

335 **APPENDIX**

336 *A.1. Sensitivity analysis of the non-dimensional equations for stretch growth*

337 Our goal in this section of the appendix is to show how the solutions of the non-dimensional equations written in
338 section 4 are affected by changes in the parameters χ_1 , χ_2 and χ_3 . Recall that we used $\chi_1 = 5.7$, $\chi_2 = 0$ and $\chi_3 = 5.2$
339 in the main text . A change in the diffusion coefficient is reflected in χ_1 , a change in passive (advective) transport is
340 reflected in χ_2 , and a change in geometry is reflected in χ_3 . In figure .6 we plot the curves of $L(t)$ and $Q_t(t)$ versus
341 time t for the same initial conditions, but different dimensionless parameters χ_1 , χ_2 and χ_3 . In particular, increasing χ_1
342 by three orders of magnitude has negligible effect on the curves for $L(t)$ and $Q_t(t)$. This suggests that diffusion plays
343 a minor role in the growth process. The transport parameter χ_2 and the geometric parameter χ_3 are more important
344 since small changes in them cause big shifts in the $L(t)$ and $Q_t(t)$ profiles.

345 *A.2. Isotropic tension in axon membrane*

346 We mention in the main text that the isotropic membrane tension τ is related to the axon cross-sectional area
347 $A = \pi R^2$ and the pressure difference p between the inside and outside of a cell through [26]

$$\tau = pR, \tag{A-1}$$

348 where R is the radius of the axon. We will now discuss the conditions under which this equation is valid. To begin we
 349 recall a study on red blood cell membranes by Evans and Hochmuth [7] in which they consider a cylindrical portion of
 350 the membrane (such as one sucked into a micropipette). They recognize that the membrane is a viscoelastic material
 351 undergoing large deformations and give the following relations for the stress components T_{11} and T_{22} respectively
 352 along the longitudinal and circumferential directions in terms of the stretches λ_1 and λ_2 :

$$T_{11} = -P_m + \frac{\mu}{2}(\lambda_1^2 - 1) + 2\eta_e \frac{\dot{\lambda}_1}{\lambda_1}, \quad (\text{A-2})$$

$$T_{22} = -P_m + \frac{\mu}{2}(\lambda_2^2 - 1) + 2\eta_e \frac{\dot{\lambda}_2}{\lambda_2}, \quad (\text{A-3})$$

353 where μ is the shear modulus of the membrane, η_e is a viscosity and P_m is an isotropic tension that enforces the
 354 constraint that the red cell membrane is inextensible so that $\lambda_1\lambda_2 = 1$. By virtue of inextensibility the equation for T_{22}
 355 above can be written as

$$T_{22} = -P_m + \frac{\mu}{2}(\lambda_1^{-2} - 1) - 2\eta_e \frac{\dot{\lambda}_1}{\lambda_1}. \quad (\text{A-4})$$

356 If these relations are assumed valid for the viscoelastic membrane of an axon then when we stretch it in the longitudinal
 357 direction $\lambda_1 > 1$ and $\dot{\lambda}_1 > 0$, so $\lambda_2 < 1$ and $\dot{\lambda}_2 < 0$. Thus, on short time scales, when growth has not occurred, the
 358 axon diameter will become smaller if its length is increased. We also see from (A-2) and (A-3) that when $\lambda_1 > 1$ and
 359 $\dot{\lambda}_1 > 0$ the stress T_{11} increases while T_{22} decreases. Now, the increase in T_{11} will cause mechanosensitive ion channels
 360 to open, which will result in an increase in the production rate of monomers I (as we explain in the main text) and
 361 eventually cause growth. Thus, over long time scales when new material is added to the axon the stress T_{11} will go
 362 down.

363 For the red cell membrane Hochmuth *et al.* [18] measured $\eta_e = 10^{-6}$ Ns/m and $\mu = 6 \times 10^{-6}$ N/m. We will use
 364 these numbers to make estimates for axonal membranes because it has been shown recently [46] that underneath the
 365 axon membrane are spectrin filaments connected by actin rings. These are the same components that make up red cell
 366 membranes [1]. Now, for an axon $\lambda_1 = 1 + \frac{\Delta L}{L}$ where L is the length of the cylinder and ΔL is the change in length
 367 caused by pulling in the absence of growth. Hence, the strain rate $\dot{\lambda}_1 = \frac{U}{L}$ where U is the pulling velocity which is on
 368 the order of 1 mm/day in the experiments described in Pfister *et al.* [31] and Smith [40]. For a 1 mm long axon the
 369 viscous term cannot be larger (since $\lambda_1 > 1$ in tension) than $2 \times 10^{-6} \times \frac{1}{(24 \times 3600)}$ N/m $\approx 0.02 \times 10^{-6}$ N/m. This is orders
 370 of magnitude smaller than 0.04×10^{-3} N/m measured by Dai *et al.* [4] in experiments on molluscan neurons. Hence,
 371 viscous effects can be neglected for our stretch grown axons and the process can be assumed quasistatic.

372 What about the elastic term? In the experiments described in [40] the axons are stretched in steps of $3.5\mu\text{m}$ every
 373 5 minutes. For a 1 mm long axon in the absence of growth this corresponds to $\lambda_1 = 1.0035$. Hence, the elastic
 374 contribution to the stress is $6 \times 10^{-6} \times (1.007 - 1) = 42 \times 10^{-9}$ N/m which is again negligible in comparison to the
 375 0.04×10^{-3} N/m in [4]. If membrane is being added due to growth then λ_1 over a 5 minute period will be still smaller
 376 and we can safely neglect it. Hence, for long axons we can approximate $T_{11} = T_{22} = \tau$ where τ is an isotropic tension

377 in the axon membrane.

378 For a cylindrical membrane of radius R (like an axon) under isotropic tension the equilibrium equation can be
379 obtained following [24] and is given by:

$$p - \frac{\tau}{R} - \frac{K_b}{2R^3} = 0. \quad (\text{A-5})$$

380 Here, p (pressure) is a Lagrange multiplier that enforces a constraint of constant volume enclosed by the membrane
381 (due to osmotic considerations), τ (tension) is a Lagrange multiplier that enforces a constraint of membrane inex-
382 tensibility and K_b is the membrane bending modulus. K_b for a red cell membrane is $20kT$ [1] while R for an axon is
383 about $1\mu\text{m}$. The tension τ is on the order of $0.05 \times 10^{-3}\text{N/m}$. Hence, the bending term above is about two orders of
384 magnitude smaller than the tension term. If we neglect the bending term then we recover (A-1).

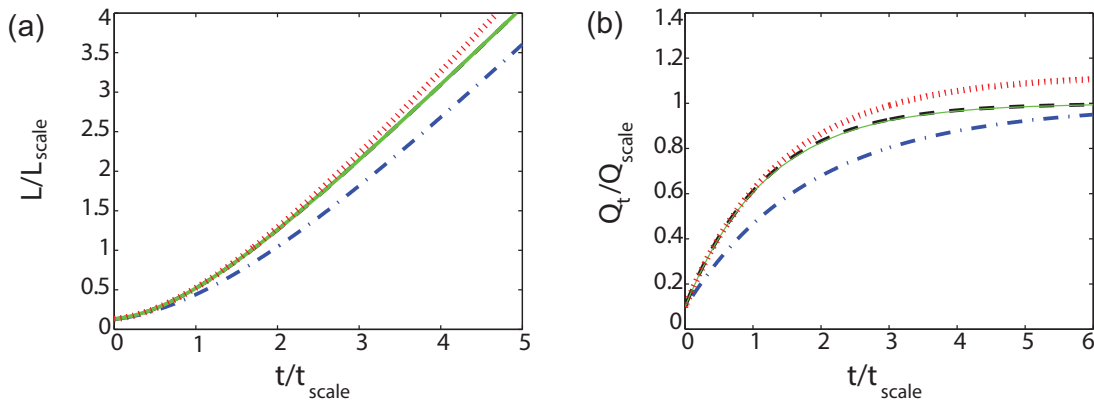


Figure .6: Sensitivity of (a) $L(t)$, and (b) $Q_t(t)$ profiles to changes in non-dimensional parameters χ_1, χ_2 and χ_3 (see the appendix). The green lines in (a) and (b) show the $L(t)$ and $Q_t(t)$ curves, respectively, for $\chi_1 = 5.7, \chi_2 = 0.0, \chi_3 = 5.2$, black dashed lines for $\chi_1 = 5700, \chi_2 = 0.0, \chi_3 = 5.2$, blue dot-dashed lines for $\chi_1 = 5.7, \chi_2 = 0.0, \chi_3 = 1.2$ and red dotted lines for $\chi_1 = 5.7, \chi_2 = 0.1, \chi_3 = 5.2$. Changing χ_1 by three orders of magnitude has negligible effect on these trajectories. This means that diffusion plays a very minor role in the growth process.

References

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