Mathematical Cell Biology Graduate Summer Course

University of British Columbia, May 1-31, 2012

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Models for cell shape and actin filament distribution

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Analysis of actin dynamics at the leading edge of crawling cells: implications for the shape of keratocyte lamellipodia

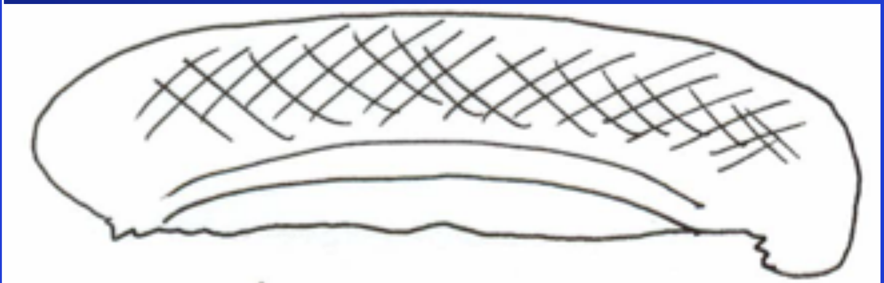
Eur Biophys J (2003) 32: 563–577

- steady-state graded actin distribution across cell edge resulting from branching, growth and capping

http://www.math.ucdavis.edu/~mogilner/CellMov.html

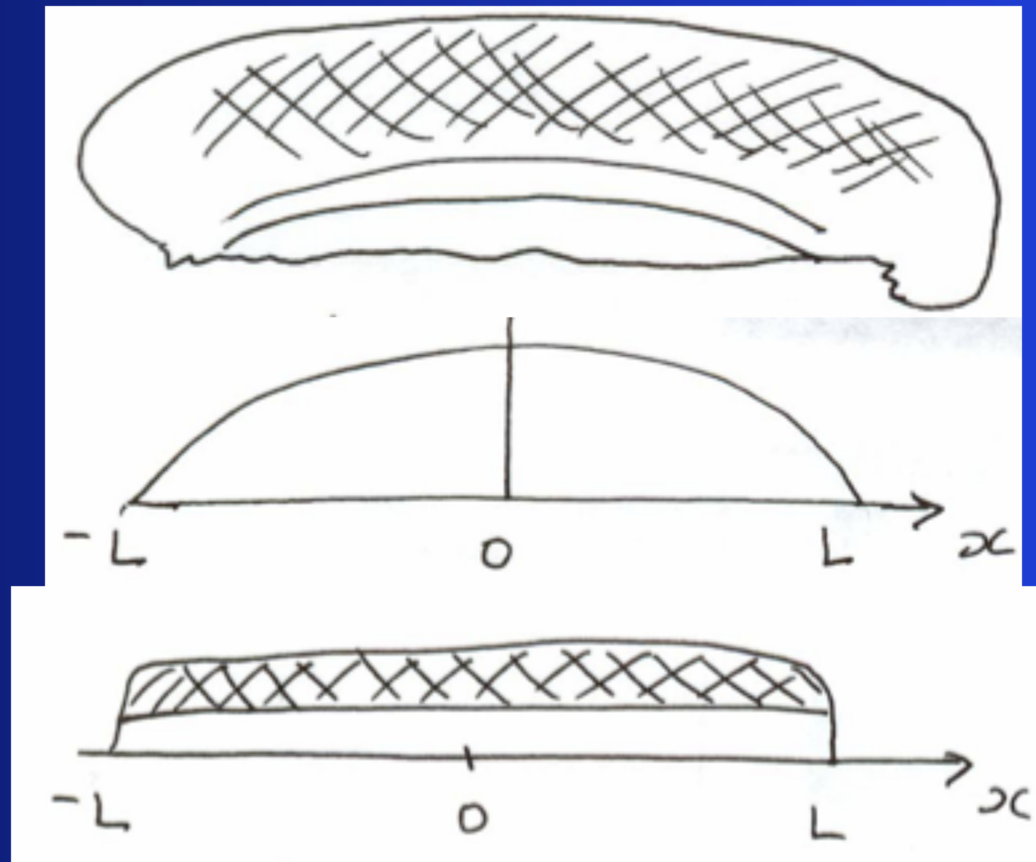
Keratocyte shape and actin distribution

Images removed due to copyright issues.. See original paper for keratocyte shape and actin density distribution



Actin filaments along front edge

- Distribution of angles – two peaks
- Flat front edge

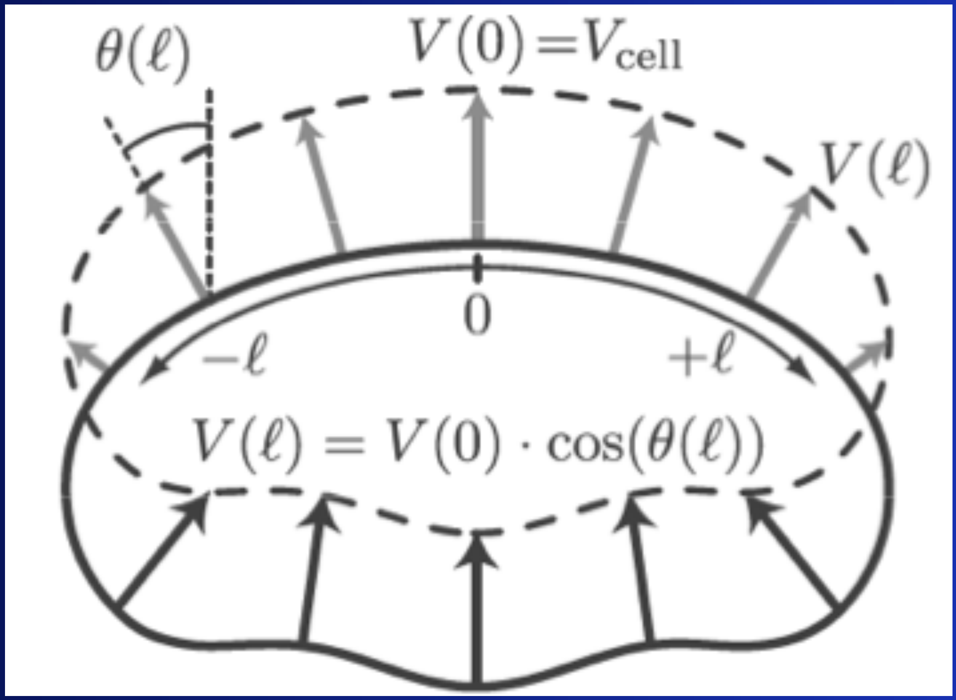


Model components

Images removed due to copyright issues.. See original paper for schematic diagram of model components

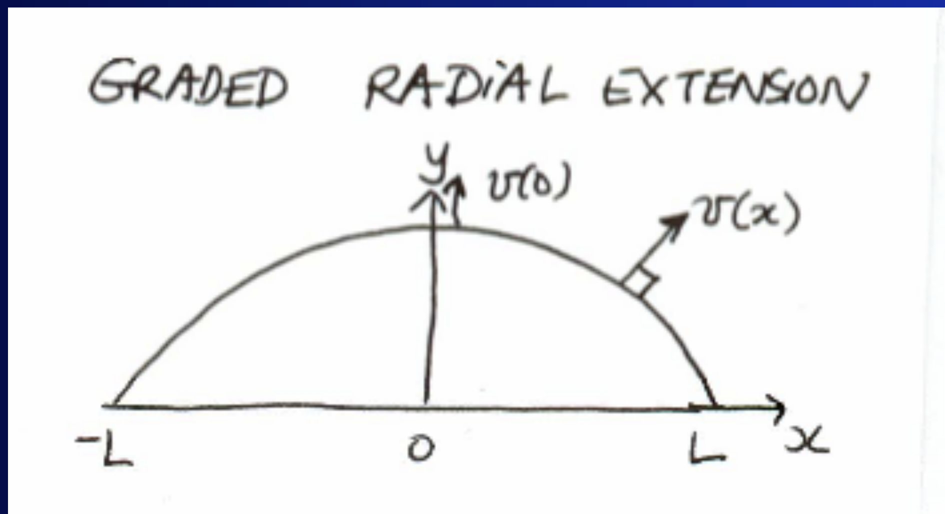
Graded radial extension:

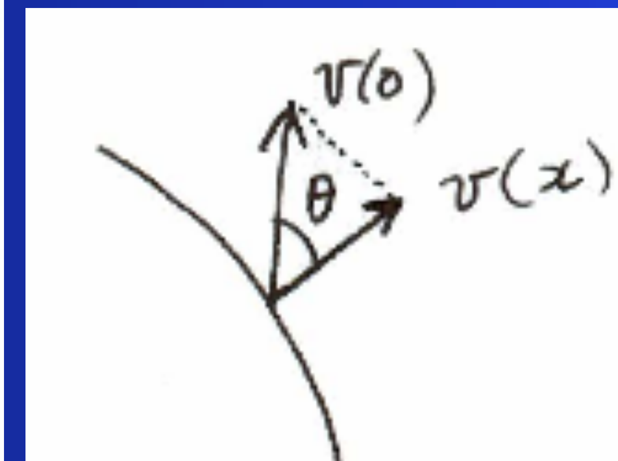
- Lee, Theriot, Jacobson et al 93:



To preserve shape, forward extension must be graded along the front (rear) edge of the cell

Graded radial extension

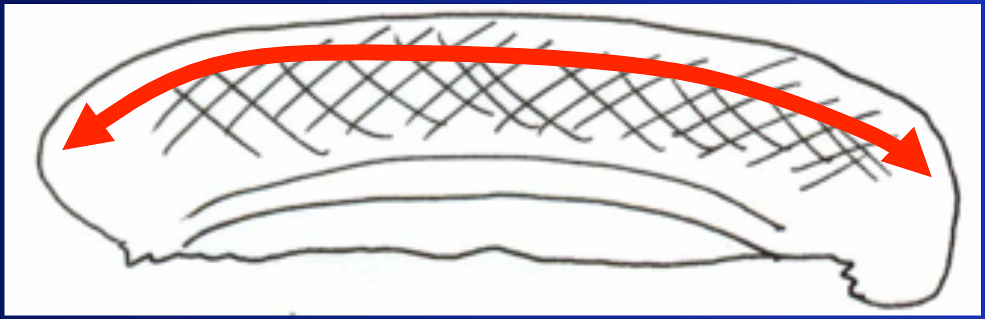




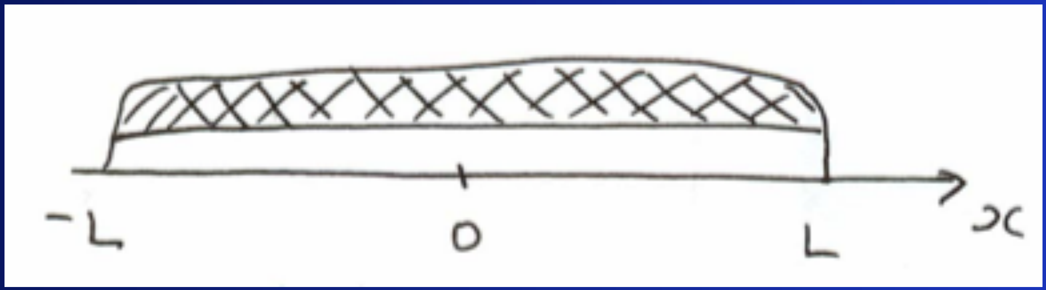
$$\frac{v(x)}{v(0)} = \cos(\theta(x))$$

$$\theta(x) = \arccos\left(\frac{v(x)}{v(0)}\right)$$

Model for actin filament distribution along front edge



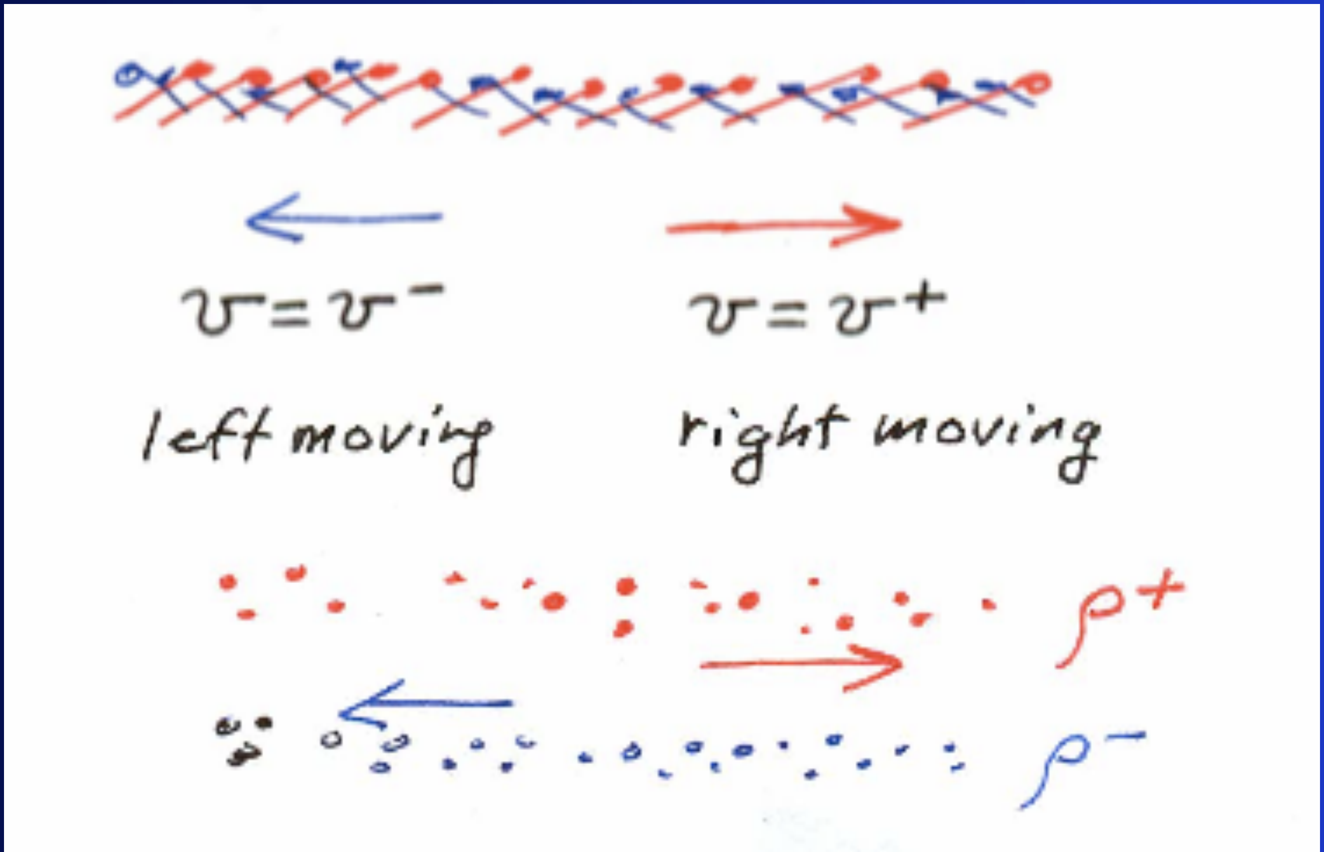
- Two filament populations (facing right/left)



- Flat front edge – reduction to 1D

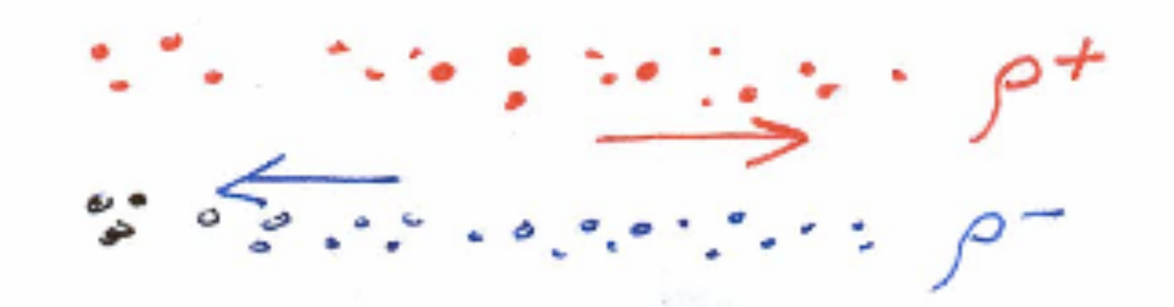
1D projection: two types

$$\rho^+(x,t) = \text{right facing filaments}$$
$$\rho^-(x,t) = \text{left facing filaments}$$



Formulating the equations

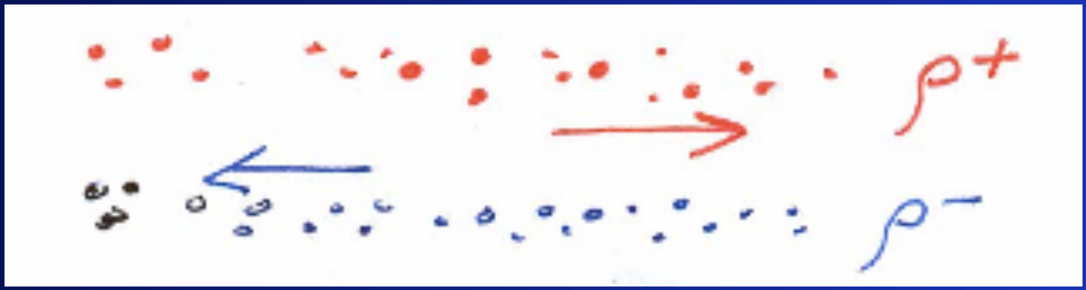
- 1D balance equations:



$$\frac{\partial \rho^+}{\partial t} = -\frac{\partial}{\partial x}(v^+\rho^+) + \text{branching} - \text{capping}$$

$$\frac{\partial \rho^-}{\partial t} = \frac{\partial}{\partial x}(v^-\rho^-) + \text{branching} - \text{capping}$$

Model equations



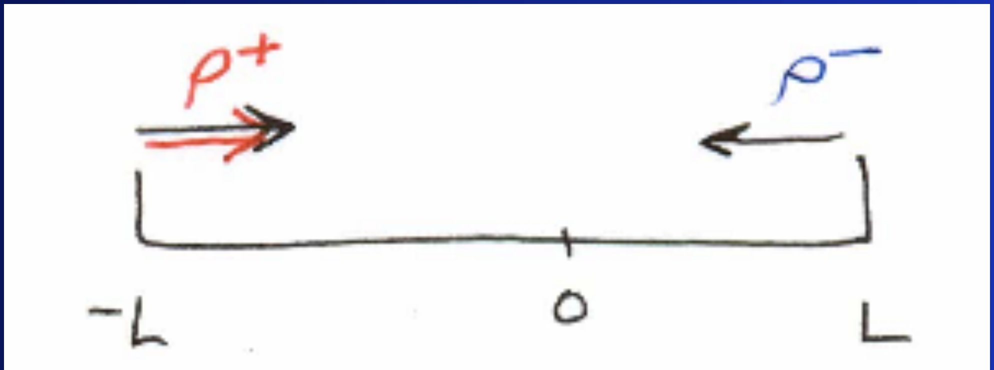
$$\frac{\partial \rho^+}{\partial t} = -v \frac{\partial}{\partial x}\rho^+ + \beta b_{1,2}(\rho^-) - \gamma \rho^+$$

$$\frac{\partial \rho^-}{\partial t} = v \frac{\partial}{\partial x}\rho^- + \beta b_{1,2}(\rho^+) - \gamma \rho^-$$

Model equations

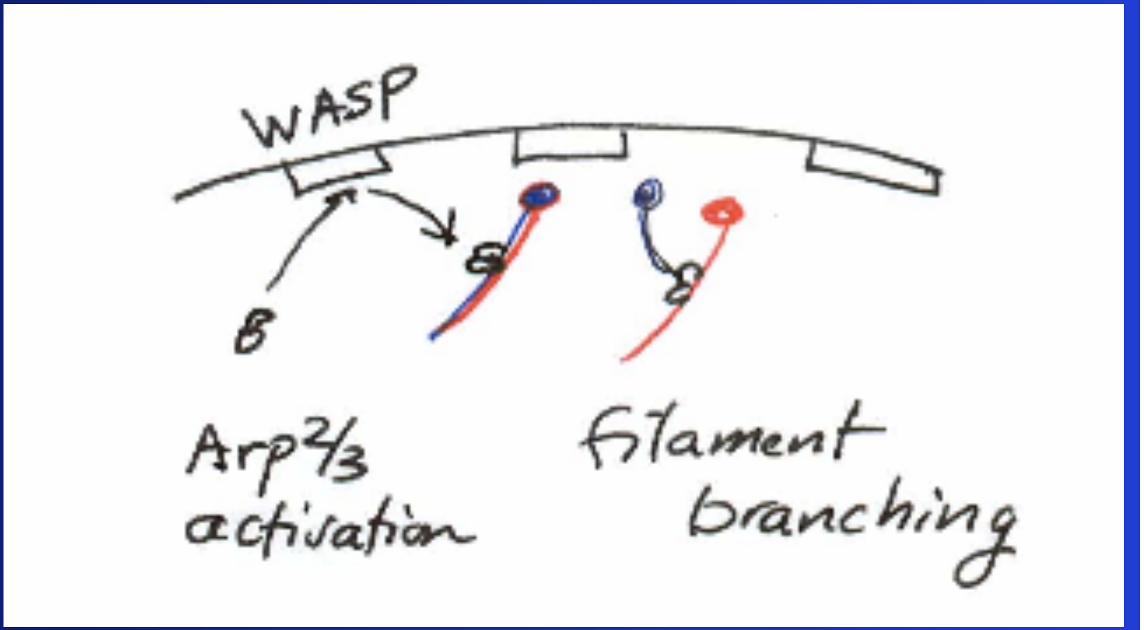
- BCs:

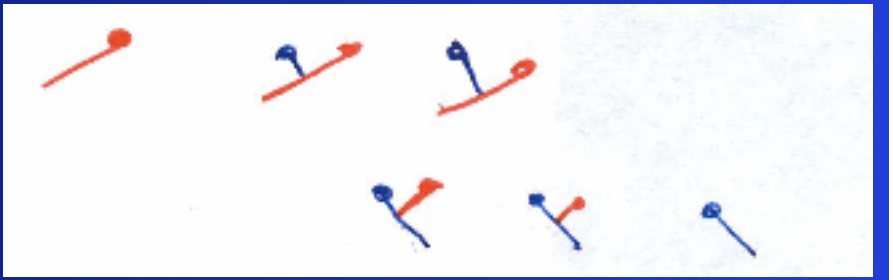
$$\rho^+(-L) = 0, \quad \rho^-(L) = 0$$



Branching by Arp2/3

- New filaments formed by Arp2/3
- Each type of filament produces daughters of other type





Scaling the model

$$x = x^* \bar{x}, \quad t = t^* \tau, \quad \rho_i = \rho_i^* \bar{\rho}$$

$$\bar{x} = L, \quad \tau = L/v, \quad \bar{\rho} = \beta L/v$$

$$\frac{\partial \rho^+}{\partial t} = -\frac{\partial}{\partial x}\rho^+ + b_{1,2}(\rho^-) - \epsilon\rho^+$$

$$\frac{\partial \rho^-}{\partial t} = \frac{\partial}{\partial x}\rho^- + b_{1,2}(\rho^+) - \epsilon\rho^-$$

$$\epsilon = \gamma L/v.$$

Competition for Arp2/3

	(1) Local		(2) Global
•	Slow	Arp2/3 diffusion	Fast
•		Branching	
	$b_1(\rho^{\pm}) = \frac{\rho^{\pm}}{\rho^{+} + \rho^{-}}$		$b_2(\rho^{\pm}) = \frac{\rho^{\pm}}{\bar{\rho}/L}$

Competition for Arp2/3

- (1) Local (2) Global
- Slow Arp2/3 diffusion Fast
- Branching

$$b_1(\rho^{\pm}) = \frac{\rho^{\pm}}{\rho^{+} + \rho^{-}}$$

$$b_2(\rho^{\pm}) = \frac{\rho^{\pm}}{\bar{\rho}/L}$$

Steady state filament distribution

- Consider the case of slow capping $\epsilon = \gamma L/v << 1$
- Equations are:

$$0 = -\frac{\partial}{\partial x}\rho^+ + \frac{\rho^-}{\rho^+ + \rho^-}$$

$$0 = \frac{\partial}{\partial x}\rho^- + \frac{\rho^+}{\rho^+ + \rho^-}$$

- BCs:

$$\rho^+(-1) = 0, \quad \rho^-(1) = 0$$

Solving the equations

- Define new variables and transform the eqs

$$s(x) = \rho^+(x) - \rho^-(x),$$
$$p(x) = \rho^+(x) + \rho^-(x)$$

(Why do this? – Because it is a very cute trick to simplify the equations and solve them)

Solving the equations

- New variables

$$s(x) = \rho^{+}(x) - \rho^{-}(x),$$
$$p(x) = \rho^{+}(x) + \rho^{-}(x)$$

- New eqs:

$$\frac{\partial s}{\partial x} = 1$$
$$\frac{\partial p}{\partial x} = -\frac{s}{p}$$

- New BCs:

$$s(1) = p(1),$$
$$s(-1) = -p(-1)$$

New eqs easily solved:

$$\frac{\partial s}{\partial x} = 1$$

$$\frac{\partial p}{\partial x} = -\frac{s}{p}$$

$$s(x) = x,$$

$$p(x) = \sqrt{2 - x^2}$$

Solutions:

- In terms of s,p

$$s(x) = x,$$
$$p(x) = \sqrt{2 - x^2}$$

- In terms of original variables:

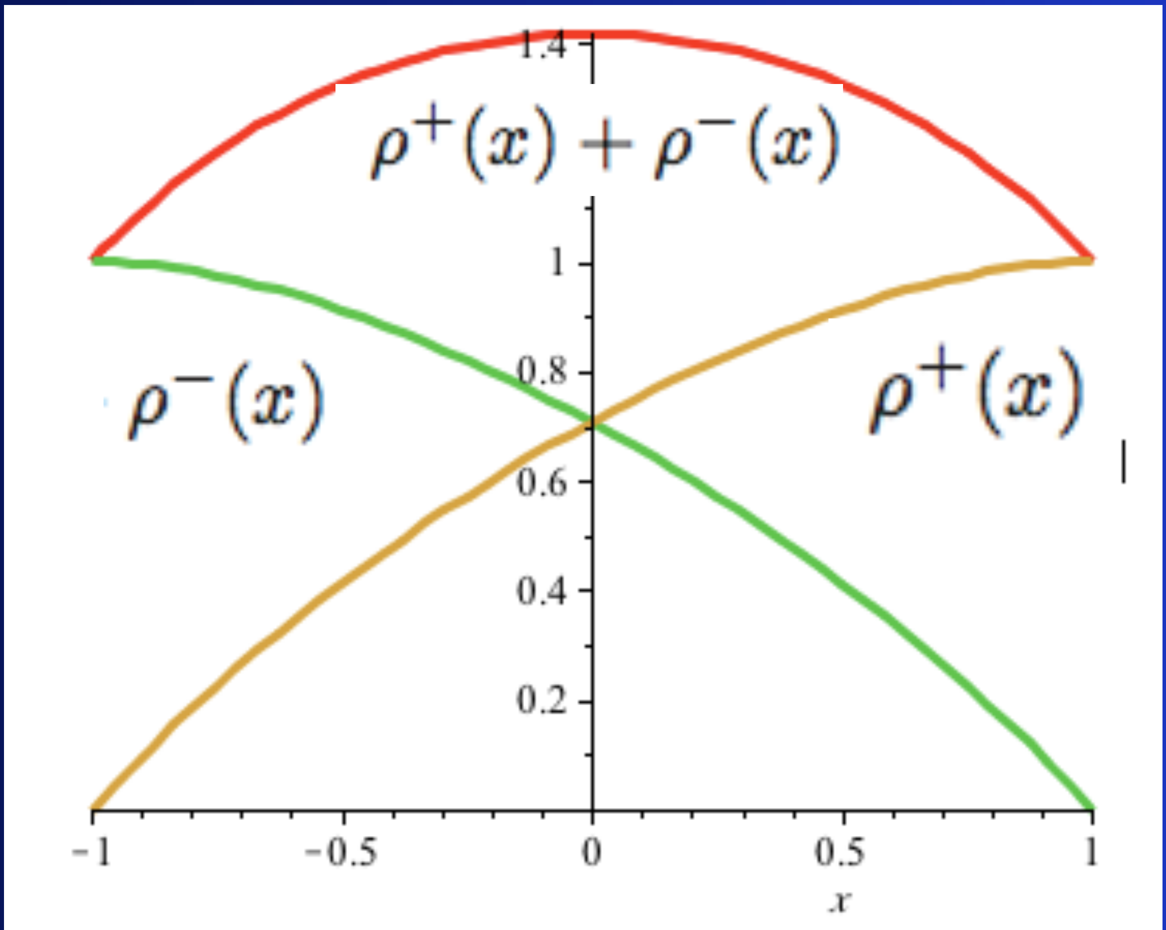
$$\rho^+(x) = \frac{p(x) + s(x)}{2}$$
$$\rho^-(x) = \frac{p(x) - s(x)}{2}$$

$$\rho^+(x) = \frac{1}{2}\left(\sqrt{2 - x^2} + x\right),$$
$$\rho^-(x) = \frac{1}{2}\left(\sqrt{2 - x^2} - x\right)$$

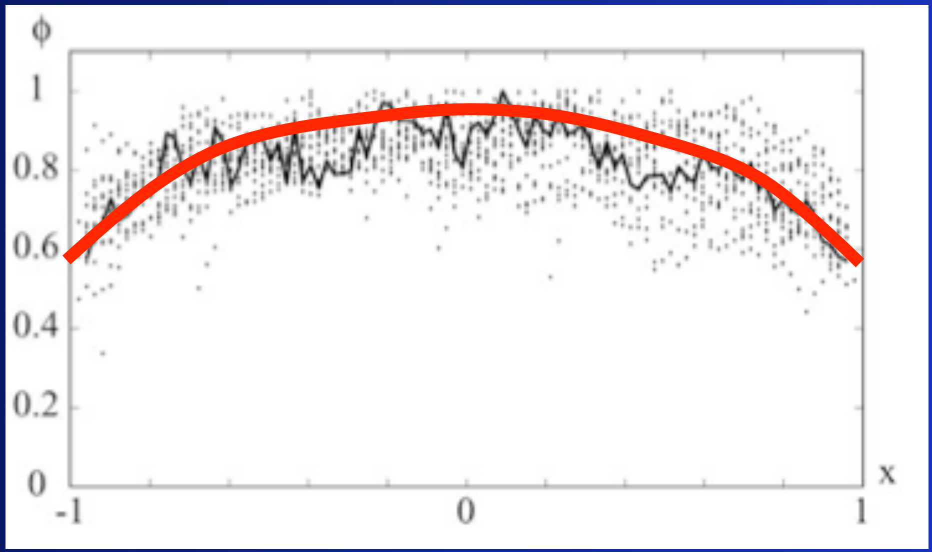
- Total density:

$$\rho^+(x) + \rho^-(x) = \sqrt{2 - x^2}$$

Actin density



Agrees with experimental results



Other results

- Slow capping, global Arp2/3 model:

$$p \approx \frac{\beta L}{\sqrt{2}V}\cos\left(\frac{\pi x}{4L}\right)$$

- Fast capping:

$$\underbrace{p \approx \frac{\beta}{\gamma}}_{\text{local model}}, \qquad \underbrace{p \approx \frac{\pi\beta}{4\gamma}}_{\text{global model}} \cos\left(\frac{\pi x}{2L}\right),$$

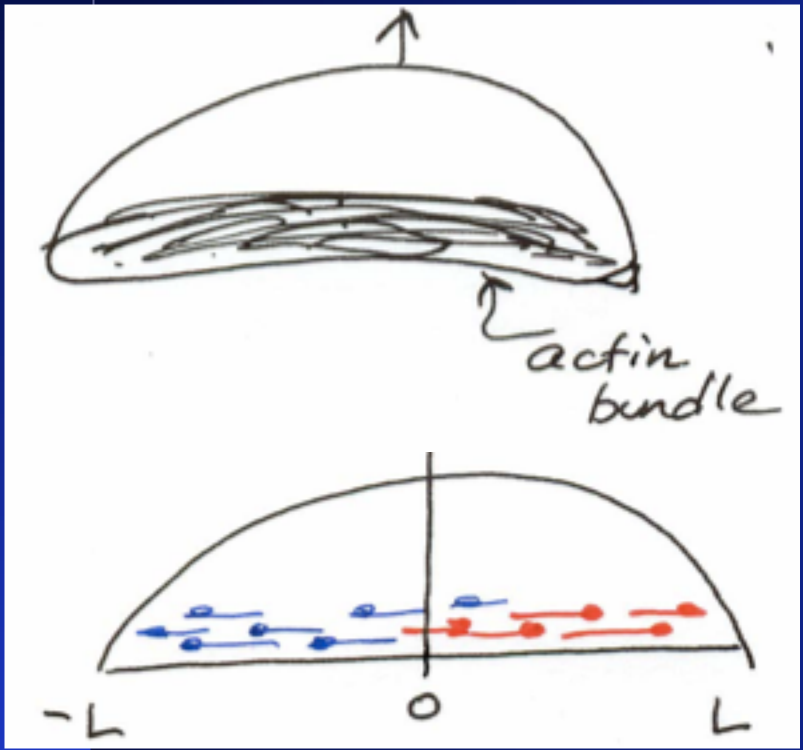
Other results

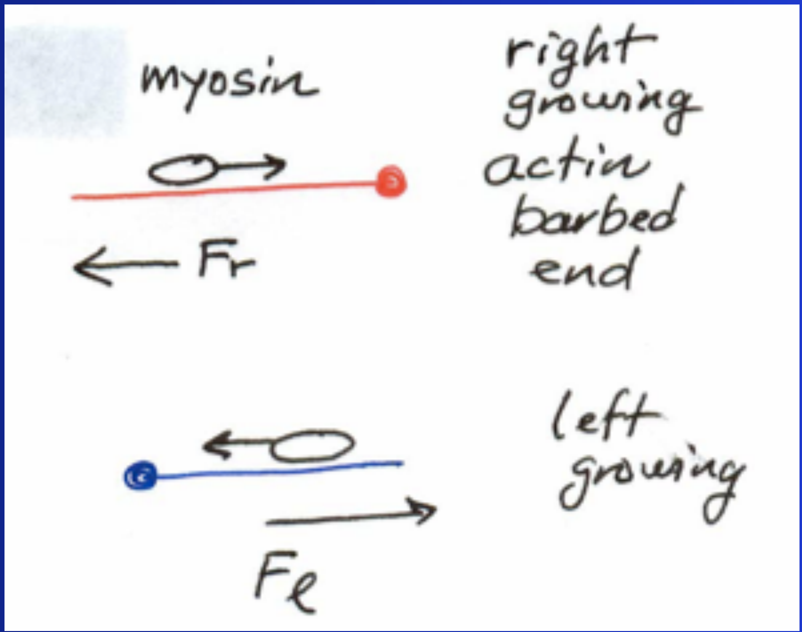
Images removed due to copyright issues.. See original paper for graphs of these model predictions

- Shape of the edge (graded radial extension)
- Actin filament density:
- Protrusion velosity

Other applications

- Actomyosin bundle at back of keratocyte





Rubinstein B, Jacobson K, Mogilner A (2005) Multiscale two-dimensional modeling of a motile simple-shaped cell. Multiscale ModelSimul 3: 413-439.

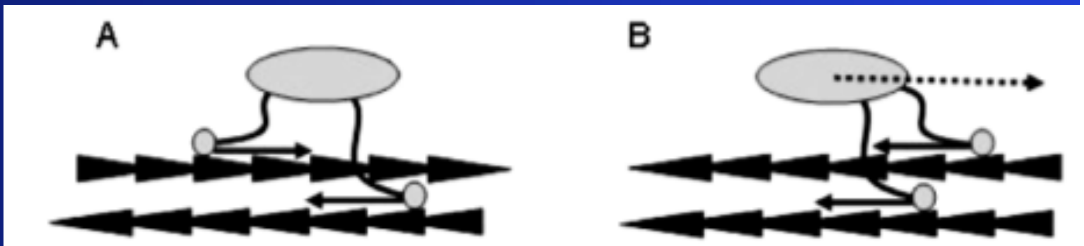
Similar equations

- Right facing filaments
- Left facing
- Myosin motors

$$\frac{\partial r}{\partial t} = n_r(x) - \gamma_b r + \frac{\partial}{\partial x}(v_r r),$$

$$\frac{\partial l}{\partial t} = n_l(x) - \gamma_b l - \frac{\partial}{\partial x}(v_l l),$$

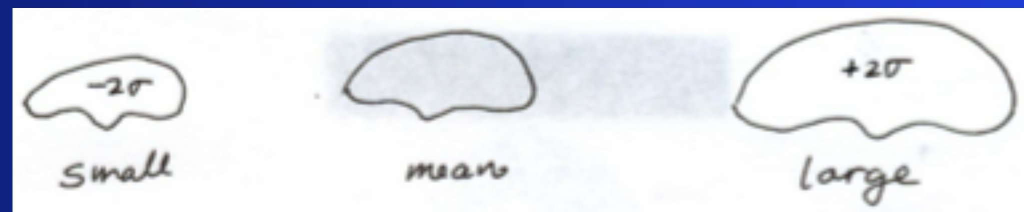
$$\frac{\partial m}{\partial t} = n_m - \gamma_m m - \frac{\partial}{\partial x}(v_m m),$$



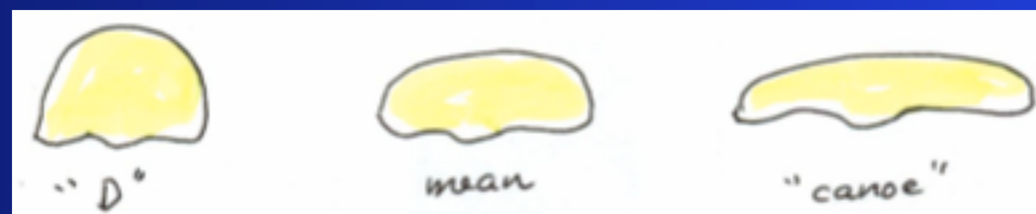
- $V_{l,r} = \pm \dfrac{F_m m}{\zeta_a (r + l)}$

Cell shape “modes”

- Area



- D vs canoe



- Tail shape

- L vs R

K. KEREN, Z. PINCUS, G. M. ALLEND, E. L. BARNHART, G. MARRIOTT, A. MOGILNER, AND J. THERIOT, *Mechanism of shape determinaztion in motile cells*, Nature, 453 (2008), pp. 475–480.

Later appearance: in study of Vasp, a protein that competes with capping

Lacayo CI, Pincus Z, VanDuijn MM, Wilson CA, Fletcher DA, et al. (2007) Emergence of large-scale cell morphology and movement from local actin filament growth dynamics. PLoS Biol 5(9): e233. doi:10.1371/journal.pbio.0050233

$$
\begin{cases}
\underbrace{\dfrac{\partial b^{\pm}}{\partial t}}_{\text{rate of density change}} = \underbrace{\mp V \dfrac{\partial b^{\pm}}{\partial x}}_{\text{lateral flow}} + \underbrace{\dfrac{\beta(b^{\mp} + \tilde{b}^{\mp})}{B}}_{\text{branching}} \underbrace{- \gamma b^{\pm}}_{\text{capping}} \underbrace{+ k_2 \tilde{b}^{\pm}}_{\text{VASP dissociation}} \underbrace{- k_1 b^{\pm}}_{\text{VASP association}} \\
\underbrace{\dfrac{\partial \tilde{b}^{\pm}}{\partial t}}_{\text{rate of density change}} = \underbrace{\mp V \dfrac{\partial \tilde{b}^{\pm}}{\partial x}}_{\text{lateral flow}} \underbrace{- k_2 \tilde{b}^{\pm}}_{\text{VASP dissociation}} \underbrace{+ k_1 b^{\pm}}_{\text{VASP association}} \\
\underbrace{B(t) = \int_{-L}^{L} [b^{+}(x,t) + b^{-}(x,t) + \tilde{b}^{+}(x,t) + \tilde{b}^{-}(x,t)]dx}_{\text{total number of filaments at the leading edge}}
\end{cases}
$$