First-passage dynamics of obstructed tracer particle diffusion in one-dimensional systems

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Abstract. The standard setup for single-file diffusion is diffusing particles in one dimension which cannot overtake each other, where the dynamics of a tracer (tagged) particle is of main interest. In this article we generalize this system and investigate first-passage properties of a tracer particle when flanked by crowder particles which may, besides diffuse, unbind (rebind) from (to) the one-dimensional lattice with rates $k_{\text{off}}$ ($k_{\text{on}}$). The tracer particle is restricted to diffuse with rate $k_D$ on the lattice. Such a model is relevant for the understanding of gene regulation where regulatory proteins are searching for specific binding sites on a crowded DNA. We quantify the first-passage time distribution, $f(t)$ ($t$ is time), numerically using the Gillespie algorithm, and estimate it analytically. In terms of our key parameter, the unbinding rate $k_{\text{off}}$, we study the bridging of two known regimes: (i) when unbinding is frequent the particles may effectively pass each other and we recover the standard single particle result $f(t) \sim t^{-5/2}$ with a renormalized diffusion constant, (ii) when unbinding is rare we recover well-known single-file diffusion result $f(t) \sim t^{-7/4}$. The intermediate cases display rich dynamics, with the characteristic $f(t)$-peak and the long-time power-law slope both being sensitive to $k_{\text{off}}$.

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1. Introduction

In first-passage processes one investigates when a stochastic variable crosses a given threshold value for the first time \[1,2\]. Such processes are applicable to many areas, for example two molecules meeting to form a chemical bond \[3\], binding of two free ends of a polymer (so called cyclization) \[4\], extinction of diseases \[5\], escape problems \[6\], arrival times of news and emails \[7\], or when a stock market share crosses a preset market value \[8\]. Here we revisit the first-passage problem focusing on a modified version of a single-file diffusion system where particles not only diffuse and collide, but also unbind and rebind via a surrounding bulk. Such a model has relevance for gene regulation where a transcription factor (protein) searches for its binding site along a crowded DNA \[9–13\].

Tracer particle motion in interacting many-body systems is an interesting case of non-Markovian dynamics \[14\]; memory effects have profound impact on the system’s dynamics. A prototypical example is single-file diffusion where one studies the tracer particle motion in a system where particles are confined to one dimension and unable to pass each other (hardcore repulsion). This restriction leads to correlations between consecutive jumps of a single particle: if the particle jumps to the right of its equilibrium position it is on average more likely to move left in the subsequent jump. Clearly this process is not memoryless and it has been shown that a tracer particle explores the system under such crowded conditions subdiffusively (e.g. \[15\]); the ensemble averaged tracer mean squared displacement (MSD) is \(\sigma^2(t) \sim \sqrt{t}\) as a function of time \(t\) \[17\]. Even though the microscopic dynamics in a single-file system is non-Markovian some macroscopic observables exhibit Markovian behaviour; the centre-of-mass MSD and the dynamic structure factor are two examples of such slow variables \[16\]. The intuitive explanation is that it is irrelevant for such macroscopic observables whether two particles, assumed identical, bounce of each other or pass through each other. Single-file diffusion, has attracted great interest for at last 50 years and the body of work is substantial, both on the theoretical \[15, 17–32\], and experimental \[33–37\] side.

In this paper we are interested in the first-passage time density (FPTD), \(f(t)\), for a tracer particle in a single-file system where all particles, except for the tracer, are allowed to detach from the line and rebind at a random location. The detachment rate, \(k_{\text{off}}\), is the main parameter of consideration since it allows us to study the transition between two known regimes:

1. **Single-particle regime:** For large unbinding rates particles may pass each other and the no-passing condition is violated. The tracer particle is therefore diffusing as if it was free \[1\].

2. **Single-file regime:** When the unbinding rate is small (compared to the diffusion rate) the non-passing condition is only weakly broken. Here we expect to recover the known FPTD for single-file diffusion \[14,38\].

We also propose a closed form expression for \(f(t)\) based on a Markovian assumption which allow us to quantify the increase in non-Markovian effects as \(k_{\text{off}}\) is lowered.

The organization of the paper is as follows: In Section 2 we define our model. In Section 3 we provide a simple analytical treatment to increase the understanding of our numerical results which are presented and discussed in Section 4. Details of the
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2. The model

Consider a one dimensional lattice on which crowder particles and the tracer particle diffuse (Figure 1). The crowder particles can in addition to diffuse, unbind and rebind to the lattice. Rebinding occurs to a random unoccupied lattice site. The lattice constant is denoted $a$ and the diffusion rate $k_D$ is assumed equal in both direction and for all particles. Double occupancy is forbidden and a particle cannot overtake a flanking neighbor (single-file condition). Binding and unbinding dynamics of crowders are characterized by the rates $k_{on}$ and $k_{off}$; they are chosen such that the particle concentration on the line is in equilibrium with the bulk. We keep the the average filling fraction at 25% during the simulations. The ends of the lattice are reflecting but the number of lattice sites chosen sufficiently large such that boundary effects do not affect our results.

To consider the first-passage properties of the tagged particle in the aforementioned system, we introduce a perfectly absorbing target site (see Figure 1). This site reacts only with the tracer and remains inert for all other particles. In this scenario we seek to understand the FPTD of the tracer to the target site as a function of $k_{off}$.

We implemented the model described above using the Gillespie algorithm; details are deferred to Appendix A. Briefly, in a simulation we initially place the particles randomly (thermal initial condition) where the initial position of the tracer particle is 70 sites away from the target site. Also, due to recent interest in non-thermal initial conditions in single-file diffusion [39][40] we in addition investigate the case when the particles are placed equidistantly for $k_{off} = 0$. We run the simulation until the tagged particle hits the absorbing target and make a record of the absorption time. From many such runs we then determine the ensemble averaged FPTD (normalized histogram of absorption times) as a function of our key parameter $k_{off}$. In this way

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$\S$ There is nothing preventing us from letting $k_D$ be different for all particles, similar to [31].

$\parallel$ Particles in the bulk rebind to a random unoccupied lattice site. This means that we model the bulk in an effective way and neglect that rebinding close to the unbinding site is more probable [11]. This would be particularly important if the surrounding bulk was crowded as is the likely scenario in the interior of a living cell.
we interpolate between the single-file regime \((k_{\text{off}} \ll k_D)\) to the unobstructed single particle regime \((k_{\text{off}} \gg k_D)\).

3. Analytical estimates

In this section we provide analytical estimates to corroborate the numerical results in the next section. First, we put bounds on the tracer’s MSD, denoted by \(\sigma^2(t)\), in the absence of the absorbing site. Second, we also put bounds on the FPTD by discussing established results. Third, we relate \(\sigma^2(t)\) to the first-passage time density, based on a Markovian approximation. These estimates allow us to quantify non-Markovian effects in the FPTD simulations in the Results section.

3.1. Bounds and estimates for \(\sigma^2(t)\)

Let us now provide estimates for the MSD for the process as considered here and depicted in Figure 1. Clearly the obstructed diffusion process can never be faster than if there were no surrounding particles at all. Therefore an upper bound on \(\sigma^2(t)\) is the unobstructed (single particle) diffusion result

\[
\dot{\sigma}_{\text{SP}}^2(t) = 2D_{\text{SP}} t^{2H_{\text{SP}}}
\]

(1)

with a diffusion constant \(D_{\text{SP}} = 2k_D a^2\). The, so called, Hurst exponent \(H = H_{\text{SP}} = 1/2\) relates the distance “explored” by the particle to time, \(t\).

The lower bound on \(\sigma^2(t)\) is reached when no particles unbind at all. This is the single-file (SFD) regime where

\[
\dot{\sigma}_{\text{SFD}}^2(t) = \gamma \left(1 - \rho a\right) \frac{4D_{\text{SP}}}{\pi} \sqrt{\frac{2}{\pi}} t^{2H_{\text{SFD}}}
\]

(2)

with a Hurst exponent \(H = H_{\text{SFD}} = 1/4\) and \(\rho\) is the particle density. We point out that tracer particle motion in a single-file system is dominated by long-time memory (non-Markovian) effects, manifested through a subdiffuse Hurst exponent \((H < 1/2)\). For equidistant initial conditions \(\gamma = 1/\sqrt{2} \) \([31, 40, 41]\), whereas \(\gamma = 1\) for thermal initial conditions. In our single-file simulations we address both cases.

3.2. Established results for the FPTD

Here we give an explicit expression for the FPTD which is valid for the single-particle and single-file regimes. For a freely diffusing particle the first-passage time density is well-known \([1]\). Also, rather recently, extensive simulations led to a proposed form \([14]\) for single-file diffusion. The results for these two cases are contained in the following expression \([14]\)

\[
f(t) = Ct^{-1} \left[ \frac{\Delta x}{\sqrt{2} \sigma(t)} \right]^{(1-H)/H} \exp \left[ -\frac{\Delta x^2}{2\sigma^2(t)} \right],
\]

(3)

with normalization constant \(C = 2H/\Gamma[(1-H)/(2H)]\), where \(\Gamma(z)\) is the gamma-function, and \(\Delta x\) is distance to target at \(t = 0\). The single particle result is found when \(H = 1/2\), and the single file result is \(H = 1/4\). The mean square displacements, \(\sigma^2(t)\), are given in equations \([1]\) and \([2]\) respectively. The functional form above provides a long time tail \(t^{-3/2}\) for a single particle \([1]\) as it should, and is in agreement with the exact asymptotic result \(t^{-7/4}\) \([38]\) for single file diffusion.
3.3. Markovian approximation for the FPTD

It is unclear to what extent equation (3) holds when $0 < k_{\text{off}} < \infty$, i.e., when we are in neither the single-particle regime ($k_{\text{off}} = \infty$) nor in the single-file regime ($k_{\text{off}} = 0$). In particular, direct application of equation (3) is complicated by the fact that for general $k_{\text{off}}$, the Hurst exponent $H$, appearing in equation (3), does not take a universally valid value for all times (see MSD simulations in the next section). Below we therefore provide a useful form for the FPTD which will allow us to quantify non-Markovian effects in our FPTD simulations (see Section 4). To that end, we define:

$$Q(t) = \frac{\Delta x}{\sqrt{2\sigma^2(t)}},$$

(4)

where $\Delta x$, as before, is the initial distance to the target. In terms of $Q(t)$ we express the FPTD for standard diffusion (Markovian process) as

$$f(t) = A \frac{Q(t)}{t} \exp[-Q^2(t)],$$

(5)

with normalization constant $A = 1/\int_0^\infty [Q(t)/t] \times \exp[-Q^2(t)]dt$. If $\sigma^2(t) \propto t$, then $A = 1/\sqrt{\pi}$. Equation (5) can be obtained by putting $H = 1/2$ in equation (3) or from using the method of images [1]. Method of images is an appealingly simple way to solve first-passage problems to perfectly absorbing boundaries, but, it has limited applicability for non-Markovian dynamics [14, 44]. Nevertheless, this method been used previously for a similar setup to ours [9].

When $k_{\text{off}} \to \infty$ our system is Markovian whereas in the opposite limit $k_{\text{off}} \to 0$ it is highly non-Markovian. Since equation (5) is based on a Markovian assumption it cannot be used to calculate the correct $f(t)$ for single-file diffusion, only to quantify deviations from non-Markovian dynamics. To see this explicitly, using $\sigma^2(t) \propto t$ in equation (5), yields $f(t) \sim t^{-5/4}$, rather than the exact result $f(t) \sim t^{-7/4}$ [14, 38]. If we instead use $\sigma^2(t) \propto t$ we obtain the proper $f(t) \sim t^{-3/2}$ for standard diffusion to an absorbing boundary.

In the next section we utilize equations (4) and (5) in the following way: first, we run simulations to numerically determine the MSD for different parameter sets. Subsequently we use the raw data from those simulations as $\sigma^2(t)$ which we substitute into equations (4) and (5). In this way we calculate an approximation for the FPTD. Finally, we perform explicit FPTD simulations and compare those to the Markovian approximation for the FPTD given by equations (4) and (5).

4. Results

In this Section we present the results of stochastic simulations (Gillespie algorithm) of the model outlined in section 2. The main quantity of interest is the FPTD to a perfectly absorbing target site for different unbinding rates $k_{\text{off}}$. But first, we characterize our system in terms of the tracer particle MSD. The MSD simulations are subsequently used to test for non-Markovian deviations in our first-passage simulations using equation (3).

In Figure 2 we show the tracer particle MSD as a function of time for different $k_{\text{off}}$ (keeping all other parameters fixed). We notice that as $k_{\text{off}}$ is increased the MSD is increased; the larger the unbinding rate, the less obstructed the tracer particle motion is. All MSD simulations are within the upper and lower bounds as provided by the single-particle limit [equation (1)] and the single-file diffusion limit [equation (2)] as
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Figure 2. Tracer particle MSD vs. time in an obstructed diffusion system, for different off-rates. As the off-rate is increased the MSD of the tracer particle approaches the single-particle result $2Dt$ (solid light blue line). In all simulations we used: diffusion rate $k_D = 1$, lattice spacing $a = 1$ and number of lattice sites $L = 1001$. The data was ensemble averaged over 2000 simulation runs. The unbinding rates are listed in the figure legend, and the binding rates were chosen to maintain the average filling fraction 0.25 (see Appendix A).

expected. For small $k_{off}$ the system behaves just as a single-file system up to a crossover time $\tau^*$, after which the MSD is linear in time. For the case that $k_{off}$ is the rate limiting parameter, we simply estimate the crossover time as the (average) time for an unbinding event to take place, i.e., $\tau^* \approx 1/k_{off}$; this prediction for $\tau^*$ is in agreement with our simulation results for $k_{off} \leq 0.1$.

Figure 2 also shows the MSD for single-file diffusion when particles placed equidistantly at $t = 0$ (non-thermal initial condition). The result shows that the asymptotic form of the MSD is well described by equation (2), with $\gamma = 1/\sqrt{2}$. We are the first to numerically verify this result which, up to now, only was known on analytical grounds [31,40,41].

Figure 3 shows simulation results for the probability density of first-passage times $f(t)$ for different $k_{off}$ (small symbols). For clarity, the top panel shows the results for large $k_{off}$ whereas the bottom panel holds the results for small $k_{off}$. We notice that as $k_{off}$ increases $f(t)$ approaches that for a single particle (top panel). As $k_{off}$ gets smaller the maximum of the curve is shifted towards longer times and the power-law exponent of tail decreases. This agrees with the fact that longtime exponent should change from $-3/2$ to $-7/4$ as $k_{off}$ decreases.

We also compare simulations to analytical approximations in figure 3. First, we find that for the case of a single particle (top panel), equation (3) with $H = 1/2$ agrees well with simulations as it should. For the case of single-file diffusion with equidistant initial conditions (bottom panel), $\gamma = 1/\sqrt{2}$, we find good agreement between simulations and equation (3) with $H = 1/4$ (the case $\gamma = 1$ was considered...
Figure 3. First-passage time density of a tracer particle in an obstructed diffusion system for (top) large unbinding rates $k_{\text{off}}$ and (bottom) small $k_{\text{off}}$. Large symbols denote normalized first-passage time histograms when the target (placed in the middle of the lattice) was initially 70 lattice sites away from the tracer particle’s initial position. The same parameters as listed in Figure 2 were used here ($k_D = 1$, $a = 1$ and $L = 1001$). The first-passage data is ensemble averaged over $9.6 \cdot 10^5$ ($k_{\text{off}} = 10^{-4}$ and $k_{\text{off}} = 10^{-3}$), $10^4$ ($k_{\text{off}} = 0.01$ and $k_{\text{off}} = 0.1$), $4.8 \cdot 10^3$ ($k_{\text{off}} = 5$), $10^3$ ($k_{\text{off}} = 0$, SFD), and $5 \cdot 10^3$ ($k_{\text{off}} = \infty$, single particle) simulation runs. Small symbols show the performance of the Markovian approximation, equation (5), where we used the MSD simulations as $\sigma(t)$ in equation (4). Notice that as $k_{\text{off}}$ is lowered non-Markovian effects become more pronounced.
extensively in [14]). Our study therefore extends the applicability of this expression to a more general setting than considered previously [14], where only thermal initial conditions were employed. Equation (3) can, however, not be used for general off rates; as noted earlier, for general $k_{\text{off}}$ it is not straightforward to choose a proper Hurst exponent that characterises our system for all times. Instead we compare our simulations to the Markovian approximation (5) (large symbols), with $\sigma^2(t)$ extracted from Figure 2. We find that for all large $k_{\text{off}}$ values considered (top panel), the discrepancy between the simulations and equation (5) are small. This indicates that non-Markovian effects are small in this regime. On the other hand, when $k_{\text{off}}$ gets smaller (bottom panel) the deviations from equation (5) grow and the non-Markovian nature of the problem becomes increasingly prominent.

5. Concluding remarks and outlook

We studied first-passage statistics of a tracer particle in a single-file diffusion system which can exchange particles with a surrounding bulk. We focused mainly on the probability density of first-passage times, $f(t)$, which we quantified numerically and estimated analytically. We distinguished two limiting behaviors as a function of our main parameter $k_{\text{off}}$. When the unbinding rate is small ($k_{\text{off}} \ll k_D$) we recover single-file results. When the unbinding is large ($k_{\text{off}} \gg k_D$) the no-passing condition is effectively violated and we recover the result for a single particle. The transient function connecting these two regimes is non-trivial and was characterized in terms of $k_{\text{off}}$. For the single-particle and the single-file cases our simulations further established the validity of equation (3). For general off-rates, equation (5) was used as a quantifier of non-Markovian effects, and we find that such effects become more prominent as $k_{\text{off}}$ is lowered.

Single-file diffusion is a useful model system to study effects of crowding in diverse (bio)physical media. It has received much of attention over the last five decades partly due to its analytical tractability. However, in its original formulation particles are under no conditions allowed to pass each other, which in real systems rarely is the state of affairs. One example is target-finding problems on DNA where most studies known to the authors omit crowding, see for example [9, 10, 12]. It is therefore a challenge to extend current knowledge on single-file diffusion to reach a wider applicability. We hope that our work will inspire future progress in this direction.

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Appendix A. Numerical implementation

The model, as depicted in Figure 1, is implemented numerically using Gillespie’s algorithm [42]. Each particle on the lattice is given rates corresponding to its allowed actions: a rate of jumping left or right ($k_D$) and a rate for unbinding ($k_{\text{off}}$). The binding rate $k_{\text{on}}$ is adjusted during the simulation such that the average number of
occupied lattice sites $\rho$ is kept fixed. Detailed balance gives

$$k_{\text{on}} = k_{\text{off}} \bar{\rho}(t) / \rho_{\text{bulk}}, \quad (A.1)$$

where $\bar{\rho}(t)$ is the instantaneous particle concentration of the lattice (number of particles divided by the system’s length), and $\rho_{\text{bulk}}$ is the concentration in the bulk. Relation (A.1) simply means that the bulk acts as a particle reservoir. Low copy number fluctuations in the surrounding volume can, in this way, not be captured with our implementation. The no-passing condition between particles is implemented by setting the jump rate to zero in the direction of a flanking particle. The tracer particle is different from all others since the binding and unbinding rates are put to zero ($k_{\text{off}} = k_{\text{on}} = 0$) throughout the simulation. Its diffusive motion is otherwise the same. In the simulations we used $\rho = 0.25$, $k_D = 1$, $a = 1$, $\Delta x = 70$, and used $k_{\text{off}}$ as the free parameter in the simulation.

Below follows a few technical details on the implementation. First, we define a binary occupation vector $X$ with the same length as the number of lattice sites $L$. A '0' ('1') entry indicates vacant (occupied) sites. Second, we define a rate vector $K$ containing all particle rates. This vector contains $3L+1$ entries ordered in the following way. If for example $X_j = 1$ and $X_{j+1} = 0$ then we put $K_{2j-1} = k_D$, $K_{2j} = k_D$ for jumping, and $K_{j+2L} = k_{\text{off}}$ for unbinding. If, on the other hand, a neighbouring site was occupied, say $X_{j+1} = 1$, then we must put $K_{2j} = 0$ (and $K_{2j+1} = 0$ for the particle at site $j+1$), such that the particles are not allowed to pass each other. The rate for adding a new particle to the lattice (i.e. binding) is for convenience placed in the last element $K_{3L+1}$. Below is a schematic outline of our algorithm:

(i) Place the tracer 70 sites away from the target. The remaining particles are placed randomly to the left and right of the tracer particle. Reset the simulation time $t_{\text{tot}} = 0$. For the single-file case with $\gamma = 1/\sqrt{2}$ the particle are placed equidistantly at the start of the simulation.

(ii) Assign to each particle their corresponding rates, sum all elements in $K$, $k_{\text{tot}} = \sum_i K_i$.

(iii) Draw two uniformly distributed random numbers $r_1$ and $r_2$ between 0 and 1.

(iv) From $r_1$, calculate time until next event $\tau$, according to $\tau = -(1/k_{\text{tot}}) \ln r_1$, and update time $t_{\text{tot}} \rightarrow t_{\text{tot}} + \tau$.

(v) From $r_2$, determine the particle event by finding the index $\mu$ in $K$ that satisfies

$$\sum_{i=0}^{\mu-1} K_i < k_{\text{tot}} r_2 \leq \sum_{i=0}^{\mu} K_i.$$

Each $\mu$ corresponds to one particle doing one of its allowed actions both of which are inferred from the index $\mu$ of $K$. If a particle is at site $j$ ($X_j = 1$) and unbinds then we simply put $X_j = 0$. Or, if the same particle jumps right, then we set $X_j = 0$ and $X_{j+1} = 1$.

(vi) Return to step 2 and repeat until the tracer particle has reached its target. The ensemble average is obtained by repeating the steps 1-6 many ($\sim 10^3 - 10^4$) times.

The absorbing target is omitted in step 6 when we are only interested in the tracer particle’s MSD.

What we describe above is a generalization of the so-called direct method for single-file diffusion systems. For the single-file simulations ($k_{\text{off}} = 0$) displayed herein we employ a computationally improved approach, the trial and error method, which
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is based on the idea that the sum of $K$ is carried out only once. This method cannot be directly applied for $k_{\text{off}} \neq 0$ since the sum over $K$ must be recalculated every time a new particle associates or dissociates.

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