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Hydrodynamic modeling of 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 such neurodegenerative diseases as Alzheimer's disease and Down syndrome. Hence, it is of particular interest to mathematically model the formation of traffic jams in axons. This paper adopts the hydrodynamic continuity equations for intracellular transport of organelles as developed by Smith and Simmons [1] whereas the Kerner and Konhäuser [2] model for traffic jams in highway traffic is applied to predict the velocity field. It is observed that combination of the two sets of equations can comprehensively predict the traffic jams in axons without the need to any additional assumption or modification.

Keywords: Numerical, Molecular motors, Motor-assisted transport, Neurons, Axons and dendrites, Intracellular organelles, Traffic jams

Nomenclature

c_0^2	dimensionless variance of the velocity distribution, $\frac{\tilde{c}_0^2}{\tilde{V}_{+0}^2}$
$\tilde{c}_0^2$	variance of the velocity distribution
D_0	dimensionless diffusivity of a free particle, $\frac{\tilde{D}_0\tilde{k}_+}{\tilde{V}_{+0}^2}$
$\tilde{D}_0$	diffusivity of a free particle

k_- dimensionless binding rate to MTs for particles that move in the negative direction, $\frac{\tilde{k}_-}{\tilde{k}_+}$

$\tilde{k}_\pm$ first order rate constants for binding to MTs for particles that move in the positive (+) and negative (−) directions, respectively

$k'_\pm$ dimensionless detachment rate from MTs for particles that move in the (+)/(−) directions, respectively, $\frac{\tilde{k}'_\pm}{\tilde{k}_+}$

$k'_{\pm 0}$ dimensionless detachment rate from MTs for particles that move in the (+)/(−) directions for the case when concentration of particles riding on microtubules is very low

$\tilde{k}'_\pm$ first order rate constants for detachment from MTs for particles that move in the (+)/(−) directions, respectively

L dimensionless axon length, $\frac{\tilde{L}\tilde{k}_+}{\tilde{V}_{+0}}$

$\tilde{L}$ axon length

n_0 dimensionless free particle concentration, $\tilde{n}_0 \frac{\tilde{V}_{+0}^3}{\tilde{k}_+^3}$

$\tilde{n}_0$ free particle concentration

$n_\pm$ dimensionless concentration of particles moving on MTs in the (+)/(−) directions, respectively, $\tilde{n}_\pm \frac{\tilde{V}_{+0}^3}{\tilde{k}_+^3}$

$\tilde{n}_\pm$ concentration of particles moving on MTs in the (+)/(−) directions, respectively

N_0 dimensionless concentration of free particles maintained at $x = 0$, $\tilde{N}_0 \frac{\tilde{V}_{+0}^3}{\tilde{k}_+^3}$

$\tilde{N}_0$ constant concentration of free particles maintained at $\tilde{x} = 0$

N_L dimensionless concentration of free particles maintained at $x = L$, $\tilde{N}_L \frac{\tilde{V}_{+0}^3}{\tilde{k}_+^3}$

$\tilde{N}_L$ constant concentration of free particles maintained at $\tilde{x} = \tilde{L}$

$\tilde{t}$ time

t dimensionless average relaxation time, $\tilde{\tau}\tilde{k}_+$

$v_\pm$ dimensionless velocity of a particle moving on a MT in the (+)/(−) directions, respectively $\frac{\tilde{v}_\pm}{\tilde{V}_{+0}}$

$\tilde{v}_\pm$ velocity of a particle moving on a MT in the (+)/(−) directions, respectively

$\tilde{V}_\pm$ average motor velocity of the anterograde (+) and retrograde (−) transport, respectively

$\tilde{V}_{+0}$ average motor velocity of the anterograde (+) transport for the case when concentration of particles riding on MTs is very low

x dimensionless particle displacement in the axon, $\frac{\tilde{x}\tilde{k}_+}{\tilde{V}_{+0}}$

$\tilde{x}$ particle displacement in the axon

Greek symbols

μ dimensionless viscosity of the traffic flow, $\frac{\tilde{\mu}V_{+0}}{\tilde{k}_+^2}$

$\tilde{\mu}$ viscosity of the traffic flow

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

$\tilde{\tau}$ average relaxation time

1. Introduction

Neurons are known to be highly specialized cells with long arms (processes). An axon is an arm which transmits electrical signals. This arm is called a dendrite (see Fig. 1 of Alberts et al. [3]) if it receives electrical signals. Axons in a human body can be up to one meter in length. They support little synthesis of proteins or membrane; hence, materials must be imported constantly from the synthetically active cytoplasm of the cell body (Hurd and Saxton [4]) and be 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 for 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-limited intracellular transport in axons and dendrites axons rely on the "railway system" whereby 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 (MTs)).

All MTs in an axon have the same polarity (their plus ends point toward the axon terminal); the MTs 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 MTs. 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 MTs 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 MTs toward their minus-ends). In dendrites the MT 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 MT, 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 [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 (Hurd and Saxton [4], Goldstein [5], Martin et al. [6]). Hurd and Saxton [4] 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.

Traffic jams in intracellular transport in axons are similar to those in highway traffic [7-10]. Moving in a step-like manner on MTs, kinesin and dynein use energy obtained from ATP hydrolysis to generate force. Experimental observations have been made that step sizes of dynein motors depend on the hindrance force against forward movement of these motors. Based on these observations, Mallik et al. [11] proposed a molecular gear mechanism for them. In a recent study,

Kunwar et al. [12] presented a cellular automata model for intracellular traffic of dynein motors based on the aggressive driving model of vehicular traffic. Fortunately, traffic jams in highway traffic have been studied in great detail using different models including, cellular automation, gas kinetic, and car-following (Nagatani [13]).

The aim of this paper is to simulate traffic jams in an axon by applying numerical techniques. The combination of the molecular motor-assisted transport equations reported in [1] and the hydrodynamic model of traffic jams in highway traffic proposed in [2] form the governing (continuity and momentum, respectively) equations. The model developed by Kuznetsov and Hooman [7] relies exclusively on the first set of equations, i.e. the continuity equations. There, it was assumed that either the detachment rate or the velocity is an exponential function of the number density while the other remains uniform along the axon. That is, no equation was solved to obtain the velocity distribution. The present work, on the other hand, uses the momentum equations of [2] to find the velocity distribution. Hence, it can shed some light on the traffic jams in axons, over a wide range of key parameters, both qualitatively and quantitatively.

2. Governing equations

The molecular-motor-assisted transport equations suggested in Smith and Simmons [1] are

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

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

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

where $\tilde{D}_0$ is the diffusivity of a free particle; $\tilde{t}$ is the time; $\tilde{n}_0$ is the free particles concentration; $\tilde{n}_+, \tilde{n}_-$ is the concentration of particles moving on MTs in the positive and negative direction (away from/toward the cell body) respectively; $\tilde{x}$ is the linear coordinate along the axon; $\tilde{v}_-, \tilde{v}_+$ is the velocity of a particle moving on a MT toward and away from the cell body (in an axon this is the motor velocity generated by a dynein/kinesin -family molecular motor) respectively; $\tilde{k}_+$ and $\tilde{k}_-$ are the first order rate constants for binding to MTs 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 MTs for particles that move in the positive and negative directions, respectively.

These equations are supplemented by equations of motion, which state that the product of particle density and acceleration equals the sum of acting forces (Kerner and Konhäuser [2]), i.e.

$$\frac{\partial \tilde{v}_-}{\partial \tilde{t}} + \tilde{v}_- \frac{\partial \tilde{v}_-}{\partial \tilde{x}} = -\frac{\tilde{c}_0^2}{\tilde{n}_-}\frac{\partial \tilde{n}_-}{\partial \tilde{x}} + \frac{\tilde{V}_-(\tilde{n}_-) - \tilde{v}_-}{\tilde{\tau}} + \frac{1}{\tilde{n}_-}\frac{\partial}{\partial \tilde{x}}\left(\tilde{\mu}\frac{\partial \tilde{v}_-}{\partial \tilde{x}}\right) \tag{4}$$

$$\frac{\partial \tilde{v}_+}{\partial \tilde{t}} + \tilde{v}_+ \frac{\partial \tilde{v}_+}{\partial \tilde{x}} = -\frac{\tilde{c}_0^2}{\tilde{n}_+}\frac{\partial \tilde{n}_+}{\partial \tilde{x}} + \frac{\tilde{V}_+(\tilde{n}_+) - \tilde{v}_+}{\tilde{\tau}} + \frac{1}{\tilde{n}_+}\frac{\partial}{\partial \tilde{x}}\left(\tilde{\mu}\frac{\partial \tilde{v}_+}{\partial \tilde{x}}\right) \tag{5}$$

where $\tilde{\tau}$ is the average relaxation time, $\tilde{c}_0^2$ is the variance of the velocity distribution, $\tilde{\mu}$ is the viscosity of the traffic flow, and $\tilde{V}_\pm$ is the average motor velocity of the anterograde/retrograde (+/-) transport, respectively.

The terms on the right side of the above equations should be interpreted as statistical anticipation functions [8]. Hence, the pressure terms [2], $-\frac{\tilde{c}_0^2}{\tilde{n}_-}\frac{\partial \tilde{n}_-}{\partial \tilde{x}}$ and $-\frac{\tilde{c}_0^2}{\tilde{n}_+}\frac{\partial \tilde{n}_+}{\partial \tilde{x}}$, model the anticipated behavior of molecular motors to accelerate or decelerate if the density (in this case $\tilde{n}_-$ and $\tilde{n}_+$, respectively) decreases or increases. The diffusion (viscous) terms, $\frac{1}{\tilde{n}_-}\frac{\partial}{\partial \tilde{x}}\left(\tilde{\mu}\frac{\partial \tilde{v}_-}{\partial \tilde{x}}\right)$ and $\frac{1}{\tilde{n}_+}\frac{\partial}{\partial \tilde{x}}\left(\tilde{\mu}\frac{\partial \tilde{v}_+}{\partial \tilde{x}}\right)$, model the anticipated behavior to go with the flow of other molecular motors: accelerate or decelerate when the traffic is in the state of special acceleration [17], i.e. $\frac{\partial^2 \tilde{v}_\pm}{\partial \tilde{x}^2} > <0$.

The appropriate boundary conditions for Eqns. (1-5) are

$$\tilde{x} = 0 \quad \tilde{n}_0 = \tilde{N}_0\ \tilde{n}_+ = \sigma_0 \tilde{N}_0\ \frac{\partial(\tilde{v}_{+/-})}{\partial \tilde{x}} = 0 \tag{6}$$

$$\tilde{x} = \tilde{L} \quad \tilde{n}_0 = \tilde{N}_L\ \tilde{n}_- = \sigma_L \tilde{N}_L\ \frac{\partial(\tilde{v}_{+/-})}{\partial \tilde{x}} = 0 \tag{7}$$

According to the Pi theorem, the maximum reduction is equal to two (the number of dimensions describing the variables, length and time). Introducing the appropriate scales, similar to [7,8], and assuming constant and uniform traffic properties (viscosity, relaxation time, and velocity

variance), the dimensionless steady-state (as a large timescale involved in their formation) form of the governing equations are

$$D_0 \frac{d^2 n_0}{dx^2} - \left(k_+ + k_-\right) n_0 + k'_+ n_+ + k'_- n_- = 0 \tag{8}$$

$$k_+ n_0 - k'_+ n_+ - \frac{d\left(v_+ n_+\right)}{dx} = 0 \tag{9}$$

$$k_- n_0 - k'_- n_- - \frac{d\left(v_- n_-\right)}{dx} = 0 \tag{10}$$

$$v_- \frac{dv_-}{dx} = -\frac{c_0^2}{n_-}\frac{dn_-}{dx} + \frac{V_-\left(n_-\right) - v_-}{t} + \frac{\mu}{n_-}\frac{d^2 v_-}{dx^2} \tag{11}$$

$$v_+ \frac{dv_+}{dx} = -\frac{c_0^2}{n_+}\frac{dn_+}{dx} + \frac{V_+\left(n_+\right) - v_+}{t} + \frac{\mu}{n_+}\frac{d^2 v_+}{dx^2} \tag{12}$$

Dimensionless boundary conditions are

$$x = 0 \quad \frac{d(v_{+/-})}{dx} = 0 \;\; n_0 = N_0 \;\; n_+ = \sigma_0 N_0 \tag{13}$$

$$x = L \quad \frac{d(v_{+/-})}{dx} = 0 \;\; n_0 = N_L \;\; n_- = \sigma_L N_L \tag{14}$$

Then, the dimensionless flux of intracellular organelles can be given by

$$j = -D_0 \frac{dn_0}{dx} + v_+ n_+ + v_- n_- \tag{15}$$

Finite difference approximation is used to solve the non-linear system of equations, i.e. Eqns. (8-12), iteratively subject to the appropriate boundary conditions, i.e. Eqns. (13-14). The governing equations are discretized using the Central Difference Scheme (CDS) using a uniform grids of size Δx=0.025. Grid independence is verified by running the code on different grid sizes. It is observed that moving Δx from 0.025 to 0.015, 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 [7,8].

3. Results and Discussion

In the light of Dinh et al [14], 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 [1,7] where the authors assumed that typical molecular motor velocities are $\tilde{v}_{\pm}=\pm 1$ μm/s and that the Einstein relation for a 1-μm sphere in water gives $\tilde{D}_0=0.4$ μm^2/s. As estimations of transport properties for different types of organelles are given in Table 1 of [15] and in supplementary material for [16], they are not repeated here. An axon with a dimensionless length of L=20 is modeled in this research. We have also assumed that N_0=N_L =σ_0= σ_L=0.1, and $V_{+,-}$=+,-1.

Figures 2-4 display dimensionless number density concentrations of free particles, n_0, those riding on microtubules toward and away from the neuron body, n_- and n_+, and the anterograde and retrograde velocities for different values of the controlling parameters. Figures 2(a,b) correspond to t=0.01 and μ=100 with different values of c_0. It can be seen in the figure that as c_0 changes, by even order of magnitude, with the mentioned values for the other parameters, velocities (in either direction) are close to their average values throughout the axon hinting that traffic jams are not forming.

With figures 3(a-d), on the other hand, where μ was made to change from 0.01 to 100, with t and c_0 being fixed (at 1 and 0.1, respectively), a different phenomenon is observed. As the dimensionless viscosity increases, all three number density concentrations increase. Interestingly, the local velocities, still almost uniformly distributed, tend to be half of their average values.

A traffic jam for n_+ is evident in Fig. 3(c); it occurs at approximately x=2.0 which is, surprisingly, the same location as that reported in [7] based on their simplified model. The traffic of organelles toward the axon terminal becomes more jammed as μ 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 while those in the intracellular flow of organelles are steady [7].

Figures 4(a-d), that show the effect of changing the relaxation time, with fixed viscosity and velocity variance, illustrate clearly that the model is capable of predicting the traffic jam. For the highest relaxation time, the number density concentrations are almost doubled (except for regions near the two ends of the axon where boundary conditions are to be satisfied) compared to the lower values of t. Interestingly, the velocity values approach zero (to be more specified reduce by

90% for v_- and 60% for v_+) for high t values. Surprisingly, the velocity distribution tends to be almost indistinguishable when $t>1$ while the changes in the number density concentrations (when t=1) are not as severe as those of t=10 compared to t=0.1. A notable observation is that v_- seems to be more sensitive to a change in relaxation time compared to v_+. This is a very important observation that the anterograde and retrograde velocities do not mirror about the x-axis. This is, however expected as the boundary conditions are different for number density concentrations at the two axon ends despite being identical for the two velocities. The reader should be reminded that the nature of the problem is a coupled one, i.e. the number density concentrations are functions of the velocities (see Eqns. (1-3)) while the velocities are, in turn, affected by the number density concentrations; see Eqns. (4-5).

Figure 5 illustrates how the (dimensionless) flux j, on the vertical axis, changes when the controlling parameters (c_0^2, t, and μ) vary. The horizontal axis represents one of these independent variables (mentioned in the legend in the figure insert) with the other two being fixed. Observe that increasing either of c_0 or t leads to higher j values. This seems to be the case for low viscosity values while for higher viscosities, say μ>10, the converse is true as j decreases with μ. According to this figure, traffic jam results in reducing the flux of organelles toward axon terminal with the reduction being more significant as μ increases.

4. Conclusions

This research demonstrates that modified Smith-Simmons equations if supplemented by Kerner-Konhäuser equations are capable of modeling traffic jams in molecular-motor-assisted transport of intracellular organelles in axons. Effect of different combination of the key parameters, on number densities and velocities, is examined. It was observed that not only the increase in the number density can slow down the traffic jam but also the interaction between different terms in the momentum equations can play a key role. This can be worse in the regions occupied by axonal swelling, where organelles with attached molecular motors compete for the same limited space close to the microtubule. Traffic jams as well as sharp reduction in local velocities can result 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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Figure captions

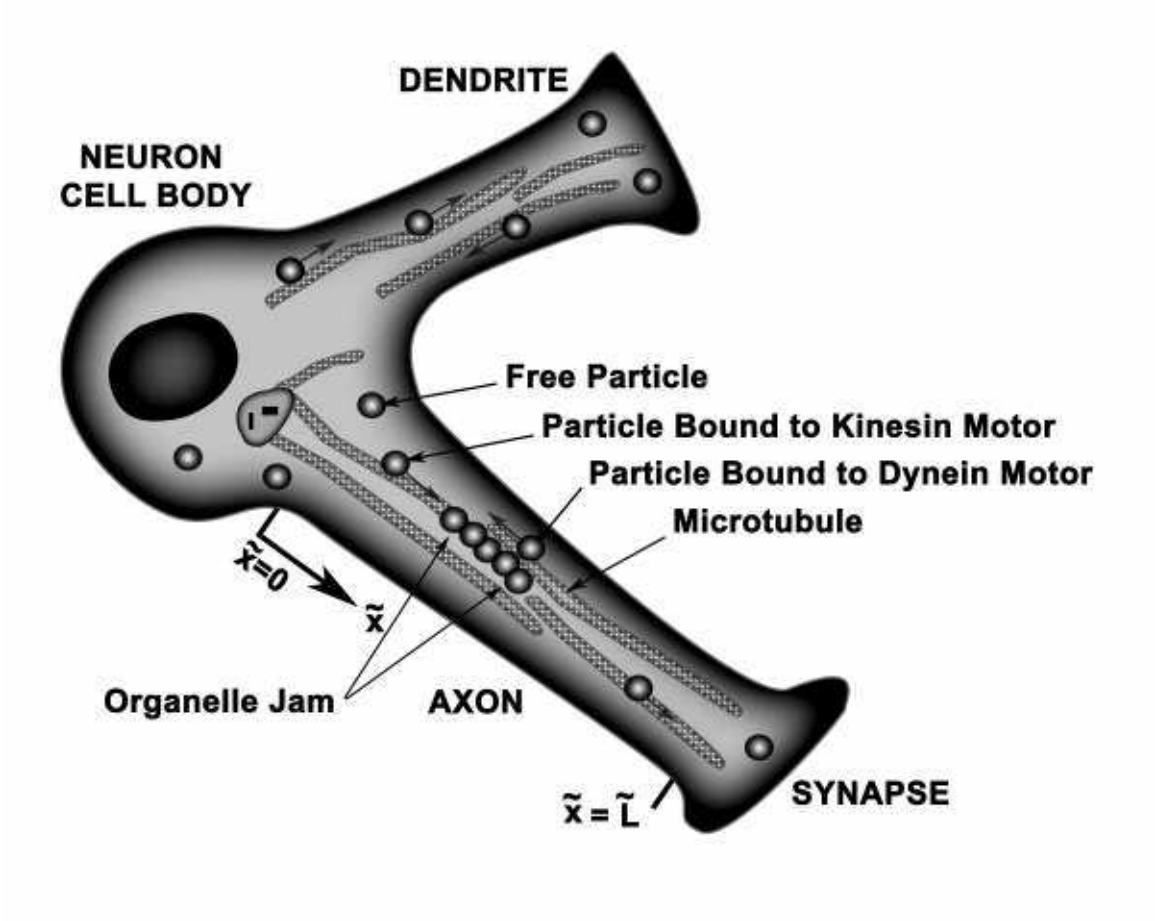
Fig. 1. Schematic diagram of a neuron cell with a dendrite and axon; also, a traffic jam in the axon resulting from crowding of organelles at a certain location in the axon.

Fig. 2. Effect of velocity variance on the molecular-motor assisted transport along microtubules on number density concentrations of free particles, n_0, particles riding on microtubules toward the neuron body, n_-, particles riding on microtubules away from the cell body, n_+ (a), and anterograde/retrograde velocities (b) computed for μ=100 and t=0.01.

Fig. 3. Effect of dimensionless viscosity on number density concentrations of free particles, n_0 (a), particles riding on microtubules toward the neuron body, n_- (b), particles riding on microtubules away from the cell body, n_+ (c), and anterograde/retrograde velocities (d) computed for c_0^2=0.01and t=1.

Fig. 4 Effect of dimensionless relaxation time on number density concentrations of free particles, n_0 (a), particles riding on microtubules toward the neuron body, n_- (b), particles riding on microtubules away from the cell body, n_+ (c), and anterograde/retrograde velocities (d) computed for c_0^2=1and μ=10.

Fig. 5 Effects of velocity variance, viscosity, and relaxation time on the flux. Solid line corresponds to c_0^2=0.1and μ=1. For dashed line t=0.01and μ=100 while with dash-dotted one c_0^2=0.1and t=1



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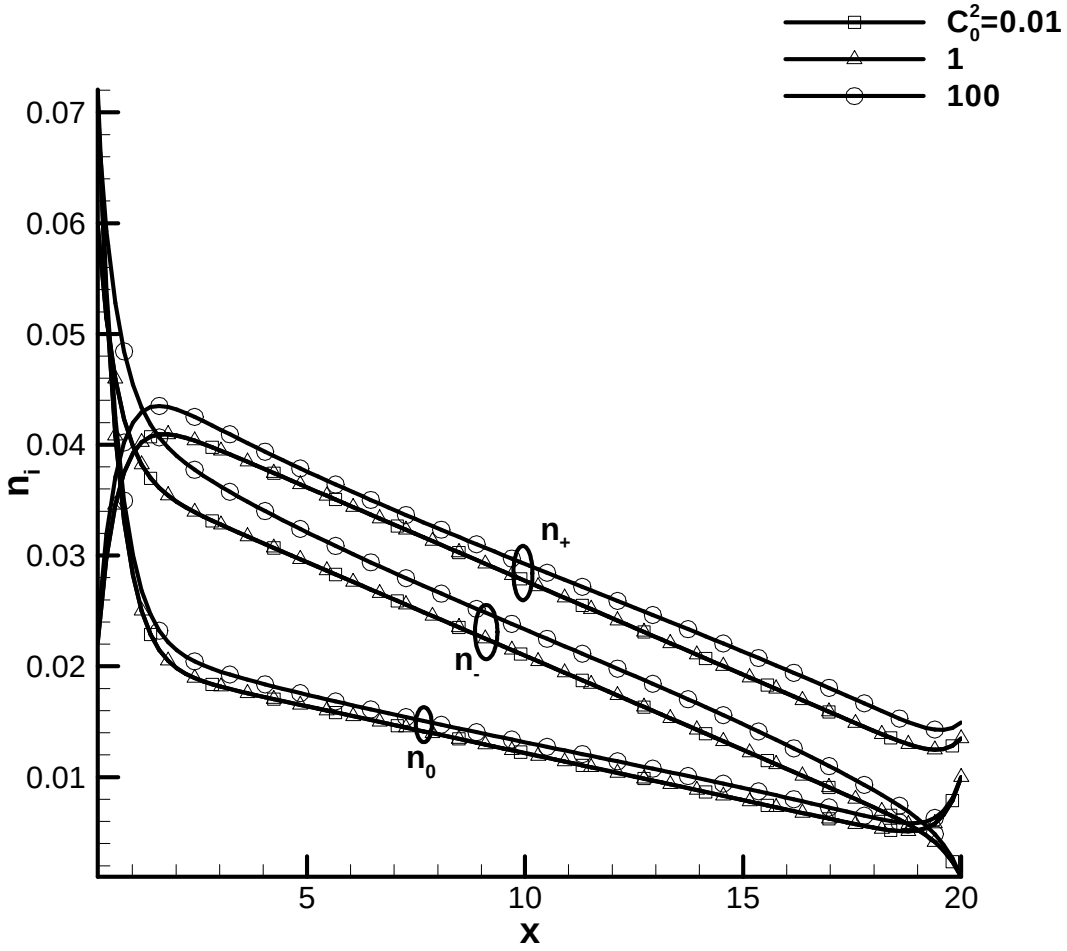

Fig. 2-a

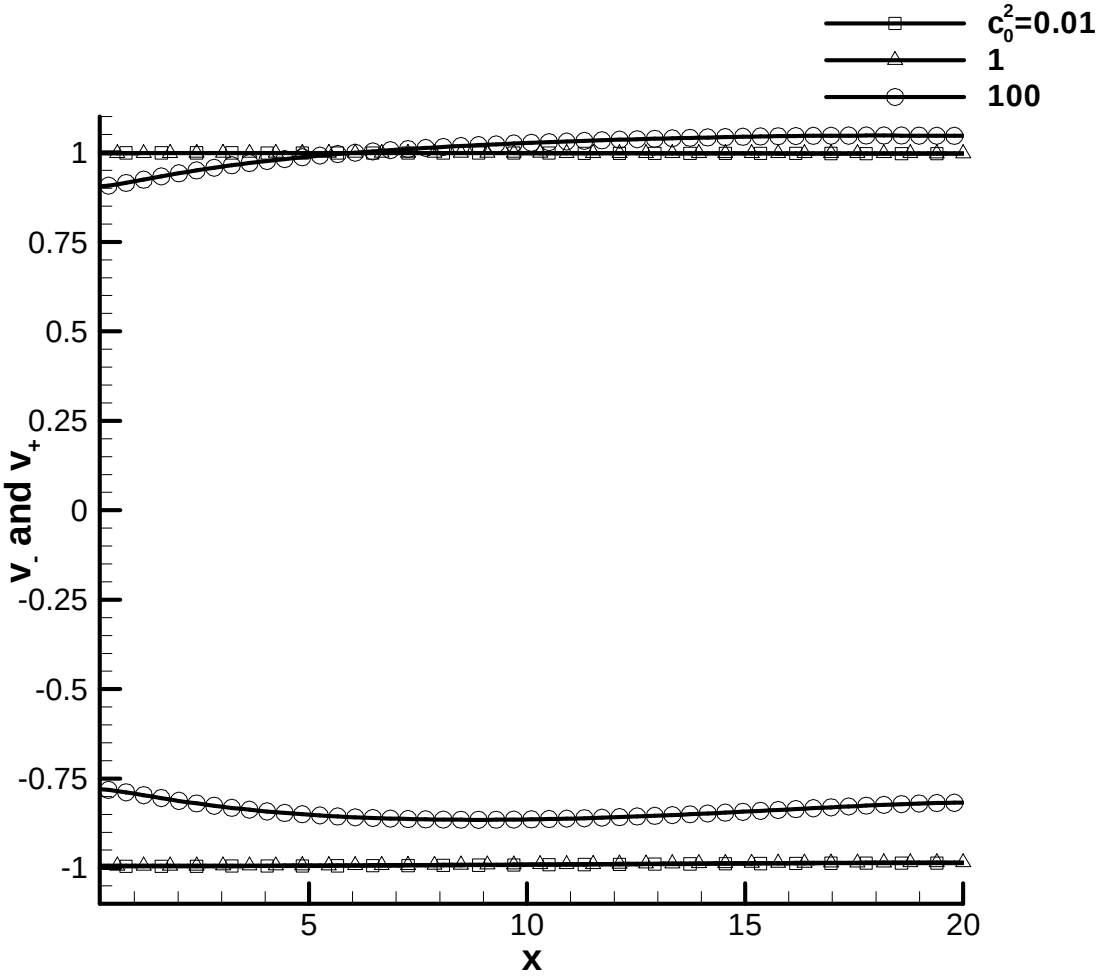

Fig. 2-b

Fig. 2. Effect of velocity variance on the molecular-motor assisted transport along microtubules on number density concentrations of free particles, n_0, particles riding on microtubules toward the neuron body, n_-, particles riding on microtubules away from the cell body, n_+ (a), and anterograde/retrograde velocities (b) computed for μ=100 and t=0.01.

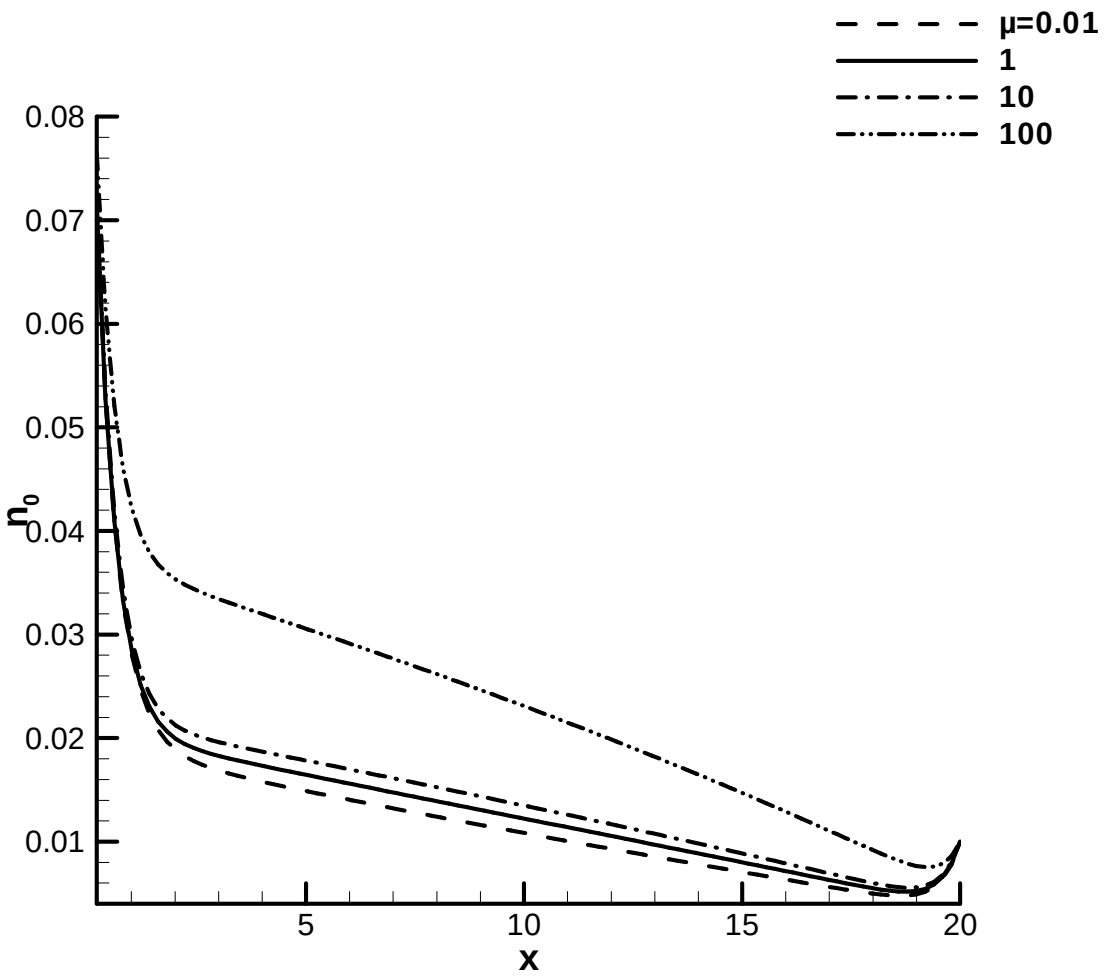

Fig. 3-a

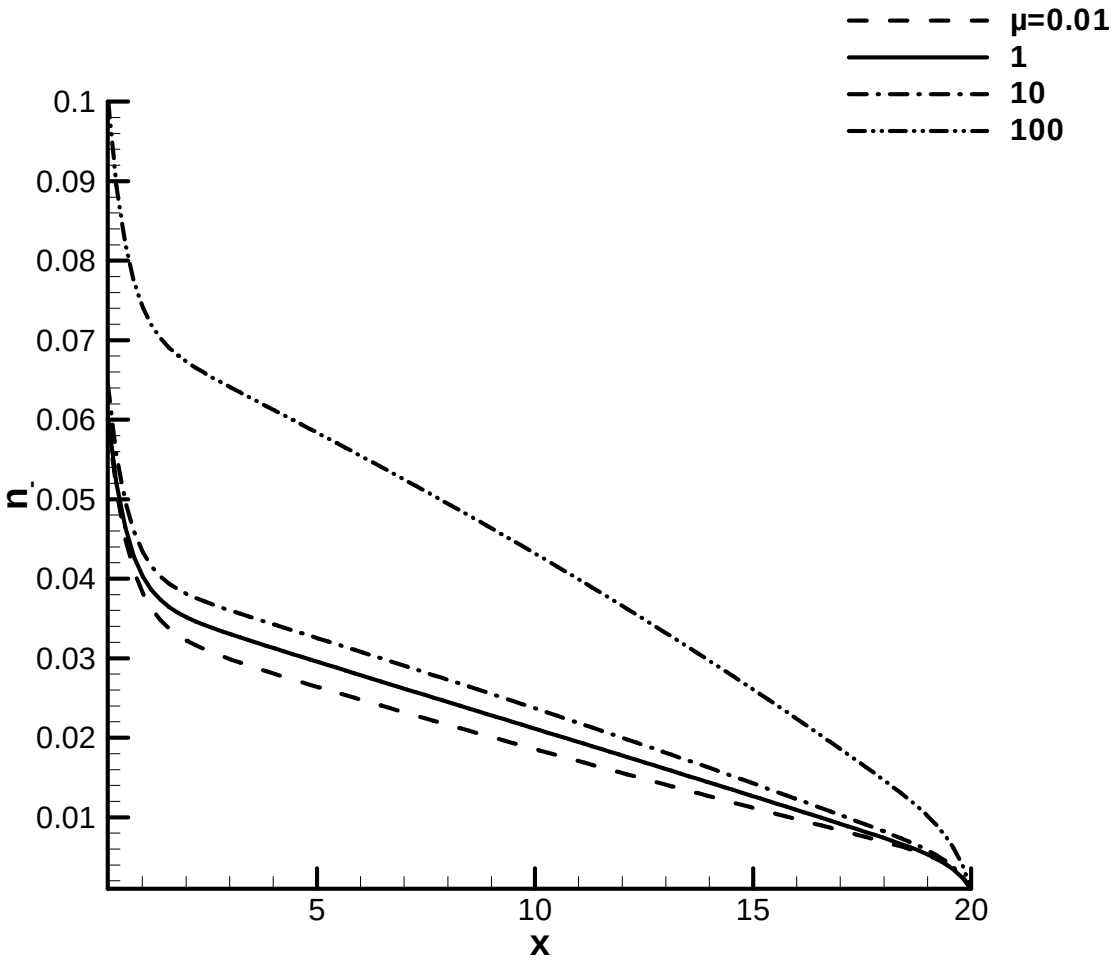

Fig. 3-b

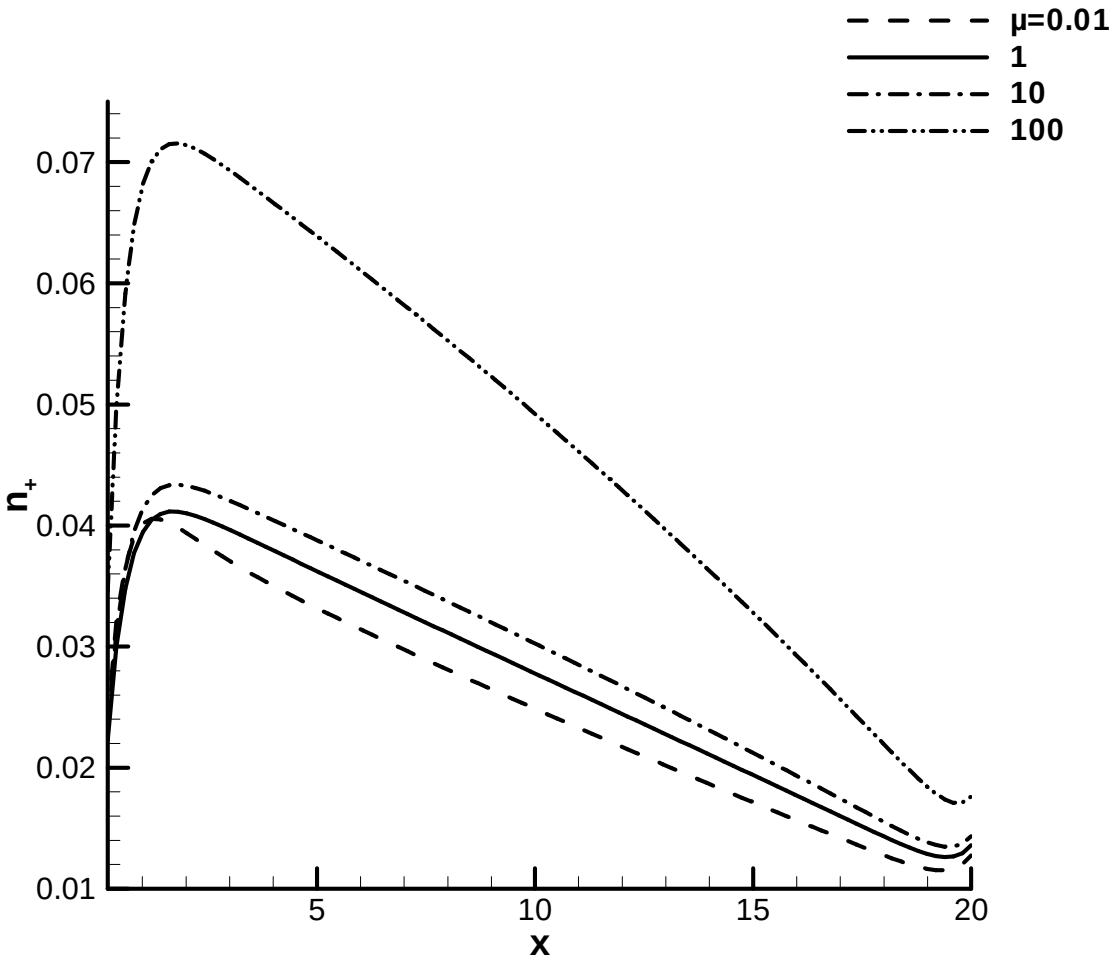

Fig. 3-c

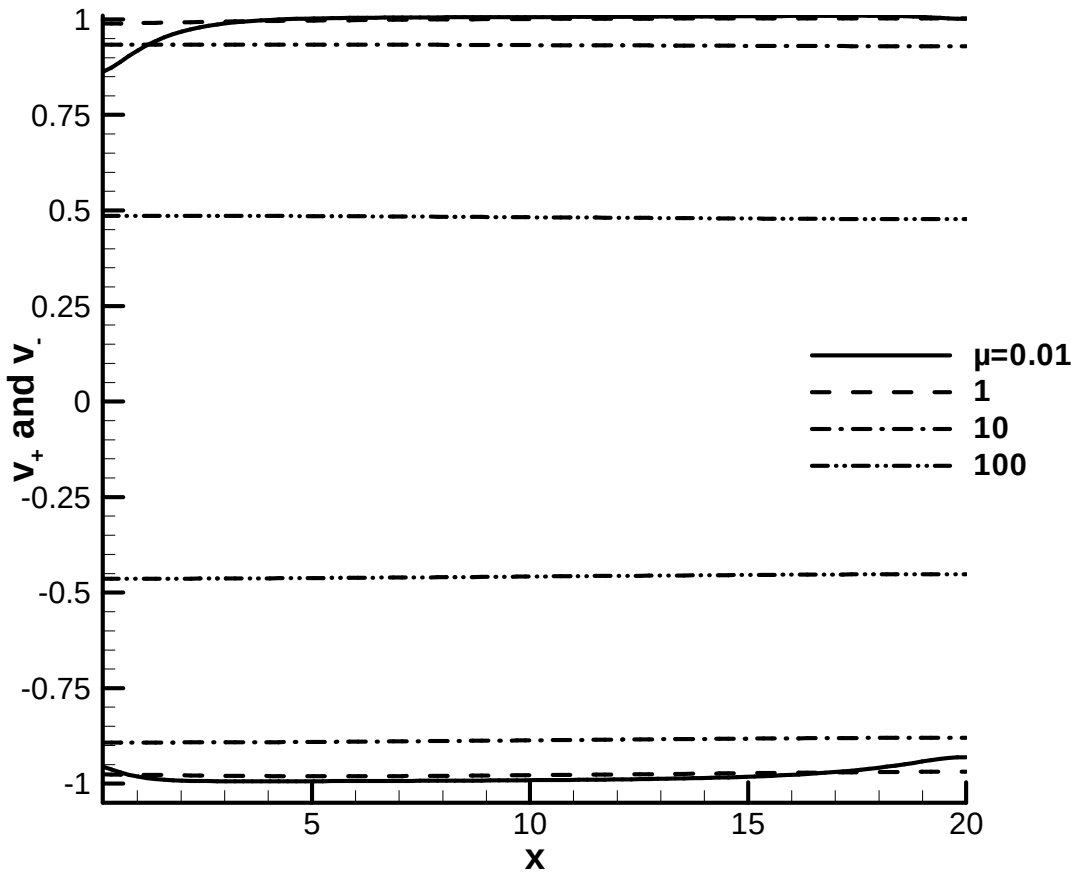

Fig. 3-d

Fig. 3. Effect of dimensionless viscosity on number density concentrations of free particles, n_0 (a), particles riding on microtubules toward the neuron body, n_- (b), particles riding on microtubules away from the cell body, n_+ (c), and anterograde/retrograde velocities (d) computed for c_0^2=0.01and t=1.

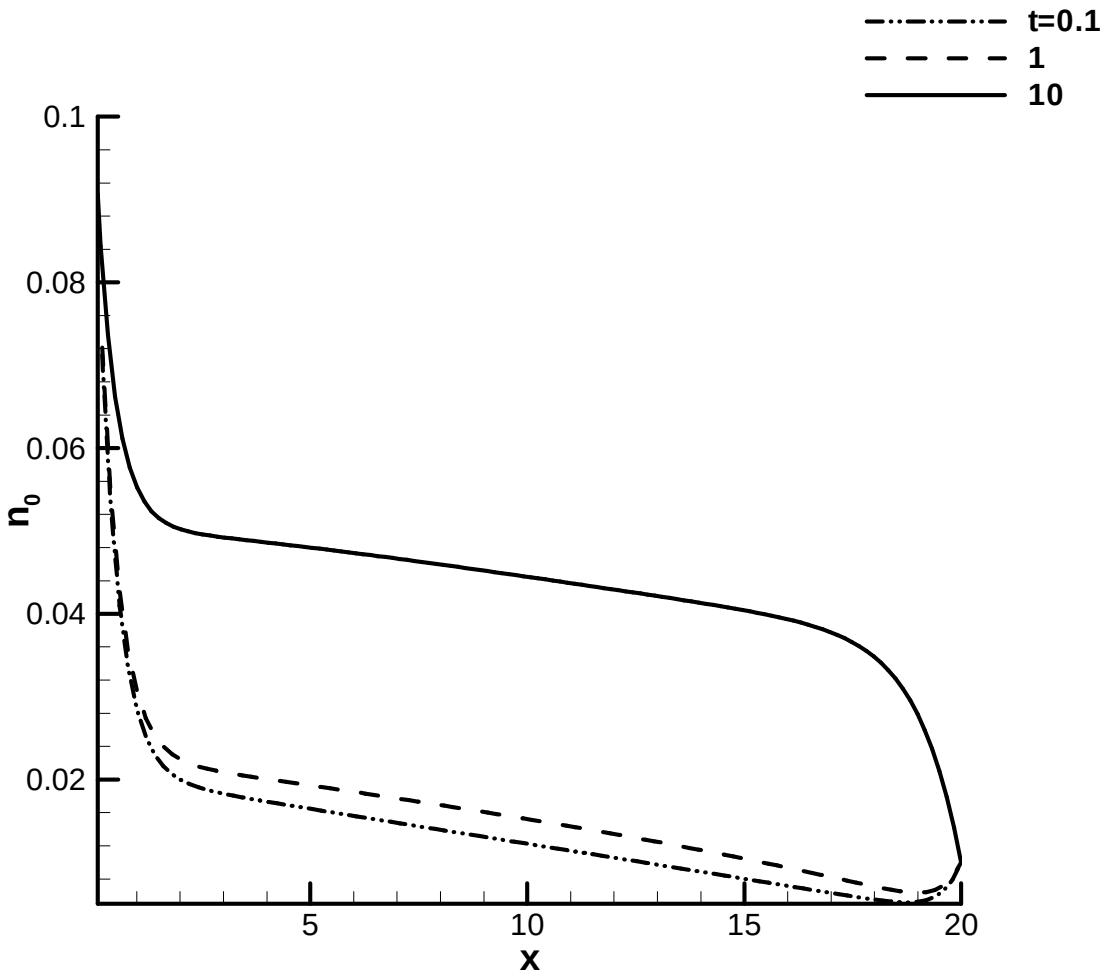

Fig. 4-a

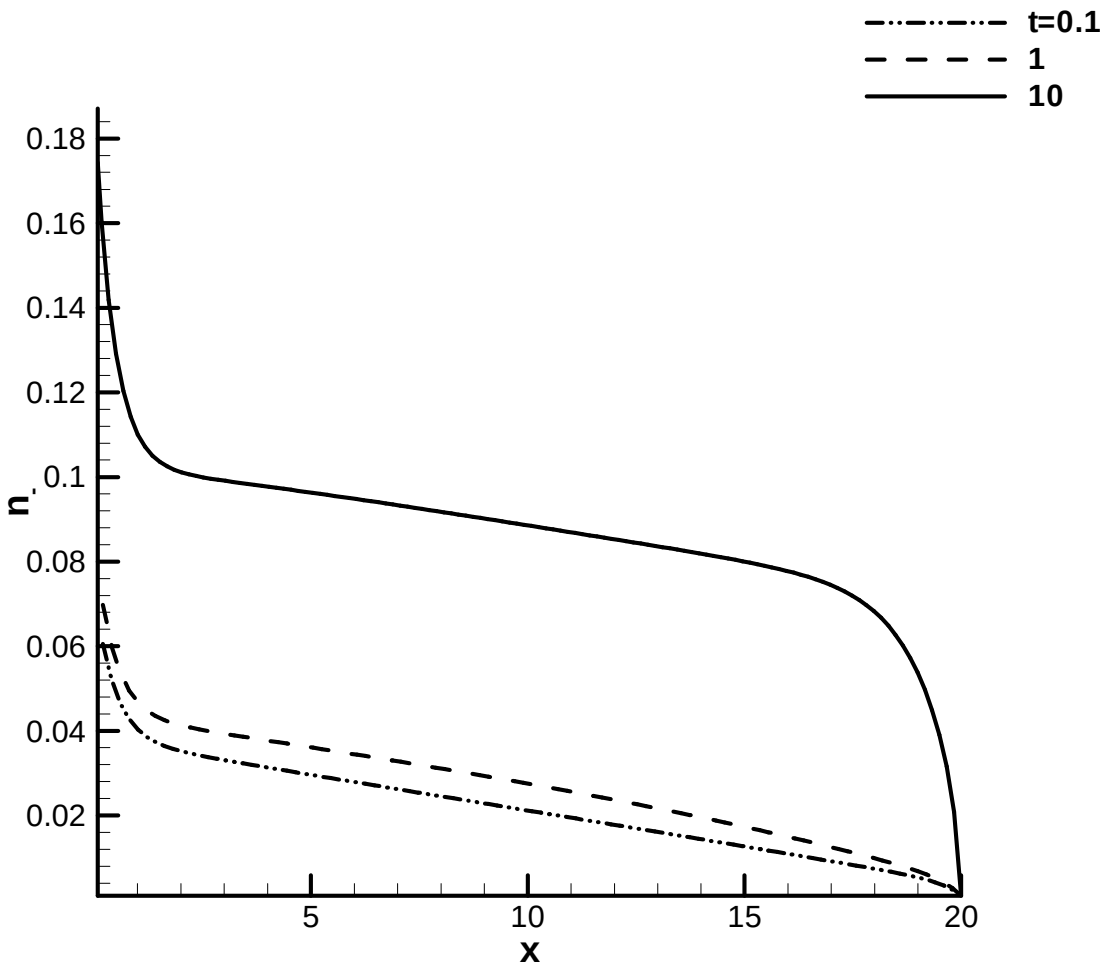

Fig. 4-b

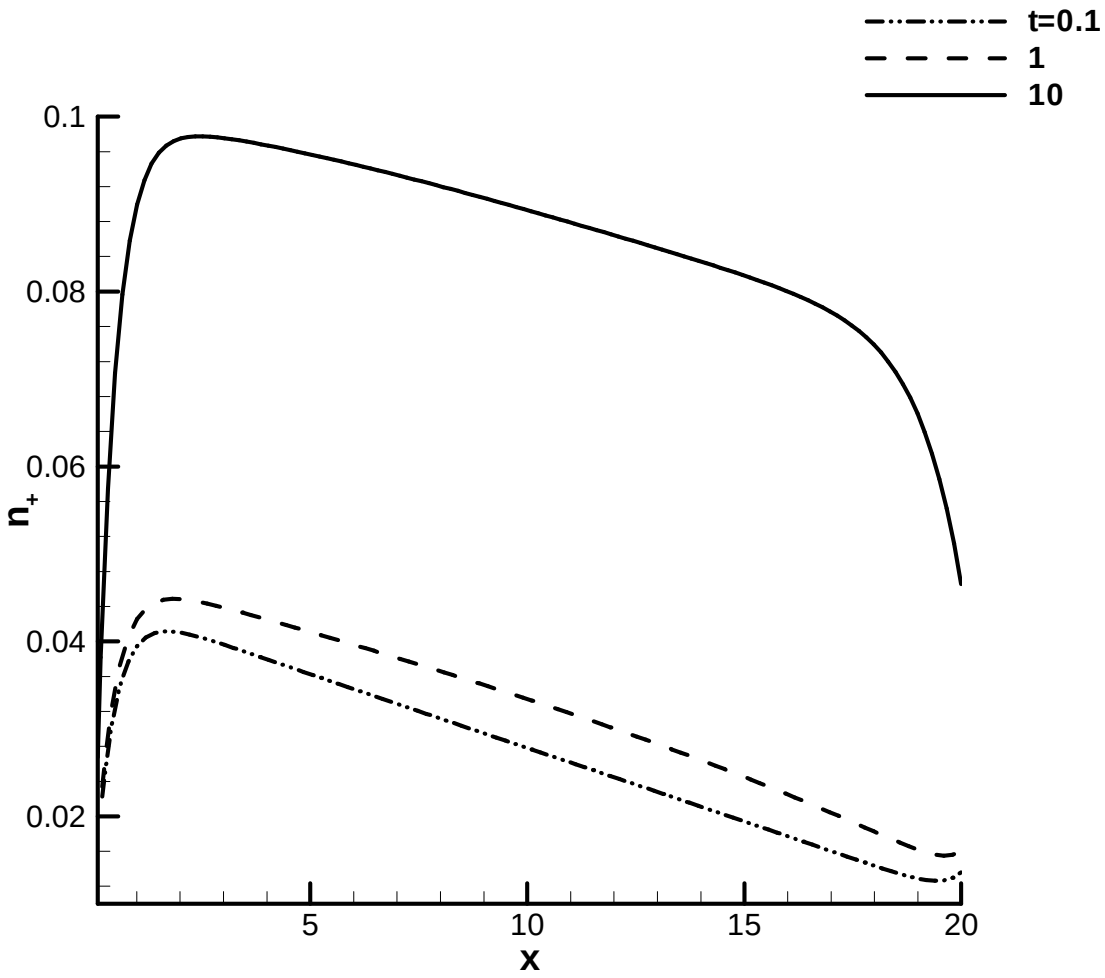

Fig. 4-c

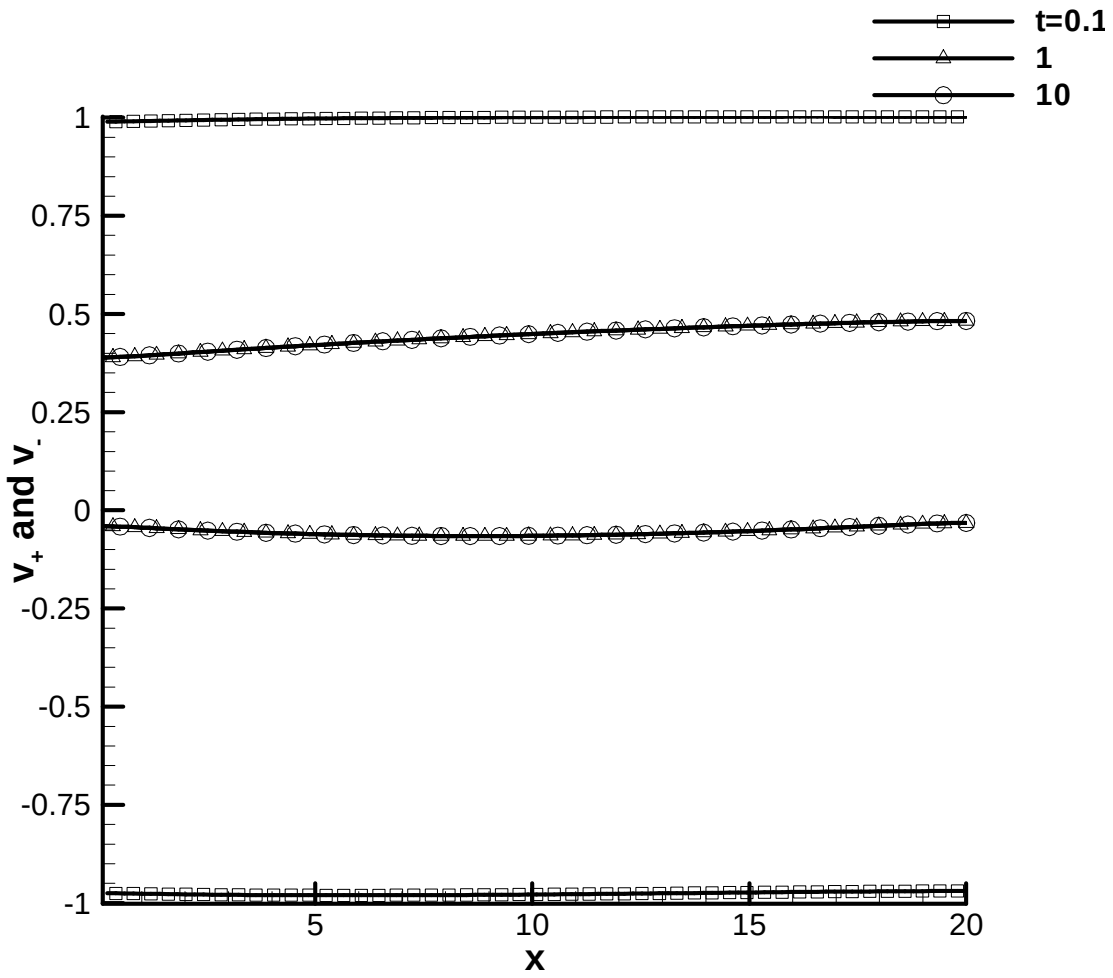

Fig. 4-d

Fig. 4 Effect of dimensionless relaxation time on number density concentrations of free particles, n_0 (a), particles riding on microtubules toward the neuron body, n_- (b), particles riding on microtubules away from the cell body, n_+ (c), and anterograde/retrograde velocities (d) computed for c_0^2=1and μ=10.

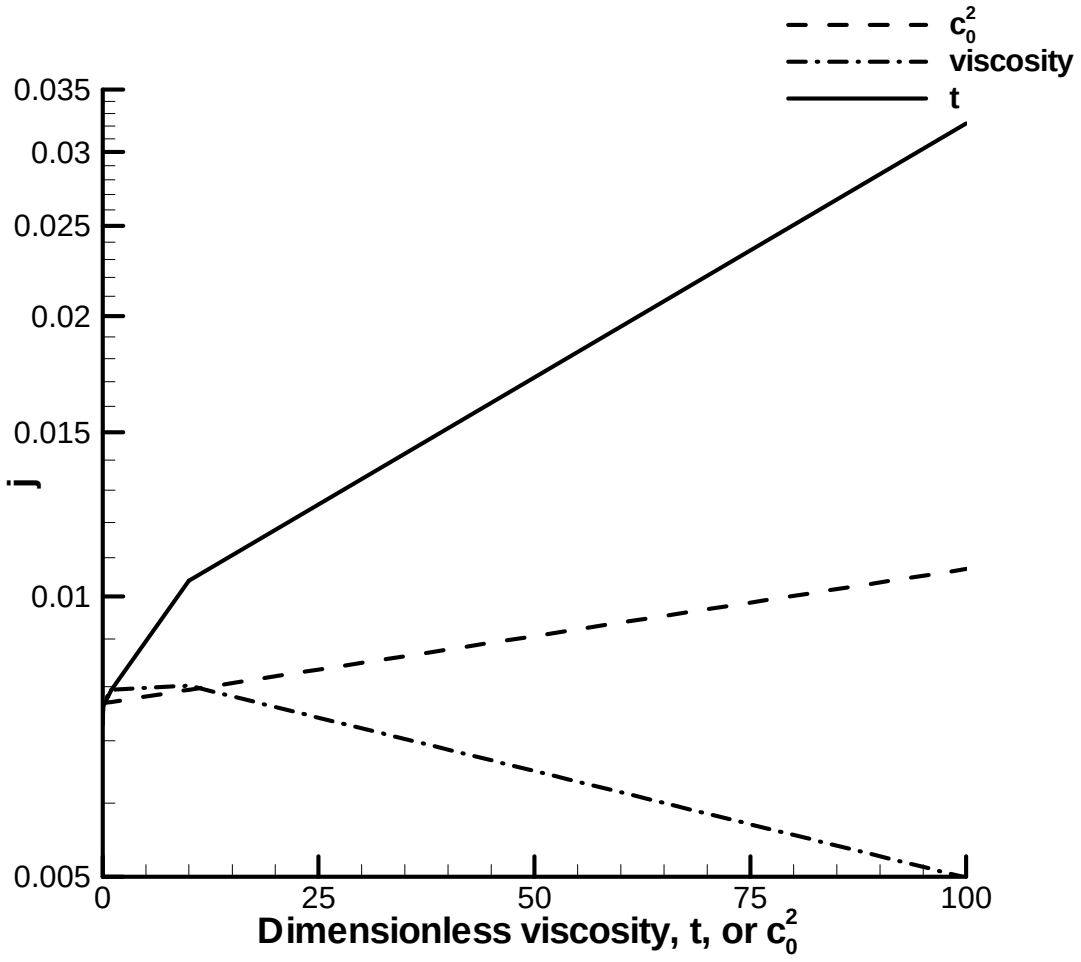

Fig. 5 Effects of velocity variance, viscosity, and relaxation time on the flux. Solid line corresponds to c_0^2=0.1and μ=1. For dashed line t=0.01and μ=100 while with dash-dotted one c_0^2=0.1and t=1