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Coupling a dynein transport model with a model of anterograde and retrograde transport of intracellular organelles ☆

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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.

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 $\tilde{x} = 0$, and axonal synapse, located at $\tilde{x} = \tilde{L}$ (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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