Committors, first-passage times, fluxes, Markov states, milestones, and all that

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ABSTRACT

Milestoning on a one-dimensional potential starts by choosing a set of points, called milestones, and initiating short trajectories from each milestone, which are terminated when they reach an adjacent milestone for the first time. From the average duration of these trajectories and the probabilities of where they terminate, a rate matrix can be constructed and then used to calculate the mean first-passage time (MFPT) between any two milestones. All these MFPTs turn out to be exact. Here we adopt a point of view from which this remarkable result is not unexpected. In addition, we clarify the nature of the “states” whose interconversion is described by the rate matrix constructed using information obtained from short trajectories and provide a microscopic expression for the “equilibrium population” of these states in terms of equilibrium averages of the committors.

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I. INTRODUCTION

Many recent advances in the theory of rare events were not made algebraically but rather by analyzing the behavior of trajectories. Both transition path theory^{1–3} and milestoning^{4–6} can be regarded as part of the emerging field of “statistical mechanics of trajectories.” This paper grew out of our efforts to understand Elber’s milestoning in the simplest context.

Operationally, Elber’s milestoning for one-dimensional diffusive dynamics on a potential can be formulated as follows: Choose an arbitrary set of points labeled by the index i , $i = 1, 2, \dots, N$. Point i is called milestone i . Run Brownian dynamics trajectories starting from milestone i and terminate them when they reach either milestone $i - 1$ or milestone $i + 1$ for the first time. The average duration of these trajectories, denoted by t_i , is by construction the mean first-passage time (MFPT) from milestone i to one of the two milestones, $i - 1$ and $i + 1$. In addition, the fraction of trajectories terminated at milestone $i + 1$ is determined. This is the splitting probability or committor denoted by $\varphi(i \rightarrow i + 1)$. Clearly, $\varphi(i \rightarrow i - 1) = 1 - \varphi(i \rightarrow i + 1)$.

This information is then used to construct an $N \times N$ rate matrix $\mathbf{R}$ that describes the interconversion of yet unspecified “states” I , $I = 1, 2, \dots, N$. This is a three-diagonal matrix with off-diagonal matrix elements $R_{I, I \pm 1} = \varphi(i \rightarrow i \pm 1)/t_i$ and diagonal elements $R_{I, I} = -1/t_i$. This guarantees that the mean lifetime of state I , given by $(R_{I, I+1} + R_{I, I-1})^{-1}$, is t_i and the probability to go from state I to state $I + 1$, given by $R_{I, I+1}/(R_{I, I+1} + R_{I, I-1})$, is $\varphi(i \rightarrow i + 1)$, where t_i and $\varphi(i \rightarrow i + 1)$ were obtained by running many short trajectories. It is important to emphasize that the distributions of lifetimes of states I are single-exponential, whereas the exact distributions of the MFPTs in general are not. Nevertheless, the MFPT between any two states obtained by using the rate matrix $\mathbf{R}$ turns out to be exact! The importance of this result is that the exact MFPT can be obtained, for example, for two milestones separated by a high barrier. To directly obtain this MFPT by running Brownian dynamics simulations would take virtually forever. On the other hand, using milestoning, all one has to do is run many relatively short trajectories starting from milestones.

Thus, milestoning maps the diffusive dynamics onto a nearest-neighbor continuous-time Markov state model. The fact that the MFPT's between the states, obtained using the rate matrix, are identical to the MFPT's between the corresponding milestones calculated using the Smoluchowski equation was initially surprising to us. One goal of this paper is to find a way of thinking that makes this, at first sight, remarkable result not unexpected. To do this, we need to understand the nature of the “states” whose interconversion is described by the rate matrix $\mathbf{R}$, and the meaning of their “equilibrium populations” obtained from the eigenvector of this rate matrix corresponding to zero eigenvalue.

The outline of this paper is as follows: In Sec. II, we consider just two milestones. This may seem too trivial to provide any insight because the MFPT's of the two-state model are exact by construction. However, it turns out to be the simplest context where one can understand what the states are and what their equilibrium populations mean. In Sec. III, we consider three milestones, which is the simplest case that involves splitting probabilities. Some concluding remarks are presented in Sec. IV. In the Appendix, we algebraically derive some identities that have been obtained in Sec. II by analyzing a long equilibrium trajectory.

II. TWO MILESTONES

We begin by analyzing the simplest possible example of milestoning. Consider a particle diffusing in a bounded one-dimensional potential $U(x)$, $U(x \rightarrow \pm\infty) = \infty$. Choose two arbitrary points (milestones), $x = a$, and $x = b$, $a < b$. The average duration of trajectories, initiated at point a and terminated at point b , is the mean first-passage time (MFPT) from a to b , $\tau(a \rightarrow b)$. Similarly, the MFPT $\tau(b \rightarrow a)$ can be obtained by starting trajectories from point b and terminating them when they reach point a .

If points a and b were located at the minima of two deep wells, A and B, of a bistable potential, separated by a high barrier, then the distributions of both first-passage times would be very nearly exponential. In this case, it would make sense to describe the dynamics of the system in terms of Markovian transitions between the two wells, i.e., by a two-state model

where the rate constants for inter-well transitions are given by

$$k_{A \rightarrow B} = \frac{1}{\tau(a \rightarrow b)}, \quad k_{B \rightarrow A} = \frac{1}{\tau(b \rightarrow a)}. \quad (2.2)$$

If the two points are arbitrary, then the distributions of the first-passage times are no longer exponential. Nevertheless, one can formally adopt the above two-state description, i.e., use the MFPT's and build a two-state model as discussed above. At least the mean lifetimes of the two states, A and B, $k_{A \rightarrow B}^{-1}$ and $k_{B \rightarrow A}^{-1}$, will be correct. The equilibrium populations, π_A and π_B , of these states are

$$\pi_A = \frac{k_{B \rightarrow A}}{k_{A \rightarrow B} + k_{B \rightarrow A}} = \frac{\tau(a \rightarrow b)}{\tau(a \rightarrow b) + \tau(b \rightarrow a)}, \quad \pi_B = 1 - \pi_A. \quad (2.3)$$

The equilibrium unidirectional flux between them, i.e., the number of A-to-B (or B-to-A) transitions per unit time at equilibrium, $J_{AB} = J_{A \rightarrow B} = J_{B \rightarrow A}$, is

$$J_{AB} = \pi_A k_{A \rightarrow B} = \pi_B k_{B \rightarrow A}. \quad (2.4)$$

For future reference, note that the rate constants in this model can be expressed as “flux-over-population,” i.e., $k_{A \rightarrow B} = J_{AB}/\pi_A$, $k_{B \rightarrow A} = J_{AB}/\pi_B$. Substituting in Eq. (2.4) the rate constants and equilibrium populations given in Eqs. (2.2) and (2.3), we find that

$$J_{AB} = \frac{1}{\tau(a \rightarrow b) + \tau(b \rightarrow a)}. \quad (2.5)$$

The sum of the MFPT's in the denominator has been called the mean round-trip time between points a and b .⁷ Thus the equilibrium unidirectional flux is the inverse mean round-trip time. However, it is not at all obvious what the two “states,” A and B, associated with milestones a and b are, what the equilibrium populations of these states mean, and what the unidirectional flux corresponds to.

A. Coloring an equilibrium trajectory

To answer these questions, consider a long equilibrium trajectory, $x(t)$, of duration T , $T \rightarrow \infty$. One way of obtaining the first passage times between points a and b is to use the trajectory coloring procedure introduced by Vanden-Eijnden and Venturoli⁸ (see also Ref. 3). Let us color the trajectory either red or blue using the following rules: the trajectory changes color from red to blue when it comes to point b from point a , and from blue to red when it comes to point a from point b , as show in the upper panel of Fig. 1. This is similar to the procedure used by Buchete and Hummer⁹ to define states when constructing Markov state models. In addition, a referee pointed out that it is closely related to transition interface sampling.^{10,11} Let T_a (T_b) be the total time the trajectory is red (blue) so that $T_a + T_b = T$. Let N_{ab} be the number of times the color of the trajectory changes from red-to-blue or equivalently from blue-to-red during time T . The MFPT's $\tau(a \rightarrow b)$ and $\tau(b \rightarrow a)$ are the average durations of the red and blue segments,

$$\tau(a \rightarrow b) = \frac{T_a}{N_{ab}}, \quad \tau(b \rightarrow a) = \frac{T_b}{N_{ab}}. \quad (2.6)$$

Thus the mean lifetimes of the red and blue segments, $\tau(a \rightarrow b)$ and $\tau(b \rightarrow a)$, are equal to the mean lifetimes of states A and B, $k_{A \rightarrow B}^{-1}$ and $k_{B \rightarrow A}^{-1}$, respectively.

The probability that the trajectory is red, π_a , is the fraction $T_a/T = T_a/(T_a + T_b)$, while the probability that the trajectory is blue, π_b , is the fraction $T_b/T = T_b/(T_a + T_b)$. Using the relations between the MFPT's and times T_a and T_b , Eq. (2.6), these can be written as

$$\pi_a = \frac{T_a}{T_a + T_b} = \frac{\tau(a \rightarrow b)}{\tau(a \rightarrow b) + \tau(b \rightarrow a)}, \quad \pi_b = 1 - \pi_a. \quad (2.7)$$

FIG. 1. Upper panel: A long equilibrium trajectory generated by Brownian dynamics simulations that is colored red and blue. The color changes from red to blue when the trajectory from a reaches b for the first time and remains blue until it reaches a for the first time whereupon it turns red. The color of the trajectory depends on the last milestone it touched: the color is red (blue), if the last touched milestone is a (b). Lower panel: The colored trajectory $x(t)$ is converted into a two-state trajectory where the lifetime of state A (B) is equal to the time during which the trajectory $x(t)$ is red (blue).

These are identical to the equilibrium populations in Eq. (2.3) obtained using the two-state model with rate constants given in Eq. (2.2). Therefore, state A (B) associated with milestone a (b) corresponds to red (blue) trajectory segments, as shown in the lower panel of Fig. 1. Note that states A and B are not thermodynamic states. The reason is that the trajectory can be both red and blue in the region between the milestones, $a < x < b$. The color is red (blue) if the last milestone touched by the trajectory before coming to point x is point a (b). Therefore, when $a < x < b$, the trajectory can be sometimes red (state A) and sometimes blue (state B) (see Fig. 1), while in thermodynamics any spatial point can belong to only one state. Thus, states A and B associated with the milestones are states of the trajectory rather than thermodynamic states.

The unidirectional flux between points a and b at equilibrium, $J_{ab} = J_{a \rightarrow b} = J_{b \rightarrow a}$, by definition, is

$$J_{ab} = \frac{N_{ab}}{T} = \frac{N_{ab}}{T_a + T_b}. \quad (2.8)$$

Using Eq. (2.6), this flux can be written in terms of the MFPT's $\tau(a \rightarrow b)$ and $\tau(b \rightarrow a)$ as

$$J_{ab} = \frac{1}{\tau(a \rightarrow b) + \tau(b \rightarrow a)}. \quad (2.9)$$

This is identical to the flux J_{AB} , Eq. (2.5), obtained in the framework of the two-state model. Thus, the equilibrium unidirectional flux between points a and b is the same as with the number of transitions from trajectory state A to state B (and vice versa) per unit time, at equilibrium, $J_{ab} = J_{AB}$.

To summarize, using the trajectory coloring procedure, we found that states A and B, associated with milestones a and b , indicate the color of the trajectory (red in state A and blue in state B). The equilibrium populations of these states, π_A and π_B , are the fractions of time when the trajectory is red and blue, π_a and π_b , respectively. Finally, the equilibrium unidirectional flux between these states, J_{AB} , is the equilibrium unidirectional flux, J_{ab} , between the two milestones.

The two-state model using the rate constants defined as the reciprocals of the MFPT's is remarkably successful in describing transitions between the trajectory segments of different color. While the MFPT's calculated from the two-state model are exact by construction, this model gives the exact relation between the unidirectional flux at equilibrium and the MFPT's, Eq. (2.9). Although at first glance this might seem surprising, there is a point of view from which it is not unexpected. The trajectory corresponding to the two-state model can be exactly generated using the Gillespie algorithm, where the lifetimes of states A and B are chosen from the exponential distributions. For example, for state A, the distribution is $k_{A \rightarrow B} \exp(-k_{A \rightarrow B}t) = \exp(-t/\tau(a \rightarrow b))/\tau(a \rightarrow b)$. While these exponential distributions differ from the exact lifetime distributions of the red and blue trajectory segments, the corresponding lifetimes are equal on average (the mean lifetimes are the same by construction). Thus, on average, the two-state trajectory is equivalent to the red-blue trajectory obtained by coloring the initial trajectory shown in the lower panel of Fig. 1. Therefore, the average number of unidirectional transitions per unit time calculated from the two-state trajectory must be the same as that obtained from the colored trajectory. As we shall see in Sec. III, this is the simplest way of understanding why a three-state model exactly gives all the MFPT's and equilibrium unidirectional fluxes for three milestones.

B. Microscopic interpretation of equilibrium populations of states A and B

Next, we discuss a microscopic interpretation of the equilibrium populations of states A and B. According to the coloring rules, the trajectory is always red when $x \leq a$ and blue when $x \geq b$. In the intermediate region, $a < x < b$, the color of the trajectory depends on the prehistory. The trajectory is red, if it entered the intermediate region through point a , and blue, if it entered through point b . Because of detailed balance or time-reversal symmetry, the probability that the trajectory reaches x coming from a is equal to the probability that starting from x , the trajectory reaches a before touching b . This probability, denoted by $\varphi(x \rightarrow a)$, is referred to as the committor or splitting probability. Similarly, the probability that the trajectory reaches x having entered the intermediate region from b is equal to the probability that starting from x , the trajectory reaches b before touching a . This probability, denoted by $\varphi(x \rightarrow b)$, is $\varphi(x \rightarrow b) = 1 - \varphi(x \rightarrow a)$.

The probability that the trajectory is colored red (state A) at an arbitrary point x , denoted by $\varphi_a(x)$, is

$$\varphi_a(x) = \begin{cases} 1, & x \leq a \\ \varphi(x \rightarrow a), & a \leq x \leq b. \\ 0, & b \leq x \end{cases} \quad (2.10a)$$

The probability that the trajectory at point x is colored blue (state B), denoted by $\varphi_b(x)$, is

$$\varphi_b(x) = \begin{cases} 0, & x \leq a \\ \varphi(x \rightarrow b), & a \leq x \leq b. \\ 1, & b \leq x \end{cases} \quad (2.10b)$$

Since we are dealing with an equilibrium trajectory, the probability of finding the trajectory at point x is given by the Boltzmann distribution, $\exp(-\beta U(x))/Z$, where $Z = \int_{-\infty}^{\infty} \exp(-\beta U(x)) dx$ with $\beta = 1/(k_B T)$, where k_B and T denote the Boltzmann constant and the absolute temperature. Therefore, the equilibrium probability densities that an arbitrary point x is red or blue are $\varphi_i(x) \exp(-\beta U(x))/Z$, $i = a, b$. As a consequence, the equilibrium probability of finding the trajectory red (blue) is the Boltzmann average of $\varphi_a(x)$ ($\varphi_b(x)$),

$$\pi_i = \langle \varphi_i \rangle = \frac{\int_{-\infty}^{\infty} \varphi_i(x) e^{-\beta U(x)} dx}{\int_{-\infty}^{\infty} e^{-\beta U(x)} dx}, \quad i = a, b. \quad (2.11)$$

This probability is also the equilibrium population π_i of state I , $I = A, B$. Thus, the equilibrium population of state I is the Boltzmann average of the probability $\varphi_i(x)$, $\pi_I = \langle \varphi_i \rangle$.

C. MFPT's, rate constants, and equilibrium unidirectional flux

The MFPT's between points a and b , given in Eq. (2.6), can be written in terms of equilibrium populations, Eqs. (2.7) and (2.11), and the equilibrium unidirectional flux, Eq. (2.8),

$$\tau(a \rightarrow b) = \frac{T_a}{N_{ab}} = \frac{T_a}{T_a + T_b} \frac{T_a + T_b}{N_{ab}} = \frac{\langle \varphi_a \rangle}{J_{ab}}, \quad \tau(b \rightarrow a) = \frac{\langle \varphi_b \rangle}{J_{ab}}. \quad (2.12)$$

These are exact identities which are verified in the Appendix using analytical expressions obtained in the framework of the theory of first-passage processes. It should be pointed out that the mean transition path or direct-transit time between points a and b , denoted by $\tau(a \leftrightarrow b)$, can be written² as $\tau(a \leftrightarrow b) = \langle \varphi_a \varphi_b \rangle / J_{ab}$.

Using the above results for the MFPT's in Eq. (2.2), the rate constants for transitions between states A and B, defined by the color of the trajectory, can be written as

$$k_{A \rightarrow B} = \frac{J_{ab}}{\langle \varphi_a \rangle}, \quad k_{B \rightarrow A} = \frac{J_{ab}}{\langle \varphi_b \rangle}. \quad (2.13)$$

These expressions have been previously obtained by Vanden-Eijnden and Venturoli.⁸ The relation between our notation and theirs is $J \leftrightarrow \nu_R$ (unidirectional flux at equilibrium), $\varphi_a(x) \leftrightarrow q_-(x)$ (the probability that the trajectory at point x is colored red), and $\langle \varphi_a \rangle = \rho_a$ (the equilibrium probability that the trajectory is red).

D. Relation to Kramers theory

When the milestones a and b happen to be at the minima of two deep wells separated by a high barrier, the above expressions for the rate constants reduce to those of the Kramers theory. Kramers used flux divided by thermodynamic well population as the definition the rate constant.¹² In the case of two deep wells, the probability $\varphi_a(x)$ is unity not only when $x \leq a$ but also is essentially unity for a wider range of x , $a < x < x^*$, where x^* is a point between point a and the barrier top, chosen so that the potential energy $U(x^*)$ is several $k_B T$'s above the potential energy at the well bottom, $U(a)$. Therefore, $\langle \varphi_a \rangle$ is essentially $\int_{-\infty}^{x^*} e^{-\beta U(x)} dx / \int_{-\infty}^{\infty} e^{-\beta U(x)} dx$. The value of the integral in the numerator is determined by the potential near the well bottom at $x = a$ and is insensitive to the location of point x^* as long as it lies sufficiently far from point a (the energy difference $U(x^*) - U(a)$ exceeds several $k_B T$'s). Consequently, the equilibrium population of non-thermodynamic state A, $\langle \varphi_a \rangle$, is equal to the equilibrium thermodynamic population of well A. This happens because the interval, where points may have both colors, is located in the barrier region. When the barrier is high, the equilibrium population in this interval is vanishingly small.

As shown in the Appendix, the equilibrium unidirectional flux between points a and b is given by $J_{ab} = \left[\left(\int_{-\infty}^{\infty} e^{-\beta U(x)} dx \right) \left(\int_a^b e^{\beta U(x)} dx / D(x) \right) \right]^{-1}$, where $D(x)$ is the position-dependent diffusivity. Substituting J_{ab} and $\langle \varphi_a \rangle$ above into Eq. (2.13), we arrive at

$$k_{A \rightarrow B} = \frac{1}{\left(\int_{-\infty}^{x^*} e^{-\beta U(x)} dx \right) \left(\int_a^b e^{\beta U(x)} dx / D(x) \right)}. \quad (2.14)$$

While the value of the first integral in the denominator is determined by the behavior of the potential near the A-well bottom, the value of the second integral is determined by the behavior of the potential near the barrier top. The value of the latter integral is insensitive to the integration limits when the potential energies $U(a)$ and $U(b)$ are several $k_B T$'s below the barrier top. Assuming that $U(x)$ is quadratic near the A-well bottom and the barrier top, and the diffusivity is position-independent, we replace $U(x)$ in the integrands by the corresponding quadratic approximations, then let $x^* \rightarrow \infty$, $a \rightarrow -\infty$, and $b \rightarrow \infty$, and perform the integrations. In this way, we recover the celebrated Kramers formula for the rate constant for diffusive barrier crossing (high-friction regime).

III. THREE MILESTONES

We now consider the much more interesting case of three milestones located at points $x = a$, $x = b$, and $x = c$, $a < b < c$. By starting trajectories at points a or c and terminating them when they reach point b , we can find the MFPT's $\tau(a \rightarrow b)$ and $\tau(c \rightarrow b)$ as before. The milestone located at point b is different because it has milestones on both sides. Here we initiate trajectories at point b and terminate them when they reach either point a or point c . In this way, we determine the MFPT, $\tau(a \leftarrow b \rightarrow c)$, required to reach points a or c for the first time starting from point b . In addition, we determine the

committor or splitting probability that a trajectory starting at point b reaches point a before point c , denoted by $\varphi(b \rightarrow a)$. Clearly, $\varphi(b \rightarrow c) = 1 - \varphi(b \rightarrow a)$.

We use these MFPT's and splitting probabilities to build a three-state model of the dynamics

Here A , B , and C are yet unspecified "states" associated with milestones a , b , and c . The transitions between them are described by the rate constants defined as

$$\begin{aligned} k_{A \rightarrow B} &= \frac{1}{\tau(a \rightarrow b)}, & k_{B \rightarrow A} &= \frac{\varphi(b \rightarrow a)}{\tau(a \leftarrow b \rightarrow c)}, \\ k_{C \rightarrow B} &= \frac{1}{\tau(c \rightarrow b)}, & k_{B \rightarrow C} &= \frac{\varphi(b \rightarrow c)}{\tau(a \leftarrow b \rightarrow c)}. \end{aligned} \quad (3.2)$$

The rate constants $k_{B \rightarrow A}$ and $k_{B \rightarrow C}$ are defined so as to ensure that (1) the splitting probabilities for $B \rightarrow A$ and $B \rightarrow C$ transitions, $k_{B \rightarrow A}/(k_{B \rightarrow A} + k_{B \rightarrow C})$ and $k_{B \rightarrow C}/(k_{B \rightarrow A} + k_{B \rightarrow C})$, are $\varphi(b \rightarrow a)$ and $\varphi(b \rightarrow c)$, and (2) the mean lifetime of state B , $(k_{B \rightarrow A} + k_{B \rightarrow C})^{-1}$, is $t_B = \tau(a \leftarrow b \rightarrow c)$. The mean lifetimes of states A and C , $k_{A \rightarrow B}^{-1}$ and $k_{C \rightarrow B}^{-1}$, respectively, are $t_A = \tau(a \rightarrow b)$ and $t_C = \tau(c \rightarrow b)$. The time evolution of the probability of finding the system in state I , $p_I(t)$, $I = A, B, C$, is given by

$$\frac{d\mathbf{p}}{dt} = \mathbf{R}\mathbf{p}, \quad (3.3)$$

where $\mathbf{p}$ is the column vector, (p_A, p_B, p_C) , and the rate matrix, $\mathbf{R}$, is

$$\mathbf{R} = \begin{pmatrix} -k_{A \rightarrow B} & k_{B \rightarrow A} & 0 \\ k_{A \rightarrow B} & -(k_{B \rightarrow A} + k_{B \rightarrow C}) & k_{C \rightarrow B} \\ 0 & k_{B \rightarrow C} & -k_{C \rightarrow B} \end{pmatrix}. \quad (3.4)$$

The normalized equilibrium populations of the three states, π_A , π_B , and π_C , $\pi_A + \pi_B + \pi_C = 1$, are solutions of $\mathbf{R}\boldsymbol{\pi} = 0$. Solving this equation and replacing the rate constants by the MFPT's and splitting probabilities, using Eq. (3.2), we find

$$\begin{aligned} \pi_A &= \frac{\varphi(b \rightarrow a)\tau(a \rightarrow b)}{\Delta}, & \pi_B &= \frac{\tau(a \leftarrow b \rightarrow c)}{\Delta}, \\ \pi_C &= \frac{\varphi(b \rightarrow c)\tau(c \rightarrow b)}{\Delta}, \end{aligned} \quad (3.5)$$

where Δ is

$$\Delta = \varphi(b \rightarrow a)\tau(a \rightarrow b) + \tau(a \leftarrow b \rightarrow c) + \varphi(b \rightarrow c)\tau(c \rightarrow b). \quad (3.6)$$

Given the rate matrix, $\mathbf{R}$, we can calculate the MFPT's between any two states by solving

$$\mathbf{R}^T \boldsymbol{\tau} = -\mathbf{1} \quad (3.7)$$

subject to the appropriate boundary condition (i.e., if we are interested in the MFPT's to state I , then $\tau(I \rightarrow I) = 0$). In this equation, which is the discrete analog of Eq. (A6) in the Appendix, $\mathbf{R}^T$ is the transpose of matrix $\mathbf{R}$, $\boldsymbol{\tau}$ is a column vector of the MFPT's, and $\mathbf{1}$ is a column vector with components equal to unity. Solving Eq. (3.7) and using Eq. (3.2), we can express the MFPT's between any two states in terms of the

MFPT's and splitting probabilities obtained from the simulations. For example, one can show that $\tau(A \rightarrow B) = \tau(a \rightarrow b)$, as to be expected, and more interestingly, that

$$\tau(B \rightarrow C) = \frac{\varphi(b \rightarrow a)\tau(a \rightarrow b) + \tau(a \leftarrow b \rightarrow c)}{\varphi(b \rightarrow c)}. \quad (3.8)$$

The MFPT between states A and C is given by $\tau(A \rightarrow C) = \tau(A \rightarrow B) + \tau(B \rightarrow C)$.

Since matrix $\mathbf{R}^T$ can be expressed as

$$\mathbf{R}^T = \begin{pmatrix} -t_A^{-1} & 0 & 0 \\ 0 & -t_B^{-1} & 0 \\ 0 & 0 & -t_C^{-1} \end{pmatrix} \begin{pmatrix} 1 & -1 & 0 \\ -\varphi(b \rightarrow a) & 1 & -\varphi(b \rightarrow c) \\ 0 & -1 & 1 \end{pmatrix}, \quad (3.9)$$

we can write Eq. (3.7) in the form⁵

$$(\mathbf{I} - \boldsymbol{\Phi})\boldsymbol{\tau} = \mathbf{t}. \quad (3.10)$$

Here $\mathbf{t}$ is the vector of mean lifetimes, and $\boldsymbol{\Phi}$ is the matrix of the splitting probabilities,

$$\boldsymbol{\Phi} = \begin{pmatrix} 0 & 1 & 0 \\ \varphi(b \rightarrow a) & 0 & \varphi(b \rightarrow c) \\ 0 & 1 & 0 \end{pmatrix}. \quad (3.11)$$

Equations (3.7) and (3.10) must be solved subject to the same boundary conditions. Alternatively, matrix $\boldsymbol{\Phi}$ can be redefined so as to explicitly incorporate these boundary conditions.

A. Coloring an equilibrium trajectory

As in the case of two milestones, we are interested in determining the nature of the "states" associated with the milestones and microscopic meaning of their equilibrium populations, π_A , π_B , and π_C , that are normalized solutions of $\mathbf{R}\boldsymbol{\pi} = 0$. To this end, as before, consider how the MFPT's can be obtained from a long equilibrium trajectory $\mathbf{x}(t)$ of duration T , $T \rightarrow \infty$, by coloring it in red, blue, and orange, using the rules proposed by Vanden-Eijnden and Venturoli.⁸ The trajectory changes its color from red to blue when it comes to point b from point a and from orange to blue when it comes to this point from point c . Then the trajectory remains blue until it touches point a or c for the first time, when it turns red or orange, respectively, as shown in the upper panel of Fig. 2.

Denote the total times when the trajectory is red, blue, and orange by T_a , T_b , and T_c , and the numbers of times the trajectory changed color from red to blue and from blue to orange and vice versa by N_{ab} and N_{bc} , respectively. The MFPT's $\tau(a \rightarrow b)$, $\tau(a \leftarrow b \rightarrow c)$, and $\tau(c \rightarrow b)$ are the average durations of the red, blue, and orange segments,

$$\tau(a \rightarrow b) = \frac{T_a}{N_{ab}}, \quad \tau(a \leftarrow b \rightarrow c) = \frac{T_b}{N_{ab} + N_{bc}}, \quad \tau(c \rightarrow b) = \frac{T_c}{N_{bc}}. \quad (3.12)$$

The splitting probability $\varphi(b \rightarrow a)$ ($\varphi(b \rightarrow c)$) is the number of times a blue segment turned red (orange), N_{ab} (N_{bc}), divided by the total number of times it changed color,

$$\varphi(b \rightarrow a) = \frac{N_{ab}}{N_{ab} + N_{bc}}, \quad \varphi(b \rightarrow c) = \frac{N_{bc}}{N_{ab} + N_{bc}}. \quad (3.13)$$

FIG. 2. The same as Fig. 1 but for three milestones. Upper panel: The trajectory $x(t)$ colored red, blue, and orange. Blue changes to orange (red) when the trajectory $x(t)$ reaches point c (a) for the first time. When $b < x < c$ ($a < x < b$), the trajectory can be either blue or orange (blue or red). The color of the trajectory depends on the last milestone it touched: the color is red (blue or orange), if the last touched milestone is a (b or c). Lower panel: A three-state trajectory corresponding to the colored trajectory $x(t)$.

Using the relations in Eqs. (3.12) and (3.13), we can write the total observation time as

$$\begin{aligned} T &= T_a + T_b + T_c = \\ &= N_{ab}\tau(a \rightarrow b) + (N_{ab} + N_{bc})\tau(a \leftarrow b \rightarrow c) + N_{bc}\tau(c \rightarrow b) \\ &= (N_{ab} + N_{bc})\Delta, \end{aligned} \quad (3.14)$$

where Δ is given in Eq. (3.6).

B. Equilibrium populations and MFPT's

The relations in Eqs. (3.12) and (3.13) link the MFPT's and splitting probabilities obtained from the short simulations initiated from the milestones with information obtained from a long trajectory. We use this to find the fractions of time when the trajectory is red, blue, and orange, $\pi_i = T_i/T$, $i = a, b, c$, and show that these fractions are equal to the equilibrium populations of states I , π_I , $I = A, B, C$, obtained from the rate matrix, $\mathbf{R}$, i.e., $\pi_i = \pi_I$. For example, the fraction of time when the trajectory is red, $\pi_a = T_a/T$, can be recast as

$$\pi_a = \frac{T_a}{T} = \frac{N_{ab}\tau(a \rightarrow b)}{(N_{ab} + N_{bc})\Delta}, \quad (3.15)$$

where we have used Eq. (3.12) for T_a and Eq. (3.14) for T . Finally, using Eq. (3.13), we obtain

$$\pi_a = \frac{T_a}{T} = \frac{\varphi(b \rightarrow a)\tau(a \rightarrow b)}{\Delta}. \quad (3.16)$$

Comparing this with π_A in Eq. (3.5), we see that $\pi_a = \pi_A$. Similarly, it can be shown that $\pi_b = T_b/T = \pi_B$ and $\pi_c = T_c/T = \pi_C$.

In summary, the mean durations of the red, blue, and orange segments of the trajectory are equal to the mean lifetimes of states A, B, and C of the three-state model. In addition, the fractions of time when the trajectory is red, blue, and orange are equal to the equilibrium populations, π_A , π_B , and π_C , of the three states. Consequently, states A, B, and C of the three-state model, associated with the milestones, correspond to red, blue, and orange segments of the long trajectory, respectively.

Times, T_a , T_b , and T_c , and the numbers of color changes, N_{ab} and N_{bc} , obtained from the long trajectory can be used to find the exact MFPT's between any two milestones, not just those in Eq. (3.12). For example, suppose we are interested in the MFPT between milestones b and c , $\tau(b \rightarrow c)$. If the color of the red trajectory fragments is changed to blue, then we are faced with a two (b and c) milestone problem where the duration of the blue trajectories is now $T_a + T_b$, and so

$$\tau(b \rightarrow c) = \frac{T_a + T_b}{N_{bc}}. \quad (3.17)$$

Now we use Eq. (3.12) to write T_a and T_b in terms of the MFPT's, i.e., $T_a = N_{ab}\tau(a \rightarrow b)$ and $T_b = (N_{ab} + N_{bc})\tau(a \leftarrow b \rightarrow c)$. Substituting this into Eq. (3.17) and using the definitions of the splitting probabilities $\varphi(b \rightarrow a)$ and $\varphi(b \rightarrow c)$ in terms of the numbers of color changes in Eq. (3.13), we arrive at

$$\tau(b \rightarrow c) = \frac{\varphi(b \rightarrow a)}{\varphi(b \rightarrow c)}\tau(a \rightarrow b) + \frac{1}{\varphi(b \rightarrow c)}\tau(a \leftarrow b \rightarrow c). \quad (3.18)$$

Comparing this with $\tau(B \rightarrow C)$ in Eq. (3.8), obtained using the three-state model, we see that $\tau(b \rightarrow c) = \tau(B \rightarrow C)$. Thus, the three-state model predicts the exact MFPT between points b and c even though this MFPT was not used to determine any of the rate constants. In a similar way, one can show that all possible MFPT's predicted by the three-state model are exact.

How can we understand this remarkable success of the three-state model? Any quantity that can be calculated using the rate matrix $\mathbf{R}$ can also be obtained from a long equilibrium trajectory in the space of states A, B, and C generated using the Gillespie algorithm. All input parameters for this algorithm (i.e., the lifetimes of the states and splitting probabilities) can be obtained from the rate matrix $\mathbf{R}$. Let us compare such a trajectory with the exact one shown in the lower panel of Fig. 2. The most dramatic difference is in the distributions of the state lifetimes and those of the durations of the colored segments. In the trajectory generated using the Gillespie algorithm, the distributions of the state lifetimes are single-exponential, while the distributions of the durations of the colored segments are in general not. However, the mean lifetimes and the splitting probabilities in both trajectories are the same because the Gillespie algorithm used the exact MFPT's and splitting probabilities as input. Therefore, any average quantity (e.g., the MFPT's) calculated using the rate matrix must be exact.

C. Microscopic interpretation of “equilibrium populations”

We will now express the equilibrium populations given by the three-state model, π_i , (which are identical to the fractions of time, π_i , when the trajectory is red, blue, and orange) in terms of the Boltzmann equilibrium averages of the committors. Let $\varphi_i(x)$ be the probabilities and $p_i(x)$ be the probability densities that the trajectory at point x has the color associated with the milestone i , $i = a, b, c$. Just as in the two-milestone case, $p_i(x)$, are given by the products of the Boltzmann distribution and the probabilities $\varphi_i(x)$, $p_i(x) = \varphi_i(x)\exp(-\beta U(x))/Z$. The probabilities $\varphi_i(x)$ are

$$\varphi_a(x) = \begin{cases} 1, & x \leq a \\ \varphi(x \rightarrow a), & a \leq x \leq b, \\ 0, & b \leq x \end{cases} \quad (3.19)$$

$$\varphi_b(x) = \begin{cases} 0, & x \leq a \\ \varphi(x \rightarrow b), & a \leq x \leq c, \\ 0, & c \leq x \end{cases} \quad (3.20)$$

and

$$\varphi_c(x) = \begin{cases} 0, & x \leq b \\ \varphi(x \rightarrow c), & b \leq x \leq c. \\ 1, & c \leq x \end{cases} \quad (3.21)$$

Here $\varphi(x \rightarrow a)$ ($\varphi(x \rightarrow c)$) is the probability of reaching point a (c) starting from point x , $a \leq x \leq b$ ($b \leq x \leq c$), before reaching point b , and $\varphi(x \rightarrow b) = 1 - \varphi(x \rightarrow a)$, for $a \leq x \leq b$, and $\varphi(x \rightarrow b) = 1 - \varphi(x \rightarrow c)$, for $b \leq x \leq c$. One can see that the probabilities $\varphi_i(x)$ are normalized at every point x , $\varphi_a(x) + \varphi_b(x) + \varphi_c(x) = 1$. The equilibrium populations of states I , π_I , $I = A, B, C$, given in terms of the Boltzmann equilibrium averages of the committors $\varphi_i(x)$, are

$$\pi_I = \pi_i = \int_{-\infty}^{\infty} p_i(x) dx = \langle \varphi_i(x) \rangle, \quad I = A, B, C, \quad i = a, b, c. \quad (3.22)$$

D. Unidirectional fluxes and rate constants

It should be no surprise by now that unidirectional fluxes at equilibrium (i.e., the numbers of transitions per unit time) between states A and B , $J_{AB} = J_{A \rightarrow B} = J_{B \rightarrow A}$, and between states B and C , $J_{BC} = J_{B \rightarrow C} = J_{C \rightarrow B}$, calculated in the framework of the three-state model, are the same as those between the points a and b , $J_{ab} = J_{a \rightarrow b} = J_{b \rightarrow a}$, and points b and c , $J_{bc} = J_{b \rightarrow c} = J_{c \rightarrow b}$, calculated from the long trajectory. To see this, consider the equilibrium unidirectional flux J_{BC} ,

$$J_{BC} = \pi_B k_{B \rightarrow C} = \frac{\pi_b \varphi(b \rightarrow c)}{\tau(a \leftarrow b \rightarrow c)}, \quad (3.23)$$

where we have used the fact that $\pi_B = \pi_b$ and the expression for $k_{B \rightarrow C}$ given in Eq. (3.2). The equilibrium unidirectional flux J_{bc} between milestones b and c , by definition, is

$$J_{bc} = \frac{N_{bc}}{T} = \frac{T_b}{T} \cdot \frac{N_{bc}}{N_{ab} + N_{bc}} \cdot \frac{N_{ab} + N_{bc}}{T_b} = \frac{\pi_b \varphi(b \rightarrow c)}{\tau(a \leftarrow b \rightarrow c)}, \quad (3.24)$$

where we have used the relations in Eqs. (3.12) and (3.13). Thus $J_{BC} = J_{bc}$ and similarly, $J_{AB} = J_{ab}$. Because of this and since $\pi_I = \pi_i = \langle \varphi_i \rangle$, all the rate constants in Eq. (3.2) can be written as “flux-over-population”

$$\begin{aligned} k_{A \rightarrow B} &= \frac{J_{ab}}{\langle \varphi_a \rangle}, & k_{B \rightarrow A} &= \frac{J_{ab}}{\langle \varphi_b \rangle}, \\ k_{C \rightarrow B} &= \frac{J_{bc}}{\langle \varphi_c \rangle}, & k_{B \rightarrow C} &= \frac{J_{bc}}{\langle \varphi_b \rangle}, \end{aligned} \quad (3.25)$$

just as in the two-milestone case [see Eq. (2.13)].

The mean lifetime of state B , t_B , or the mean duration of the blue trajectory segment, t_b , is $t_B = t_b = (k_{B \rightarrow A} + k_{B \rightarrow C})^{-1} = \tau(a \leftarrow b \rightarrow c)$. Using the expressions for the rate constants in Eq. (3.25), we obtain the following relation among the MFPT, $\tau(a \leftarrow b \rightarrow c)$, the Boltzmann averaged committor, $\langle \varphi_b \rangle$, and the equilibrium unidirectional fluxes:

$$\tau(a \leftarrow b \rightarrow c) = \frac{\langle \varphi_b \rangle}{J_{ab} + J_{bc}}, \quad (3.26)$$

which is to be compared with the results in Eq. (2.12) for $\tau(a \rightarrow b)$ and $\tau(b \rightarrow a)$ in the case of two milestones. The sum of fluxes, $J_{ab} + J_{bc}$, is denoted by q_b in the milestone literature.⁶ The identity in Eq. (3.26) can be proved the old-fashioned way, algebraically, using the formalism given in the Appendix: $\tau(a \leftarrow x_0 \rightarrow c)$ is the solution of Eq. (A6), in which $\tau(x_0 \rightarrow b)$ should be replaced by $\tau(a \leftarrow x_0 \rightarrow c)$, with boundary conditions $\tau(a \leftarrow a \rightarrow c) = \tau(a \leftarrow c \rightarrow c) = 0$, while $\varphi(x \rightarrow b)$ is the solution of Eq. (A11), in which $\varphi(x \rightarrow a)$ should be replaced by $\varphi(x \rightarrow b)$, with boundary conditions $\varphi(b \rightarrow b) = 1$ and $\varphi(a \rightarrow b) = \varphi(c \rightarrow b) = 0$.

IV. CONCLUDING REMARKS

The above analysis can be readily generalized to an arbitrary number of milestones in one dimension. Thus, by running short trajectories starting from one milestone and stopping at an adjacent milestone, one can calculate the exact MFPT between any two milestones no matter how far apart they are. The importance of this result is that one can obtain very long MFPTs, say, between two milestones separated by a high barrier, that would be virtually impossible to simulate directly. In simplest terms, the reason for this remarkable result is that a long trajectory generated by the Gillespie algorithm with parameters obtained from the rate matrix is “on the average” equivalent to the exact trajectory (i.e., the lower panels in Figs. 1 and 2). By “on the average,” we mean that while the distribution of the lifetimes of the various states are different, the average lifetimes as well as other average properties such as equilibrium populations, unidirectional fluxes, and MFPTs will be the same.

How can this be generalized to multidimensional diffusive dynamics? In this case, milestones are no longer points but rather surfaces, and the first-passage times between the milestones depend on the location of the starting points on the surface. If we could choose the distribution of starting points in such a way that the MFPTs obtained by running

short trajectories would be identical to those obtained by coloring a long equilibrium trajectory, then all our arguments would immediately carry over. This distribution is related to the probability that the equilibrium trajectory crosses or hits a particular point on the surface (for an algebraic derivation, see the end of the [Appendix](#)). How this distribution can be found iteratively by running only short trajectories for non-diffusive dynamics is the focus of an extensive literature that can be accessed through some recent references¹³⁻¹⁵ and earlier ones therein. We hope that our work will help to reduce the “activation barrier” encountered in trying to understand these papers.

Finally, we would like to mention that once we did something¹⁶ in the context of solute transport through a membrane channel, which in retrospect was closely related to milestone-ing. We considered two models of solute transport through a membrane channel, one, where a solute diffuses through the channel in the presence of a potential of mean force, and the other, where the solute simply jumps between two sites located at the channel ends. We showed that the fluxes calculated within the framework of these models are identical when the jump rates between the two states are chosen as the reciprocal of the MFPT's to diffuse from one end of the channel to the other. In this way, we provided a microscopic interpretation of the phenomenological rate constants of the widely used two-site model of the solute dynamics in the channel.

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APPENDIX: ALGEBRAIC DERIVATION OF THE RELATION AMONG THE MFPT, FLUX, AND COMMITTOR

Here we will algebraically derive the relation among the MFPT, $\tau(a \rightarrow b)$, the equilibrium-averaged committor, $\langle \varphi_a \rangle$, and the equilibrium unidirectional flux, J_{ab} .

Consider a particle diffusing in a potential $U(x)$, $U(x \rightarrow \pm\infty) = \infty$, with position-dependent diffusivity, $D(x)$. The probability density of finding the particle at point x at time t , given that it was initially (at $t = 0$) at point x_0 , $p(x, t|x_0, 0)$, satisfies the Smoluchowski equation

$$\frac{\partial p}{\partial t} = \mathcal{L}_x p = \frac{\partial}{\partial x} \left[D(x) e^{-\beta U(x)} \frac{\partial}{\partial x} (e^{\beta U(x)} p) \right] \quad (\text{A1})$$

subject to the initial condition $p(x, 0|x_0, 0) = \delta(x - x_0)$. It follows from the detailed balance condition that $p(x, t|x_0, 0) = p(x_0, t|x, 0)e^{\beta(U(x_0) - U(x))}$. Substituting this into Eq. (A1) and interchanging the notations of the variables $x \leftrightarrow x_0$, one finds

that $p(x, t|x_0, 0)$ satisfies

$$\frac{\partial p}{\partial t} = \mathcal{L}_{x_0}^+ p = e^{\beta U(x_0)} \frac{\partial}{\partial x_0} \left[D(x_0) e^{-\beta U(x_0)} \frac{\partial p}{\partial x_0} \right], \quad (\text{A2})$$

which is the adjoint or backward Smoluchowski equation.

Let us now choose point $x = b$ to be an absorbing boundary, i.e., $p(b, t|x_0, 0) = 0$. The survival probability of a particle starting from x_0 , $x_0 < b$, at $t = 0$, denoted by $S(t|x_0)$, is defined as

$$S(t|x_0) = \int_{-\infty}^b p(x, t|x_0, 0) dx. \quad (\text{A3})$$

Integrating both sides of Eq. (A2) over x from $-\infty$ to b , we find that the survival probability satisfies

$$\frac{\partial S(t|x_0)}{\partial t} = \mathcal{L}_{x_0}^+ S(t|x_0) = e^{\beta U(x_0)} \frac{\partial}{\partial x_0} \left[D(x_0) e^{-\beta U(x_0)} \frac{\partial S(t|x_0)}{\partial x_0} \right] \quad (\text{A4})$$

subject to the initial condition $S(0|x_0) = 1$. The mean particle lifetime is the MFPT from point x_0 to point b , $\tau(x_0 \rightarrow b)$,

$$\tau(x_0 \rightarrow b) = \int_0^\infty t \left(-\frac{dS(t|x_0)}{dt} \right) dt = \int_0^\infty S(t|x_0) dt. \quad (\text{A5})$$

Integrating both sides of Eq. (A4) over time from 0 to ∞ and using the facts that $S(\infty|x_0) = 0$ and $S(0|x_0) = 1$, we find that the MFPT satisfies

$$\mathcal{L}_{x_0}^+ \tau(x_0 \rightarrow b) = e^{\beta U(x_0)} \frac{\partial}{\partial x_0} \left[D(x_0) e^{-\beta U(x_0)} \frac{\partial \tau(x_0 \rightarrow b)}{\partial x_0} \right] = -1. \quad (\text{A6})$$

This must be solved subject to the boundary condition $\tau(b \rightarrow b) = 0$.

Multiplying both sides of Eq. (A6) by $\exp(-\beta U(x_0))$, integrating over x_0 from $-\infty$ to x , where $x < b$, and using the fact that $U(-\infty) = \infty$, we obtain

$$D(x) e^{-\beta U(x)} \frac{\partial \tau(x \rightarrow b)}{\partial x} = - \int_{-\infty}^x e^{-\beta U(y)} dy. \quad (\text{A7})$$

Dividing both sides by $D(x) \exp(-\beta U(x))$, integrating the resulting equation from x to b , and using the fact that $\tau(b \rightarrow b) = 0$, we arrive at

$$\tau(x \rightarrow b) = \int_x^b e^{\beta U(z)} \frac{dz}{D(z)} \int_{-\infty}^z e^{-\beta U(y)} dy. \quad (\text{A8a})$$

Similarly, for the MFPT from x to a , $x \geq a$, we have

$$\tau(x \rightarrow a) = \int_a^x e^{\beta U(z)} \frac{dz}{D(z)} \int_z^\infty e^{-\beta U(y)} dy. \quad (\text{A8b})$$

According to Eq. (2.5), the equilibrium unidirectional flux J_{ab} between milestones a and b is $J_{ab} = (\tau(a \rightarrow b) + \tau(b \rightarrow a))^{-1}$. Using Eqs. (A8a) and (A8b), it can be shown that this flux is given by

$$J_{ab} = \frac{1}{\tau(a \rightarrow b) + \tau(b \rightarrow a)} = \frac{1}{\left(\int_a^b e^{\beta U(z)} \frac{dz}{D(z)} \right) \left(\int_{-\infty}^\infty e^{-\beta U(y)} dy \right)}. \quad (\text{A9})$$

This result can also be obtained from

$$J_{ab} = -D(x)e^{-\beta U(x)} \frac{\partial}{\partial x} (e^{\beta U(x)} p(x)), \quad a \leq x \leq b, \quad (\text{A10})$$

where the probability density $p(x)$ at the end points is $p(a) = \exp(-\beta U(a)) / \int_{-\infty}^{\infty} \exp(-\beta U(x)) dx$ and $p(b) = 0$, i.e., milestone b is absorbing and point a is kept at equilibrium. Dividing both sides of Eq. (A10) by $D(x) \exp(-\beta U(x))$ and then integrating both sides of the resulting equation from a to b , we recover the result for the flux in Eq. (A9).

The committor (splitting probability) $\varphi(x \rightarrow a)$, $a \leq x \leq b$, satisfies the Onsager equation, $\mathcal{L}_x^+ \varphi(x \rightarrow a) = 0$, subject to the boundary conditions $\varphi(a \rightarrow a) = 1$ and $\varphi(b \rightarrow a) = 0$. Using $\mathcal{L}_x^+$, defined in Eq. (A2), we can write the Onsager equation as

$$\frac{d}{dx} \left[D(x) e^{-\beta U(x)} \frac{d\varphi(x \rightarrow a)}{dx} \right] = 0. \quad (\text{A11})$$

Consequently, we have

$$D(x) e^{-\beta U(x)} \frac{d\varphi(x \rightarrow a)}{dx} = C, \quad (\text{A12})$$

where C is a constant to be determined using the boundary conditions at $x = a$ and $x = b$. Dividing both sides by $D(x) \exp(-\beta U(x))$, integrating both sides of the resulting equation from x to b , and using the boundary condition at point b , $\varphi(b \rightarrow a) = 0$, we arrive at

$$\varphi(x \rightarrow a) = C \int_x^b e^{\beta U(z)} \frac{dz}{D(z)}. \quad (\text{A13})$$

Using the boundary condition at point a , $\varphi(a \rightarrow a) = 1$, to find C , we finally obtain

$$\varphi(x \rightarrow a) = \frac{\int_x^b e^{\beta U(z)} \frac{dz}{D(z)}}{\int_a^b e^{\beta U(z)} \frac{dz}{D(z)}}, \quad a \leq x \leq b. \quad (\text{A14})$$

Now we are ready to calculate $\langle \varphi_a \rangle$, where $\varphi_a(x)$ is given in Eq. (2.10a),

$$\begin{aligned} \langle \varphi_a \rangle &= \left[\int_{-\infty}^a e^{-\beta U(x)} dx + \int_a^b \varphi(x \rightarrow a) e^{-\beta U(x)} dx \right] / \int_{-\infty}^{\infty} e^{-\beta U(y)} dy \\ &= J_{ab} \left[\left(\int_a^b e^{\beta U(z)} \frac{dz}{D(z)} \right) \left(\int_{-\infty}^a e^{-\beta U(x)} dx \right) \right. \\ &\quad \left. + \int_a^b \left(\int_x^b e^{\beta U(z)} \frac{dz}{D(z)} \right) e^{-\beta U(x)} dx \right]. \end{aligned} \quad (\text{A15})$$

In the last step, we used Eq. (A9) for J_{ab} and Eq. (A14) for $\varphi(x \rightarrow a)$. The sum in the square brackets is $\tau(a \rightarrow b)$. To see this, one has to change the order of integration in the second term in the square brackets, write the sum of integrals as a single double integral, and then compare with $\tau(a \rightarrow b)$ obtained from Eq. (A8a). Thus, we have derived the result for $\tau(a \rightarrow b)$ in Eq. (2.12), $\tau(a \rightarrow b) = \langle \varphi_a \rangle / J_{ab}$.

This can be done simpler in a way that can be readily generalized to many dimensions. Multiplying both sides of Eq. (A6)

by $\varphi_a(\mathbf{x}_0) \exp(-\beta U(\mathbf{x}_0))$, where $\varphi_a(x)$ is given in Eq. (2.10a), and integrating both sides over all $\mathbf{x}_0$, one has

$$\begin{aligned} &\int_{-\infty}^{\infty} \varphi_a(\mathbf{x}_0) \frac{\partial}{\partial \mathbf{x}_0} \left[D(\mathbf{x}_0) e^{-\beta U(\mathbf{x}_0)} \frac{\partial \tau(\mathbf{x}_0 \rightarrow b)}{\partial \mathbf{x}_0} \right] d\mathbf{x}_0 \\ &= - \int_{-\infty}^{\infty} \varphi_a(\mathbf{x}_0) e^{-\beta U(\mathbf{x}_0)} d\mathbf{x}_0. \end{aligned} \quad (\text{A16})$$

Integrating the left-hand side by parts and taking advantage of the fact that $U(\pm\infty) = \infty$, we find

$$\int_{-\infty}^{\infty} \left(D(\mathbf{x}_0) e^{-\beta U(\mathbf{x}_0)} \frac{\partial \varphi_a(\mathbf{x}_0)}{\partial \mathbf{x}_0} \right) \frac{\partial \tau(\mathbf{x}_0 \rightarrow b)}{\partial \mathbf{x}_0} d\mathbf{x}_0 = \langle \varphi_a \rangle \int_{-\infty}^{\infty} e^{-\beta U(y)} dy, \quad (\text{A17})$$

where we have used the definition of the equilibrium average, $\langle \varphi_a \rangle$, in Eq. (2.11). Since the derivative of $\varphi_a(x)$ is $\partial \varphi(x \rightarrow a) / \partial x_0$ inside the interval $a < x_0 < b$ and zero outside, Eq. (A17) becomes

$$\begin{aligned} &\int_a^b \left(D(\mathbf{x}_0) e^{-\beta U(\mathbf{x}_0)} \frac{\partial \varphi(x \rightarrow a)}{\partial \mathbf{x}_0} \right) \frac{\partial \tau(\mathbf{x}_0 \rightarrow b)}{\partial \mathbf{x}_0} d\mathbf{x}_0 \\ &= \langle \varphi_a \rangle \int_{-\infty}^{\infty} e^{-\beta U(y)} dy. \end{aligned} \quad (\text{A18})$$

Integrating the right-hand side by parts, using Eq. (A11) and the fact that $\tau(b \rightarrow b) = 0$, we obtain

$$-D(a) e^{-\beta U(a)} \frac{\partial \varphi(x \rightarrow a)}{\partial \mathbf{x}_0} \bigg|_{\mathbf{x}_0=a} \tau(a \rightarrow b) = \langle \varphi_a \rangle \int_{-\infty}^{\infty} e^{-\beta U(y)} dy. \quad (\text{A19})$$

By differentiating Eq. (A14) for $\varphi(x \rightarrow a)$ and using the expression for the flux J_{ab} in Eq. (A9), one can see that the factor in front of $\tau(a \rightarrow b)$ on the left-hand side of the above equation is the product $J_{ab} \int_{-\infty}^{\infty} e^{-\beta U(y)} dy$. Thus, we recover the expression for $\tau(a \rightarrow b)$ in Eq. (2.12), $\tau(a \rightarrow b) = \langle \varphi_a \rangle / J_{ab}$.

Let us now generalize this to many dimensions with two milestones that are infinite non-intersecting surfaces Σ_a and Σ_b that divide the space into three regions: Ω_a (left of Σ_a), Ω_{ab} (between Σ_a and Σ_b), and Ω_b (right of Σ_b). The multidimensional generalization of Eq. (A16) is

$$\begin{aligned} &\int \varphi_a(\mathbf{x}_0) \nabla \cdot \mathbf{D}(\mathbf{x}_0) e^{-\beta U(\mathbf{x}_0)} \cdot \nabla \tau(\mathbf{x}_0 \rightarrow \Sigma_b) d\mathbf{x}_0 \\ &= - \int \varphi_a(\mathbf{x}_0) e^{-\beta U(\mathbf{x}_0)} d\mathbf{x}_0. \end{aligned} \quad (\text{A20})$$

Here $\varphi_a(\mathbf{x}_0) = 1$ for $\mathbf{x}_0 \in \Omega_a$, $\varphi_a(\mathbf{x}_0) = \varphi(\mathbf{x}_0 \rightarrow \Sigma_a)$ for $\mathbf{x}_0 \in \Omega_{ab}$, and $\varphi_a(\mathbf{x}_0) = 0$ for $\mathbf{x}_0 \in \Omega_b$ is the multidimensional analog of $\varphi_a(x)$ in Eq. (2.10a), $\mathbf{D}(\mathbf{x}_0)$ is the position-dependent diffusivity tensor at point $\mathbf{x}_0$, and $\tau(\mathbf{x}_0 \rightarrow \Sigma_b)$ is the MFPT from point $\mathbf{x}_0$ located in regions Ω_a or Ω_{ab} to the surface Σ_b . Integrating the left-hand side of Eq. (A20) by parts and using the fact that the surface term vanishes, we obtain

$$\int \nabla \varphi(\mathbf{x}_0) \cdot \mathbf{D}(\mathbf{x}_0) e^{-\beta U(\mathbf{x}_0)} \cdot \nabla \tau(\mathbf{x}_0 \rightarrow \Sigma_b) d\mathbf{x}_0 = \langle \varphi_a \rangle \int e^{-\beta U(y)} dy, \quad (\text{A21})$$

where $\langle \varphi_a \rangle$ is the Boltzmann average of $\varphi_a(\mathbf{x})$ analogous to that in Eq. (2.11). Equation (A21) is the multidimensional generalization of Eq. (A17).

Now $\nabla \varphi_a(\mathbf{x}_0)$ is non-zero only in the region Ω_{ab} between the two surfaces, where $\varphi_a(\mathbf{x}_0) = \varphi(\mathbf{x}_0 \rightarrow \Sigma_a)$. Thus Eq. (A21) becomes

$$\int_{\Omega_{ab}} \nabla \varphi(\mathbf{x}_0 \rightarrow \Sigma_a) \cdot \mathbf{D}(\mathbf{x}_0) e^{-\beta U(\mathbf{x}_0)} \cdot \nabla \tau(\mathbf{x}_0 \rightarrow \Sigma_b) d\mathbf{x}_0 = \langle \varphi_a \rangle \int e^{-\beta U(\mathbf{y})} d\mathbf{y}. \quad (\text{A22})$$

If we integrate the left-hand side by parts and apply Gauss's divergence theorem, only the integral over the surface Σ_a survives because $\tau(\mathbf{x} \rightarrow \Sigma_b)|_{\mathbf{x} \in \Sigma_b} = 0$ and $\varphi(\mathbf{x}_0 \rightarrow \Sigma_a)$ satisfies, $\nabla \cdot \mathbf{D}(\mathbf{x}_0) e^{-\beta U(\mathbf{x}_0)} \cdot \nabla \varphi(\mathbf{x}_0 \rightarrow \Sigma_a) = 0$, which is the multidimensional version of the Onsager equation in Eq. (A11). As a result, Eq. (A22) reduces to

$$-\int_{\Sigma_a} [\mathbf{n}(\mathbf{x}_0) \cdot \mathbf{D}(\mathbf{x}_0) e^{-\beta U(\mathbf{x}_0)} \cdot \nabla \varphi(\mathbf{x}_0 \rightarrow \Sigma_a)] \tau(\mathbf{x}_0 \rightarrow \Sigma_b) d\mathbf{x}_0 = \langle \varphi_a \rangle \int e^{-\beta U(\mathbf{y})} d\mathbf{y}, \quad (\text{A23})$$

where $\mathbf{n}(\mathbf{x}_0)$ is a unit vector perpendicular to the surface Σ_a , pointing towards Σ_b .

It can be shown that the total unidirectional equilibrium flux J_{ab} between the two surfaces is given by¹⁷

$$J_{ab} = -\int_{\Sigma_a} \mathbf{n}(\mathbf{x}_0) \cdot \mathbf{D}(\mathbf{x}_0) e^{-\beta U(\mathbf{x}_0)} \cdot \nabla \varphi(\mathbf{x}_0 \rightarrow \Sigma_a) d\mathbf{x}_0 \bigg/ \int e^{-\beta U(\mathbf{y})} d\mathbf{y}. \quad (\text{A24})$$

Using this, Eq. (A23) can be written as

$$\tau(\Sigma_a \rightarrow \Sigma_b) = \frac{\langle \varphi_a \rangle}{J_{ab}}. \quad (\text{A25})$$

Here $\tau(\Sigma_a \rightarrow \Sigma_b)$ is the MFPT between the two surfaces defined by

$$\tau(\Sigma_a \rightarrow \Sigma_b) = \int_{\Sigma_a} p_{\text{flux}}(\mathbf{x}_0) \tau(\mathbf{x}_0 \rightarrow \Sigma_b) d\mathbf{x}_0, \quad (\text{A26})$$

where $p_{\text{flux}}(\mathbf{x}_0)$, $\mathbf{x}_0 \in \Sigma_a$, defined as

$$p_{\text{flux}}(\mathbf{x}_0) = \frac{\mathbf{n}(\mathbf{x}_0) \cdot \mathbf{D}(\mathbf{x}_0) e^{-\beta U(\mathbf{x}_0)} \cdot \nabla \varphi(\mathbf{x}_0 \rightarrow \Sigma_a)}{\int_{\Sigma_a} \mathbf{n}(\mathbf{x}_0) \cdot \mathbf{D}(\mathbf{x}_0) e^{-\beta U(\mathbf{x}_0)} \cdot \nabla \varphi(\mathbf{x}_0 \rightarrow \Sigma_a) d\mathbf{x}_0}, \quad (\text{A27})$$

is the normalized distribution of the unidirectional flux from surface Σ_a to surface Σ_b passing through the point $\mathbf{x}_0$ on surface Σ_a at equilibrium.

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