

A dynamical system model of neurofilament transport in axons

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Abstract

We develop a dynamical system model for the transport of neurofilaments in axons, inspired by Brown's "stop-and-go" model for slow axonal transport. We use fast/slow time-scale arguments to lower the number of relevant parameters in our model. Then, we use experimental data of Wang and Brown to estimate all but one parameter. We show that we can choose this last remaining parameter such that the results of our model agree with pulse-labeling experiments from three different nerve cell types, and also agree with stochastic simulation results.

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1. Introduction

Most axonal proteins are synthesized in the nerve cell body and are transported along axons by the mechanisms of axonal transport in association with discrete cargo structures that move at different rates (Brown, 2003). One type of cargo structure are neurofilaments, which are neuron-specific cytoskeletal polymers that function as space-filling structures in axons (Williamson et al., 1996). Studies on populations of neurofilaments in vivo on a time scale of weeks and months using radioisotopic pulse-labeling have demonstrated that these cytoskeletal polymers move along axons in the slowest component of axonal transport at average rates of about 0.002–0.035 $\mu\text{m/s}$, i.e. about 0.25–3 mm/day (Lasek et al., 1992); this average rate is different in different neuronal populations and it also depends on age. The radiolabeled proteins in these experiments distribute along the axon in the form of a bell-shaped wave that spreads as it moves distally. Defects in the transport of neurofilaments may contribute to their

accumulation in some neurodegenerative diseases, such as ALS (Al-chalabi and Miller, 2003).

A mathematical model for slow axonal transport has been proposed by Blum and Reed (1989). The model assumed the existence of a hypothetical engine that moves at a constant velocity. Proteins were considered to move by reversible association with the engine, either by binding directly to the engine or by piggy-backing on other structures that bind directly to the engine. Microtubules were considered to interact directly with the engine and neurofilaments were considered to move by piggy-backing on the moving microtubules. According to this model, the average velocity of neurofilaments was dependent on the equilibrium constants of the interactions between neurofilaments and microtubules and between microtubules and the engine. By computer simulation of the equations of the model, the authors demonstrated that they could account for the profile of the bell-shaped waves of labeled proteins observed in the radio-isotopic pulse labeling experiments.

Since the development of the Blum–Reed model 15 years ago, considerable progress has been made in the experimental study of neurofilament transport in axons. It is now possible to observe the movement of neurofilaments directly in cultured nerve cells, on a time

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scale of seconds or minutes, using fluorescence microscopy. These observations have demonstrated that the movement of neurofilaments is not slow, after all; neurofilaments actually move at fast rates (about $0.5\mu\text{m/s}$), and the movements are also infrequent, bidirectional and highly asynchronous (see Wang et al., 2000; Roy et al., 2000; Wang and Brown, 2001). To explain these data, Brown proposed the “stop and go” model of slow axonal transport, in which the slow rate of movement is considered to be an average of rapid bidirectional movements interrupted by prolonged pauses (Brown, 2000, 2003). In subsequent work, Brown et al. (2005) used a discrete model to show that the rapid intermittent movement of single neurofilaments observed by fluorescence microscopy in cultured nerve cells can account for the slow overall movement of populations of neurofilaments observed by radio-isotopic pulse labeling in vivo.

In the present paper, we develop a new dynamical system model for the transport of neurofilaments in axons, based on the fast time-scale observations in cultured nerve cells. Some parameters in the model are computed from the measurements in Wang and Brown (2001). We then show, by simulation, that our dynamical system model can match the population profiles of pulse-labeled neurofilaments obtained experimentally in rat and mouse lumbar spinal motor neurons (Hoffman et al., 1985; Xu and Tung, 2000) and in mouse optic nerve (Yabe et al., 2000). Thus, our model and the discrete stochastic model developed by Brown et al. (2005), although they use completely different approaches, both rely on experimental measurements in cultured neurons of Wang and Brown (2001), and both provide a very good agreement with the in vivo experimental data.

2. The model

We view neurofilament polymers as cargo structures that move along cytoskeletal tracks powered by molecular motor proteins. However, note that the model that we are about to describe could apply equally well to neurofilament proteins moving in a non-filamentous form. We assume that neurofilaments can interact with anterograde motor proteins, which move them towards the axon tip, or with retrograde motor proteins, which move them towards the cell body. The identity of the motors that move neurofilaments is not clearly established, but there is evidence that dynein, KIF 5A and myosin Va may all play a role (Shah et al., 2000; Xia et al., 2003; Helfand et al., 2003; Wagner et al., 2004; Rao et al., 2002). Our model does not make any assumptions about the identity of these motor proteins, or about the mechanism or kinetics of motor binding to neurofilaments. However, for the purposes of discussion we will

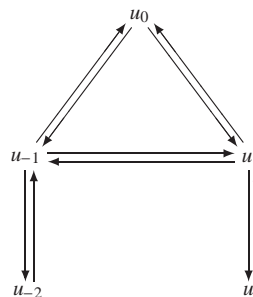
consider that neurofilaments can bind only one type of motor at a time and that reversal occurs when one type of motor dissociates and another type binds.

As discussed by Brown et al. (2005), we assume that anterograde and retrograde neurofilaments can each exist in two states: those adjacent to a cytoskeletal track (“on track”) and those further away (“off track”). At any point in time some neurofilaments are on track and others are off track. Neurofilaments are only capable of movement in the longitudinal dimension of the axon when they are on track but they can switch on and off track by diffusion or active movement in the radial dimension of the axon (our model only considers longitudinal movements and makes no particular assumption about the mechanism of lateral movement). When off track, neurofilaments pause for long periods until they get back on track. When on track, neurofilaments alternate between short bouts of movement and short pauses. Thus we divide the on track population of neurofilaments into those that are moving and those that are making a short pause. Moreover, we designate separately the population of anterograde moving neurofilaments and the population of retrograde moving neurofilaments. In this manner, we divide the neurofilaments into five populations:

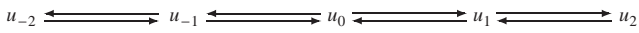
- u_2 : neurofilaments bound to anterograde motors, moving anterogradely, on track,
- u_1 : neurofilaments bound to anterograde motors, pausing, on track,
- u_0 : neurofilaments bound to anterograde or retrograde motors, pausing, off track,
- u_{-1} : neurofilaments bound to retrograde motors, pausing, on track.
- u_{-2} : neurofilaments bound to retrograde motors, moving retrogradely, on track.

We also denote by $u_{-2}, u_{-1}, u_0, u_1, u_2$ the concentrations of these five populations of neurofilaments along the axon.

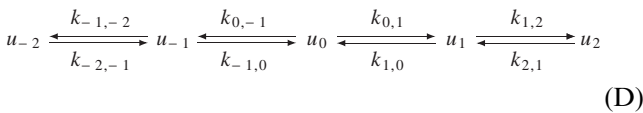
We assume that neurofilaments can reverse direction (i.e. switch motors) when they are pausing, either on track or off track. Thus we obtain the following diagram of possible transitions between the five neurofilament populations:



According to experimental results by Wang and Brown (2001), the rate of change from u_1 to u_{-1} should be much smaller than the rate of change from u_1 to u_2 , and the population u_0 is much larger than u_1 . Therefore, the contribution of this rate in the numerical simulations will be negligible. Analogously, the contribution of the rate of change from u_{-1} to u_1 in the numerical simulations will be negligible. This leads us to the following diagram:



If we denote by $k_{i,j}$ the rate of change from u_i to u_j we have



These relations, together with mass conservation laws, yield the following dynamical system for $0 < x < L$, where L is the length of the axon:

$$\begin{aligned} \frac{\partial u_2}{\partial t} &= -v_A \frac{\partial u_2}{\partial x} + k_{1,2}u_1 - k_{2,1}u_2, \\ \frac{\partial u_1}{\partial t} &= k_{2,1}u_2 + k_{0,1}u_0 - (k_{1,2} + k_{1,0})u_1, \\ \frac{\partial u_0}{\partial t} &= k_{1,0}u_1 + k_{-1,0}u_{-1} - (k_{0,1} + k_{0,-1})u_0, \\ \frac{\partial u_{-1}}{\partial t} &= k_{0,-1}u_0 + k_{-2,-1}u_{-2} - (k_{-1,0} + k_{-1,-2})u_{-1}, \\ \frac{\partial u_{-2}}{\partial t} &= v_R \frac{\partial u_{-2}}{\partial x} + k_{-1,-2}u_{-1} - k_{-2,-1}u_{-2}, \end{aligned} \tag{T}$$

where v_A is the velocity of neurofilaments moving anterograde, and v_R is the velocity of neurofilaments moving retrograde. It is known (Wang and Brown, 2001) that the average velocities excluding pauses, v_A and v_R , are

$$v_A = 0.56 \mu\text{m/s}, \quad v_R = 0.62 \mu\text{m/s}.$$

Strictly speaking, one needs to complement the system (T) with boundary conditions. However, we are modeling the distribution of labeled neurofilament proteins in pulse-labeling experiments, which decays to zero near the endpoints (Brown et al., 2005). Consequently, our numerical results will deal with concentrations of neurofilaments which are negligible near $x = 0$ and L , so that the particular form of the boundary conditions will not enter into our simulation.

Remark. As we mentioned above, the system (T) will be applied to densities of neurofilaments which have been radioactively tagged. Although the measured concentrations of neurofilaments will have a wave-like profile, this wave of tagged neurofilaments does not move in an empty axon. In fact, the concentrations of *all* neurofilaments is at equilibrium locally; what we see are radioactive neurofilaments replacing non-radioactive

neurofilaments. So, the wave of radioactivity will be governed by linear equations, as in the system (T).

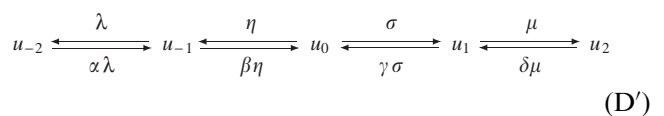
In order to be able to use the system (T) for computational purposes, we must identify the rate coefficients $k_{i,j}$.

2.1. Fast/slow time scales

We regard the transitions in Eq. (D) as happening on a “fast time scale”, as suggested by experimental observations of individual neurofilament movement made by Wang and Brown (2001). On the other hand, we regard the total neurofilament population transport observed in radioisotopic pulse-labeling experiments as taking place on a relatively “slow time scale”. We wish to use the dynamical system (T) to explain the results of radioisotopic pulse-labeling experiments, for example the results of Xu and Tung (2000). The experiments of Xu and Tung have been carried out over a period of several weeks, i.e. each experimental datum was taken after one or several weeks from the initial setup. By contrast, the experimental observations made by Wang and Brown (2001) were carried out over a period of a few minutes. During this short time interval, although some individual neurofilaments were in motion, the total neurofilament population of each u_j changed very little. In other words, both the dynamics and transport terms in Eqs. (T) could be neglected for the values u_j in Wang and Brown (2001). Thus, if we equate the terms $\partial u_j / \partial t$, $v_A \partial u_2 / \partial x$ and $v_R \partial u_{-2} / \partial x$ to zero in Eqs. (T), and note that the last equation is then a consequence of the first four equations, we find the following four relations:

$$\frac{u_{-1}}{u_{-2}} = \frac{k_{-2,-1}}{k_{-1,-2}}, \quad \frac{u_0}{u_{-1}} = \frac{k_{-1,0}}{k_{0,-1}}, \quad \frac{u_0}{u_1} = \frac{k_{1,0}}{k_{0,1}}, \quad \frac{u_1}{u_2} = \frac{k_{2,1}}{k_{1,2}}. \tag{*}$$

Furthermore, let us replace the rates $k_{-1,-2}$ and $k_{-2,-1}$ in diagram (D) by λ and $\lambda k_{-2,-1} / k_{-1,-2}$, respectively, provided that λ is “large enough” to keep the flow chart (D) within the fast time scale (e.g. $\lambda \geq 10$). Since the ratio of the new rates is the same, this replacement will not affect the average distance traveled by the neurofilaments. In the same way we replace $k_{-1,0}$ and $k_{0,-1}$ in diagram (D) by η and $\eta k_{0,-1} / k_{-1,0}$, where η is large enough, etc. The average distance traveled by the neurofilaments is unaffected by these rescalings of the rates $k_{i,j}$. Thus, we replace diagram (D) with



where $\lambda, \eta, \sigma, \mu$ can be any numbers which are large enough to keep this flow chart within the fast time scale.

Together with diagram (D') we also have, as in Eq. (*),

$$\frac{u_{-1}}{u_{-2}} = \alpha, \quad \frac{u_0}{u_{-1}} = \beta, \quad \frac{u_0}{u_1} = \gamma, \quad \frac{u_1}{u_2} = \delta. \quad (**)$$

2.2. Parameter values

We now need to determine the rates $\alpha, \beta, \gamma, \delta$, and, at this point we use the experimental results by Wang and Brown (2001).

If we look at the Wang and Brown (2001) data we notice that, in most cases, individual neurofilaments moving anterogradely switch back and forth between populations u_1 (short pause) and u_2 (moving). If individual neurofilaments moving anterograde make more short pauses, then u_2 decreases and u_1 increases. The ratio u_1/u_2 depends on the time spent pausing and the time spent in processive motion. From the experimental measurements by Wang and Brown (2001) we have $u_1/u_2 = (u_{-1})/(u_{-2}) = \frac{67}{33}$. Hence

$$\alpha = \delta = \frac{67}{33}. \quad (1)$$

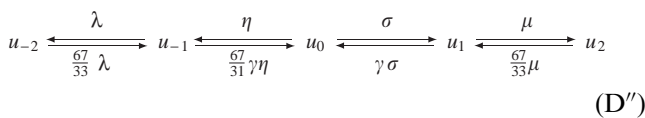
Also, Wang and Brown (2001) established that the ratio between neurofilaments moving anterograde and neurofilaments moving retrograde is $\frac{69}{31}$, i.e.

$$\frac{u_1 + u_2}{u_{-1} + u_{-2}} = \frac{69}{31}.$$

Using Eq. (**) and the equality $\alpha = \delta$ we find that the left-hand side in the last equation is equal to β/γ . Hence

$$\beta = \frac{69}{31} \gamma. \quad (2)$$

From Eqs. (1) and (2) we see that the flow chart (D') can be written in the form



As explained above, the choice of parameters $\lambda, \eta, \sigma, \mu$ will not affect the average distance traveled by neurofilaments for the system (T). But we still have the unresolved parameter γ . This parameter will be determined in a way that provides the best fit with pulse-labeling experimental results.

3. Numerical results

To compare our model to the experimental radioisotopic pulse-labeling data, we begin with the published data of Xu and Tung (2000) for the axonal transport of neurofilament protein L in motor axons of the mouse ventral root and sciatic nerve. In this study, profiles of the neurofilament protein L distribution along the axon

were obtained at one week intervals after injection of radioisotope. Interestingly, the average velocity was found to be approximately constant during the first three weeks, but then slowed at later times. These data indicate that the effective velocity of neurofilament transport (including movement and pauses) can vary along the length of axons. For simplicity, we chose to focus on the initial 3 week period. Our strategy was to start with a distribution of neurofilaments that matches the experimental data at week 1 and then run the simulation and optimize the parameters to obtain the best possible match with the data at week 3.

Given that the distribution of labeled neurofilament proteins in the pulse labeling experiments is approximately gaussian (Xu and Tung, 2000), we take the initial condition to be such that the total population of neurofilaments has a concentration $Ae^{-(x-x_0)^2/M}$, where A, x_0, M were chosen such that the gaussian $Ae^{-(x-x_0)^2/M}$ best estimates the experimental measurements of Xu and Tung (2000) for week 1 (see blue curve in Fig. 1). Given our assumption that most neurofilaments are pausing off track, and since small changes in the initial conditions will not affect the population concentration after a relatively long time (for example, after 1 or 2 weeks), we take initial conditions $u_0(x, 0) = Ae^{-(x-x_0)^2/M}$, and $u_j(x, 0) = 0$ for all other j . We then solve the system (T) with the flow chart (D''), taking

$$\lambda = \eta = \sigma = \mu = 10^2$$

and choose γ such that the profile of the total population of neurofilaments best fits the experimental results of Xu and Tung (2000) for week 3. We find that $\gamma = 19.9$ gives

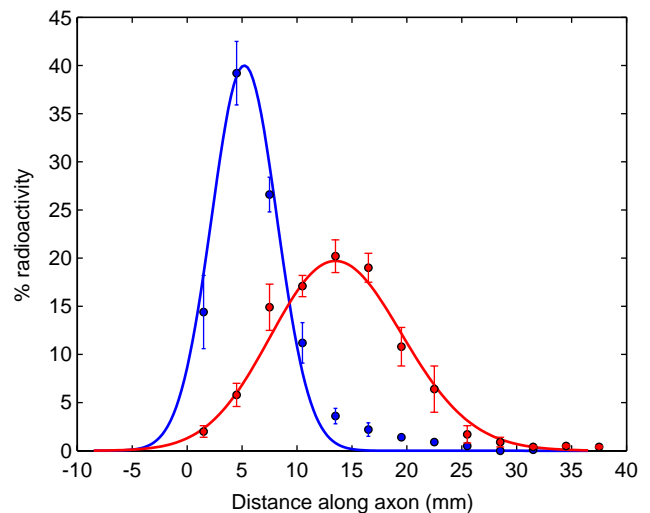


Fig. 1. Population profiles of neurofilament protein in mouse lumbar ventral root and sciatic nerve: the dots represent the experimental data of Xu and Tung (2000); blue is week 1, and red is week 3. The segment length is 3mm. Each point is the mean of 3–5 nerves. The bars represent standard error of the mean (SEM). The blue curve is the initial condition for our model; the red curve then follows from our dynamical system model.

a good fit, as shown in Fig. 1. We have tried other choices of $\lambda, \eta, \sigma, \mu$ in the range $10-10^4$, and found hardly any change in the average distance traveled by neurofilaments, for the same value of γ . This fits perfectly well with the fast time-scale assumption we made in the previous section.

3.1. Comparison with the model of Brown et al. (2005)

Brown et al. (2005) describe a discrete stochastic model for this problem. One of their model predictions is that, overall, neurofilaments spend 97% of the time pausing, i.e.

$$\frac{u_{-2} + u_2}{u_{-1} + u_0 + u_1} = \frac{3}{97}.$$

Using Eq. (**) and our choice of $\gamma = 19.9$, we can compute the left-hand side in terms of the parameters in our model, and we find that it is equal to 0.033, which is in good agreement with the value $\frac{3}{97}$.

Another model prediction by Brown et al. (2005) is that, on average, only 8% of the neurofilaments are on track, i.e.

$$\frac{u_{-2} + u_{-1} + u_1 + u_2}{u_0} = \frac{8}{92}.$$

Again using Eq. (**) and the choice $\gamma = 19.9$, we can compute the left-hand side in terms of the parameters in our model, and we get the value 0.108, which is in good agreement with the value $\frac{8}{92}$.

3.2. Numerical results for other experimental data

Our numerical results for the data of Xu and Tung at week 3 can also be extended to the data at week 2. What we find again is a good fit between our model and the experimental data, but for a different value of the parameter, namely $\gamma = 39.2$. This rather large difference could reflect spatial or temporal differences in neurofilament transport kinetics in these axons, but inspection of the standard errors in the original data suggests that it is more likely due to statistical error (see Fig. 4 in Xu and Tung, 2000).

To determine whether our model is more generally applicable, we attempted to match the radioisotopic pulse labeling data in other neuronal cell types. In Fig. 2, we present numerical results obtained by trying to fit our model to mouse optic nerve experimental data of Yabe et al. (2000) for day 14, using day 3 as the starting point. We find that $\gamma = 1187$ gives a good fit. In Fig. 3 we present numerical results obtained by trying to fit our model to rat sciatic nerve data of Hoffman et al. (1985) for day 20, using day 6 as the starting point. We find that with $\gamma = 67.7$ gives a good fit. In both cases, we were also able to fit the experimental data at other time points, but with different values for γ (not shown).

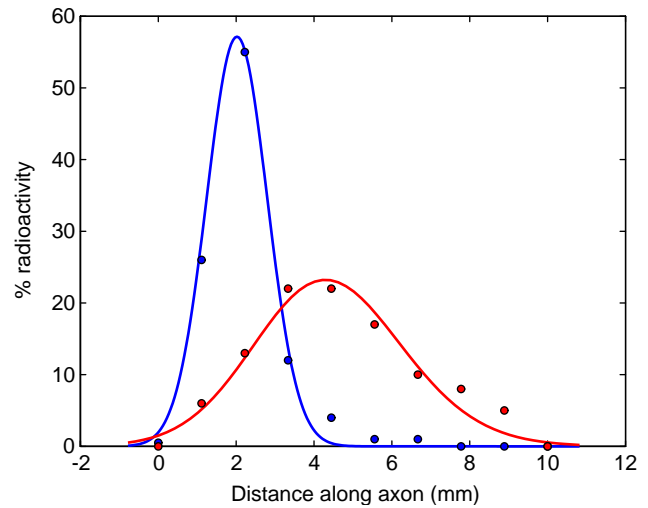


Fig. 2. Population profiles of neurofilament protein in mouse optic nerve: the dots represent the experimental data of Yabe et al. (2000); blue is day 3, and red is day 14. The first segment corresponds to the retina (average axon length = 1 mm; Nixon et al., 1994); subsequent segments correspond to the optic nerve (segment length = 1.1 mm). The blue curve is the initial condition for our model; the red curve then follows from our dynamical system model.

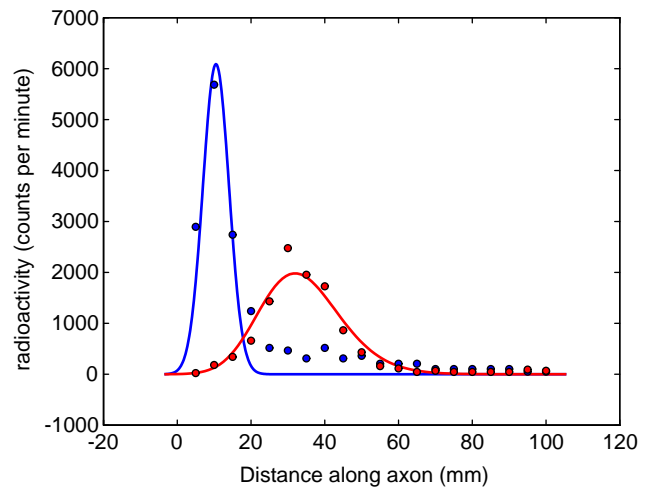


Fig. 3. Population profiles of neurofilament protein in rat lumbar ventral root and sciatic nerve: the dots represent experimental data of Hoffman et al. (1985); blue is day 6, and red is day 20. The segment length is 5 mm. The blue curve is the initial condition for our model; the red curve then follows from our dynamical system model.

Unlike the data of Xu and Tung (2000), no statistics are available for these pulse labeling profiles, so the contribution of statistical error to the variation in γ is not clear. However, in the case of the data of Hoffman et al. (1985) the changes in γ were consistent with the reported slowing of neurofilament transport observed in that system.

Larger γ corresponds to slower overall transport rate, since γ measures the ratio between “off track” and “on track” neurofilament populations. For example, the

very large value of γ obtained for optic nerve data in mouse is consistent with the fact that neurofilament transport rate is significantly slower in the optic nerve, versus ventral root and sciatic nerve in mouse and rat.

4. Conclusions

In this paper, we developed a dynamical system model of transport of neurofilaments in an axon. The model is based on mass conservation of concentrations of the various populations of neurofilaments. All but one of the parameters in our model, namely γ , are determined from experimental measurements by Wang and Brown (2001). We showed that we can then choose γ such that the model produces profiles that are in good agreement with in vivo experiments of Xu and Tung (2000), Yabe et al. (2000) and Hoffman et al. (1985). A discrete stochastic model, entirely different from ours, was used by Brown et al. (2005) to generate profiles which also fit the results of Xu and Tung (2000) for the distribution of neurofilaments. That model predicts some relations among the concentrations u_i . We have shown that our model makes the same predictions.

While we were able to obtain a good fit with the experimental data for any pair of time points in the three data sets that we modeled, we found that each pair of time points required a different value for the parameter γ . Since it is only possible to generate one time point per animal using radioisotopic pulse labeling, there is considerable potential for statistical error in such experiments. Thus it is likely that some of the variation in γ may be due to experimental error. However, it is clear that transport kinetics do vary spatially and/or temporally in some axons. In mouse lumbar spinal motor axons, Xu and Tung reported an abrupt slowing after 3 weeks corresponding to the point at which the axons emerge from the vertebral foramen and enter the periphery (Xu and Tung, 2000, 2001). In rat lumbar spinal motor axons, Hoffman et al. reported a more continuous slowing (Hoffman et al., 1985). According to our model, such changes in transport velocity along axons could be caused by changes in the size of the on- and off-track pools or the anterograde and retrograde pools. For example, a decrease in the proportion of time spent on track or an increase in the proportion of time spent moving retrogradely could both cause a slowing of neurofilament transport. We plan to address the slowing mechanism in the future.

Our model assumes that neurofilament transport is bidirectional in vivo. This assumption is based primarily on the observation that neurofilaments move both anterogradely and retrogradely in axons of cultured neurons. While it is possible that this bidirectionality is unique to neurons in culture, it should be noted that there is also experimental evidence for bidirectional

movement of neurofilaments in vivo (Watson et al., 1993; Glass and Griffin, 1994). The idea that neurofilaments can move retrogradely in vivo is also supported by studies on transgenic mice over-expressing the p50/dynamitin subunit of dynactin, which exhibit axonal neurofilament accumulations (LaMonte et al., 2002). Moreover, we have shown here that a model based on rapid intermittent and bidirectional movement can explain the kinetics of movement in vivo.

Our numerical results raise a very interesting mathematical question about long time behavior of linear systems of reaction-hyperbolic equations. Reed et al. (1990) considered $n + 1$ species, with the first n species, p_1, \dots, p_n , stationary, and the last one, q , moving with velocity v . They show, by a singular perturbation argument, that there exists a traveling wave solution, determined by the heat equation, similar to our numerical results. There are important similarities between the setting in Reed et al. and ours: (a) they work with linear reaction-hyperbolic dynamical systems similar to ours, and (b) they work in a regime of very high transition rates between species (which we called “fast time scale”). The main differences between their setting and ours are: (a) we have two moving populations with different velocities and different directions of movement, and (b) the initial conditions and the boundary conditions (at the axon soma) are different. The argument of Reed et al. (1990) was subsequently made rigorous by Brooks (1999) in the case $n = 1$, by using a probabilistic method which resembles the stochastic setup of Brown et al. (2005). It would be interesting to extend the asymptotic results of Reed et al. (1990) and Brooks (1999) to the case of an arbitrary number of species and velocities.

Our dynamical system approach can easily be refined to include diffusion, and it can also be extended to other transport problems, such as the transport of vesicles in an axon (Friedman and Craciun, 2005). This approach should extend also to models of neurofilament distribution along axons during axon growth, and hopefully also to models of neurofilament distribution at particular regions along the length of axons, such as at nodes of Ranvier.

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References

- Al-chalabi, A., Miller, C.C., 2003. Neurofilaments and neurological disease. *BioEssays* 24, 346–355.
- Blum, J.J., Reed, M.C., 1989. A model for slow axonal transport and its application to neurofilamentous neuropathies. *Cell Motil. Cytoskel.* 12, 53–65.
- Brooks, E.A., 1999. Probabilistic methods for a linear reaction-hyperbolic system with constant coefficients. *Ann. Appl. Probab.* 9 (3), 719–731.
- Brown, A., 2000. Slow axonal transport: stop and go traffic in the axon. *Nat. Rev. Mol. Cell Biol.* 1, 153–156.
- Brown, A., 2003. Axonal transport of membranous and nonmembranous cargoes: a unified perspective. *J. Cell Biol.* 160 (6), 817–821.
- Brown, A., Wang, L., Jung, P., 2005. Stochastic simulation of neurofilament transport in axons: the ‘stop and go’ hypothesis. *Mol. Biol. Cell*, in press.
- Friedman, A., Craciun, G., 2005. A model of intracellular transport of particles in an axon. *J. Math. Biol.*, in press.
- Glass, J.D., Griffin, J.W., 1994. Retrograde transport of radiolabeled cytoskeletal proteins in transected nerves. *J. Neurosci.* 14, 3915–3921.
- Helfand, B.T., Loomis, P., Yoon, M., Goldman, R.D., 2003. Rapid transport of neural intermediate filament protein. *J. Cell Sci.* 116 (Part 11), 2345–2359.
- Hoffman, P.N., Griffin, J.W., Gold, B.G., Price, D.L., 1985. Slowing of neurofilament transport and the radial growth of developing nerve fibers. *J. Neurosci.* 5, 2920–2929.
- LaMonte, B.H., Wallace, K.E., Holloway, B.A., Shelly, S.S., Ascano, J., Tokito, M., Van Winkle, T., Howland, D.S., Holzbaur, E.L., 2002. Disruption of dynein/dynactin inhibits axonal transport in motor neurons causing late-onset progressive degeneration. *Neuron* 34 (5), 715–727.
- Lasek, R.J., Paggi, P., Katz, M.J., 1992. Slow axonal transport mechanisms move neurofilaments relentlessly in mouse optic axons. *J. Cell Biol.* 117, 607–616.
- Nixon, R.A., Paskevich, P.A., Sihag, R.K., Thayer, C.Y., 1994. Phosphorylation on carboxyl terminus domains of neurofilament proteins in retinal ganglion cell neurons in vivo: influences on regional neurofilament accumulation, interneurofilament spacing, and axon caliber. *J. Cell Biol.* 126, 1031–1046.
- Rao, M.V., Engle, L.J., Mohan, P.S., Yuan, A., Qiu, D., Cataldo, A., Hassinger, L., Jacobsen, S., Lee, V.M., Andreadis, A., Julien, J.P., Bridgman, P.C., Nixon, R.A., 2002. Myosin Va binding to neurofilaments is essential for correct myosin Va distribution and transport and neurofilament density. *J. Cell Biol.* 159 (2), 279–289.
- Reed, M.C., Venakides, S., Blum, J.J., 1990. Approximate traveling waves in linear reaction-hyperbolic equations. *SIAM J. Appl. Math.* 50 (1), 167–180.
- Roy, S., Coffee, P., Smith, G., Liem, R.K., Brady, S.T., Black, M.M., 2000. Neurofilaments are transported rapidly but intermittently in axons: implications for slow axonal transport. *J. Neurosci.* 20, 6849–6861.
- Shah, J.V., Flanagan, L.A., Janmey, P.A., Leterrier, J.F., 2000. Bidirectional translocation of neurofilaments along microtubules mediated in part by dynein/dynactin. *Mol. Biol. Cell* 11, 3495–3508.
- Wagner, O.I., Ascano, J., Tokito, M., Leterrier, J.-F., Janmey, P.A., Holzbaur, E.L., 2004. The interaction of neurofilaments with the microtubule motor cytoplasmic dynein. *Mol. Biol. Cell* 15, 5092–5100.
- Wang, L., Brown, A., 2001. Rapid intermittent movement of axonal neurofilaments observed by fluorescence photobleaching. *Mol. Biol. Cell* 12, 3257–3267.
- Wang, L., Ho, C.-L., Sun, D., Liem, R.K.H., Brown, A., 2000. Rapid movement of axonal neurofilaments interrupted by prolonged pauses. *Nat. Cell Biol.* 2, 137–141.
- Watson, D.F., Glass, J.D., Griffin, J.W., 1993. Redistribution of cytoskeletal proteins in mammalian axons disconnected from their cell bodies. *J. Neurosci.* 13, 4354–4360.
- Williamson, T.L., Marszalek, J.R., Vechio, J.D., Bruijn, L.I., Lee, M.K., Xu, Z., Brown, R.H., Cleveland, D.W., 1996. Neurofilaments, radial growth of axons, and mechanisms of motor neuron disease. *Cold Spring Harbor Symp. Quant. Biol.* 61, 709–723.
- Xia, C.H., Roberts, E.A., Her, L.S., Liu, X., Williams, D.S., Cleveland, D.W., Goldstein, L.S., 2003. Abnormal neurofilament transport caused by targeted disruption of neuronal kinesin heavy chain KIF5A. *J. Cell Biol.* 161 (1), 55–66.
- Xu, Z., Tung, V., 2000. Overexpression of neurofilament subunit M accelerates neurofilament transport. *Brain Res.* 866, 326–332.
- Xu, Z., Tung, V., 2001. Temporal and spatial variations in slow axonal transport velocity along peripheral motoneuron axons. *Neuroscience* 102, 193–200.
- Yabe, J.T., Jung, C., Chan, W.K., Shea, T.B., 2000. Phospho-dependent association of neurofilament proteins with kinesin in situ. *Cell Motil. Cytoskel.* 45, 249–262.