Active and Passive Transport of Cargo in a Corrugated Channel: A Lattice Model Study

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Inside cells, cargos such as vesicles and organelles are transported by molecular motors to their correct locations via active motion on microtubule tracks and passive, Brownian diffusion. During the transportation of cargos, motor-cargo complexes (MCC) navigate the confining and crowded environment of the cytoskeletal network. Motivated by this, we study a minimal two-state model of motor-driven cargo transport in confinement and predict transport properties that can be tested in experiments. We assume that the motion of the motor is directly affected by the entropic barrier due to confinement when it is in the passive, unbound state, but not in the active, bound state. Confinement can further modulate the motor’s binding kinetics. We construct a lattice model based on a Fokker Planck description of the two-state system, and study it using a kinetic Monte Carlo method. We compute transport properties such as the average velocity and the effective diffusivity of the MCC. For constant binding and unbinding rates, we find that introducing confinement effectively enhances the unbinding rate and thereby reduces the motor processivity, leading to smaller effective diffusivity and average velocity. For spatially varying binding rates that depend on confinement, the average velocity is further reduced when the average binding rate is equal to the constant binding rate without confinement. However, confinement may lead to an enhancement in the average velocity if it results in a greater average binding rate than in the absence of confinement.

I. INTRODUCTION

Intracellular transport of cargos by molecular motors is critical to development, maintenance, and homeostasis in most eukaryotic cells [1]. There exist several motors, such as kinesin-1 and cytoplasmic dynein, that use ATP, the energy currency of the cell, to move cargo through the cell using microtubules [1–9]. Some motors have direction bias on microtubules; some carry larger, and some smaller cargos. Examples of intracellular cargo include organelles such as mitochondria and nucleus, and dysfunctional or damaged protein aggregates that occur in disease states [2–4, 10–12]. While the transport of the former is essential to proper functioning of the cell, the latter need to be cleared out of the cell to prevent cell damage and disease progression. Understanding the mechanistic principles underlying intracellular cargo transport will help to elucidate how cells move or clear cargo, and aid in the creation of new drugs or agents to help regain function in disease states.

Microtubules, the filaments which provide the pathway for the motors to walk during intracellular transport, are rigid, filamentous biopolymers that are found throughout the cell interior and can grow as long as 50 microns in length [1, 7, 13]. Over the past two decades, there have been many studies, both experimental and theoretical, on cargo transport by motors on single microtubules in-vitro. The speed and travel distance of molecular motors on surface-immobilized microtubules is very well understood [14]; examples include the molecular motor kinesin pulling fluid membranes on a microtubule [15], multiple motors transporting a single cargo [16], and motors carrying cargos to multiple targets in neurons [17]. Within cells, however, microtubules rarely exist as individual filaments. Instead, they are found as networks of filaments that provide a long-distance highway system for intracellular cargo transport [3]. Despite decades of studies of motors moving and carrying cargos on single microtubule tracks, cargo transport in complex and dynamic cytoskeletal architectures in cells is not well understood. In fact, experimental [18–19] and theoretical studies [20–22] have only recently begun to investigate how intracellular transport is affected by the physical properties of the cytoskeletal network and crowded cellular environments, and there remain many open questions.

Here we ask: How does confinement due to the cytoskeletal network affect motor-driven cargo transport? We address this question by developing a minimal two-state model that describes cargo transport in the presence of confinement. The two states are: (i) an active state when the motor-cargo complex (MCC) is attached to the microtubule and moves with a constant speed, and (ii) a passive state when it is unattached and undergoes diffusive motion. Such two-state models have been useful in elucidating active transport of brownian particles in confined geometries [23, 24], specifically how the cooperative rectification between geometric constraints and Brownian ratchets impacts net particle motion. The interplay between passive and active transport and confinement, as is common in intracellular transport, however, remains poorly understood. In this paper, we combine a Fokker Planck description with a lattice model framework to study how confinement, and motor dynamics and binding kinetics interact to modify directed
transport of cargos by motors.

The paper is organized as follows. We write down the Fokker Planck Equations (FPE) for the two-state model and propose a lattice model that can capture the physics described by the FPE and reduces to the FPE in the continuum limit. We simulate the lattice model using a kinetic Monte Cargo method, and show that it reproduces known analytical results for passive (diffusive) transport in confinement. Thereafter we investigate the full two state problem in confinement, and calculate transport properties such as mean squared displacement (MSD), average velocity, and effective diffusivity for the MCC, and discuss the implications of our results.

II. MODEL AND METHOD

We model and study the active and passive transport of cargo by a motor moving unidirectionally on a microtubule track and confined in a corrugated channel as schematically shown in Fig. 1. The motor can move micrometer-long distances along the microtubule before detaching. Kinesin motors, a well-characterized family of motor proteins that move organelles (e.g., mitochondria, nucleus, etc.) and macromolecules (e.g. RNA) in many cell types \[25\] are good examples of such motors. While the confinement faced by an MCC in a live cell is heterogeneous and dynamic, for simplicity, we consider a confining channel described by

\[ w(x) = a \sin(2\pi x/L) + b, \]

where \( L \) is the periodicity, \( a \) and \( b \) control the width of the channel, and the bottleneck width is given by \( 2(b - a) \) \[26\]. The channel width and periodicity are set by the length scales associated with localized cages and network mesh sizes.

The basic assumptions of the model are as follows:

1. Over long time scales, the MCC alternates between two states: (i) An active state which phenomenologically represents the MCC being bound to a microtubule and moving along the microtubule in the forward direction with a speed \( v_b \), and (ii) an passive state where the MCC is detached from the microtubule and undergoes overdamped Brownian motion with a bare diffusion constant \( D_0 \).

2. The binding rate, \( k_{on}(x) \), of the motor can be constant or it can vary inversely with the width of the confining channel in Fig. 1. The latter represents the case where tighter confinement leads to greater likelihood of the motor attaching to the microtubule due to increased proximity to binding sites.

3. The unbinding rate, \( k_{off}(x) \), of the motor is assumed to be constant.

The channel is symmetric, and hence there is no confinement-induced symmetry-breaking for purely diffusive motion as in some Brownian Ratchet models \[27\].

\[ \frac{\partial P(x,t)}{\partial t} = D_0 \frac{\partial}{\partial x} \left( e^{-\beta A(x)} \frac{\partial}{\partial x} e^{\beta A(x)} P(x,t) \right). \] (1)

Here, \( P(x,t) \) represents the probability density at a given position \( x \) along the axial direction of the channel at time \( t \), \( D_0 \) is the diffusion coefficient in the absence of confinement, and \( \beta = 1/k_B T \), where \( k_B \) is the Boltzmann constant and \( T \) is the temperature. To derive the above equation, rapid equilibration is assumed in the transverse direction of the channel. The confinement is incorporated through an effective free energy.
\[ A(x) = V(x) - TS(x), \] where \( S(x) \) is the entropy barrier due to confinement and \( V(x) \) is an external energy barrier. The entropy due to the confining wall \( w(x) \) is \( S(x) = k_B \log(2w(x)/w_{ave}), \) where \( w_{ave} = 2 \int_0^L w(x) \, dx \) is the average width of the channel. In the absence of any external potential, the free energy is purely entropic, \[ A(x) = -k_B T \log(2w(x)/w_{ave}). \]

Now, we return to the problem of two-state transport. The MCC walks with a velocity \( v_b \) when it is bound, diffuses with a bare diffusion constant \( D_0 \) when unbound, and alternates between the two states with rates \( k_{off}(x) \) and \( k_{on}(x) \), respectively. The Fokker-Planck equation for the probability densities for the bound state \( P_b(x,t) \) and unbound state \( P_{ub}(x,t) \) are given by:

\[ \frac{\partial P_b(x,t)}{\partial t} = k_{on}(x) P_{ub}(x,t) - k_{off}(x) P_b(x,t) - v_b \frac{\partial P_b(x,t)}{\partial x}, \] (2a)

\[ \frac{\partial P_{ub}(x,t)}{\partial t} = -k_{on}(x) P_{ub}(x,t) + k_{off}(x) P_b(x,t) + D_0 \frac{\partial}{\partial x} \left( e^{-\beta A(x)} \frac{\partial}{\partial x} e^{\beta A(x)} P_{ub}(x,t) \right). \] (2b)

The first two terms in Eqs. 2a and 2b correspond to binding and unbinding transitions respectively. The third term in Eq. 2a represents active motion of the MCC, while the third term in Eq. 2b describes passive motion of the MCC under confinement. Given kinesin is a highly processive motor and can take over a hundred steps along a microtubule before dissociating [30, 31], we neglect diffusion in the active state. However, one can easily incorporate diffusive behavior for other motor types by adding a diffusion term in Eq. 2a. The analytical solutions of Eq. 2 are difficult, and have closed form expressions only in the passive limit [26] and in a mean field limit for two-state transport discussed later in the paper. We, therefore, construct the corresponding lattice model which reduces to Eq. 2 in the continuum limit and evolve the system using a kinetic Monte Carlo method as discussed below.

### B. Lattice Model

We study the dynamics of a two-state MCC described by the continuum Fokker-Planck equation (Eq. 2) using an equivalent lattice model. The model is schematically shown in Fig. 1 and consists of an MCC on a one-dimensional lattice. The MCC can switch between a bound and an unbound state. The bound MCC can further hop to its forward neighboring site while the unbound MCC can hop to both its backward and forward neighboring sites. The spacing between neighboring lattice sites is \( \ell \).

Consider that the MCC is at the lattice site at position \( x \) at time \( t \) in a particular state. The transition rates from the unbound state to bound state is \( k_{on}(x) \) and from the bound state to unbound state is \( k_{off}(x) \). The MCC in the bound state can either hop to its forward neighbor \((x + \ell)\) with rate \( \lambda_+(x) \), or it can switch to the unbound state with rate \( k_{off}(x) \). The MCC in the unbound state can hop either to its forward neighbor \((x + \ell)\) with rate \( \lambda_{ub}^+(x) \), backward neighbor \((x - \ell)\) with rate \( \lambda_{ub}^-(x) \), or switch to the bound state with rate \( k_{on}(x) \).

The master equations describing the time evolution of the probability densities for the bound state \( P_b(x,t) \) and the unbound state \( P_{ub}(x,t) \) for this process are

\[ \frac{\partial P_b(x,t)}{\partial t} = k_{on}(x) P_{ub}(x,t) - k_{off}(x) P_b(x,t) + \lambda_+(x - \ell) P_b(x - \ell, t) - \lambda_v(x) P_b(x, t), \] (3a)

\[ \frac{\partial P_{ub}(x,t)}{\partial t} = -k_{on}(x) P_{ub}(x,t) + k_{off}(x) P_b(x,t) + \lambda_{ub}^+(x - \ell) P_{ub}(x - \ell, t) + \lambda_{ub}^-(x + \ell) P_b(x + \ell, t) - (\lambda_{ub}^+(x) + \lambda_{ub}^-(x)) P_{ub}(x, t). \] (3b)

As the bound velocity \( v_b \) in our model is independent of position, the bound state hopping rate \( \lambda_v(x) \) is also position independent and is given by \( \lambda_v(x) = v_b/\ell \). We incorporate the effect of confinement using position dependent hopping rates \( \lambda_{ub}^\pm(x) \) for the unbound state. The hopping rates \( \lambda_{ub}^\pm(x) \) depend on the free-energy \( A(x) \) which has a contribution from the entropic barrier due to confinement. In the presence of an external potential, it also has an energy contribution. The hopping rates are given by \( \lambda_{ub}^\pm(x) = (D_0/\ell^2) e^{-\beta (A(x) \pm \ell - A(x))}/2. \) The factor 1/2 in the exponent ensures local detailed balance. With these choice of rates, for \( \ell \to 0 \), the Eq. 3 reduces to Eq. 2 (see Supporting Information for details).

We use a kinetic Monte Carlo algorithm to evolve the system. For the MCC at the lattice site \( x \) at time \( t \), we choose an event out of all possible events at random with a probability proportional to its rate, and increase the time by \( \Delta t = 1/\Gamma(x) \), where \( \Gamma(x) \) is the total rate. For the bound MCC, the event space consists of a forward hopping event with probability \( \lambda_+ \Gamma \), and a transition to the unbound state with probability \( k_{off}(x)/\Gamma \), where the total rate in the bound state \( \Gamma = k_{off}(x) + \lambda_v(x) \).
For the unbound MCC, the event space consists of a hopping event in the forward direction, a hopping event in the backward direction, and a transition to the bound state, with probabilities \( \lambda_+^u(x)/\Gamma \), \( \lambda_-^u(x)/\Gamma \), and \( k_{on}(x)/\Gamma \) respectively, where the total rate in the bound state is \( \Gamma = k_{on}(x) + \lambda_+^u(x) + \lambda_-^u(x) \). For simplicity and efficiency, the mean of the exponential distribution \( \Gamma(x) \exp(-\delta t \Gamma(x)) \) is used as the time step in our simulations. Although a time step drawn at random from the exponential distribution would have been more appropriate, we have checked that the choice of the mean does not change any of our results, while it makes the simulation more efficient. This was also verified by one of the authors in a study of a lattice model for ballistic aggregation in [32].

C. Simulation Details and Parameters

Throughout this study, the lengthscales associated with the corrugated channel are taken to be \( L = 1 \mu m \), \( a = 1/(2\pi) \mu m \), and \( b = 1.02/(2\pi) \mu m \). The parameter values for the two-state motion of the MCC are informed by experiments [15, 16, 33]. The value of the step size or lattice spacing \( \ell = 8 \) nm. The simulations are performed with the bare diffusion constant of the unbound MCC \( D_0 = 0.64 \mu m^2 s^{-1} \) and the off-rate \( k_{off} = 0.42 s^{-1} \), unless otherwise specified. The on-rate and bound velocity are varied over wide ranges, \( k_{on} = 0.05 - 50 s^{-1} \) and \( 0.04 - 1.6 \mu m s^{-1} \).

For the binding (on) rate, we study two cases: (i) \( k_{on} = k_{on}^0 \), and (ii) \( k_{on}(x) \propto k_{on}^0/(w(x)) \). In the latter case, we further investigate two situations – when the spatial average of \( k_{on} \), in the interval \( L \) is \( k_{on}^0 \), to allow for comparison with (i), and when it is greater than \( k_{on}^0 \). All the data presented in this paper are averaged over 25000 or more realizations.

III. RESULTS

We characterize the motor-driven cargo transport in our model by the mean squared displaced, \( \langle \delta x^2(t) \rangle = \langle (x(t + t_0) - x(t_0))^2 \rangle \), the average velocity, \( \langle \dot{x} \rangle \), and the effective diffusion coefficient, \( D_{eff} \) of the MCC. The last two quantities are defined in the asymptotic limit as \( \langle \dot{x} \rangle = \lim_{t \to \infty} \frac{\langle x(t) - x(0) \rangle}{t} \), and \( D_{eff} = \lim_{t \to \infty} \frac{(\langle x^2(t) \rangle - \langle x(t) \rangle^2)}{2t} \), where \( x(t) \) is the position of the particle at time \( t \) and \( \langle \cdot \rangle \) represents ensemble averages.

A. Passive Transport in a Confining Channel

We first study the passive, diffusive transport of a particle in confinement using kinetic Monte Carlo simulations of the lattice model. We demonstrate that the lattice model correctly incorporates hopping rates through the entropic barrier dependent free energy, and discuss properties which will be used to compare and understand the results of two-state transport in the next section. In this case, a particle at the lattice site can hop to one of its neighboring sites \((x \pm \ell)\) with rate \( \lambda_{\pm} = (D_0/\ell^2) e^{-\beta(\mathcal{A}(x \pm \ell) - \mathcal{A}(x))/2} \). For Brownian motion under constant force \( F \), \( \mathcal{A}(x) = -Fx - TS(x) \), which gives \( \lambda_{\pm}(x) = (D_0/\ell^2) e^{\pm 3\beta F/2} \sqrt{w(x \pm \ell)/w(x)} \).

In the absence of any confinement, the rates of hopping then become, \( \lambda_{\pm}(x) = (D_0/\ell^2) e^{\pm 3\beta F/2} \), i.e. independent of \( x \). Confinement makes the hopping probabilities \( x \) dependent, which are given by \( \lambda_{\pm}(x)/\Gamma(x) \), where \( \Gamma(x) = \lambda_{+}(x) + \lambda_{-}(x) \).

In Fig. 2(a) and (b), we present the lattice model results for the scaled mobility \( \mu_{eff}/\mu_0 \) and scaled diffusion coefficient \( D_{eff}/D_0 \) and compare them with the corresponding analytical predictions. The latter are obtained by solving the Fick-Jacobs equation (Eq. 1) for a particle undergoing 2D overdamped Brownian motion under an external driving force \( F \) in a corrugated channel \( w(x) \) with peri-
odicty $L$ and given by

$$\mu_{\text{eff}} := \frac{\langle \dot{x} \rangle}{F} = \frac{D_0}{k_B T} \int_0^L \frac{dx}{x} I(x, f) e^{-f(x)/k_B T} - f^{-1}.$$  \hspace{1cm} (4a)

$$\frac{D_{\text{eff}}}{D_0} = \int_0^L \frac{dx}{L} \frac{\int_{x-L}^x dx e^{A(x)/k_B T} \int_{x-L}^x dx e^{-A(y)/k_B T} I^2(z, f)}{\int_{x-L}^x dx I(x, f) e^{-A(y)/k_B T}} .$$  \hspace{1cm} (4b)

where $I(z, f) := e^{A(z)/k_B T} \int_{x-L}^x \frac{dy}{L} e^{-A(y)/k_B T}$.

We now discuss the results shown in Fig. 2 in more detail. The scaled mobility shown in Fig. 2(a) is always less than 1, approaching 1 asymptotically as $f$ is increased. This suggests that a symmetric confinement without any rectification mechanism cannot enhance the mobility of a purely diffusive system. The behavior of the scaled effective diffusivity $D_{\text{eff}}/D_0$ in Fig. 2(b) is non-monotonic with a peak at a critical value of $f$, suggesting that while at small $f$ confinement causes the effective diffusivity to decrease, at large $f$ the interplay of the force and confinement leads to enhanced diffusivity. In Fig. 2(c) and (d), we show the MSD for $f = 0$ and $f = 25$ respectively, and compare the results with the corresponding no-confinement case. In the absence of any external force, i.e. $f = 0$, confinement leads to a significant decrease in the MSD compared to the no-confinement case at intermediate and large times as seen in Fig. 2(c); the particle’s motion changes from free diffusion with $D_0$ at early times to an intermediate sub-diffusive regime, and finally to effective diffusive behavior with $D_{\text{eff}} < D_0$ at large times. The intermediate sub-diffusive regime presumably emerges due to the slowing down of motion near the neck of the channel. Presence of an external driving force ($f = 25$) noticeably reduces the effect of confinement (Fig. 2(d)) – the separation between the MSDs for confined and unconfined cases is much smaller in (d) compared to (c). The motion of the particle now undergoes a change from free diffusion at very early times to force-driven ballistic motion at large times. Once again, there is a visible slowing down in at intermediate times for the confined case, but the gap between the two asymptotic MSDs decreases as $f$ is increased. As we will see in the next section, this intermediate slowing down due to confinement plays a critical role in two-state cargo transport.

![Figure 3](image3.png)

FIG. 3. MSD with time for $k_{\text{off}} = 0.42 \text{s}^{-1}$, and $D_0 = 0.64 \text{µm}^2\text{s}^{-1}$, with confinement (C) and without confinement (NC). Figures (a) & (b) show data for a large binding rate ($k_{\text{on}} = 4.7 \text{s}^{-1}$) of the motor to the microtubule. (a) For a small bound velocity ($v_b = 0.04 \text{µm s}^{-1}$), the MSDs for both C and NC grow as $2D_0 t$ initially, deviating at intermediate times, and asymptotically converging to ballistic motion ($\langle \dot{x} \rangle t^2$) at large times. (b) For a large bound velocity ($v_b = 0.8 \text{µm s}^{-1}$), the small $t$ diffusive motion and large $t$ ballistic motion are the same for both C and NC, but the intermediate behavior are different. Figures (c) & (d) show data for a small binding rate ($k_{\text{on}} = 0.2 \text{s}^{-1}$), for a small velocity ($v_b = 0.04 \text{µm s}^{-1}$) in (c) and a large velocity ($v_b = 0.04 \text{µm s}^{-1}$) in (d); the observed MSDs are similar to (a) and (b) respectively, but with the crossover from diffusive to ballistic motion occurring at larger times.

### B. Active and Passive Transport in a Confining Channel

We now discuss the transport properties, namely MSD, average velocity, and effective diffusivity of the MCC for the two state model with confinement, and compare them with the results for the no-confinement case. Where appropriate, we also compare our results with corresponding steady state values in the mean field limit without any confinement. The following sections we refer to this limit as the Mean Field No Confinement (MFNC) limit. In this limit, the probabilities of bound and unbound states are given by $P_b = k_{\text{on}}/(k_{\text{on}} + k_{\text{off}})$ and $P_{\text{off}} = k_{\text{off}}/(k_{\text{on}} + k_{\text{off}})$, respectively, and the average velocity and effective diffusivity can be written as,

$$V_l = \tilde{P}_b v_b = \frac{k_{\text{on}} v_b}{k_{\text{on}} + k_{\text{off}}} \hspace{1cm} (5)$$

$$D_l = \tilde{P}_{\text{off}} D_0 = \frac{k_{\text{off}} D_0}{k_{\text{on}} + k_{\text{off}}} \hspace{1cm} (6)$$
FIG. 4. Scaled average velocity $\langle \dot{x} \rangle / v_b$ of the MCC as a function of the binding rate $k_{on}$ (a) without confinement and (b) with confinement for various values of $v_b$. We have set $k_{off} = 0.42 \text{s}^{-1}$, and $D_0 = 0.64 \mu m^2 s^{-1}$. Solid lines represent MFNC limit. The data for $v_b = 0.04$, and $0.1 \mu m s^{-1}$ do not follow MFNC limit. The dashed line is a fit of $0.04 \mu m s^{-1}$ data to Eq. 5 which yields $k_{eff}^{on} = 0.57 \text{s}^{-1}$ and $v_b^{eff} = 0.019 \mu m s^{-1}$. The dotted line is a fit of $0.1 \mu m s^{-1}$ data with $k_{eff} = 0.49 \text{s}^{-1}$ and $v_b^{eff} = 0.08 \mu m s^{-1}$.

Below we discuss our main results.

Mean Squared Displacements (MSD): In Fig. 3 we present the MSD for small and large bound velocities $v_b$ for two different binding rates $k_{on}$. At very small time $t$, the MSD behaves as $\langle \delta x^2(t) \rangle \approx 2D_0t$. This behavior suggests that below a crossover time scale, say $t_{c1}$, the effect of binding/unbinding kinetics and confinement are negligible such that the MCC can diffuse freely. For $t > t_{c1}$, it shows a transition from free diffusion to “sub-diffusion”. In the absence of confinement, the sub-diffusive behavior is due to the time spent by the MCC alternately transitioning between bound and unbound states, and the crossover time scale, $t_{c1}$, mainly depends on the transition rates. In the confined case, in addition to transition events, the motion of the MCC slows down even further due to the strong entropic barrier in the diffusive state close to a neck of the channel. Consequently, the crossover time $t_{c1}$ becomes even smaller for the confined case than that without any confinement. There is a second crossover from sub-diffusive to ballistic behavior i.e., for $t > t_{c2}$, $\langle \delta x^2(t) \rangle \approx \langle \dot{x} \rangle^2 t^2$. A representative case of the locations of $t_{c1}$ and $t_{c2}$ are shown in Fig. 3 (a). From the Fig. 3 it is clear that confinement impacts the motion of the MCC more strongly for small $v_b$ – it spends longer times in the intermediate sub-diffusive regime leading to smaller asymptotic velocities at large times compared to the no-confinement case. For larger $v_b$, the sub-diffusion regime shrinks and the MCC has the same asymptotic velocities with and without confinement.

Average velocity: We find that confinement reduces the average velocity of the MCC for small bound velocities $v_b$ while for large $v_b$ the results follow the MFNC limit. In Fig. 4(a) and (b), we show the results for the scaled average velocity for various values of $v_b$ without and with confinement, respectively. We observed that the scaled average velocities grow monotonically with $k_{on}$. In the absence of confinement, the data for all $v_b$ follow Eq. 5. For small $v_b (0.04, \text{and} 0.1 \mu m s^{-1})$, confinement leads to a reduction in the scaled average velocity and it stays below the MFNC limit described by Eq. 5. However, the data can be fitted to Eq. 5 with an effective $k_{eff}^{on}$, and an effective $v_b^{eff}$. We find that $k_{eff}^{on} > k_{eff}$ and $v_b^{eff} < v_b$ suggesting that confinement renormalizes the bound velocity and the unbinding rate to values lower than without confinement, and therefore effectively reduces the processivity of the motor. For large $v_b (0.5, 0.8, \text{and} 1.6 \mu m s^{-1})$, the scaled average velocities are unaffected by confinement. These results are consistent with MSDs discussed earlier.

Effective Diffusivity: Confinement has a much more striking impact on the effective diffusivity of the MCC. Unlike for the average velocity, we do not find a data collapse in this case. We show the scaled diffusion coefficient as a function of $k_{on}$ for the no-confinement case in Fig. 5(a). We observed that scaled diffusion coefficient shows a maximum for $v_b = 1.6 \mu m s^{-1}$ at $k_{on} = 0.2 s^{-1}$. In the case of confinement (Fig. 5 (b)), the effective diffusion coefficient become smaller than for the case without confinement, but they are well separated with prominent peaks, and the presence of a maximum at $k_{on} = 0.2 s^{-1}$ is now seen for small $v_b$. The observed maximum in diffusivity is reminiscent of similar behavior for a particle undergoing diffusion in a tiled washboard potential [35], or in a periodic confined profile [26]. There the appearance of a peak in the diffusivity is associated with a “locked-to-running” transition [35]. In the locked state, the particle shows no net movement over a significant amount of time, while in the running state the particle has a net drift velocity. Transitions between the two states can be induced via occasional large kicks due to noise. We observe peaks in the two-state model even without any confinement, with the passive (unbound) and active (bound) states corresponding to the locked and running states respectively. The transition between the two states are induced by the binding kinetics of
the motors to the microtubule. Confinement makes the peaks much more pronounced, and leads to greater separation between the scaled effective diffusivity curves for different \(v_b\).

The qualitative behavior of the average velocity and effective diffusivity does not depend on the bare diffusion constant \(D_0\). We have checked this by studying a system with \(D_0 = 0.064 \mu m^2 s^{-1}\) (results not presented here).

C. Active and Passive Transport in a Confining Channel with Spatially Varying Binding Rates

Next we study cargo transport by motors with a spatially varying binding rate that depends on the local width of the confining channel. We have studied the following two cases: (i) \(k_{on}(x) = k_{on}^0 \sqrt{b^2 - a^2}/w(x)\), where the binding rate is normalized to ensure that the spatial average \(\langle k_{on}(x) \rangle = k_{on}^0\), and (ii) \(k_{on}(x) = k_{on}^0/w(x)\), where the binding rate is not normalized, and its spatial average \(\langle k_{on}(x) \rangle = k_{on}^0/\sqrt{b^2 - a^2}\). For both (i) and (ii), the unbinding rate \(k_{off}\) is assumed to be independent of the spatial variation of the channel width.

Let us first consider the case (i) with the normalized spatially varying binding rate. We present the scaled velocities against \(k_{on}^0\) for two different values of unbinding rates \(k_{off} = 0.42\) and \(0.0955 s^{-1}\) in Fig. 6(a). For each value of the unbinding rate, we consider three different bound velocities \(v_b\). For each unbinding rate, the average velocity data collapse onto a single curve, suggesting that unlike for constant binding rates the scaled velocities do not depend on \(v_b\). We further find that for both unbinding rates, the average velocities of the MCC stay below the corresponding velocities \(V_l\) in the MFNC limit given by Eq. 5 and that confinement does not lead to any enhancement of the average velocity.

Although these observations may be intriguing at first look, they can be explained as follows. The probability of the MCC binding to the microtubule is very high near the neck of the channel where \(k_{on}(x) >> k_{on}^0\), reaching its maximum value at the neck. Concomitantly, for all locations other than the channel neck, we must have \(k_{on}(x) < k_{on}^0\) such that the condition \(\langle k_{on}(x) \rangle = k_{on}^0\) is satisfied over the channel length. Recall that confinement impairs the diffusive motion of motors in the unbound state but does not affect the directed motion in the bound state. Therefore, in regions where confinement is the most tight, the MCC is more likely to be in a state (bound) where it is unaffected by confinement. This leads to a reduced impact of confinement on the net movement of the MCC leading to the data collapse of the average velocity observed in Fig. 6(a). Furthermore, since \(k_{on}(x) < k_{on}^0\) across most of the channel length, the probability of the MCC being in the bound state is smaller than for the case with a constant \(k_{on}^0\) in those regions. Since the contribution to the average velocity comes from the directed motion in the bound state, the average velocity is now smaller and well below the MFNC limit as seen in Fig. 6(a).

Next we compare case (i) with the un-normalized case (ii) where the average \(\langle k_{on}(x) \rangle\) is not set to be equal to \(k_{on}^0\) and is, in fact, larger than \(k_{on}^0\). In Fig. 6(b), we show the scaled velocities against \(k_{on}^0\) for case (i) and case (ii), for a given unbinding rate \(k_{off} = 0.42 s^{-1}\) along with the corresponding MFNC prediction (Eq. 5). We observe that for both cases, the data for all bound velocities show a good collapse as in Fig. 6(a). More interestingly, the average velocity of the MCC for case (ii) is greater than the MFNC velocity \(V_l\), unlike case (i) where it is always less than \(V_l\). This enhancement in the average velocity is because of \(\langle k_{on}(x) \rangle\) being larger than \(k_{on}^0\) by a factor of \(1/\sqrt{b^2 - a^2}\); multiplying \(k_{on}^0\) by this factor can collapse both data onto a single curve which stays below \(V_l\) (Fig. 6(c)). Nevertheless, this suggests that if confinement were to cause an enhancement of the average binding rate \(\langle k_{on}(x) \rangle\), it would lead to larger average velocities of the MCC. In fact, in a study similarly to (ii) but for Brownian ratchets in confined media, the authors found an enhancement of the net particle for non-processive motors with a confinement dependent binding rate 23 24.
IV. CONCLUSIONS

We have studied cargo transport by molecular motors in a two-dimensional corrugated channel using an equivalent one dimensional lattice model. The effect of confinement is incorporated through a position dependent entropy barrier. At any given time, the MCC can be in one of two states: an active state where it moves on a microtubule track with a constant speed, and a passive state when it is detached from the microtubule and undergoes diffusive motion. We assume small cargo sizes such that while the diffusive motion is impaired by confinement, the bound state directed motion is not. In the lattice model, when in the active state, a bound particle hops in the forward direction with a rate proportional to its bound velocity, while in the passive state, an unbound particle can hop in both directions with position dependent hopping rates. For purely diffusive motion in confinement, the results from the lattice model exactly match known analytical results, demonstrating that the Arrhenius description for hopping rates works for our system and other similar systems with entropic barriers. Moreover, the lattice based approach and simple evolution rules make our model computationally more efficient for simulating two state transport in complex confinement profiles than numerical simulations of the corresponding 2D Langevin equations.

In order to understand and quantify how confinement impacts two-state transport, we compute and compare the mean squared displacements, as well as the average velocity and effective diffusivity of the MCC scaled by the mean squared displacements, as well as the average velocity differently depending on whether the average binding rate is equal to or greater than that in the absence of confinement. In the former case, we find further slowing down of the MCC, while in the later we find an enhancement in its scaled average velocity. Our results suggest that the impact of confinement on cargo transport strongly depends on if and how it modulates the binding kinetics of the motors. The impact of confinement on binding kinetics can be obtained in the enclosed microchannel experiments [37] by measuring the MCC residence times in the bound and unbound states for different channel widths. The same experimental set up can be used to obtain the scaled average velocity, and thus test the predictions of our study.

In addition to studying motor driven cargo transport in confinement, such microfabricated enclosed channels can be potentially used to deliver specific proteins or to separate DNA or RNA strands from a complex mixture by binding them to microtubules and transporting them to desired locations. Our results therefore may not only be useful in understanding cargo transport in cells, but also may help in advancing the nanoscale drug delivery system within cells and sequencing techniques for DNA and RNA. Our model can also be easily extended to study bidirectional cargo transport [38].

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Active and Passive Transport of Cargo in a Corrugated Channel: Supporting Information

I. CONTINUOUS LIMIT OF THE LATTICE MODEL

As discussed in the main text, the master equations describing the time evolution of the probability densities of the bound (active) and unbound (passive) states are given by,

\[ \frac{\partial P_\text{on}(x,t)}{\partial t} = k_\text{on}(x)P_\text{ub}(x,t) - k_\text{off}(x)P_\text{b}(x,t) + \lambda_+P_\text{b}(x-\ell,t) - \lambda_-P_\text{b}(x,t) \]  
\[ \frac{\partial P_\text{ub}(x,t)}{\partial t} = -k_\text{on}(x)P_\text{ub}(x,t) + k_\text{off}(x)P_\text{b}(x,t) + \lambda_+\text{ub}(x-\ell)P_\text{ub}(x-\ell,t) + \lambda_-\text{ub}(x+\ell)P_\text{b}(x+\ell,t) \]

\[ - (\lambda_+\text{ub}(x) + \lambda_-\text{ub}(x)) P_\text{ub}(x,t), \]

where \( k_\text{on}(x) \) and \( k_\text{off}(x) \) are binding and unbinding rates respectively, \( \lambda_+ = v_+/\ell \) is the hopping rate in the forward direction when the motor-cargo complex is in the bound state, and \( \lambda_{\pm}\text{ub}(x) = (D_0/\ell^2)e^{-\beta(A(x+\ell)-A(x))/2} \) are the unbound state hopping rates for the forward (+) and backward (−) directions. Using Taylor’s expansion for \( P_{b,\text{ub}}(x\pm \ell) \)
ℓ, t) and \( \lambda^\pm_\pm(x \pm \ell) \) around \( x \) and keeping the terms up to 2\(^{nd}\) order in \( \ell \), we get

\[
\frac{\partial P_b(x,t)}{\partial t} = \left. k_{\text{on}} P_{ub} - k_{\text{off}} P_b - v_b \frac{\partial P_b}{\partial x} + D_v \frac{\partial^2 P_b}{\partial x^2} + \mathcal{O}(\ell^3), \right. \\
\frac{\partial P_{ub}(x,t)}{\partial t} = -k_{\text{on}} P_{ub} + k_{\text{off}} P_b + \ell P_{ub} \left[ -\frac{d\lambda^\pm_{ub}}{dx} + \ell \left( \frac{d\lambda^\pm_{ub}}{dx} - \frac{d\lambda^\pm_{ub}}{dx} \right) \right] \\
+ \ell \frac{\partial P_{ub}}{\partial x} \left[ -\lambda^\pm_{ub} + \ell \left( \frac{d\lambda^\pm_{ub}}{dx} \right) \right] + \frac{\ell^2}{2} \frac{\partial^2 P_{ub}}{\partial x^2} \left( \lambda^\pm_{ub} + \lambda^\pm_{ub} \right) + \mathcal{O}(\ell^3),
\]

(S3)

where \( D_v \equiv \ell^2 \lambda_v/2 = \ell v_b/2 \). In \( \ell \rightarrow 0 \) limit, neglecting the term with \( D_v \) in Eq. (S5) we recover the continuum Fokker-Planck equation for the bound state (Eq. (2a) in the main text)

\[
\frac{\partial P_b(x,t)}{\partial t} = k_{\text{on}} P_{ub} - k_{\text{off}} P_b - v_b \frac{\partial P_b}{\partial x}.
\]

(S5)

Considering the leading order contributions for the coefficients of \( P_{ub} \) and \( \frac{\partial P_{ub}}{\partial x} \) in Eq. (S6) we get

\[
\frac{\partial P_{ub}(x,t)}{\partial t} = -k_{\text{on}} P_{ub} + k_{\text{off}} P_b + \ell P_{ub} \left[ -\frac{d\lambda^\pm_{ub}}{dx} + \ell \left( \frac{d\lambda^\pm_{ub}}{dx} \right) \right] + \ell \frac{\partial P_{ub}}{\partial x} \left[ -\lambda^\pm_{ub} + \ell \left( \frac{d\lambda^\pm_{ub}}{dx} \right) \right] + \frac{\ell^2}{2} \frac{\partial^2 P_{ub}}{\partial x^2} \left( \lambda^\pm_{ub} + \lambda^\pm_{ub} \right).
\]

(S6)

In the \( \ell \rightarrow 0 \) limit, \( \lambda^\pm_{ub}(x) = (D_0/\ell^2) e^{\pm \ell \lambda^\pm_{ub}/\ell} \). In this limit, the coefficients of \( P_{ub} \), \( \frac{\partial P_{ub}}{\partial x} \), and \( \frac{\partial^2 P_{ub}}{\partial x^2} \) are given by, \( \ell \left( -\frac{d\lambda^\pm_{ub}}{dx} + \frac{d\lambda^\pm_{ub}}{dx} \right) \simeq D_0 \beta \frac{d^2 A}{dx^2}, \ell \left( -\lambda^\pm_{ub} + \lambda^\pm_{ub} \right) \simeq D_0 \beta \frac{d^2 A}{dx^2}, \) and \( \ell^2 \left( \lambda^\pm_{ub} + \lambda^\pm_{ub} \right)/2 \simeq D_0 \) respectively. Using these expressions in Eq. (S6) we recover the continuum Fokker-Planck equation for the unbound state (Eq. (2b) in the main text),

\[
\frac{\partial P_{ub}(x,t)}{\partial t} = -k_{\text{on}} P_{ub}(x,t) + k_{\text{off}} P_b(x,t) + D_0 \beta \frac{\partial}{\partial x} P_{ub}(x,t) \frac{dA}{dx} + D_0 \frac{\partial^2 P_{ub}(x,t)}{\partial x^2} \\
= -k_{\text{on}} P_{ub} + k_{\text{off}} P_b + D_0 \frac{\partial}{\partial x} \left( e^{-\beta A(x)} \frac{\partial}{\partial x} e^{\beta A(x)} P_{ub}(x,t) \right).
\]

(S7)