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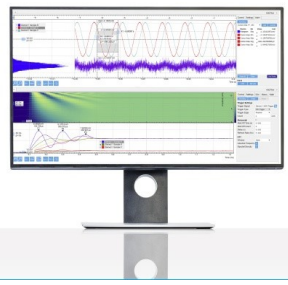

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One of the main experimental tools in studying the microscopic mechanisms of complex phenomena is measuring transition times for individual particles.[1] These observations are frequently analyzed using a random walk approach, which is one the simplest theoretical models that accounts for stochasticity at the molecular level.[2] In the presence of a bias, a random walker moves preferentially along the bias; however, the jumps' waiting time is the same in both directions as a consequence of microscopic reversibility.[3] We have recently shown that the symmetry of the downhill (along with the bias) and uphill (against the bias) transition times can be broken in multi-particle systems.[4,5] Here, we explain that such symmetry can be also broken even for a single particle at non-equilibrium conditions for the systems with complex internal transitions.

Consider a particle moving on a two-lane lattice, as illustrated in Fig. 1. In lane 1, the hopping rates are u and w to the right and left, respectively. In lane 2, u' and w' are the corresponding right and left rates. The particle can also transition between two lanes with the rate a (from lane 2 to lane 1) and b (from lane 1 to lane 2). We define the forward motion as the motion to the right along any lane, and, correspondingly, the backward motion is any motion to the left.

We start with the transition to the right through lane 1. Since the transition time is defined only between two neighboring sites, we consider six sites on the lattice marked −1, 0, 1, 2, 3, and 4 in Fig. 1. It is assumed that the particle is placed either at the site 1 or at the site 2 at time $t = 0$, and the system is transitionally invariant. Now we define first-passage probability-density distribution functions $F_{i,3}(t)$ ($i = 1, 2, 3$) to reach state 3 starting at the site i at time t before making any forward/backward transition via other paths. These functions follow the backward master equations,[6,7]

$$\frac{dF_{1,3}(t)}{dt} = -(u+w+b)F_{1,3}(t) + bF_{2,3}(t) + uF_{3,3}(t), \tag{1}$$

$$\frac{dF_{2,3}(t)}{dt} = -(u'+w'+a)F_{2,3}(t) + aF_{1,3}(t), \tag{2}$$

and $F_{3,3}(t) = \delta(t)$. Applying the Laplace transformation, $\widetilde{F}_{i,3}(s) \equiv \int_0^\infty F_{i,3}(t)\exp(-st)dt$, we derive

$$(s+u+w+b)\widetilde{F}_{1,3}(s) = b\widetilde{F}_{2,3}(s) + u, \tag{3}$$

$$(s+u'+w'+a)\widetilde{F}_{2,3}(s) = a\widetilde{F}_{1,3}(s). \tag{4}$$

These equations can be solved, allowing us to obtain the probabilities to reach state 3 before reaching other states (−1, 0, and 4) starting from the state 1, $\Pi_{1,3}$, or starting from the state 2, $\Pi_{2,3}$,

$$\Pi_{1,3} = \frac{u(a+u'+w')}{a(u+w)+(b+u+w)(u'+w')}, \tag{5}$$

$$\Pi_{2,3} = \frac{au}{a(u+w)+(b+u+w)(u'+w')}. \tag{6}$$

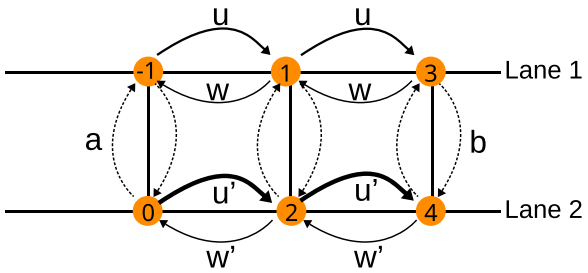

FIG. 1. A model for a single particle hopping on a two-lane lattice. The transition rates are u and w to move to the right and to the left, respectively, in lane 1, and the corresponding rates in lane 2 are u' and w'. The particle can also jump between the lanes with the rates a and b.

The (conditional) mean-first passage times $T_{1,3}$, $T_{2,3}$ for such events can be also found from the first-passage distributions,[6,7] producing

$$T_{1,3} = \frac{a^2 + (u'+w')^2 + a[b + 2(u'+w')]}{(a+u'+w')[a(u+w) + (b+u+w)(u'+w')]}, \tag{7}$$

$$T_{2,3} = \frac{a+b+u+u'+w+w'}{a(u+w) + (b+u+w)(u'+w')}. \tag{8}$$

Similarly, we determine the forward transition times via lane 2 by evaluating the first-passage distribution functions $F_{1,4}(t)$ and $F_{2,4}(t)$ to reach state 4, yielding

$$\Pi_{1,4} = \frac{bu'}{a(u+w) + (b+u+w)(u'+w')}, \tag{9}$$

$$\Pi_{2,4} = \frac{u'(b+u+w)}{a(u+w) + (b+u+w)(u'+w')}, \tag{10}$$

$$T_{1,4} = \frac{a+b+u+u'+w+w'}{a(u+w) + (b+u+w)(u'+w')}, \tag{11}$$

$$T_{2,4} = \frac{ab + (b+u+w)^2}{(b+u+w)[a(u+w) + (b+u+w)(u'+w')]}. \tag{12}$$

Finally, the mean forward transition time can be calculated by averaging over all the possible forward paths and initial states,

$$T_+(u,w,u',w') = \frac{\sum_{i=1,2}\sum_{j=3,4} p_i \Pi_{i,j} T_{i,j}}{\sum_{i=1,2}\sum_{j=3,4} p_i \Pi_{i,j}}, \tag{13}$$

where p_i (i = 1, 2) is the probability for the particle to start at lane 1 or lane 2, respectively. Measuring the transition events for long times gives $p_1 = \frac{a}{a+b}$ and $p_2 = 1 - p_1$.[5] The backward transition times can be obtained from symmetry considerations, $T_-(u, w, u', w') = T_+(w, u, w', u')$. Note that as we measure the transition dynamics along the horizontal direction, the effective dynamics is non-Markovian, while the individual transitions are Markovian.[8]

We found that the forward and backward transition times are different in general. As an illustration, they are shown in Fig. 2 for a specific set of parameters. Even though that for these parameters, the particle preferably moves to the right in both lanes, either forward or backward transition time can be faster.

In order to understand these surprising observations, we consider a cyclic network of states (1, 3, 4, 2). The thermodynamic affinity for this loop, which can be viewed as a driving force for the system to be out of equilibrium, can be evaluated as[3,9]

$$A = k_B T \ln\left(\frac{ubw'a}{wbu'a}\right) = k_B T \ln\left(\frac{uw'}{u'w}\right). \tag{14}$$

Only at equilibrium, we have $A = 0$, and $A \neq 0$ corresponds to a net current in the system. With the choice of our parameters in Fig. 2, we have $A > 0$ (<0) for $w < 1/4$ (>1/4). Figure 2 shows that for the clockwise current ($A > 0$ and $w < 1/4$), the forward transition time is longer than the backward transition time. The particle preferentially moves forward through lane 1, where the transition is slower than through lane 2. On the other hand, for the backward transition, the particle moves preferentially through the lane 2. That is why the forward transition is slower in this case. The situation is opposite for $w > 1/4$ when there is a net counter-clockwise current. Only at equilibrium, $w = 1/4$, there is no net current along the cycle, and the symmetry of the forward/backward transition times is recovered.[8]

Our results can be applied to motor proteins that undergo conformational changes during the motion along linear tracks.[7,10] The possibility of conformational transitions is typically not accounted for because it is difficult to detect them experimentally. Our study suggests that experiments might be used to clarify the existence of the conformational states: if the motor protein exhibits the asymmetry in transition times, it indicates that there are several internal states.

In summary, we showed that the symmetry of forward/backward transition times could be broken even for a single particle. Using a random walk approach, it is found that the transition times are the same only at equilibrium. In out-of-equilibrium, the direction of the loop current determines which transition times

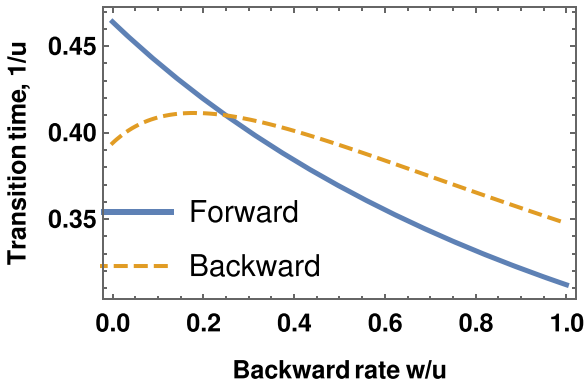

FIG. 2. Forward and backward transition times. The following parameters are used in calculations: u = 1, u' = 4, w' = 1, and a = b = 1. Only the rate w is varied.

are shorter. This is the result of different contributions for forward and backward paths. Since the asymmetry of transition forward/backward times arises when the system is out-of-equilibrium and non-Markovian due to underlying molecular mechanisms,[8] our analysis suggests that the asymmetry can be used as a measure of deviation from equilibrium in complex molecular systems.[11] In addition, our analysis provides the way to quantify the complexity of internal transitions in molecular systems.

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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