

Continuum model for tubulin-driven neurite elongation

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Abstract

The formulation and numerical solution of a continuum (PDE) model of neurite elongation is presented. This model describes elongation as a function of the production, transport and (dis)assembly of tubulin into microtubules in a single growing neurite. It provides an important extension to previous ODE models of neurite elongation by allowing the incorporation of protein degradation and the calculation of the tubulin concentration gradient along the extent of the neurite. Simulation results indicate that the tubulin gradient can be flat, linearly decreasing, or significantly nonlinear. Elongation rate may be constant, or decrease until growth stops.

Key words: neuronal morphology; neurite outgrowth; tubulin; PDE model

1 Introduction

The growth of a neuron during its development is a complex process involving the construction of the cytoskeleton and the insertion of new membrane. As neurites grow out, their rate and direction of elongation are regulated by the external environment, as is the propensity for the growth cone at the end of the growing neurite to split to form new daughter branches. A wide variety of mathematical models have been proposed to describe aspects of neurite outgrowth (for a review of such models see [4].) Particular models have examined the dynamics of neurite elongation as determined by the construction of the cytoskeleton [2,3,5]. These models have investigated the rate and extent of elongation as a function of the transport of tubulin and its (dis)assembly into the microtubules that form the rigid internal structure of the neurite. These models are a simple steady-state analysis [2,5] or a coupled ordinary differential equation (ODE) description of the concentration of tubulin in the soma

and the growth cone [3,5]. These latter models, whilst examining the dynamics of outgrowth, of necessity assume a linear gradient of tubulin along the neurite and uniform conditions for tubulin transport. Degradation of tubulin can only be considered at the soma and growth cone.

In this paper we present a full partial differential equation (PDE) model of tubulin-driven neurite elongation. This model includes the production of tubulin in the soma and its transport by diffusion and active transport to the growth cone. Elongation is determined by the rate of (dis)assembly of the tubulin onto the ends of microtubules at the growth cone. As such this model is of the same form as previous models [3,5]. However, the PDE solution allows the calculation of the tubulin concentration and degradation along the length of the neurite. Simulation results show that the tubulin gradient along the neurite is not necessarily linear. Nonlinear interactions between tubulin degradation and microtubule (dis)assembly rates are revealed.

2 Formulation of the continuum (PDE) model

Governing Equation. We consider the one-dimensional concentration of tubulin along the length of a single, growing neurite. Tubulin is transported by diffusion (D), and active transport (a), which is positive and constant along the length of the neurite. Tubulin may degrade at a constant rate (g). The governing equation for this system is

$$\frac{\partial c}{\partial t} + a \frac{\partial c}{\partial x} = D \frac{\partial^2 c}{\partial x^2} - gc \quad (1)$$

defined on the domain $\Omega_{xt} \equiv \{(x, t) : x \in [0, l], t \geq 0\}$ where the soma/neurite interface is situated at $x = 0$ and $x = l$ is the maximum extent of neurite growth. At $x = l$, there is a flux of tubulin across this boundary which is used, in turn, to “grow” the neurite. Hence l is some function of time t defined by the ordinary differential equation

$$\frac{dl}{dt} = r_g c \Big|_{x=l} - s_g, \quad l(0) = l_0 \quad (2)$$

where r_g is the elongation rate and s_g is the (constant) retraction rate.

Boundary Conditions. For all $t \geq 0$ we assume that there is a steady flux of tubulin into the domain Ω_{xt} at $x = 0$ and that the flux of tubulin out of Ω_{xt} at $x = l$ is proportional to the quantity of tubulin there. The flux of tubulin from *left to right* across the boundaries at $x = 0, l$ is

$$\frac{\partial c}{\partial x} = -\epsilon_0 c_0 \quad \text{at } x = 0 \quad \text{and} \quad \frac{\partial c}{\partial x} = \zeta_l - \epsilon_l c \quad \text{at } x = l \quad (3)$$

for a typical tubulin scale c_0 , microtubule disassembly rate ζ_l , flux-source rate $\epsilon_0 > 0$ and flux-sink (microtubule assembly) rate $\epsilon_l > 0$. Usually we take the microtubule (dis)assembly rates to be equal to the neurite retraction and elongation rates ($\epsilon_l = r_g$; $\zeta_l = s_g$).

Initial Conditions. The simplest initial condition $c(x, 0) \equiv c^{(0)}(x)$, $x \in [0, l_0]$, which satisfies the boundary conditions, but not the governing equation, is linear in x :

$$c^{(0)}(x) = c_0 \epsilon_0 \left(l_0 + \frac{1}{\epsilon_l} - x \right) + \frac{\zeta_l}{\epsilon_l}$$

Numerical Solution. Numerical simulations of this model have been achieved via a finite difference approach. The equations were first nondimensionalised, then a spatial transformation was applied to give a governing equation defined on the new domain $\Omega_{yt} \equiv \{(y, t) : y \in [0, 1], t \geq 0\}$. The parameters of this equation are now functions of the length of the neurite. The transformed system is given by:

$$\frac{\partial C}{\partial t} + \frac{\alpha}{l} \frac{\partial C}{\partial y} = \frac{1}{l^2} \frac{\partial^2 C}{\partial y^2} - \beta C + \frac{y}{l} \frac{\partial C}{\partial y} \left(\left[C \right]_{y=1} - \gamma \right) \quad (4)$$

$$\text{and} \quad \frac{dl}{dt} = \left[C \right]_{y=1} - \gamma \quad (5)$$

where $\alpha = \frac{a}{r_g c_0}$, $\beta = \frac{gD}{r_g^2 c_0^2}$ and $\gamma = \frac{s_g}{r_g c_0}$. The boundary conditions are:

$$\frac{\partial C}{\partial y} = -\phi l \quad \text{at } y = 0 \quad \text{and} \quad \frac{\partial C}{\partial y} = \phi l (\sigma - \rho C) \quad \text{at } y = 1 \quad (6)$$

where $\phi = \frac{\epsilon_0 D}{r_g c_0}$, $\rho = \frac{\epsilon_l}{\epsilon_0}$ and $\sigma = \frac{\zeta_l}{\epsilon_0 c_0}$. The linear initial conditions are:

$$C^{(0)}(y) = \phi l_0 \left(1 + \frac{1}{\phi \rho l_0} - y \right) + \frac{\sigma}{\rho}. \quad (7)$$

For numerical implementation, the spatial domain $y \in [0, 1]$ was discretized into N equal subintervals, giving a constant spacing $\Delta y \equiv 1/N$. This corresponds to a changing spacing $\Delta x \equiv l/N$ in the original domain $x \in [0, l]$.

A predictor-corrector step was used to time-integrate the length equation (5) and a 2nd order accurate finite difference scheme was used in the spatial integration of the governing equation (4). There, a Crank-Nicholson approach was used to deal with the (nonlinear) diffusive term whilst an Euler approach was used for the time-derivative and remaining terms. Simulation has been carried out in MATLAB.

3 Simulation results

Numerical simulation of the model reveals that elongation can proceed in a variety of ways determined by the production, transport, decay and (dis)assembly of tubulin. With no decay and transport by diffusion only, elongation eventually proceeds at a constant rate, with the soma tubulin concentration continuing to increase and the growth cone concentration at steady state, given that production is faster than tubulin assembly into microtubules [5]. Low production rates give a near linear concentration gradient down the neurite, while higher production results in a nonlinear (concave) gradient. Inclusion of active transport raises the elongation rate and gives a nonlinear, but convex gradient. Addition of tubulin degradation (decay) returns the gradient to near linear and reduces the elongation rate. Elongation will eventually stop in the presence of decay. These results are shown in figures 1 and 2.

Without decay in the model, the tubulin disassembly rate (γ) acts in a purely additive way to the tubulin concentration. Higher disassembly raises the concentration level along the neurite without altering the slope or the elongation rate. This situation is radically different in the presence of decay, as illustrated in figure 3. Now increasing the disassembly rate flattens the concentration gradient and reduces growth, even though concentration levels are still raised.

4 Conclusions

The use of a continuum model for tubulin-driven neurite elongation allows the calculation of conditions along the growing neurite, revealing possible nonlinear gradients of tubulin. The major work here has been the formulation and numerical simulation of the PDE in which the space dimension changes with time. Further work is needed to generalise this approach to allow the modelling of the development of branching structures and the incorporation of inhomogeneous elements, such as variation in transport rates, along the growing neurite. The aim is to specify numerically accurate techniques for general compartmental modelling of developing neurons [1].

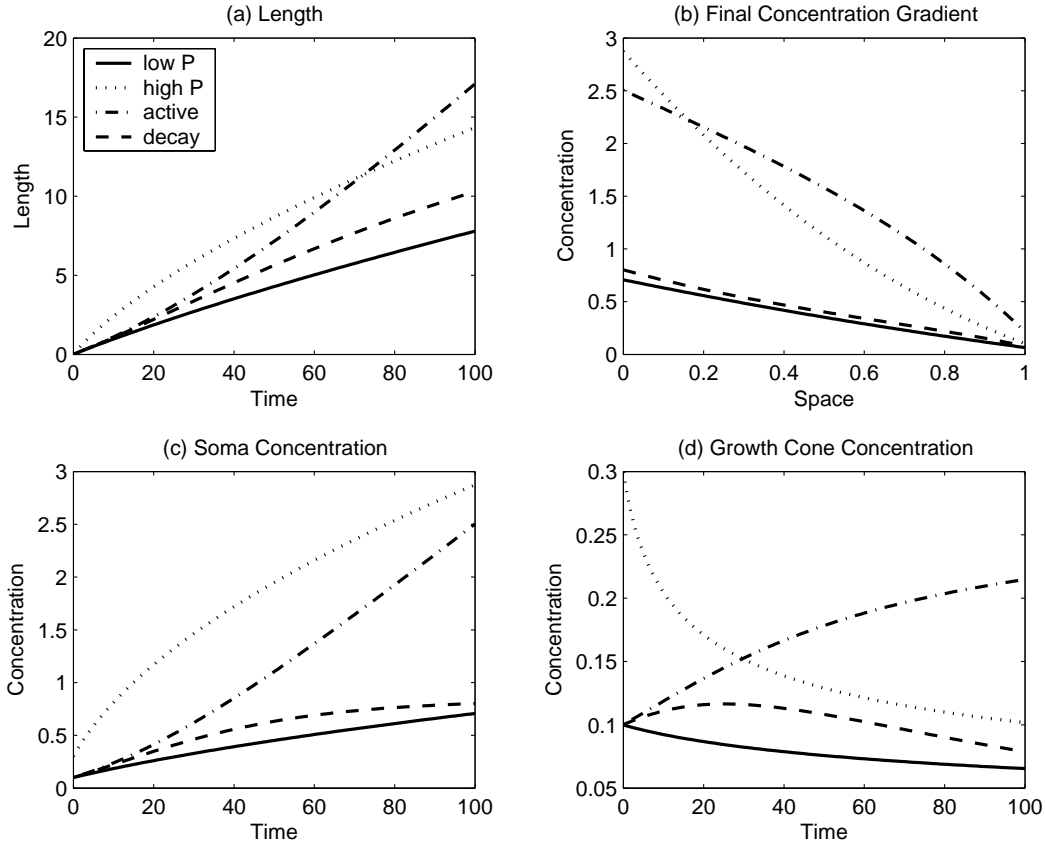


Fig. 1. Neurite elongation in different conditions. (1) Low production ($\phi = 0.1$) (2) High production ($\phi = 0.3$) (3) Active transport ($\alpha = 0.3$, $\phi = 0.1$) (4) Decay ($\alpha = 0.3$, $\beta = 0.05$, $\phi = 0.1$).

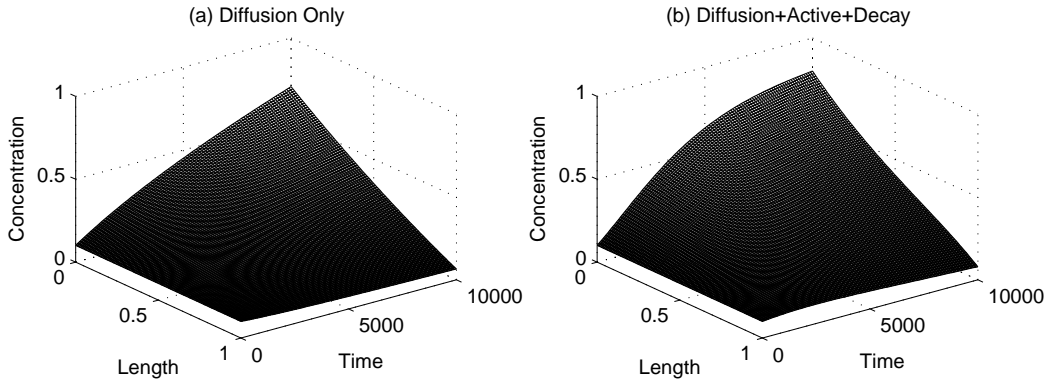


Fig. 2. Concentration gradients over time and space. (1) Low production with transport by diffusion only ($\phi = 0.1$) (2) Diffusion, active transport and decay ($\alpha = 0.3$, $\beta = 0.05$, $\phi = 0.1$).

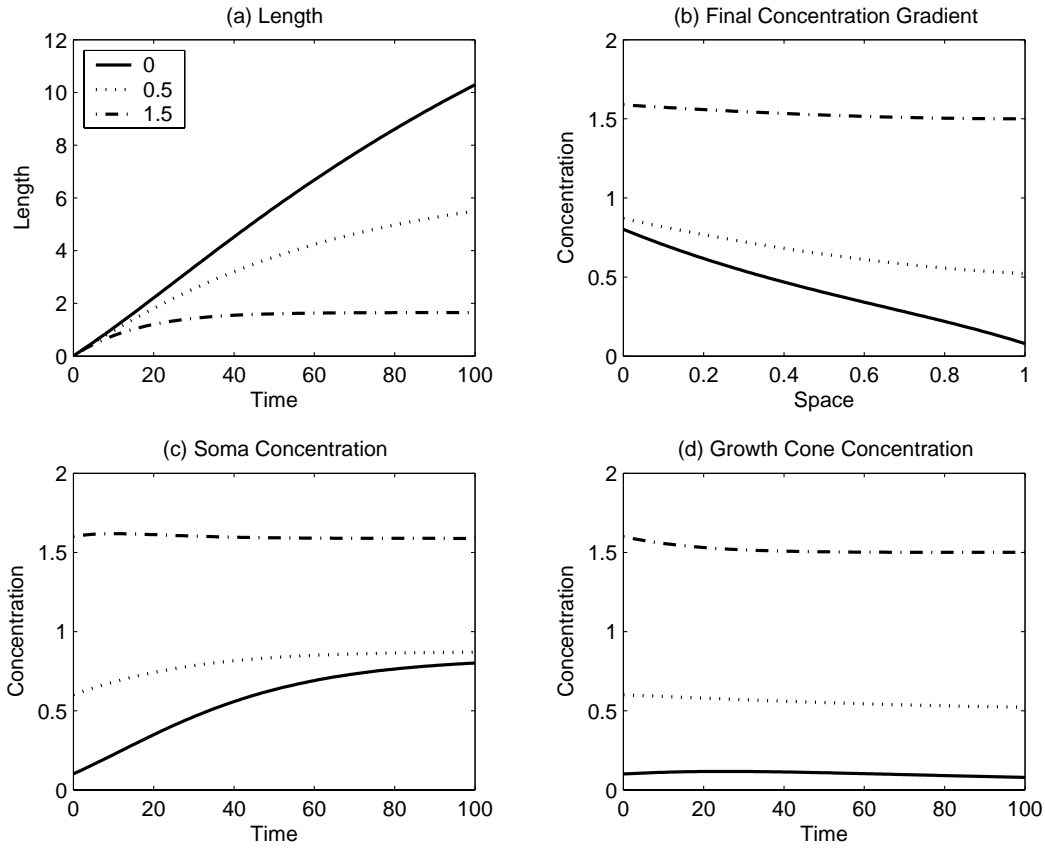


Fig. 3. Effect of microtubule disassembly rate on neurite elongation. Diffusion, active transport and decay ($\alpha = 0.3$, $\beta = 0.05$, $\phi = 0.1$). Disassembly rate (γ) set to 0, 0.5 or 1.5.

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