



# Coupling a dynein transport model with a model of anterograde and retrograde transport of intracellular organelles<sup>☆</sup>

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## ABSTRACT

A model of fast axonal transport of organelles that accounts for dynein transport in an inactive state toward the axonal synapse is developed. It is assumed that anterograde transport of inactive dynein in an axon is powered by kinesin motors. It is further assumed that the probability of organelle attachment to a dynein motor is directly proportional to the concentration of free dynein motors available at a particular location in the axon. The results predicted by two models (the first one is that which incorporates dynein transport and the second one is the traditional model that does not incorporate dynein transport) are compared. The obtained results suggest that the availability of dynein motors in a particular location in an axon can be a factor limiting fast axonal transport.

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## 1. Introduction

Neurons are unique cells in terms of the size of their processes, axons and dendrites, which can be 1000 times larger in volume than the body of a neuron [1]; axons transmit signals while dendrites receive signals. Since organelles are almost exclusively synthesized in the cell body, they need to be transported through these very long processes to a particular location where they are needed. Used organelles also need to be returned to the neuron body for recycling. Since diffusion is not fast enough for this task, transport of organelles is accomplished by a complicated “railway” system, where various organelles are propelled by molecular motors moving on microtubule (MT) tracks and, to a degree, on actin cables. In axons, there are three modes of anterograde transport (fast, slow component A, and slow component B) and only one (fast) mode of retrograde transport. This paper concentrates on fast axonal transport, which transports various membrane-bound organelles and vesicles. Fast anterograde transport is propelled mainly by kinesin-1 motors while retrograde transport is powered mainly by cytoplasmic dynein [2–6]. Understanding fast axonal transport is important because its defects are linked to various neurodegenerative diseases [7,8].

Due to biomedical relevance of this problem, there is significant interest in modeling fast anterograde and retrograde transport in axons and dendrites [9–13]. However, to the best of the author's knowledge, one important aspect of fast axonal transport has never been addressed in modeling. Neuron molecular motors, like any other

proteins, are synthesized in the cell body. Kinesin motors, which move organelles from the neuron body to the tip of the axon, are abundant at the axon base, and once kinesin motors reach the synapse of the axon, they are probably destroyed or inactivated [1,14]. Dynein motors, which drive retrograde axonal transport, are also synthesized in the cell body. In order to transport organelles from the axonal synapse to the cell body dynein must be first transported to the synapse. This is probably done by kinesin motors that transport dynein, while it is in an inactive state, to the axonal synapse [1]. This implies that a complete model of fast axonal transport must include equations describing dynein transport to the axon tip.

There is evidence that there are two pools of dynein motors: about 10% are transported to the synapse by fast axonal transport and about 90% by slow component B. However, since fast axonal transport (which drives organelles at rates of about 200 mm/day) is much faster than slow component B (which transports elements at rates of only about 5 mm/day), 85% of retrograde activity is attributed to dynein transported to the synapse by fast axonal transport [15]. Also, there is data that suggest that dynein from the slowly transported pool may serve some specialized purposes, such as transport of specific organelles or neurofilaments [16]. Therefore, in this paper only the dynein pool transported anterogradely by the fast mode of axonal transport is simulated.

## 2. Governing equations

Transport of organelles between the axon base, located at  $\bar{x} = 0$ , and axonal synapse, located at  $\bar{x} = \bar{L}$  (Fig. 1a), is simulated. Governing equations are based on molecular motor-assisted transport model developed in Smith and Simmons [17]. Three populations of organelles are considered in the model: organelles propelled by

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### Nomenclature

$a$	parameter in Eq. (6) defining how the kinetic constant $k_{0-}$ depends on the concentration of free dynein motors $n_{d0}$
$b$	parameter in Eq. (7) defining how the kinetic constant $k_-$ depends on the concentration of free dynein motors $n_{d0}$
$\tilde{D}_0$	diffusivity of free organelles
$\tilde{D}_{d0}$	diffusivity of dynein motors in the cytoplasm
$j$	total dimensionless flux of organelles (due to diffusion and motor-driven transport)
$\tilde{k}_+$	first order rate constant describing the rate of switching of organelles propelled by dynein motors to those propelled by kinesin motors
$\tilde{k}_-$	first order rate constant describing the rate of switching of organelles propelled by kinesin motors to those propelled by dynein motors
$\tilde{k}_{0+}$	first order rate constant describing the rate at which free organelles attach to MTs and become organelles propelled by kinesin motors
$\tilde{k}_{0-}$	first order rate constant describing the rate at which free organelles attach to MTs and become organelles propelled by dynein motors
$\tilde{k}'_+$	first order rate constant describing the rate at which organelles propelled by kinesin motors detach from MTs
$\tilde{k}'_-$	first order rate constant describing the rate at which organelles propelled by dynein motors detach from MTs
$\tilde{k}_{d0+}$	first order rate constant describing the rate at which free dynein motors attach to MTs to be transported anterogradely (in an inactive state) by kinesin motors
$\tilde{k}'_{d0+}$	first order rate constant describing the rate at which dynein motors that are transported in an inactive state by kinesin motors detach from MTs to become free dynein motors
$\tilde{L}$	axon length
$\tilde{n}_+$	number density of MT-bound organelles propelled by kinesin motors
$\tilde{n}_-$	number density of MT-bound organelles propelled by dynein motors
$\tilde{n}_0$	number density of free organelles
$\tilde{n}_{d+}$	number density of dynein motors transported anterogradely in an inactive state by kinesin
$\tilde{n}_{d0}$	number density of free dynein motors
$\tilde{N}_0$	number density of free organelles at $x=0$
$\tilde{N}_{d0}$	number density of free dynein motors at $x=0$
$\tilde{N}_L$	number density of free organelles at $x=L$
$\tilde{N}_{dL}$	number density of free dynein motors at $x=L$
$\tilde{t}$	time
$\tilde{v}_-$	average velocity of organelles propelled by dynein motors
$\tilde{v}_+$	average velocity of organelles propelled by kinesin motors
$\tilde{v}_{d+}$	average velocity of dynein motors (in an inactive state) propelled by kinesin motors
$\tilde{x}$	linear coordinate along the axon

### Greek symbols

$\sigma_0$	degree of organelle loading at $x=0$
$\sigma_L$	degree of organelle loading at $x=L$
$\sigma_{d0}$	degree of dynein loading (to be transported in an inactive state by kinesin motors) at $x=0$

### Abbreviation

MT	microtubule
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kinesin motors (the concentration of such organelles is denoted by  $\tilde{n}_+$ ), organelles propelled by dynein motors (the concentration of such organelles is denoted by  $\tilde{n}_-$ ), and free organelles that are in the state of Brownian diffusion (the concentration of such organelles is denoted by  $\tilde{n}_0$ ). It is assumed that an organelle may have both kinesin and dynein motors attached to it, but can be propelled by only one type of motors at a given time. When kinesin motors detach from an organelle and dynein motors attach to an organelle (as a result, an organelle changes the direction of its motion), the concentration of plus-end-directed organelles,  $\tilde{n}_+$ , decreases, and the concentration of minus-end-directed organelles,  $\tilde{n}_-$ , increases. The rate of this process is characterized by the kinetic constant  $\tilde{k}_-$  (see the kinetic diagram in Fig. 1b). The rate of the opposite process (when dynein motors detach from an organelle and kinesin motors attach to it) is characterized by the kinetic constant  $\tilde{k}_+$ . Organelles propelled by either kinesin or dynein motors can completely detach from MTs and become free organelles, the rates of these processes are characterized by kinetic constants  $\tilde{k}'_+$  and  $\tilde{k}'_-$ , respectively. When organelles attach to MTs and become kinesin or dynein-driven organelles, concentrations  $\tilde{n}_+$  and  $\tilde{n}_-$  increase and  $\tilde{n}_0$  decreases; the rates of these processes are characterized by kinetic constants  $\tilde{k}_{0+}$  and  $\tilde{k}_{0-}$ , respectively.

The dimensionless equations describing the conservation of free, kinesin-driven, and dynein-driven organelles are, respectively:

$$\frac{\partial n_0}{\partial t} = D_0 \frac{\partial^2 n_0}{\partial x^2} - [k_{0+} + k_{0-}(n_{d0})]n_0 + k'_{0+}n_+ + k'_{0-}n_-, \quad (1)$$

$$\frac{\partial n_+}{\partial t} = -k_-(n_{d0})n_+ + n_- + k_{0+}n_0 - k'_{0+}n_+ - \frac{\partial n_+}{\partial x}, \quad (2)$$

$$\frac{\partial n_-}{\partial t} = k_-(n_{d0})n_+ - n_- + k_{0-}(n_{d0})n_0 - k'_{0-}n_- - v_- \frac{\partial n_-}{\partial x}, \quad (3)$$

where the dimensionless variables and parameters in Eqs. (1)–(3) are defined as follows:

$$D_0 = \frac{\tilde{D}_0 \tilde{k}_+}{\tilde{v}_+^2}, \quad k_- = \frac{\tilde{k}_-}{k_+}, \quad k_{0\pm} = \frac{\tilde{k}_{0\pm}}{k_+}, \quad k'_{0\pm} = \frac{\tilde{k}'_{0\pm}}{k_+}, \quad L = \frac{\tilde{L} \tilde{k}_+}{\tilde{v}_+}, \quad (4)$$

$$v_- = \frac{\tilde{v}_-}{\tilde{v}_+}, \quad x = \frac{\tilde{x} \tilde{k}_+}{\tilde{v}_+}, \quad t = \tilde{t} \tilde{k}_+, \quad n_0 = \tilde{n}_0 \frac{\tilde{v}_+^3}{k_+}, \quad n_{\pm} = \tilde{n}_{\pm} \frac{\tilde{v}_+^3}{k_+}. \quad (5)$$

In Eqs. (4) and (5)  $\tilde{D}_0$  is the diffusivity of free organelles,  $\tilde{t}$  is the time,  $\tilde{v}_+$  is the average velocity of an organelle propelled by kinesin motors ( $\tilde{v}_+$  is positive),  $\tilde{v}_-$  is the average velocity of an organelle propelled by dynein motors ( $\tilde{v}_-$  is negative), and  $\tilde{x}$  is the linear coordinate along the axon.

It is assumed that the rate at which organelles switch the direction of their motion from anterograde to retrograde is proportional to the dimensionless concentration of free dynein motors in a particular location in an axon,  $n_{d0}(x)$ :

$$k_{0-}(n_{d0}) = a n_{d0}. \quad (6)$$

It is further assumed that the rate at which free organelles attach to MTs and become dynein-driven organelles is also proportional to the dimensionless concentration of free dynein motors,  $n_{d0}(x)$ :

$$k_-(n_{d0}) = b n_{d0}. \quad (7)$$

With respect to dynein transport toward the synapse, two populations of dynein motors are considered in the model: dynein motors (in an inactive state) that are transported by kinesin motors (the concentration of such dynein motors is denoted by  $\tilde{n}_{d+}$ ) and free dynein motors that are in the state of Brownian diffusion (the concentration of such dynein motors is denoted by  $\tilde{n}_{d0}$ ). It is assumed

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