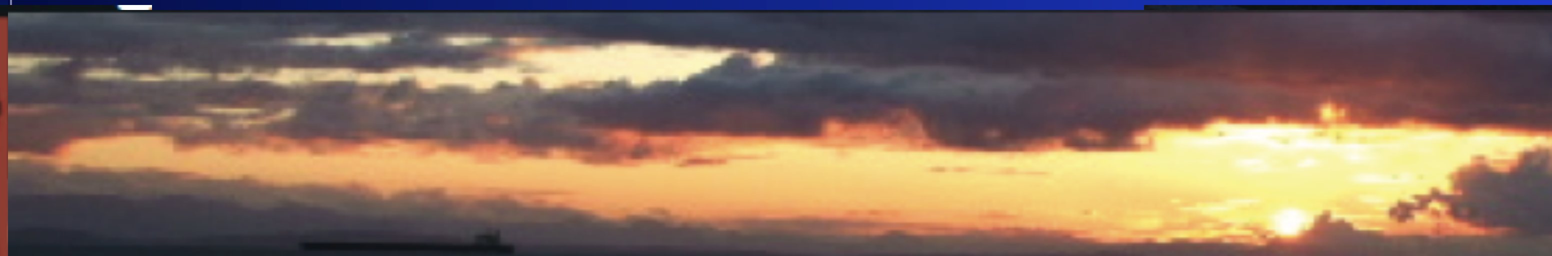
Mathematical Cell Biology Graduate Summer Course

University of British Columbia, May 1-31, 2012

Leah Edelstein-Keshet

Three short stories about Molecular Motors



mprime

PIMS

www.math.ubc.ca/~keshet/MCB2012/

With thanks to Alex Mogilner
for advice and material

Regulation of size in cell structures

Length of flagellum

Size control in dynamic organelles

Wallace F. Marshall

Control of flagellar length in Chlamydomonas

TRENDS in Cell Biology Vol.12 No.9 September 2002

Intraflagellar transport balances continuous turnover of outer doublet microtubules

implications for flagellar length control

Wallace F. Marshall and Joel L. Rosenbaum

JCB vol. 155 no. 3 405-414

http://jcb.rupress.org/content/155/3/405.full

What is the problem?

How can the cell control the size of a structure?

1. Create protein of "just the right size"
2. Use a "ruler".
3. Use a sensor to signal when the size is correct
4. Dynamic regulation (balance assembly/disassembly)

If structure is continually turned over

1. Create protein of “just the right size”
2. Use a “ruler”.
3. Use a sensor to signal when the size is correct
4. Dynamic regulation (balance assembly/disassembly)

Chlamydomonas flagellae

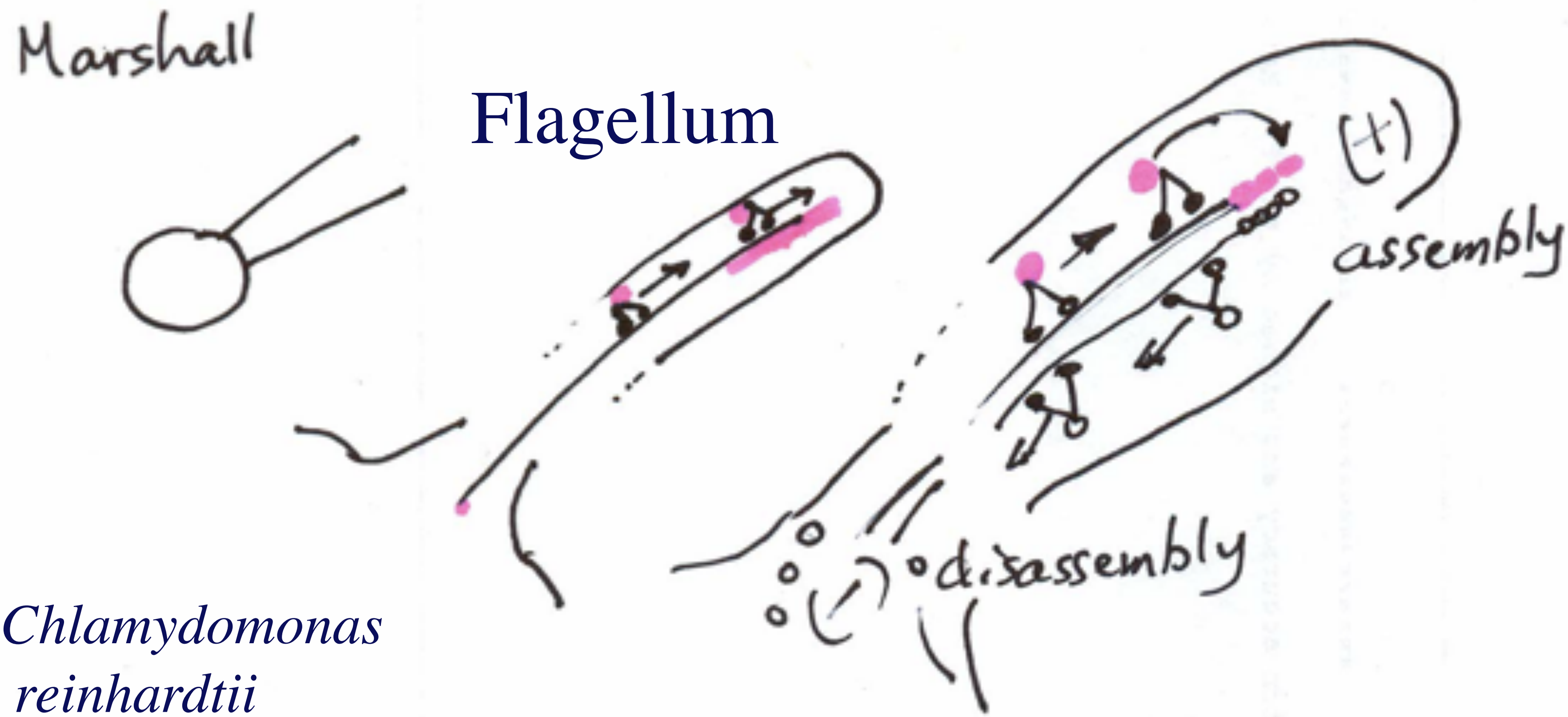
See movie at:

http://www.youtube.com/watch?v=QGAm6hMysTA&feature=related

Observations and facts

1. In Chlamidomonas, 2 flagella, continuous turnover.
2. Tubulin made in cell body, delivered to tip of flagellum.
3. Motors (IFT's) transport tubulin to and from flagellum tip with constant velocity v.
4. Assembly rate depends on delivery of cargo to the tip.
5. Assembly is length-dependent, disassembly is constant.

Flagellum length tightly controlled



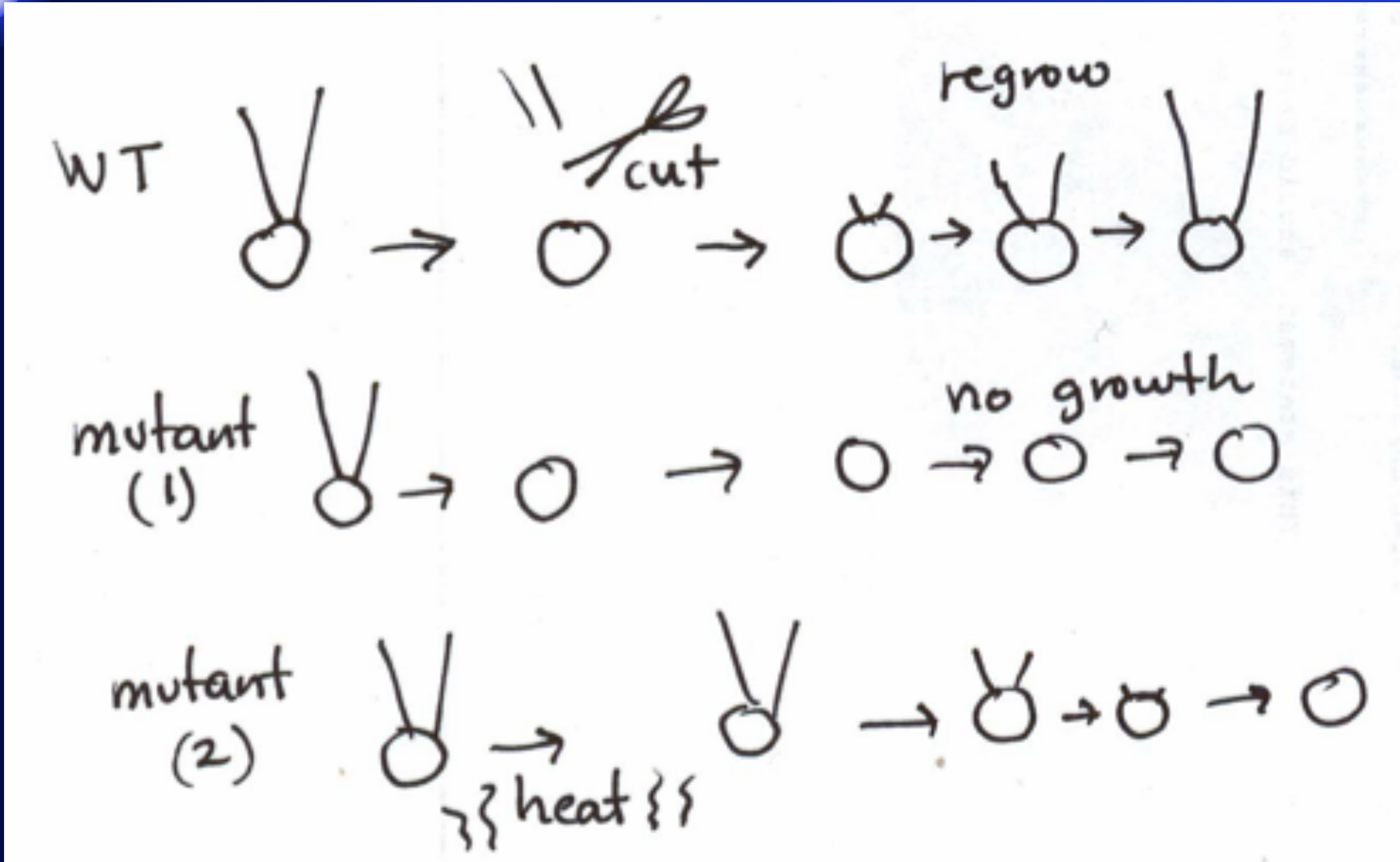
Chlamydomonas reinhardtii

Constant number of transporters

The number of IFT’s in flagellum is constant and length-independent.

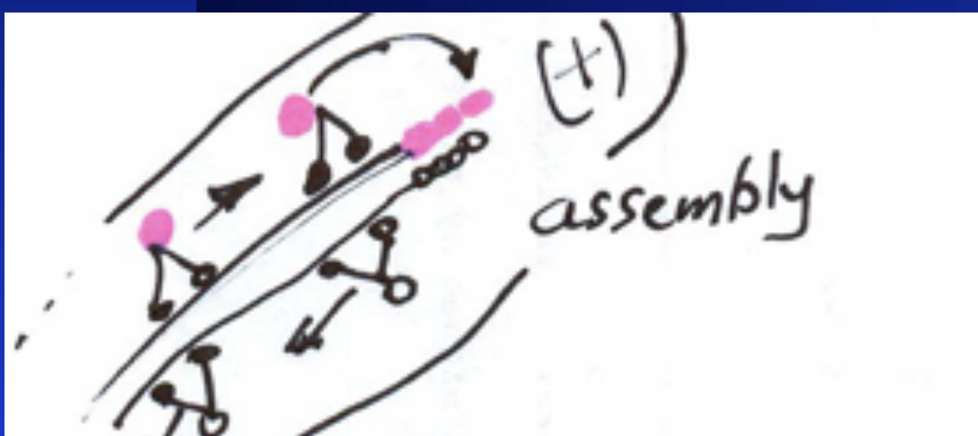
http://jcb.rupress.org/content/155/3/405/F7.large.jpg

Experiments



Transporters carry tubulin

L= length of flagellum (in μm)
T = Total amount of flagellar protein (in length equivalents) μm
M= number of IFT transporters = $\boxed{\text{constant (Observed)}}$
v= speed of transport μm/s



Assembly rate

Each IFT binds available tubulin with some affinity α.

M IFT's can deliver: $\alpha M(T-2L)$ length-units in 1 round-trip

Trip time $= 2L/V$ seconds

$$\text{Assembly rate} = \frac{\Delta L}{\Delta t} = \alpha M(T-2L)\frac{V}{2L}$$

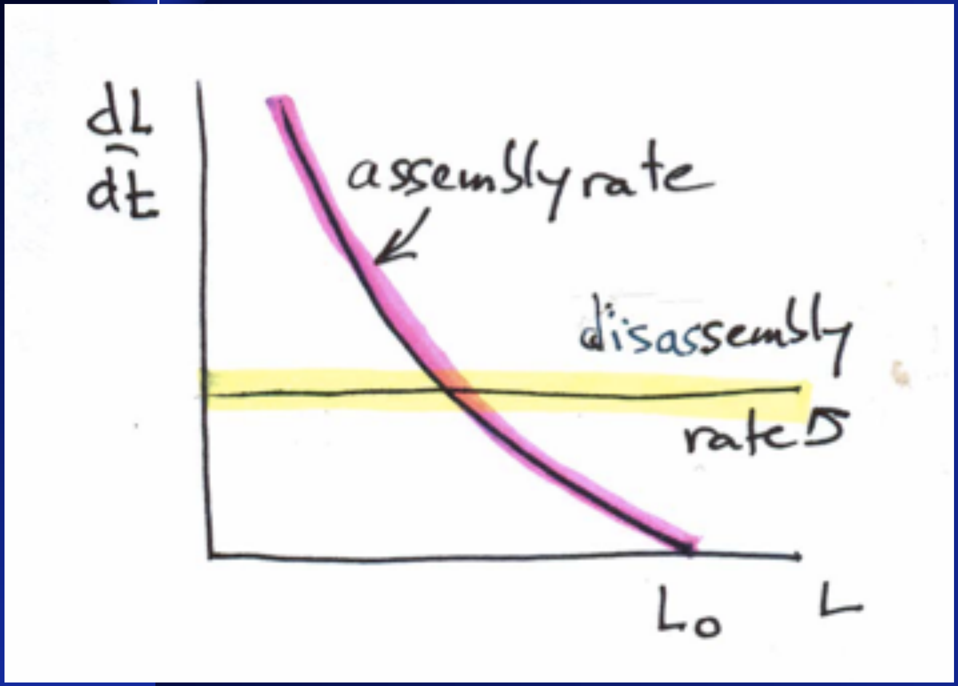
Flagellum length

$$\frac{dL}{dt} = \text{Assembly rate} - \text{Disassembly rate}$$

$$\frac{dL}{dt} = \alpha M(T - 2L)\frac{V}{2L} - D$$

$$\frac{dL}{dt} = \alpha MV\left(\frac{T}{2L} - 1\right) - D$$

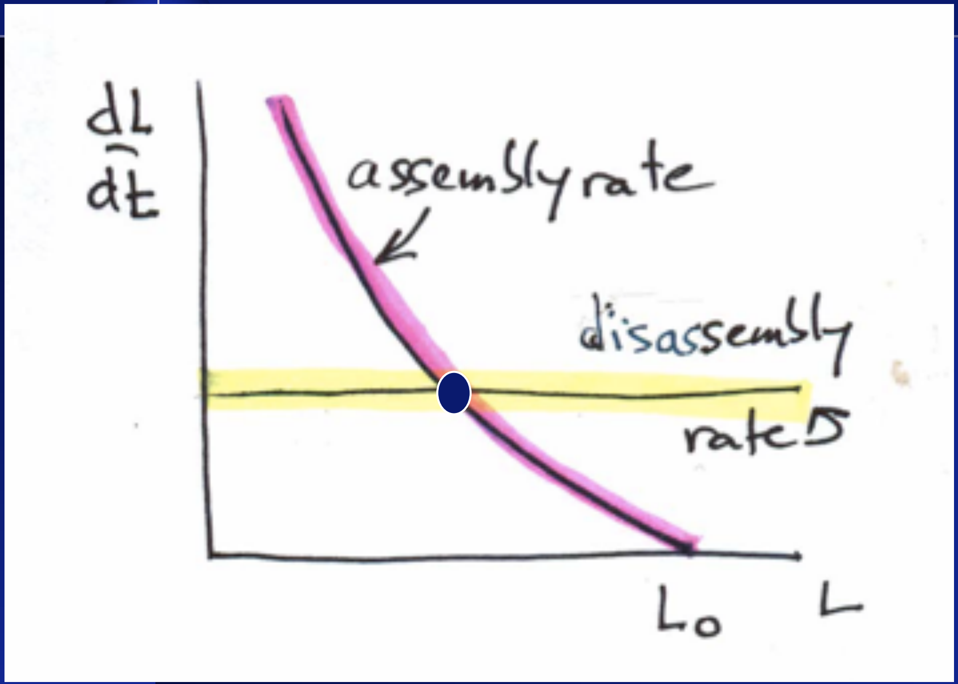
Regulation stems from balance of assembly and disassembly



$$\frac{dL}{dt} = A\left(\frac{L_0}{L} - 1\right) - D$$

$$A = \alpha M v, \quad L_0 = \frac{T}{2}$$

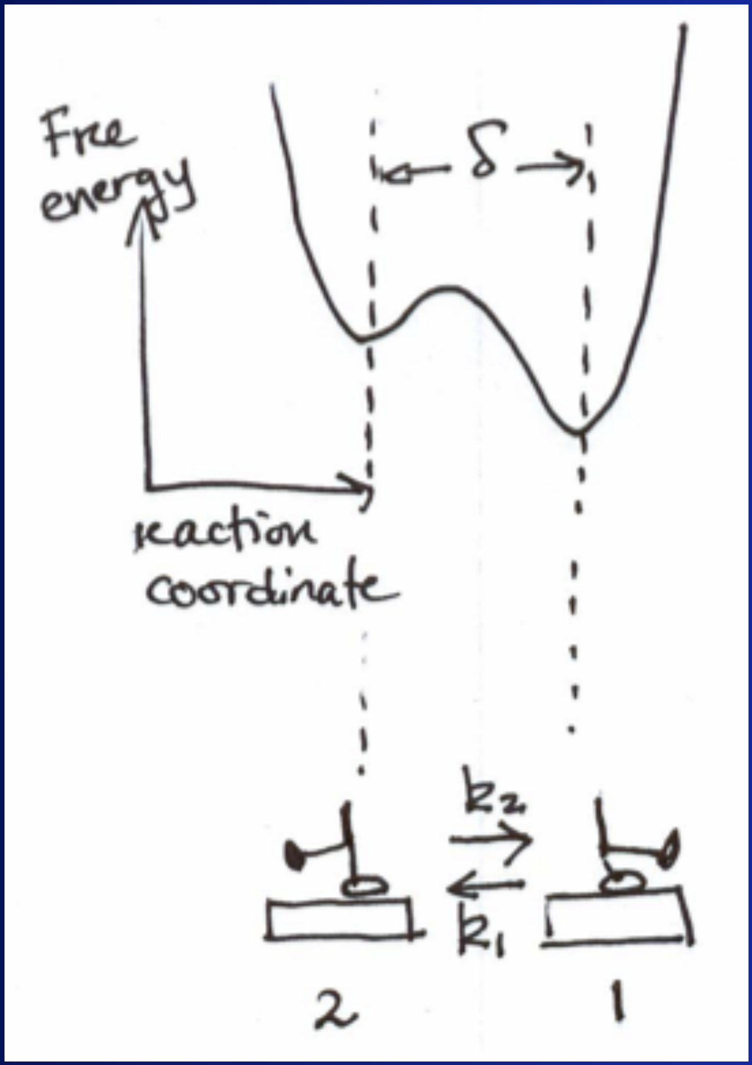
Equilibrium length



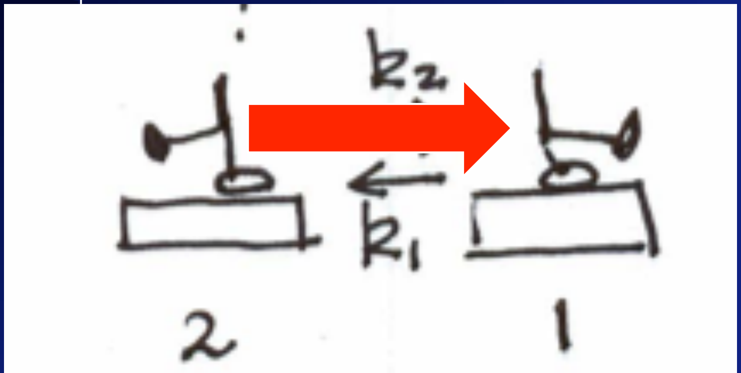
$$\frac{dL}{dt} = 0 \quad \Rightarrow \quad \frac{L_0}{L} - 1 = \frac{D}{A}, \quad \Rightarrow \quad L = \frac{L_0 A}{D + A}$$

Short derivation of a force-velocity relation in simple power-stroke motor

Two-step motor (by Alex Mogilner)



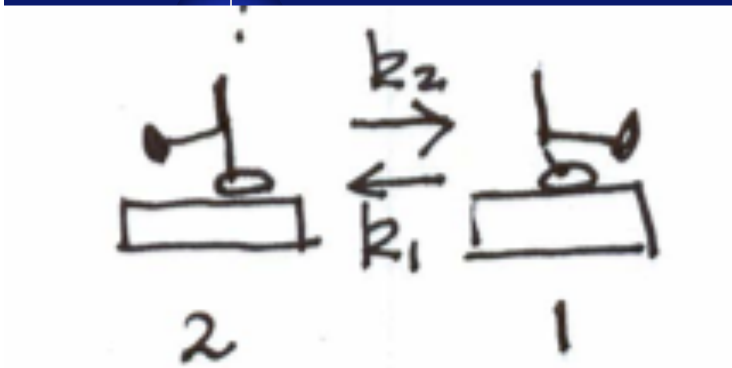
Powerstroke



Suppose the transition 2 → 1 is the power-stroke.

$$k_2 = k_2^0 \exp\left(-\frac{f\delta}{k_B T}\right)$$

Master equations



$p_1(t), p_2(t)$ = probabilities of states 1 and 2.

$$
\begin{aligned}
\frac{dp_1}{dt} &= -k_1 p_1 + k_2 p_2, \\
\frac{dp_2}{dt} &= k_1 p_1 - k_2 p_2
\end{aligned}
$$

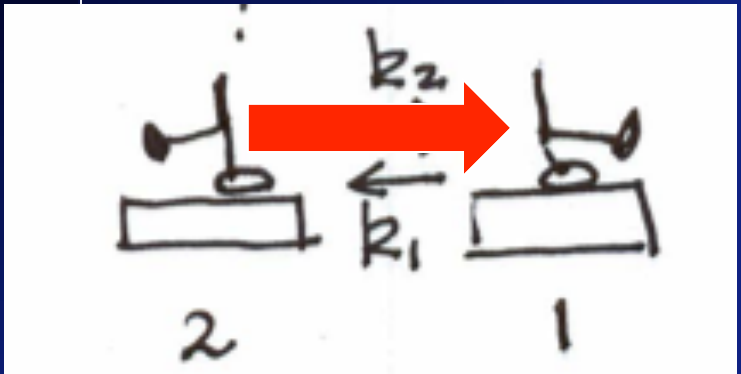
At equilibrium

$$k_1 p_1 = k_2 p_2 \quad \Rightarrow$$

$$p_1 = \frac{k_2}{k_1} p_2 \quad \Rightarrow \quad p_2 \left(1 + \frac{k_2}{k_1}\right) = 1$$

$$p_2 = \frac{k_1}{k_1 + k_2}$$

Velocity



$$V = \delta k_2 p_2$$

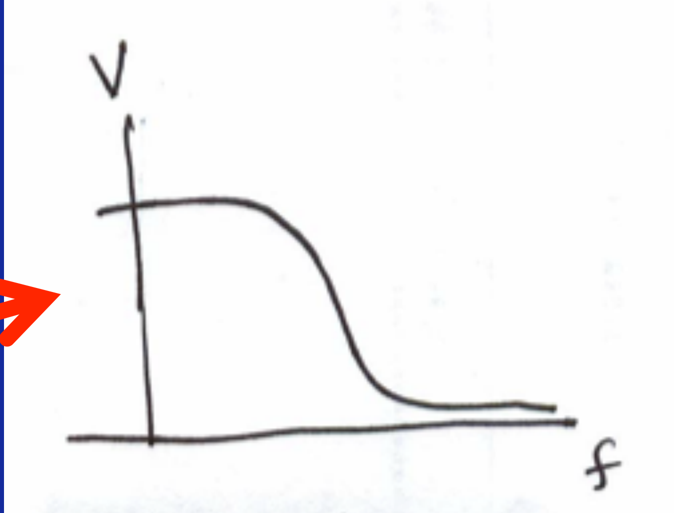
$$V = \delta k_2 \frac{k_1}{k_1 + k_2} = \delta \frac{k_1 k_2}{k_1 + k_2}$$

$$k_2 = k_2^0 \exp\left(-\frac{f\delta}{k_B T}\right)$$

This leads to Force-velocity relation:

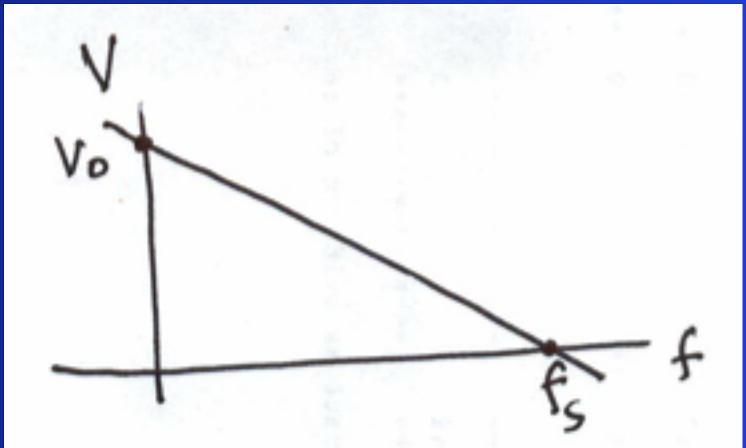
$$V = \frac{\delta k_1 k_2^0 \exp\left(-\frac{f\delta}{k_B T}\right)}{k_1 + k_2^0 \exp\left(-\frac{f\delta}{k_B T}\right)}$$

$$V = \frac{\delta k_1 k_2^0}{k_1 \exp\left(\frac{f\delta}{k_B T}\right) + k_2^0}$$



Linear approximation

$$V = V_0\left(1 - \frac{f}{f_s}\right)$$



Motors and MT tug of war

Self-Organization of Dynein Motors Generates Meiotic Nuclear Oscillations

Sven K. Vogel[1☯], Nenad Pavin[2,3☯], Nicola Maghelli[1], Frank Jülicher[2], Iva M. Tolić-Nørrelykke[1*]

PLoS Biology | www.plosbiology.org

April 2009 | Volume 7 | Issue 4 | e1000087

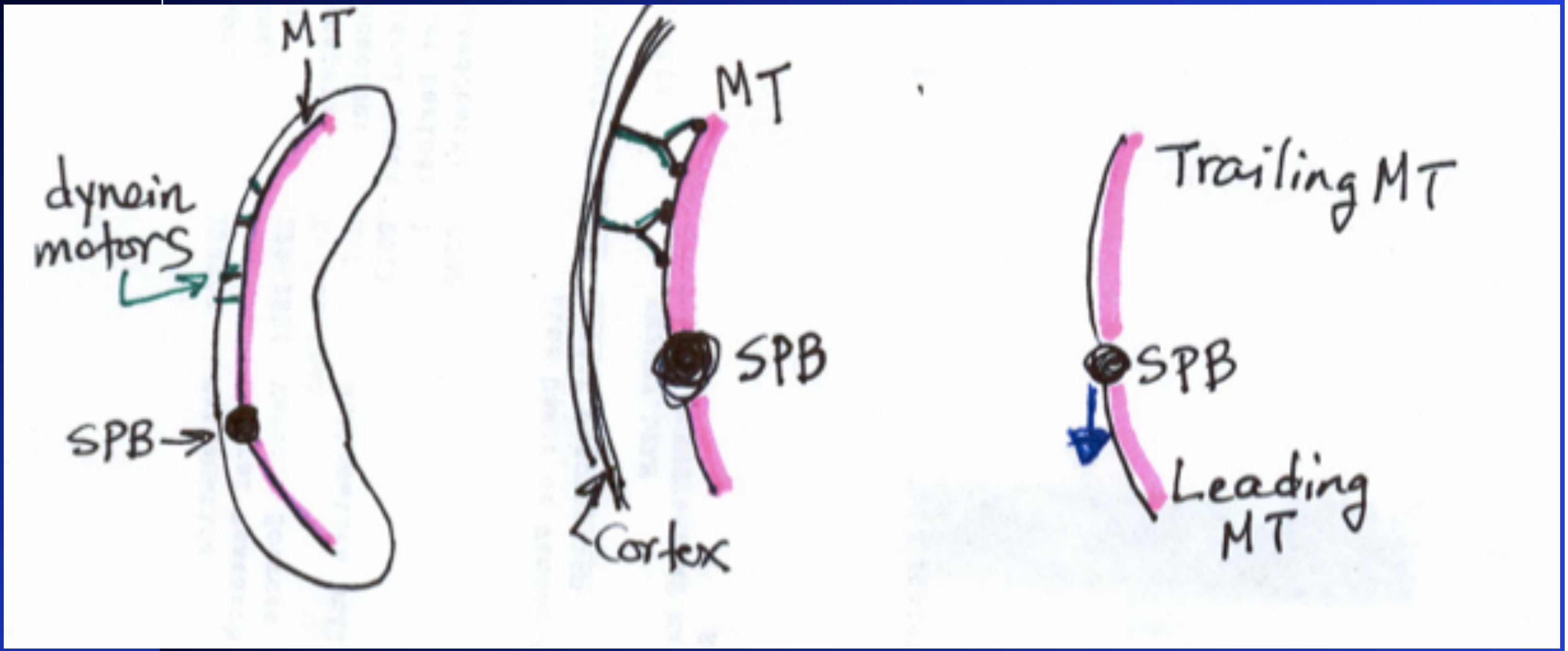
Oscillating spindle-pole body

"In fission yeast, S. pombe, two cells … fuse at their tips forming a banana- shaped zygote. Subsequently, the two nuclei of the parental cells fuse into one, which starts to oscillate from one end of the cell to the other."

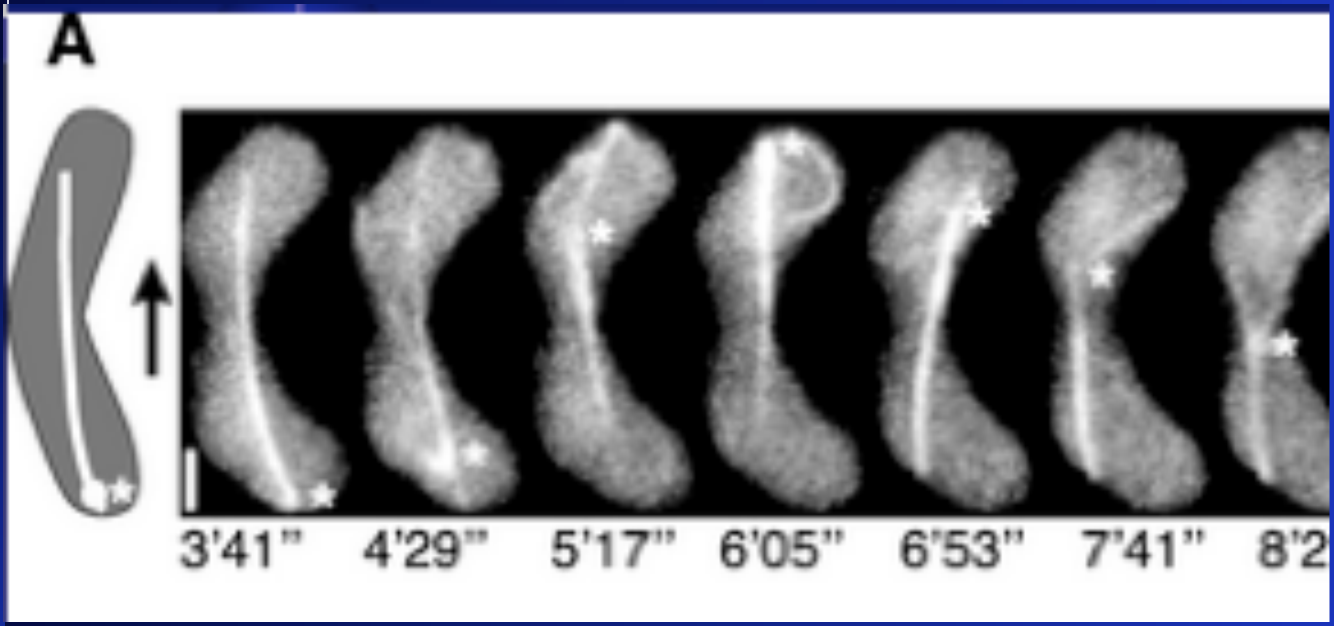
Movies

Vogel SK, Pavin N, Maghelli N, Jülicher F, Tolić-Nørrelykke IM (2009). PLoS Biol 7 (4): e1000087. doi:10.1371/journal.pbio.1000087

What is the biology?

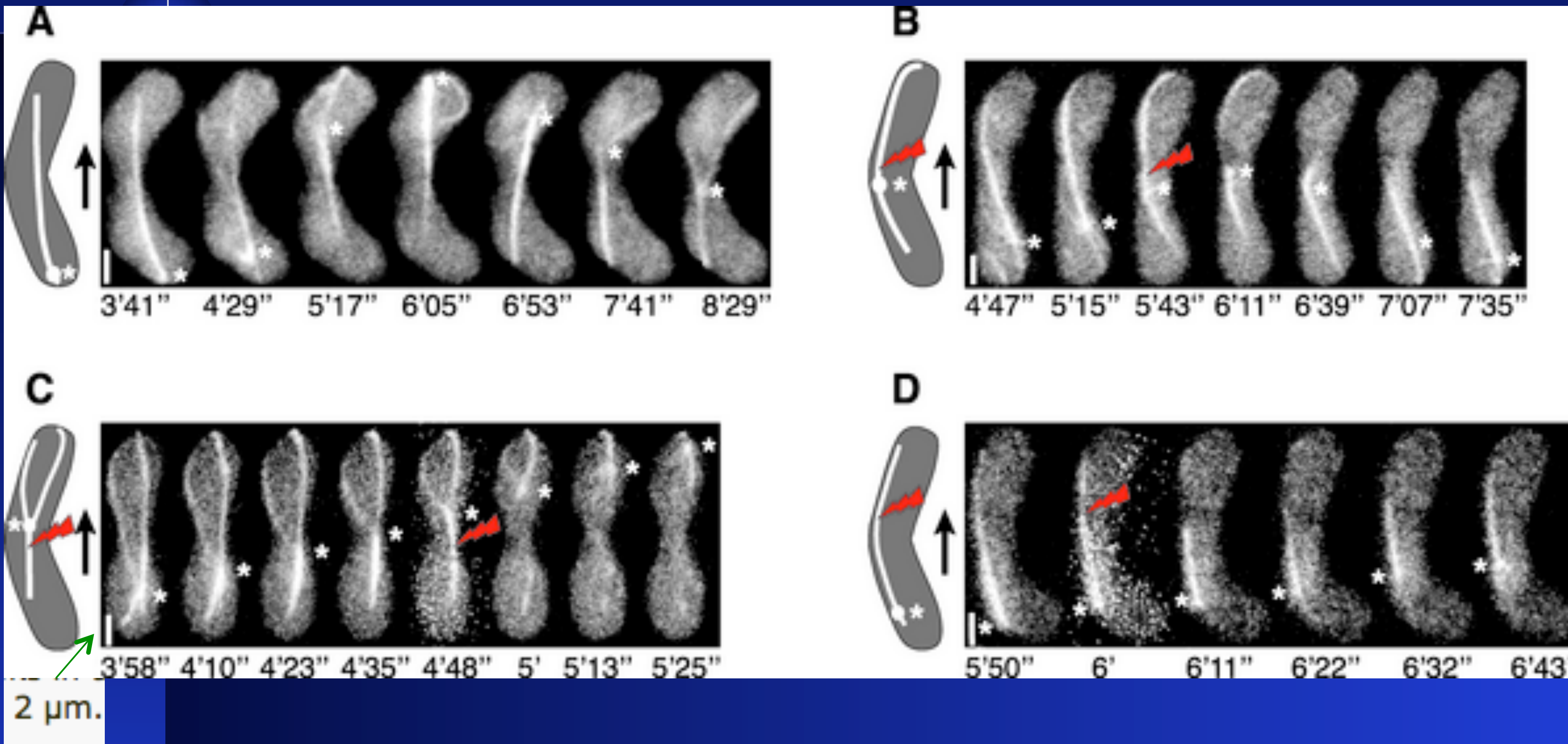


Oscillations of spindle pole body



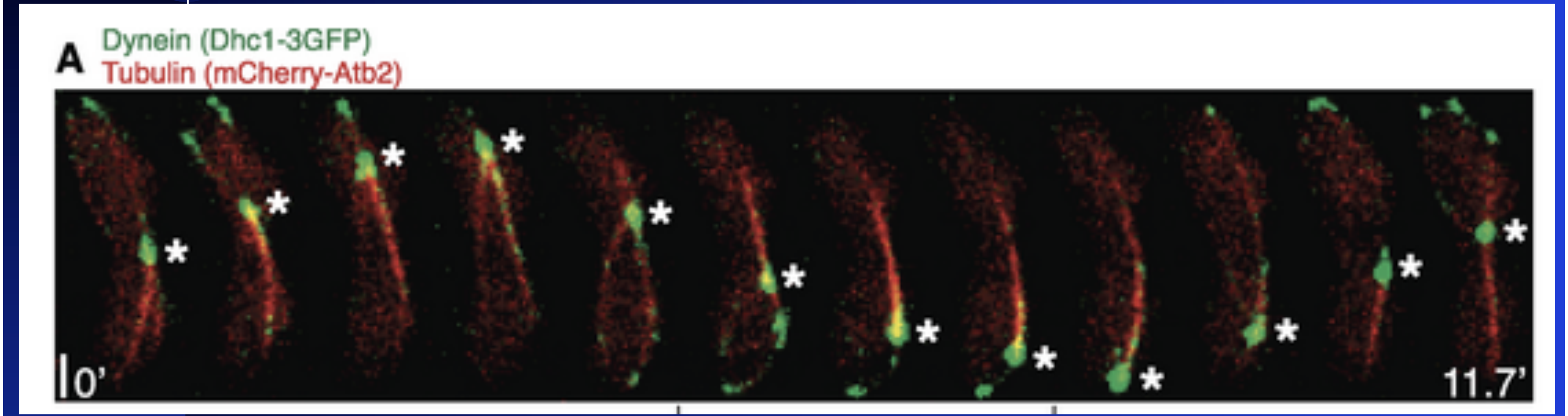
Vogel SK, Pavin N, Maghelli N, Jülicher F, Tolić-Nørrelykke IM (2009). PLoS Biol 7 (4): e1000087. doi:10.1371/journal.pbio.1000087

Laser ablation experiments



Vogel SK, Pavin N, Maghelli N, Jülicher F, Tolić-Nørrelykke IM (2009). PLoS Biol 7 (4): e1000087. doi:10.1371/journal.pbio.1000087

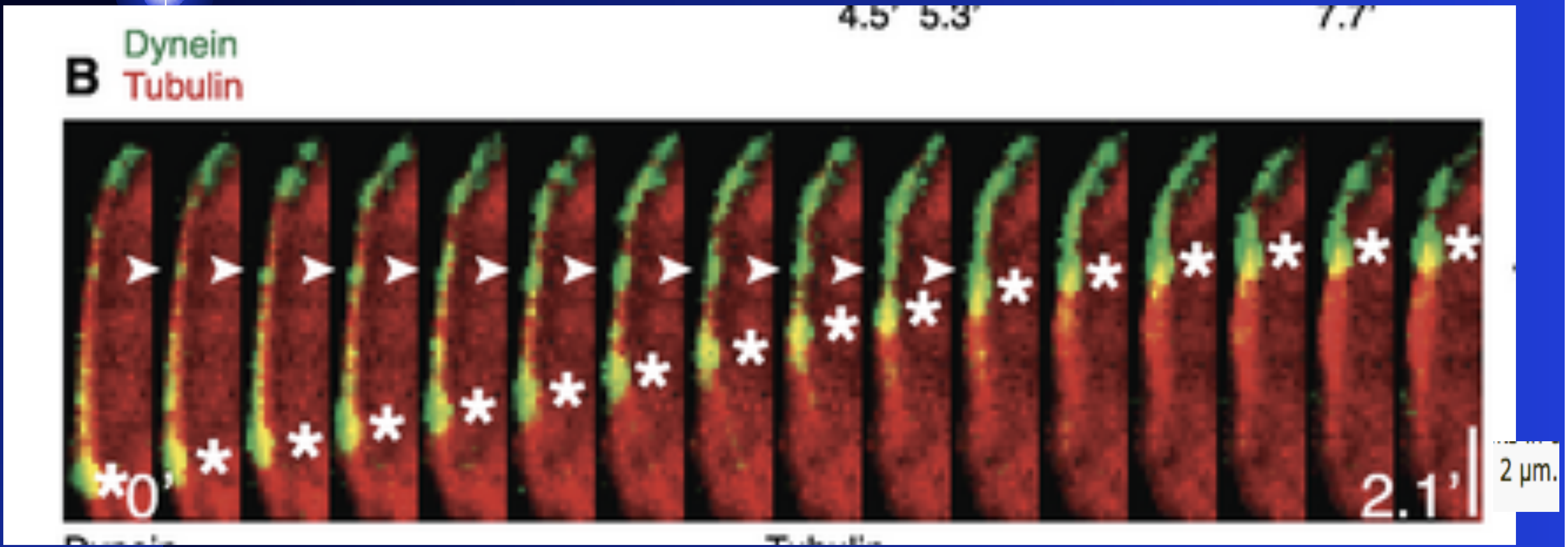
Dynein stronger on leading MT



Time in min

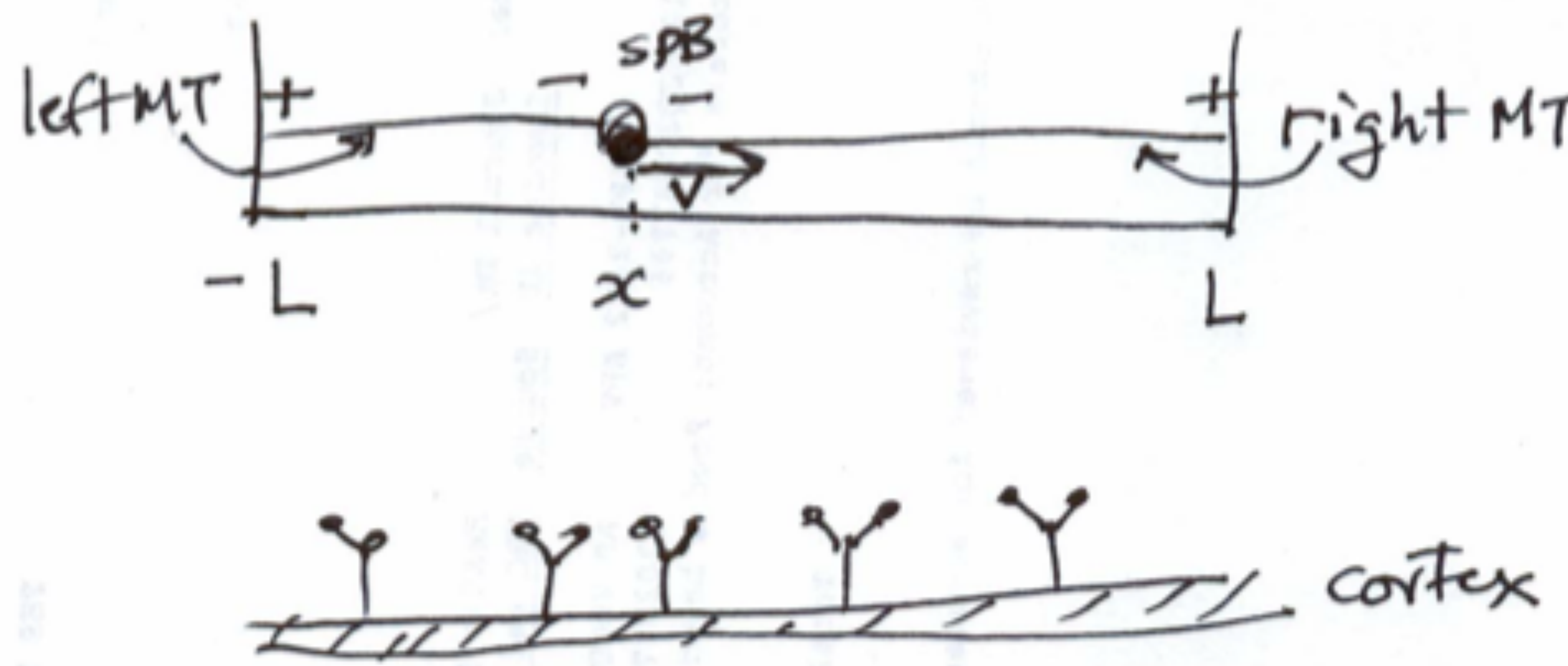
Vogel SK, Pavin N, Maghelli N, Jülicher F, Tolić-Nørrelykke IM (2009. PLoS Biol 7 (4): e1000087. doi:10.1371/journal.pbio.1000087

Dynein also attached to cortex

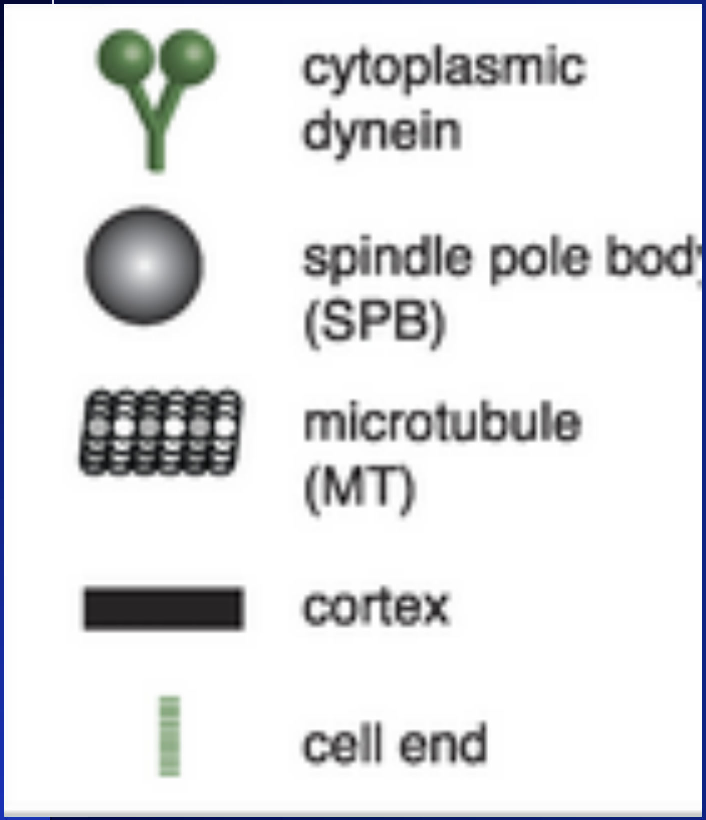


Vogel SK, Pavin N, Maghelli N, Jülicher F, Tolić-Nørrelykke IM (2009. PLoS Biol 7 (4): e1000087. doi:10.1371/journal.pbio.1000087

1D model



Bits and pieces

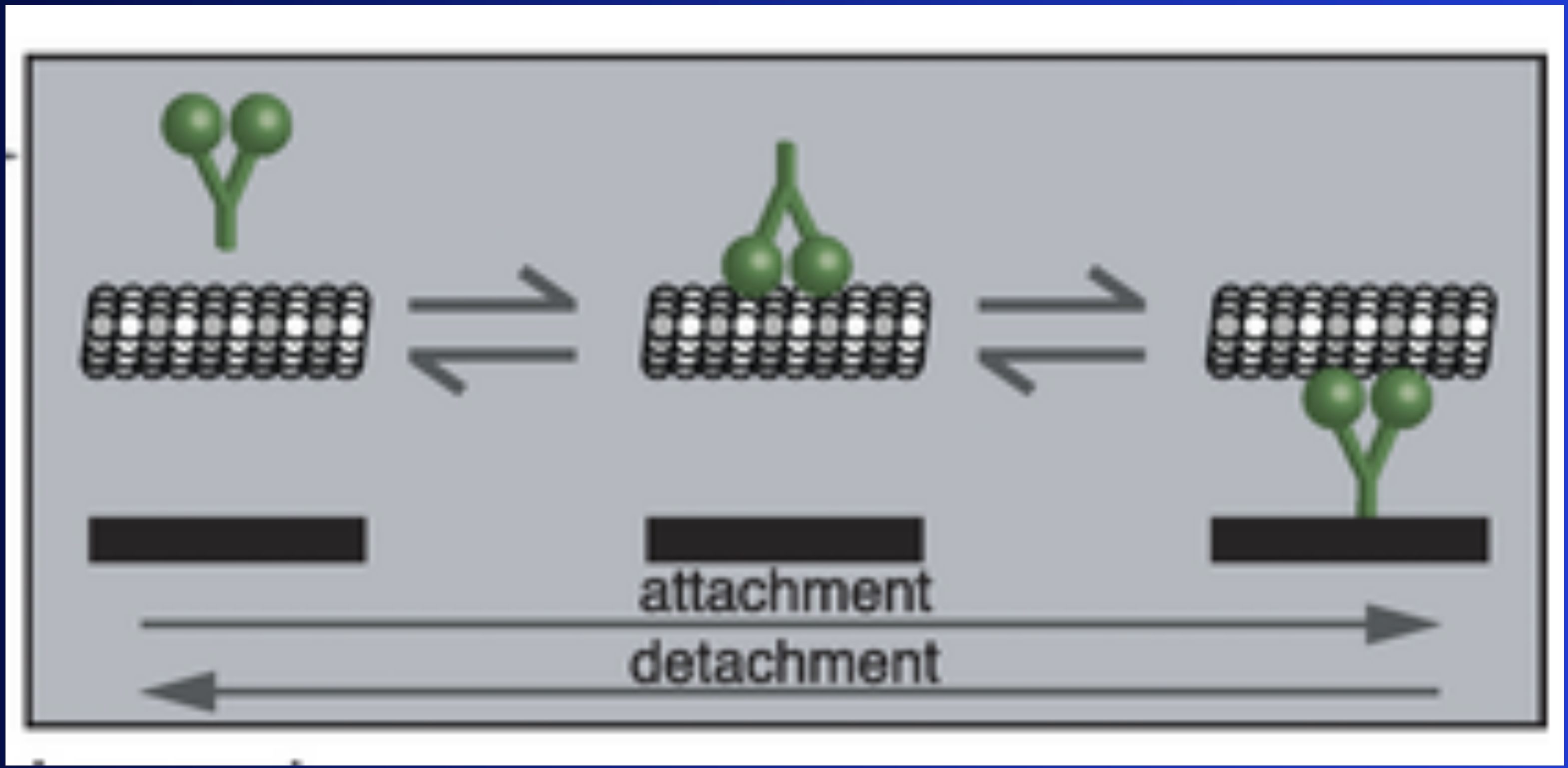


Vogel SK, Pavin N, Maghelli N, Jülicher F, Tolić-Nørrelykke IM (2009. PLoS Biol 7 (4): e1000087. doi:10.1371/journal.pbio.1000087

Dynein attachment-detachment

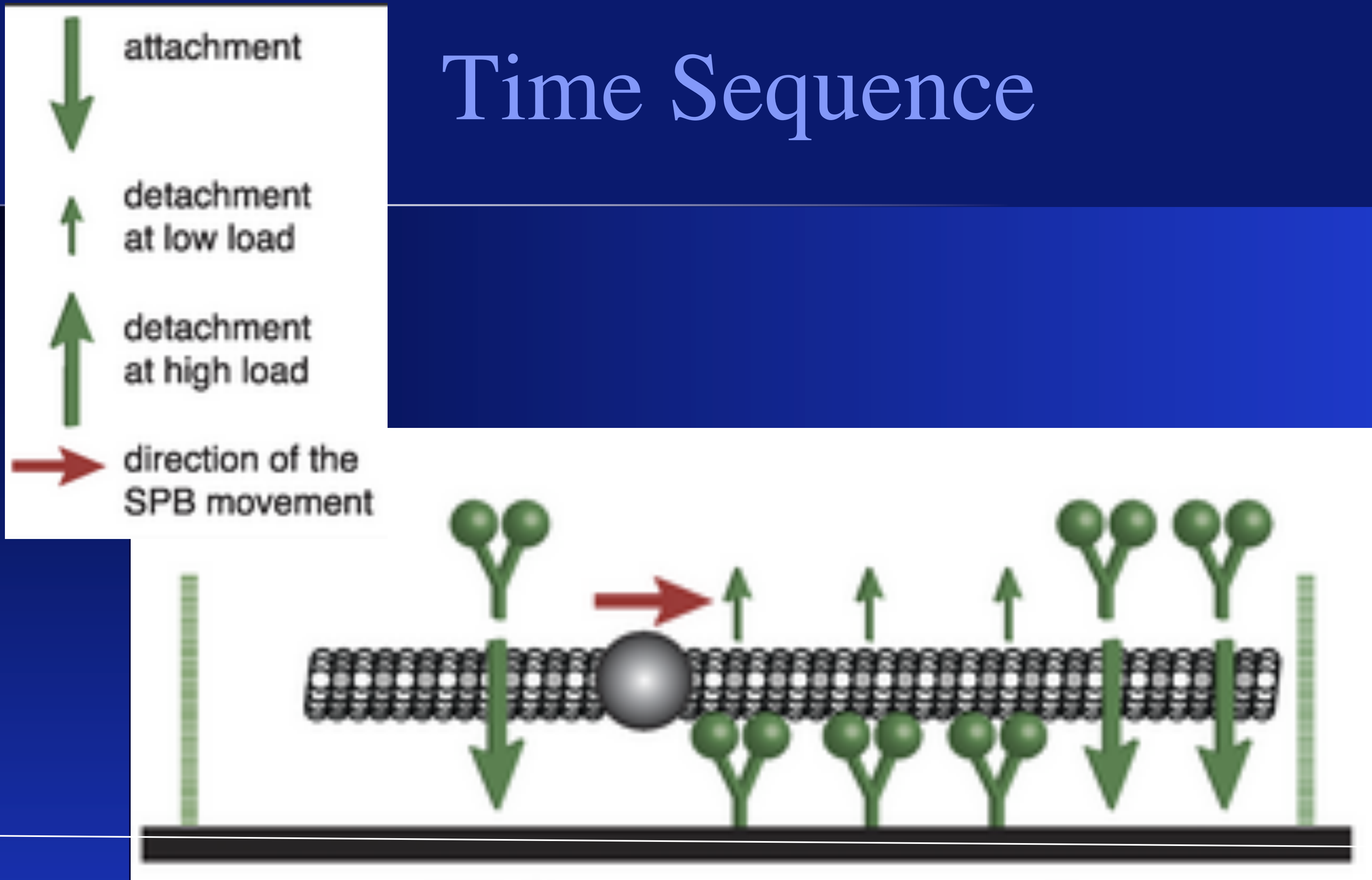
MT

cortex



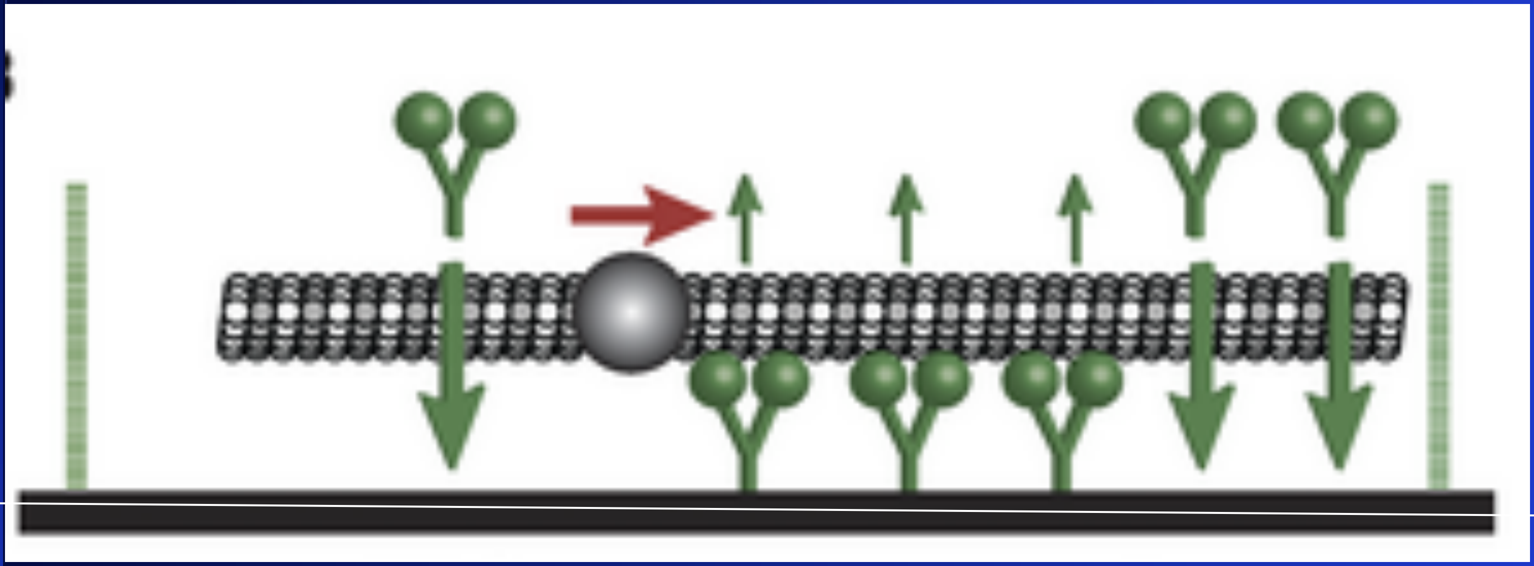
Vogel SK, Pavin N, Maghelli N, Jülicher F, Tolić-Nørrelykke IM (2009. PLoS Biol 7 (4): e1000087. doi:10.1371/journal.pbio.1000087

Time Sequence



Vogel SK, Pavin N, Maghelli N, Jülicher F, Tolić-Nørrelykke IM (2009. PLoS Biol 7 (4): e1000087. doi:10.1371/journal.pbio.1000087

(1)



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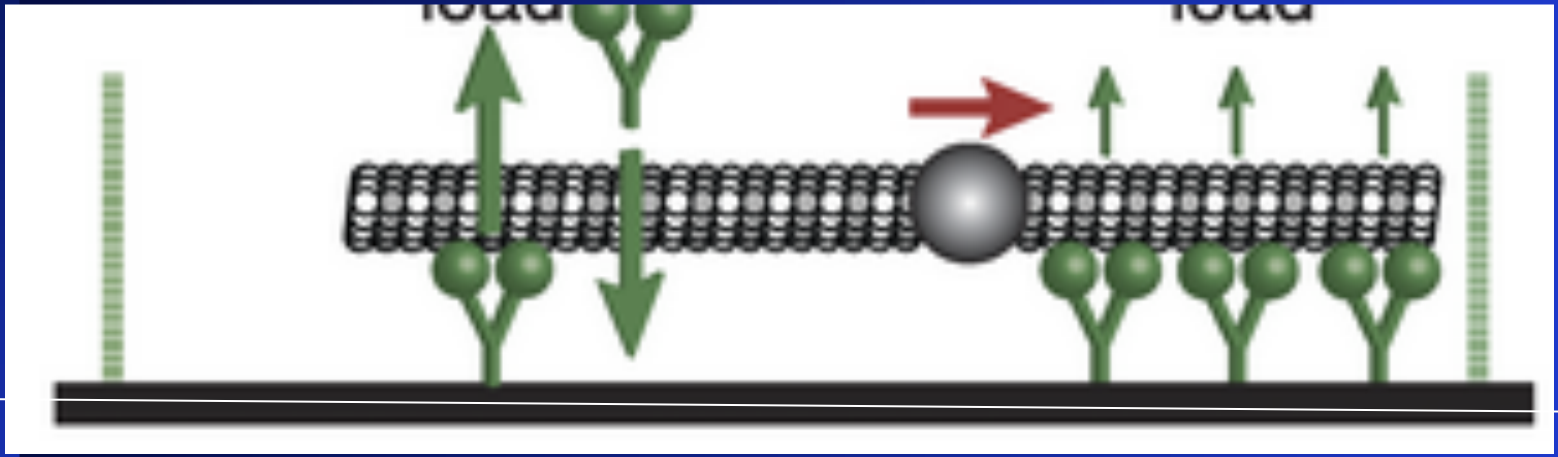
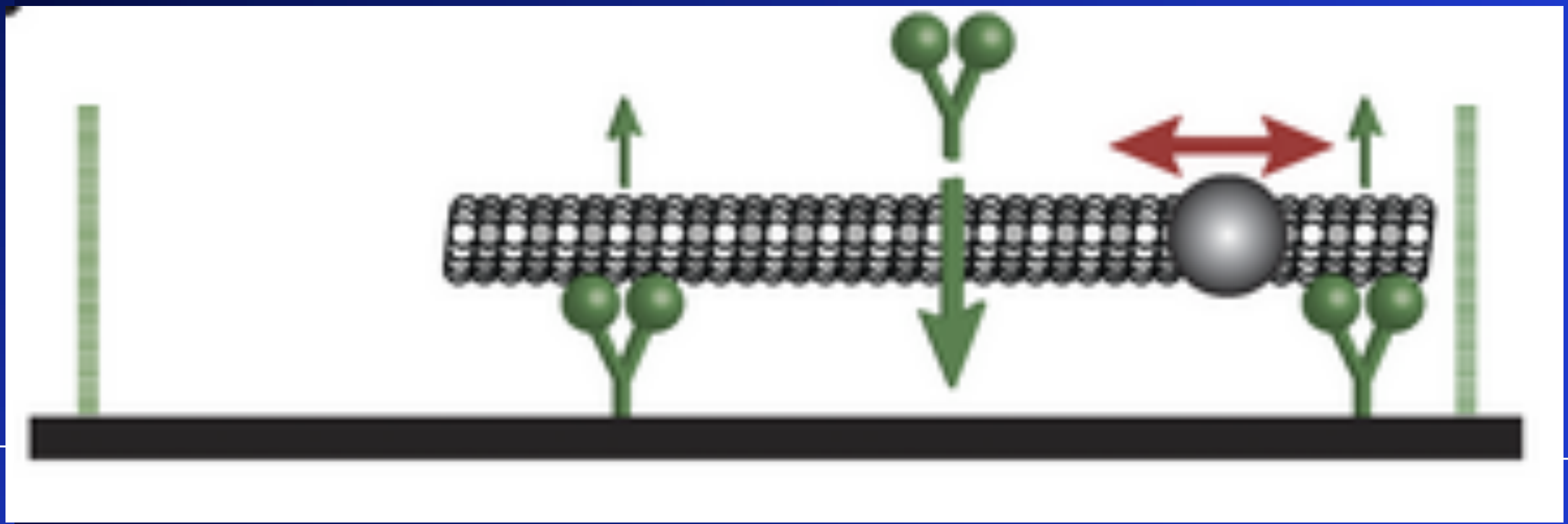
(2)



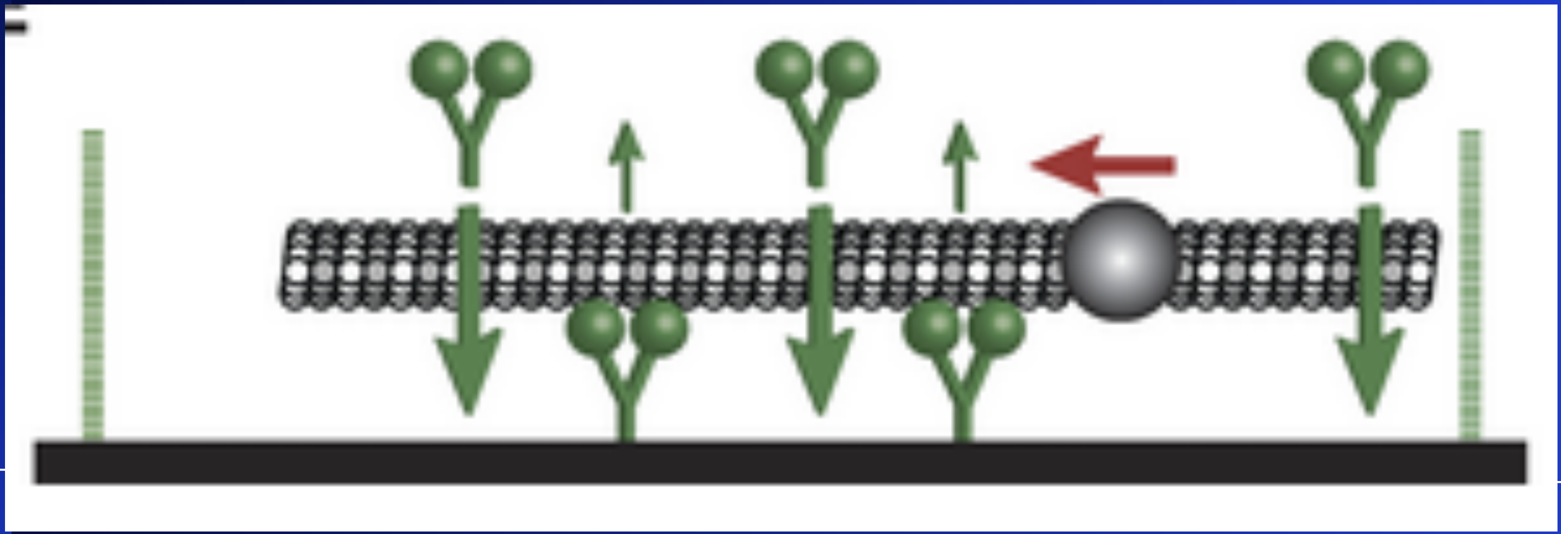
Vogel SK, Pavin N, Maghelli N, Jülicher F, Tolić-Nørrelykke IM (2009. PLoS Biol 7 (4): e1000087. doi:10.1371/journal.pbio.1000087

(3)



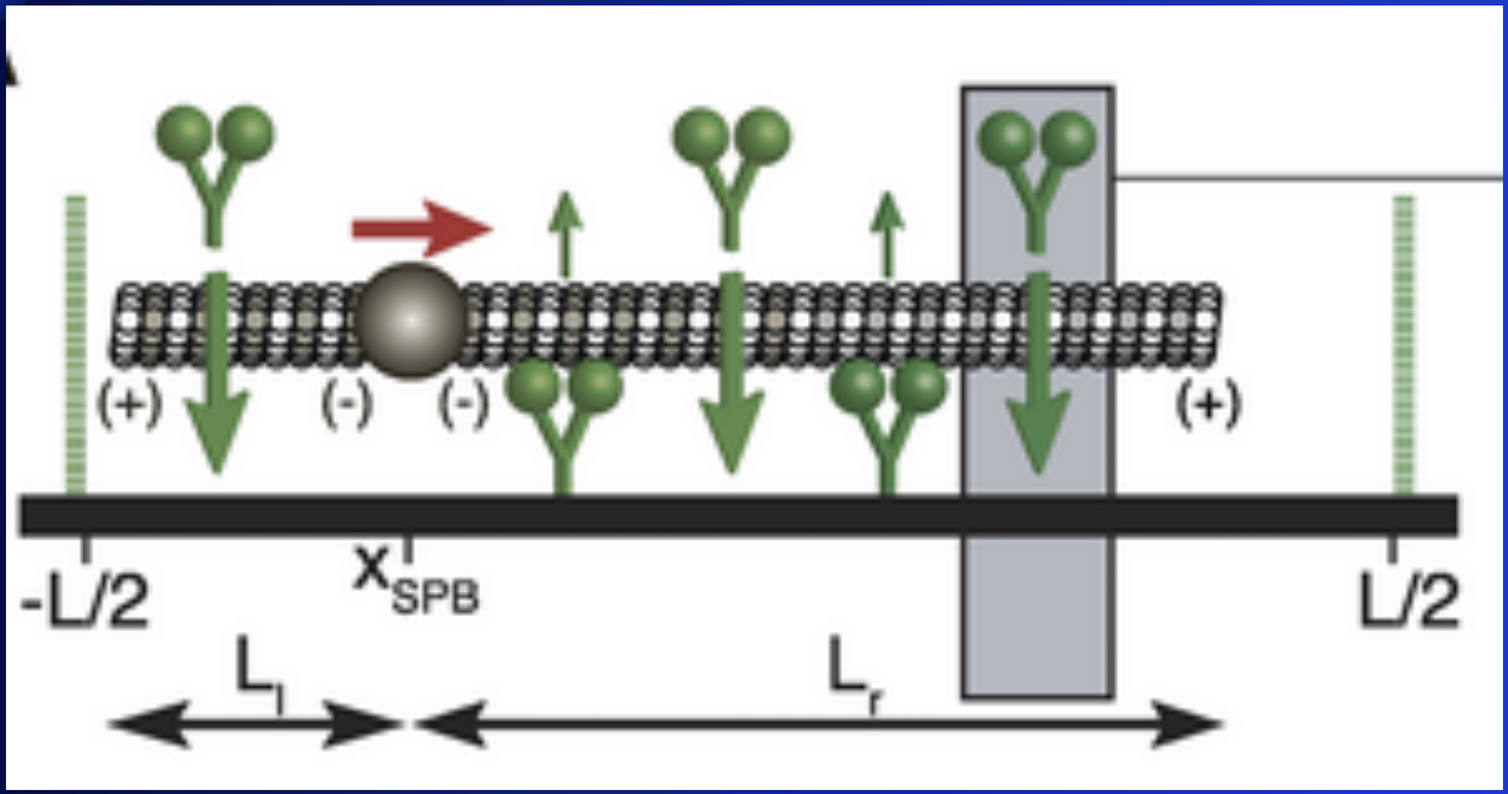
Vogel SK, Pavin N, Maghelli N, Jülicher F, Tolić-Nørrelykke IM (2009. PLoS Biol 7 (4): e1000087. doi:10.1371/journal.pbio.1000087

(4)



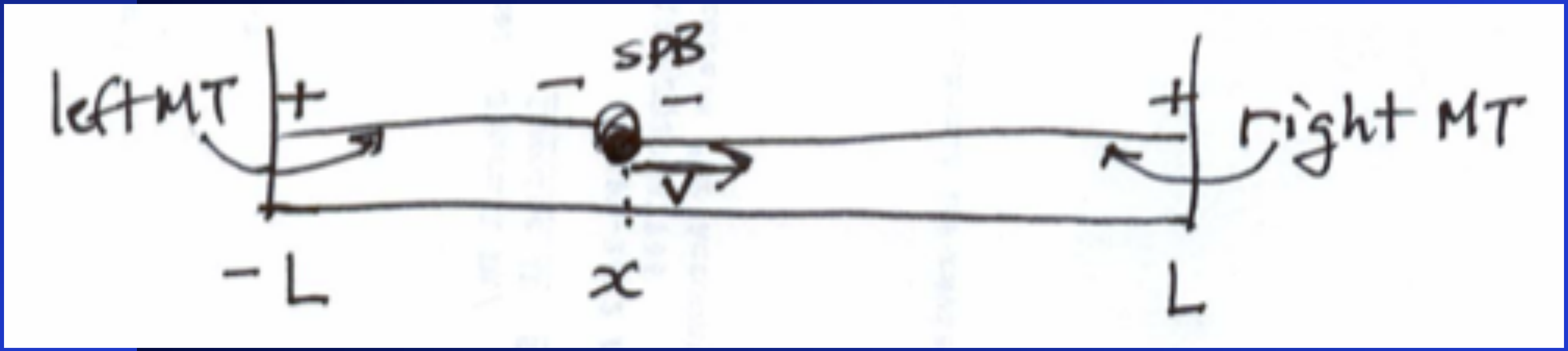
Vogel SK, Pavin N, Maghelli N, Jülicher F, Tolić-Nørrelykke IM (2009. PLoS Biol 7 (4): e1000087. doi:10.1371/journal.pbio.1000087

Model



Vogel SK, Pavin N, Maghelli N, Jülicher F, Tolić-Nørrelykke IM (2009. PLoS Biol 7 (4): e1000087. doi:10.1371/journal.pbio.1000087

N_r = number of dynein motors attached to right MT,
N_l = number of dynein motors attached to left MT
N = Number of motors per unit length attached to cortex.
X =position of the spindle body.



Forces and motors

$$F_l = \text{Net force to left,}$$
$$F_r = \text{Net force to right}$$

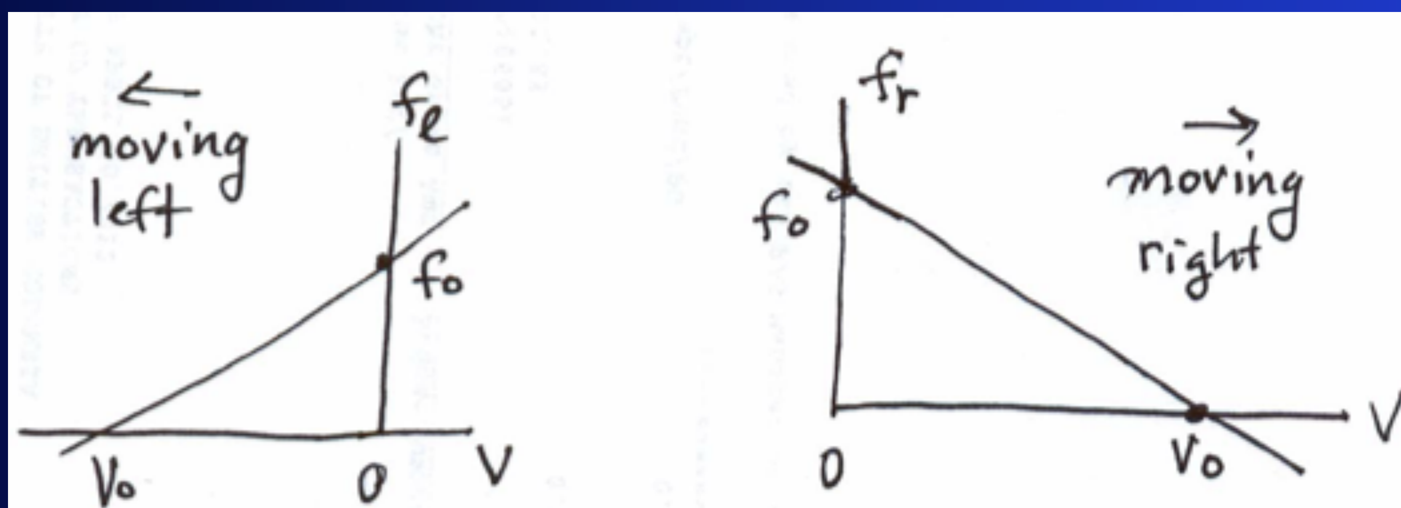
$$f_l = \text{force per motor to left,}$$
$$f_r = \text{force per motor to right}$$

$$F_l = N_l f_l, \quad F_R = N_r f_r$$

Motors' force-velocity relation

$$f_l = f_0\left(1 - \frac{V}{V_0}\right),$$

$$f_r = f_0\left(1 + \frac{V}{V_0}\right)$$



Load force causes motors to unbind faster

$$k_{off} = k^0_{off} \exp\left(\frac{f_{r,l}\delta}{E_0}\right) = k \exp\left(\frac{f_{r,l}}{f_d}\right)$$

$$\frac{dN_r}{dT} = k(\underbrace{N(L-x) - N_r}_{\text{Unattached motors available to bind}}) - k\exp(f_r/f_d))\underbrace{N_r}_{\text{Attached motors}}$$

= Rate of binding – Rate of unbinding

Force balance on SPB

Net force due to all motors pulling left and right (neglecting inertial terms, as usual).

$$\xi \frac{dX}{dT} = F = F_r - F_l = N_r f_r - N_l f_l$$

Position of SPB:

$$\frac{dX}{dT} = \frac{F}{\xi} = \frac{1}{\xi}(N_r f_r - N_l f_l)$$

Full model

$$\frac{dN_r}{dT} = k(N(L-x) - N_r) - k\exp(f_r/f_d))N_r$$

$$\frac{dN_l}{dT} = k(N(L+x) - N_l) - k(\exp(f_l/f_d)N_l$$

$$\frac{dX}{dT} = \frac{F}{\xi} = \frac{1}{\xi}(N_r f_r - N_l f_l)$$

Scaled equations

$$x = \frac{X}{L}, \quad v = \frac{V}{V_0}, \quad t = \frac{V_0 T}{L}, \quad n_{r,l} = \frac{N_{r,l}}{NL}$$

$$w\frac{dn_r}{dt} = (1-x) - n_r(1+\exp(\epsilon(1-v)))$$
$$w\frac{dn_l}{dt} = (1+x) - n_l(1+\exp(\epsilon(1+v)))$$
$$\frac{dx}{dt} = v, \quad v = \frac{n_r - n_l}{\lambda + n_r + n_l}$$

Two dimensionless parameters:

$$\epsilon = \frac{f_0}{f_d}, \quad w = \frac{V_0}{kL}$$

Values

Typical values

$$f_0 \approx 1\text{pN}, \quad \xi \approx 30\text{pN sec}/(\mu\text{m}), \quad V_0 \approx 0.1\mu\text{m}/\text{sec},$$

$$N \approx 30, \quad L \approx 1\mu\text{m}, \quad k \approx 1/\text{sec}$$

Dimensionless parameter values are then

$$\epsilon \approx 1, \quad w \approx 0.1 \ll 1, \quad \lambda \approx 0.1 \ll 1.$$

XPP file

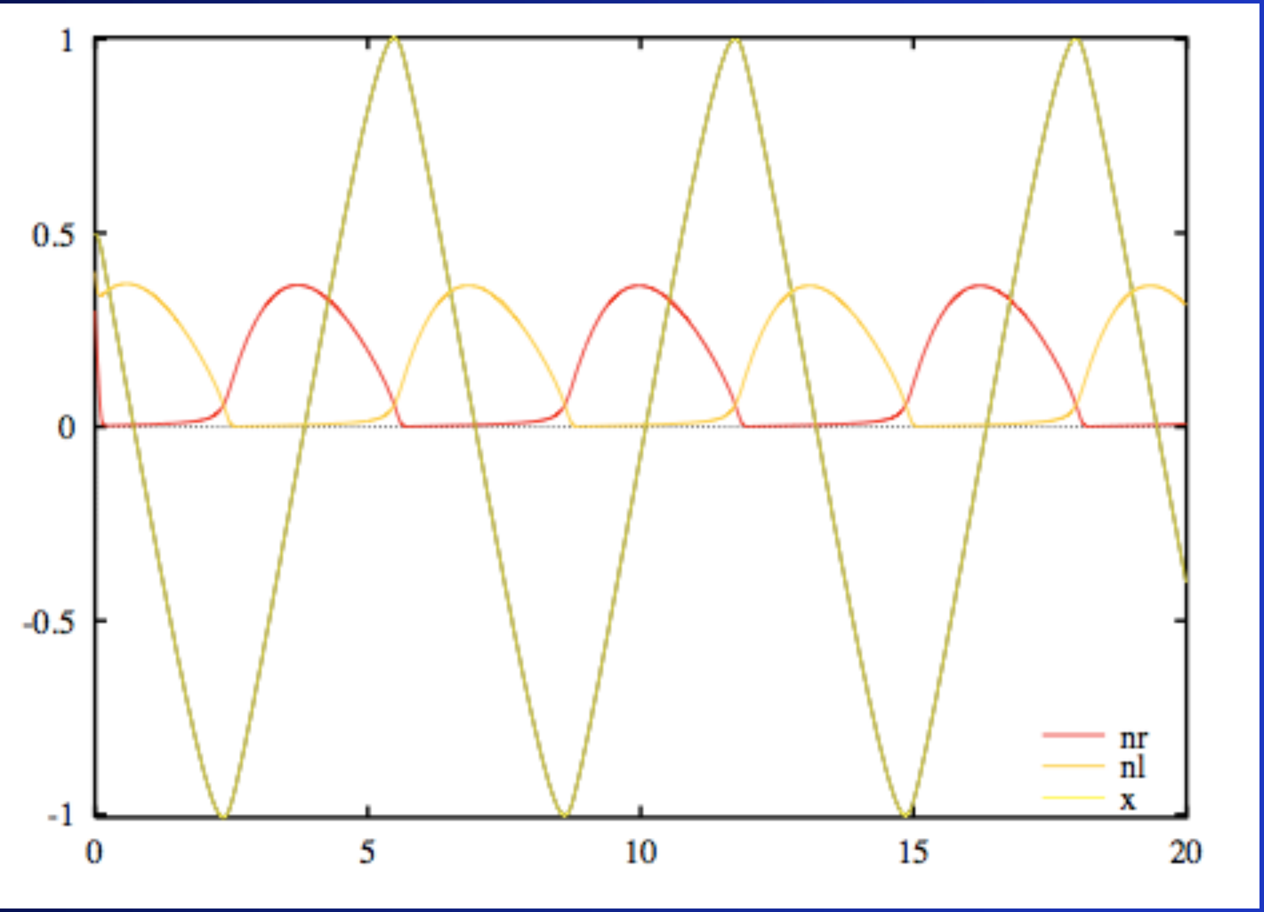
```
#MTVogelMogilner.ode
#Vogel MT simplified by Alex Mogilner
#simulates dimensionless model with
# nl motors pulling left
# and
# nr motors pulling right
# with k_off depending on the load force per motor


# x= position of the SPB (spindle pole body)

nr'=(1/w)*(1-x-nr*(1+exp(eps*(1-v(nr,nl)))))
nl'=(1/w)*(1+x-nl*(1+exp(eps*(1+v(nr,nl)))))
x'=(nr-nl)/(lam+nr+nl)
v(p,q)=(p-q)/(lam+p+q)

init nr=0.3,nl=0.4,x=0.5
par w=3,eps=3,lam=0.1
@ dt=0.01
done
```

Simulations



Time