A model of axonal transport drug delivery

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Abstract: In this paper a model of targeted drug delivery by means of active (motor-driven) axonal transport is developed. The model is motivated by recent experimental research by Filler et al. (A.G. Filler, G.T. Whiteside, M. Bacon, M. Frederickson, F.A. Howe, M.D. Rabinowitz, A.J. Sokoloff, T.W. Deacon, C. Abell, R. Munglani, J.R. Griffiths, B.A. Bell, A.M.L. Lever, Tri-partite complex for axonal transport drug delivery achieves pharmacological effect, Bmc Neuroscience 11 (2010) 8) that reported synthesis and pharmacological efficiency tests of a tri-partite complex designed for axonal transport drug delivery. The developed model accounts for two populations of pharmaceutical agent complexes (PACs): PACs that are transported retrogradely by dynein motors and PACs that are accumulated in the axon at the Nodes of Ranvier. The transitions between these two populations of PACs are described by first-order reactions. An analytical solution of the coupled system of transient equations describing conservations of these two populations of PACs is obtained by using Laplace transform. Numerical results for various combinations of parameter values are presented and their physical significance is discussed.

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1. Introduction

Neurons are nerve cells that have two types of long processes, axons and dendrites; axons transmit signals and dendrites receive signals. In a human body axons can be up to one meter in length. Most organelles are synthesized in the neuron soma, and they have to be transported to a particular location in an axon or dendrite where they are needed. In order to transport them in a timely fashion cells developed a sophisticated network, where organelles are pulled by molecular motors running on microtubules (MTs) (Goldstein and Yang [1], Goldstein [2], Alberts et al. [3]). In axons, anterograde transport is powered by kinesin motors while retrograde transport is powered by dynein motors (Ally et al. [4], Gallant [5], Gross [6], Pilling et al. [7], Welte [8], Mallik et al. [9]).

In addition to organelles, various chemical signals (for example, trophic factors) are also transported by molecular motors (Deckwerth et al. [10], Deshmukh and Johnson [11], Riccio et al. [12], Vogelbaum et al. [13], Zweifel et al. [14], Altick et al. [15], Chan and Haschke [16], Chan et al. [17]). Also, many harmful viruses and prions utilize the axonal transport machinery to spread in the neural system (Lancaster and Pfeiffer [18], Mazarakis et al. [19], Miranda-Saksena et al. [20], Tan et al. [21], Encalada and Goldstein [22]). Axonal transport can be potentially used...
to deliver drugs to treat various neurological disorders. Von Bartheld [23] discussed similarities in trafficking of trophic factors and pathogenic proteins and also reviewed research on the utilization of axonal transport for targeted drug delivery for treating neurological diseases (see also Kaplan et al. [24]).

Possible applications of axonal transport for targeted drug delivery have been discussed in Bizzini et al. [25], Filler [26], Filler and Bell [27], Filler et al. [28], Haschke et al. [29]. Potential benefits include the reduction of drug toxicity and increase of its half life. The present research is motivated by recent work by Filler et al. [30] who chemically synthesized a tripartite complex that consisted of an axon transport facilitator molecule, a polymer linker, and a large number of drug molecules, for targeted drug delivery to neurons. Filler et al. [30] reported that they were able to load up to 100 drug molecules per complex; the obtained results indicate a tenfold increase in the drug half life and a 300 fold decrease in the necessary dose compared to systemic administration.

The research of Filler et al. [30] indicated that a significant amount of transported drug accumulated in the axon. The explanation of this phenomenon proposed in [30] is based on the fact that the material from the axoplasm can be endocytosed by paranodal complexes of Schwann cells at the Nodes of Ranvier (Gatzinsky and Berthold [31], see also Gatzinsky [32]). Filler et al. [30] also reported that accumulated drug was subsequently re-released (rather than entering the degenerative pathway [31]). Proceeding from this evidence, the goal of this paper is to develop a mathematical model that accounts for drug accumulation as it is transported retrogradely down the axon and then is re-released and to obtain an analytical solution of model equations for the transient case. This would fill the existing gap in the literature concerning modeling of axonal transport drug delivery. The analysis of the model reveals conditions when a long-term accumulation of PACs is possible and also provides a mechanistic interpretation of the results of [30] in terms of how the accumulation could occur.

The solution method developed in this paper relies on mathematical techniques developed in [33, 34] for modeling retrograde transport of neurotropic viruses, in [35] for modeling the propagation of injury signals in axons, and in [36] for modeling retrograde transport of nerve growth factors; however, the above papers dealt with the situation when there was only one population of particles. The problem solved here is much more complex because two populations of particles are included in the model, and the model accounts for transitions between these two populations. A corresponding steady-state problem was considered in [37] and effects of degradation and diffusivity of PACs were considered in [38, 39], respectively.

2. Governing equations

A sketch of the problem is displayed in Fig. 1a. It is assumed that the axon terminal is exposed to PACs for the time \( t^* \). During that time PACs enter the axon terminal at a constant rate (see Fig. 1c). After they enter, PACs are transported by dynein motors toward the neuron soma. During their transport, PACs can be absorbed at the Nodes of Ranvier and then be re-released; the absorption and re-release processes are described by first-order reactions. Thus there are two populations of PACs in the model: PACs that are transported in the axon retrogradely by dynein motors and PACs that are accumulated in the axon (Fig. 1b). The situation is thus different from that analyzed in Smith and Simmons [40] where no population of accumulated particles was considered. The purpose of the presented modeling is, by building on the experimental results reported in [30], to show how the interplay between PAC transport and accumulation in the axon could occur.

Due to a large number of the Nodes of Ranvier, the discrete spacing of the Nodes of Ranvier is neglected and it
is assumed that PACs are continuously absorbed and then re-released along the axon length. This assumption is reasonable, given that the spacing of the Nodes of Ranvier is ∼100 μm [41] while drug delivery problems typically involve distances ∼1 cm. Under these assumptions, equations describing the conservation of the two populations of PACs are

\[ \frac{\partial n_0^*}{\partial t^*} = -k^*_n n_0^* + k^*_d n^* \]  

\[ \frac{\partial n^*}{\partial t^*} = k^*_n n_0^* - k^*_d n^* - v^* \frac{\partial n^*}{\partial x^*}, \]  

where \( k^*_n \) is the first order rate constant characterizing the rate at which PACs are re-released from the accumulated state \((s^{-1})\); \( k^*_d \) is the first order rate constant characterizing the rate at which PACs are absorbed at the Nodes of Ranvier \((s^{-1})\); \( n_0^* \) is the number density of PACs accumulated at a particular location in the axon \((1/\mu m^3)\); \( n^* \) is the number density of PACs transported retrogradely by dynein motors \((1/\mu m^3)\); \( t^* \) is the time \((s)\); \( v^* \) is the average velocity of dynein motors \((\mu m/s)\); and \( x^* \) is the linear coordinate that starts at the axon terminal and is directed toward the neuron soma \((\mu m)\), see Fig. 1a. Asterisks denote dimensional variables. Eq. (1) expresses the conservation of PACs accumulated in the axon while Eq. (2) expresses the conservation of PACs that are transported by dynein motors. These two equations are coupled through the kinetic terms that describe transitions between these two populations of PACs (see Fig. 1b).

Since PACs are assumed to be driven by dynein motors, their flux, measured in \(1/\mu m^2s\), is given by

\[ j^* = v^* n^*. \]  

The boundary condition at \( x^* = 0 \) is

\[ j^*(0, t^*) = v^* n^*(0, t^*) = j_0^* \left[ 1 - H(t^* - t^*_c) \right], \]  

where \( H(\eta) \) is the Heaviside step function [42]; \( j_0^* \) is the PAC flux at the axon terminal during the exposure \((1/\mu m^2s)\), see Fig. 1c; and \( t^*_c \) is the duration of the PAC exposure \((s)\). It is assumed that the neuron soma acts as a perfect absorber of PACs (no wave reflection at the axon hillock, [43]), which means that the solution is identical to that obtained for a semi-infinite domain.

It is assumed that at \( t^* = 0 \) there are no PACs in the axon, \( n_0^* (x^*, 0) = 0 \) and \( n^* (x^*, 0) = 0 \).

The dimensionless forms of Eqs. (1) and (2) are

\[ \frac{\partial n_0}{\partial t} = -n_0 + k_n n_-. \]  

where the dimensionless variables are defined as follows:

\[ x = \frac{x^* k^*_r}{v^*}, \quad n_0 = \frac{n_0^* v^*}{j_0^*}, \quad n_- = \frac{n^* v^*}{j_0^*}, \quad t = t^* k^*_r. \]  

and the dimensionless kinetic constant is defined as

\[ k_n = \frac{k^*_n}{k^*_r}. \]  

The dimensionless form of boundary condition is

\[ n_-(0, t) = 1 - H(t - t_c), \]  

where

\[ t_c = t^*_c k^*_r. \]  

Eqs. (5) and (6) with boundary condition (9) and zero initial conditions (it is assumed that initially there were no PACs in the axon) are solved by Laplace transform. The subsidiary equations are

\[ sN_0 = -N_0 + k_a N_- \]  

\[ sN_- = N_0 - k_a N_- - \frac{\partial N_-}{\partial x}, \]  

where \( N_0(x, s) \) and \( N_-(x, s) \) are the Laplace transforms of the functions \( n_0(x, t) \) and \( n_-(x, t) \), respectively.

The Laplace transform of boundary condition (9) is

\[ N_-(0, s) = \frac{1 - e^{-st_c}}{s}. \]  

The solutions of subsidiary Eqs. (11) and (12) subject to boundary condition (13) are

\[ N_0(x, s) = \frac{-1 + \exp[st_c] k_a}{s(1 + s)} \times \exp \left[ -st_c - \frac{s + k_a + s}{1 + s} x \right] \]  

\[ N_-(x, s) = \frac{-1 + \exp[st_c]}{s} \times \exp \left[ -st_c - \frac{s + k_a + s}{1 + s} x \right]. \]  

Calculating the inverse Laplace transforms [42, 44] of the right-hand sides of Eqs. (14) and (15), the following solutions for the PA concentrations are obtained:
of magnitude estimates of different model parameters are than on the dynamics of their transport in neurons. Order-pharmacological efficiency of tripartite complexes rather from Filler et al. [30] whose focus was on synthesis and It is not possible to estimate values of model parameters 

\[ n_0(x, t) = k_{a} \exp[-(t - k_{a}x)](\exp[t] - \exp[x])H[t - x] \]

\[ + \int_{0}^{t} \exp[-(t - k_{a}x)](1 - \exp[-t + \tau + x]) \times H[t - \tau - x] \sqrt[k_{a}x]{\frac{k_{a}x}{\tau}} f(2\sqrt{\tau k_{a}x}) d\tau \]

\[ - H[t - t_{c}] \{ \exp[-(t - k_{a}x)]H[t - t_{c} - x] \times \exp[t - t_{c} - x] H[t - x] \}

\[ + \int_{0}^{t} \exp[-(t - k_{a}x)]H[t - x] \sqrt[k_{a}x]{\frac{k_{a}x}{\tau}} f(2\sqrt{\tau k_{a}x}) d\tau \]

\[ \times \sqrt[k_{a}x]{\frac{k_{a}x}{\tau}} f(2\sqrt{\tau k_{a}x}) d\tau \]

where \( f(\cdot) \) is the modified Bessel function of the first kind of order 1.

3. Parameter estimation

It is not possible to estimate values of model parameters from Filler et al. [30] whose focus was on synthesis and pharmacological efficiency of tripartite complexes rather than on the dynamics of their transport in neurons. Order-of-magnitude estimates of different model parameters are therefore based on other published work. According to King and Schroer [45] and Toba et al. [46], cytoplasmic dynein walks to the MT minus-end with an average velocity of approximately 1 \( \mu m/s \). It is assumed that a pulse contains 500 PACs. Since the problem is linear, this assumption does not affect the generality of the trends displayed in the figures. In order to estimate the flux of PACs from the axon terminal, \( \mu_{p} \), one needs to know the duration of the pulse, \( t'_{c} \). Using, for example, a 600 s duration of the pulse and estimating the average axonal diameter as 1.1 \( \mu m \) based on Bergers et al. [47] one obtains \( \mu_{p} = 0.88 \) particles/(\( \mu m s \)). This value is rounded up to \( \mu_{p} = 1 \) particles/(\( \mu m s \)), and the latter value is used in computations.

Estimating kinetic constants characterizing the dynamics of PAC absorption/release at the Nodes of Ranvier is difficult. For cytoplasmic dynein, the average attachment rate to MTs is estimated as 1.5 s\(^{-1}\) (Carter and Cross [48], Vale et al. [49]) while the average detachment rate from MTs is estimated as 0.25 s\(^{-1}\) (King and Schroer [45], Reck-Peterson et al. [50]). Smith and Simmons [40] used the same value of 1 s\(^{-1}\) for all attachment/detachment rates in a standard set of primary parameters that they used in computations. However, values of kinetic constants characterizing absorption/release at the Nodes of Ranvier are expected to be several orders of magnitude smaller than the above values characterizing the dynamics of organelle interaction with MTs. This point is demonstrated in Fig. 2, which is computed for \( \mu_{p} = 1 \mu m^{-2}s^{-1}, \nu = 1 \mu m/s, t'_{c} = 600s, k^{*}_{a} = 1s^{-1}, \) and \( k^{*}_{d} = 1s^{-1} \). (All computed figures display dimensionless concentrations along the \( y \)-axes and dimensional coordinate \( x^{*} \) along the \( x \)-axis. The dimensional coordinate \( x^{*} \) is used for the ease of comparison between the figures; otherwise, figures with different \( k^{*}_{d} \) would have different ranges of the \( x \)-axis; this is because \( k^{*}_{d} \) is used in scaling of the \( x \)-coordinate, see Eq. (7). For the same reason, dimensional rather than dimensionless times are given in the legends.) For the case when kinetic constants in the numerical model are large, both concentrations of accumulated PACs (displayed in Fig. 2a) and those transported by dynein motors (displayed in Fig. 2b) form pulses that have the same shape and move with the same velocity. Fig. 2 demonstrates that: (1) If values of kinetic constants were large, no drug accumulation would be observed (which contradicts [30]), PACs would be absorbed and then immediately re-released resulting in the formation of two waves, the concentration wave of accumulated PACs being a footprint of the concentration wave of PACs transported by dynein motors. (2) The propagation velocity of the two concentration waves would be smaller than the velocity of a PAC transported by dynein motors. This is explained as follows. In the case of large kinetic constants a PAC is part time transported by dynein motors (this is similar to being in a moving state in the model developed in Jung and Brown [51] and part time attached to the axon at the Nodes of Ranvier (this is similar to being in the pausing state in the model developed in [51]). This means that the PAC moves only part time, resulting...
Figure 2. The case of large kinetic constants: (a) Dimensionless number density of PACs accumulated at the Nodes of Ranvier; (b) Dimensionless number density of PACs transported retrogradely by dynein motors. Computations are performed for $\gamma_0 = 1 \mu m^{-2} s^{-1}$, $\nu^* = 1 \mu m/s$, $t_c^* = 600 s$, $k_r^* = 10^{-4} s^{-1}$ and $k_a^* = 10^{-4} s^{-1}$. The situation is now very different from that displayed in Fig. 2. Indeed, the pulse showing the concentration of PACs that are transported by dynein motors in Fig. 3b moves much faster than that in Fig. 2b. This is because a PAC now spends most of its time in the moving state and only a small portion of its time in the accumulated state. Interestingly, the top of the pulse in Fig. 3b is a straight line with a negative slope, which indicates that the concentration of dynein-transported PACs decreases within the pulse because PACs transition to the accumulated state. There is also a small amount of dynein-driven PACs after the main pulse, those are PACs re-released from the accumulated state. Also, the concentration of PACs in the accumulated state (see Fig. 3a) now propagates as a front. As the front propagates, the concentration of PACs accumulated at the Nodes of Ranvier decreases because these PACs are re-released and picked up by dynein motors.

Fig. 4 is similar to Fig. 3, but it is computed for a smaller value of the kinetic constant characterizing the rate of re-release of accumulated PACs, $k_r^* = 10^{-5} s^{-1}$ (the value of $k_r^*$ has been decreased by a factor of 10 compared to Fig. 3). One can see that there is almost no effect on the concentration of PACs transported by dynein motors; this concentration is displayed in Fig. 4b. This is because the concentration of accumulated PACs is much smaller than the concentration of dynein-transported PACs, and a small change in the concentration of accumulated PACs does not result in a visible change in the concentration of dynein-driven PACs. The concentration of accumulated PACs displayed in Fig. 4a is a little larger than that displayed in Fig. 3a. Also, the shape of the lines is different; Fig. 4a displays a linear decrease of the concentration of accumulated PACs as $x^*$ increases. This is because now the re-release of accumulated PACs is negligible; $n_0$ decreases as $x^*$ increases not because of the re-release, but because the concentration of dynein-driven PACs, displayed in Fig. 4b, decreases as $x^*$ increases, and these two concentrations of PACs are coupled through the kinetic diagram displayed in Fig. 1b.
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Figure 3. The case of small kinetic constants: (a) Dimensionless number density of PACs accumulated at the Nodes of Ranvier; (b) Dimensionless number density of PACs transported retrogradely by dynein motors. Computations are performed for $\kappa_*^0 = 1 \mu m^{-2} s^{-1}$, $\nu^* = 1 \mu m/s$, $t^*_c = 600 s$, $k^*_a = 10^{-4} s^{-1}$, $k^*_r = 10^{-4} s^{-1}$ (corresponding dimensionless parameter values are $k_a = 1$, $t_c = 0.06$).

Fig. 5 is similar to Fig. 3, but it is computed for a smaller value of the kinetic constant characterizing the rate of PAC absorption at the Nodes of Ranvier, $k^*_a = 10^{-5} s^{-1}$ (the value of $k^*_a$ has been decreased by a factor of 10 compared to Fig. 3). The concentration of dynein-driven PACs, displayed in Fig. 5b, is now a little larger than that displayed in Fig. 3b. Also, the tops of the pulses in Fig. 5a are closer to horizontal lines; this indicates a smaller loss of moving PACs due their transition to the accumulated state. The concentration of accumulated PACs, displayed in Fig. 5a, is now very small.

Fig. 6 is similar to Fig. 3, but it is computed for a smaller pulse duration, $t^*_c = 300s$ (the duration of the pulse has been decreased by a factor of 2 compared to Fig. 3). The pulse in Fig. 6b is twice more narrow than in Fig. 3b, as
expected. However, the height of the pulse and the rate of its decay are approximately the same in these two figures. This is because these parameters are controlled by kinetic constants (which are the same in both cases presented in Figs. 6 and 3), and not by the pulse duration. The shapes of the concentrations of accumulated PACs in Fig. 6a are similar to those in Fig. 3a, but the concentrations are approximately twice smaller in amplitude. This is because the number of dynein-transported PACs in Fig. 6 is half of that in Fig. 3 (due to a shorter pulse), and, as a result of that, less PACs are absorbed at the Nodes of Ranvier.

5. Conclusions

A minimal mechanistic mathematical model describing axonal transport drug delivery is developed. The model accounts for two populations of PACs: those transported by
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