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Second-year Group Research Project

Random walk models of polymers and molecular motors

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Abstract

The work in this research project may broadly be summarised to be the study of stochastic models of cell behaviour, specifically in the modelling of different realisations of the biological mechanism called polymerisation. In modelling polymerisation, continuous random walks are particularly important constituents of models, as they are connected to diffusive motion, and it is frequently diffusive motion which enables the polymerisation mechanism to be activated. In many ways, this well-studied connection between diffusion and random walks can be directly manipulated in the problems we consider. On the other hand, cells, as well as important biological mechanisms activated by polymerisation, have greatly heterogeneous qualities, and these can often require a more subtle approach. It is these subtle solving techniques, alongside important techniques both for dealing with properties of stochastic processes and the solution of relevant PDEs, which constituted the research of our group in the duration of this project.

Contents

1 The Biology of Polymers

The eukaryotic cytoskeleton is built from three classes of protein filaments— *actin filaments*, *microtubules*, and *intermediate filaments* (with characteristic diameters approximately 6 nm, 23 nm, and 10 nm, respectively) [7]. These structures fulfil distinct mechanical roles, but a common feature is that two of them (actin and microtubules) are *polarised polymers*. They elongate preferentially at a chemically distinct (+) end and shorten, faster at the (−) end [7]. This elongation and shortening is caused by processes called polymerisation and depolymerisation respectively; polymerisation occurs when the end of chain– called a polymer– of subunits– called monomers– attaches another monomer in the cell to one of its ends, effectively becoming 1 monomer "longer" [7]. Depolymerisation occurs simply when detaching of existing monomers at an end of a chain occurs rather than attaching [7].

Polymerisation is crucial because it allows these filaments to dynamically regulate their length. For our purposes, there are two main functions of such filaments and this dynamic regulation of their structures [7]:

- These polymers can lengthen or shorten based on polymerisation/ depolymerisation. This effectively moves the position of the polymer, and since these polymers are important structures in holding a cell together, this may also allow the cell to move or change its shape and structure [7].
- These polymers may also serve as 1D "tracks" [7], upon which so-called molecular motors travel in order to actively (that is, in a fashion requiring energy input) transport important macromolecules. This is highly necessary as without these active mechanisms of transport simply allowing macromolecules to diffuse across cells by themselves is usually too slow [13]. Thus polymerisation is a key process in cells as it dictates the shapes of the paths actively transported molecules take.

Modelling Assumptions for Polymerisation

The precise mechanism for polymerisation can vary depending on the situation and the specific polymer being considered. For the purposes of our research, we generally made a few modelling assumptions, which aimed to produce tractable problems without sacrificing biological realism.

Generally speaking, the main assumption we made was to assume that polymerisation happens as a result of random diffusion: in particular, that polymerisation occurs with some probability if monomers floating around the cell in a diffusive motion contacted the end of an existing polymer. This entails the following simplifications:

1. For the most part, we assume that the length of a polymer chain does not affect the likelihood of a new monomer attaching, and our random walks are constructed from the assumption that this step probability in the underlying discrete random walk remains the same throughout.

   This assumption is reasonable for many cases of polymers [13]. Moreover, if we want to create constraints upon the length of a polymer chain becoming too large, this is often not too difficult to remodel. The bounded growth section of Model II (Dogterom-Leibler) provides an example of this exact constraining.

2. Related to the previous assumption, we mostly assumed that the process of polymerisation can be modelled by a Markovian stochastic process [13]. In biological terms, that is to say

that we assume the history of the length of the polymer is not relevant to the likelihood of a new monomer attaching itself, except the current length when this new attachment occurs. This is a very intuitive and reasonable assumption [13], as indeed there is no biological reason why a polymer should not be memoryless in the variation of its length under polymerisation.

3. Finally, we make the simplification that we only consider polymerisation at one end of the polymer. This is not a realistic assumption, as polymerisation or depolymerisation will occur at both ends, but it is clearly one which is not a barrier to understanding, as the analysis of dynamics may be easily reproduced to consider the other end as well if necessary.

Stochastic Models for Polymerisation

Throughout the report, much focus will be given to motivating the use of stochastic models to model polymerisation. In short, we may consider this to be due to the fact that at cellular length scales ($\lesssim 1\,\mu$m) and monomer numbers ($\sim 10^2 - 10^4$), intrinsic noise and variability is not negligible [13] and even examining the mean "expected" case may not be sufficient to understand models. Some examples of these stochastic characteristics include:

1. **Switching statistics.** The waiting-time distributions for catastrophe and rescue in microtubules (important processes, as studied in Model II of this report) exhibit broad, non-exponential tails that can only be explained by stochastic cap loss rather than deterministic thresholds [7]. Indeed, there are in general many tail events in biological processes which suggest the need for a careful stochastic treatment rather than simple deterministic approximations [13].

2. **Length fluctuations.** Filament length fluctuations influence network mechanics and have measurable consequences for cell migration speed and direction [7] [13]. It is important therefore to model these fluctuations carefully and accurately.

Consequently, the mathematical toolkit spans master equations, first-passage-time theory, and continuum approximations (Langevin or Fokker–Planck descriptions) [13]. These methods form the backbone of the stochastic models analysed in the main body of this paper.

1.1 Scope and Outlook

In the research which follows, we exploited the biological facts summarised above to derive, analyse, and simulate minimal stochastic models of polymerisation processes in different settings. The emphasis is on analytically (or numerically) tractable formulations that nonetheless retain enough realism to predict experimentally measurable quantities such as length distributions, catastrophe frequencies, and mean first passage times. In the 4 central models of this paper, various heterogeneities, unique constraints and insightful biological mechanisms were investigated. The thread throughout remained the careful derivation and solution of stochastic models and the investigation of consequences of such models, as well as numerical simulations to complement the analytical solutions obtained.

2 Mathematical Preliminaries

Our goal is to model the biological processes which occur in certain cells. While this requires subtlety, it does give us important indicators for the efficacy of our models. In particular,

we must have models which predict evolutionarily useful behaviour. For example, consider modelling the behaviour of neurons, which may reach the length of 1m in the human body. In order for chemical or electrical impulses to travel across neurons, therefore, we must have a model of transport which allows this to happen quickly[13]. We cannot for example use a random walk/ diffusive model, where chemical molecules will take on average hundreds of hours to travel the distance of 1m, since it would be evolutionarily useless to have for example pain receptors which takes hundreds of hours to process an injury like that of a sudden burn[13].

To this end, important *stochastic* models and properties present themselves as particularly useful quantities to study within our models. This section introduces such quantities and their relevance within the biological framework of the phenomena we are attempting to model.

A. Continuous-Time Random Walk:

Our specific goal is to model the process of polymerisation. To do this, we assume that monomers floating around the cell follow some stochastic paths, which in turn makes the process of polymerisation itself a stochastically modelled phenomenon as polymerisation depends on these monomers attaching to the end of an existing chain [13]. As mentioned previously, we only consider one end of the chain in our polymer models, as similar dynamics may be extrapolated on the other end. In order to study the number of monomers forming a polymer at any given time, then, we can treat the rightmost end of the polymer as having a value as a 1D lattice site; by definition this value is nonnegative (as the rightmost end is to the right of the leftmost end, and we define the leftmost end to be $r = 0$) [13]. So each time there is polymerisation the rightmost end gets a $+1$ contribution to its lattice site (that is, it moves right on the lattice, and therefore the polymer chain size increases by 1); each time there is depolymerisation the contribution instead becomes -1, so the polymer chain reduces in size by 1.

Equally importantly, we are modelling a real-time process, and hence must have continuous time. We do not expect and cannot justifiably model that polymerisation occurs in evenly spaced time intervals [13]. So there is a continuity in time, even though the number of monomers in a chain must be a natural number and hence is a discrete value.

These two requirements dictated that the core mathematical object of this research was the continuous-time random walk on a 1D lattice. This continuous-time random walk (CTRW) is the time-continuous limit of what is perhaps the most fundamental discrete stochastic process, the discrete random walk (DRW). Crucially, there is a discreteness in value (lattice site/position) which is preserved even though we incorporate a continuity in time, for the reasons previously explained. This is exactly what we need in modelling polymerisation [13].

The DRW is defined as follows: one first defines the variables

$$Y_i = \begin{cases} 1, & \text{with probability } p \\ -1, & \text{with probability } 1-p \end{cases}$$

and then the DRW is defined as the sum:

$$X_N := \sum_{i=1}^{N} Y_i$$

whence can be derived several important properties. Perhaps the most important of these is that the DRW is clearly a Markov chain: that is,

$$\mathbb{E}[X_{N+1}|\mathcal{F}(N)] = \mathbb{E}[X_{N+1}|X_N]$$

under the shorthand $\mathcal{F}(N) := \{X_1, ..., X_N\}$. This is indeed clear as the next step of the DRW is ± 1 from the immediately prior step; hence the "memoryless" property of Markovian processes holds. Indeed, we can go further because of the simplicity of the summed iid random variables Y_i, and produce the *master equation* for $P_N(r)$ the probability that the DRW has value r at time step N. We now however want to obtain a version of the discrete random walk where time steps may occur at any time but lattice sites are discrete. In order to do this, we first need to factor in a probability that nothing occurs at all in a given time step, since we will be taking the limit as this time step becomes infinitesimally small. This is clearly a fairly simple modification to the previous discrete random walk. We just redefine the DRW as follows

$$X_N := \sum_{i=1}^{N} Y_i \quad \text{for } Y_i := \begin{cases} 1 & \text{with probability } \alpha \\ -1 & \text{with probability } \beta \\ 0 & \text{with probability } 1-(\alpha+\beta) \end{cases}$$

Now, we must scale by the size of the time step Δt, instead of assuming the steps are $t \in \mathbb{N}$ as we did previously for the discrete random walk. So during one step we have an increase by 1 with probability $\alpha\Delta t$, a decrease by 1 with probability $\beta\Delta t$, and nothing happening with probability $1-(\alpha+\beta)\Delta t$. With $t/N = \Delta t$ (so we will be taking the large N limit) and $P(r,t) = P_N(r)$ the new master equation therefore is

$$P(r,t) = \alpha\Delta t\, P(r-1, t-\Delta t) + \beta\Delta t\, P(r+1, t-\Delta t) + \big[1-(\alpha+\beta)\Delta t\big] P(r, t-\Delta t). \tag{1}$$

[13] We first subtract $P(r, t-\Delta t)$, and then divide by Δt. Subsequently, taking the limit as $\Delta t \to 0$ gives us the formula for the derivative of $P(r,t)$:

$$\frac{\mathrm{d}P(r,t)}{\mathrm{d}t} = \alpha P(r-1,t) + \beta P(r+1,t) - (\alpha+\beta)P(r,t) \tag{2}$$

Multiplying by $\exp\big[(\alpha+\beta)t\big]$ and integrating gives

$$P(r,t) = e^{-(\alpha+\beta)t}P(r,0) + \int_0^t \psi(t-\tau)\left[\frac{\alpha}{\alpha+\beta}P(r-1,\tau) + \frac{\beta}{\alpha+\beta}P(r+1,\tau)\right]\mathrm{d}\tau, \tag{3}$$

for $\psi(s) := (\alpha+\beta)e^{-(\alpha+\beta)s}$ [13]. This is a very rich form, with many further limiting cases and characteristics which may be investigated, for example the phenomenon of so-called *anomalous diffusion*, where motion does not resemble usual diffusion but rather is markedly super-diffusive or sub-diffusive [13]. Indeed, it is due to the complexity of this model that a wide-range of investigations may be considered for any model which is underlied by CTRW processes; our report contains some of the paradigmatic investigations and models in the modelling of polymerisation.

B. Continuous Random Walk and Diffusion

We have now constructed the continuous-time random walk, based off a time-continuous limit of the discrete random walk. While this satisfies our requirement of keeping spatial discretisation but having time continuity, it has not been fully explained why we chose a random-walk based model in the first place. The reason why we did so was due to a connection with diffusion, a key underlying biological process as that is largely the mechanism by which monomers would float in the cell. Indeed, the connection between the (fully) continuous random walk and diffusion is well known, for example being briefly touched on in the Year 2 PDE's module. We show now how this connection arises simply by taking a continuum limit of the master equation (1) for the DRW, following steps similar to the derivation in [13].

To do this we first define the space and time infinitesimals, δx and δt, and then we set

$$P_N(r) = p(x,t)\,\delta x, \quad \text{for } x = r\,\delta x, \quad t = N\,\delta t.$$

Assuming $p = 1 - p = 1/2$ (the unbiased DRW, also known as the simple random walk), we can substitute into the DRW master equation and get following equation for the continuous probability density $p(x,t)$:

$$\begin{aligned} p(x,t) &= \tfrac{1}{2}\, p(x - \delta x,\, t - \delta t) + \tfrac{1}{2}\, p(x + \delta x,\, t - \delta t) \\ &\approx \left[p(x,t) - \tfrac{\partial p}{\partial t}\, \delta t\right] + \tfrac{1}{2}\, \frac{\partial^2 p}{\partial x^2}\, \delta x^2, \end{aligned}$$

where p has been Taylor expanded to first order in δt and to second order in δx. Defining

$$D \;:=\; \lim_{\delta x, \delta t \to 0} \frac{\delta x^2}{2\,\delta t},$$

and dividing through by δt before taking the continuum limit $\delta x, \delta t \to 0$, we get the canonical Diffusion Equation with diffusivity D:

$$\frac{\partial p(x,t)}{\partial t} = D\, \frac{\partial^2 p(x,t)}{\partial x^2}. \tag{4}$$

Indeed, this Diffusion Equation was covered in the Year 2 PDE's Module, so we know that we obtain the solution

$$p(x,t) = \frac{1}{\sqrt{4\pi D t}} \int_{-\infty}^{\infty} e^{\frac{-(x-y)^2}{4Dt}}\, f(y)\, dy$$

when we have the initial condition $p(x,0) = f(x)$. But since $p(x,t)$ is a probability density we have that $f(x)$ is the initial distribution. In the majority of cases within models of polymerisation there is a deterministic initial position which we define to be $x = 0$. Hence, in this case we get that the density of the CRW is

$$p(x,t) = \frac{1}{\sqrt{4\pi D t}} e^{-x^2/4Dt}$$

which is the Fundamental Solution to the diffusion equation.

Indeed, this derivation makes it fully clear why the main focus of this project was on random-walk based models. Understanding that the underlying process affecting the process of polymerisation is randomised motion in a diffusive manner makes it clear that another limiting version of the DRW, our previously derived CTRW, is important, as it keeps the relevant dynamics but gives the continuous-time/discrete-space combination we need for modelling polymer lengths in real time.

C. First Passage Time:

A **First-Passage Time** is an important member of the family of random variables which derive themselves from an underlying stochastic process. Studying this random variable, and its distribution, is extremely useful for providing insights into the accuracy of stochastic transport and biological mechanism models [13]. We define it with respect to a measurable event $A \in \mathcal{S}$ the state space of a stochastic process, and it is simply

$$\tau_A := \inf\{t \geq 0 :\; X_t(\omega) \in A\}$$

which is clearly a well-defined random variable. As A may be any event, we do not talk about a canonical first-passage time for a stochastic process, as no such canonical event exists in generality, but rather we can fashion any first-passage time given a relevant event we are studying [13]. Given well-chosen and important events, the distribution of this random variable is critical

for problems in cell transport and diffusion [13].

For example, the **Mean First Passage Time** (also often called expected absorption time) $\mathbb{E}[\tau_A]$, where A is some semi-infinite interval $A := (L, \infty)$ and the underlying stochastic process is displacement valued, is an indicator of how fast the transportive process reaches the point defined as displacement L away from the origin of displacement (starting position). This specific MFPT defined with respect to such an event is a crucial metric, because in many biological processes there are crucial thresholds upon the reaching of which a transport process may activate a biological mechanism. Examples include:

- Setting L to be the end of a cell (considering 1D transport), upon which the MPFT is the mean time it takes for a particle to be transported across the length of the cell. This is clearly a useful concept, for example in the scenario of the transport of impulses along neurons [13].
- Setting L to be the boundary of membrane, as many processes in cell biology involve the activation of certain biological mechanisms upon certain biomolecules crossing across certain membranes; then, the MPFT $\mathbb{E}[\tau_{\{>L\}}]$ (shorthand for the MPFT as defined above) is the mean time it takes for such a biological mechanism to be activated as it is the mean time it takes for at least one biomolecule to cross the membrane [13].

Of course, we may not only consider the mean of a FPT, but also its other moments. One of these could be its variance– a huge variance for a diffusive process would entail high uncertainty over when a particle reaches a location, which may or may not be evolutionarily unviable, depending on whether the living organism requires this transport to be targeted and precise [13]. We may also construct correlators with other FPT random variables based on other important events, hence indicating whether the activation of one process may trigger or causally the activation of another process in a cell.

While the concept of an FPT is fairly intuitive, the problem of calculating its distribution is challenging, because the calculations may vary highly and usually involve familiarity with Fokker-Planck Equations or stochastic calculus [13]. For the most part of our project, this was circumvented as it was beyond the scope of difficulty. When required, for example in calculation and simulation of MPFT in the Dogterom-Leibler model for MT Catatstrophes, we assumed formulae which had been derived [13] from Fokker-Planck Equations.

3 Model I - Random walk model of actin polymerisation

3.1 Biological Background

The cytoskeleton is a dynamic structural network found in eukaryotic cells, essential for maintaining shape, enabling intracellular transport, and driving cell movement and division. It is composed of three main types of filamentous proteins: microtubules, intermediate filaments, and actin filaments. Among these, **actin filaments** are the most flexible and versatile. [6]

Actin exists in two forms:

- **G-actin**: Monomeric form that diffuses freely in the cytoplasm.
- **F-actin**: Polymerised chains of G-actin subunits, forming helical filaments.

These F-actin filaments grow and shrink dynamically through the addition and removal of G-actin monomers, and due to the inherently stochastic nature of molecular events such as binding and unbinding, a probabilistic framework is appropriate for modelling actin dynamics.

3.2 Mathematical setup

Consider, for simplicity, monomers binding or unbinding at the + end of a single stranded filament, see Figure 1 below. Suppose that the minimum length of the polymer is either a single monomer or a critical nucleus of M monomers, which for the moment is considered stable. Let $N(t), N(t) \geq 0$, denote the number of monomers added to this critical nucleus, and take the rate of monomer binding and unbinding to be π and ϵ, respectively. The probability $P_n(t)$ that the filament contains $N(t) = n$ additional monomers at time t satisfies a continuous time version of a random walk master equation [13][5], which we will be diving into below.

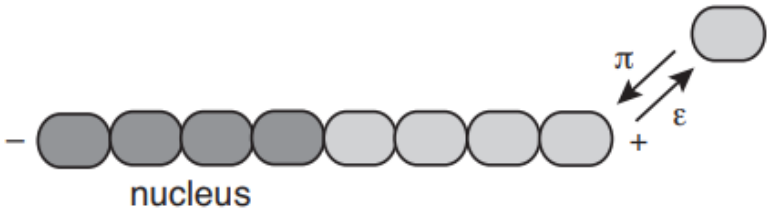


Figure 1 Simple model of F-actin undergoing polymerisation at one end. [13]

3.3 Investigating steady state solutions of the master equation

This section will be investigating the steady state solutions of the master equation, as well as using stochastic simulation to generate our own data and compare it to the solutions derived.

For $n \geq 1$, the master equation is:

$$\frac{dP_n}{dt} = \pi P_{n-1}(t) + \varepsilon P_{n+1}(t) - (\pi + \varepsilon)P_n(t) \tag{5}$$

The boundary condition at $n = 0$ is:

$$\frac{dP_0}{dt} = \varepsilon P_1(t) - \pi P_0(t)$$

We also have the normalisation condition that:

$$\sum_{n=0}^{\infty} P_n = 1$$

At a steady state, $\frac{dP_n}{dt} = 0$. The master equations become:

- For $n \geq 1$:
$$0 = \pi P_{n-1} + \epsilon P_{n+1} - (\pi + \epsilon)P_n$$
- For $n = 0$ (boundary condition):
$$0 = \epsilon P_1 - \pi P_0$$

Solution via Recurrence Relation

The steady state master equation yields a recurrence relation, we will solve it using the characteristic equation of a 2nd order recurrence relation:

$$\epsilon r^2 - (\pi + \epsilon)r + \pi = 0$$

Solving the quadratic equation:

$$r = \frac{(\pi + \epsilon) \pm \sqrt{(\pi + \epsilon)^2 - 4\epsilon\pi}}{2\epsilon}$$

$$\Rightarrow r = \frac{(\pi + \epsilon) \pm \sqrt{(\pi^2 + 2\pi\epsilon + \epsilon^2 - 4\epsilon\pi}}{2\epsilon} = \frac{(\pi + \epsilon) \pm \sqrt{(\pi - \epsilon)^2}}{2\epsilon}$$

$$\Rightarrow r = \frac{(\pi + \epsilon) \pm (\pi - \epsilon)}{2\epsilon} \Rightarrow r = \frac{\pi}{\epsilon}, 1$$

Thus, the general solution is:

$$P_n = A\left(\frac{\pi}{\epsilon}\right)^n + B$$

for some constants A and B that we need to find using the constraints established.

We can plug in our general solution into the normalisation condition as follows:

$$\sum_{n=0}^{\infty} P_n = \sum_{n=0}^{\infty} [A\left(\frac{\pi}{\epsilon}\right)^n + B] = \sum_{n=0}^{\infty} A\left(\frac{\pi}{\epsilon}\right)^n + \sum_{n=0}^{\infty} B$$

Now if B is some constant > 0, then $\lim_{x\to\infty} \sum_{n=0}^{x} B \ = \infty$, thus $B = 0$.

We now assume that $A \neq 0$ since otherwise P_n is always 0 which defies the normalisation condition. If $\pi \geq \epsilon$ then $\lim_{x\to\infty} A \sum_{n=0}^{x} (\frac{\pi}{\epsilon})^n \ = \infty$ which also defies the normalisation condition, hence we have to have that $\pi < \epsilon$.

To find A we take the sum from $n = 0$ to ∞:

$$A \sum_{n=0}^{\infty} \left(\frac{\pi}{\epsilon}\right)^n = 1 \Rightarrow \sum_{n=0}^{\infty} \left(\frac{\pi}{\epsilon}\right)^n = \frac{1}{A}$$

This geometric series converges if $\frac{\pi}{\epsilon} < 1$, and thus:

$$\sum_{n=0}^{\infty} \left(\frac{\pi}{\epsilon}\right)^n = \frac{1}{1 - \frac{\pi}{\epsilon}} = \frac{\epsilon}{\epsilon - \pi}$$

Therefore,

$$A = \frac{\epsilon - \pi}{\epsilon}$$

Final Result

The steady-state probability distribution is:

$$\boxed{P_n = \left(\frac{\pi}{\epsilon}\right)^n \left(1 - \frac{\pi}{\epsilon}\right)} \quad \text{for } \pi < \epsilon, \quad n \geq 0$$

This is a geometric distribution for the probabilities, with a steady state solution only existing when we have $\pi < \epsilon$.

3.4 Deriving a differential equation for the mean polymer length

For $n \geq 1$, the master equation is:

$$\frac{dP_n}{dt} = \pi P_{n-1}(t) + \varepsilon P_{n+1}(t) - (\pi + \varepsilon)P_n(t)$$

The boundary condition at $n = 0$ is:

$$\frac{dP_0}{dt} = \varepsilon P_1(t) - \pi P_0(t)$$

Mean Polymer Length

Define the mean polymer length as:

$$\langle N(t) \rangle = \sum_{n=0}^{\infty} n P_n(t)$$

Taking the time derivative:

$$\frac{d}{dt}\langle N(t) \rangle = \sum_{n=0}^{\infty} n \frac{dP_n}{dt}$$

For $n \geq 1$, substitute the master equation:

$$\frac{d}{dt}\langle N(t) \rangle = \sum_{n=1}^{\infty} n \left(\pi P_{n-1} + \varepsilon P_{n+1} - (\pi + \varepsilon)P_n\right)$$

Distribute the sum:

$$= \pi \sum_{n=1}^{\infty} n P_{n-1} + \varepsilon \sum_{n=1}^{\infty} n P_{n+1} - (\pi + \varepsilon) \sum_{n=1}^{\infty} n P_n$$

Evaluate each of the summation terms

First term: Let $m = n - 1 \Rightarrow n = m + 1$

$$\sum_{n=1}^{\infty} n P_{n-1} = \sum_{m=0}^{\infty} (m+1) P_m = \langle N \rangle + \sum_{m=0}^{\infty} P_m$$

$$\Rightarrow \langle N \rangle + 1$$

Second term: Let $m = n + 1 \Rightarrow n = m - 1$

$$\sum_{n=1}^{\infty} nP_{n+1}$$

$$\Rightarrow \sum_{m=0}^{\infty}(m-1)P_m - (1-1)P_1 - (0-1)P_0 = \sum_{m=0}^{\infty}(m-1)P_m + P_0$$

Using as before the fact that:

$$\sum_{m=0}^{\infty} mP_m = \langle N \rangle, \quad \sum_{m=0}^{\infty} P_m = 1$$

$$\Rightarrow \sum_{n=1}^{\infty} nP_{n+1} = \langle N \rangle - 1 + P_0$$

Third term:

$$\sum_{n=1}^{\infty} nP_n = \langle N \rangle$$

Final Expression

Putting it all together:

$$\frac{d}{dt}\langle N(t) \rangle = \pi(\langle N \rangle + 1) + \varepsilon(\langle N \rangle + P_0 - 1) - (\pi + \varepsilon)\langle N \rangle$$

Simplifying:

$$= \pi + \varepsilon P_0 - \varepsilon$$

$$\boxed{\frac{d}{dt}\langle N(t) \rangle = \pi - \varepsilon(1 - P_0(t))}$$

If $P_0 = 1$, then you get that the change in the mean polymer length is just equal to π, which would make sense since if you have no added monomers the only possible action is to add a monomer, since the stable polymer with no added monomers can't have anything removed from it. Conversely, if $P_0 = 0$, then you find that the change is just the rate of unbinding − binding, which makes sense if there is zero probability of having no added monomers at some time t.

3.5 Solving the original master equation using Euler's direct method

Overview of Euler's Method

Euler's method is a numerical technique used to solve ODEs of the form

$$\frac{dy}{dt} = f(y, t),$$

given an initial condition $y(0) = y_0$. The method proceeds by discretising time into small intervals Δt, and updating the solution iteratively as:

$$y_{n+1} = y_n + \Delta t \cdot f(y_n, t_n).$$

Application to the Master Equation

In this case, we consider a stochastic model of polymer growth and shrinkage, where the probability $P_n(t)$ of a polymer having n monomers evolves according to a master equation:

$$\frac{dP_n}{dt} = \pi P_{n-1} + \varepsilon P_{n+1} - (\pi + \varepsilon)P_n.$$

We solve this using Euler's method with the initial condition $P_n(0) = \delta_{n,10}$, binding rate $\pi = 0.4$, unbinding rate $\varepsilon = 0.7$, and time range $t \in [0, 2]$. A finite maximum polymer length $N_{\max}$ is chosen since we can't work with infinite arrays on a computer, with 25 being chosen since it is enough to give a varied set of probabilities, with the plot still being legible.

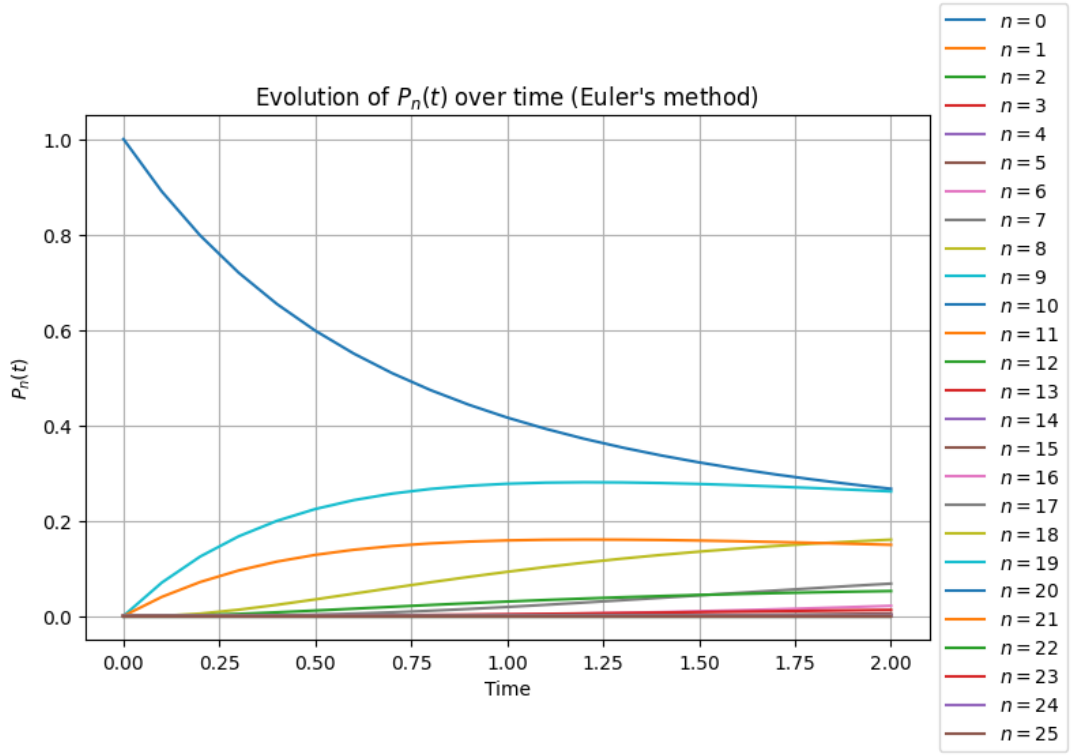


Figure 2 Plot of P_n values over time

3.6 Using the Gillespie algorithm to generate sample paths for polymer length

The Gillespie algorithm is a stochastic simulation method often used in biochemical modelling. It is ideal for systems where the discrete nature of individual events is significant, and the number of events is relatively small.

Given a set of possible reactions each with an associated rate, the algorithm is as follows [13]:

1. Calculates the total rate $R = \sum_i r_i$.
2. Samples the time until the next reaction from an exponential distribution with mean $1/R$.
3. Selects which reaction occurs based on the relative rates.

Application to Polymer Growth

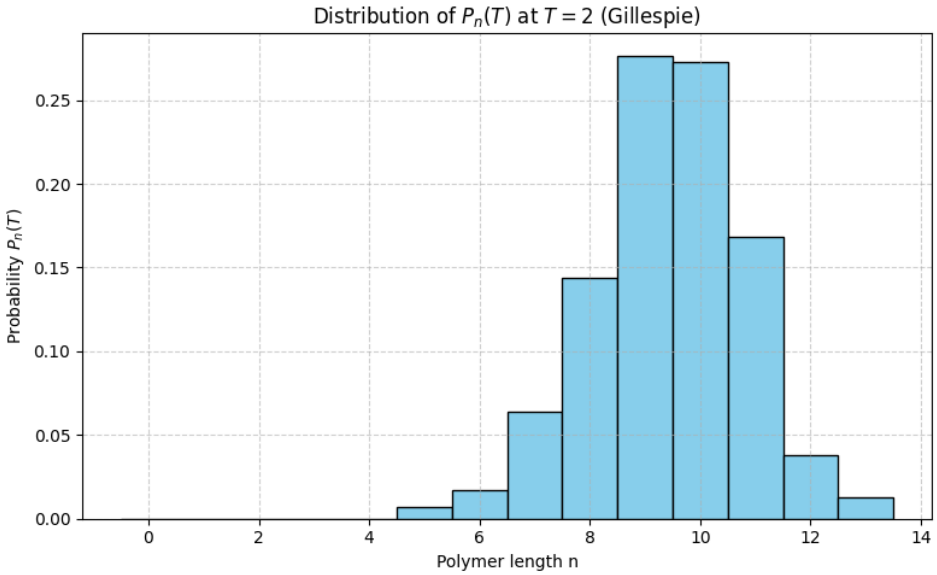
We model a single-ended polymer where monomers are added or removed with rates π and ϵ, respectively. Let $N(t)$ be the number of monomers added to a critical nucleus at time t. The two reactions are:

$$\begin{aligned} \text{Addition:} \quad & n \to n+1 \quad \text{at rate } \pi, \\ \text{Removal:} \quad & n \to n-1 \quad \text{at rate } \epsilon. \end{aligned}$$

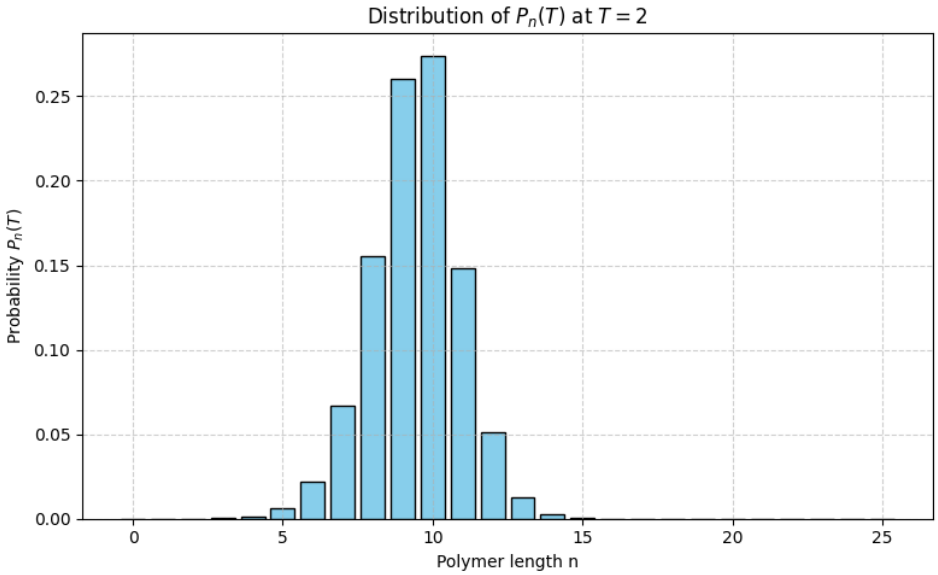
To simulate this using Gillespie:

- Start with $N(0) = 10$. This is to compare to the earlier Euler method solution of the differential equation.
- At each step, compute total rate $R = \pi + \epsilon$.
- Sample time to the next event using the exponential distribution as $\Delta t \sim \text{Exp}(R)$.
- Choose addition with probability π/R, removal with ϵ/R.
- Repeat until $t > T$.

If we use the method above to generate 1000 samples of the polymer length with the same starting conditions as with the Euler solution, we get the histogram below.

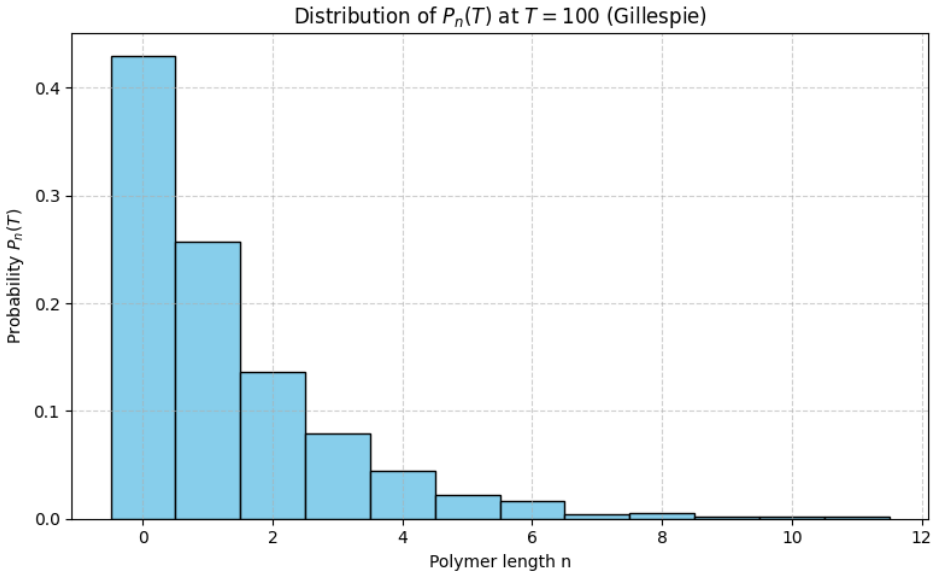


If we compare this with our Euler method solution to the ODE below we see a very similar distribution, resembling a normal distribution with mean length 10 and a probability P_n of around 0.25 at $n = 10$.

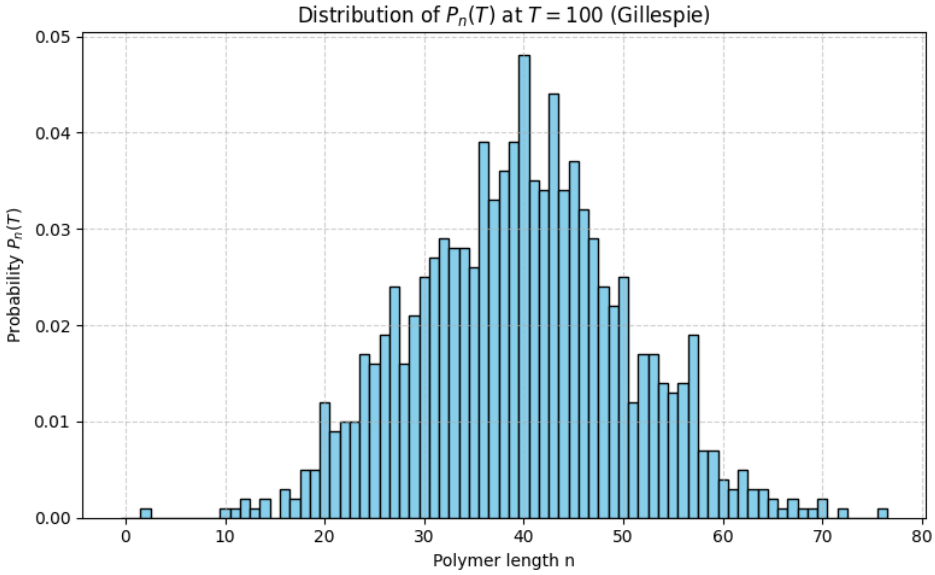


We now look at the long term behavior of the system with $\epsilon = 0.7$ and $\pi = 0.4$ using the Gillespie algorithm, which in this case is setting $T = 100$, since that should give us a much better idea of long term trends without taking too much computational power.

The plot below shows the histogram of the simulations for $T = 100$, and as we can see the probability distribution of added polymer length is tending to 0. This does make sense intuitively as in this case $\epsilon > \pi$, so we would expect over a longer time period for there to be more removal and addition, which leads to a polymer of (added) length 0.



Similarly computing the long term behaviour for $\epsilon = 0.4$ and $\pi = 0.7$ yields the histogram below.



Since in this case $\pi > \epsilon$, as $t \to \infty$ you expect the mean polymer length to also $\to \infty$, so our limited time solutions won't necessarily provide the whole picture, though it shows the data is approximately normally distributed as we would expect. If we were to run the simulation for longer time frames you would see a similar shape just with a larger mean polymer length.

4 Extension of Model I - A polymerisation ratchet model

4.1 Model Setup

Similar to the previous model, we have monomers binding or unbinding at one end of an actin filament. In this model, we assume the rate to be k_+m and k_- respectively, where m is the background concentration of monomers. We made the following modifications/assumptions

[13][4]:

- add a section of a cell membrane wall that is undergoing Brownian motion in the presence of a resistive force F due to stretching, see Fig 3.
- assume the gap x between the membrane wall and the end of the filament is sufficiently large for the addition of actin monomers.
- assume the mean time between attachments is sufficiently large so that the Brownian particle reaches thermal equilibrium.

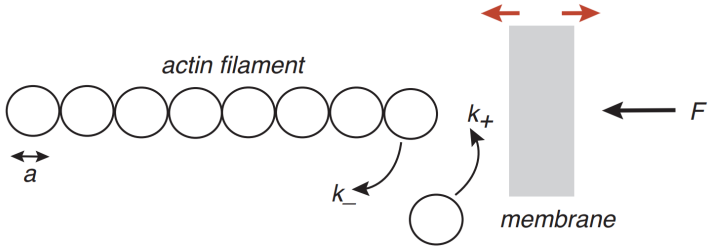


Figure 3 Cartoon of a polymerisation ratchet model [13]

Langevin equation

It is known that the distance $X(t)$ between the membrane and actin polymer tip evolves according to the Langevin equation [13]:

$$\Delta X(t) = -\frac{F}{\gamma}\Delta t + \sqrt{2D}\Delta W(t), \quad X(t) > 0 \tag{6}$$

with a reflecting boundary at $X(t) = 0$, where γ is a friction coefficient, D is the diffusivity, and $\Delta W(t)$ is a Gaussian variable with zero mean and variance $\sigma^2 = \Delta t$.

Advection-diffusion equation

The corresponding probability density for particle position satisfies the advection-diffusion equation [13]:

$$\frac{\partial p(x,t)}{\partial t} = -\frac{\partial J(x,t)}{\partial x}, \quad x > 0 \tag{7}$$

with probability flux:

$$J(x,t) = -D\frac{\partial p(x,t)}{\partial x} - \frac{F}{\gamma}p(x,t) \tag{8}$$

and the reflecting boundary condition: $J(0,t) = 0$.

4.2 Derivation of Steady State Density

A variable of interest is the steady state density $p(x,t)$. This arises when an equilibrium has been reached, and the probability density for particle position no longer changes with time. For its derivation, we set $\frac{\partial p(x,t)}{\partial t} = 0$. It follows from (7) that

$$\begin{aligned} &\frac{\partial J(x,t)}{\partial x} = 0 \\ \implies &J(x,t) = c(t) \\ \implies &J(x,t) = 0 \end{aligned}$$

where we have used the boundary condition $J(0,t) = 0$. This means that for steady state density, the probability flux $J(x,t)$ equals to 0. Using (8), we get a first order linear differential equation:

$$\frac{\partial p(x,t)}{\partial x} + \frac{F}{D\gamma}p(x,t) = 0$$

which we can solve by using the method of integrating factor:

$$\frac{d}{dx}\left(p(x,t)e^{\frac{Fx}{D\gamma}}\right) = 0$$
$$p(x,t) = C(t)e^{-\frac{Fx}{D\gamma}}$$

Since $p(x,t)$ is a probability density function on the domain $x \in (0,\infty]$, it must integrate to 1:

$$\begin{aligned}
C(t)\int_0^\infty e^{-\frac{Fx}{D\gamma}}dx &= 1 \\
\left[\frac{e^{-\frac{Fx}{D\gamma}}}{-\frac{F}{D\gamma}}\right]_0^\infty &= \frac{1}{C(t)} \\
\frac{-1}{-\frac{F}{D\gamma}} &= \frac{1}{C(t)} \\
\implies C(t) &= \frac{F}{D\gamma} \\
\implies p(x,t) = p(x) &= \frac{F}{D\gamma}e^{-\frac{Fx}{D\gamma}}
\end{aligned}$$

By using the Einstein relation $D\gamma = k_B T$ [13], where k_B is the Boltzmann constant and T is the temperature in Kelvin, we get a final expression for $p(x,t)$:

$$p(x) = \frac{F}{k_B T}e^{\frac{-Fx}{k_B T}} \tag{9}$$

4.3 Analysis of the mean polymerisation velocity v

We have an estimate of the mean polymerisation velocity v to be

$$v = a\left[k_+ m P(x > a) - k_-\right] \tag{10}$$

where a is the size of a monomer [13]. By using (9), we first derive an expression for $P(x > a)$:

$$\begin{aligned}
P(x > a) &= 1 - P(x < a) \\
&= 1 - \int_0^a \frac{F}{k_B T}e^{\frac{-Fx}{k_B T}}dx \\
&= 1 - \frac{F}{k_B T}\left[\frac{e^{\frac{-Fx}{k_B T}}}{\frac{-F}{k_B T}}\right]_0^a \\
&= 1 + \left[e^{\frac{-Fa}{k_B T}} - 1\right] \\
&= e^{\frac{-Fa}{k_B T}}
\end{aligned}$$

It is also known that for an equilibrium temperature T, we have

$$\frac{k_+ m}{k_-} = e^{\Delta G/k_B T} \tag{11}$$

where ΔG is the binding energy when a monomer binds to a polymer [13]. Note that (11) implies that a large, positive ΔG corresponds to faster polymer growth.

Using the expression for $P(x > a)$, combined with (10) and (11) to get:

$$\begin{aligned} v &= a[k_+ mP(x > a) - k_-] \\ &= a[k_- e^{\frac{\Delta G}{k_B T}} P(x > a) - k_-] \\ &= ak_-[e^{\frac{\Delta G}{k_B T}} P(x > a) - 1] \\ &= ak_-[e^{\frac{\Delta G}{k_B T}} e^{\frac{-Fa}{k_B T}} - 1] \\ &= ak_-[e^{\frac{\Delta G - Fa}{k_B T}} - 1] \end{aligned}$$

We would like to investigate how the mean polymerisation velocity v changes with F (recall that F is a resistive force applied on the cell membrane wall). Without loss of generality, we set $\Delta G/k_B T = 6$, and plot v/ak_- as a function of $Fa/k_B T$:

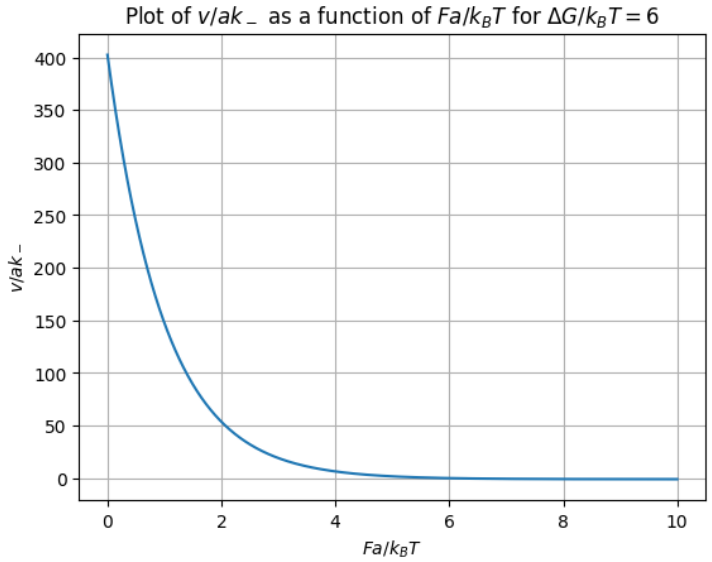


Figure 4 A plot to investigate the relationship between v and F

From Fig 4, we can see that as F increases, v decreases. This result can be interpreted in a physical sense:

- when $Fa < \Delta G$: v is positive, polymerisation is favourable because the work done by F is less than the binding energy.
- when $Fa = \Delta G$: $v = 0$, the work done by F is balanced by the binding energy, so polymerisation stops.
- when $Fa > \Delta G$: v becomes negative, this means the force F is large enough for depolymerisation to occur.

5 Model II - The two-state model of the microtubule catastrophe

5.1 Background

Microtubules are among the most important structural components of a biological cell [7]. They can be thought of as forming a dynamic scaffolding that both shapes the structure of a cell and powers essential processes. In particular, alongside providing structural rigidity, they serve as rigid "tracks" for motor proteins to transport important biomolecules; both of these processes are crucial to the function and regulation of the cell [13]. Equally importantly to their uses in rigid states, they can also rapidly assemble and disassemble, which is vital for the regulation of the structure of a cell, because it provides dynamic flexibility [7].

It is precisely this assembly-disassembly process which we study in our second model of polymerisation [13]. In particular, microtubules undergo a process called *microtubule catastrophe*, where microtubules which previously were growing suddenly switch to a phase of shrinking. Microtubules grow by the addition of GTP-tubulin subunits add on to the microtubule's plus end, which form a stabilizing "GTP cap". That cap is lost if GTP is been hydrolyzed to GDP faster than new subunits can be added—the GDP-tubulin: hence, the speed of polymerisation (as opposed to depolymerisation via hydrolysation) is critical [13]. Upon the hydrolysation of the GTP-cap, the lattice becomes unstable and the filament undergoes catastrophe, which is the technical term for rapidly disassembling and shrinking of microtubules [13]. Conversely, if enough GTP-tubulin rebinds, the microtubule can be "rescued" and switch back into a growth phase [13]. It is this balance of growth, catastrophe and rescue which underlies how cells remodel their cytoskeleton so dynamically [7].

5.2 The 2-State Dogterom-Leibler Model

[2] [10] In modelling the MT Catastrophe, we used the classic 2-state RW model, the Dogterom-Leibler model of the MT catastrophe. This takes the form of the two partial differential equations:

$$\frac{\partial p^+}{\partial t} = -v^+ \frac{\partial p^+}{\partial x} - k_c p^+ + k_r p^-$$
$$\frac{\partial p^-}{\partial t} = v^- \frac{\partial p^-}{\partial x} - k_r p^- + k_c p^+$$

which govern the growing $(+)$ state and shrinking $(-)$ state respectively. This equation explicitly models the time evolution of the crucial quantity

$$p^{\pm}(x,t)$$

which is the time-evolving probability density function over space for the $\pm$ states. We understand it to be a spatial-valued density, but which is different at different times. The additional parameters are

$$v^{\pm} \quad \text{the average growth and shrink speed}$$

and

$$k_c,\ k_r \quad \text{the catastrophe and rescue rates}$$

Our boundary condition is

$$v^+ p^+(0,t) = v^- p^-(0,t)$$

this is because we are treating $x = 0$ as the fixed ('leftmost') end of the microtubule; hence, we may not have shrinking beyond $x = 0$, requiring this reflecting boundary condition.

Steady-State Solution

We begin by solving the steady-state equations. That, is, we set

$$\frac{\partial p^+}{\partial t} = 0 = \frac{\partial p^-}{\partial t}$$

Then, the equations reduce to

$$0 = -v^+ \frac{\partial p^+}{\partial x} - k_c p^+ + k_r p^- \tag{12}$$

$$0 = v^- \frac{\partial p^-}{\partial x} - k_r p^- + k_c p^+ \tag{13}$$

but indeed we are solving a steady state equation so the partial derivatives became ordinary position derivatives. Thus we get the linear system:

$$\begin{pmatrix} \frac{dp^+}{dx} \\ \frac{dp^-}{dx} \end{pmatrix} = \begin{pmatrix} -k_c/v^+ & k_r/v^+ \\ -k_c/v^- & k_r/v^- \end{pmatrix} \begin{pmatrix} p^+ \\ p^- \end{pmatrix}$$

As seen in the Year 2 ODEs module, since this equation has constant coefficients and is a linear system, we may solve this system by use of the matrix exponential method. Defining $\mathbf{p} = (p^+, p^-)^T$, we have that this is

$$\dot{\mathbf{p}} = A\mathbf{p} \quad \text{for} \quad A := \begin{pmatrix} -k_c/v^+ & k_r/v^+ \\ -k_c/v^- & k_r/v^- \end{pmatrix}$$

where the dot indicates differentiation wrt x. To do this, we first find the eigenvalues of the A. The characteristic polynomial of A is

$$\begin{aligned} c_A(x) &= (x + \frac{k_c}{v^+})(x - \frac{k_r}{v^-}) + \frac{k_c k_r}{v^+ v^-} = x^2 + \left(\frac{k_c}{v^+} - \frac{k_r}{v^-}\right)x \\ &= x\left(x + \frac{k_c v^- - k_r v^+}{v^+ v^-}\right) \end{aligned}$$

so indeed the eigenvalues are the roots

$$\lambda \in \{0, \ \frac{k_r v^+ - k_c v^-}{v^+ v^-}\}$$

and again k_c, k_r, v^+, v^- are real constants. Hence, we clearly have the that Jordan Normal Form of A is

$$J(A) = \begin{pmatrix} c & 0 \\ 0 & 0 \end{pmatrix}$$

for $c := \frac{k_r v^+ - k_c v^-}{v^+ v^-}$. Then, the matrix exponential of A is

$$e^{Ax} = T e^{Jx} T^{-1} = T \begin{pmatrix} e^{cx} & 0 \\ 0 & 1 \end{pmatrix} T^{-1}$$

for T the change of basis matrix. T is simple to find, as $J(A) \equiv J$ is a diagonal matrix, so we only need to find eigenvectors. Indeed,

$$A \begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix} \implies \frac{k_r y - k_c x}{v^+} = 0 = \frac{k_r y - k_c x}{v^-}$$

which is

$$k_c x = k_r y \implies y = \frac{k_c}{k_r} x$$

so this gives an eigenvector corresponding to $\lambda = 0$ as

$$\begin{pmatrix} 1 \\ k_c/k_r \end{pmatrix}$$

Similarly

$$A\begin{pmatrix} x \\ y \end{pmatrix} = c\begin{pmatrix} x \\ y \end{pmatrix} \implies \frac{k_r y - k_c x}{cv^+} = x \quad \text{and} \quad \frac{k_r y - k_c x}{cv^-} = y$$

so we get

$$y = \frac{cv^+ + k_c}{k_r} x$$

giving the eigenvector

$$\begin{pmatrix} 1 \\ (cv^+ + k_c)/k_r \end{pmatrix}$$

so the change of basis matrix is

$$T = \begin{pmatrix} 1 & 1 \\ \frac{cv^+ + k_c}{k_r} & \frac{k_c}{k_r} \end{pmatrix}$$

but $c = \frac{k_r v^+ - k_c v^-}{v^+ v^-}$ so

$$\frac{cv^+ + k_c}{k_r} = \frac{\frac{k_r v^+ - k_c v^-}{v^-} + k_c}{k_r} = \frac{v^+}{v^-}$$

so the change of basis matrix is

$$T = \begin{pmatrix} 1 & 1 \\ \frac{v^+}{v^-} & \frac{k_c}{k_r} \end{pmatrix}$$

which has inverse

$$T^{-1} = \frac{1}{(\frac{k_c v^- - k_r v^+}{k_r v^-})} \begin{pmatrix} \frac{k_c}{k_r} & -1 \\ -\frac{v^+}{v^-} & 1 \end{pmatrix}$$

hence giving that the matrix exponential of A as

$$\begin{aligned} e^{Ax} = Te^{Jx}T^{-1} &= \left(\frac{k_r v^-}{k_c v^- - k_r v^+}\right) \begin{pmatrix} 1 & 1 \\ \frac{v^+}{v^-} & \frac{k_c}{k_r} \end{pmatrix} \begin{pmatrix} e^{cx} & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \frac{k_c}{k_r} & -1 \\ -\frac{v^+}{v^-} & 1 \end{pmatrix} \\ &= \left(\frac{k_r v^-}{k_c v^- - k_r v^+}\right) \begin{pmatrix} 1 & 1 \\ \frac{v^+}{v^-} & \frac{k_c}{k_r} \end{pmatrix} \begin{pmatrix} \frac{k_c}{k_r} e^{cx} & -e^{cx} \\ -\frac{v^+}{v^-} & 1 \end{pmatrix} \\ &= \left(\frac{k_r v^-}{k_c v^- - k_r v^+}\right) \begin{pmatrix} \frac{k_c}{k_r} e^{cx} - \frac{v^+}{v^-} & 1 - e^{cx} \\ \frac{k_c v^+}{k_r v^-}(e^{cx} - 1) & \frac{k_c}{k_r} - \frac{v^+}{v^-} e^{cx} \end{pmatrix} \\ &= \left(\frac{1}{k_c v^- - k_r v^+}\right) \begin{pmatrix} k_c v^- e^{cx} - k_r v^+ & k_r v^- - k_r v^- e^{cx} \\ k_c v^+ (e^{cx} - 1) & k_c v^- - k_r v^+ e^{cx} \end{pmatrix} \end{aligned}$$

Using, this, we have that the steady state solution is found by

$$\mathbf{p}(x) = e^{Ax}\mathbf{p}(0)$$

But our reflecting boundary condition is

$$v^+ p^+(0,t) = v^- p^-(0,t)$$

so indeed for the steady state solution we have

$$p^-(0) = \frac{v^+}{v^-} p^+(0)$$

whence we get that

$$\mathbf{p}(0) = A\begin{pmatrix} 1 \\ \frac{v^+}{v^-} \end{pmatrix}$$

for some scaling constant A, which requires further boundary conditions to fix. Hence, our final general solution is

$$\begin{aligned}
\mathbf{p}(x) = \begin{pmatrix} p^+(x) \\ p^-(x) \end{pmatrix} &= A\left(\frac{1}{k_c v^- - k_r v^+}\right)\begin{pmatrix} k_c v^- e^{cx} - k_r v^+ & k_r v^- - k_r v^- e^{cx} \\ k_c v^+(e^{cx}-1) & k_c v^- - k_r v^+ e^{cx} \end{pmatrix}\begin{pmatrix} 1 \\ \frac{v^+}{v^-} \end{pmatrix} \\
&= A\left(\frac{1}{k_c v^- - k_r v^+}\right)\begin{pmatrix} (k_c v^- e^{cx} - k_r v^+) + (k_r v^+ - k_r v^+ e^{cx}) \\ k_c - (k_c (v^+)^2/v^-)e^{cx} \end{pmatrix} \\
&= A\left(\frac{1}{k_c v^- - k_r v^+}\right)\begin{pmatrix} (k_c v^- - k_r v^+)e^{cx} \\ k_c v^+ - (k_c (v^+)^2/v^-)e^{cx} \end{pmatrix} \\
&= A e^{cx}\begin{pmatrix} 1 \\ \frac{k_c v^+ - \frac{k_r (v^+)^2}{v^-}}{k_c v^- - k_r v^+} \end{pmatrix} \\
&= A e^{cx}\begin{pmatrix} 1 \\ \frac{v^+}{v^-} \end{pmatrix}
\end{aligned}$$

where A is a scaling constant to be determined by further boundary conditions.

5.3 Existence of General Solution

It is not so clear at this stage whether our model matches biological intuition. To tackle this, we consider a reasonable test of validity. In particular, we expect the steady-state solution should be valid if and only if we have the following condition on the mean speed of microtubular growth V:

$$V := \frac{k_r v^+ - k_c v^-}{k_c + k_r} < 0$$

[13]. This is true because otherwise we expect the microtubule to be in a consistent growth phase with very few catastrophes, thereby inhibiting the existence of a steady state solution [13]. Indeed, we can show this quite easily. This is because for the density

$$p_\Sigma(x) := p^+(x) + p^-(x)$$

we must have that the integral over the semi-infinite domain of this density does not diverge, since our microtubule is defined on a semi-infinite domain and indeed our probability must integrate to 1 over the domain of definition. Hence we in particular we require

$$\int_0^\infty e^{cx} < \infty$$

Then, this occurs if and only if $c < 0$. But

$$c \equiv \frac{k_r v^+ - k_c v^-}{v^+ v^-}$$

so

$$c < 0 \iff k_r v^+ - k_c v^- < 0$$

in particular, this then clearly means, after dividing both sides by $(k_r + k_c) > 0$, that

$$c < 0 \iff V < 0$$

Hence, we have shown that as required our general solution only exists if the mean growth velocity is negative, which matches biological intuition and indeed shows when a rough balance between catastrophe and rescue is achieved.

5.4 The 3-State Model of Constrained MT Growth-Catastrophe

In the introduction to this report, it was mentioned how heterogenous cell geometries affect the diffusive process assumed in the RW models. We now reach one simpler example of imposing such a geometry on the Dogterom-Leibler equations. In particular, we consider the assumption that there is a sticky wall at $x = L$. We first restate the relevant DL equations:

$$\frac{\partial p^+}{\partial t} = -v^+ \frac{\partial p^+}{\partial x} - k_c p^+ + k_r p^- \tag{14}$$

$$\frac{\partial p^-}{\partial t} = v^- \frac{\partial p^-}{\partial x} - k_r p^- + k_c p^+ \tag{15}$$

However, we now also must factor in the sticky wall at $x = L$ (preventing growth beyond that point). We do this by introducing a third state, denoted b, which is governed by

$$v^- p^-(L,t) = r_b p_b(t) \tag{16}$$

$$\frac{dp_b}{dt} = v^+ p^+(L,t) - r_b p_b(t) \tag{17}$$

for r_b the rate of the shrinking which occurs when the microtubule reaches length $x = L$ [11]. Indeed, our entire solution must be confined to the spatial bounds $[0, L]$. We once again look for a steady state solution. To do this, we defined our desired solution to be the vector of respective probabilities

$$\tilde{\mathbf{p}}(x) := \begin{pmatrix} p^+(x) \\ p^-(x) \\ p_b(x) \end{pmatrix}$$

Then, since p_b is solely time-dependent (as it is defined for a fixed position $x = L$ so has no position dependence), a steady state solution must entail that p_b is constant, as it is unchanging in time. So we may write under this assumption that

$$v^- p^-(L) = r_b p_b \implies v^- p^-(L) = v^+ p^+(L) = r_b p_b$$

Clearly, the steady state solution for the Dogterom Leibler model on a semi-infinite unbounded domain still solves the same differential equations constituting the models. Thus, the task is merely to incorporate the boundary conditions at $x = L$. First of all, we note that it is clear that our original solution for $p^+(x)$ and $p^-(x)$ in the unbounded case satisfy the condition

$$v^- p^-(x) = v^+ p^+(x) \quad \forall\, x$$

as is clear from inspecting the solutions. So in particular,

$$v^- p^-(L) = v^+ p^+(L)$$

does indeed hold. Therefore,

$$v^- p^-(L) = v^+ p^+(L) = r_B p_B \implies P_B = \frac{v^+}{r_B} p^+(L) = A \frac{v^+}{r_B} e^{cL}$$

for c defined as previously. The true difference to our solution is that the introduction of the boundary conditions means that the global normalisation constant A must be affected. We have that

$$p_+(x) = A\, e^{cx}, \tag{18}$$

$$p_-(x) = \alpha\, A\, e^{cx}, \qquad \alpha \equiv \frac{v^+}{v^-}. \tag{19}$$

$$P_b = \frac{v^+}{r_b}\, p_+(L) = \frac{v^+}{r_b}\, A\, e^{cL}. \tag{20}$$

However, our normalisation condition has changed. Indeed, the probability that the microtubule tip has position in $(0, L)$ must be 1! Therefore, we have a disjoint partition of possible states:

$$p^+(x), \quad x \in (0, L) \quad ; \quad p^-(x), \quad x \in (0, L) \quad ; \quad p_B$$

which therefore means we have the normalisation condition

$$\int_0^L \big(p_+(x) + p_-(x)\big)\, dx \;+\; p_B \;=\; 1. \tag{21}$$

We can then solve this, as follows:

$$\int_0^L \big(p_+ + p_-\big)\, dx = A\,(1+\alpha) \int_0^L e^{cx}\, dx \tag{22}$$

$$= A\,(1+\alpha) \left[\frac{e^{cx}}{c}\right]_0^L \tag{23}$$

$$= A\,(1+\alpha)\, \frac{e^{cL} - 1}{c}. \tag{24}$$

Therefore,

$$A\,(1+\alpha)\, \frac{e^{cL} - 1}{c} \;+\; \frac{v^+}{r_b}\, A\, e^{cL} \;=\; 1. \tag{25}$$

which gives

$$A = \frac{1}{(1+\alpha)\, \dfrac{e^{cL} - 1}{c} \;+\; \dfrac{v^+}{r_b}\, e^{cL}}$$

and therefore, substituting the full form of $\alpha = \frac{v^+}{v^-}$, this is

$$A = \frac{1}{\dfrac{(v^- + v^+)(e^{cL} - 1)}{cv^-} \;+\; \dfrac{v^+}{r_b}\, e^{cL}}$$

So substituting into our form of the solution, we finally get a steady state solution:

$$\tilde{\mathbf{p}}(x) = \begin{pmatrix} p^+(x) \\ p^-(x) \\ p_B(x) \end{pmatrix} = \frac{1}{\dfrac{(v^- + v^+)(e^{cL} - 1)}{cv^-} \;+\; \dfrac{v^+}{r_b}\, e^{cL}} \begin{pmatrix} e^{cx} \\ \frac{v^+}{v^-} e^{cx} \\ \frac{v^+}{r_b} e^{cL} \end{pmatrix}$$

Indeed, there are other ways to solve this problem of a constrained geometry [8] which do not involve a 3-state approach, but the result is the same as in our approach, which is a method adapted from the approach in [11].

5.5 Mean Passage Times and Survival Probabilities

Throughout we use the parameters

$$V = \frac{k_r v^+ - k_c v^-}{k_c + k_r}, \qquad D = \frac{v^+ v^-}{k_c + k_r}.$$

which are clearly related to the previously derived solutions ($c = V/D$ is the rate of the exponential in the solution).

We let

$$q_{\pm}(x,t\,|\,y,m) = p\big(x,\pm,t\,\big|\,y,m,0\big), \qquad m\in\{+,-\},$$

be the *backward* transition densities, that is, the probability density for being at x in state $\pm$ at time t given that the process started at y in state m at $t=0$. This is relevant to us as we are considering first passage times and survival probabilities. The governing backward equations ((3.6) in the notes) were derived in the notes to be:

$$\frac{\partial q_+}{\partial t} = v_+\frac{\partial q_+}{\partial y} - k_c[q_+ - q_-], \tag{B1a}$$

$$\frac{\partial q_-}{\partial t} = -v_-\frac{\partial q_-}{\partial y} + k_r[q_+ - q_-], \tag{B1b}$$

with the additional boundary conditions (3.7)

$$q_-(0,t) = 0, \qquad q_+(L,t) = 0.$$

First we need to show that the mean first passage time (MFPT) and survival probability are related according to

$$\tau_m(y) := \mathbb{E}[T_m(y)] = \int_0^\infty S_m(y,t)dt.$$

By definition of expectation, we know that

$$\tau_m(y) := \mathbb{E}[T_m(y)] = \int_0^\infty t\cdot f_m(y,t)dt,$$

where $f_m(y,t)$ is the probability density function of the first passage time of the MT.
Since $S_m(y,t) = \int_0^L p(x,t|y,m,0)dx$ represents the probability that the MT hasn't reached $x=L$ by the time t, then $\mathbb{P}(T_m(y)>t) = S_m(y,t)$ so the CDF of T_m is

$$F_m(t) = \mathbb{P}(T_m(y)\le t) = 1 - S_m(y,t).$$

Hence,

$$f_m(y,t) = \frac{d}{dt}F_m(t) = \frac{d}{dt}(1-S_m(y,t)) = -\frac{d}{dt}S_m(y,t),$$

Therefore,

$$\tau_m(y) = \int_0^\infty t\cdot f_m(y,t)dt = [-tS_m(y,t)]_0^\infty + \int_0^\infty S_m(y,t)dt,$$

and since as $t\to\infty$, $S_m(y,t)\to 0$ so we arrive at the required result

$$\tau_m(y) = \int_0^\infty S_m(y,t)dt.$$

To derive the required pair of equations for the MFPTs, we first begin with the backward equation, letting $q_m(y,t) = p(x,t|y,m,0)$ for fixed x,

$$\frac{\partial q_+}{\partial t} = v_+\frac{\partial q_+}{\partial y} - k_c[q_+ - q_-],$$

$$\frac{\partial q_-}{\partial t} = -v_-\frac{\partial q_-}{\partial y} + k_r[q_+ - q_-],$$

with the boundary conditions

$$q_-(0,t) = 0, \qquad q_+(L,t) = 0.$$

Then defining

$$\tau_+(y) = \int_0^\infty q_+(y,t)dt, \quad \tau_-(y) = \int_0^\infty q_-(y,t)dt,$$

and using the definition of q_m as survival probabilities that begin at 1 and decay to 0, we can find the integrals from 0 to ∞ of each of the terms in the backward equation as

$$\int_0^\infty v_+ \frac{\partial q_+}{\partial y}dt = v_+ \frac{d\tau_+}{dy}, \quad \int_0^\infty k_c(q_+ - q_-)dt = k_c(\tau_+ - \tau_-),$$

$$\int_0^\infty v_- \frac{\partial \tau_-}{\partial y}dt = v_- \frac{d\tau_-}{dy}, \quad \int_0^\infty k_r(q_+ - q_-)dt = k_r(\tau_+ - \tau_-).$$

Looking at

$$\int_0^\infty \frac{\partial q_+}{\partial t}dt = q_+(y,\infty) - q_+(y,0), \quad \int_0^\infty \frac{\partial q_-}{\partial t}dt = q_-(y,\infty) - q_-(y,0).$$

Since q represents the survival probability, that being the probability of not being absorbed at the boundary $x = L$ for time t, we see that

$$q_+(y,\infty) = q_-(y,\infty) = 0.$$

Then $q_+(y,0) = 1$ since at time 0 the survival probability is 1. However, looking at q_-, since here we are in the $-$ state, we are moving away from the absorbing boundary so the survival probability here is 0 as we have not 'started the clock of time t' so we have $q_-(y,0) = 0$.
Now looking at boundary conditions,

$$\tau_+(L) = \int_0^\infty q_+(L,t)dt = \int_0^\infty 0dt = 0.$$

Since at $y = 0$, we are at the reflecting boundary, if you start in the $-$ state, you are immediately reflected. So at $y = 0$, starting in the $-$ state is equivalent to starting in the $+$ state so $q_+(0,t) = q_-(0,t) \implies \tau_+(0) = \tau_-(0)$. Now putting all of this together we get the required pair of equations for the MFPTs:

$$-1 = v_+ \frac{d\tau_+}{dy} - k_c(\tau_+ - \tau_-), \quad 0 = -v_- \frac{d\tau_-}{dy} + k_r(\tau_+ - \tau_-),$$

together with the boundary conditions

$$\tau_+(0) = \tau_-(0), \quad \tau_+(L) = 0.$$

Solution of the coupled ODEs

First we need to combine the two equations into one to solve for τ_-,

$$-1 = v_+ \frac{d\tau_+}{dy} - k_c(\tau_+ - \tau_-), \quad 0 = -v_- \frac{d\tau_-}{dy} + k_r(\tau_+ - \tau_-),$$

$$\implies \tau_+ - \tau_- = \frac{v_-}{k_r}\frac{d\tau_-}{dy} \implies -1 = v_+ \frac{d\tau_+}{dy} - \frac{k_c v_-}{k_r}\frac{d\tau_-}{dy}$$

By differentiating the second of the pair of equations

$$\frac{d}{dy}(\tau_+ - \tau_-) = \frac{v_-}{k_r}\frac{d^2\tau_-}{dy^2} \implies \frac{d\tau_+}{dy} + \frac{v_-}{k_r}\frac{d^2\tau_-}{dy^2}$$

$$\implies -1 = \left(v_+ - \frac{k_c v_-}{k_r}\right)\frac{d\tau_-}{dy} + \frac{v_+ v_-}{k_r}\frac{d^2\tau_-}{dy^2}$$

Now plugging in $V = \frac{k_r v_+ - k_c v_-}{k_c + k_r}$ and $D = \frac{v_+ v_-}{k_c + k_r}$, we find the ODE for τ_- is

$$D\frac{d^2\tau_-}{dy^2} + V\frac{d\tau_-}{dy} = -\frac{k_r}{k_c + k_r}$$

First we find the solution to $D\frac{d^2\tau_-}{dy^2} + V\frac{d\tau_-}{dy} = 0$ as

$$\tau_-(y) = -\frac{D}{V}Ce^{-\frac{V}{D}y} + C_2$$

Now we find a particular solution using a linear ansatz letting $\tau_- = \alpha y + \beta$ so $\frac{d\tau_-}{dy} = \alpha$, $\frac{d^2\tau_-}{dy^2} = 0$ so solving for α gives $\alpha = -\frac{k_r}{V(k_c+k_r)}$. This gives a general solution of τ_- as

$$\tau_-(y) = B - \frac{D}{V}Ce^{-\frac{V}{D}y} - \frac{k_r}{V(k_c + k_r)}y,$$

where $B = \beta + C_2$. Applying the initial and boundary conditions, noting from earlier that $\tau_+ = \tau_- + \frac{v_-}{k_r}\tau_-'$ so since $\tau_+(0) = \tau_-(0)$,

$$\tau_+(0) = \tau_-(0) + \frac{v_-}{k_r}\tau_-'(0) = \tau_-(0) \implies \tau_-'(0) = 0.$$

Also,

$$\tau_+(L) = 0 \implies \tau_-(L) + \frac{v_-}{k_r}\tau_-'(L) = 0.$$

Now differentiating our general solution,

$$\tau_-'(y) = Ce^{-\frac{V}{D}y} - \frac{k_r}{V(k_c + k_r)}.$$

- at $y = 0$, $\tau_-'(0) = 0$ so
$$C = \frac{k_r}{V(k_c + k_r)}$$
- at $y = L$, $\tau_-(L) + \frac{v_-}{k_r}\tau_-'(L) = 0$ so
$$0 = B - \frac{D}{V}Ce^{-\frac{V}{D}L} - \frac{k_r}{V(k_c + k_r)}L + \frac{v_-}{k_r}\left(Ce^{-\frac{V}{D}L} - \frac{k_r}{V(k_c + k_r)}\right)$$
$$\implies Ce^{-\frac{V}{D}L}\left(\frac{v_-}{k_r} - \frac{D}{V}\right) - \frac{k_r}{V(k_c + k_r}\left(\frac{v_-}{k_r} + L\right) + B = 0$$
$$\implies B = \frac{k_r}{V(k_c + k_r)}\left(\frac{v_-}{k_r} + L\right) - Ce^{-\frac{V}{D}L}\left(\frac{v_-}{k_r} - \frac{D}{V}\right)$$

Therefore

$$\tau_-(y) = \frac{k_r}{V(k_c + k_r)}\left(\frac{v_-}{k_r} + L\right) - \frac{k_r}{V(k_c + k_r)}e^{-\frac{V}{D}L}\left(\frac{v_-}{k_r} - \frac{D}{V}\right) - \frac{D}{V}\frac{k_r}{V(k_c + k_r)}e^{-\frac{V}{D}y} - \frac{k_r}{V(k_c + k_r)}y$$

Now we can rearrange this to get it into the required form using the function $I(y)$ defined as:

$$I(y) := \frac{D}{V}y - \left(\frac{D}{V}\right)^2\left(1 - e^{-\frac{V}{D}y}\right)$$

Looking term by term,

- linear y term:
$$\frac{k_r}{V(k_c+k_r)} = \frac{k_r}{v_+v_-}\frac{v_+v_-}{V(k_c+k_r)} = \frac{k_r}{v_+v_-}\frac{D}{V}$$
- linear L term:
$$\frac{k_r}{V(k_c+k_r)} = \frac{1}{v_+}\frac{V(k_c+k_r)+k_cv_-}{V(k_c+k_r)} = \frac{1}{v_+}\left(\frac{k_cD}{v_+V}+1\right) = \frac{k_c}{v_+}\frac{1}{v_+}\frac{D}{V}+\frac{1}{v_+}$$
- constant term:
$$\frac{v_-}{V(k_c+k_r)} = \frac{D}{V}\frac{1}{v_+} = \left(\frac{D}{V}\right)^2\frac{1}{v_+}\left(\frac{k_rv_+-k_cv_-}{v_+v_-}\right) = -\frac{k_c}{v_+}\frac{1}{v_+}\left(\frac{D}{V}\right)^2+\frac{k_r}{v_+v_-}\left(\frac{D}{V}\right)^2$$
- exponential L term:
$$-\frac{k_r}{V(k_c+k_r)}\left(\frac{v_-}{k_r}-\frac{D}{V}\right) = \frac{Dk_r}{V^2(k_c+k_r)}-\frac{v_-}{V(k_c+k_r)}$$
Then using what we have just found from the constant term,
$$\left(\frac{D}{V}\right)^2\frac{k_r}{v_+v_-}-\left(-\frac{k_c}{v_+}\frac{1}{v_+}\left(\frac{D}{V}\right)^2+\frac{k_r}{v_+v_-}\left(\frac{D}{V}\right)^2\right) = \frac{k_c}{v_+}\frac{1}{v_+}\left(\frac{D}{V}\right)^2$$
- exponential y term:
Using a section of the simplification from the previous exponential L term, we see that
$$-\frac{D}{V}\frac{k_r}{V(k_c+k_r)} = -\frac{k_r}{v_+v_-}\left(\frac{D}{V}\right)^2$$

Now combining all of these rearrangements, we arrive at
$$\tau_-(y) = \frac{k_c}{v_+}\left(\frac{1}{v_+}\left(\frac{D}{V}L-\left(\frac{D}{V}\right)^2\left(1-e^{-\frac{V}{D}L}\right)\right)+\frac{L}{k_c}\right)$$
$$-\frac{k_r}{v_+v_-}\left(\frac{D}{V}y-\left(\frac{D}{V}\right)^2\left(1-e^{-\frac{V}{D}y}\right)\right)$$
and using the $I(y)$ function defined above we finally reach the required form of the result
$$\tau_-(y) = \frac{k_c}{v_+}\left[\frac{I(L)}{v_+}+\frac{L}{k_c}\right]-\frac{k_rI(y)}{v_+v_-}.$$
To find the solution to $\tau_+(y)$, we recall that
$$\tau_+ = \tau_- + \frac{v_-}{k_r}\tau_-',$$
so we can simply substitute in our solution for $\tau_-(y)$ to find our result.
$$\tau_-'(y) = -\frac{k_r}{v_+v_-}\left(\frac{D}{V}-\left(\frac{D}{V}\right)^2\left(\frac{V}{D}e^{-\frac{V}{D}y}\right)\right)$$
$$= \frac{k_r}{V(k_c+k_r)}\left(e^{-\frac{V}{D}y}-1\right)$$
So
$$\tau_+(y) = \frac{k_c}{v_+}\left[\frac{I(L)}{v_+}+\frac{L}{k_c}\right]-\frac{k_rI(y)}{v_+v_-}+\frac{v_-}{V(k_c+k_r)}\left(e^{-\frac{V}{D}y}-1\right).$$
Both expressions automatically satisfy the required boundary conditions and reduce to the well-known drift–diffusion limit when $k_c, k_r \to \infty$ with fixed D, V.

6 Model III - Discrete model of polymer chaperone-assisted translocation

6.1 Background

The transport of a polymer through a translocation pore can be modelled using a translocation ratchet model, see Fig. 5.

For a perfect ratchet, the polymer can only move backward (to the left in Fig. 5). In this model, we are mainly interested in an imperfect ratchet, where we introduce some probability of reflection to allow forward movement to occur.

On one side of the membrane, there are proteins known as chaperones that can bind to a polymer ratchet site. The size of a chaperone is assumed to be larger than the size of the translocation pore. Thus, it rectifies the movement of the polymer when it is bound to a site immediately next to the translocation pore, resulting in forward movement of the polymer [3].

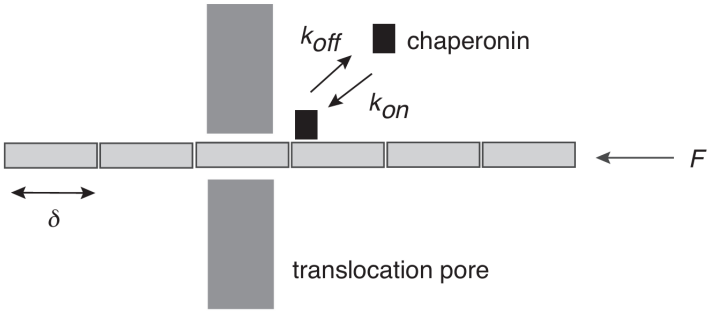


Figure 5 Cartoon of a translocation ratchet model [13]

6.2 Model Setup

Consider a (rigid) polymer chain that moves through a membrane nanopore located at $x = 0$. We will focus on the segment of the polymer to the right of the pore. Suppose that the region to the right of the pore has a fixed density of chaperones that bind irreversibly to unoccupied monomeric sites on the polymer at a rate λ. The movements of the polymer and the adsorption of a chaperone are summarised as below [13] (see also Fig. 6):

(a) If the site immediately next to the pore is chaperone-free, then the polymer can hop in either direction (unbiased random walk).

(b) If the site immediately next to the pore is occupied by a chaperone, the polymer can hop only to the right because an adsorbed chaperone is too large to enter the pore.

(c) Adsorption of a new chaperone (shaded) can occur at any site on the leftmost chaperone-free segment of length m

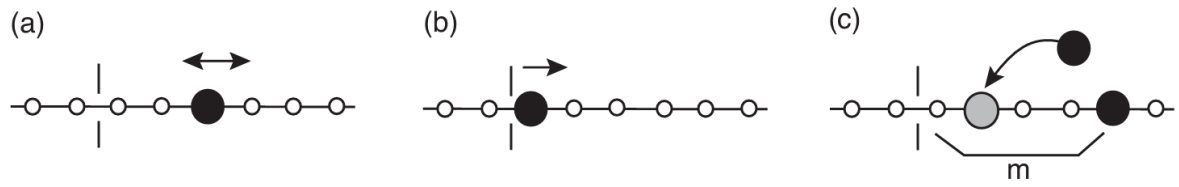


Figure 6 Schematic of chaperone-assisted translocation model. [13]

Let $E_m(t)$ be the probability that the first m monomer sites to the right of the pore are free of chaperones at time t. We also define the segment probability:

$$S_m = E_m - E_{m+1} \tag{26}$$

which represents the probability that the leftmost chaperone is located at site $m+1$. For the purpose of this model, we will use $\sum_{m=0}^{\infty} S_m = 1$ as the normalisation condition, with boundary condition $E_0 = 1$.

6.3 Derivation of an ODE for the rate of change of $E_m(t)$

The rate of change of $E_m(t)$ is influenced by:

- Gain from configurations where the leftmost chaperone is at site m, and the polymer steps right, meaning that we went from $m-1$ clear sites to m clear sites, hence contributing to a positive increase in E_m: $+S_{m-1}$
- Loss to configurations where the leftmost chaperone is at site $m+1$ and the polymer steps left, thus making a configuration that did fall under E_m no longer do so: $-S_m$
- Absorption of a chaperone at any of the m monomers in the chaperone-free segment of length m just to the right of the pore: $-\lambda m E_m$

Any other configurations will still either fall under E_m or not after a move forward or backward, with the move itself having no effect unless the chaperones are in the specific positions outlined above. The extra case for an additional chaperone being added is handled by the last term.

Putting everything together, we get the differential equation:

$$\frac{dE_m}{dt} = S_{m-1} - S_m - \lambda m E_m, \quad m \geq 1 \tag{27}$$

Using the definition of S_m in (26), we substitute into (27):

$$\frac{dE_m}{dt} = (E_{m-1} - E_m) - (E_m - E_{m+1}) - \lambda m E_m \tag{28}$$

$$\implies \frac{dE_m}{dt} = E_{m-1} + E_{m+1} - 2E_m - \lambda m E_m, \quad m \geq 1 \tag{29}$$

6.4 Bessel Function Solution and Steady-State Verification

We want to verify that a solution for E_m of the form below in terms of Bessel Functions satisfies the steady state requirement [13]:

$$E_m = \frac{J_{m+\nu}(\nu)}{J_\nu(\nu)}, \tag{30}$$

where $\nu = \frac{2}{\lambda}$, and $J_\nu(x)$ is the Bessel function of the first kind. In other words, we would like to show that for E_m in (30), we have:

$$E_{m-1} + E_{m+1} - 2E_m = \lambda m E_m \tag{31}$$

We substitute the Bessel-form expression in (30) into each term in (31):

$$E_{m-1} = \frac{J_{m-1+\nu}(\nu)}{J_\nu(\nu)},$$
$$E_{m+1} = \frac{J_{m+1+\nu}(\nu)}{J_\nu(\nu)},$$
$$E_m = \frac{J_{m+\nu}(\nu)}{J_\nu(\nu)}.$$

Plugging into the left-hand side of (31):

$$E_{m-1} + E_{m+1} - 2E_m = \frac{J_{m-1+\nu}(\nu) + J_{m+1+\nu}(\nu) - 2J_{m+\nu}(\nu)}{J_\nu(\nu)}. \tag{32}$$

We now use the identity for Bessel functions of the first kind:

$$J_{\nu-1}(x) + J_{\nu+1}(x) = \frac{2\nu}{x} J_\nu(x).$$

Or equivalently,

$$J_{m-1+\nu}(\nu) + J_{m+1+\nu}(\nu) = \frac{2(m+\nu)}{\nu} J_{m+\nu}(\nu).$$

Substitute into equation (32):

$$E_{m-1} + E_{m+1} - 2E_m = \frac{1}{J_\nu(\nu)} \left(\frac{2(m+\nu)}{\nu} J_{m+\nu}(\nu) - 2J_{m+\nu}(\nu) \right).$$

Factor out $J_{m+\nu}(\nu)$:

$$= \frac{J_{m+\nu}(\nu)}{J_\nu(\nu)} \left(\frac{2(m+\nu)}{\nu} - 2 \right) = E_m \cdot \left(\frac{2(m+\nu) - 2\nu}{\nu} \right) = E_m \cdot \left(\frac{2m}{\nu} \right).$$

Now recall $\nu = \frac{2}{\lambda} \Rightarrow \frac{1}{\nu} = \frac{\lambda}{2}$, so:

$$\frac{2m}{\nu} = 2m \cdot \frac{\lambda}{2} = \lambda m.$$

Thus,

$$E_{m-1} + E_{m+1} - 2E_m = \lambda m E_m,$$

which confirms that the form of E_m in (30) satisfies the steady-state requirement.

6.5 Expression for the Mean Translocation Speed V

We define the mean translocation speed V as the probability that the polymer moves one unit to the right, per unit time. This occurs precisely when the monomer site immediately to the right of the pore (site 1) is occupied by a chaperone.

Let E_1 denote the probability that the first site to the right of the pore is chaperone-free. Then, the probability that it is *occupied* is $1 - E_1$, which is also the probability that the polymer is prevented from diffusing backward through the pore due to the chaperone.

Since this rectification leads to a net forward motion, the average speed is given by:

$$V = 1 - E_1$$

From the Bessel-function solution derived earlier, we have:

$$E_1 = \frac{J_{1+\nu}(\nu)}{J_\nu(\nu)}$$

where $\nu = \frac{2}{\lambda}$. Substituting this in, we obtain:

$$V = 1 - \frac{J_{\nu+1}(\nu)}{J_\nu(\nu)}$$

This expression gives the mean speed of the polymer as a function of the chaperone absorption rate λ, via $\nu = 2/\lambda$.

We can plot the relationship between the speed V and the chaperone absorption rate λ using Python and the scientific computation library Scipy.

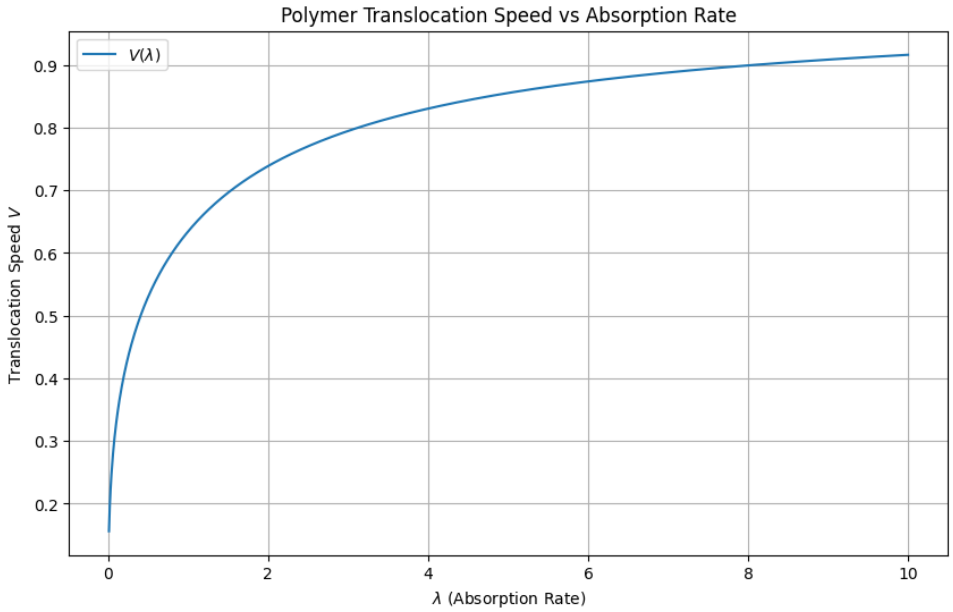


Figure 7 A plot to investigate the relationship between V and λ

Figure 7 illustrates that as the absorption rate λ rises, the polymer translocation speed V increases and eventually approaches 1. This occurs because a higher λ leads to a higher probability that the first site to the right of the pore is occupied by a chaperone. As a result, this favours the movement of the polymer to the right, which explains the increase in mean translocation speed V.

7 Model IV - Modelling length control in axons

7.1 Introduction

Axons are neurones that transmit electrical impulses from the cell body (soma) to other neurones, muscles, or glands. They play a fundamental role in the nervous system by enabling rapid and precise communication between distant regions of the body and the brain. Once target connections are established, maintaining appropriate axonal length is critical for ensuring accurate signal transmission and the functional integrity of neural circuits. The problem of length control is particularly acute for the axons, which exhibit the most significant size differences of any cell type, ranging from several microns to over a metre in humans.[12]

7.2 Biological Background

Tubulin is a globular protein that polymerises to form microtubules. In neurones, tubulin is synthesised in the cell body and transported along the axon towards the distal end. There, it undergoes polymerisation to extend the microtubule network and drive axonal elongation. Conversely, microtubules can depolymerise, releasing tubulin back into the cytoplasm. The dynamic balance between these two processes regulates axon length. [12]

7.3 Schematic and Model Description

Figure 8 [13] illustrates a schematic of a growing axon. Tubulin is introduced at $x = 0$ at a rate σ, and is transported towards the distal end $x = L(t)$ via advection-diffusion mechanisms. At the distal tip, tubulin is polymerised into microtubules, contributing to the elongation of the axon.

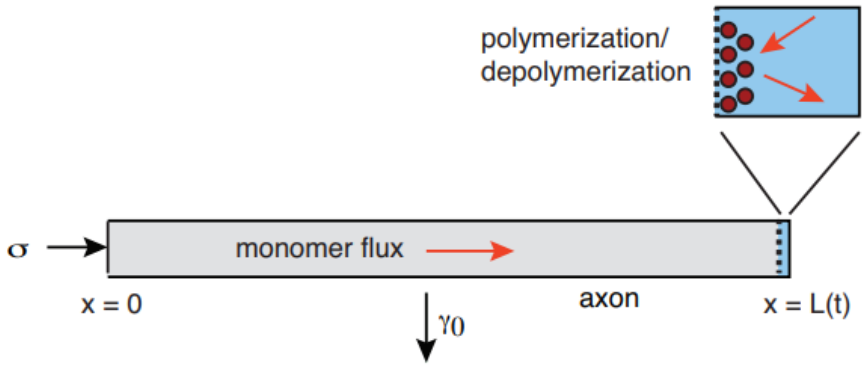


Figure 8 Schematic diagram of a growing neurite of length $L(t)$. Tubulin is inserted at $x = 0$ at a rate σ, transported to the distal end via advection-diffusion, and is then absorbed via polymerisation.

Consider a one-dimensional model of the diffusive transport of monomers along an axon of a neurone. Let $c(x,t)$ denote the concentration of monomers at position x along the axon at time t. Suppose that at time t, the axon has length $L(t)$ so that $x \in [0, L(t)]$. The transport of monomers is modelled macroscopically in terms of an advection-diffusion equation with an additional decay term representing degradation at a rate γ:[9]

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - V\frac{\partial c}{\partial x} - \gamma c$$

Suppose that there is a constant flux of newly synthesised monomers at $x = 0$, so that

$$-D\frac{\partial c}{\partial x}\bigg|_{x=0} = \sigma$$

The flux at the growing end $x = L(t)$ is equal to the difference between the fluxes associated with polymer assembly and disassembly:

$$-D\frac{\partial c}{\partial x}\bigg|_{x=L(t)} = \epsilon_l c(L(t), t),$$

where ϵ_l and γ_l are the rates of polymerisation and depolymerisation, respectively. Finally, the rate of growth is taken to be proportional to the difference between these two fluxes, according to

$$\frac{dL}{dt} = \epsilon_l c(L(t), t) - \gamma_l$$

7.4 Finding the steady state solution for concentration

In the steady state, all time derivatives are zero. Thus, $\frac{\partial c}{\partial t} = 0$ and $\frac{dL}{dt} = 0$.

The advection-diffusion equation becomes an ODE:

$$D\frac{d^2 c}{dx^2} - V\frac{dc}{dx} - \gamma c = 0$$

The condition for the rate of growth, $\frac{dL}{dt} = 0$, gives a boundary condition at $x = L$:

$$\frac{dL}{dt} = \epsilon_L c(L) - \gamma_L = 0 \implies \epsilon_L c(L) = \gamma_L \implies c(L) = \frac{\gamma_L}{\epsilon_L}$$

We will set a constant $c_L = \frac{\gamma_L}{\epsilon_L}$. The flux boundary condition at $x = L$ is $-D\frac{dc}{dx}\Big|_{x=L} = \epsilon_L c(L) - \gamma_L$. Substituting $c(L) = c_L$, the right-hand side becomes zero:

$$-D\frac{dc}{dx}\bigg|_{x=L} = \epsilon_L c_L - \gamma_L = \epsilon_L\left(\frac{\gamma_L}{\epsilon_L}\right) - \gamma_L = 0$$

This gives the second boundary condition at $x = L$:

$$\frac{dc}{dx}\bigg|_{x=L} = 0$$

The boundary condition at $x = 0$ remains:

$$-D\frac{dc}{dx}\bigg|_{x=0} = \sigma$$

7.4.1 General Solution of the ODE

The characteristic equation for the steady-state ODE is:

$$D\lambda^2 - V\lambda - \gamma = 0$$

The roots $\lambda_\pm$ are given by the quadratic formula:

$$\lambda_\pm = \frac{V \pm \sqrt{V^2 - 4(D)(-\gamma)}}{2D} = \frac{V \pm \sqrt{V^2 + 4D\gamma}}{2D} = \frac{V}{2D}\left[1 \pm \sqrt{1 + \frac{4D\gamma}{V^2}}\right]$$

The general solution for $c(x)$ is therefore:

$$c(x) = Ae^{\lambda_+ x} + Be^{\lambda_- x}$$

where A and B are constants. Its derivative is:

$$\frac{dc}{dx} = A\lambda_+ e^{\lambda_+ x} + B\lambda_- e^{\lambda_- x}$$

7.4.2 Applying Boundary Conditions at x=L

We apply the two conditions $c(L) = c_L$ and $\frac{dc}{dx}(L) = 0$ to form a system of equations for A and B:

$$Ae^{\lambda_+ L} + Be^{\lambda_- L} = c_L \tag{1}$$
$$A\lambda_+ e^{\lambda_+ L} + B\lambda_- e^{\lambda_- L} = 0 \tag{2}$$

From equation (2), we express A in terms of B:

$$A = -B\frac{\lambda_-}{\lambda_+}\frac{e^{\lambda_- L}}{e^{\lambda_+ L}} = -B\frac{\lambda_-}{\lambda_+}e^{(\lambda_- - \lambda_+)L}$$

Substitute this expression for A into equation (1):

$$\left(-B\frac{\lambda_-}{\lambda_+}e^{(\lambda_- - \lambda_+)L}\right)e^{\lambda_+ L} + Be^{\lambda_- L} = c_L$$
$$-B\frac{\lambda_-}{\lambda_+}e^{\lambda_- L} + Be^{\lambda_- L} = c_L$$
$$Be^{\lambda_- L}\left(1 - \frac{\lambda_-}{\lambda_+}\right) = c_L$$
$$Be^{\lambda_- L}\left(\frac{\lambda_+ - \lambda_-}{\lambda_+}\right) = c_L$$
$$\implies B = \frac{c_L\lambda_+}{\lambda_+ - \lambda_-}e^{-\lambda_- L}$$

Now, we find A by substituting the expression for B back:

$$A = -\left(\frac{c_L\lambda_+}{\lambda_+ - \lambda_-}e^{-\lambda_- L}\right)\frac{\lambda_-}{\lambda_+}e^{(\lambda_- - \lambda_+)L} = -\frac{c_L\lambda_-}{\lambda_+ - \lambda_-}e^{-\lambda_- L + \lambda_- L - \lambda_+ L} = -\frac{c_L\lambda_-}{\lambda_+ - \lambda_-}e^{-\lambda_+ L}$$

Substituting the expressions for A and B back into the general solution for $c(x)$:

$$c(x) = \left(-\frac{c_L\lambda_-}{\lambda_+ - \lambda_-}e^{-\lambda_+ L}\right)e^{\lambda_+ x} + \left(\frac{c_L\lambda_+}{\lambda_+ - \lambda_-}e^{-\lambda_- L}\right)e^{\lambda_- x}$$
$$c(x) = \frac{c_L}{\lambda_+ - \lambda_-}\left(-\lambda_- e^{\lambda_+(x-L)} + \lambda_+ e^{\lambda_-(x-L)}\right)$$

7.4.3 Deriving a transcendental equation for L

Finally, we apply the boundary condition at $x = 0$: $-D\frac{dc}{dx}(0) = \sigma$. First, we evaluate $\frac{dc}{dx}(0)$:

$$\begin{aligned}\frac{dc}{dx}(0) &= A\lambda_+ + B\lambda_- \\ &= \left(-\frac{c_L\lambda_-}{\lambda_+ - \lambda_-}e^{-\lambda_+ L}\right)\lambda_+ + \left(\frac{c_L\lambda_+}{\lambda_+ - \lambda_-}e^{-\lambda_- L}\right)\lambda_- \\ &= -\frac{c_L\lambda_-\lambda_+}{\lambda_+ - \lambda_-}e^{-\lambda_+ L} + \frac{c_L\lambda_+\lambda_-}{\lambda_+ - \lambda_-}e^{-\lambda_- L} \\ &= \frac{c_L\lambda_+\lambda_-}{\lambda_+ - \lambda_-}\left(e^{-\lambda_- L} - e^{-\lambda_+ L}\right)\end{aligned}$$

From Vieta's formulas for the characteristic equation $D\lambda^2 - V\lambda - \gamma = 0$, the product of the roots is $\lambda_+\lambda_- = -\frac{\gamma}{D}$, which implies $D\lambda_+\lambda_- = -\gamma$. Substituting this into the boundary condition at $x = 0$:

$$\begin{aligned}-D\left[\frac{c_L\lambda_+\lambda_-}{\lambda_+ - \lambda_-}\left(e^{-\lambda_- L} - e^{-\lambda_+ L}\right)\right] &= \sigma \\ -(-\gamma)\left[\frac{c_L}{\lambda_+ - \lambda_-}\left(e^{-\lambda_- L} - e^{-\lambda_+ L}\right)\right] &= \sigma \\ \gamma\frac{c_L}{\lambda_+ - \lambda_-}\left(e^{-\lambda_- L} - e^{-\lambda_+ L}\right) &= \sigma\end{aligned}$$

Rearranging the terms yields the final transcendental equation for L:

$$e^{-\lambda_- L} - e^{-\lambda_+ L} = \frac{\sigma}{\gamma c_L}(\lambda_+ - \lambda_-)$$

where $c_L = \gamma_L/\epsilon_L$ and

$$\lambda_\pm = \frac{V}{2D}\left[1 \pm \sqrt{1 + \frac{4D\gamma}{V^2}}\right].$$

7.5 Exploring how L depends on other parameters

We start with the transcendental equation derived previously:

$$e^{-\lambda_- L} - e^{-\lambda_+ L} = \frac{\sigma}{\gamma c_L}(\lambda_+ - \lambda_-)$$

To simplify the setup, we fix the units of space and time by setting $D = 1$ and $\gamma = 1$. The equation becomes:

$$e^{-\lambda_- L} - e^{-\lambda_+ L} = \frac{\sigma}{c_L}(\lambda_+ - \lambda_-)$$

The parameters $\lambda_\pm$ become:

$$\lambda_\pm = \frac{V}{2}\left[1 \pm \sqrt{1 + \frac{4}{V^2}}\right]$$

7.5.1 Approximation for small L

In the regime where L is small, we can use the first-order Taylor series expansion for the exponential function, $e^z \approx 1 + z$, for a small argument z. We apply this approximation to the

LHS of the transcendental equation:

$$\begin{aligned} e^{-\lambda_- L} - e^{-\lambda_+ L} &\approx (1 - \lambda_- L) - (1 - \lambda_+ L) \\ &= 1 - \lambda_- L - 1 + \lambda_+ L \\ &= (\lambda_+ - \lambda_-)L \end{aligned}$$

Now, we substitute this approximation back into the main equation:

$$(\lambda_+ - \lambda_-)L \approx \frac{\sigma}{c_L}(\lambda_+ - \lambda_-)$$

Since $\lambda_+ \neq \lambda_-$, we can divide both sides by the term $(\lambda_+ - \lambda_-)$, which yields the approximation for L in the small L regime:

$$\boxed{L \approx \frac{\sigma}{c_L}}$$

7.5.2 Approximation for Large L and Large V

In the regime where both L and V are large, we first find approximations for $\lambda_\pm$ in the large V limit. We use the binomial approximation $(1 + x)^a \approx 1 + ax$ for small x. Since V is large, the term $4/V^2$ is small.

$$\sqrt{1 + \frac{4}{V^2}} = \left(1 + \frac{4}{V^2}\right)^{1/2} \approx 1 + \frac{1}{2}\left(\frac{4}{V^2}\right) = 1 + \frac{2}{V^2}$$

Substituting this into the expressions for $\lambda_\pm$:

$$\begin{aligned} \lambda_+ &= \frac{V}{2}\left[1 + \left(1 + \frac{2}{V^2}\right)\right] = \frac{V}{2}\left[2 + \frac{2}{V^2}\right] = V + \frac{1}{V} \approx V \\ \lambda_- &= \frac{V}{2}\left[1 - \left(1 + \frac{2}{V^2}\right)\right] = \frac{V}{2}\left[-\frac{2}{V^2}\right] = -\frac{1}{V} \end{aligned}$$

The difference is $\lambda_+ - \lambda_- \approx V - (-1/V) = V + 1/V \approx V$.

Now we examine the terms in the transcendental equation. As L and V are large, the exponent in the term $e^{-\lambda_+ L} \approx e^{-VL}$ is a large negative number. This makes the term vanishingly small, so it can be neglected. The equation simplifies to:

$$e^{-\lambda_- L} \approx \frac{\sigma}{c_L}(\lambda_+ - \lambda_-)$$

Substituting the large-V approximations for λ_- and $(\lambda_+ - \lambda_-)$:

$$\begin{aligned} e^{-(-1/V)L} &\approx \frac{\sigma}{c_L}(V) \\ e^{L/V} &\approx \frac{\sigma V}{c_L} \end{aligned}$$

To solve for L, we take the natural logarithm of both sides:

$$\begin{aligned} \log(e^{L/V}) &\approx \log\left(\frac{\sigma V}{c_L}\right) \\ \frac{L}{V} &\approx \log\left(\frac{\sigma V}{c_L}\right) \end{aligned}$$

This gives the final approximation for L in the large L and large V regime:

$$\boxed{L \approx V \log\left(\frac{\sigma V}{c_L}\right)}$$

7.6 Numerical analysis of approximations

7.6.1 Objective

The goal is to numerically investigate how the steady-state axon length, L, depends on the key model parameters: the advection velocity, V, and the dimensionless flux, σ/c_L. This is achieved by solving the governing transcendental equation for L while varying one parameter and holding the other constant. The chosen numerical method for finding the root L is the Newton-Raphson iteration. We can then compare the numerical results to the approximations we found earlier.

7.6.2 Numerical Method: The Newton-Raphson method

The Newton-Raphson method is an iterative root-finding algorithm for a real-valued function. To solve an equation of the form $f(x) = 0$, the method starts with an initial guess x_0 and successively generates better approximations x_{n+1} using the formula:

$$x_{n+1} = x_n - \frac{f(x_n)}{f'(x_n)}$$

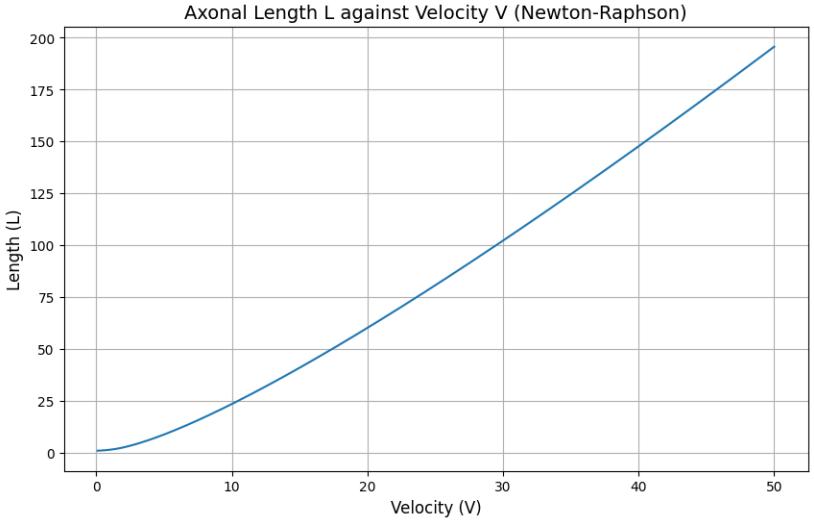
where $f'(x_n)$ is the derivative of the function evaluated at x_n.

7.6.3 Plots and results

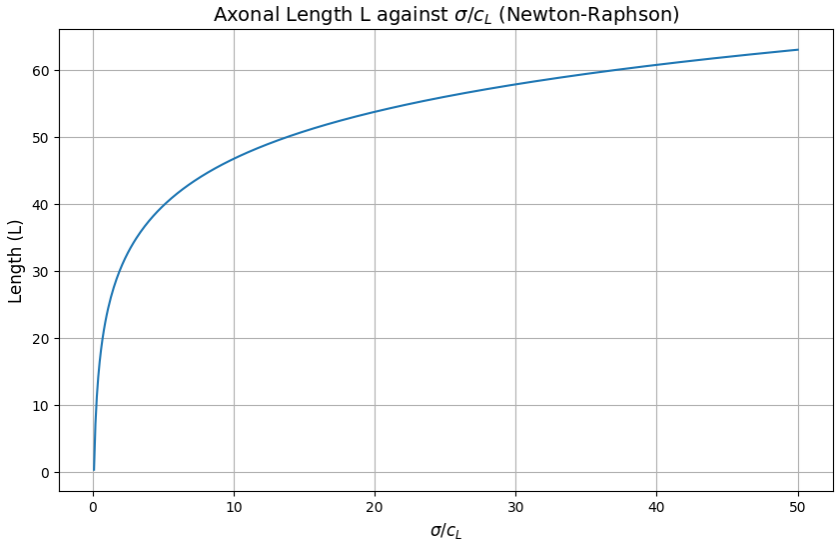
In the first experiment, we studied the dependence of L on V.

- The parameter group σ/c_L was held at a fixed value.
- A range of values for the advection velocity, V, was selected.
- For each value of V, the transcendental equation $f(L) = 0$ was solved for L using the Newton-Raphson method.

This method results in the plot below, with the trend line looking linear as our approximation would suggest.



In the second experiment, we studied the dependence of L on σ/c_L in a similar fashion, with the plot below showing the results. The relationship seems to be logarithmic, which we would expect from the approximations derived earlier.



7.7 Analysing the system when not at steady state

We consider the growth of an axon in a regime far from its steady-state length (i.e., $L(t) \ll L^*$). In this scenario, the system's dynamics are governed by the following key assumptions[12]:

- **Diffusion Dominance:** The transport of monomers is dominated by diffusion. The advection (V) and monomer degradation (γ) terms from the more general advection-diffusion-reaction equation are considered negligible. After rescaling the spatial coordinate, the diffusion coefficient is set to unity, $D = 1$.
- **Fixed Source Concentration:** The concentration of monomers at the base of the axon ($x = 0$) is held at a constant value, c_0.
- **Perfect Absorption at the Tip:** Monomers that reach the growing end of the axon at $x = L(t)$ are immediately and completely absorbed. This corresponds to an assumption of infinitely fast polymerisation with no depolymerisation. This implies that the concentration of free monomers at the tip is always zero.

This physical model describes a moving boundary problem, where the consumption of monomers at the tip drives the growth of the domain itself.

7.7.1 Governing equations as a result of assumptions

The mathematical formulation of the model is given by the diffusion equation

$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2}, \qquad 0 < x < L(t),$$

with the boundary conditions

$$c(0,t) = c_0, \qquad c(L(t),t) = 0,$$

and the interface condition

$$-\frac{\partial c}{\partial x}\bigg|_{x=L(t)} = \beta \frac{dL(t)}{dt},$$

for some constant of proportionality given by β.

This mathematical setup is actually analogous to the classic Stefan problem, which we will provide some background for and solve in the following sections.

7.8 The Stefan Problem

The Stefan problem is a classical moving boundary problem that models the evolution of an interface between two phases, typically governed by diffusion, with melting ice being a classic example of the problem. The defining feature of a Stefan problem is that the location of the interface separating regions (e.g., solid and liquid, or diffused and undiffused zones) is not known ahead of time—it must be determined as part of the solution. [1]

In our case, we study a one-phase Stefan problem in the context of diffusion, where the concentration $c(x,t)$ satisfies a diffusion equation front that moves over time:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}, \quad 0 < x < L(t)$$

with $c(x,t)$ subject to suitable boundary conditions, such as:

$$c(0,t) = c_0, \quad c(L(t),t) = 0$$

The key unknown is the moving boundary $L(t)$, which must be solved for along with $c(x,t)$. The condition that determines how $L(t)$ evolves is called the **Stefan condition**.

7.8.1 Explanation of the Stefan Condition

The Stefan condition expresses a conservation principle at the moving interface. It can be understood as a balance between the diffusive flux of the quantity (e.g., heat, concentration) and the rate at which the interface moves. Intuitively, it says that the interface advances at a rate proportional to the net amount of diffusing material arriving at the boundary. If more material arrives at the front, the boundary moves forward faster.

Mathematically, it takes the form:

$$\frac{dL}{dt} = -\beta \left.\frac{\partial c}{\partial x}\right|_{x=L(t)}$$

Here:

- β is a constant that incorporates material and phase-change properties (e.g., latent heat or concentration jump),
- $\frac{\partial c}{\partial x}|_{x=L(t)}$ is the gradient of the concentration just to the left of the front,
- The negative sign reflects that a positive concentration gradient corresponds to material flux toward the front.

This condition ensures mass (or energy) conservation: the accumulation or depletion of material at the interface must match the rate at which the phase boundary moves. In physical terms, the interface moves precisely because material is being added or removed at that point through diffusion.

7.8.2 Application to our problem

In this problem, we consider a diffusion process in a medium where one end ($x = 0$) is held at fixed concentration c_0, while a sharp interface at $x = L(t)$ moves into the medium over time. The boundary conditions are:

$$c(0,t) = c_0, \quad c(L(t),t) = 0, \quad \text{and} \quad \frac{dL}{dt} = -\beta \left.\frac{\partial c}{\partial x}\right|_{x=L(t)}$$

7.9 Constructing a Neumann solution to the problem

To solve the problem, we seek a similarity solution of the form: [1]

$$c(x,t) = f(\eta), \quad \text{where } \eta = \frac{x}{2\sqrt{t}}$$

which reduces the PDE to an ODE in the similarity variable η, and transforms the moving boundary into a fixed location η_s in this coordinate system.

Applying the Stefan condition in similarity coordinates ultimately leads to a transcendental equation for η_s, which determines the evolution of the moving front.

We now compute the necessary derivatives using the chain rule:

$$\begin{aligned}
\frac{\partial c}{\partial x} &= \frac{df}{d\eta} \cdot \frac{\partial \eta}{\partial x} = f'(\eta) \cdot \frac{1}{2\sqrt{t}} \\
\frac{\partial^2 c}{\partial x^2} &= \frac{d}{dx}\left(f'(\eta) \cdot \frac{1}{2\sqrt{t}}\right) = f''(\eta) \cdot \left(\frac{1}{2\sqrt{t}}\right)^2 = \frac{1}{4t} f''(\eta) \\
\frac{\partial c}{\partial t} &= \frac{df}{d\eta} \cdot \frac{\partial \eta}{\partial t} = f'(\eta) \cdot \left(-\frac{x}{4t^{3/2}}\right) = -\frac{\eta}{2t} f'(\eta)
\end{aligned}$$

Deriving the ODE for $f(\eta)$

Substituting into the heat equation:

$$\frac{\partial c}{\partial t} = \frac{\partial^2 c}{\partial x^2} \quad \Rightarrow \quad -\frac{\eta}{2t} f'(\eta) = \frac{1}{4t} f''(\eta)$$

Multiply both sides by $4t$:

$$-2\eta f'(\eta) = f''(\eta) \quad \Rightarrow \quad f''(\eta) + 2\eta f'(\eta) = 0$$

This is a second-order linear ODE. Letting $u = f'(\eta)$, we get:

$$u' + 2\eta u = 0 \quad \Rightarrow \quad \frac{du}{u} = -2\eta d\eta \Rightarrow \ln u = -\eta^2 + C_1 \Rightarrow u = f'(\eta) = C_1 e^{-\eta^2}$$

Integrating:

$$f(\eta) = C_1 \int e^{-\eta^2} d\eta + C_2 = C_1 \cdot \operatorname{erf}(\eta) + C_2$$

Thus, the general solution is:

$$c(x,t) = A \cdot \operatorname{erf}\left(\frac{x}{2\sqrt{t}}\right) + B$$

Applying Boundary Conditions

At $x = 0 \Rightarrow \eta = 0$:

$$c(0,t) = A \cdot \operatorname{erf}(0) + B = B = c_0 \Rightarrow B = c_0$$

At $x = L(t) \Rightarrow \eta = \eta_s = \frac{L(t)}{2\sqrt{t}}$:

$$c(L(t),t) = A \cdot \operatorname{erf}(\eta_s) + c_0 = 0 \Rightarrow A = -\frac{c_0}{\operatorname{erf}(\eta_s)}$$

Hence the solution becomes:

$$c(x,t) = c_0 \left(1 - \frac{\operatorname{erf}\left(\frac{x}{2\sqrt{t}}\right)}{\operatorname{erf}(\eta_s)}\right)$$

Applying the Stefan Condition

We now apply the Stefan condition:

$$-\left.\frac{\partial c}{\partial x}\right|_{x=L(t)} = \beta \frac{dL}{dt}$$

First, compute $\frac{\partial c}{\partial x}$ using the chain rule:

$$\frac{\partial c}{\partial x} = f'(\eta) \cdot \frac{1}{2\sqrt{t}} = \frac{A}{2\sqrt{t}} \cdot \frac{2}{\sqrt{\pi}} e^{-\eta^2} = \frac{A}{\sqrt{\pi t}} e^{-\eta^2}$$

Evaluated at $x = L(t) \Rightarrow \eta = \eta_s$, we get:

$$-\left.\frac{\partial c}{\partial x}\right|_{x=L(t)} = -\left(\frac{A}{\sqrt{\pi t}} e^{-\eta_s^2}\right) = \frac{c_0}{\sqrt{\pi t}} \cdot \frac{e^{-\eta_s^2}}{\operatorname{erf}(\eta_s)}$$

Now, we express $\frac{dL}{dt}$. Since:

$$L(t) = 2\eta_s\sqrt{t} \quad \Rightarrow \quad \frac{dL}{dt} = \frac{\eta_s}{\sqrt{t}}$$

Thus, the Stefan condition becomes:

$$\frac{c_0}{\sqrt{\pi t}} \cdot \frac{e^{-\eta_s^2}}{\text{erf}(\eta_s)} = \beta \cdot \frac{\eta_s}{\sqrt{t}}$$

Multiplying both sides by $\sqrt{t}$:

$$\frac{c_0}{\sqrt{\pi}} \cdot \frac{e^{-\eta_s^2}}{\text{erf}(\eta_s)} = \beta \eta_s$$

Final Result for Neumann Solution

We arrive at the final form of the solution:

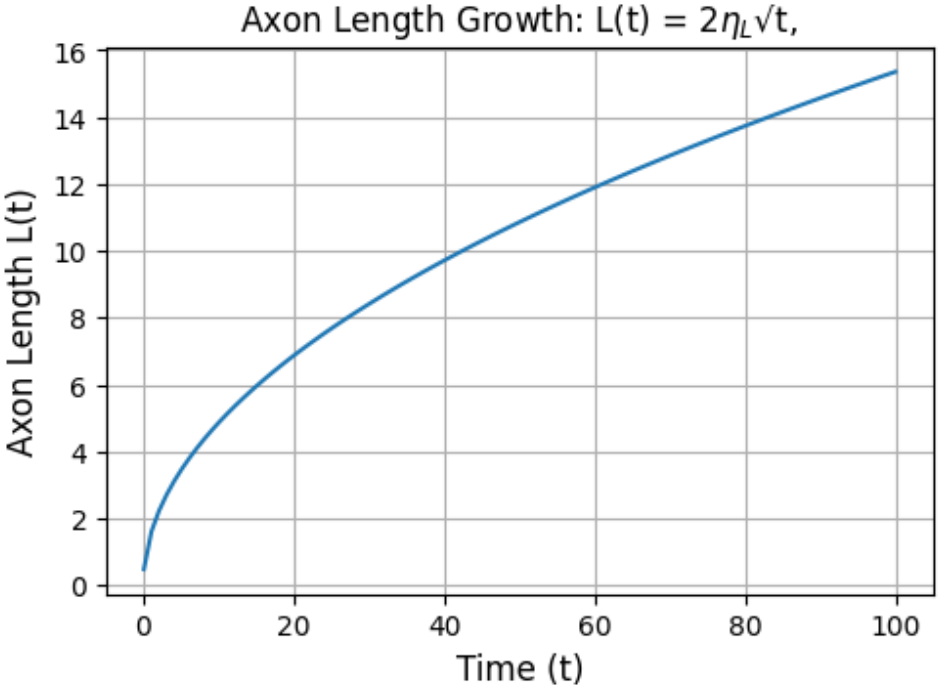
$$c(x,t) = c_0 \left(1 - \frac{\text{erf}\left(\frac{x}{2\sqrt{t}}\right)}{\text{erf}(\eta_s)}\right)$$

$$L(t) = 2\eta_s \sqrt{t}$$

with η_s satisfying the transcendental equation: $\boxed{\eta_s \cdot \text{erf}(\eta_s) = \frac{c_0}{\beta\sqrt{\pi}} e^{-\eta_s^2}}$

7.10 Analytical solution of transcendental equation

In a similar way as done in section 7.5, we use Newton-Raphson iteration to solve for η_s, and then used that value in our solution for $L(t)$. The iteration yielded a value of $\eta_s \approx 0.7677514365$, and the plot below shows how L changes with time for this value of η_s.



A Appendix A: Code

The Python scripts/notebooks that have been used to generate plots and simulations are available at https://github.com/WeiSiangLai/M2R

Bibliography

[1] F. G. Collins B. N. Antar and A. E. Aumalis. "An Exact Solution for the Solidification of a Liquid Slab of Binary Mixture". In: *NASA* (1986).

[2] S. Leibler M. Dogterom. "Physical Aspects of the Growth and Regulation of Microtubule Structures". In: *Phys. Rev. Lett. 70, 1347* (1993).

[3] Oster GF Peskin CS Odell GM. "Cellular motions and thermal fluctuations: the Brownian ratchet". In: *Biophys J* (1993).

[4] Oster G Mogilner A. "Cell motility driven by actin polymerization". In: *Biophys J* (1996).

[5] G.B. Ermentrout L. Edelstein-Keshet. "Models for the length distribution of actin filaments: simple polymerization and fragmentation". In: *Bull of Math Bio* (1998).

[6] Geoffrey M Cooper. *The Cell, 2nd edition*. A Molecular Approach. Sunderland, 2000. ISBN: 0-87893-106-6.

[7] Jonathon Howard. *Mechanics of Motor Proteins and the Cytoskeleton*. Oxford University Press, 2001. ISBN: 9780878933334.

[8] W. B. Spillman Jr B. Govindan. "Steady states of a microtubule assembly in a confined geometry". In: *Phys. Rev. E 70, 032901* (2004).

[9] B.P Graham D.R Mclean. "Mathematical formulation and analysis of a continuum model for tubulin-driven neurite elongation". In: *The Royal Society* (2004).

[10] M. Dogterom C. Tischer P.R ten Wolde. "Providing positional information with active transport on dynamic microtubules". In: *Biophys. J. 99, 726–35* (2010).

[11] J. Kerfield B. Zelinski N. Muller. "Dynamics and length distribution of microtubules under force and confinement". In: *Phys. Rev. E 86, 041918* (2012).

[12] Paul C. Bressloff Bhargav R. Karamched. "Delayed Feedback Model of Axonal Length Sensing". In: *Biophysical Journal* (2015). DOI: 10.1016/j.bpj.2015.03.055.

[13] Paul C. Bressloff. *Stochastic Processes in Cell Biology*. Interdisciplinary Applied Mathematics. Springer Charm, 2016. ISBN: 978-3-319-35494-1.