\alpha(t)$ for $t \in [0, T_{\text{max}}]$ we can then use standard Bayesian inference methods to estimate the rate matrix $k_{i,j}$, e.g., by maximising the likelihood function of this trajectory over all $k_{i,j}$. The maximum likelihood estimator is

$$k_{i,j}^{(MLE)} = \frac{N_{i,j}^{T_{\text{max}}}}{T_{i,j}^{T_{\text{max}}}} \quad (i \neq j), \quad (\text{C2})$$

where $N_{i,j}^{T_{\text{max}}}$ is the total number of jumps the trajectory made from B_i to B_j in the interval $[0, T_{\text{max}})$, and $T_{i,j}^{T_{\text{max}}}$ is the total time this trajectory spent in B_i in this interval. The difficulty with this procedure is that the MLE estimate $k_{i,j}^{(MLE)}$ typically overestimates the rate constant. This is because $\mathbf{x}(t)$ usually recrosses the boundary of the cells B_i frequently, in a non-Markov (correlated) way, before committing to one specific cell. For example, in the case of overdamped dynamics, this procedure fails completely, since the trajectory $\mathbf{x}(t)$, being non-differentiable in time, crosses any boundary infinitely often. The only way to get around this difficulty is to either process the trajectory at finite lag (i.e., construct a discrete-time Markov chain first), or use core or target sets^{44,52} that do not partition space and assign the trajectory to the last such set visited.

APPENDIX D: ANOTHER MODIFICATION OF THE CHAIN

Here, we show why it is important to sample both cells B_i and B_j to calculate the rate constant $k_{i,j}$ and why an approach based on integration of the relaxation time is typically more accurate than an approach based only on observing the first exit out of a cell. To this end, notice first that another possible modification of the chain that can be used to estimate the rate matrix consists in picking a state i_* and letting all states

FIG. 5. Schematic representation of the modification of the chain use in this work (right), in which we artificially isolate two states/cells from the system and observe the relaxation toward equilibrium of this modified chain. The modification introduced in (D1) is on the left.

connected to it become sinks (Fig. 5 left), i.e., for $i \neq j$ set

$$k_{i,j}^0 = \begin{cases} k_{i,j}, & \text{if } i = i_*, \\ 0, & \text{otherwise.} \end{cases} \quad (\text{D1})$$

If we start the system at $i = i_*$ in this modified chain, it is easy to see that it will jump eventually to another state, then stay there forever. In particular, the solution to

$$p_i^0(t) = \sum_{j=1}^N p_j^0(t) k_{j,i}^0, \quad p_i^0(0) = \delta_{i,i_*} \quad (\text{D2})$$

is such that $p_{i_*}^0(t)$ gives the probability that the system has not yet left state i_* at time t (since otherwise it would have reached another state $j \neq i_*$, without any possibility to come back to i_*), that is, the probability that the first exit time out of i_* is larger than t ; and $\lim_{t \rightarrow \infty} p_j^0(t)$ with $j \neq i_*$ gives the probability that the state reached right after i_* is j . Simple calculations then imply that (denoting now i_* by i since we can pick any i_* and repeat the argument for each),

(a) with probability

$$\pi_{j|i}^0 = \frac{k_{i,j}^0}{\sum_{l \neq i} k_{i,l}^0} \quad (\text{D3})$$

state $j (\neq i)$ will be the one visited by the chain directly after state i , and

(b) the time it takes the chain to leave state i after first arrival in this state is exponentially distributed by mean

$$\tau_i^{\text{wait}} = \frac{1}{\sum_{j \neq i} k_{i,j}^0}. \quad (\text{D4})$$

Note that property (b) holds regardless of which state is hit after i . This property can in principle be used as a test of Markovianity. Note also that if we know $\pi_{j|i}^0$ and τ_i^{wait} , we can recover $k_{i,j}^0$ (for $i \neq j$) from

$$k_{i,j}^0 = \frac{\pi_{j|i}^0}{\tau_i^{\text{wait}}}. \quad (\text{D5})$$

At the MD level, this procedure amounts to identifying τ_i^{wait} in (D5) with the total mean exit time τ_i^E out of B_i , defined as

$$\tau_i^E = \sum_j \tau_{i,j}^e p_{i,j}^e. \quad (\text{D6})$$

This estimate, however, leads to difficulties when the distribution of first passage times is not exponential. In this case, the mean exit time is not equal to the reciprocal equilibrium flux through the dividing surface, and the rate constant given by

(D5) with τ_i^{wait} approximated by τ_i^E does not satisfy detailed balance. In addition, this estimator is quite sensitive to the precise location of the boundaries of the cells, because it only accounts for the exit of these cells and not the commitment to another cell—for example, an exit can be followed by a quick correlated reentrance if the boundary of cell B_i is badly placed. The estimator in (42) does not have this problem.

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