Brownian Ratchets Driven by Asymmetric Nucleation of Hydrolysis Waves

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We propose a stochastic process wherein molecular transport is mediated by asymmetric nucleation of domains on a one-dimensional substrate, in contrast with molecular motors that hydrolyze nucleotide triphosphates and undergo conformational change. We show that asymmetric nucleation of hydrolysis waves on a track can also result in directed motion of an attached particle. Asymmetrically cooperative kinetics between hydrolyzed and unhydrolyzed states on each lattice site generate moving domain walls that push a particle sitting on the track. We use a novel fluctuating-frame, finite-segment mean field theory to accurately compute steady-state velocities of the driven particle and to discover parameter regimes yielding maximal domain wall flux, leading to optimal particle drift.

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Molecular motors such as kinesins, myosins, helicases, and polymerases convert part of the free energy of, e.g., ATP hydrolysis to a conformational change [1]. The resulting molecular deformation leads to motion of the motor against a load on a track. Although the literature on such molecular motors is vast, much less attention has been paid to the theory of molecular motions that exploit the dynamics of the track on which translation occurs. Such loads are propelled by the track, which itself is undergoing catalyzed state changes by, e.g., hydrolysis.

Two biological strategies involving track-propelled particles are collagenase catalysis and Holliday junction transport. Collagenase MMP-1, an enzyme that associates with collagen, cleaves its track asymmetrically as it diffuses, thus biasing its motion [2]. The dynamics of this track-driven propulsion has been modeled using burnt bridge models [3–5].

Another system where substrate reactions may lead to biased motion is the translocation of Holliday junctions [6]. The Holliday junction at which two double-stranded DNA molecules exchange one of their strands may be moved by the dynamics of hydrolysis states of the DNA binding protein RecA. RecA polymerizes on at least one of the strand-exchanging dsDNA molecules, assembling into a long nucleoprotein filament. The RecA monomers hydrolyze ATP and can exist in different states, much like the intermediate hydrolysis states of myosin motors. The dynamics of the interconversion among these hydrolysis states may provide the force necessary to rotate DNA strands about each other during Holliday junction translocation. An especially promising model of this process exploits asymmetric cooperativity in the hydrolysis of the ATP cofactors associated with each RecA monomer. This intrinsic asymmetry of the filament gives rise to “waves” of hydrolyzed monomers with a preferred direction, thereby moving the junction by virtue of its preferential attachment to the hydrolyzed segment of the RecA filament [6,7]. These examples constitute only two of many mechanisms by which chemical energy may be harnessed by the substrate, rather than directly by a molecular motor, to perform mechanical work. In this Letter, we develop a general stochastic theory of track-driven, hydrolysis wave-mediated transport. In addition to analyzing our model using Monte Carlo (MC) simulations, we also formulate a moving-frame mean field theory (MFT) that accurately predicts novel features of the transport.

As in models of the ATP cycle of myosin motors, in RecA hydrolysis wave-mediated transport the RecA subunits can exist in a number of substates corresponding to sites that have bound ATP, ADP + Pi, ADP, or are empty. To simplify our model, we will assume that each site of the substrate lattice exists in one of only two possible states, “hydrolyzed” (σ = 1) and “unhydrolyzed” (σ = 0). Any lattice site i can transition from state σi = 1 to state σi = 0 with rate k0. The reverse process, physically corresponding to “hydrolysis” or “nucleation”, fills an empty site. In our model, an asymmetry arises in the nucleation transitions. If site i − 1 is also in the state σi−1 = 0, then the transition σi = 0 → σi = 1 occurs with rate k−. However, if σi−1 = 1, then the transition σi = 0 → σi = 1 occurs with rate k+. If k+ ≠ k−, the process is asymmetric and can lead to a net steady-state current of domain walls. If a particle is associated with the lattice, it will be pushed each

\[ \begin{align*}
1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 \\
 0 & k_0 & k_{k+} & k_{k-} & k_0 & & & & & & \\
 \end{align*} \]

FIG. 1 (color online). Schematic of the asymmetric nucleation process. An intrinsic asymmetry in the lattice sites gives rise to asymmetric cooperativity and nucleation. The transported particle is represented by a triangle.
time a domain wall passes it. Thus, a net flux of domain walls will lead to directed particle transport. The kinetics of the lattice is outlined in Fig. 1.

The corresponding master equation is similar to that which describes Glauber dynamics of a one-dimensional Ising model, except that the asymmetry in the transition rates prevents this system from supporting an equilibrium state. Since no exact solutions are known, we employ a hybrid finite-segment MFT and MC simulations to obtain quantitative results and physical understanding.

First, consider a translationally invariant (infinite or periodic) lattice in the absence of an associated load particle. In the fixed laboratory frame, the master equation provides unclosed moments $\langle \sigma_0 \sigma_j \cdots \rangle$ of the hydrolysis states. For example, the equation $\langle \sigma_0 \rangle = (k_+ + k_0)(\langle \sigma_0 \rangle + \Delta \langle \sigma_{-1} \rangle - \Delta \langle \sigma_{-1} \sigma_{-1} \rangle)$ (where $\Delta = k_+ - k_-$ is the hydrolysis asymmetry), depends on higher correlations $\langle \sigma_i \sigma_{-1} \rangle$. For a statistically uniform lattice, the simplest mean field approximation assumes $\langle \sigma_i \sigma_{-1} \rangle = \langle \sigma \rangle^2$, giving a steady-state mean hydrolysis level $\Delta \langle \sigma_0 \rangle = k_+ - 2k_- - k_0 + \sqrt{(k_+ - k_0)^2 + 4k_+ k_0}$. As shown by the dotted curves in Fig. 2(a), this mean field result is only in qualitative agreement with the mean hydrolysis level obtained from MC simulations on a lattice with periodic boundary conditions and $N = 1000$ sites (open circles).

The locality of the asymmetric interactions suggests that correlations are short-ranged. Thus, more accurate approximations can be systematically implemented by considering small clusters in which all possible configurations are identified, and enumerating all the transitions among them. The densities at both ends of this cluster are then self-consistently matched to bulk values inferred by the statistics within the cluster. This finite-segment mean field approach has been used to study the nonequilibrium steady states of related models [8,9]. For example, consider all possible configurations in a segment of $m = 2$ lattice sites.

If we enumerate the states corresponding to the binary representation of the state number, (i.e., $P_0 = 00$, $P_1 = 01$, $P_2 = 10$, $P_3 = 11$), the $2^3 \times 2^3$ transition matrix in the Master equation $\mathbf{P} = \mathbf{M} \mathbf{P}$ is

$$
\mathbf{M} = \begin{bmatrix}
-2k_- - s\Delta & k_0 & 0 & 0 \\
-k_+ - k_- - s\Delta & 0 & k_0 & 0 \\
k_+ + s\Delta & 0 & -k_+ - k_- & 0 \\
0 & k_+ + s\Delta & 0 & -2k_0
\end{bmatrix}
$$

where $\mathbf{P} = (P_0, P_1, P_2, P_3)^T$ is the probability vector and $s$ is the mean occupancy of the site immediately to the left of the explicitly enumerated pair. Since $s$ represents the mean occupation of the rightmost site of the preceding segment, we impose self-consistency by setting $\sum_{i=odd} P_i = s$ and solving for $s$ numerically. The simplest mean field approximation corresponds to $m = 1$.

Figure 2(a) shows the increasing accuracy in determining $\langle \sigma \rangle$ upon using larger $m$ in the finite-segment mean field approach. Although $m = 1$ (simple MFT) can give results appreciably disparate from MC simulation results, larger clusters significantly improve convergence to the correct mean density level. Note that simple MFT is exact in the symmetric, equilibrium limit $k_+ = k_-$. Now consider a lattice-associated particle that can be moved by the nonequilibrium fluctuations inherent in the substrate. Simple kinetic rules are defined in Fig. 3. Without loss of generality, we also assume that the particle does not have intrinsic fluctuations. Since its stochastic motion is caused only by the domain walls fluctuating past it, we must determine the domain wall probability in the frame of the moving particle. The thick solid black curves in Fig. 2(b) show the mean hydrolysis level, determined by MC simulation, in the particle frame. The particle position is arbitrary, but the hydrolysis level near it differs significantly from the uniform bulk away from the
particle (or in the laboratory frame). Since the particle statistically moves ahead of a domain wall, spending more time ahead of it, the mean hydrolysis level \((\sigma_{i+1})\) just before (after) it is higher (lower), as shown by the simulated data displayed in the load frame [Fig. 2(b)].

The mean velocity and dispersion (defined here as twice the diffusivity) of the driven particle are computed from

\[
V = k_+ f_+ Q_{100} - k_- f_- Q_{001},
\]

\[
D = k_+ f_+ Q_{100} + k_- f_- Q_{001},
\]

where \(Q_{100}\) and \(Q_{001}\) are the steady-state probabilities, determined by the kinetic rates, that the segment of three sites centered about the driven particle is in the indicated configuration (cf. Fig. 3). In order to compute \(Q_{100}\) and \(Q_{001}\) (defined in the frame of the particle), we use finite-segment MFT in the moving frame of the transported particle. We consider a sliding window of \(m\) sites always centered about the driven particle [10]. As before, we explicitly enumerate all configurations of the \(m\) sites surrounding the particle and assign appropriate rates to create the transition matrix \(M\). Transitions generated by the motion of the particle are reflected in the modifications of \(M\) to include terms corresponding to sliding of the \(m\)-site window. For example, for \(m = 5\), one term in the \(2^5 \times 2^5\) transition matrix specific to particle motion and window sliding is shown in Fig. 4. The leftmost site is removed from the window, while one from the bulk in state \(s\) is added on the right.

Provided \(m\) is large enough that \(s\) takes on the uniform bulk value, all local correlations near the driven particle will be captured. In our subsequent analyses, we use an \(m = 5\) site segment that yields sufficiently accurate results for the parameters explored. Henceforth, we rescale time in units of \(k_0^{-1}\) (normalizing all rates with respect to \(k_0\)), and set \(f_\pm = 1\).

Figure 5(a) shows the mean velocity \(V\) derived from MC simulations and finite-segment MFT applied in the moving frame of the transported particle. For \(k_- > k_+\), the hydrolyzed domains grow backward more rapidly than forward, and the mean velocity \(V < 0\). The velocity is positive and increases once \(k_+\) increases past \(k_-\). However, if \(k_+\) becomes too large, \(V\) decreases, despite an increase in the hydrolysis asymmetry along the track. This behavior can be understood by considering Eq. (2) and Fig. 6. When both \(k_\pm \ll 1\), dehydration dominates, domains are quickly dissipated, and the particle is kicked by a rare 100 domain wall as shown in Fig. 6(a).

Increasing the value of \(k_+ \geq k_-\) modestly increases the asymmetry and hence \(V\). However, if \(k_+\) is too large, the hydrolyzed domains merge into each other, as depicted in Fig. 6(c), reducing the domain wall density \(Q_{100}\) and ultimately \(V\). There is a value of \(k_+\) that gives an optimally combined domain wall density and nucleation asymmetry, as shown in Fig. 6(b), resulting in a maximum mean velocity \(V_{\text{max}}\).

For all values of \(k_-\), an extremely large \(k_+\) will ultimately decrease the particle velocity. Although \(D = k_+ - k_-\) might be large, \(Q_{100}\) decreases sufficiently that \(V\) decreases. The decrease of the mean velocity \(V\) in the \(k_+ \rightarrow \infty\) limit can be determined by considering a “virial” approximation where only transitions among 111, 110, 101, and 100 need be considered. Nearly all sites are hydrolyzed and we use \(s = 1\). Since 100 configurations along the lattice are rare and spaced far apart, we can consider each triplet of sites as independent and find

\[
Q_{100} = 2(k_0/k_+)^2 + O(k_+^3).\]

Therefore, \(V \sim 2f_+ k_0^2/k_+\) as \(k_+ \rightarrow \infty\).

The observation from Fig. 5(b) that for small or large \(k_-\) the dispersion is maximal near the maximum of \(|V|\) is consistent with Eq. (2). The first term \(k_+ f_+ Q_{100}\), common to \(V\) and \(D\), dominates at small \(k_-\) because \(Q_{001}\) is only weakly dependent on \(k_-\). Similarly, the second term \(k_- f_- Q_{001}\) dominates at large \(k_-\) where \(|V|_{\text{max}}\) occurs at \(k_+ = 0\), and \(D = -V\). In either regime, the optimizations of \(D\) and \(|V|\) coincide. We may expect this to be the case unless there is an additional, intrinsic dispersion with some dependence on \(k_+\).

In Fig. 7 we show \(V_{\text{max}}\) and the value of \(k_+\) that yields \(V_{\text{max}}\) (designated \(k^*_+\)) as functions of \(k_-\). We find \(V_{\text{max}}\) and \(k^*_+\) by accurately fitting the MC simulations of \(V\) in Fig. 5 with Padé approximants and indicate these optimum values in Fig. 7 with open circles. For large \(k_-\), the hydrolysis level is high and domain merging prevails throughout the lattice [Fig. 6(c)], requiring ever-higher \(k^*_+\) to arrive at a \(V_{\text{max}}\) that is smaller. Lowering \(k_-\) to intermediate values

![FIG. 4 (color online). A moving-frame-specific transition out of state \(P_{25}\) where the window of five sites has slid forward with rate \(k_+ f_+\). The destination state is \(P_{26}\) if \(s = 0\) and \(P_{27}\) if \(s = 1\).](248302-3)
MFT results are plotted as solid curves and for $k_+$, $k_\leq 1$, $V \ll 1$

Note that for the case $k_+$ are in close agreement with those from MC simulations. For $k_+$ or $k_-$ extremely large, the hydrolyzed domains coalesce, diminishing the number of domain walls. Even though the rate $k_+$ is large, the quantity $k_+ Q_{100}$ slowly diminishes.

increases both the asymmetry $\Delta = k_+ - k_-$ and delays the onset of domain merging, giving rise to larger $V_{\text{max}}$ at smaller values of $k_+^*$. However, for $k_- \leq 0.1$, the hydrolyzed fraction and the onset of domain merging become insensitive to $k_-$ and $k_+^* \rightarrow 3.3$. The $m = 5$ finite-segment MFT results are plotted as solid curves and for $k_- > 0.1$ are in close agreement with those from MC simulations. Note that for the case $k_- \rightarrow 0$ before the system size $N \rightarrow \infty$, $\sigma_i = 0 \forall i$ is an absorbing but unstable condition accessible only by large deviations from the stable steady-state that are exponentially unlikely in the system size. Nonetheless, for a large system a well defined steady state can be found and $V_{\text{max}}$ and $k_+^*$ are accurately fit using the expressions plotted as dashed curves in Fig. 7.

In summary, we have presented a paradigm for substrate-driven particle motion which has been a relatively understudied mode of subcellular transport. Our model captures the salient aspects of hydrolysis waves and exhibits rich transport behavior. Specifically, we find short-ranged state correlations, allowing us to accurately compute nonequilibrium steady-state particle velocities. For fixed backward hydrolysis rate $k_-$, the velocities show a maximum as a function of the forward hydrolysis rate $k_+$. The maximum possible velocities and their associated rates can be accurately described by the simple universal fitting equations (Fig. 7). For the application to RecA-mediated Holliday junction transport, $k_- \sim 0.3 \text{ s}^{-1}$, $k_+ \sim 2 \text{ s}^{-1}$, and $\langle \sigma_i \rangle \sim 0.1$ [7]. Our model therefore predicts $V \leq 1$ lattice sites per second ($\sim 1 \text{ nm/s}$), which is 2 orders of magnitude slower than conventional dedicated molecular motors, as well as MMP-1, which is thought to use a similar track-driven mechanism. In our model, velocities are small because they are limited by merging of domains, reducing the number of domain walls that propel the particle. Nonetheless, our predicted recombination junction velocity is measurable using traveling wave tracking [11].

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