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. Track-driven mechanisms of molecular transport arise in biophysical applications such as Holliday junction positioning and collagenase processivity. In contrast to molecular motors that hydrolyze nucleotide triphosphates and undergo a local molecular 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 which yield maximal domain wall flux, leading to optimal particle drift.

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Molecular motors such as kinesins, myosins, helicases, and polymerases typically convert part of the free energy of ATP or GTP hydrolysis to a conformational change. This 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 and cleaves collagen, is propelled by proteolysis of the collagen track. The cleaving of bonds prevents the collagenase from diffusing back across the broken bond, resulting in biased transport of the collagenase. Thus the statistical dynamics of the track propels the enzyme. This dynamic has been modeled by a burnt bridge model. Another system where substrate modification possibly leads to biased motion is the translocation of Holliday junctions. 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 appear to 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 nucleotide triphosphate 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.

These examples constitute only two of many mechanisms through which chemical energy may be harnessed to perform mechanical work by the substrate rather than a motor protein. 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+P, or are empty. To simplify our model, we will assume that each site of the substrate lattice exists in only one of two possible states, “hydrolyzed” \((\sigma = 1)\) and “unhydrolyzed” \((\sigma = 0)\). Any lattice site \(i\) can transition from state \(\sigma_i = 1\) to state \(\sigma_i = 0\) with rate \(k_0\). The reverse process, \(\sigma_i = 0\) to \(\sigma_i = 1\), fills an empty site. In our model, an asymmetry arises in the nucleation transitions \(\sigma_i = 0 \rightarrow \sigma_i = 1\) occurs with rate \(k_+\). However, if
\( \sigma_{i-1} = 1 \), then the transition \( \sigma_i = 0 \rightarrow \sigma_i = 1 \) occurs with rate \( k_+ \). If \( k_+ \neq k_- \), the process is asymmetric and can lead to a steady-state current of domain walls. If a particle is associated with the lattice, it will be pushed each 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 mean field theory (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 moments \( \langle \sigma_i \sigma_{j} \rangle \) of the hydrolysis states can be derived from the Master equation. These hierarchical moment equations are not closed. For example, the equation for the first moment

\[
\frac{d\langle \sigma_i \rangle}{dt} = k_- - (k_- + k_0)\langle \sigma_i \rangle + \Delta \langle \sigma_{i-1} \rangle - \Delta \langle \sigma_i \sigma_{i-1} \rangle,
\]

where \( \Delta \equiv k_+ - k_- \) is the hydrolysis asymmetry, depends on correlations \( \langle \sigma_i \sigma_{i-1} \rangle \). The simplest mean field approximation assumes \( \langle \sigma_i \sigma_{i-1} \rangle = \langle \sigma_{i-1} \rangle \langle \sigma_i \rangle \), which, when combined with the steady-state limit \( (d\langle \sigma_i \rangle/dt = 0) \) of Eq. (1) gives a steady-state mean hydrolysis level

\[
\langle \sigma_i \rangle = \frac{k_+ - 2k_- - k_0}{2\Delta} + \frac{\sqrt{(k_+ - k_0)^2 + 4k_- k_0}}{2\Delta}.
\]

As shown by the dotted curves in Fig. 2a, this result is only in qualitative agreement with the mean hydrolysis level obtained from MC simulations on a lattice with \( N = 1000 \) sites (open circles).

The locality of the asymmetric interactions suggests that correlations are short-ranged as in the totally asymmetric exclusion process. 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 such as the asymmetric exclusion process. 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, \( \text{i.e., } P_0 = 00, P_1 = 01, P_2 = 10, P_3 = 11 \), the \( 2^2 \times 2^2 \) transition matrix defined by \( \mathbf{P} = \mathbf{M} \mathbf{P} \) is

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

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 \( \sum_i s_i = s \) and solving for \( s \) numerically. The simple mean field approximation (Eq. (2)) corresponds to \( m = 1 \).

FIG. 2: (a) Mean densities computed from finite-segment MFT and from MC simulation. The three groups of densities correspond to \( k_- = 0.1, 1.0 \). Within each group, finite-segment mean field results with sizes \( m = 1, 2, 3, 4 \) (denoted MFT \( m \)) are compared with results from MC simulations (open circles). (b) Density profiles (for \( k_+ = 1.8, 3 \) in the lab frame (thin light curves) and in a frame moving with the load particle (thick dark curves) that follows the rules indicated in Eq. (2).

Fig. 2b shows the increasing accuracy in determining \( \langle \sigma \rangle \) upon using larger \( m \) (shown are \( m = 1, 2, 3, 4 \)) in the finite-segment mean field approach. Although \( m = 1 \) (simple mean field theory) can give results appreciably disparate from MC simulation results, larger clusters \( (m = 2, 3, 4, \ldots) \) significantly improve convergence to the correct mean density level. Moreover, simple MFT (Eq. (2)) is exact in the symmetric, equilibrium limit \( k_+ \rightarrow k_- \), where the moment equations are closed.

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. 2b. Without loss of generality, we also assume that the particle does not have intrinsic fluctuations. Since its stochastic motion is caused only by the asymmetric 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. 2b 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). As we follow the stochastically driven particle, the mean hydrolysis level \( \langle \sigma_i \rangle \) just before (after) it is higher (lower); the particle statistically moves ahead of a domain wall, spending more time ahead of it.

The mean velocity and dispersion of the driven particle are computed from

\[
V = k_+ f_+ Q_{100} - k_- f_- Q_{001} \quad \text{and} \quad D = k_+ f_+ Q_{100} + k_- f_- Q_{001},
\]

where \( Q_{100} \) and \( Q_{001} \) are the steady-state probabilities that the segment of three sites centered about the driven particle is in the indicated configuration (cf. Fig. 5). In order to use mean field theory to compute \( Q_{100} \) and \( Q_{001} \), we must use either moment equations or a finite-sized mean field transition matrix in the moving, fluctuating frame of the transported particle. In analogy to Eq. 1, we can consider the evolution equation of the first moment \( \langle \sigma_i \rangle \) of the hydrolysis level at the site of the driven particle. In addition to the state transitions represented by rates \( k_\pm \) (hydrolysis) and \( k_0 \) (dehydration), transition terms also arise from motion of the driven particle:

\[
\frac{d\langle \sigma_i \rangle}{dt} = k_- - (k_- + k_0)\langle \sigma_i \rangle + \Delta \langle \sigma_{i-1} \rangle - \Delta \langle \sigma_{i+1} \rangle
\]

\[
+ (p_+ (\sigma_i - \sigma_{i+1}) - p_- (\sigma_i - \sigma_{i-1})),
\]

where \( p_\pm \) are the effective forward and backward hopping rates of the particle. Since the particle moves only via motion of domain walls defined by \( Q_{100} \) and \( Q_{001} \),

\[
p_+ = k_+ f_+ Q_{100} = k_+ f_+ \sigma_{i-1} (1 - \sigma_i) (1 - \sigma_{i+1})
\]

\[
p_- = k_- f_- Q_{001} = k_- f_- (1 - \sigma_{i-1}) (1 - \sigma_i) \sigma_{i+1}.
\]

Upon substitution of \( p_\pm \) in Eq. (6) into Eq. (5) and neglecting all correlations, we obtain a simple, single-site, moving-frame mean field approach to finding \( \langle \sigma_i \rangle \approx \langle \sigma_{i\pm 1} \rangle \) as a root of a cubic equation. This simple mean field solution is only in qualitative agreement with MC simulations. In analogy to the finite-sized segment approach implemented through the transition matrix \( M \), we can also improve the simple moving-frame mean field theory by considering a sliding window of sites always centered about the driven particle \([11]\).

Within these sites, the configurations are explicitly enumerated, transitions involving sliding the segment as it follows the driven particle are included, and steady-states are found. 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 \( f_\pm = 1 \).

Fig. 4 shows the mean velocity \( V \) derived from MC simulations and from finite-segment mean field theory applied in the moving frame of the convected particle. The agreement between MC simulation and the finite-segment MFT is quite good provided \( k_- \ll 0.1 \). For \( k_- > k_+ \), the hydrolyzed domains grow backward at a higher rate 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. (5) and Fig. 5. When both \( k_+ \ll 1 \), dehydration dominates, domains are quickly dissipated, and the particle is kicked by a rare 100 domain wall as shown in Fig. 5b. Increasing values 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. 5c, reducing the domain wall density \( Q_{100} \) and ultimately \( V \). Thus, there is a value of \( k_+ \) that gives an optimally combined domain wall density and nucleation asymmetry, as shown in Fig. 5d, resulting in a maximum

FIG. 3: The kinetic rules for domain wall-driven particle motion. A particle is pushed forward with probability \( f_+ \) whenever a \( \ldots \\ldots 100 \ldots \) domain wall tries to move past it from left to right. Similarly, the particle moves backward with rate \( k_- f_- \).

FIG. 4: (a) The mean velocity \( V \) as a function of the forward hydrolysis rate \( k_+ \) for various \( k_- \). (b) The dispersion \( D \) for the same values of \( k_- \). The symbols mark the values obtained from MC simulation and the solid curves are results from a 5-site finite-segment mean field approach.
mean velocity $V_{\text{max}}$.

For all values of $k_-$, an extremely large $k_+$ will ultimately decrease the particle velocity. Although $\Delta = k_+ - k_-$ might be large, $Q_{100}$ decreases sufficiently that $V$ decreases. The decrease of the mean velocity $V$ in the $k_+ \to \infty$ limit can be determined by considering a “virial” approximation where only transitions among intermediary, and the mean velocity is maximal. (c) 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.

In Fig. 5a, $k_+ < k_- \ll 1$, the most of the lattice remains unhydrolyzed and there are few domain walls to push the particle. (b) When $k_+ > k_- \ll 1$, the mean velocity $V$ asymptotically approaches $V_{\text{max}} \simeq 0.315 (k_- + 0.469)$, $k_+ \simeq 2.67 k_- > 1$, and $V_{\text{max}} \simeq 1.68 \exp(-1.84 k_-^{0.29})$, $k_+ \approx 3.3$ for $k_- < 0.1$. These expressions are plotted as dashed curves in Fig. 6 and provide accurate, universal approximations on the maximum velocity possible $V_{\text{max}}$ as a function of $k_-$, and the value of $k_+^{*\text{max}}$ required for maximal particle velocity, for each $k_-$. 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 value $k_+^{*\text{max}}$ approaches its minimum near $\sim 3.3$ when $k_- \lesssim 0.2$. The maximum velocities and the associated rates can be accurately described by the simple universal fitting equations (7).

Additional details such as slippage ($f_\pm < 1$) and an external load can be readily implemented. A load on the particle would bias the motion of the motor backwards and impart a negative drift velocity in addition to that shown in Fig. 4b. The force-velocity relationship follows directly from the functional form of the force-dependent drift.
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