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Macroscopic modeling of slow axonal transport of rapidly diffusible soluble proteins ☆

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ABSTRACT

The purpose of this paper is to develop a macroscopic model of slow axonal transport of soluble proteins which may be transported in axons by both diffusion and active molecular-motor-assisted transport mechanisms. The model relies on the "stop-and-go" hypothesis put forward by Brown et al. [A. Brown, L. Wang, P. Jung, Stochastic simulation of neurofilament transport in axons: the "stop-and-go" hypothesis, Molecular Biology of the Cell 16 (2005) 4243–4255.] according to which the motion of neurofilaments in slow axonal transport does not occur at a constant velocity; instead, neurofilaments move along microtubules alternating between short periods of rapid movement, short on-track pauses, and prolonged off-track pauses, when they temporarily disengage from microtubules. For soluble proteins, diffusion may also play an important role in overall slow axonal transport; to account for this effect governing equations of the dynamic system model developed in Craciun et al. [G. Craciun, A. Brown, A. Friedman, A dynamical system model of neurofilament in axons, Journal of Theoretical Biology 237 (2005) 316–322.] are extended to incorporate diffusivity of off track proteins (proteins unbound to a stationary matrix). The model correctly predicts that the total concentration of organelles forms the bell-shaped wave that spreads out as it propagates toward the axon tip.
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1. Introduction

Neurons are highly specialized cells that communicate with other cells by extending cytoplasmic arms (processes). If a neuron's arm transmits electrical signals, it is called an axon, whereas if it receives electrical signals, it is called a dendrite (Fig. 1, Alberts et al. [1]). Axons in a human body can be up to one meter in length; however, they lack ribosomes and Golgi complexes, therefore materials must be constantly imported from the synthetically active cytoplasm of the cell body (Brown [2], Hurd and Saxton [3]) and transported to the axons' terminals; this axonal transport is essential for both maintenance and growth of the axon at the growth cone. Diffusion alone is not sufficiently fast mechanism for transporting large intracellular organelles and therefore, intracellular transport in axons and dendrites also relies on the "railway system": large intracellular organelles bind with 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)) that transport them along MTs.

Transport of organelles in axons is divided into fast and slow axonal transport. In fast axonal transport organelles move at average rates of approximately 2–4 μm/s (200–400 mm/day); slow axonal transport is divided into two components: "slow component-a" transports proteins that form microtubules and neurofilaments at average rates of 0.002–0.01 μm/s (0.2–1 mm/day) while "slow component-b" transports various proteins (such as actin, glycolytic enzymes, and synaptic proteins) at average rates of 0.02–0.09 μm/s (2–8 mm/day) (Brown [2], Vallee and Bloom [4], Roy et al. [5]). Both fast and slow axonal transport are essential for axonal growth and survival; defects in axonal transport are linked to such neurodegenerative diseases as Alzheimer's and Parkinson's diseases and Down syndrome (Stokin et al. [6], Vallee and Bloom [4], Roy et al. [5]). There is general agreement that molecular motors kinesin and cytoplasmic dynein are responsible for generating forces necessary to move organelles along MTs in fast axonal transport. Kinesin is responsible for anterograde transport while dynein is responsible for retrograde transport.

According to the "stop-and-go" hypothesis put forward by Brown et al. [7] and Craciun et al. [8], the same molecular motors kinesin and dynein are responsible for slow axonal transport of neurofilaments; the difference is that in slow axonal transport the motion does not occur at a constant velocity; instead, neurofilaments move along MTs alternating between short periods of rapid movement, short on-track pauses, and prolonged off-track pauses, when they temporarily disengage from MTs. According to Trivedi et al. [9], during slow axonal transport neurofilaments spend 92% of their time in the stationary state. This explains low average velocity of the slow axonal transport.

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Nomenclature

D_0	dimensionless diffusivity of off track proteins, $\frac{\tilde{D}_0\tilde{k}_{0,1}}{\tilde{v}_A^2}$
$\tilde{D}_0$	diffusivity of off track proteins
$\tilde{k}_{i,j}$	first order rate constants describing transitions between protein population i and protein population j
$k_{i,j}$	dimensionless value of $\tilde{k}_{i,j}$, $\frac{\tilde{k}_{i,j}}{\tilde{k}_{0,1}}$
L	dimensionless axon length, $\frac{\tilde{L}\tilde{k}_{0,1}}{\tilde{v}_A}$
$\tilde{L}$	axon length
n_i	dimensionless value of $\tilde{n}_i$ $(i=-2,-1,0,1,2)$, $\tilde{n}_i\frac{\tilde{v}_A^3}{\tilde{k}_{0,1}^3}$
n_t	total concentration of protein particles (the quantity accessible to experiments), $n_2+n_1+n_0+n_{-1}+n_{-2}$
$\tilde{n}_2$	number density of proteins bound to anterograde motors, moving anterogradely, on track
$\tilde{n}_1$	number density of proteins bound to anterograde motors, pausing, on track
$\tilde{n}_0$	number density of proteins bound to anterograde and retrograde motors, pausing, off track
$\tilde{n}_{-1}$	number density of proteins bound to retrograde motors, pausing, on track
$\tilde{n}_{-2}$	number density of proteins bound to retrograde motors, moving retrogradely, on track
t	dimensionless time, $\tilde{t}\tilde{k}_{0,1}$
$\tilde{t}$	time
$\tilde{v}_A$	velocity of the anterograde transport
v_R	dimensionless velocity of the retrograde transport, $\frac{\tilde{v}_R}{\tilde{v}_A}$
$\tilde{v}_R$	velocity of the retrograde transport
x	dimensionless linear coordinate along the axon, $\frac{\tilde{x}\tilde{k}_{0,1}}{\tilde{v}_A}$
$\tilde{x}$	linear coordinate along the axon

Greek symbols

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

Abbreviations

MT	microtubule

According to Roy et al. [5], the same "stop-and-go" hypothesis is also applicable to transport of "slow component-b" proteins.

According to Miller and Heidemann [10], molecular motors will move anything they bind to (unless it is tightly associated with the cytoskeletal framework), including various soluble proteins. Due to a smaller size of soluble proteins, the contribution of diffusion to their transport in axons is expected to be larger compared with that of polymers. For example, whether tubulin is transported in axons as a polymer or as a monomer (and then assembled into polymers at the axon's growth cone) is still been discussed (Sabry et al. [11]). Van Veen and Van Pelt [12] argued that for monomeric tubulin the effect of diffusion may be significant.

The purpose of this paper is to supplement a model proposed in Craciun et al. [8] with a diffusion model for off track proteins, and apply this model to the investigation of slow axonal transport of rapidly diffusible soluble proteins.

2. Governing equations

Schematic diagram of the problem is depicted in Fig. 1. To account for the effect of diffusion, governing equations presented by Craciun et al. [8] are supplemented with a diffusion model for proteins bound to off track molecular motors, resulting in the following equations:

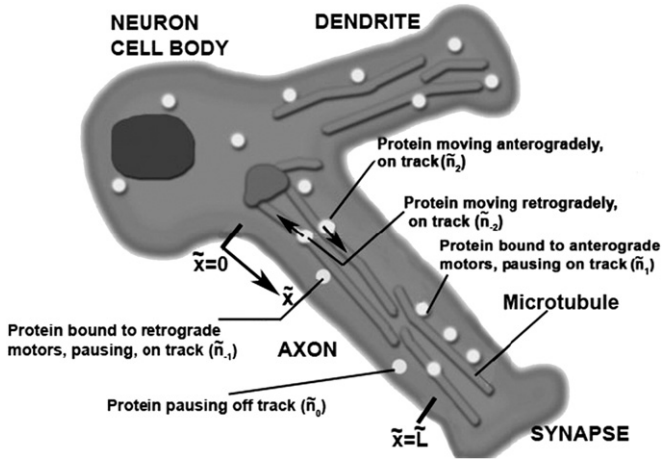

Fig. 1. Schematic diagram of a neuron cell with a dendrite and axon; also, various populations of proteins transported in the axon by slow axonal transport.

$$\frac{\partial\tilde{n}_2}{\partial\tilde{t}} = -\tilde{v}_A\frac{\partial\tilde{n}_2}{\partial\tilde{x}} + \tilde{k}_{1,2}\tilde{n}_1 - \tilde{k}_{2,1}\tilde{n}_2 \tag{1}$$

$$\frac{\partial\tilde{n}_1}{\partial\tilde{t}} = \tilde{k}_{2,1}\tilde{n}_2 + \tilde{k}_{0,1}\tilde{n}_0 + \tilde{k}_{-1,1}\tilde{n}_{-1} - \left(\tilde{k}_{1,2} + \tilde{k}_{1,0} + \tilde{k}_{1,-1}\right)\tilde{n}_1 \tag{2}$$

$$\frac{\partial\tilde{n}_0}{\partial\tilde{t}} = \tilde{D}_0\frac{\partial^2\tilde{n}_0}{\partial\tilde{x}^2} + \tilde{k}_{1,0}\tilde{n}_1 + \tilde{k}_{-1,0}\tilde{n}_{-1} - \left(\tilde{k}_{0,1} + \tilde{k}_{0,-1}\right)\tilde{n}_0 \tag{3}$$

$$\frac{\partial\tilde{n}_{-1}}{\partial\tilde{t}} = \tilde{k}_{0,-1}\tilde{n}_0 + \tilde{k}_{-2,-1}\tilde{n}_{-2} + \tilde{k}_{1,-1}\tilde{n}_1 - \left(\tilde{k}_{-1,0} + \tilde{k}_{-1,-2} + \tilde{k}_{-1,1}\right)\tilde{n}_{-1} \tag{4}$$

$$\frac{\partial\tilde{n}_{-2}}{\partial\tilde{t}} = \tilde{v}_R\frac{\partial\tilde{n}_{-2}}{\partial\tilde{x}} + \tilde{k}_{-1,-2}\tilde{n}_{-1} - \tilde{k}_{-2,-1}\tilde{n}_{-2} \tag{5}$$

where $\tilde{n}_2$ is the number density of proteins bound to anterograde motors, moving anterogradely, on track; $\tilde{n}_1$ is the number density of proteins bound to anterograde motors, pausing, on track; $\tilde{n}_0$ is the number density of proteins bound to anterograde and retrograde motors, pausing, off track; $\tilde{n}_{-1}$ is the number density of proteins bound to retrograde motors, pausing, on track; $\tilde{n}_{-2}$ is the number density of proteins bound to retrograde motors, moving retrogradely, on track; $\tilde{D}_0$ is the diffusivity of off track proteins; $\tilde{v}_A$ is the velocity of the

Table 1
Dimensionless parameter values utilized in computations

Parameter	Description	Value
v_R	Retrograde velocity	1.107
D_0	Diffusivity of off track proteins	0.004
L	Axon length	50
σ_0	Degree of loading at $x=0$	0.1
σ_L	Degree of loading at $x=L$	0.1
$k_{-2,-1}$	First order rate constant	$\frac{67}{33}$
$k_{-1,0}$	First order rate constant	44.29
$k_{1,0}$	First order rate constant	19.9
$k_{2,1}$	First order rate constant	$\frac{67}{33}$
$k_{-1,1}$	First order rate constant	0
$k_{1,-1}$	First order rate constant	0
$k_{-1,-2}$	First order rate constant	1
$k_{0,-1}$	First order rate constant	1
$k_{1,2}$	First order rate constant	10
A	Parameter in Eq. (18)	0.4
M	Parameter in Eq. (18)	2
x_0	Parameter in Eq. (18)	15

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