

Mechanism of Diffusive Transport in Molecular Spider Models

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Recent advances in single-molecule chemistry have led to designs for artificial multi-pedal walkers that follow tracks of chemicals. We investigate the motion of a class of walkers, called *molecular spiders*, which consist of a rigid chemically inert body and several flexible enzymatic legs. The legs can reversibly bind to chemical substrates on a surface, and through their enzymatic action convert them to products. The legs can also reversibly bind to products, but at a different rate. Antal and Krapivsky have proposed a model for molecular spider motion over regular 1D lattices [T. Antal, P. Krapivsky, Phys. Rev. E **76**, 2 (2007)]. In the model the legs hop from site to site under constraints imposed by connection to a common body. The first time a leg visits a site, the site is an uncleaved substrate and the leg hops from this site only once it has cleaved it into a product. This cleavage happens at a rate $r < 1$, slower than dissociation from a product site, $r = 1$. The effect of cleavage is to slow down the hopping rate for legs that visit a site for the first time. Along with the constraints imposed on the legs, this leads to an effective bias in the direction of unvisited sites that decreases the average time needed to visit n sites. The overall motion, however, remains diffusive in the long time limit. We have reformulated the Antal-Krapivsky model as a continuous-time Markov process, and simulated many traces of this process using kinetic Monte Carlo techniques. Our simulations show a previously unpredicted transient behavior wherein spiders with small r values move superdiffusively over significant distances and times. We explain this transient period of superdiffusive behavior by describing the spider process as switching between two metastates: a diffusive state D wherein the spider moves in an unbiased manner over previously visited sites; and a boundary state B wherein the spider is on the boundary between regions of visited and unvisited sites and experiences a bias in the direction of unvisited sites. We show that while the spider remains in the B state it moves ballistically in the direction of unvisited sites, and while the spider is in the D state it moves diffusively. The relative amount of time the spider spends in the two states determines how superdiffusively the spider moves. We show that the B state is Markovian, but the D state is non-Markovian because the duration of a D period depends on how many sites have been visited previously. As time passes the spider spends progressively more time in the D state (moving diffusively) and less time in the B state (moving ballistically). This explains both the transient superdiffusive motion and the eventual decay to diffusive motion as $t \rightarrow \infty$.

I. INTRODUCTION

Controlling the transport of individual molecules is a central problem in nanotechnology. Any molecule free in solution is subject to thermally driven diffusion. To enable directed movement of molecules, a nanoscale system can use a chemical scaffold and associated chemical walkers that traverse the scaffold as a molecular transport mechanism. Such structures are ubiquitous in biological systems—cells accomplish many of their complex tasks using self-assembled filament tracks and molecular motors that walk directionally along the filaments [1].

In addition to naturally occurring molecular

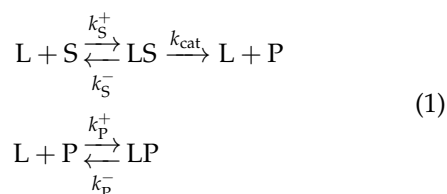
walkers, several synthetic walker systems have been studied. Our work is inspired by *molecular spiders* [2]. A molecular spider consists of a rigid, inert chemical body to which are attached multiple flexible enzymatic legs. The legs are deoxyribozymes—enzymatic sequences of single-stranded DNA that can bind to and cleave complementary strands of a DNA substrate. When a molecular spider is placed on a surface coated with the single-stranded DNA substrate, its legs bind to the substrate (Fig. 1). A bound leg can either detach from the substrate without modifying it, or it can catalyze the cleavage of the substrate, creating two product strands. The “lower” product remains bound to the surface, while the “upper” product is free to float away in solution. Because the lower product is complementary to the nether part of the spider’s leg, there is a residual binding of the leg to the product, although this is typically much weaker than the leg-substrate binding and thus much shorter lived. The leg kinetics are described by the five chemical reactions in Eq. 1 relating legs (L), substrates (S), and products

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(P). In these equations we ignore the upper product strand, and P refers to only the lower part of the cleaved substrate that remains bound to the surface. Additionally, we have combined the catalysis reaction together with all of the subsequent dissociation reactions (not shown) into a single k_{cat} rate.



Molecular walkers, including molecular spiders, have many potential applications [3, 4]. Walkers can be used as molecular shuttles [5], moving cargo between sites over molecular tracks [6, 7]. They can aid in the self-assembly of molecular structures [8] that are otherwise thermodynamically unfavorable, and proposals have been made to use the actions of walkers to effect molecular communication [9] and computation [10, 11]. More recently, molecular spiders have been shown to follow prefabricated tracks of DNA substrates across a surface [12]. In each of these applications, different statistical properties of the walker motion (mean squared displacement, first passage time, etc.) determine the usefulness of a particular walker design.

Recently, Antal and Krapivsky introduced an abstract model of molecular spider motion [13, 14].

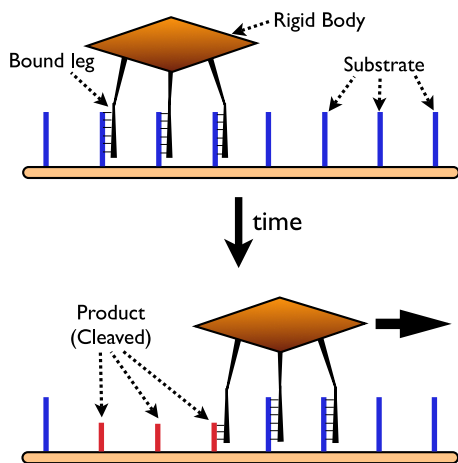


FIG. 1: (Color online) A molecular spider system. The spider moves over a surface of chemical sites as the legs attach and detach. A leg cleaves a substrate site, turning it into a product site when it detaches.

The Antal-Krapivsky (AK) model simplifies the reaction rates in Eq. 1, setting the on-rates to be infinite, and the substrate dissociation rate to be 0, so that substrates are always cleaved to products before detachment. Essentially, the AK model defines

$$\begin{aligned}
 k_S^+ &= k_P^+ = \infty, \\
 k_{\text{cat}} &= r \leq 1, \\
 k_S^- &= 0, \text{ and} \\
 k_P^- &= 1.
 \end{aligned}
 \tag{2}$$

Under these conditions the spider motion can be studied as a function of the single rate parameter $r \leq 1$, which represents the ratio between the substrate cleavage and product detachment rates. Hence, a *residency-time bias* is established, where legs detach faster from previously visited sites than from unvisited sites. Antal and Krapivsky showed that the asymptotic behavior of this spider model is diffusive for all values of r . Thus, in the long time limit the AK spiders cannot be used as a faster-than-diffusion transport mechanism. However, our numerical simulations of the AK model reveal that when there is a residency-time difference between previously visited and unvisited sites, the spiders can move superdiffusively for time periods that span many orders of magnitude. While the asymptotic behavior of molecular spiders remains diffusive, there is a possibility of exploiting their transient superdiffusive behavior to perform useful work in experimentally relevant situations where spiders need only move for a finite time or over a finite distance.

In Section II we formalize the description of the AK model as a continuous-time Markov process so that it is amenable to simulation using the kinetic Monte Carlo method. Section III gives the numerical results of our simulations, carried out to very long simulated times, and demonstrates the dichotomy between the superdiffusive transient and the diffusive asymptotic behavior.

Understanding the mechanism of the transition from short-time to long-time behavior is essential for designing nanoscale transport systems using walkers such as molecular spiders. In Section IV we show how the states of the AK Markov process can be partitioned into two metastates. A spider is in the *diffusive* metastate D when it is moving over the region of previously visited sites. It is in the *boundary* metastate B when it is attached to sites at the boundary between regions of visited and unvisited sites. The spider moves diffusively in metastate D and ballistically in metastate B , and alternates between D and B over time. We show that the B state

is Markovian, but the D state is not. As the region of cleaved products grows, so does the proportion of time the spider spends moving diffusively in the D state. Thus the observed transient superdiffusive behavior of the spiders can be explained by the gradual transition from a predominance of B periods to a predominance of D periods.

II. THE ANTAL-KRAPIVSKY MODEL

Antal and Krapivsky abstract away many of the details of molecular spiders to arrive at a simplified model that can explain how walkers with multiple uncoordinated but collectively constrained legs might move over a 1D lattice of sites [13], and how this movement is affected by allowing the legs to irreversibly modify the sites as they move [14]. The model simplifies the chemical kinetics of Eq. 1, assuming the rates of Eq. 2. Under these conditions the legs are always attached to the surface, because the on-rates are infinite, so legs detach and then immediately reattach, hopping from one site to the next. Additionally, because $k_S^- = 0$, a leg bound to a substrate will always cleave the substrate into a product. This simplification focuses attention on the two rates k_{cat} and k_P^- and how their ratio $r < 1$ controls the motion of the spiders through a residency-time bias, i.e., longer residency times on newly visited sites.

The model effectively but not explicitly describes spider movement as a continuous-time Markov process. We reformulate the model more precisely to emphasize the states and transitions, and the Markovian nature of the transitions when the state is defined to include both the state of the spider and the state of the surface sites.

We consider a system with a single k -legged spider. The legs step over sites on a regular lattice (\mathbb{Z}). The states in the process are the combined state of the lattice sites and the state of the spider. Each lattice site is a substrate (uncleaved) or a product (cleaved). Initially all sites are substrates, so the state of the surface can be described by the set $P \subset \mathbb{Z}$ of sites that have been cleaved. The state of the spider is described by the set $F \subset \mathbb{Z}$ of foot locations—lattice sites with a leg attached. Together P and F completely define the state of the spider system, i.e., the state of the Markov process is $X = (P, F)$.

We call F a *configuration* of the legs. The *gait* of a spider is defined by what configurations and what transitions between configurations are allowed in the model. There are considerable possibilities for

variations on the spider gait. Antal and Krapivsky describe the gait of a spider with the kinetics of Eq. 2. With $k_S^+ = k_P^+ = \infty$, a leg immediately reattaches after it detaches. Thus in any state $X = (P, F)$ of the process, all k legs are attached. Together with the restriction that at most one leg may be attached to a site, this implies that

$$|F| = k. \quad (3)$$

Additionally, the legs are constrained by their attachment to a common body. If the spider has a point body with flexible, string-like legs of length $s/2$, then any two feet can be separated by at most distance s , thus

$$\max(F) - \min(F) \leq s. \quad (4)$$

This restriction is that of the “global spiders” of Antal and Krapivsky [13].

The transitions in the process correspond to individual legs unbinding and rebinding. When a spider is in configuration F , any foot $i \in F$ can unbind and move to a nearest-neighbor site $j \in \{i+1, i-1\}$ to form a new configuration $F' = (F \setminus \{i\}) \cup \{j\}$ provided the new configuration does not violate one of the constraints of Eqs. 3 and 4. A transition $i \rightarrow j$ is called *feasible* if it meets these constraints. The feasible transitions determine the gait of the spider. The nearest-neighbor hopping combined with the mutual exclusion of legs leads to a shuffling gait, wherein legs can slide left or right if there is a free site, but legs can never move over each other, and a leg with both neighboring sites occupied cannot move at all. If the legs of such a spider were distinguishable, they would always remain in the same left-to-right ordering.

The rate at which feasible transitions take place depends on the state of the site i . If i is a product the transition rate is 1, but if i is a substrate the transition occurs at a slower rate $r < 1$. This is meant to model the realistically slower dissociation rates from substrates corresponding to chemical kinetics where $k_{\text{cat}}/k_P^- = r < 1$. The effect of substrate cleavage is also captured in the transition rules. If for state $X = (P, F)$ where $i \in F \setminus P$, the process makes the feasible transition $i \rightarrow j$, then the leg will cleave site i before leaving, and the new state will have $P' = P \cup \{i\}$.

In order to compactly represent the state of a spider process, Antal and Krapivsky introduced a graphical notation. The symbol \circ represents an unoccupied site and \bullet represents an occupied site. All sites initially have a hat $\hat{}$ indicating they are uncleaved (substrate) sites. A site is cleaved into a

product when a leg detaches from it for the first time, denoted by removing the hat. For example, a spider in the B state (Fig. 12) with a configuration of legs $F = \{i, i + 2\}$ can be illustrated thus:

$$\cdots \hat{\circ}_{i-4} \hat{\circ}_{i-3} \circ_{i-2} \circ_{i-1} \bullet_i \circ_{i+1} \hat{\bullet}_{i+2} \hat{\circ}_{i+3} \cdots$$

Since the transition rates are translationally invariant on the lattice, we can generally omit the indexes on the sites.

Antal and Krapivsky have analytically studied the expectation of the random variable $T(n)$, which for the bipedal spider with $s = 2$ is defined as the time when a leg steps onto an uncleaved site after $n + 2$ sites have already been cleaved. When this event occurs the spider is always in the following position (or its reflection),

$$\cdots \hat{\circ} \hat{\circ} \underbrace{\circ \circ \cdots \circ \bullet \circ}_{n+2} \hat{\bullet} \hat{\circ} \cdots$$

One can alternatively think of $T(n)$ as the time at which the spider first visits n distinct sites not counting the three sites its legs span at that time. Since a spider always cleaves a substrate site it visits, $T(n)$ is equivalent to the time for $n + 2$ products to be formed. For the case $s = 2, k = 2$, when $r = 1$, it was found that

$$\langle T(n) \rangle = n^2 + n, \quad (5)$$

but more generally, when $0 < r \leq 1$, the leading coefficient is reduced to

$$\langle T(n) \rangle = \frac{3}{2} \frac{1+r}{2+r} n^2 + \frac{1}{r} n. \quad (6)$$

This implies that a large residency-time bias between unvisited and visited sites, corresponding to small values of r , leads to a faster mean time to visit n sites for large enough n . Antal and Krapivsky also showed that one-legged spiders do not exhibit this behavior. Thus, it is the combination of having more than one leg and the ability to irreversibly change the sites and hence rates that allows the spider to move faster. While for small r values $T(n)$ is smaller, it is still $\mathcal{O}(n^2)$, and hence not asymptotically faster than an ordinary diffusive process.

Antal and Krapivsky note that with $r < 1$ there is an effective bias in the spider's motion when it

has one leg on a substrate at the boundary between cleaved and uncleaved sites. In such a situation the spider moves with probability p_+ in the direction away from previously visited sites and with probability p_- towards previously visited sites. Antal and Krapivsky calculated that the strongest bias is in the $r \rightarrow 0$ limit when $p_- = 3/8$ and $p_+ = 5/8$. In the next section we show via simulation that spiders experience an initial period of superdiffusive behavior when $r < 1$, and in Section IV we show how this behavior is caused by the effective bias, yet asymptotically dominated by diffusive motion over previously visited sites in the limit as $t \rightarrow \infty$.

III. SIMULATION RESULTS

We use the Kinetic Monte Carlo method [15] to numerically sample traces of the spider Markov process. In our simulations, a single two-legged ($k = 2$) spider with maximum leg separation constraint $s = 2$ is placed on a one-dimensional infinite lattice of substrates and allowed to move according to the model. We vary the rate r to see how it influences the motion. The case $r = 1$ corresponds to ordinary diffusion because there is no effective difference between substrates and products.

A. Simulation Description

For each value of $r \in \{1, 0.5, 0.1, 0.05, 0.01, 0.005\}$ we simulate 5000 traces of the Markov process. We record samples of several random variables (e.g., mean squared displacement and first passage time) that are functions of time, distance, or the number of sites visited. To ensure that each simulation trace provides a sample for each measured value of the random variables, we run each simulation until all of the following conditions are met: (1) the time is greater than $t_{\max} = 10^8$ time units; (2) the spider has visited at least $c_{\max} = 10^4$ sites; and (3) the spider has moved at least a distance $d_{\max} = 10^4$ sites away from the origin. We sample so that each of the plots with time on the x -axis that follow is obtained from 6000 measurement points equispaced for the independent variable axis of the plot (linear or logarithmic). For plots that have distance and number of cleaved sites on the x -axis we use 10^4 measurement points each.

B. Agreement with Analytical Results

We are primarily interested in using the simulations to obtain estimates of random variables for which we do not already have analytical results. However, we should also show our simulations agree with Antal and Krapivsky's calculations for $\langle T(n) \rangle$ (Eq. 6).

Figs. 2 and 3 show simulation results for $\langle T(n) \rangle$ and its dual quantity $\langle N(t) \rangle$, respectively. These quantities show how fast a spider cleaves the substrates and are especially relevant because for real molecular spiders it has been possible, using surface plasmon resonance, to measure the loss of mass due to cleavage [2].

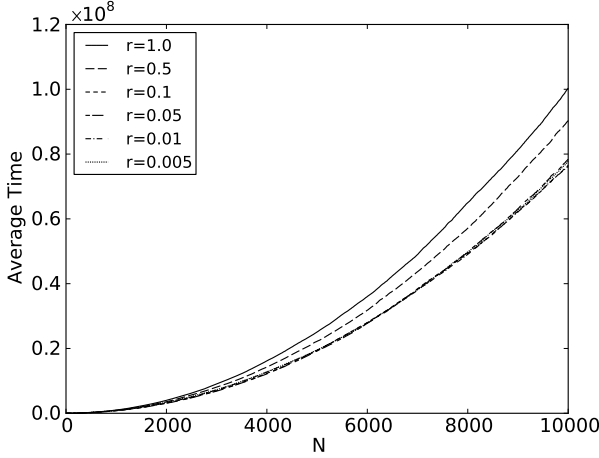


FIG. 2: Simulation estimates for $\langle T(n) \rangle$.

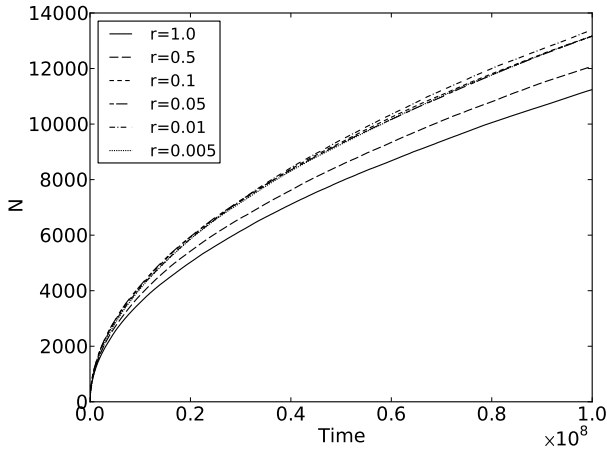


FIG. 3: Simulation estimates for $\langle N(t) \rangle$.

We can estimate how well the simulation results fit the analytical formula using the R^2 statistic

$$R^2 = 1 - \frac{\sum_{i=1}^n (\langle T(i) \rangle - t(i))^2}{\sum_{i=1}^n (t(i) - \bar{t})^2}.$$

Here n is the number of measured points, $\langle T(i) \rangle$ is given analytically by Eq. 6, $t(i)$ is the mean of the i -th observed value for each trace, and $\bar{t} = \sum_{i=1}^n t(i)/n$. We found the R^2 values were greater than 0.999 for all measured values of r , indicating excellent agreement between theory and simulation.

C. Observed Instantaneous Superdiffusion of Spiders

Superdiffusive motion can be quantified by analyzing the mean square displacement of a spider as a function of time. For diffusion in 1D space with diffusion constant D , the mean squared displacement is given by Eq. 7.

$$\text{msd}(t) = 2Dt^\alpha \begin{cases} \alpha = 0 & \text{stationary} \\ 0 < \alpha < 1 & \text{subdiffusive} \\ \alpha = 1 & \text{diffusive} \\ 1 < \alpha < 2 & \text{superdiffusive} \\ \alpha = 2 & \text{ballistic or linear} \end{cases} \quad (7)$$

We shall say that the spider is moving *instantaneously superdiffusively* at a given time t if

$$\alpha(t) = \frac{d(\log_{10} \text{msd}(t))}{d(\log_{10} t)} > 1. \quad (8)$$

This definition is similar to that used by Lacasta et al. [16] to describe transient superdiffusive behavior.

Fig. 4 shows $\text{msd}(t)$ for different r values. In this log-log plot, straight lines correspond to power laws, that is, to Eq. 7, and the parameter α is given by the slope. A reference line for diffusion is shown to illustrate that the $r = 1$ spider is ordinary diffusive, and all spiders eventually become ordinary diffusive asymptotically. A reference line proportional to t^2 is also shown for comparison to ballistic motion, which shows that spiders with small r values experience significant periods of superdiffusive behavior.

We use finite difference methods to estimate $\alpha(t)$ (Eq. 8). Fig. 5 shows the result of using the Savitzky-Golay smoothing filter [17] on these estimates. The

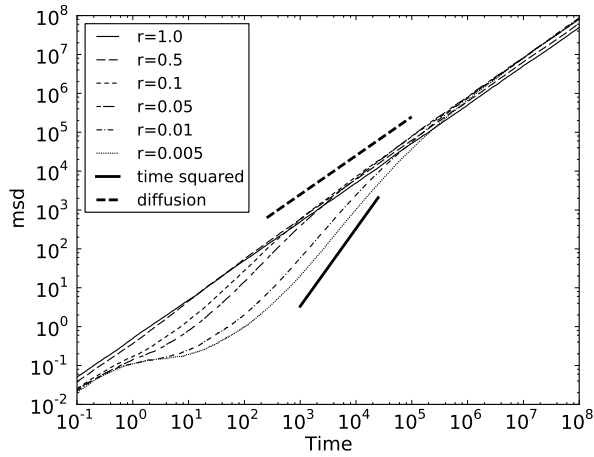


FIG. 4: Mean squared displacement, $\text{msd}(t)$.

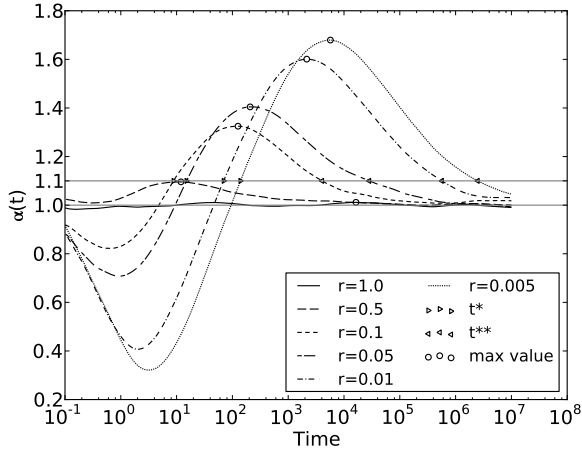


FIG. 5: Finite difference approximation of $\alpha(t)$.

spiders with $r = 1$ indeed move diffusively, with $\alpha(t) \approx 1$ for all times. However, the spiders with $r < 1$ show a pattern of three distinct diffusion regimes at different time scales. The first of these is an *initial regime* when the times are small enough that the mean number of cleavages is less than 1 and the spiders show significantly *subdiffusive* behavior. This can be explained by considering that the spider starts in the configuration defined by Antal and Krapivsky,

$$\cdots \hat{0} \bullet \circ \hat{1} \hat{0} \cdots$$

From this state either the right leg moves at rate r or the left leg moves at rate 1, but if $r \ll 1$ the mean time to move the right leg is large. Until the right leg has moved, the left leg is restricted to hopping between sites -1 and 0 . Thus, the parameter r determines the time scale of this initial period as $0 \leq t \leq 1/r$.

When $t > 1/r$, the average number of cleavages is greater than one. After this time, the spider has taken several steps, and has cleaved out a small region (sea) of products which defines a boundary between regions of visited and unvisited sites. As Antal and Krapivsky noted, there is an effective outward bias for bipedal spiders near this boundary when $r < 1$. Fig. 5 shows that spiders with small r values move significantly superdiffusively in the period of time after the initial regime. Hence, we call this the *superdiffusive regime*. We quantify this regime as the period of time when $\alpha(t) > 1.1$. The choice of 1.1 is arbitrary, but is a sensible threshold that corresponds to a spider moving significantly superdiffusively. Using this threshold, we define t^* and t^{**} as the time when the spider enters and exits the regime of superdiffusive motion. Table I summarizes these values. We also compute the maximum value of $\alpha(t)$, and the time t at which the maximum is reached. These values show an increasingly significant superdiffusive regime for smaller values of r . These effects were not predicted by analytical methods as they are only transient effects—eventually all spiders move diffusively. However, the fact that these transient behaviors last several decades in time means that spiders could potentially be exploited to achieve faster-than-diffusion transport over experimentally practical times.

As predicted by Eq. 6, the spiders must eventually move diffusively. This leads to the third and final *diffusive regime*, in which all spiders asymptotically move with $\text{msd}(t) \propto t$. Thus while the process is not mathematically identical to unbiased diffusion, it is practically no faster than diffusion for transport over very long times.

To quantify when a particular r -value spider is faster than the $r = 1$ spider (in terms of $\text{msd}(t)$), we define $\hat{t}(r)$ as the first time when $\text{msd}_r(t) > \text{msd}_1(t)$, and summarize the values in Table I. Between the times \hat{t} and t^{**} the spider is farther on average than a diffusive spider and it is still moving faster by more than a constant factor. Thus during this interval, the spider is more efficient in every respect than an ordinary diffusive spider.

r	$\max \alpha(t)$	$\operatorname{argmax} \alpha(t)$	t^*	t^{**}	\hat{t}
0.5	1.10	1.20×10^1	-	-	2.25×10^1
0.1	1.32	1.26×10^2	8.83×10^1	4.06×10^3	5.89×10^2
0.05	1.40	2.08×10^2	1.51×10^2	2.83×10^4	2.67×10^3
0.01	1.60	2.15×10^3	6.89×10^2	5.68×10^5	5.59×10^4
0.005	1.68	5.70×10^3	1.39×10^3	2.49×10^6	2.44×10^5

TABLE I: Properties of the mean squared displacement and the superdiffusive regime defined by $\alpha(t) > 1.1$.

D. First Passage Time

We also measured the mean first passage time, Fig. 6. This property is useful for describing how efficiently spiders can be used to transport cargo from the origin to a destination—when the spider reaches the destination point for the first time it has completed the task. The $r < 1$ spiders reach new unvisited sites faster than the diffusive $r = 1$ spider, and so they are more efficient as a transport mechanism. However, as with the average number of cleaved sites, there is a limit on how much one can reduce the first passage time by decreasing r .

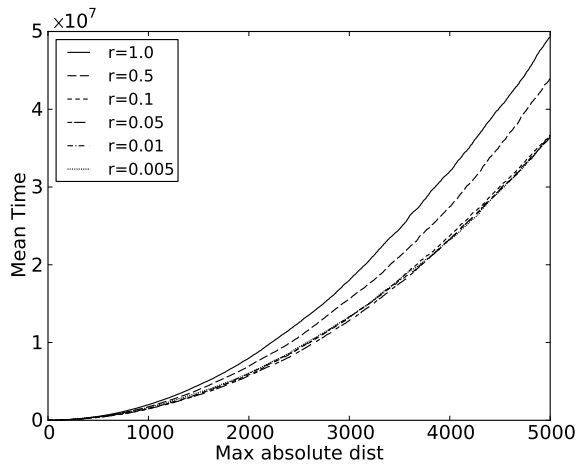


FIG. 6: Mean first passage time.

E. Asymptotic Behavior and Distributions

To describe a process as unbiased ordinary diffusive, one must show not just that the mean squared displacement increases linearly with time, but more specifically that the distribution of the displacement is Gaussian. Initially this is not true for spiders with $r < 1$. The bias at the boundary tends

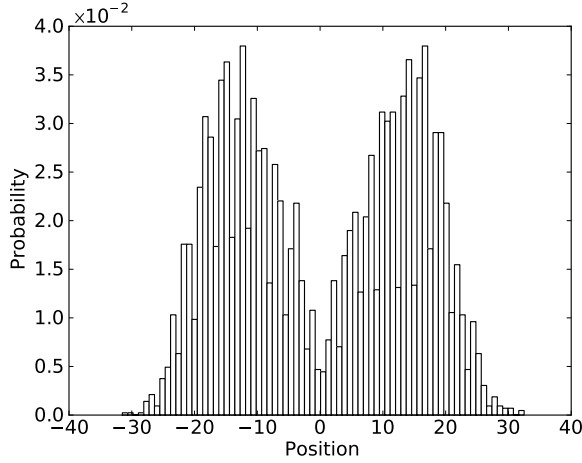
to keep spiders towards the outside of the region of cleaved products, leading to a bimodal distribution peaked around the average locations of the boundaries at that time. However, as time increases and the size of the sea of products grows, spiders spend increasingly more time moving in an unbiased, diffusive manner over these sites. This eventually leads to a more Gaussian-shaped distribution. Fig. 7 shows the displacement distributions for the $r = 0.01$ spider at three times: at $\operatorname{argmax}(\alpha(t))$, when the spider is moving most superdiffusively; at \hat{t} , when the spider mean squared displacement overtakes the $r = 1$ spider; and at t_{\max} , when the spider is in the diffusive regime. Fig. 8 shows a comparison of the distributions at the same three times for the $r = 0.01$ and the $r = 0.005$ spiders. The spider with the smaller r value has a sharper peak near the boundary at time $t = \operatorname{argmax}(\alpha(t))$, corresponding to the slower release from substrates.

At $t_{\max} = 10^8$, most of the spiders have $\alpha(t) \approx 1$. Table II shows the results of using the Shapiro-Wilk normality test [18] to test the hypothesis that the displacement distribution is Gaussian at time t_{\max} . The p -values are significant enough to support this hypothesis. However, note that the p -values are increasingly small for small r values. This likely indicates that the spider processes for small r values are still slowly moving towards ordinary diffusion, and hence are not quite normal, especially near the ends of the distribution due to the bias at the boundary.

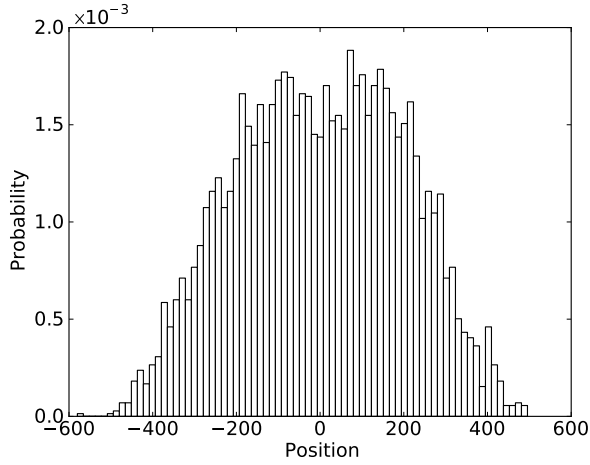
Nevertheless, all the spiders are sufficiently close to normally distributed at time t_{\max} so that we can use

$$D(t) = \frac{\operatorname{msd}(t)}{2t} \quad (9)$$

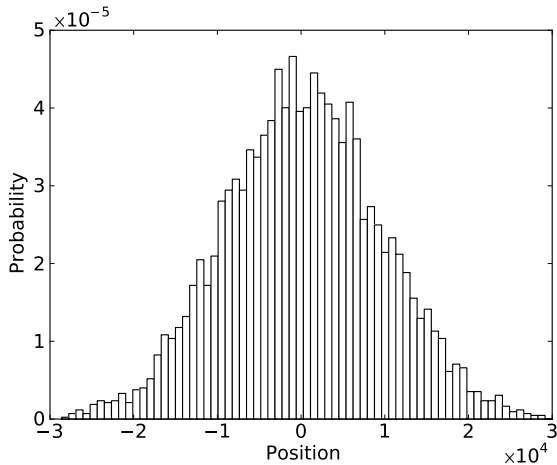
as an approximation to the effective diffusion rate of the spiders. The value $D(t_{\max})$ should be thought of as the diffusion constant an ordinary diffusive process would need in order to have the same mean squared displacement at time t_{\max} as the given spider process. In this way it can make sense to compute $D(t)$ even at times when the spider processes are significantly subdiffusive or su-



(a) Distribution at time $t = \text{argmax}(\alpha(t))$



(b) Distribution at time $t = \hat{t}$



(c) Distribution at time $t = t^{**}$

FIG. 7: Displacement distribution for $r = 0.01$ at three characteristic times.

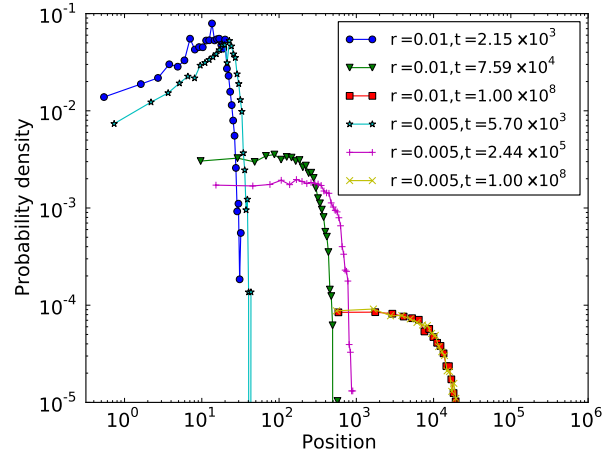


FIG. 8: (Color online) Comparison of displacement distributions for $r = 0.01$ and $r = 0.005$ at three characteristic times $\text{argmax}(\alpha(t))$, \hat{t} , and t_{\max} .

perdiffusive. For these times we interpret the $D(t)$ value as a measure relating the msd of the spider process to that of an ordinary diffusive process with diffusion constant D . In Fig. 9, we use Eq. 9 to compute $D(t)$ for all times. Finally, in Table II we estimate $D(t_{\max})$ with 95% confidence bounds for each value of r . The analytical value for $r = 1$ is $1/4$, which is within the error bounds of our estimate. We should expect these values to be monotonically increasing with decreasing r , and this is true (within confidence intervals). However, the $D(t_{\max})$ value for the $r = 0.005$ spiders is not representative of their true long-term behavior, as these spiders still have not moved for long enough for their $\langle T(n) \rangle$ value to surpass that of the $r = 0.01$ spiders. The $r = 0.005$ spiders are still moving superdiffusively enough at t_{\max} that the $D(t_{\max})$ value is substantially smaller than its asymptotic value. The same would be true of the $D(t_{\max})$ value for any spider with an even smaller r .

Of practical interest, from these diffusion rates we estimate that at time t_{\max} a spider with $r = 0.005$ will be approximately 31% farther from the origin on average than an ordinary-diffusive spider with $r = 1$ (or equivalently an ordinary random walker with $D = 0.25$). Thus, given enough time, a spider with *slower* enzymatic rate k_{cat} can transport objects significantly *farther*.

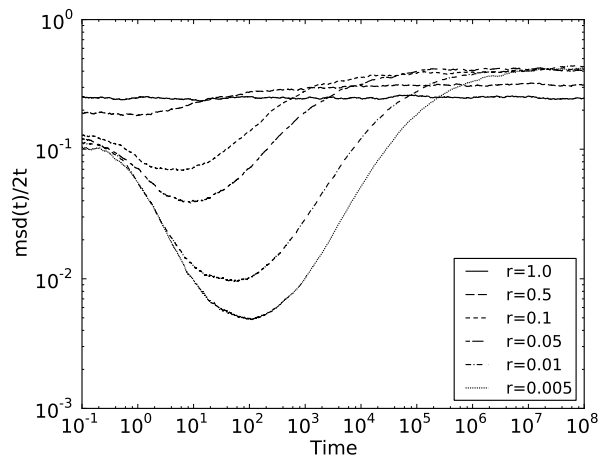


FIG. 9: $D(t)$ as computed by Eq. 9.

r	$D(t_{\max} = 10^8)$	Shapiro-Wilk p-value (at $t_{\max} = 10^8$)
1.0	0.247 ± 0.010	0.747
0.5	0.313 ± 0.012	0.518
0.1	0.413 ± 0.016	0.620
0.05	0.407 ± 0.016	0.677
0.01	0.435 ± 0.017	0.250
0.005	0.417 ± 0.016	0.206

TABLE II: The estimated diffusion coefficient D for different r values with 95% confidence bounds, and the p -value for Shapiro-Wilk normality test at time 10^8 , showing the distributions are reasonably normal at this time.

IV. MECHANISM OF TRANSIENT SPIDER SUPER-DIFFUSION

Our simulation results have shown that the spiders of the AK model for $s = 2$, $k = 2$ move superdiffusively over a significant distance and time, and that this effect increases with decreasing values of r . Eventually, however, the motion decays to an ordinary diffusive walk.

In this section, we argue that there is a general principle underlying spider motion that can be understood by viewing spiders as existing in one of two metastates, a diffusive metastate D wherein a spider moves over visited sites, or a boundary metastate B wherein a spider moves ballistically away from the origin when it is on the boundary of uncleaved sites. Because the duration of a B period remains independent of the past, but the duration of a D period grows with time, eventually the spider will approach an ordinary diffusive motion.

The $s = 2$, $k = 2$, $r < 1$ AK spider model is the simplest model exhibiting the boundary/diffusive state decomposition and the resulting superdiffusive behavior.

A. The Boundary and Diffusive Metastates

As explained in Section II, in the AK model legs only hop to nearest-neighbor sites and cannot hop over one another. This leads to a shuffling gait. If the legs were distinguishable their ordering would not change. Thus for concreteness we can refer to a leftmost and a rightmost leg. Because the legs only move to nearest-neighbor sites, they cannot jump over any site; and because a leg always cleaves a substrate into a product, a spider cannot leave any substrates behind. Thus a spider with this shuffling gait will cleave out an interval of products so that for state $X = (P, F)$, we find

$$P = \{b_L(t) + 1, \dots, b_R(t) - 1\}, \quad (10)$$

where

$$b_L = \min(P) - 1, \quad \text{and} \quad b_R = \max(P) + 1. \quad (11)$$

We call b_L and b_R the left and right boundaries, as they define the interval of products (Eq. 10) we call the *product sea*. This product sea includes the origin and contains no substrates within it. Thus, a spider in the product sea has all its legs on products so it must hop without bias at rate 1, and its motion is diffusive. Any state in which all the spider's legs are contained within the product sea belongs to the diffusive or D metastate. Formally, for state $X = (P, F)$, $X \in D$ if and only if $F \subseteq P$.

The only other possible state is for the spider to have a single leg on a substrate at one of the boundaries. This must be either the leftmost leg on b_L or the rightmost leg on b_R . No other situation is possible because of the shuffling gait of the legs enforced by nearest-neighbor hopping. In either of these cases, we say that the spider is in the boundary or B metastate, so that for $X = (P, F)$, we have $X \in B$ if and only if $b_L \in F$ or $b_R \in F$.

Together B and D form a partition of the state space for the spider Markov process. Thus, we can view a spider process as a (non-Markovian) stochastic process that moves between a B state and a D state (Fig. 10).

For a particular realization of the spider Markov process, we define a *B period* as an interval of time during which the spider is in the B metastate and a *D period* as an interval of time spent in the D state.

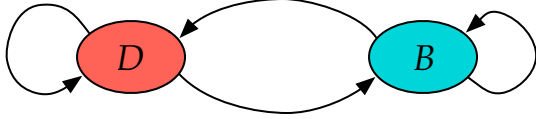


FIG. 10: (Color online) A spider process moves between two metastates, a B state in which the spider is on the boundary between substrates and products, and a D state in which the spider is diffusing in the product sea.

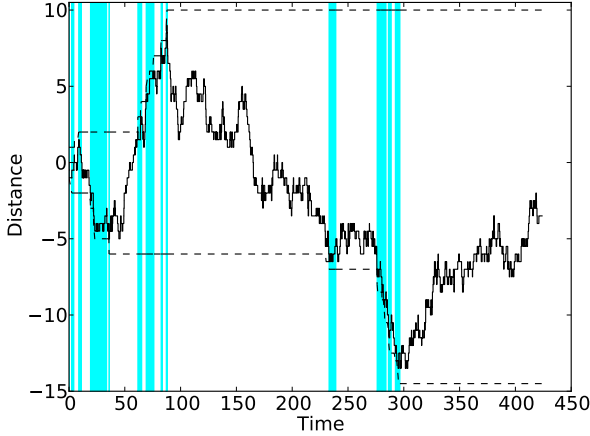


FIG. 11: (Color online) A realization $X = (P, F)$ of the spider Markov process. We plot the mean body position as the mean of the feet locations, $\sum_{i \in F} i / |F|$. At each time the spider is in a B (shaded area) or D (white area) metastate. The top and bottom dashed lines show b_R and b_L respectively. Thus, at any time t the sites below the bottom dashed line and above the top dashed line have not yet been visited.

Fig. 11 shows a particular simulated trace of the Markov process and the partitioning of time into B and D periods.

B. The Diffusive Metastate D

The D metastate is the simpler state, as it corresponds to an unbiased diffusion over the product sea, and no sites can be cleaved while in the D state. Let $\langle \tau_D(t) \rangle$ be the mean duration of a D period that begins at time t . This quantity depends only on the size of the product sea P .

To derive $\langle \tau_D(t) \rangle$ we follow the analysis of Antal and Krapivsky [14], and consider that the spider always begins a D period in the state

$$\dots \hat{o} \hat{o} \underbrace{\dots \circ \bullet \bullet \circ \hat{o} \hat{o}}_N \dots$$

From here it executes an unbiased random walk on the product sea in which each step corresponds to a $\pm 1/2$ step in the mean of the leg locations. Thus, the process of exiting the D state is equivalent to that of a normal random walker exiting an interval of size $M = 2N + 4$, starting at position $x = 2N + 1$. For general M and x this time is

$$T(M, x) = \frac{x(M - x)}{2},$$

whence we obtain

$$T(2N + 4, 2N + 1) = \frac{3(2N + 1)}{2}. \quad (12)$$

Antal and Krapivsky [14] calculated that asymptotically

$$\langle N(t) \rangle = \sqrt{t} \frac{\Gamma\left(\frac{3+3r}{4+2r}\right)}{\Gamma\left(\frac{5+4r}{4+2r}\right)}. \quad (13)$$

Now, combining Eqs. 12 and 13, allows us to show that asymptotically

$$\langle \tau_D(t) \rangle = \frac{3}{2} \left(2\sqrt{t} \frac{\Gamma\left(\frac{3+3r}{4+2r}\right)}{\Gamma\left(\frac{5+4r}{4+2r}\right)} + 1 \right). \quad (14)$$

Notice that $\langle \tau_D \rangle$ grows with time, hence the D state is non-Markovian.

C. The Boundary Metastate B

In contrast to the D state, the B state is Markovian. For a B period we can compute the number of steps a spider takes (S_B), the length of the B period (τ_B), and the number of cleavages the spider performs (C_B). We find that each of these random variables is independent of time, independent of the size of product sea, and independent of the absolute position of the boundary. These conclusions show that the spider walking in a B period is essentially Markovian—independent of the past history of the spider, and translationally invariant. This means that as soon as the spider cleaves the boundary site and moves onto the new boundary site the process is renewed.

When $s = 2$ and $k = 2$, legs can either be on adjacent sites or separated by a single unoccupied site.

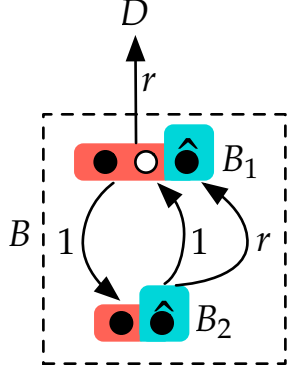


FIG. 12: (Color online) To compute S_B and τ_B we consider in detail the two states contained within the B state. A spider always enters the B state by moving to state B_1 . It can leave the B state by moving its right leg, cleaving the site, and moving to the D state as there are no longer any legs on the boundary. If a spider in state B_1 moves its left leg instead, it goes to state B_2 . From B_2 the spider can move either leg. It moves its right leg at rate r which cleaves the current boundary site, moving the boundary to the right and the spider back to state B_1 . Also from state B_2 the spider can move its left leg which moves the spider back to state B_1 without changing the boundary.

By definition, in the B state one of the legs is always on a substrate at the boundary. Without loss of generality, assume the spider is on the right boundary, so that the right leg is at b_R . Then the B metastate can be partitioned into two smaller metastates (Fig. 12), a state B_1 in which the legs are separated by one site, and a state B_2 in which the legs are adjacent. In either B_1 or B_2 each leg has exactly one transition it can make, and since one leg is on a product and one leg is on a substrate the total rate of transition out of either B_1 or B_2 is

$$R = 1 + r.$$

A spider can only leave the B metastate when it is in state B_1 and the next action is to move the rightmost leg off the substrate. In the state B_2 , either leg moving results in the spider moving to state B_1 .

To derive the distribution for S_B , the number of steps the spider makes in the B state, we note that each B period begins with the spider moving into state B_1 . From B_1 the spider has a r/R probability of moving off the boundary into the D metastate. But with the remaining $1/R$ probability, the spider moves to state B_2 and subsequently back to B_1 . Thus a B period can be thought of as $Y \geq 0$ loops $B_1 \rightarrow B_2 \rightarrow B_1$, ending at state B_1 , and a final move to state D , meaning that the number of steps

taken in the B state will be

$$S_B = 2Y + 1. \quad (15)$$

Each time the spider is at B_1 it has an independent $1/R$ probability of making a loop through B_2 , thus Y is geometrically distributed with mean $1/R$,

$$\mathbf{P}[Y = y] = \left(\frac{1}{R}\right)^y \left(\frac{r}{R}\right) = \frac{r}{R^{y+1}}. \quad (16)$$

Combining Eqs. 15 and 16 gives

$$\mathbf{P}[S_b = s] = \begin{cases} 0, & s \text{ even} \\ \frac{r}{R^{\frac{s+1}{2}}}, & \text{sodd} \end{cases} \quad (17)$$

Each of these S_B steps occurs with total rate R , hence the time for the i -th step is exponentially distributed with scale parameter $1/R$. Therefore, the duration of a B period, conditioned on the event that $S_B = s$ steps are made in the period is gamma-distributed with probability distribution function

$$f_{\tau_B|S_B}(t|s) = \text{Gamma}(s, 1/R). \quad (18)$$

Using the distribution of Y , we find the marginal probability distribution function as

$$\begin{aligned} f_{\tau_B}(t) &= \sum_{y=0}^{\infty} \text{Gamma}(2y + 1, 1/R) (\mathbf{P}[Y = y]) \\ &= \sum_{y=0}^{\infty} \left(\frac{t^{2y} e^{-Rt}}{R^{-(2y+1)} \Gamma(2y + 1)} \right) \left(\frac{r}{R^{y+1}} \right) \\ &= e^{-Rt} \sum_{y=0}^{\infty} \frac{t^{2y}}{(2y)!} \frac{r}{R^{-y}} \\ &= r e^{-Rt} \sum_{y=0}^{\infty} \frac{(t\sqrt{R})^{2y}}{(2y)!} \\ &= r e^{-Rt} \cosh(t\sqrt{R}). \end{aligned} \quad (19)$$

To compute C_B , the number of cleavages in a B period, we must pay closer attention to the transitions out of state B_2 in Fig. 12. In state B_2 either leg can move. If the leftmost leg moves, it is constrained to move left and the spider moves back to B_1 without cleaving a site. If the rightmost leg moves, it cleaves the substrate, moves the boundary ($b_R \rightarrow b_R + 1$), and the leg is constrained to move right onto the new boundary, leaving the spider in state B_1 again but at a new absolute position.

A spider always enters a B period in state B_1 . From this state there are two ways to cleave exactly one site. Either (1) the spider follows a sequence

of non-cleaving moves ending in state B_2 and then moves its right leg, cleaving that site and moving back to state B_1 ; or (2) the spider follows a sequence of non-cleaving moves ending in state B_1 and then moves its right leg, cleaving that site and exiting to the D metastate. Let Z_1 and Z_2 be the events (1) and (2) respectively. Then, for $c \geq 1$ we can compute the distribution of C_B as

$$\mathbf{P}[C_B = c] = (\mathbf{P}[Z_1])^{c-1} \mathbf{P}[Z_2]. \quad (20)$$

Note that $\mathbf{P}[C_B = 0] = 0$ since at least one substrate will be cleaved when the spider leaves the boundary.

To compute $\mathbf{P}[Z_1]$ we must account for all the ways a spider can cleave exactly one substrate and return to B_1 . The spider must first move to B_2 with probability $1/R$, then it can move $B_2 \rightarrow B_1 \rightarrow B_2$ an arbitrary number of times *without cleaving* by moving the left leg in state B_2 with probability $1/R$ and subsequently moving its left leg again when in state B_1 with probability $1/R$. Finally, the spider will move its right leg with probability r/R , cleaving a site and returning to B_1 . Thus,

$$\begin{aligned} \mathbf{P}[Z_1] &= \frac{1}{R} \times \sum_{i=0}^{\infty} \left(\frac{1}{R^2}\right)^i \times \frac{r}{R} \\ &= \frac{r}{R^2} \frac{R^2}{R^2 - 1} \\ &= \frac{r}{R^2 - 1} = \frac{1}{r+2}. \end{aligned} \quad (21)$$

For event Z_2 , the spider can leave the boundary by first moving $B_1 \rightarrow B_2 \rightarrow B_1$ an arbitrary number of times *without cleaving* by moving the left leg with probability $1/R$ when in state B_1 and again moving the left leg with probability $1/R$ when in state B_2 , and finally in state B_1 moving the right leg with probability r/R to exit to state D . Thus,

$$\begin{aligned} \mathbf{P}[Z_2] &= \sum_{i=0}^{\infty} \left(\frac{1}{R^2}\right)^i \times \frac{r}{R} \\ &= \frac{rR}{R^2 - 1} = \frac{r+1}{r+2}. \end{aligned} \quad (22)$$

Therefore,

$$\begin{aligned} \mathbf{P}[C_B = c] &= (\mathbf{P}[Z_1])^{c-1} \mathbf{P}[Z_2] \\ &= \left(\frac{1}{r+2}\right)^{c-1} \left(\frac{r+1}{r+2}\right). \end{aligned} \quad (23)$$

Hence, C_B is geometrically distributed with mean

$$\langle C_B \rangle = \frac{r+2}{r+1}. \quad (24)$$

Together these random variables characterize most of the important characteristics of the B periods. Each of τ_B , S_B , and C_B is independent of the state of the process when it enters the B period. For this reason we say that the B state is Markovian with respect to the B/D state decomposition of Fig. 10.

D. How B and D States Explain Spider Motion

The random variable C_B is important because sites can only be cleaved during a B period. Also, because C_B is independent of the state of the system when it enters a B period, the only thing that affects the number of sites cleaved at time t is the number of B periods that have occurred. Let $B(t)$ be the random variable giving the number of completed B periods at time t , and if the spider is in the middle of a B period, let $K(t)$ be the number of sites it has cleaved up to time t in that period ($K(t) = 0$ if the spider is in the D state). Recall Antal and Krapivsky's definition of $N(t)$ as the number of sites cleaved at time t , to see that

$$N(t) = \sum_{i=1}^{B(t)} C_{B_i} + K(t). \quad (25)$$

Therefore,

$$\langle N(t) \rangle = \langle B(t) \rangle \langle C_B \rangle + \langle K(t) \rangle. \quad (26)$$

Eqs. 26 and 13 together allow us to show

$$\langle B(t) \rangle = \left(\sqrt{t} \frac{\Gamma\left(\frac{3+3r}{4+2r}\right)}{\Gamma\left(\frac{5+4r}{4+2r}\right)} - \langle K(t) \rangle \right) \frac{r+1}{r+2}. \quad (27)$$

Note that asymptotically $\langle K(t) \rangle \rightarrow 0$, because, as we have shown, $\langle \tau_D \rangle$ (Eq. 14) increases with time while $\langle \tau_B \rangle$ (Eq. 19) and $\langle C_B \rangle$ (Eq. 24) are independent of time. As $t \rightarrow \infty$, the probability to be in a B period will tend to 0, and so also must $\langle K(t) \rangle$. Thus for large t , Eq. 27 simplifies to

$$\langle B(t) \rangle = \sqrt{t} \frac{r+1}{r+2} \frac{\Gamma\left(\frac{3+3r}{4+2r}\right)}{\Gamma\left(\frac{5+4r}{4+2r}\right)}. \quad (28)$$

The only way the spider can cleave substrates and increase its maximum distance from the origin is for it to be in a B state. In fact, if the spider never left the boundary (i.e., if $\mathbf{P}[B \rightarrow D] = 0$), it would move ballistically away from the origin.

Thus, the B/D decomposition of Fig. 10 shows how the spider process is in essence a constant alternation between two types of motion: a ballistic motion away from the origin in the B state, and an ordinary diffusive motion over the contiguous sea of products. The spider repeatedly switches between these states, and the average amount of time spent in each state determines the average behavior of the spider (ballistic vs. diffusive). Because

$$\lim_{t \rightarrow \infty} \frac{d\langle B(t) \rangle}{dt} = 0,$$

the spider initiates fewer and fewer B periods over time, and in the limit spends all of its time in the D state moving diffusively. *It is for this reason that the asymptotic behavior is diffusive.* However, because at least initially the spider spends a significant fraction of its time in the B period, there is a superdiffusive transient.

V. DISCUSSION

Using Kinetic Monte Carlo simulations of the Markov process defined by Antal and Krapivsky we showed the unanticipated result that spiders move superdiffusively over a significant span of time and distance before eventually moving diffusively as had been predicted analytically. This phenomenon can be explained by considering the natural decomposition of the process as switching between two metastates: a diffusive state D where a spider moves over the contiguous sea of product sites, and a boundary state B where the spider has a leg attached to a substrate at the boundary between visited and unvisited sites. This decomposition partitions the underlying continuous-time Markov process into B periods and D periods. The spider moves ballistically away from the origin during B periods, but moves diffusively over visited sites during D periods. The B state is Markovian in that the transitions from the B state are independent of the state of the system when it entered the B state. However, the transitions from the D -state depend on the size of the contiguous sea of products, and this size increases with time. This explains the apparent superdiffusion at short times when the spider spends more time moving ballistically in the B state, and the decay to ordinary diffusion at long times, as the spider spends nearly all of its time diffusing over previously visited sites in the D state. The AK model with $k = 2$, $s = 2$, $r < 1$ is the simplest model of spider motion with this B/D state decomposition and the resulting superdiffusive ef-

fect. With $k = 1$, there is no bias at the boundaries, and without irreversible cleavage of sites and a rate $r < 1$ there is no biasing effect at the boundaries. Thus, the superdiffusive effect depends on spiders having multiple legs and on the legs having the ability to modify sites so that future steps on those sites have different rates.

It is important to note that neither analysis nor finite-time simulations will necessarily give the full picture of the motion of spiders. Analytical calculations estimate the values of random variables in the limit as $t \rightarrow \infty$, which is the correct way to mathematically characterize processes as diffusive or superdiffusive. However, analysis may miss interesting transient behavior that is especially important in the context of real experiments that last for a finite time and where spiders cover a finite distance. If the transient behavior is particularly long-lasting, as it is with the AK spider model, then the characteristics of the transient behavior will be important to experimental designs. Indeed, the B/D characterization offers an insight to developers of new experimental designs: the designs should embody gait and chemistry rules that minimize the rate of escape from the B to the D metastate.

On the other hand, simulations can provide accurate estimates of behavior for short times. However, care must be taken when drawing conclusions from simulation results. All simulations are necessarily finite and can only definitively determine the behavior over the time span they are evaluated over. The final behavior of simulations cut off at a finite time is not the same thing as the asymptotic behavior of the mathematical process. For example, if one were to run the simulations of Section III only up until time $t = 10^4$ (avoiding the enormous computational expense which we incurred), one might well conclude that small values of r are superdiffusive *in the long-time limit*, and this would obviously not be correct.

Recently, another model of molecular spider motion was proposed by Samii et al. [19]; we shall call it S-spiders to avoid confusion with the AK spiders discussed in this paper. The model incorporates dissociation rates of each leg, and permits S-spiders to detach from the surface if all of their legs detach simultaneously. S-spiders can also detach from a substrate without cleaving. In consequence, the region of products between the left and right boundaries is not necessarily free of substrates. Because S-spiders can detach, they move only over finite distances, hence direct comparisons between this model and the AK model are difficult. The focus of Samii et al. was on the short-time behavior

of spiders and the effects of spider gait, substrate cleavage, and spider dissociation on the initial motion of spiders. This focus on short times is born of necessity, since when on-rates are rather slow, most S-spiders will detach quickly.

In contrast, our work explores the medium- to long-time behavior of spider-like systems. For any non-zero asymptotic behavior to exist, spiders cannot dissociate from the surface. This can be enforced by a model where either (I) the feasible transitions of the leg are restricted such that when a leg detaches no other leg may detach until the first one has reattached; or (II) the rates are set to $k_S^+ = k_P^+ = \infty$ (the choice made in the AK-model). Both of these assumptions will lead to the same qualitative behavior. To see this, observe that even with infinite on-rates, the spider's legs never move from site to site infinitely fast. The finite dissociation rates mean that a leg must stay bound to a new site for a finite amount of time before moving again, even in model (II). In model (I) we can incorporate finite k^+ rates by asserting that an attached leg can detach with rate k_P^- (or k_{cat}), but then the only allowable transition will be for that same leg to attach (at some free site) with a finite rate $k^+ = k_P^+ = k_S^+$. Let us define the *hop time* (H_P) for product sites as the elapsed time from when a leg steps on a product

site to when it steps onto the next site. In terms of hop times, the difference is that in model (I) $H_P \sim \text{Exp}(1/k_P^-)$ whereas in model (II) $H_P = H_P^- + H_P^+$ and $H_P^- \sim \text{Exp}(1/k_P^-)$, $H_P^+ \sim \text{Exp}(1/k^+)$ (a similar relationship holds for H_S where k_P^- is replaced by k_{cat}). But as $k^+ \rightarrow \infty$, $\langle H_P^+ \rangle \rightarrow 0$, so there will be no effective difference in mean displacement between the alternative models. Hence, the infinite k^+ rates are not in and of themselves responsible for the superdiffusive behavior—they merely act to prevent the possibility of detachment, which in turn permits the characterization of the asymptotic behavior of such systems and the comparison with ordinary diffusive processes.

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