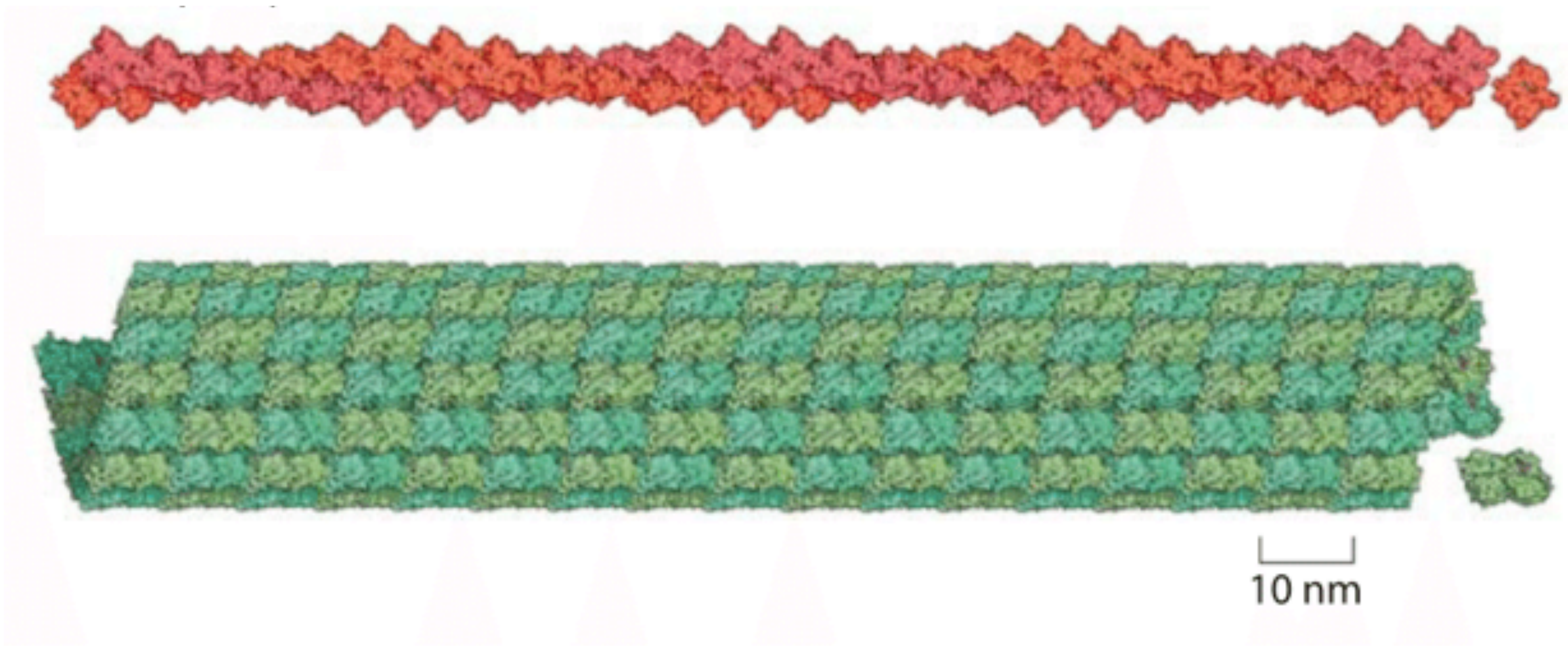
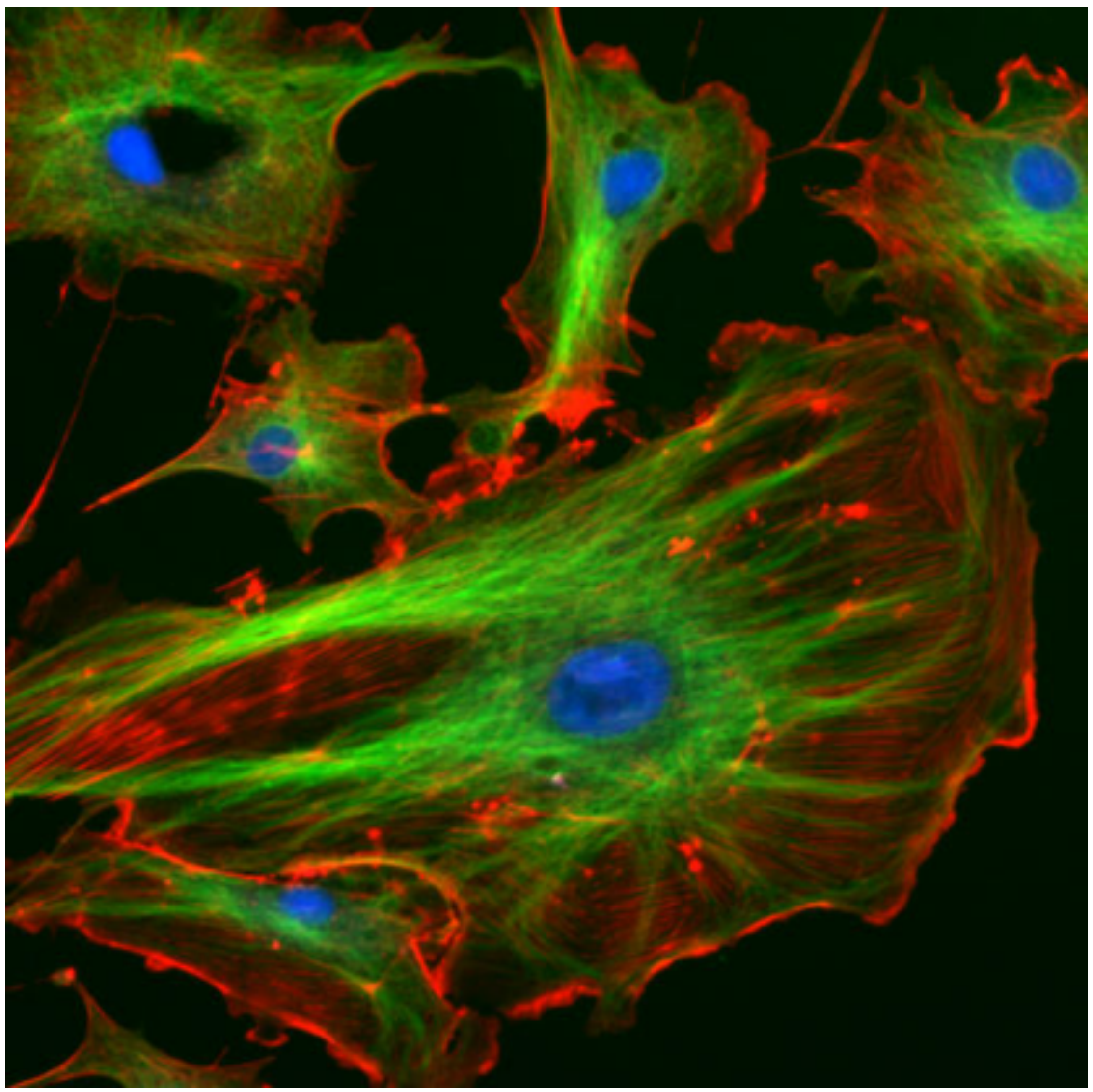
MAE 545: Lecture 6 (10/6)

Growth dynamics of actin filaments and microtubules



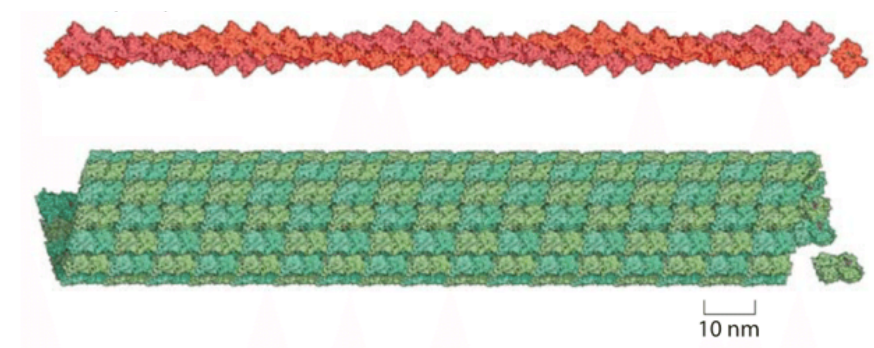
Cytoskeleton in cells

Cytoskeleton matrix gives the cell shape and mechanical resistance to deformation.



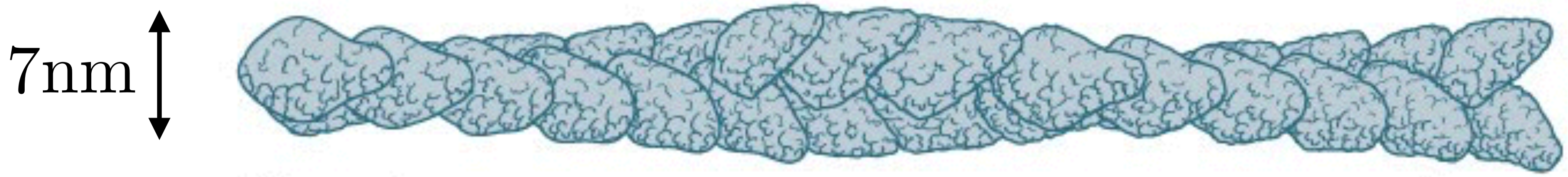
(wikipedia)

Actin filament



Microtubule

Actin filaments



actin monomer

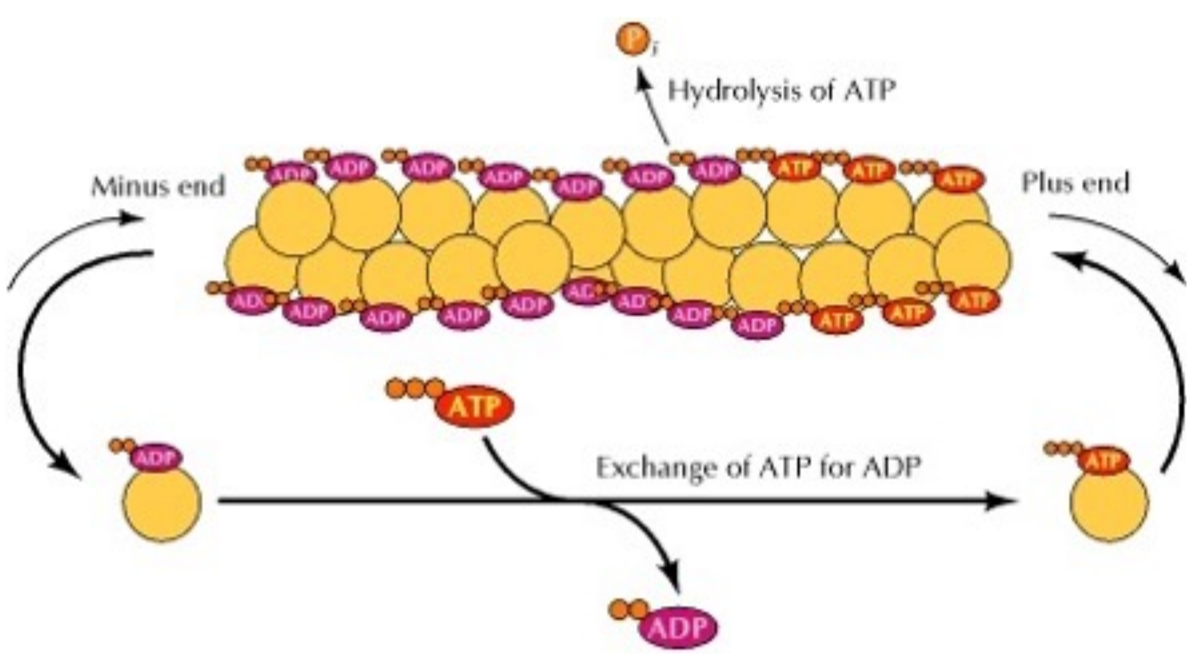
Minus end (pointed end)

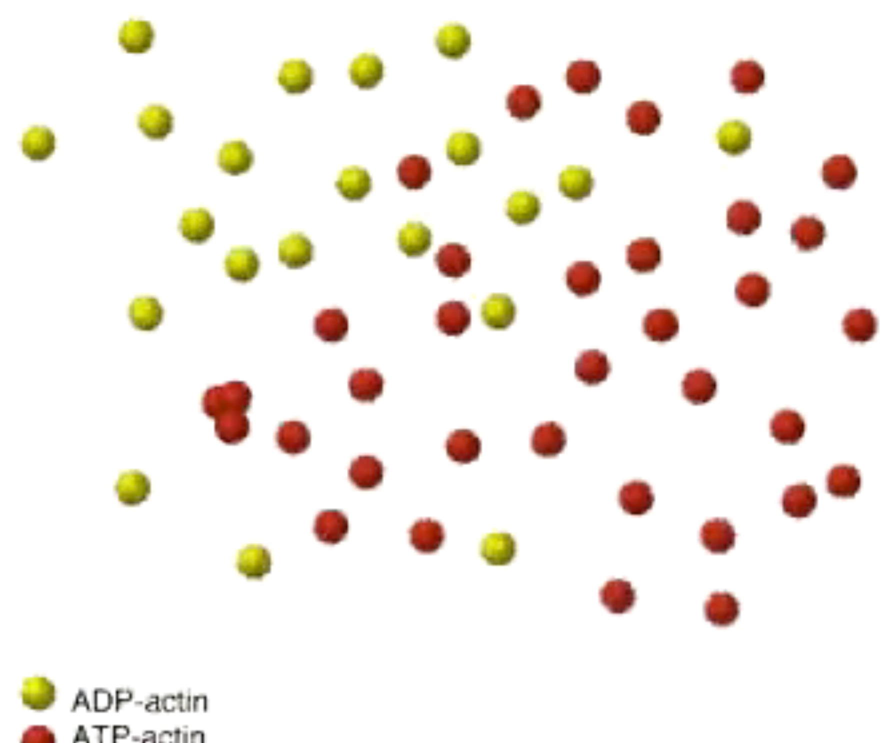
Plus end (barbed end)

Persistence length $\ell_p \sim 10\mu\text{m}$

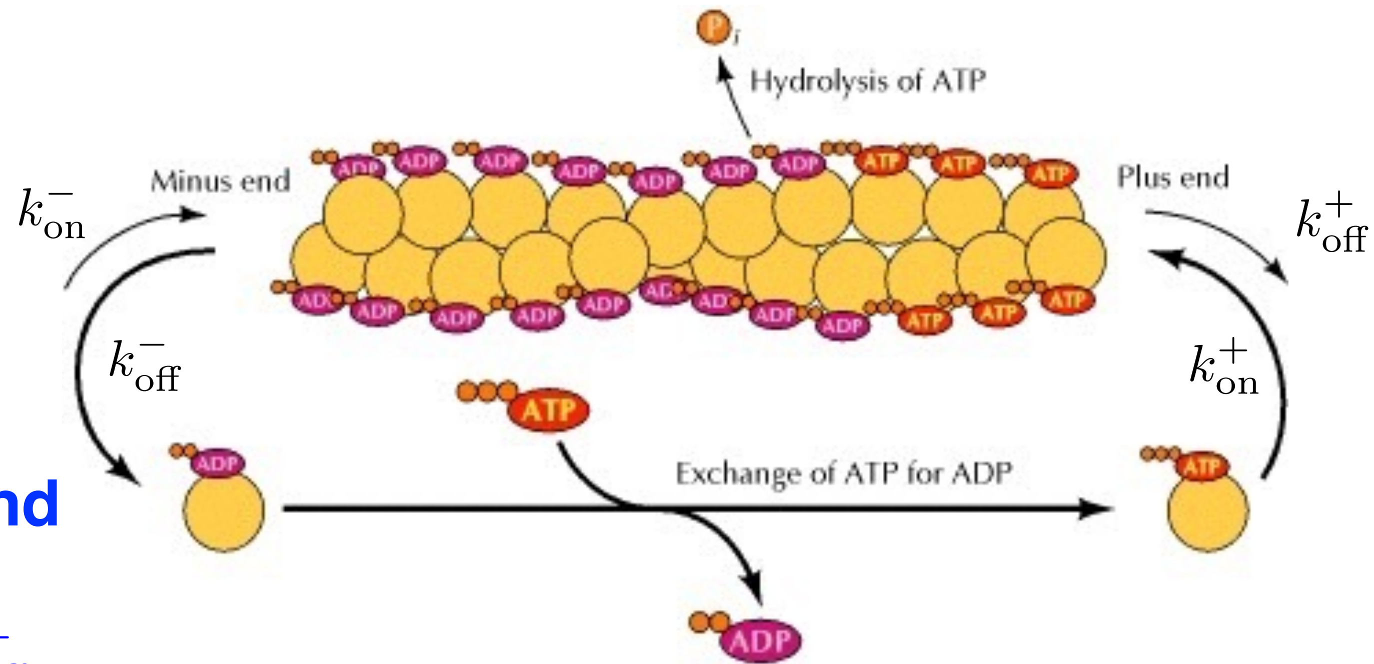
Typical length $L \lesssim 10\mu\text{m}$

Actin treadmilling





Actin growth



growth of minus end

$$\frac{dn^-}{dt} = k_{\text{on}}^-[M] - k_{\text{off}}^-$$

no growth at

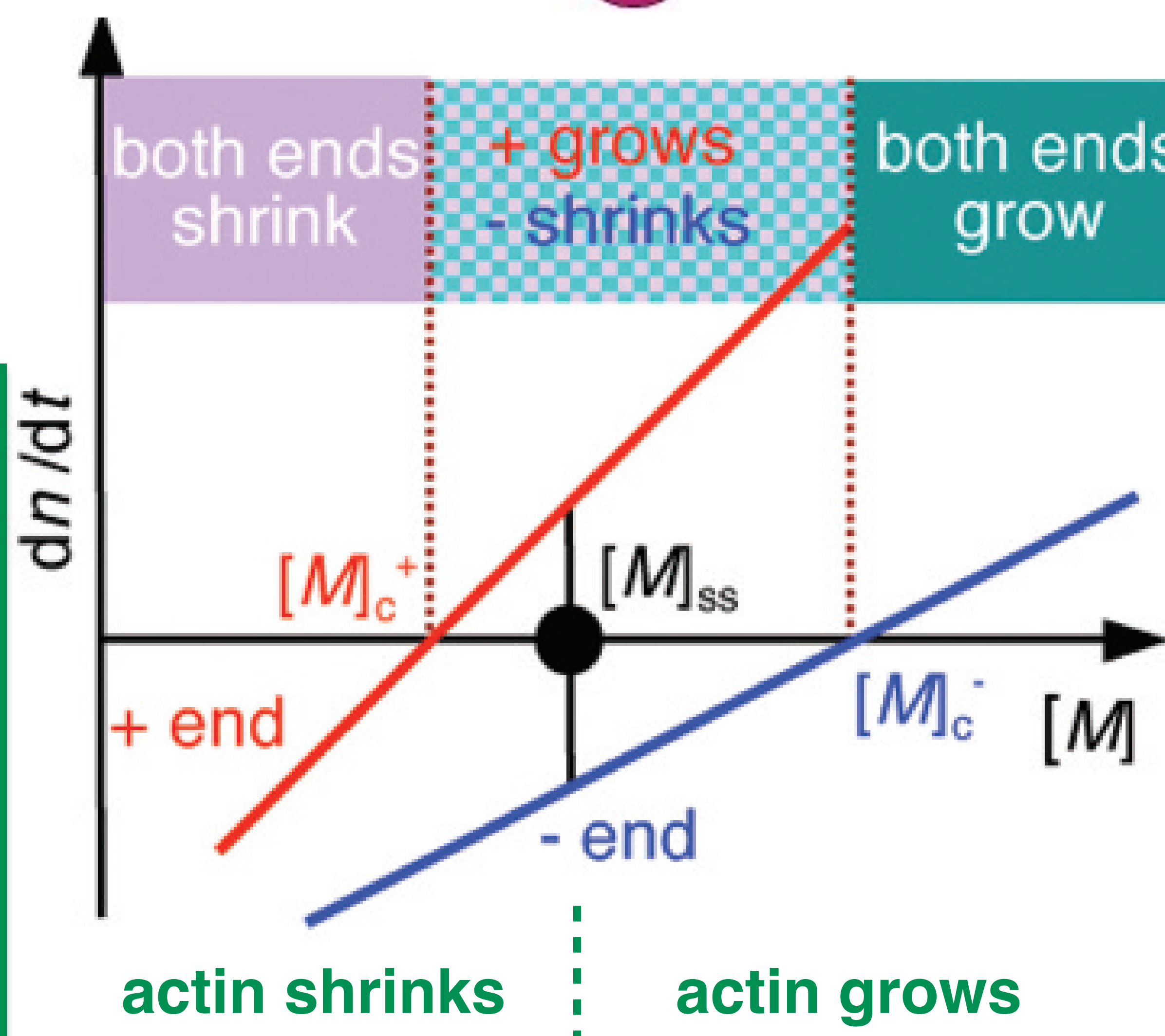
$$[M]_c^- = \frac{k_{\text{off}}^-}{k_{\text{on}}^-}$$

growth of plus end

$$\frac{dn^+}{dt} = k_{\text{on}}^+[M] - k_{\text{off}}^+$$

no growth at

$$[M]_c^+ = \frac{k_{\text{off}}^+}{k_{\text{on}}^+}$$



concentration of free actin monomers

Steady state regime

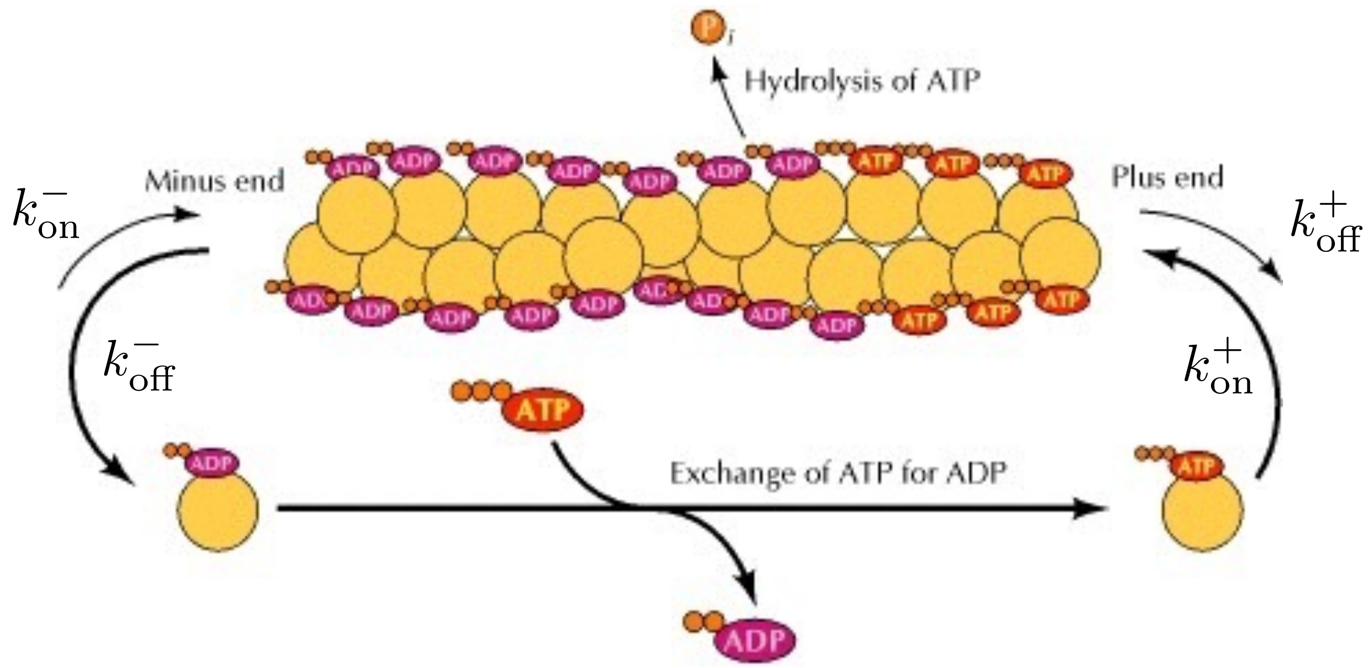
$$\frac{dn^+}{dt} = -\frac{dn^-}{dt}$$

$$[M]_{\text{ss}} = \frac{k_{\text{off}}^+ + k_{\text{off}}^-}{k_{\text{on}}^+ + k_{\text{on}}^-} \approx 0.17\mu\text{M}$$

front speed

$$\frac{dn^+}{dt} = \frac{k_{\text{on}}^+ k_{\text{off}}^- - k_{\text{on}}^- k_{\text{off}}^+}{k_{\text{on}}^+ + k_{\text{on}}^-} \approx 0.6\text{s}^{-1}$$

Distribution of actin filament lengths



total rate of actin monomer addition $k_{\rm on} = k_{\rm on}^+ + k_{\rm on}^-$

total rate of actin monomer removal $k_{\rm off} = k_{\rm off}^+ + k_{\rm off}^-$

Master equation

$$\frac{\partial p(n,t)}{\partial t} = k_{\rm on}[M]p(n-1,t) + k_{\rm off}\, p(n+1,t) - k_{\rm on}[M]p(n,t) - k_{\rm off}\, p(n,t)$$

Continuum limit

$$\frac{\partial p(n,t)}{\partial t} = -v\frac{\partial p(n,t)}{\partial n} + D\frac{\partial^2 p(n,t)}{\partial n^2}$$

drift velocity $v = k_{\rm on}[M] - k_{\rm off}$

diffusion constant $D = (k_{\rm on}[M] + k_{\rm off})/2$

at large concentrations

actin grows ($v > 0$)

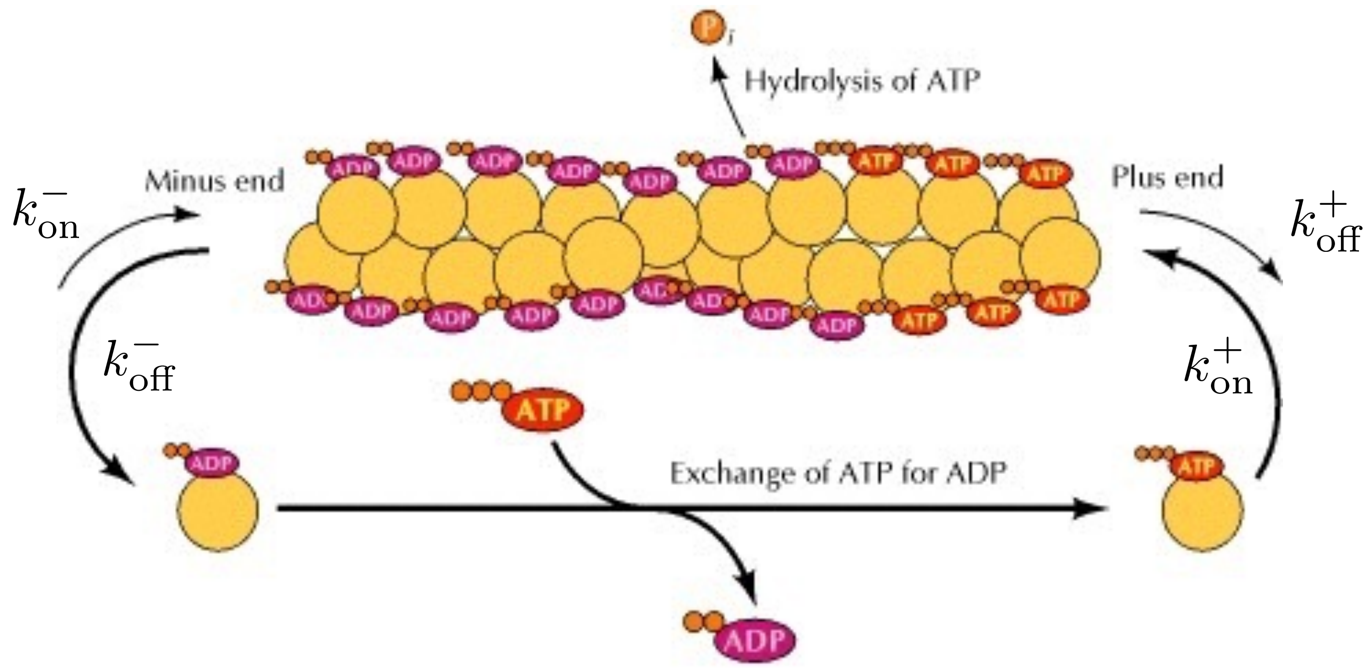
$$[M] > \frac{k_{\rm off}}{k_{\rm on}} = [M]_{\rm ss}$$

at low concentrations

actin shrinks ($v < 0$)

$$[M] < \frac{k_{\rm off}}{k_{\rm on}} = [M]_{\rm ss}$$

Distribution of actin filament lengths



total rate of actin monomer addition $k_{\rm on} = k_{\rm on}^+ + k_{\rm on}^-$

total rate of actin monomer removal $k_{\rm off} = k_{\rm off}^+ + k_{\rm off}^-$

What is steady state distribution of actin filament lengths at low concentration?

$$\frac{\partial p^*(n,t)}{\partial t} = -v\frac{\partial p^*(n,t)}{\partial n} + D\frac{\partial^2 p^*(n,t)}{\partial n^2} = 0$$

drift velocity $v = k_{\rm on}[M] - k_{\rm off} < 0$

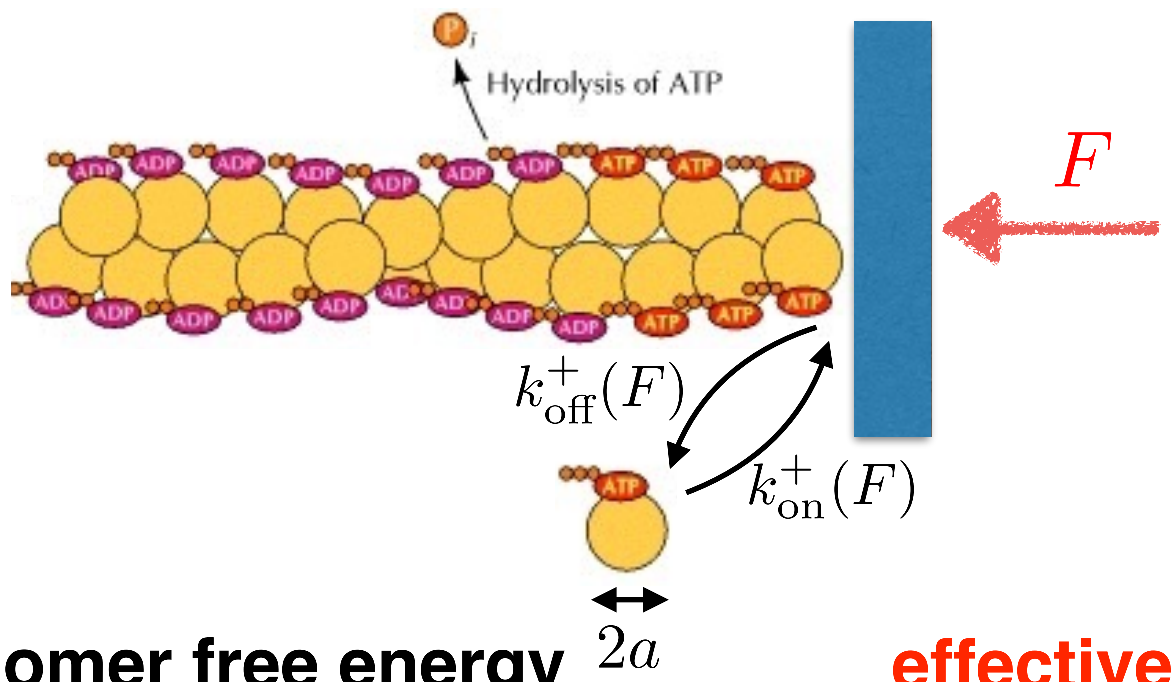
diffusion constant $D = (k_{\rm on}[M] + k_{\rm off})/2$

$$p^*(n) = \frac{|v|}{D}e^{-|v|n/D} = \frac{1}{\overline{n}}e^{-n/\overline{n}}$$

average actin filament length

$$\overline{n} = \frac{D}{|v|} = \frac{(k_{\rm off} + k_{\rm on}[M])}{2(k_{\rm off} - k_{\rm on}[M])}$$

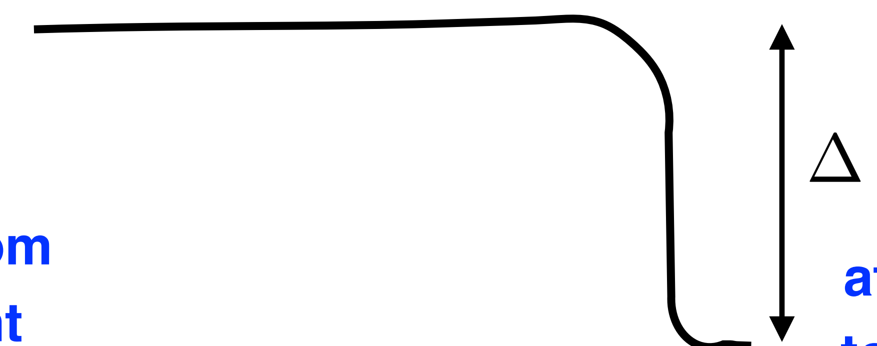
Actin filament growing against the barrier



work done against the barrier for insertion of new monomer

$$W = Fa$$

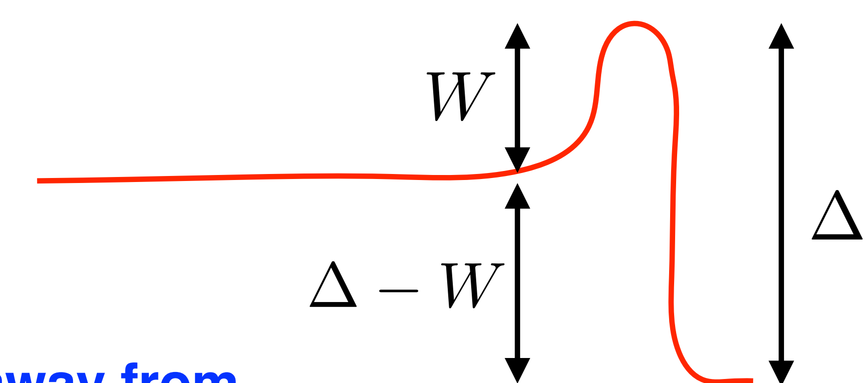
effective monomer free energy potential without barrier



$$k_{\text{on}}^{+} \sim 4\pi D_3 a$$

$$k_{\text{off}}^{+} \propto e^{-\Delta/k_B T}$$

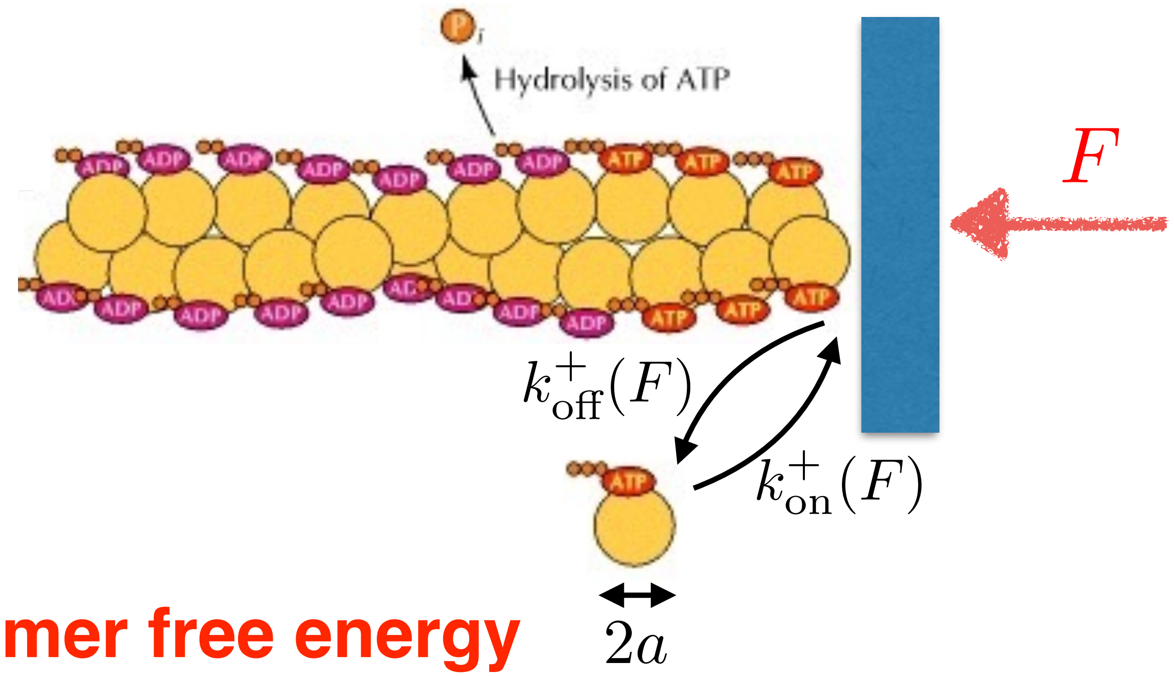
effective monomer free energy potential with barrier



$$k_{\text{on}}^{+}(F) \sim k_{\text{on}}^{+} e^{-Fa/k_B T}$$

$$k_{\text{off}}^{+}(F) \sim k_{\text{off}}^{+}$$

Actin filament growing against the barrier



work done against the barrier for insertion of new monomer

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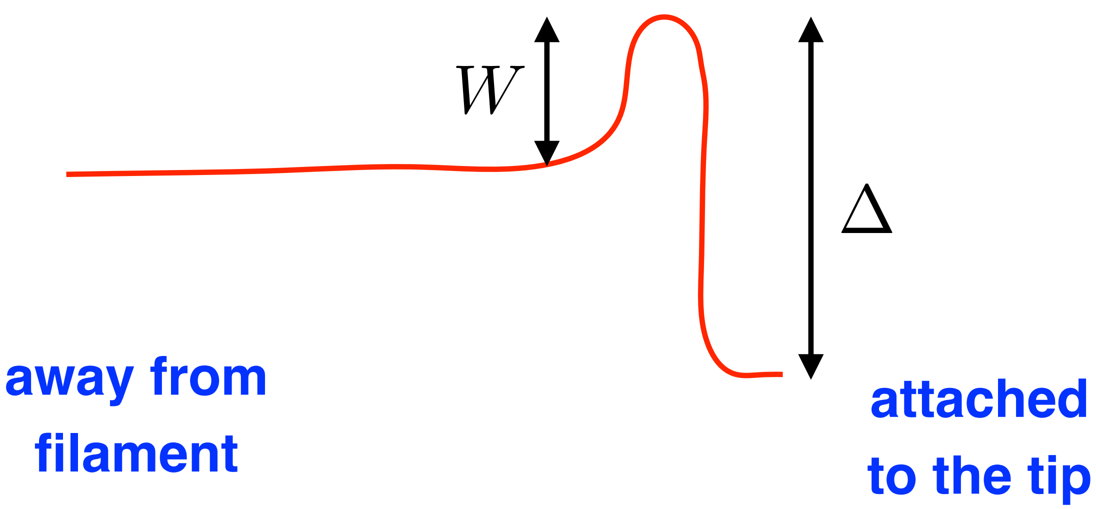
effective monomer free energy potential with barrier



$$k_{\rm on}^{+}(F) \sim k_{\rm on}^{+} e^{-Fa/k_BT}$$

$$k_{\rm off}^{+}(F) \sim k_{\rm off}^{+}$$

Growth speed of the tip

$$v^{+}(F) = \frac{dn^{+}(F)}{dt} = k_{\rm on}^{+}[M]e^{-Fa/k_BT} - k_{\rm off}^{+}$$

Maximal force that can be balanced by growing filament

(stall force)

$$v^{+}(F_{\rm max}) = 0 \longrightarrow F_{\rm max} = \frac{k_BT}{a}\ln\left(\frac{k_{\rm on}^{+}[M]}{k_{\rm off}^{+}}\right)$$

$k_{\rm on}^{+} \sim 10\mu{\rm M}^{-1}{\rm s}^{-1}$

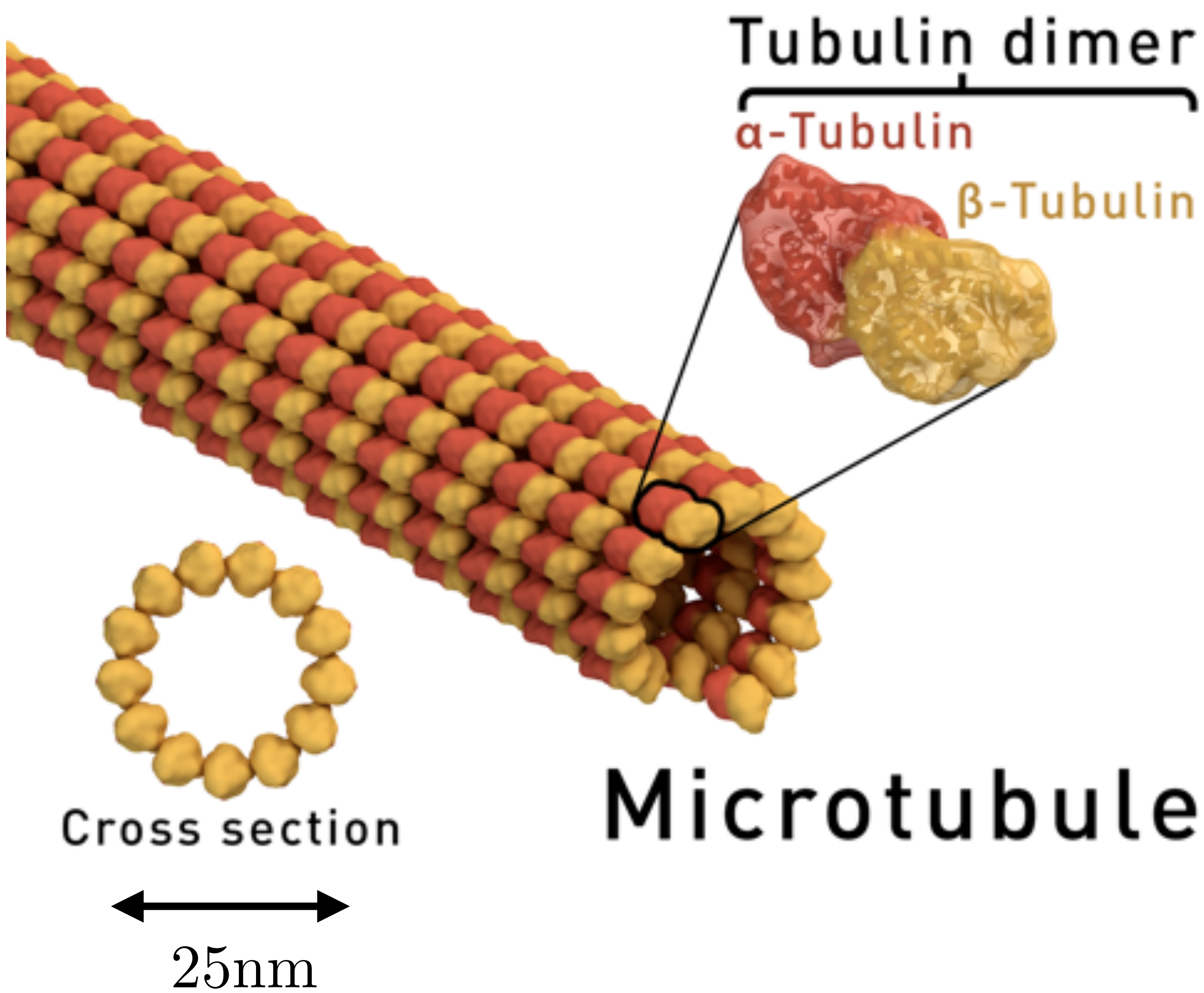
$k_{\rm off}^{+} \sim 1{\rm s}^{-1}$

$[M] \sim 10\mu{\rm M}$

$a \approx 2.5{\rm nm}$

$F_{\rm max} \sim 8{\rm pN}$

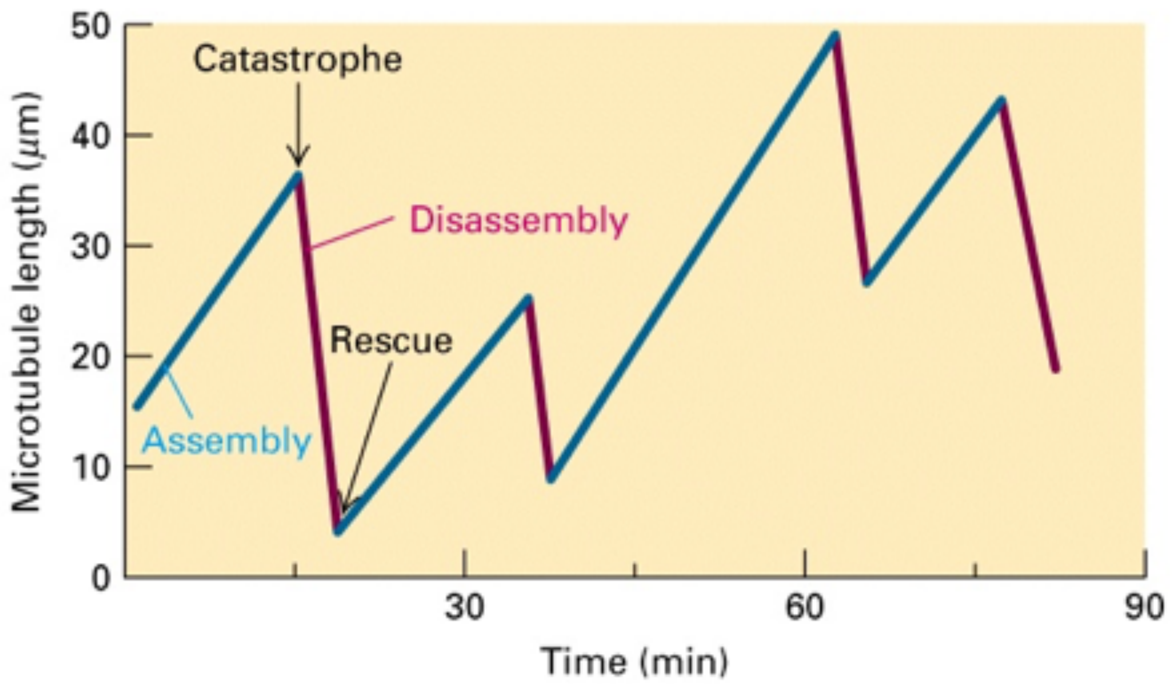
Microtubules

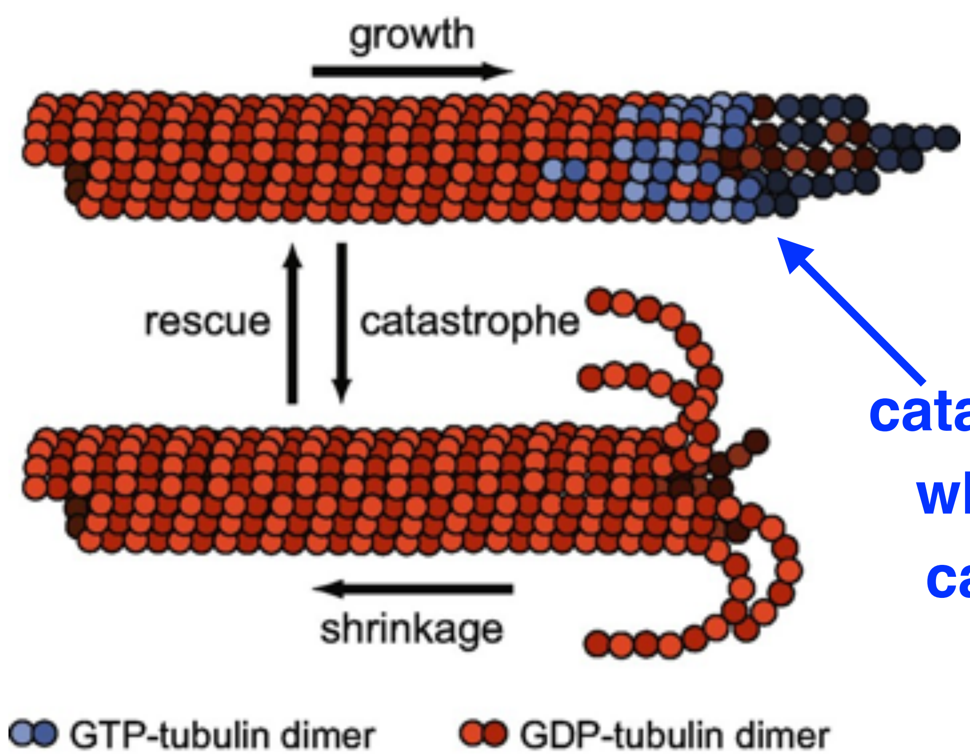


Persistence length $\ell_p \sim 1\text{mm}$

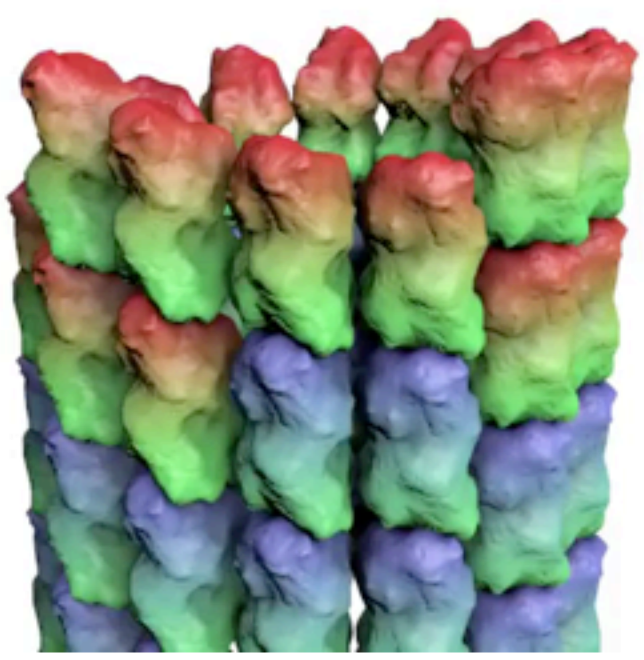
Typical length $L \lesssim 50\mu\text{m}$

Microtubule dynamic instability



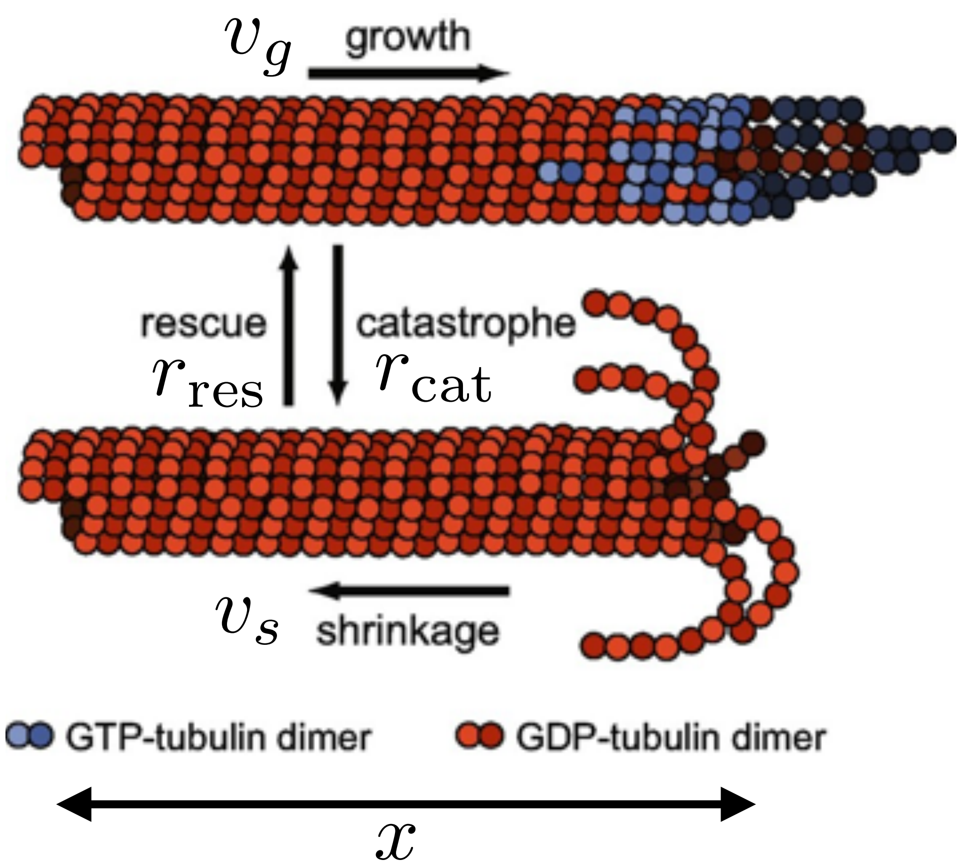


catastrophe occurs when protective cap disappears



Wikipedia

Simple model of microtubule growth



Typical values in a tubilin solution of concentration $10\mu\mathrm{M}$:

$$v_g \approx 2\mu\mathrm{m}/\mathrm{min}$$

$$v_s \approx 20\mu\mathrm{m}/\mathrm{min}$$

$$r_{\rm cat} \approx 0.24\mathrm{min}^{-1}$$

$$r_{\rm res} \approx 3\mathrm{min}^{-1}$$

First let's ignore all molecular details and assume that microtubules switch at fixed rates between growing and shrinking phases

$$\frac{\partial p_g(x,t)}{\partial t} = -v_g \frac{\partial p_g(x,t)}{\partial x} - r_{\rm cat} p_g(x,t) + r_{\rm res} p_s(x,t)$$

$$\frac{\partial p_s(x,t)}{\partial t} = +v_s \frac{\partial p_s(x,t)}{\partial x} + r_{\rm cat} p_g(x,t) - r_{\rm res} p_s(x,t)$$

(for simplicity ignore diffusion during individual growing or shrinking event)

What is the average growth speed and average diffusion constant for such dynamic system?

M. Dogterom and S. Leibler, PRL 70, 1347-1350 (1993)

Fokker-Plank equation in Fourier spectrum

Master equation

$$\frac{\partial p(x,t)}{\partial t} = -v\frac{\partial p(x,t)}{\partial x} + D\frac{\partial^2 p(x,t)}{\partial x^2}$$

Fourier spectrum $p(x,t) = \int dk d\omega\, e^{i\omega t - ikx}\tilde{p}(k,\omega)$

$$i\omega\tilde{p}(k,\omega) = +ivk\tilde{p}(k,\omega) - Dk^2\tilde{p}(k,\omega)$$

$$i\left[\omega - vk - iDk^2\right]\tilde{p}(k,\omega) = 0$$

Only those Fourier modes $\tilde{p}(k,\omega)$ are nonzero that satisfy dispersion relation

$$\omega(k) = vk + iDk^2$$

Initial condition

$$p(x,0) = \int dk\, e^{-ikx}\tilde{p}(k,\omega(k))$$

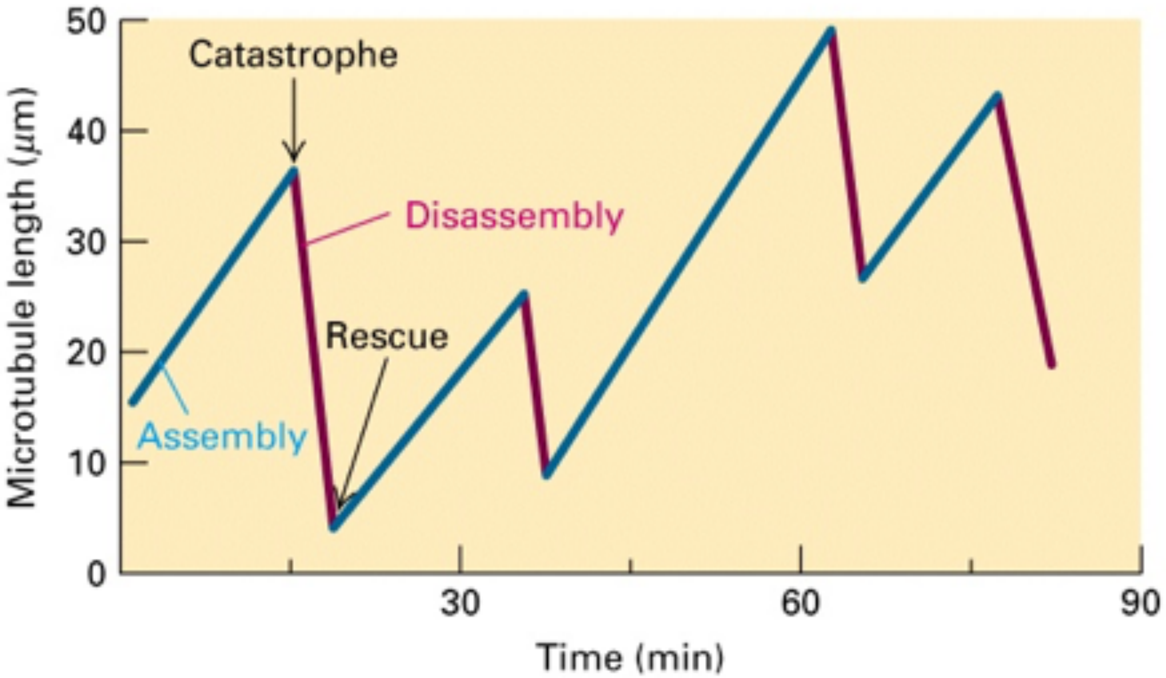
→

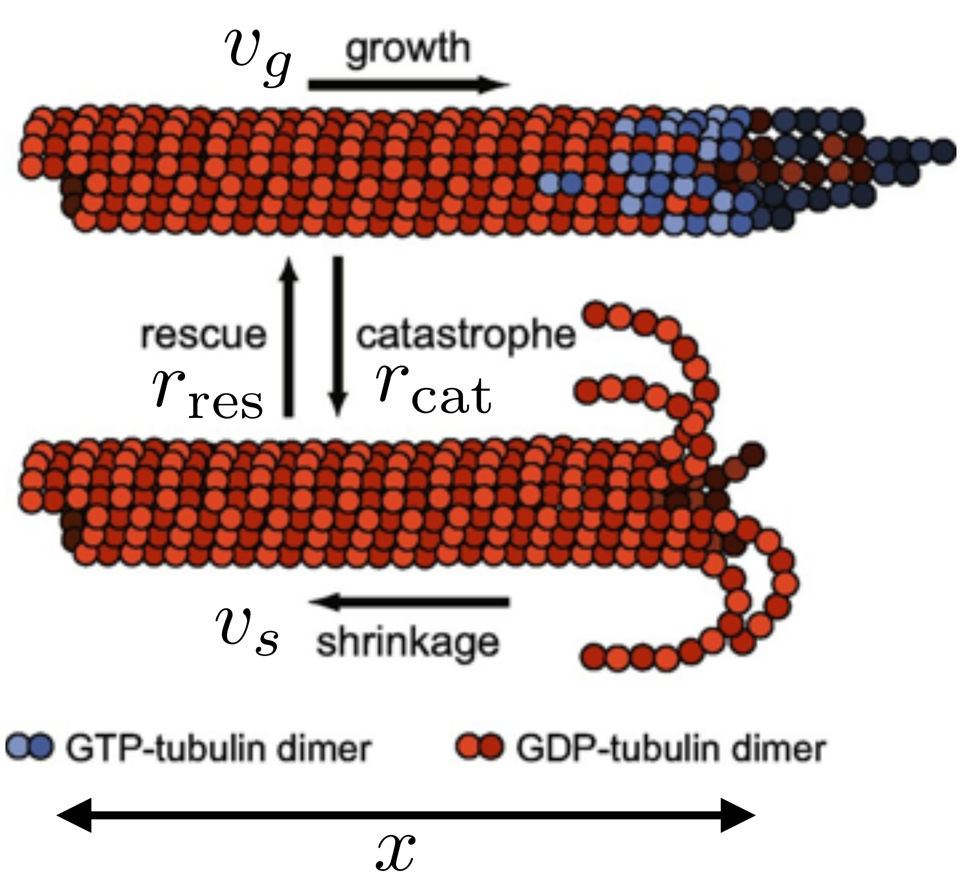
Time evolution

$$p(x,t) = \int dk\, e^{-ik(x-vt)}e^{-Dk^2 t}\tilde{p}(k,\omega(k))$$

At large times only small k components are relevant!

Simple model of microtubule growth





Master equation

$$\frac{\partial p_g(x,t)}{\partial t} = -v_g \frac{\partial p_g(x,t)}{\partial x} - r_{\text{cat}} p_g(x,t) + r_{\text{res}} p_s(x,t)$$

$$\frac{\partial p_s(x,t)}{\partial t} = +v_s \frac{\partial p_s(x,t)}{\partial x} + r_{\text{cat}} p_g(x,t) - r_{\text{res}} p_s(x,t)$$

Average growth speed and average diffusion constant can be determined from dispersion relation for such system:

$$\omega(k) = \overline{v} k + i \overline{D} k^2 + \cdots$$

Simple model of microtubule growth

Master equation

$$\frac{\partial p_g(x,t)}{\partial t} = -v_g \frac{\partial p_g(x,t)}{\partial x} - r_{\text{cat}} p_g(x,t) + r_{\text{res}} p_s(x,t)$$

$$\frac{\partial p_s(x,t)}{\partial t} = +v_s \frac{\partial p_s(x,t)}{\partial x} + r_{\text{cat}} p_g(x,t) - r_{\text{res}} p_s(x,t)$$

Fourier spectrum

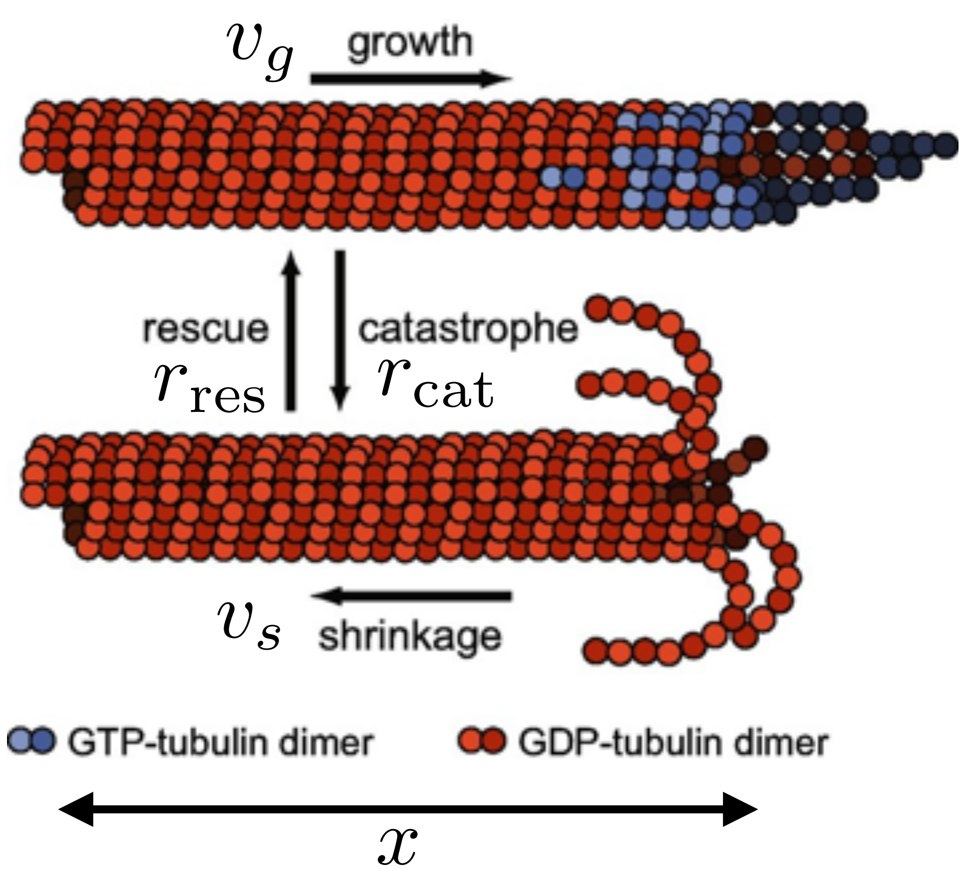
$$p_{g,s}(x,t) = \int dk d\omega e^{i\omega t - ikx} \tilde{p}_{g,s}(k,\omega)$$

$$i \begin{pmatrix} \omega - v_g k - i r_{\text{cat}} & i r_{\text{res}} \\ i r_{\text{cat}} & \omega + v_s k - i r_{\text{res}} \end{pmatrix} \begin{pmatrix} \tilde{p}_g(k,\omega) \\ \tilde{p}_s(k,\omega) \end{pmatrix} = 0$$

Only those Fourier modes are nonzero, that correspond to the matrix with zero determinant!

$$(\omega - v_g k - i r_{\text{cat}})(\omega + v_s k - i r_{\text{res}}) + r_{\text{res}} r_{\text{cat}} = 0$$

Simple model of microtubule growth



Dispersion relation

$$\omega(k) = \frac{1}{2}\Big(k(v_g - v_s) + i r_{\text{cat}} + i r_{\text{res}}\Big) \pm \frac{i}{2}\sqrt{(r_{\text{cat}} + r_{\text{res}})^2 + 2ik(r_{\text{cat}} + r_{\text{res}})(v_g + v_s) - k^2(v_g + v_s)^2}$$

We are interested in effective behavior at large timescales, which correspond to small ω. Taylor expand for small *k* to find:

$$\omega(k) = \overline{v}k + i\overline{D}k^2 + \cdots$$

average growth speed

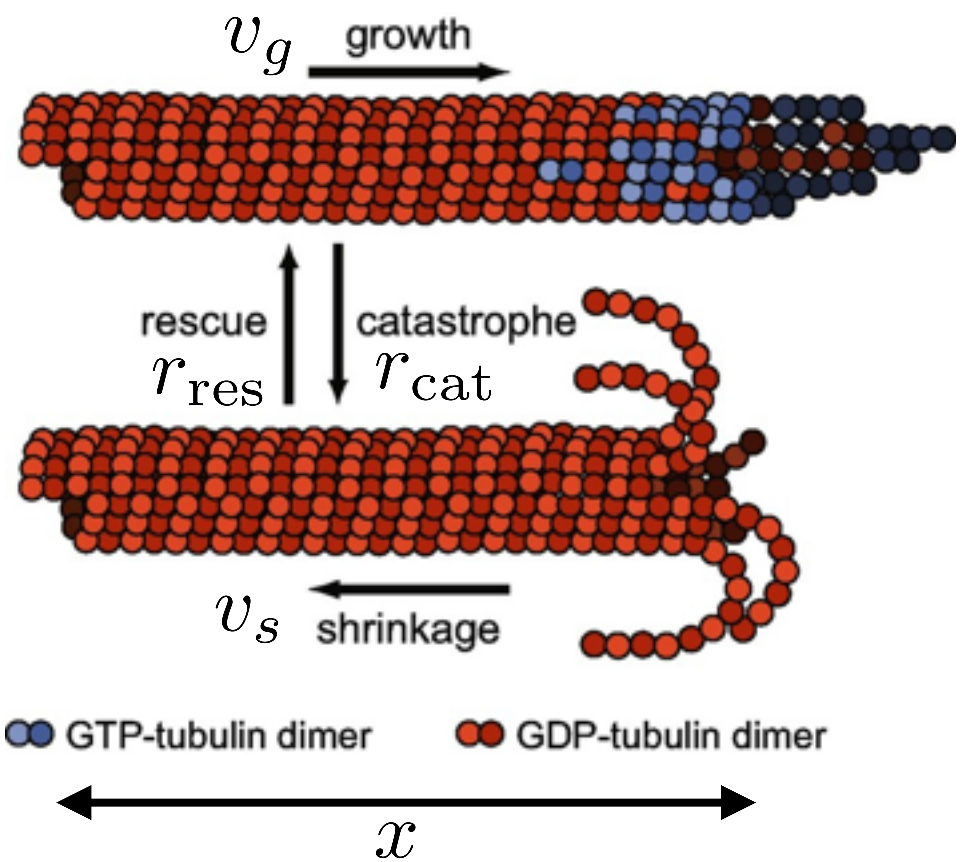
$$\overline{v} = \frac{r_{\text{res}}}{(r_{\text{res}} + r_{\text{cat}})} v_g - \frac{r_{\text{cat}}}{(r_{\text{res}} + r_{\text{cat}})} v_s$$

probability of growing — **probability of shrinking**

average diffusion constant

$$\overline{D} = \frac{r_{\text{res}} r_{\text{cat}} (v_g + v_s)^2}{(r_{\text{res}} + r_{\text{cat}})^3}$$

Simple model of microtubule growth



average growth speed

$$\overline{v} = \frac{r_{\rm res}}{(r_{\rm res} + r_{\rm cat})} v_g - \frac{r_{\rm cat}}{(r_{\rm res} + r_{\rm cat})} v_s$$

bounded growth $\overline{v} < 0$

$$p_g^*(x) = \frac{v_s}{(v_g + v_s)} \frac{1}{\overline{L}} e^{-x/\overline{L}}$$

$$p_s^*(x) = \frac{v_g}{(v_g + v_s)} \frac{1}{\overline{L}} e^{-x/\overline{L}}$$

$$\overline{L} = \frac{v_g v_s}{(v_s r_{\rm cat} - v_g r_{\rm res})} \propto \frac{1}{|\overline{v}|}$$

average filament length