A general one-dimensional traffic model for motion of molecular motors on microtubules of variable length

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Abstract. We present a traffic model inspired by the motion of molecular motors along microtubules, represented by particles moving along a one-dimensional track of variable length. As the particles move unidirectionally along the track, several processes can occur: particles already on the track can move to the next open site, additional particles can attach at unoccupied sites, or particles on the track can detach. We study the model using mean-field theory and Monte Carlo simulations, with a focus on the steady-state properties and the time evolution of the particle density and particle currents. For a specific range of parameters, the model captures the microtubule instability observed experimentally and reported in the literature. This model is versatile and can be modified to represent traffic in a variety of biological systems.

1. Introduction

From the perspective of a physicist, the traffic of molecular motors represents an interesting non-equilibrium system directly amenable to analysis using methods of non-equilibrium statistical physics. In the past twenty years, the non-equilibrium physics community demonstrated an increased interest in modeling molecular motors using the driven lattice gas approach, with many studies using the totally-asymmetric exclusion process (TASEP) model as a paradigm [1, 2, 3, 4]. These models were studied using both computer simulation techniques and analytical means [5, 6]. A special interest was shown in describing the movements of molecular motors on cytoskeletal filaments as random walks on a track [7].

Most traffic models assume tracks with fixed length over time, but there are processes in nature for which these tracks have variable length. The most common example in biology is the traffic of molecular motors [8, 9] on cellular tracks called microtubules [10, 11]. In eukaryotic cells, microtubules are linear, polarized polymers that contribute to intracellular transport, cell motility, division and differentiation [10]. Microtubules are formed from the polymerization of alpha-beta tubulin dimers into thirteen linear protofilaments, which interact longitudinally to form a polarized cylinder. The positively charged alpha-tubulin end is more dynamic, where guanosine tri-phosphates (GTP) rapidly attach to form a GTP cap that regulates the polymerization of additional dimers. Conversely, GTP hydrolysis weakens the adjacent protofilaments’ affinity for new tubulin dimers, thus increasing the rate of depolymerization and shrinking the
microtubule. Influenced by microtubule-associated proteins, transitions between polymerization and depolymerization are referred to as dynamic instability [12, 13]. At an extreme state of instability, the removal of the stabilizing GTP cap results in rapid dissociation known as microtubule catastrophe [6].

We present a general, versatile model in which the motors travel along a one-dimensional track of variable length. The change in length captures microtubule instability and rescue, the transition between polymerization and depolymerization. Usually this process is caused by the loss of the GTP cap, but it is occasionally triggered by depolymerizing motors at the end of the microtubules, such as kinesins [12, 14]. In section 2, we introduce our general model in the context of the traffic of kinesin motors on microtubules. In section 3 we derive the mean-field equations for the model and discuss some of its features. In section 4 we present other possible applications and extensions of the model including the limitations of the mathematical techniques used in our work.

2. The model

Inspired by these complicated coupled dynamics of the motors motion and the microtubules, we define our model on a one-dimensional lattice of variable length (the microtubule) with \( N \) sites. \( N \) is not constant. Each site can be empty or occupied by a particle (the representation of our molecular motor) and is described by an occupation number \( n_i = 0 \) for empty and \( n_i = 1 \) for occupied. The right end is fixed (site \( N \)), and the left end (site 1) can extend, remain the same or contract. Following the same method as in [15, 16], we choose a reference frame attached to the growing tip of the filament, with site 1 being the leftmost site. Any site “\( i \)” measures the distance of that site from the fluctuating tip. When the lattice grows or shrinks due to the attachment or detachment of a new site at the tip, respectively, all the site labels are updated \( i \rightarrow i \pm 1 \).

Particles traffic flows from right to left. We assumed unidirectionality as a first approximation. Almost all kinesins undergo unidirectional motion, as interactions of polar structures between kinesins and microtubule subunits energetically favor the microtubule plus-end [17]. This phenomenon is not consistent through all molecular motors, evident by the bidirectionality of some fungal members of the Kinesin-5 subfamily and the dynein family of motors [18]. Consequently, this assumption of unidirectionality can be adapted to better represent other physical models.

The system evolves according to the following rules (depicted in Fig. 1):

At sites 1 and 2:

- \( 10 \rightarrow 00 \) with rate \( \beta \): particles leave the track with exit rate \( \beta \);
- \( 01 \rightarrow 10 \) with rate 1: particles move from right to left if the neighboring site is empty;
- \( 00 \rightarrow 000 \) with rate \( \gamma \): the length of the track increases by one unit when the two first sites are empty; this is equivalent to spontaneous polymerization of a microtubule;
- \( 11 \rightarrow 0 \) with rate \( \delta \): the length of the track decreases by one unit when two particles (occupying site 1 and 2) are present; at the same time, the particles leaves the track; this is equivalent to motor-induced depolymerization for a microtubule;

Two terminal tubulin dimers are depicted as unoccupied to demonstrate that spontaneous
polymerization is a motor-independent process made possible by stability provided by the GTP cap. The mechanism of the motors’ steps is electrostatically dependent on the tubulin dimers [19]. Consequently, during spontaneous polymerization, the presence of the GTP cap prevents motors from occupying terminal sites of the microtubule.

Depolymerization of the microtubule can occur due to the loss of the GTP cap (a motor-independent process) or from stimulation by depolymerizing motors (a motor-dependent process). In Fig. 1(c), we depict motor-induced depolymerization with the terminal sites of the microtubule occupied by depolymerizing motors. In the case of spontaneous depolymerization, (often referred to as catastrophe) the loss of tubulin subunits is attributed to instability from the loss of the GTP cap, not the presence of kinesins, and thus would occur with terminal sites vacant.

In bulk (sites $n_i = 3...N - 1$):

- $01 \rightarrow 10$ with rate 1: particles move to the left with rate 1 as long as the neighbor to the left is empty;
- $1 \rightarrow 0$ with rate $\omega_D$: if site is occupied, remove particle with rate $\omega_D$;
- $0 \rightarrow 1$ with rate $\omega_A$: if site is empty, add particle with rate $\omega_A$;

At site N:

- $00 \rightarrow 01$ with rate $\alpha$: particles enter the track with entrance rate $\alpha$;
- $01 \rightarrow 10$ with rate 1: diffusion to the left with rate 1;

3. Mean-field analysis and Monte Carlo results

We present below the evolution equations for the site occupation numbers. For boundary sites 1, 2, 3 and N the equations are:

$$\frac{dn_1}{dt} = -\beta n_1(1 - n_2) + n_2(1 - n_1) - \delta n_1 n_2 \quad (1)$$
$$\frac{dn_2}{dt} = n_3(1 - n_2) - n_2(1 - n_1) - \delta n_1 n_2 + \delta n_1 n_2 n_3$$
$$\frac{dn_3}{dt} = n_4(1 - n_3) - n_3(1 - n_2) - \omega_D n_3 + \omega_A (1 - n_3) - \gamma (1 - n_1)(1 - n_2)n_3 + \delta n_1 n_2 (n_4 - n_3)$$
$$\frac{dn_N}{dt} = \alpha (1 - n_N) - n_N (1 - n_{N-1})$$

The evolution of occupation of sites “1” and “2” in time is dictated by the exit of particles with rate $\beta$, the diffusion of particles from site “2” into site “1” with rate 1, the spontaneous polymerization of the microtubule with rate $\gamma$ and the motor-induced depolymerization of the tubule with rate $\delta$. For example, if both sites (1 and 2) are occupied, the microtubule may shrink due to depolymerization, with the loss of both sites reflected in the “–” sign of the $\delta$ terms. Similarly, the $\gamma$ term in the evolution equation for site 3 captures the spontaneous polymerization of the microtubule if the first two sites are empty. In this case, site “3” becomes site
And for the bulk sites, $n_i = 4...N - 1$:

$$\frac{dn_i}{dt} = n_{i+1}(1-n_i)-n_i(1-n_{i-1})+\gamma (1-n_1)(1-n_2)(n_{i-1}-n_i)+\delta n_1n_2(n_{i+1}-n_i)+\omega_D n_i+\omega_A (1-n_i)$$

(2)

In the bulk the additional processes considered are the attachment and detachment of particles with rates $\omega_A$ and $\omega_D$, according to Langmuir dynamics.
In analyzing these equations we are using the mean-field method presented in [15, 16, 20, 21]. We start by defining the mean local densities as the mean ensemble values of the site occupation numbers $\rho_i = < n_i >$ and replacing the mean correlations between site occupation numbers with the product of their averages: $< n_i n_j > = \rho_i \rho_j$. With these assumptions in mind, the equations above become:

\[
\begin{align*}
\frac{d\rho_1}{dt} &= -\beta \rho_1 (1 - \rho_2) + \rho_2 (1 - \rho_1) - \delta \rho_1 \rho_2 \\
\frac{d\rho_2}{dt} &= \rho_3 (1 - \rho_2) - \rho_2 (1 - \rho_1) - \delta \rho_1 \rho_2 + \delta \rho_1 \rho_2 \rho_3 \\
\frac{d\rho_3}{dt} &= \rho_4 (1 - \rho_3) - \rho_3 (1 - \rho_2) - \omega_D \rho_3 + \omega_A (1 - \rho_3) - \gamma (1 - \rho_1) (1 - \rho_2) \rho_3 + \delta \rho_1 \rho_2 (\rho_4 - \rho_3)
\end{align*}
\]  

The evolution equation for site $N$ is:

\[
\frac{d\rho_N}{dt} = \alpha (1 - \rho_N) - \rho_N (1 - \rho_{N-1})
\]  

And for the bulk sites, $n_i = 4...N - 1$:

\[
\frac{d\rho_i}{dt} = \rho_{i+1} (1 - \rho_i) - \rho_i (1 - \rho_{i-1}) + \gamma (1 - \rho_1) (1 - \rho_2) (\rho_{i-1} - \rho_i) + \delta \rho_1 \rho_2 (\rho_{i+1} - \rho_i) - \omega_D \rho_i + \omega_A (1 - \rho_i)
\]

In order to extract information about the system’s behavior, we study the system in the thermodynamic limit, $N \to \infty$. Based on the Monte Carlo simulation results that we will discuss later in the paper, it is worth noting that the system is mostly in a growth phase, unless the shrink rate $\delta > 0.1$. Sites 1, 2 and 3 are the sites affected by the particle dynamics at the fluctuating tip. The approximation $\rho_4 = \rho_3$ serves two purposes: it permits an analytical solution for the four densities ($\rho_1$, $\rho_2$, and $\rho_3 = \rho_4$) by closing the system of equations and it also captures the behavior of the system in the thermodynamic limit of $N \to \infty$, when the bulk phase adjoining the fluctuating tip is a high-density phase. The analytical expressions for $\rho_1$, $\rho_2$, and $\rho_3 = \rho_4$ are too complicated to report here, so we will continue our analysis using these symbols as placeholders for densities obtained numerically for specific sets of parameters.

To obtain a continuous equation for the bulk density ($n_i = 4...N - 1$) we follow the standard method presented in [3, 20]. We define the following variables: $\epsilon = \frac{L}{x}$, the spacing of the lattice given the length of the lattice $L$ and the number of sites $N$; and $x = \frac{L}{\xi}$, which measures the relative position of the particle in the variable lattice (measured with respect to the left end). The lattice length and the number of lattice sites increase or decrease due to the polymerization/depolymerization processes which occurs at tip of the filament (the left end) in such a way that their ratio $\epsilon$ remains constant. We also introduce the reduced rates, $\Omega_A = N \omega_A$ and $\Omega_D = N \omega_D$ as the total bulk attachment and detachment rates of particles for the entire system. We use the series approximation: $\rho(x \pm \epsilon) = \rho(x) \pm \epsilon \partial_x \rho(x) \pm \frac{1}{2} \epsilon^2 \partial_x^2 \rho(x) + O(\epsilon^3)$ and will keep just the two first terms in the series.
The continuous expression of Eq. 5 for the steady state becomes:

\[(C - 2\rho(x)) \left( \frac{d\rho(x)}{dx} \right) - (\Omega_A + \Omega_D)\rho(x) + \Omega_A = 0\] (6)

where \(C = \gamma(1 - \rho_2)(\rho_1 - 1) + \delta\rho_1\rho_2 + 1\). This constant will have a numerical value for every set of parameters.

This equation can be rewritten as a continuity equation:

\[\frac{dJ(x)}{dx} - (\Omega_A + \Omega_D)\rho(x) + \Omega_A = 0 \] (7)

where the particle current is defined as \(J(x) = \rho(C - \rho)\).

The continuous version of the evolution equation for the fixed tip (re-scaled as \(x = 1\) with the approximation \(N - 1 \approx N\) in the thermodynamic limit) is:

\[\frac{d\rho(1)}{dt} = \alpha(1 - \rho(1)) - \rho(1)(1 - \rho(1)) \] (8)

We now study in more detail the general equation for the bulk density in the steady-state case, Eq. 6. With the notations: \(u(x) = C - 2\rho(x)\) and \(\Omega = \Omega_A + \Omega_D\), the equation becomes:

\[u(x) \left( \frac{du(x)}{dx} - \Omega \right) = 2\Omega_A - \Omega C\] (9)

If we introduce the extra constraint \(2\Omega_A - \Omega C = 0\), the equation above leads to solutions similar to the ones presented in [20]. The correction due to variation in length represented by \(\delta\) and \(\gamma\) affects the bulk density, which is still a constant for a given set of parameters.

\[\rho(x) = \begin{cases} 
\Omega x + \rho_3 & \text{if } 0 \leq x \leq x_{left} \\
\frac{\gamma(1-\rho_2)(\rho_1-1)+\delta\rho_1\rho_2+1}{2} & \text{if } x_{left} \leq x \leq x_{right} \\
\Omega(x-1) + \alpha & \text{if } x_{right} \leq x \leq 1 
\end{cases} \] (10)

And for the steady-state current:

\[J(x) = \begin{cases} 
(\Omega x + \rho_3)(C - \Omega x - \rho_3) & \text{if } 0 \leq x \leq x_{left} \\
\frac{(\gamma(1-\rho_2)(\rho_1-1)+\delta\rho_1\rho_2+1)^2}{4} & \text{if } x_{left} \leq x \leq x_{right} \\
(\Omega(x-1) + \alpha)(C - \Omega(x-1) - \alpha) & \text{if } x_{right} \leq x \leq 1 
\end{cases} \] (11)

A specific set of parameters for which the extra constraint \(2\Omega_A - \Omega C = 0\) is obeyed is: \(\beta = 0.5, \delta = 0.5, \alpha = 0.5, \Omega_A = \Omega_D = 0.5, \gamma = 0.25\). The mean-field predicts the following numerical values: \(\rho_1 = 0.439, \rho_2 = 0.392, \rho_3 = 0.440\) and \(\rho_{bulk} = 0.5\). The \(x_{left}\) and \(x_{right}\) boundaries are found by equating the left and the bulk solutions and the right and the bulk solutions. These boundaries will change with the change of the parameters. For this special case, \(x_{left} = 0.06\) and \(x_{right} = 1\), which means that the bulk solution for the density is a good
approximation for the whole system. Because of the multitude of parameters, building a phase
diagram for the general case becomes a messy endeavor. Reference [20] is a good resource that
outlines the steps one needs to follow in order to identify the regions of high and low density, the
maximum current phase and the position of the domain walls (found by matching $J_{\text{left}} = J_{\text{right}}$).
We would like to emphasize, however, that due to the effect of correlations between sites at the
tip of the microtubule, the mean-field solutions are able to qualitatively match the Monte Carlo
solutions only for specific cases.

The Monte Carlo simulations for densities and currents are presented in Fig. 2 for the two
cases of systems with and without parameters obeying the constraint. We can see from the plots
that the behavior of the system is very different for the two situations. When the constraint is
obeyed, the system is in a growing regime, as opposed to a switch between growth and shrinkage
as seen in Fig. 2(e).

If we don’t introduce the extra constraint $2\Omega_A - \Omega C = 0$, we solve the general equation using
separation of variables methods. The integration of this equation leads to:

$$\frac{K \ln(K - \Omega u(x)) + \Omega u(x)}{\Omega^2} = (x - x_b)$$

with the new constant $K = \Omega C - 2\Omega A$.

In a more compact form, the solution can be reported using LambertW special function:

$$u(x) = -\frac{K}{\omega} \left( \text{LambertW} \left( -\frac{1}{K} e^{-1 - \frac{\kappa x^2}{K}} \frac{x^2}{\kappa} \right) + 1 \right)$$

where $K_1$ is a new constant of integration found by matching the boundary conditions. This
leads to a solution for $\rho(x)$:

$$\rho(x) = \frac{1}{2} \left( C + \frac{K}{\omega} \left( \text{LambertW} \left( -\frac{1}{K} e^{-1 - \frac{\kappa x^2}{K}} \frac{x^2}{\kappa} \right) + 1 \right) \right)$$

Although we have a somewhat qualitative agreement between simulations and mean-field theory
for the general case with the constraint in place, the mean-field theory fails to capture the
intricacies of the model dynamics when the constraint is lifted, as seen in Fig. 2.

4. Conclusions

We presented a versatile traffic model on dynamic tracks motivated by the motion of molecular
motors on microtubules of variable length. The model captures the interplay between polymer-
ization and depolymerization of the microtubule, consistent with the microtubule instability
observed in lab experiments [13, 22]. The model can be adapted to a particular motor (such
as Kinesin-8 or Kinesin-13), but is general enough to be applied to other physical systems. We
also see value in studying this model as an abstract non-equilibrium statistical physics model
that can shed light on the new features of a traffic model defined on dynamic tracks.

From a theoretical point of view, the model is rich in its dynamics and can lead to more
in-depth studies of its special cases or extensions. We used the mean field and hydrodynamics
approach to study it analytically, and compared our results to the Monte Carlo simulations
Figure 2: General case. Sample Monte Carlo results for the case of $\gamma \neq \delta \neq 0$ and $\omega_D \neq 0$, $\omega_A \neq 0$, initial length $N = 100$ and maximum number of 700 sites. (a) average density along the track; (b) average current along the track; (c) the time evolution of the total density; (d) the time evolution of the total current; (e) the time evolution of the length.
with various degrees of success. Due to the high correlation effects between the sites at the tip of the microtubule that trigger the change in length, the mean-field approach worked for only a few cases, when the microtubule can be easily approximated as being constant in length. For other sets of parameters, the mean-field theory fails, and other analysis methods need to be explored. The first step in addressing the shortcomings of the mean-field theory is to include particle correlations into the equations, starting with two and three point correlations for the boundary sites. Another avenue of study may be a kinetic approach to small-size systems by solving numerically the governing master equation.

With a few exceptions (for example [15], [16], and others), traditional TASEP studies for motion of molecular motors on microtubules consider the track as fixed in length. The value of our paper is in considering three competing processes that occur at the biological level: (1) the track variable in length due to both growth and shrinkage; (2) TASEP dynamics; (3) Langmuir dynamics. We hope this study can be useful for biologists and biophysicists working in the molecular motors field. We also hope that this is an interesting enough non-equilibrium statistical physics model worthy of further studies and extensions to other physical systems.

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