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Modeling traffic jams in intracellular transport in axons

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ABSTRACT

Irregularities in intracellular traffic in axons caused by mutations of molecular motors may lead to "traffic jams", which often result in swelling of axons causing various neurodegenerative diseases. The purpose of this paper is to suggest a model of the formation of traffic jams in axons during molecular-motor-assisted transport of intracellular organelles utilizing transport equations developed in Smith and Simmons [D.A. Smith, R.M. Simmons, Models of motor-assisted transport of intracellular particles, Biophys. J. 80 (2001) 45–68], which describe the motion of intracellular particles under the combined action of diffusion and motor-driven transport. According to this model, large intracellular organelles are transported in the cytoplasm by a combined action of diffusion and motor-driven transport. In an axon, organelles are transported away from the neuron's body toward the axon's terminal by kinesin-family molecular motors running on tracks composed by microtubules; old and used components are carried back toward neuron's body by dynein-family molecular motors. Binding/detachment kinetic processes between the organelles and microtubules are specified by first rate reaction constants; these lead to coupling between the three organelle concentrations.

1. Introduction

Neurons are highly specialized cells that have long arms (processes). If the arm transmits electrical signals, it is called an axon, whereas if it receives electrical signals, it is called a dendrite (Fig. 1) [1]. Axons in a human body can be up to one meter in length. Axons support little synthesis of proteins or membrane, therefore materials must be constantly imported from the synthetically active cytoplasm of the cell body ([2]) and transported to arms' terminals. Diffusion is not a sufficiently fast mechanism for transporting large intracellular particles (organelles), such as large protein particles or intracellular vesicles carrying different types of cargo. This is because according to Einstein's relation that determines the diffusivity of small particles due to the Brownian motion, the diffusivity is inversely proportional to the particles' radius, which means that larger particles have smaller diffusivity. To overcome the diffusion limitation, intracellular transport in axons and dendrites relies on the "railway system": large intracellular particles attach themselves to molecular motors (specialized proteins that as a result of a chemical process, usually ATP hydrolysis, undergo conformational changes "walking" along intracellular filaments, such as microtubules) that transport them along microtubules.

All microtubules (MT) in an axon have the same polarity (their plus ends point toward the axon terminal); the microtubules do not stretch the entire length of the axon so that the continuous path along the axon is composed by short overlapping segments of parallel microtubules. Transport vesicles loaded with specific proteins are carried away from the neuron body toward the synapse (the axon terminal) by kinesin-family molecular motors (this family of molecular motors is responsible for the transport on microtubules toward their plus-ends). Used and old intracellular organelles are carried from the axon terminal toward the body of the neuron by dynein-family molecular motors (this family of molecular motors is responsible for the transport on microtubules toward their minus-ends). In dendrites the microtubule polarities are mixed; some of them point their plus ends toward the dendrite tip and some point those toward the neurons' body. Therefore, in a dendrite, depending on the polarity of a particular microtubule, transport in a certain direction (to the neuron's body or away from it) can be carried out by either kinesin or dynein molecular motors ([1,3]).

Irregularities in intracellular traffic in axons caused by mutations of molecular motors may lead to "traffic jams", which may result in swelling of axons causing various neurodegenerative diseases ([2,4,5]). Hurd and Saxton [2] published electron micrographs of cross-sections through axonal swellings. The micrographs show that the swellings, caused by traffic jams induced by a mutation of a gene encoding the force-producing heavy chain of the kinesin molecular motor, are packed with mitochondria, large multi-vesicular bodies, and other types of intracellular organelles.

The purpose of this paper is to suggest a model of the formation of traffic jams in axons during molecular-motor-assisted transport

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Nomenclature

D_0	dimensionless diffusivity of a free particle, $\frac{\widetilde{D}_0\tilde{k}_+}{\tilde{v}_+^2}$
$\widetilde{D}_0$	diffusivity of a free particle
k_-	dimensionless binding rate to microtubules for particles that move in the negative direction, $\frac{\tilde{k}_-}{\tilde{k}_+}$
$\tilde{k}_\pm$	first order rate constants for binding to microtubules for particles that move in the positive (+) and negative (−) directions, respectively
$k'_\pm$	dimensionless detachment rate from microtubules for particles that move in the positive (+) and negative (−) directions, respectively, $\frac{k'_\pm}{\tilde{k}_+}$
$k'_{\pm 0}$	dimensionless detachment rate from microtubules for particles that move in the positive (+) and negative (−) directions for the case when concentration of particles riding on microtubules is very low
$\tilde{k}'_\pm$	first order rate constants for detachment from microtubules for particles that move in the positive (+) and negative (−) directions, respectively
L	dimensionless axon length, $\frac{\widetilde{L}\tilde{k}_+}{\tilde{v}_+}$
$\widetilde{L}$	axon length
n_0	dimensionless free particle concentration, $\tilde{n}_0\frac{\tilde{v}_+^3}{\tilde{k}_+^3}$
$\tilde{n}_0$	free particle concentration
$n_\pm$	dimensionless concentration of particles moving on microtubules in the positive (+) and negative (−) directions, respectively, $\tilde{n}_\pm\frac{\tilde{v}_+^3}{\tilde{k}_+^3}$
$\tilde{n}_\pm$	concentration of particles moving on microtubules in the positive (+) and negative (−) directions, respectively
N_0	dimensionless concentration of free particles maintained at $x = 0$, $\widetilde{N}_0\frac{\tilde{v}_+^3}{\tilde{k}_+^3}$
$\widetilde{N}_0$	constant concentration of free particles maintained at $\tilde{x} = 0$
N_L	dimensionless concentration of free particles maintained at $x = L$, $\widetilde{N}_L\frac{\tilde{v}_+^3}{\tilde{k}_+^3}$
$\widetilde{N}_L$	constant concentration of free particles maintained at $\tilde{x} = \widetilde{L}$
$\tilde{t}$	time
v_-	dimensionless velocity of a particle moving on a microtubule toward the cell body, $\frac{\tilde{v}_-}{\tilde{v}_+}$
v_{-0}	dimensionless velocity of a particle moving on a microtubule in the negative (−) direction for the case when concentration of particles riding on microtubules is very low
$\tilde{v}_\pm$	velocity of a particle moving on a microtubule in the positive (+) and negative (−) directions, respectively
x	dimensionless particle displacement in the axon, $\frac{\tilde{x}\tilde{k}_+}{\tilde{v}_+}$
$\tilde{x}$	particle displacement in the axon

Greek symbols

σ_0	degree of loading at $\tilde{x} = 0$
σ_L	degree of loading at $\tilde{x} = \widetilde{L}$

of intracellular organelles utilizing transport equations developed in Smith and Simmons [6] which describe motion of intracellular particles under the combined action of diffusion and motor-driven transport. According to this model, the organelle either diffuses freely in the cytosol or moves on a filament at a motor velocity; the organelle can bind to or detach from a filament. Depending on the type of a molecular motor (or several motors) attached to the particle, the motion along the microtubule can occur in either direction. Dinh et al. [7] presented numerical solutions of Smith–Simmons equations to describe intracellular trafficking of adenoviruses between the cell membrane and cell nucleus. Other relevant aspects of intracellular transport of cell organelles and vesicles along microtubules are considered in [8–15].

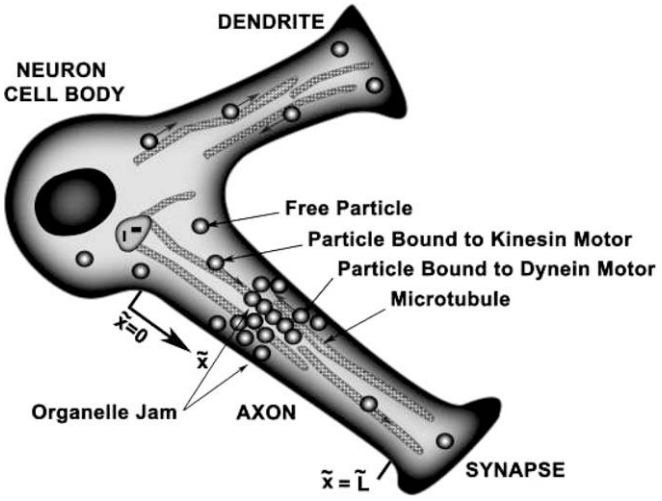

Fig. 1. Schematic diagram of a neuron cell with a dendrite and axon; also, a traffic jam in the axon resulting from crowding of organelles at a certain location in the axon.

2. Governing equations

The molecular-motor-assisted transport equations suggested in Smith and Simmons [6] are

$$\frac{\partial\tilde{n}_0}{\partial\tilde{t}} = \widetilde{D}_0\frac{\partial^2\tilde{n}_0}{\partial\tilde{x}^2} - (\tilde{k}_+ + \tilde{k}_-)\tilde{n}_0 + \tilde{k}'_+\tilde{n}_+ + \tilde{k}'_-\tilde{n}_- \tag{1}$$

$$\frac{\partial\tilde{n}_+}{\partial\tilde{t}} = \tilde{k}_+\tilde{n}_0 - \tilde{k}'_+\tilde{n}_+ - \frac{\partial(\tilde{v}_+\tilde{n}_+)}{\partial\tilde{x}} \tag{2}$$

$$\frac{\partial\tilde{n}_-}{\partial\tilde{t}} = \tilde{k}_-\tilde{n}_0 - \tilde{k}'_-\tilde{n}_- - \frac{\partial(\tilde{v}_-\tilde{n}_-)}{\partial\tilde{x}} \tag{3}$$

where $\widetilde{D}_0$ is the diffusivity of a free particle; $\tilde{t}$ is the time; $\tilde{n}_0$ is the free particles concentration; $\tilde{n}_+$ is the concentration of particles moving on microtubules in the positive direction (away from the cell body); $\tilde{n}_-$ is the concentration of particles moving on microtubules in the negative direction (toward the cell body); $\tilde{x}$ is the linear coordinate along the axon; $\tilde{v}_-$ is the velocity of a particle moving on a microtubule toward the cell body (in an axon this is the motor velocity generated by a dynein-family molecular motor), $\tilde{v}_-$ is negative; $\tilde{v}_+$ is the velocity of a particle moving on a microtubule away from the cell body (in an axon this is the motor velocity generated by a kinesin-family molecular motor), $\tilde{v}_+$ is positive; $\tilde{k}_+$ and $\tilde{k}_-$ are the first order rate constants for binding to microtubules for particles that move in the positive and negative directions, respectively; and $\tilde{k}'_+$ and $\tilde{k}'_-$ are the first order rate constants for detachment from microtubules for particles that move in the positive and negative directions, respectively. Eqs. (1)–(3) to be solved subject to the following boundary conditions:

$$\tilde{x} = 0, \quad \tilde{n}_0 = \widetilde{N}_0, \quad \tilde{n}_+ = \sigma_0\widetilde{N}_0 \tag{4}$$

$$\tilde{x} = \widetilde{L}, \quad \tilde{n}_0 = \widetilde{N}_L, \quad \tilde{n}_- = \sigma_L\widetilde{N}_L \tag{5}$$

where $\widetilde{N}_0$ and $\widetilde{N}_L$ are fixed concentrations of particles at $\tilde{x}=0$ and $\tilde{x}=\widetilde{L}$, respectively; and σ_0 and σ_L are the degrees of loading at $\tilde{x}=0$ and $\tilde{x}=\widetilde{L}$, respectively.

Since the time scale for the development of neurodegenerative diseases (for the formation of traffic jams) is large, the transient terms in Eqs. (1)–(3) are neglected, and axonal transport is considered at steady-state conditions.

According to the Pi theorem, the maximum variable reduction is equal to two (the number of dimensions describing the variables, length and time). Dimensionless variables are introduced as follows:

$$D_0=\frac{\widetilde{D}_0\tilde{k}_+}{\tilde{v}_{+0}^2},\quad k_-=\frac{\tilde{k}_-}{\tilde{k}_+},\quad k'_\pm=\frac{\tilde{k}'_\pm}{\tilde{k}_+},\quad L=\frac{\widetilde{L}\tilde{k}_+}{\tilde{v}_{+0}},\quad n_0=\tilde{n}_0\frac{\tilde{v}_{+0}^3}{\tilde{k}_+^3} \tag{6}$$

$$n_\pm=\tilde{n}_\pm\frac{\tilde{v}_{+0}^3}{\tilde{k}_+^3},\quad N_0=\widetilde{N}_0\frac{\tilde{v}_{+0}^3}{\tilde{k}_+^3},\quad N_L=\widetilde{N}_L\frac{\tilde{v}_{+0}^3}{\tilde{k}_+^3},\quad v_-=\frac{\tilde{v}_-}{\tilde{v}_{+0}},\quad x=\frac{\tilde{x}\tilde{k}_+}{\tilde{v}_{+0}} \tag{7}$$

In order to simulate traffic jams in axons, two physical modeling approaches are investigated

1. The increase of concentration of particles riding on microtubules results in decreasing the molecular motor velocity; this behavior may be related to mutations of genes coding the structure of molecular motors. The slowdown is modeled here by the exponential functions:

$$\tilde{v}_+=\tilde{v}_{+0}\exp(-An_+),\quad \tilde{v}_-=\tilde{v}_{-0}\exp(-An_-) \tag{8}$$

   where $\tilde{v}_{+0}$ and $\tilde{v}_{-0}$ are values of $\tilde{v}_+$ and $\tilde{v}_-$ for the case when concentration of particles riding on microtubules is very low.
2. Alternatively, it may be a better physical approach to assume that molecular motor velocity is independent of particle concentration (this is done by setting $A=0$ in Eq. (8)), but as number densities of organelles riding on microtubules (n_+ and n_-) increase, the probability of them falling off the microtubules and becoming free particles increases. Indeed, molecular motors operate in a very noisy environment (constantly experiencing thermally excited collisions with water molecules); organelles with attached molecular motors compete for the same space close to the microtubule [16]. Therefore, it is reasonable to assume that the increase of number density concentration of intercellular particles riding on a microtubule results in larger probability for a molecular motor to fall off the microtubule thus increasing the detachment rate constants, $\tilde{k}'_\pm$. This is modeled by representing the detachment rate constants as:

$$k'_+=k'_{+0}\exp(Bn_+),\quad k'_-=k'_{-0}\exp(Bn_-) \tag{9a}$$

   where k'_{+0} and k'_{-0} are values of k'_+ and k'_- for the case when concentration of particles riding on microtubules is very low.This should be particularly true in the regions occupied by axonal swelling. An organelle-filled axonal swelling can be modeled by locally increasing the value of constant B in the region occupied by the swelling. For example, if the swelling is located in the region $x_1\leqslant x\leqslant x_2$, this can be modeled by the following step function:

$$0\leqslant x<x_1\quad\text{and}\quad x_1<x\leqslant x_2: B=0 \tag{9b}$$

$$x_1\leqslant x\leqslant x_2:\quad B=B_0 \tag{9c}$$

   where B_0 is a positive constant.

Under these assumptions, the dimensionless steady-state governing equations are

$$D_0\frac{\mathrm{d}^2n_0}{\mathrm{d}x^2}-(1+k_-)n_0+k'_{+0}\exp(Bn_+)n_++k'_{-0}\exp(Bn_-)n_-=0 \tag{10}$$

$$n_0-k'_{+0}\exp(Bn_+)n_+-\frac{\mathrm{d}(\exp(-An_+)n_+)}{\mathrm{d}x}=0 \tag{11}$$

$$k_-n_0-k'_{-0}\exp(Bn_-)n_--v_{-0}\frac{\mathrm{d}(\exp(-An_-)n_-)}{\mathrm{d}x}=0 \tag{12}$$

The dimensionless boundary conditions are

$$x=0,\quad n_0=N_0,\quad n_+=\sigma_0N_0 \tag{13}$$

$$x=L,\quad n_0=N_L,\quad n_-=\sigma_LN_L \tag{14}$$

The dimensionless flux of intracellular organelles is

$$j=-D_0\frac{\mathrm{d}n_0}{\mathrm{d}x}+\exp(-An_+)n_++v_{-0}\exp(-An_-)n_- \tag{15}$$

By adding Eqs. (10)–(12) and integrating the result once with respect to x it is readily proven that for the steady-state situation j is a constant (independent of x).

Finite difference approximation is used to solve the non-linear system of equations, i.e., Eqs. (10)–(12), iteratively subject to the appropriate boundary conditions, i.e., Eqs. (13) and (14). As seen, two boundary conditions are available for the second order differential equation, Eq. (10), when solved for n_0. On the other hand, while one of the first order equations, Eq. (11), has its only boundary condition at $x=0$, the other one, when solved for n_-, is solved subject to a known value at the other end of the axon, i.e., at $x=L$. Hence, Eq. (10) is discretized by a central difference scheme (CDS) while a forward/backward one is implemented for Eqs. (11) and (12). Uniform grids of size $\Delta x=0.02$ are used. Grid independence is verified by running the most stringent cases (associated with the highest B or the lowest A values) on different grid sizes. It is observed that moving Δx from 0.02 to 0.01, the change in the results is less than 1%. The convergence criterion (maximum relative error in the values of the dependent variables between two successive iterations) in all runs is set at 10^{-7}. As a test on the accuracy of the numerical procedure the results are compared (successfully) with those obtained by a numerical solution of the same equations

Table 1
Dimensionless parameters utilized in computations

Parameter	Description	Value
D_0	Diffusivity of free particles	0.4
k_-	Binding rate to microtubules for particles that move in the negative direction (toward the cell body)	1
$k'_{\pm0}$	Detachment rate from microtubules for particles that move in the positive (+) and negative (−) directions for the case when concentration of particles riding on microtubules is very low	0.5
L	Axon length	20
N_0	Concentration of free particles at $x=0$	0.1
N_L	Concentration of free particles at $x=L$	0.01
v_{-0}	Motor speed of a particle moving on a microtubule in the negative (−) direction for the case when concentration of particles riding on microtubules is very low	−1
σ_0	Degree of loading at $x=0$	0.1
σ_L	Degree of loading at $x=L$	0.1

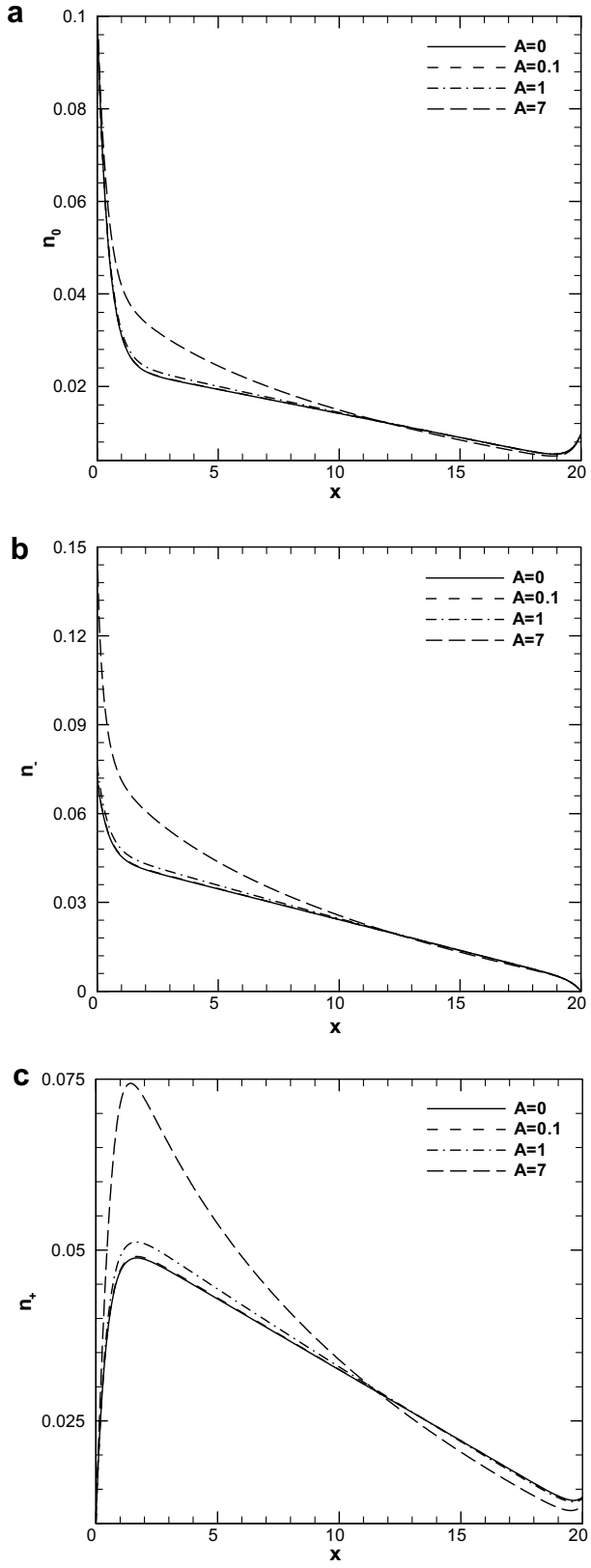

Fig. 2. Effect of slowing down the molecular-motor assisted transport along microtubules (see Eq. (8)) on number density concentrations of free particles, n_0 (a), particles riding on microtubules toward the neuron body, n_- (b), and particles riding on microtubules away from the cell body, n_+ (c). Computed for $B = 0$.

using the Mathematica software package for the case when the system of equations is linear, i.e., $A = B = 0$.

Table 2
Effect of the traffic jam due to velocity decrease at larger concentration of organelles riding on microtubules on the flux of the organelles toward the axon terminal, computed for $B = 0$

A	j
0	0.0087
0.1	0.0086
1	0.0083
7	0.0063

3. Results and discussion

In the light of Dinh et al [7], the detachment rate constants, $\tilde{k}'_{\pm}$, for trafficking adenoviruses of type 2 in HeLa cells are estimated as 0.5 s^{-1}. The corresponding binding rates, $\tilde{k}_{\pm} = 1$, are taken to be equal to 1 s^{-1} based on [6]. According to [6], typical molecular motor velocities are $\tilde{v}_{\pm} = \pm 1$ μm/s; the Einstein relation for a 1 μm sphere in water gives $\tilde{D}_0 = 0.4$ $\mu m^2/s$. Estimations of transport properties for different types of organelles are also given in Table 1 of [9] and in supplementary material for [12] and are not repeated here. A relatively short axon whose length is 20 μm is modeled in this research. This explains the choice of dimensionless parameter values summarized in Table 1.

Fig. 2a–c displays dimensionless number density concentrations of free particles, n_0, particles riding on microtubules toward the neuron body, n_-, and particles riding on microtubules away from the neuron body, n_+. The effect of slowing down the molecular motor velocity as number density concentration of particles riding on microtubules increases is investigated. Computations are performed for $B = 0$ (the detachment rates from microtubules, $k'_{\pm}$, are assumed to remain constant, independent of organelle concentration) for various values of A (see Eq. (8)). A traffic jam for n_+ is evident in Fig. 2c; it occurs at approximately $x = 2.0$. The traffic of organelles toward the axon terminal becomes more jammed as A increases. This is as expected because larger A corresponds to more significant slowdown of molecular-motor-assisted transport as density of the traffic increases. This is similar to the formation of a cluster of cars in traffic flow [17], with the difference that traditional traffic flows are essentially unsteady, and clusters of cars (traffic jams) often form in a homogeneous flow and are highly dynamic objects. Traffic jams in the intracellular flow of organelles, on the contrary, are steady-state objects because of a large timescale involved in their formation. As one can see from Table 2, this traffic jam results in the reduction of the dimensionless flux of intracellular organelles, j (see Eq. (15)), thus reducing the supply of proteins to the axon terminal (synapse, see Fig. 1), which eventually may lead to a disruption of normal functioning of the neuron.

Fig. 3a–c is similar to Fig. 2a–c, but it investigates the possible effect of an organelle-filled axonal swelling (positioned in the region of $10 \leqslant x \leqslant 11$) on organelle transport in axons. The effect of axonal swelling is modeled by locally increasing the value of constant B in the region occupied by the swelling (see Eqs. (9b) and (9c)). The traffic jam in the region of axonal swelling, $10 \leqslant x \leqslant 11$, is clearly visible. Table 3 shows that this traffic jam results in reducing the flux of organelles toward axon terminal; the reduction becomes more significant as B_0 increases.

4. Conclusions

This research demonstrates that modified Smith–Simmons equations are capable of modeling traffic jams in molecular-motor-assisted transport of intracellular organelles in axons. Two approaches to modeling traffic jams in axons are discussed

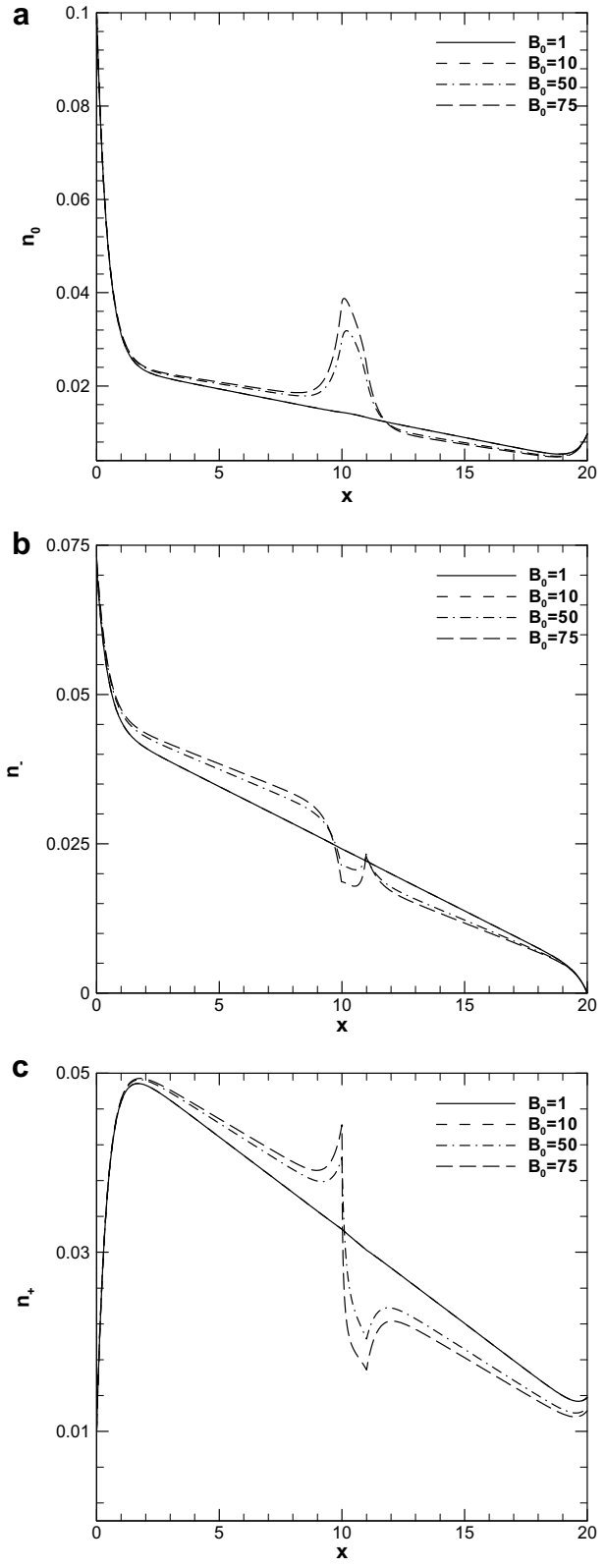

Fig. 3. Effect of increasing the detachment rate from microtubules (see Eqs. (9a)–(9c)) on number density concentrations of free particles, n_0 (a), particles riding on microtubules toward the neuron body, n_- (b), and particles riding on microtubules away from the cell body, n_+ (c). Computed for $A = 0$, B is increased locally in the region $10 < x < 11$ (the value of B in this region is set to B_0), otherwise $B = 0$.

Table 3
Effect of the traffic jam due to increased probability of the organelles to fall off the microtubules on the flux of the organelles toward the axon terminal, computed for $A = 0$

B in the region $10 < x < 11$ ($B = 0$ otherwise)	j
1	0.0087
10	0.0085
50	0.0073
75	0.0068

(1) Traffic jam is obtained by assuming that the increase of concentration of particles riding on microtubules results in decreasing the molecular motor velocity; this behavior may be related to mutations of genes coding the structure of molecular motors.
(2) It is also shown that traffic jam can be caused by the assumption that as number density of organelles riding on microtubules increases, the probability of them falling off the microtubules and becoming free particles increases.

This is particularly true in the regions occupied by an axonal swelling, where organelles with attached molecular motors compete for the same limited space close to the microtubule. The effect of an organelle-filled axonal swelling is modeled by locally increasing the value of constant B in the region occupied by the swelling. It is shown that traffic jam results in reducing the flux of organelles toward axon terminal, which may eventually lead to a disruption of normal functioning of the neuron.

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