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Spatial pattern formation in microtubule post-translational modifications and the tight localization of motor-driven cargo

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Abstract

Microtubule (MT) “age” can be interpreted as nucleotide state, lattice defects, or post-translational modification (PTM) such as acetylation and de-tyrosination. In all three cases, these have been recently shown to have functionally-important effects on the dynamics of MT arrays, and can present spatial and temporal heterogeneity. While mathematical models for MT array densities are well-established, here we present equations describing MT age, defined as the mean time since the MT’s building blocks (tubulin) were polymerized from their soluble dimer state. We derive the age equations using a mean first-passage time calculation and two complementary approaches: The continuum limit of spatial discretization model, and an adjoint operator approach. These equations can recapitulate the observation that the oldest (most de-tyrosinated) tubulin in axons is near the middle of axons during neuronal development in chick embryos. Furthermore, PTMs influence motor kinetics up to approximately twofold for off-rates and velocities. Our simulations demonstrate that this relatively weak dependence of motor kinetics is sufficient to target motor cargo to a specific location along the array. This localization is tightly peaked in a way that magnifies the relatively small signal of PTM spatial heterogeneity. Thus, MT age can produce long-range spatial patterning without feedbacks or diffusing signals.

Keywords

Pattern formation; First passage time; Microtubules; Kinesin; Dynein; De-tyrosination; 92C37 Cell biology; 97M60 Biology, chemistry, medicine; 35Q92 PDEs in connection with biology and other natural sciences

1 Introduction

A fundamental question in cell biology is how cells form robust spatial patterns, transitioning from a homogenous (or random) initial state to one in which a molecular participant is tightly and robustly localized. One example occurs in neuronal processes such as axons and dendrites, where cargo such as AMPA receptor (Hoernkli et al. 2013) must be delivered to a specific location along the 100 $\sim \mu\text{m}$ of axonal length. Other examples include

the Cdc42 cell polarity program (Mogilner et al. 2012) which plays a role in cell migration, budding and ciliogenesis, and PAR localization in *C. elegans* development (Goehring et al. 2011). Above the length scale of individual cells, a similar phenomenon of spatial localization occurs in fish melanophores (Mahalwar et al. 2014) and heterogeneity in tissues, including tumors (Konstorum et al. 2013).

Mathematical biology has played a particularly important role in deciphering general mechanisms of spatial localization. Several mechanisms have been studied theoretically and there is mounting evidence that they operate in cells. These including: Turing and other local-activation, global-inhibition mechanisms that govern cell motility (Huang et al. 2013); Depletion mechanisms (Mogilner et al. 2012) like wave-pinning (Mori et al. 2008; Goehring et al. 2011); and diffusion gradients like the “French flag” mechanism (Umulis and Othmer 2013). In this work, we present a distinct mechanism for robust spatial localization. This mechanism is based on micro-tubule motor response to post-translational modification, and we speculate it could govern cargo localization in neurons.

Neurons have multiple cellular protrusions, collectively termed neurites or neuronal processes. These include axons, dendrites, and minor processes during development. These protrusions all contain microtubules (MTs), linear polymers made of the protein tubulin that are 25 nm in diameter and range in length from zero to tens of microns. The MT array is continually assembling and disassembling, therefore individual tubulin molecules continually transition from being in the MT array to being in solution. In addition to these non-trivial internal dynamics, MTs also act as tracks for molecular motors in the kinesin and dynein families, which transport cargo bi-directionally on the MT array. Both MT and motor dynamics have been extensively and successfully described in mathematical models, using continuum approaches (Dogterom and Leibler 1993; Gou et al. 2014; Bicout 1997; Bicout and Rubin 1999; Cytrynbaum et al. 2004) and discrete approaches (Seetapun and Odde 2010; Lin et al. 2011; Newby and Bressloff 2010) and combinations of these (Ando et al. 2015).

In addition to the dynamics of MTs, individual tubulin molecules also undergo post-translational modification (PTM), a chemical event in which the tubulin is modified by, e.g, removal or addition of a tyrosine. Certain PTMs, such as de-tyrosination and acetylation, only occur when tubulin is polymerized (in a MT), and are only reversed when tubulin is in solution. Therefore, these PTMs act as a proxy for the age of that region of a MT. Two recent reports hint at an important role for PTMs. The first, Seetapun and Odde (2010), demonstrates that PTMs are spatially heterogeneous in the neuronal MT arrays. Specifically, there is a shallow peak of de-tyrosination near, but not at, the middle of the array. A second report, Sirajuddin et al. (2014), demonstrates that motors respond differentially to MTs with and without PTMs. Taking these two reports together, one wonders whether MT PTM could assist in localizing motor-driven cargo. However, both the spatial peak in PTM and the influence of PTMs on motor behavior are fairly weak (10 % above baseline and twofold, respectively). A careful quantitative treatment is therefore of value.

Here we develop a mathematical model demonstrating that these two phenomena can indeed combine to allow cargo localization under some conditions. As discussed below, our model

is specific to neurites that have bidirectional MT arrays and in which MTs remain dynamic. Therefore, it applies to neurites during development, proximal regions of dendrites, and other specialized neuronal processes and non-neuronal processes with bidirectional MTs. The paper is organized as follows. In Section 2 we adapt existing partial-differential equation models of MT density and use this continuum formulation to compute the local age, and thereby the level of PTM, at locations along the array. In Sect. 3, we demonstrate that this model recapitulates the shallow peak in MT age along the neurite observed experimentally, along with other quantitative features. Section 4 deals with motor transport along this array. In Sect. 4.1, we develop a model of cargo transport in which motors respond to the spatially heterogeneous age patterns found in the previous section. In Sect. 4.2, we simulate the motor model numerically. Since specific motor responses are not known, there are combinatorially many possible models, and we explore them exhaustively. We find conditions under which a robust peak of cargo density forms. In Sect. 4.3 we demonstrate that model parameters can be tuned to move the cargo localization peak. Since these parameters correspond to dynamics at the cell body, they could provide the cell with a mechanism by which to locally control long-range cargo placement. Finally, Sect. 5 contains discussions and specific model predictions.

2 Microtubule continuum equations

2.1 Tubulin density equations

We use advection-reaction equations that, when used to represent MT plus-end densities, are commonly referred to as the Dogterom-Leibler equations (Dogterom and Leibler 1993; Cytrynbaum et al. 2004; Gou et al. 2014; Eren et al. 2015; Yarahmadian et al. 2010; Dauvergne and Edelstein-Keshet 2015). In these equation, the dynamic variables represent an ensemble of microtubule plus-ends that grow and shrink with velocities v_g and v_s , respectively, and undergo catastrophe and rescue at rates k_{cat} and k_{res} , respectively. We modify the basic equations to include:

- Bidirectional arrays, meaning that there is a subpopulation of MTs facing towards the distal end, which we refer to as anterograde or, for convenience, “right-facing”, and another subpopulation with plus-end towards the cell body, referred to as retrograde or “left-facing”. The left-facing MT plus-ends can travel a distance L_2 past the edge of the neuronal process into the cell body. This is the case for neurites during development (Seetapun and Odde 2010) and other MT arrays, but not for fully-developed axons, which have unidirectional (anterograde) arrays.
- Distributed nucleation by γ -tubulin throughout the length of the neurite.
- Nucleation in the cell body. We assume these originate from a distance L_1 into the cell body, at approximately the location of the MT organizing center.

These MTs are shown in the schematic Fig. 1. We model the densities of anterograde and retrograde MTs in a neurite with length L , such that the MTs minus end is at position x^m and plus end at position x^p , denoted by $\rho^R(x^p, x^m, t)$ and $\rho^L(x^p, x^m, t)$ respectively. Furthermore, we keep track of growing and shrinking subpopulations and denote the

densities with a subscript g or s , respectively. We further assume MTs undergo catastrophe upon encountering the distal end, and that minus ends remain fixed in space at the site of nucleation.

These assumptions lead to advection-reaction equations

$$\frac{\partial \rho_g^R}{\partial t} = -v_g \frac{\partial \rho_g^R}{\partial x^p} + k_{res} \rho_s^R - k_{cat} \rho_g^R \quad (1)$$

$$\frac{\partial \rho_s^R}{\partial t} = v_s \frac{\partial \rho_s^R}{\partial x^p} - k_{res} \rho_s^R + k_{cat} \rho_g^R \quad (2)$$

$$\frac{\partial \rho_g^L}{\partial t} = v_g \frac{\partial \rho_g^L}{\partial x^p} + k_{res} \rho_s^L - k_{cat} \rho_g^L \quad (3)$$

$$\frac{\partial \rho_s^L}{\partial t} = -v_s \frac{\partial \rho_s^L}{\partial x^p} - k_{res} \rho_s^L + k_{cat} \rho_g^L. \quad (4)$$

In this framework, distributed nucleation is included via boundary conditions. When nucleation occurs, the MT has zero length, thus $x^p = x^m$. A right-facing MT must have $x^p > x^m$, therefore $\rho^R(x_m, x_p) = 0$ wherever $x_p < x_m$, and similarly for ρ^L . If nucleation is equally likely to occur in either direction, we obtain boundary conditions

$$v_g \rho_g^R(x^p, x^p) = \frac{k_{nuc}}{2} \quad (5)$$

$$-v_g \rho_g^L(x^p, x^p) = \frac{k_{nuc}}{2}, \quad (6)$$

where k_{nuc} (in $s^{-1} \mu m^{-1}$) is the rate of nucleation. Further conditions arise from the observation that MTs undergo catastrophe at the boundaries (Seetapun and Odde 2010; Ambrose et al. 2011). This leads to

$$v_g \rho_g^R(L, x^p) = v_s \rho_s^R(L, x^p) \quad (7)$$

$$v_g \rho_g^L(-L_2, x^p) = v_s \rho_s^L(-L_2, x^p). \quad (8)$$

The steady state solutions for Eqs. 1–4, shown in Fig. 2, provide solutions that can be used to obtain theoretical predictions to compare to experimental data, such as plus end densities, cross sectional numbers along a neurite, and number of MTs in a neurite of length L . These ancillary quantities are obtained from the solutions of the $\rho(x, t)$'s as follows.

The plus-end density $p^R(x)$ of anterograde MTs at position x , comprises MTs whose minus end is to the left of x and are therefore given by

$$p^R(x) = \int_{-L_1}^x \rho_g^R(x^p, x^m) + \rho_s^R(x^p, x^m) dx^m. \quad (9)$$

Similarly, the density of retrograde plus ends at position x is

$$p^L(x) = \int_x^L \rho_g^L(x^p, x^m) + \rho_s^L(x^p, x^m) dx^m. \quad (10)$$

These correspond to integrating lines across Fig. 2. Note the ρ variable have units of μm^{-2} , meaning the p variables have units of μm^{-1} as desired.

The cross sectional number of the anterograde MTs at position x , $N^R(x)$, is found by counting any MT with plus end to the right of x and minus end to the left of x ,

$$N^R(x) = \int_0^x \int_x^L \rho_g^R(x^p, x^m) + \rho_s^R(x^p, x^m) dx^p dx^m. \quad (11)$$

Similarly, we obtain the left-facing MTs as

$$N^L(x) = \int_0^x \int_x^L \rho_g^L(x^p, x^m) + \rho_s^L(x^p, x^m) dx^m dx^p. \quad (12)$$

Lastly, we can obtain the total number of MTs in a neurite of length L by integrating over all of space,

$$\mathcal{N} = \int_0^L \int_0^L \rho_g^R(x^p, x^m) + \rho_s^R(x^p, x^m) dx^p + \rho_g^L(x^p, x^m) + \rho_s^L(x^p, x^m) dx^p dx^m. \quad (13)$$

This continuum modeling approach provides computationally efficient solutions and is more amenable to analysis than, e.g., stochastic simulation. For more details, see Gou et al. (2014).

We solve the above system to steady state to provide theoretical results and compare to experimental work by Seetapun and Odde (2010). Parameters were experimentally measured and we use these in all results presented here, except where otherwise noted. These are: $L = 30 \mu\text{m}$, $L_2 = 10 \mu\text{m}$, $L_1 = 0 \mu\text{m}$, $v_g = 150 \text{ nm s}^{-1}$, $v_s = 250 \text{ nm s}^{-1}$, $k_{cat} = 0.1 \text{ s}^{-1}$, $k_{res} = 0.154 \text{ s}^{-1}$, $k_{nuc} = 8.6 \times 10^{-6} \text{ s}^{-1} \text{ nm}^{-1}$.

2.2 Tubulin age equations

While mathematical models for MT array densities are well-established, here we derive equations describing MT age $A(x)$, defined here as the mean time since tubulin was polymerized from their soluble dimer state. We derive the age equations from mean first-passage time (MFPT) equations $T(x_i, x_f)$ describing how long, on average, a plus-end takes to be in state x_i until it is in state x_f . The Dogterom–Leibler equations themselves are derived from the biophysically-precise spatially discrete models, since MTs grow one tubulin dimer at a time. For this reason, the MFPT equations can be derived either from the limit of a discrete-space model, or using an adjoint operator (Bicout 1997). The derivation schemes are shown in Fig. 3b. Each has advantages and limitations, so we present both derivations here.

2.2.1 Tubulin mean age from spatial discretization—First we present the discretization approach, which involves two steps shown in blue arrows in Fig. 3b. Using the schematic in Fig. 3a, we derive a differential equation to describe the average time spent in a specific location in space for the growing population. If we consider a discrete point x_i during a short time interval Δt , the MT has the ability to grow Δx with probability P_1 , transition to the shrinking state with probability P_2 , or stay at position x_i with probability P_3 . These transition probabilities are given by $P_1 = v_g \Delta t / \Delta x$, $P_2 = k_{cat} \Delta t$, and $P_3 = 1 - P_1 - P_2$. From this, we obtain a discrete master equation

$$T_g^R(x_i, x_f) = (T_g^R(x_i, x_f) + \Delta t)P_3 + (T_g^R(x_i + \Delta x, x_f) + \Delta t)P_1 + (T_s^R(x_i, x_f) + \Delta t)P_2. \quad (14)$$

for the mean time, T , for a plus-end to be growing at x_i until it first passes through a target state. A similar equation arises for T_s to describe shrinking states. After rearranging the equations and taking the limit first as $\Delta t \rightarrow 0$, then as $\Delta x \rightarrow 0$, we obtain the system of equations

$$-1 = v_g \frac{\partial T_g^R(x_i, x_f)}{\partial x_i} + k_{cat} (T_s^R(x_i, x_f) - T_g^R(x_i, x_f)) \quad (15)$$

$$-1 = -v_s \frac{\partial T_s^R(x_i, x_f)}{\partial x_i} + k_{res}(T_g^R(x_i, x_f) - T_s^R(x_i, x_f)) \quad (16)$$

$$-1 = -v_g \frac{\partial T_g^L(x_i, x_f)}{\partial x_i} + k_{cat}(T_s^L(x_i, x_f) - T_g^L(x_i, x_f)) \quad (17)$$

$$-1 = v_s \frac{\partial T_s^L(x_i, x_f)}{\partial x_i} + k_{res}(T_g^L(x_i, x_f) - T_s^L(x_i, x_f)). \quad (18)$$

Boundary conditions arising from catastrophe at the distal end and into the cell body are

$$T_g^R(L, x_f) = T_s^R(L, x_f) \quad (19)$$

$$T_g^L(-L_2, x_f) = T_s^L(-L_2, x_f). \quad (20)$$

The target state is defined by a boundary condition where T is set to zero. This defines a second boundary condition per subpopulation, $T_s^R(x_f, x_f) = 0$ and $T_s^L(x_f, x_f) = 0$.

2.2.2 Tubulin mean age and higher moments from adjoint operator approach

—An alternative derivation that leads more directly to Eqs. 15–18 is provided by using the adjoint operator of the Dogterom–Leibler equations, involving a single step shown as a green arrow in Fig. 3b. This calculation was presented by Bicout (1997) to describe the lifetime of an entire MT polymer. We point out that the same equations describe the local age of a given region of tubulin polymer.

The Dogterom–Leibler equations can be re-written in matrix form

$$\frac{\partial}{\partial t} \begin{pmatrix} \rho_g \\ \rho_s \end{pmatrix} = \mathcal{L} \begin{pmatrix} \rho_g \\ \rho_s \end{pmatrix} \quad (21)$$

where

$$\mathcal{L} = \begin{pmatrix} -v_g \frac{\partial}{\partial x} - k_{\text{cat}} & k_{\text{res}} \\ k_{\text{cat}} & v_s \frac{\partial}{\partial x} - k_{\text{res}} \end{pmatrix} \quad (22)$$

is a linear operator. Its adjoint is given by

$$\mathcal{L}^\dagger = \begin{pmatrix} +v_g \frac{\partial}{\partial x} - k_{\text{cat}} & k_{\text{cat}} \\ k_{\text{res}} & -v_s \frac{\partial}{\partial x} - k_{\text{res}} \end{pmatrix}. \quad (23)$$

From the adjoint operator, first-passage time moments can be computed using a formula from the classical theory of stochastic processes. For a useful description, see, e.g., Chou and D'Orsogna (2014). The m -th first-passage moment T_m satisfies the equation

$$\mathcal{L}^\dagger T_m = -m T_{m-1} \quad (24)$$

with the convention that $T_0 = 1$. For the first moment, i.e., the mean, this yields Eqs. 15–18. One advantage of the adjoint approach is that it allows calculation of higher moments including the second moment T_2 , which provides us with the standard deviation of age

$$\sigma = \sqrt{T_2 - (T_1)^2}. \quad (25)$$

We note that the mean age of a region of polymerized tubulin at position x is given by the mean time for a plus-end to grow past position $x^i = x$ until it shrinks past position $x^f = x$. Therefore,

$$A^R(x) = T_g^R(x, x) \quad (26)$$

and similarly for $A^L(x)$.

3 Application to microtubule arrays in developing neurons

The above derivation is for general MT arrays. One biologically-important example is offered by neuronal processes. In this section, we demonstrate agreement with experimental data from Seetapun and Odde (2010) on neurons from chick embryos. Since the model comprises linear PDEs for densities and linear boundary-value problems for ages, we can solve them without appealing to numerics (although Sect. 4 presents numerical results for the cargo transport model). We use the computer algebra package Mathematica in this section. The explicit functional forms of solutions are unwieldy and not presented here.

3.1 Continuum model recapitulates MT density in neurites

The growing population of plus-ends can be monitored experimentally using EB1, a processive plus-end tracking protein. In Fig. 4a, b, the plus-end density from our model, $p_g^R(x)$ from Eq. 9, is compared to experimental results from Seetapun and Odde (2010). We find good agreement for both short and long neurites, where we use the terminology that short neurites are minor processes with typical lengths of 7 μm and long neurites are developing axons with lengths 30 μm . The total number of MTs, computed from Eq. 13, also agrees for both short and long neurites (Fig. 4c). Seetapun and Odde (2010) also performed agent-based stochastic simulation in which tubulin dimers were explicitly assembled and disassembled, using a fixed-timestep Monte Carlo scheme (for more details on their simulation, see their Supplemental Material). They find good agreement with their experimental data, after including distributed, bidirectional nucleation. Our continuum model also agrees with their stochastic simulation, in both the number of MTs, as shown in Fig. 4d, and with the proportion of anterograde-to-retrograde MTs (not shown).

3.2 Tubulin age and standard deviation recapitulate PTM pattern in neurites

Using the continuum equations for MT age, we obtain an analytic expression for the mean age of tubulin at all locations along the array. This involves left-and right-facing subpopulations, weighted by the local relative number of left-and right-facing MT cross-sections, leading to

$$A(x) = \frac{N^R(x)}{N^R(x) + N^L(x)} \cdot A^R(x) + \frac{N^L(x)}{N^R(x) + N^L(x)} \cdot A^L(x) \quad (27)$$

where N^R and N^L are defined in Eqs. 11 and 12.

The MFPTs giving rise to the age are shown in Fig. 5a along with their standard deviation. To confirm our work, we performed Gillespie simulation of MT dynamic instability in continuous space using a stochastic version of the Dogterom-Leibler model. Plotted in solid circles is the standard deviation of the first-passage times for 10,000 simulated MT growth trajectories. We find good agreement with the analytically-derived curve.

Our model predicts that the oldest polymerized tubulin will not be found at either cell body or distal end, but rather at a location near, but not at, the middle of the array, as shown in Fig. 5b blue curve. This peak is shallow, ~10 % above baseline, and is consistent with previous experimental measurements of heterogeneity in PTMs along axons (Seetapun and Odde 2010) shown in Fig. 5b, orange data points. We note, however, that while we qualitatively match the experimentally-observed peak over a wide range of parameters, we could not match the experimental PTMs using the same parameter set as the MT densities. In particular, the parameter k_{arr} representing the arrival rate of MTs from the cell body was reduced by a factor of ~50. This could be for several reasons, including that the PTM assay used in Seetapun and Odde (2010) does not scale linearly with age, as would be expected if de-tyrosination is in the dynamic regime in which it saturates.

3.3 Peak in age arises from combination of dynamic instability and a bidirectional array

Since a shallow peak is difficult to resolve experimentally, and is of possible biological functional significance (see next section), we seek to understand whether it is a robust prediction of our model. Heuristically, where does this peak come from? If MT dynamic instability is removed from our simulation (by setting $k_{\text{cat}} = k_{\text{res}} = 0$), we find the peak vanishes. Since MT age is determined by the mean time for a plus-end to return to its site of nucleation (its minus-end), we examine this mean time in Fig. 6d as dynamic instability is modulated. In the absence of dynamic instability (solid lines), motion is deterministic and the mean times (and therefore age) are linear functions of space. However, as dynamic instability is introduced (dotted and dashed lines), the transport process become more diffusion-like and therefore concave-down. When the anterograde and retrograde concave-down functions are averaged, as shown in Fig. 6a–c, the result is a peak. Thus, heuristically, the peak in age is a robust consequence of dynamic instability, which leads to a diffusion-like concave-down MFPT, and a bidirectional array, which averages these two concave-down functions.

4 Influence of weak spatial non-uniformity on motor transport

4.1 Model of bidirectional microtubule-motor transport of cargo

Recent experiments (Sirajuddin et al. 2014) examined the influence of PTMs such as de-tyrosination on motor dynamics, finding that de-tyrosination can accelerate or decelerate kinesin velocity (for kinesin-2 and kinesin-13, respectively), can accelerate or decelerate kinesin detachment (for *C. elegans* and human kinesin-2, respectively), and has a negligible effect on dynein. In all cases, the difference between fully-tyrosinated and fully-de-tyrosinated MTs was approximately twofold.

To explore the effects of collective cargo transport along a microtubule array with PTM heterogeneity, we hierarchically extend our model to include cargo transport. Cargo can exist in four states, as shown in Fig. 7: dynein-driven or kinesin-driven on anterograde or retrograde MTs. These have local densities u^{DL} , u^{DR} , u^{KL} , u^{KR} respectively. The base equations have been used before by us and others (Cytrynbaum et al. 2004; Gou et al. 2014; White et al. 2015) and comprise a set of four coupled advection-reaction equations

$$\frac{\partial}{\partial t} \begin{pmatrix} u^{KR} \\ u^{KL} \\ u^{DR} \\ u^{DL} \end{pmatrix} = - \frac{\partial}{\partial x} \begin{pmatrix} v^K \cdot u^{KR} \\ v^K \cdot u^{KL} \\ v^D \cdot u^{DR} \\ v^D \cdot u^{DL} \end{pmatrix} + M \begin{pmatrix} u^{KR} \\ u^{KL} \\ u^{DR} \\ u^{DL} \end{pmatrix} \quad (28)$$

where transitions between the states have rates f^i , of which there are twelve. These appear in the transition matrix

$$M = \begin{pmatrix} -\left(\sum_{i=KRXX} f^i\right) & f^{KLKR} & f^{DRKL} & f^{DLKR} \\ f^{KRKL} & -\left(\sum_{i=KLXX} f^i\right) & f^{DRKL} & f^{DLKL} \\ f^{KRDR} & f^{KLDR} & -\left(\sum_{i=DRXX} f^i\right) & f^{DLDR} \\ f^{KRDL} & f^{KLDL} & f^{DRDL} & -\left(\sum_{i=DLXX} f^i\right) \end{pmatrix}.$$

The most conservative assumption we can make is that age scales linearly with PTM modification, which in turn has a linear influence on motor properties (this assumption is relaxed below). A 20 % modulation in age would thus imply a 10 % acceleration or deceleration in motor dynamics, since Sirajuddin et al. (2014) find twofold changes. Therefore we extend the model to have spatially-dependent transition rates and velocities, described by

$$f^i(A(x)) = f_{\min}^i + (f_{\max}^i - f_{\min}^i) \left(1 - \frac{A(x)}{A_{\max}}\right) \quad \text{Increasing} \quad (29)$$

$$f^i(A(x)) = f_{\max}^i + (f_{\min}^i - f_{\max}^i) \left(1 - \frac{A(x)}{A_{\max}}\right) \quad \text{Decreasing} \quad (30)$$

and

$$v^i(A(x)) = v_{\min}^i + (v_{\max}^i - v_{\min}^i) \left(1 - \frac{A(x)}{A_{\max}}\right) \quad \text{Increasing} \quad (31)$$

$$v^i(A(x)) = v_{\max}^i + (v_{\min}^i - v_{\max}^i) \left(1 - \frac{A(x)}{A_{\max}}\right) \quad \text{Decreasing} \quad (32)$$

respectively.

Spatially-averaged parameters for transitions and the two motor velocities are available for certain systems including the fungus *Ustilago maydis* (Lin et al. 2011), but not for PTM-dependent effects. Here, we use single-motor parameters from Sirajuddin et al. (2014) as a starting point. For dynein, we use $f^{DXXX} = 0.13 \text{ s}^{-1}$ and $v^D = 100 \text{ nm/s}$. For kinesin, we assume transition rates vary between $f_{\min}^i = 0.4 \text{ nm/s}$ and $f_{\max}^i = 0.92 \text{ nm/s}$ and $v_{\min}^K = 5.3 \text{ nm/s}$ and $v_{\max}^K = 11.6 \text{ nm/s}$. For simulations with constant, non-PTM-dependent rates, we use the average of these.

4.2 Weak spatial pattern in PTMs with linear influence on motors leads to tight localization of cargo

Although the equations are linear, the coefficients are spatially non-uniform. We solve the system numerically with a standard backwards-Euler scheme with finite difference discretization in space and a forward-Euler scheme with finite difference discretization in the transition rates. In the absence of age-dependent transition rates and velocities, cargo remains uniformly distributed along the MT array, as shown in Fig. 8a. For age-dependent rates and velocities, a variety of cargo distributions are observed.

There are twelve transition rates. However, our model does not exploit any assumed asymmetry in the MT array. Therefore, upon imposing left-right symmetry, there are six independent rates. Following experimental evidence that dynein detachment rates are not age-dependent (Sirajuddin et al. 2014), we assume transitions away from dynein states are not age-dependent. Therefore there are three rates with possible age-dependence, each of which could be increasing, decreasing or constant with age, leading to 27 possibilities. We simulate all of these and summarize the results in Table 1.

What choice of transition rate dependency is most biophysically likely? The mechanism of directional changes is under intense investigation (Ando et al. 2014; Shubeita and Gross 2012; Kunwar et al. 2011; Leidel et al. 2012; Muller et al. 2010; Soppina et al. 2009; Hendricks et al. 2010). In the absence of molecular mechanism, we can distinguish two classes of transitions: (*KLDR*, *KRDL*) are transitions that can take place on the same MT, whereas (*KLDR*, *KRDR*) and (*KLKR*, *KRKL*) necessarily involve switching MTs. We therefore focus on combinations in which same-MT transitions have one dependence and switch-MT transitions have another (Lines 4, 8, 11, 15, 17, 22, 23 and 27 in Table 1). Of these, several resulted in cargo accumulation and peak formation. We show one in Fig. 8c in which same-MT transitions decrease with age, and switch-MT transition rates increase with age.

To quantify the localization, we measure the full-width at half-max of total cargo $u_{tot}(x)$. The aforementioned age dependence results in accumulation within $\sim 10 \mu\text{m}$, one-third of the total length. For other combinations, we observed tighter localization (Lines 1 and 6 in Table 1) and looser localization, for example when all rates decrease with age (Line 2 and Fig. 8d). For yet other combinations, cargo accumulated at the ends of the MT array (Line 19 and Fig. 8f).

We next explored the effect of motor velocities with a dependence on age. When both transition rates and velocities depend on age, the cargo distribution is only weakly different from distributions with only transition rate dependence. For example, Fig. 8e is identical to Fig. 8c but assumes kinesin velocity decreases with de-tyrosination. The curves are similar in localization.

Heuristically, the magnification of the small changes in transition rates into large vabidirectionriation in cargo density comes from the exponential character of solutions to advection-reaction equations. Conceptually, consider the simple first-degree advection reaction equation

$$\frac{\partial u}{\partial t} = -\frac{\partial}{\partial x}(vu) - fu. \quad (33)$$

This has steady-state solution

$$u(x) = u_0 \exp(-xf/v) \quad (34)$$

for f uniform in space. This depends exponentially on f . Thus, small changes in transition rates are expected to have a large influence on cargo density. The sensitivity we observe is consistent to previously reported motor-cargo localization (Newby and Bressloff 2010).

In the above results, we have assumed that de-tyrosination is linearly proportional to age. *A priori*, there are three possible regimes: If the saturation timescale is much less than the age timescale (~ 100 s), then all tubulin will be fully de-tyrosinated, and the experimentally-observed heterogeneity would need an alternative explanation. If the saturation timescale is much longer than the age timescale, then we assume it is still in a linear regime, leading to our current functional form, where age and de-tyrosination are linearly related. Finally, the saturation timescale could be comparable to the age timescale. While data on the in vivo de-tyrosination timescale is not readily available, there is in vivo data on another, similar post-translational modification, acetylation. There, it has been shown to have a timescale of 30 min (Kalebic et al. 2013), which is much larger than the ~ 100 s timescale of tubulin age. Nonetheless, to explore the possibility of a saturation timescale comparable to the age timescale, we have performed limited simulations using a saturating function for de-tyrosination $D(x)$,

$$D(x) = D(A(x)) = \frac{A(x)}{T_{\text{PTM}} + A(x)} \quad (35)$$

where T_{PTM} is the saturation timescale of the de-tyrosination reaction. The de-tyrosination level $D(x)$ is then substituted for $A(x)$ in Eqs. 29 and 30. These results are shown in Fig. 9. We find that the peak in cargo remains, but is slightly broader. This makes intuitive sense, since the peak should be completely abolished the smaller the saturation timescale.

4.3 Cargo localization can be tuned by relative rates of microtubule nucleation from cell body

For a localization mechanism to be a suitable candidate mechanism in cells, it must be tuneable, meaning that the position of the cargo density peak can be changed by changing model parameters. In Fig. 10 we show simulations in which L_2 and k_{arr} are varied.

The parameter L_2 corresponds to how retrograde MT plus-ends entering the cell body experience catastrophe. As L_2 is increased, the peak in cargo density moves toward the cell body. For intermediate values of L_2 , there is a second accumulation of motors near the cell

body. For high values of L_2 , the middle peak vanishes. To understand why the peak moves, we plot the average age $A(x)$ and the weighted age of right-and left-facing MTs,

$$A_{\text{weighted}}^L(x) = \frac{N^L(x)}{N^R(x) + N^L(x)} \cdot A^L(x), \quad (36)$$

$$A_{\text{weighted}}^R(x) = \frac{N^R(x)}{N^R(x) + N^L(x)} \cdot A^R(x) \quad (37)$$

in Fig. 10a (bottom row). Since the age peak arises from the averaging of the two subpopulations, modifying either subpopulation changes overall motor transport. In the case of L_2 modification, only left-facing MTs are affected, changing directly $A^L(x)$ and $N^L(x)$. This in turn changes the weighting of the two sub-populations, increasing the importance of the left-facing MTs at the expense of right-facing MTs and moving the peak to the left.

The parameter k_{arr} represents how MTs are nucleated from the cell body and arrive as right-facing MTs in the array. As this parameter is increased in Fig. 10b, we find that the cargo peak moves to the right. Similarly to above, this can be understood by examining the weighted ages of left-and right-facing subpopulations. The right-facing MT subpopulation gains in weighting, moving the peak to the right.

5 Discussion

We develop and investigate a mathematical model of MT density, MT age and cargo transport using partial differential equations and mean first-passage time calculations and apply the model to MT arrays in neurons. We find closed-form exact solutions for the MT models and numerically simulate the cargo model. Our analysis demonstrates that a bidirectional array of MTs undergoing dynamic instability leads naturally to a weak spatial heterogeneity in tubulin age, and that MT motors responding weakly to PTMs can magnify this peak into a mechanism to localize molecular cargo to a specific, tunable location along a MT array.

Our approach harnesses an underlying mathematical simplicity: The MT density, MT age and cargo density equations are all linear, so numerical methods and solution structure are well-understood. This simplicity does not arise from linearization of a non-linear model, but rather naturally from assuming first-order kinetics, an assumption with abundant experimental support (Komarova et al. 2002; Janson et al. 2003). The non-trivial features arise from the spatially heterogeneity that emerges when the equations are coupled together.

The mechanism of localization we find is distinct from Turing, wave-pinning and French Flag pattern formation. In contrast, it is similar to other motor-cargo models where spatial heterogeneity in motor parameters localizes cargo towards its target (Newby and Bressloff 2010). One possible biological advantage is its long-range character: Since MTs span $\sim 10 \mu\text{m}$, localization can be effected over this distance without the limitation in length-or time-

scale of alternative mechanisms based on diffusion. Another feature is the ability to tune the placement from afar. That is, cargo that is localized $\sim 10\ \mu\text{m}$ distal into an axon can be moved, inwards or outwards, by modifying nucleation or catastrophe rates of MTs at the cell body. This type of long-range control is distinct from the external cue that tunes localization by other mechanisms, many of which need the cue to be modulated at the site of localization. We note that this mechanism produces peaks that are still too wide to explain the punctate localization of protein, for example, in synaptic boutons. Like other coarse localization schemes, it would need to be coupled to a finer-scale localization mechanism such as spontaneous clustering or, in the case of the synaptic bouton, diffusional bottlenecks or cooperative recruitment (Hoerndli et al. 2013).

This hypothesized mechanism is speculative. However, we note that, first, it arises naturally from two assumptions with strong experimental support: that tubulin PTM exhibits heterogeneity due to MT age, and that PTMs differentially influence motors. Second, the model make several testable predictions. If a particular cargo is localized by this mechanism, stabilizing the MT array from assembly/disassembly, for example with taxol (Vanburen et al. 2005), will result in eventually homogenizing PTMs, abrogating the signal to motors. The model also predicts that replacing motors with a motor species that responds differently to PTM would also result in loss of cargo localization.

Axons, dendrites and other neurites are spatially patterned by extrinsic cues, such as contact with the neurite of another cell, but also *intrinsic* cues, as evidenced by experiments on single, isolated neurons grown in culture (Katsuki et al. 2011). In the simplest case, isolated cells create a sharply-defined boundary between proximal and distal regions in both axons and dendrites. Our mechanism could apply to intrinsic spatial patterning, for example, to localize the molecules that acts as a receptor diffusion barrier at the sharp boundary.

The concept of MT “age” is becoming increasingly prevalent, since it is manifest by different biophysical phenomena such as nucleotide state (Tropini et al. 2012), structural changes (Coombes et al. 2013), lattice defects (Liang et al. 2016), or the PTMs we focus on here. In all four cases, age has been recently shown to have functionally-important effects on the dynamics of MT arrays, and can present spatial and temporal heterogeneity. The mathematical description of MT densities have fostered significant contribution to MT biology, and we augment these with a mathematical description of local tubulin age. As different markers of age are discovered to be implicated in further cellular processes, models such as ours will be of increasing importance.

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Fig. 1.

A schematic representation of MT arrangement in a neuron. MT nucleation occurs uniformly along the neurite through the γ tubulin nucleation sites, shown as *black dots*. The plus-end, denoted by *plus signs*, face either retrograde (*left*) or anterograde (*right*). The total length of the neurite is L . In addition to MTs nucleated in the neurite, MTs are nucleated from the cell body a distance L_1 from the neurite entrance, denoted by *gray bar*. Retrograde MTs travel a distance L_2 into the cell body before undergoing catastrophe

Fig. 2. Density of MTs whose minus end is at x^m and whose plus end is at position x^p along a 30 μm neurite at steady state for anterograde (*right*) and retrograde (*left*) MT subpopulations. Ancillary quantities are computed from these solutions, for example, the density of plus-ends at location x_p is obtained by integrating along a line of constant x_p as described in Eq. 9

Fig. 3.

Two approaches for computing first passage times and tubulin age. The Dogterom–Leibler equations are derived from a microscopic model in which the length of a MT is discretized to individual tubulin dimers. Equations 1–4 comprise a continuum limit of the discrete model. To compute the mean first passage time, we either return to the discrete model, derive the MFPT equations, and compute the continuum limit (*blue arrows*). Alternatively, we can compute first-passage statistics directly from the continuum model using an adjoint operator (*green arrow*)

Fig. 4.

The continuum model provides MT densities that match experimental data and previous stochastic simulation. **a, b** The density model recapitulates the experimental distribution of EB1, which tracks growing plus-ends, along a short neurite (**a**) and long neurite (**b**). **c, d** The total number of MTs agrees with previous discrete stochastic simulation (**c**) and experimental observation, with ranges shown as *rectangles* in **d**. Here, short neurites are minor processes with typical lengths of 7 μm and long neurites are developing axons with lengths 30 μm

Fig. 5.

Tubulin age recapitulates pattern in neurite. **a** Using the adjoint operator approach, one can obtain the standard deviation and mean for the age of anterograde MT. This agrees with results of stochastic simulation using the Gillespie algorithm as expected (*filled circles*). **b** The theoretical age distribution along a neurite recapitulates the experimental data obtained by (Seetapun and Odde 2010). We use parameters $L = 30 \mu\text{m}$, $L_2 = 10 \mu\text{m}$, $L_1 = 6 \mu\text{m}$, $v_g = 160.3 \text{ nm s}^{-1}$, $v_s = 109.5 \text{ nm s}^{-1}$, $k_{\text{cat}} = 0.1545 \text{ s}^{-1}$, $k_{\text{res}} = 0.1 \text{ s}^{-1}$, $k_{\text{arr}} = 0.025 \text{ s}^{-1}$, $k_{\text{nuc}} = 0.1 \text{ s}^{-1} \text{ nm}^{-1}$

Fig. 6.

Dynamic instability and bidirectional arrays provide a robust age peak. **a–c** The age of right-facing (anterograde) MTs is a decreasing, concave-down function of x , while the *left-facing* (retrograde) MTs is symmetrically increasing and concave-down. The mean age, shown in **c**, exhibits a peak. **d** Using the solutions of Eqs. 15 and 16, we vary the dynamic instability parameters (k_{res} , k_{cat}) given that the initial position of interest is at $10\mu\text{m}$. *Black curves* Growing plus-ends; *blue curves* shrinking plus-ends. Setting the dynamic instability parameters to zero (*solid*), we obtain a linear age distribution that does not result in a peak when coupled with Eqs. (12) and (13). As we turn on the dynamic instability parameters (*dash* and *dot dashed*), we begin to observe concavity. Thus, coupling Eqs. 15–18, we would have a robust peak as the retrograde MTs are symmetric to T_g^R and T_s^R . $L_1 = 0$, $L_2 = 0$ for all simulations. *Solid* $k_{cat} = 0$, $k_{res} = 0$, *dashed dotted* $k_{cat} = 0.01$, $k_{res} = 0.01458$, *dashed* $k_{cat} = 0.1$, $k_{res} = 0.154$

Fig. 7.

A schematic that represents the four possible states a cargo can be in. The cargo can be kinesin-driven on retrograde (u^{KL}) or anterograde (u^{KR}) MTs or dynein-driven on retrograde (u^{DR}) or anterograde (u^{DL}) MTs. The f^{ij} s represent the transition rate from the i th state to the j th state

Fig. 8.

Cargo transport by MT motors on a MT array with PTM-dependence. There are four subpopulations of cargo: driven by dynein or kinesin, and on anterograde (“R”) or retrograde (“L”) MTs shown schematically in Fig. 7. The total density profile at steady state is shown in *green*. **a** No age-dependence. **b** Kinesin velocity decreases with age, while transition rates are independent. **c** Transition rates on the same MT decrease with age, while transitions requiring a change of MT increase with age. Velocities are independent. **d** All kinesin transition rates decrease with age. **e** Same as **c** but with kinesin velocity decreasing with age. **f** Combination of increasing and decreasing rates leads to cargo accumulation at edges

Fig. 9. Different assumptions for de-tyrosination timescale, leading to different age-dependencies. All simulations use the dependence on de-tyrosination from Fig. 8c. For $T_{PTM} = 5s$ (left), de-tyrosination rapidly homogenizes in space, broadening the cargo peak. This effect diminishes as T_{PTM} increases above the age timescale of ~ 100 s (right)

Fig. 10.

Location of cargo accumulation can be tuned by biophysical parameters in the cell body. In **a**, the parameter L_2 , representing how far retrograde MTs can persist into the cell body, is increased. In **b**, the parameter k_{arr} , representing the nucleation rate of MTs in the cell body, is increased. *Top row of a and b*: cargo density. *Bottom row of a and b*: weighted age of total (black), left-facing (blue) and right-facing (red) MTs using Eqs. 36 and 37

Table 1

Combinations of motor-dependence on PTM and their influence on cargo localization

	f^{KLDL} and f^{KRDL}	f^{KLDL} and f^{KRKL}	f^{KLDL} and f^{KRDR}	Full width at half max width (μm)	Panel in Fig. 8
1	Decreasing	Decreasing	Increasing	9.42	–
2	Decreasing	Decreasing	Decreasing	20.10	d
3	Decreasing	Decreasing	Constant	12.36	–
4	Decreasing	Increasing	Increasing	10.26	c, e
5	Decreasing	Increasing	Constant	13.74	–
6	Decreasing	Constant	Increasing	9.84	–
7	Decreasing	Constant	Decreasing	20.40	–
8	Decreasing	Constant	Constant	13.08	–
9	Constant	Decreasing	Increasing	14.04	–
10	Constant	Decreasing	Constant	20.76	–
11	Constant	Increasing	Increasing	15.30	–
12	Constant	Constant	Increasing	14.64	–
13	Decrease	Increasing	Decreasing	No peak	–
14	Increasing	Decreasing	Increasing	No peak	–
15	Increasing	Decreasing	Decreasing	No peak	–
16	Increasing	Decreasing	Constant	No peak	–
17	Increasing	Increasing	Increasing	No peak	–
18	Increasing	Increasing	Decreasing	No peak	–
19	Increasing	Increasing	Constant	No peak	f
20	Increasing	Constant	Increasing	No peak	–
21	Increasing	Constant	Decreasing	No peak	–
22	Increasing	Constant	Constant	No peak	–
23	Constant	Decreasing	Decreasing	No peak	–
24	Constant	Increasing	Decreasing	No peak	–
25	Constant	Increasing	Constant	No peak	–
26	Constant	Constant	Decreasing	No peak	–
27	Constant	Constant	Constant	No peak	a, b

Of the possible 27 combinations of motor-dependence parameters, 12 combinations gave rise to peaks. The decreasing, increasing, and constant represents their linear dependence with age. For example, “decreasing” represents a linear decreasing transition rate with respect to age. The last column refers to the cargo density profiles shown in Fig. 8