Modeling organelle transport in branching dendrites with a variable cross-sectional area

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Abstract The purpose of this paper is to develop a method for calculating organelle transport in dendrites with a non-uniform cross-sectional area that depends on the distance from the neuron soma. The model is based on modified Smith–Simmons equations governing molecular motor-assisted organelle transport. The developed method is then applied to simulating organelle transport in branching dendrites with two particular microtubule (MT) orientations reported from experiments. It is found that the rate of organelle transport toward a dendrite's growth cone heavily depends on the MT orientation, and since there is experimental evidence that the MT orientation in a particular region of a dendrite may depend on the dendrite's developmental stage, the obtained results suggest that a rearrangement of the MT structure may depend on the amount of organelles needed at the growth cone.

Keywords Molecular motors • Motor-assisted transport • Neurons • Axons and dendrites • Intracellular organelles

1 Introduction

Neurons have two types of long specialized processes, axons that transmit signals and dendrites that receive signals. Neither axons nor dendrites contain enough synthetic machinery to produce organelles they need on their own. Most organelles needed for the growth and maintenance of axons and dendrites are synthesized in the neuron body; synthesized organelles are transported from the cell body toward distal parts of axons and dendrites while used components are transported back to the neuron body for reprocessing. Organelles are transported by the combined effect of diffusion and molecular-motor-driven transport (the latter component is essential because diffusion is not a sufficiently fast mode

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for transport of large organelles; indeed, diffusivity of particles is inversely proportional to their radius). Molecular-motor-driven transport of intracellular cargo in axons and dendrites occurs along MTs. Active transport toward MT plus-ends is powered by kinesin molecular motors while that toward MT minus-ends is powered by dynein molecular motors (Vallee and Bloom [1], Holzbaur [2], Linial [3]).

The diameter of axons is relatively constant, and does not decrease with branching (Rolls et al. [4]). The MT polarity orientation in axons is uniform; the plus-end of each MT is directed away from the neuron soma toward the axon terminal (Alberts et al. [5]). Unlike axons, dendrites are relatively thick at their bases, decrease in diameter with increasing distance from the cell body, and are relatively short; for example dendrites of hippocampal neurons terminate within a distance of about 150 μm from the soma (Bartlett and Banker [6]). Baas et al. [7] reported that in dendrites of cultured rat hippocampal neurons in the mid-region of the dendrite the MT orientation is mixed, roughly half of MTs have their plus-ends facing outward away from the soma, and half have their minus-ends out. In the distal dendrite region, the MT polarity orientation in dendrites is similar to that in axons; MT plus-ends are uniformly directed toward the growth cone. Based on their research of cultural pyramidal neurons, Takahashi et al. [8] found another possible MT arrangement in dendrites: in their experiments they found the mixed MT orientation in both proximal and distal dendritic regions. To explain the difference with previous results of Baas et al. [7], Takahashi et al. [8] suggested that the MT polarity pattern along the length of a dendrite may depend on whether the dendrite is growing or not. There are also indications that in invertebrate neurons the MT orientation in dendrites may be different. Recently, Stone et al. [9] mapped MT orientations in dendrites of *Drosophila* sensory neurons, interneurons, and motor neurons and established the minus-end-out rather than mixed MT orientation in these dendrites.

The purpose of this paper is to develop a method for calculating transport of organelles in dendrites with a non-uniform cross-sectional area; this is important because the cross-sectional area of a dendrite depends on the distance from the neuron soma. The size and shape of dendrites are major characteristics that define neuronal types; in fact, the dendrite morphology can be considered as a neuron's anatomical fingerprint (Gao [10], Cuntz et al. [11]). The method developed in this paper is applied to dendrites in which a proximal dendrite branches to produce two distal dendrites. Two particular MT arrangements are simulated: one reported in Baas et al. [7] (displayed in Fig. 1a) and the other reported in Takahashi et al. [8] (displayed in Fig. 1b), although the method can be easily reformulated for any other dendritic MT arrangement as well as for dendrites with a more complex morphology. For example, simulations for dendrites with a uniform cross-section for MT arrangements typical for *Drosophila* dendrites and axons (based on experimental results presented in Stone et al. [9]) have been recently reported in Kuznetsov [12, 13].

2 Governing equations

The model utilized in this research is based on the continuum approach to modeling molecular-motor-assisted transport of organelles developed in Smith and Simmons [14]. Continuum-based models developed utilizing Smith–Simmons equations have been recently applied to different situations in intracellular transport in [15–19]. The model developed in this paper assumes that organelles can be in one of four kinetic states, and the number density of organelles in each kinetic state is denoted as $\tilde{n}_{0+}$, $\tilde{n}_{0-}$, $\tilde{n}_{+}$, and

$\tilde{n}_-$, respectively. A kinetic diagram showing various organelle populations and kinetic processes between them is displayed in Fig. 1c (the idea of presenting this diagram is motivated by Fig. 4 in Jung and Brown [20], but the diagram is adjusted for the fast mode of organelle transport). Two of the four kinetic states ($\tilde{n}_{0+}$ and $\tilde{n}_{0-}$) correspond to free (off-track) organelles (off-track organelles are thus denoted by a subscript 0) and the other two kinetic states ($\tilde{n}_+$ and $\tilde{n}_-$) correspond to organelles that are transported on MTs by molecular motors. If an organelle is attached to a plus-end (kinesin) motor, it is denoted by a subscript + ($\tilde{n}_{0+}$ and $\tilde{n}_+$), if it is attached to a minus-end (dynein) motor, it is denoted by a subscript - ($\tilde{n}_{0-}$ and $\tilde{n}_-$). The reason for separating free (off-track) organelles into free plus-end-directed organelles ($\tilde{n}_{0+}$) and free minus-end-directed organelles ($\tilde{n}_{0-}$) is the fact that switching the type of a molecular motor (or molecular motors, if an organelle is pulled by more than one motor) requires an elaborate molecular mechanism and cannot not occur

Fig. 1 **a** Schematic diagram of the MT orientation in a dendrite with a mixed polarity orientation in a proximal dendrite and plus-end-out orientation in distal dendrites (dendrite 1), **b** Schematic diagram of the MT orientation in a dendrite with a mixed polarity orientation in both proximal and distal dendrites (dendrite 2), **c** kinetic diagram showing various organelle populations and kinetic processes between them

very often; in fact, available biological data (at least for slow axonal transport) suggest that such switching occurs much less frequently than the attachment of free organelles to MTs. For modeling diffusion transport, it is assumed that the cross-sectional area of the dendrite $\tilde{A}$ is a given function of the distance from the neuron soma $\tilde{x}$; it is also assumed that at the branch point section the sum of cross-sectional areas of two distal dendrites is equal to the cross-sectional area of the proximal dendrite.

2.1 Dendrite 1, $0 < x < L_1 + L_2$, mixed MT polarity orientation in a proximal dendrite and plus-end-out orientation in distal dendrites

A schematic diagram for this case is shown in Fig. 1a. In order to minimize the number of parameters involved in the model, governing equations have been converted to their dimensionless form. According to the Buckingham Pi theorem (White [21]), the maximum reduction is equal to two (the number of dimensions describing the variables, length and time). The dimensionless variables and dimensionless groups utilized in the model are defined in Eqs. 7–9 below.

It is assumed that the variation of organelle concentrations occurs only in the axial direction; this assumption makes it possible to reduce the problem to a one-dimensional problem. Since the length of the dendrite is much larger than its diameter, MTs are aligned along the dendrite length, and any change of dendrite diameter is gradual, this assumption is a reasonable one. Equations governing concentrations of intracellular organelles in different kinetic states in a dendrite with a mixed MT orientation in a proximal dendrite and plus-end-out orientation in distal dendrites are as follows.

Region 1, proximal dendrite, $0 < x < L_1$

$$D_{0+} \frac{\partial^2 n_{0+}^{(1)}}{\partial x^2} + D_{0+} \left(\frac{1}{A} \frac{dA}{dx} \right) \frac{\partial n_{0+}^{(1)}}{\partial x} - (2 + k_{0-}) n_{0+}^{(1)} + k_{0+} n_{0-}^{(1)} + k'_+ (n_+^{(1,1)} + n_+^{(1,2)}) = 0, \quad (1)$$

$$D_{0-} \frac{\partial^2 n_{0-}^{(1)}}{\partial x^2} + D_{0-} \left(\frac{1}{A} \frac{dA}{dx} \right) \frac{\partial n_{0-}^{(1)}}{\partial x} - (2k_- + k_{0+}) n_{0-}^{(1)} + k_{0-} n_{0+}^{(1)} + k'_- (n_-^{(1,1)} + n_-^{(1,2)}) = 0, \quad (2)$$

$$n_{0+}^{(1)} - k'_+ n_+^{(1,1)} + \frac{\partial n_+^{(1,1)}}{\partial x} + \frac{1}{A} \frac{dA}{dx} n_+^{(1,1)} = 0, \quad (3)$$

$$n_{0+}^{(1)} - k'_+ n_+^{(1,2)} - \frac{\partial n_+^{(1,2)}}{\partial x} - \frac{1}{A} \frac{dA}{dx} n_+^{(1,2)} = 0, \quad (4)$$

$$k_- n_{0-}^{(1)} - k'_- n_-^{(1,1)} + v_- \frac{\partial n_-^{(1,1)}}{\partial x} + v_- \frac{1}{A} \frac{dA}{dx} n_-^{(1,1)} = 0, \quad (5)$$

$$k_- n_{0-}^{(1)} - k'_- n_-^{(1,2)} - v_- \frac{\partial n_-^{(1,2)}}{\partial x} - v_- \frac{1}{A} \frac{dA}{dx} n_-^{(1,2)} = 0. \quad (6)$$

In Eqs. 1–6, superscript (1) and the first numeral in superscripts (1,1) and (1,2) refer to the proximal dendrite region, $0 < x < L_1$. The second numeral in superscripts (1,1) and (1,2) on n_+ and n_- refers to two groups of MTs in the proximal dendrite (MTs corresponding to the (1,1) group have minus-ends out while MTs corresponding to the (1,2) group have plus-ends out). In the proximal dendrite, these groups of MTs have opposite orientations (Fig. 1a, b); this is the reason why the last two terms on the right-hand sides of Eqs. 3 and 4 have opposite signs, as well as those in Eqs. 5 and 6.

Dimensionless variables in Eqs. 1–6 are introduced as follows:

$$D_{0\pm} = \frac{\tilde{D}_{0\pm}\tilde{k}_+}{\tilde{v}_+^2}, \quad k_- = \frac{\tilde{k}_-}{\tilde{k}_+}, \quad k'_\pm = \frac{\tilde{k}'_\pm}{\tilde{k}_+}, \quad k_{0\pm} = \frac{\tilde{k}_{0\pm}}{\tilde{k}_+} \quad (7)$$

$$L_i = \frac{\tilde{L}_i\tilde{k}_+}{\tilde{v}_+} \quad (i = 1, 2), \quad n_{0\pm} = \tilde{n}_{0\pm}\frac{\tilde{v}_+^3}{\tilde{k}_+^3}, \quad n_\pm = \tilde{n}_\pm\frac{\tilde{v}_+^3}{\tilde{k}_+^3} \quad (8)$$

$$v_- = \frac{\tilde{v}_-}{\tilde{v}_+}, \quad x = \frac{\tilde{x}\tilde{k}_+}{\tilde{v}_+}, \quad A = \frac{\tilde{A}\tilde{k}_+^2}{\tilde{v}_+^2} \quad (9)$$

where $\tilde{D}_{0+}$ is the diffusivity of free (off-track) organelles with plus-end-directed motors attached to them (motors transporting organelles toward the MT plus-ends, kinesin motors); $\tilde{D}_{0-}$ is the diffusivity of free (off-track) organelles with minus-end-directed motors attached to them (motors transporting organelles toward the MT minus-ends, dynein motors); $\tilde{n}_{0+}$ is the number density of free organelles with plus-end-directed motors attached to them; $\tilde{n}_{0-}$ is the number density of free organelles with minus-end-directed motors attached to them; $\tilde{n}_+$ is the number density of organelles transported on MTs by plus-end-directed motors; $\tilde{n}_-$ is the number density of organelles transported on MTs by minus-end-directed motors; $\tilde{x}$ is the linear coordinate; $\tilde{L}_1 + \tilde{L}_2$ is the total length of the axon or dendrite ($\tilde{L}_1$ is the length of a proximal dendrite and $\tilde{L}_2$ is the length of a distal dendrite); $\tilde{v}_-$ is the average velocity of organelles moving toward the MT minus end (this motor velocity is generated by dynein-family molecular motors), $\tilde{v}_-$ is negative; $\tilde{v}_+$ is the average velocity of organelles moving toward the MT plus end (this motor velocity is generated by kinesin-family molecular motors), $\tilde{v}_+$ is positive; $\tilde{k}_+$ is the first order rate constant for binding to MTs for plus-end-oriented organelles (organelles with kinesin motors attached to them), $\tilde{k}_-$ is the first order rate constant for binding to MTs for minus-end-oriented organelles (organelles with dynein motors attached to them); $\tilde{k}'_+$ and $\tilde{k}'_-$ are the first order rate constants for detachment from MTs for plus-end-oriented and minus-end-oriented organelles, respectively; $\tilde{k}_{0+}$ is the first order rate constant describing the probability for a free minus-end-oriented organelle to become a free plus-end oriented organelle (to detach from a dynein molecular motor and attach to a kinesin molecular motor), $\tilde{k}_{0-}$ is the first order rate constant describing the probability for a free plus-end-oriented organelle to become a free minus-end oriented organelle (to detach from a kinesin molecular motor and attach to a dynein molecular motor), and $\tilde{A}$ is the cross-sectional area of the dendrite in the proximal dendrite region and the sum of cross-sectional areas of two distal dendrites in the distal dendrite region ($\tilde{A}$ depends on the distance from the soma, $\tilde{x}$).

Region 2, distal dendrite, $L_1 < x < L_1 + L_2$

$$D_{0+} \frac{\partial^2 n_{0+}^{(2)}}{\partial x^2} + D_{0+} \left(\frac{1}{A} \frac{dA}{dx} \right) \frac{\partial n_{0+}^{(2)}}{\partial x} - (4 + k_{0-}) n_{0+}^{(2)} + k_{0+} n_{0-}^{(2)} + 4k'_+ n_+^{(2)} = 0, \quad (10)$$

$$D_{0-} \frac{\partial^2 n_{0-}^{(2)}}{\partial x^2} + D_{0-} \left(\frac{1}{A} \frac{dA}{dx} \right) \frac{\partial n_{0-}^{(2)}}{\partial x} - (4k_- + k_{0+}) n_{0-}^{(2)} + k_{0-} n_{0+}^{(2)} + 4k'_- n_-^{(2)} = 0, \quad (11)$$

$$n_{0+}^{(2)} - k'_+ n_+^{(2)} - \frac{\partial n_+^{(2)}}{\partial x} - \frac{1}{A} \frac{dA}{dx} n_+^{(2)} = 0, \quad (12)$$

$$k_- n_{0-}^{(2)} - k'_- n_-^{(2)} - v_- \frac{\partial n_-^{(2)}}{\partial x} - v_- \frac{1}{A} \frac{dA}{dx} n_-^{(2)} = 0. \quad (13)$$

In Eqs. 10–13, superscript (2) refers to the proximal dendrite region, $L_1 < x < L_2$.

At the base of the proximal dendrite, $x = 0$, the boundary conditions are

$$n_{0+}^{(1)} = N_{+,x=0}, \quad n_{0-}^{(1)} = N_{-,x=0}, \quad n_-^{(1,1)} = \sigma_{x=0} N_{-,x=0}, \quad n_+^{(1,2)} = \sigma_{x=0} N_{+,x=0}, \quad (14)$$

New dimensionless parameters in Eq. 14 are defined as:

$$N_{+,x=0} = \tilde{N}_{+,x=0} \frac{\tilde{v}_+^3}{\tilde{k}_+^3}, \quad N_{-,x=0} = \tilde{N}_{-,x=0} \frac{\tilde{v}_+^3}{\tilde{k}_+^3}, \quad (15)$$

where $\tilde{N}_{+,x=0}$ and $\tilde{N}_{-,x=0}$ are constant number densities of free organelles with kinesin/dynein motors attached to them, respectively, maintained at $x = 0$, and $\sigma_{x=0}$ is the degree of loading of organelles at $x = 0$.

At the growth cones of the distal dendrites, $x = L_1 + L_2$, the boundary conditions are

$$n_{0+}^{(2)} = N_{+,x=L_1+L_2}, \quad n_{0-}^{(2)} = N_{-,x=L_1+L_2}, \quad n_-^{(2)} = \sigma_{x=L_1+L_2} N_{-,x=L_1+L_2} \quad (16)$$

New dimensionless parameters in Eq. 16 are defined as:

$$N_{+,x=L_1+L_2} = \tilde{N}_{+,x=L_1+L_2} \frac{\tilde{v}_+^3}{\tilde{k}_+^3}, \quad N_{-,x=L_1+L_2} = \tilde{N}_{-,x=L_1+L_2} \frac{\tilde{v}_+^3}{\tilde{k}_+^3} \quad (17)$$

where $\tilde{N}_{+,x=L_1+L_2}$ and $\tilde{N}_{-,x=L_1+L_2}$ are constant number densities of free organelles with kinesin/dynein motors attached to them, respectively, maintained at $x = L_1 + L_2$, and $\sigma_{x=L_1+L_2}$ is the degree of loading of organelles at $x = L_1 + L_2$.

At the proximal/distal dendrite branch point, $x = L_1$, the boundary conditions are

$$n_{0+}^{(1)} \Big|_{x=L_1-} = n_{0+}^{(2)} \Big|_{x=L_1+} \quad (18)$$

$$n_{0-}^{(1)} \Big|_{x=L_1-} = n_{0-}^{(2)} \Big|_{x=L_1+} \quad (19)$$

$$n_+^{(1,1)} \Big|_{x=L_1-} = \sigma_{x=L_1} n_{0+}^{(2)} \Big|_{x=L_1+} \quad (20)$$

$$n_+^{(1,2)} \Big|_{x=L_1-} = 4n_+^{(2)} \Big|_{x=L_1+} \quad (21)$$

$$n_-^{(1,2)} \Big|_{x=L_1-} = 4n_-^{(2)} \Big|_{x=L_1+} \quad (22)$$

$$\left(-D_{0+} \frac{dn_{0+}^{(1)}}{dx} - n_{+}^{(1,1)} + n_{+}^{(1,2)} \right) \Big|_{x=L_1-} = \left(-D_{0+} \frac{dn_{0+}^{(2)}}{dx} + 4n_{+}^{(2)} \right) \Big|_{x=L_1+} \quad (23)$$

$$\left(-D_{0-} \frac{dn_{0-}^{(1)}}{dx} - v_{-} n_{-}^{(1,1)} + v_{-} n_{-}^{(1,2)} \right) \Big|_{x=L_1-} = \left(-D_{0-} \frac{dn_{0-}^{(2)}}{dx} + 4v_{-} n_{-}^{(2)} \right) \Big|_{x=L_1+} \quad (24)$$

where $\sigma_{x=L_1}$ is the degree of loading at $x = L_1$ for minus-end-out MTs that terminate at the branch point.

Factors four on the right-hand sides of Eqs. 21 and 22 (and in the last terms on the right-hand sides of Eqs. 23 and 24) are due to the assumption that MTs of the second group (the plus-end-out MTs) are divided equally between the two distal dendrites when MTs cross the branch point section.

For a dendrite with a mixed polarity orientation, the total number density of organelles is calculated as follows. In a proximal dendrite:

$$n_t = n_{0+}^{(1)} + n_{0-}^{(1)} + n_{+}^{(1,1)} + n_{+}^{(1,2)} + n_{-}^{(1,1)} + n_{-}^{(1,2)} \quad (25)$$

In a distal dendrite:

$$n_t = n_{0+}^{(2)} + n_{0-}^{(2)} + 4n_{+}^{(2)} + 4n_{-}^{(2)} \quad (26)$$

The total rate of organelle transfer is calculated as:

$$j = j_{\text{diff}} + j_{\text{motor}} \quad (27)$$

where in a proximal dendrite the transfer rate by diffusion is calculated as:

$$j_{\text{diff}} = -D_{0+} A \frac{dn_{0+}^{(1)}}{dx} - D_{0-} A \frac{dn_{0-}^{(1)}}{dx} \quad (28)$$

and in a distal dendrite region it is calculated as:

$$j_{\text{diff}} = -D_{0+} A \frac{dn_{0+}^{(2)}}{dx} - D_{0-} A \frac{dn_{0-}^{(2)}}{dx}. \quad (29)$$

Equation 29 gives the combined transfer rate by diffusion that goes into both distal dendrites (exactly half of that goes into each distal dendrite). This comes from the fact that there are two distal dendrites and the assumption that the cross-sectional area of each of the distal dendrites equals half of that of the proximal dendrite at the branch point.

The motor-driven rate of organelle transfer is now calculated as follows. In a proximal dendrite it is calculated as:

$$j_{\text{motor}} = -An_{+}^{(1,1)} + An_{+}^{(1,2)} - v_{-} An_{-}^{(1,1)} + v_{-} An_{-}^{(1,2)} \quad (30)$$

and in a distal dendrite it is calculated as:

$$j_{\text{motor}} = 4An_{+}^{(2)} + 4v_{-} An_{-}^{(2)} \quad (31)$$

(exactly half of what is given by Eq. 31 goes into each distal dendrite).

The number density of organelles transported anterogradely by motor-driven transport now is

$$n_{\text{motor,anter}} = n_-^{(1,1)} + n_+^{(1,2)} \quad \text{for } 0 < x < L_1 \text{ (proximal dendrite)} \quad (32)$$

$$n_{\text{motor,anter}} = 4n_+^{(2)} \quad \text{for } L_1 < x < L_1 + L_2 \text{ (distal dendrite)} \quad (33)$$

The number density of organelles transported retrogradely by motor-driven transport is

$$n_{\text{motor,ret}} = n_+^{(1,1)} + n_-^{(1,2)} \quad \text{for } 0 < x < L_1 \text{ (proximal dendrite)} \quad (34)$$

$$n_{\text{motor,ret}} = 4n_-^{(2)} \quad \text{for } L_1 < x < L_1 + L_2 \text{ (distal dendrite)} \quad (35)$$

2.2 Dendrite 2, $0 < x < L_1 + L_2$, mixed MT polarity orientation in both proximal and distal dendrites

A schematic diagram for this case is shown in Fig. 1b. Equations governing transport of intracellular organelles in a dendrite with a mixed MT orientation are as follows.

Region 1, proximal dendrite, $0 < x < L_1$

$$D_{0+} \frac{\partial^2 n_{0+}^{(1)}}{\partial x^2} + D_{0+} \left(\frac{1}{A} \frac{dA}{dx} \right) \frac{\partial n_{0+}^{(1)}}{\partial x} - (2 + k_{0-}) n_{0+}^{(1)} + k_{0+} n_{0-}^{(1)} + k'_+ \left(n_+^{(1,1)} + n_+^{(1,2)} \right) = 0, \quad (36)$$

$$D_{0-} \frac{\partial^2 n_{0-}^{(1)}}{\partial x^2} + D_{0-} \left(\frac{1}{A} \frac{dA}{dx} \right) \frac{\partial n_{0-}^{(1)}}{\partial x} - (2k_- + k_{0+}) n_{0-}^{(1)} + k_{0-} n_{0+}^{(1)} + k'_- \left(n_-^{(1,1)} + n_-^{(1,2)} \right) = 0, \quad (37)$$

$$n_{0+}^{(1)} - k'_+ n_+^{(1,1)} + \frac{\partial n_+^{(1,1)}}{\partial x} + \frac{1}{A} \frac{dA}{dx} n_+^{(1,1)} = 0, \quad (38)$$

$$n_{0+}^{(1)} - k'_+ n_+^{(1,2)} - \frac{\partial n_+^{(1,2)}}{\partial x} - \frac{1}{A} \frac{dA}{dx} n_+^{(1,2)} = 0, \quad (39)$$

$$k_- n_{0-}^{(1)} - k'_- n_-^{(1,1)} + v_- \frac{\partial n_-^{(1,1)}}{\partial x} + v_- \frac{1}{A} \frac{dA}{dx} n_-^{(1,1)} = 0, \quad (40)$$

$$k_- n_{0-}^{(1)} - k'_- n_-^{(1,2)} - v_- \frac{\partial n_-^{(1,2)}}{\partial x} - v_- \frac{1}{A} \frac{dA}{dx} n_-^{(1,2)} = 0. \quad (41)$$

Region 2, distal dendrite, $L_1 < x < L_1 + L_2$

$$D_{0+} \frac{\partial^2 n_{0+}^{(2)}}{\partial x^2} + D_{0+} \left(\frac{1}{A} \frac{dA}{dx} \right) \frac{\partial n_{0+}^{(2)}}{\partial x} - (4 + k_{0-}) n_{0+}^{(2)} + k_{0+} n_{0-}^{(2)} + 2k'_+ \left(n_+^{(2,1)} + n_+^{(2,2)} \right) = 0, \quad (42)$$

$$D_{0-} \frac{\partial^2 n_{0-}^{(2)}}{\partial x^2} + D_{0-} \left(\frac{1}{A} \frac{dA}{dx} \right) \frac{\partial n_{0-}^{(2)}}{\partial x} - (4k_- + k_{0+}) n_{0-}^{(2)} + k_{0-} n_{0+}^{(2)} + 2k'_- \left(n_-^{(2,1)} + n_-^{(2,2)} \right) = 0, \quad (43)$$

$$n_{0+}^{(2)} - k'_+ n_+^{(2,1)} + \frac{\partial n_+^{(2,1)}}{\partial x} + \frac{1}{A} \frac{dA}{dx} n_+^{(2,1)} = 0, \quad (44)$$

$$n_{0+}^{(2)} - k'_+ n_+^{(2,2)} - \frac{\partial n_+^{(2,2)}}{\partial x} - \frac{1}{A} \frac{dA}{dx} n_+^{(2,2)} = 0, \quad (45)$$

$$k_- n_{0-}^{(2)} - k'_- n_-^{(2,1)} + v_- \frac{\partial n_-^{(2,1)}}{\partial x} + v_- \frac{1}{A} \frac{dA}{dx} n_-^{(2,1)} = 0, \quad (46)$$

$$k_- n_{0-}^{(2)} - k'_- n_-^{(2,2)} - v_- \frac{\partial n_-^{(2,2)}}{\partial x} - v_- \frac{1}{A} \frac{dA}{dx} n_-^{(2,2)} = 0. \quad (47)$$

In the case of dendrite 2, MTs corresponding to the (2,1) group in distal dendrites have minus-ends out while MTs corresponding to the (2,2) group have plus-ends out.

At the base of the proximal dendrite, $x = 0$, the boundary conditions are

$$n_{0+}^{(1)} = N_{+,x=0}, \quad n_{0-}^{(1)} = N_{-,x=0}, \quad n_-^{(1,1)} = \sigma_{x=0} N_{-,x=0}, \quad n_+^{(1,2)} = \sigma_{x=0} N_{+,x=0} \quad (48)$$

At the growth cones of the distal dendrites, $x = L_1 + L_2$, the boundary conditions are

$$n_{0+}^{(2)} = N_{+,x=L_1+L_2}, \quad n_{0-}^{(2)} = N_{-,x=L_1+L_2} \quad (49)$$

$$n_+^{(2,1)} = \sigma_{x=L_1+L_2} N_{+,x=L_1+L_2}, \quad n_-^{(2,2)} = \sigma_{x=L_1+L_2} N_{-,x=L_1+L_2} \quad (50)$$

At the proximal/distal dendrite branch point, $x = L_1$, the boundary conditions are

$$n_{0+}^{(1)} \Big|_{x=L_1-} = n_{0+}^{(2)} \Big|_{x=L_1+} \quad (51)$$

$$n_{0-}^{(1)} \Big|_{x=L_1-} = n_{0-}^{(2)} \Big|_{x=L_1+} \quad (52)$$

$$n_+^{(1,1)} \Big|_{x=L_1-} = 2n_+^{(2,1)} \Big|_{x=L_1+} \quad (53)$$

$$n_-^{(1,1)} \Big|_{x=L_1-} = 2n_-^{(2,1)} \Big|_{x=L_1+} \quad (54)$$

$$n_+^{(1,2)} \Big|_{x=L_1-} = 2n_+^{(2,2)} \Big|_{x=L_1+} \quad (55)$$

$$n_-^{(1,2)} \Big|_{x=L_1-} = 2n_-^{(2,2)} \Big|_{x=L_1+} \quad (56)$$

$$\left(-D_{0+} \frac{dn_{0+}^{(1)}}{dx} - n_+^{(1,1)} + n_+^{(1,2)} \right) \Big|_{x=L_1-} = \left(-D_{0+} \frac{dn_{0+}^{(2)}}{dx} - 2n_+^{(2,1)} + 2n_+^{(2,2)} \right) \Big|_{x=L_1+} \quad (57)$$

$$\left(-D_{0-} \frac{dn_{0-}^{(1)}}{dx} - v_- n_-^{(1,1)} + v_- n_-^{(1,2)} \right) \Big|_{x=L_1-} = \left(-D_{0-} \frac{dn_{0-}^{(2)}}{dx} - 2v_- n_-^{(2,1)} + 2v_- n_-^{(2,2)} \right) \Big|_{x=L_1+} \quad (58)$$

Factors two on the right-hand sides of Eqs. 53–56 are due to the assumption that MTs in each of the MT groups (the plus-end-out and minus-end-out groups, respectively) are divided equally between the two distal dendrites when MTs cross the branch point section.

For a dendrite with a mixed polarity orientation the total number density of organelles is calculated as follows. In a proximal dendrite:

$$n_t = n_{0+}^{(1)} + n_{0-}^{(1)} + n_+^{(1,1)} + n_+^{(1,2)} + n_-^{(1,1)} + n_-^{(1,2)} \quad (59)$$

In a distal dendrite:

$$n_t = n_{0+}^{(2)} + n_{0-}^{(2)} + 2n_+^{(2,1)} + 2n_+^{(2,2)} + 2n_-^{(2,1)} + 2n_-^{(2,2)} \quad (60)$$

The total organelle transfer rate is still given by Eq. 27, where the diffusion rate is given by Eq. 28 in a proximal dendrite and by Eq. 29 in a distal dendrite region (exactly half of what is given by Eq. 29 goes into each distal dendrite).

The motor-driven rate of transfer is now calculated as follows. In a proximal dendrite, it is calculated as:

$$j_{\text{motor}} = -An_+^{(1,1)} + An_+^{(1,2)} - v_- An_-^{(1,1)} + v_- An_-^{(1,2)} \quad (61)$$

and in a distal dendrite it is calculated as:

$$j_{\text{motor}} = -2An_+^{(2,1)} - 2v_- An_-^{(2,1)} + 2An_+^{(2,2)} + 2v_- An_-^{(2,2)} \quad (62)$$

(exactly half of what is given by Eq. 62 goes into each distal dendrite).

The number density of organelles transported anterogradely by motor-driven transport now is

$$n_{\text{motor,anter}} = n_-^{(1,1)} + n_+^{(1,2)} \quad \text{for } 0 < x < L_1 \text{ (proximal dendrite)} \quad (63)$$

$$n_{\text{motor,anter}} = 2n_-^{(2,1)} + 2n_+^{(2,2)} \quad \text{for } L_1 < x < L_1 + L_2 \text{ (distal dendrite)} \quad (64)$$

The number density of organelles transported retrogradely by motor-driven transport is

$$n_{\text{motor,retr}} = n_+^{(1,1)} + n_-^{(1,2)} \quad \text{for } 0 < x < L_1 \text{ (proximal dendrite)} \quad (65)$$

$$n_{\text{motor,retr}} = 2n_+^{(2,1)} + 2n_-^{(2,2)} \quad \text{for } L_1 < x < L_1 + L_2 \text{ (distal dendrite)} \quad (66)$$

3 Results and discussion

The selection of parameter values utilized in computations is based on the following data reported in the literature. Carter and Cross [22] and Vale et al. [23] reported that kinesin-1

(conventional kinesin) walks to the MT plus-end with the average velocity ($\tilde{v}_+$) of 1 $\mu\text{m/s}$. King and Schroer [24] and Toba et al. [25] reported that cytoplasmic dynein walks to the MT minus-end with approximately the same average velocity ($\tilde{v}_-$) of 1 $\mu\text{m/s}$. It should be noted that the above values are for the case when an organelle is moved by a single molecular motor. The organelle velocity can be larger if it is moved by several molecular motors pulling in the same direction; maximum velocities of organelles in neurons ($\tilde{v}_+$ or $\tilde{v}_-$) are reported to be between 3.5 and 5 $\mu\text{m/s}$ (Kural et al. [26], Hill et al. [27]). The average attachment rate of kinesin-1 to MTs ($\tilde{k}_+$) is estimated to be 5 s^{-1} (Beeg et al. [28], Leduc et al. [29]) while its average detachment rate from MTs ($\tilde{k}'_+$) is estimated to be 1 s^{-1} (Schnitzer et al. [30], Vale et al. [23]). The average attachment rate of cytoplasmic dynein to MTs ($\tilde{k}_-$) is estimated to be 1.5 s^{-1} (Carter and Cross [22], Vale et al. [23]) while its average detachment rate from MTs ($\tilde{k}'_-$) is estimated to be 0.25 s^{-1} (King and Schroer [24], Reck-Peterson et al. [31]). Smith and Simmons [14] used the value of 1 s^{-1} for all attachment/detachment rates ($\tilde{k}_+$, $\tilde{k}'_+$, $\tilde{k}_-$, and $\tilde{k}'_-$) in a standard set of primary parameters for numerical work. Jung and Brown [20] estimated the rate of transition of off-track organelles attached to minus-end-directed motors to those attached to plus-end-directed motors ($\tilde{k}_{0+}$) as $1.4 \times 10^{-5} \text{ s}^{-1}$ and backwards ($\tilde{k}_{0-}$) as $4.2 \times 10^{-6} \text{ s}^{-1}$. However, these estimates are for slow axonal transport and the rates are probably larger for fast axonal transport. Using the Einstein–Stokes relation, Smith and Simmons [14] estimated the diffusivity ($\tilde{D}_{0+}$ or $\tilde{D}_{0-}$) of a 1- μm sphere in water to be 0.4 $\mu\text{m}^2/\text{s}$, then they rounded this value down to 0.1 $\mu\text{m}^2/\text{s}$ to account for an irregular surface topology and a larger cytoplasmic viscosity. According to Bartlett and Banker [6], the average diameter of a dendrite ($\tilde{d}$) of a hippocampal neuron at the base is about 2.5 μm while 100 μm from the base is about 0.5 μm (see Fig. 7 in their paper). These data have been used to estimate the cross-sectional area of a dendrite as $\tilde{A} = \frac{\pi \tilde{d}^2}{4}$ and the dependence of $\tilde{A}$ on the distance from the base of the dendrite, $\tilde{x}$.

Although utilized parameter values fall into biologically reasonable ranges, simulations performed in this research do not attempt to model a transport situation in a particular dendrite, but are rather aimed at understanding, at the fundamental level, effects of the variation of the cross-sectional area of the dendrite in branching dendrites with two particular MT orientations reported from experiments.

Based on the analysis of the above data, the following values of dimensionless parameters have been selected for modeling transport in two types of dendrites (see Fig. 1a, b) presented in this research: $D_{0+} = D_{0-} = 0.5$, $k_{0+} = k_{0-} = 0.05$, $k'_\pm = 0.5$, $k_- = 1$, $L_1 = 8$, $L_2 = 2$, $N_{+,x=0} = 0.2$, $N_{-,x=0} = 0.2$, $N_{+,x=L_1+L_2} = 0.01$, $N_{-,x=L_1+L_2} = 0.01$, $v_- = -1$, $\sigma_{x=0} = 0.1$, $\sigma_{x=L_1} = 0.1$, and $\sigma_{x=L_1+L_2} = 0.1$ (in order to convert dimensional parameters to dimensionless the use of Eqs. 7–9 has been made). The following dependencies for the cross-sectional area of a dendrite (based on the data presented in Bartlett and Banker [6]) are utilized: $A(x) = 0.785(2.5 - 0.02x)^2$ and $dA/dx = -0.0785 + 0.000628x$. In simulations, $N_{+,x=0}$ and $N_{-,x=0}$ are assumed high (both equal to 0.2) since components are being synthesized at the neuron soma while $N_{+,x=L_1+L_2}$ and $N_{-,x=L_1+L_2}$ are assumed low (both equal to 0.01) since components are being utilized at the dendrite growth cones.

Figure 2a shows distributions of the number density of free organelles with plus-end-directed motors attached to them, n_{0+} , in two types of dendrites. Distributions of n_{0+} in both dendrites are very close. There is a relatively thick diffusion boundary layer adjacent to the neuron soma where the slope of $n_{0+}(x)$ is very large, but even after that the slope of $n_{0+}(x)$ is not zero (the curve never becomes horizontal), which indicates that diffusion is important over the whole dendrite length. Figure 2b displays distributions of the number density of free organelles with minus-end-directed motors attached to them, n_{0-} . The

Fig. 2 **a** Distributions of the number density of free organelles with plus-end-directed motors attached to them, n_{0+} , **b** Distributions of the number density of free organelles with minus-end-directed motors attached to them, n_{0-}

distribution of $n_{0-}(x)$ in dendrite 2 is quite similar to distribution of $n_{0+}(x)$ in that dendrite, but the distribution of $n_{0-}(x)$ in dendrite 1 is remarkably different: there is a significant accumulation of n_{0-} organelles near the branch point. The reason for this accumulation is a mismatch of the MT polarity at the branch point: the proximal dendrite contains both plus-end-out and minus-end-out MTs while the distal dendrites contain only plus-end-out MTs. This implies that plus-end-out MTs must terminate on the proximal dendrite side near the

branch point. This creates good conditions for the removal of plus-end-directed organelles from the branch point area, but minus-end-directed organelles that are transported to this area by dynein motors get stuck there. This phenomenon is similar to the phenomenon of organelle trap formation in a region with opposing MT polarities that was found and explained in Erez et al. [32], Erez and Spira [33], and Shemesh et al. [34].

Figure 3a shows distributions of the number density of organelles transported on MTs by plus-end-directed motors, n_+ . In dendrite 1 (Fig. 1a), there are two groups of MTs (minus-end-out, group 1, and plus-end-out, group 2) in the proximal dendrite but there are only

Fig. 3 **a** Distributions of the number density of organelles transported on MTs by plus-end-directed motors, n_+ , **b** Distributions of the number density of organelles transported on MTs by minus-end-directed motors, n_-

plus-end-out MTs in the distal dendrites. In dendrite 2 (Fig. 1b), there are two differently oriented groups of MTs in both proximal and distal dendrites. The jump in n_+ at the branch point ($x = L_1$) is caused not by a physical discontinuity but by the fact that plus-end-directed organelles are split between two distal dendrites (see boundary condition at the branch point given by Eq. 21 for dendrite 1 and by Eqs. 53 and 55 for dendrite 2). Figure 3b displays distributions of the number density of organelles transported on MTs by minus-end-directed

Fig. 4 **a** Distributions of the number densities of organelles transported on MTs anterogradely, $n_{\text{anterograde}}$, **b** Distributions of the number densities of organelles transported on MTs retrogradely, $n_{\text{retrograde}}$

motors, n_- . Again, in dendrite 1, there is an accumulation of minus-end directed organelles near the branch point section, caused by the fact that the minus-end-directed MTs coming from the proximal dendrite terminate at this section.

Figure 4a shows distributions of the number densities of organelles transported on MTs anterogradely, $n_{\text{anterograde}}$ (this represents the total number density of organelles transported by kinesin motors on plus-end-out directed MTs and by dynein motors on minus-end-out directed MTs). In dendrite 2 this curve is smooth but in dendrite 1 there is a jump at the branch point. This is because in dendrite 1 only half of MTs (the plus-end-out MTs) continue from the proximal into the distal dendrites, all minus-end-out MTs terminate at the

Fig. 5 **a** Distributions of the rate of organelle transfer due to diffusion, j_{diff} , **b** Distributions of the rate of organelle transfer due to motor-driven transport, j_{motor}

branch section. Because of that, all organelles that are transported on minus-end-out MTs in the proximal dendrite by dynein motors must detach before the branch point, and cannot continue in the anterograde direction on MTs because there are no minus-end-out MTs in the distal dendrites (Fig. 1a). Figure 4b displays distributions of the number densities of organelles transported on MTs retrogradely, $n_{\text{retrograde}}$. Unlike $n_{\text{anterograde}}$, $n_{\text{retrograde}}$ is continuous through the branch point, even for dendrite 1. This is because the major motor-driven component of retrograde transport is driven by dynein motors pulling organelles on plus-end-out MTs, and these MTs continue through the branch point and go into distal dendrites. Another component that contributes to retrograde transport is represented by the

Fig. 6 **a** Distributions of the total number density of organelles, n_t , **b** distributions of the total rate of organelle transfer (due to diffusion and motor-driven transport), j

motion of organelles that are driven by kinesin motors pulling organelles on minus-end-out MTs. However, n_+ at $x = L_1$ for dendrite 1 is very low (see Fig. 3a), because in accord with Eq. 20 n_+ is determined as the concentration of free organelles, n_{0+} , multiplied by the degree of loading at $x = L_1$ ($\sigma_{x=L_1} = 0.1$). n_{0+} at the branch point is low (see Fig. 2a) because diffusion plays an important role in organelle transport in dendrites, and since diffusion is driven by the gradient of organelle concentration, n_{0+} decreases significantly from the base of the dendrite to the branch point.

Figure 5a shows distributions of the rate of organelle transfer due to diffusion, j_{diff} . For dendrite 1, there is a jump at the branch point. This can be related to the peak of n_{0-} that occurs at $x = L_1$ (see Fig. 2b). Diffusion moves organelles with minus-end-directed motors from the point of their accumulation at the branch point into the distal dendrites as well as back to the neuron soma. Figure 5b displays distributions of the rate of organelle transfer due to motor-driven transport, j_{motor} . Again, for dendrite 1 j_{motor} exhibits a jump at the branch point that is related to the jump in anterograde transport of organelles exhibited in Fig. 4a (caused by minus-end-out MTs terminating at $x = L_1$).

Figure 6a shows distributions of the total number density of organelles, n_t . For dendrite 2, the curve exhibits a gradual decay that shows that in dendrites diffusion is an important transport mechanism (unlike in axons where transport of organelles is mostly motor-driven). For dendrite 1, $n_t(x)$ almost levels off toward the branch point, but in the distal dendrites it decays very fast. Unlike $n_{0-}(x)$, $n_t(x)$ does not exhibit a local maximum at $x = L_1$; the maximum is averaged out between different concentrations composing n_t . Figure 6b displays distributions of the total rate of organelle transfer (due to diffusion and motor-driven transport), j . One notable feature is that in both dendrites $j(x)$ is uniform and independent of x . This is a consequence of the steady-state formulation of the problem (in order for a control volume to remain at steady-state, the total transfer rate of organelles into the control volume must equal to that out of the control volume); this result can be viewed as a validation of the numerical code. The important result displayed in Fig. 6b is that j in dendrite 2 is approximately twice that in dendrite 1, which means that the MT arrangement displayed in Fig. 1b can support a much larger organelle transfer rate than that displayed in Fig. 1a. This supports the hypothesis put forward in Takahashi et al. [8] that the MT polarity arrangement in different dendritic compartments may depend on the stage of dendrite's development. For example, if a dendrite is growing, it needs the MT structure that would allow for a larger organelle transfer rate to its growth cone.

4 Conclusions

Based on the analysis of computational results, the following conclusions can be drawn.

There is a relatively thick diffusion boundary layer adjacent to the neuron soma where the diffusion mode of organelle transfer is dominant; however, even deeper into the dendrite diffusion remains important; unlike in axons, in dendrites the motor-driven transport of organelles never becomes the dominant mechanism of organelle transfer.

In a dendrite with a mixed MT orientation in the proximal region and plus-end-out MT orientation in distal dendrites, an area with a significant accumulation of free organelles with minus-end-directed motors attached to them is found near the branch point. This accumulation is explained by a mismatch of the MT polarity at the branch point: the proximal dendrite contains both plus-end-out and minus-end-out MTs while the distal dendrites contain only plus-end-out MTs. This implies that plus-end-out MTs must

terminate on the proximal dendrite side near the branch point. As a result of this MT arrangement, the minus-end-directed organelles that are transported to this area by dynein motors are unable to move out and remain in this area.

In a dendrite with a mixed MT orientation in the proximal region and plus-end-out MT orientation in distal dendrites, a curve displaying the number density of organelles transported on MTs anterogradely exhibits a jump at the branch point. This is because in such a dendrite only the plus-end-out MTs continue from the proximal into the distal dendrites while all minus-end-out MTs terminate at the branch section. Because of that, all organelles that are transported on minus-end-out MTs in the proximal dendrite by dynein motors must detach before the branch point.

The curves depicting the total number density of organelles exhibit a non-zero slope which indicates that in dendrites (unlike in axons) diffusion is an important transport mechanism. In both dendrites, the total organelle transfer rate is uniform and independent of x , which is a consequence of the steady-state formulation of the problem. In a dendrite with a mixed MT orientation in both proximal and distal regions the total organelle transfer rate is about twice the rate in a dendrite with a mixed MT orientation in the proximal region and plus-end-out MT orientation in the distal region. This means that by rearranging its MT structure, depending on its growth needs and the stage of its development, a dendrite can control the organelle transfer rate toward its growth cone.

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