Multiple Scales in Molecular Motor Models

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2.28.2013

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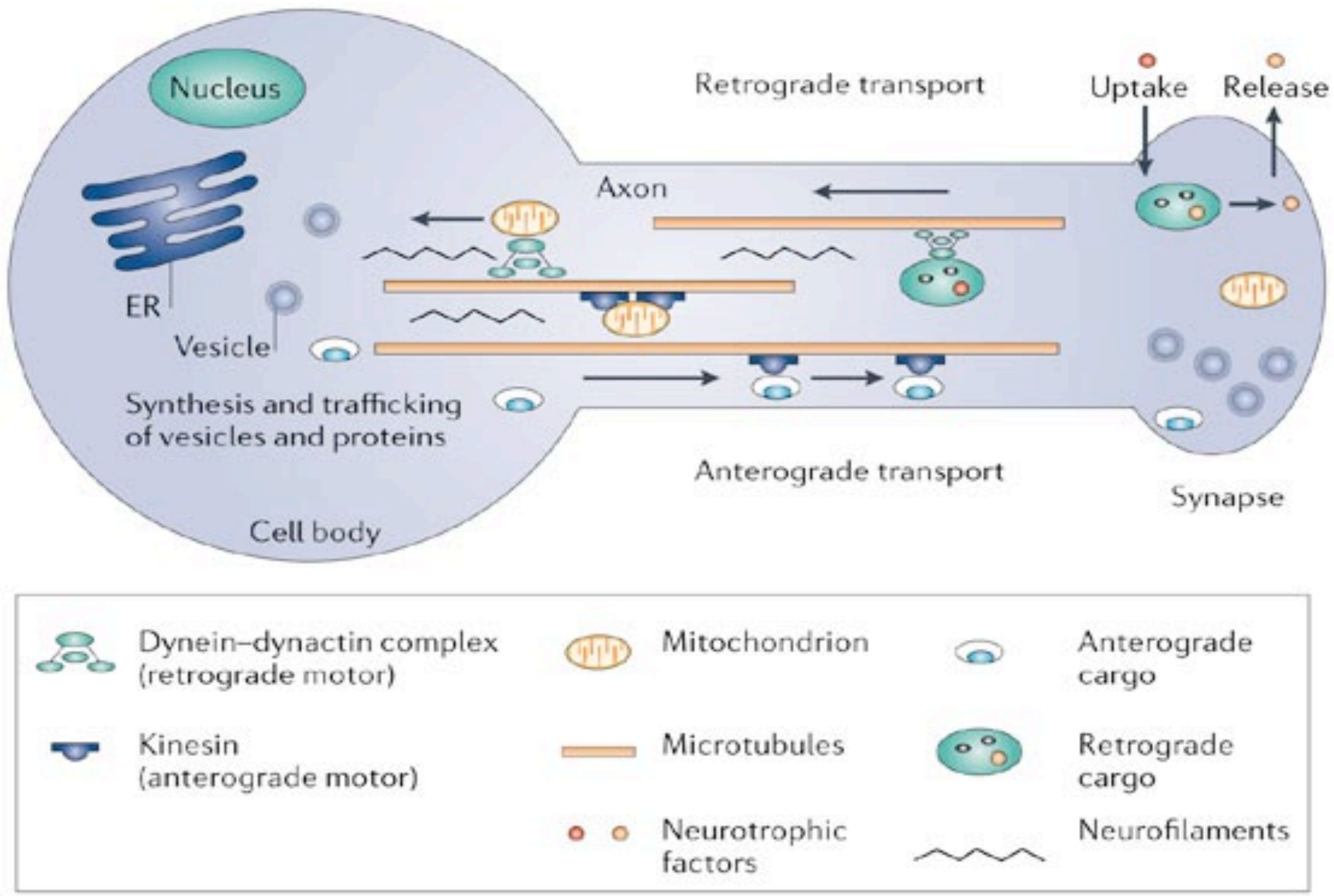
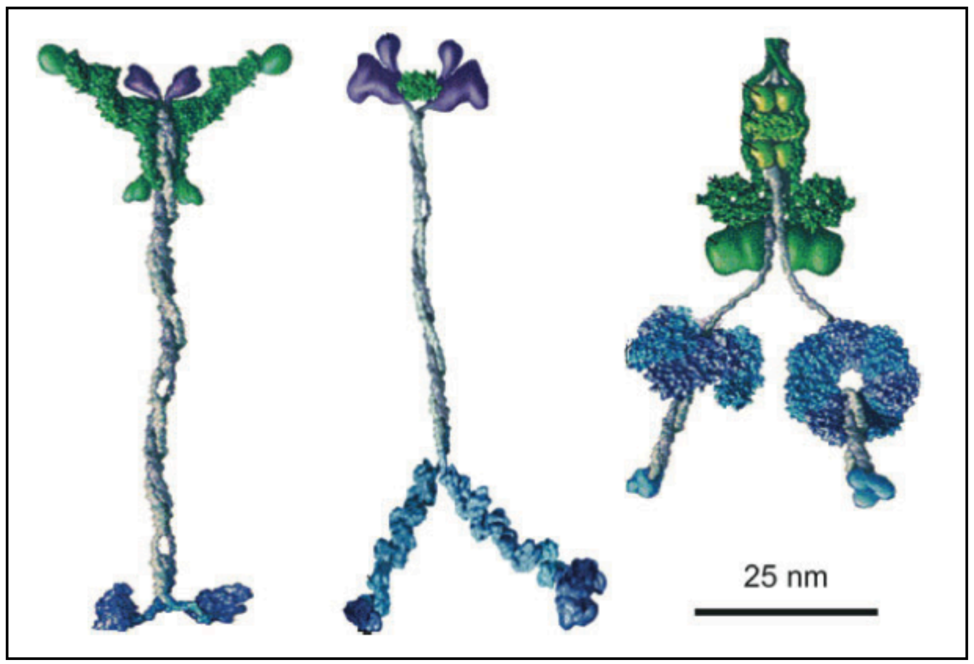
Microtubule-based Transport



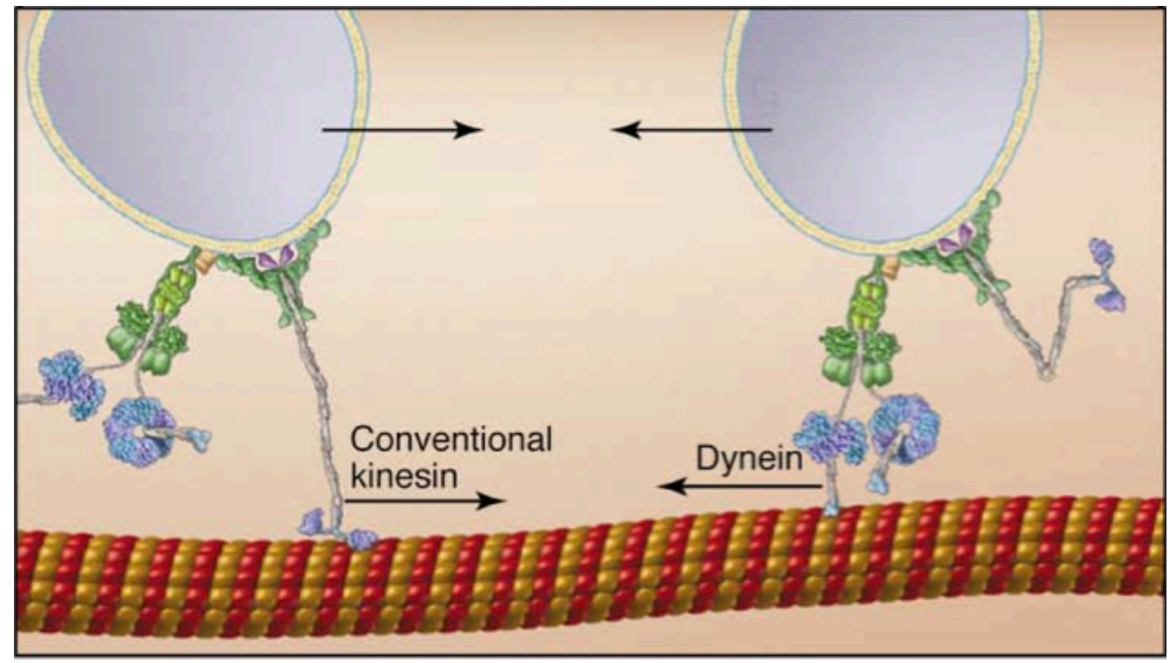
Nature Reviews | Neuroscience

Pasinelli and Brown *Nature Reviews Neuroscience* **7**, 710–723 (September 2006) | doi:10.1038/nrn1971

Examples of Motors

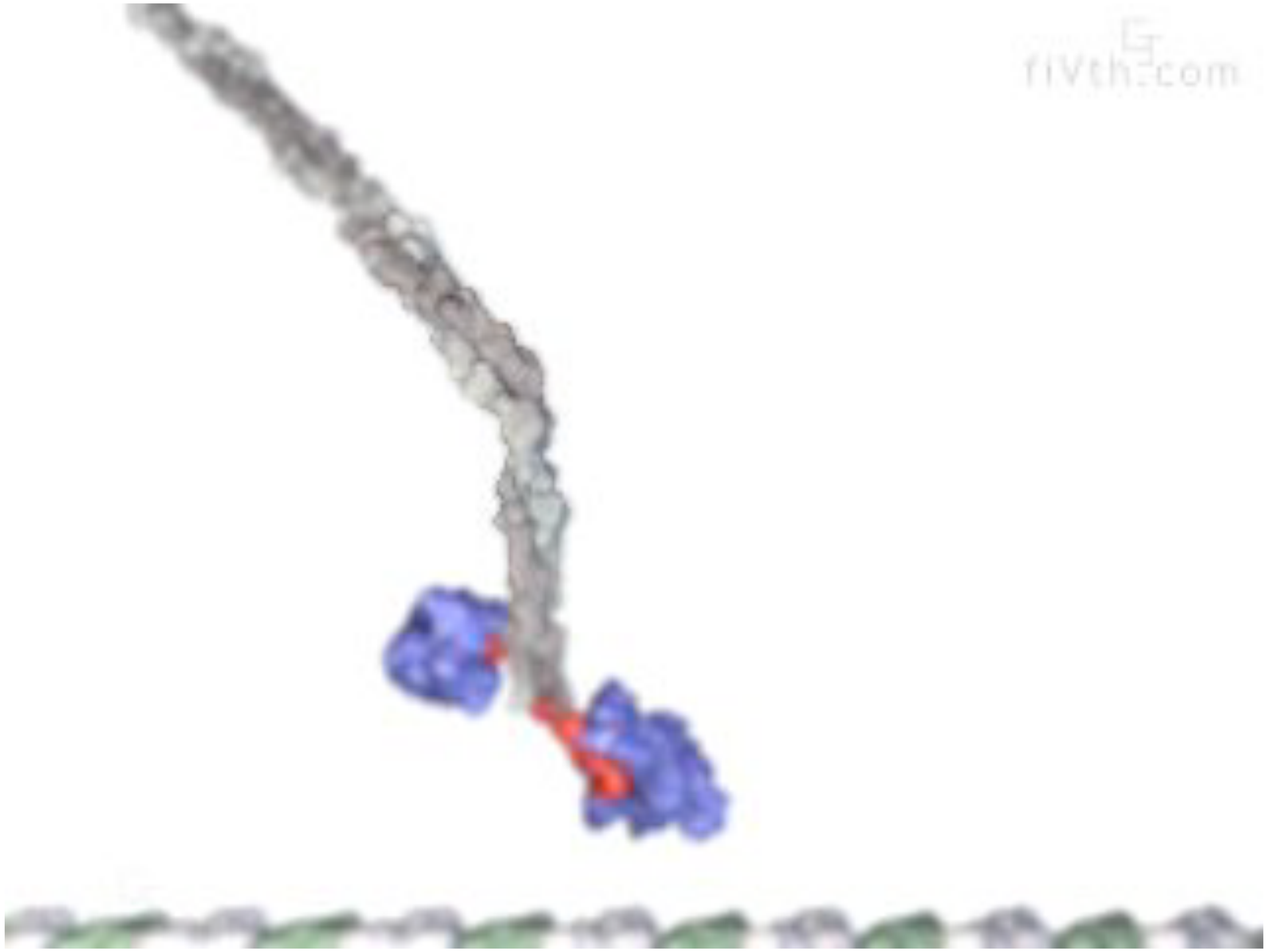


A Kolomeisky, M Fisher, Ann Rev Phys Chem, 2007



R Vale, Cell, 2003

Kinesin Dynamics



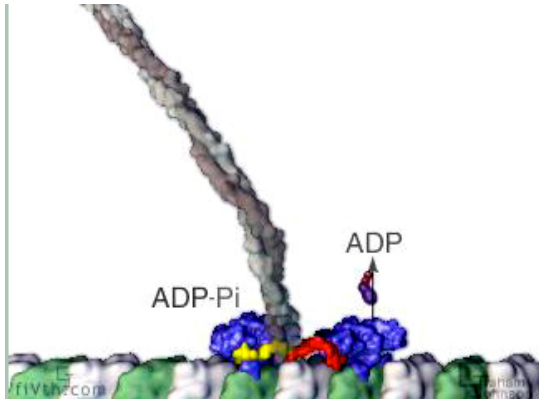
Vale lab, web video
http://valelab.ucsf.edu/

Scales

- nanoscale

- mesoscale: tens of nanometers to micron

- microscale: microns to centimeters



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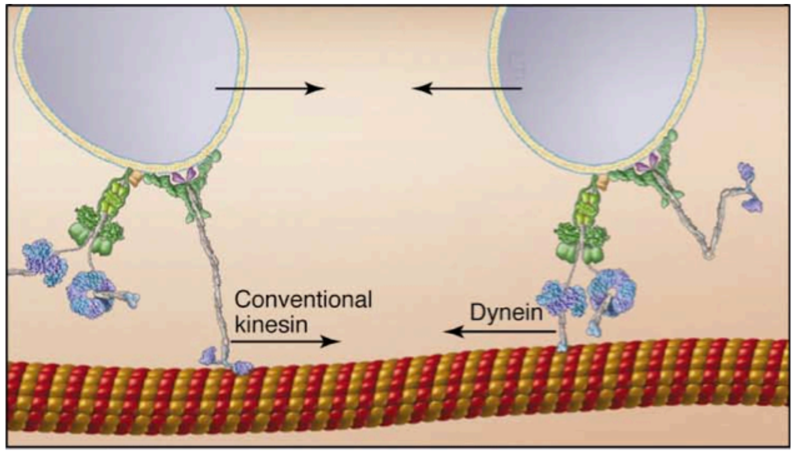
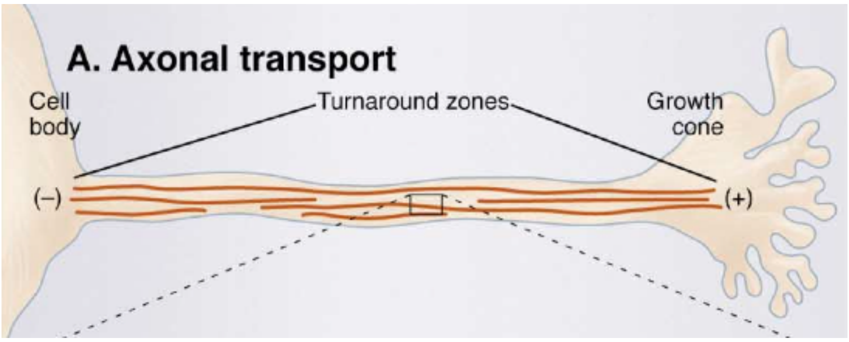


R Vale, Cell, 2003



S Gross, Phys. Biol., 2004

Why?

- When an axon is severed, it must be regenerated from a dendrite.

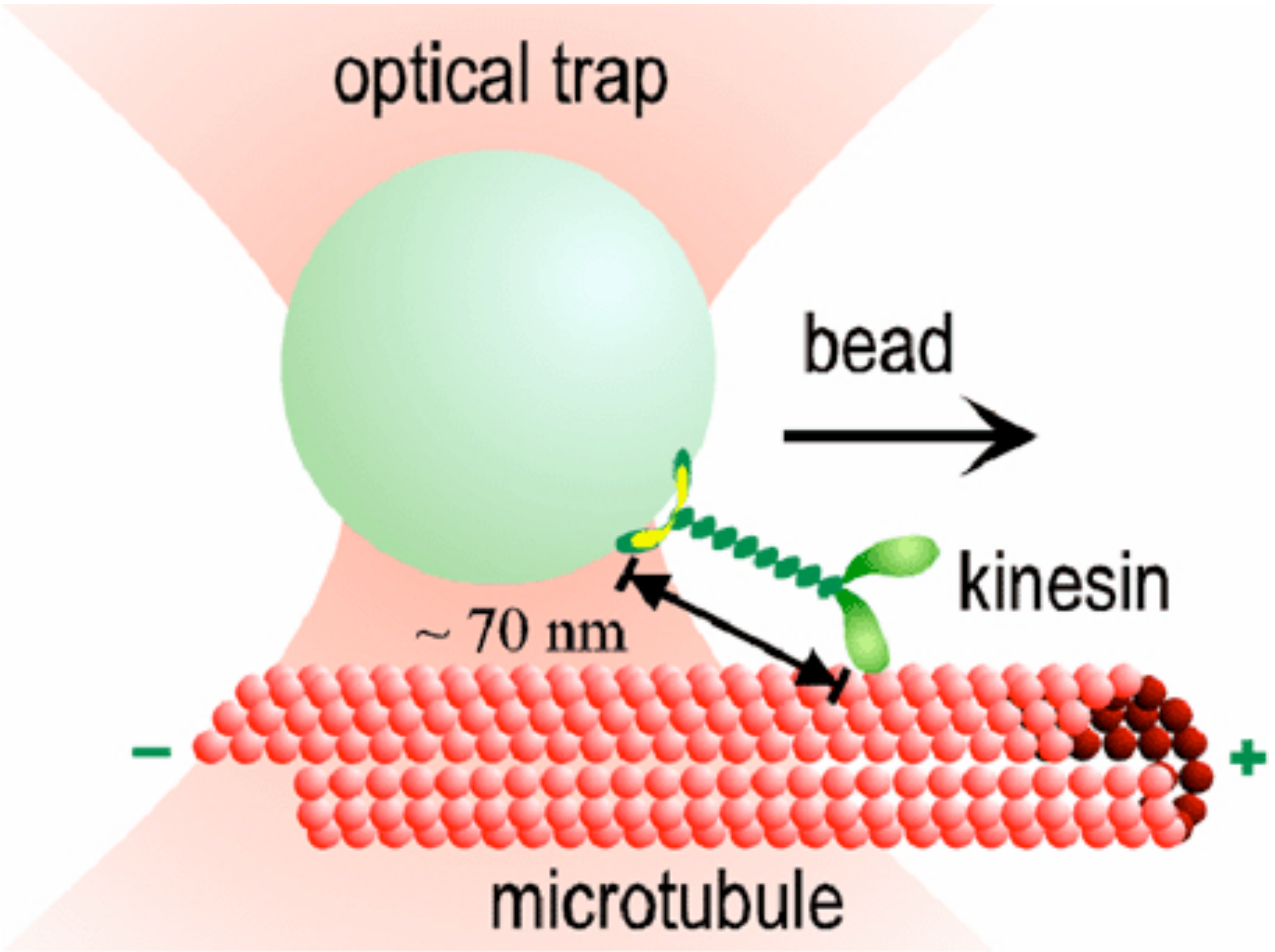
- The microtubules near the regeneration site realign in a mixed polarity.

- What effect does this have on kinesin-dynein transport? Is the effect on transport restorative?

Orientation

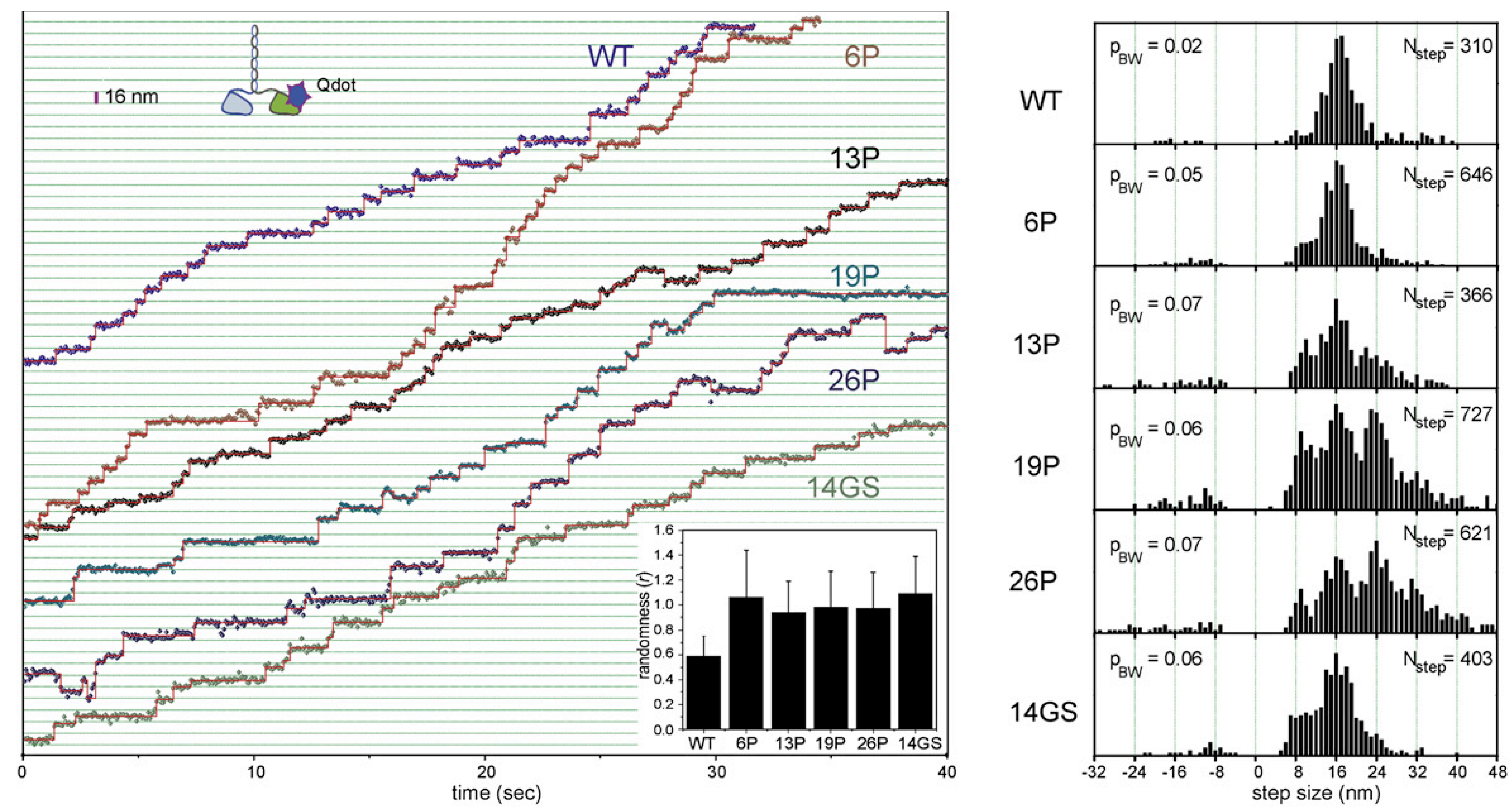
- How is the process regulated?
- At the nanoscale?
- Interactions up through the scales?
- Through MAPS, Post-translational modifications, etc?

Laser Trap



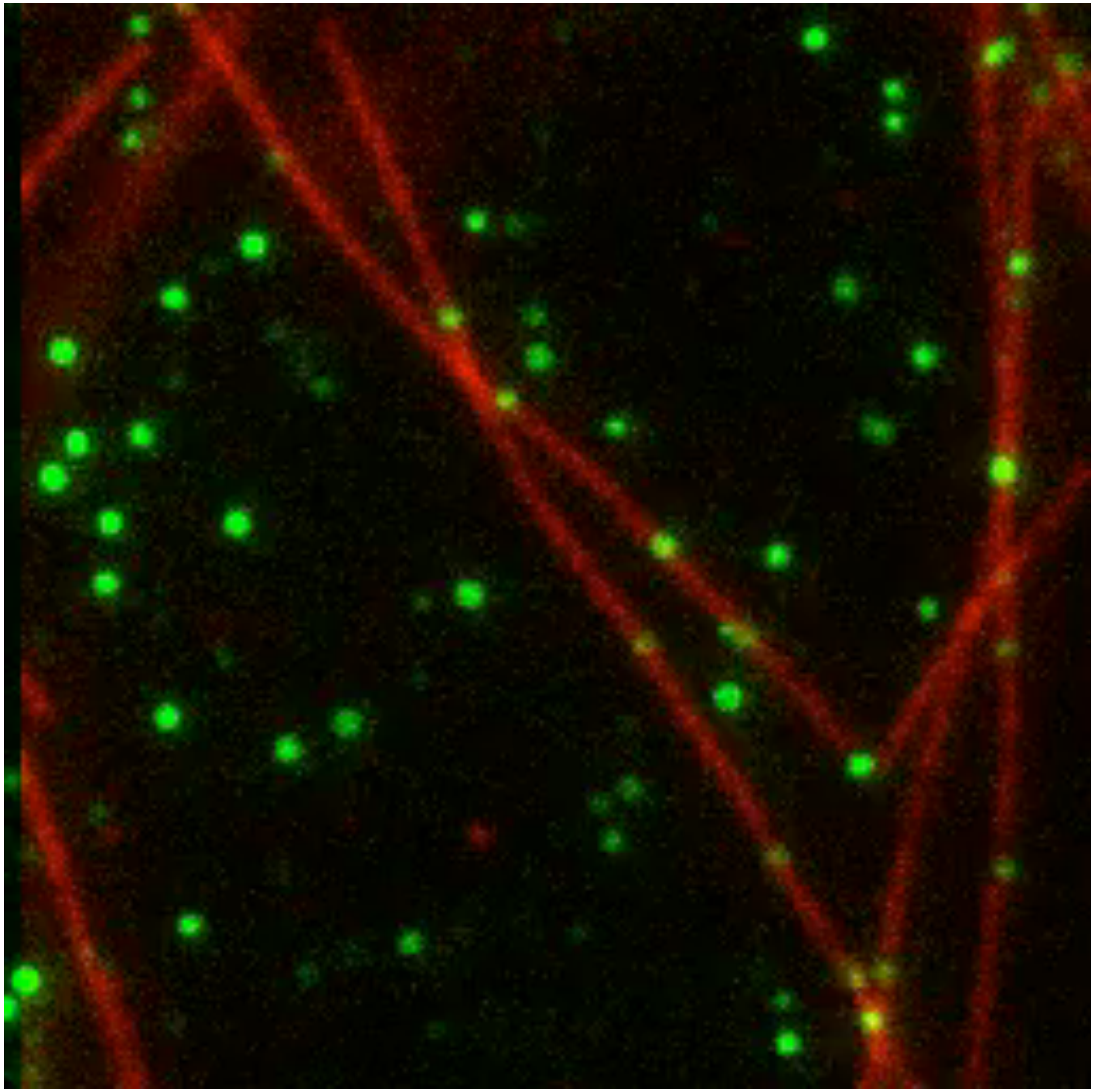
Block Lab:http://www.stanford.edu/group/blocklab/kinesin/kinesin.html

Yildiz et al.



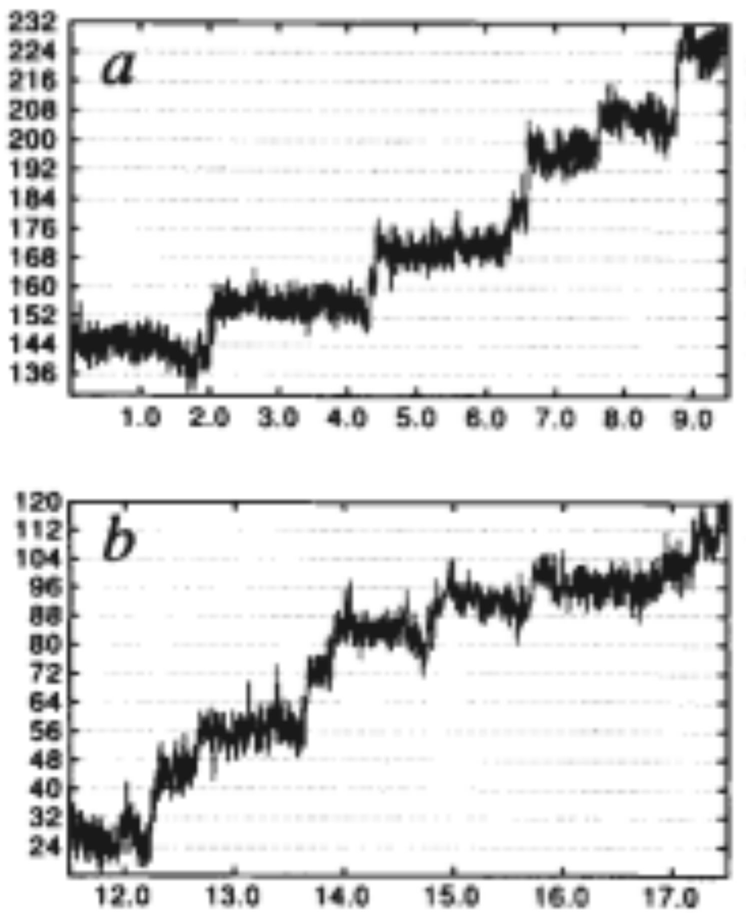
Yildiz, A. and Tomishige, M. and Gennerich, A. and Vale, R.D.

Fluorescence Experiment



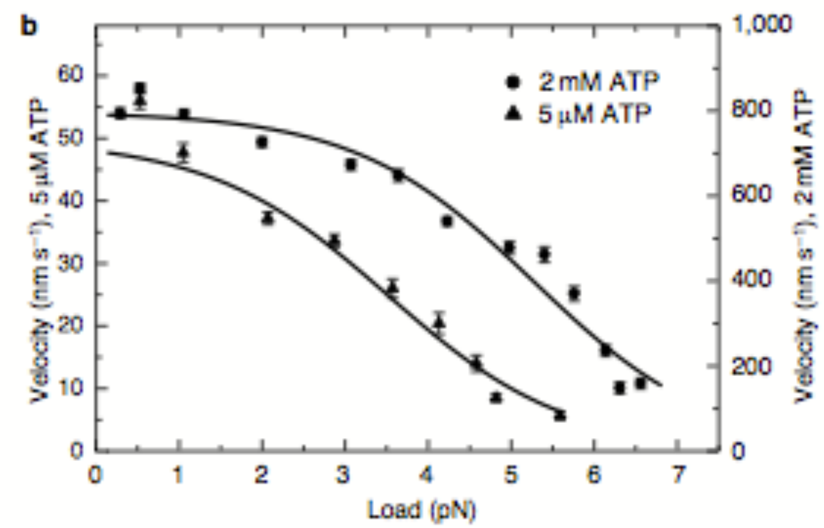
Data at Multiple Scales

Nanoscale



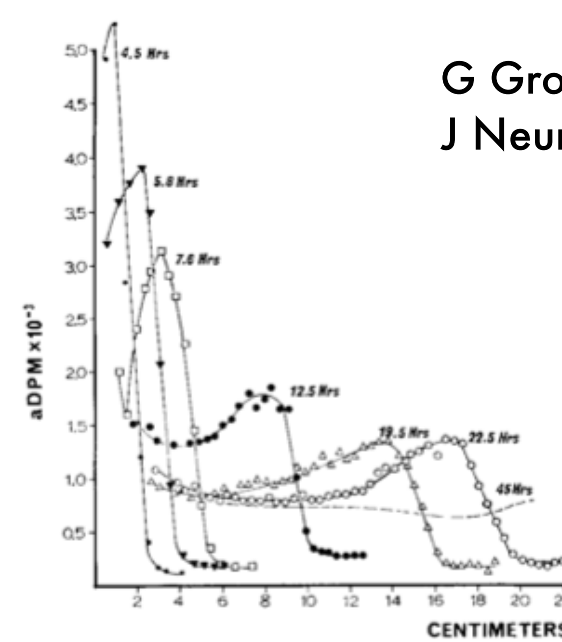
Svoboda et al, Nature, 1993

Mesoscale



M Schnitzer et al, Nature Cell Biology, 2000

>Microscale



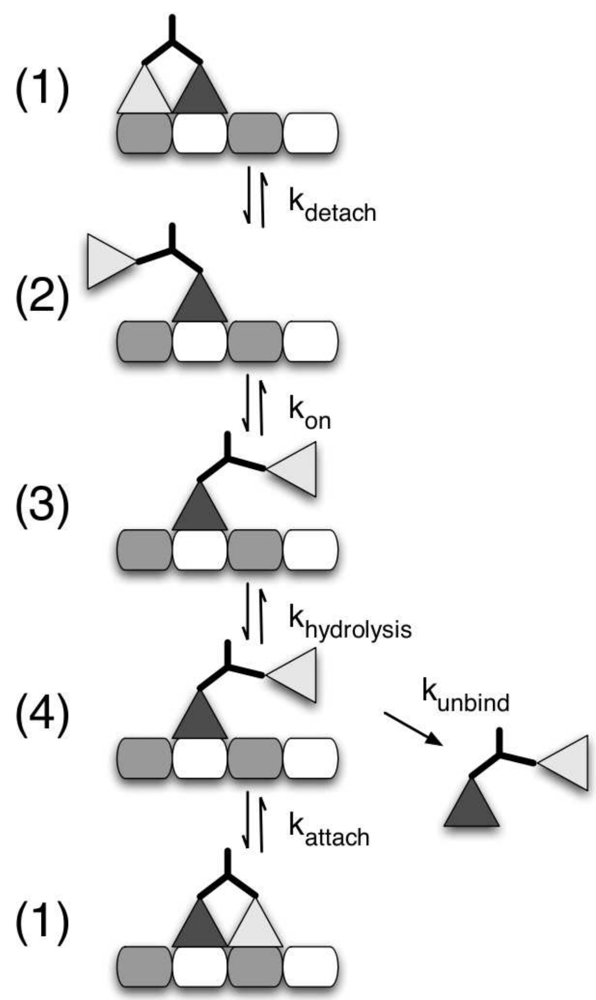
G Gross and L Beidler
J Neurobiology, 1975

Nanoscale to Mesoscale Perturbations

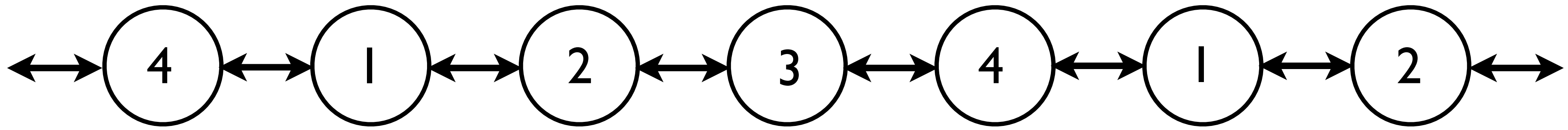
- Investigate Dynamics at Nanoscale.
- Example of Perturbation at Nanoscale.
- First Model. Intrastep Diffusion of Heads.
  - John Hughes, William O. Hancock, and John Fricks (2011). A Matrix Computational Approach to Kinesin Neck Linker Extension. *Journal of Theoretical Biology*. **269**, No. 1, 181-194.

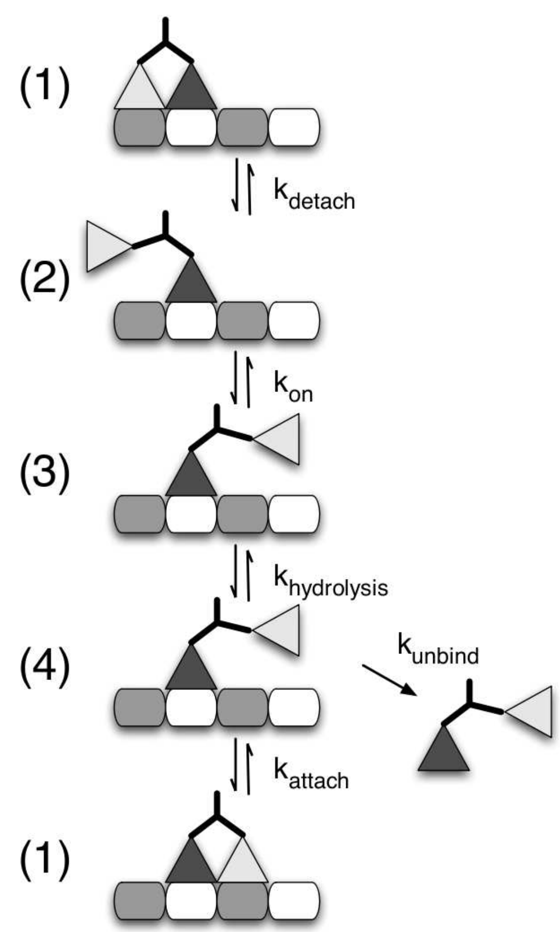
  - Matthew L. Kutys, John Fricks, and William O. Hancock (2010). Monte Carlo Analysis of Neck Linker Extension in Kinesin Molecular Motors. *PLoS Computational Biology*. **6**, No. 11.
- Second Model. Variable Length Stepping.
  - John Hughes, William O. Hancock, and John Fricks (2012). Kinesins with Extended Neck Linkers: A Chemomechanical Model for Variable-Length Stepping. *Bulletin of Mathematical Biology*. **74**, No. 5, 1066-1097.

Diffusion and Kinetics of a Step

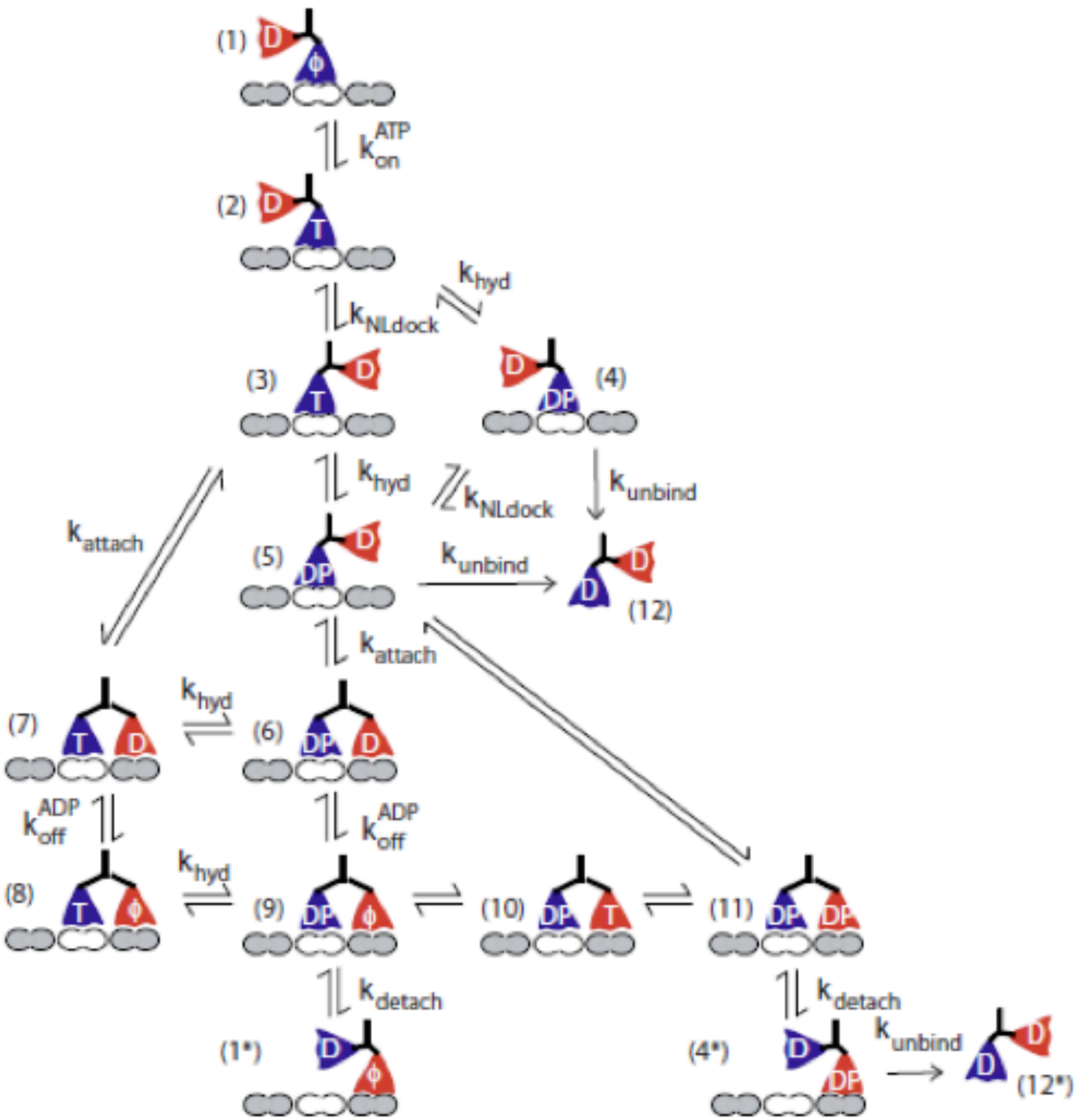


Discrete Space Markov Process

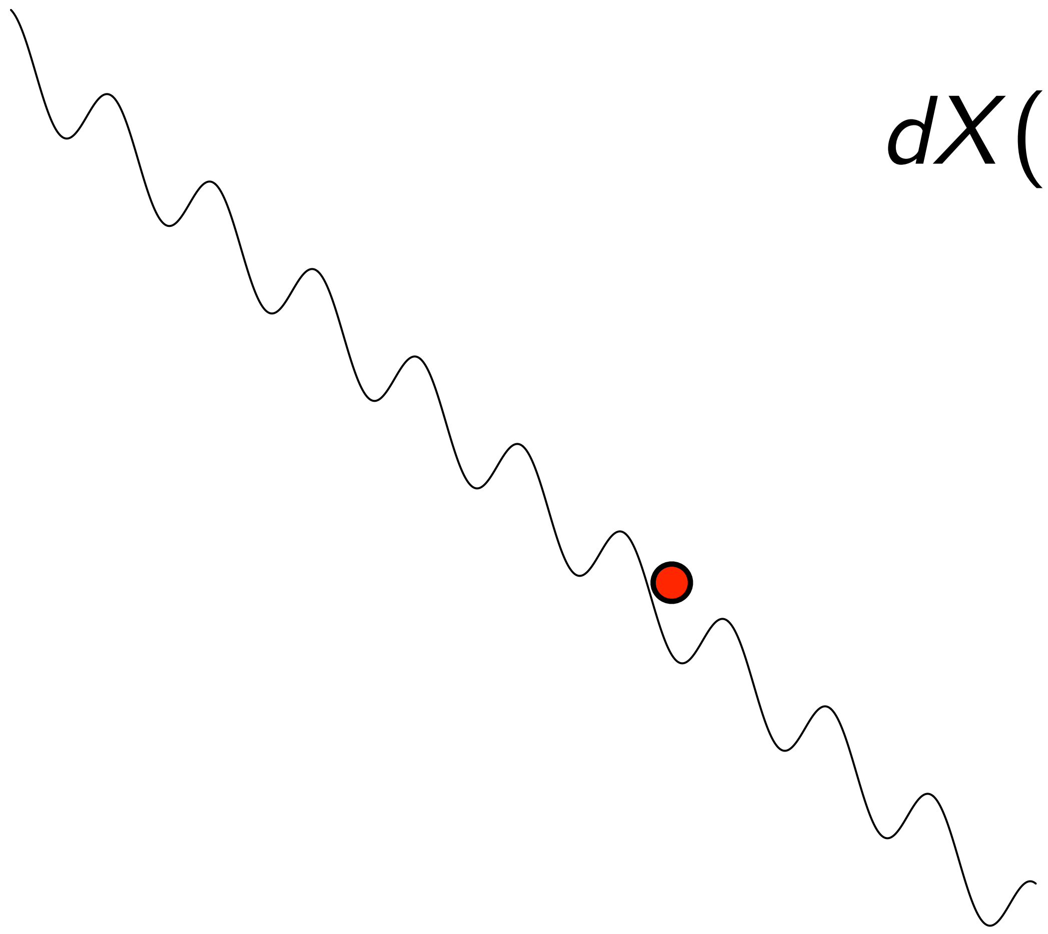




More Complex

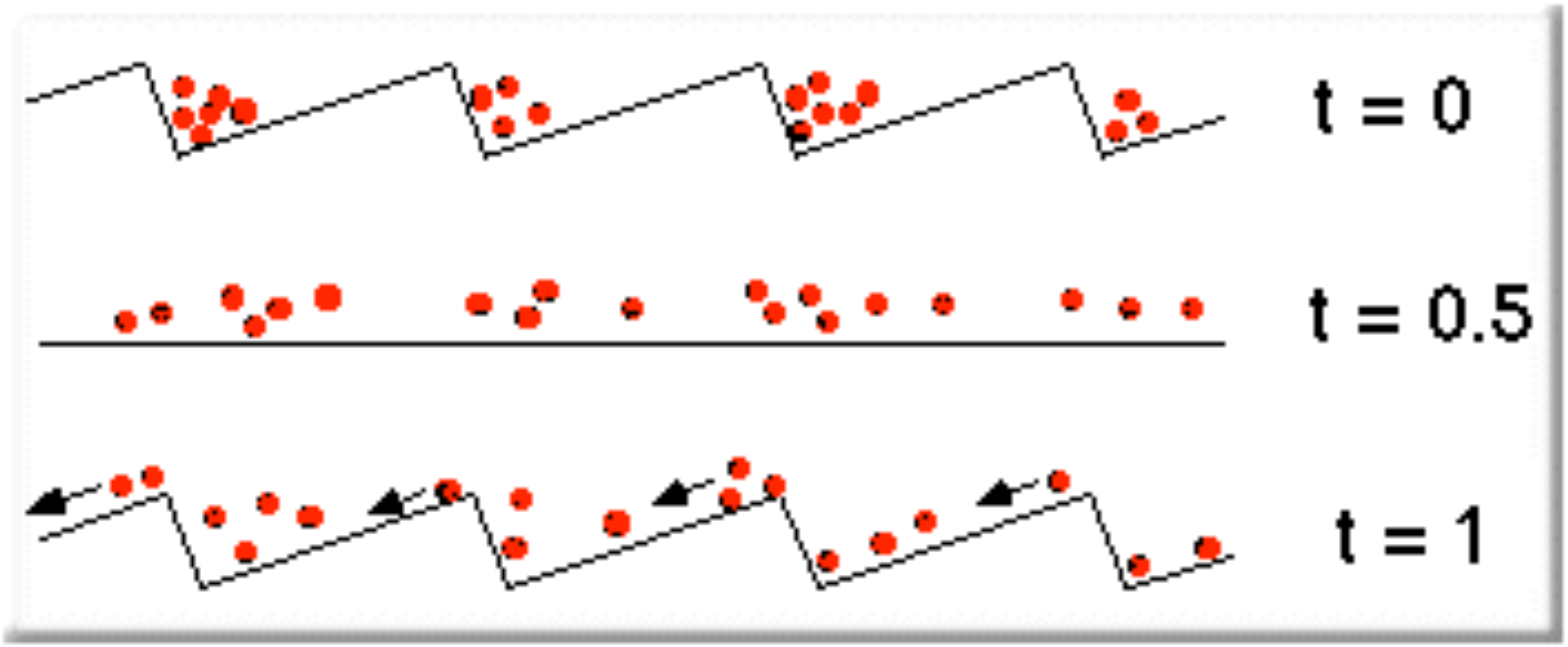


Stochastic Differential Equation



$$dX(t) = a(X(t))dt + \sigma dB(t)$$

Flashing Ratchet



Heiner Linke (http://www.phys.unsw.edu.au/STAFF/RESEARCH/linke.html)

$$dX(t) = a_{K(t)}(X(t))dt + \sigma dB(t)$$

Quantities of Interest

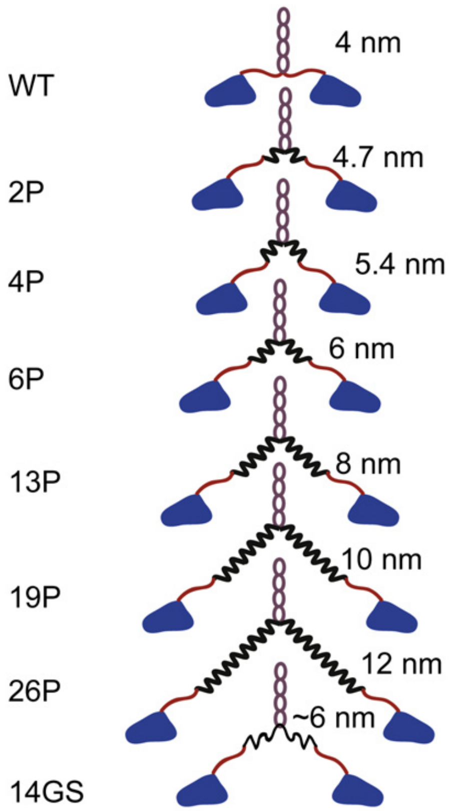
- Asymptotic Velocity $V_a = \lim_{t \to \infty} \frac{E[X(t)]}{t}$ *or* $V_a = \lim_{t \to \infty} \frac{X(t)}{t}$

- Effective Diffusion $D_{eff} = \lim_{t \to \infty} \frac{Var[X(t)]}{2t}$

- Randomness Parameter (Fano Factor) $R = \frac{2D_{eff}}{LV_a}$

- Processivity

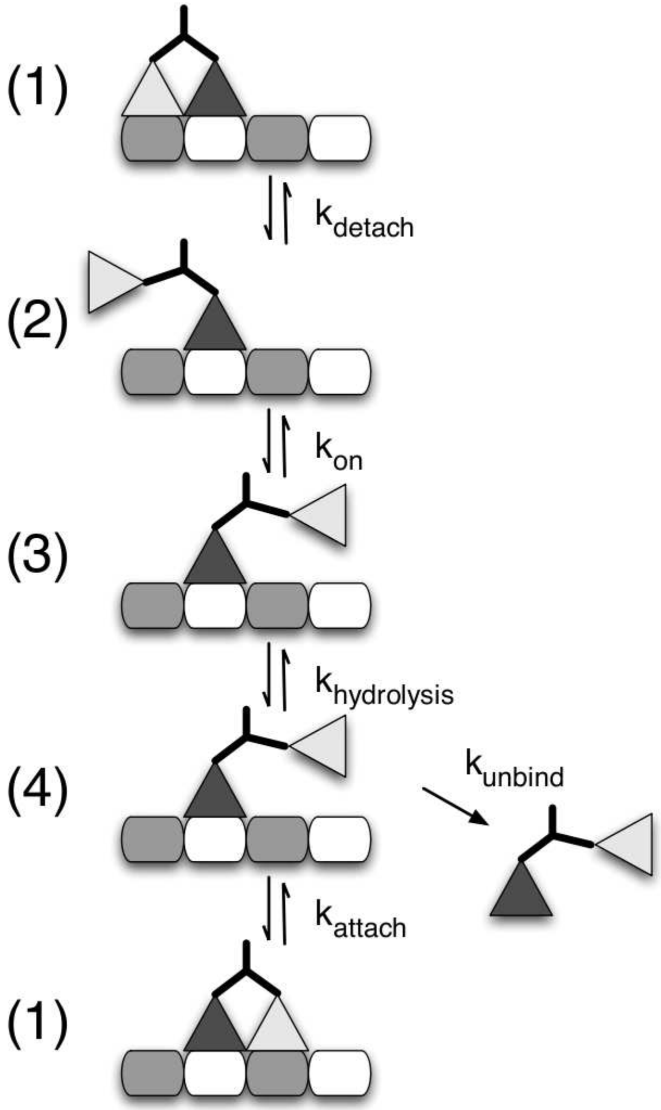
Engineered Motors



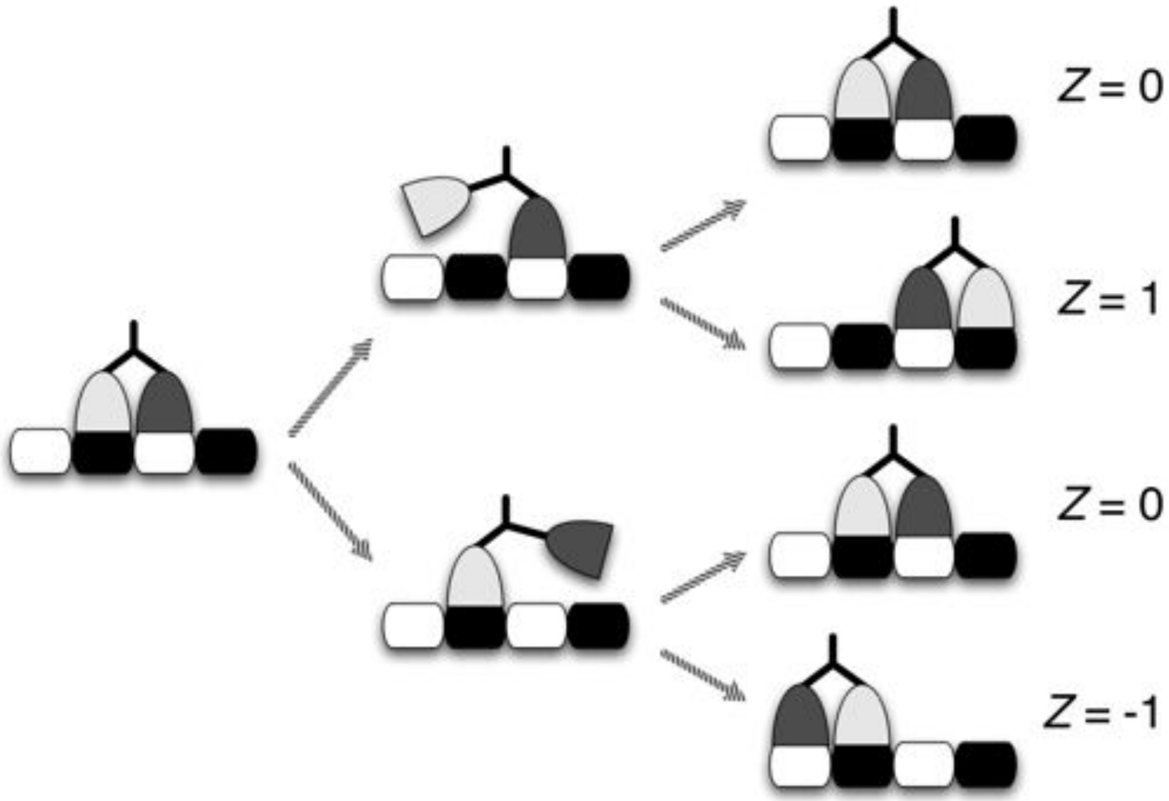
- Extensions range from 1 to 12 nm.
- Hackney and Hancock
  - reduced processivity
- Hancock
  - velocity was reduced
- Yildiz et al
  - processivity unaffected
  - velocity reduced

Mathematical Model–First Try

- What about incorporating diffusion into the free head?
- State 1 corresponds to both heads down.
- State 2 corresponds to the rear head free. Negative or neutral bias.
- States 3 and 4 correspond to a forward bias due to the binding of ATP.



Mathematical Model–First Try



Mathematical Model-First Try

- Position of free motor head is governed by

$$Y(t) = y + \int_0^t a_{K(s)}(Y(s))ds + \sigma B(s)$$

- Associate with each free binding site

$$N_j\left(\int_0^t g_j\left(Y(s)\right)ds\right)$$

- The time and location of absorption

$$\tau \qquad Y(\tau)$$

Mathematical Model-First Try

$Y(t) = x + \int_0^t a_{K(s)}(Y(s))ds + \sigma B(s)$

Linear Spring

$$a_k(y) = -\kappa(y - c)$$

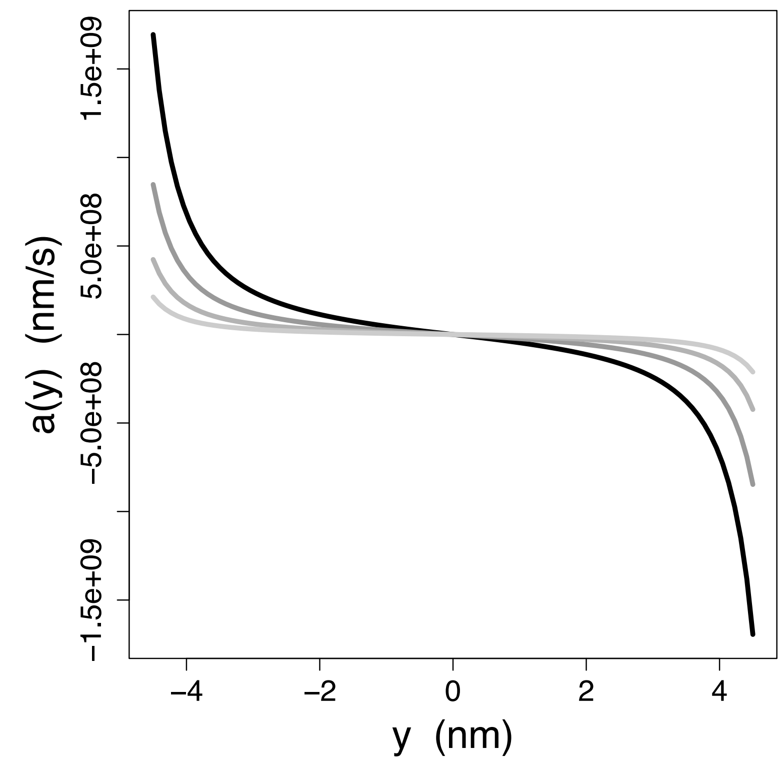
WLC

$$a_k(y) = \kappa \left(\frac{1}{4}\left(1 - \frac{y}{L_c}\right)^{-2} - \frac{1}{4} + \frac{y}{L_c} \right)$$

FENE

$$a_k(y) = -\kappa(y - c)$$

but with reflecting barriers at L_c and $-L_c$.



Model within step dynamics

$$Q = \left(\begin{array}{c|c} A & B \\ \hline 0 & 0 \end{array}\right)$$

$$\mathbf{A} = \begin{pmatrix}
k_{1_+,1_+} & k_{1_+,2_+} & 0 & 0 & k_{1_+,4_-} & 0 & 0 \\
0 & k_{2_+,2_+} & k_{2_+,3_+} & 0 & 0 & 0 & 0 \\
0 & k_{3_+,2_+} & k_{3_+,3_+} & k_{3_+,4_+} & 0 & 0 & 0 \\
0 & 0 & k_{4_+,3_+} & k_{4_+,4_+} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & k_{4_-,4_-} & k_{4_-,3_-} & 0 \\
0 & 0 & 0 & 0 & k_{3_-,4_-} & k_{3_-,3_-} & k_{3_-,2_-} \\
0 & 0 & 0 & 0 & 0 & k_{2_-,3_-} & k_{2_-,2_-} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix}$$

and

$$\mathbf{B} = \begin{pmatrix}
0 & 0 & 0 \\
0 & K_{2_+,1_*} & 0 \\
0 & 0 & 0 \\
k_{4_+,1_{++}} & 0 & 0 \\
0 & k_{4_-,1_*} & 0 \\
0 & 0 & 0 \\
0 & 0 & k_{2_-,1_-}
\end{pmatrix}.$$

Aggregated Markov Chains

$$\mu_\tau = -aA^{-1}\mathbf{1}'$$

$$\sigma_\tau^2 = 2aA^{-1}A^{-1}\mathbf{1}' - \left(\nu A^{-1}\mathbf{1}'\right)^2$$

Wang and Qian on kinetic models for motors.

Milescu et al on MLE for motor dwell time.

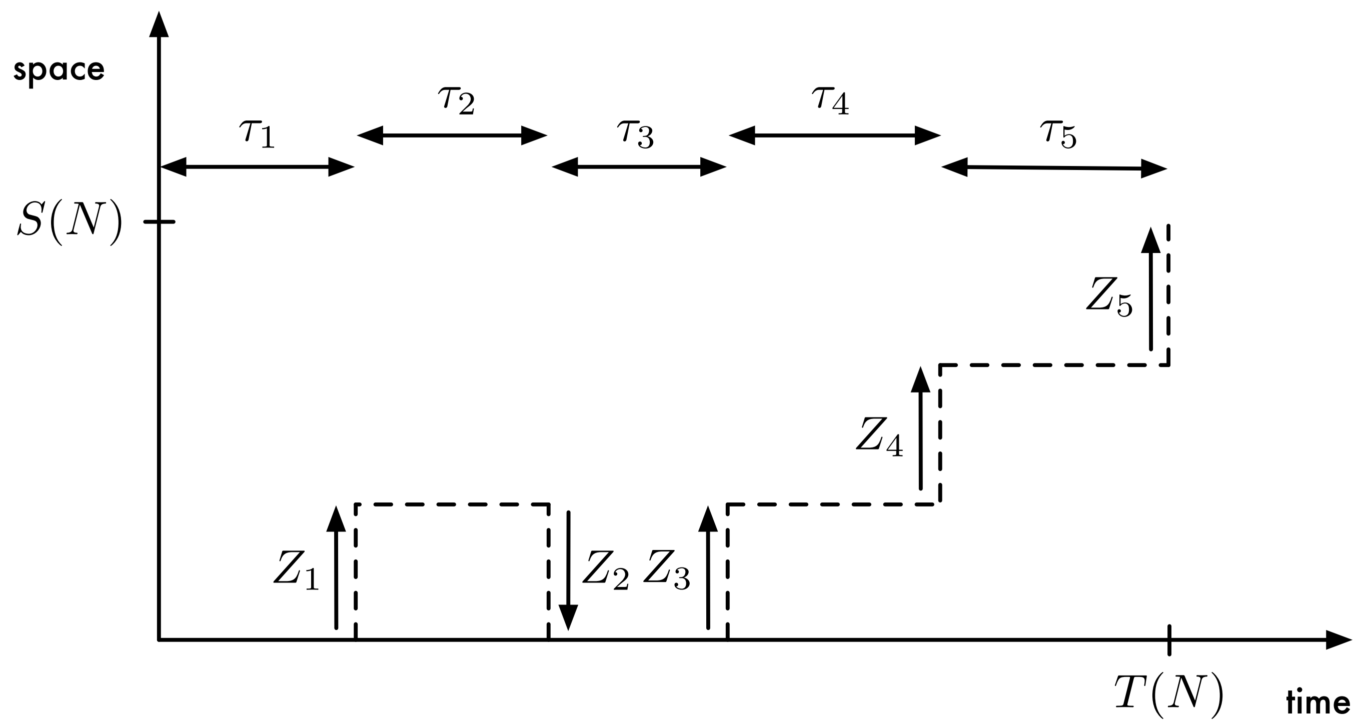
Fredkin and Rice a comprehensive look.

Colquhoun and Hawkes with ion channels.

Queueing Literataure–Asmussen, Neuts+others

A Semi-Markov Framework

$$X(t) = \sum_{i=1}^{N(t)} Z_i \qquad N(t) = \max\{n : \textstyle\sum_{i=1}^{n} \tau_i \leq t\}$$



Standard Quantities

$$V_\infty = \lim_{t\to\infty} \frac{X(t)}{t} = \lim_{t\to\infty} \frac{L\sum_{i=1}^{N(t)} Z_i}{t} = L\frac{\mu_Z}{\mu_\tau}$$

$$D = \frac{L^2}{2}\left(\frac{\mu_Z^2\sigma_\tau^2}{\mu_\tau^3} + \frac{\sigma_Z^2}{\mu_\tau} - 2\frac{\mu_Z\sigma_{Z,\tau}}{\mu_\tau^2}\right)$$

$$n^{-1/2}\left(X(nt) - V_\infty nt\right) \Rightarrow \sqrt{2D}B(t)$$

Functional Central Limit Theorem

Define

$$S(t) = \sum_{i=0}^{\lfloor t \rfloor} Z_i \quad T(t) = \sum_{i=0}^{\lfloor t \rfloor} \tau_i$$

$$n^{-1/2} \begin{pmatrix} S(nt) - \mu_Z nt \\ T(nt) - \mu_\tau nt \end{pmatrix} \Rightarrow \begin{pmatrix} B_1(t) \\ B_2(t) \end{pmatrix}$$

where the covariance matrix is

$$\Sigma = \begin{pmatrix} \sigma_Z^2 & \sigma_{Z,\tau} \\ \sigma_{Z,\tau} & \sigma_\tau^2 \end{pmatrix}$$

FCLT and Delta Method

Note that $X(t) = S(T^{-1}(t))$.
Now, if we define

$$X_n(t) = n^{-1/2}\left(S(T^{-1}(nt)) - \frac{\mu_Z}{\mu_\tau}nt\right),$$

and we apply a continuous mapping theorem.

$$X_n(t) \Rightarrow B_1\left(\frac{t}{\mu_\tau}\right) - \frac{\mu_Z}{\mu_\tau}B_2\left(\frac{t}{\mu_\tau}\right).$$

Or

$$X_n(t) = n^{-1/2}\left(X(nt) - \frac{\mu_z}{\mu_\tau}nt\right) \Rightarrow \sqrt{\frac{\sigma_Z^2}{\mu_\tau} + \frac{\mu_z^2\sigma_\tau^2}{\mu_\tau^3} - 2\frac{\mu_Z\sigma_{Z,\tau}}{\mu_\tau^2}}\,B(t).$$

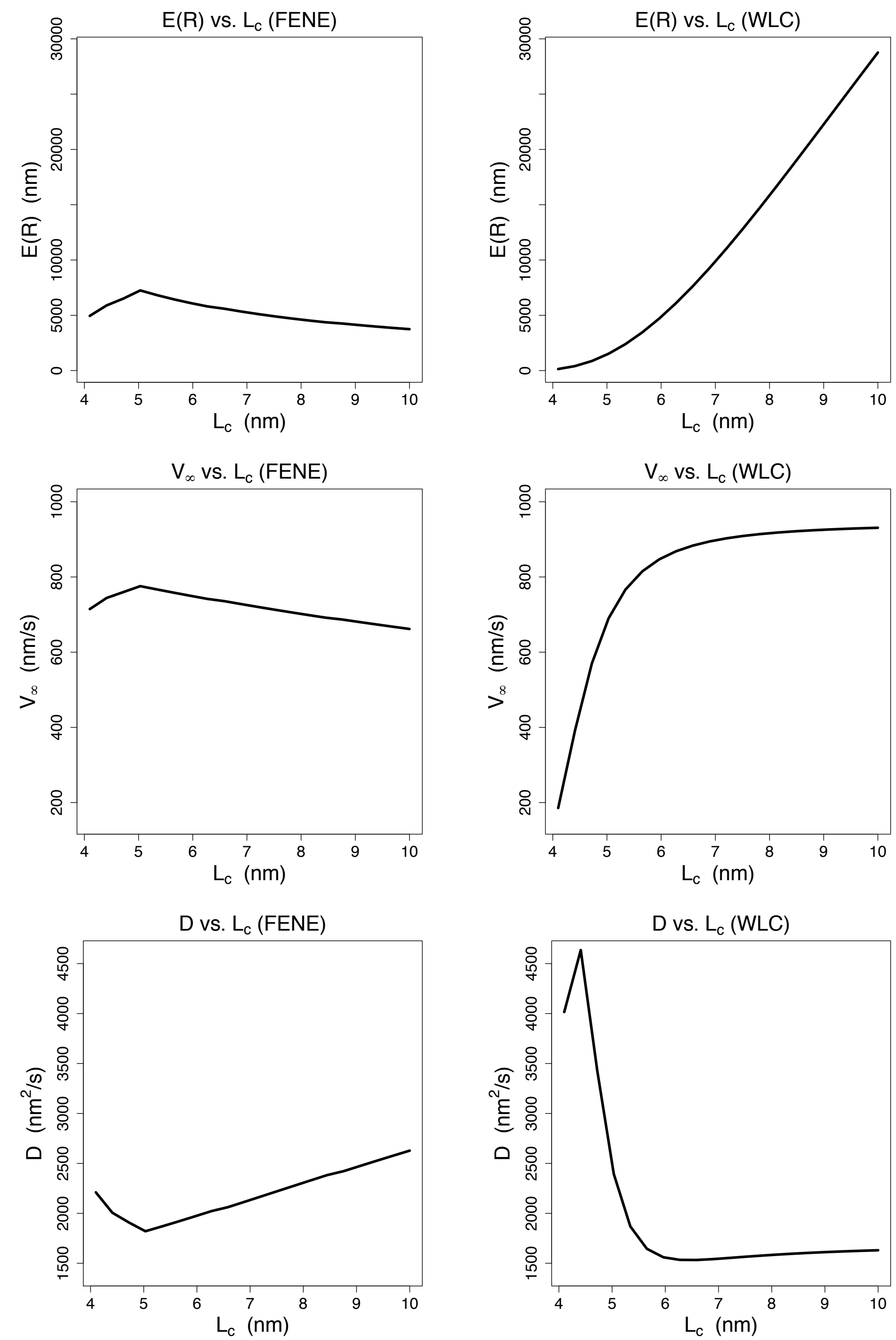
$$X(nt) \approx \frac{\mu_z}{\mu_\tau}nt + n^{1/2}\sqrt{\frac{\sigma_Z^2}{\mu_\tau} + \frac{\mu_z^2\sigma_\tau^2}{\mu_\tau^3} - 2\frac{\mu_Z\sigma_{Z,\tau}}{\mu_\tau^2}}\,B(t).$$

Results for First Model

- Run length is unaffected/reduced in experiments.

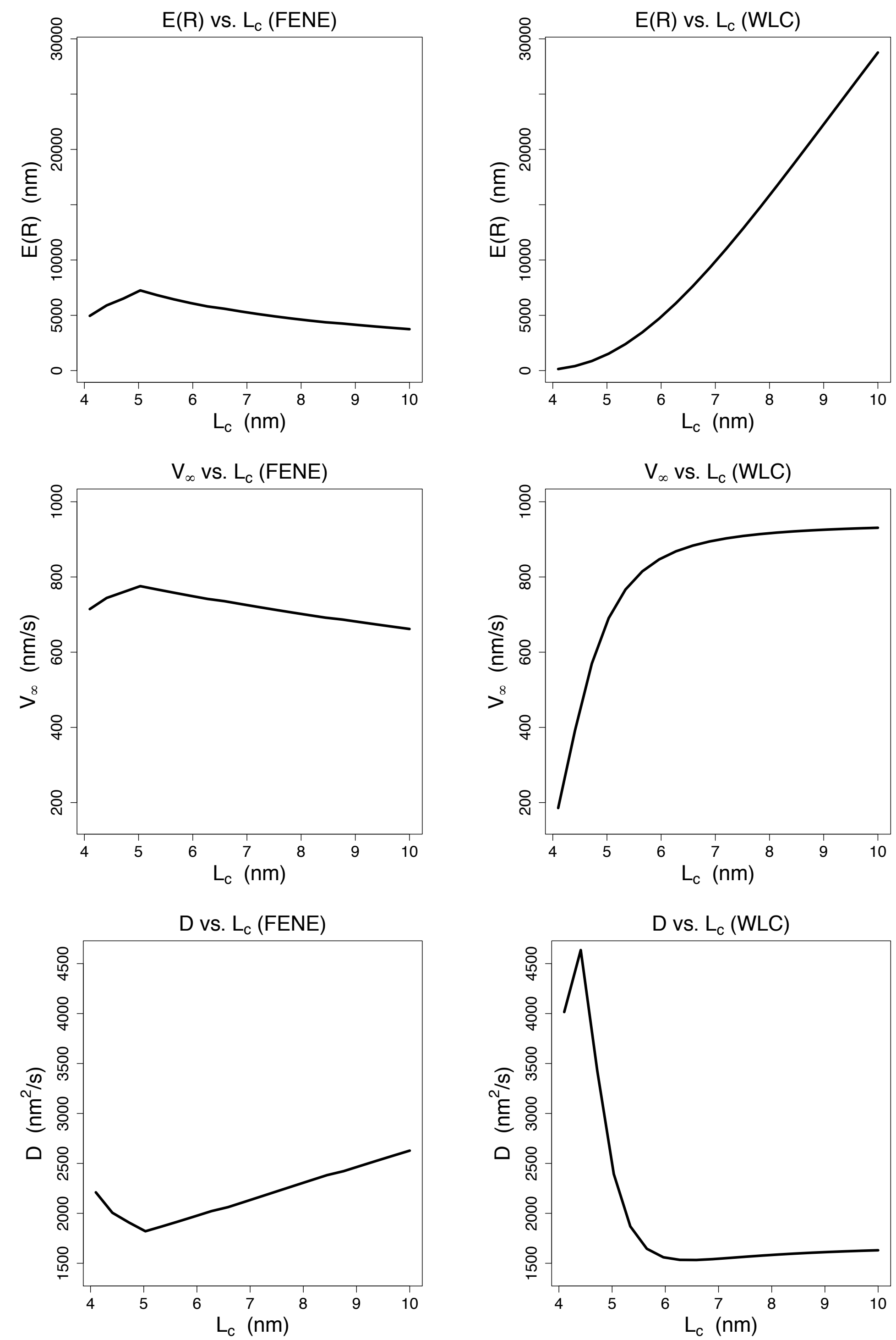
- Run length decreases mildly in FENE

- Run length increases rapidly for WLC.

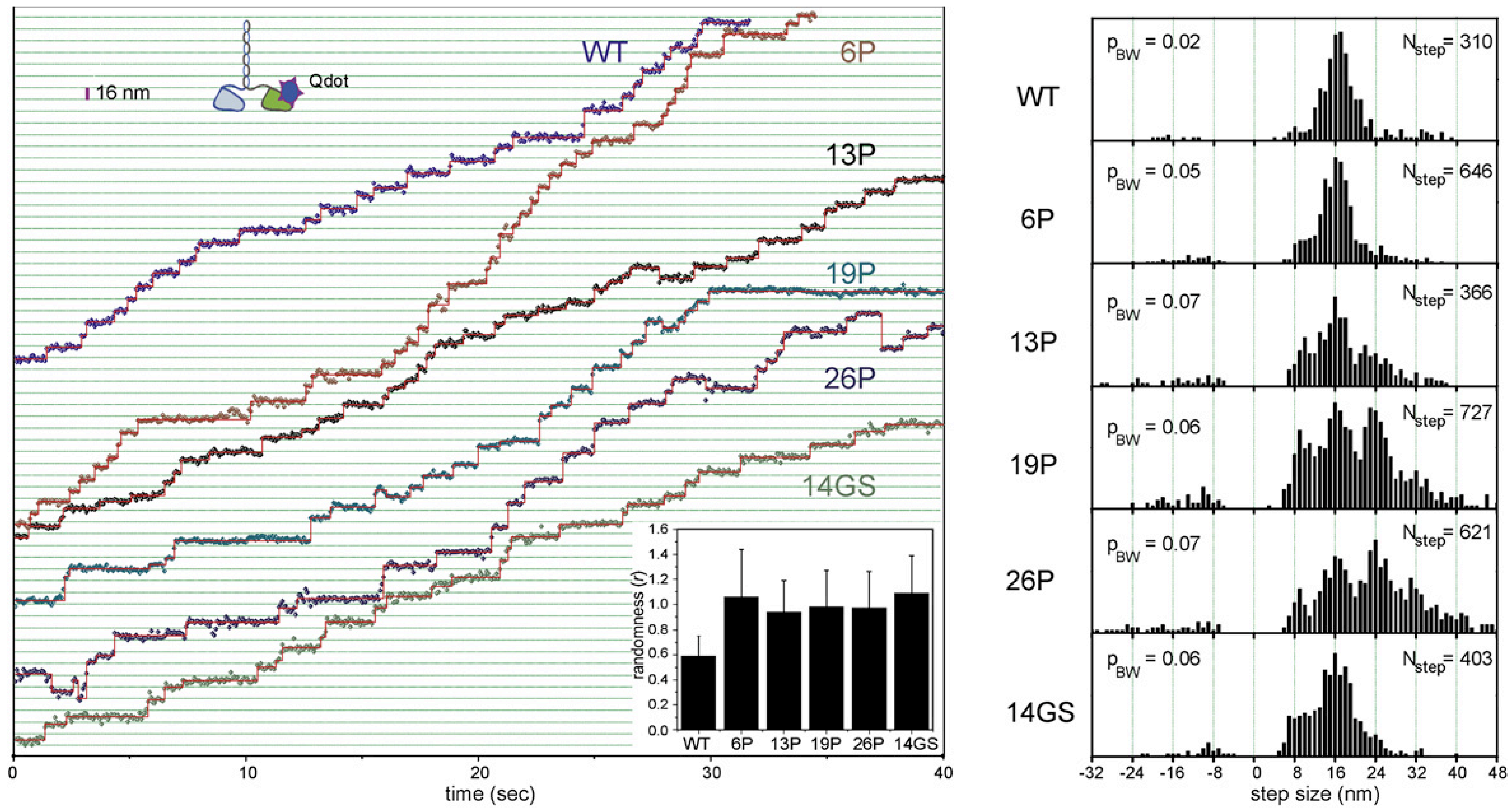


Results for First Model

- Velocity decreases for experiments.
- Velocity decreases for FENE.
- Velocity increases for WLC.

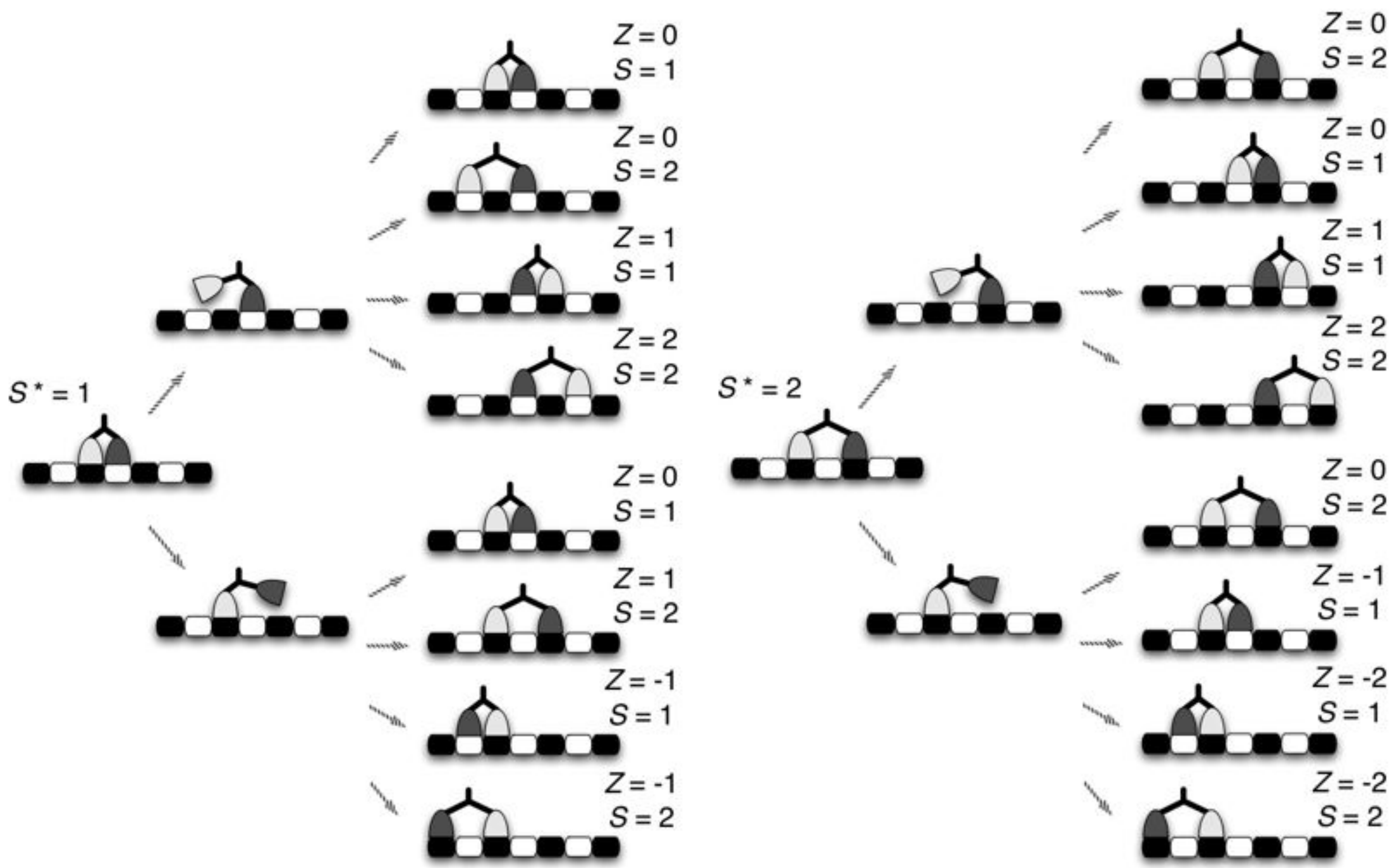


Yildiz et al.



Yildiz, A. and Tomishige, M. and Gennerich, A. and Vale, R.D.

Mathematical Model–Second Attempt



Mathematical Model–Second Attempt

- The tension between the heads will be different depending on the distance.
- We include this tension in the rate to unbind when both heads are bound.

Mathematical Model–Second Attempt

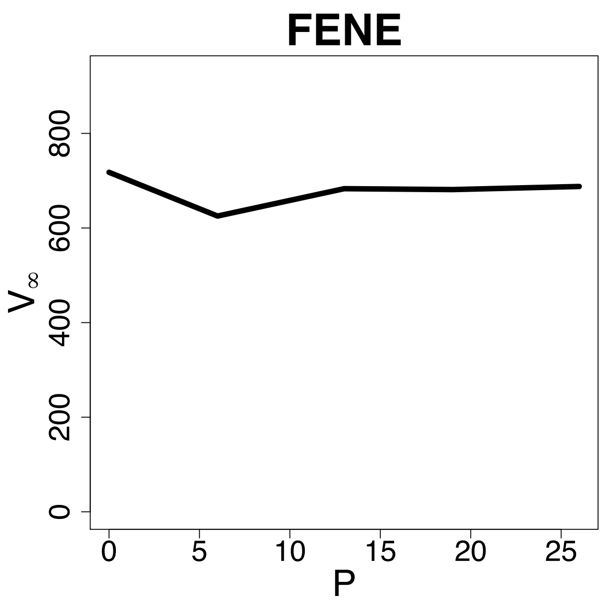
$$\begin{pmatrix} Z_i \\ \tau_i \\ S_i \end{pmatrix}$$

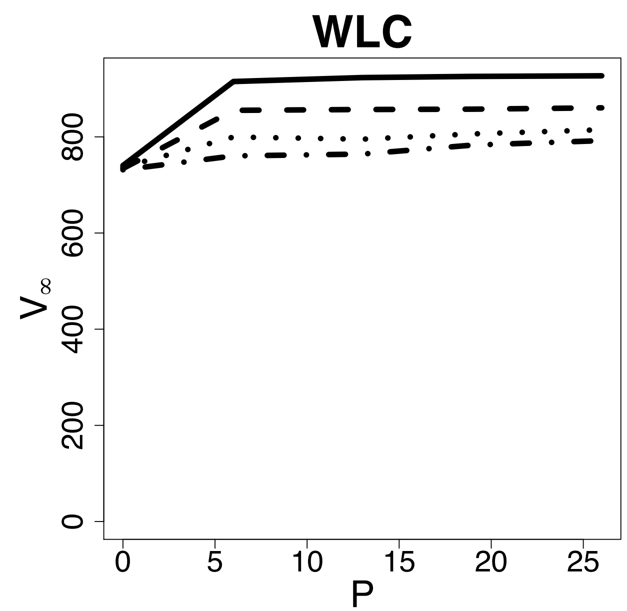
S_i is a Markov chain describing the distance between heads after previous cycle.

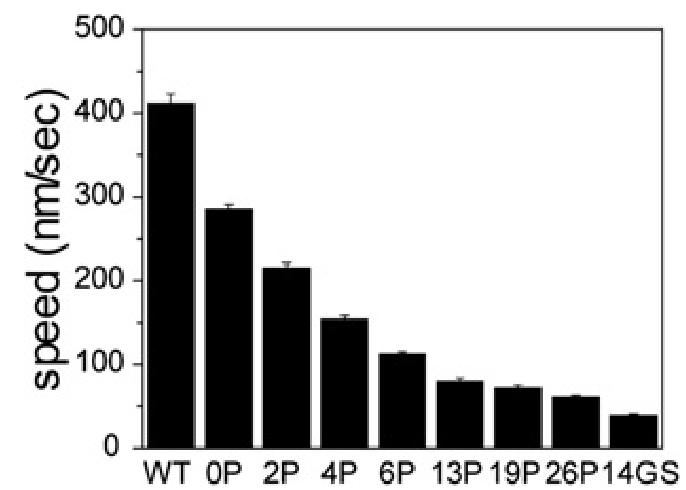
The position of the front head after a full cycle

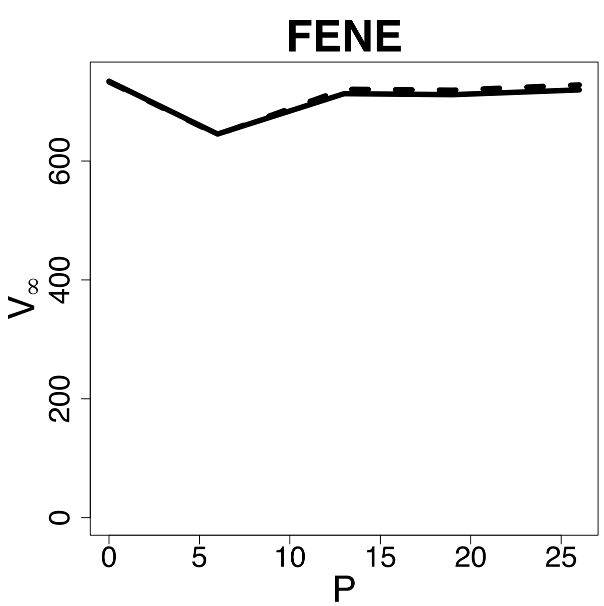
$$X(t) = \sum_{i=1}^{N(t)} Z_i$$

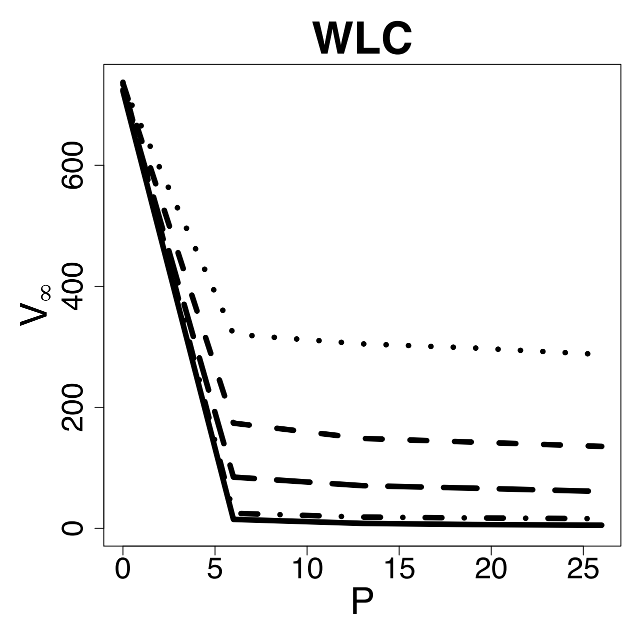
Results for Second Attempt



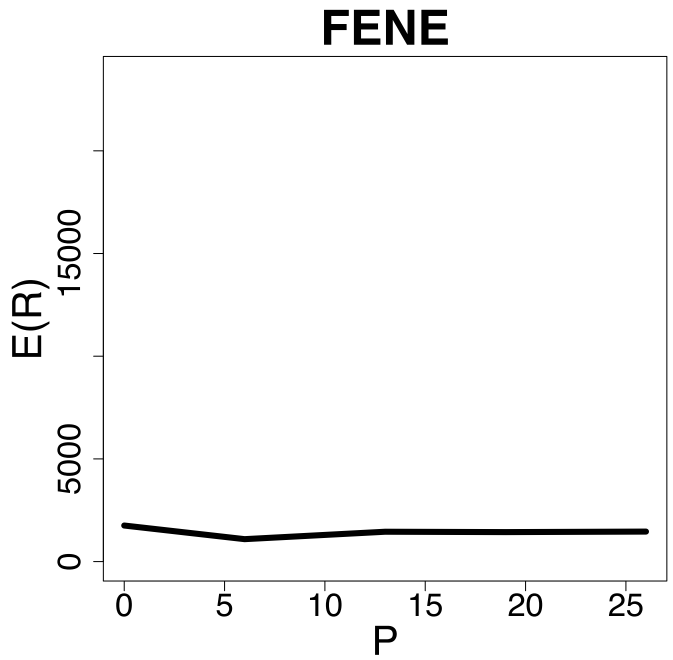


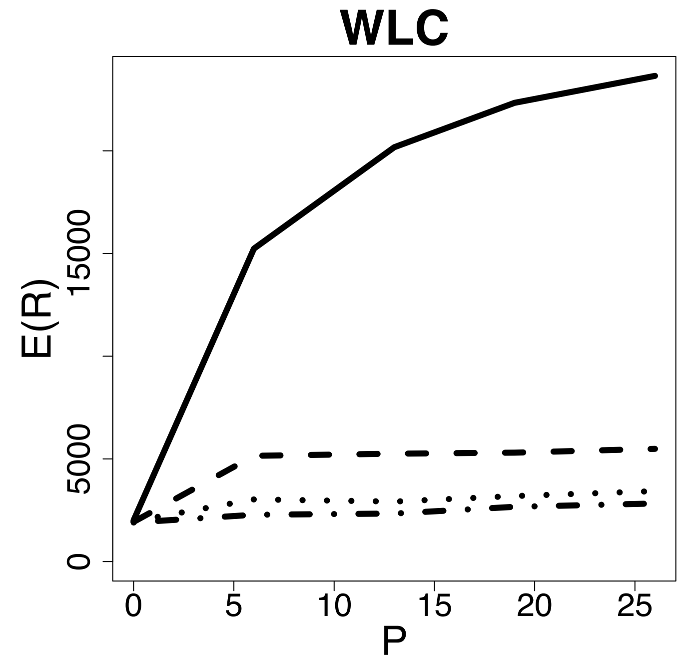


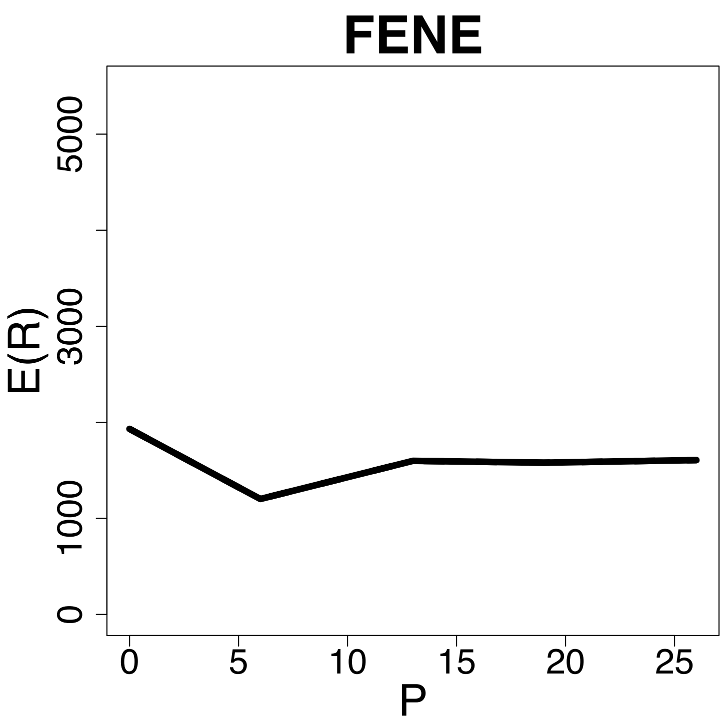


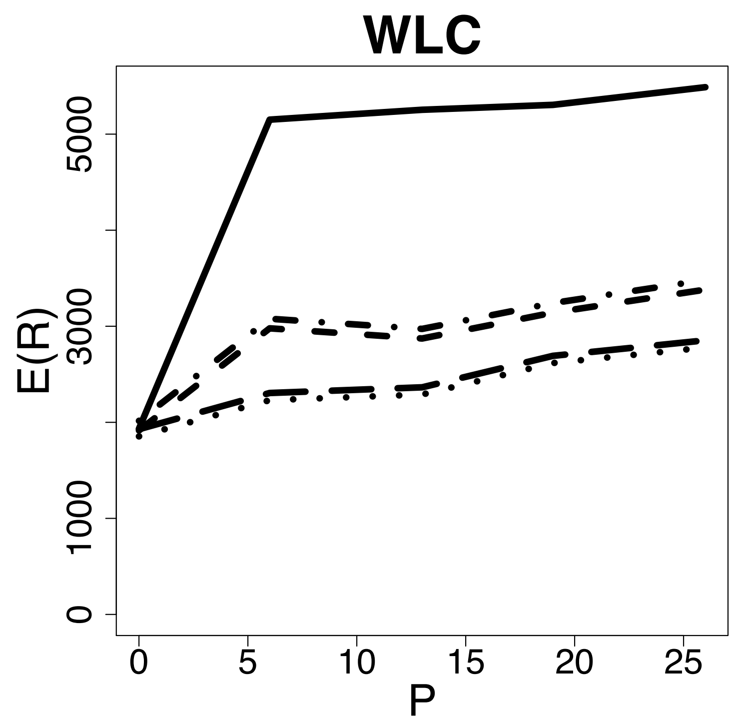


Results for Second Attempt

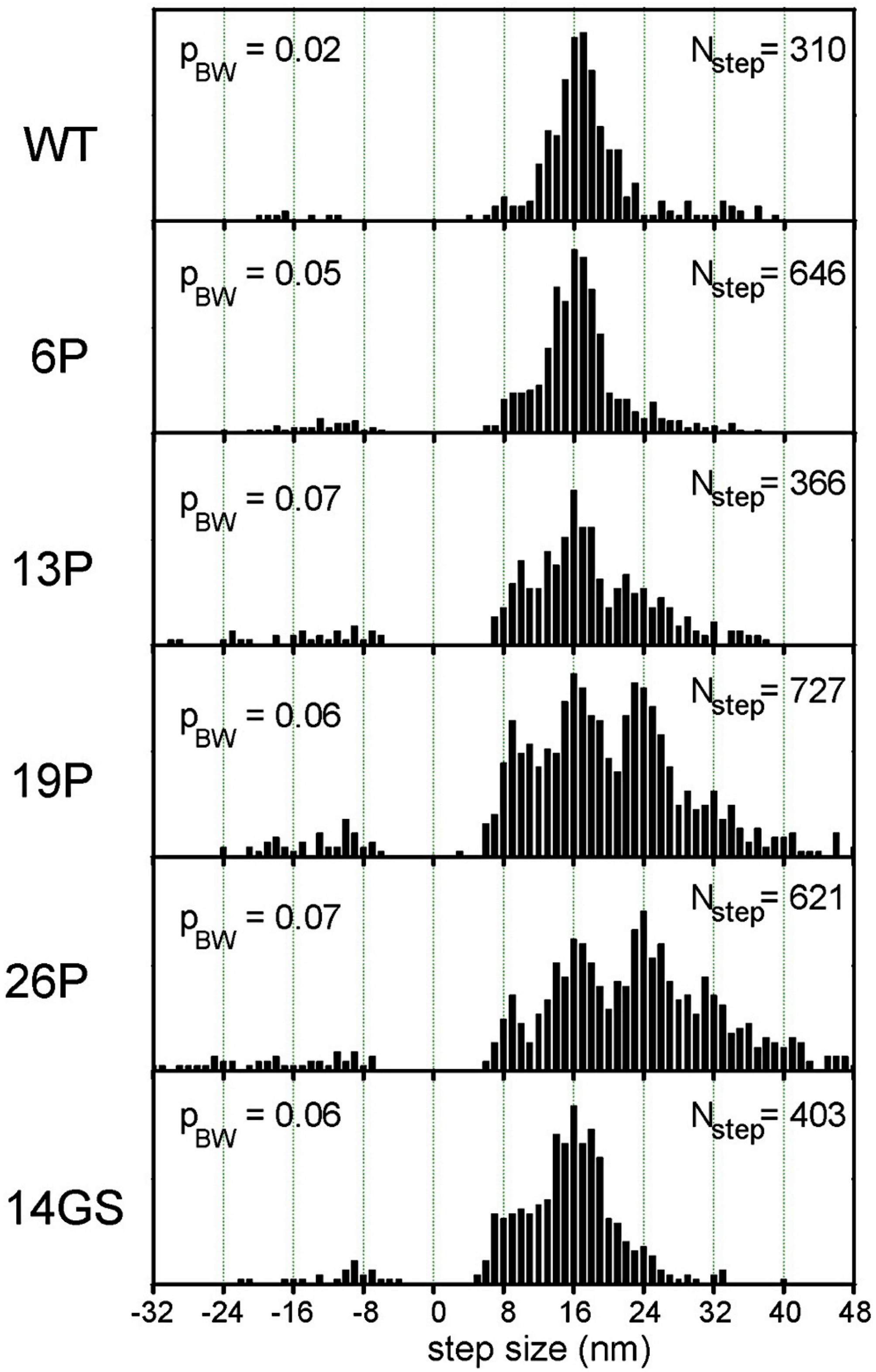


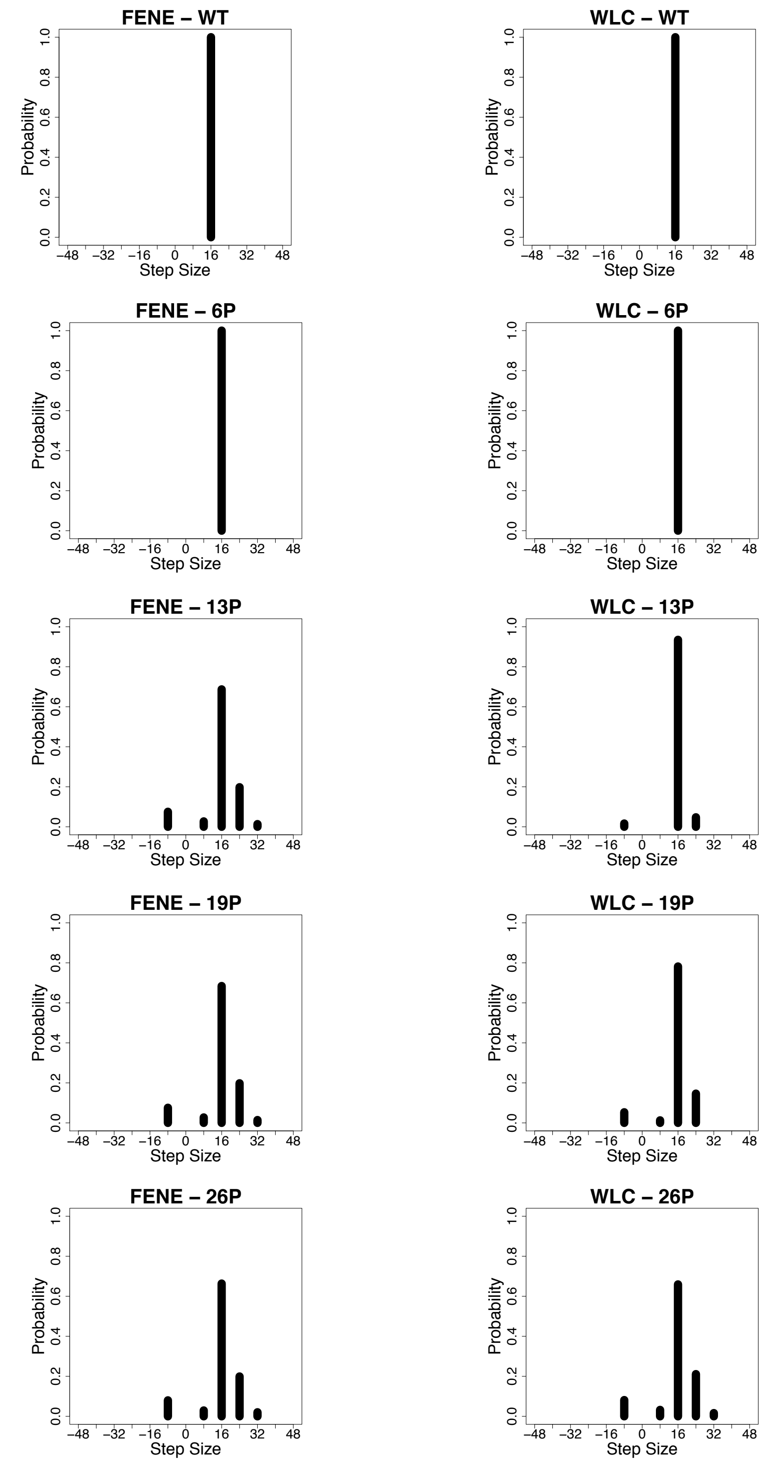






Results for Second Attempt





Random Stopping

- asymptotic distribution of empirical asymptotic velocity

$$\widehat{V} = \frac{\sum_{i=1}^{N} Z_i}{\sum_{i=1}^{N} \tau_i}$$

- the Pearson VII distribution

$$\frac{1}{\sqrt{n}} \left(\widehat{V} - \frac{\mu_Z}{\mu_\tau} \right) \Rightarrow P_{VII}$$

Why it works

Recall

$$S(t) = \sum_{i=0}^{\lfloor t \rfloor} Z_i \quad T(t) = \sum_{i=0}^{\lfloor t \rfloor} \tau_i$$

$$\eta_n = \frac{1}{n} T(N) \Rightarrow \eta = \mu_\tau \varepsilon$$

$$\frac{X_n(t)}{t} = n^{-1/2} \left(\frac{S(T^{-1}(nt))}{t} - \frac{\mu_Z}{\mu_\tau} n \right) \Rightarrow \sqrt{2D} \frac{B(t)}{t}$$

So,

$$\frac{X_n(\eta_n)}{\eta_n} = n^{-1/2} \left(\frac{S(T^{-1}(n\eta_n))}{\eta_n} - \frac{\mu_Z}{\mu_\tau} n \right) \Rightarrow \sqrt{2D} \frac{B(\eta)}{\eta}$$

or

$$\frac{X_n(\eta_n)}{\eta_n} = n^{-1/2} \left(\frac{S(N)}{T(N)} - \frac{\mu_Z}{\mu_\tau} \right) \Rightarrow \sqrt{2D} \frac{B(\eta)}{\eta}$$

Random Stopping

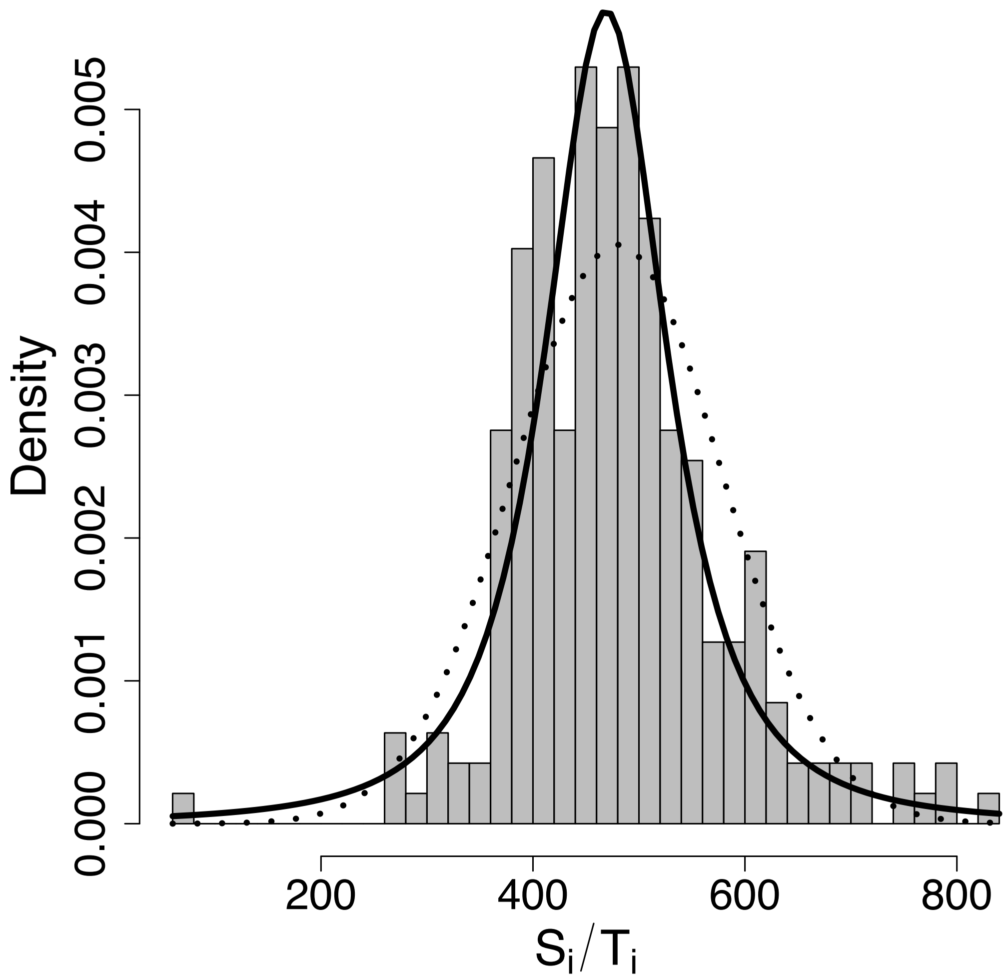
- The Pearson VII distribution

$$f(x) = \frac{1}{\sigma\beta\left(\alpha - \frac{1}{2}, \frac{1}{2}\right)} \left(1 + \left(\frac{x-\mu}{\sigma}\right)^2\right)^{-\alpha}$$

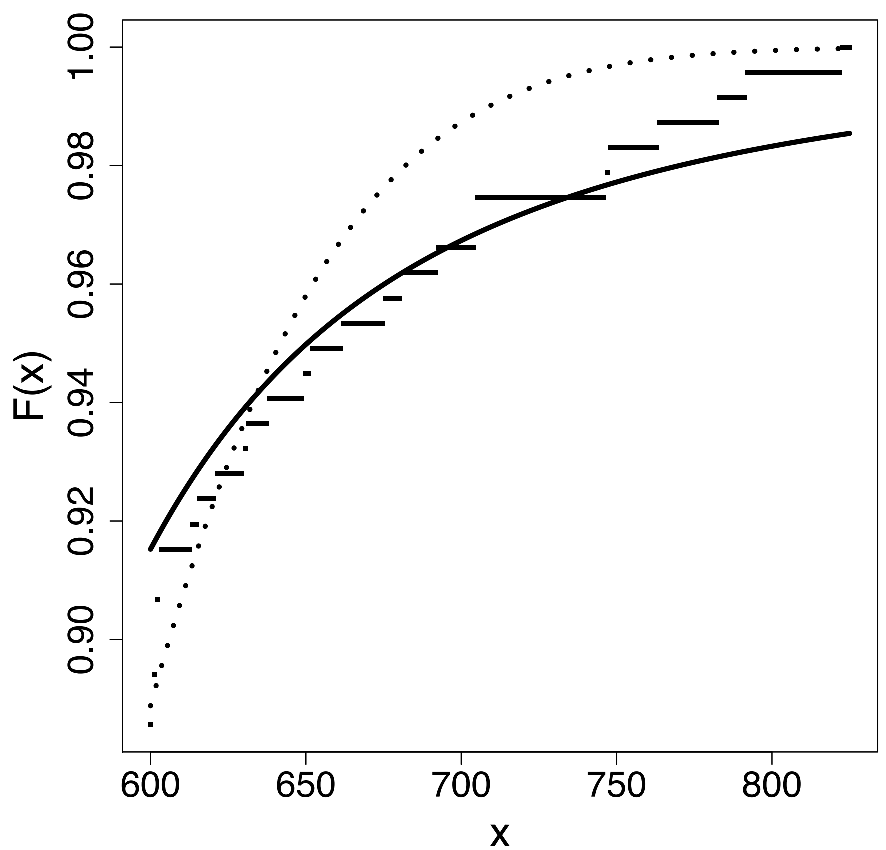
$$f(x) = \frac{1}{2\sigma} \left(1 + \left(\frac{x-\mu}{\sigma}\right)^2\right)^{-3/2}$$

Pearson VII

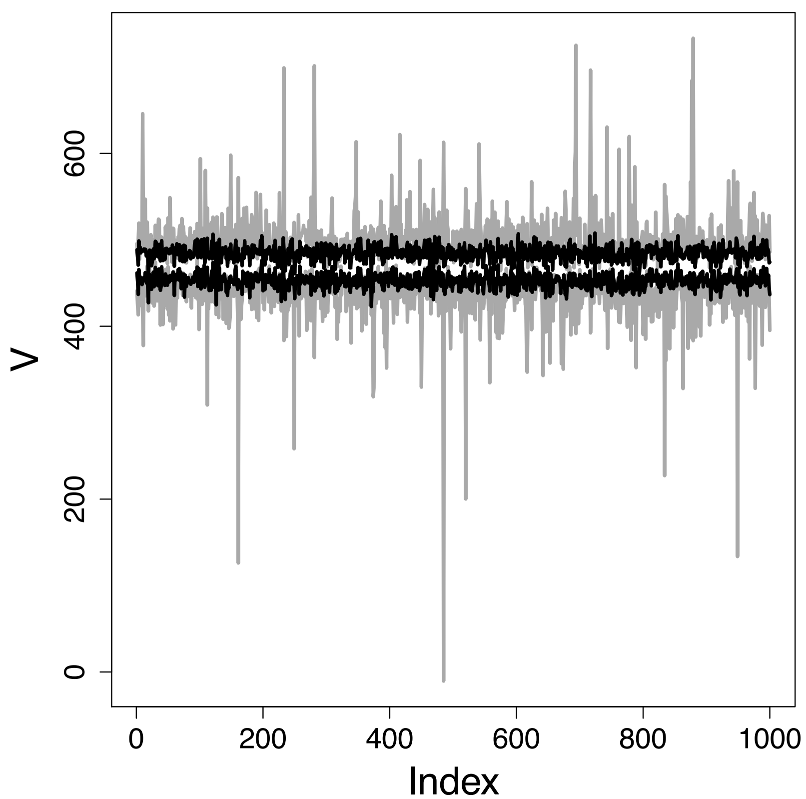
- The mean exists and equals the asymptotic velocity.
- Variance is infinite.
- Confidence intervals on the order of half the width.



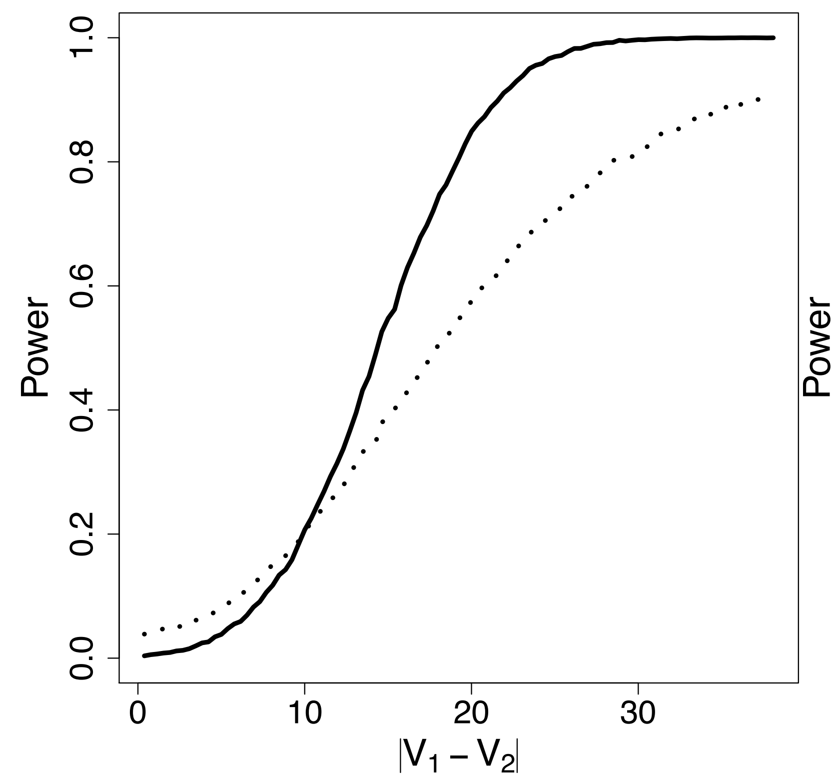
F(x)



Pearson VII



V
0
200
400
600
0
200
400
600
800
1000
Index



Power
0.0
0.2
0.4
0.6
0.8
1.0
0
10
20
30
$|V_1 - V_2|$
Power

Conclusions Nanoscale to Mesoscale

- The WLC model gives qualitatively similar behavior to experiments.

- Matrix based methods allow for computationally efficient sensitivity analysis with respect to parameters and modeling choices.

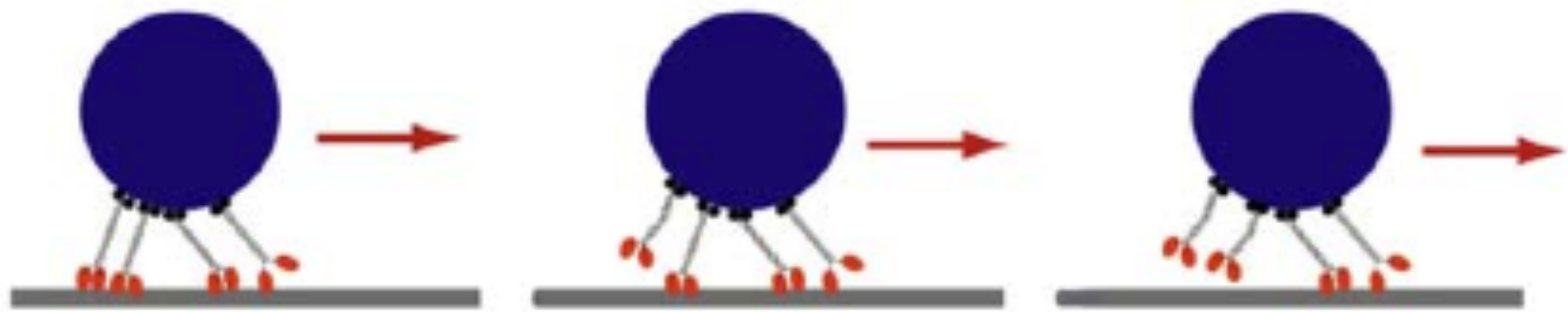
- A general Semi-Markov structure allows for concrete statistical models.

Conclusions Nanoscale to Mesoscale

- Nanoscale features give rise to a mesoscale model–Brownian motion.

- What happens if there is feedback such as an imposed force (cargo, laser trap, etc)?

Multiple Motors



$$\mathrm{d}X_i(t) = vg(F(X_i(t) - Z(t))/F_*)\,\mathrm{d}t + \sigma h(F(X_i(t) - Z(t))/F_*)\,\mathrm{d}W_i(t)$$

$$\gamma \mathrm{d}Z(t) = \left[\sum_{i=1}^{N} F(X_i(t), Z(t)) - \theta\right] \mathrm{d}t + \sqrt{2k_B T\gamma}\,\mathrm{d}W_z(t).$$

v average velocity of unconstrained motor $\sim 50nm/s$

F_* stall force $\sim 7pN$

θ optical track force ~ 0 *to* $10pN$

$F(\cdot)$ spring force function linear with spring constant $\sim 0.34pN/m$

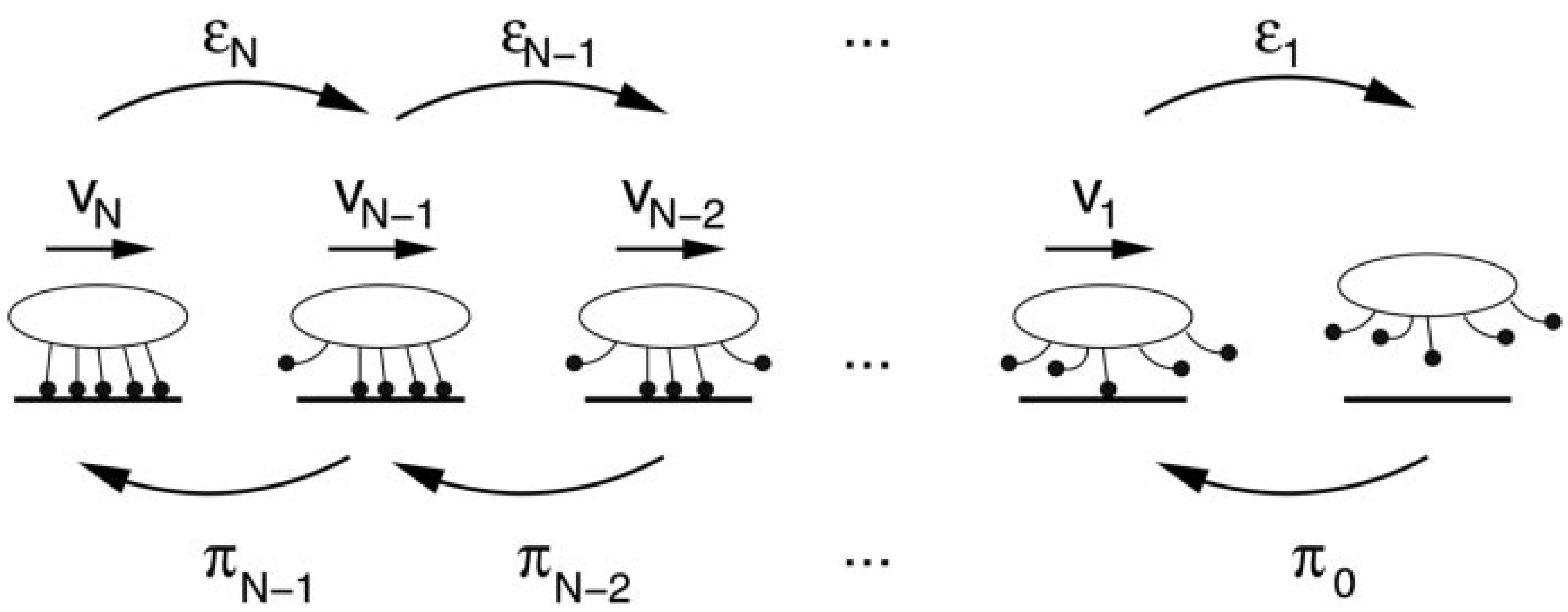
$g(\cdot)$ non-dimensional instantaneous force-velocity function.

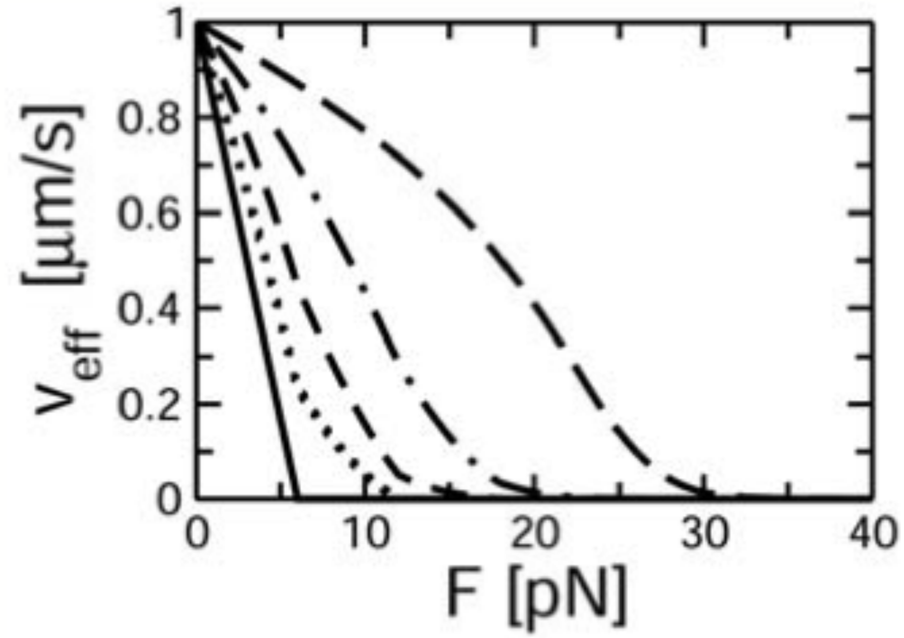
$h(\cdot)$ non-dimensional instantaneous force-diffusivity function.

σ^2 effective diffusivity $\sim 500nm/s$

Scott A. McKinley, Avanti Athreya, John Fricks, and Peter R. Kramer (2012). Asymptotic Analysis of Microtubule-Based Transport by Multiple Identical Molecular Motors. *Journal of Theoretical Biology.* **305**, 54-69.

Motor Cargo Systems

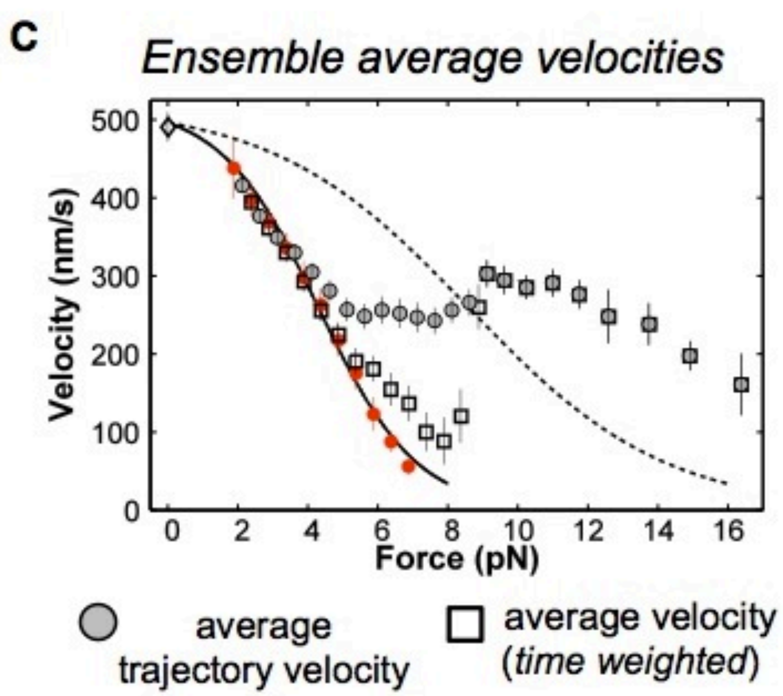




Klumpp,Lipowsky 2006

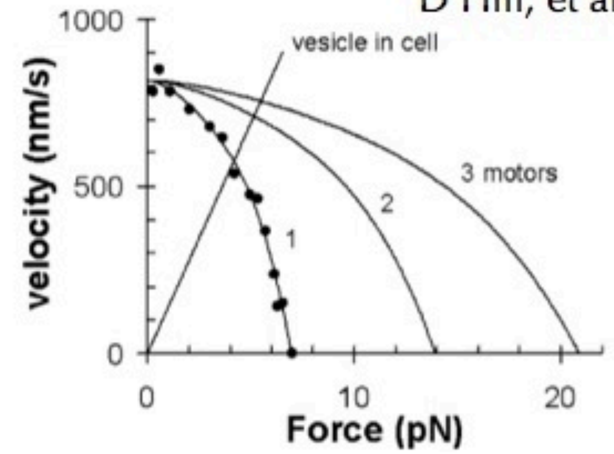
Some Data

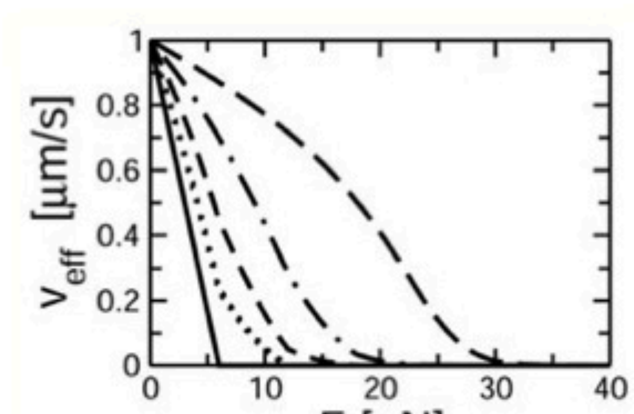
External force vs. average velocity curves



Diehl Lab, Biophys J.2010

D Hill, et al, 04





S Klumpp

Averaged Equations

$$\mathrm{d}\tilde{X}_i(\tilde{t}) = \epsilon g(s(\tilde{X}_i(\tilde{t}) - \tilde{Z}(\tilde{t})))\,\mathrm{d}\tilde{t} + \sqrt{\epsilon\rho}\,\mathrm{d}W_i(\tilde{t})$$

$$\mathrm{d}\tilde{Z}(\tilde{t}) = \sum_{i=1}^{N}\left(\tilde{X}_i(\tilde{t}) - \tilde{Z}(\tilde{t}) - \frac{\tilde{\theta}}{N}\right)\mathrm{d}\tilde{t} + \mathrm{d}W_z(\tilde{t}).$$

$$\tilde{t} = \kappa/\gamma t.$$

$\epsilon = \frac{v\gamma}{\sqrt{2k_B T\kappa}}$ friction force/thermal force $\sim 10^{-4}$

$s = \frac{\sqrt{2k_B T\kappa}}{F_s}$ stallability ~ 0.1

$\rho = \frac{\sigma^2\sqrt{2\kappa}}{v\sqrt{k_B T}}$

Special Case

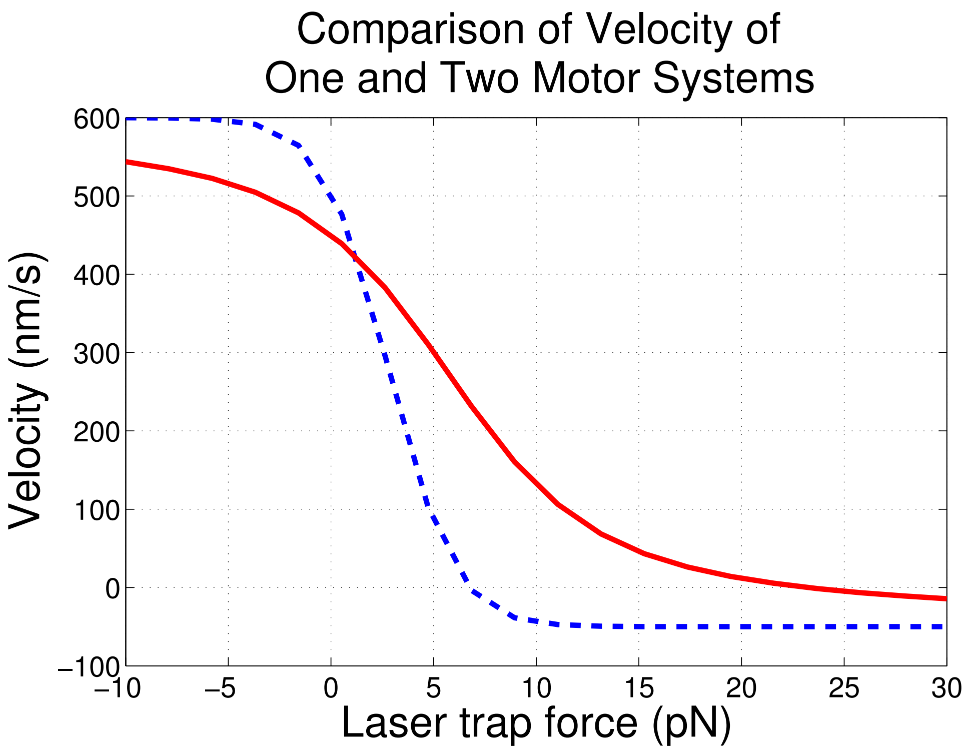
$$\mathrm{d}M(\bar{t}) = \frac{1}{2}\left[G(R(\bar{t}) - \tilde{\theta}) + G(-R(\bar{t}) - \tilde{\theta}))\right]\mathrm{d}\bar{t} + \sqrt{\frac{\rho}{2}}\,\mathrm{d}W_m(\bar{t}),$$

$$\mathrm{d}R(\bar{t}) = -\left[G(R(\bar{t}) - \tilde{\theta}) - G(-R(\bar{t}) - \tilde{\theta})\right]\,\mathrm{d}\bar{t} + \sqrt{2\rho}\,\mathrm{d}W_r(\bar{t}).$$

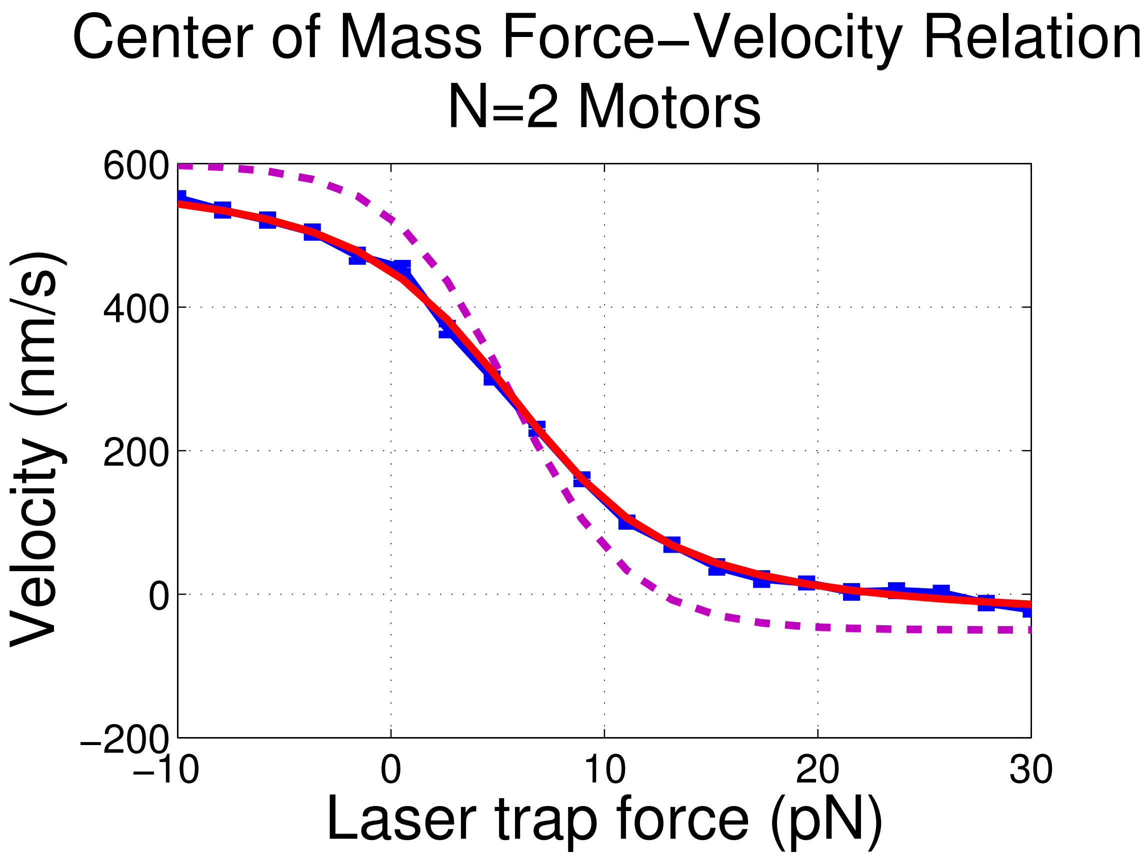
$$\hat{\mathcal{V}}_2(\tilde{\theta}) := \lim_{\bar{t}\to\infty} \frac{M(\bar{t})}{\bar{t}} = \int_{\mathbb{R}} \frac{1}{2} G_+(r;\theta)\pi_R(r;\tilde{\theta})\mathrm{d}r.$$

$$\hat{\mathcal{D}}_2(\tilde{\theta}) := \frac{\rho}{4} + \int_{-\infty}^{\infty}\left(\int_{-\infty}^{r}\left(\frac{1}{2}G_+(r';\theta) - \hat{\mathcal{V}}_2(\tilde{\theta})\right)\pi_R(r';\tilde{\theta})\mathrm{d}r'\right)^2 \frac{1}{\rho\pi_R(r;\tilde{\theta})}\mathrm{d}r.$$

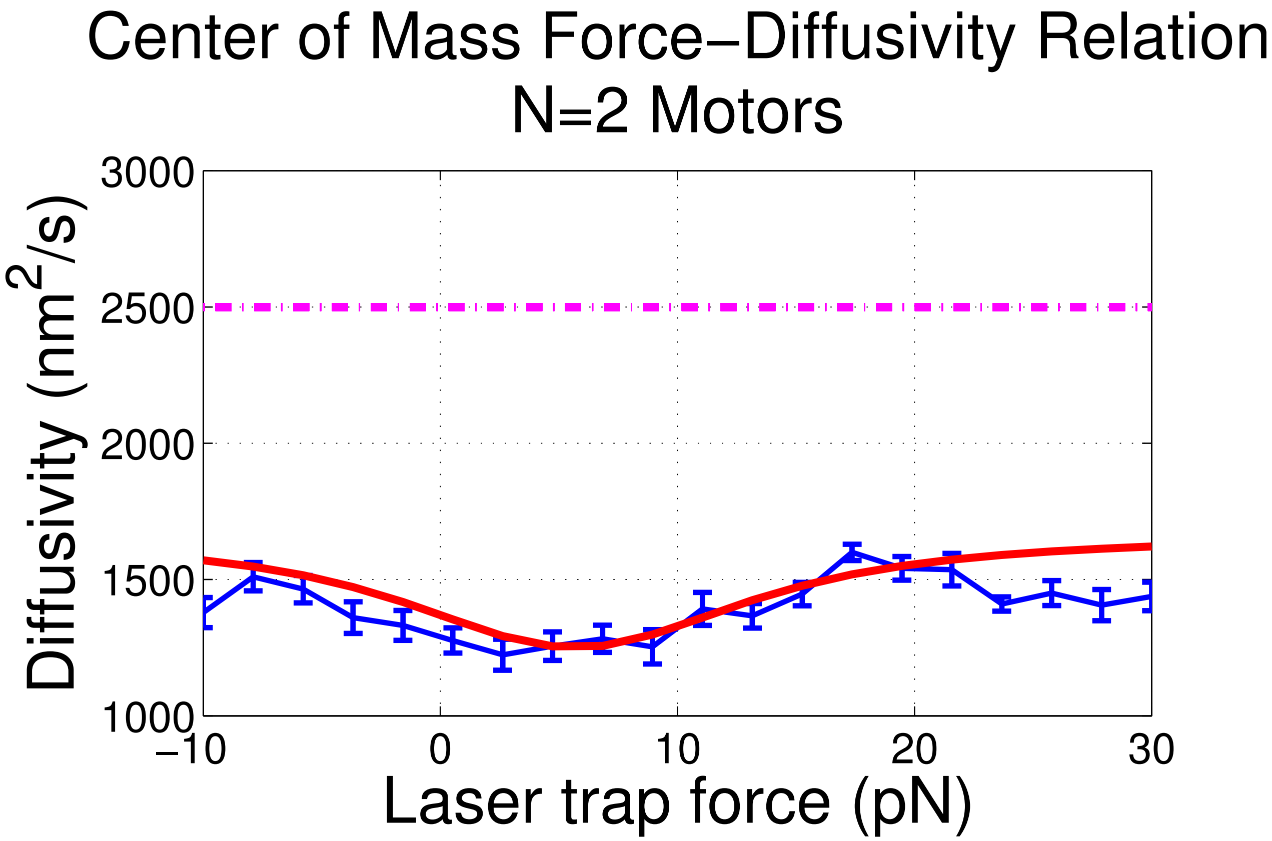
Results


Comparison of Velocity of
One and Two Motor Systems
Velocity (nm/s)
600
500
400
300
200
100
0
−100
−10
−5
0
5
10
15
20
25
30
Laser trap force (pN)

Results



Center of Mass Force−Velocity Relation
N=2 Motors
Velocity (nm/s)
600
400
200
0
−200
−10
0
10
20
30
Laser trap force (pN)



Center of Mass Force−Diffusivity Relation
N=2 Motors
Diffusivity (nm^2/s)
3000
2500
2000
1500
1000
−10
0
10
20
30
Laser trap force (pN)

High Viscosity

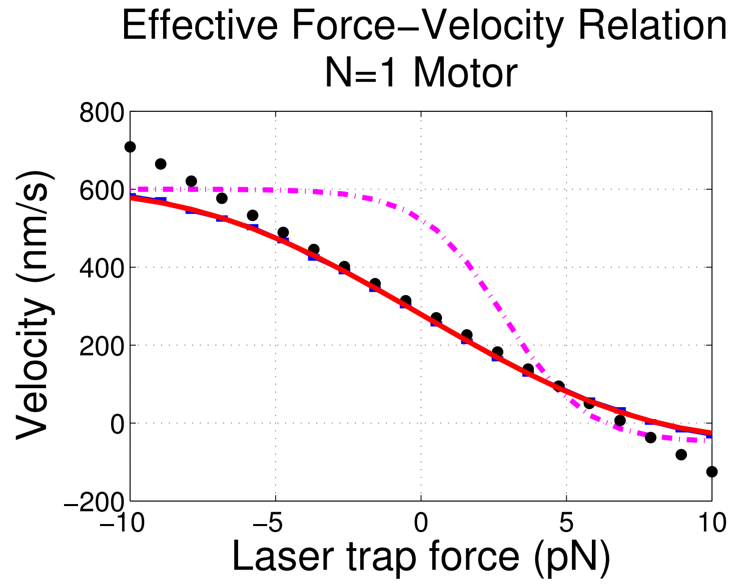
$$\mathrm{d}\check{X}(\bar{t}) = g(s\check{Y}(\bar{t}))\,\mathrm{d}\bar{t} + \sqrt{\rho}\,\mathrm{d}W_x(\bar{t})$$

$$\mathrm{d}\check{Y}(\bar{t}) = [g(s\check{Y}(\bar{t})) - \frac{1}{\epsilon}(\check{Y}(\bar{t}) - \tilde{\theta})]\,\mathrm{d}\bar{t} + \sqrt{\rho + 1/\epsilon}\,\mathrm{d}W_y(\bar{t}).$$

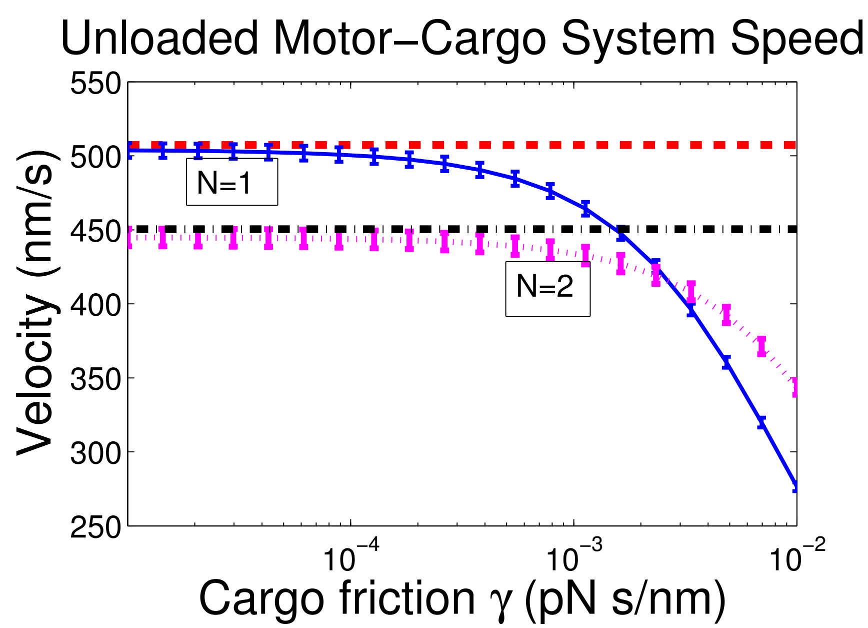
$$\lim_{t\to\infty} \frac{X(t)}{t} = v \int_{\mathbb{R}} \frac{1+\epsilon\rho}{2\epsilon} \left[\frac{\partial \pi_Y(y)}{\partial y} + \frac{2(y-\tilde{\theta})}{1+\epsilon\rho} \pi_Y(y) \right] \mathrm{d}y$$

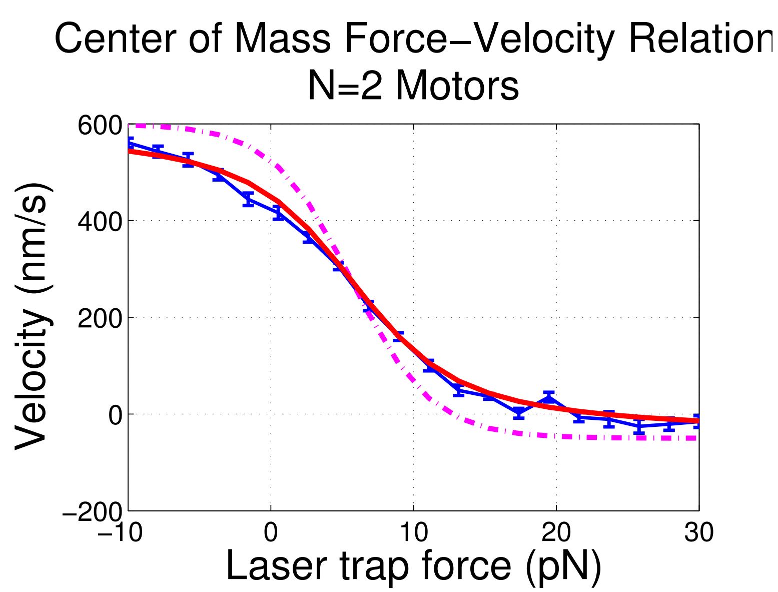
$$= \frac{v}{\epsilon} \left(\int_{\mathbb{R}} (y-\tilde{\theta}) \pi_Y(y)\,\mathrm{d}y \right) = \frac{v(\langle \check{Y} \rangle - \tilde{\theta})}{\epsilon} = \frac{\kappa \langle Y \rangle - \theta}{\gamma}$$

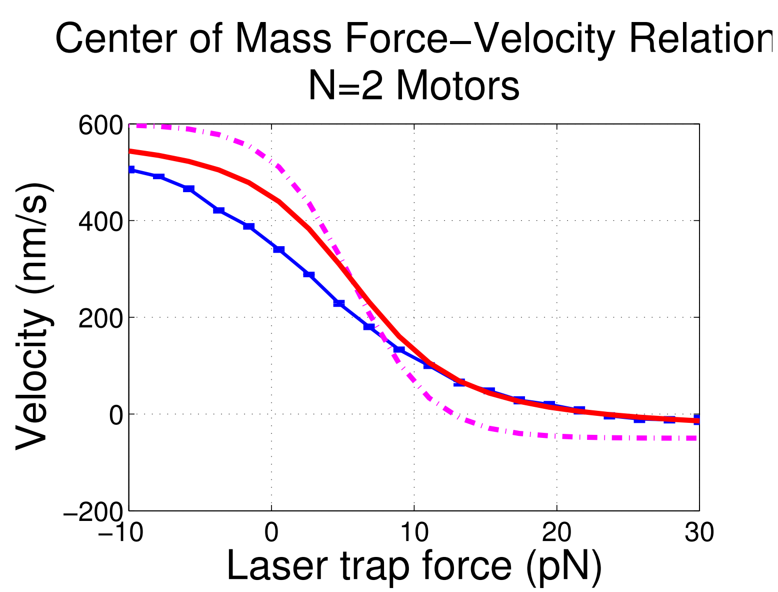
$$V_1(\theta) \approx \frac{v(1-\theta/F_*)}{1+\gamma v/F_*}$$



Results


Unloaded Motor−Cargo System Speed
550
500
450
400
350
300
250
Velocity (nm/s)
N=1
N=2
10^{-4}
10^{-3}
10^{-2}
Cargo friction γ (pN s/nm)


Center of Mass Force−Velocity Relation
N=2 Motors
600
400
200
0
−200
Velocity (nm/s)
−10
0
10
20
30
Laser trap force (pN)


Center of Mass Force−Velocity Relation
N=2 Motors
600
400
200
0
−200
Velocity (nm/s)
−10
0
10
20
30
Laser trap force (pN)

Multimotor Conclusions

- Dynamics of the cargo is faster than the velocity of the motor.

- Can give precise conditions on force-velocity curve when two motors are slower than one.

- Have explicit formulas for asymptotic velocity and effective diffusion of motor cargo complexes.

- Behavior breaks down in certain viscosity regimes. *in vivo* vs *in vitro*

Future Directions

- Switching. How do the dynamics change as motors become attached and detached?

- Tug-of-war. How do the dynamics change with more than one type of motor?

- Build feedback explicitly into nanoscale model of the motor. (Nanoscale to mesoscale.)

- How do these motor complexes interact with complex microtubule dynamics? (Mesoscale to microscale and higher)

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