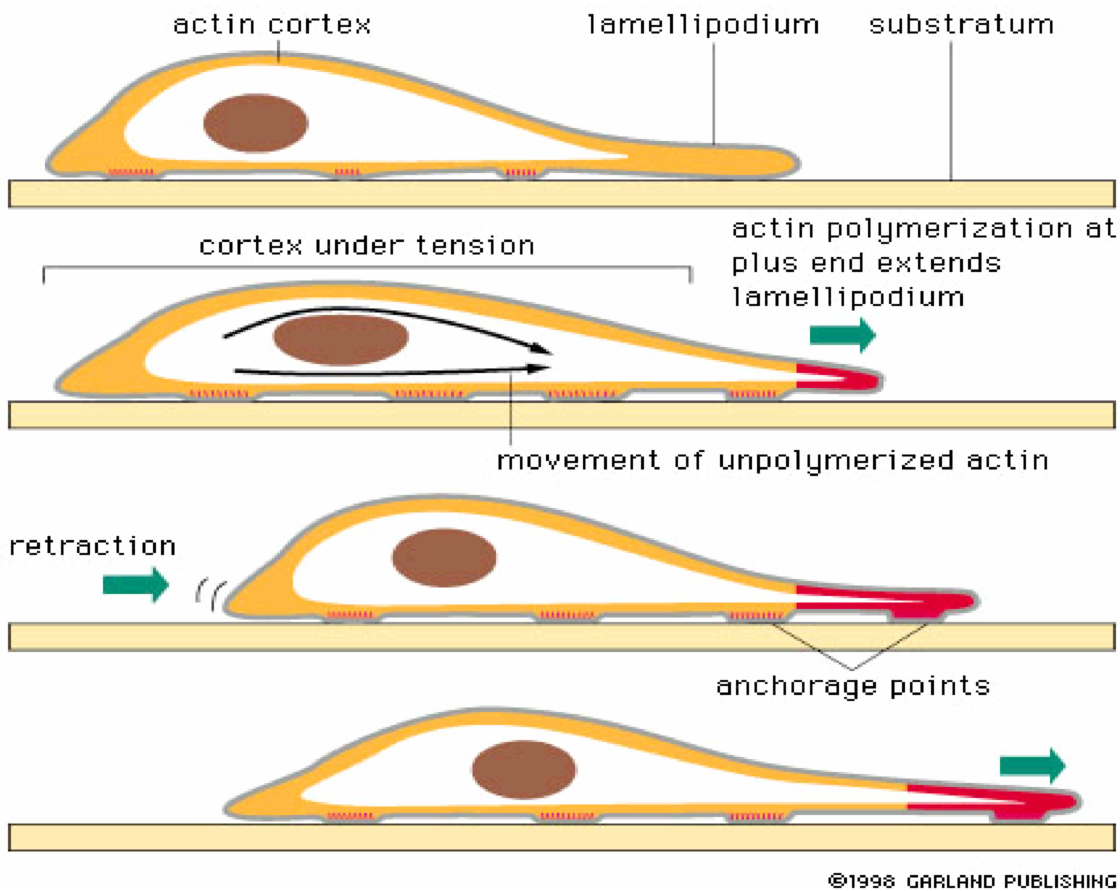
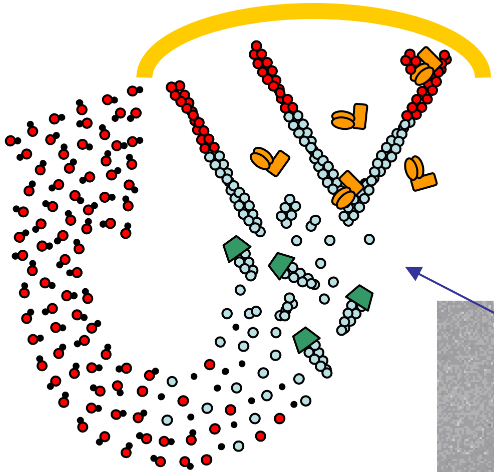
Laboratory of Cell and Computational Biology
Department of Mathematics & Center for Genetics and Development
University of California at Davis

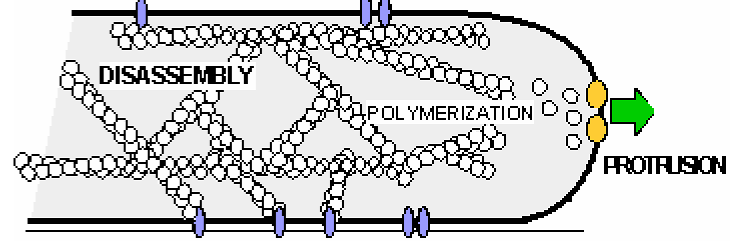
Lamellipodial and filopodial protrusions
Alex Mogilner

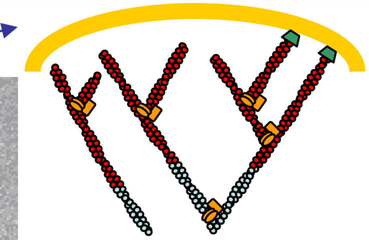


Relevant papers: http//www.math.ucdavis.edu/~mogilner/

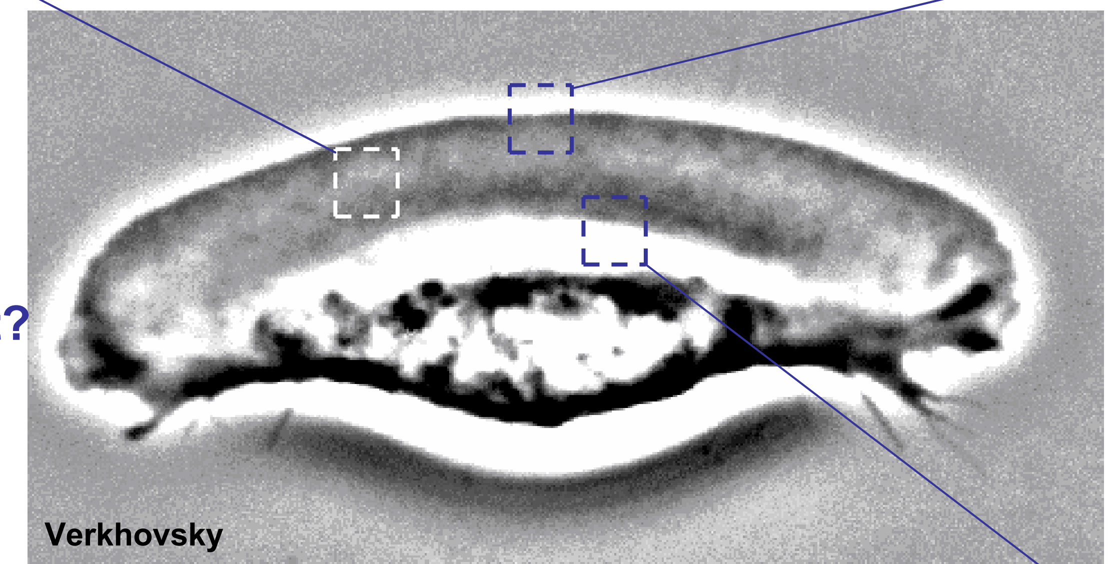


1) Force at the leading edge?

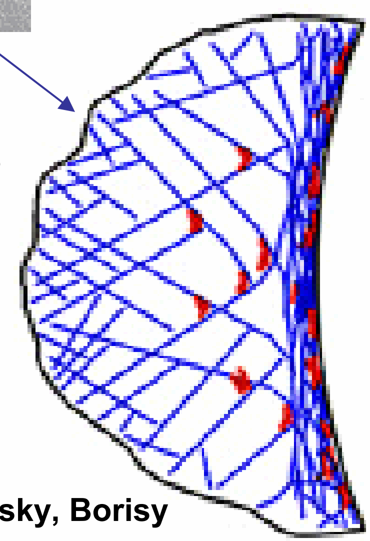




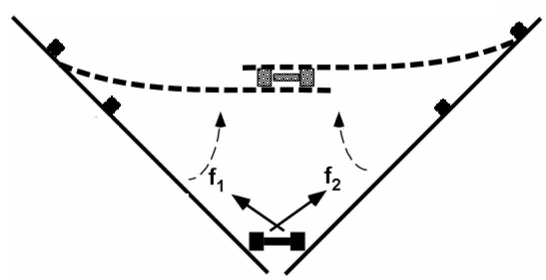
3) Actin transport?



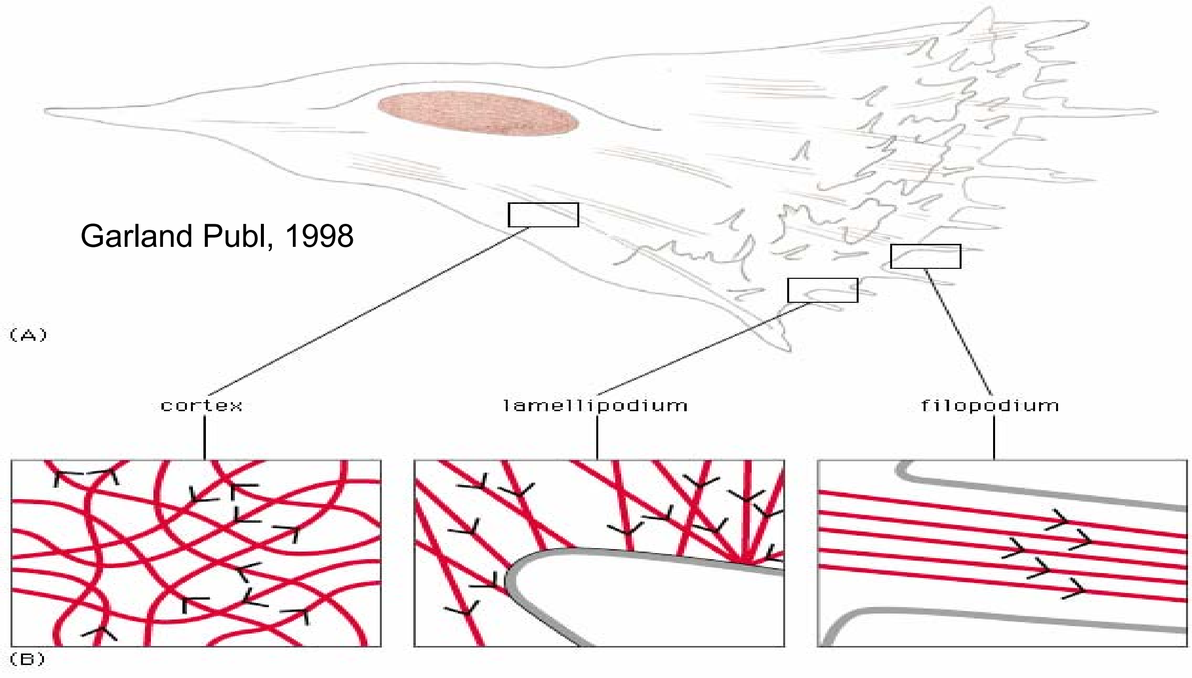
2) Dynamics at the rear?



4) Integration and cell shape?

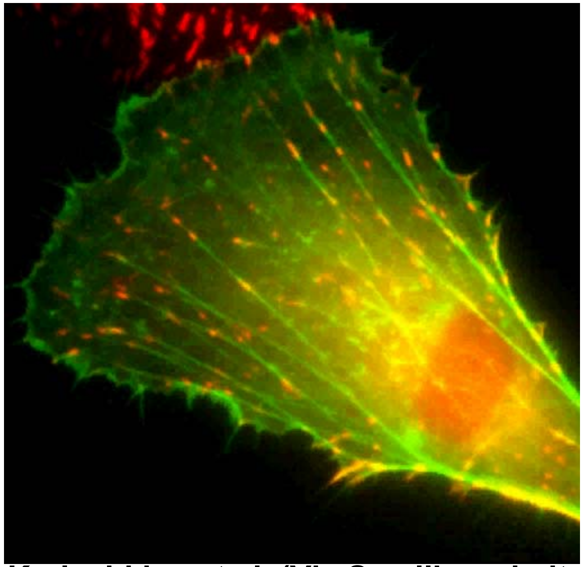


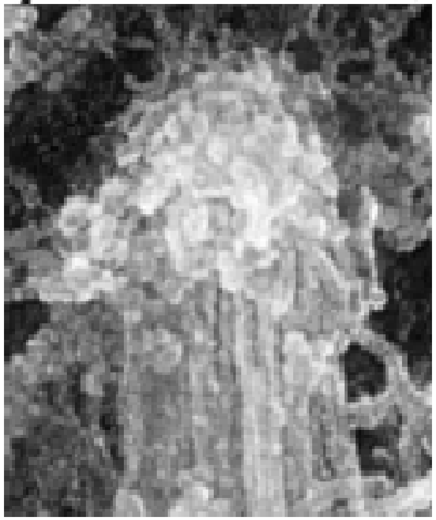
Svitkina, Verkhovsky, Borisy



Garland Publ, 1998


Steketee et al,
MBC 12: 2378 (2001)

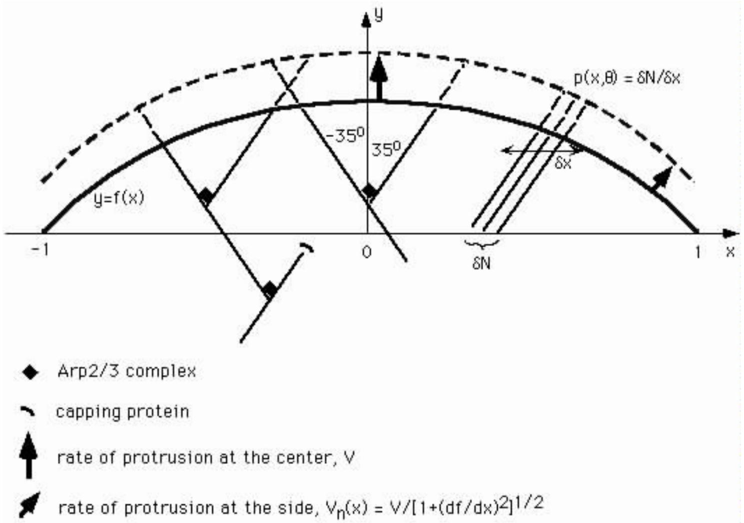

Krylyshkina et al. (Vic Small's website)

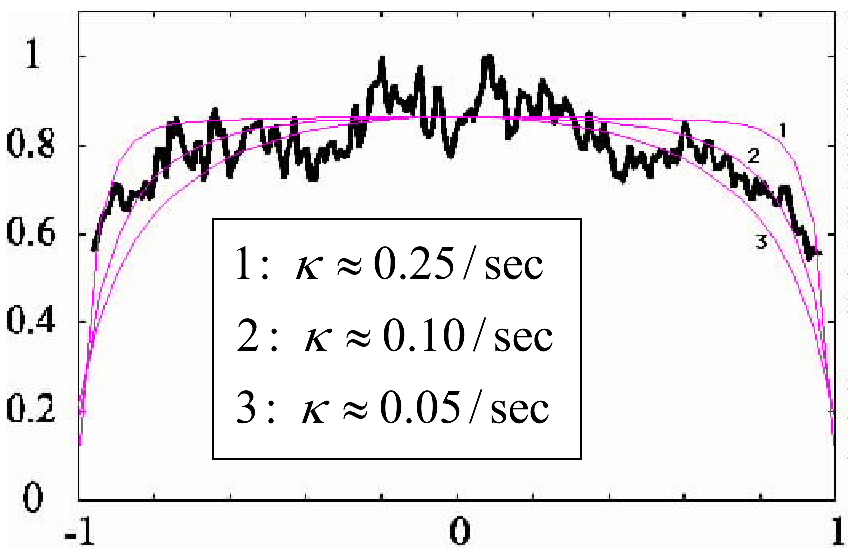

Svitkina et al, JCB 2003

F-actin dynamics at the front

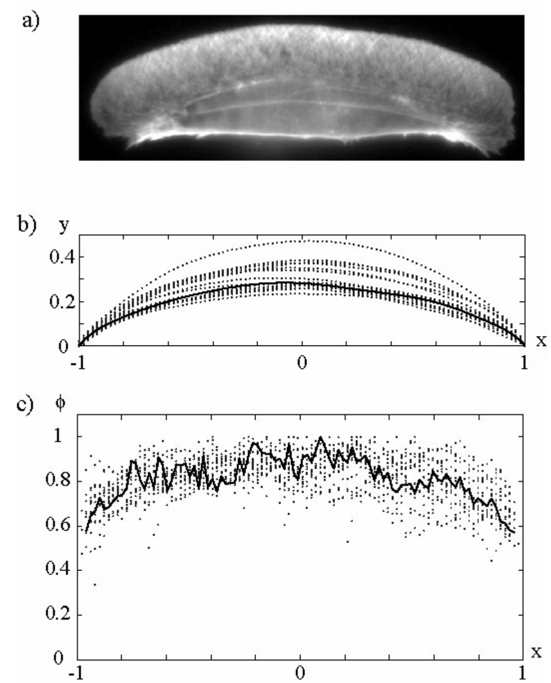
Grimm et al., *Eur. Biophys. J.*, **32**, 563-577 (2003)

Hypothesis: branching, capping and lateral flow organize actin at the edge:



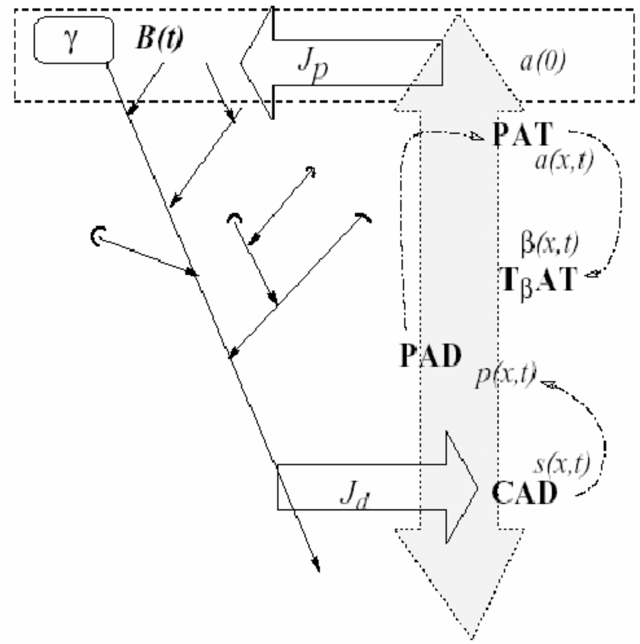


Leading edge and actin density are convex and symmetric:



$$\underbrace{\frac{\partial B^{\pm}}{\partial t}}_{\text{density change}} = \mp \underbrace{\frac{\partial}{\partial x}\left(v^{\pm} B^{\pm}\right)}_{\text{lateral flow}} + \underbrace{\frac{\beta B^{\mp}}{B^{+}+B^{-}}}_{\text{branching}} - \underbrace{\kappa B^{\pm}}_{\text{capping}}$$

$$v^{\pm} = \frac{V}{\cot(35^{o}) \mp (\partial f/\partial x)}, B^{-}(L) = 0, B^{+}(-L) = 0$$



$$\frac{\partial s}{\partial t} = -V\frac{\partial s}{\partial x} + D\frac{\partial^2 s}{\partial x^2} - k_1 s + k_{-1} p + J_d(x)$$

$$\frac{\partial p}{\partial t} = -V\frac{\partial p}{\partial x} + D\frac{\partial^2 p}{\partial x^2} + k_1 s - k_{-1} p - k_2 p$$

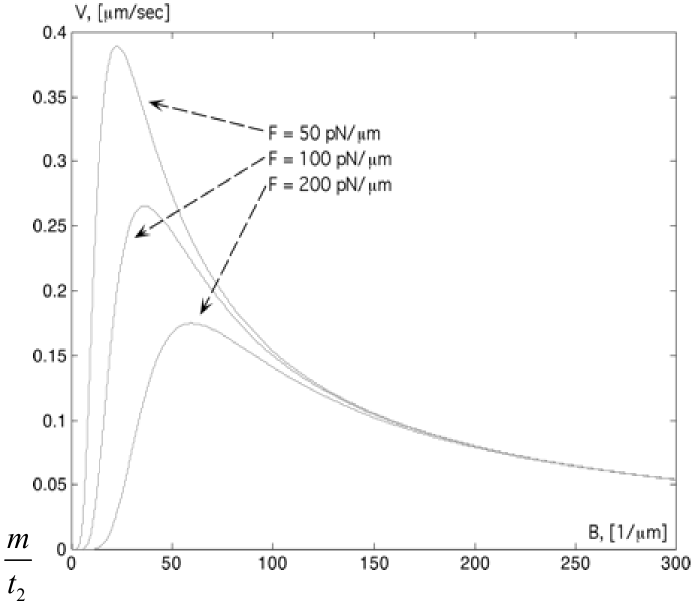
$$\frac{\partial \beta}{\partial t} = -V\frac{\partial \beta}{\partial x} + D\frac{\partial^2 \beta}{\partial x^2} - k_{-3}\beta + k_3 a$$

$$\frac{\partial a}{\partial t} = -V\frac{\partial a}{\partial x} + D\frac{\partial^2 a}{\partial x^2} + k_{-3}\beta - k_3 a + k_2 p$$

$$-D\frac{\partial a}{\partial x} + Va = -\frac{VB}{\delta}\Big|_{x=0} \qquad \frac{dB}{dt} = n - \gamma B$$

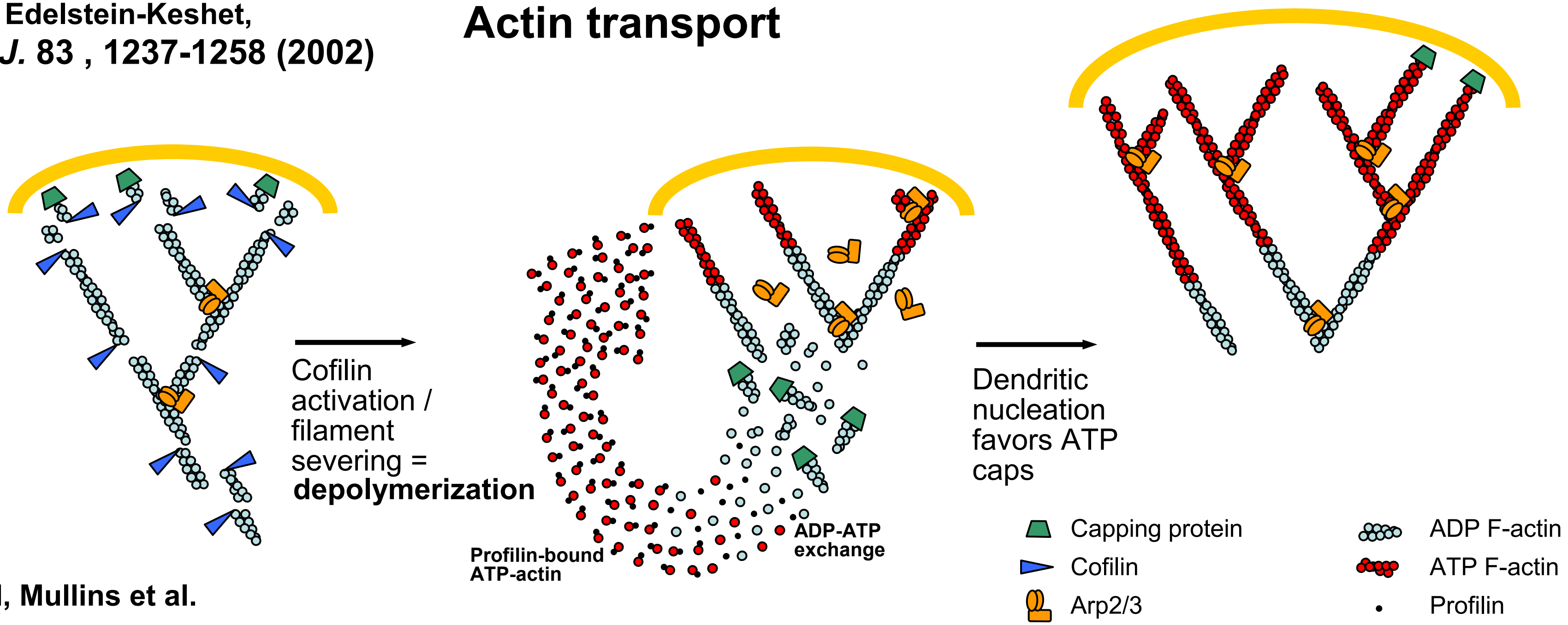
$$V = k_{on}\delta a \exp\left[\frac{-F\delta}{k_B T B(x)}\right] \qquad J_d = k_{off} m$$

$$\frac{\partial m_c}{\partial t} = -V\frac{\partial m_c}{\partial x} - \frac{m_c}{t_1} \qquad \frac{\partial m}{\partial t} = -V\frac{\partial m}{\partial x} + \frac{m_c}{t_1} - \frac{m}{t_2}$$

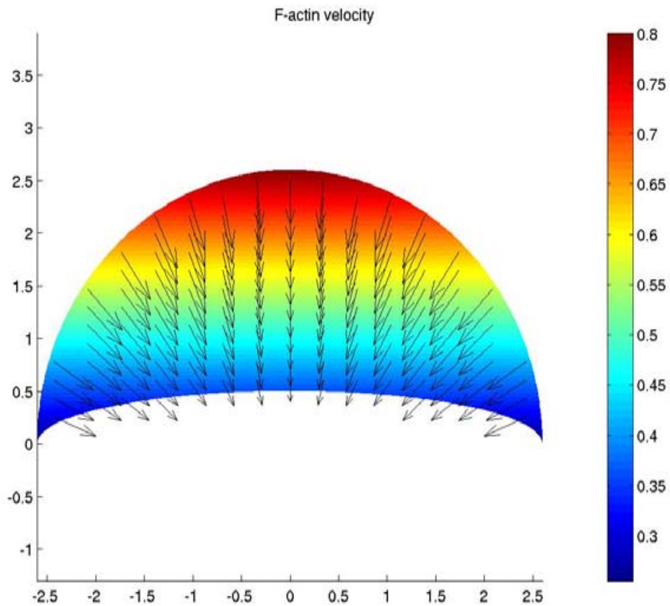


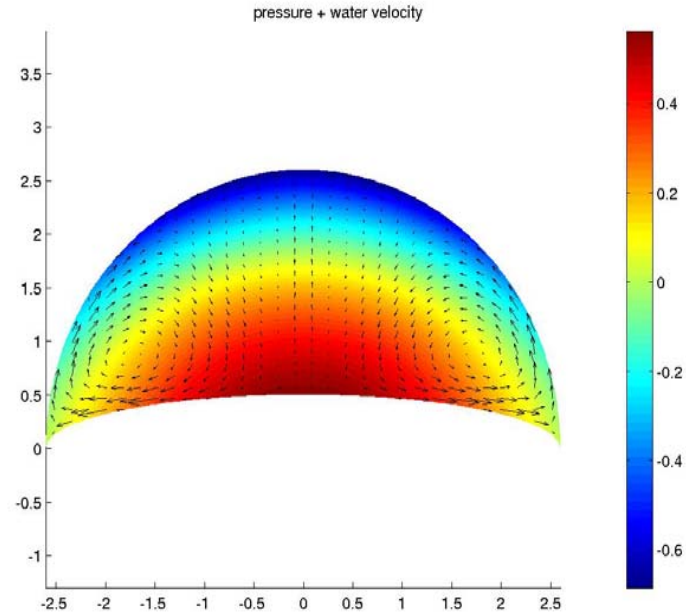
Mogilner & Edelstein-Keshet,
***Biophys. J.* 83 , 1237-1258 (2002)**

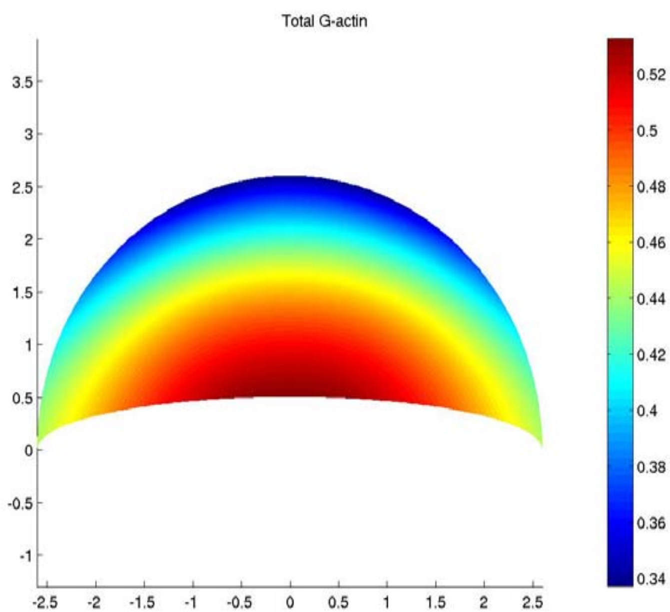
Actin transport



Pollard, Mullins et al.







$$\frac{\partial b}{\partial t} = -k_1 b + k_2 a + D\Delta b - \nabla \cdot (\mathbf{V}_c b),$$

$$\frac{\partial a}{\partial t} = k_1 b - k_2 a + \gamma f + D\Delta a - \nabla \cdot (\mathbf{V}_c a).$$

$$([-D(\nabla a) + \mathbf{V}_c a] \cdot \mathbf{n})(\mathbf{x}) = -\frac{V(\mathbf{x}) f(\mathbf{x})}{\delta v}.$$

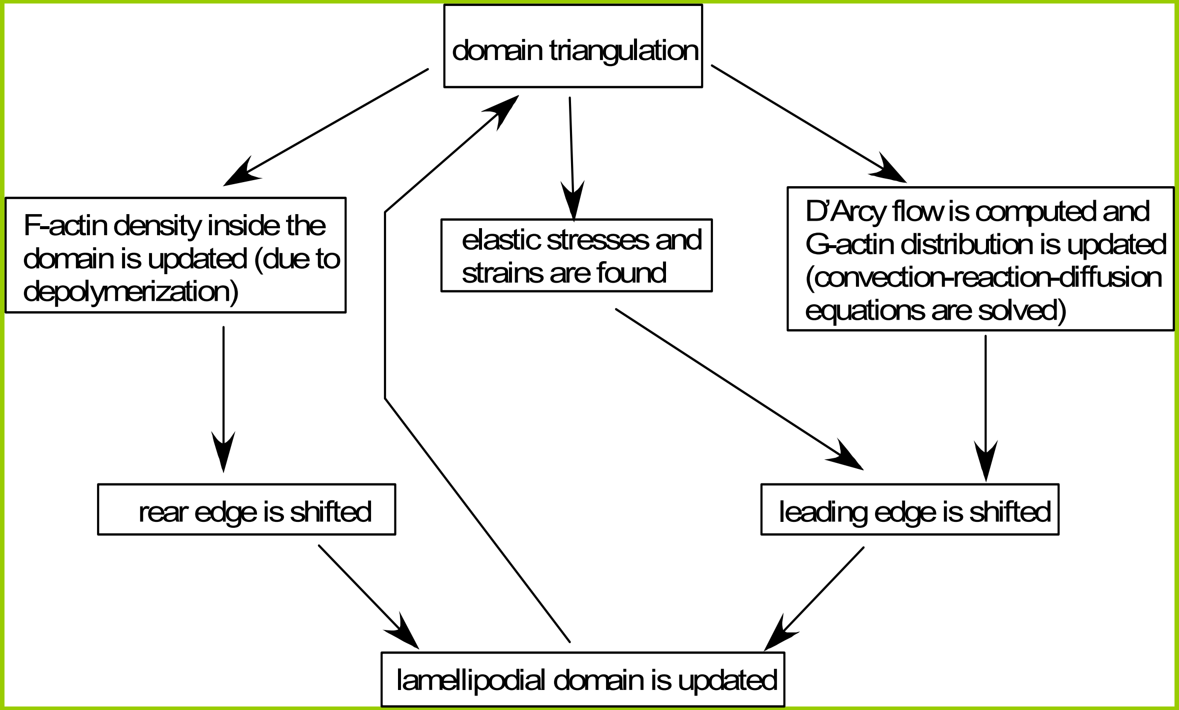
$$\frac{\partial f}{\partial t} = -\gamma f.$$

$$(\mathbf{V}_c - \mathbf{V}_f) = -\frac{K}{\phi\eta}\nabla P, \quad \phi \approx 1 - 0.1 f, \quad K \approx \frac{d^2\phi^3}{(1-\phi)^2},$$

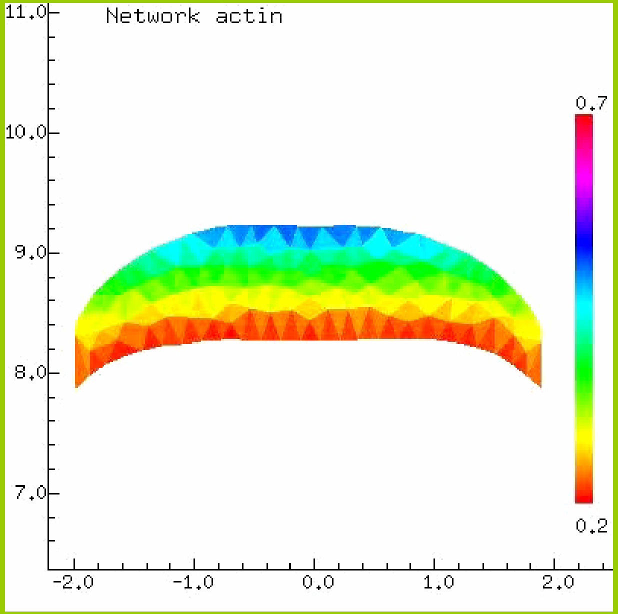
$$\nabla \cdot [\mathbf{V}_c \phi + \mathbf{V}_f (1-\phi)] = 0.$$

B. Rubinstein, K. Jacobson, A. Mogilner, *SIAM J. MMS*, In Press:
http://www.math.ucdavis.edu/~mogilner/CellMov.html

Assembling the modules into a virtual cell



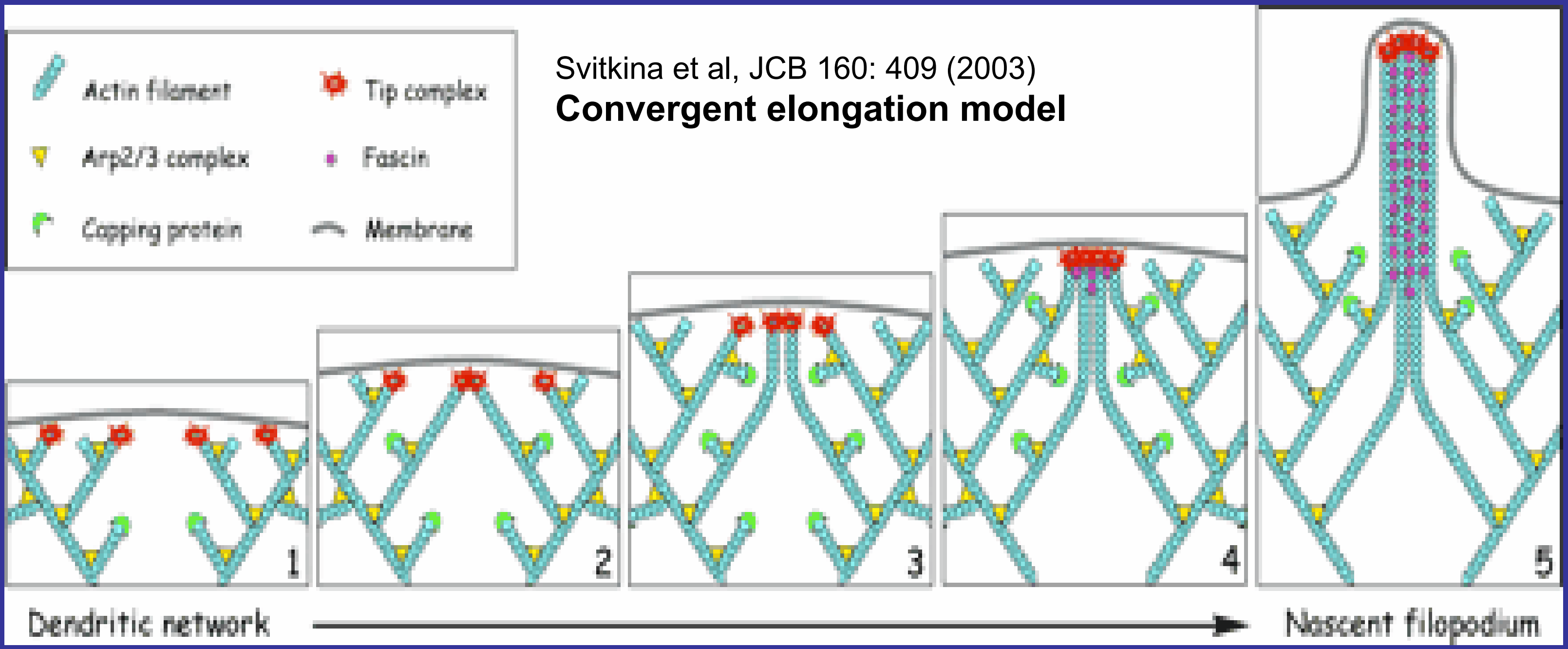
Fragment simulation is at:
http://www.math.ucdavis.edu/~mogilner/CompKerat1.mpg



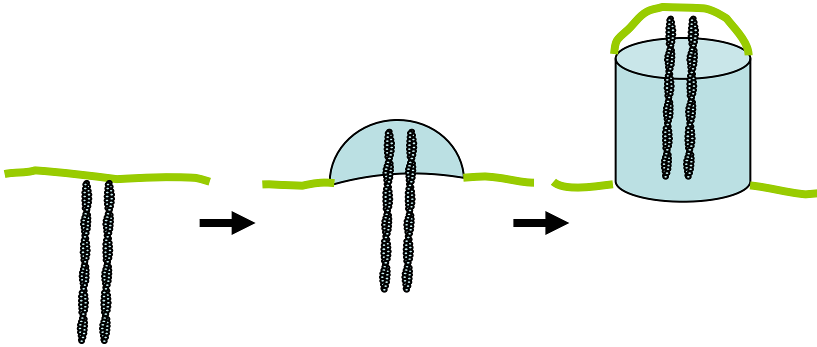
B. Rubinstein, K. Jacobson, A. Mogilner, *SIAM J. MMS*, In Press:
http://www.math.ucdavis.edu/~mogilner/CellMov.html

Filopodia as:
- Scaffold for lamellipodia (implies mechanical strength)
- Signaling/probing antennae (implies mechanical weakness)

Questions:
What is the mechanism of the protrusion force generation?
How are filopodia initiated?
How are filopodia maintained: actin transport?
Do filopodia have a mechanical role?

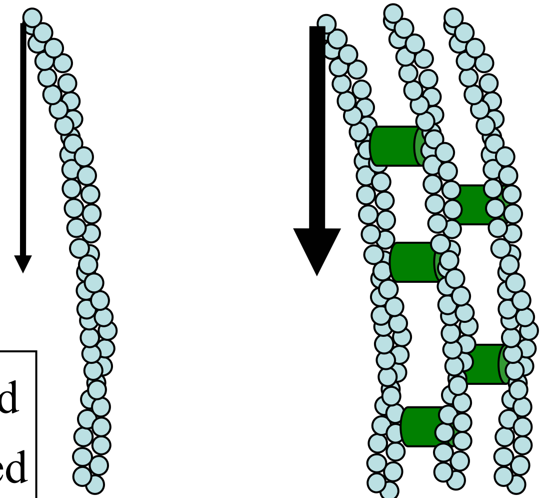


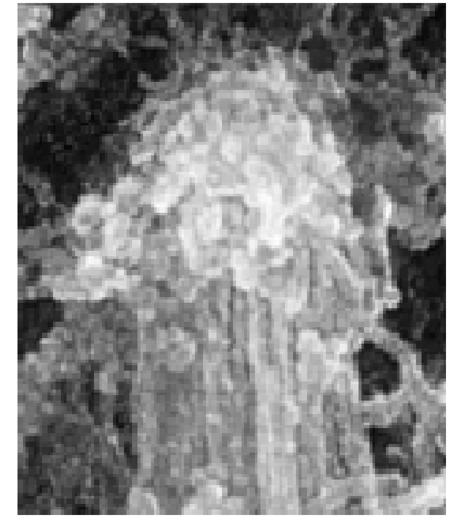
Buckling force:



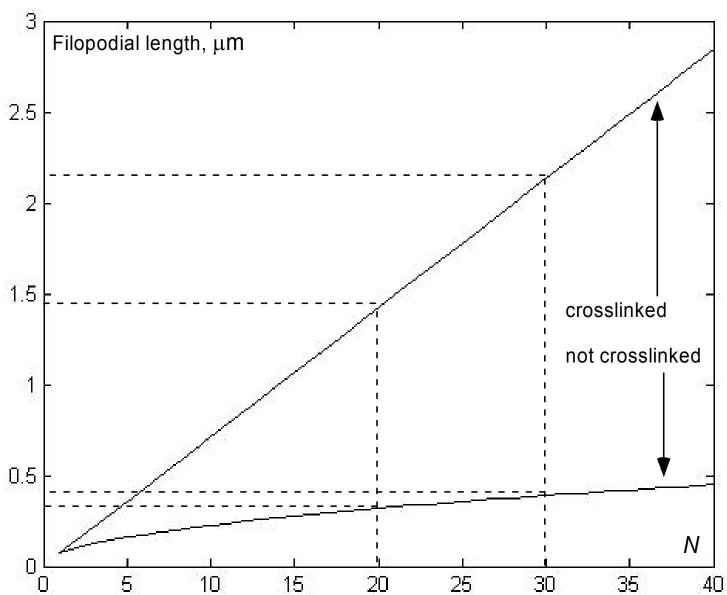
$F_1 \sim 100\,pN$ $F_2 \sim 100\,pN$

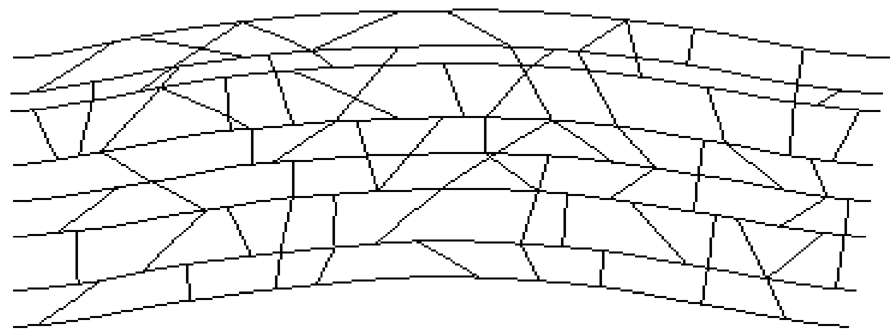
$$L_{\max} = \frac{\pi}{2}\sqrt{\frac{k_B T \lambda}{F}} \times \begin{cases} \sqrt{N} & \text{weakly crosslinked} \\ N & \text{strongly crosslinked} \end{cases}$$





Svitkina et al, JCB 2003

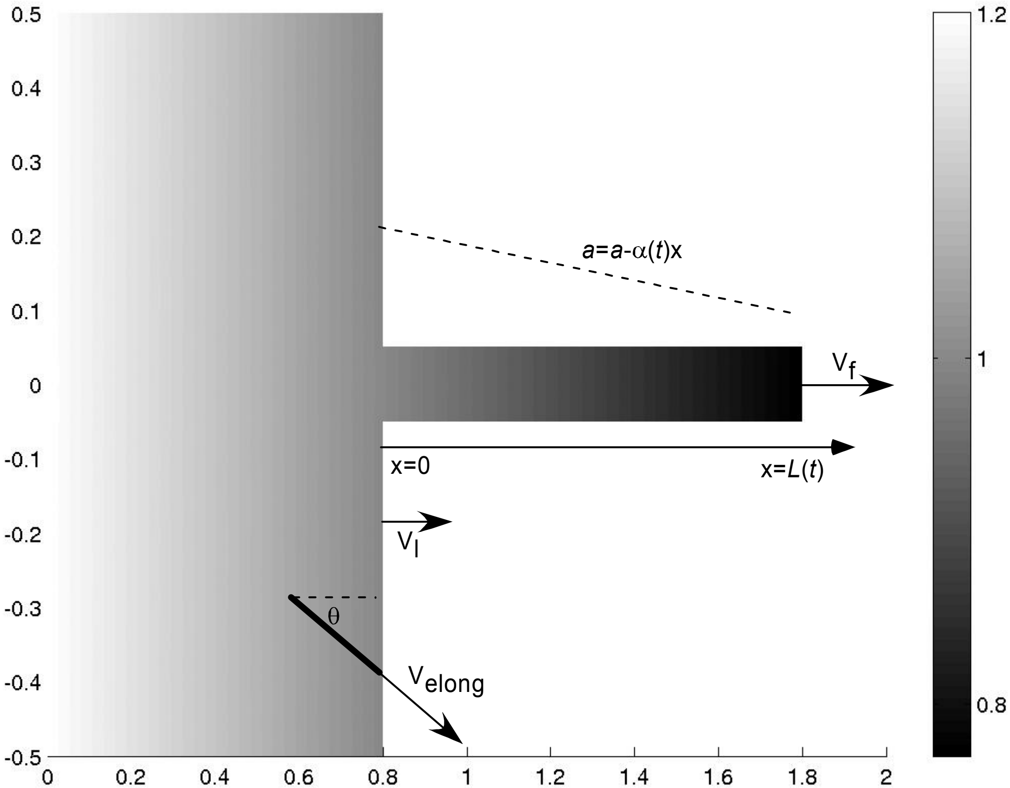


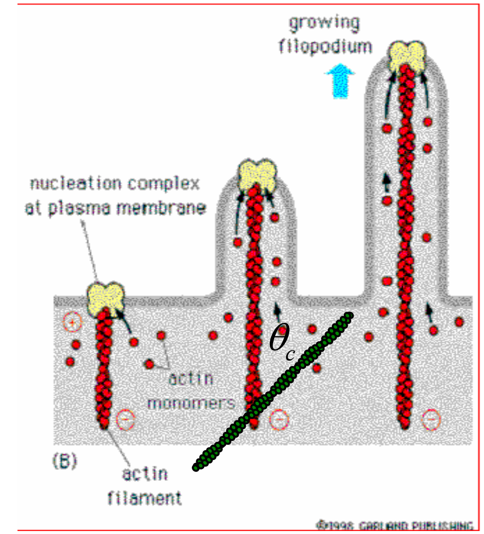


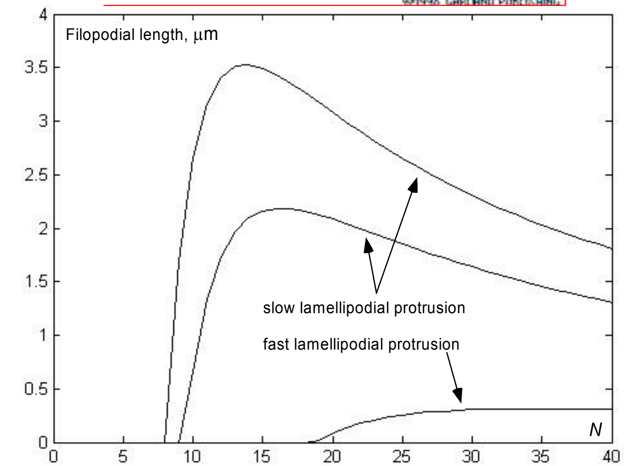
$\lambda_1 \approx 10\,\mu m,\ \lambda_N \approx \lambda_1 \cdot N^2,\ N \approx 25,\ \lambda_N \approx 6mm$

Experiment: $\lambda_N \approx 14mm$ (D. Mullins)

Membrane resistance and G-actin diffusion:







$$\frac{\partial a}{\partial t} = D\frac{\partial^2 a}{\partial x^2} - \frac{\partial}{\partial x}\left[\left(\frac{dL}{dt}\right)a\right],$$

$$a(0) = a_0, \quad -D\frac{\partial a}{\partial x}\Big|_{x=L(t)} = \frac{NV_f}{\eta\delta}$$

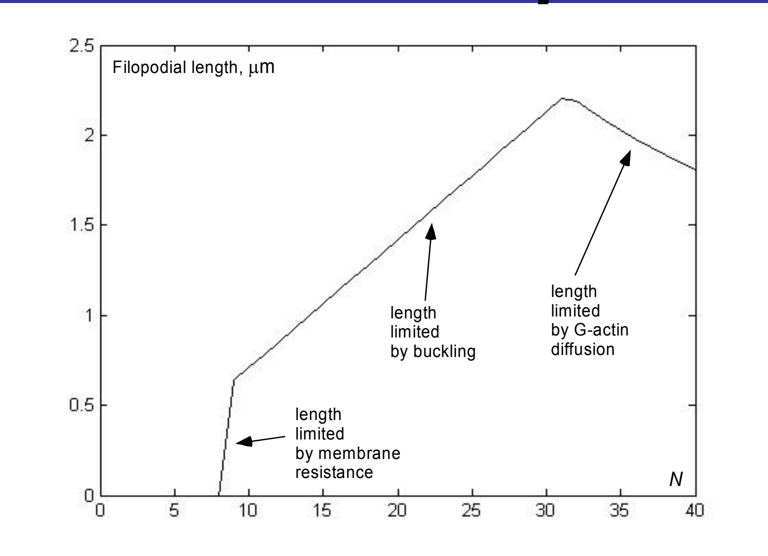
$$\frac{dL}{dt} = V_f - V_l, \; V_l = k_{on}\delta a_0 \cos\theta_c$$

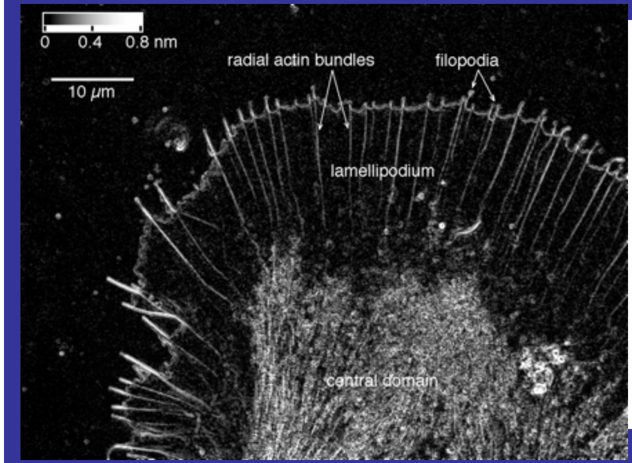
$$V_f = k_{on}\delta a(L)\exp\left[-F\delta / k_B TN\right]$$

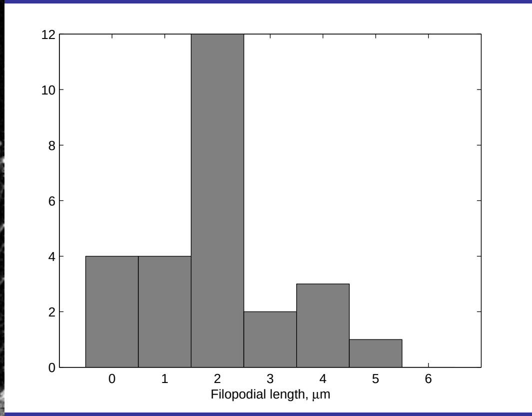
$$L_{\max} = \left(\frac{D\eta}{k_{on}}\right)\times\frac{1}{N}\times\left(\frac{1}{\cos\theta_c} - e^{N_0/N}\right) \sim \frac{D\eta}{k_{on}N} \sim 1\mu m$$

$5\mu m^2/s$ (D), $20\mu M^{-1}\mu m^{-1}$ (η), $10\mu M^{-1}s^{-1}$ (k_{on}), 10 (N)

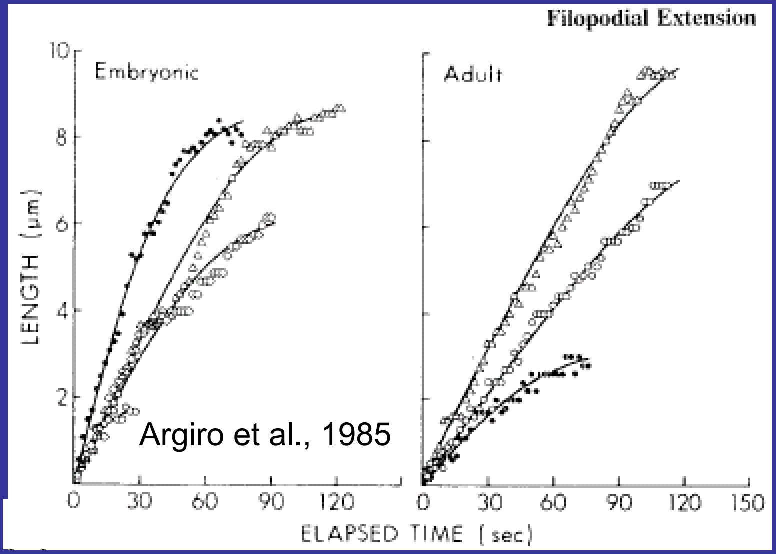
Comparison to experimental data:



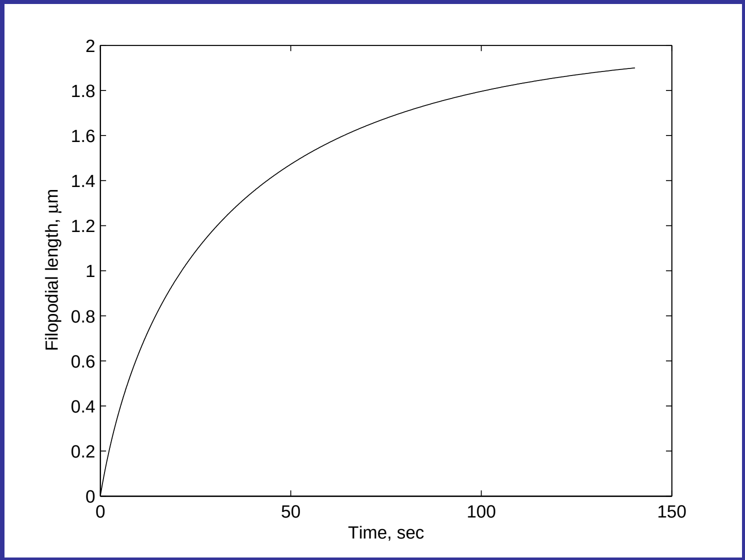




Oldenburg et al., 2000



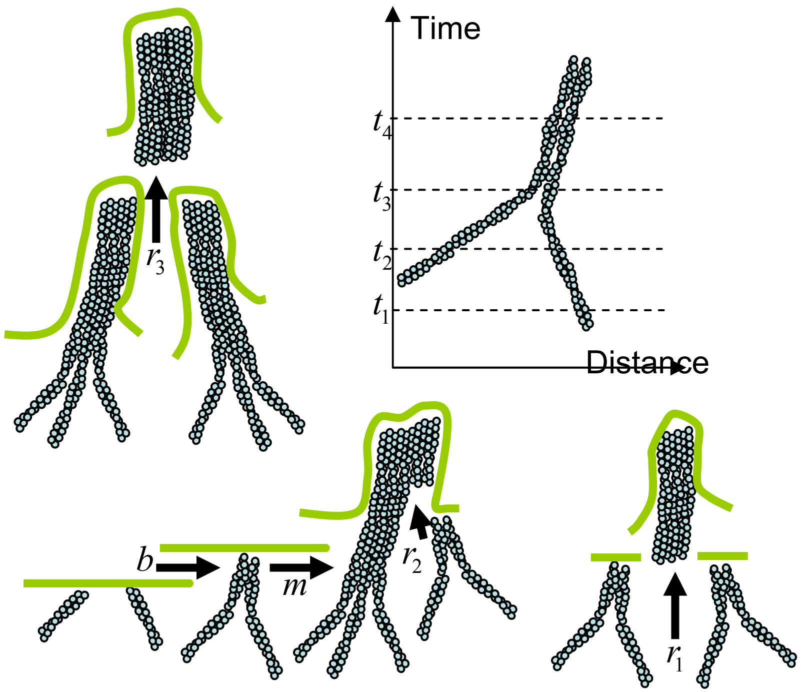
Argiro et al., 1985

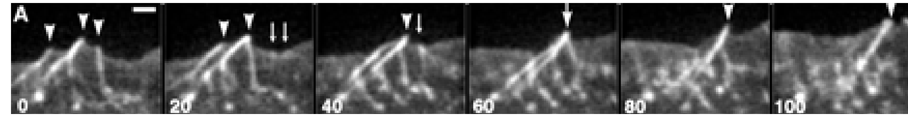


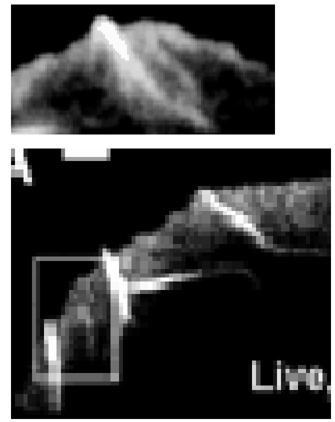
Inter-filopodial distance:

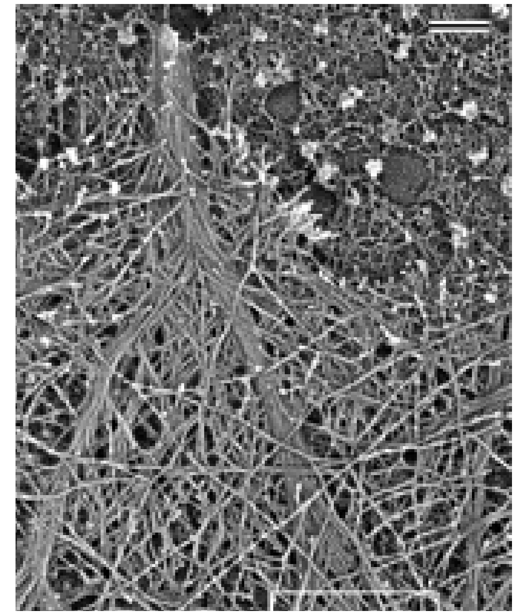
$$\frac{d\lambda}{dt} = b - m\lambda - 2\left(v_{ld}\lambda\right)\lambda - \left(v_{ld}\lambda\right)f$$

$$\frac{df}{dt} = m\lambda + \left(v_{ld}\lambda\right)\lambda - \left(v_{ld}f\right)f$$









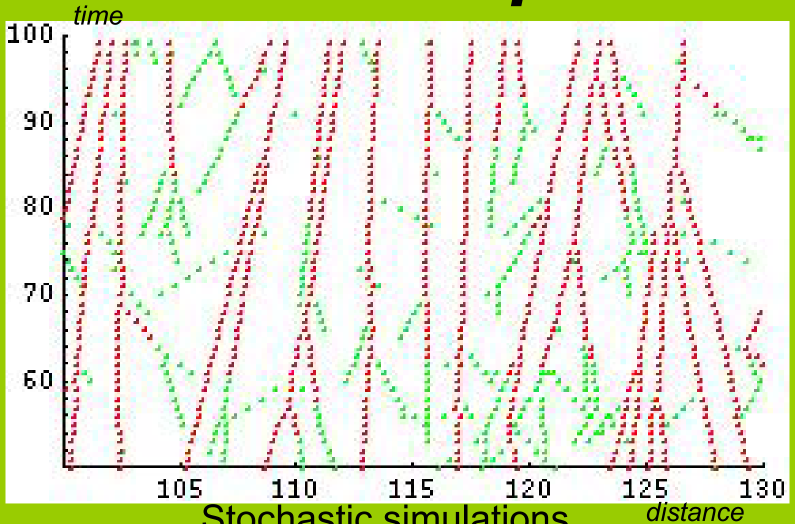
Svitkina et al, JCB 2003

$$f \sim \sqrt{b / v_{ld}},$$

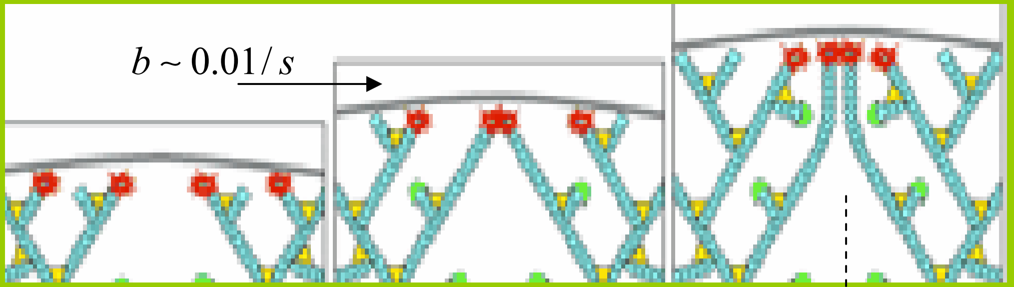
$$f \sim 1/\mu m, v_{ld} \sim 0.01 \mu m / s,$$

$$b \sim 0.01 / s$$

Comparison to experimental data:



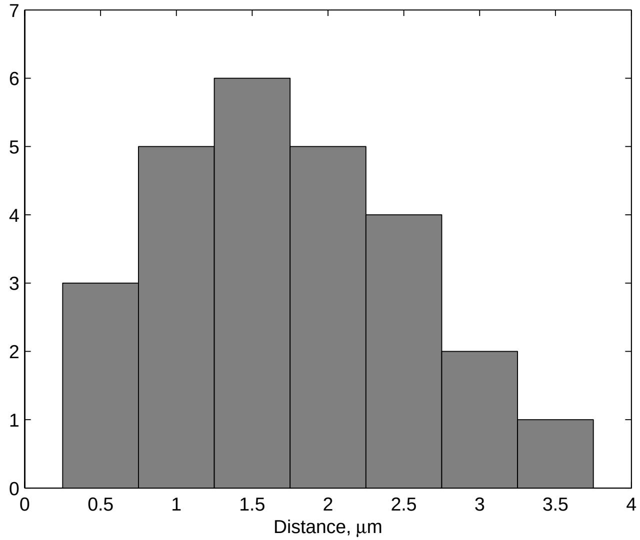
Stochastic simulations



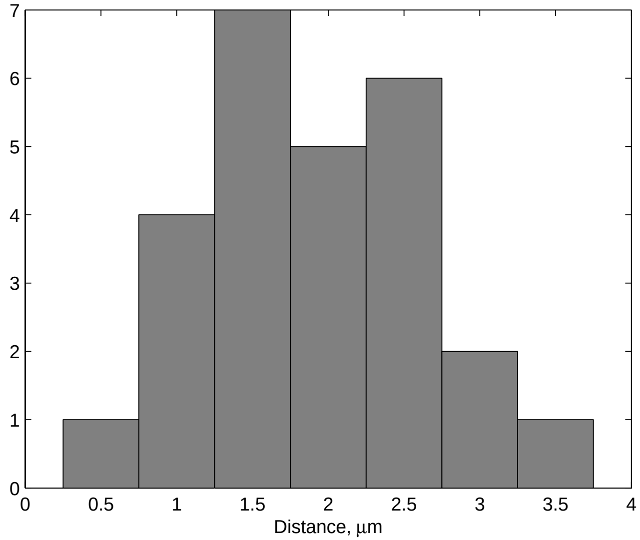
$$\frac{dN}{dt} = b - cN \qquad N = \frac{b}{c} \sim 10$$

$c - ?$

$$c = \frac{b}{N} \sim 0.01/s$$



Theory



Experiment

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Ken Jacobson

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