Bioengineering Day 2015

Princeton University October 2

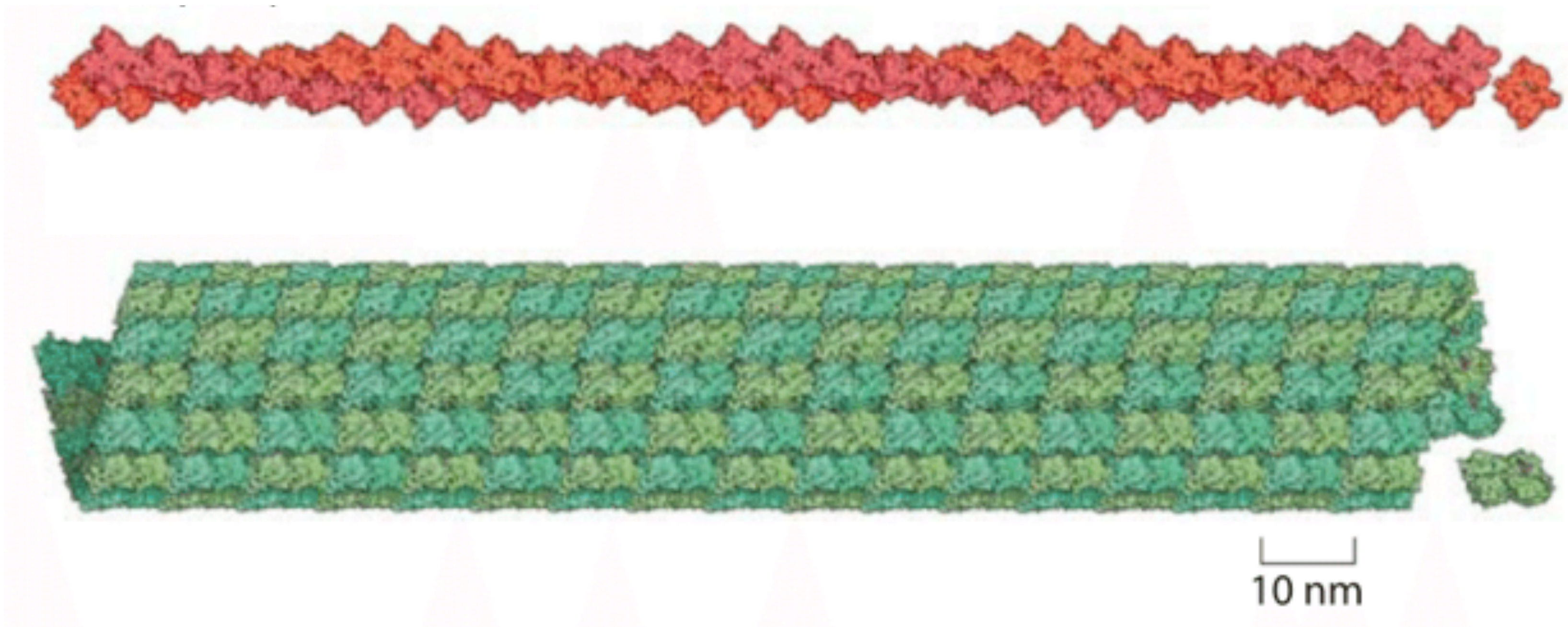
http://bioeng.princeton.edu/bioenginering-day/

MAE 545: Lecture 5 (10/1)

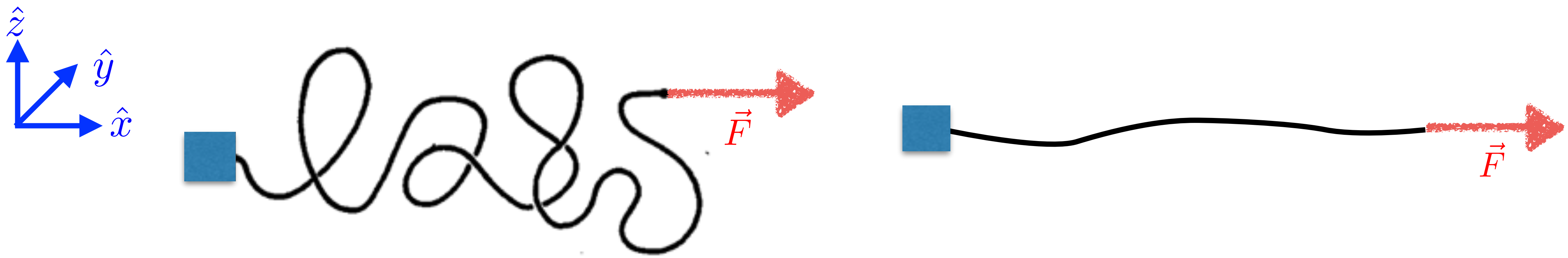
Statistical mechanics of proteins

(continued)

Dynamics of actin filaments and microtubules



Stretching of worm-like chains



Small force

$$F\ell_p \ll k_B T$$

$$\langle x \rangle \approx L \, \frac{2F\ell_p}{3k_B T}$$

Large force

$$F\ell_p \gg k_B T$$

$$\langle x \rangle \approx L \left[1 - \sqrt{\frac{k_B T}{4F\ell_p}} \right]$$

Approximate expression that interpolates between both regimes

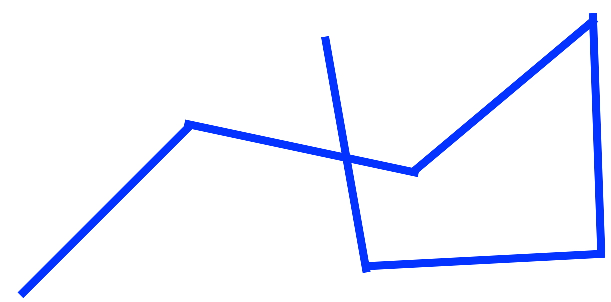
$$\frac{F\ell_p}{k_B T} = \frac{1}{4}\left(1 - \frac{\langle x \rangle}{L}\right)^{-2} - \frac{1}{4} + \frac{\langle x \rangle}{L}$$

J.F. Marko and E.D. Siggia,
Macromolecules 28, 8759-8770 (1995)

Steric interactions

So far we ignored interactions between different chain segments, but in reality the chain cannot pass through itself due to steric interactions.

Example of forbidden configuration in 2D



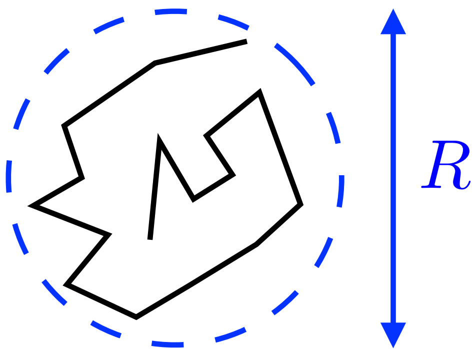
Polymer chains are realizations of self-avoiding random walks!

Steric interactions are important for long polymers in the absence of pulling forces

Steric interactions are not important in the presence of pulling forces.

Mean field estimate for the radius of self-avoiding polymers

Paul Flory



Approximate partition function: estimate number of self-avoiding random walks of *N* steps of size *a* that are restricted to a sphere of radius *R*.

$$Z(R,N) \approx g^N \times \frac{e^{-3R^2/2Na^2}}{[2\pi N a^2/3]^{3/2}} \times \underbrace{\left[1 \cdot \left(1 - \frac{a^3}{R^3}\right) \cdot \left(1 - \frac{2a^3}{R^3}\right) \cdots \left(1 - \frac{(N-1)a^3}{R^3}\right)\right]}_{C_{\mathrm{ev}}}$$

total number of random walks

reduction in entropy when constrained to sphere of radius R

reduction in entropy due to excluded volume

Excluded volume effect

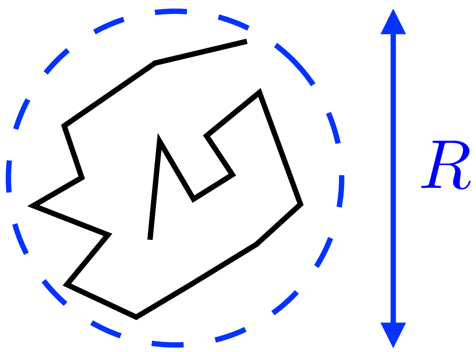
$$\ln C_{\mathrm{ev}} = \sum_{k=1}^{N-1} \ln\left(1 - \frac{ka^3}{R^3}\right) \approx \sum_{k=1}^{N-1}\left(-\frac{ka^3}{R^3} - \frac{k^2a^6}{2R^6} - \cdots\right) \approx -\frac{N^2a^3}{2R^3} - \frac{N^3a^6}{6R^6}$$

Approximate partition function

$$\ln Z(R,N) \approx N \ln g - \frac{3}{2}\ln(2\pi N a^2/3) - \frac{3R^2}{2Na^2} - \frac{N^2a^3}{2R^3} - \frac{N^3a^6}{6R^6}$$

Relation between partition function and free energy

Paul Flory



Statistical mechanics

$$Z = \sum_c e^{-E_c/k_B T} = e^{-G/k_B T} \longrightarrow G = -k_B T \ln Z$$

Approximate partition function

$$\ln Z(R,N) \approx N \ln g - \frac{3}{2}\ln(2\pi N a^2/3) - \frac{3R^2}{2Na^2} - \underbrace{\frac{N^2a^3}{2R^3} - \frac{N^3a^6}{6R^6}}$$

reduction in entropy when constrained to sphere of radius R

reduction in entropy due to excluded volume interactions

Free energy cost for constraining polymer to sphere of radius *R*

$$\Delta G(R,N) = G_{\text{ent}}(R,N) + G_{\text{int}}(R,N)$$

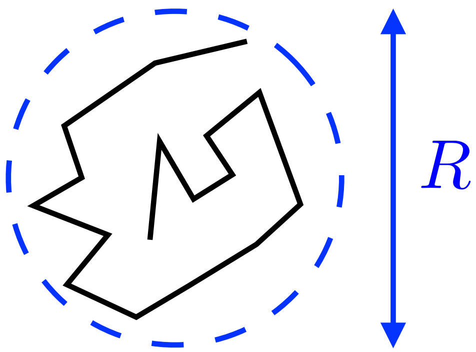
$$G_{\text{ent}}(R,N) = \frac{3k_B T R^2}{2Na^2}$$

$$G_{\text{int}}(R,N) = \frac{k_B T N^2 a^3}{2R^3} + \frac{k_B T N^3 a^6}{6R^6}$$

Estimate polymer radius by maximizing the partition function or equivalently by minimizing the free energy!

Mean field estimate for the radius of self-avoiding polymers

Paul Flory



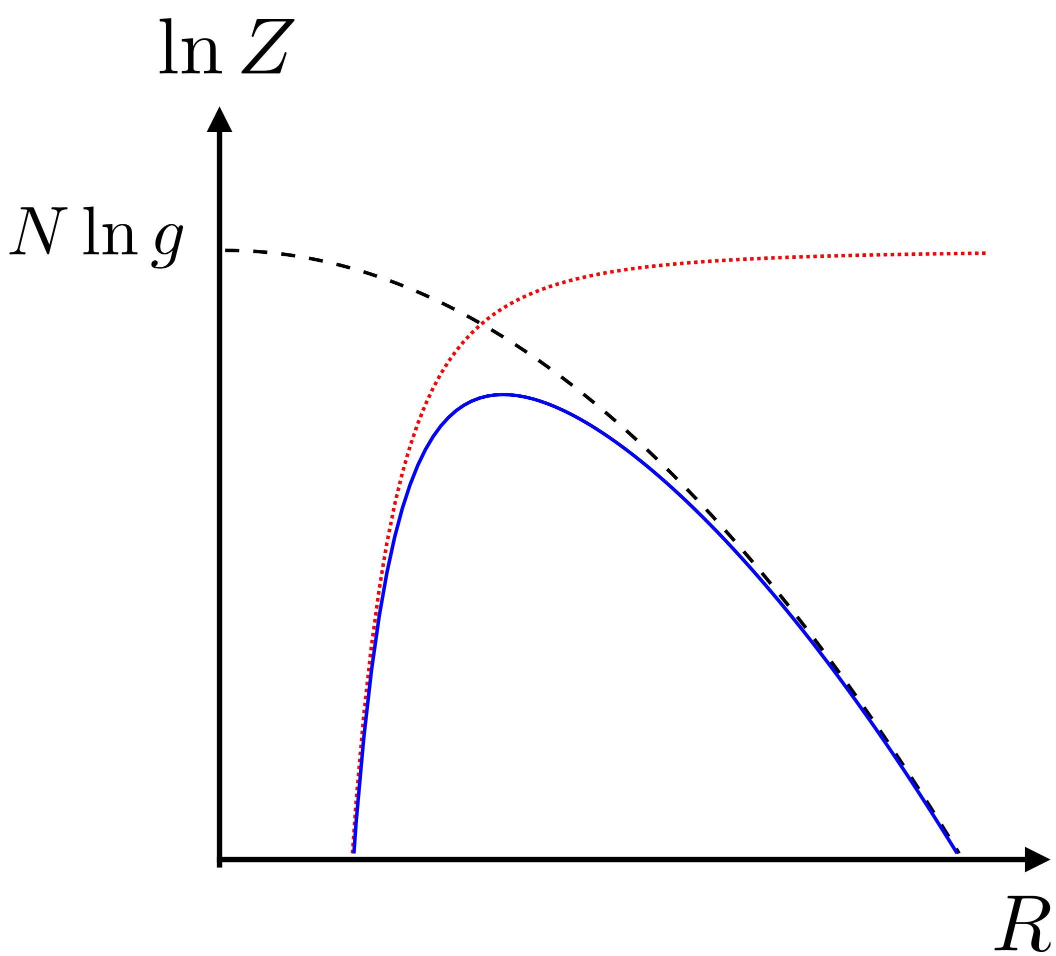
(higher order term can be ignored)

Approximate partition function

$$\ln Z(R,N) \approx N \ln g - \frac{3}{2}\ln(2\pi N a^2/3) - \frac{3R^2}{2Na^2} - \frac{N^2 a^3}{2R^3} - \frac{N^3 a^6}{6R^6}$$

Estimate polymer radius by maximizing the partition function

$$\frac{\partial \ln Z(R,N)}{\partial R} \approx -\frac{3R}{Na^2} + \frac{3}{2}\frac{N^2 a^3}{R^4} = 0$$



$$R \sim a N^{\nu} \sim \ell_p \left(\frac{L}{\ell_p}\right)^{\nu}$$

Flory exponent $\nu = 3/5$

Exact result from more sophisticated methods

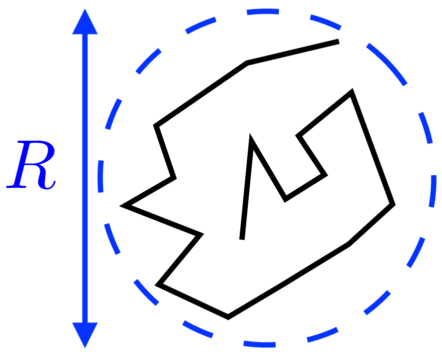
$\nu \approx 0.591$

non-avoiding random walks

$\nu = 1/2$

Paul Flory

Self-avoiding walks in *d* dimensions



Approximate partition function

$$Z(R,N) \approx g^N \times \frac{e^{-dR^2/2Na^2}}{[2\pi N a^2/d]^{d/2}} \times \left[1 \cdot \left(1 - \frac{a^d}{R^d}\right) \cdot \left(1 - \frac{2a^d}{R^d}\right) \cdots \left(1 - \frac{(N-1)a^d}{R^d}\right)\right]$$

$$\ln Z(R,N) \approx N \ln g - \frac{d}{2} \ln(2\pi N a^2/d) - \frac{dR^2}{2Na^2} - \frac{N^2 a^d}{2R^d}$$

Estimate *R* by maximizing the partition function

$$\frac{\partial \ln Z(R,N)}{\partial R} \approx -\frac{dR}{Na^2} + \frac{d}{2} \frac{N^2 a^d}{R^{d+1}} = 0$$

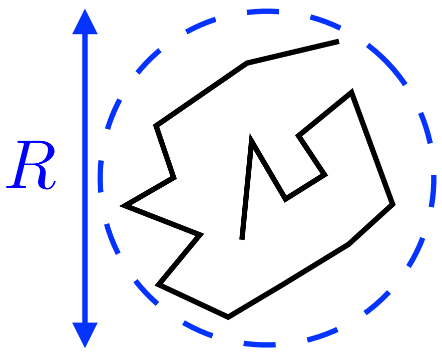
$$\boxed{R \sim a N^{\nu} \qquad \nu = \frac{3}{d+2}}$$

For $d \geq 4$ Flory exponent is $\nu \leq 1/2$, but for non-avoiding walk $\nu = 1/2$.

What is then the expected scaling for radius *R*?

Self-avoiding walks in *d* dimensions

Paul Flory



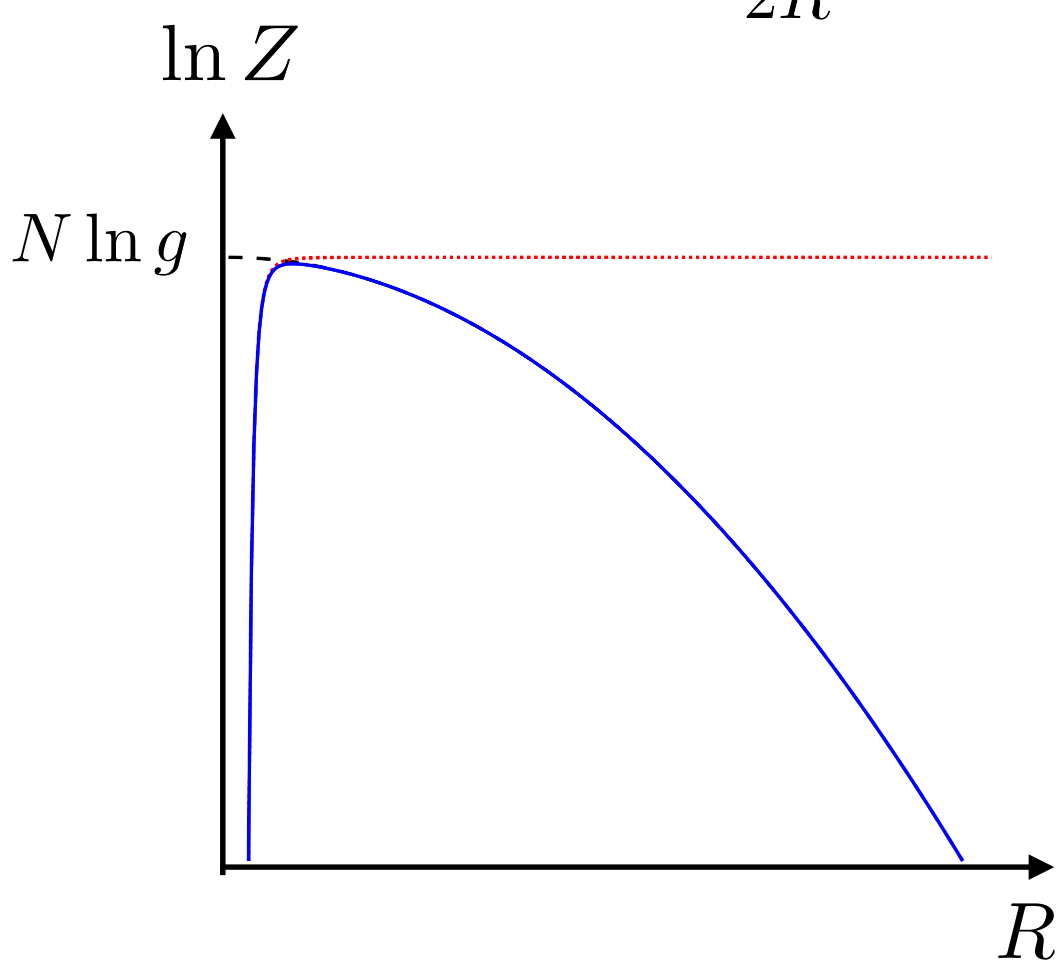
Approximate partition function

$$\ln Z(R,N) \approx N \ln g - \frac{d}{2}\ln(2\pi N a^2/d) - \frac{dR^2}{2Na^2} - \frac{N^2 a^d}{2R^d}$$

Estimate free energy contributions when $R \sim aN^{1/2}$

$$G_{\mathrm{ent}} = k_B T\,\frac{dR^2}{2Na^2} \sim k_B T$$

$$G_{\mathrm{int}} = k_B T\,\frac{N^2 a^d}{2R^d} \sim k_B T N^{(4-d)/2}$$



Excluded volume interactions are only important for *d* < 4!

Flory estimate

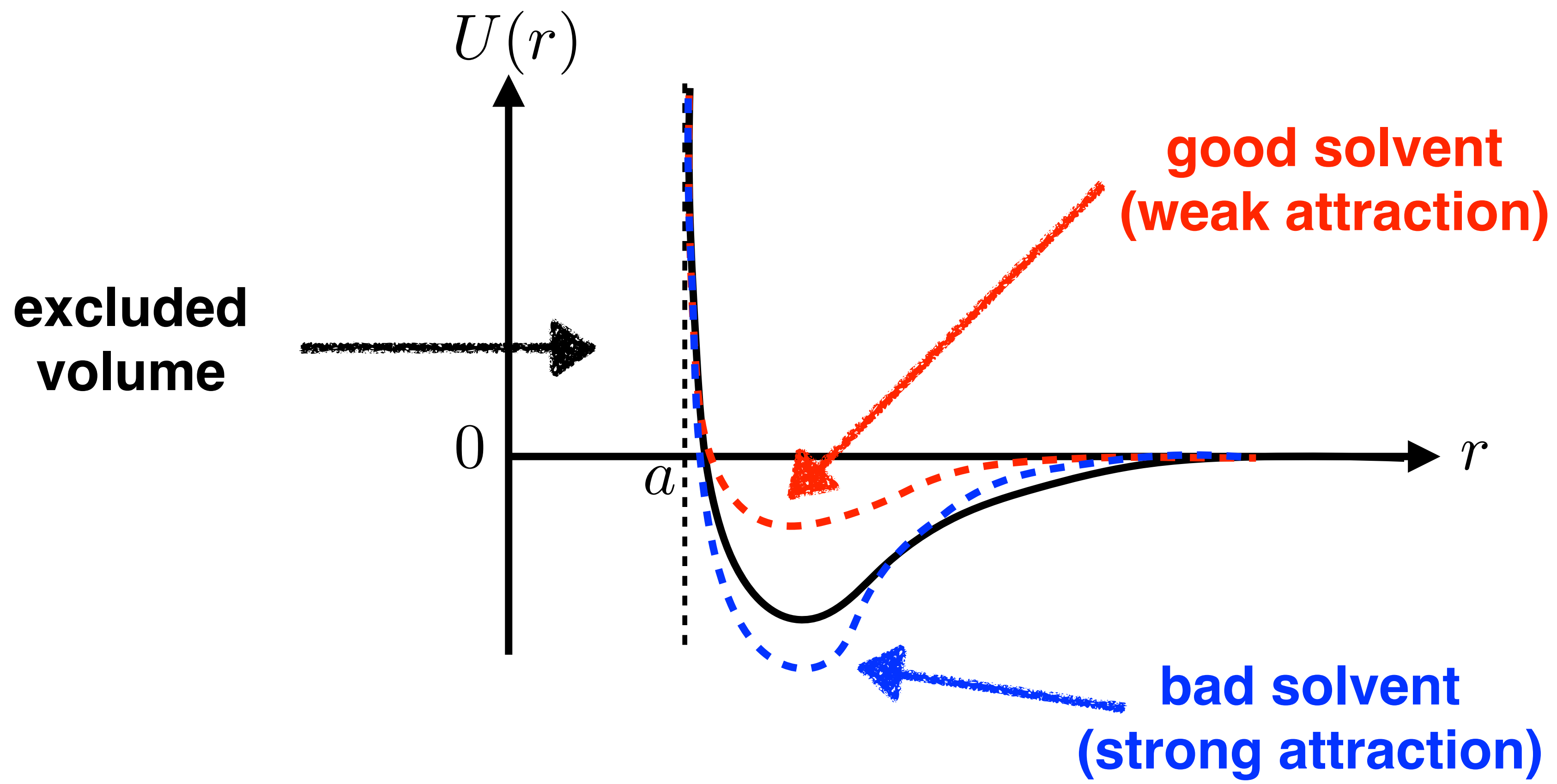
$$R \sim aN^{\nu} \qquad d \le 4 \quad \nu = \frac{3}{d+2} \qquad d \ge 4 \quad \nu = \frac{1}{2}$$

d	1	2	3	≥ 4
ν	1	$3/4$	$3/5$	$1/2$

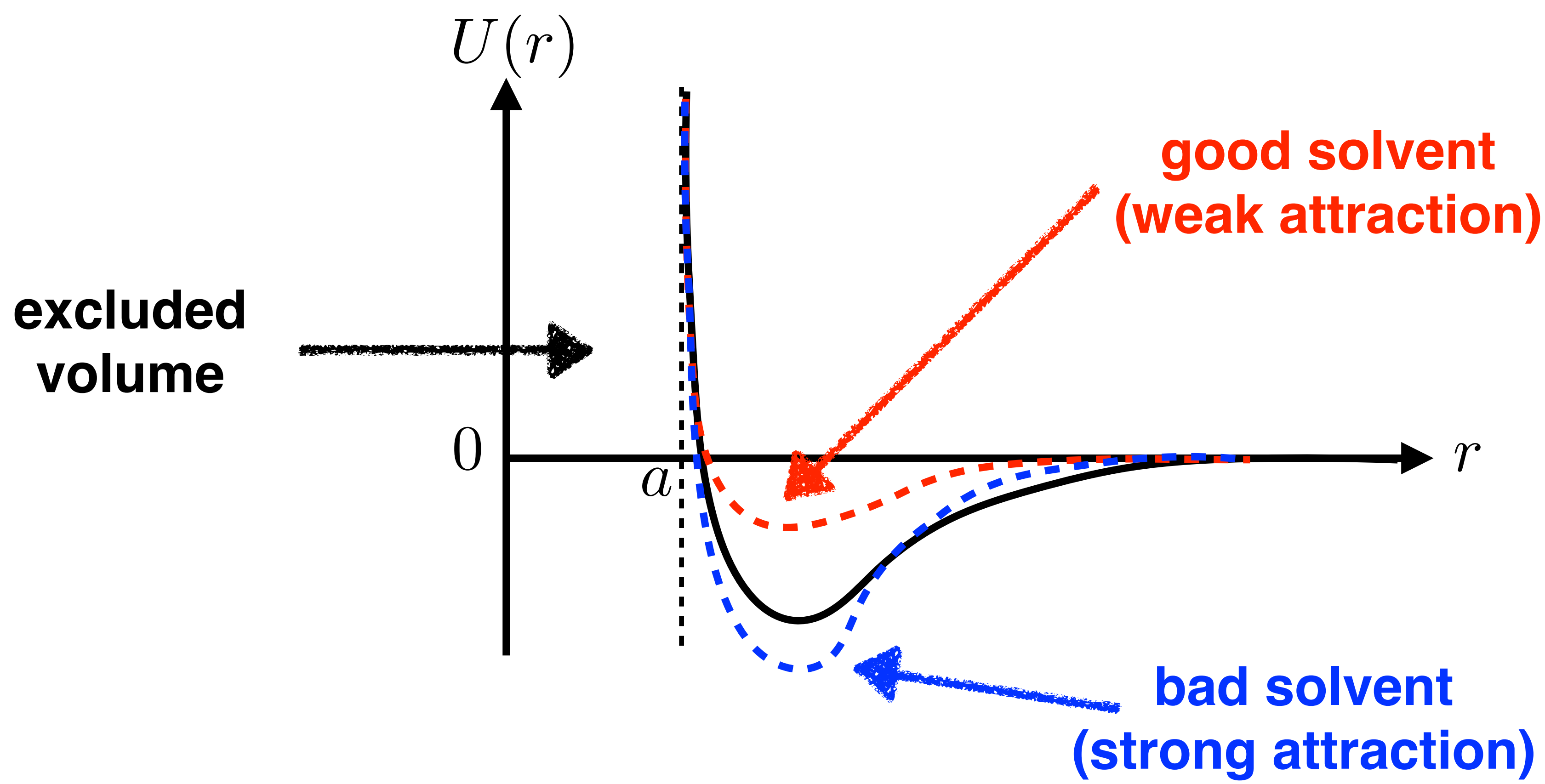
Note: except for *d*=3 these exponents are exact!

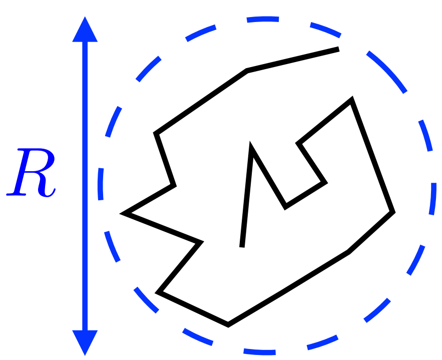
Interacting polymers

Now let us include also other interactions between polymer chains, e.g. van der Waals interactions. Interactions are typically attractive and their magnitude can be modulated by the choice of solvent.



Interacting polymers





Mean field approximation for the total attraction energy

$$E_{\text{att}} = \frac{1}{2}\sum_{i\neq j} U(\vec{r}_i - \vec{r}_j) \approx \frac{1}{2}\int d^3\vec{r}\, d^3\vec{r}\,'\, \rho(\vec{r})\rho(\vec{r}\,')U(\vec{r}-\vec{r}\,')$$

$\rho(\vec{r})$
polymer density

Assuming uniform polymer density $\rho(\vec{r}) = N/V \sim N/R^3$

$$E_{\text{att}} = \frac{N^2}{2V}\int_{r>a} d^3\vec{r}\; U(\vec{r}) \equiv -k_B T \chi N^2 a^3/R^3$$

Excluded volume effects will be treated separately.

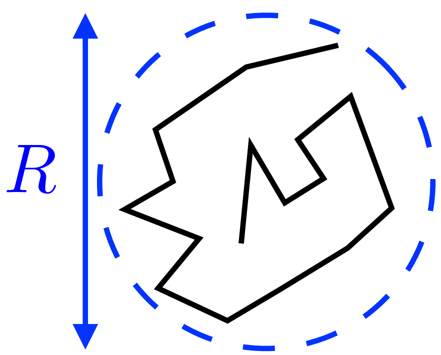
Flory-Huggins parameter $\chi = -\dfrac{\int_{r>a} d^3\vec{r}\, U(\vec{r})}{2a^3 k_B T}$

Interacting polymers

Mean field approximation for the partition function

$$Z(R,N) \approx g^N \times \frac{e^{-3R^2/2Na^2}}{[2\pi N a^2/3]^{3/2}} \times \left[1 \cdot \left(1 - \frac{a^3}{R^3}\right) \cdot \left(1 - \frac{2a^3}{R^3}\right) \cdots \left(1 - \frac{(N-1)a^3}{R^3}\right)\right] \times e^{-E_{\rm att}/k_B T}$$

$$\ln Z(R,N) \approx N \ln g - \frac{3}{2}\ln(2\pi N a^2/3) - \frac{3R^2}{2Na^2} - \frac{N^2 a^3}{2R^3} - \frac{N^3 a^6}{6R^6} + \chi N^2 \frac{a^3}{R^3}$$



attraction

$$\ln Z(R,N) \approx N \ln g - \frac{3}{2}\ln(2\pi N a^2/3) - \frac{3R^2}{2Na^2} - \left(\frac{1}{2} - \chi\right)\frac{N^2 a^3}{R^3} - \frac{N^3 a^6}{6R^6}$$

Note: $\chi(T)$ is typically a decreasing function of temperature and the coefficient $(1/2 - \chi)$ in equation above changes sign at the so called θ temperature, where $\chi(\theta) = 1/2$.

At large temperatures, where $\chi < 1/2$, polymers are in swollen coil state.

$$\boxed{R \sim (1/2 - \chi)^{1/5} a N^{3/5}}$$

average density $\bar{\rho} \sim \frac{N}{R^3} \sim N^{-4/5} \to 0$

Exactly at θ temperature, where $\chi = 1/2$, attractive interactions and excluded volume are balanced.

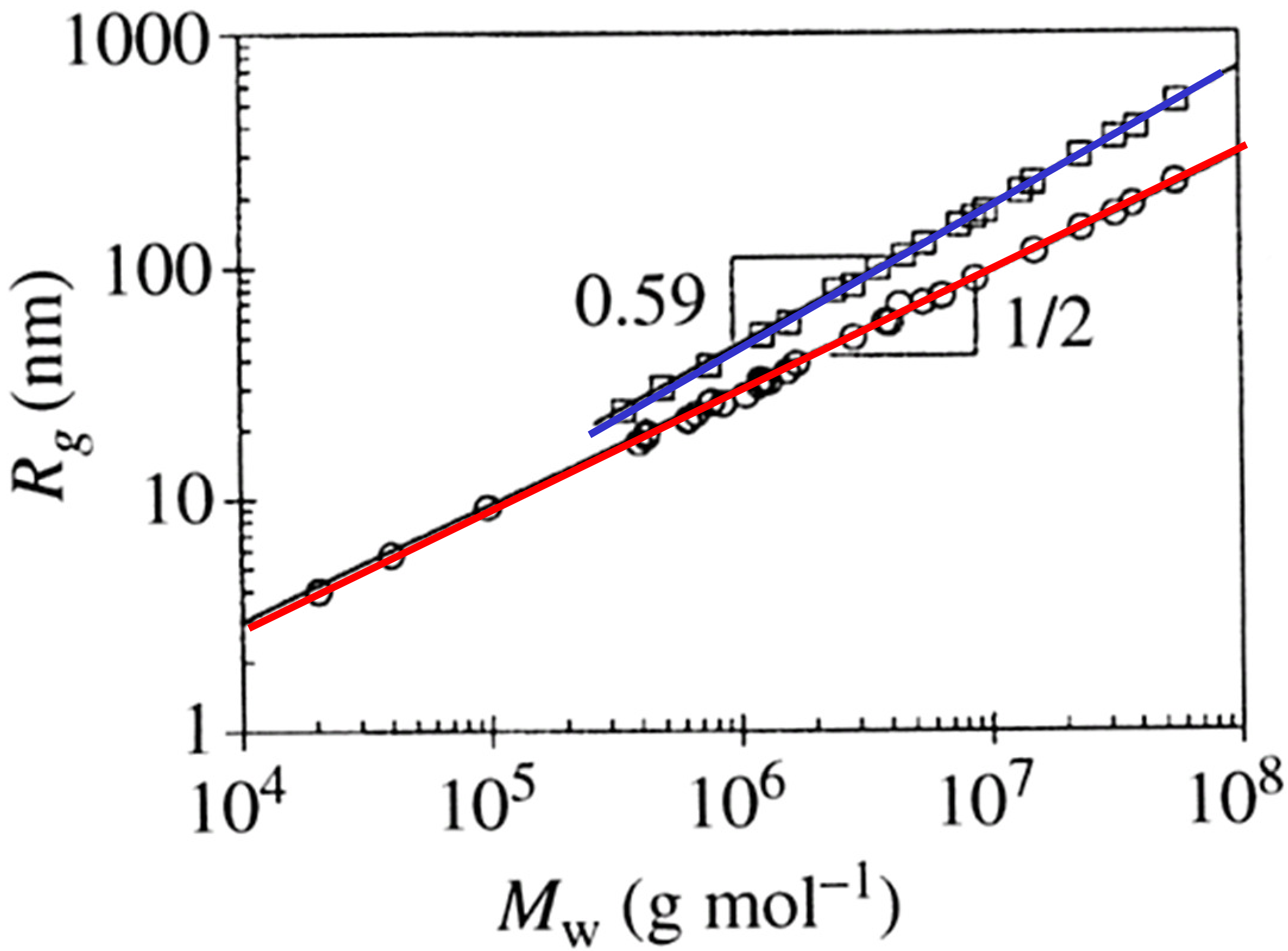
$$\boxed{R \sim a N^{1/2}}$$

average density $\bar{\rho} \sim N^{-1/2} \to 0$

Good solvent - theta solvent

gyration radius

$$R_g^2 = \frac{1}{N}\left\langle \sum_{k=1}^{N} (\vec{r}_k - \vec{r}_{\mathrm{mean}})^2 \right\rangle \qquad \vec{r}_{\mathrm{mean}} = \frac{1}{N}\sum_{k=1}^{N} \vec{r}_k$$



polystyrene in benzene (good solvent)

$\chi < 1/2$

$R \sim N^{0.59}$

polystyrene in cyclohexane (theta solvent)

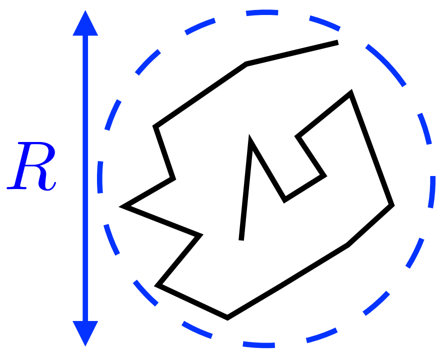
$\chi = 1/2$

$R \sim N^{1/2}$

molecular weight of polystyrene $\sim N$

L.J. Fetters *et al.*, J. Phys. Chem. 23, 619-640 (1994)

Swollen coil to globule transition



At low temperatures, where $\chi > 1/2$, polymers are in compact globule state with finite density $\rho \sim N/R^3$

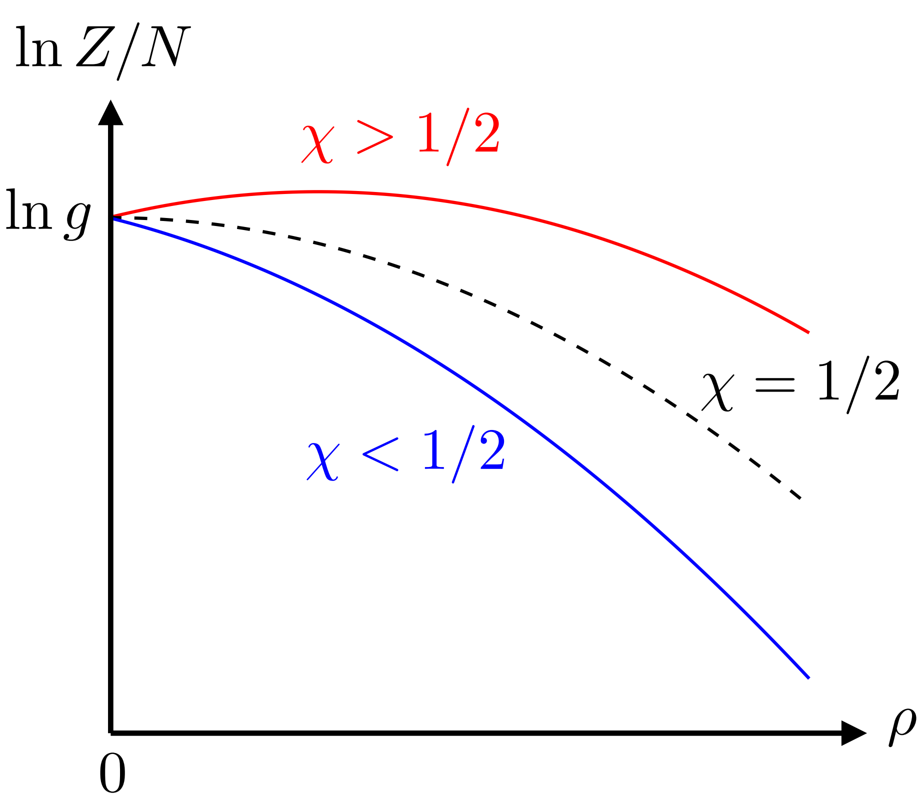
$$\frac{\ln Z(R,N)}{N} \approx \ln g - \frac{3R^2}{2N^2a^2} - \left(\frac{1}{2} - \chi\right)\frac{Na^3}{R^3} - \frac{N^2a^6}{6R^6}$$

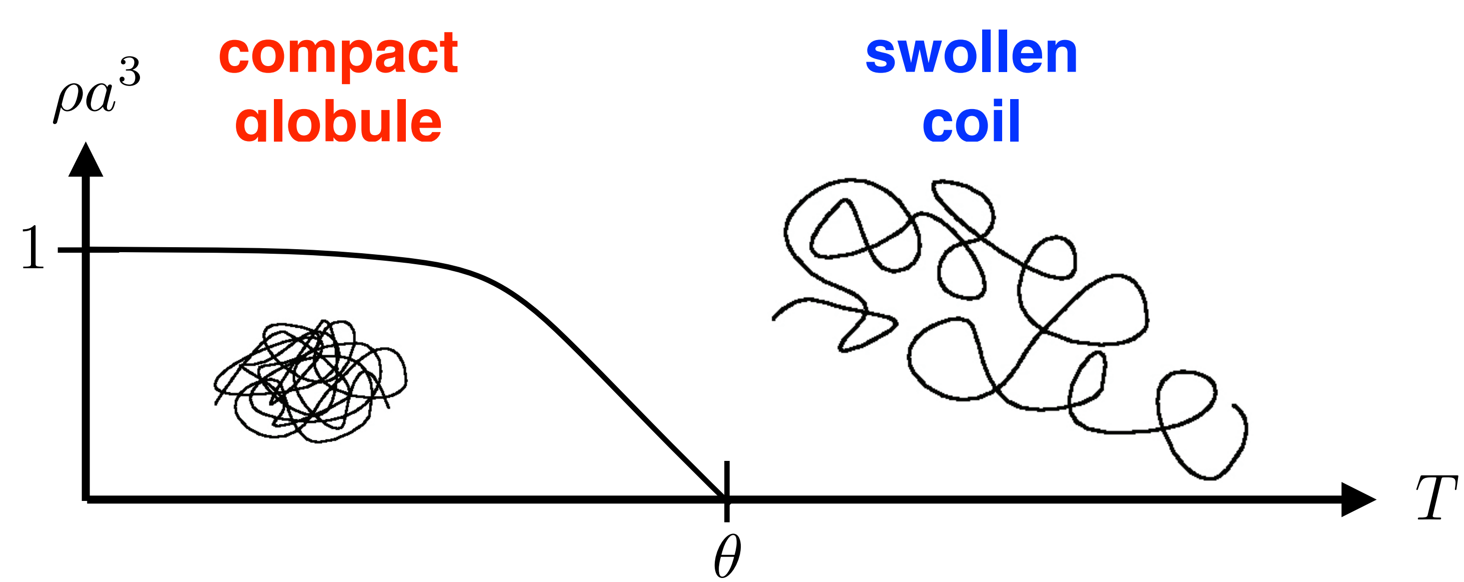
(higher order term can be ignored)

$$\frac{\ln Z(\rho,N)}{N} \approx \ln g + \left(\chi - \frac{1}{2}\right)\rho a^3 - \frac{\rho^2 a^6}{6}$$

Average density of the compact globule is obtained by maximizing entropy

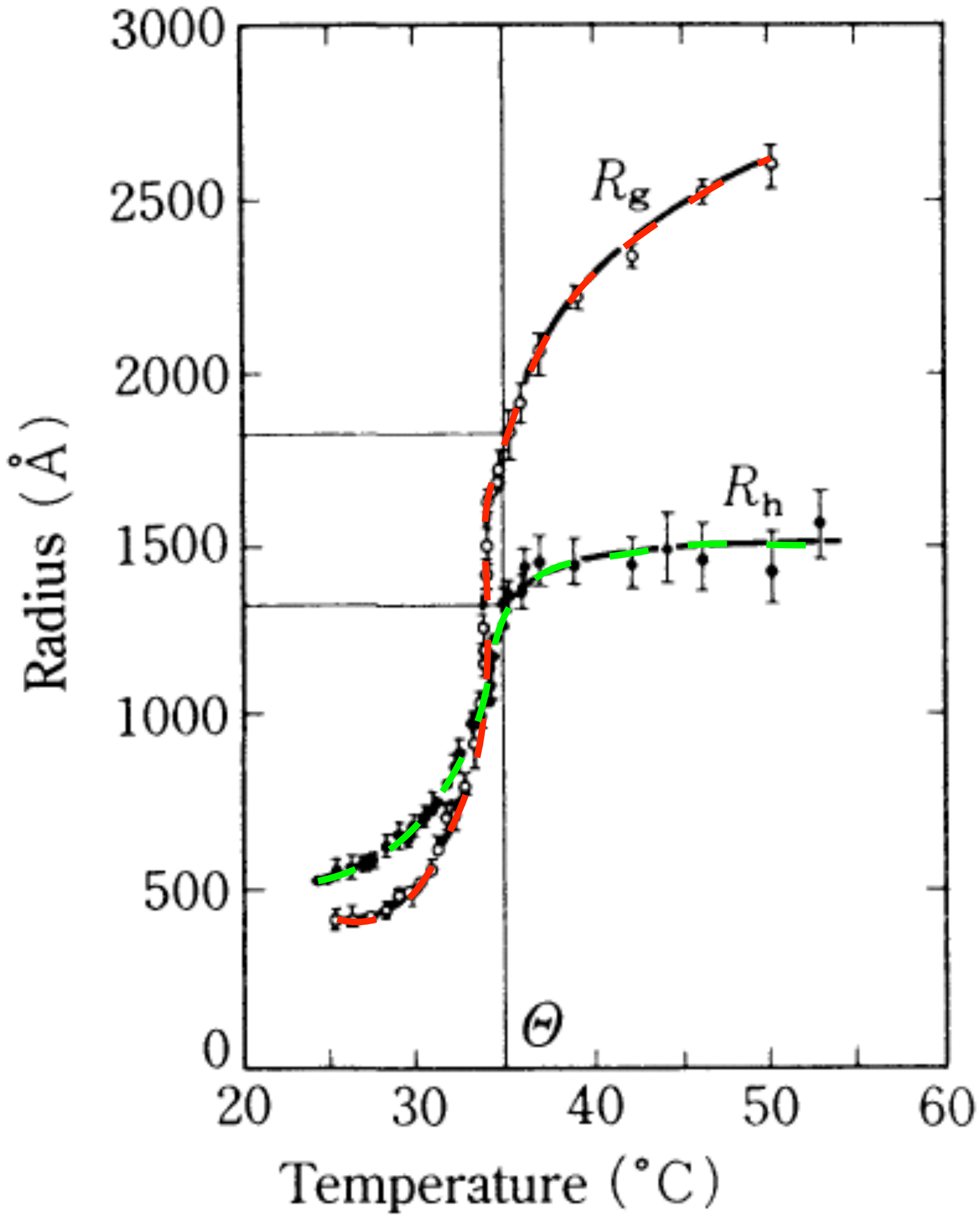
$$\boxed{\rho \sim \left(\chi - \frac{1}{2}\right) a^{-3}}$$





Swollen coil to globule transition

polystyrene in cyclohexane



gyration radius

$$R_g^2 = \frac{1}{N}\left\langle \sum_{k=1}^{N} (\vec{r}_k - \vec{r}_{\text{mean}})^2 \right\rangle$$

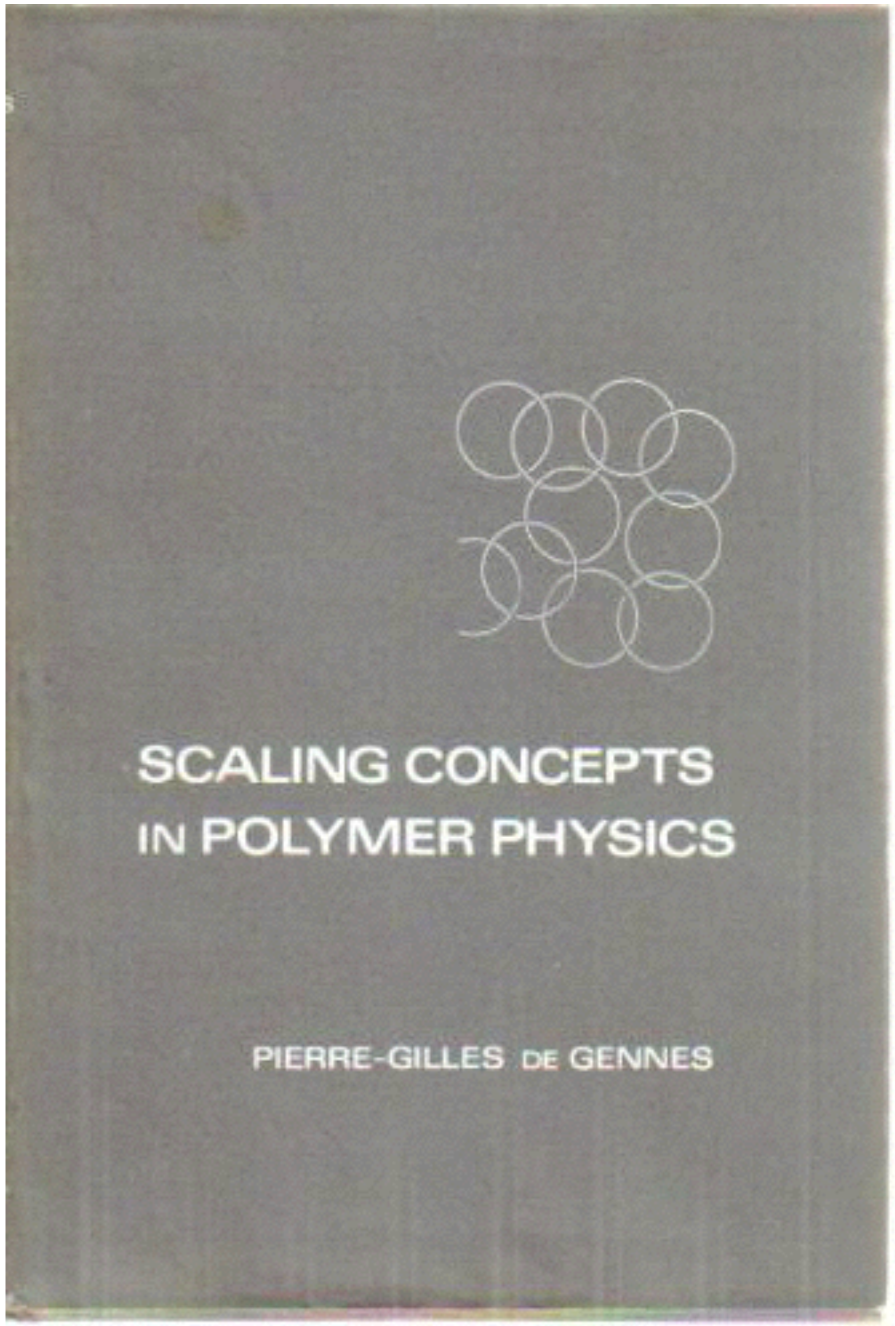
$$\vec{r}_{\text{mean}} = \frac{1}{N}\sum_{k=1}^{N} \vec{r}_k$$

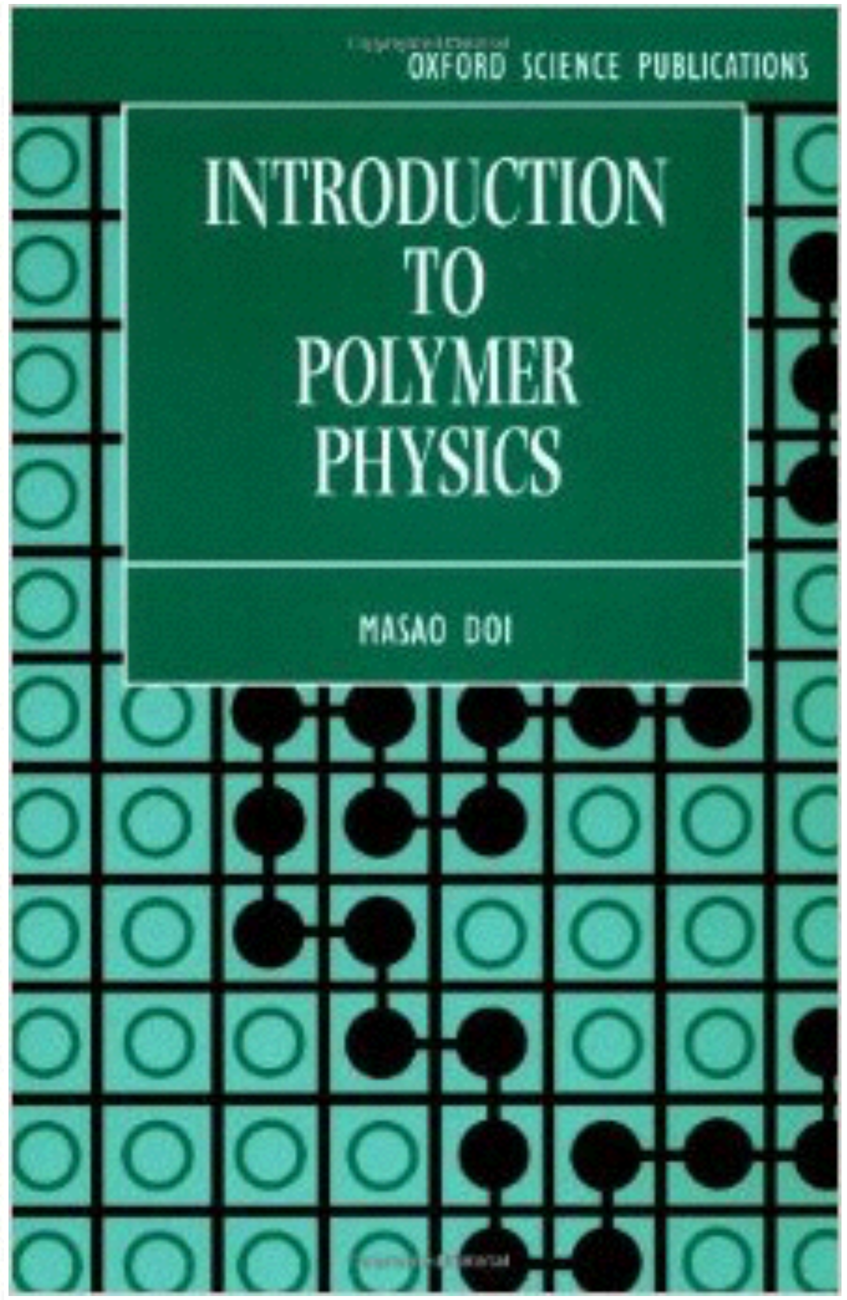
hydrodynamic radius

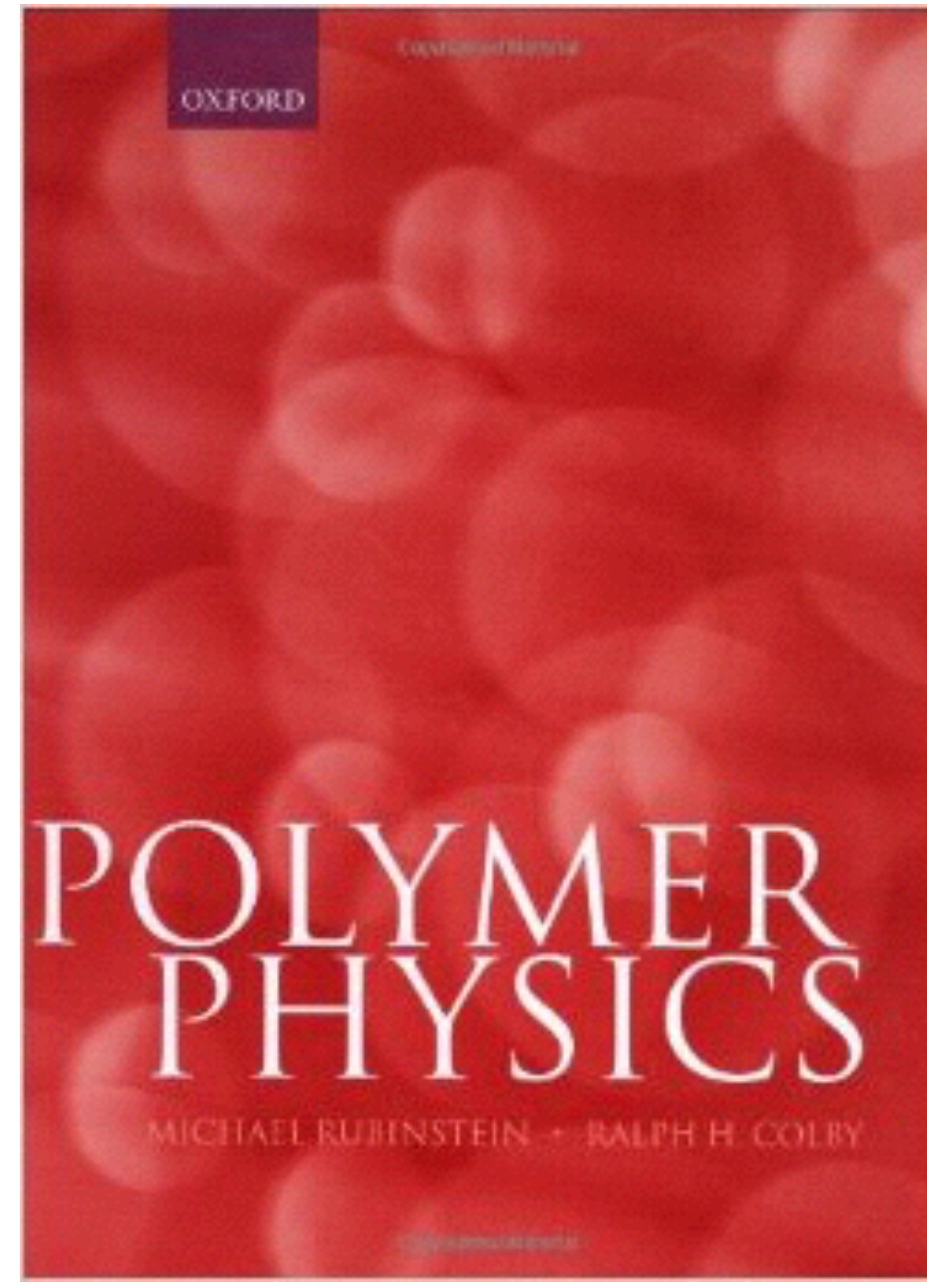
$$R_h = \frac{k_B T}{6\pi\eta D}$$

S.T. Sun *et al.*, J. Chem. Phys. 73, 5971 (1980)

Further reading



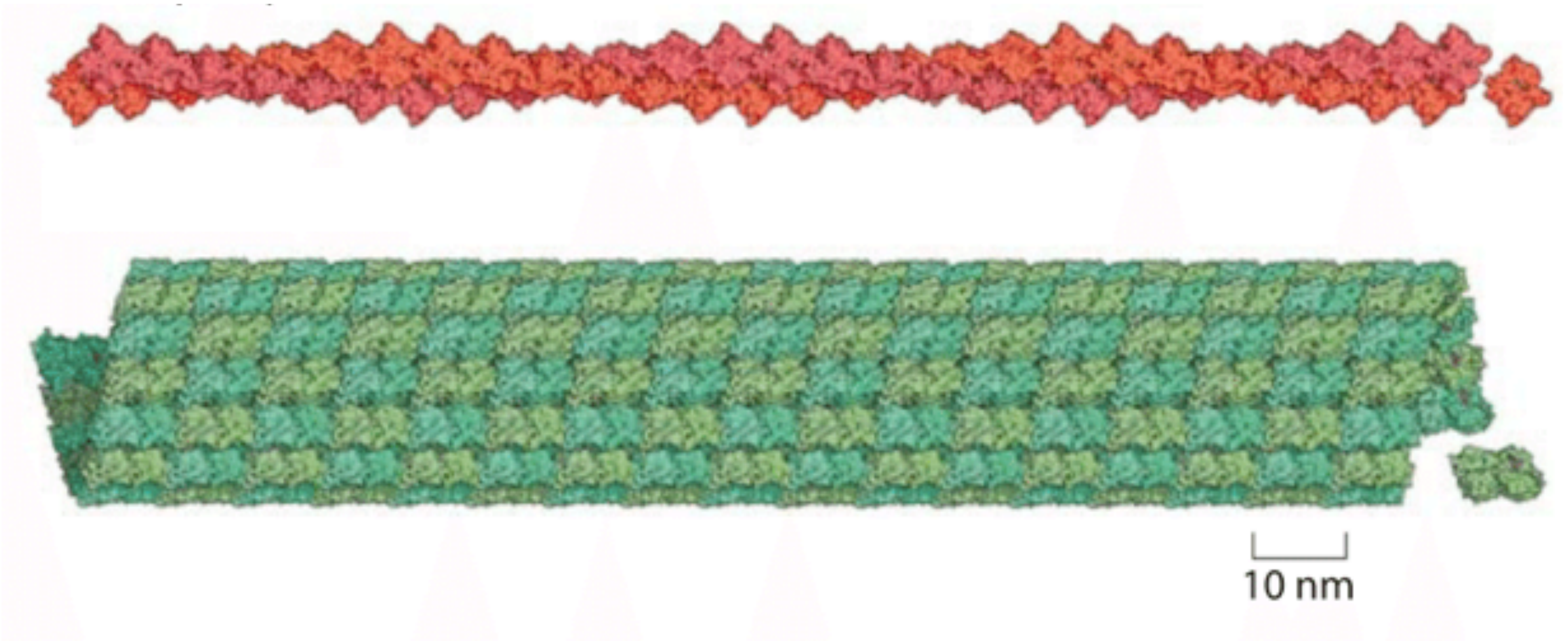




Dynamics of actin filaments and microtubules

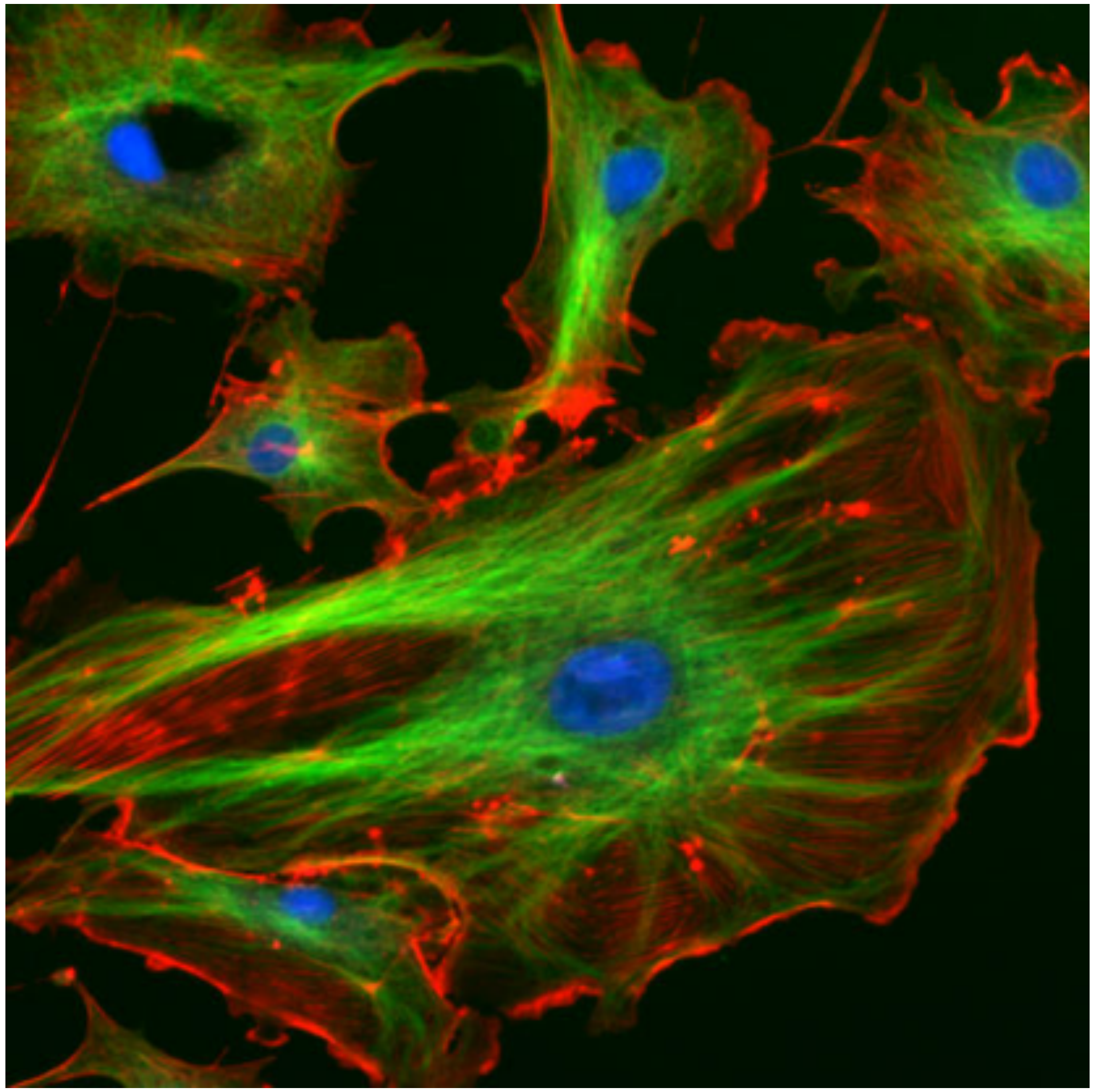
Actin filament

Microtubule



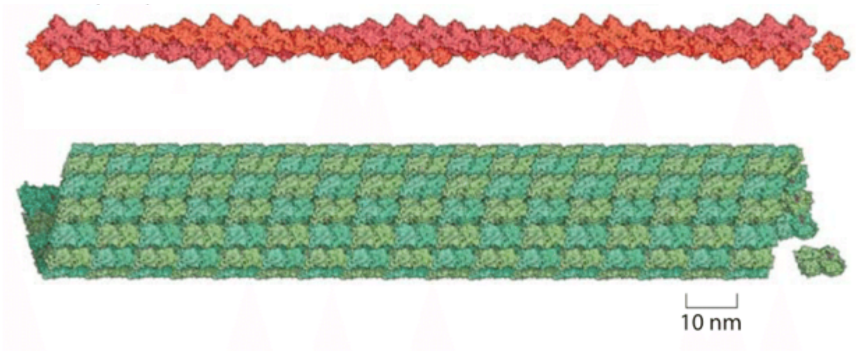
Cytoskeleton in cells

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



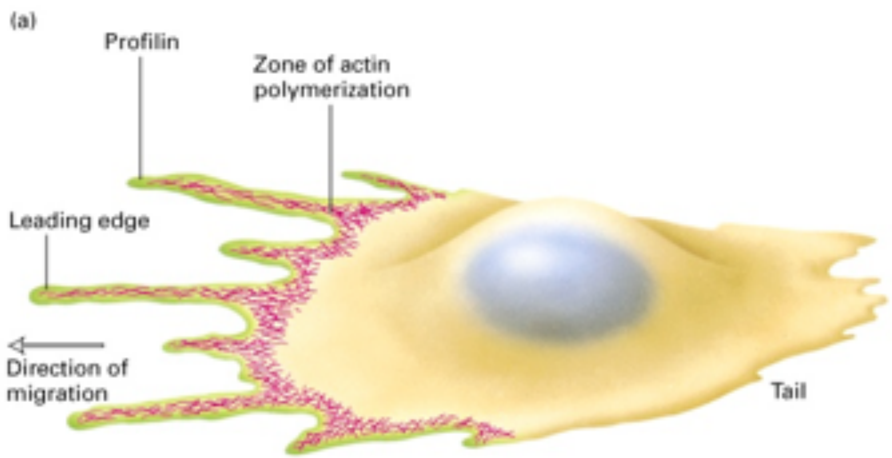
(wikipedia)

Actin filament



Microtubule

Crawling of cells



migration of skin cells during wound healing

spread of cancer cells during metastasis of tumors

amoeba searching for food

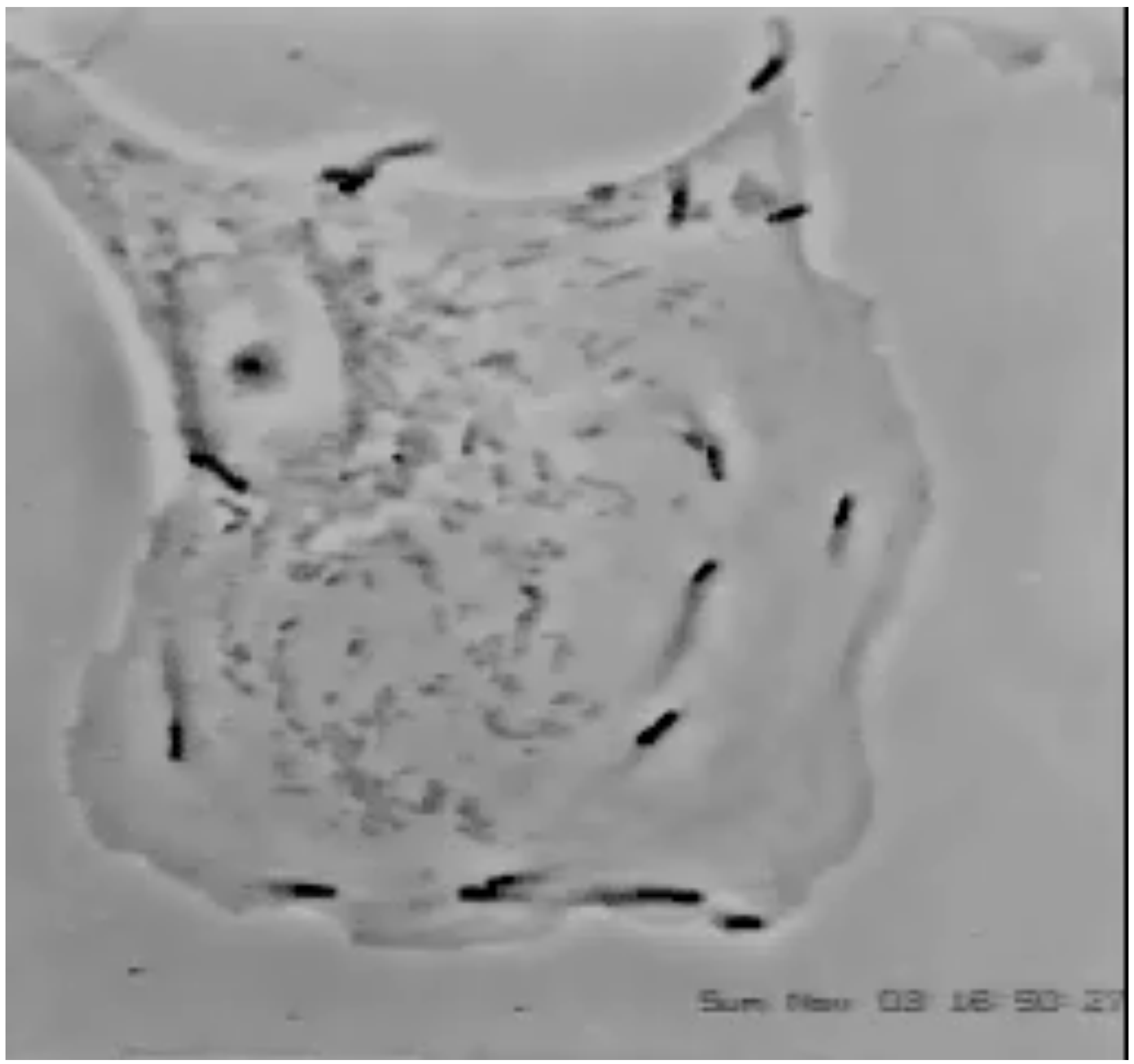
Immune system:
neutrophils chasing bacteria

David Rogers, 1950s

$v \sim 0.1 \mu\mathrm{m/s}$

Movement of bacteria

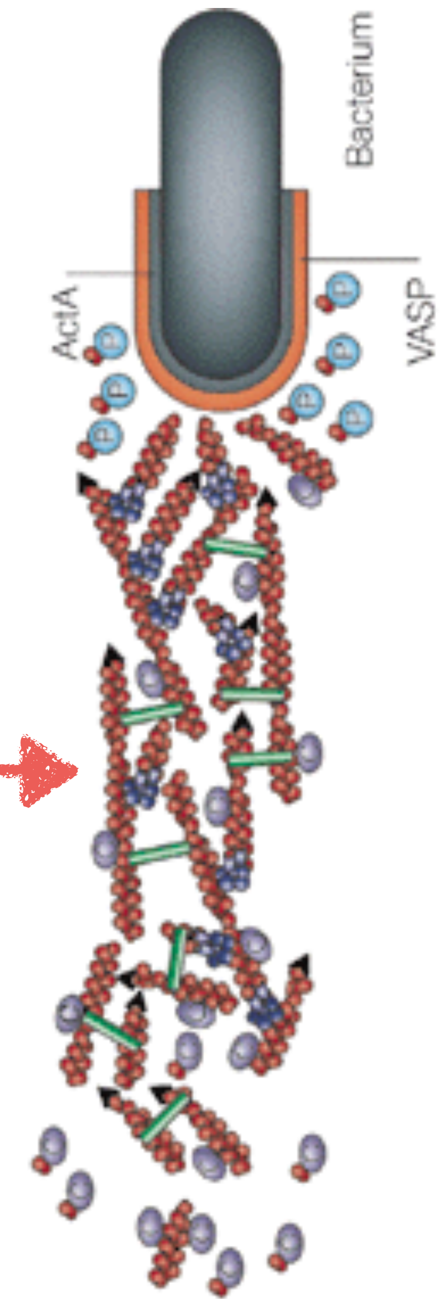
Listeria monocytogenes
moving in PtK2 cells



Julie Theriot **(speeded up 150x)**

$$v \sim 0.1 - 0.3 \mu\mathrm{m/s}$$

Actin



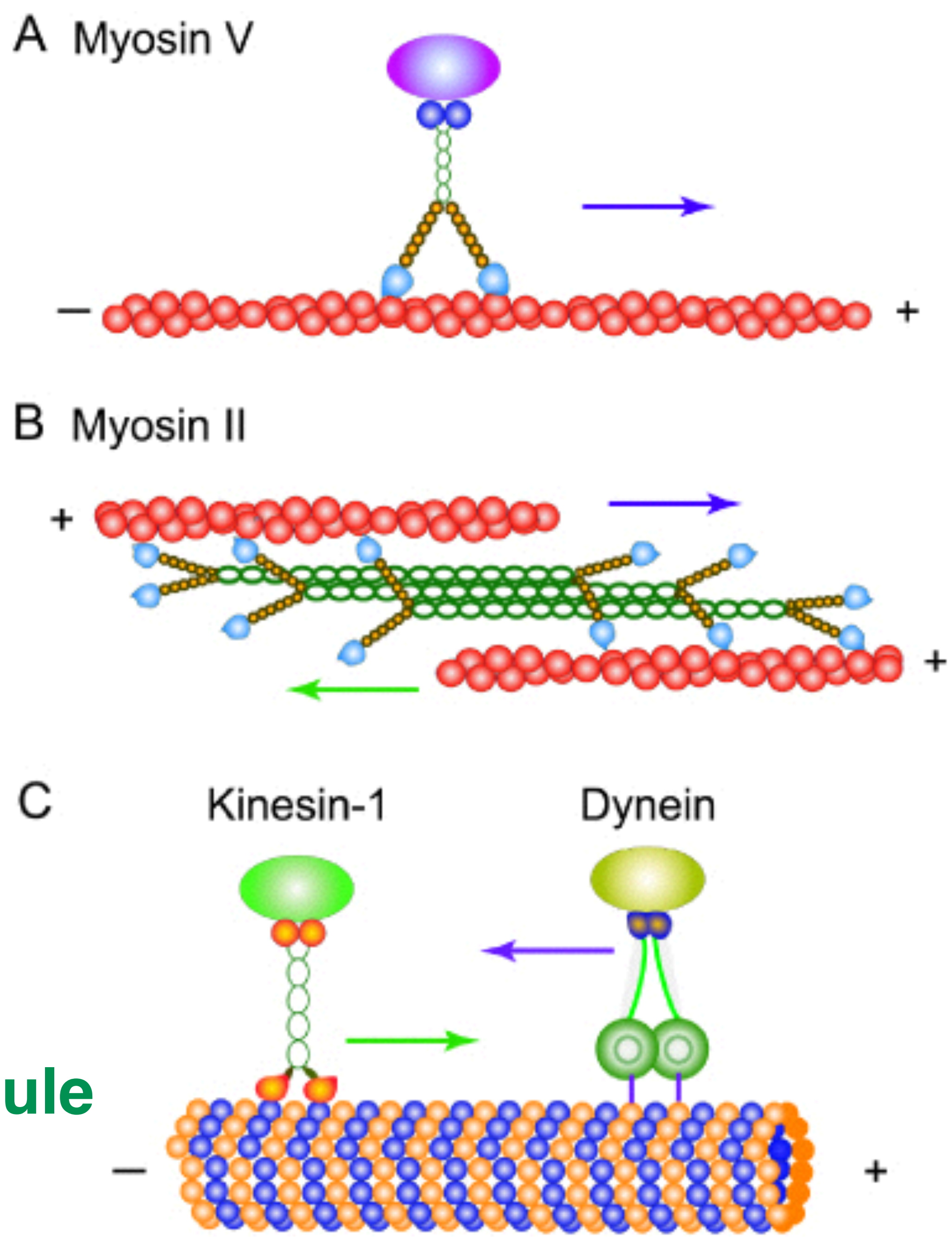
L. A. Cameron *et al.*, Nat. Rev. Mol. Cell Biol. 1, 110 (2000)

Molecular motors

Actin

Actin

Microtubule

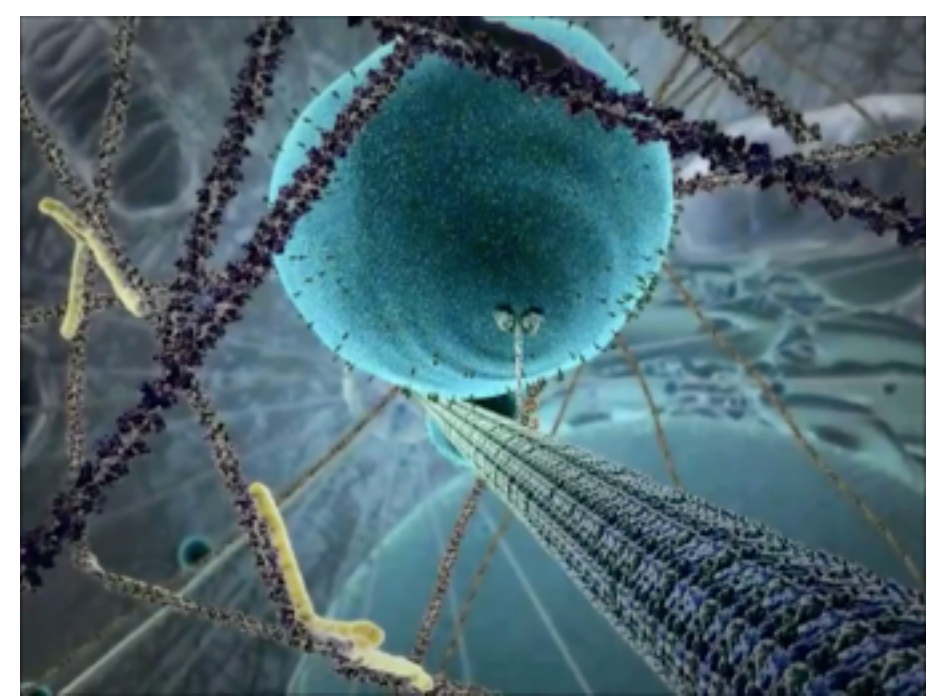


A.B. Kolomeisky, J. Phys.: Condens. Matter 25, 463101 (2013)

Transport of large molecules around cells (diffusion too slow)

$v \sim 1\mu\mathrm{m/s}$

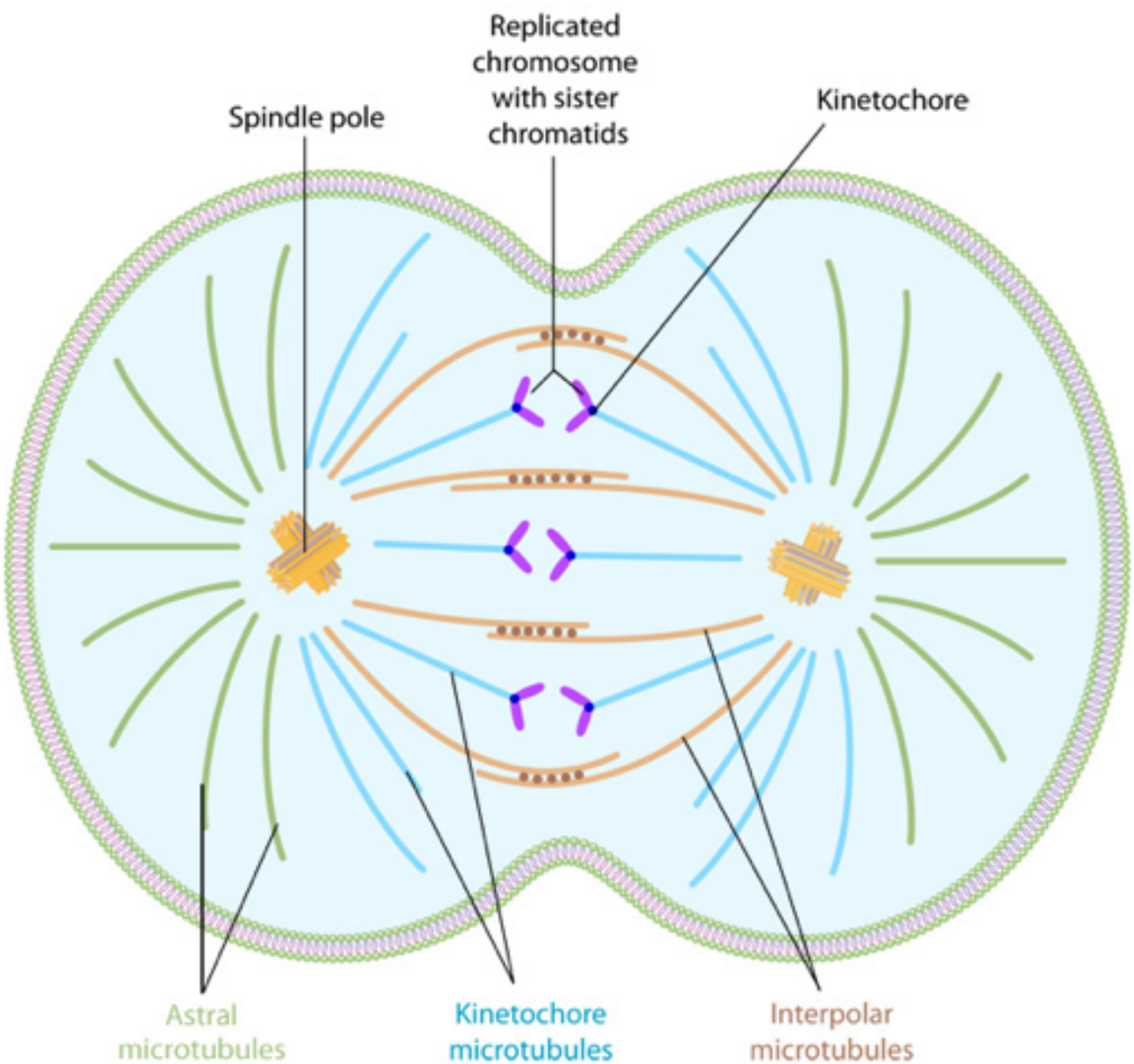
Contraction of muscles



Harvard BioVisions

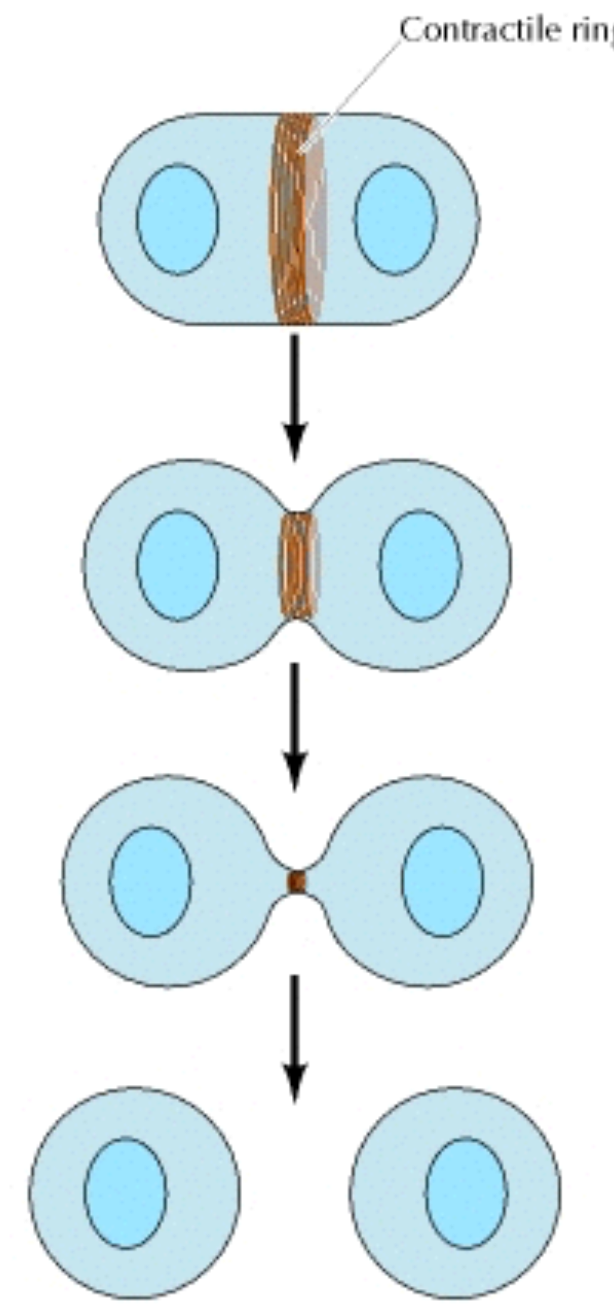
Cell division

Segregation of chromosomes



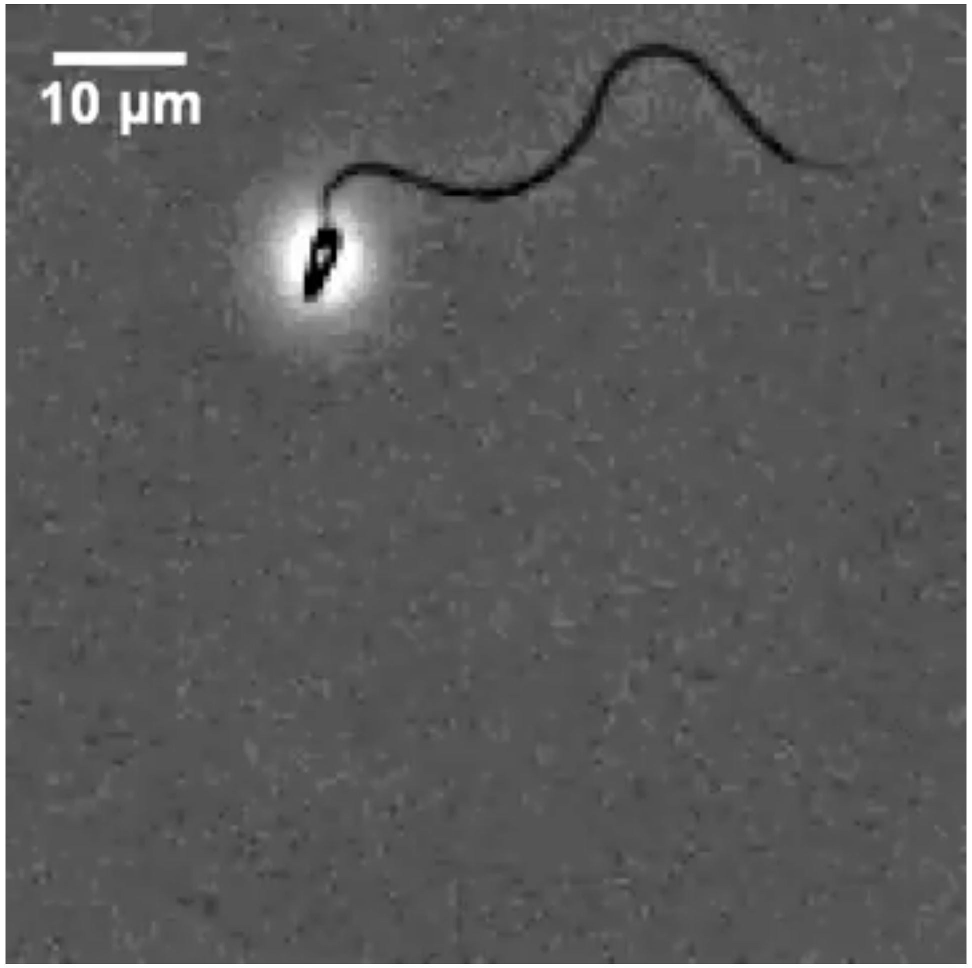
Microtubules

Contractile ring divides the cell in two



Actin

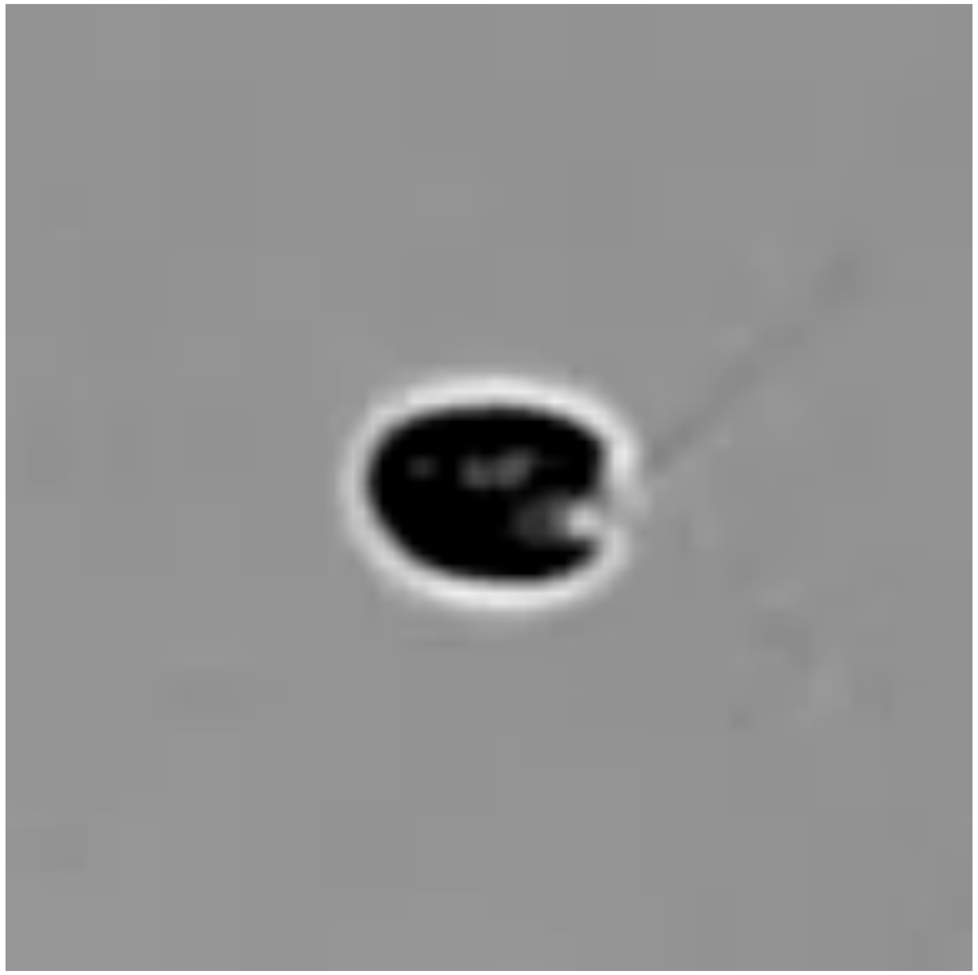
Swimming of sperm cells



Jeff Guasto

$v \sim 50 \mu\mathrm{m/s}$

Swimming of Chlamydomonas (green alga)

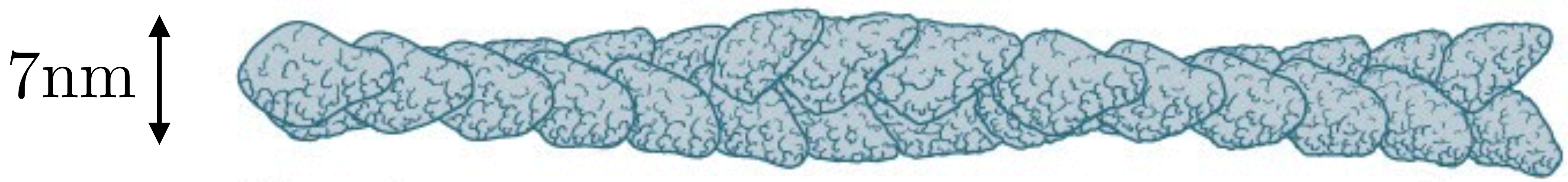


Jeff Guasto

$v \sim 60 \mu\mathrm{m/s}$

Bending is produced by motors walking on neighboring microtubule-like structures

Actin filaments



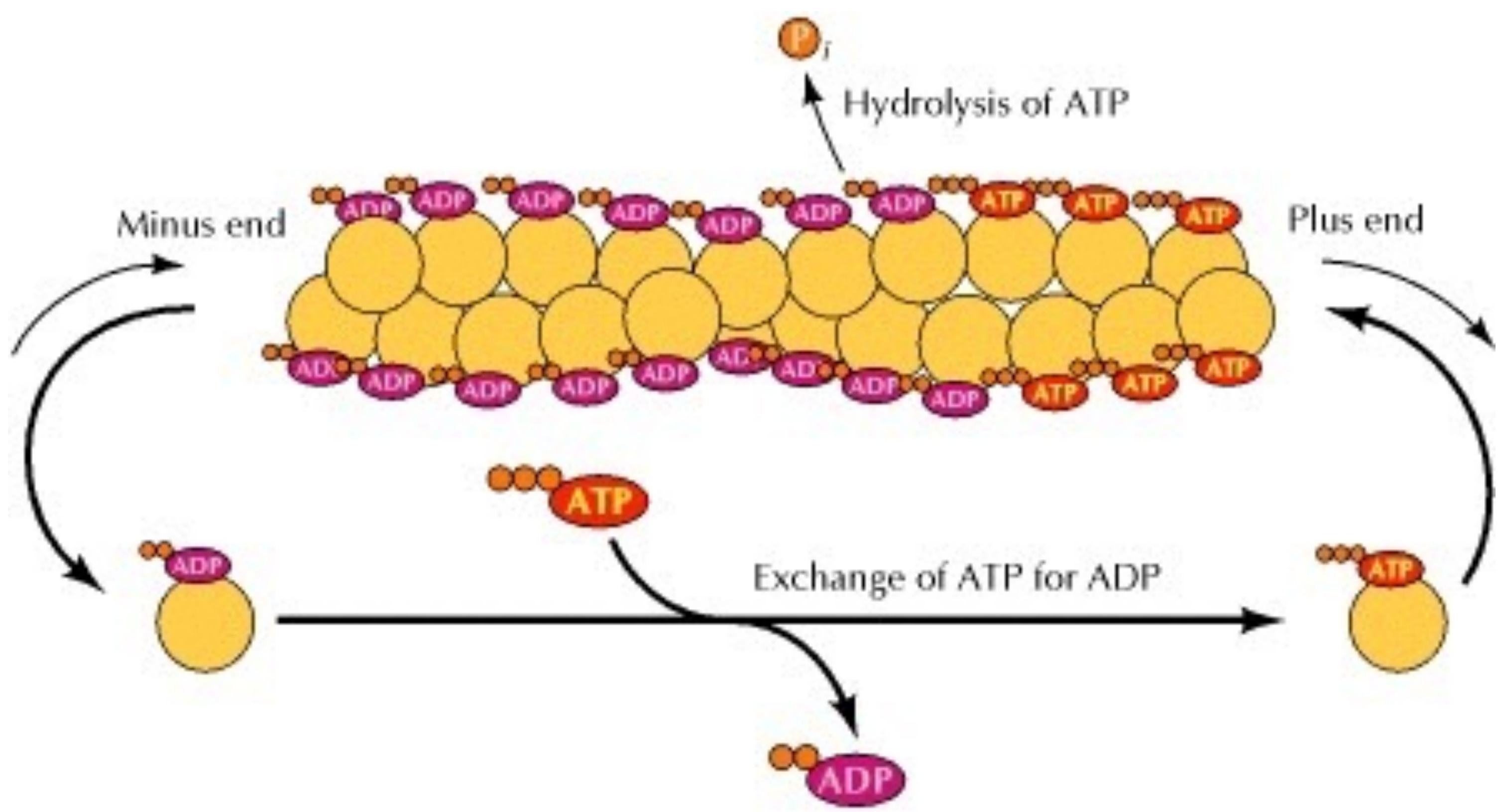
Minus end (pointed end)

Plus end (barbed end)

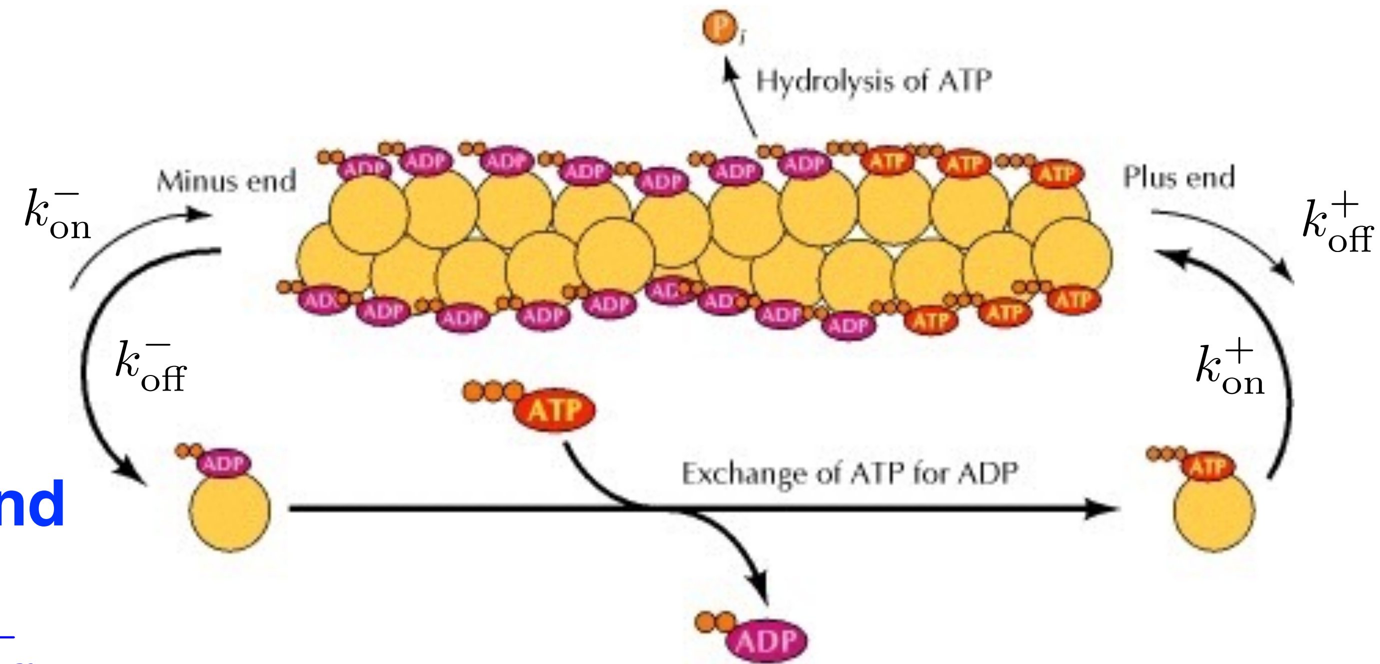
Persistence length $\ell_p \sim 10\mu\mathrm{m}$

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

Actin treadmilling



Actin growth



growth of minus end

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

no growth at

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

growth of plus end

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

no growth at

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

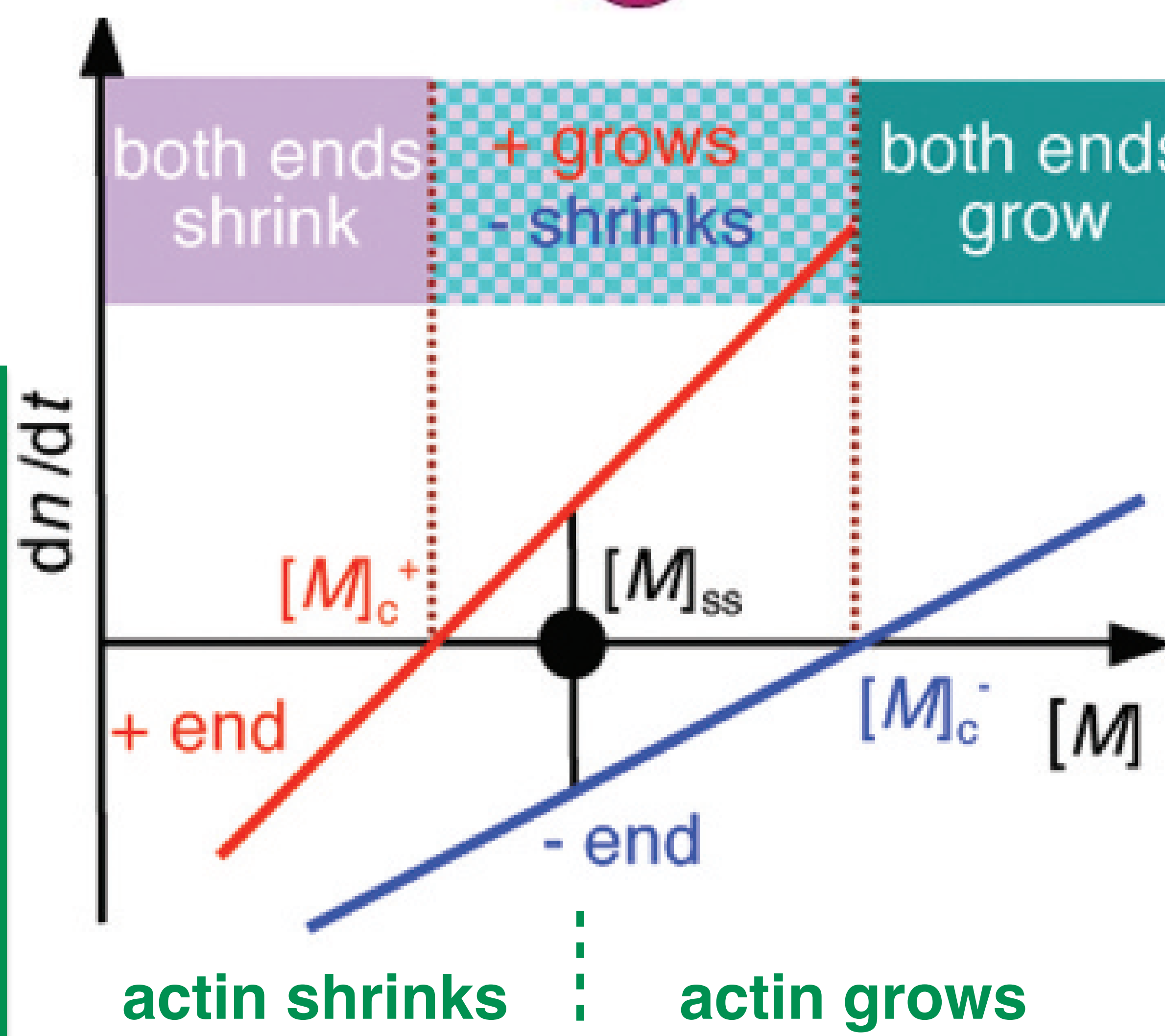
Steady state regime

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

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

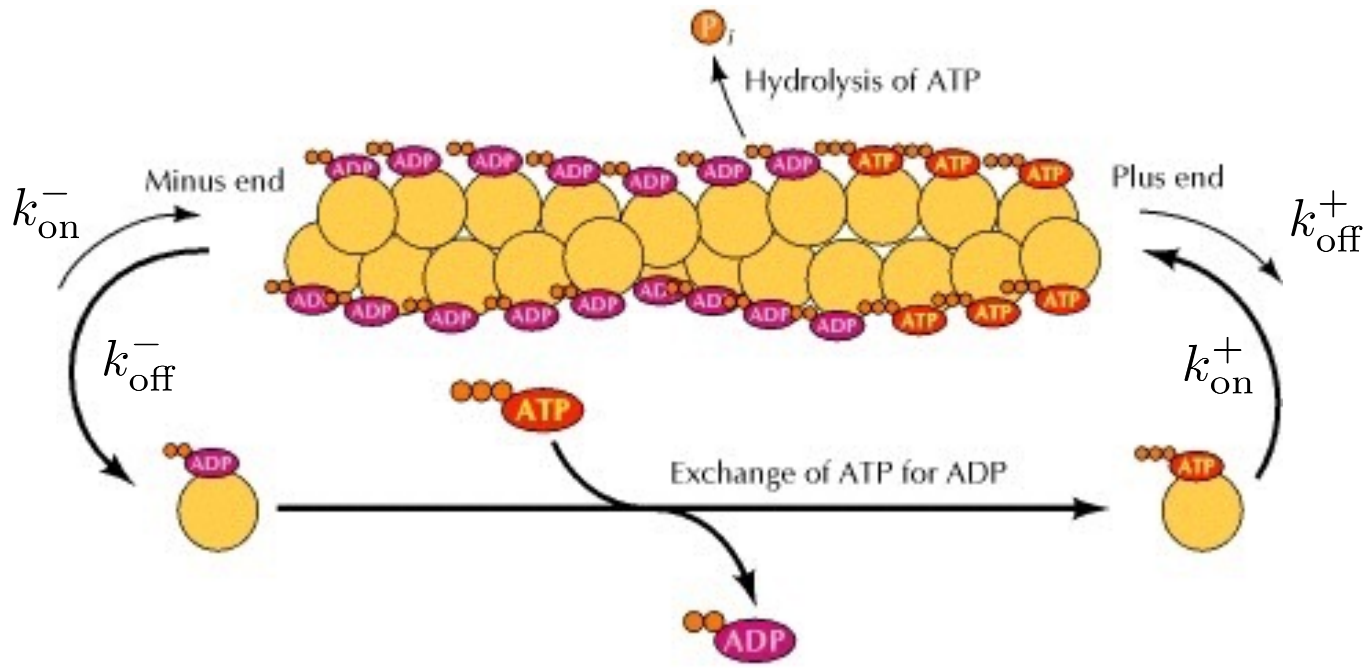
front speed

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



concentration of free actin monomers

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

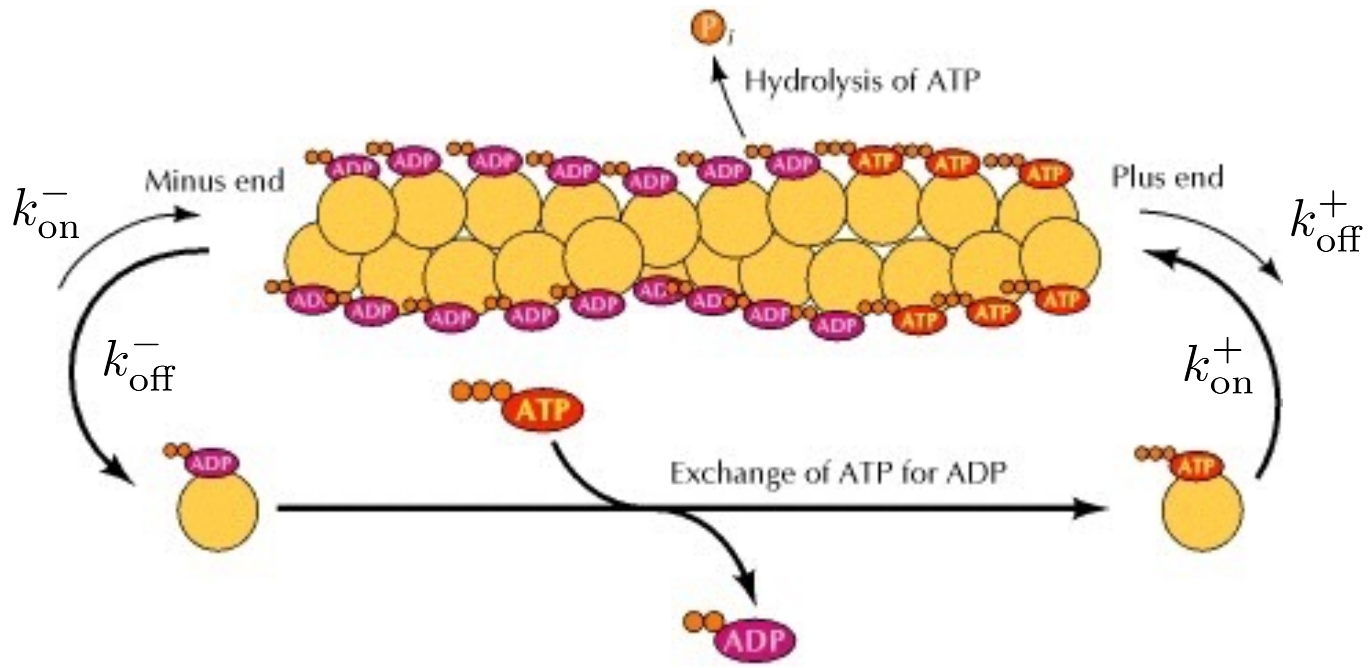
at large concentrations
actin grows ($v > 0$)

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

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?

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

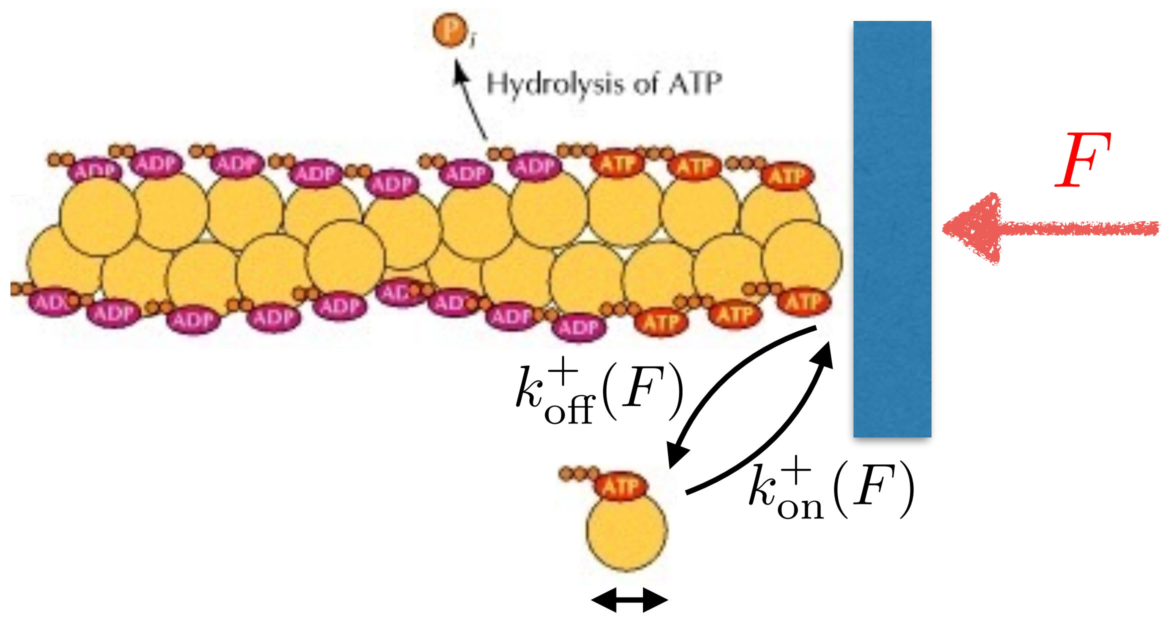
drift velocity $v = k_{\rm on}[M] - k_{\rm off} < 0$

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

$$\boxed{\begin{aligned} p^*(n) &= \frac{|v|}{D}e^{-|v|n/D} = \frac{1}{\overline{n}}e^{-n/\overline{n}} \\ \overline{n} &= \frac{D}{|v|} = \frac{(k_{\rm off} + k_{\rm on}[M])}{2(k_{\rm off} - k_{\rm on}[M])} \end{aligned}}$$

average actin filament length

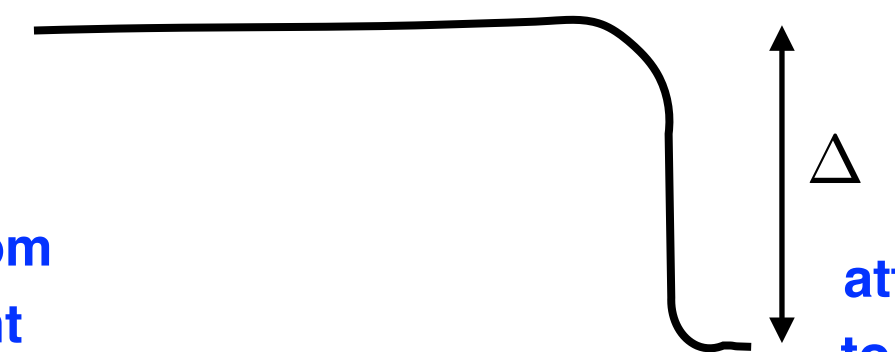
Actin filament growing against the barrier



work done against the barrier for insertion of new monomer

$$W = Fa$$

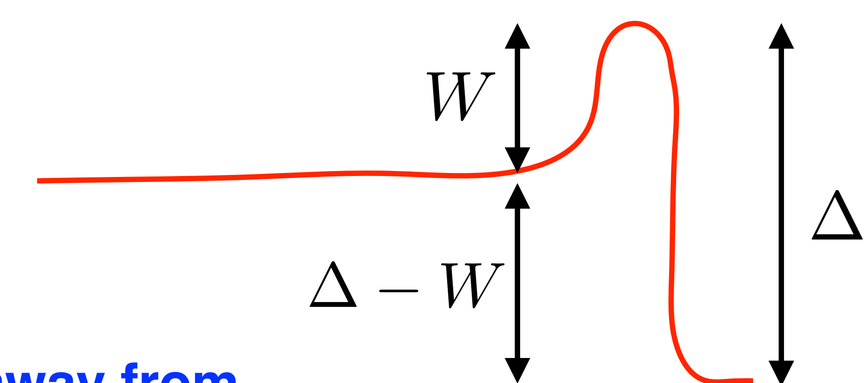
effective monomer free energy potential without barrier



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

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

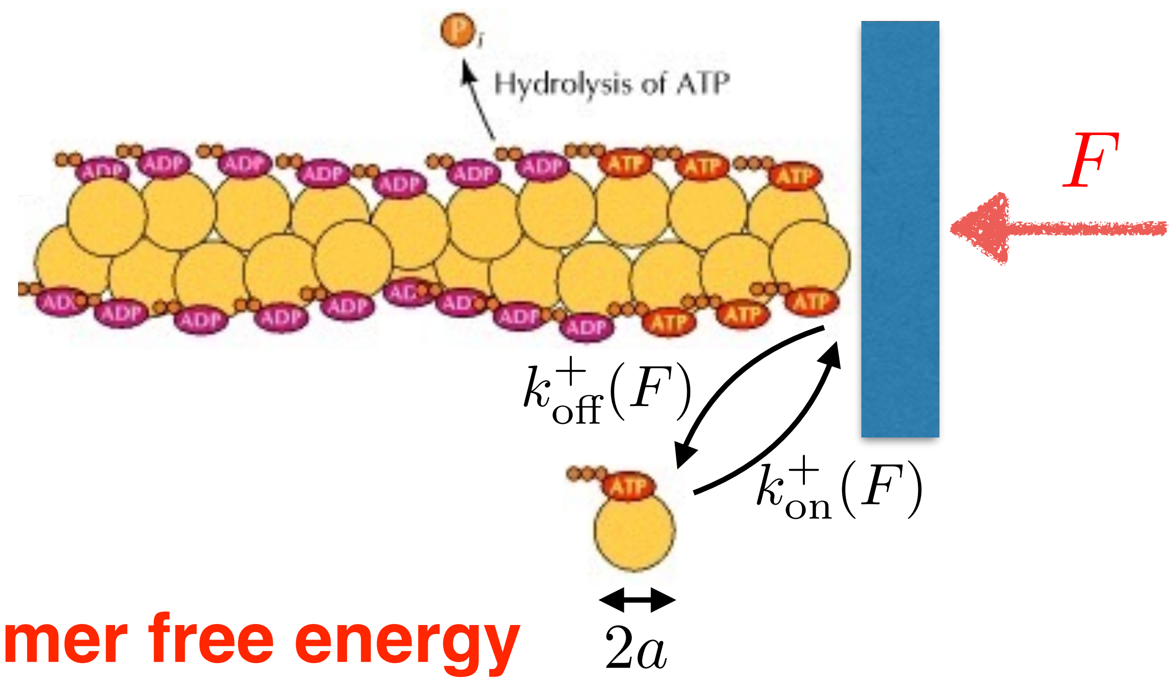
effective monomer free energy potential with barrier



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

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

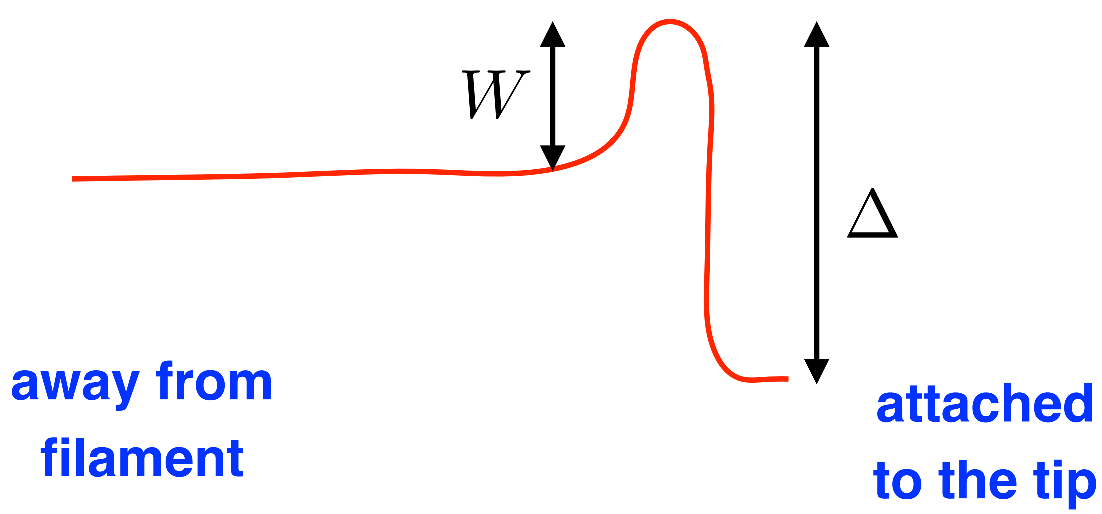
Actin filament growing against the barrier



work done against the barrier for insertion of new monomer

$$W = Fa$$

effective monomer free energy potential with barrier



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

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

Growth speed of the tip

$$v^{+}(F) = k_{\text{on}}^{+}[M] e^{-Fa/k_B T} - k_{\text{off}}^{+}$$

Maximal force that can be balanced by growing filament

$$\boxed{v^{+}(F_{\max}) = 0 \quad \longrightarrow \quad F_{\max} = \frac{k_B T}{a} \ln\left(\frac{k_{\text{on}}^{+}[M]}{k_{\text{off}}^{+}}\right)}$$