Modelling Axonal Growth

Modelling Case Study report
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Contents

1 Introduction

This case study concerns the modelling of the growth of axons. Modelling of axonal growth is not only interesting to predict what affect the growth of neurons, but could only give insight into the growth mechanisms, or be used as a baseline to understand the effect of neurological diseases.

We first consider biological background for axonal growth. Then we consider models that correspond to the two prevailing theories. Subsequently we derive and analyse a model that combines them. Finally, an extended model is derived under that discretely models both types of growth.

2 Biological background

Neuronal cells initially grow extensions called neurites, one of which differentiates into an axon, whose growth profile is modelled in this report. To model axonal growth it is imperative to have an understanding of the structure of an axon, is the growth mechanism, and the processes that influence it.

2.1 Axonal cell structure

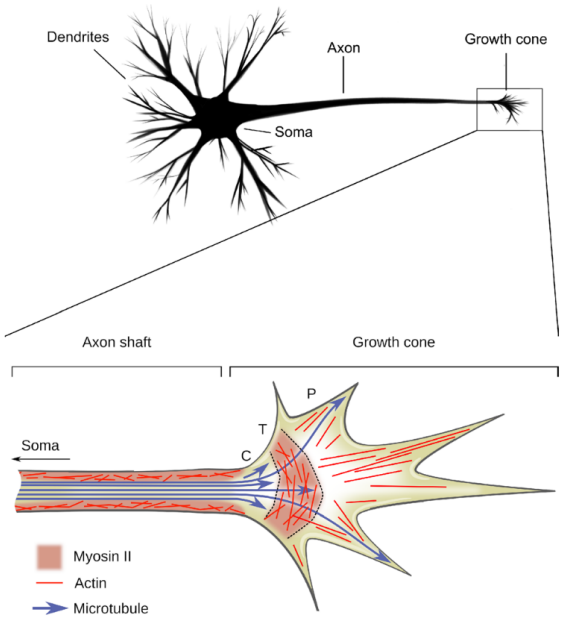

Figure 1: Schematic of a typical neuron showing the soma, the dendrites and the axon along with a close-up of the growth cone [5].

An axonal cell consists of a cell body (soma), and neurites, Figure 1. One of these neurites differentiates by length, becoming an axon, while the rest become dendrites. The axonal shaft consists mainly of stabilized microtubules, cross-linked by microtubule-associated proteins. At tip of the axon is a highly dynamic actin-supported extension called the growth cone. It has two main functions: sense its environment to determine in which direction the neuron ought to grow, and to advance in that direction, yielding growth, [5].

2.2 Axonal growth

Axonal growth is defined as the irreversible elongation of the neurite shaft supported by addition of new cellular material [1]. To reach its functional target, an axon must extend along a precise path, determined by the growth cone, in a growth stage called axonal guidance. Once the target is reached, the axon tip forms synapses with it, and is chemically bound, such that the axon must extend to accommodate the animal's growth, in a growth phases called stretch growth. This report considers the growth of an axon along a given path during axon guidance.

As part of the growth of the axon, free microtubule monodimers are synthesized in the cell body, transported along the axon and constructed into the cytoskeleton [6]. Where and how these tubulin are added is a debated research question [5].

Tip growth. An important theory in the 80s and 90s is that the microtubules along the shaft are stationary and that the shaft only extends through microtubule assembly at the tip. Models assuming this form of growth are called tranport limited models. The process along which the the cytoskeletal proteins (such as neurofilaments, actin and tubulin) are moved along the axis is called slow axonal transport [3]. Direct observations of tip growth are lacking.

Shaft growth. Another theory, mechanically mediated growth, assumes that growth is a response to an applied mechanical force. It postulates that the growth cone generates a tensile force during its migration, which creates internal tension and yields growth along the entire axon. Models assuming this type of growth are called mechanically mediated models. Experimental results [4] indicate that shaft growth is possible.

3 Transport Model

Transport models assume that the transport of free tubulin towards the tip of the axon is the limiting factor for axonal growth. We shall review the one-dimensional model presented by McLean [2].

3.1 Governing equations

Mass conservation governs the spatio-temporal distribution of tubulin. It states that the concentration of tubulin can be changed by either an outgoing flux $\mathbf{J}$ or by a source term S. In three dimensions this yields:

$$\frac{\mathrm{d}}{\mathrm{d}t}\int_V c(\mathbf{x},t)dV = -\int_{\partial V}\mathbf{J}\cdot d\mathbf{V} + \int_V S(\mathbf{x},t)dV$$

Applying the divergence theorem allows the simplification to:

$$\int_V \left(\frac{\partial c(\mathbf{x},t)}{\partial t} + \nabla\cdot\mathbf{J} - S(\mathbf{x},t)\right)dV = 0$$

which holds for an arbitrary volume. We shall be considering a single dimension only, in which case the equation reduces to:

$$\frac{\partial c(x,t)}{\partial t} + \frac{\partial J(x,t)}{\partial x} = S(x,t) \tag{3.1}$$

The flux considered is both active transport $J_{active} = ac(x)$ and diffusion $J_{diffusion} = -D\nabla c$, yielding a total flux $J = (a(x) - D\nabla)c$, with $a(x)$ and D proportionality factors. The source term consists here merely of the degradation proportional to the concentration: $S = -\kappa\cdot c$, for $\kappa > 0$ a positive constant. This yields the following governing equation:

$$\frac{\partial c}{\partial t} - D\frac{\partial^2 c}{\partial x^2} + a\frac{\partial c}{\partial x} = -\kappa c \tag{3.2}$$

on a domain $\Omega := \{(x,t)|x\in[0,l(t)], t\geq 0\}$. As the domain is time dependent, we also need an equation for the length of the neuron. The rate change of the length is assumed to be balanced by the assembly of microtubule $\gamma c|_{x=l}$ and the disassembly β:

$$\frac{\mathrm{d}l}{\mathrm{d}t} = \gamma c|_{x=l} - \beta \quad \text{with} \quad l(0) = l_0 \tag{3.3}$$

3.2 Boundary conditions

We assume that there is an influx of microtubule from the soma ($x = 0$), and outflux at the growth cone ($x = l$). In both cases, that is a flux from left to right: $-\mathbf{e}_l \cdot \nabla c = -\partial c/\partial x$, hence:

$$\frac{\partial c}{\partial x} = \begin{cases} -\epsilon_0 c_0 & \text{at } x = 0, \\ -\epsilon_l c + \zeta_l & \text{at } x = l \end{cases} \tag{3.4}$$

where $\epsilon_0 > 0$ is the tubulin production rate, ϵ_l the flux sink rate, ζ_l the returned flux (due to the disassembly process, related to s_g) and c_0 a typical tubulin scale.

4 Mechanical Model

O'Toole [2] presents a model based on shaft growth, generated by a tensile force F_0 in the axon. The proximal end of the axon, the soma, is kept fixed, and the axon is embedded in a substrate which creates dissipative forces $f_\eta(x)$, Figure 2.

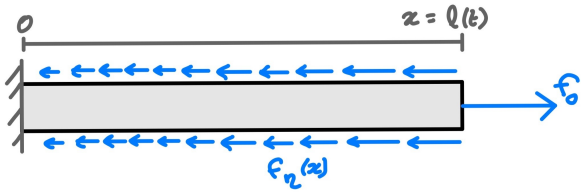

Figure 2: Setup of axonal model as dashpot with a force F_0 applied at $x = l(t)$ and a dissipative force f_η along the axon.

The axon is loosely modelled as a dashpot, such that the velocity (in the local reference frame) is given by $v_x(x, l(t)) = f(x, l(t))/G$ where f is the local force, and G is the dashpot constant. We can use this to find the velocity of any point in the global reference frame (choosing $v(x, l(t)) = 0$, i.e. the soma doesn't move):

$$v(x, l(t)) = \int_0^x v_x(x, l(t))dt = \frac{1}{G}\int_0^x f(\tilde{x}, l(t))d\tilde{x} \tag{4.5}$$

We note that f is the local resultant force, with contributions from both the applied tip force, and the dissipation from the substrate: $f(x, l(t)) = F_0 - f_\eta(x, l(t))$. We can relate the spatial derivative of the dissipative force, f_{η_x}, to the point's velocity with respect to the substrate: $f_{\eta_x} = -\eta v(x, l(t))$. Note that the minus sign is because

the dissipative force reduces towards the soma. Integrating:

$$f_\eta(x, l(t)) = f_\eta(x = l(t), l(t)) + \int_{l(t)}^{x} -\eta v(x, l(t))dt = 0 + \eta \int_{x}^{l(t)} v(x, l(t))dt \quad (4.6)$$

Combining (4.5) and (4.6):

$$f_\eta(x, l(t)) = \frac{\eta}{G} \int_{x}^{l(t)} \int_{0}^{\bar{x}} f(\tilde{x}, l(t))d\tilde{x}d\bar{x}$$

Then we remember $f(x, l(t))) = F_0 - f_\eta(x, l(t))$, and hence find the following integral equation:

$$f(x, l(t)) = F_0 - \frac{\eta}{G} \int_{x}^{l(t)} \int_{0}^{\bar{x}} f(\tilde{x}, l(t))d\tilde{x}d\bar{x}$$

which we can reduce into ODE form, and also recover boundary conditions by evaluating f and f' at carefully chosen points such that the integral vanishes, yielding the following boundary value problem:

$$\begin{aligned} \frac{\partial^2 f}{\partial x^2} &= \frac{\eta}{G} f \\ f(x = L(t), L(t)) &= F_0 \\ \frac{\partial f}{\partial x}(x = 0, l(t)) &= 0 \end{aligned}$$

We thus have a second order ODE with 2 boundary conditions: we can solve this! The general solution of the ODE is given by:

$$f(x) = A\cosh(\alpha x) + B\sinh(\alpha x)$$

where $\alpha = \frac{\eta}{G}$. We then plug in the boundary conditions:

$$\begin{aligned} f_x(x = 0) = 0 \quad &\rightarrow \quad 0 = \alpha A \sinh(0) + \alpha B \cosh(0) \rightarrow B = 0 \\ f(x = l(t)) = F_0 \quad &\rightarrow \quad F_0 = A\cosh(\alpha\, l(t)) \rightarrow A = \frac{F_0}{\cosh(\alpha\, l(t))} \end{aligned}$$

which then yields the final form of the resultant internal force f:

$$f(x, l(t)) = \frac{F_0 \cosh(\alpha x)}{\cosh(\alpha l(t))} \quad (4.7)$$

which leaves us with the unknown $l(t)$. However, we know $\frac{dl}{dt} = v(x = l(t))$, and also have an expression for v, (4.5), hence:

$$\begin{aligned} \frac{\mathrm{d}l}{\mathrm{d}t} &= \frac{1}{G} \int_{0}^{l(t)} f(x, l(t))dx = \frac{F_0}{G\cosh(\alpha l(t))} \int_{0}^{l(t)} \cosh(\alpha x)dx \\ &= \frac{F_0 \left[\sinh(\alpha x)\right]_0^{l(t)}}{\alpha G \cosh(\alpha l(t))} = \frac{F_0 \sinh(\alpha l(t))}{\alpha G \cosh(\alpha l(t))} \end{aligned}$$

which is an ODE we can solve:

$$\begin{aligned}
\frac{\mathrm{d}l}{\mathrm{d}t}\cosh(\alpha l(t)) &= \frac{F_0}{\alpha G}\sinh(\alpha l(t)) \\
\frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{\sinh(\alpha l(t))}{\alpha}\right) &= \frac{F_0}{\alpha G}\sinh(\alpha l(t)) \\
\sinh(\alpha l(t)) &= He^{\frac{F_0}{G}t} \\
l(t) &= \frac{1}{\alpha}\mathrm{arcsinh}\left(He^{\frac{F_0}{G}t}\right)
\end{aligned}$$

where we then plug in the initial condition $l(0) = L_0$ to find $\sinh(\alpha L_0) = He^0$, and hence we have the following final expression for the length of the axon over time:

$$l(t) = \mathrm{arcsinh}\left(\sinh(\alpha L_0)e^{F_0 t/G}\right)/\alpha \tag{4.8}$$

Experimental results tracking the movement of docked mitochondria (which are attached to the axon) show that the axon indeed moves, substantiating this assumed form of growth, and hence the model, as can be seen in Figure 3.

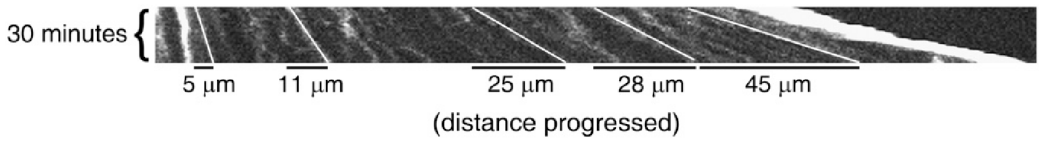

Figure 3: Mitochondria positions (white) along the axon (horizontal-axis) and over time (vertical axis). It shows increasing velocity of the axonal shaft towards the tip.

5 Combined Model

To build a combined model, we shall use the mechanical model to find the deformation, and then use a (modified) tubulin conservation equation, similar to the transport model, to find the required tubulin concentration distribution.

5.1 Mechanically mediated growth

The mechanical part of this model consists of the 1D mechanical model described in Section 4. From this model we need the axonal length $l(t)$, the velocity $v(x, l(t))$ and its first spatial derivative $v_x(x, l(t))$. The last two can be calculated from $f(x, l(t))$ in (4.7). We then have:

$$l(t) = \operatorname{arcsinh}\left(\sinh(\alpha L_0)e^{F_0 t/G}\right)/\alpha \tag{5.9}$$

$$v(x, l(t)) = \frac{F_0 \sinh(\alpha x)}{G\alpha \cosh(\alpha l(t))} \tag{5.10}$$

$$v_x(x, l(t)) = \frac{F_0 \cosh(\alpha x)}{G \cosh(\alpha l(t))} \tag{5.11}$$

5.2 Transport mediated growth

For the derivation of the second part, we continue from the 1D mass conservation equation derived in Section 3

$$\frac{\partial c(x,t)}{\partial t} + \frac{\partial J(x,t)}{\partial x} = S(x,t) \tag{5.12}$$

We shall consider three different sources of flux:

1. Diffusion: $J_D = -D\frac{\partial c}{\partial x}$
2. Active transport: $J_a = ac$
3. Stretch: $J_s = vc$ (this is the transport of tubulin due to the movement of the axon within which the tubulin moves).

For the source term, we shall consider two contributions:

1. Non-local degradation of tubulin $S_d = -\kappa c$
2. Consumption of tubulin to construct the axon. It is derived from the continuity equation, which expresses the conservation of mass in a fixed volume:

   $$\frac{\partial \rho}{\partial t} = \frac{\partial}{\partial x}(\rho v) + S(x,t)$$

   We then make the assumption that the linear density of the microtubule in the axon ($\neq$ the density of free tubulin) is constant in both space and time. Then the equation reduces to give the source term that corresponds to the consumption of tubulin due to the growth velocity v:

   $$S_c(x,t) = -\rho\frac{\partial v(x,t)}{\partial x}$$

Plugging all these terms into the PDE (3.1) yields:

$$\frac{\partial}{\partial t}c - D\frac{\partial^2}{\partial x^2} + \frac{\partial}{\partial x}\left((a+v)c\right) = -\kappa c - \rho\frac{\partial v}{\partial x} \tag{5.13}$$

Boundary conditions We choose to specify the concentration at the soma, and a no flux boundary condition at the growth cone:

$$c(x=0,t) = c_0(t) \tag{5.14}$$

$$(J_d + J_a + J_s)|_{x=l(t)} = 0 \rightarrow \frac{\partial c}{\partial x}(x=l(t),t) = \frac{a + v(x=l(t),t)}{D} \tag{5.15}$$

Initial condition Not having any information to prescribe an initial condition, we set the simplest initial condition that meets the boundary conditions, and make the assumption that for long time, the effect of this initial condition is zero.

$$c_1(x,t) = c_0(t) + \frac{a + v(x=l(t),t)}{D}x \tag{5.16}$$

5.3 Solving the combined model

Given that the mechanical model is explicitly solved, to find a solution to the model, we must solve the transport model for the space-time distribution of the concentration of free tubulin. We will justify and analyse two simplified models.

5.3.1 Model 1: Simple ODE.

For this first model we do not consider the transient component ($\partial/\partial t \rightarrow 0$, as growth is much slower than the transport processes), nor do we consider diffusion ($D = 0$, as it is much slower than active transport), or tubulin degradation ($\kappa = 0$), resulting in:

$$\frac{\partial}{\partial x}\left((a+v)c\right) = -\rho\frac{\partial v}{\mathrm{d}x} \tag{5.17}$$

As it is a first order ODE we only need to prescribe one boundary condition, but we have two. We choose to apply the no flux boundary condition, and then recover the required concentration at the soma to make this deformation possible. Due to $D = 0$, the no flux boundary condition is changed:

$$(J_s + J_a)|_{x=l} = 0 \quad \rightarrow \quad (a+v)c|_{x=l} = 0 \quad \rightarrow \quad c(x=l) = 0 \tag{5.18}$$

Note that we while v and v_x depend on time, and the concentration is also time varying, we solve only for one specific point in time.

Analytic solution Recognising both sides of the ODE as being the derivative w.r.t. x, we can solve it exactly:

$$\frac{\partial}{\partial x}\left((a+v(x))c\right) = \frac{\partial}{\partial x}(-\rho v(x)) \quad \rightarrow \quad c(x) = \frac{P-\rho v(x)}{a+v(x)} \tag{5.19}$$

Then we apply $c(x=l)=0$:

$$0 = P - \rho v(l) \quad \rightarrow \quad c(x) = \rho\frac{v(l)-v(x)}{a+v(x)} \tag{5.20}$$

We can also recover c_0:

$$c_0 = c(x=0) = \rho\frac{v(l)-v(0)}{a+v(0)} = \frac{\rho v(l)}{a} \tag{5.21}$$

as the velocity at the soma is zero (it is chosen as the reference point).

Numerical solution While numerically solving the ODE is not necessary as we have the analytic solution, it is useful for validating the numerical approximation technique. We have chosen to use finite differences, outlined in Subsection A.1, yielding Figure 4.

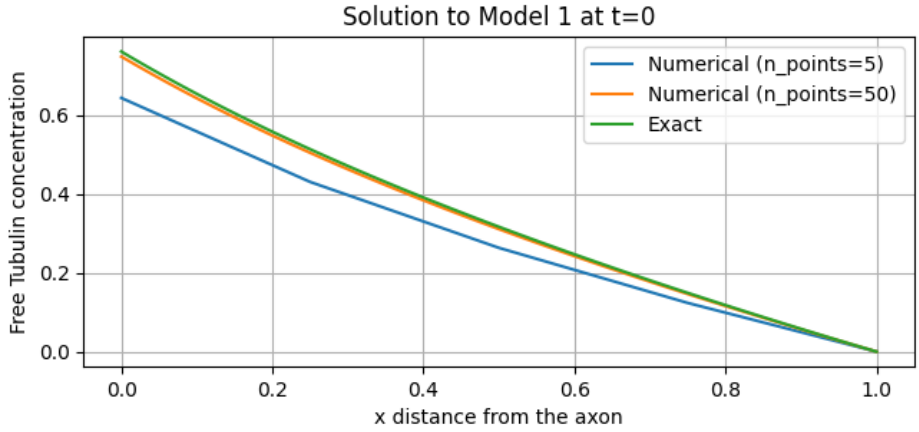

Figure 4: Comparison of the numerical solution and the exact solution, when all coefficients are set to 1. Note that as the number of points is increased, the numerical approximation approaches the analytical solution.

5.3.2 Model 2: Adding diffusion

We can create a second order model by adding diffusion ($D \neq 0$):

$$-D\frac{\partial^2 c}{\partial x^2} + \frac{\partial}{\partial x}((a+v(x)c(x)) = -\rho\frac{\partial v}{\partial x} \tag{5.22}$$

which also changes the no flux ($J(x = l) = 0$) boundary condition:

$$D\frac{\partial c}{\partial x} = (a + v)c \quad \rightarrow \quad \left.\frac{\partial c}{\partial x}\right|_{x=l} = \frac{a + v}{D}c \tag{5.23}$$

Numerical solution We can discretise (5.22) and the boundary conditions using finite differences, as outlined in Subsection A.2 to find Figure 5.

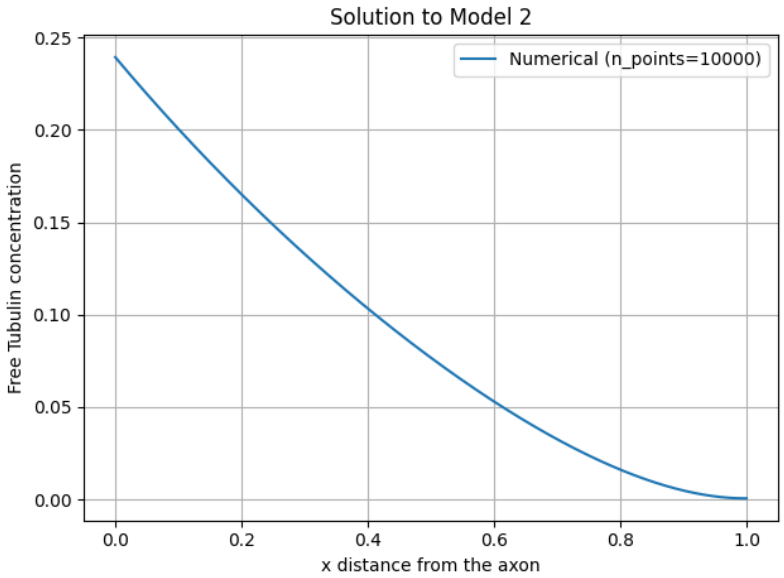

Figure 5: Numerical solution of Model 2 with all coefficients set to 1, except c_0, which was numerical optimized to yield $c(x = l) = 0$

5.3.3 Results

Let us perform some sanity checks on the results. Comparing the results from Model 1 (Figure 6) to Model 2 (Figure 7), we notice:

1. When adding another transport mechanism (diffusion), going from Model 1 to Model 2, the concentration at every point in space (for a given point in time) is lower. This is expected because more transport means the tubulin consumption for growth is more easily satisfied.

2. The length, as a function of time, is identical between both models. They have identical deformation because only the concentration PDE simplification differs between them.

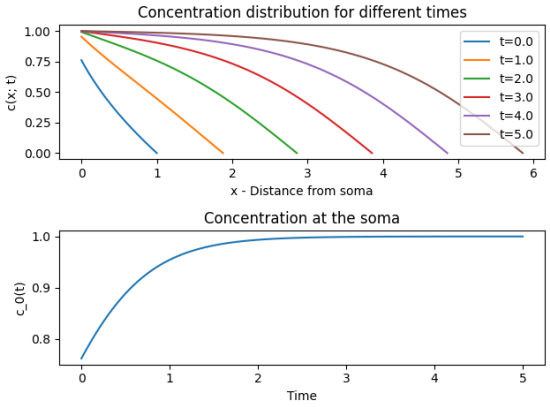

Figure 6: Model 1

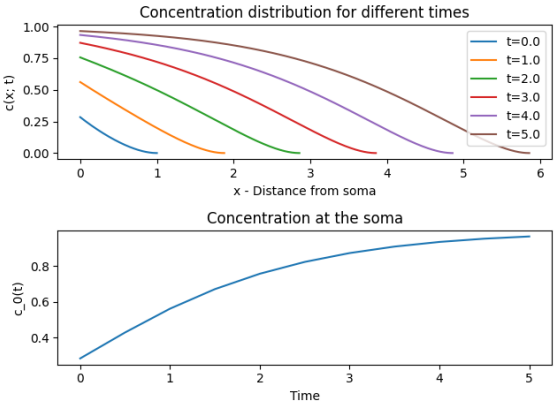

Figure 7: Model 2

By varying the model coefficients, for either model, we can perform further sanity checks. In Figure 8 note:

1. The top three graphs show that increasing the force increases the length (though only for $t > 0$), in both models equally. This corresponds to an increased tubulin consumption and hence a higher concentration is required.

2. The bottom left graph shows that by adding diffusion, a lower free tubulin concentration is needed.

3. The last two graphs show that if we decrease the transport mechanism coefficients, more free tubulin is required.

5.4 Analytical analysis

To perform asymptotic analysis, let $\epsilon = \sqrt{\eta/G}$ and $\sigma = F_0/\sqrt{\eta G}$. We then consider a deformation that changes ϵ while keeping σ constant (thus assuming $\eta \propto 1/G$). If we let $\epsilon \to 0$, that implies either the substrate force dissipation disappears ($\eta \to 0$), or the axon becomes very stiff ($G \to \infty$). This sets:

$$v(x) = \sigma \frac{\sinh(x\epsilon)}{\cosh(l\epsilon)} = \sigma \frac{\epsilon x + \mathcal{O}((\epsilon x)^3)}{1 + \mathcal{O}((\epsilon l)^2)} \quad \to \quad \lim_{\epsilon \to 0} v(x) = \sigma \epsilon x = \frac{F_0}{G} x \tag{5.24}$$

Thus for small ϵ, the mechanical model reduces to uniform linear growth. On the other hand, large ϵ corresponds either to very strong adhesion ($\eta \to \infty$), or a very

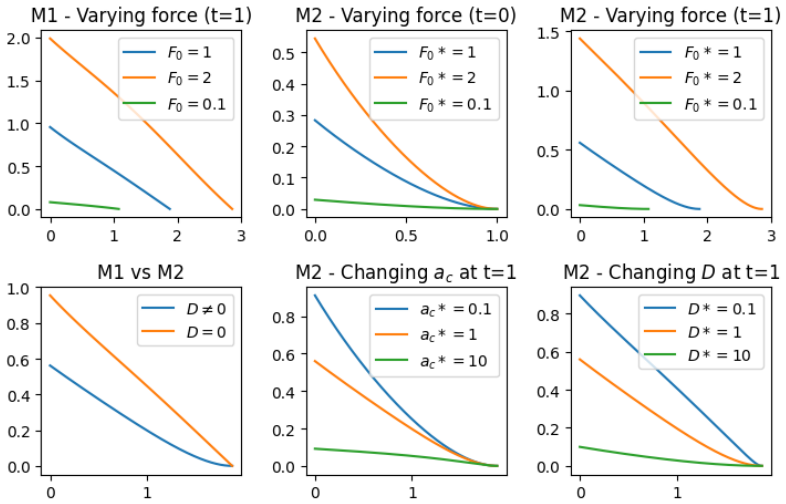

Figure 8: Variations on the model coefficients of both Model 1 (M1) and Model 2 (M2)

ductile axon ($G \to 0$). The velocity then becomes:

$$\begin{aligned} x \ll \epsilon \quad &\to \quad v(x) \approx 0 \\ x \approx l \quad &\to \quad v(x) \approx \tanh(\epsilon l) \to \infty \end{aligned}$$

and hence for large ϵ, the velocity $v(x)$ approaches the delta function $\delta(x - l)$. This implies tip growth. Hence, in the case where $\epsilon \to \infty$ and σ is constant, the combined model reduces to tip growth.

5.5 Extended Model

As an extension to the combined model, we add a discrete compartment at the tip that enables tip growth. This model has thus both shaft and tip growth, whose relative strength is determined by (unknown) coefficients. While the combined model exhibits tip growth asymptotically, it does not have a discrete tip growth process for finite coefficients. The aim of this model is to allow fitting of experimental to determine which of the two growth theories is more likely.

Biologically, the growth cone has an inherently different structure that the rest, as can be seen in Figure 1. Hence, one could potentially consider both shaft and tip growth.

5.5.1 Model derivation

To add tip growth to the combined model, we add a discrete compartment at the growth cone, which consumes tubulin and extends the axon, similar to end growth cone compartment in a 0D transport model, as presented by Oliveri [5, Section 3.1.1]. We keep the mechanical model up to the equations for velocity and its special derivative:

$$v(x, l(t)) = \frac{F_0}{G\alpha} \frac{\sinh(\alpha x)}{\cosh(\alpha l(t))} \qquad v_x(x, l(t) = \frac{F_0}{G} \frac{\cosh(\alpha x)}{\cosh(\alpha l(t))} \tag{5.25}$$

Then we want to find $l(t)$ and $c(x, t)$. We assume that the change in axonal length is due to both the velocity of the growth cone w.r.t. the substrate and due to the assembly and disassembly of microtubules at the growth cone:

$$\frac{\mathrm{d}l}{\mathrm{d}t} = v(x, l(t)) + \gamma c|_{x=l} - \beta \tag{5.26}$$

where $\beta > 0$ represents a constant rate of disassembly, $\gamma > 0$ is a proportionality constant for the rate of assembly, and $v(x = l, t)$ is the velocity of the axonal tip w.r.t. the substrate. Then we need an equation for the distribution of the concentration, which is where the transport model comes in. We add a source term to subtract the tubulin used for growth:

$$\frac{\partial c}{\partial t} + \frac{\partial}{\partial x}\left((a + v)c - D\frac{\partial c}{\partial x}\right) = -\rho\frac{\partial v}{\partial x} + \delta(x - l) \cdot (\beta - \gamma c) \tag{5.27}$$

We consider the PDE in 2 domains:

Domain 1: $0 \leq x < l(t)$ Just as in Model 1, presented in Subsubsection 5.3.1, let us neglect $\partial c/\partial x$, and diffusion, finding:

$$\frac{\partial}{\partial x}\left((a + v)c\right) = \frac{\partial}{\partial x}(-\rho v) \quad \rightarrow \quad c(x, t) = \frac{\tilde{c}_1(t) - \rho v(x, t)}{a + v(x, t)}$$

To simplify comparison with the combined model, let $\tilde{c}_1(t) = c_1(t) + \rho v(l, t)$:

$$c(x, t) = \frac{c_1(t) + \rho(v(l, t) - v(x, t))}{a + v(x, t)} \quad \text{in} \quad 0 \leq x < l(t) \tag{5.28}$$

where we thus require $c_1(t) \geq 0$.

Domain 2: $x = l(t)$ Neglecting diffusion ($D \rightarrow 0$) and assuming continuity of c (though not of $\partial c/\partial x$):

$$\frac{\partial c}{\partial t} + \frac{\partial}{\partial x}((a + v)c) = -\rho v_x + \beta - \gamma c \quad \text{at } x = l. \tag{5.29}$$

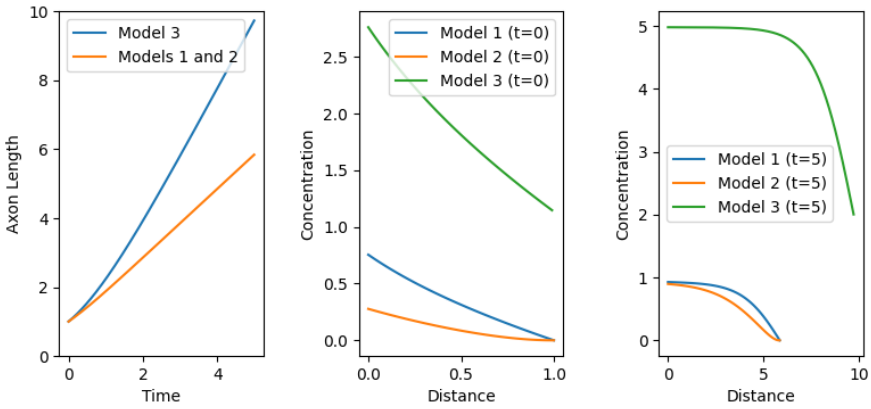

Figure 9: Comparison of Models 1, 2 and 3. Note that the deformation of models 1 and 2 is the same, as they are governed by $l(t)$ given in (4.8)

Expanding an rearranging yields:

$$\frac{\partial c}{\partial t} = -\frac{\partial v}{\partial x}(\rho + c) - (a + v)\frac{\partial c}{\partial x} + \beta \quad \text{at } x = l \tag{5.30}$$

Then we make the assumption that $\partial c/\partial x|_{x=l}$ is a constant. Since $c(x,t)$ is strictly monotonously decreasing towards the growth cone, we find it must be strictly negative. Note that by (5.28) and continuity of c, we have: $c(l,t) = c_1(t)/(a + v(l,t))$.

Governing equations We then find a system of 2 first order ODEs in time with two unknowns for the extended model (which we call Model 3):

$$\frac{\mathrm{d}c_1}{\mathrm{d}t} = (a + v)\left(-(a + v)\frac{\partial c}{\partial x} - \rho\frac{\partial v}{\partial x} - \gamma\frac{c_1}{a + v} + \beta\right) \tag{5.31}$$

$$\frac{\mathrm{d}l}{\mathrm{d}t} = v + \gamma\frac{c_1}{a + v} - \beta \tag{5.32}$$

Numerical solution Setting $\partial c/\partial x = -1$, $l(t = 0) = 1$, $c_1(t = 0) = 2$, and all other coefficients 1, we can solve the first order system numerically, and compare it with Model 1 (5.3.1), and Model 2 (5.3.2), yielding Figure 9.

5.5.2 Discussion

Considering Figure 9, we can perform some sanity checks. From the left-most figure we can see that, as expected, adding another growth mechanism and keeping all other coefficients equal yields faster growth. From the middle figure we see that indeed the concentration at the growth cone is nonzero, such that it can consume

tubulin. From the two rightmost pictures we can see that this extra growth (without a higher transport coefficients) means a higher concentration is needed. From the rightmost picture we can see that indeed, Model 3 has a very similar shape to Model 1 (both first order models without diffusion), but with a longer axon at $t = 5$ and a higher concentration.

This extended model provides a pathway for discerning which of the two proposed growth techniques is more likely. There are however, some further steps that must be taken before being able to do this. Most importantly, the validity of $\partial c/\partial x|_{x=l}$ must be investigated, and justified. Secondly, it would be interesting to add diffusion and tubulin degradation to the model.

6 Conclusion

We have first reviewed the two prevailing types of models: transport limited and mechanically mediated. Then, we have derived a combined model, whereby the deformation is presecribed by the mechanically mediated model, and the spatio-temporal concentration distribution is prescribed by a modified set of equations from the transport model.

Finally, we have extended this model by adding a discrete compartment at the tip. This model exhibits both shaft and tip growth, whose relative proportions are determined by unknown coefficients. The hope is that this model could be used, through fitting of experimental data, to determine which of the two growth modes is more likely.

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A Finite Difference Discretisations

A.1 Model 1

We discretise

$$(a + v(x))\frac{\mathrm{d}c}{\mathrm{d}x} + \frac{\mathrm{d}v}{\mathrm{d}x}c = -\rho\frac{\mathrm{d}v}{\mathrm{d}x}$$

on a homogeneous mesh $\Omega : x \in [0, l]$ with step size Δx as

$$(a + v(x_i))\frac{c_{i+i} - c_i}{\Delta x} + \frac{\mathrm{d}v(x_i)}{\partial x}c_i = -\rho\frac{\mathrm{d}v(x_i)}{\partial x}$$
$$c_i\left(\Delta x\frac{\partial v}{\partial x}(x_i) - (a + v(x_i))\right) + c_{i+1}(a + v(x_i)) = -\rho\frac{\partial v}{\partial x}(x_i)$$

where $c_i = c(x_i) = c(\Delta x \cdot i)$. The applied boundary condition is $c_N = 0$. This then yields the following matrix equation:

$$\begin{bmatrix} a_1 & b_1 & & & \\ & a_2 & b_2 & & \\ & & \ddots & \ddots & \\ & & & a_{N-2} & b_{N-2} \\ & & & & a_{N-1} \end{bmatrix} \begin{bmatrix} c_1 \\ c_2 \\ \vdots \\ c_{N-2} \\ c_{N-1} \end{bmatrix} = \begin{bmatrix} d_1 \\ d_2 \\ \vdots \\ d_{N-2} \\ d_{N-1} \end{bmatrix} \tag{A.33}$$

which can be solved to find $\mathbf{c}$, shown in Figure 4.

A.2 Model 2

$$-D\frac{c_{i+1} - 2c_i + c_{i-1}}{(\Delta x)^2} + (a + v(x_i)\frac{c_{i+1} - c_i}{\Delta x} + c_i\left(\frac{\partial v}{\partial x}(x_i)\right)) = -\rho\frac{\partial v(x_i)}{\partial x}$$
$$c_{i-1}(-D) + c_i\left(2D - (a + v(x_i))\Delta x + (\Delta x)^2\left(\frac{\partial v}{\partial x}(x_i)\right)\right)$$
$$+c_{i+1}(-D + \Delta x(a + v(x_i))) = -\rho\frac{\partial v(x_i)}{\partial x}$$
$$c_{i+1}a_i + c_i b_i + c_{i-1}d_i = g_i$$

On the left end of the domain we simply apply the robin boundary condition $c_{i=0} = c_0$. On the right side however, we need to derive an appropriate expression

using finite differences:

$$\frac{c_i - c_{i-1}}{\Delta x} = \frac{a + v(x_i)}{D} c_i$$

$$C_N - C_{N-1} = \frac{\Delta x}{D}(a + v(x_i))C_N$$

$$C_{N-1}(-1) + C_N \left(1 - \frac{\Delta x}{D}(a + v(x_i))\right) = 0$$

This can again be write in matrix form and solved for $\mathbf{c}$, yielding Figure 5.