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Biased Random Walk in Crowded Environment: Breaking Uphill/Downhill Symmetry of Transition Times

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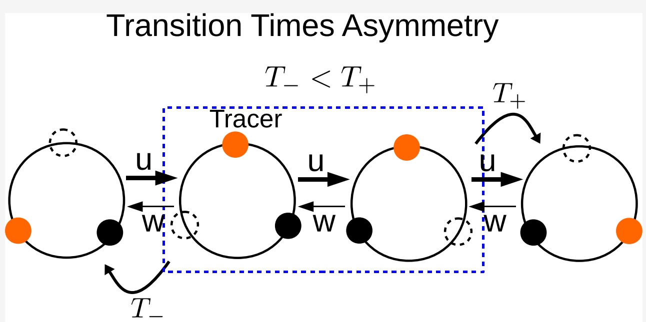
ABSTRACT: Various natural processes can be analyzed using the concept of random walks. For a single random walker, the mean waiting times for uphill and downhill transitions between neighboring sites are equal. Here we investigate the uphill/downhill symmetry of waiting times for transitions of a tracer in crowded environment using exactly solvable one-dimensional stochastic models. It is found that, unexpectedly, the time to move in the direction of the bias (downhill) is always longer than the time to move against the bias (uphill). The degree of asymmetry depends on the particle density, the strength of the bias, and the size of the system. The microscopic origin of the symmetry breaking is discussed.



Recent advances in experimental techniques allowed researchers to monitor and probe complex chemical, biological, and physical processes with unprecedented temporal and spatial resolutions.[1−5] One of the key measured properties in these studies are times for transitions between the states along the reaction coordinates. These measurements are important since they reflect the dynamics and potential interactions in the system, clarifying the underlying molecular mechanisms.[2,5] In recent years, there have been multiple theoretical studies on the role of transition times for understanding the microscopic details of complex systems.[1,6−14]

Many natural processes can be successfully analyzed using random-walk models.[13,15,16] The advantage of such an approach is the ability to explain the dynamic processes in these systems at the molecular level. For a single walker, it is known that the mean times to jump to the neighboring sites are identical for all directions, even in the presence of the bias.[13,17] At the same time, the bias affects the probability of transition events in each direction. The majority of natural processes, however, involve multiple particles interacting with each other. It has been suggested that in such systems the symmetry of uphill/downhill waiting times for transitions along the reaction coordinates might not be preserved.[18] Recent computational study of biased single-file diffusion in a periodic potential reports a surprising finding that for tracer particles the transitions between neighboring potential wells occur faster uphill than downhill.[18] This is important since in many single-molecule studies of chemical and biological systems the information about their properties is obtained by monitoring the dynamics of specifically labeled particles in the crowded environment of unlabeled particles.[3,4,19] These observations are raising several crucial questions. More specifically, it is unclear what are the microscopic mechanisms of the symmetry breaking, and how the degree of symmetry breaking is related to the microscopic transition rates, particle densities, and the sizes of the systems.

To answer these questions, in this Letter we investigate one-dimensional nonequilibrium discrete-state stochastic models with multiple particles that perform a biased random walk and interact with each other only via hard-core exclusion. This is a simple version of a more general class of models known as asymmetric simple exclusion processes (ASEP), which have been widely utilized in analyzing complex processes in chemistry, physics, and biology.[20−23] Using the method of first-passage probabilities, it is shown that transition times are symmetric about changing the transit direction if initial and final states are precisely known. However, the situation is different when we consider a tracer particle, as typically done in experiments. It is found that in this case the symmetry of transition times in downhill (along the bias) and uphill (against the bias) directions is broken. Surprisingly, the tracer particle moves faster in the direction opposite to the bias. The amplitude of symmetry breaking depends on the density of particles, the strength of the bias, and the size of the system. The random-walk approach gives the exact description for

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dynamics, allowing us to explain the asymmetry at the microscopic level.

Let us consider a stochastic model with multiple particles that preferentially move in one direction on the lattice of discrete sites, as illustrated in Figure 1A. There are L sites and

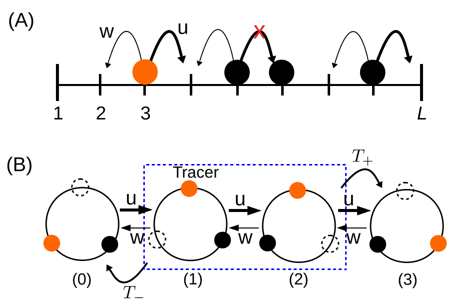

Figure 1. (A) Schematic view of the model: N particles are moving on the lattice of size L with the hopping rate u (w) to the right (left). Due to the exclusion, two particles cannot occupy the same site simultaneously. (B) For the case of $L = 3$ and $N = 2$ with the periodic boundary conditions, the system can be viewed as two particle in the ring with three sites. The filled circles represent particles (orange circle is the tracer), and the dashed circle represents an empty site. The dashed box describes the states in which the tracer particle did not move.

N particles in the system ($L > N$), and periodic boundary conditions are assumed. In each time step, a particle is randomly chosen, and it can make a jump to the right or left site with the rates u and w ($w < u$), respectively, if the corresponding site is empty. If it is occupied, the particle does not move at all. In experimental studies, the motion of specific tracer particles, which can be, for example, fluorescently labeled or tagged in the other way, is monitored. For this model, the dynamics of a tracer particle is investigated (see Figure 1A). We focus on the mean downhill (to the right) and uphill (to the left) transition times, T_+ and T_-, of the tracer. The transition time is defined as the time it takes for the tracer to step in any direction after the previous step. For the system with a single random walker ($N = 1$), the mean transition times in both directions are equal and determined by the mean residence time at each site, $T_+ = T_- = 1/(u + w)$. But the probabilities of transitions in each directions are different, $p_+ = u/(u + w)$ and $p_- = w/(u + w)$, respectively.

To understand how the exclusion interactions break the symmetry, we focus first on the simplest but still nontrivial case of $L = 3$ and $N = 2$, which can be viewed as two particles moving on the ring with three sites (see Figure 1B). The clockwise motion of the particles is considered to be in the downhill (along the bias) direction, and the counterclockwise motion is in the uphill (against the bias) direction. We choose one of the particles as a tracer and follow its dynamics. As shown in Figure 1B, for a given tracer position, the system can be found in one of two distinct states. In state 1, the tracer is behind the nontracer particle, while in state 2 the nontracer particle is behind the tracer. The tracer stepping occurs when the system moves from state 1 to the left to state 0 or from state 2 to the right to state 3 (see Figure 1B). Transitions between states 1 and 2 do not involve the motion of the tracer particle and thus experimentally cannot be observed.

The dynamics of the tracer particle can be quantitatively described using a method of first-passage probabilities.[15,24] One can define $F_n(t)$ ($n = 1, 2, 3$) as the (non-normalized) probability distribution function for the tracer particle to reach state 3 at time t if the system started in state $n = 1$, 2, or 3 at $t = 0$. It is obvious that $F_3(t) = \delta(t)$ since the system is already in state 3 at $t = 0$. All first-passage probabilities can be evaluated from the backward master equations,[15,24] and the details of calculations are given in the Supporting Information.

The knowledge of first-passage probability functions allows us to obtain the explicit expressions for all dynamic properties in the system. For example, the probability of the tracer particle to step forward (downhill) before stepping backward (uphill), starting from the state 1 or from the state 2 are given by

$$\Pi_{1+} = \frac{u^2}{u^2 + uw + w^2} \tag{1}$$

and

$$\Pi_{2+} = \frac{u(u + w)}{u^2 + uw + w^2} \tag{2}$$

The mean forward transition times from states 1 or 2 can be calculated as

$$T_{1+} = \frac{2(u + w)}{u^2 + uw + w^2} \tag{3}$$

and

$$T_{2+} = \frac{u^2 + 3uw + w^2}{(u^2 + uw + w^2)(u + w)} \tag{4}$$

One can see that $\Pi_{1+} < \Pi_{2+}$ and $T_{1+} > T_{2+}$ because it takes two transitions for the tracer to step if it starts in state 1 and only one transition if it starts in state 2. Similar calculations can be done for the backward (uphill) transitions, i.e., for transitions from states 1 or 2 to the state 0. Here we obtain for the probabilities,

$$\Pi_{1-} = \frac{w(u + w)}{u^2 + uw + w^2} \qquad \Pi_{2-} = \frac{w^2}{u^2 + uw + w^2} \tag{5}$$

while for the mean transition times we obtained $T_{1-} = T_{2+}$ and $T_{2-} = T_{1+}$. These results lead to the conclusion that although the uphill/downhill probabilities times are not equal to each other, the symmetry is preserved when the transitions occur between *exactly* known initial and final states of the system.

However, as we track only the tracer particle, the precise configuration of the system is unknown. For instance, there are two possibilities of the nontracer particle position for a given tracer position (see the dashed box in Figure 1B). This leads to multiple paths for the transition of the tracer. In this case, to calculate the mean downhill transition time, we need to take the average over two different initial states of the system, which can be written as

$$T_+ = \frac{p_1\Pi_{1+}T_{1+} + p_2\Pi_{2+}T_{2+}}{p_1\Pi_{1+} + p_2\Pi_{2+}} \tag{6}$$

The parameters p_1 and p_2 are the probabilities for the system to start in state 1 or 2, respectively. Then, $p_1\Pi_{1+}/(p_1\Pi_{1+} + p_2\Pi_{2+})$ and $p_2\Pi_{2+}/(p_1\Pi_{1+} + p_2\Pi_{2+})$ are the fractions of successful trajectories for the forward step of the system starting from state 1 or 2. Similar expression for the mean uphill transition time is given by

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$$T_- = \frac{p_1 \Pi_{1-} T_{1-} + p_2 \Pi_{2-} T_{2-}}{p_1 \Pi_{1-} + p_2 \Pi_{2-}} \tag{7}$$

One can see that explicit values of the downhill and uphill transition times are determined by the probabilities to start in state 1 or 2. Let us monitor the tracer particle dynamics by considering long-time trajectories. This is a procedure that is frequently employed in experimental studies. In such a case, multiple steps of the tracer particle are observed in single long-time trajectories, which are used then to evaluate the dynamic properties of the system. The probabilities of starting in state 1 or in state 2 in this case are not the same ($p_1 \neq p_2$), and they are determined by the frequencies of the forward and backward steps. Specifically, they satisfy

$$p_1 = p_1 \Pi_{1+} + p_2 \Pi_{2+} \qquad p_2 = p_1 \Pi_{1-} + p_2 \Pi_{2-} \tag{8}$$

which leads to

$$p_1 = \frac{u}{u+w} = \frac{1}{1+x} \qquad p_2 = 1 - p_1 \tag{9}$$

where $x \equiv w/u$ characterizes the degree of the bias. Substituting p_1 and p_2 into eqs 6 and 7, we obtain explicit expressions for the mean transition times,

$$T_+ = \frac{1}{u} \frac{x+2}{(x^2+x+1)} \qquad T_- = \frac{1}{u} \frac{2x+1}{(x^2+x+1)} \tag{10}$$

As shown in Figure 2, the downhill waiting times are always larger than the uphill waiting times, in contrast to naive expectations that the motion in the bias direction occurs faster than the motion against the bias. This asymmetry can be quantified by a parameter A given by the ratio of mean downhill and uphill transition times,

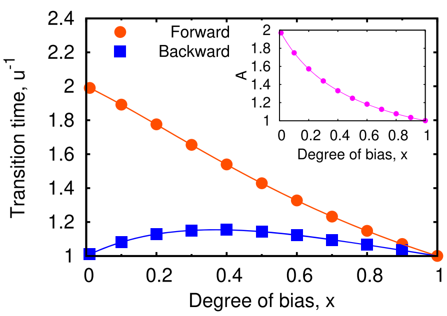

Figure 2. Forward and backward transition times as a function of the bias $x = w/u$. The transition times are measured from a long-time trajectory. The forward transition times T_+ (orange lines) are always larger than or equal to the backward transition times T_- (blue lines). In the insets, we show the ratio of the forward and backward transition times. The solid lines are from theory, and the symbols are simulation data.

$$A \equiv \frac{T_+}{T_-} = \frac{x+2}{2x+1} \tag{11}$$

Because our approach provides the exact analytical description of the dynamics, we are able to rationalize the microscopic arguments to explain the symmetry breaking phenomena by analyzing eqs 6 and 7. One can see that the relative contributions to the fast (T_{2+} and T_{1-}) and slow paths (T_{1+} and T_{2-}) are not the same for the forward and backward transitions. For the forward transition, the contribution of the slow path is given by $p_1\Pi_{1+}/(p_1\Pi_{1+} + p_2\Pi_{2+}) = 1/(x^2 + x + 1)$. The contribution for the backward transition is $p_2\Pi_{2-}/(p_1\Pi_{1-} + p_2\Pi_{2-}) = x^2/(x^2 + x + 1)$. Clearly, the fraction of the slow paths for the forward transitions is always larger than that for the backward transitions $[1/(x^2 + x + 1) \geq x^2/(x^2 + x + 1)$ for $0 \leq x \leq 1]$. Oppositely, the contribution of the fast paths to the forward transition is always smaller than that for the backward transition. In the limiting case of strong bias $x \to 0$, while only the slow paths contribute to the forward transition ($T_+ \simeq T_{1+}$), only the fast paths contribute to the backward transition ($T_- \simeq T_{1-}$).

This argument explains why the mean forward waiting times are longer than the mean backward waiting times, and it also emphasizes that the symmetry breaking is more pronounced for the stronger bias. Thus, the main reason for the symmetry breaking of mean uphill/downhill transition times in the crowded environment is the combination of the excluded volume effect and the bias in the microscopic dynamics of particles. It increases the contribution of slower trajectories with multiple sequential transitions more for the forward steps than for the backward steps.

Our analysis can be extended to larger systems. For example, if we consider a more general situation with L lattice sites and $N = L - 1$ particles, one can notice that there are N different initial states of the system corresponding to different relative positions of the tracer particle and the empty site. Then, employing the first-passage calculations as shown in the Supporting Information, we obtain the splitting probabilities for the forward and backward directions,

$$\Pi_{n+} = \frac{1 - x^n}{1 - x^L} \qquad \Pi_{n-} = \frac{x^n - x^L}{1 - x^L} \tag{12}$$

$n = 1, 2, ..., L - 1$, assuming that the empty site is at n sites behind the tracer (in the counterclockwise direction), which occupies the site L. The calculations of the mean transition times from specific states lead to

$$T_{n+} = \frac{1}{u} \frac{(L-n)(1-x^{L+n}) - (L+n)(x^n - x^L)}{(1-x)(1-x^L)(1-x^n)} \tag{13}$$

and

$$T_{n-} = \frac{1}{u} \frac{n(1-x^{2L-n}) - (2L-n)(x^{L-n} - x^L)}{(1-x)(1-x^L)(1-x^{L-n})} \tag{14}$$

Note that the results for the backward transitions can be obtained via symmetry arguments from those for the forward transitions with $n \to L - n$, $x \to 1/x$, and $u \to w$ transformations.

Now we can estimate the mean forward and backward transition times for the tracer by generalizing eqs 6 and 7. This leads to the following formal expressions for the mean uphill and downhill waiting times,

$$T_+ = \frac{\sum_{n=1}^{L-1} p_n \Pi_{n+} T_{n+}}{\sum_{n=1}^{L-1} p_n \Pi_{n+}} \qquad T_- = \frac{\sum_{n=1}^{L-1} p_n \Pi_{n-} T_{n-}}{\sum_{n=1}^{L-1} p_n \Pi_{n-}} \tag{15}$$

where p_n is the probability for the tracer to start in state n. However, because we are monitoring long-time trajectories of the tracer particles, only two starting configurations are possible: $n = 1$ if the previous step was downhill (forward) or $n = L - 1$ if the previous step was uphill (backward). Then the mean forward and backward transition times are

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$$T_+ = \frac{p_1\Pi_{1+}T_{1+} + p_{L-1}\Pi_{(L-1)+}T_{(L-1)+}}{p_1\Pi_{1+} + p_{L-1}\Pi_{(L-1)+}} \quad (16)$$

$$T_- = \frac{p_1\Pi_{1-}T_{1-} + p_{L-1}\Pi_{(L-1)-}T_{(L-1)-}}{p_1\Pi_{1-} + p_{L-1}\Pi_{(L-1)-}} \quad (17)$$

The probabilities p_1 and p_{L-1} satisfy the following relations,

$$p_1 = p_1\Pi_{1+} + p_{L-1}\Pi_{(L-1)+}$$
$$p_{L-1} = p_1\Pi_{(L-1)-} + p_{L-1}\Pi_{(L-1)-} \quad (18)$$

which result in $p_1 = 1/(1 + x)$ and $p_{L-1} = 1 - p_1$. Finally, combining the above expressions we arrive at

$$T_+ = \frac{1}{u}\frac{L - 1 + x^L - Lx}{(1 - x)(1 - x^L)} \quad (19)$$

and

$$T_- = \frac{1}{u}\frac{1 + (L - 1)x^L - Lx^{L-1}}{(1 - x)(1 - x^L)} \quad (20)$$

These results are illustrated in Figure 3. One can see then that the asymmetry parameter (A) approaches asymptotically $L - 1$ for the strongest bias $(x \to 0)$, while the for the weak bias $(x \to 1)$ the breaking of uphill/downhill symmetry in waiting times is much smaller $(A \to 1)$. This observation can be explained again by pointing out to the importance of the bias, which makes trajectories with the tracer starting behind other nontracer particles more probable. Then it takes, at least, $L - 1$ transitions to move downhill, and these transitions determining the overall downhill transition time are the slowest. This leads to the symmetry breaking in waiting times that increases with the size of the system L.

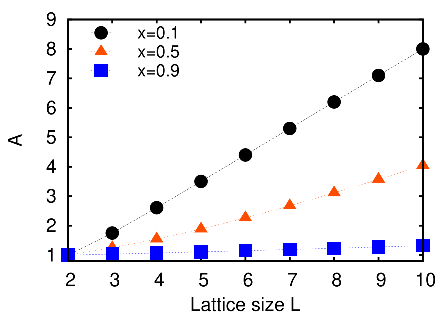

Figure 3. Asymmetry parameter $A = T_+/T_-$ as a function of the lattice size L (with $N = L - 1$). Lines are analytical predictions, symbols are simulation results.

Another important parameter that governs the symmetry breaking is the density of particles in the system. Since an analytical solution for the mean transition times in systems with arbitrary L and N are not available, we performed Monte Carlo simulations. As shown in Figure 4, at the fixed size L of the system, the higher asymmetry parameter is observed for increasing the particle density. The bias leads to dominating the particle conformations with the tracer being behind of other nontracer particles. For higher densities there are more particles that have to move forward before the tracer can step forward, and this clearly increases the asymmetry.

It is important to note that similar observations have been recently made in the Brownian dynamics simulation study of single-file diffusion in a biased periodic potential.[18] While the physical mechanisms of the symmetry breaking in this system might differ from that discussed above because of much more complex nature of interactions, we nevertheless believe that the bias mechanism identified in the present work still plays an important role there. It is worth emphasizing that because the random-walk framework is adopted, our consideration provides a much more detailed microscopic analysis of the symmetry breaking for waiting times.

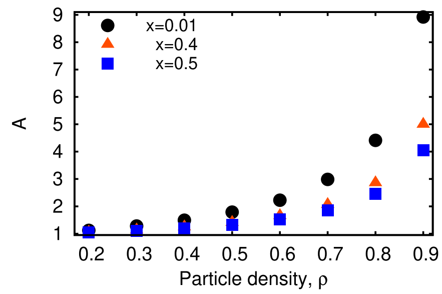

Figure 4. Asymmetry parameter $A = T_+/T_-$ as a function of the particle density $\rho = N/L$ from computer simulations. $L = 10$ and long-time trajectories were used in calculations.

We note that the symmetry (and symmetry breaking) of forward/backward transition-path times in a general reaction network was discussed recently in ref 25. Although these phenomena might look similar to the symmetry breaking discussed in our work, they are qualitatively different: the former is due to the time reversibility of the random-walk dynamics, whereas in our system the symmetry breaking is due to many-body effects. In addition, ref 25 deals with forward and backward transitions between different discrete states on a network; however, our investigation focuses on the uphill and downhill transitions of the system from the same state.

To clarify the microscopic details of the symmetry breaking for transition times, we considered only a limited range of theoretical models that can be solved analytically. However, in order to understand better the physics of symmetry breaking phenomena, more general situations need to be considered. It seems reasonable to generalize and extend the presented analysis in several directions by considering (i) an arbitrary number of random walkers N $(<L)$ for a given lattice of size L, (ii) the dynamics of a tracer on a high dimensional lattice, and (iii) open boundary conditions.

Although we analyzed very simple random-walk models, it can be argued that the obtained results on asymmetry of transition times might have strong implications for investigating various physical, chemical, and biological processes. The reason for this is that in many experimental studies the information on dynamic processes is obtained by monitoring the motion of single labeled particles that move in the crowded environment of unlabeled particles under the effect of external forces.[3,4,19,22] Our theoretical analysis suggests that measuring the transition times might provide an important information on the system, such as the degree of crowding, the strength of effective potentials, and the deviation from the equilibrium. It will be important to extend our theoretical studies to more realistic systems in order to provide a better quantitative description of the underlying molecular processes.

To summarize, we investigated the microscopic mechanisms of the symmetry breaking in uphill/downhill waiting times by considering biased random-walk models with crowding. Exact solutions via first-passage calculations allow us to obtain a full

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dynamic description of these systems. Our analysis shows that the symmetry of the mean downhill and uphill transition times is preserved if the initial and final states of the system are exactly known. However, recording the dynamics of only the tracer particles, as typically done in experiments, leads to the symmetry breaking in the mean uphill/downhill transition times. We identified the bias in the motion of individual particles as the main driving force in this phenomena. The asymmetry in transition times appears because the bias leads to a larger fraction of slow trajectories in the forward direction in comparison with that in the motion in the backward direction. It is also found that the symmetry breaking increases with the bias, the particle density and the size of the system. The advantage of the random-walk approach is that it allows us to obtain analytical results. Our theoretical predictions can be tested experimentally, for instance, using colloids with optical tweezers.[26] It has been argued also that the asymmetry in transition times might be utilized in current experimental studies of various systems to obtain a better microscopic description of underlying complex processes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpclett.0c01113.

Details of calculations for the forward/backward transition times (PDF)

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Notes

The authors declare no competing financial interest.

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