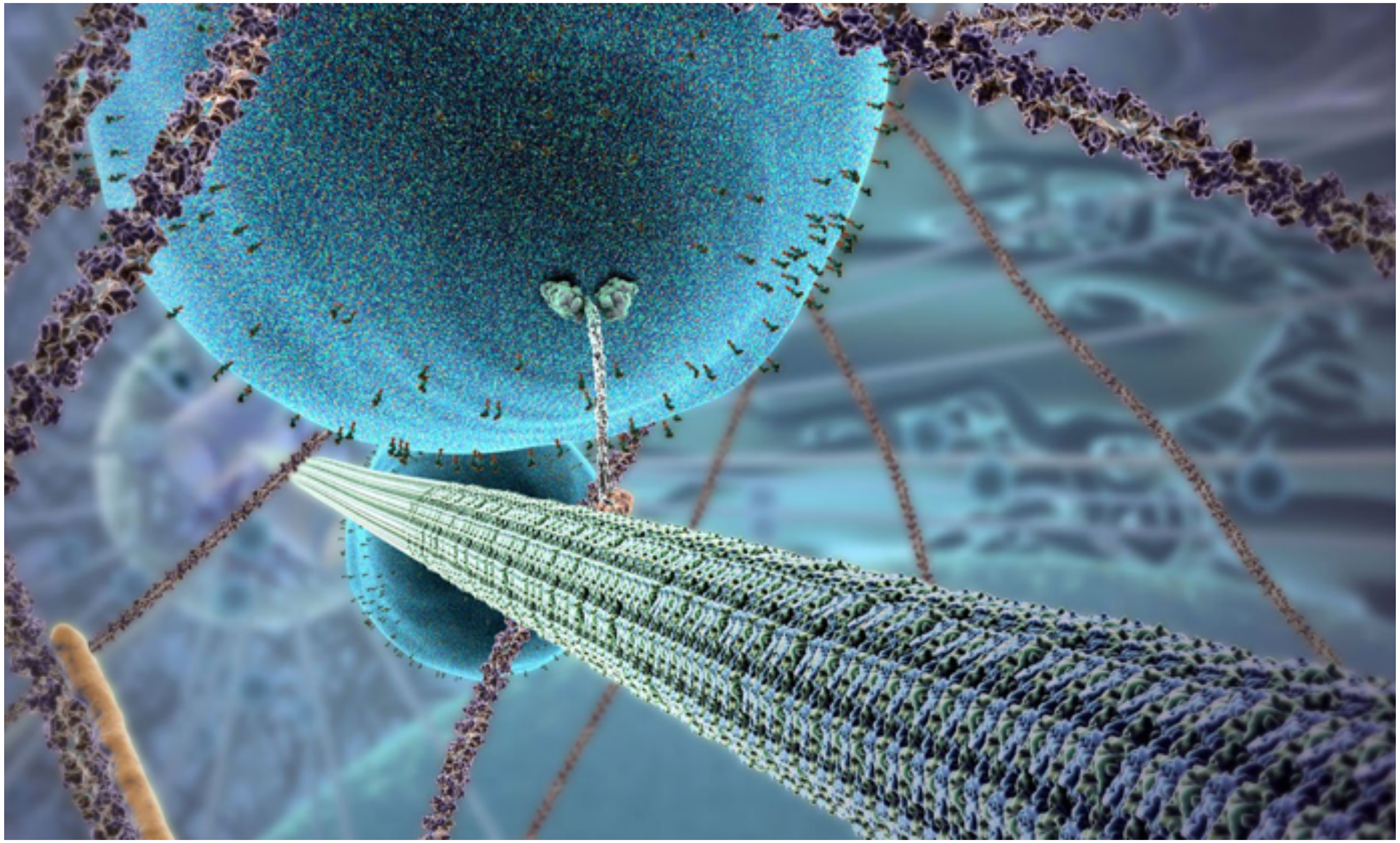
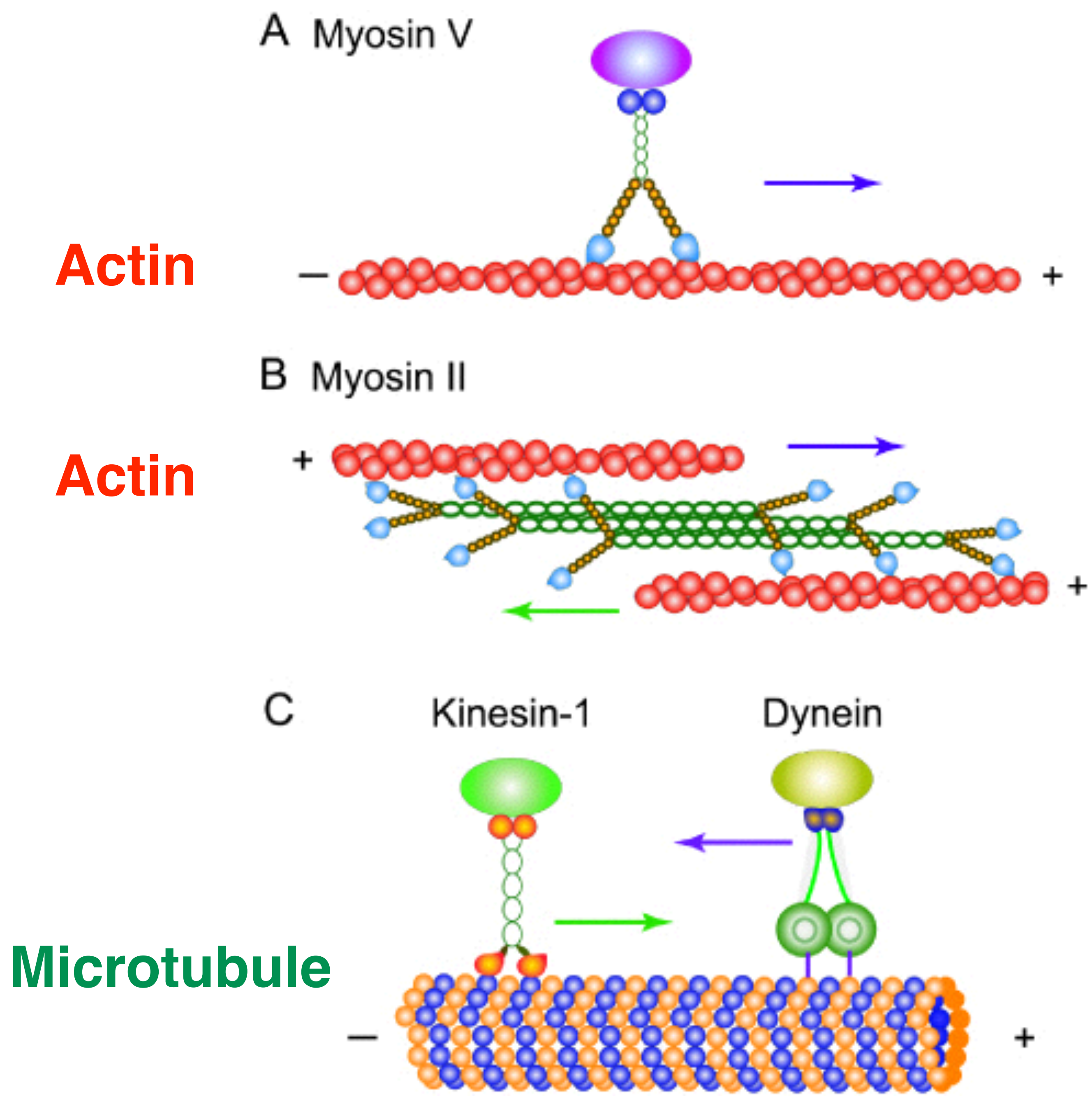
MAE 545: Lecture 8 (10/13)

Dynamics of molecular motors



Molecular motors



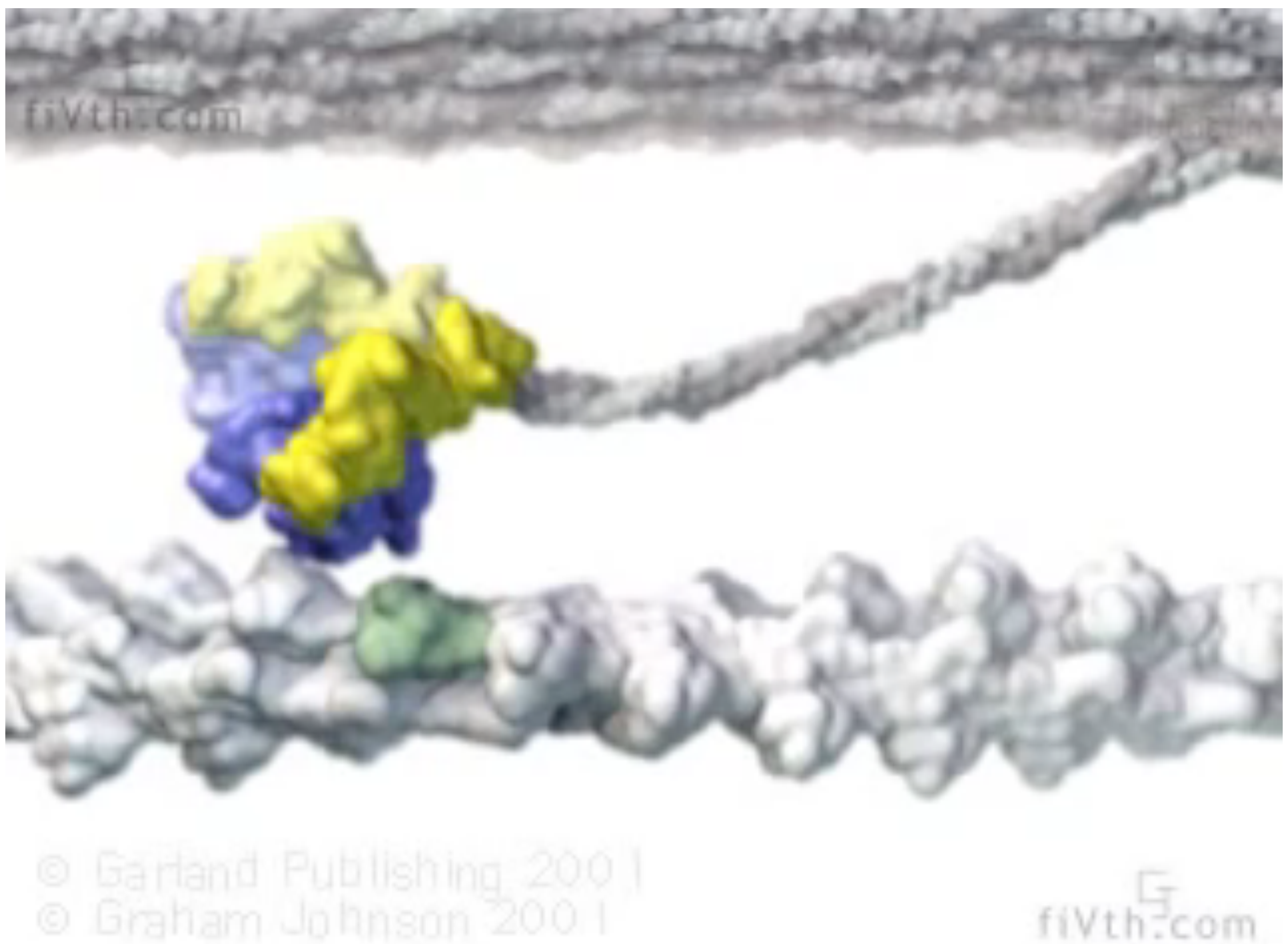
Typical motor speeds

$$v \sim 10^{-2}\text{-}1\,\mu\mathrm{m/s}$$

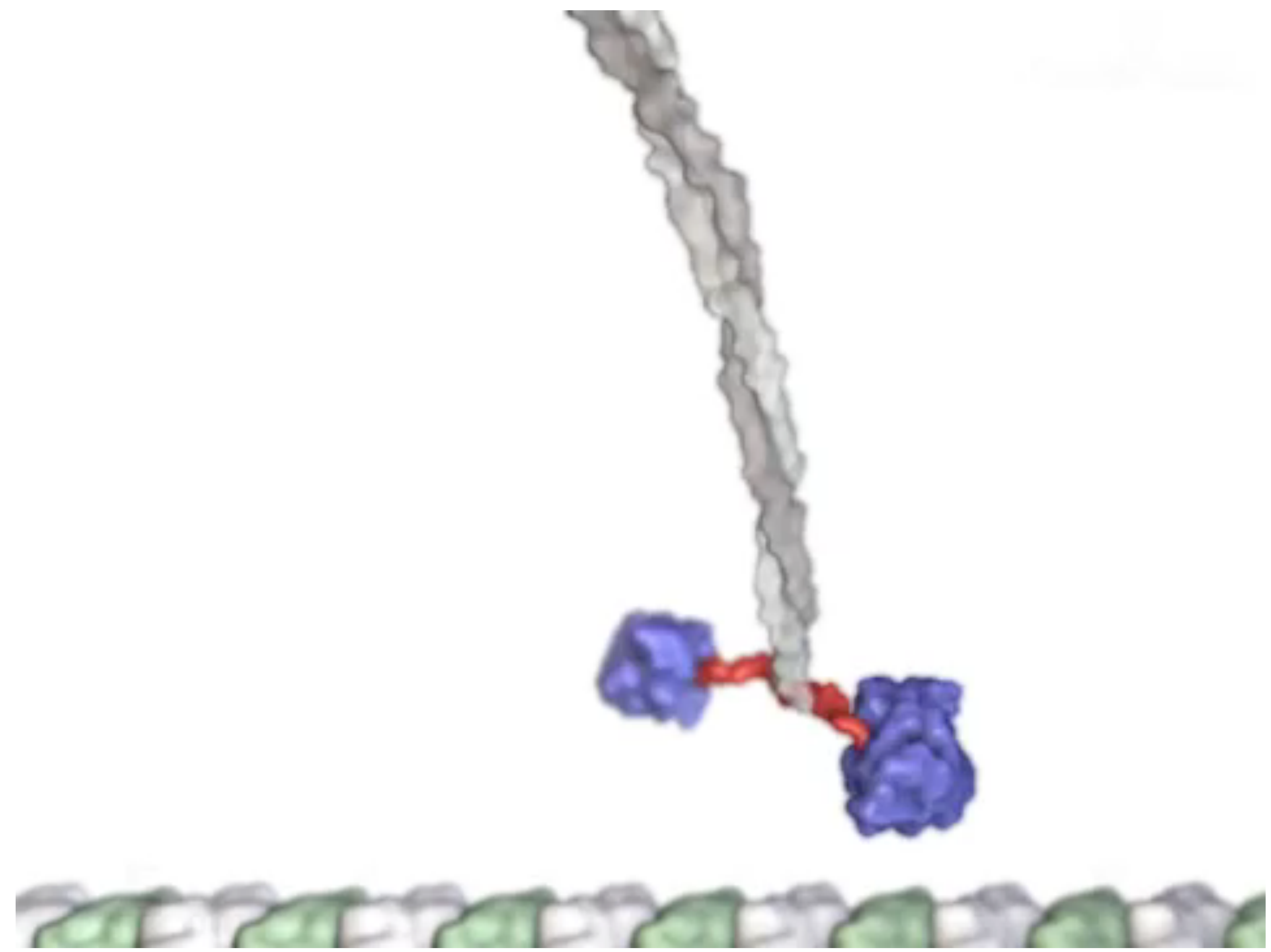
A.B. Kolomeisky, J. Phys.: Condens. Matter 25, 463101 (2013)

Movement of molecular motors is powered by ATP molecules

Myosin motor walking on actin in muscles



Kinesin motor walking on microtubule

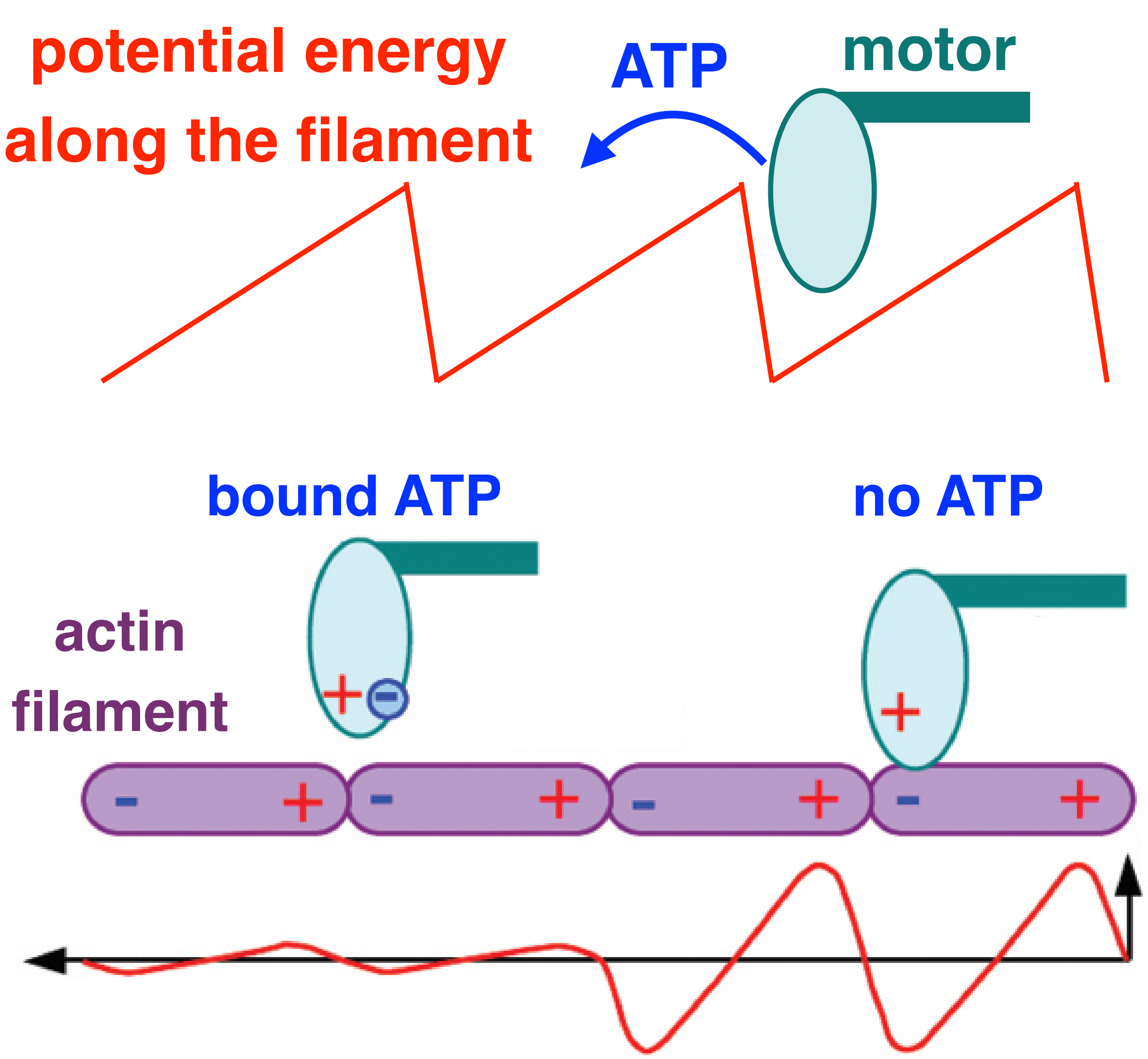


Graham Johnson

Molecular motors vs Brownian ratchets

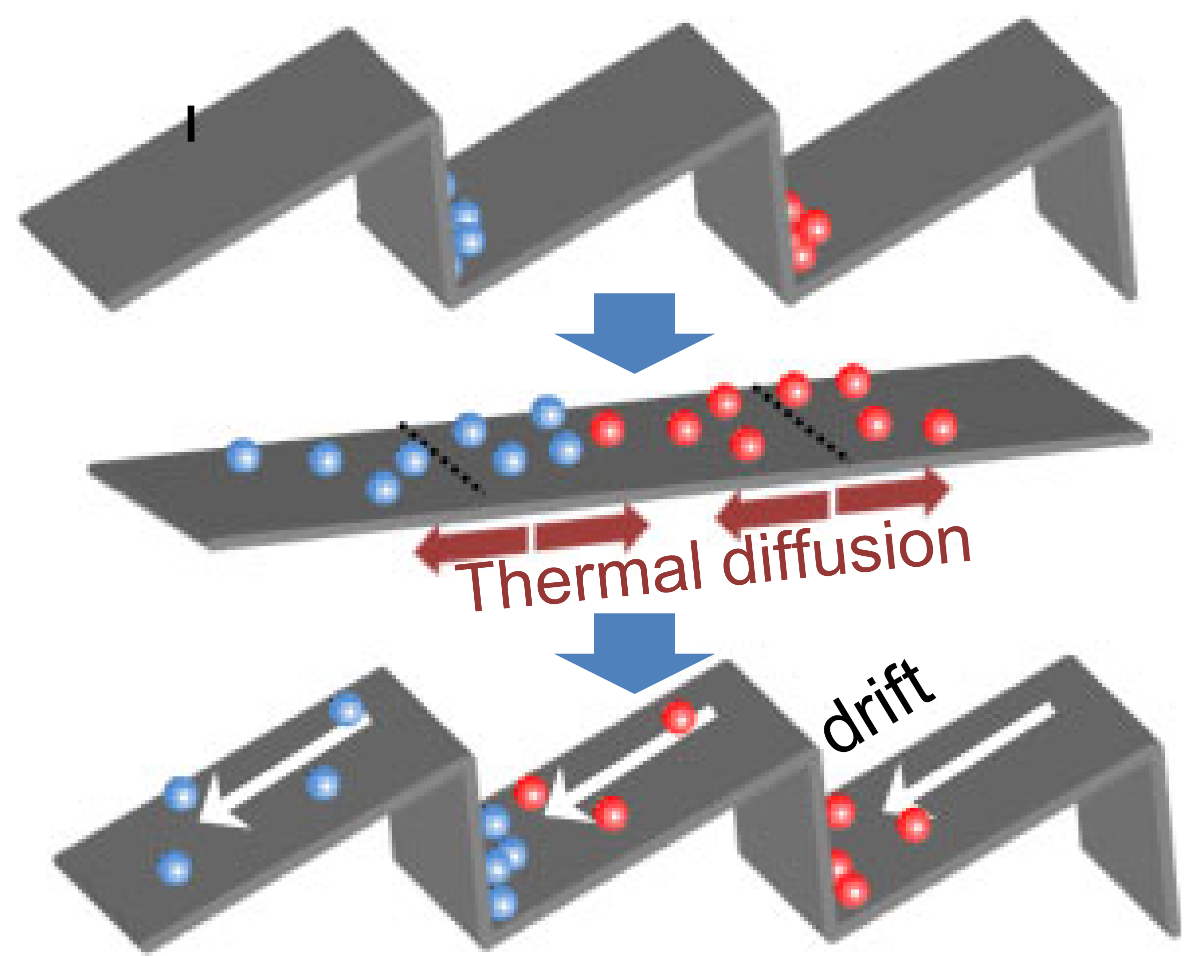
Myosin motor

ATP driven process drives molecular motors along the filaments

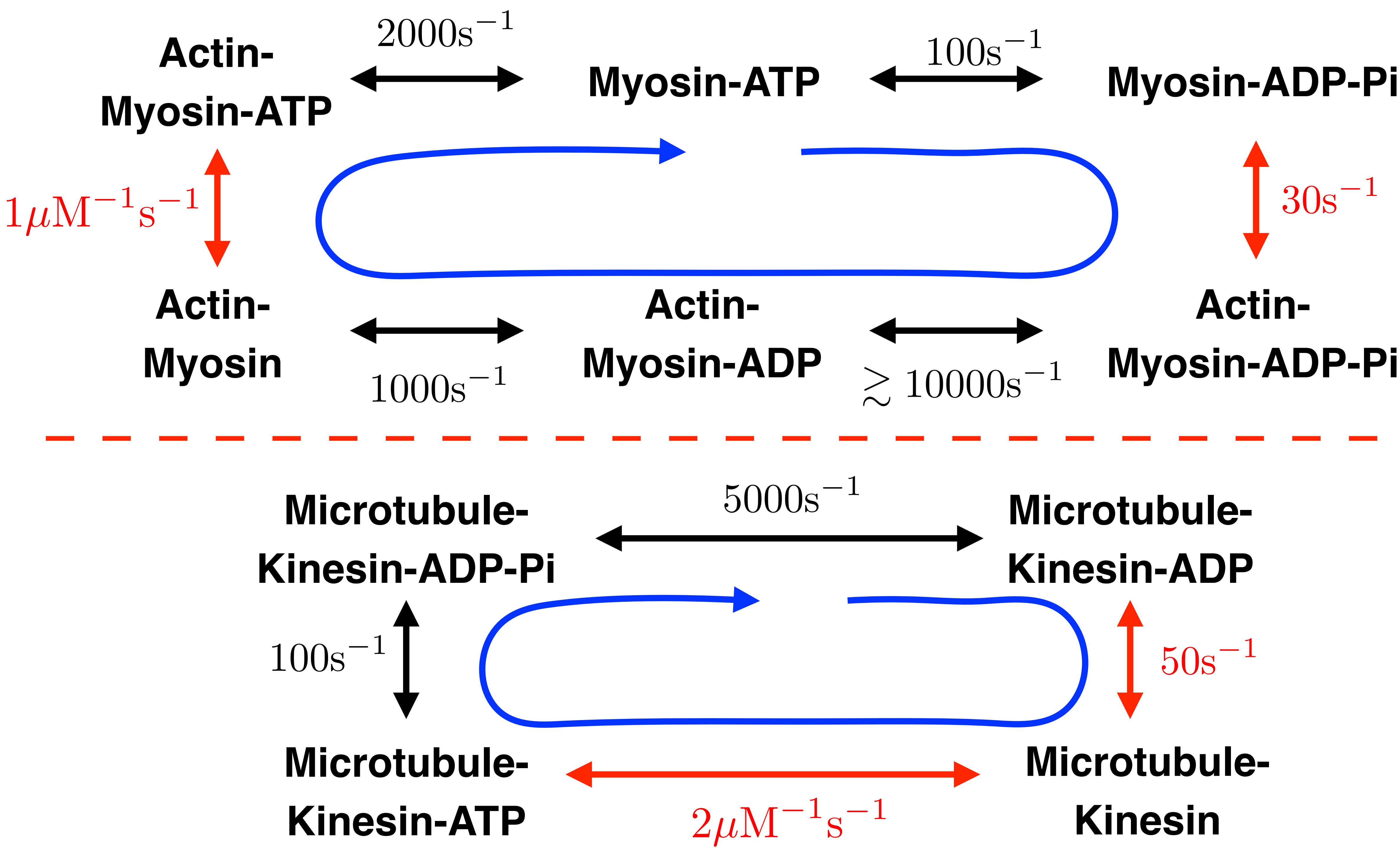


Brownian ratchet

net movement of particles is achieved by periodic modulation of asymmetric external potential



Typical rates (timescales)



timescale=1/rate

stepping motion for kinesin: ~100 μs

F. Fulga *et al.*, Integr. Biol. 1, 150-169 (2009)

Internal states are revealed by dwell times

Let's assume that for walking of molecular motors there are two subprocesses A and B with time distributions

$$p_A(t) = \frac{1}{t_A} e^{-t/t_A}$$

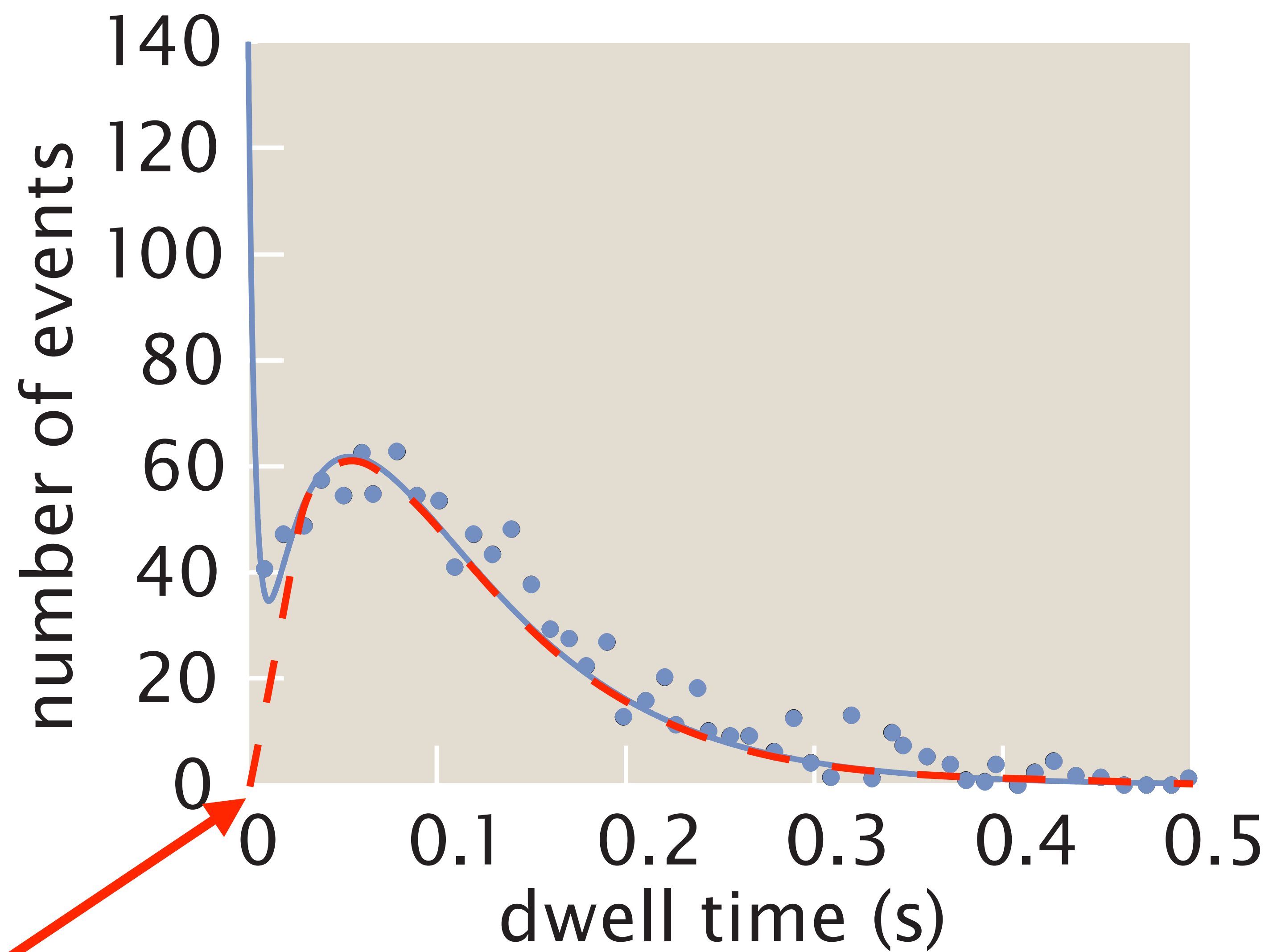
$$p_B(t) = \frac{1}{t_B} e^{-t/t_B}$$

Distribution of time to complete both subprocesses

$$p(t) = \int_0^t d\tau \, p_A(\tau) p_B(t-\tau)$$

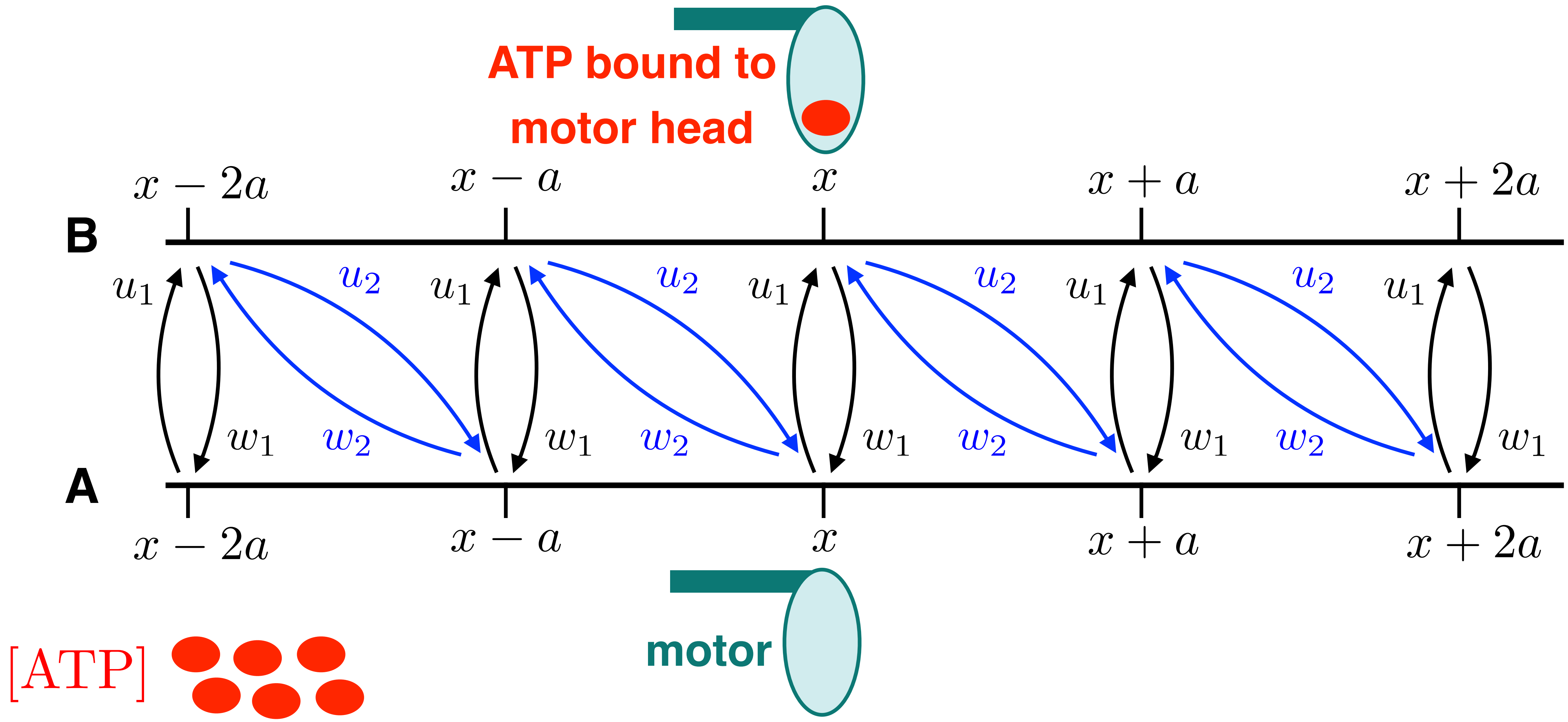
$$p(t) = \frac{e^{-t/t_B} - e^{-t/t_A}}{t_B - t_A}$$

Distribution of time needed for one cycle of myosin V walking on actin at 10 μM ATP



R. Phillips et al., Physical Biology of the Cell

Two state model for molecular motor



Forward rate *u₁* depends on concentration of ATP

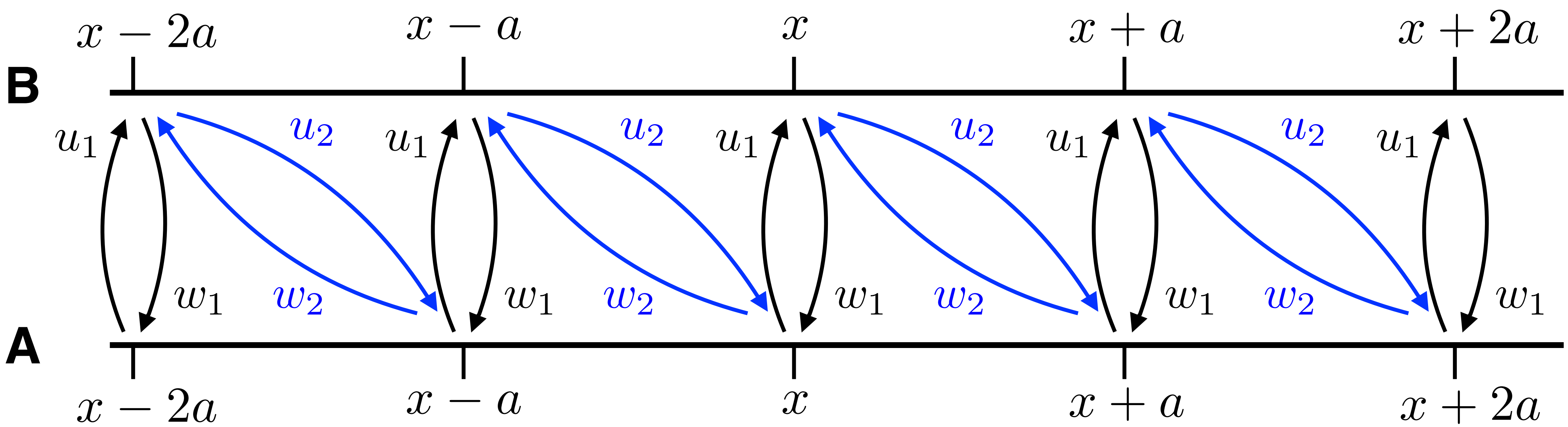
$$u_1 = k_{\mathrm{on}}[\mathrm{ATP}]$$

Forward rate u_2 corresponds to the slow rate limiting process.

Backward rates w_1 and w_2 are assumed to be small but non zero.

What is the speed of molecular motor in such model?

Two state model for molecular motor



Master equation

$$\frac{\partial p_A(x,t)}{\partial t} = u_2 p_B(x-a,t) + w_1 p_B(x,t) - (u_1 + w_2) p_A(x,t)$$

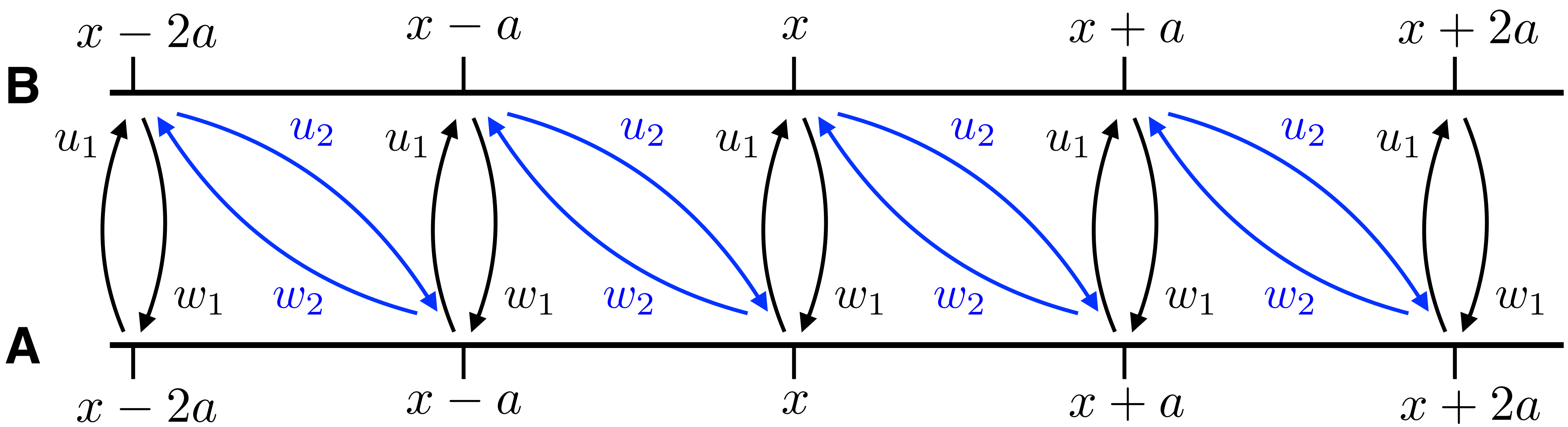
$$\frac{\partial p_B(x,t)}{\partial t} = u_1 p_A(x,t) + w_2 p_A(x+a,t) - (u_2 + w_1) p_B(x,t)$$

Continuum limit

$$\frac{\partial p_A(x,t)}{\partial t} = -(u_1 + w_2) p_A(x,t) + (u_2 + w_1) p_B(x,t) - a u_2 \frac{\partial p_B(x,t)}{\partial x} + \frac{a^2 u_2}{2} \frac{\partial^2 p_B(x,t)}{\partial x^2}$$

$$\frac{\partial p_B(x,t)}{\partial t} = -(u_2 + w_1) p_B(x,t) + (u_1 + w_2) p_A(x,t) + a w_2 \frac{\partial p_A(x,t)}{\partial x} + \frac{a^2 w_2}{2} \frac{\partial^2 p_A(x,t)}{\partial x^2}$$

Two state model for molecular motor



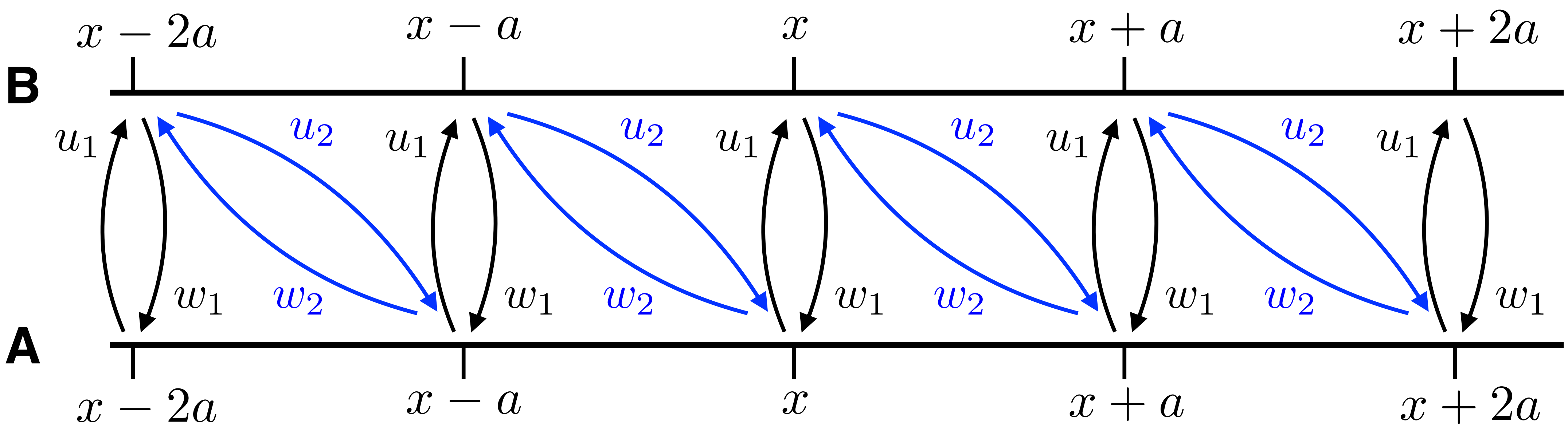
Fourier transform $p_{A,B}(x,t) = \int dk d\omega e^{i\omega t - ikx} \tilde{p}_{A,B}(k,\omega)$

$$i \begin{pmatrix} \omega - iu_1 - iw_2, & iw_1 + iu_2(1 + ika - k^2a^2/2) \\ iu_1 + iw_2(1 - ika - k^2a^2/2), & \omega - iu_2 - iw_1 \end{pmatrix} \begin{pmatrix} \tilde{p}_A(\omega,k) \\ \tilde{p}_B(\omega,k) \end{pmatrix} = 0$$

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

$$\begin{aligned} &(\omega - iu_1 - iw_2)(\omega - iu_2 - iw_1) \\ &+ \left(w_1 + u_2(1 + ika - k^2a^2/2)\right)\left(u_1 + w_2(1 - ika - k^2a^2/2)\right) = 0 \end{aligned}$$

Two state model for molecular motor



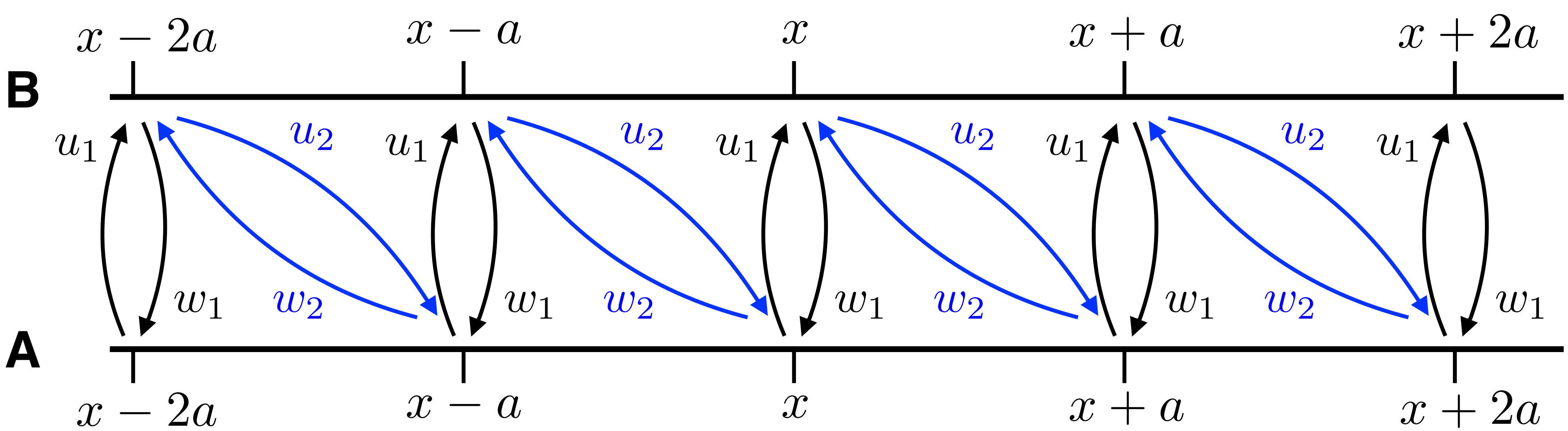
Dispersion relation

$$\omega(k) = \frac{i}{2}\left(u_1 + u_2 + w_1 + w_2\right)$$
$$\pm\frac{i}{2}\sqrt{(u_1 + u_2 + w_1 + w_2)^2 + 4ika(u_1u_2 - w_1w_2) - 2k^2a^2(u_1u_2 + w_1w_2) + k^4a^4u_2w^2}$$

Obtain motor velocity and diffusion constant by Taylor expansion

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

Two state model for molecular motor



Speed of molecular motor

$$\boxed{v = a\frac{(u_1u_2 - w_1w_2)}{(u_1+u_2+w_1+w_2)}}$$

Diffusion constant for molecular motor

$$D = a^2\left(\frac{(u_1u_2+w_1w_2)}{2(u_1+u_2+w_1+w_2)} - \frac{(u_1u_2-w_1w_2)^2}{(u_1+u_2+w_1+w_2)^3}\right)$$

"Einstein force"

$$v = \mu F_E \qquad D = \mu k_B T$$

$$\boxed{F_E = k_B T\frac{v}{D}}$$

Fictitious force acting on the motor

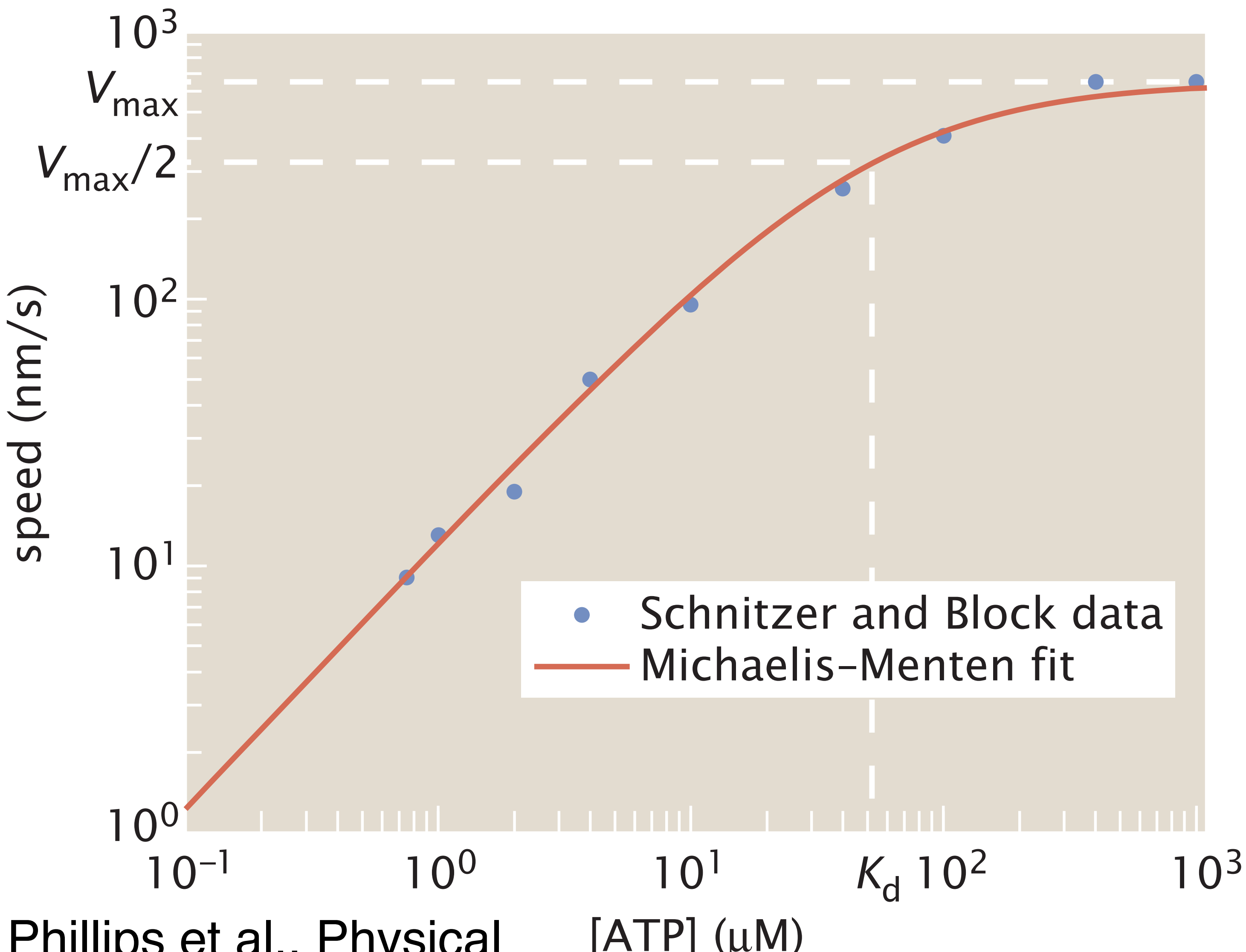
ATP concentration dependent speed of motors

Ignoring backward rates and assuming

$$u_1 = k_{\mathrm{on}}[\mathrm{ATP}]$$

$$\boxed{v \approx a\frac{u_1 u_2}{(u_1 + u_2)} = v_{\max}\frac{[\mathrm{ATP}]}{([\mathrm{ATP}] + K_d)}}$$

Kinesin motor on microtubules



R. Phillips et al., Physical Biology of the Cell

Maximal speed

$$v_{\max} = a u_2 \approx 0.6\mu\mathrm{m/s}$$

ATP concentration at half the maximal speed

$$K_d = \frac{u_2}{k_{\mathrm{on}}} \approx 50\mu\mathrm{M}$$

Measured constants

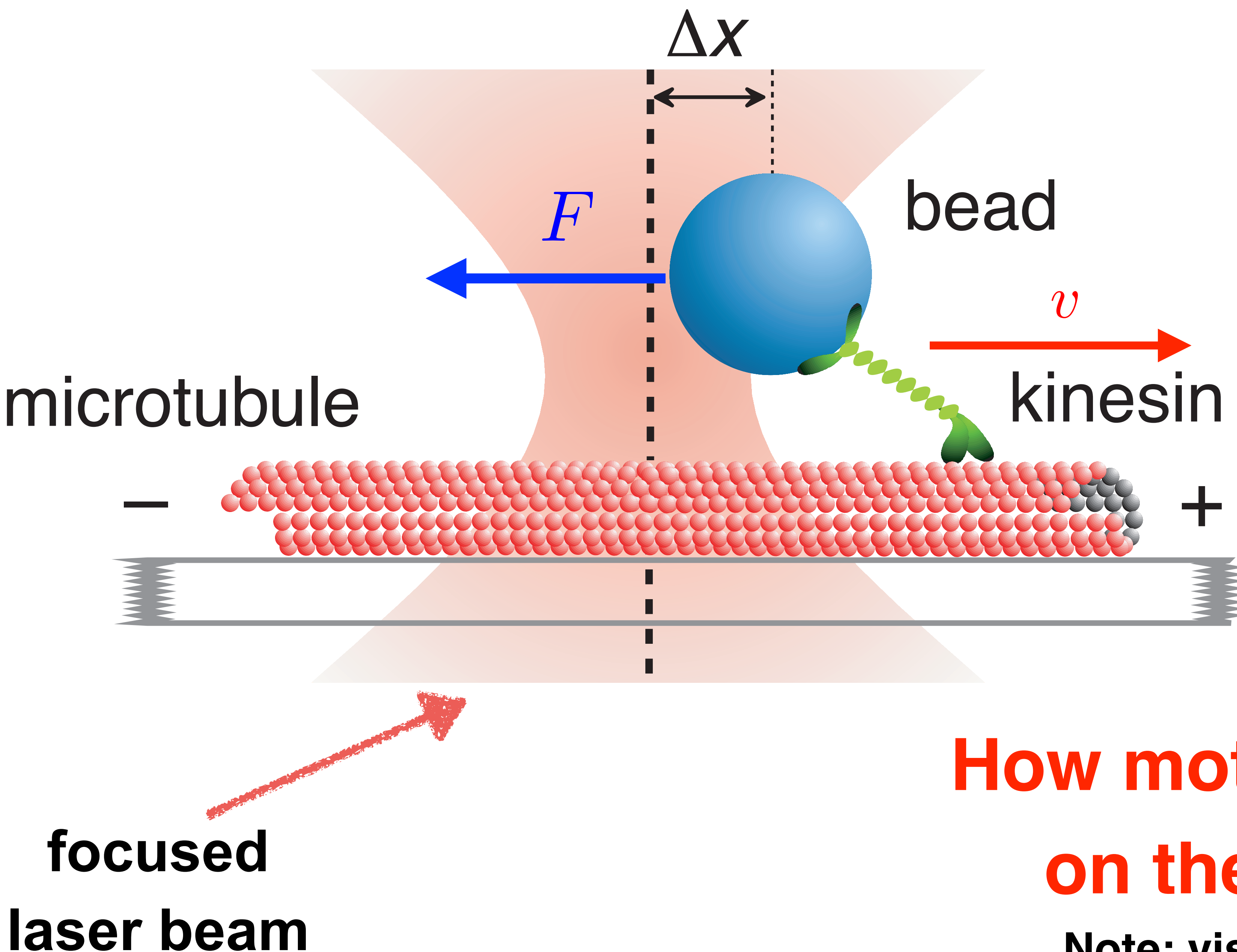
$$a \approx 8\mathrm{nm}$$

$$u_2 \approx 70\mathrm{s}^{-1}$$

$$k_{\mathrm{on}} \approx 1\mu\mathrm{M}^{-1}\mathrm{s}^{-1}$$

Motors carrying the load

Force exerted on kinesin motors carrying plastic beads can be controlled with optical tweezers



$$F \approx k\Delta x$$

Effective spring constant *k* depends on the bead size, refractive indices of the bead and surrounding medium, and the gradient of laser intensity

How motor speed depends on the loading force?

Note: viscous drag is negligible

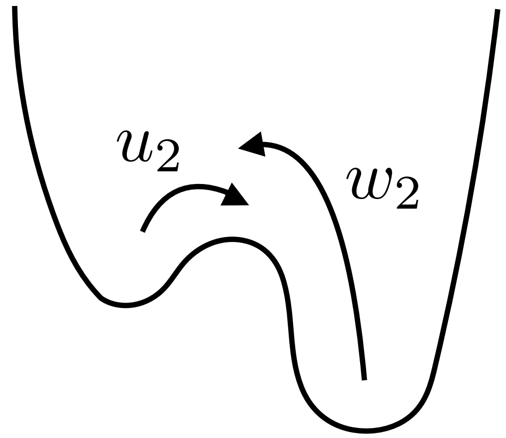
$$F_{\text{drag}} = 6\pi\eta R v$$

$$F_{\text{drag}} \sim 6\pi 10^{-3}\text{kgm}^{-1}\text{s}^{-1} \cdot 1\mu\text{m} \cdot 1\mu\text{m/s} \sim 10^{-2}\text{pN}$$

K. Visscher et al., Nature 400, 184-189 (1999)

Motor velocity dependence on the load

Free energy profile in the absence of load



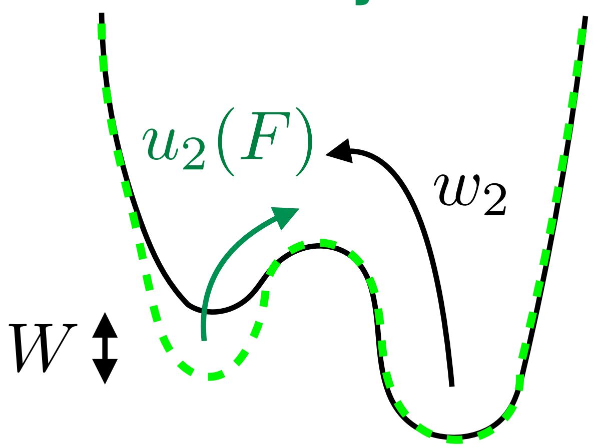
Work against the load force

$$W = Fa$$

motor velocity

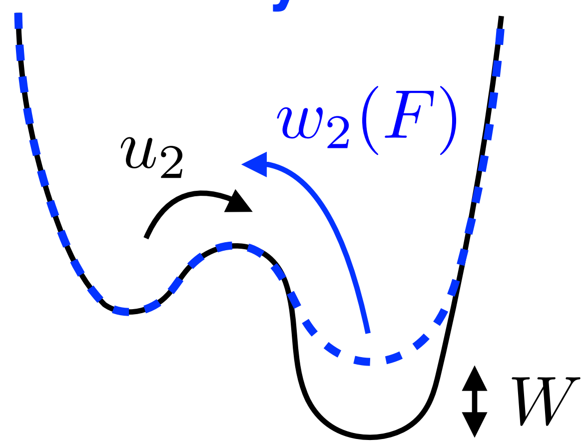
$$v(F) = a\frac{(u_1 u_2(F) - w_1 w_2(F))}{(u_1 + u_2(F) + w_1 + w_2(F))}$$

Assuming forward rate affected by the load



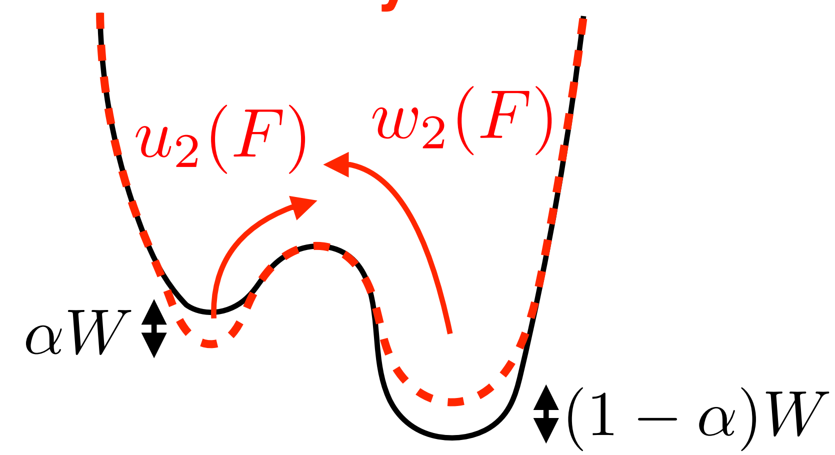
$$u_2(F) = u_2 e^{-Fa/k_BT}$$

Assuming backward rate affected by the load

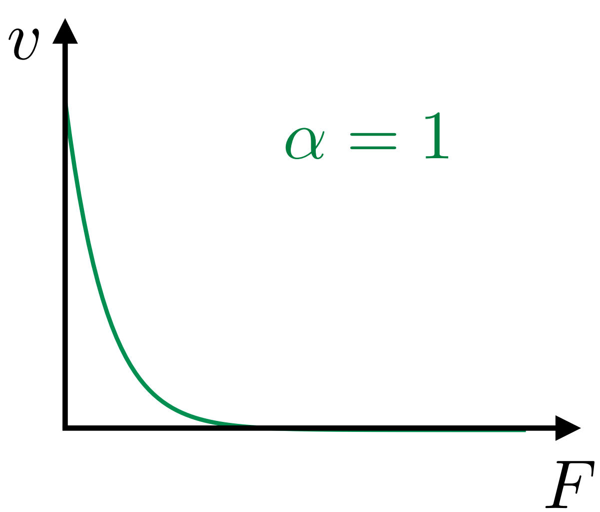


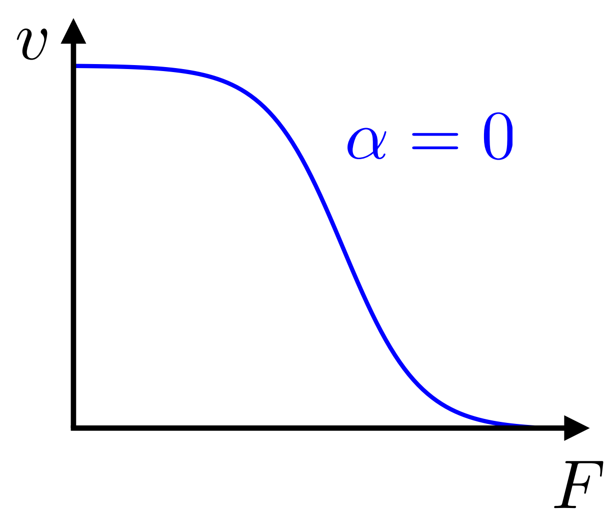
$$w_2(F) = w_2 e^{+Fa/k_BT}$$

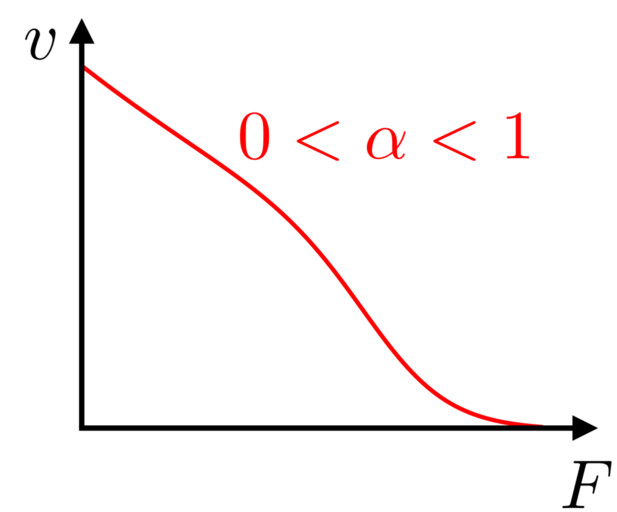
Assuming both rates affected by the load



$$u_2(F) = u_2 e^{-\alpha Fa/k_BT}$$
$$w_2(F) = w_2 e^{+(1-\alpha)Fa/k_BT}$$

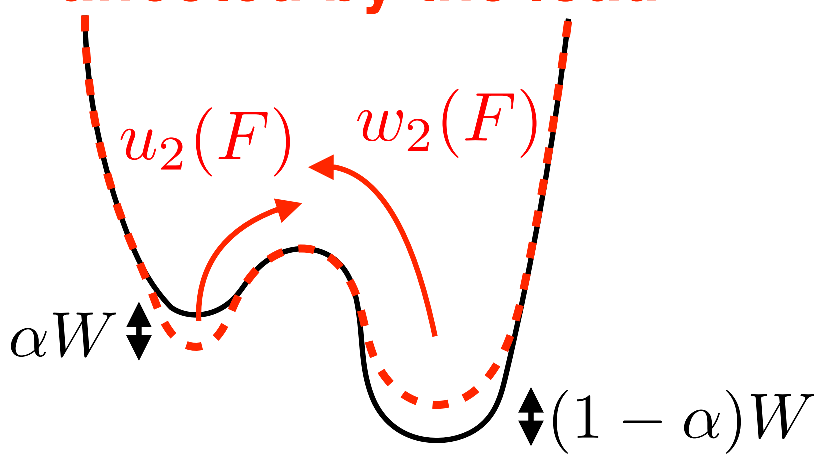




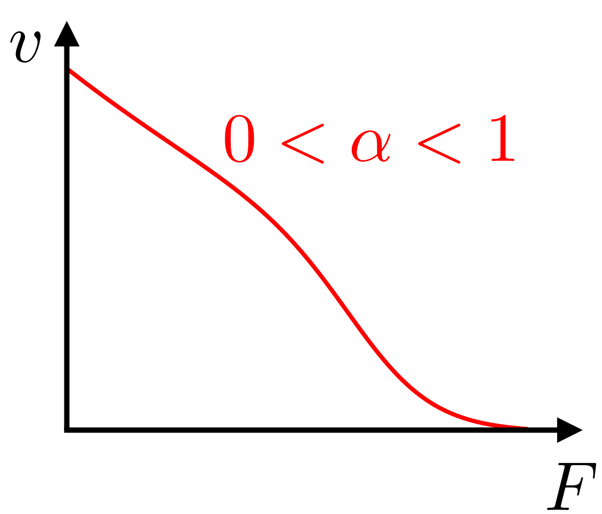


Motor velocity dependence on the load

Assuming both rates affected by the load

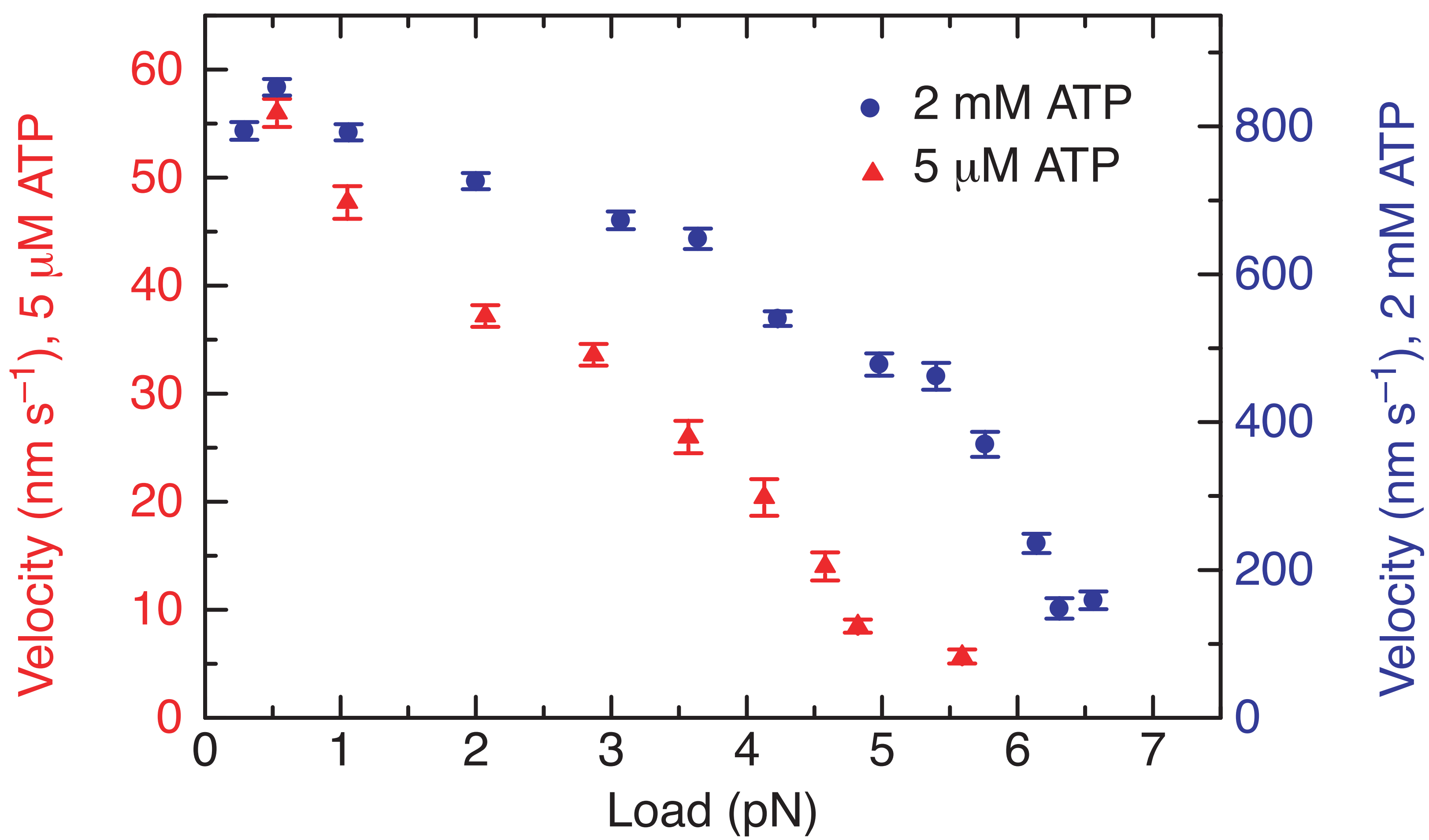


$$u_2(F) = u_2 e^{-\alpha F a / k_B T}$$
$$w_2(F) = w_2 e^{+(1-\alpha) F a / k_B T}$$



$$v(F) = a \frac{\left(k_{\mathrm{on}}[\mathrm{ATP}] u_2 e^{-\alpha F a / k_B T} - w_1 w_2 e^{+(1-\alpha) F a / k_B T}\right)}{\left(k_{\mathrm{on}}[\mathrm{ATP}] + u_2 e^{-\alpha F a / k_B T} + w_1 + w_2 e^{+(1-\alpha) F a / k_B T}\right)}$$

kinesin walking on microtubules



K. Visscher et al., Nature 400, 184-189 (1999)

Stall force

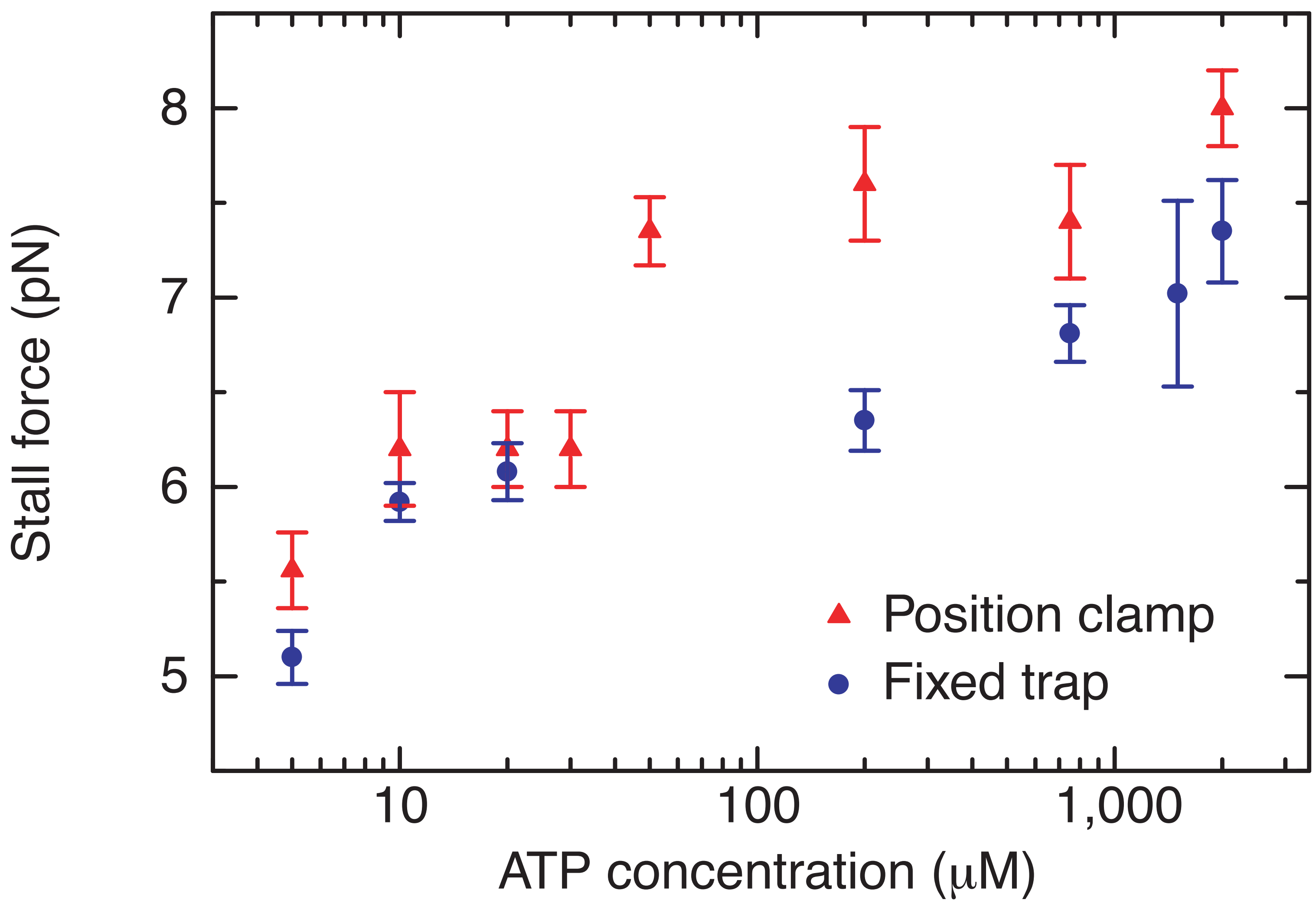
$$v(F_s) = 0$$

$$\boxed{F_s = \frac{k_B T}{a} \ln\left(\frac{k_{\text{on}}[\text{ATP}]u_2}{w_1 w_2}\right)}$$

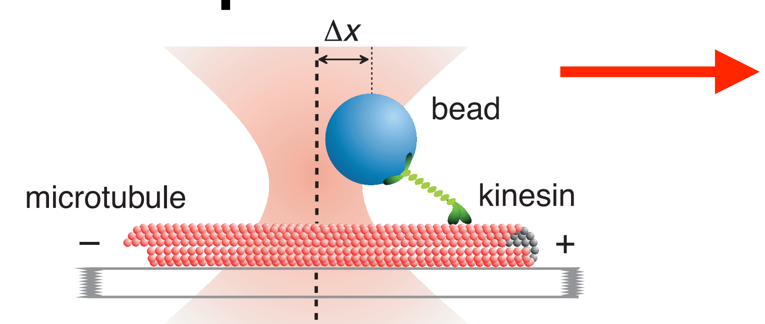
maximal possible force from energy conservation

$$F_{\max} = \frac{\Delta G_{\text{ATP}}}{a} \approx \frac{20 k_B T}{8\text{nm}} \sim 10\text{pN}$$

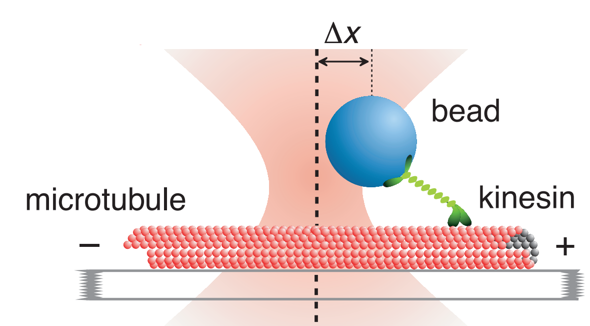
kinesin walking on microtubules



Position clamp
laser follows the bead and keeps fixed force

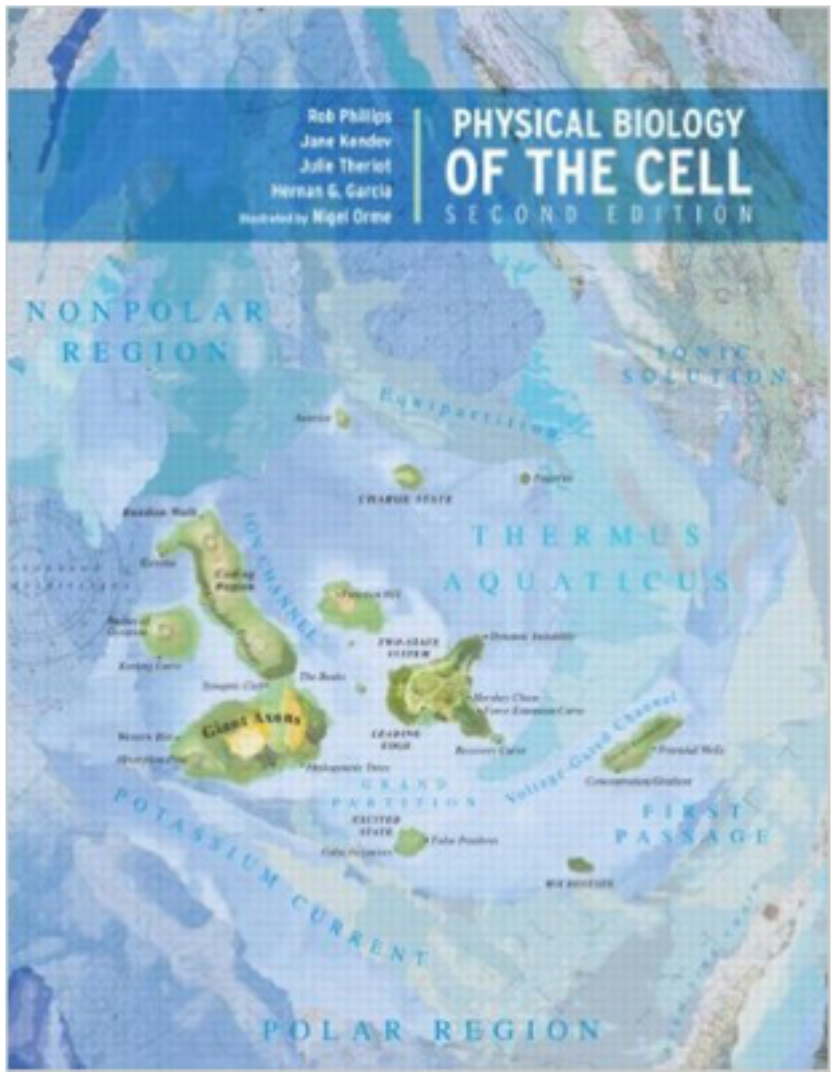


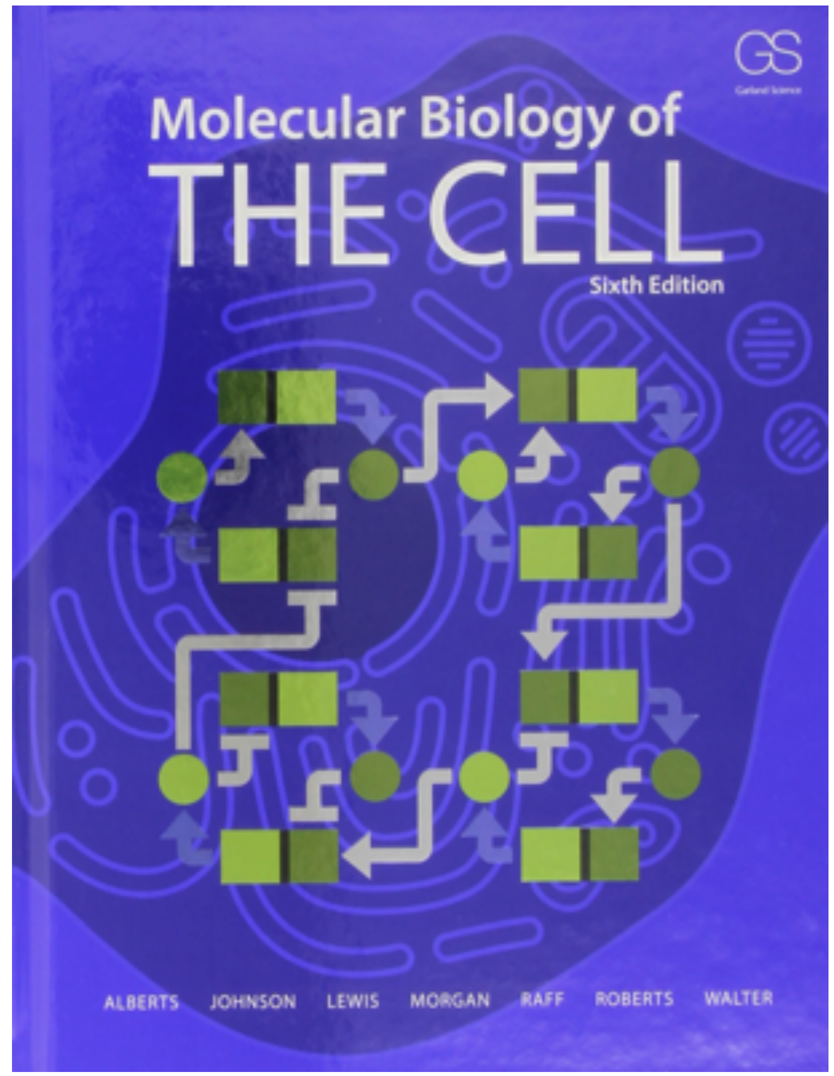
Fixed trap
laser position is is fixed

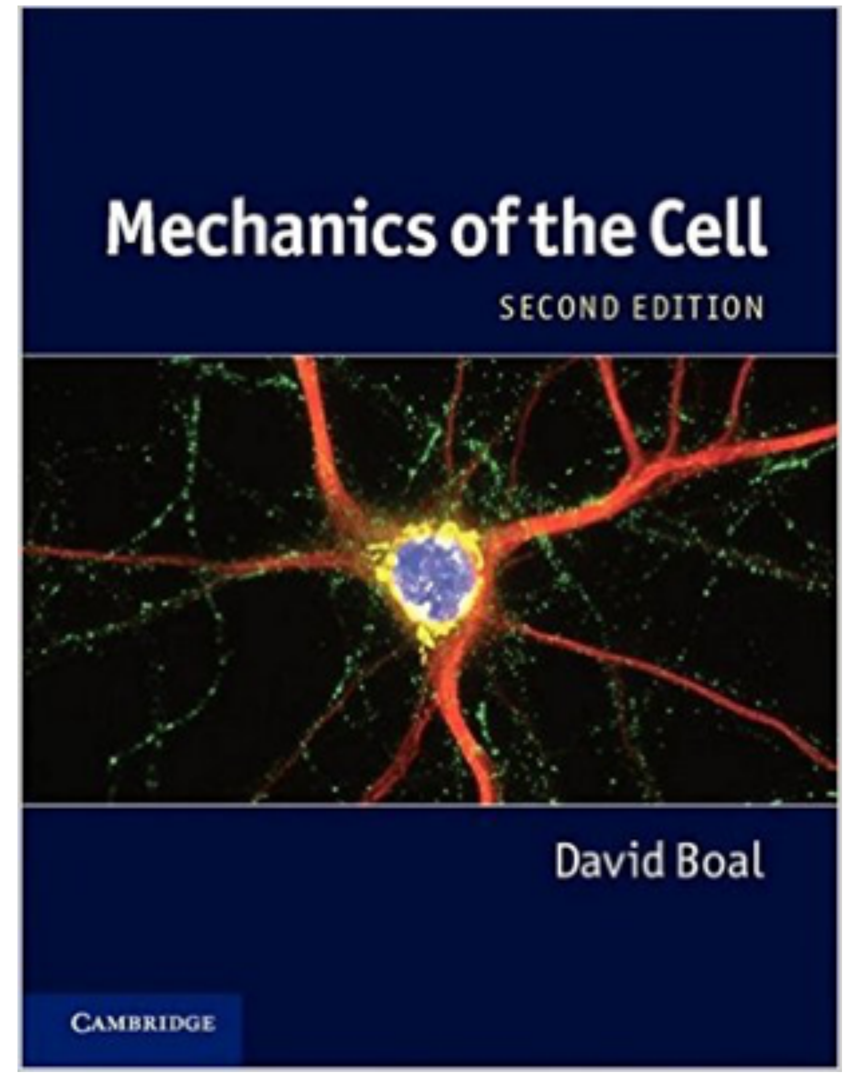


K. Visscher et al., Nature 400, 184-189 (1999)

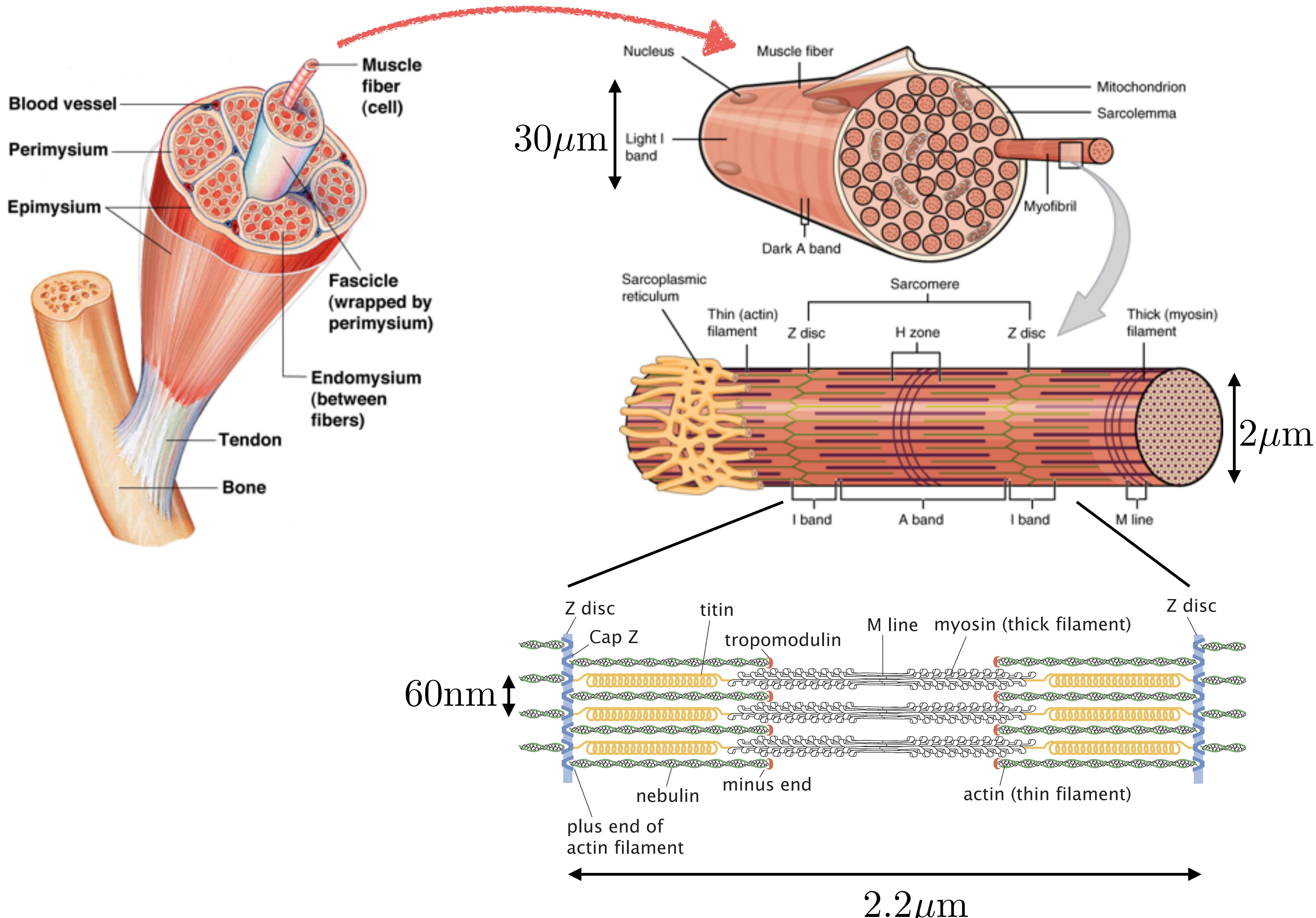
Further reading



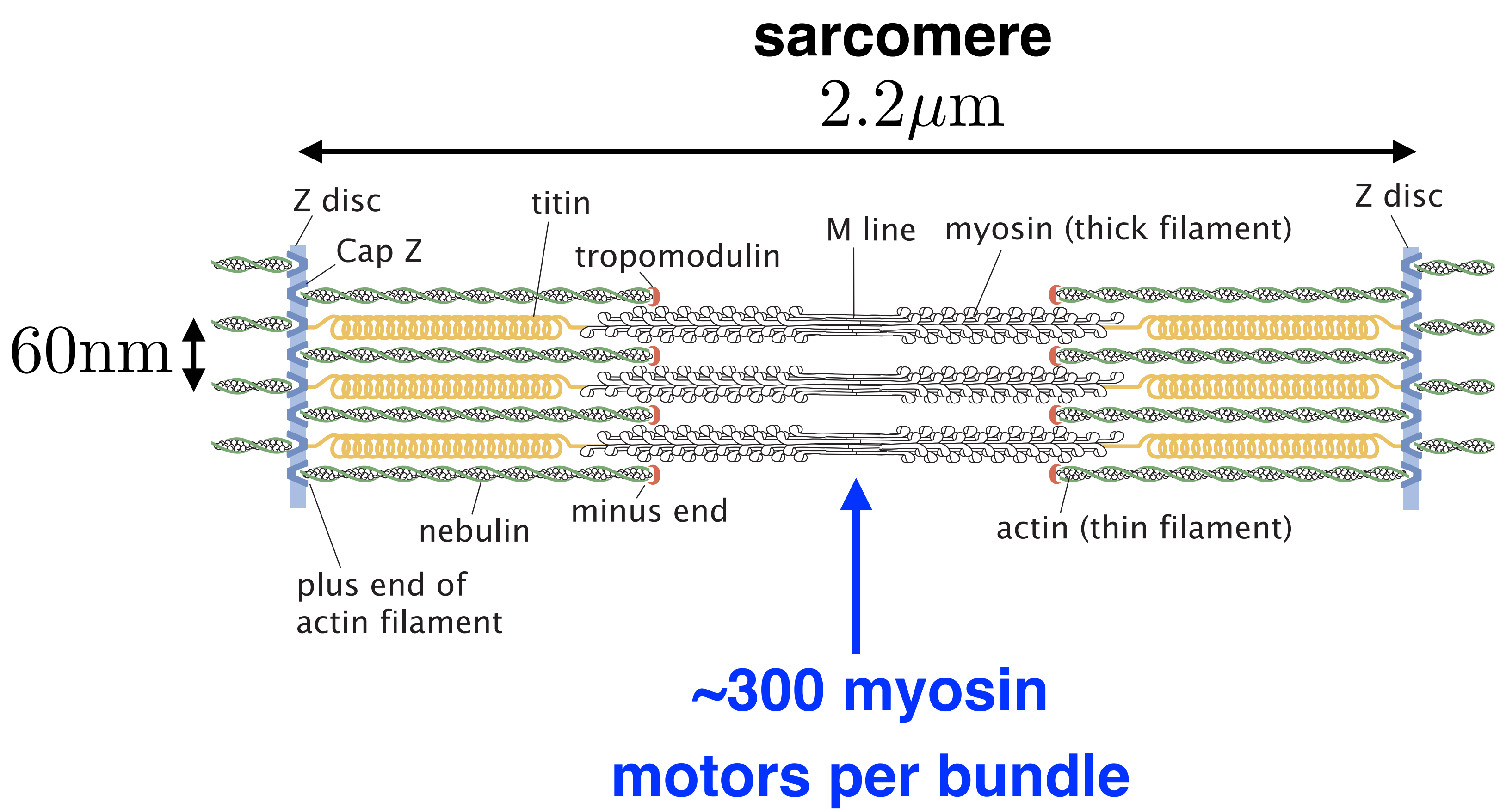




Skeletal muscle contraction by myosin motors



Skeletal muscle contraction by myosin motors



Estimated force generated by myosin motors

$$300 \times \frac{2\text{pN}}{\pi(30\text{nm})^2} \sim 20\text{N}/\text{cm}^2$$

Muscles contract at twice the speed of myosin motors

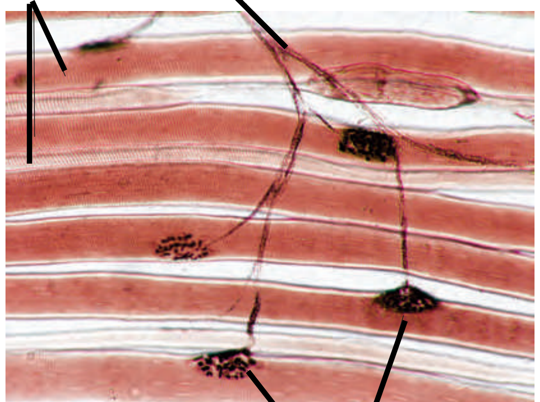
$$\sim 0.1\text{-}1\mu\text{m}/\text{s}$$

Muscles may contract by 5%-45% per second!

Skeletal muscle contraction is controlled by nerve cells

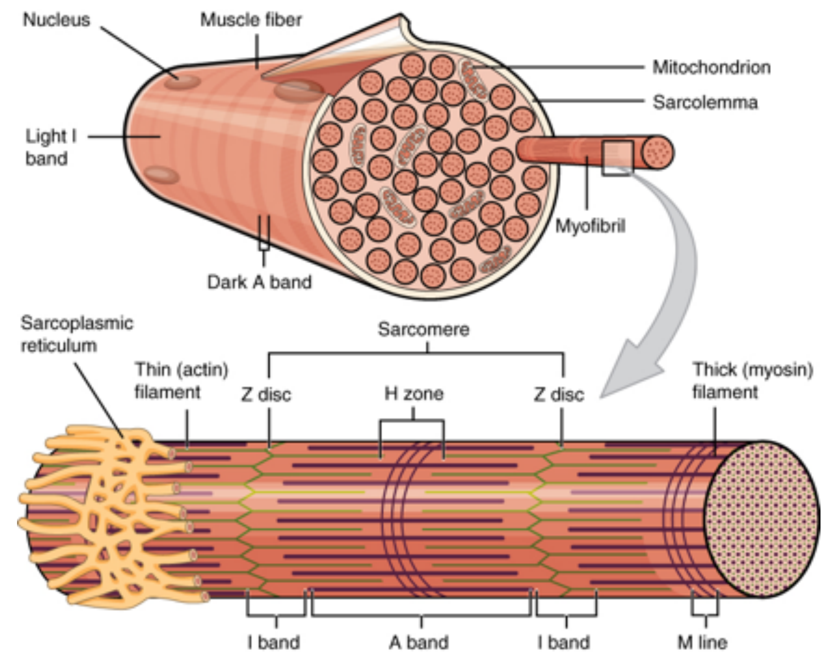
muscle cells

nerve cell

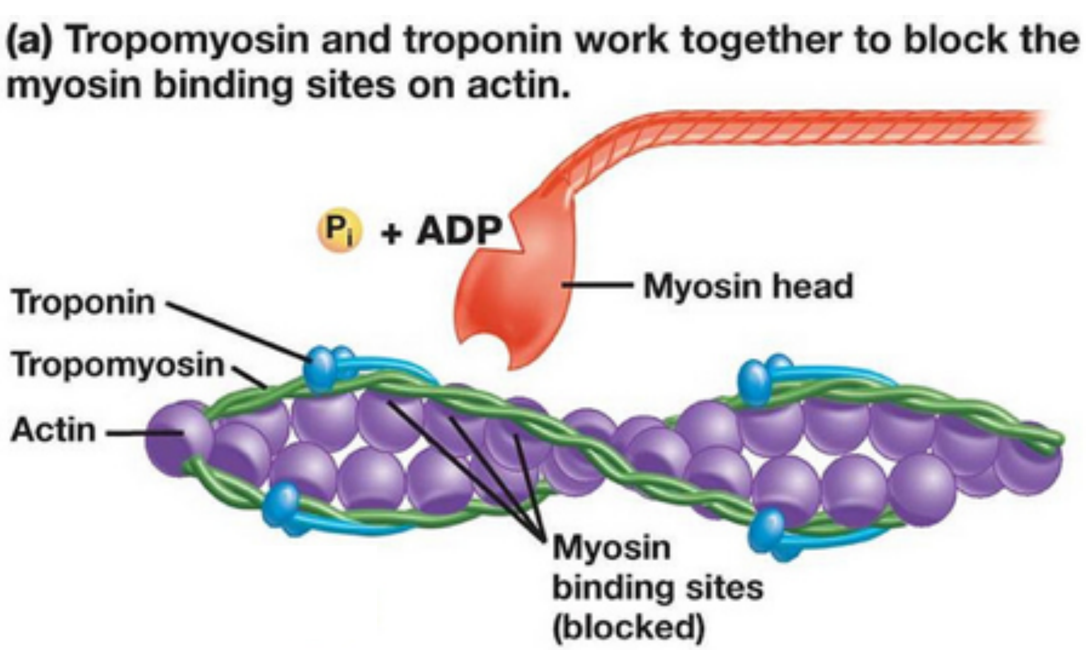


synapses

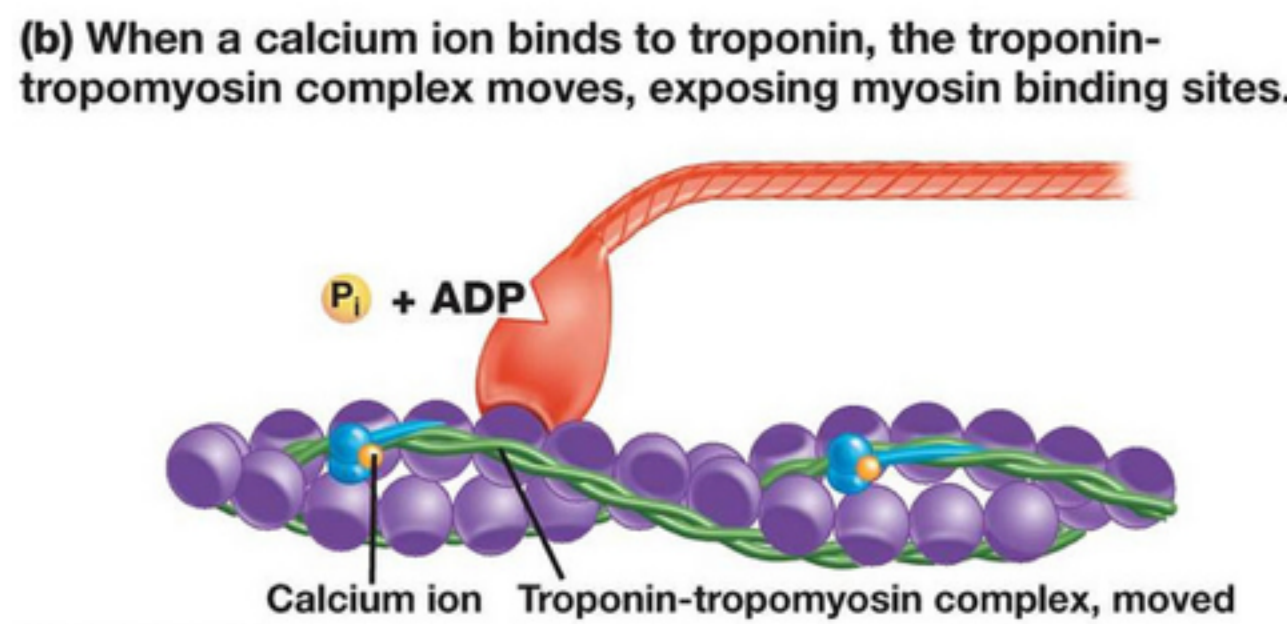
Electric signal from nerve cells releases Ca^{2+} from sarcoplasmic reticulum



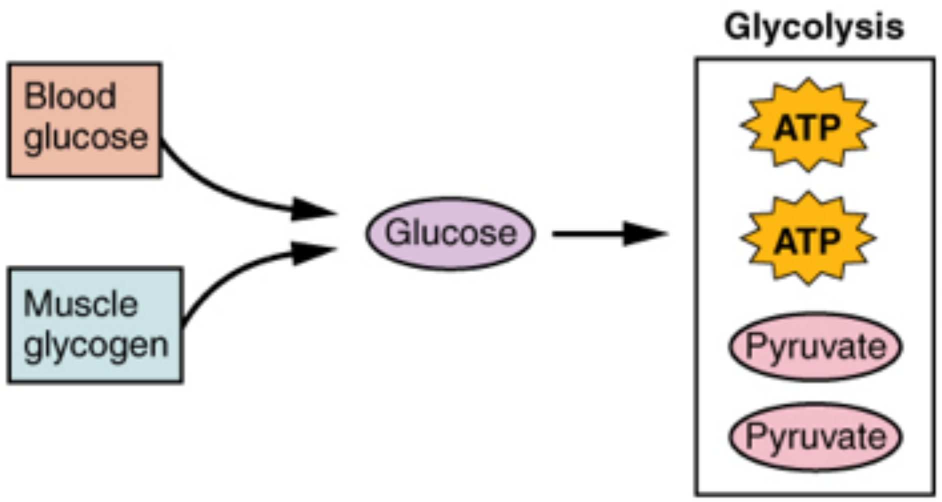
Low Ca^{2+}, muscles are relaxed



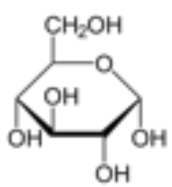
High Ca^{2+}, muscles are contracted

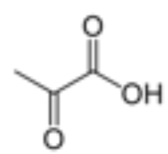


How muscles get ATP energy?



glucose **pyruvate**





O_2

Aerobic respiration

$$C_6H_{12}O_6 + 6O_2 \Longrightarrow 6CO_2 + 6H_2O + 36\text{ATP}$$

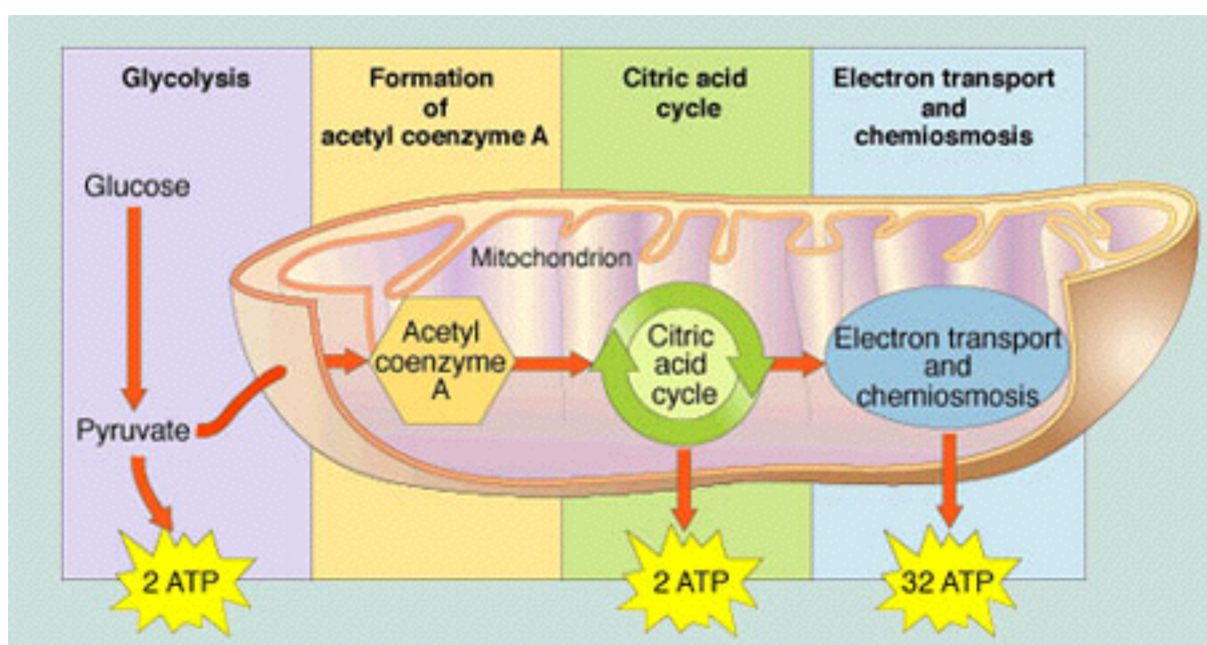
no O_2

Anaerobic respiration

$$C_6H_{12}O_6 \Longrightarrow 2 \text{ Lactic Acids} + 2\text{ATP}$$

(muscle fatigue)

Aerobic respiration



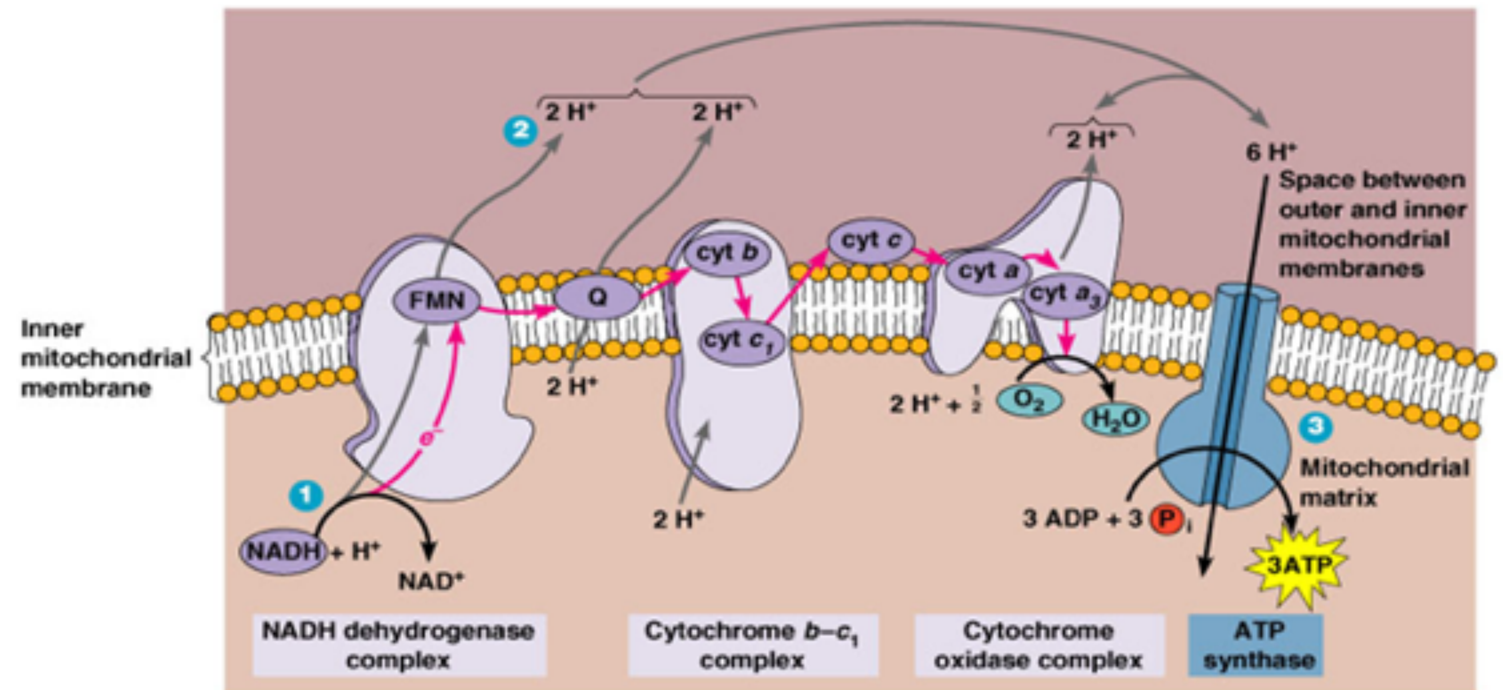
Note:

Citric acid cycle

= Krebs cycle

Electron transport chain

Mitochondrion



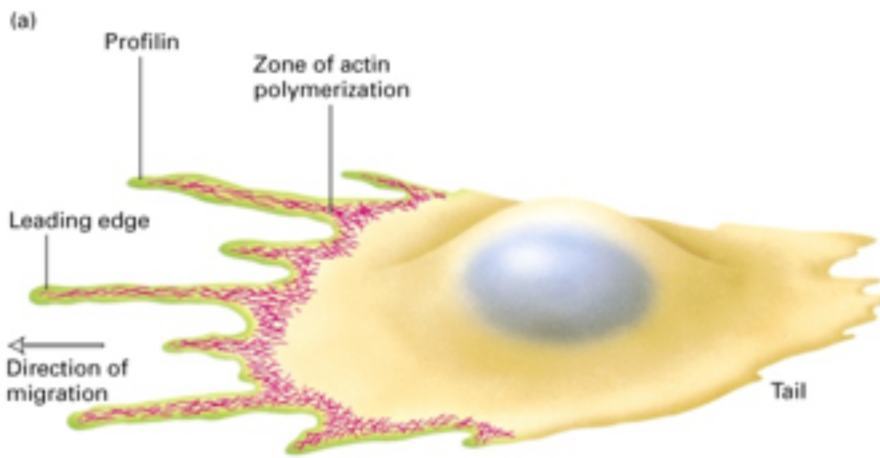
NADH products of the Cytric acid cycle are used to pump H+ to the space between outer and inner mitochondrial membrane.

Gradient of H+ concentration drives the ATP synthase motor that converts ADP to ATP.

Note: ATP synthase can run in reverse and use ATP to pump H+ at low concentrations.

ATP synthase

Crawling of cells



Immune system:
neutrophils chasing bacteria

David Rogers, 1950s

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

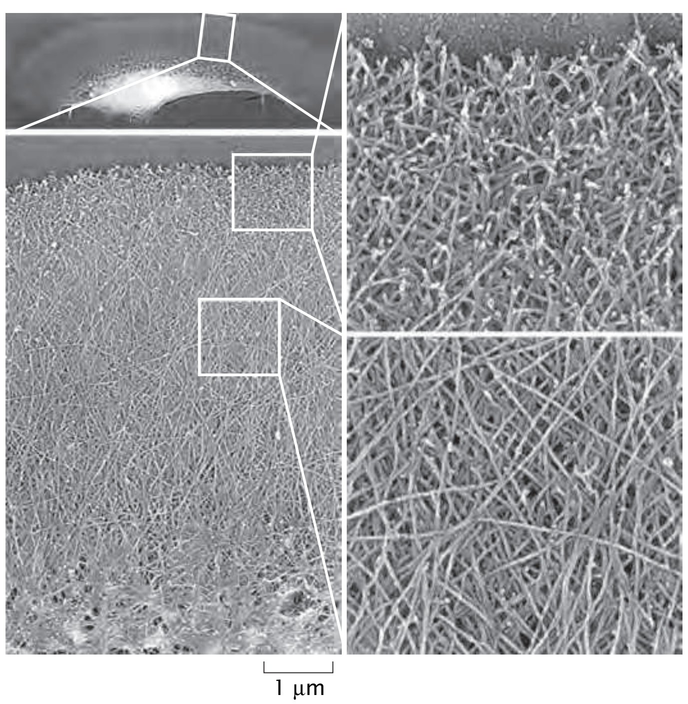
migration of skin cells during wound healing

spread of cancer cells during metastasis of tumors

amoeba searching for food

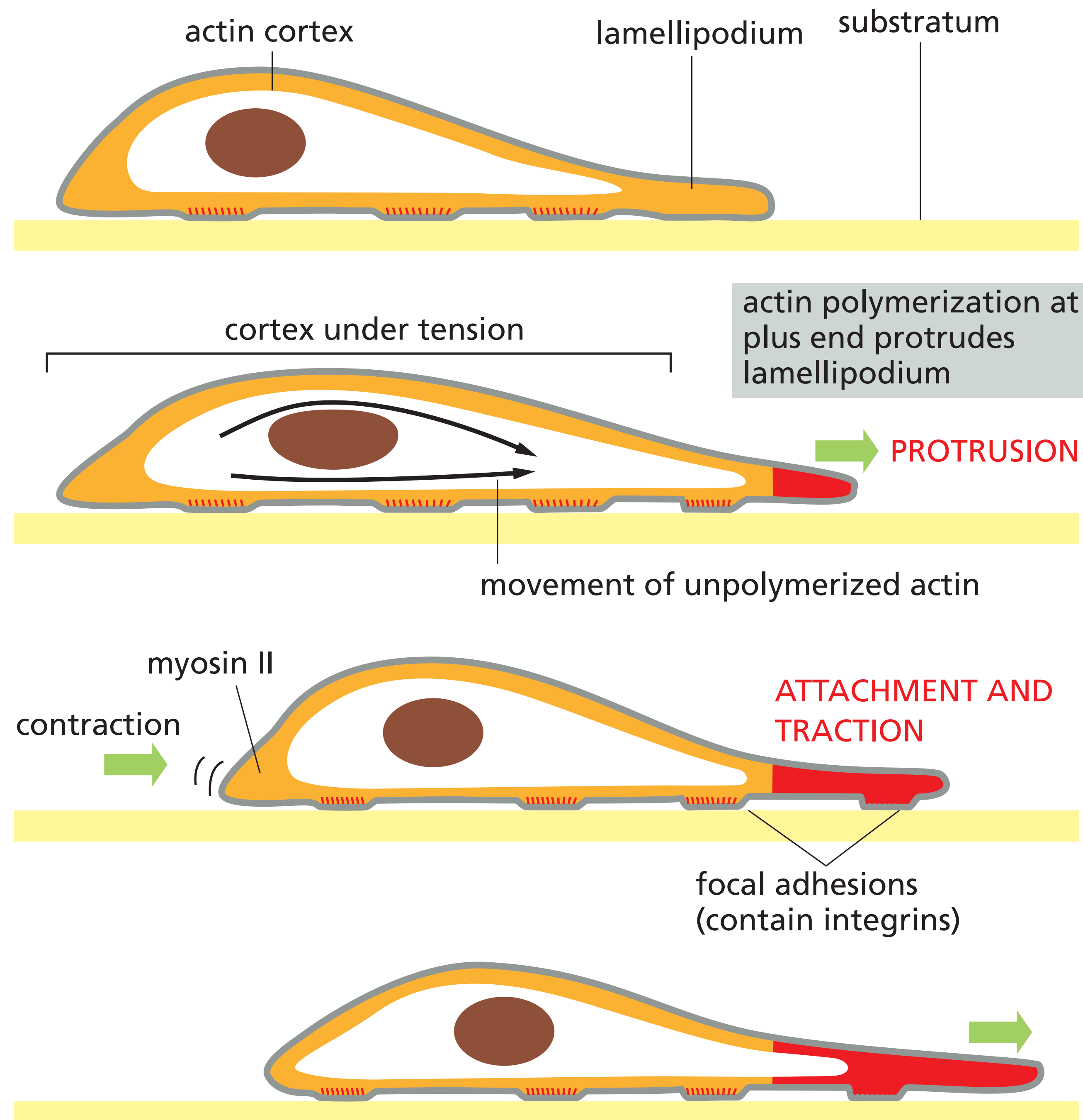
Crawling of cells

fish skin cell $v = 0.2\mu\mathrm{m/s}$



actin

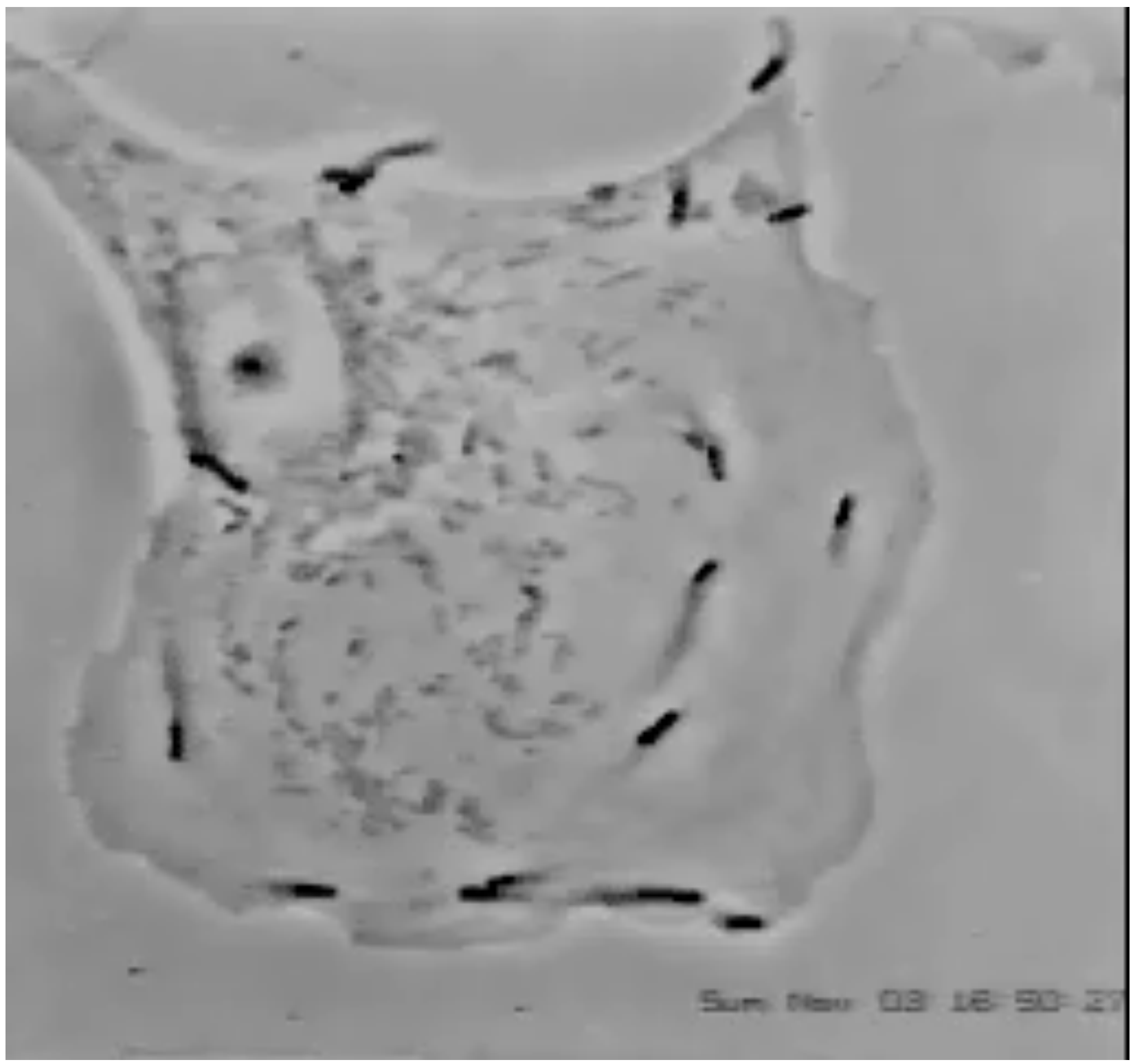
R. Phillips et al., Physical Biology of the Cell



Alberts et al., Molecular Biology of the Cell

Movement of bacteria

Listeria monocytogenes
moving in PtK2 cells



(speeded up 150x)

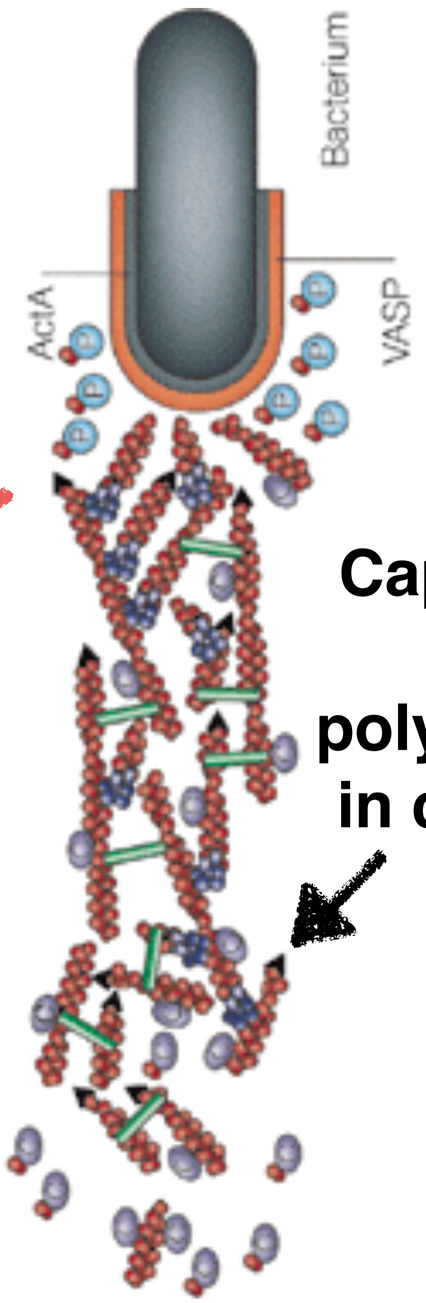
Julie Theriot

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

Actin polymerization is pushing bacteria

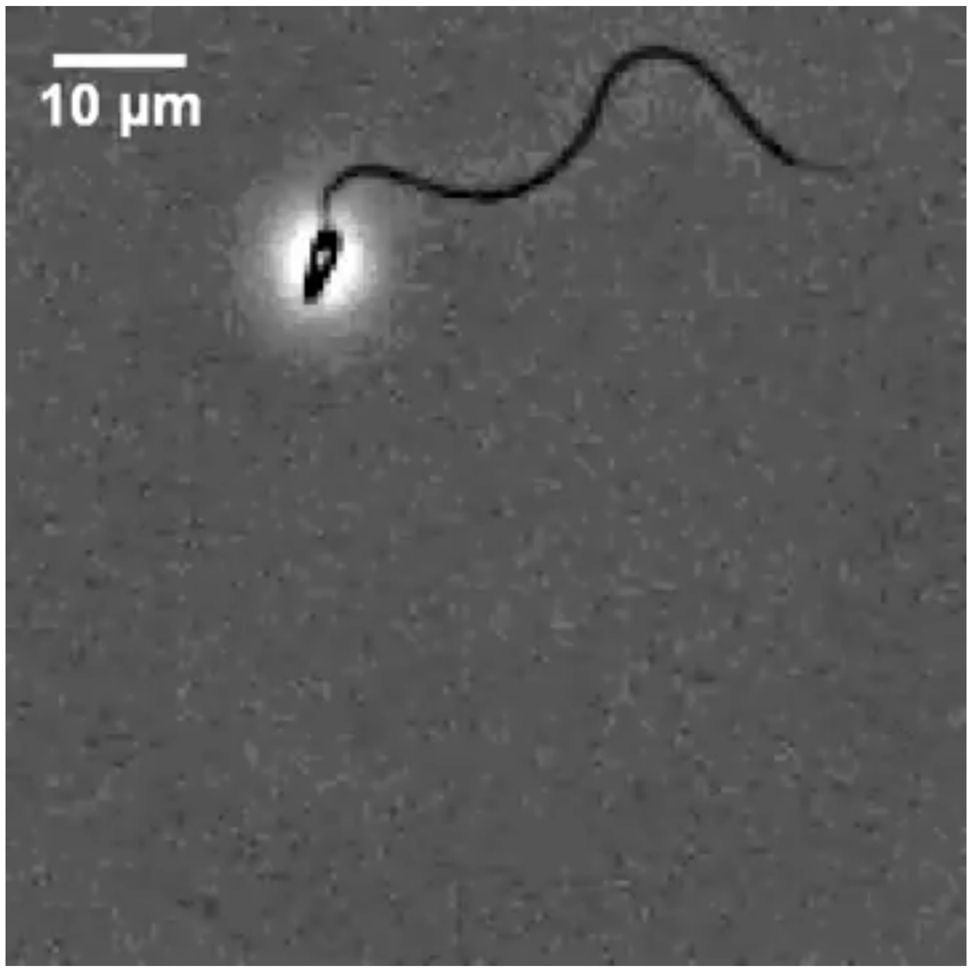
Caps prevent further polymerization in comet tails

Actin is randomly depolymerized in comet tails



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

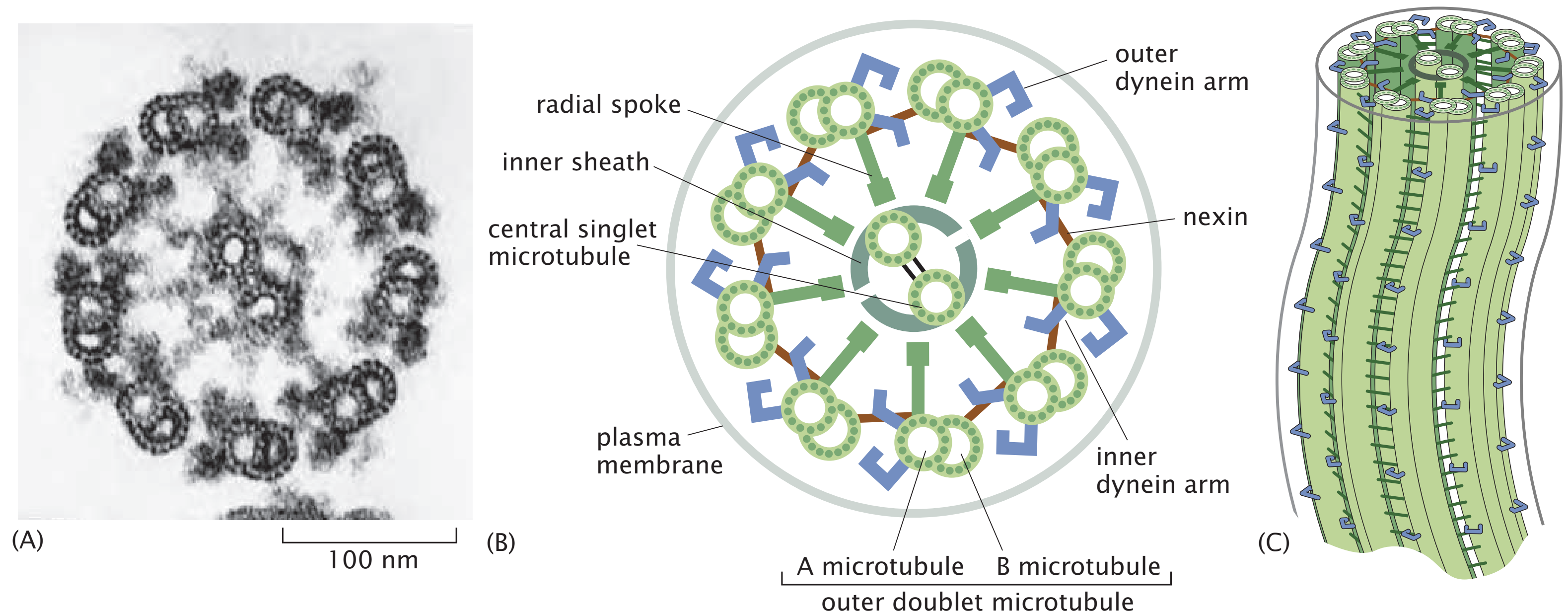
Swimming of sperm cells

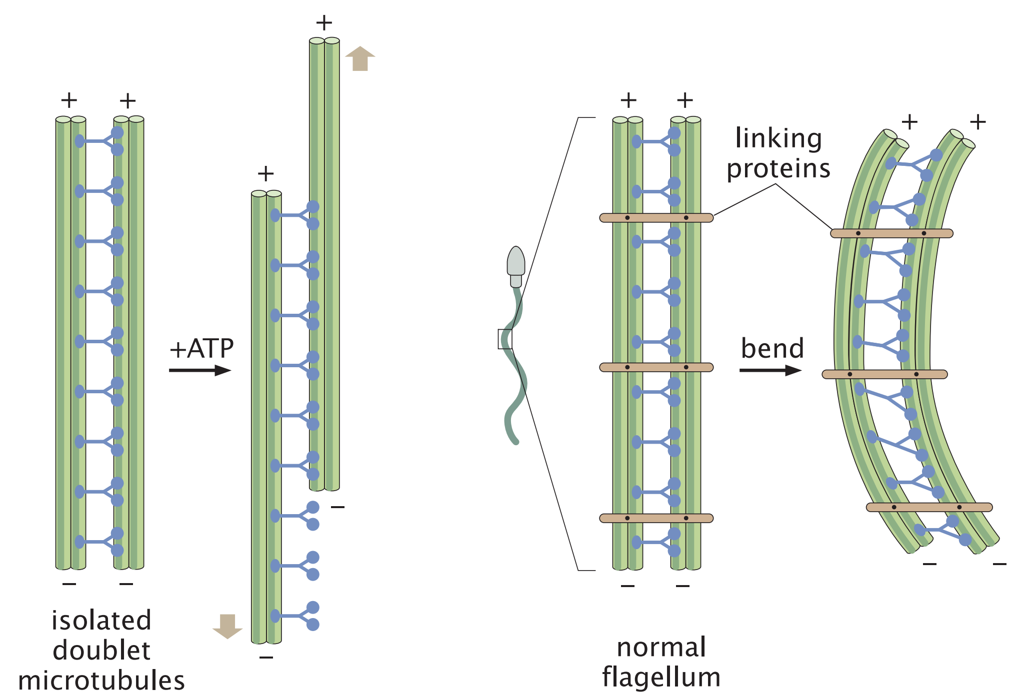


Jeff Guasto

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

Sperm flagellum is constructed from microtubules





R. Phillips et al., Physical Biology of the Cell