Mathematical Cell Biology Graduate Summer Course

University of British Columbia, May 1-31, 2012

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Pacific Institute for the
Mathematical Sciences

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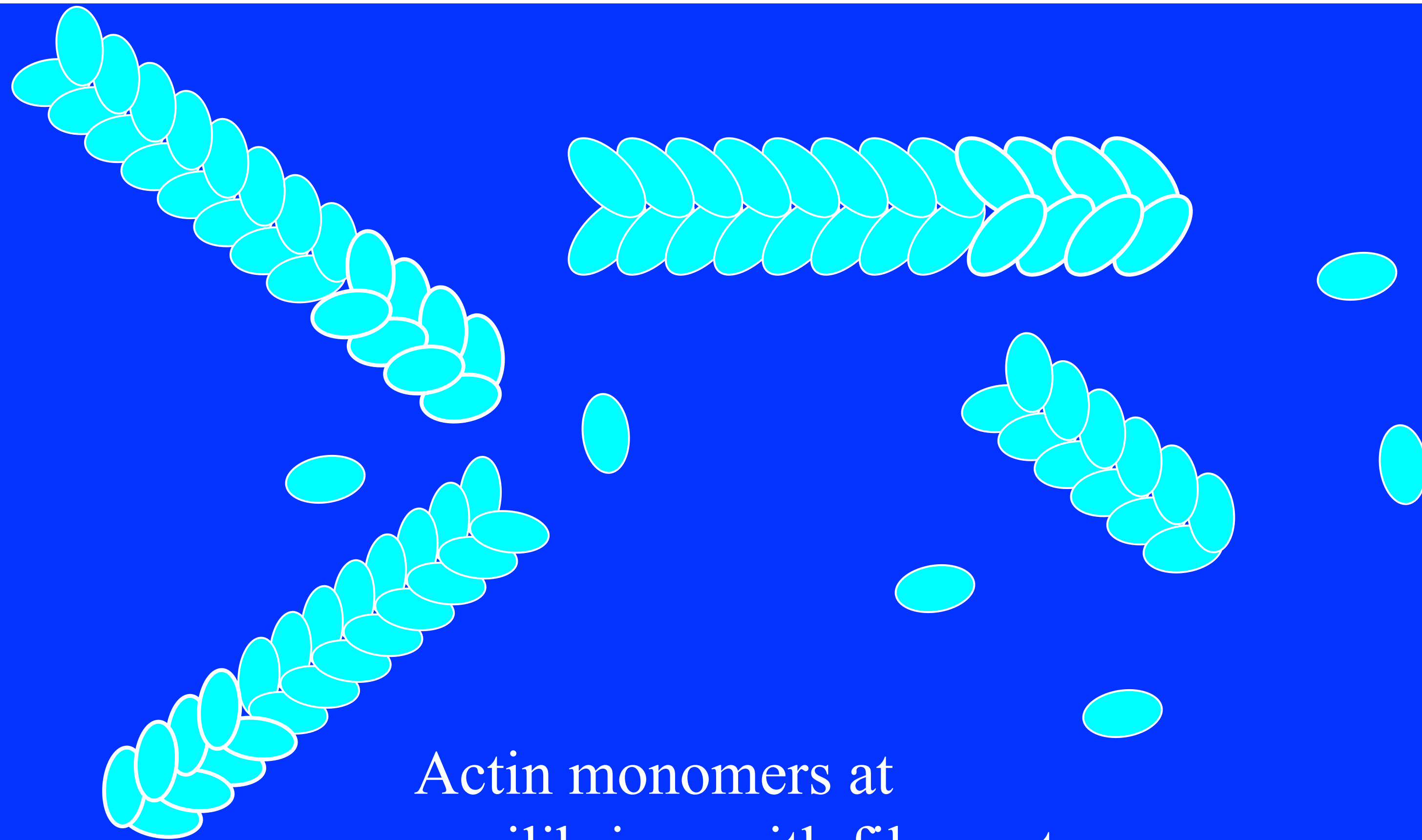
Actin filament length distribution

Models for filament length distributions

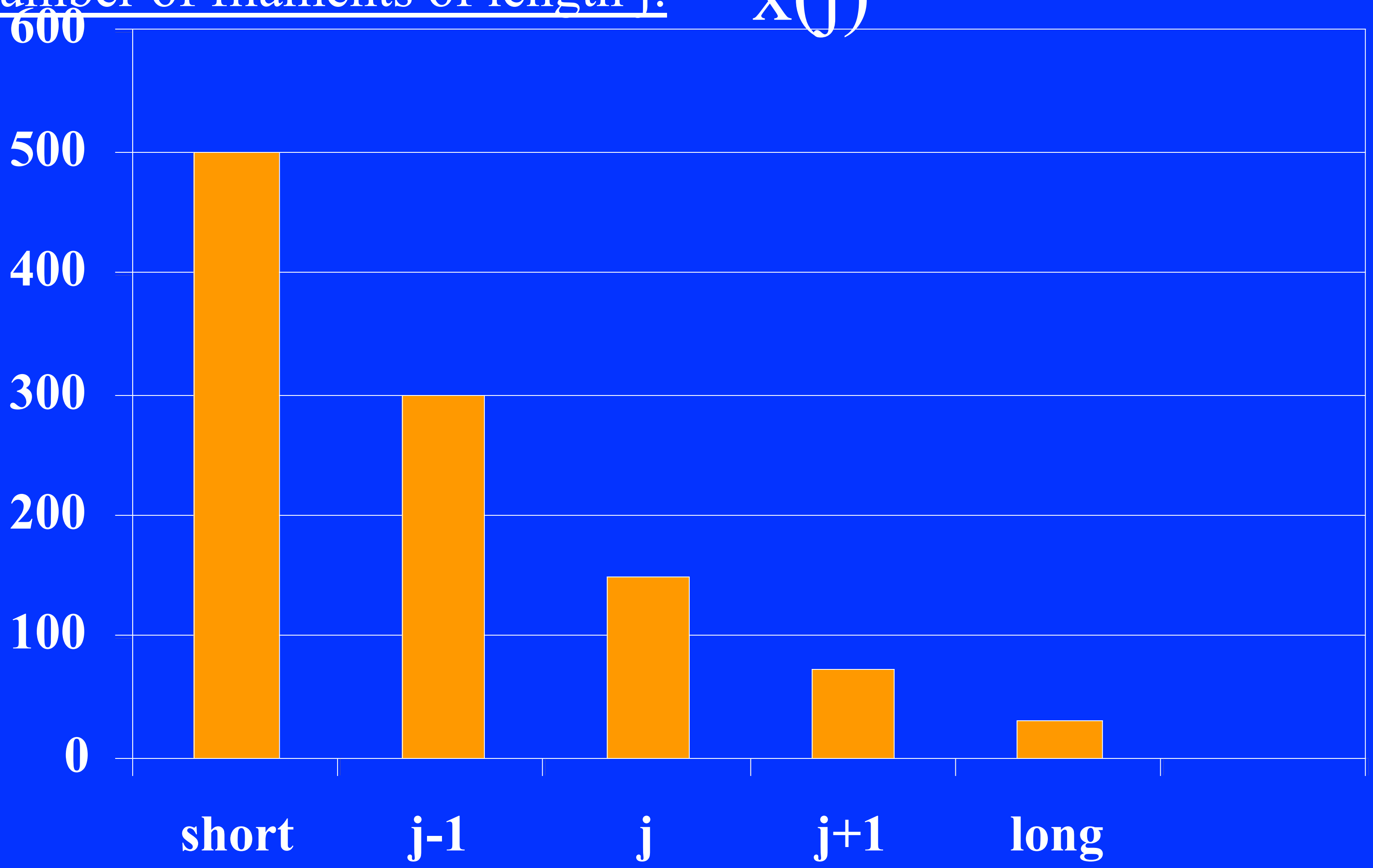
- How are filaments distributed in the lamellipod ?
- How would cutting, capping, and polymerization of the filaments affect this distribution?



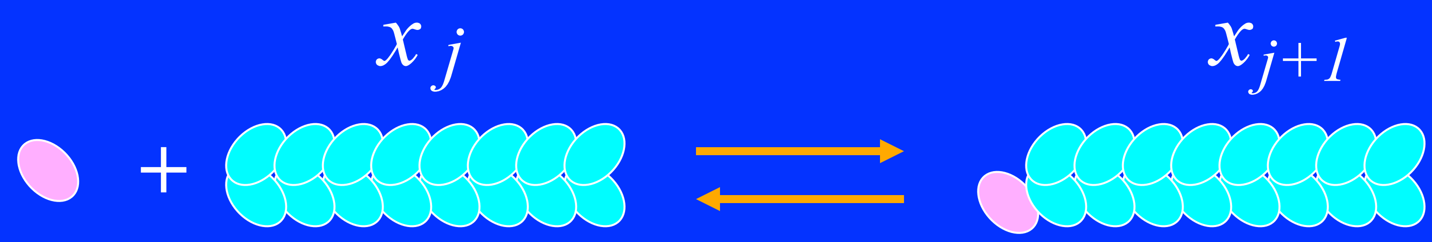
Actin monomers at equilibrium with filaments of various lengths

• What is the filament length distribution ?

Number of filaments of length j: x(j)



Number of filaments of length *j* :

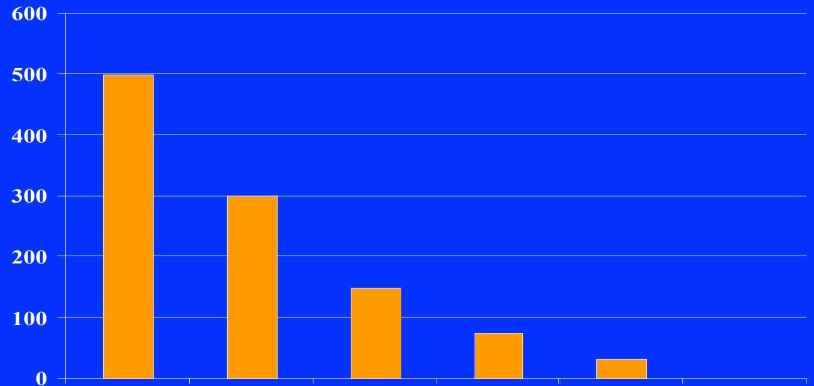


$$\frac{dx_j(t)}{dt} = \underbrace{k^{+} a x_{j-1}}_{\text{Growth of shorter filament}} - \underbrace{(k^{-} + a k^{+})}_{\text{Monomer loss or gain}} x_j + \underbrace{k^{-} x_{j+1}}_{\text{Shrinking of longer filament}}$$

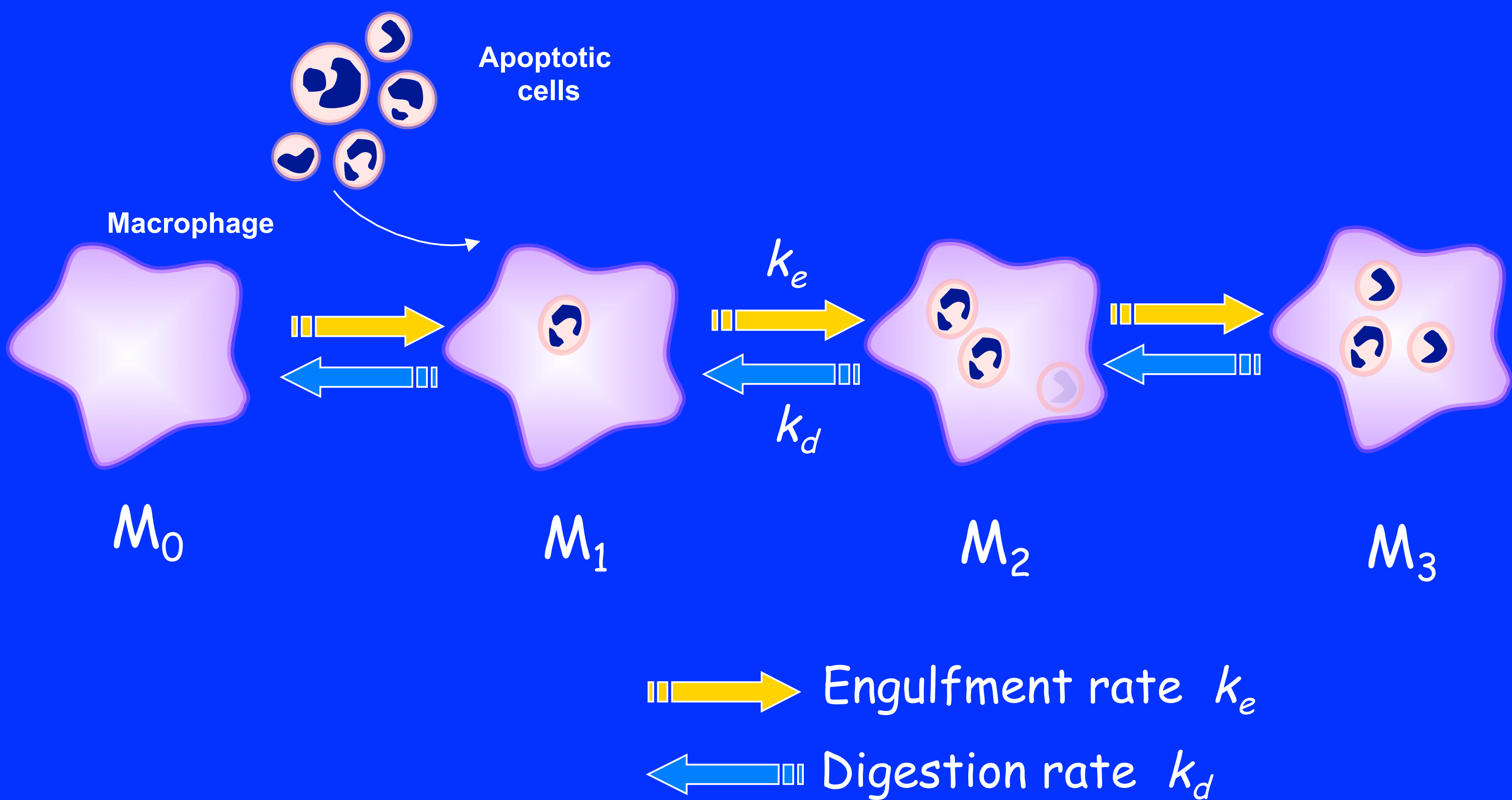
Steady state distribution of filament lengths

$$0 = k^{+}ax_{j-1} - (k^{-} + ak^{+})x_{j} + k^{-}x_{j+1}$$

For a fixed level of monomer, a , this is a simple linear difference equation. Solutions are exponential distributions

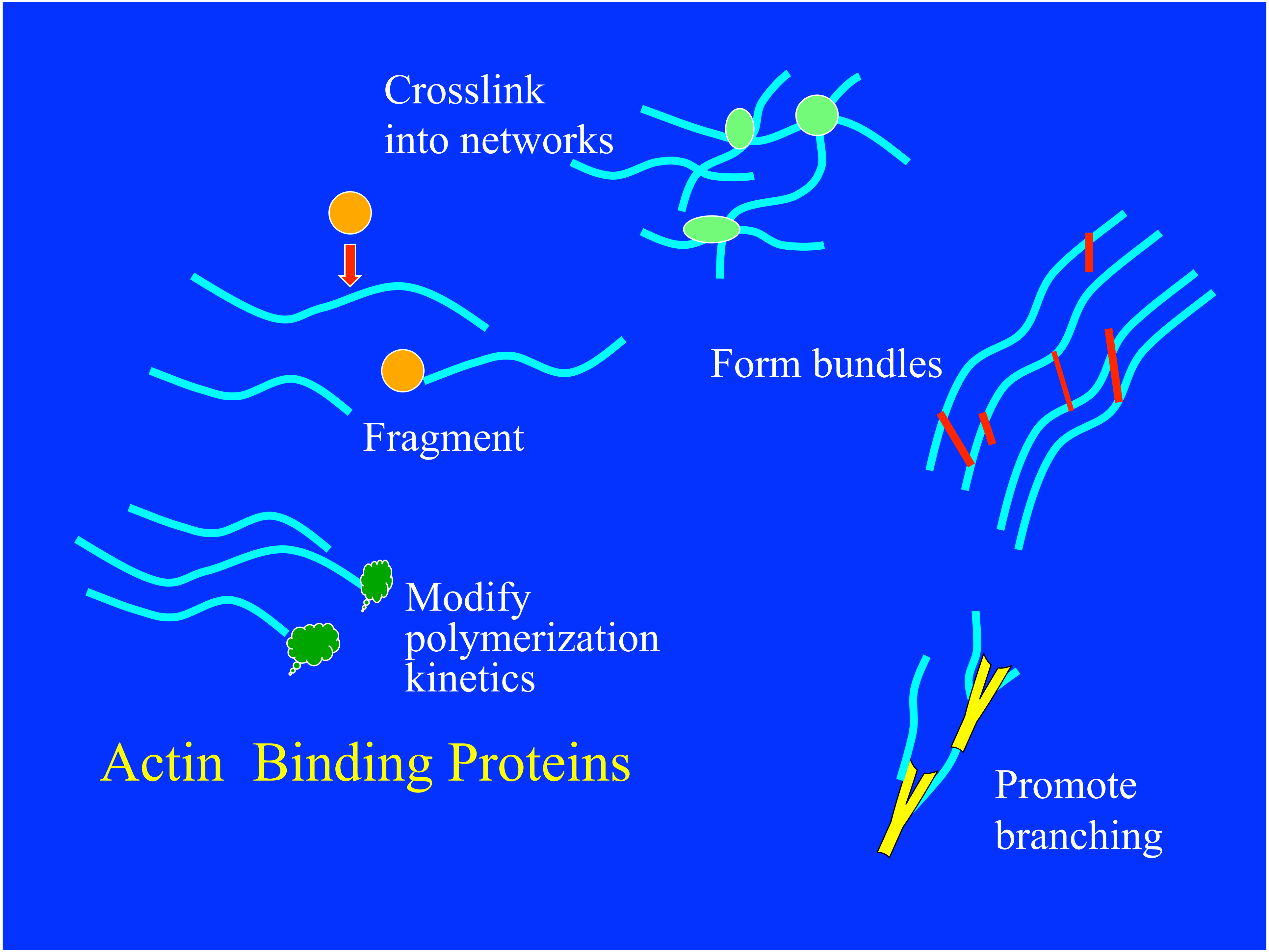


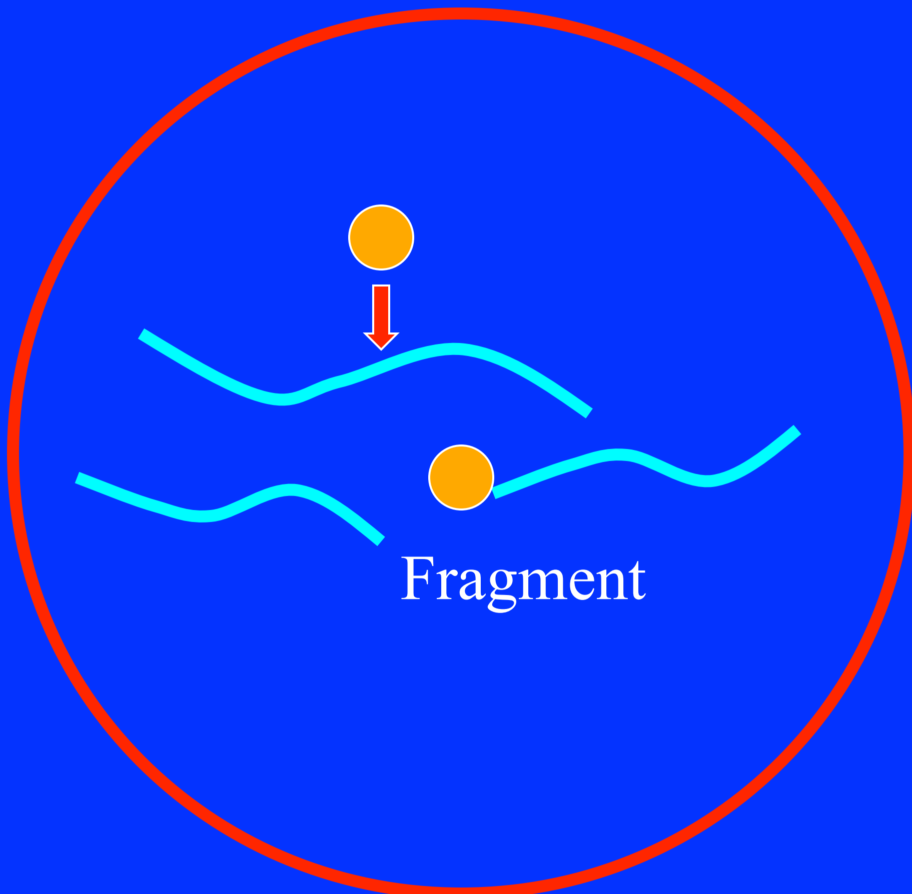
Other applications of same idea



Effect of cutting on the Actin filament length distribution

How does the length distribution change if the filaments are also being fragmented or chopped up?

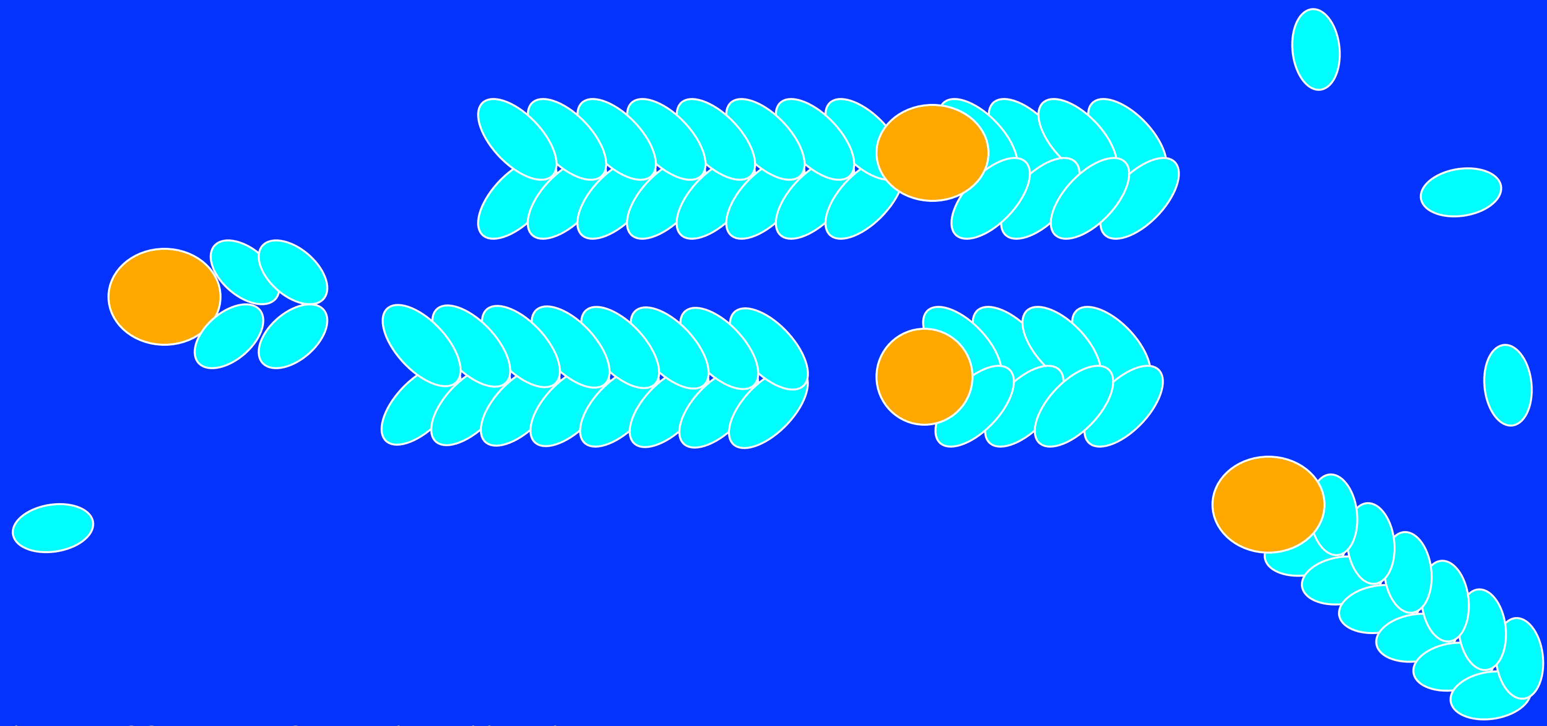

Crosslink
into networks
Fragment
Form bundles
Modify
polymerization
kinetics
Promote
branching
Actin Binding Proteins



Types:

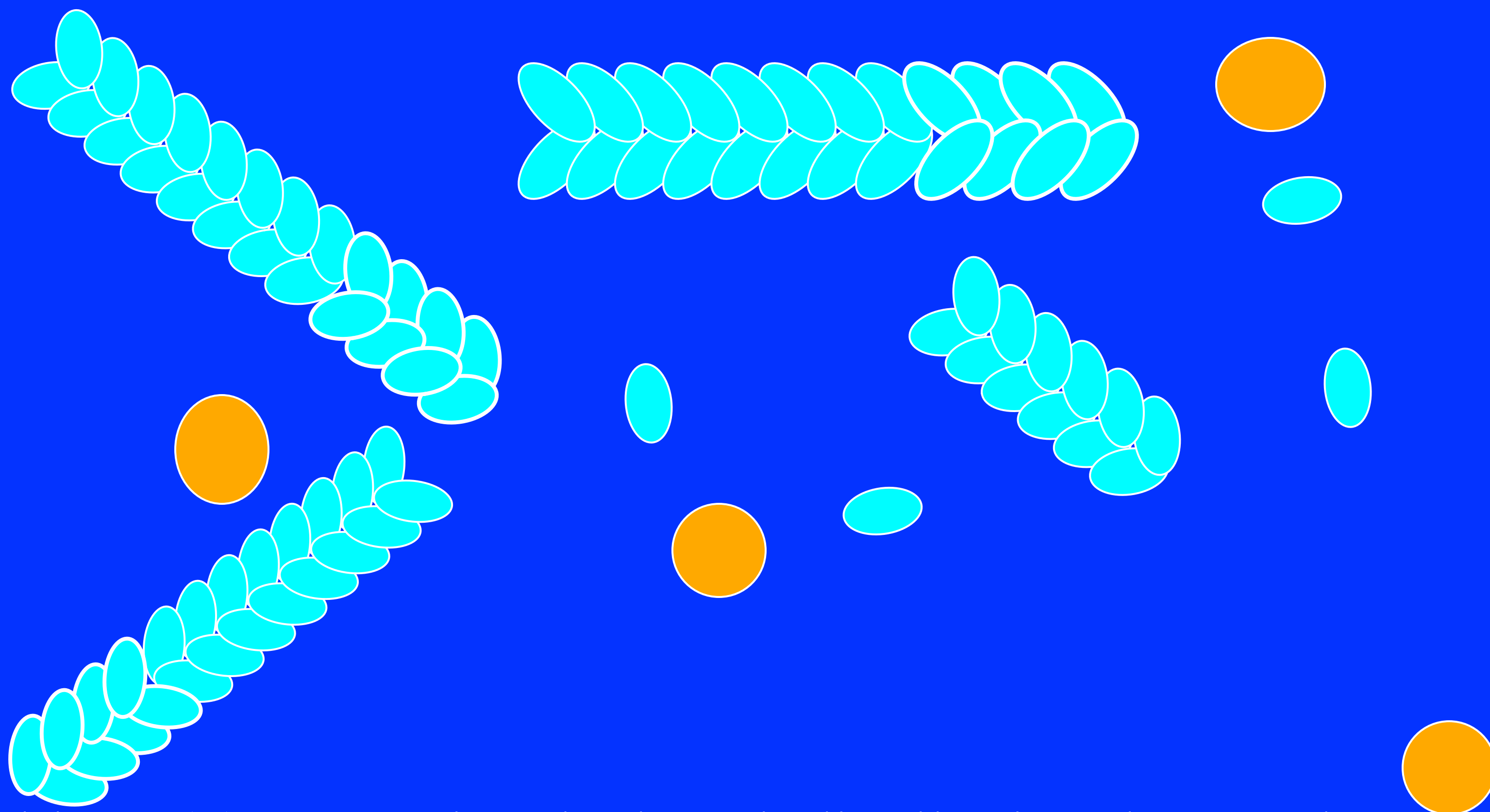
- Gelsolin : cuts a filament and caps its barbed end
- Cofilin: cuts or degrades filament; results in faster depolymerization at the pointed end

Actin Binding Proteins



The effect of Gelsolin is to:

1. Nucleate actin filaments
2. Cap the barbed ends of filaments
3. Break actin filaments



Problem: (1) Determine the length distribution that results from fragmentation alone (2) from fragmentation with the other effects such as capping, nucleating, etc (for gelsolin).

EKE & Ermentrout (1998) Bull Math Biol 60: I: 449-475; II: 477-503

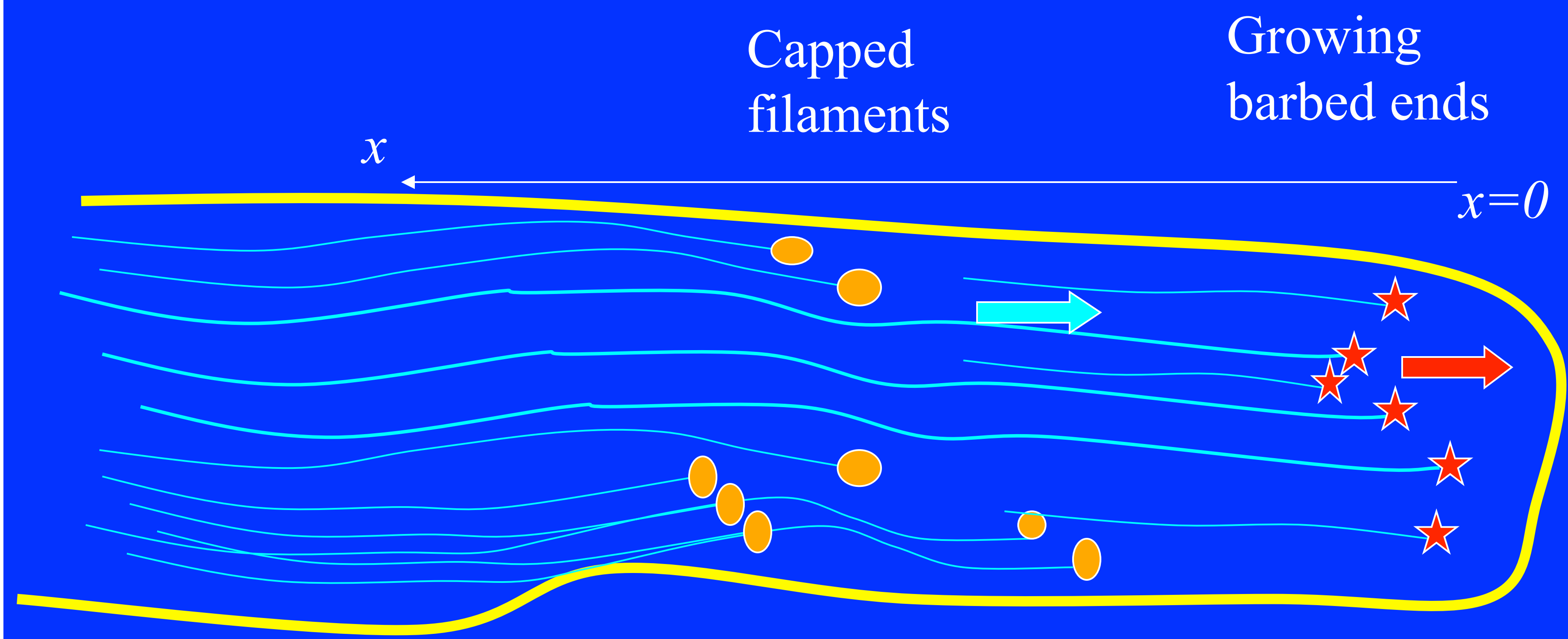
Distribution of filament lengths over a 1D spatial axis in the cell

Goal:

- To use mathematical tools to predict how filaments are distributed in the lamellipod
- To test what a variety of hypotheses about filament cutting and capping imply about this distribution.

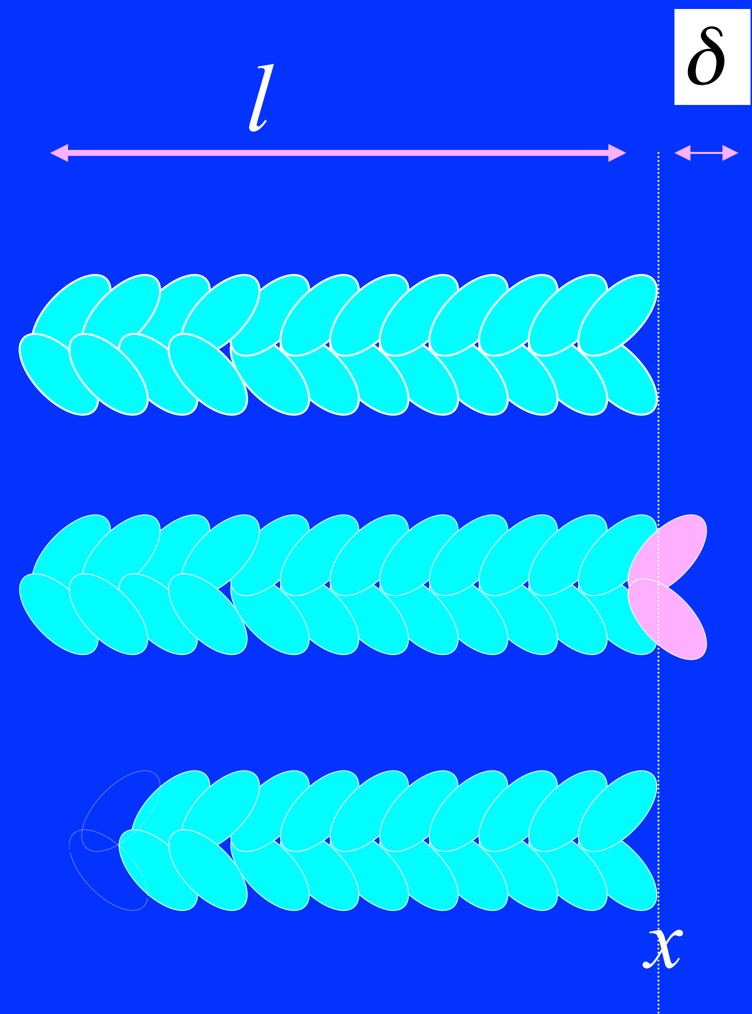
Select small piece of edge to get a roughly 1D geometry .

Assume barbed ends at $x=0$



Length-distribution model:

- Growth of filaments at barbed ends
- Fragmentation along length (dependent on ADP-ATP form of actin)
- Capping of loose ends

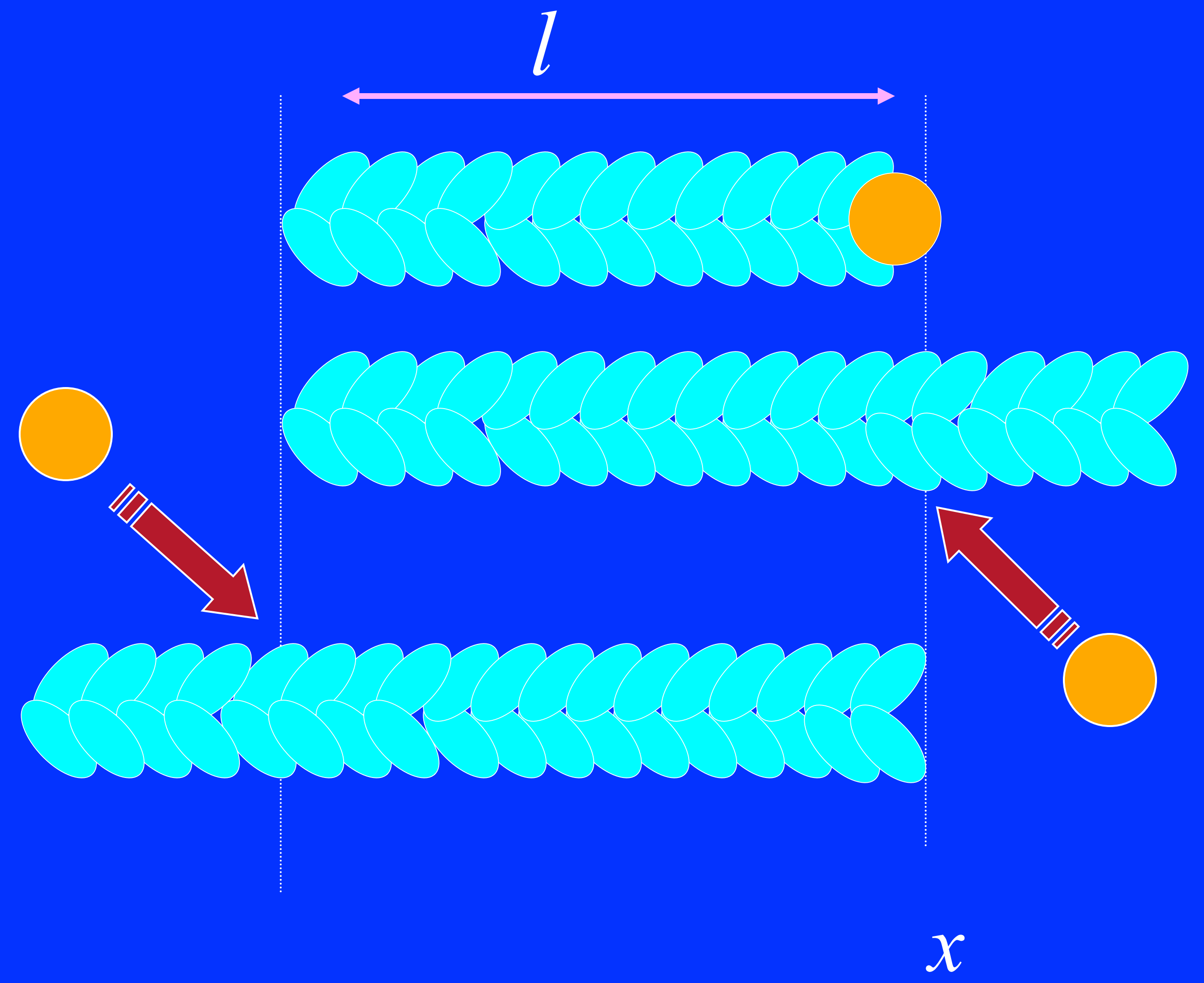


length l filament with end at x

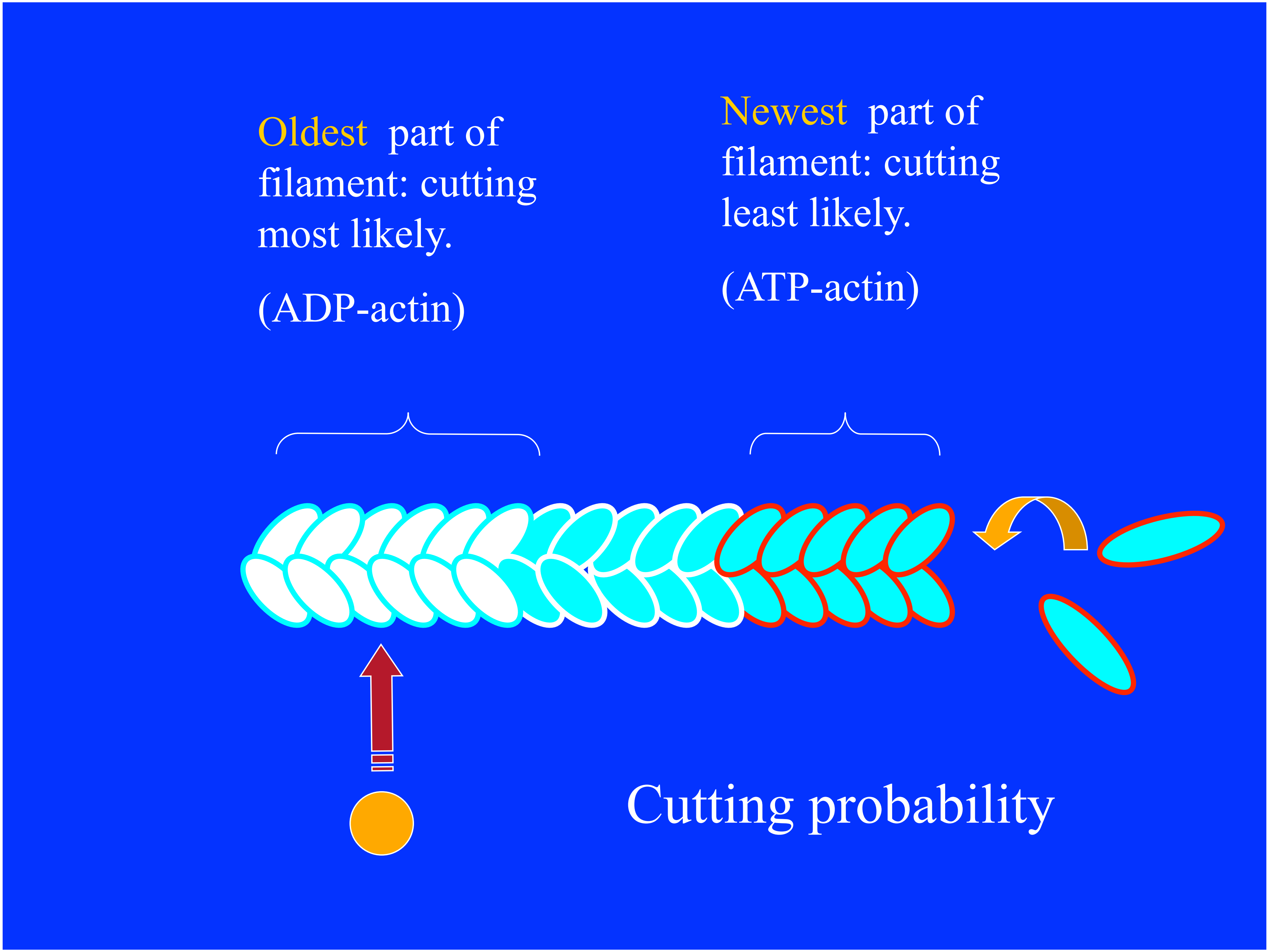
barbed end grows

or pointed end shrinks

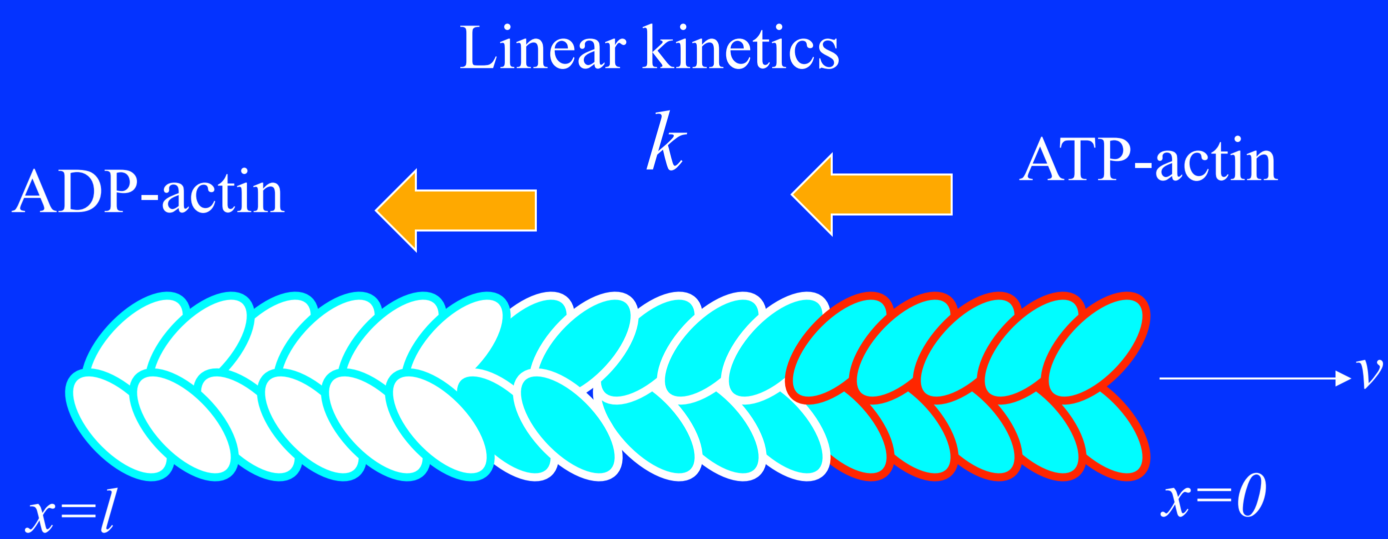
Length changes by loss or gain of monomer: $\boxed{\delta}$



Length changes via cutting at either end


Oldest part of filament: cutting most likely.
(ADP-actin)
Newest part of filament: cutting least likely.
(ATP-actin)
Cutting probability

Cutting probability depends on position



$$P(x) = 1 - e^{(-kx/v)}$$

probability of cutting at x

Let $b(l, t)$ = number of active tips of length l filaments

$P(l)$ = probability that filament will be fragmented at distance l from its end

$$b_a(x,l,t)\begin{cases}\rightarrow b_a(x+\delta, l+\delta, t+dt) & \text{polymerization of barbed end}\\ \rightarrow b_a(x, l-\delta, t+dt) & \text{depolymerization of pointed end}\end{cases}$$

$$b_c(x,l,t)\begin{cases}\rightarrow b_c(x, l-\delta, t+dt) & \text{depolymerization of pointed end}\\ \leftarrow b_a(x+l', l+l', t+dt) & \text{cut and cap active filament}\\ \leftarrow b_c(x+l', l+l', t+dt) & \text{cut and cap capped filament}\\ \leftarrow b_c(x, l+l', t+dt) & \text{cut and cap capped filament}\end{cases}$$

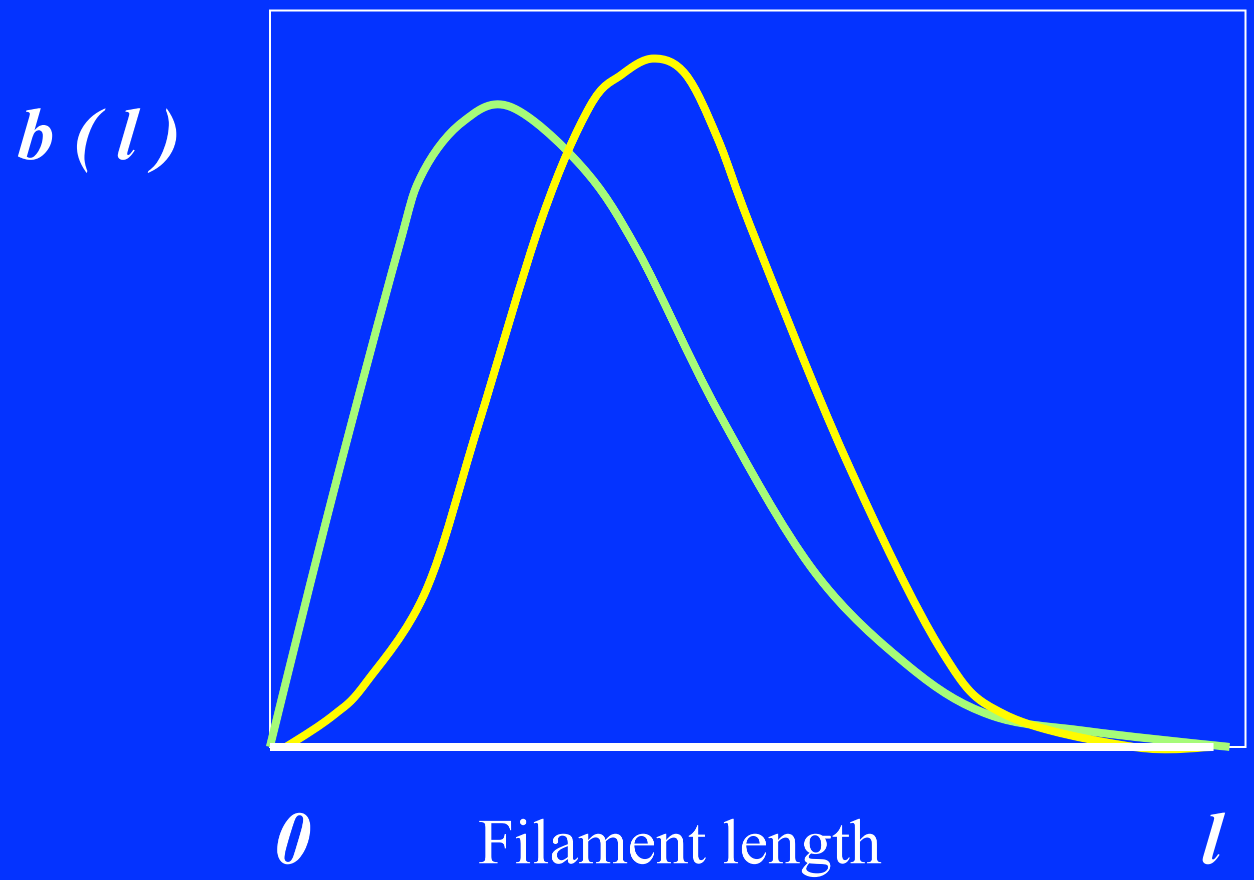
$$\frac{\partial b}{\partial t} = -c\frac{\partial b}{\partial l} + P(l)z(l,t) - b(l,t)F(l)$$

$$c = (v_b - v_p)\delta$$

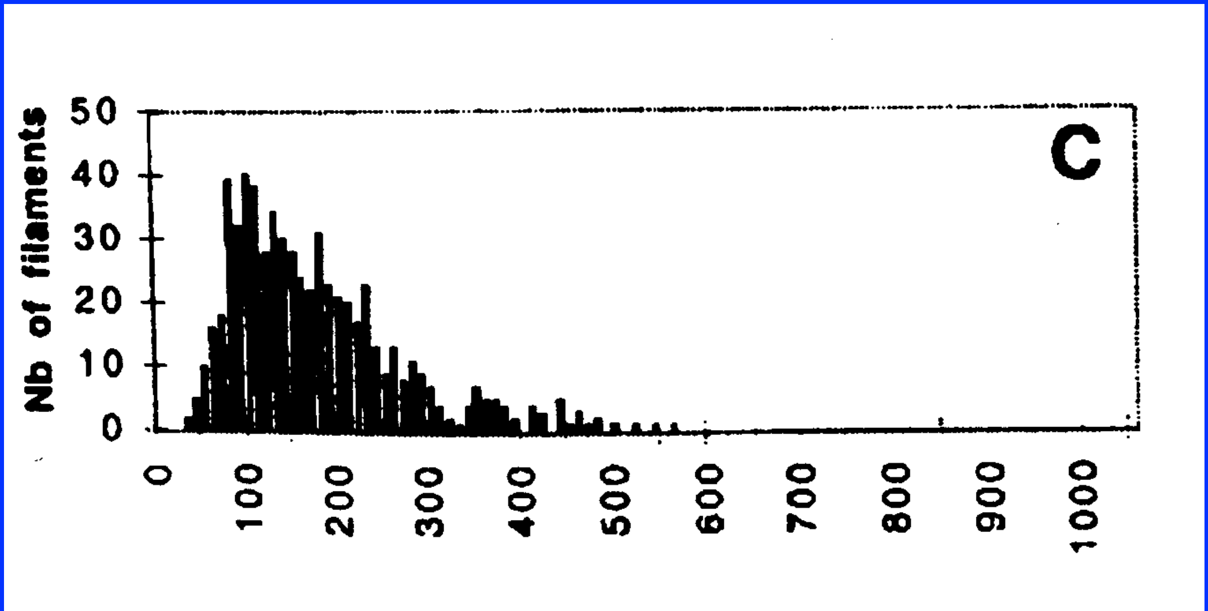
$$z(l,t) = \int_l^\infty b(s,t)\,ds$$

$$F(l) = \int_0^l P(s)\,ds$$

Typical solutions



Qualitative comparison with biological data



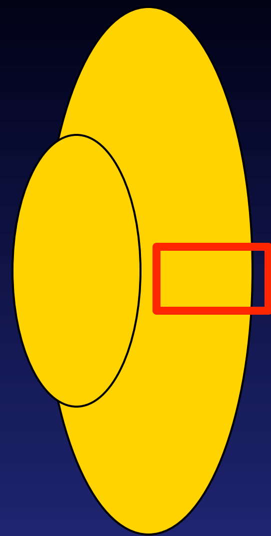
Filament length distribution within a 1 micron zone at the leading edge of a cell

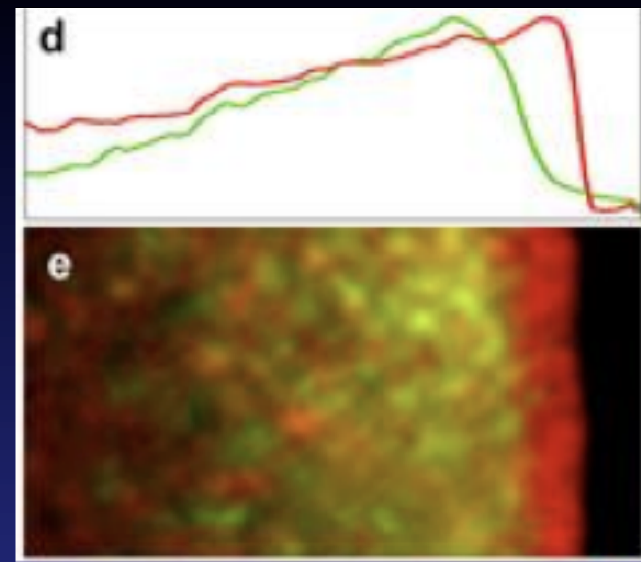
Bailey et al (1999) J Cell Biol 145:331-345

T. M. Svitkina,

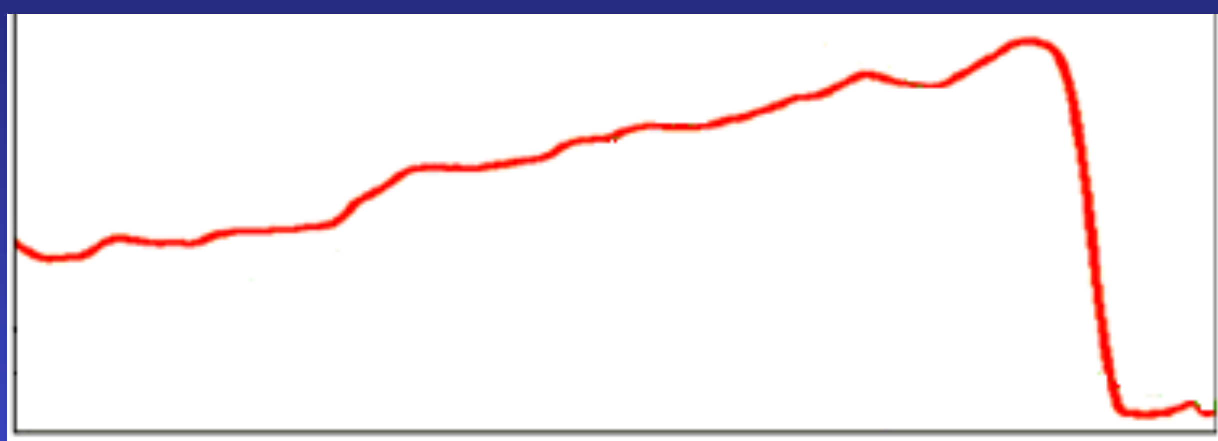
GG. Borisy
J. Cell Biol.,

145(5): 1009-1026, 1999



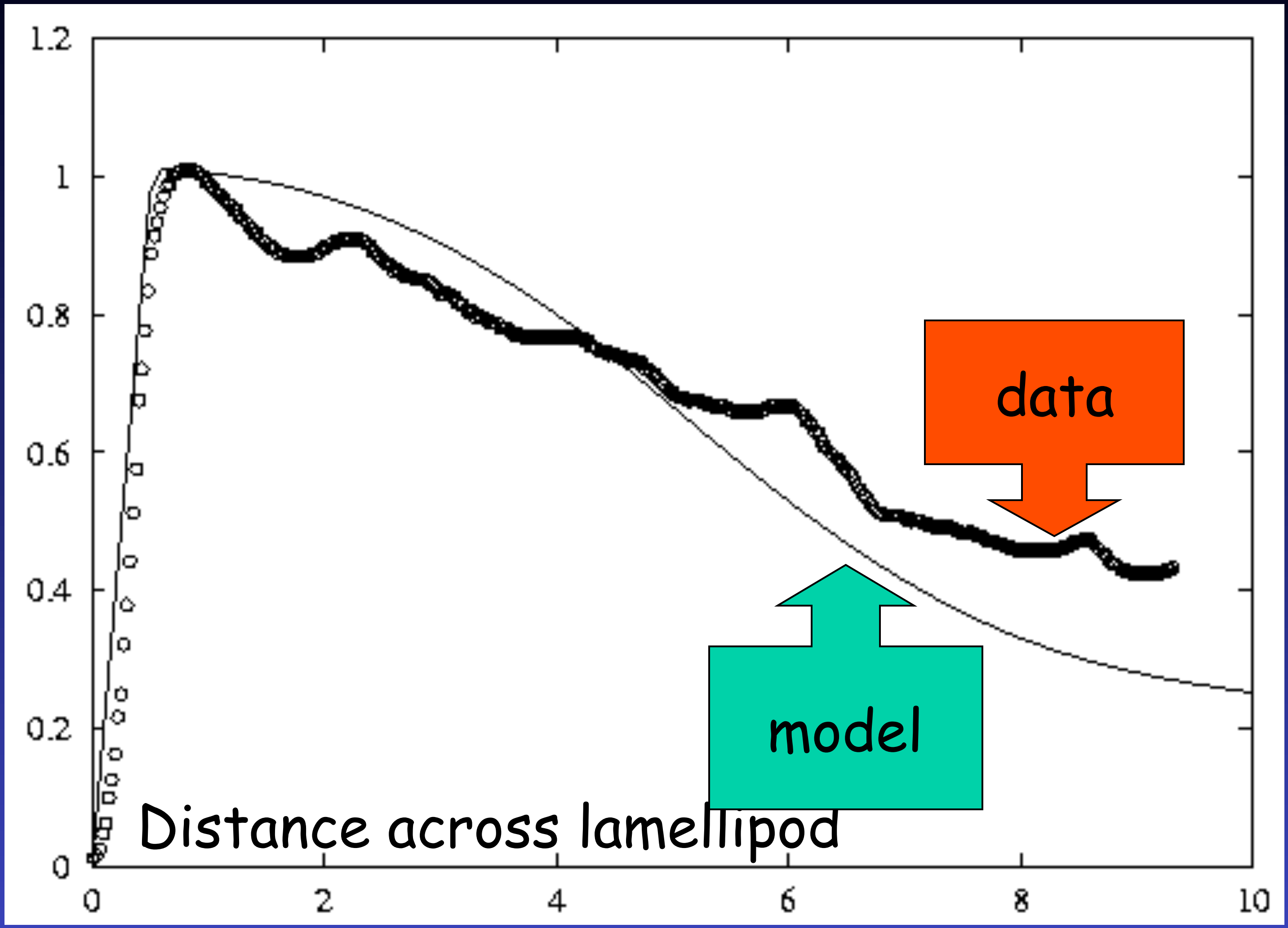


Actin filament density in keratocyte lamelipod



Distance across lamellipod

Actin filament density



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