Tug of war of molecular motors: the effects of uneven load sharing

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Abstract

We analyze theoretically the problem of cargo transport along microtubules by motors of two species with opposite polarities. We consider two different one-dimensional models previously developed in the literature: a quite widespread model which assumes equal force sharing, here referred to as the mean field model (MFM), and a stochastic model (SM) which considers individual motor–cargo links. We find that in generic situations, the MFM predicts larger cargo mean velocity, smaller mean run time and less frequent reversions than the SM. These phenomena are found to be the consequences of the load sharing assumptions and can be interpreted in terms of the probabilities of the different motility states. We also explore the influence of the viscosity in both models and the role of the stiffness of the motor–cargo links within the SM. Our results show that the mean cargo velocity is independent of the stiffness, while the mean run time decreases with such a parameter. We explore the case of symmetric forward and backward motors considering kinesin-1 parameters, and the problem of transport by kinesin-1 and cytoplasmic dyneins considering two different sets of parameters previously proposed for dyneins.

1. Introduction

Transport of cargo driven by multiple molecular motors along microtubules has become a very active subject of research because of its relevance for many cellular functions [1–4]. In recent years, a myriad of experiments and models have attempted to understand the way in which motors work together [4–9] and, still, there are many fundamental details which remain unclear and deserve further research, most particularly for the case of bidirectional transport by two motor species.

The complexity of the multiple motor systems and the difficulties for controlling the experiments are often quite important so that the connection between models and experiments must be performed carefully. Models always involve many parameters, including for instance detachment and attachment rates, stall forces, motor stiffness and viscosity of the media. Usually, many of these parameters are \textit{a priori} not well known in the experiments, and even more fundamental features, such as the number of motors, or whether more than a single species is participating on the transport, remain unclear. Thus, distinct models may provide different fitting of the experimental data and, consequently, different interpretations. Moreover, recent \textit{in vivo} experiments [10] have revealed important differences with \textit{in vitro} systems. In this context, detailed knowledge of the consequences of specific modeling assumptions as well as the comparison of different kinds of models becomes quite relevant. The aim of this paper is to contribute to these two important aspects.

The research carried out in [11] and [12] originated a modeling framework that has largely contributed to the understanding of transport by several motors. The model introduced in [11] deals with cargo transport by a single class of motors, while in [12] the formalism is extended to account for bidirectional transport associated with tug of war between two motor types with opposite polarities. Assuming certain force–velocity relations, and specific attachment and detachment probabilities for individual motors, the model enables the calculation of the probabilities of different motility states characterized by a different number of motors, and
the reproduction of trajectories and velocity distributions as well. In a series of papers [7, 13–15], the model was further developed and several effects and transport conditions have been analyzed, providing a deep physical insight into the problem. An important assumption of the model is that all the motors of the same polarity simultaneously engaged in the microtubule share the load equally. In real systems, however, fluctuations of the distances between motor–microtubule binding position and motor–cargo binding position may lead to non-negligible differences between the forces supported by the different motors [8, 16–18]. Consequently, the model would eventually fail to predict exact quantitative results. In [17], the model was referred to as mean field due to the equal sharing of load approximation. We will keep such a name throughout this work.

Several models have gone beyond the mean field approach by considering independent motor–cargo links for each motor, and incorporating different degree of detail in their description of individual motor properties [8, 9, 17, 19, 20]. Although such models generally provide less instrumental (and less elegant) formulations than the mean field model (MFM), and they mostly lack analytical results, they may be more successful in predicting numerical results for multiple motors through simulations based on individual motor parameters. In a different but related context, models in [21] and [22] consider the load applied only to the leading motor and constitute thus interesting extreme examples of models beyond mean field. Although not directly connected to our approach for processive motors on microtubules, studies on non-processive motors [23, 24] and general ratchet models [25] also provide relevant analysis of bidirectional motion in many motor systems.

In this paper, we investigate bidirectional cargo transport by two opposing teams of processive motors within two different models: the mean field model (MFM) and a recently introduced [19] stochastic model (SM) which considers independent cargo–motor links for individual motors, allowing for uneven load sharing. In this way, at the same time when we investigate how cargo transport depends on the system parameters, we are able to clearly identify the consequences of the assumption of equal load sharing. Our work follows the spirit of the paper by Kunwar and Mogilner [17]. They compared results from both kinds of models focussing on the case of cargo transport by a single team of motors, and provided also an analysis of the velocity distributions for bidirectional transport. Moreover, they studied the influence of the nonlinearities of the force–velocity relations of individual motors.

Our studies focus on analyzing the dependence of cargo transport on the number of motors of each polarity, the viscous drag and the stiffness of the motor–cargo link, while we do not consider the influence of additional load forces acting on the cargo. In section 2, we present the models. Section 3 studies the case of equal forward and backward motors. The effects of varying the number of motors to each side and the influence of viscous drag are analyzed within both models. In section 4, we present results for bidirectional transport by asymmetric motors considering system parameters compatible with kinesin-1 and cytoplasmic dynein. Section 5 is devoted to the conclusions.

2. Models and methods

As introduced in the introduction, we will consider two different models for the analysis of cargo transport by multiple motors: the MFM and our recently proposed SM. We first introduce the characteristics that are common to both.

The two models consider the cargo as a point particle which performs a continuous trajectory $x(t)$ in one dimension. The cargo is linked to $N_f$ forward motors and $N_b$ backward motors. The first of them can pull the cargo in the positive direction, while the second can pull it in the negative one. At a given time, the numbers of forward and backward motors engaged in the microtubule are respectively $n_f(t) \leq N_f$ and $n_b(t) \leq N_b$. Each engaged motor $i$ detaches from the microtubule with a probability per time unit given by $\epsilon \exp(|f_i|/F_0)$. Here $f_i$ is the instantaneous force exerted by the motor $i$ on the cargo. $\epsilon$ is the reference zero-load detachment rate and $F_0 > 0$ is the detachment force. We will call $\epsilon_f, \epsilon_b, F_{df}$ and $F_{db}$ the corresponding parameters for forward and backward motors. Conversely, a detached motor engages in the microtubule with the rate $\Pi_f$ or $\Pi_b$, according to its type.

When loaded with a force $f_i > 0$ (considered positive if exerted against the polarity of the motor), the motor $i$ advances with velocity

$$v_i = \begin{cases} v_0(1 - f_i/F_s) & \text{for } f_i \leq F_s \\ v_1(1 - f_i/F_s) & \text{for } f_i > F_s. \end{cases}$$

Here $F_s > 0$ is the stall force, $v_0$ is the zero-load velocity and $v_1$ is a reference backward velocity. Considering both motor species, we have the system parameters $F_{sf}, F_{sb}, v_{0f}, v_{0b}, v_{1f}$ and $v_{1b}$. The linear force–velocity relation for single motors of equation (1) is a natural choice for comparing the SM and MFM since it is used in most works on the MFM [7, 12, 13] and is also a common assumption in other theoretical models [17, 26, 27]. Studies in [17] suggest that the consideration of general nonlinear relations would lead to no relevant qualitative changes in the results. It is important to mention that, while equation (1) is taken as instantaneously exact in the MFM, within the SM it is only valid in terms of time averages, i.e. $v_1$ is the mean velocity of a motor subject to a constant force $f_i$.

The way to compute the forces $f_i$ and the cargo motion depends on the model as we explain in the following subsections.

2.1. Cargo dynamics in the MFM

The MFM [12] assumes that all the motors (backward and forward) move with the same velocity than the cargo at any time, and that motors of the same polarity share the force equally. It also assumes that the total force acting on the cargo vanishes at almost any time (it has discontinuities at the times at which the number of engaged motors changes). With such hypotheses, by performing a force balance and using the force–velocity relation for single motors of equation (1), it is possible to obtain the cargo velocity as a function of the numbers of engaged motors $n_f$ and $n_b$ [12]. We thus have a discrete set of allowed cargo velocities.
Langevin equation for the cargo is
\[ \gamma_x = \sum_i f_i + \xi(t). \]
Here \( \gamma \) is the viscous drag, \( f_i \) (\( i = 1, \ldots, N = N_f + N_b \)) is the force exerted by the \( i \)th motor and \( \xi(t) \) is the white thermal noise. The viscous drag is defined through the Stokes relation \( \gamma = 6\pi r \eta \) [8, 17], where \( \eta \) is the viscosity of the medium and \( r \) is the radius of the cargo for which we consider \( r = 500 \text{ nm} \) throughout the paper. The thermal noise satisfies \( \langle \xi(t) \rangle = 0 \) and the correlation formula \( \langle \xi(t_1)\xi(t_2) \rangle = 2D\delta(t_1 - t_2) \) [29]. Here \( \langle \rangle \) represents ensemble average, \( \delta(t) \) is the Dirac delta and \( D \) the diffusion coefficient satisfying the fluctuation–dissipation relation \( D = k_B T / \gamma \) [29], with \( k_B \) the Boltzmann constant and \( T \) the temperature. In all our calculations, we consider \( T = 300 \text{ K} \).

Each motor is modeled as a particle that can occupy discrete positions separated by \( \Delta x = 8 \text{ nm} \) along the same spatial coordinate used for the cargo. Its dynamics is governed by a Monte Carlo algorithm [19] that rules the elementary processes of step forward, step back, detachment and attachment. At each time step of duration \( \delta t \), an engaged forward motor has a probability \( P_{\text{jump}} = \delta t / \tau_D(F) \) of performing an 8 nm step, which may be forward (right) with probability \( P_r(F) = [R(F)/(1 + R(F))] \) or backward (left) with probability \( P_l(F) = [1/(1 + R(F))] \). Here \( \tau_D(F) \) is the dwell time [30, 31] and \( R(F) \) is the forward–backward ratio of jumps [30–32]. The resulting mean velocity for a single forward motor with constant load \( F \) is \( \langle v(F) \rangle = \Delta x (P_r(F) - P_l(F)) / \tau_D(F) \). In [19], the model was developed assuming certain specific formulas for \( F \) and \( \tau_D(F) \) based on experimental data for kinesins-1, while \( \langle v(F) \rangle \) was left free.

Here, in order to compare results with the MFM, we consider \( \langle v(F) \rangle \) as a known relation instead of \( \tau_D(F) \). Then, the value of \( \tau_D(F) \) entering into the algorithm is determined by inverting the corresponding formulas. We consider the formula \( R(F) = A \exp(-\log(A)|F|/F_s) \), based on the experiments in [30–32], with \( A = 1000 \) and \( F_s \) the above-mentioned single motor stall force that leads to \( F_r = F_l \). For the backward motors, we consider the same single motor model but interchanging right and left. The forces \( f_i \) are computed assuming that the cargo is linked to each motor by a nonlinear spring [8, 17] which produces only attractive interactions, and only for distances larger than a critical one. Let us call \( x \) the position of the motor \( i \) and \( \Delta_i = x_i - x_\text{c} \). We define \( f_i = k(\Delta_i - x_0) \) for \( \Delta_i \geq x_0 \), \( f_i = 0 \) for \( -x_0 < \Delta_i < x_0 \) and \( f_i = k(\Delta_i + x_0) \) for \( \Delta_i \leq -x_0 \), with \( x_0 = 110 \text{ nm} \) [8, 17]. Here, \( k \) is the stiffness of the motor for which we consider the values \( k_f \) and \( k_b \) for forward and backward motors, respectively. Note that while in [19] we have included volume excluded interaction between motors, here we consider only interactions mediated through the cargo.

The detachment and attachment processes occur according to the probabilities per time unit indicated at the beginning of this section. The attachment of detached motors occurs with equal probability in any of the discrete sites \( x_j \) satisfying \( |x_j - x_\text{c}| < x_0 \).

### 2.3. Relevant quantities and numerical simulations

We study the cargo dynamics within the MFM and SM by performing numerical simulations of the evolution of the system for different values of the parameters. As an initial condition (at time \( t_{\text{ini}} = 0 \)), we consider a random number of motors of each species engaged in the microtubule. Each realization finishes when all the motors are detached (at the time referred to as \( t_{\text{end}} \)). The numerical simulations of the SM are performed as explained in [19] using time steps between \( \delta t = 2 \times 10^{-5} \) and \( \delta t = 3 \times 10^{-7} \) s depending on the value of \( \gamma \). For the MFM, we use our implementation of the Gillespie algorithm explained in [12, 28].

In order to characterize the long-time properties of cargo dynamics, we compute the following quantities.

- **Cargo mean velocity.** Defined as the average over realizations of the ratio \( (x_{\text{end}} - x_{\text{ini}}) / (t_{\text{end}} - t_{\text{ini}}) \).
- **Run length.** Defined as the average over realizations of \( (x_{\text{end}} - x_{\text{ini}}) \).
- **Run time.** Denoted as \( t_r \), equal to the average of \( (t_{\text{end}} - t_{\text{ini}}) \).

Concerning the analysis of the dynamical properties during forward and backward stages of the motion, we compute the **mean forward run length** (\( r_f \)) and the **mean backward run length** (\( r_b \)). We define them as the average...
Figure 1. Trajectories. (a) Typical cargo and motors trajectories for the SM considering \(N_f = 2\), \(N_b = 1\). (b) Cargo trajectories for \(N_f = N_b = 2\) for the SM and MFM. (c) Several different cargo trajectories for \(N_f = 3\) and \(N_b = 2\) for the SM. (d) Same as (c) but for the MFM. In all the cases, the viscosity considered is 100 times the water viscosity.

3. Results for symmetric motors

First we analyze the results for both models considering equal parameters for forward and backward motors. For shortness, we speak of equal or symmetric motors. Except when specially stated, we consider single motor parameters compatible with kinesin-1 [12] for both models: \(F_s = 6\) pN, \(v_0 = 1000\) nm s\(^{-1}\), \(v_1 = 6\) nm s\(^{-1}\), \(\epsilon = 1\) s, \(F_d = 3.18\) pN and \(\Pi_T = 5\) s. We left the numbers of motors \(N_f\) and \(N_b\) and the viscosity as free parameters. For the SM, except when indicated, we consider the parameter \(k = 0.32\) pN nm\(^{-1}\) usually taken as a reference value for kinesin-1 [17].

3.1. Trajectories

As a first step in our study, we glance at the trajectories within both models. Figure 1(a) shows cargo and motor trajectories for a system with \(N_f = 2\) and \(N_b = 1\) computed using the SM. Regions of tug of war leading to pauses and reversions of the cargo motion can be appreciated. In figure 1(b), we show MFM and SM cargo trajectories for \(N_f = N_b = 2\). At a first glance, we see that both models produce similar trajectories for such parameters. Thus, we can expect that this may lead to compatible results for ensemble averaged quantities. In contrast, results in figures 1(c) and (d) indicate us that, in the case \(N_f = 3\), \(N_b = 2\), both models predict very different results even at the level of single trajectories. Thus, depending on the parameters we may expect that the two models give results which may or may not be statistically equivalent.

3.2. Results for negligible viscous drag

Now we begin our systematic analysis of both models focussing on the behavior of the cargo mean velocity, run length and run time. We analyze first the dynamics for negligible viscous drag. To do so, we consider the MFM without viscous drag [12], and the SM with a very small value...
of $\gamma$, so that the system is essentially at the zero viscosity limit. Actually, we use $\gamma = 9.42 \times 10^{-6}$ pNs nm$^{-1}$, calculated using the Stokes formula [8, 17] with water viscosity and a radius of the cargo equal to 0.5 $\mu$m. Note that for such a value of $\gamma$, even if we consider a fast cargo velocity of $10^3$ nm s$^{-1}$, we obtain a viscous drag of order $10^{-2}$ pN which is quite small compared to the typical forces on the scale of 1 pN involved in motor dynamics.

In figure 2, we study the case of a single species of motors considered with forward polarity. We plot the run length and the velocity as functions of the number of motors. The results are already well known from a number of previous works: the velocity is independent of the number of motors (for negligible viscosity), while the run length grows exponentially. Our contribution here is to show that both models agree in their numerical results. As the analysis of single trajectories suggest and we will shortly confirm, this is not always the case when we consider two species of motors.

In figure 3(a), we show results for the cargo velocity as a function of the number of backward motors $N_b$ for fixed $N_f = 3$ in the symmetrical case. It can be seen that both models coincide only for $N_b = 0$ and $N_b = N_f$, while for the intermediate values of $N_b$, the MFM predicts considerably larger velocities. These differences are a consequence of the load sharing hypothesis. Note that, while in the MFM all engaged motors contribute equally to pulling the cargo, in the SM only those motors which are instantaneously beyond the limit distance $x_0$ from the cargo exert non-vanishing forces. Hence, each of such pulling motors is more loaded than motors in the MFM and, thus, their velocity is smaller. Clearly, this causes a smaller cargo velocity, since cargo velocity is essentially controlled by such leading motors. It is interesting to realize that for the SM we obtain the simple linear behavior $v = v_{0_f}(N_f - N_b)/N_f$, regardless of the value of the motor stiffness $k$. This demonstrates a certain degree of robustness of the motor team performance independently of the stalk stiffness. However, as we will see, other relevant quantities do depend on $k$. In figure 3(b), we show the run time $\tau_r$ as a function of $N_b$ for the same system as in figure 3(a). We see that, within the SM, $\tau_r$ increases with $N_b$ and decreases with $k$. Except for vanishing $N_b$, the SM predicts sensibly larger values of $\tau_r$ than the MFM. Note that, while the cargo velocity is controlled by the pulling motors, the run time is expected to be essentially determined by the total number of engaged motors, regardless of its polarity. This is because forward and backward motors contribute equally to linking the cargo to the microtubule (at least for symmetric motors). The relevance of differentiating between engaged and pulling motors was discussed in [19] when analyzing transport by a single species against an external load. The relation between the run time and the total number of engaged motors becomes evident with the results in figure 3(c), where we show the mean number of engaged motors as a function of $N_b$ for the same systems in figures 3(a) and (b). The parallelism between curves in figures 3(b) and (c) is apparent. The total number of engaged motors increases with $N_b$, decreases when passing from the MFM to SM and decreases with $k$ within the SM. The causes of these behaviors will be explained later when studying the probabilities of the different motility states. In figure 3(d), we show the run length as a function of $N_b$ for the same parameters as those in figures 3(a) and (b). As expected, the run length decreases with $N_b$ in both models following the decrease of the mean velocity. Within the SM, the decrease of the run length with $k$ can be associated with that of the run time and to the invariance of the mean velocity. This seems compatible with a factorization of the mean values. Interestingly, the results for the MFM are similar to those for the SM with $k = 0.32$ pN nm$^{-1}$. However, this seems to be due to a compensation between the decrease of the velocity and the increase of $\tau_r$ when passing from the MFM to the SM.

Now we study the probabilities of the different states $(n_f, n_b)$ for fixed $N_f$ and $N_b$. This is relevant for finding out to what extent forward and backward motors coexist linked to the microtubule, and for evaluating the mean number of engaged motors. Let us take the case $N_f = 3$, $N_b = 1$ with $k = 0.32$ pN nm$^{-1}$ as an example. Figures 4(a) and (b) show the probabilities of the different states $(n_f, n_b)$ for the SM and MFM, respectively. Note that the state $n_f = n_b = 0$ has null probability as it determines the end of the simulation. The results clearly indicate that the states with one engaged backward motor are much more likely in the SM than in the MFM. Note that for the MFM, the states with $n_b = 0$ accumulate around an 85% of the probability. This means that the backward motor is detached most of the time. In particular, the states $(3, 0)$ and $(2, 0)$ alone dominate the dynamics an 80% of the time. In contrast, the SM predicts that the backward motor will be essentially half of the time engaged in the microtubule. Moreover, the probabilities for the states $(3, 0)$, $(3, 1)$, $(2, 0)$ and $(2, 1)$ are all similar to each other. States with the backward motor engaged are more likely in the SM than in the MFM due to the fact that, within the SM, the backward motor is unloaded a non-negligible part of the time and, when it is loaded, it is in a tug of war only with those forward motors that are beyond the limit of 110 nm from...
Figure 3. Cargo mean velocity (a), mean run time (b), mean number of engaged motors (c) and run length (d) as functions of $N_b$ for systems with $N_f = 3$. Results for mean field and SMs under conditions of negligible viscous drag. In all the cases, we consider kinesin-1 parameters both for forward and backward motors. The inset in panel (a) shows velocity results for $N_f = 4$ whose analogy with those for $N_f = 3$ indicates that the latter case (studied throughout the paper) is typical.

Figure 4. Probability of the states $(n_f, n_b)$ for a system with $N_f = 3$ and $N_b = 1$ considering the SM with $k = 0.32 \text{pN/nm}$ (a) and MFM (b). (c) The probabilities of the states $(2, 1)$ and $(3, 1)$ as functions of $k$ within the SM. In all the cases, the normalization of the probabilities is such that their sum over the eight possible states is equal to 1.

In contrast, in the MFM the engaged backward motor is all the time in a tug of war with $N_f$ motors, each of which is less loaded than the backward motor. Within the SM, the probabilities of states with a backward motor engaged are found to decrease with the stiffness $k$, as we show in figure 4(c). This is reasonable, since smaller values of $k$ lead to lower probabilities of detachment and result in more permissive tug of war states. In the case of the system with $N_f = 3$ and $N_b = 2$, the results (not shown) are completely analogous to those for $N_f = 3$ and $N_b = 1$ in figure 4. Thus, we can state generally that the probabilities of states with engaged backward motors increase when passing from the MFM to SM and, within the SM, they increase with decreasing $k$. This explains the increase of the mean number of engaged motors when changing from the MFM to SM and when decreasing $k$ (figure 3(c)) as a consequence of the contribution of the tug of war states, which have a larger total number of motors than single species states.
3.3. The influence of the viscous drag

Now we analyze bidirectional transport under non-negligible viscous drag. Figure 6(a) shows the cargo mean velocity as a function of \( N_b \) for \( N_f = 3 \) considering a viscous drag equal to 1000 times that of water, both for the MFM and SM. As expected, the velocities are smaller than those for water viscosity shown in figure 3(a) (typically by a factor 1/2). The general behavior of both models is similar to that for water viscosity, with one relevant difference. Now, MFM and SM give different results even for \( N_b = 0 \). This is because, while in the MFM all the forward motors share the load coming from the viscous drag, in the SM the load acts essentially only on the pulling motors. The same would occur when considering any other kind of external load force acting against the advance of the cargo, as the results in [17] for a single motor species suggest. Figure 6(b) shows the run times for the same systems analyzed in figure 6(a). As in the case of the velocities, we find that the differences between both models extend to the case \( N_b = 0 \). Finally, we complete our analysis of the influence of viscous drag with the results in figure 6(c), which show the dependence of the cargo velocity on \( \gamma \) for systems with and without backward motors. It can be seen that, although the general dependences on \( \gamma \) for all systems and models are similar to each other (\( r_c \) is constant for \( \gamma \lesssim 5 \times 10^{-3} \) pNs nm\(^{-1}\) and decreases exponentially for \( \gamma \gtrsim 5 \times 10^{-3} \) pNs nm\(^{-1}\)), the predictions of both models coincide only in the case of low viscosity and no backward motors. Moreover, the differences between the results from both models increase with the addition of backward motors.

4. Results for uneven forward and backward motors

Now we leave the symmetric case and study the models considering backward motor parameters that can be associated with cytoplasmic dynein. For forward motors, we continue using the kinesin-1 parameters considered in the previous section. Since the walking and detachment properties of dyneins are not as well known as for kinesin-1, the parameters for dyneins are not quite clear. Here we consider two different sets of the parameter’s values (named simply as set A and set B) based on the two proposals in [12, 13, 15]. Set A has been considered within the MFM in [12] and with small changes in [15] on the basis of previous experimental and theoretical results (see table 1 in [12], supporting material in [15] and references therein). Set B was obtained by fitting experimental data on Drosophila lipid-droplet transport [12] and is consistent with previous experimental data [35]. According to set A, the main differences between dyneins and kinesin-1 appear in the binding and unbinding rates. In contrast, set B considers also important differences on the typical velocities and stall forces of both motor types. It is interesting to investigate the biderirectional motion of the cargo transported with kinesin-1 motors and both models of dyneins.

Note that for the SM, in addition to binding, unbinding and velocity parameters, it is also necessary to specify the forward–backward ratio of jumps as a function of the load force. Since
Figure 6. The influence of the viscous drag. Cargo mean velocity (a) and run time (b) as functions of $N_b$ for fixed $N_f = 3$ considering $\gamma = 9.42 \times 10^{-3}$ pNs nm$^{-1}$ for both models. This value of $\gamma$ corresponds to a thousand times water viscosity and a cargo of 500 nm radio. (c) Cargo mean velocity as a function of $\gamma$ for $N_f = 3$ and different values of $N_b$ for both models. All calculations within the SM are for $k = 0.32$ pN nm$^{-1}$.

Figure 7. Kinesins and dyneins. Cargo mean velocity (a), cargo trajectories (b), mean run time (c) and probability of states with $n_b = 1$ (d) for a cargo pulled by kinesin-1 and dynein considering set A parameters for dyneins and negligible viscosity conditions for both models. Set A: $F_{sb} = 7$ pN, $F_{db} = 5.18$ pN, $e_b = 0.27$ s$^{-1}$, $\Pi_b = 1.6$ s$^{-1}$, $v_{0b} = 1000$ nm s$^{-1}$ and $v_{1b} = 6$ nm s$^{-1}$.

we have no experimental data for dyneins, in this work we consider the same exponential form used for kinesins. The use of any other reasonable formula is not expected to produce relevant changes in the results. In fact in [19] it was shown that even the consideration of no backward steps produces relatively small changes for the case of transport by kinesins.

In figure 7, we show results for cargo transport by kinesins-1 and set A dyneins under negligible viscous drag. Since the differences between the parameters for both types of motors are relatively small, the results are similar to those for symmetrical motors. The effects of the asymmetry are mainly notable in the case $N_f = N_b = 3$, for which we observe a net backward motion. This can be seen both in the velocities in figure 7(a) and in the trajectories in figure 7(b). The fact that set A dyneins win the tug of war for $N_f = N_b$ is mainly due to their slightly larger stall force. The differences between the predictions of the MFM and SM for the velocities (figure 7(a)) and the run times (figure 7(c)) are considerably relevant, and they occur in a similar fashion to that observed for symmetrical motors. The same happens with the probabilities of having a backward motor engaged (figure 7(d)), which are found to be larger for the SM than for the MFM. As in the case of
symmetrical motors, the latter result helps us to understand the differences in the run times from both models. Going back to figure 7(b), we see that the SM trajectories are much more winding than those from the MFM. This phenomenon is related to the reduction of \( r_f \) analyzed in the case of symmetric motors. The larger rate of reversion in the SM is due to that only some of the engaged motors pull the cargo at a given time and, in addition, it is more likely to have opposing motors engaged than in the MFM.

Now we consider dynein with parameter set B. In this case, dynein is a motor sensibly weaker than kinesin-1, since it has much lower stall force, much lower detachment force, lower attaching probability and also lower ratio \( F_s/F_d \). Thus, for the equal number of kinesin and dyneins, the kinesins win the tug of war. In fact, we find that several dyneins are needed to produce average null velocity for a cargo pulled by only one kinesin. In figure 8(a), we show the cargo mean velocity as a function of \( N_b \) for systems with \( N_f = 1 \) and \( N_f = 2 \). It can be seen that for small \( N_b \), the velocity is similar for both models (almost coincident for the case \( N_f = 1 \)). In contrast, for relatively large values of \( N_b \), the predictions of both models differ substantially. In particular, the number of dyneins needed to attain zero average velocity for a cargo pulled by one or two kinesins is considerably different. For \( N_f = 1 \), we find \( N_b \sim 8 \) for the MFM and \( N_b \sim 12 \) for the SM, while for \( N_f = 2 \) we find respectively \( N_b \sim 14 \) and \( N_b \sim 20 \).

Figure 8(b) shows the dependence of the run time on the number of dyneins for a cargo pulled by one kinesin. It can be seen that, even for \( N_b < 4 \) for which both models give similar mean velocities, they predict quite different results for \( \tau_r \). In the region \( n_b \sim 8 \), the situation is the opposite; both models give similar run times but they predict quite different velocities. For \( n_b > 8 \), the run time in the MFM grows very fast with \( n_b \) due to that dyneins win the tug of war (the mean velocity is negative). This makes dyneins to remain mostly attached, while the only kinesin detaches. Thus, the total number of engaged motors which controls the run time increases. 
In figure 8(c) we show results for the probabilities of the different states for a system with $N_f = 1$ and $N_b = 4$. For simplicity, we show only the probabilities of states with $n_f = 1$ (states with $n_f = 0$ have very small contributions in both models). Again, the SM gives a much larger probability of engagement of backward motors than the MFM.

Finally, we briefly explore the influence of the viscosity and of possible differences on the stiffness of motors from both species. In figure 8(d), we study the effective number of set B dyneins needed to achieve zero mean velocity when pulling against one kinesin. We consider different values of $\gamma$ and $k_b$. Note that our results provide non-integer effective values for $N_b$ which correspond to interpolations leading to zero cargo velocity. We see that for the MFM, the results are almost independent of $\gamma$ at a value close to $N_b = 8$. Interestingly, this value can be estimated by equating the powers produced by both motor teams considering all the motors attached at stall force. Namely, considering $N_b \times v_{sb} \times f_{sb} = v_{sf} \times f_{sf}$, we obtain $N_b = 8.39$. The behavior within the SM is much more complex. The effective number of dyneins needed to stop a kinesin depends both on the viscosity and the stiffness. Actually, it decreases with $\gamma$ and increases with $k_b$. The decrease with $\gamma$ is clearly due to that viscosity helps to stop the cargo. The increase with $k_b$ is due to the fact that the larger $k_b$ leads to less force production by dyneins, due to easier detachment. Note that we have considered a quite small value for the dynein’s stiffness ($k_b = 0.08$ pN nm$^{-1}$). The reason for this is twofold. First, it is the only way to reduce to reasonable values the effective number of set B dyneins needed to attain null velocity when pulling against one kinesin. Second, recent experiments [36] for transport mediated by dynein and kinesin-2 reported values of the stiffness in such a range.

5. Conclusions

Cargo transport along microtubules mediated by two opposing motor species provides interesting challenges both from the experimental and theoretical points of view. With the main aim of understanding the consequences of specific modeling assumptions, in this paper we have theoretically analyzed several aspects of the problem considering two different mathematical models, the mean field model (MFM) [12] and a recently introduced stochastic model (SM) [19], which share some commons with models in [8] and [17]. The main difference between the MFM and the SM stems from the assumptions of force sharing by the different motors. The MFM assumes equal load sharing by all the engaged motors of the same polarity, while the SM considers individual cargo–motor linking allowing for uneven force sharing.

Our main results indicate that both models show complete agreement only when there is essentially no load to share, that is, in systems with a single type of motors and with no relevant viscous effects. In other situations, the MFM predicts larger cargo mean velocity and smaller mean run time than the SM. We have found that the differences in the velocities are mainly due to the fact that, within the SM (and in agreement with statements in [8, 17, 18]), only some of the engaged motors pull the cargo at a given time. Moreover, the probability of engaged backward motors during forward excursions is larger in the SM than in the MFM. This leads also to a larger rate of reversions within the SM when compared with the MFM, or equivalently, to shorter excursions toward each polarity. The difference between the mean velocities predicted by both models is found to increase with the viscosity. We have also found that the mean run time is essentially controlled by the mean number of engaged motors at a given time, which depends on the probabilities of the different motility states and, ultimately, on the force sharing assumptions. Our results for the SM show that the mean cargo velocity turns out to be rather independent of the stiffness of the motor–cargo link ($k$). In contrast, the mean run time decreases with $k$ approaching the MFM results for large $k$.

These conclusions were obtained analyzing ideal systems in which motors of opposite polarities have identical dynamical properties. In addition, in section 4 we have provided results for the asymmetric case of transport driven by kinesin-1 and cytoplasmic dyneins, considering two different sets of parameters for dyneins usually found in the literature.

Finally, it is interesting to mention the possibility of considering a hybrid-modeling framework taking advantage of the benefits of both kinds of models: the simplicity and computational advantage of the Gillespie formulation of the MFM and the higher reliability of models including uneven force sharing. Note that the SM provides an alternative way to compute (numerically) the transition rates and velocities of the motility states entering into the Gillespie algorithm considering uneven load sharing. The same could be done with models such as those in [8, 17]. Thus, when fitting the single motor parameters needed to reproduce experimental trajectories, different intermediate procedures combining computations with both kinds of models could be imagined, depending on the particular problem and on the a priori knowledge of the parameters.

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