Generic Transport Mechanisms for Molecular Traffic in Cellular Protrusions

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Transport of molecular motors along protein filaments in a half-closed geometry is a common feature of biologically relevant processes in cellular protrusions. Using a lattice-gas model we study how the interplay between active and diffusive transport and mass conservation leads to localized domain walls and tip localization of the motors. We identify a mechanism for task sharing between the active motors (maintaining a gradient) and the diffusive motion (transport to the tip), which ensures that energy consumption is low and motor exchange mostly happens at the tip. These features are attributed to strong nearest-neighbor correlations that lead to a strong reduction of active currents, which we calculate analytically using an exact moment identity, and might prove useful for the understanding of correlations and active transport also in more elaborate systems.

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Linear protrusions of cells, such as, for instance, filopodia or stereocilia, perform multiple tasks in living organisms, ranging from cell migration and signal transduction to wound healing. They contain actin filaments cross-linked into bundles by actin-binding proteins [1–4], and molecular motors of the myosin family which interact with actin filaments and walk on them in a persistent, unidirectional fashion towards the tip of the protrusion [3–9]. These motors play an important role in the biological function of protrusions [1,4,5]. In particular, they are known to localize to the tips of filopodia and stereocilia, and are (jointly) responsible for length control [2–12].

Motivated by these observations, various models have been investigated. Some are detailed mathematical models addressing specific biological issues. These include the role of motor transport in shaping the concentration profile of G-actin at the base of protrusions [13], the localization of different proteins along stereocilia [14], and the effect of myosin X on filopodial growth [15]. Complementary, simplified conceptual models have been studied asking how the interplay between active and diffusive transport in open systems may lead to nonequilibrium phase transitions and ensuing steady states with interesting correlations and nontrivial density profiles [16–20]. The latter are based on the totally asymmetric simple exclusion process (TASEP) [21,22], a lattice-gas model which, despite its simple structure, has become a paradigm for nonequilibrium dynamics [23,24].

Here we present and analyze a conceptual model capturing two basic properties of the motion of persistent,

plus-end directed motors inside narrow, elongated cellular protrusions. First, there is an interplay between two genuinely different types of dynamics: directed (active) transport with steric hindrance along actin filaments, and diffusive motion in the cytoplasm. These are coupled by particle exchange between the filament and the cytoplasm. Second, the half-closed geometry of cellular protrusions is special: At one end, the protrusions are connected to the cell body and thus to a reservoir, whereas everywhere else protein diffusion is confined by the cell membrane, so that mass conservation and resource limitation play an important role there. The combination of mass conservation (closure) on the one hand and the interplay of equilibrium (diffusion) and nonequilibrium (active transport) processes on the other hand is intrinsically interesting to study as closure in a system entails no-flux boundary conditions that oppose currents from active transport. Here, we want to examine the interplay of these mechanisms with the help of an abstract model that is motivated biologically but has a level of description that makes it possible to understand all the processes accounted for. We identify generic mechanisms based on correlations and nonequilibrium physics that could be of importance for biological systems as cellular protrusions but, inevitably, predictions for biological systems are qualitative.

Specifically, we consider a two-lane lattice-gas model in a half-closed geometry [Fig. 1] in steady state, similar to Ref. [25]. One lane represents the actin filament and the second lane the cytoplasm. While there is a rich literature on the nonequilibrium dynamics of two-lane systems [20,25–43], very few of these studies address how the physics of nonequilibrium steady states is affected by a half-closed geometry [25,42]. We are interested in the limit where the actin filament and the cytoplasm are coupled weakly by attachment and detachment processes, while

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FIG. 1. Illustration of the two-lane lattice-gas model comprised of a TASEP and a SSEP with hopping rates ν and ϵ , respectively. The lanes are coupled via a symmetric attachment and detachment rate $\omega \ll \nu$. In model A, detachment from the last site is given by $\beta \gg \omega$, while in model B exchange between the lanes is fully symmetric. At the tip of the systems mass conservation holds, and at the base particles can enter the SSEP lane at rate α and exit at rate ϵ .

Ref. [25] focuses on the strong coupling limit. Our analyses show that, due to the closure of the system at the tip, there is only one type of density profile, namely, domain walls (DW) separating a high- and a low-density region. The limit where the width of the high-density region becomes microscopically small (of the order of a few lattice sites) corresponds to tip localization. Furthermore, correlations in such systems have not received much attention, and we want to investigate nearest-neighbor (NN) correlations on the filament. In a biological context, this is related to efficient transport on actin filaments and to the significance of steric hindrance of motors there. We find that those correlations reach high values close to the DW, and the transport current along the filament is strongly reduced compared to its mean-field (MF) prediction. This suggests an important role for the cytoplasm, namely, to transport the proteins to the tip. Conversely, active transport effectively sets up and maintains a gradient of motor proteins.

Our model consists of two coupled sublattices [Fig. 1], namely, a TASEP and a SSEP (symmetric simple exclusion process) lane of $L + 1$ sites $\in \{0, 1, \dots, L\}$. The dynamics on lane 1 (TASEP) are governed by a rate ν at which particles jump forward one site towards the right (tip) provided that the site in front of them is empty (exclusion). This corresponds to the directional motion of the motors on the filament that is oriented towards the tip. By convention, we measure time in units of ν (i.e., set $\nu = 1$) and length in units of the system size (i.e., the lattice spacing is $a = 1/L$ and the total length $La = 1$). In lane 2 (SSEP) particles jump nondirectionally between neighboring sites, at rate ϵ again respecting exclusion. This represents the diffusive motion in the cytoplasm that is taken to be effectively one-dimensional in the thin cylinderlike protrusions (the steady-state behavior of a system with several lanes for diffusion arranged on a cylinder around the TASEP can be reduced to the steady-state behavior of this model [44]). Particles enter or exit the system only at site 0 of lane 2 (base) but not at site 0 of lane 1. At rate α a particle is injected provided the site is empty and at rate ϵ a particle leaves the system. This reflects the exchange of motors between the protrusion base and the cell body. In the bulk both lanes are coupled via a

rate ω at which particles jump from site $i \in \{0, 1, \dots, L - 1\}$ of lane 1 to site i of lane 2 or vice versa (each respecting exclusion). Since the biochemistry at the tip is only poorly understood, at site L we consider two extreme cases: In model A, particles jump from site L of lane 1 to site L of lane 2 at rate $\beta \gg \omega$ (respecting exclusion) but not in the opposite direction. This describes a scenario where motors at the tip detach mainly due to the lack of a filament subunit in front of them. In model B, the exchange rates between the lanes at sites L are the same as in the bulk. The comparison of both models stresses that seemingly minor changes in a nonequilibrium system may have a strong influence on the dynamics [45], and highlights the relevance of the biochemistry at the filament tip for the motor density profile. In the following, when considering the continuum limit $a \rightarrow 0$, we focus on the mesoscopic limit for ω [18,19]; i.e., we keep $\Omega = \omega/a$ fixed, thus ensuring the number of jumps between lanes is of the same order as that of entry or exit events (persistent motors) and implementing weak coupling between the diffusive and the directed motion. For simplicity, we take the attachment and detachment rates to be equal. However, the qualitative results do not change for different attachment and detachment rates $\omega_A \neq \omega_D$ as long as both are still taken in the mesoscopic limit (not shown here).

A single TASEP exhibits three phases, namely, a maximal current (MC), a low- (LD) and a high-density (HD) phase [16]. Moreover, on the phase boundary between the LD and HD phase the steady-state profile is given by a DW that performs a random walk. Because of the closure at the tip, we do not find a MC phase in our system [44], but instead observe *localized* DWs [17,18]. That is, the generic steady-state TASEP profile $\rho^T(x)$ for both models is given by a localized DW separating low density at the base from high density at the tip [Fig. 2]. For generic parameters, the filament current is thus comparatively small, and restricted to a small part of the system. This might be beneficial from a biological point of view,

FIG. 2. Representative steady-state DW profile $\rho^T(x)$ (left) with covariances $\text{Cov}(x)$ (right) on the TASEP lane are shown exemplarily for model A with $L = 50$, $\beta = 0.2$, $\Omega = 0.001$, $\alpha = 0.1$, and $\epsilon = 0.025$. The covariances are nonzero only in the vicinity of the DW. Using the fluctuation-corrected profile from DW theory, our predictions (dotted green curves) fit the simulation result (filled red circles) very well. If we use the refined MF profile (dot-dashed blue) instead of a step function (dashed black curve), the width of the DW and the strength of the covariances are strongly underestimated [44].

since every motor step on the filament consumes ATP. The position of the DW depends on the model parameters, and is shifted towards the tip (base) for smaller (higher) values of $\sigma := \alpha/(\alpha + \epsilon)$ [44]. This ratio can be thought of as the motor density in the cell body, and thus the value for the cytoplasmic density at the protrusion base. The width of the DW decreases with increasing L and with increasing distance from the tip [44]. Generically, when describing the DW as a random walker (see below), we observe that its motion is mainly confined to a small part of the system. Hence, we assume for the moment that the DW is fully localized and adopt a step-function ansatz for $\rho^T(x)$ that holds to lowest order in a : $\rho^T(x) = 0$ for $x \in [0, z[$, and $\rho^T(x) = 1$ for $x \in]z, 1]$. First, we determine the position z of the DW to find out whether tip localization (i.e., $z \approx 1$) occurs for certain parameter ranges or not. For this purpose we derive a mass-balance equation relating the total average occupancies of the TASEP (T) and the SSEP (S). We denote by n_i^μ the occupation number on site $i \in \{0, \dots, L\}$ of lane $\mu \in \{T, S\}$; i.e., we write $n_i^\mu = 0$ if site i of lane μ is empty and $n_i^\mu = 1$ if it is occupied. Since $n_i^\mu \in \{0, 1\}$, we have $\langle n_i^\mu \rangle = \text{Prob}\{n_i^\mu = 1\}$; ensemble averages are denoted by $\langle \cdot \rangle$. The steady-state condition in the bulk corresponds to a flux balance [44]: $(\rho_{i-1}^T - f_{i-1}) - (\rho_i^T - f_i) = \omega(\rho_i^T - \rho_i^S)$ with the correlator $f_i = \langle n_i^T n_{i+1}^T \rangle$ and the average occupancy $\rho_i^\mu = \langle n_i^\mu \rangle$. The difference of the TASEP currents, from site $i-1$ to site i and from site i to site $i+1$, (left-hand side) must equal the current between sites i of the TASEP and SSEP, $\omega(\langle n_i^T(1 - n_i^S) \rangle - \langle n_i^S(1 - n_i^T) \rangle)$, (right-hand side). It follows that $f_i = f_0 + \rho_i^T - \rho_0^T + \omega \sum_{j=1}^i (\rho_j^T - \rho_j^S)$. At the base, there is no direct flux from the cell body into the filament; so the boundary condition is $f_0 = \rho_0^T + \omega(\rho_0^T - \rho_0^S)$ and we find the following exact *moment identity*,

$$f_i = \rho_i^T + \omega \sum_{j=0}^i (\rho_j^T - \rho_j^S). \quad (1)$$

The systems are both closed at the tip but, due to the different attachment and detachment behavior, the boundary conditions read $f_{L-1} = \rho_{L-1}^T - \beta \langle n_L^T(1 - n_L^S) \rangle$, and $f_{L-1} = \rho_{L-1}^T + \omega(\rho_L^S - \rho_L^T)$ for models A and B, respectively. Combining these with Eq. (1), the following exact *mass-balance equations* can be derived for model A,

$$\omega \sum_{j=0}^{L-1} (\rho_j^T - \rho_j^S) = -\beta(\rho_L^T - \langle n_L^T n_L^S \rangle), \quad (2)$$

and similarly for model B, $\omega \sum_{j=0}^{L-1} (\rho_j^T - \rho_j^S) = 0$. These equations relate the average occupancy on the two lanes in such a way that the total influx into the TASEP lane equals the total outflux from it [46]. Interestingly, these equations reveal that a global detailed balance holds for the total exchange between the two lanes, rather than local detailed balance for any pair of sites (cf. adsorption equilibrium in

Ref. [25]). The moment identity and the mass-balance equations are useful in two ways: (i) By using the DW ansatz, we are able to find an analytic formula for the DW position; (ii) the moment identity enables us to express covariances with respect to NNs on the TASEP lane in terms of densities.

To address the first issue, we determine the average density $\rho^S(x)$ on the SSEP lane corresponding to the fully localized DW ansatz by solving the bulk equation for the SSEP. For that, we implement the continuum limit and, for model A, assume $\langle n_L^T n_L^S \rangle \approx \rho_L^T \rho_L^S$ [44]. Note, that we only need this MF approximation for the tip densities of model A. This is due to the otherwise symmetric attachment and detachment rates and the diffusive motion in the cytoplasm, for both of which the correlations drop out in the dynamical equation. With the resulting equation for $\rho^S(x)$ we can then conclude $z = 1 - l \cosh^{-1}[\sigma \cosh(1/l)]$ and $z = 1 - l \sinh^{-1}[\sigma \sinh(1/l)]$ for models A and B, respectively, where $l := \sqrt{D/\omega}$ with $D := \epsilon a^2$ being the diffusion constant in the cytoplasm [44]; l can be understood as the typical dwell length for motors in the cytoplasm before attaching to the filament. Comparing these expressions with our stochastic simulation results [47] we find excellent agreement [Fig. 3].

The phase diagrams for the two models are qualitatively different. For model A, one can switch between the DW phase ($z \ll 1$) and the tip-localization phase ($z \approx 1$) by only slightly increasing the dwell length l . In contrast, for model B, tip localization is attained only as $\sigma \rightarrow 0$, even for large l

FIG. 3. Phase diagrams for the DW position z (color-coded) for $L = 50$ and $\Omega = 0.001$ for model A (upper panel, $\beta = 0.2$) and model B (lower panel) as a function of the typical dwell length l in the cytoplasm and the cytoplasmic density at the protrusion base σ : the simulation results are shown on the left, the theoretical predictions for the DW position are shown on the right. The black thick lines in the diagrams for model A show the phase boundary $z = 1$ as obtained from theory. The dashed black lines in the diagrams obtained from theory are, from right to left respectively, contour lines of constant $z = 0.2, 0.4, 0.6$, and additionally, $z = 0.8$ for model B.

[44]. This can be understood from the symmetry between the attachment and detachment processes in model *B*, which should also be reflected in a symmetry in occupancy between the filament and the cytoplasm. For large l , the cytoplasm becomes well-mixed with constant density σ . So, the average density on the filament is σ as well, which is realized for a DW position $z = 1 - \sigma$. For model *A*, fast diffusion in the cytoplasm leads to rapid diffusion of the motors away from the tip. Therefore, the exit rate at the tip is high and motors quickly leave the tip of the filament, thus enabling tip localization but reducing large jamming. For small but finite σ , there is tip localization also if the typical dwell length is smaller than the system size, $l \leq 1$. That is, even if the motors have a relatively small D , tip localization can occur if the tip has an enhanced detachment rate (model *A*). For model *B*, even by increasing l well beyond the system size, tip localization occurs only for very low motor density σ at the base.

These features may have interesting biological implications: A higher detachment rate at the actin filament's end would promote tip localization, but simultaneously avoid jamming. As a result, motor exchange between filament and cytoplasm occurs primarily near the tip (where the DW is located) and the motors at the tip can be continuously replenished by new ones delivered through the cytoplasm. Furthermore, energy consumption (ATP hydrolysis) is low, as the filament current is kept small and mainly restricted to the tip area. Transport to the tip is facilitated mainly by diffusion in the cytoplasm, which does not consume chemical energy. In summary, energy from ATP hydrolysis could efficiently be used to localize motors to the filament tip, while material transport is facilitated by diffusion in the cytoplasm [44].

In this regard, the model is also interesting from a theoretical point of view, as it allows for the calculation of the filament current $J_i^T = \rho_i^T - f_i$ that depends on NN correlations or, equivalently, the NN covariances

$$\text{Cov}_i := \langle n_i^T n_{i+1}^T \rangle - \rho_i^T \rho_{i+1}^T = f_i - \rho_i^T \rho_{i+1}^T \quad (3)$$

on the TASEP lane. To go beyond MF, we use Eq. (1), which relates f_i to the average densities, and find $\text{Cov}_i = \rho_i^T(1 - \rho_{i+1}^T) + \omega \sum_{j=0}^i (\rho_j^T - \rho_j^S)$, which, in the continuum limit, translates to

$$\text{Cov}(x) = \rho^T(x)[1 - \rho^T(x+a)] + \Omega \int_0^x dy (\rho^T - \rho^S). \quad (4)$$

The value of the first term in Eq. (4) depends sensitively on the width and shape of the DW (the density profile $\rho^T(x)$ is increasing with x , so that $\rho^T(x)[1 - \rho^T(x+a)]$ is maximal if both $\rho^T(x)$ and $\rho^T(x+a)$ are close to 0.5). Therefore, one needs to refine the fully localized DW ansatz, by taking into account the stochastic dynamics of the DW position. Following Refs. [48,49] we consider the DW as a random walker with (site-dependent) hopping rates depending on

currents and densities in the low- and high-density regions. For small a we find

$$\rho^T(x) \approx \frac{\text{erf}[(x-z)/W(z)] + \text{erf}[z/W(z)]}{\text{erf}[(1-z)/W(z)] + \text{erf}[z/W(z)]}, \quad (5)$$

where $W(z) = \sqrt{2\sigma a l \sinh(z/l)}$ [44]. This fluctuation-corrected DW profile, as well as the covariance obtained from it, agree very well with our simulation data [Fig. 2]. If one uses a refined MF method instead, accounting for second-order spatial derivatives, the DW width and the strength of the correlations are both markedly underestimated [44].

In general, covariances are nonzero only close to the DW, but there they can reach quite high values of around 0.2. We have $\text{Cov}_i = \rho_i^T(1 - \rho_{i+1}^T) - J_i^T$, where the first term corresponding to the MF current dominates. Therefore, the actual current $J_i^T = \omega \sum_{j=0}^i (\rho_j^S - \rho_j^T)$ can be orders of magnitude smaller than the MF current, and scales with the particle exchange rate ω [44]. That is, density correlations dominate in such a way that they suppress the TASEP current substantially. This demonstrates that, even if basic properties of the single TASEP are captured well by MF theory, correlation effects in TASEP-based systems should be studied more closely and might lead to unanticipated features [50–52].

The covariances are non-negative everywhere, $\text{Cov}_i \geq 0$, so the conditional probabilities obey the inequalities $\text{Prob}\{n_i^T = 1 | n_{i+1}^T = 1\} \geq \text{Prob}\{n_i^T = 1\}$ and $\text{Prob}\{n_{i+1}^T = 1 | n_i^T = 1\} \geq \text{Prob}\{n_{i+1}^T = 1\}$ at any site, implying that particles typically form clusters. As a result, from the DW region onwards (where the covariances are highest), the mean time a particle spends at a certain site is increased considerably compared to freely moving motors. This is due to the effective jump rate on the filament, which is decreased by excluded-volume effects. Thus, in the case of tip localization, particles spend more time near the tip than in the main part of the filament. This prolongation of the residence time is further enhanced by the exclusion in the cytoplasm that prevents motors from detaching if the cytoplasmic tip density is high. This is especially important for model *A*, where the cytoplasmic tip density takes a value of ≈ 1 , which is much higher than in the bulk [44]. Biologically, the extended residence time at the tip might facilitate the tasks of the motors or their cargo at the tip.

Our results all essentially rely on the exact moment identity and the exact mass-balance equations. The derivation of both depends on the TASEP dynamics and the coupling between the two lanes, but not at all on the dynamics of the second (here SSEP) lane. Hence, those equations do not change if this dynamics on the second lane is modified, and we expect them to be useful for other model systems in which a TASEP lane is coupled to another lattice via attachment and detachment kinetics. To our best knowledge, the moment identity has not been

mentioned before. We believe that it might open doors in the understanding of correlations and the prediction of active currents also in more elaborate models. Furthermore, both equations could easily be generalized to the case of different attachment and detachment rates.

Our models could also be varied in other interesting ways. One could account for the three-dimensional geometry or for polymerization and depolymerization of the filament and the accompanying changes in length. Nevertheless, we expect that some of the phenomena seen here should be robust against such modifications. Tip localization, which is mostly based on mass conservation at the tip, should still be present. Second, the TASEP current might still be suppressed, and the roles of the TASEP and the diffusive lane in being responsible for tip localization and motor transport, respectively, should remain untouched. This seems to be supported by more elaborate models in a related context [13,15].

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