Bidirectional, unlike unidirectional transport, allows transporting axonal cargos against their concentration gradient

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Abstract

Even though most axonal cargos are synthesized in the soma, the concentration of many of these cargos is larger at the presynaptic terminal than in the soma. This requires transport of these cargos from the soma to the presynaptic terminal or other active sites in the axon. Axons utilize both bidirectional (for example, slow axonal transport) and unidirectional (for example, fast anterograde axonal transport) modes of cargo transport. Bidirectional transport seems to be less efficient because it requires more time and takes more energy to deliver cargos. In this paper, bidirectional and unidirectional axonal transport processes are investigated with respect to their ability to transport cargos against their concentration gradient. We argue that because bidirectional axonal transport includes both the anterograde and retrograde cargo populations, information about cargo concentration at the axon entrance and at the presynaptic terminal can travel in both anterograde and retrograde directions. This allows bidirectional axonal transport to account for the concentration of cargos at the presynaptic terminal. In unidirectional axonal transport, on the contrary, cargo transport occurs only in one direction, and this disallows transport of information about the cargo concentration at the opposite boundary. For the case of unidirectional anterograde transport, this means that proximal regions of the axon do not receive information about cargo concertation in the distal regions. This does not allow for the imposition of a higher concentration at the presynaptic terminal in comparison to the cargo concentration at the axon hillock. To the best of our knowledge, our paper presents the first explanation for the utilization of seemingly inefficient bidirectional transport in neurons.

Keywords neuron; axon; mathematical modeling; slow and fast axonal transport, alpha-synuclein

1. Introduction

To ensure reliable operation over decades, neurons need to constantly replace their functional components. In neurons, the delivery of new components to distal parts of an axon is accomplished by active transport that requires involvement of molecular motors. It is likely that most neuronal proteins are replaced once every several weeks by new proteins arriving from the soma [1,2].

Cytosolic proteins are transported from the soma, where they are synthesized, to active sites, e.g. the presynaptic terminal, by slow component-b (SCb). SCb is involved in transport of ~200 proteins [3]. The average rate of SCb-transport is ~2-8 mm/day (0.023-0.093 μm/s). One of the proteins transported in SCb is α-synuclein (α-syn), which is mostly known for its involvement in Parkinson's disease (PD) [4,5]. In a healthy neuron α-syn predominantly exists as a monomer [6]. α-syn is synthesized in the soma and then is transported to the synapse, mostly in SCb [7-9]. In healthy neurons α-syn predominantly localizes in the presynaptic terminal [10-12]. As for any SCb protein, α-syn motion is characterized by periods of fast transport, pauses, and changes in movement direction [13]. Fast anterograde and retrograde motions of α-syn are propelled by kinesin and dynein motors, respectively [14].

An intriguing question is why cytosolic proteins, such as α-syn [15], are moved in SCb, which includes both anterograde and retrograde components, although the net flux of these proteins is anterograde. Transporting cargos using molecular motors requires energy [16]. Bidirectional transport takes more energy to move a cargo by the same distance compared to unidirectional transport. For some unknown reason neurons use slow axonal transport, which is inherently bidirectional, to deliver three times more protein to the presynaptic terminal than by fast axonal transport [16]. This is especially surprising because protein delivery to the presynaptic terminal is essential and a lack of presynaptic proteins can lead to synaptic degeneration [17]. Why then do proteins transported via SCb to the presynaptic terminal rely on a mode of transit that includes a retrograde component?

Back-and-forth movements of cargos with overall net directionality toward a certain destination seemingly constitute an inefficient transport mechanism. Possible explanations for the utilization of bidirectional transport include facilitating maneuvering of molecular motors around obstacles on MTs and providing an error correction mechanism for the delivery of cargo to a proper location [18]. It was also suggested that the purpose of bidirectional transport (especially of slow axonal transport) is dynamic recruitment and redistribution of cargos in response to changing metabolic needs [19].

Bidirectional transport (especially slow axonal transport) is slower than unidirectional transport. Slow axonal transport along human motor neurons can take up to a year. This may predispose neurons to being

unable to properly supply presynaptic terminal with key proteins, as slow transport acts as a bottleneck and may predispose them to proteolytic degradation in transport. Indeed, the cellular environment is quite hostile to most proteins, and most of them are short-lived, days or weeks at the most [2]. Why has evolution chosen to use something that seems to be less efficient?

Unlike previously suggested hypotheses, our hypothesis is that bidirectional transport in neurons allows for movement of cargos against their concentration gradient. Situations where cargos must be transported against their concentration gradient are common in neurons. One example is transport of tau in the axon initial segment, where tau transported from the soma has to pass the tau diffusion barrier [20]. Tau concentration in the axon is larger than in the soma, and thus, tau entry into the axon requires transport against the concentration gradient. A model of this process has recently been developed in [21]. Additionally, tau concentration at the axon tip is larger than its concentration in the proximal axon [22]. Thus, in the axon, tau is also transported against its concentration gradient [23,24].

Additionally, tau concentration at the axon tip is larger than its concentration in the proximal axon [22]. Thus, in the axon, tau is also transported against its concentration gradient [23,24]. Other examples involving anterograde protein transport against the protein's concentration gradient include dynein, which cannot move in the anterograde direction on its own [25], and synapsin, which is also enriched at synapses [26].

2. Methods and models

2.1. The model of slow (bidirectional) axonal transport of cytosolic proteins

A continuum model of slow axonal transport of neurofilaments (which move in slow component a, SCa, which is characterized by an average velocity of 0.2-1 mm/day [8]) was proposed in [27]. Refs. [28,29] extended this model to cytosolic proteins, which are transported in SCb and can diffuse in the cytoplasm.

Although our model of slow axonal transport is applicable to any of the proteins transported in SCb, all of which move bidirectionally, here we apply the model to α-syn monomer. α-syn monomer, after being synthesized in the soma, is transported to the presynaptic terminal by slow axonal transport. Slow axonal transport is characterized by short rapid movements, which can be anterograde or retrograde, and are presumably powered by kinesin and dynein motors, respectively. Kinesin and dynein motors run along microtubules (MTs). Rapid movements are interrupted by prolonged pauses, during which α-syn monomer presumably maintains some association with MTs.

Since axonal transport is mostly one-dimensional (it occurs along the axon), we characterized all concentrations in the axon by their linear number densities (number of cargoes in a certain kinetic state per unit length of the axon). The model includes two motor-driven states for α-syn monomer with concentrations n_a^* and n_r^*, respectively. Conservation of α-syn residing in motor-driven states (Fig. 2) gives the following equations:

$$-v_a^* \frac{\partial n_a^*}{\partial x^*} - \gamma_{10}^* n_a^* + \gamma_{01}^* n_{a0}^* = 0 , \tag{1}$$

$$v_r^* \frac{\partial n_r^*}{\partial x^*} - \gamma_{10}^* n_r^* + \gamma_{01}^* n_{r0}^* = 0 , \tag{2}$$

where x^* is the Cartesian coordinate along the axon (Fig. 1). Various α-syn concentrations are defined in Table 1 and various model parameters are defined in Tables 2 and 3.

The first terms on the left-hand sides of Eqs. (1) and (2) describe fast motions of α-syn monomer in the anterograde (with a velocity v_a^*) and retrograde (with a velocity v_r^*) directions, respectively, while other terms describe transitions between motor-driven and pausing kinetic states. Fig. 2 shows various kinetic states and transitions between them described by kinetic rates γ*s.

The model also includes equations for α-syn monomer in two pausing states, with concentrations n_{a0}^* and n_{r0}^*, respectively. It is assumed that despite pausing, α-syn monomer maintains some connection with MTs, but is ready to resume anterograde or retrograde motion. Equations expressing conservation of α-syn monomers in the pausing states involve only terms that describe transitions to/from other kinetic states, since no motor-driven transport or diffusion occur in the pausing states (Fig. 2):

$$-\left(\gamma_{01}^* + \gamma_{ar}^* + \gamma_{off,a}^*\right) n_{a0}^* + \gamma_{10}^* n_a^* + \gamma_{ra}^* n_{r0}^* + \gamma_{on,a}^* n_{free}^* = 0 , \tag{3}$$

$$-\left(\gamma_{01}^* + \gamma_{ra}^* + \gamma_{off,r}^*\right) n_{r0}^* + \gamma_{10}^* n_r^* + \gamma_{ar}^* n_{a0}^* + \gamma_{on,r}^* n_{free}^* = 0 . \tag{4}$$

SCb-transported proteins have diffusible fractions [30]. Free (cytosolic) α-syn monomers can thus be transported by diffusion. They also can be destroyed by degradation in proteasomes [31], which are present in various locations in the axon. Free α-syn can also transition to anterograde or retrograde biased pausing states (Fig. 2). Stating the conservation of free monomeric α-syn gives the following equation:

$$D_{n_{free}}^* \frac{\partial^2 n_{free}^*}{\partial x^{*2}} + \gamma_{off,a}^* n_{a0}^* + \gamma_{off,r}^* n_{r0}^* - \left(\gamma_{on,a}^* + \gamma_{on,r}^*\right) n_{free}^* - \frac{n_{free}^* \ln(2)}{T_{1/2,\,free}^*} = 0 . \tag{5}$$

Eqs. (1)-(5) must be solved subject to the following boundary conditions:

At $x^* = 0$: $\quad n^*_{tot} = n^*_{tot,x=0}$, $\quad j^*_{tot} = v^*_{av,estimate} n^*_{tot,x=0}$. (6a,b)

Eq. (6a) postulates the total concentration of α-syn monomer at the axon hillock and Eq. (6b) postulates the total flux of newly synthesized α-syn monomers entering the axon. In Eq. (6b)

$$j^*_{tot}\left(x^*\right) = -D^*_{n_{free}} \frac{\partial n^*_{free}}{\partial x^*} + v^*_a n^*_a - v^*_r n^*_r \tag{7}$$

is the total flux of α-syn monomer due to diffusion in the cytosol and motor-driven transport.

The total concentration of α-syn monomers (in all five kinetic states displayed in Fig. 2) is found as:

$$n^*_{tot} = n^*_a + n^*_r + n^*_{a0} + n^*_{r0} + n^*_{free}. \tag{8}$$

As we suggested in [32], the average velocity of a protein in slow axonal transport is defined as the ratio of the total protein flux to the total protein concentration:

$$v^*_{av}\left(x^*\right) = \frac{j^*_{tot}}{n^*_{tot}}. \tag{9}$$

At the axon presynaptic terminal, we imposed the following boundary conditions:

At $x^* = L^*$: $\quad \dfrac{\partial n^*_{free}}{\partial x^*} = 0$, $\quad n^*_{tot} = n^*_{tot,x=L}$. (10a,b)

We defined the dimensionless concentration of α-syn as:

$$n = n^* / n^*_{x=L}. \tag{11}$$

This equation applies to the total α-syn concentration and all α-syn concentration components (n_a, n_r, etc.). Eq. (10b) can then be recast as:

$$n_{tot,x=L} = 1. \tag{12}$$

The dimensionless total flux of α-syn is defined as:

$$j_{tot} = \frac{j^*_{tot}}{n^*_{x=L} v^*_a}. \tag{13}$$

2.2. The model of fast anterograde (unidirectional) axonal transport of various organelles

Fast anterograde axonal transport of various membranous organelles is simulated by the following equation:

$$-v_a^* \frac{\partial n_a^*}{\partial x^*} - \frac{n_a^* \ln(2)}{T_{1/2,a}^*} = 0 . \tag{14}$$

In Eq. (14) we neglected the vesicles' diffusivity due to their large size. This equation must be solved subject to the following boundary condition:

$$\text{At } x^* = 0: \qquad n_a^* = n_{tot,x=0}^* . \tag{15}$$

To enable a comparison between slow and fast axonal transport simulations, we assumed the same protein concentration at $x^* = 0$ for fast axonal transport as for slow axonal transport (compare with Eq. (6a)).

The analytical solution of Eq. (14) with boundary condition (15) is

$$n_a^* = n_{tot,x=0}^* \exp\left(-\frac{\ln(2)}{v_a^* T_{1/2,a}^*} x^* \right). \tag{16}$$

Ref. [33] have shown that neuropeptide delivery to en passant boutons in type Ib terminals of Drosophila motoneurons involves DCV circulation, in which DCVs that reached the most distal bouton in the terminal turn around and move back by retrograde transport. The concentration of retrogradely transported cargos can be modeled by the following equation:

$$v_r^* \frac{\partial n_r^*}{\partial x^*} - \frac{n_r^* \ln(2)}{T_{1/2,r}^*} = 0 . \tag{17}$$

This equation must be solved subject to the following boundary condition at the axon tip:

$$\text{At } x^* = L^*: \qquad j_r^* = \upsilon j_a^* , \tag{18}$$

where $j_a^* = v_a^* n_a^*$, $j_r^* = v_r^* n_r^*$, and υ is the fraction of vesicles entering the presynaptic terminal that turn around and return to the axon, moved by dynein motors. Under steady-state conditions, the difference, $j_a^* - j_r^*$, must be destroyed in the presynaptic terminal (or released from it). Eq. (18) can be recast as:

$$\text{At } x^* = L^*: \qquad n_r^* = \frac{\upsilon v_a^*}{v_r^*} n_a^* . \tag{19}$$

If $T^*_{1/2,a}$ is very large, then, from Eq. (16), $n^*_{a,x=0} = n^*_{a,x=L} = n^*_{tot,x=0}$, and the solution of Eq. (17) with boundary condition (19) gives the following:

$$n^*_r = n^*_{tot,x=0} \frac{\upsilon v^*_a}{v^*_r} \exp\left(-\frac{\left(L^* - x^*\right)\ln(2)}{v^*_r T^*_{1/2,r}} \right). \tag{20}$$

2.3. The model of slow axonal transport of cytosolic proteins with 15% fast component

According to [8,9,14,30], 10-15% of proteins transported in SCb are moved by fast axonal transport. In order to simulate this situation, we utilized the above models of fast and slow axonal transport, in which Eq. (6a,b) was modified as:

$$\text{At } x^* = 0: \qquad n^*_{tot} = 0.85 n^*_{tot,x=0}, \qquad j^*_{tot} = 0.85 v^*_{av,estimate} n^*_{tot,x=0}, \tag{21a,b}$$

and Eq. (15) is replaced with the following equation:

$$x^* = 0: \; n^*_a = 0.15 n^*_{tot,x=0}. \tag{22}$$

2.4. Finding values of kinetic constants by least square regression

In order to solve the problem numerically, values of eight kinetic constants given in Table 3 are needed. These values can be found by using multi-objective optimization (see, for example, [34-38]). The following objective (penalty) function was minimized:

$$err = \sum_{j=1}^{N_{fit}} \left(n_{tot,j} - n_{tot,estimate,j} \right)^2 + \omega_1 \sum_{j=1}^{N_{fit}} \left(v^*_{av,j} - v^*_{av,estimate} \right)^2 + \omega_2 . \tag{23}$$

This function combines three different effects. The first term on the right-hand side of Eq. (23) estimates how well the α-syn concentration predicted by the model, $n_{tot,j}$, fits the estimated concentration of α-syn given by the following sigmoid curve, which we obtained by modifying a logistic function

$$n_{tot,estimate,j} = n_{tot,x=0} + \left(1 - n_{tot,x=0}\right)\left(1 - \tanh\left[k\left(L - x\right)\right]\right). \tag{24}$$

The second term on the right-hand side of Eq. (23) estimates how well the average velocity of α-syn predicted by the model, $v^*_{av,j}$, fits the estimated average α-syn velocity, $v^*_{av,estimate}$. We used three values for $v^*_{av,estimate}$, which are in the range of average velocities of SCb (2-8 mm/day [3]). We used ω_1=1 s^2/μm^2. This

value was selected by numerical experimentation to avoid overfit in terms of either α-syn concentration or average velocity, as described in [39].

Physically, α-syn concentrations in various kinetic states must be non-negative. Therefore, we set $\omega_2 = 10^8$ if any of $n_{a,j}$, $n_{r,j}$, $n_{a0,j}$, $n_{r0,j}$, and $n_{free,j}$ (j=1,…, N_{fit}) are negative. If the half-life of α-syn monomer is infinitely large, its flux under steady-state conditions must stay constant. However, if the half-life of α-syn is finite, its flux decreases as x^* increases. However, since the presynaptic terminal must be supplied with α-syn monomers, physically the flux must remain positive. Therefore, we also set $\omega_2 = 10^8$ if j_{tot} (j=1,…, N_{fit}) becomes negative.

Table 1. Dependent variables in the model of α-syn monomers transport from the soma to the presynaptic terminal.

Symbol	Definition	Units
j^*_{tot}	Total flux of α-syn monomers through a given cross-section in the axon	s^{-1}
n^*_a	Concentration of on-track α-syn monomers moving along MTs anterogradely, propelled by molecular motors	μm^{-1}
n^*_r	Concentration of on-track α-syn monomers moving along MTs retrogradely, propelled by molecular motors	μm^{-1}
n^*_{a0}	Concentration of pausing on-track α-syn monomers that are still associated with molecular motors and can resume their anterograde motion	μm^{-1}
n^*_{r0}	Concentration of pausing on-track α-syn monomers that are still associated with molecular motors and can resume their retrograde motion	μm^{-1}
n^*_{free}	Concentration of free (off-track) α-syn monomers in the cytosol	μm^{-1}

Table 2. Parameters characterizing transport of α-syn monomers in the axon taken from published data or assumed on physical grounds.

Symbol	Definition	Units	Value or range	Reference(s)	Value(s) used in computations
$D^*_{n_{free}}$	Diffusivity of α-syn monomers in the cytosolic state	$\mu m^2/s$	114 [a]	[40]	114
k	The logistic growth rate, which characterizes the steepness of the *S*-shaped curve used in approximating the distribution of α-syn along the axon length				10^{-3}
L^*	Length of the axon	μm	up to 10^6 in humans	[26]	5×10^4 [b]
$n^*_{tot,x=0}$	Concentration of α-syn monomer at the axon hillock	μM	10^{-3} [c]	[41]	10^{-3}
$n^*_{tot,x=L}$	Concentration of α-syn monomer at the presynaptic terminal	μM	3.5 [c]	[42]	3.5
N_{fit}	Number of points uniformly distributed along the axon length in which α-syn concentration is matched with the assumed *S*-shaped distribution				50
$T^*_{1/2,a}$	Half-life of 15% portion α-syn monomers transported anterogradely by fast axonal transport	s	6.62×10^3 - 1.73×10^5 [d]	[43-46]	5.76×10^4, 5.76×10^5, 5.76×10^6, 5.76×10^{10}
$T^*_{1/2,free}$	Half-life of free α-syn monomers	s	6.62×10^3 - 1.73×10^5 [d]	[43-46]	5.76×10^4, 5.76×10^5, 5.76×10^6, 5.76×10^{10}
v^*_a, v^*_r	Velocities of rapid motions of α-syn monomers on MTs propelled by kinesin and dynein motors, respectively, in slow axonal transport	$\mu m\ s^{-1}$	0.7	[47]	0.7
$v^*_{av,estimate}$	Estimated average velocity of α-syn monomers in slow axonal transport	$\mu m\ s^{-1}$	0.023-0.093 [e]	[3,48,49]	0.02, 0.05, 0.1

υ	Fraction of vesicles entering the presynaptic terminal that turn around and return to the axon moved by dynein motors		0-1		0.5
ω_1	Weighting factor in Eq. (23)	$s^2/\mu m^2$		Numerical experimentation	1
ω_2	Weighting factor in Eq. (23)			Numerical experimentation	10^8

[a] The large diffusivity of α-syn monomers is explained by its small molecular weight of ~14 kDa [50].

[b] In computations, we used a representative axon length of 50 mm [26].

[c] Cellular α-syn concentration in presynaptic terminals is expected to be in micromolar range, while in other parts of the cell it can be as low as nanomolar range [41]. Ref. [42] estimated the concentration of α-syn in the presynaptic terminal to be 3.5 μM.

[d] Cellular environment is quite hostile to most proteins. A possible reason for this is damage to proteins by reactive oxygen species. Cytosolic proteins could be degraded in proteasomes, which are present in various locations in the axon. Typical half-life of cytosolic proteins is days or weeks at the most [2].

Monomeric α-syn is most likely degraded in proteasomes [43,51]. Various estimates are found in the literature; the reported values are 1.84 hrs [43], 16 hrs [44], and 48 hrs [45]. Following [44,46], we used 16 hours (5.76×10^4 s) as an estimate of half-life of an unprotected monomeric α-syn.

In large neurons, the time that it takes for a protein to travel from the soma to the synapse may exceed the lifetime of the protein. Therefore, it is likely that proteins are somehow protected from degradation during their transit in the axon [49,52]. As a result, the half-life of α-syn monomers undergoing slow axonal transport may be much larger than 16 hours. For that reason, in computations we used four estimates for α-syn monomer half-life: 5.76×10^4 s (16 hours), 5.76×10^5 s (160 hours), 5.76×10^6 s (1,600 hours), and 5.76×10^{10} s (1.6×10^7 hours).

[e] There are different estimates of the average velocity of α-syn monomers transport from the soma to the presynaptic terminal: 0.022-0.028 μm/s (1.9-2.4 mm/day) [48], 0.035-0.12 μm/s (3-10 mm/day) [49]. Since α-syn monomers are transported in SCb, we are using an estimate of 0.023-0.093 μm/s (2-8 mm/day) reported in [3].

Table 3. Kinetic constants characterizing transition of α-syn monomers between different kinetic states in slow axonal transport, which are displayed in Fig. 2. Values of these kinetic constants were obtained by finding values that give the best fit with respect to different objectives: getting the best fit (i) between the assumed concentration (based on published estimates) and computed α-syn concentration and (ii) between the value of the average α-syn transport velocity reported in literature and its computed value. These objectives were weighted in defining the objective (penalty) function, see Eq. (23). For optimizing the fit, the Least Square Regression (LSR) was utilized, as described in [39,53,54].

Symbol	Definition	Units	Initial guess used in the optimization procedure
γ_{10}^{*}	Kinetic constant describing the rate of transitions $n_a^* \to n_{a0}^*$ and $n_r^* \to n_{r0}^*$ (Fig. 2)	s^{-1}	7.19×10^{-3}
γ_{01}^{*}	Kinetic constant describing the rate of transitions $n_{a0}^* \to n_a^*$ and $n_{r0}^* \to n_r^*$ (Fig. 2)	s^{-1}	4.01×10^{-3}
γ_{ar}^{*}	Kinetic constant describing the rate of transitions $n_{a0}^* \to n_{r0}^*$ (Fig. 2)	s^{-1}	4.59×10^{-3}
γ_{ra}^{*}	Kinetic constant describing the rate of transitions $n_{r0}^* \to n_{a0}^*$ (Fig. 2)	s^{-1}	6.76×10^{-3}
$\gamma_{on,a}^{*}$	Kinetic constant describing the rate of transitions $n_{free}^* \to n_{a0}^*$ (Fig. 2)	s^{-1}	9.43×10^{-2}
$\gamma_{on,r}^{*}$	Kinetic constant describing the rate of transitions $n_{free}^* \to n_{r0}^*$ (Fig. 2)	s^{-1}	5.90×10^{-2}
$\gamma_{off,a}^{*}$	Kinetic constant describing the rate of transitions $n_{a0}^* \to n_{free}^*$ (Fig. 2)	s^{-1}	5.29×10^{-3}

$\gamma^*_{off,r}$	Kinetic constant describing the rate of transitions $n^*_{r0} \rightarrow n^*_{free}$ (Fig. 2)	s^{-1}	5.40×10^{-3}

2.5. Numerical solution

We eliminated $n^*_{a0}\left(x^*\right)$ and $n^*_{r0}\left(x^*\right)$ from Eqs. (1)-(5) using Eqs. (3) and (4). This led to a system of ordinary differential equations of the fourth order, which was solved using Matlab's BVP5C solver (Matlab R2019a, MathWorks, Natick, MA, USA). The inverse problem, which involves a determination of values of kinetic constants (Table 3), was solved by using MULTISTART with the local solver FMINCON; these routines are included in Matlab's Optimization Toolbox. 1000 random point were utilized as starting points in the search for the global minimum. The numerical procedure is described in detail in [24].

3. Results

3.1. Effect of the average velocity of α-syn monomers

A bidirectional transport model (in particular, a slow axonal transport model) can fit a protein distribution characterized by a uniform low protein concentration in the axon and a sharp concentration increase at the presynaptic terminal. For the simulated case of slow axonal transport of α-syn, the fitting is done by adjusting values of the kinetic constants characterizing protein transfer rates between different kinetic states. The model can fit such a distribution for any average velocity of α-syn transport within the SCb range (the total concentration is shown in Fig. 3a, the components of the total concentration are shown in Figs. S1-S3). This is because the bidirectional axonal transport model is described by a higher order system of differential equations (second when diffusion of free proteins in the cytosol is neglected and fourth when it is accounted for), and thus allows for the imposition of boundary conditions at the axon hillock and at the presynaptic terminal. Because the model includes both anterogradely and retrogradely transported protein populations, information about the cargo concentration in this model can propagate in both anterograde and retrograde directions, which allows a bidirectional axonal transport model to account for the imposed protein concentration at the presynaptic terminal. This enables a bidirectional axonal transport to move proteins against their concentration gradient, unlike diffusion and unidirectional fast axonal transport.

Unlike bidirectional axonal transport, unidirectional axonal transport cannot simulate the increase of protein concentration near the presynaptic terminal. If the protein half-life is infinitely large, the protein

concentration is uniform and constant (Fig. 3a). This is explained by the fact that the system of governing equations simulating unidirectional (in the simulated case, anterograde) axonal transport is of the first order, and thus can only include one boundary condition, which in the case of anterograde transport has to be imposed at the axon entrance. This is because the model of unidirectional fast anterograde axonal transport includes only transport by anterograde motors, and thus information about the cargo concentration can only propagate in the anterograde direction. Diffusion is neglected in the model of unidirectional transport because this mode of transport usually applies to fast axonal transport, in which case cargos are moved inside vesicles, which are usually too large to exhibit a significant diffusivity.

In some situations, cargos participating in fast axonal transport can turn around at the end of the axon and then move backward by retrograde transport, propelled by cytoplasmic dynein. This situation may lead to cargo circulation [33]. However, this situation does not allow for the imposition of a higher cargo concentration at the end of the axon because only a fraction of anterogradely transported cargos can turn around, and due to the conservation of cargos this fraction cannot exceed unity. The dashed curve in Fig. 3b shows the retrograde flux for the situation when half of anterogradely transported cargos turn around at the end of the axon. The velocities of fast anterograde and retrograde axonal transport components are the same (Fig. 4).

Our model shows that α-syn flux along the axon is constant and uniform if α-syn destruction during its axonal transport is neglected. Since α-syn concentration at the entrance to the axon is assumed constant, the constant value of α-syn flux increases with an increase of the average α-syn velocity. For the same α-syn concentration at the axon entrance, fast axonal transport can deliver a much larger α-syn flux due to larger average velocity (Fig. 3b).

The velocity along most of the axon length remains constant, but it decreases close to the presynaptic terminal (Fig. 4), in the region where the average α-syn concentration increases (Fig. 3a).

3.2. Effect of the half-life of α-syn monomers

If the α-syn half-life is varied, the slow axonal transport model can still fit an α-syn concentration profile with a sharp concentration increase at the presynaptic terminal (the total concentration is shown in Fig. 5a, the components of the total concentration are shown in Figs. S4-S6). The fast axonal transport model predicts a decreasing concentration toward the presynaptic terminal, due to protein degradation. The decrease becomes faster for shorter protein half-life (Fig. S4b vs Figs. S5b and S6b).

For the slow axonal transport model, the α-syn flux remains almost constant along most of the axon. (Fig. 5b). This is because in slow axonal transport model we assumed that α-syn is destroyed only in free (cytosolic) kinetic state (see Eq. (5)), and the concentration of α-syn in this kinetic state is very low in most of the axon (Fig. S4, S5, S6). Close to the presynaptic terminal the flux decreases, which is due to a sharp increase in the concentration of α-syn (including in the free state, in which α-syn can be destroyed) near the presynaptic terminal (Fig. 5a and Figs. 4b, 5b, 6b). For the fast anterograde axonal transport model, α-syn degradation during its transport along the axon results in a decrease of the α-syn flux because of α-syn destruction (Fig. 5b), see Eq. (14).

It is interesting that even if the α-syn half-life is decreased, the slow axonal transport model is capable of simulating a constant velocity along most of the axon, with the velocity decreasing close to the presynaptic terminal (Fig. 6).

3.3. Effect of a 15% fraction of α-syn monomers moved by fast axonal transport

To investigate whether transport of a fraction of α-syn by fast axonal transport may affect the α-syn distribution, we combined the slow and fast components of axonal transport and modified the boundary conditions in such way that 85% of α-syn enters the axon in slow component and 15% enters the axon by axonal transport [9,30], see Eqs. (21) and (22). The combined 15% fast plus 85% slow axonal transport model is still able to fit the α-syn concentration characterized by a uniform concentration in most of the axon, with a concentration increase only at the presynaptic terminal (Fig. 7a).

The α-syn flux in the case of combined fast plus slow axon transport is slightly (by ~17%) larger, because fast axonal transport is much more efficient than slow axonal transport, even 15% makes a difference (Fig. 7b). The average velocity of α-syn transport is also slightly (by ~15%) larger when a fraction of α-syn is transported in the fast component (Fig. 8).

4. Conclusions

In this paper, we compared bidirectional and unidirectional axonal transport models with respect to information about the cargo concentration that these models allow us to impose on the boundaries of the domain. The presented analysis uncovers an important feature of propagation of information about the cargo concentration in bidirectional and unidirectional axonal transport processes. Bidirectional axonal transport includes both anterograde and retrograde components, and hence information about the cargo

concentration can propagate in both directions. This allows for the imposition of protein concentration not only at the axon hillock, but also at the presynaptic terminal. Since any value of protein concentration can be imposed at the presynaptic terminal, bidirectional axonal transport is capable of transporting protein against its concentration gradient, allowing for a situation when the protein concentration in the beginning of the axon is low and at the presynaptic terminal is high.

Contrary to this, the unidirectional anterograde axonal transport accounts only for anterograde flow of information about the cargo concentration and thus allows for the imposition of a boundary condition specifying the protein concentration only at the axon hillock. Since no boundary condition can be imposed at the presynaptic terminal, the information about the cargo concentration at the terminal cannot be supplied in the unidirectional anterograde axonal transport model. This results in the inability of unidirectional axonal transport to move protein against its concentration gradient. Thus, unidirectional axonal transport can only enhance diffusion but it cannot change the direction of protein transport with respect to the concentration gradient. However, bidirectional axonal transport is capable of transporting proteins against their concentration gradient.

The presented results suggest why bidirectional transport, despite its much less efficient utilization of molecular motors and larger energy cost, is used by neurons to transport presynaptic proteins from the soma, where these proteins are synthesized, to the presynaptic terminal. The concentration of such proteins is much higher at the presynaptic terminal, and the utilization of bidirectional axonal transport, with its ability to transmit information about the cargo concentration both ways, allows for transport of these proteins from locations where their concentration is low (the soma and proximal axon) to locations where their concentration is high (the presynaptic terminal). We should note that to have information about the cargo concentration travel in both anterograde and retrograde directions, it is not enough to have cargos that make bidirectional movements occasionally. It is necessary to have separate populations of anterogradely and retrogradely moving cargos, which happens, for example, in slow axonal transport.

Data accessibility. Additional data accompanying this paper are available in the Supplemental Materials.

Authors' contributions. IAK and AVK contributed equally to the performing of computational work and article preparation. Both authors approved final version of the manuscript and agreed to be accountable for all aspects of the work.

Competing interests. We have no competing interests.

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Figure captions

Fig. 1. A diagram showing the coordinate system adopted in the model.

Fig. 2. A kinetic diagram showing various kinetic states in our model of α-syn transport in the axon. The diagram is based on the model of SCa transport of neurofilaments developed in [27] with modification to this model suggested in [28,29] to extend this model to SCb-transported proteins.

Fig. 3. (a) Total concentration of α-syn monomers (the sum of α-syn concentrations in motor-driven, pausing, and diffusing states). (b) Total flux of α-syn monomers due to action of molecular motors and diffusion in the cytosol. $T^*_{1/2,\,free} = 5.76 \times 10^{10}$ s, the fraction of α-syn monomers conveyed in the fast component of axonal transport is assumed to be zero. Slow (bidirectional) and fast (unidirectional) axonal transport.

Fig. 4. Average velocity of α-syn monomers in slow axonal transport along the axon. $T^*_{1/2,\,free} = 5.76 \times 10^{10}$ s, the fraction of α-syn monomers conveyed in the fast component of axonal transport is assumed to be zero. Slow (bidirectional) and fast (unidirectional) axonal transport.

Fig. 5. (a) Total concentration of α-syn monomers (the sum of α-syn concentrations in motor-driven, pausing, and diffusing states). (b) Total flux of α-syn monomers due to action of molecular motors and diffusion in the cytosol. $v^*_{av,estimate} = 0.05$ μm s^{-1}, the fraction of α-syn monomers conveyed in the fast component of axonal transport is assumed to be zero. Slow (bidirectional) and fast (unidirectional) axonal transport.

Fig. 6. Average velocity of α-syn monomers in slow axonal transport along the axon. $v^*_{av,estimate} = 0.05$ μm s^{-1}, the fraction of α-syn monomers conveyed in the fast component of axonal transport is assumed to be zero. Slow (bidirectional) and fast (unidirectional) axonal transport.

Fig. 7. (a) Total concentration of α-syn monomers (the sum of α-syn concentrations in motor-driven, pausing, and diffusing states). (b) Total flux of α-syn monomers due to action of molecular motors and diffusion in the cytosol. $T^*_{1/2,\,free} = T^*_{1/2,a} = 5.76 \times 10^{10}$ s, $v^*_{av,estimate} = 0.05$ μm s^{-1}, the fraction of α-syn monomers conveyed in the fast component of axonal transport is assumed to be 15%. Slow (bidirectional) and fast (unidirectional) axonal transport.

Fig. 8. Average velocity of α-syn monomers in slow (bidirectional) and fast (unidirectional) axonal transport along the axon. $T^*_{1/2,\,free} = T^*_{1/2,a} = 5.76 \times 10^{10}$ s, $v^*_{av,estimate} = 0.05$ μm s^{-1}, the fraction of α-syn

monomers conveyed in the fast component of axonal transport is assumed to be 15%. Slow (bidirectional) and fast (unidirectional) axonal transport.

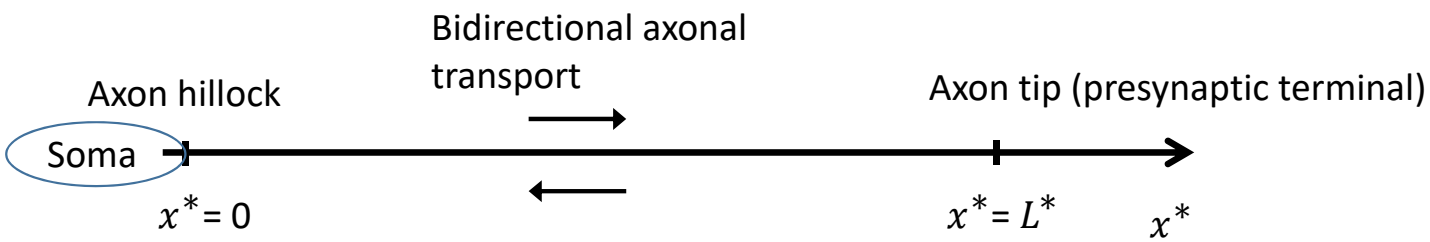

Bidirectional axonal transport
Axon hillock
Axon tip (presynaptic terminal)
Soma
$x^* = 0$
$x^* = L^*$
x^*

Figure 1

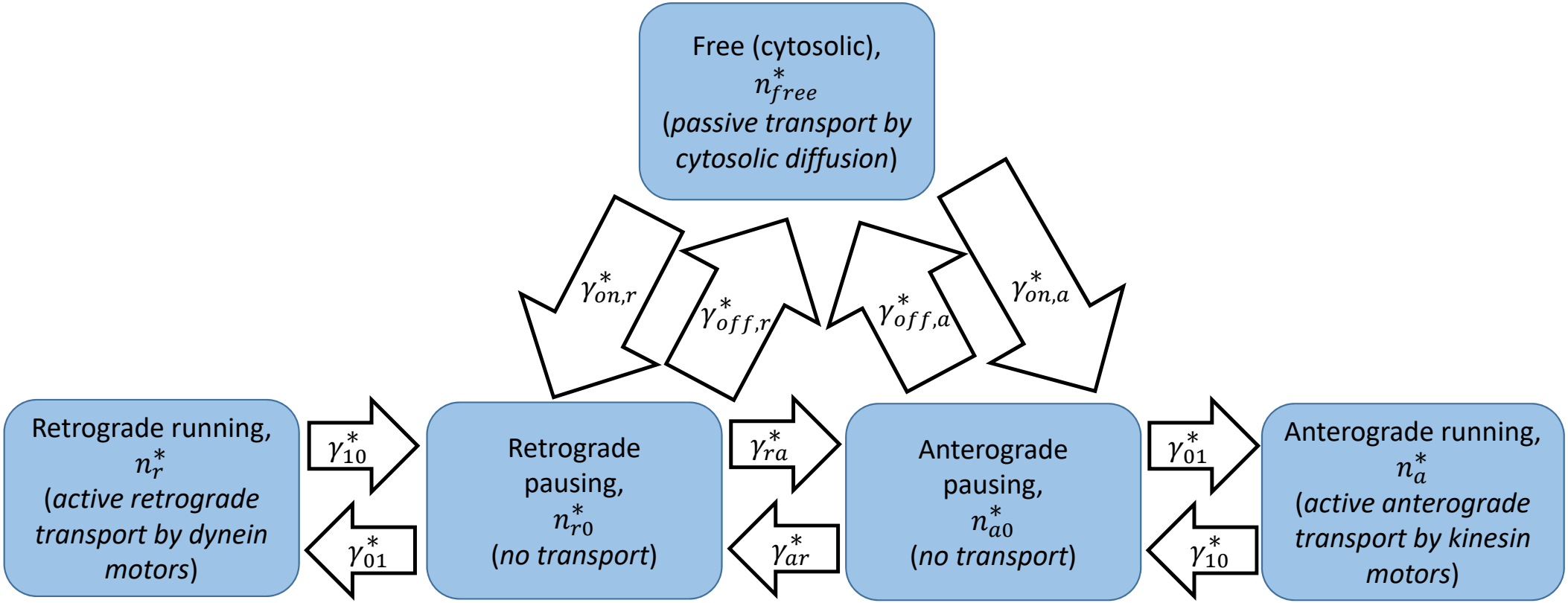
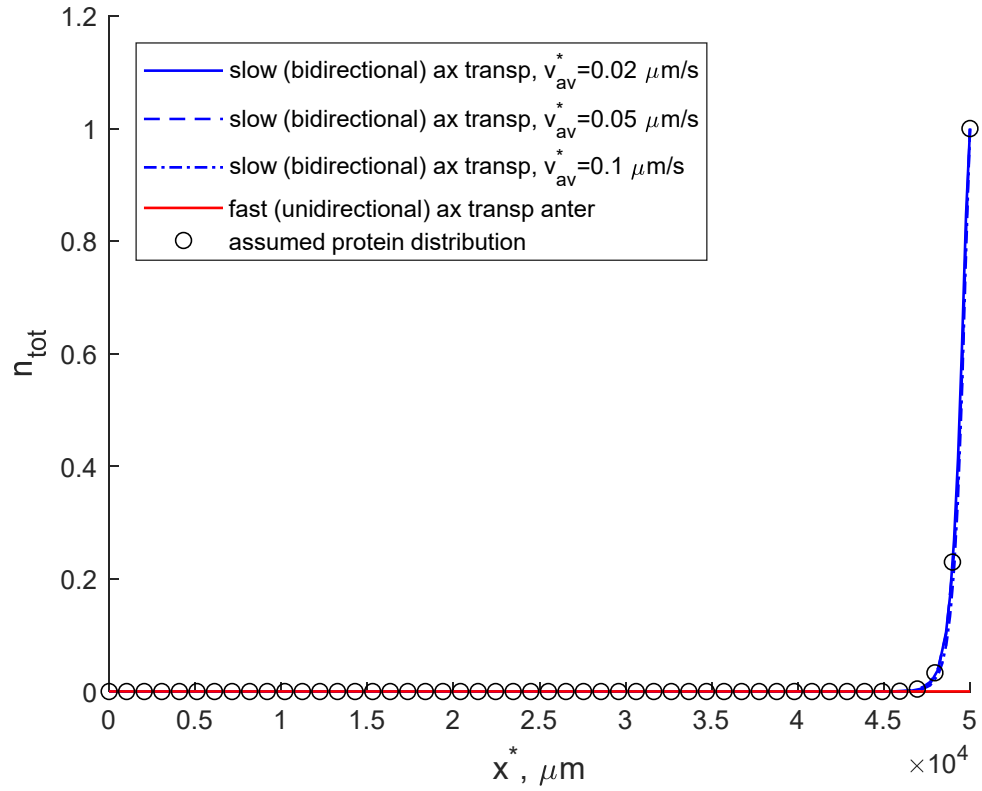

Free (cytosolic),
n^*_{free}
(*passive transport by cytosolic diffusion*)
$\gamma^*_{on,r}$
$\gamma^*_{off,r}$
$\gamma^*_{off,a}$
$\gamma^*_{on,a}$
Retrograde running,
n^*_r
(*active retrograde transport by dynein motors*)
γ^*_{10}
γ^*_{01}
Retrograde pausing,
n^*_{r0}
(*no transport*)
γ^*_{ra}
γ^*_{ar}
Anterograde pausing,
n^*_{a0}
(*no transport*)
γ^*_{01}
γ^*_{10}
Anterograde running,
n^*_a
(*active anterograde transport by kinesin motors*)

Figure 2

(a)


slow (bidirectional) ax transp, v^*_{av}=0.02 μm/s
slow (bidirectional) ax transp, v^*_{av}=0.05 μm/s
slow (bidirectional) ax transp, v^*_{av}=0.1 μm/s
fast (unidirectional) ax transp anter
assumed protein distribution
n_{tot}
x^*, μm
$\times 10^4$

(b)

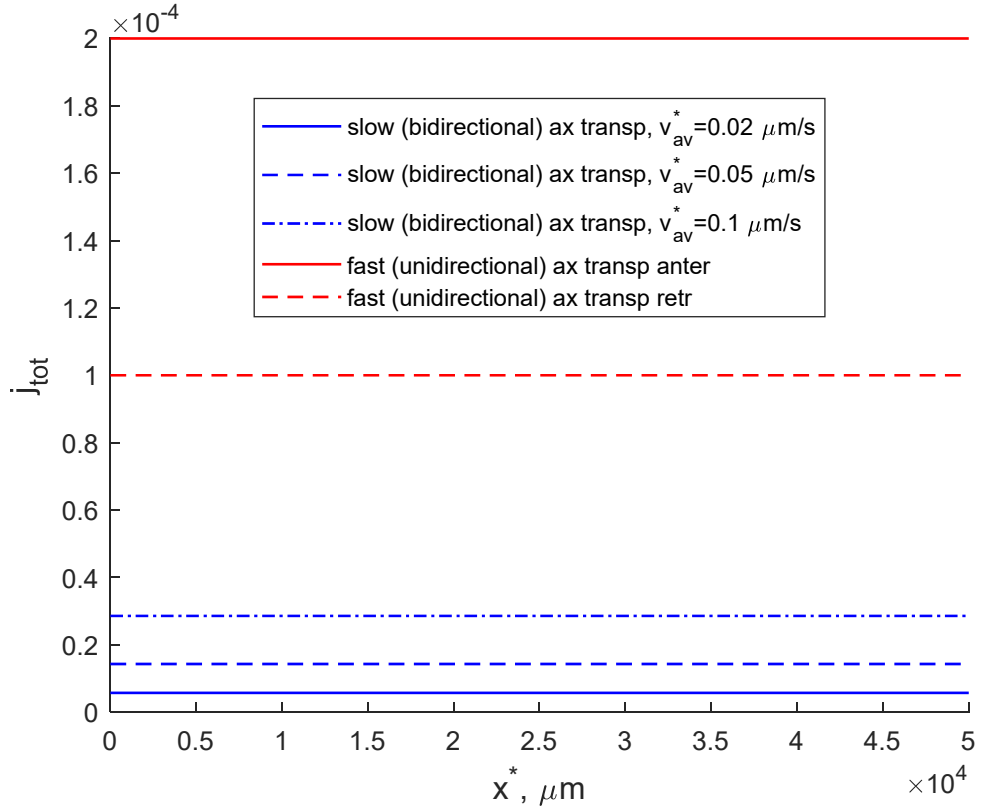

$\times 10^{-4}$
slow (bidirectional) ax transp, v^*_{av}=0.02 μm/s
slow (bidirectional) ax transp, v^*_{av}=0.05 μm/s
slow (bidirectional) ax transp, v^*_{av}=0.1 μm/s
fast (unidirectional) ax transp anter
fast (unidirectional) ax transp retr
j_{tot}
x^*, μm
$\times 10^4$

Figure 3

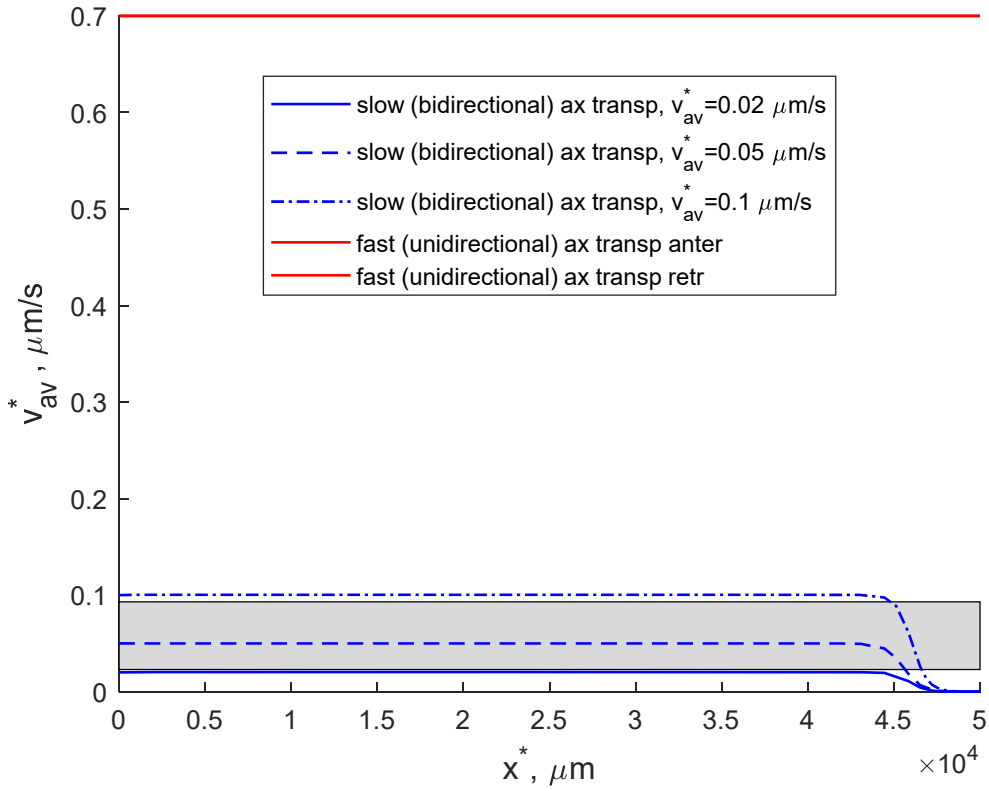
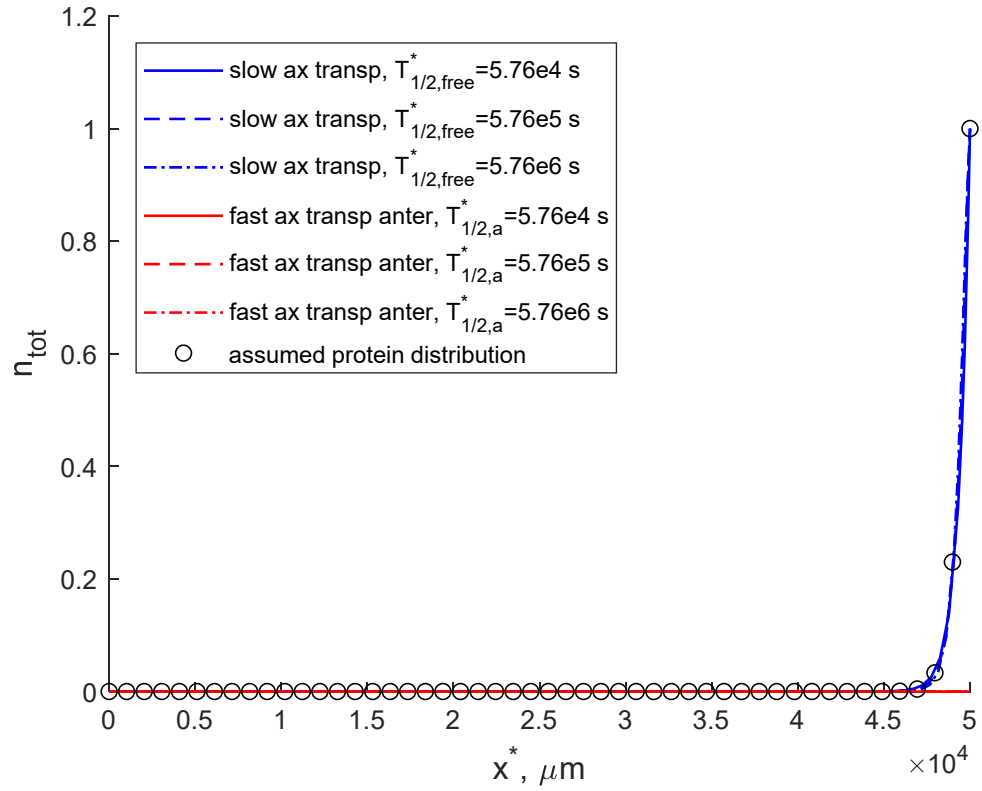

0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
×10^4
x*, μm
v*av, μm/s
slow (bidirectional) ax transp, v*av=0.02 μm/s
slow (bidirectional) ax transp, v*av=0.05 μm/s
slow (bidirectional) ax transp, v*av=0.1 μm/s
fast (unidirectional) ax transp anter
fast (unidirectional) ax transp retr

Figure 4

(a)


slow ax transp, $T^*_{1/2,free}$=5.76e4 s
slow ax transp, $T^*_{1/2,free}$=5.76e5 s
slow ax transp, $T^*_{1/2,free}$=5.76e6 s
fast ax transp anter, $T^*_{1/2,a}$=5.76e4 s
fast ax transp anter, $T^*_{1/2,a}$=5.76e5 s
fast ax transp anter, $T^*_{1/2,a}$=5.76e6 s
assumed protein distribution
n_{tot}
x^*, μm
$\times 10^4$

(b)

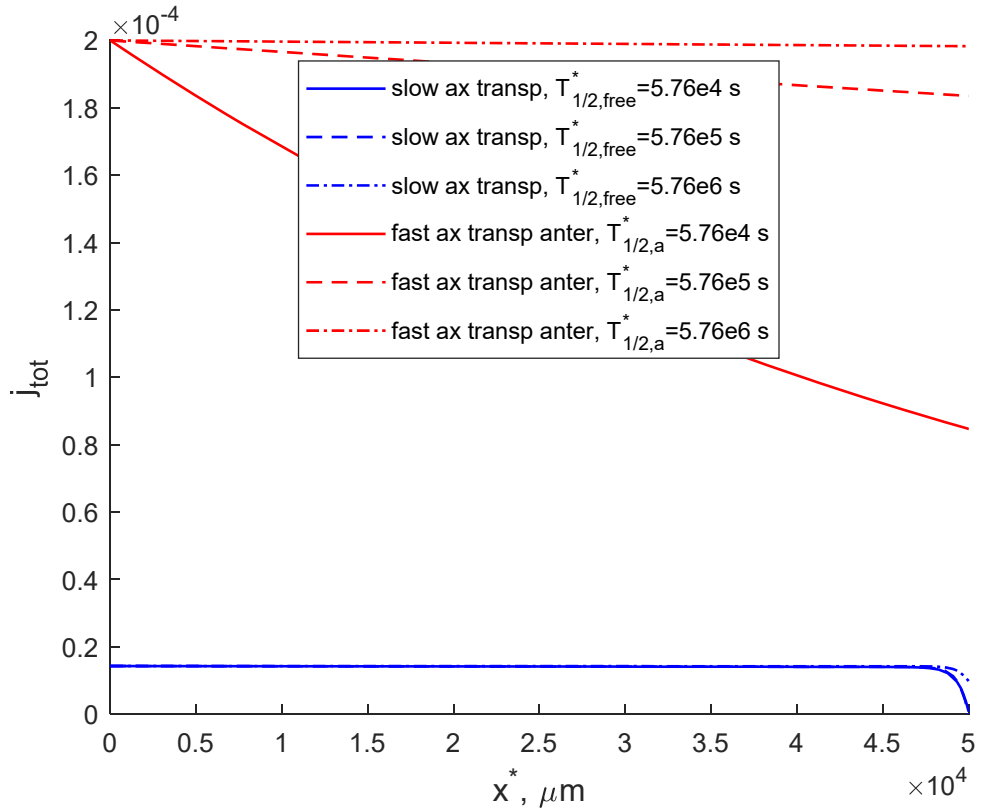

$\times 10^{-4}$
slow ax transp, $T^*_{1/2,free}$=5.76e4 s
slow ax transp, $T^*_{1/2,free}$=5.76e5 s
slow ax transp, $T^*_{1/2,free}$=5.76e6 s
fast ax transp anter, $T^*_{1/2,a}$=5.76e4 s
fast ax transp anter, $T^*_{1/2,a}$=5.76e5 s
fast ax transp anter, $T^*_{1/2,a}$=5.76e6 s
j_{tot}
x^*, μm
$\times 10^4$

Figure 5

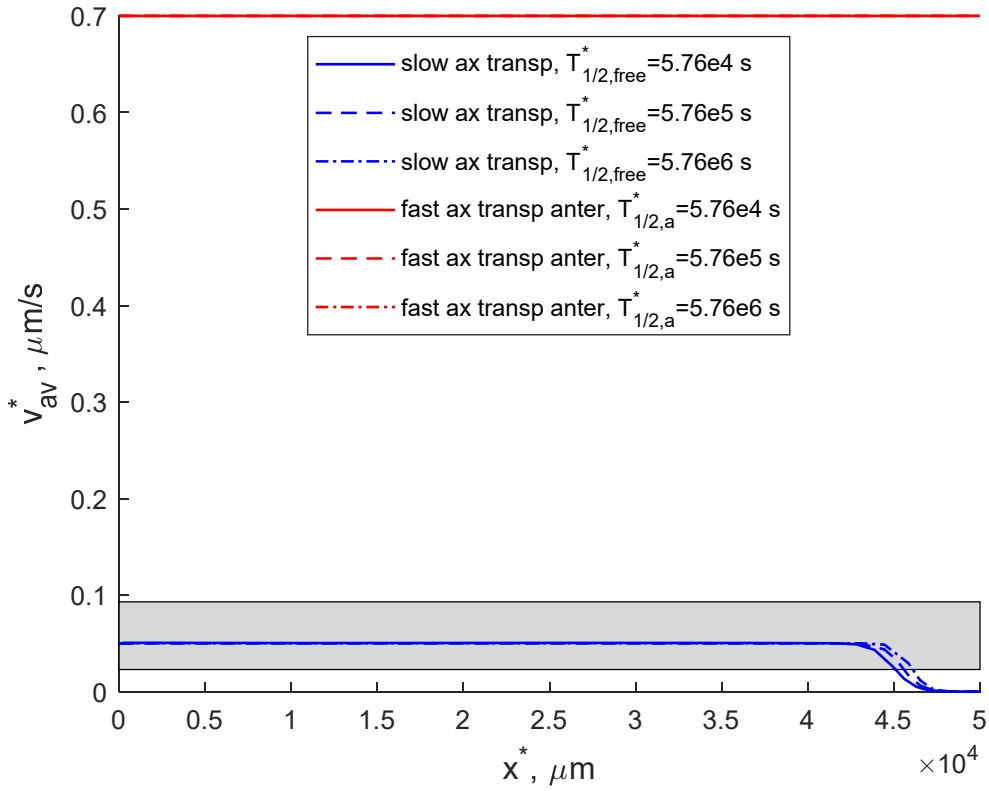
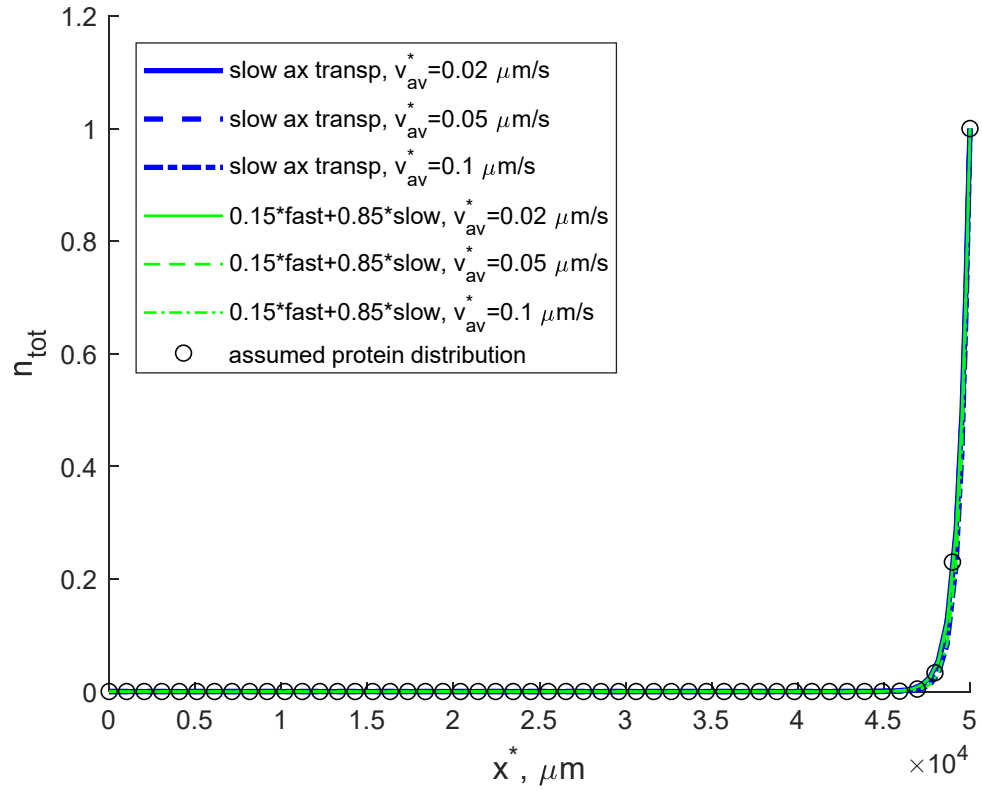

0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
×10^4
x*, μm
v*av, μm/s
slow ax transp, T*1/2,free=5.76e4 s
slow ax transp, T*1/2,free=5.76e5 s
slow ax transp, T*1/2,free=5.76e6 s
fast ax transp anter, T*1/2,a=5.76e4 s
fast ax transp anter, T*1/2,a=5.76e5 s
fast ax transp anter, T*1/2,a=5.76e6 s

Figure 6

(a)


slow ax transp, v^*_{av}=0.02 μm/s
slow ax transp, v^*_{av}=0.05 μm/s
slow ax transp, v^*_{av}=0.1 μm/s
0.15*fast+0.85*slow, v^*_{av}=0.02 μm/s
0.15*fast+0.85*slow, v^*_{av}=0.05 μm/s
0.15*fast+0.85*slow, v^*_{av}=0.1 μm/s
assumed protein distribution
n_{tot}
x^*, μm
$\times 10^4$

(b)

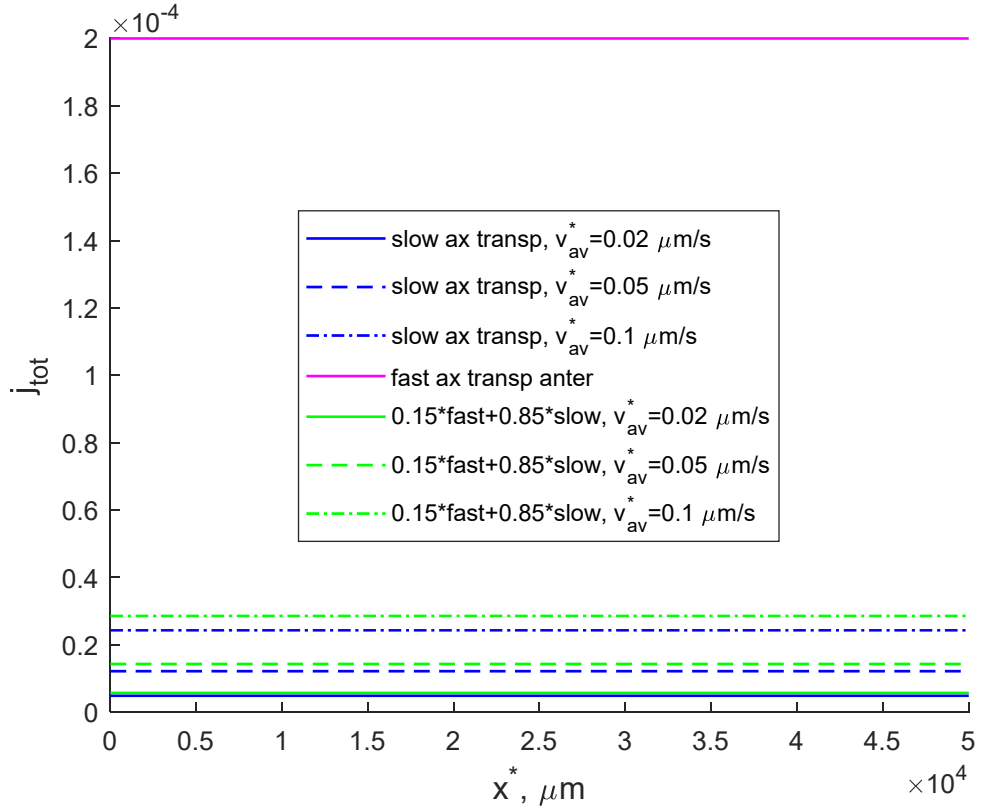

$\times 10^{-4}$
slow ax transp, v^*_{av}=0.02 μm/s
slow ax transp, v^*_{av}=0.05 μm/s
slow ax transp, v^*_{av}=0.1 μm/s
fast ax transp anter
0.15*fast+0.85*slow, v^*_{av}=0.02 μm/s
0.15*fast+0.85*slow, v^*_{av}=0.05 μm/s
0.15*fast+0.85*slow, v^*_{av}=0.1 μm/s
j_{tot}
x^*, μm
$\times 10^4$

Figure 7

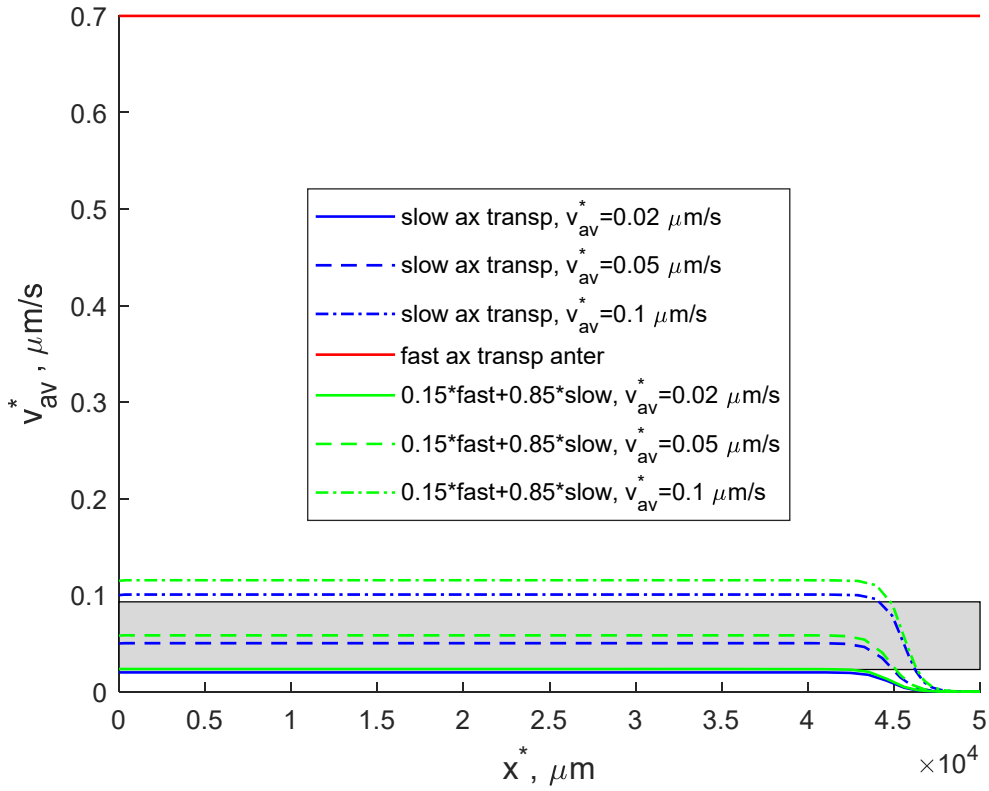

0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
×10^4
x*, μm
v*av, μm/s
slow ax transp, v*av=0.02 μm/s
slow ax transp, v*av=0.05 μm/s
slow ax transp, v*av=0.1 μm/s
fast ax transp anter
0.15*fast+0.85*slow, v*av=0.02 μm/s
0.15*fast+0.85*slow, v*av=0.05 μm/s
0.15*fast+0.85*slow, v*av=0.1 μm/s

Figure 8