

Analytical comparison between Nixon–Logvinenko's and Jung–Brown's theories of slow neurofilament transport in axons



I.A. Kuznetsov^a, A.V. Kuznetsov^{b,*}

^a Dept. of Biomedical Engineering, Johns Hopkins University, Baltimore, MD 21218-2694, USA

^b Dept. of Mechanical and Aerospace Engineering, North Carolina State University, Raleigh, NC 27695-7910, USA

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ABSTRACT

This paper develops analytical solutions describing slow neurofilament (NF) transport in axons. The obtained solutions are based on two theories of NF transport: Nixon–Logvinenko's theory that postulates that most NFs are incorporated into a stationary cross-linked network and only a small pool is slowly transported and Jung–Brown's theory that postulates a single dynamic pool of NFs that are transported according to the stop-and-go hypothesis. The simplest two-kinetic state version of the model developed by Jung and Brown was compared with the theory developed by Nixon and Logvinenko. The model for Nixon–Logvinenko's theory included stationary, pausing, and running NF populations while the model used for Jung–Brown's theory only included pausing and running NF populations. Distributions of NF concentrations resulting from Nixon–Logvinenko's and Jung–Brown's theories were compared. In previous publications, Brown and colleagues successfully incorporated slowing of NF transport into their model by assuming that some kinetic constants depend on the distance from the axon hillock. In this paper we defined the average rate of NF transport as the rate of motion of the center of mass of radiolabeled NFs. We have shown that for this definition, if all kinetic rates are assumed constant, Jung–Brown's theory predicts a constant average rate of NF transport. We also demonstrated that Nixon–Logvinenko's theory predicts slowing of NF transport even if all kinetic rates are assumed constant, and the obtained slowing agrees well with published experimental data.

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1. Introduction

Neurons have two types of long cytoplasmic processes, axons and dendrites (see Fig. 1(a)). In a human body axons can be up to 1 m in length (Goldstein and Yang [1]). Since most axonal proteins are synthesized in the neuron body, axons heavily depend on transport of various cargos from the neuron body toward the pre-synaptic terminal (Brown [2]). Axonal transport is mostly powered by two types of molecular motors, kinesin-1 and cytoplasmic dynein. Kinesin-1 is an anterograde motor and cytoplasmic dynein is a retrograde motor. These motors run on microtubules (MTs) that provide “railway tracks” for axonal transport (Goldstein and Yang [1], Alberts et al. [3]).

Depending on its velocity, axonal transport is divided into fast and slow axonal transport. Fast axonal transport moves various vesicles and organelles with velocities between 100–400 mm/day (1–5 $\mu\text{m/s}$); these velocities can be easily explained by cargo being pulled by kinesin and dynein motors. Slow axonal transport is characterized by much smaller rates. There are two components

of slow axonal transport, component ‘a’ and component ‘b’. Component ‘a’ moves neurofilaments (NFs) and tubulin with velocities between 0.2–1 mm/day (0.002–0.01 $\mu\text{m/s}$), while component ‘b’ moves actin, spectrin and many other cytosolic proteins with velocities between 2–8 mm/day (0.02–0.09 $\mu\text{m/s}$) (Vallee and Bloom [4], Brown [5], Roy et al. [6]). Since there are no molecular motors that walk on MTs with such low velocities, explaining slow axonal transport is challenging (Miller and Heidermann [7], Mitchell and Lee [8]).

NFs, which function as space-filling structures in axons, are one of the slowest axonal cargos (Williamson et al. [9]). Ochs [10] was first to suggest a single motor system for fast and slow axonal transport. Evidence of kinesin-1 involvement in NF transport was provided by Shea and colleagues [11–13] and Goldstein and colleagues [14]. Shah et al. [15], Wagner et al. [16], and He et al. [17] provided evidence that cytoplasmic dynein is also involved in NF transport.

There have been two major approaches to explaining slow axonal transport. The first approach, initially suggested in Nixon and Logvinenko [18], postulates that the majority of NFs are deposited into a stationary cross-linked cytoskeletal network that remains fixed for months, and only a small portion of NFs are transported. Nixon and colleagues developed this theory further in [19] and

* Corresponding author. Tel. +1 919 515 5292.

E-mail addresses: ikuznet1@jhu.edu (I.A. Kuznetsov), avkuznet@ncsu.edu (A.V. Kuznetsov).

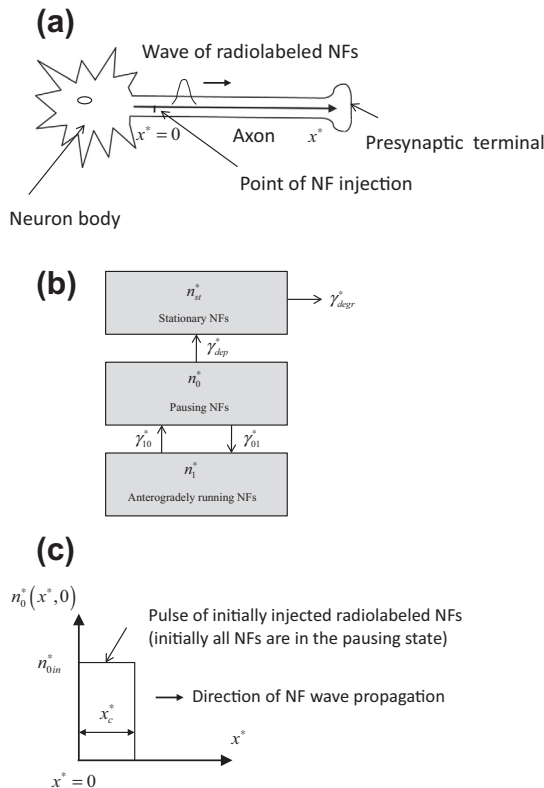


Fig. 1. (a) Sketch of the problem showing a neuron body and an axon. NFs are slowly transported from the point of injection toward the presynaptic terminal. (b) A kinetic diagram showing anterogradely running, pausing and stationary NFs and kinetic processes between them. (c) Sketch of the initial pulse. It is assumed that initially all NFs are in the pausing state.

suggested that more than 90% of NFs in mature optic axons comprise a stationary network, while less than 10% undergo slow axonal transport in the stop-and-go fashion (Brown [5]), alternating between rapid runs and pauses. Additional experimental evidence in support of Nixon–Logvinenko’s theory has recently been reported in Rao et al. [20] and Sunil et al. [21] and reviewed in Yuan et al. [22].

The second approach, developed in Brown [5], Wang et al. [23], Brown et al. [24], Craciun et al. [25], Trivedi et al. [26], Brown [27], and Lasek et al. [28], assumes that there is no stationary NF network and that NFs move relentlessly from the cell body to the axon tip. According to the stop-and-go hypothesis, which was originally put forward by Brown and colleagues in the above publications, all NFs move in an intermittent manner, alternating between relatively long pauses and short runs. Jung and Brown [29] developed three models that were based on the stop-and-go hypothesis; these models are illustrated in Figs. 1, 3, and 4 in [29], respectively. A two-kinetic state model considered two NF populations, pausing and running-antegrade. A four-kinetic state model included four NF populations, running-antegrade, pausing-antegrade, pausing-retrograde, and running-retrograde. A six-kinetic state model, in addition to the four above populations, also included off-track-antegrade and off-track retrograde populations, to account for NFs that pause for longer periods of time, probably disengaging from MT tracks. Recently, Li et al. [30] presented numerical simulations based on the six-kinetic state model developed in Jung and Brown [29] and compared the results of these simulation with experimental data reported in Nixon and Logvinenko [18] and Yuan et al. [19].

In this paper, we developed analytical solutions based on Nixon–Logvinenko’s and Jung–Brown’s theories. The developed solutions are then used to compare the NF concentrations predicted

by these two theories and to point out their characteristic features. Since our goal was to investigate how far one can advance the analytical solution techniques, when developing our modeling approach we had to rely on the two-kinetic state model suggested in Jung and Brown [29] (no practically tractable analytical solution is possible for the four and six-kinetic state models). The limitation of the two-kinetic state version of Jung–Brown’s model is that it does not include bidirectional movement of NFs and does not distinguish between short and long-term pausing states. This results in an underprediction of the NF spreading rate and an overprediction of their average rate of movement. As shown in Li et al. [30], a six-kinetic state version of Jung–Brown’s model that includes these effects gives much better quantitative agreement with experimental data. However, even a two-kinetic state version of Jung–Brown’s model makes it possible to analyze important features of slow axonal transport of NFs.

A finite cargo half-life was first incorporated into the model of slow axonal transport by Kuznetsov et al. [31]. Analytical solutions of the two-kinetic state model of Jung and Brown were obtained in Kuznetsov [32] (assuming an infinite NF half-life) and Kuznetsov [33] (assuming a finite NF half-life). Effects of kinesin velocity distribution were considered in Kuznetsov [34]. In order to enable a comparison between Nixon–Logvinenko’s and Jung–Brown’s theories, here we supplemented the two-kinetic state model developed in Jung and Brown [29] with a third kinetic state that accounts for stationary NFs. We assumed that NFs residing in the pausing state can deposit onto the stationary phase (see Fig. 1(b)). Stationary NFs can slowly degrade, as it was suggested in Nixon and Logvinenko [18] and Yuan et al. [19]. Yuan et al. [19] suggested that NFs can either degrade locally or slowly detach and be transported to another site for degradation. In our model, we had to assume the first option (local degradation). This was necessary to keep a one-way coupling between the pausing state and the stationary phase; without this condition obtaining an analytical solution is not possible. The local degradation assumption is consistent with recent results presented in Rao et al. [20].

Equations for the pausing and running kinetic states in the present model are also different from those utilized in Kuznetsov [33]. The difference is that Kuznetsov [33] assumed NF degradation with the same rate in both pausing and running states. In the present research, NFs can deposit (to the stationary phase) only from the pausing state (and not from the running state). This asymmetry between the equations makes finding the inverse Laplace transform, which is the most challenging step in obtaining the solution, more difficult.

2. Methods and models

2.0.1. A two-kinetic state formulation of Nixon–Logvinenko’s and Jung–Brown’s models

The main difference between the two models is presence (Nixon and Logvinenko) or absence (Jung and Brown) of a stationary pool of NFs. In order to develop a set of governing equations that could be used to describe both theories, a two-kinetic state model of slow axonal transport developed in Jung and Brown [29], given by Eq. (7) in their paper, was supplemented by a conservation equation for NFs residing in the stationary phase. The coordinate system in the axon is shown in Fig. 1(a). A kinetic diagram, showing three NF populations (stationary, pausing, and anterogradely running) is displayed in Fig. 1(b). The two-kinetic state model of Jung and Brown is recovered by setting the NF deposition rate from the pausing state to the stationary phase, γ_{dep}^* , to zero. The governing equations are

$$\frac{\partial n_{st}^*}{\partial t^*} = \gamma_{dep}^* n_0^* - \gamma_{degr}^* n_{st}^* \quad (1)$$

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