Matrix Calculations in Diffusion Approximations for Molecular Motors

SIAM Conference on Computational Science and Engineering
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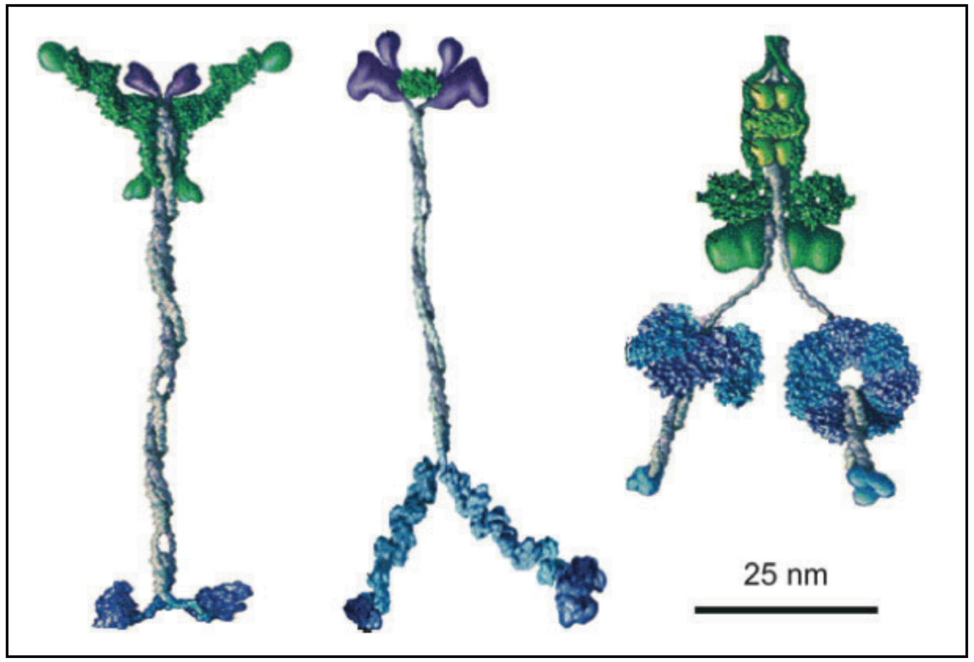
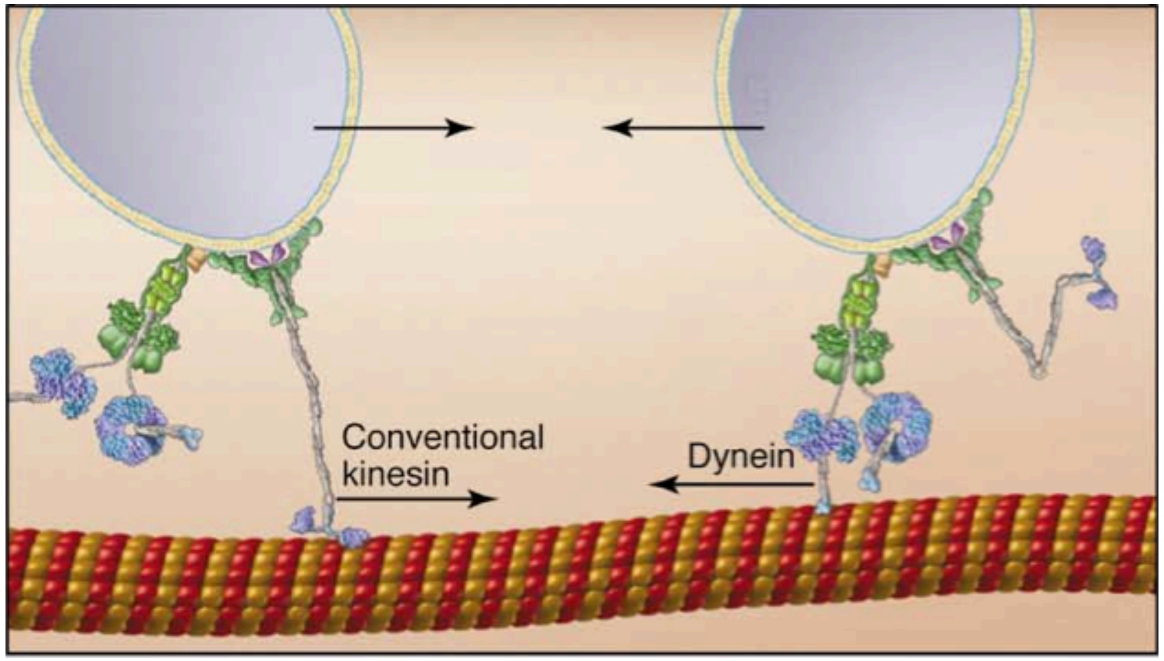
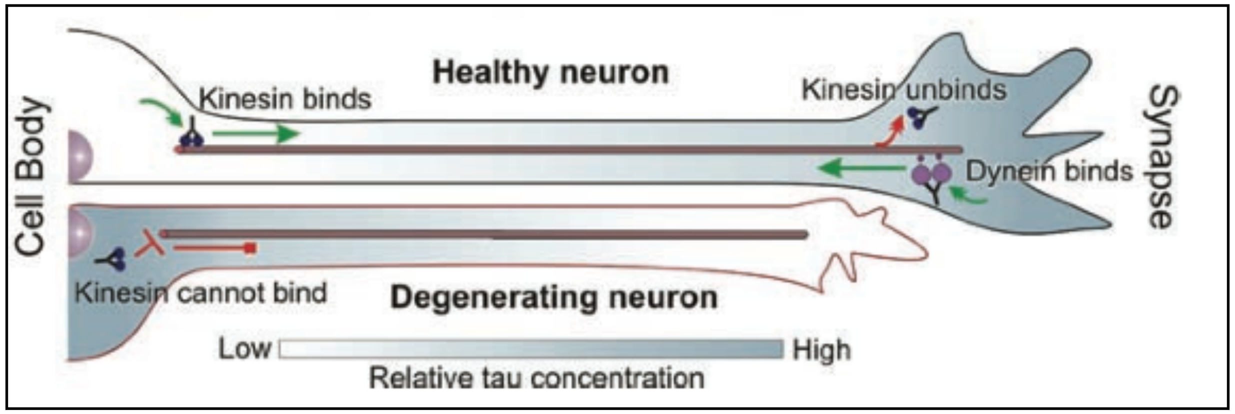
Examples of Motors



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

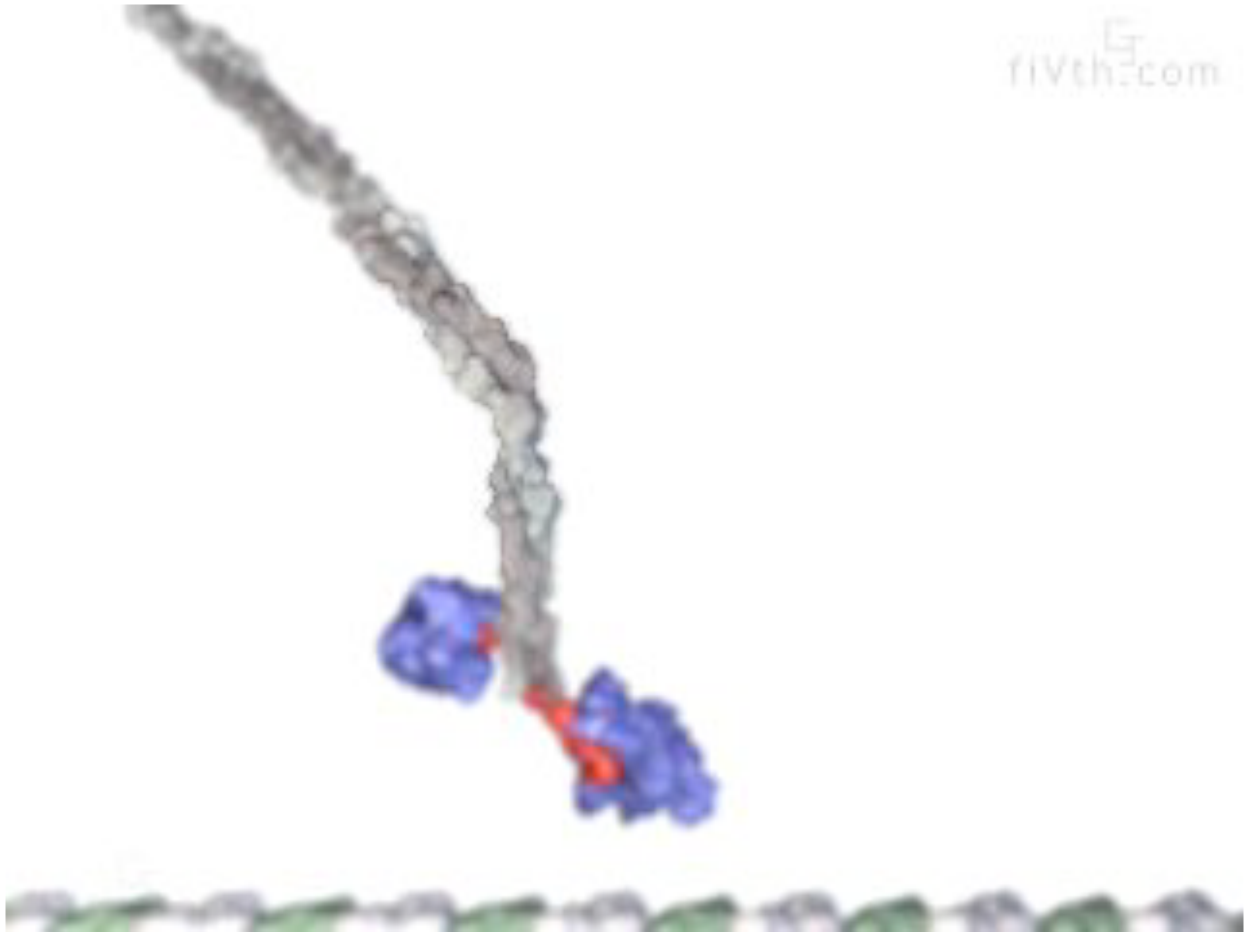


R Vale, Cell, 2003



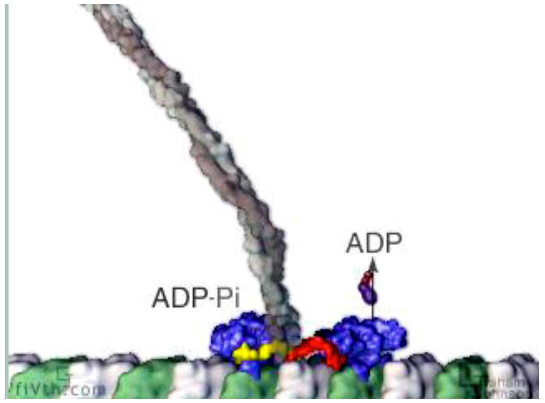
R Dixit, Science, '09

Kinesin Movie



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

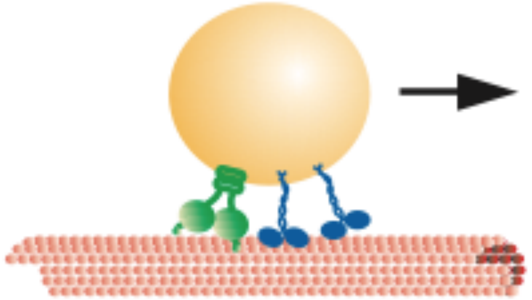
Scales



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

- **nanoscale**

(Stay for the rest of the talk.)



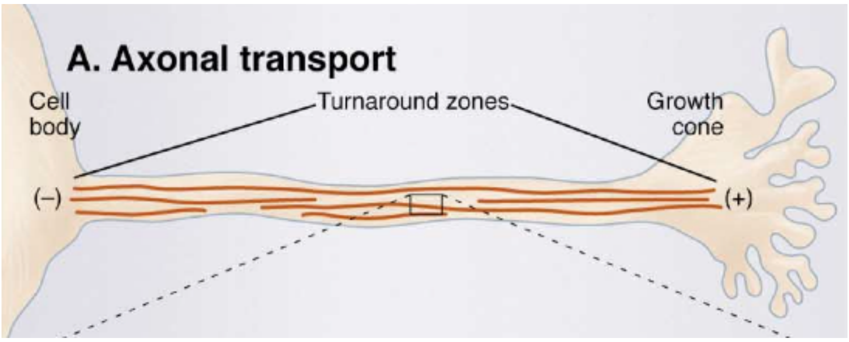
S Gross, Phys. Biol., 2004

- **mesoscale: tens of nanometers to micron**

(Come to Peter Kramer's talk at 4.)

- **microscale: microns to centimeters**

(See, for example Mckinley, Popovic, and Reed.)



S Gross, Phys. Biol., 2004

Who cares?

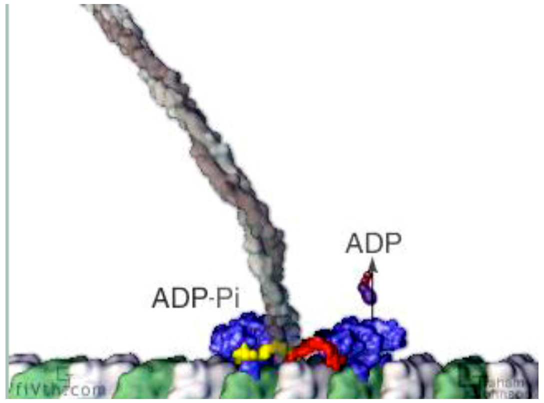
- When an axon is severed from a dendrite, it must be regenerated.

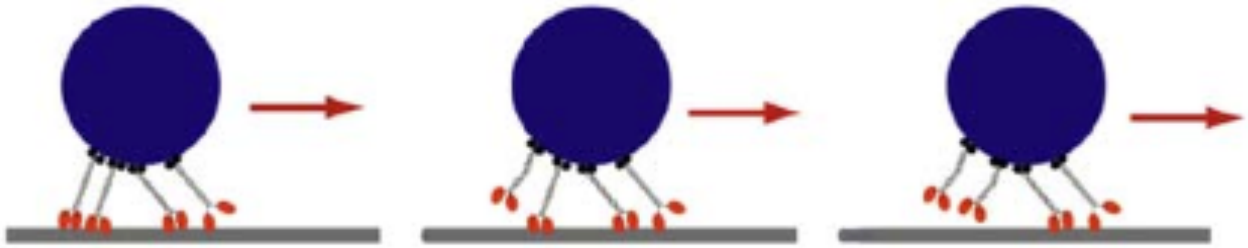
- The microtubules near the regeneration site realign in a mixed polarity.

- What effect does this have on kinesin (and dynein) transport? Does the effect on transport have a restorative role?

Orientation

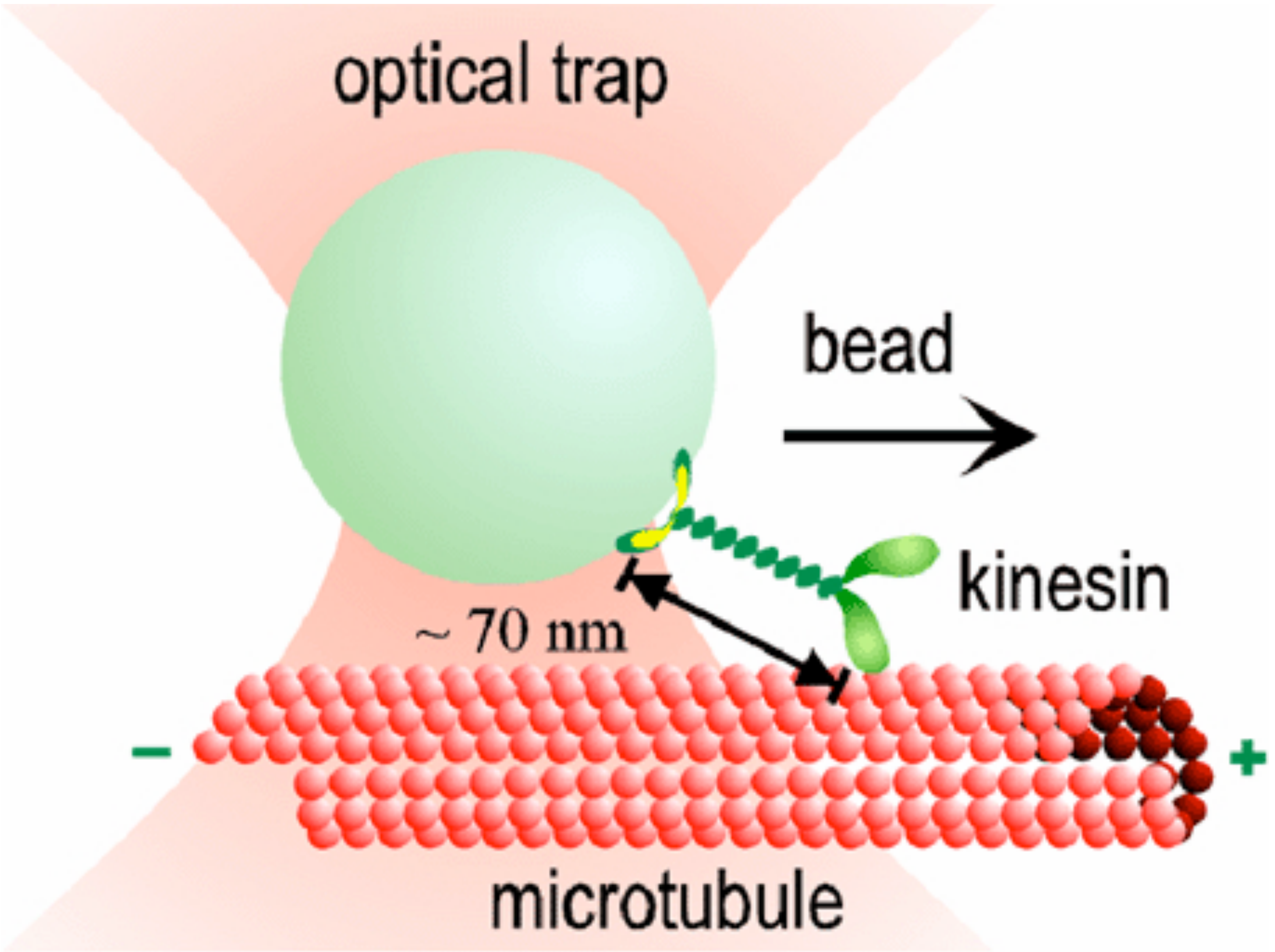
- How is the process regulated?
- At the nanoscale?
- Through MAPS, Post-translational modifications, etc?





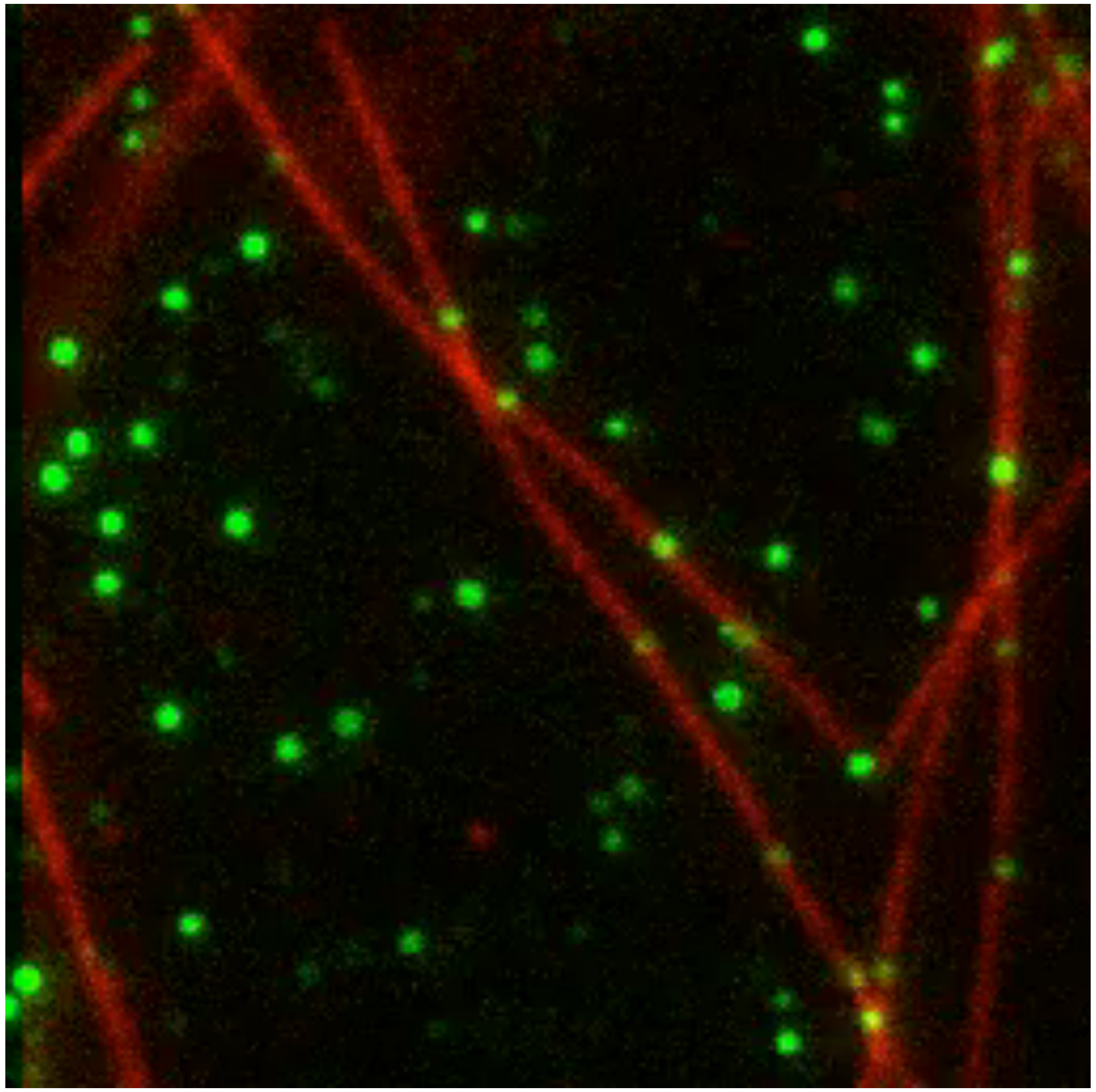
R Lipowsky, et al Phys E, 2010

Laser Trap

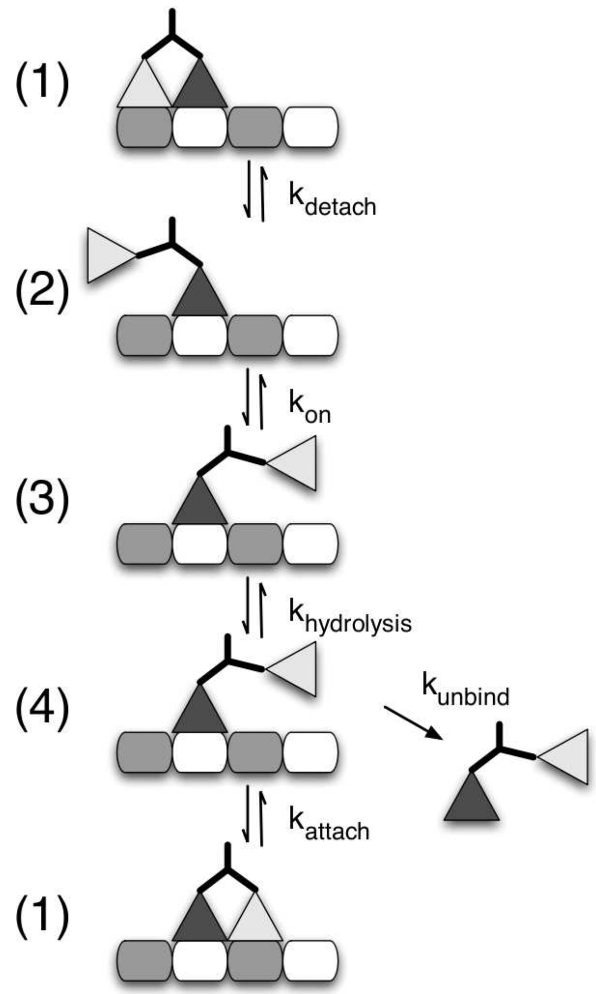


Block Lab:http://www.stanford.edu/group/blocklab/kinesin/kinesin.html

Fluorescence Experiment



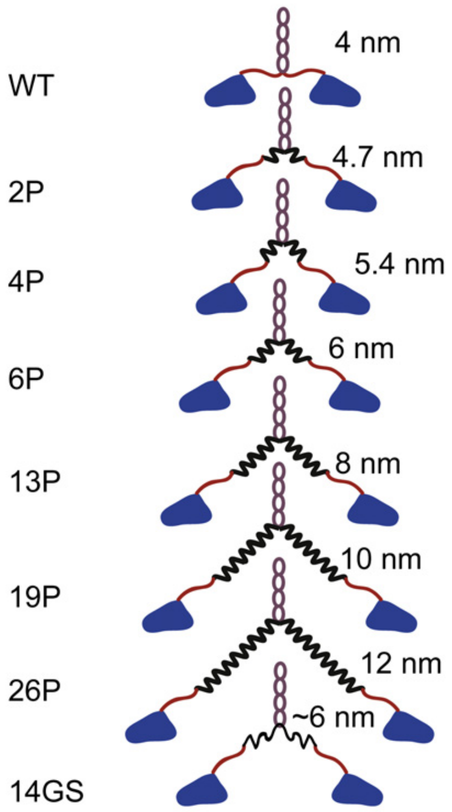
Diffusion and Kinetics of a Step



Diffusion and Kinetics of a Step

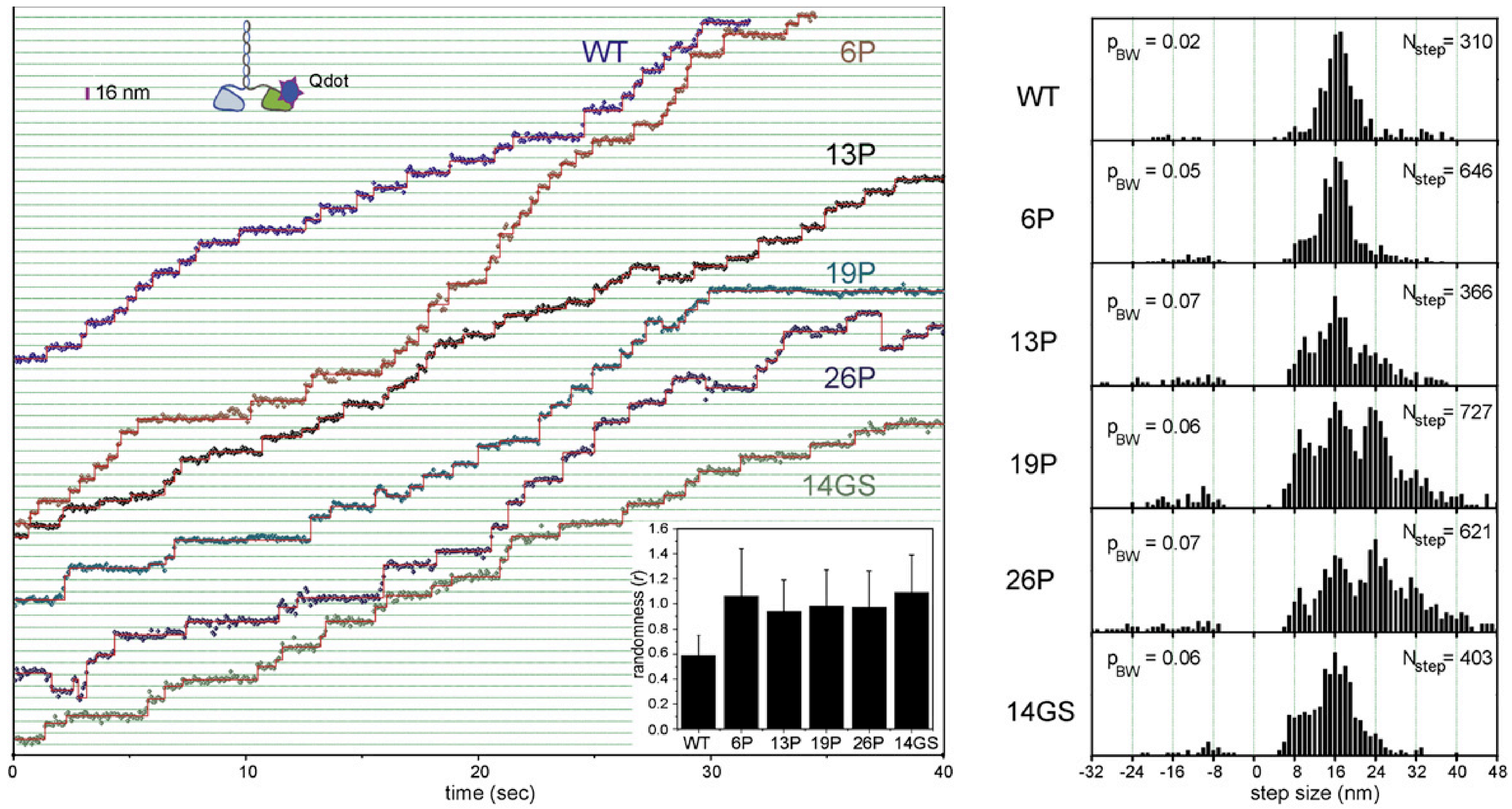
- Engineered Motors
- First Try. Intrastep Diffusion of Heads.
- Second Try. Variable Length Stepping.
- An Application to Statistics.

Engineered Motors.



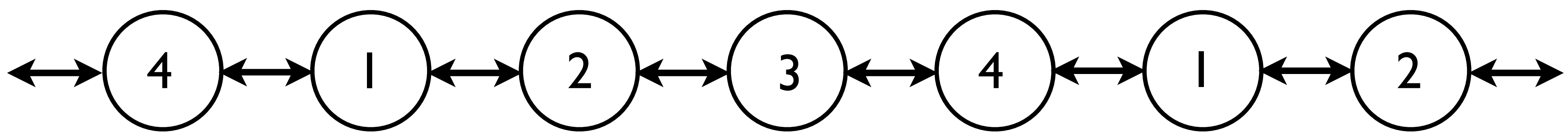
- Extensions can range from less than 1 nm up to 12 nm.
- Hackney and Hancock–extensions reduced processivity.
- Hancock–velocity was reduced.
- Yildiz et al–processivity was unaffected and velocity was reduced.

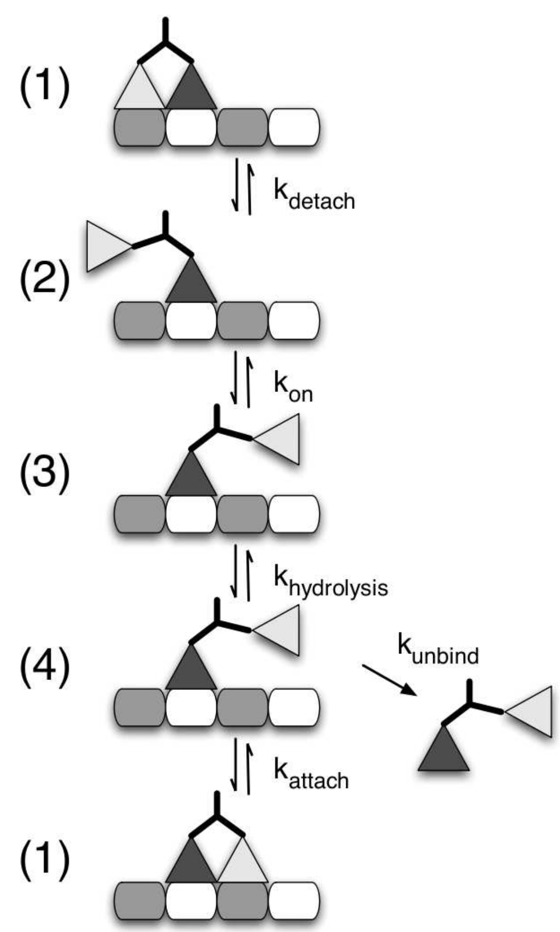
Yildiz et al.



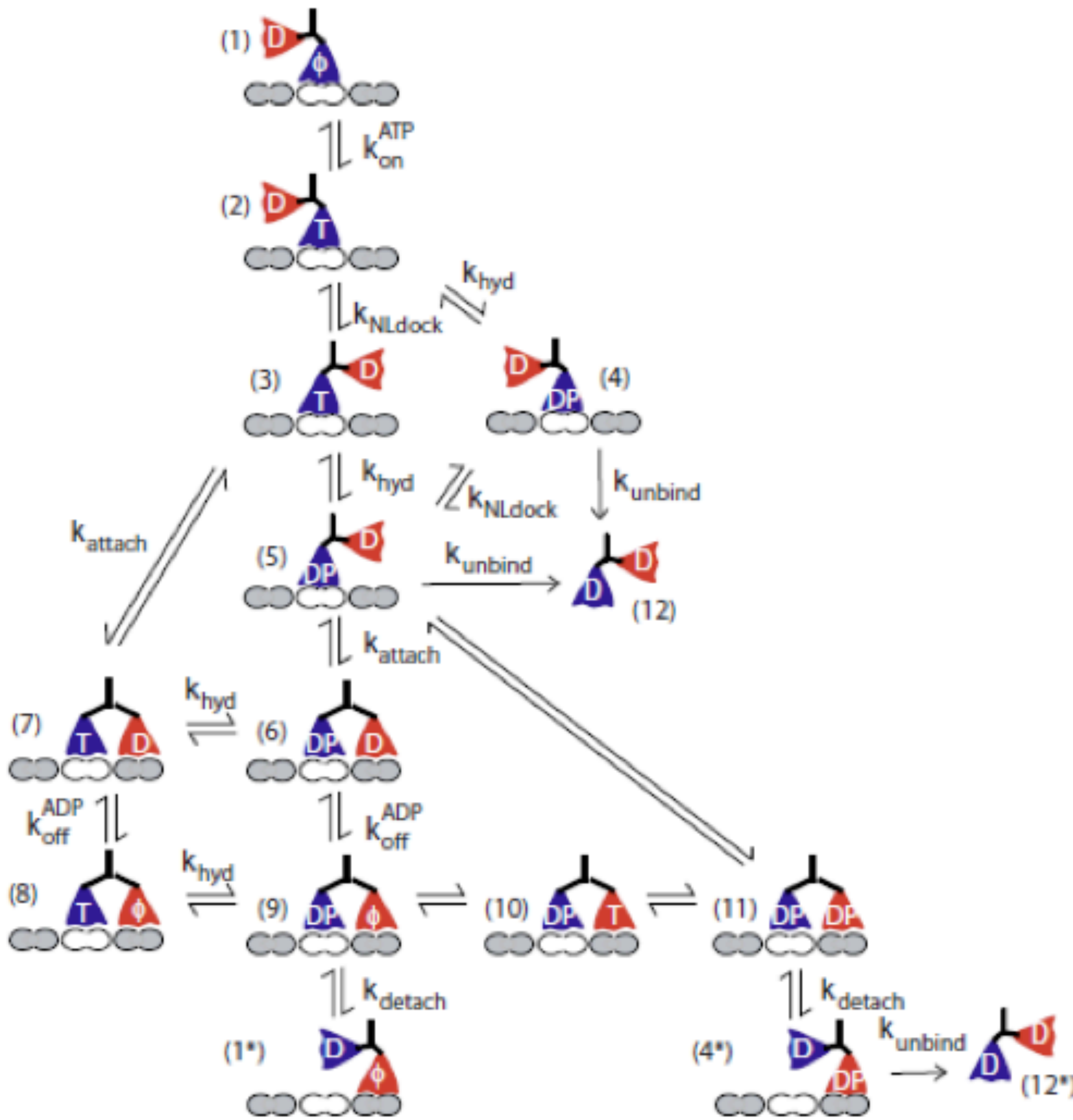
Yildiz, A. and Tomishige, M. and Gennerich, A. and Vale, R.D. correct cite

Discrete Space Markov Process

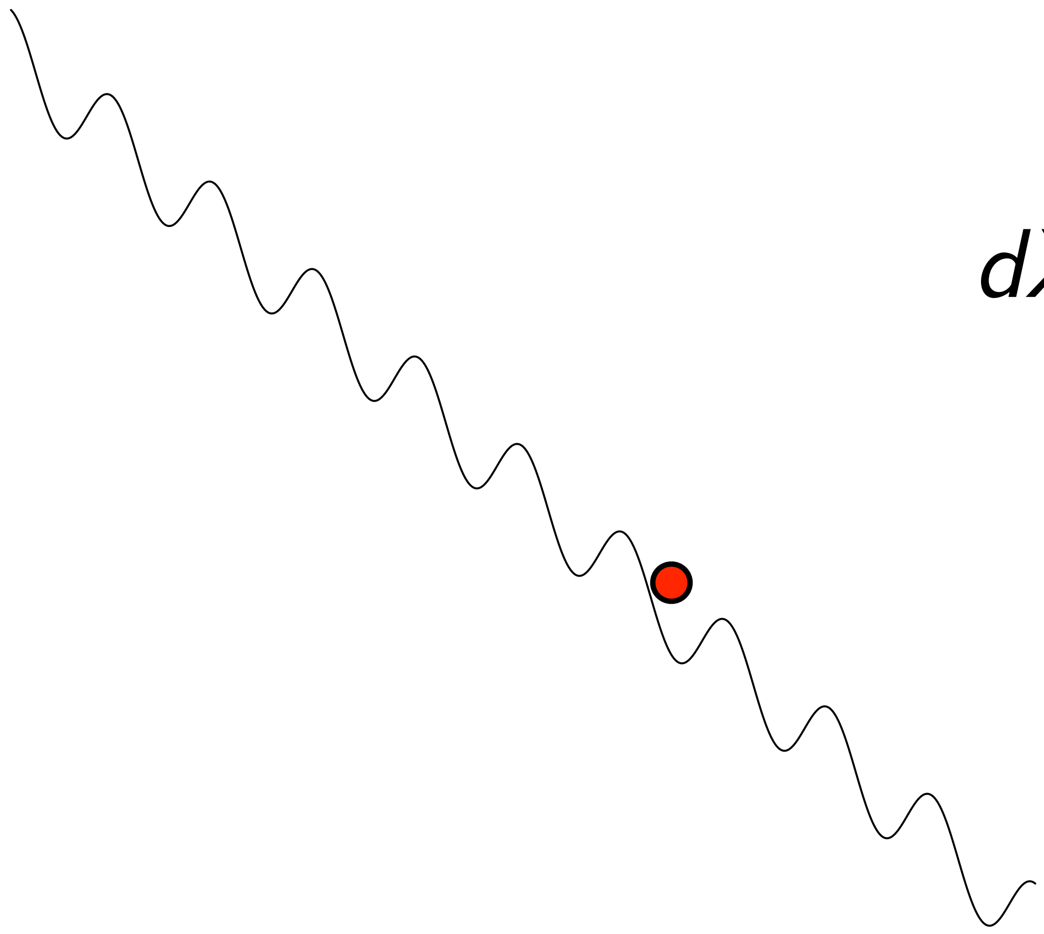




More Complex

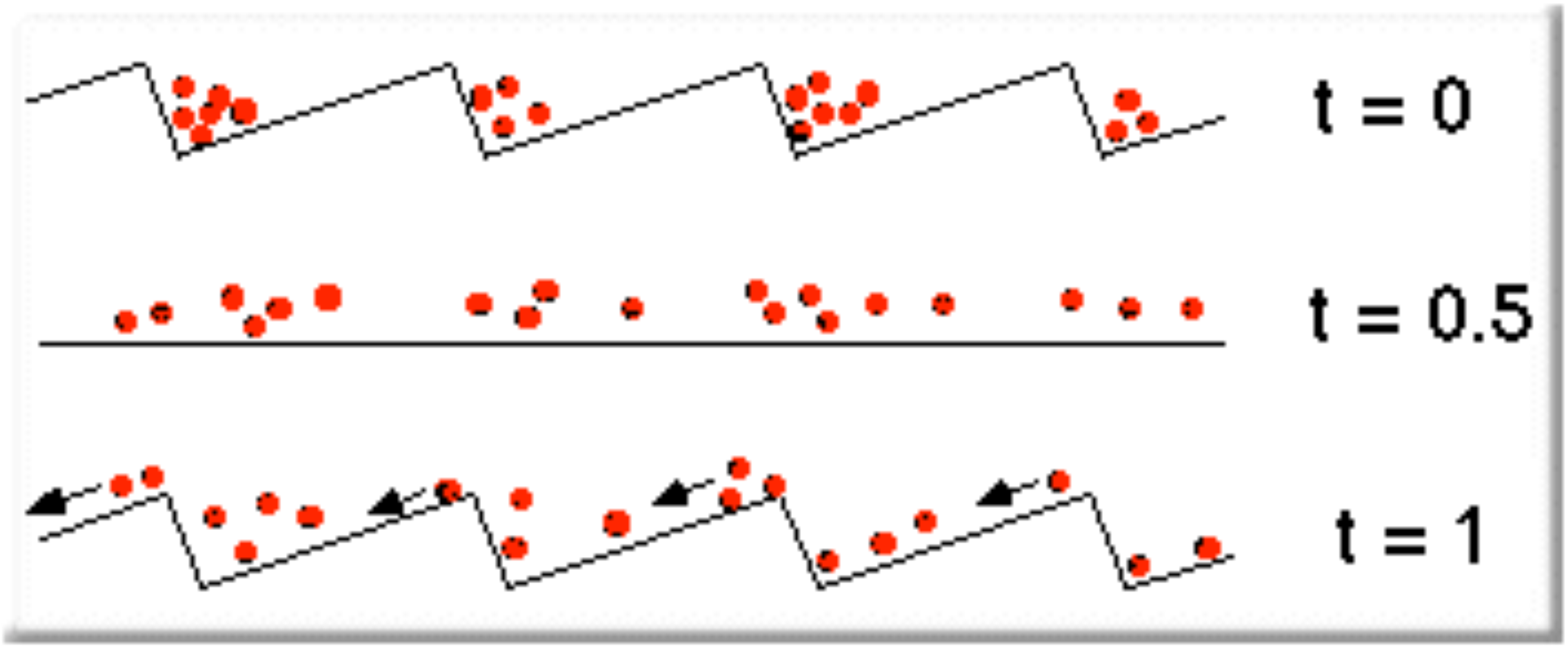


Stochastic Differential Equation



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

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

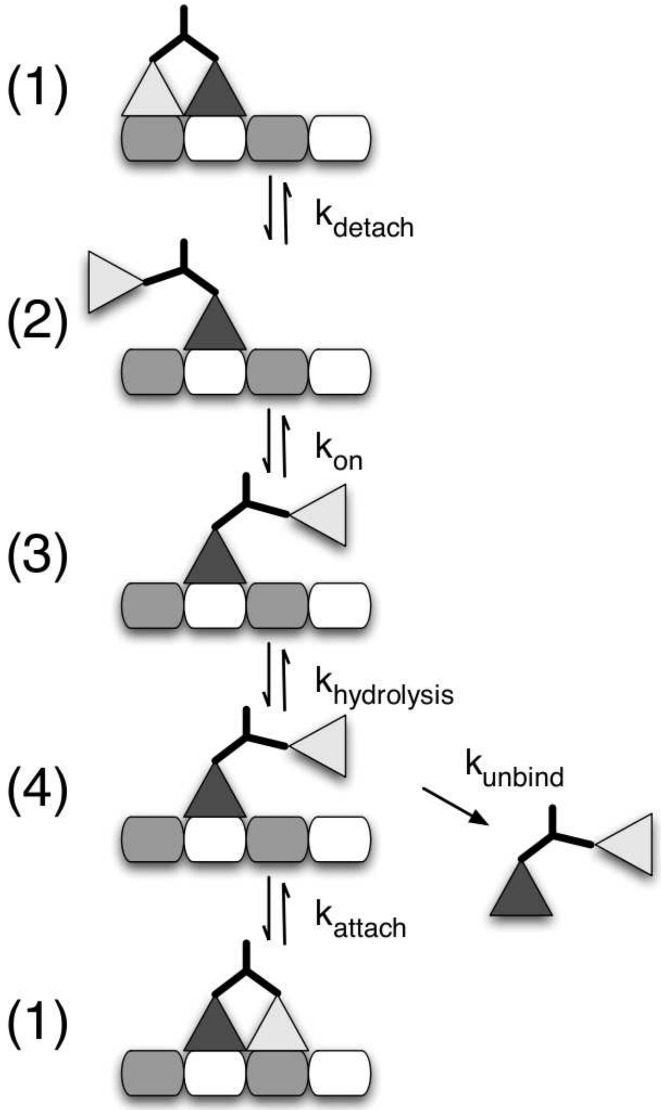
- **Effective Diffusion** $$D_{eff} = \lim_{t \to \infty} \frac{Var[X(t)]}{2t}$$

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

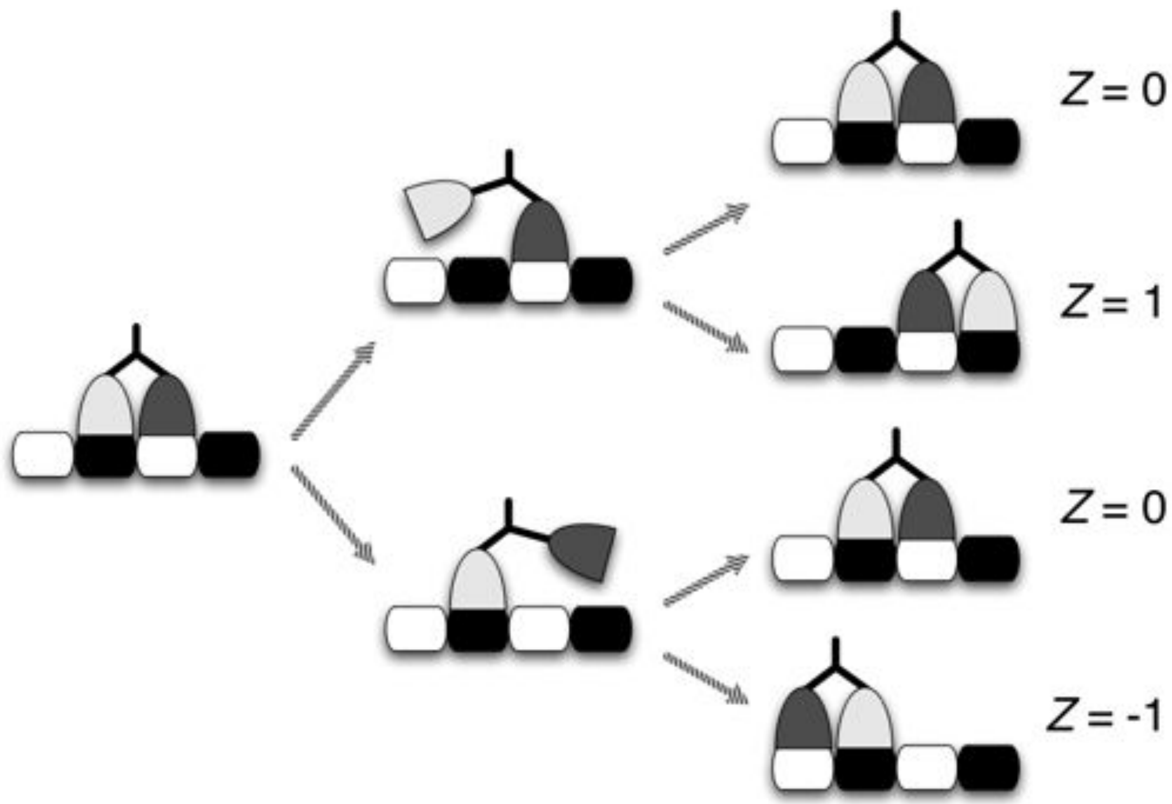
- **Processivity**

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

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

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. (Corresponding PDF file is 11 pages.)

Mathematical Model-First Try

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

Linear Spring

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

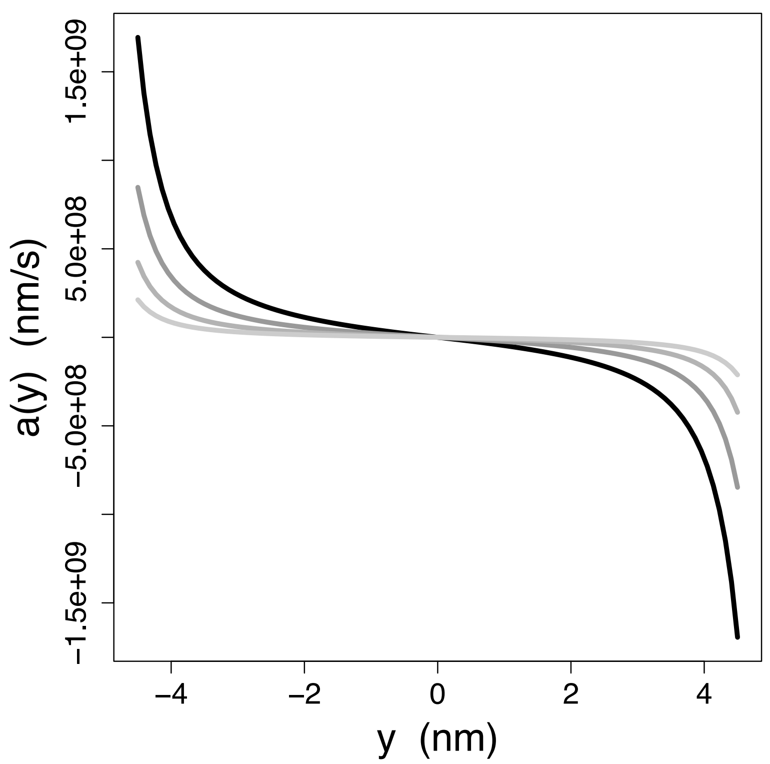
WLC

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

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.

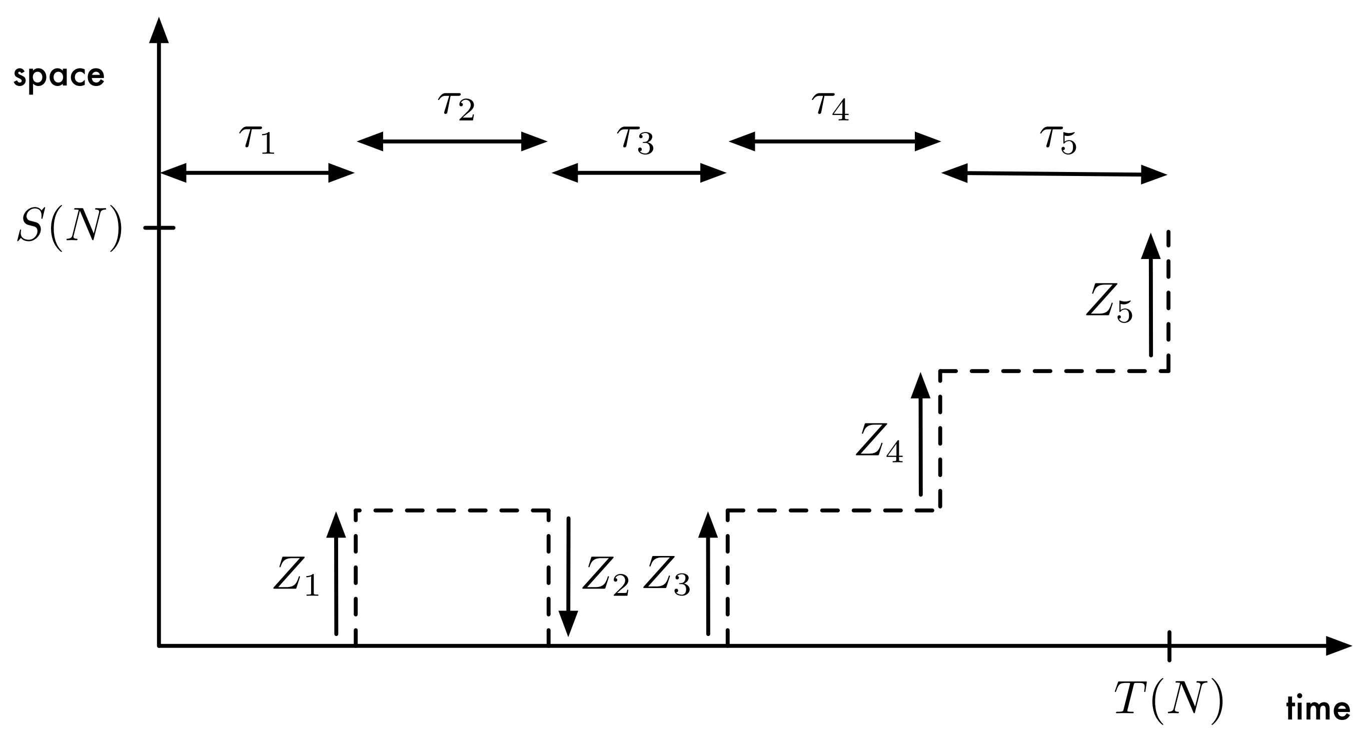
Fredkin and Rice a comprehensive look.

Colquhoun and Hawkes with ion channels.

Queueing Literataure–Asmussen, Neuts+others

A Semi-Markov Framework

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



John Hughes, William Hancock, and John Fricks (2011). A Matrix Computational Approach to Kinesin Neck Linker Extension. *Journal of Theoretical Biology.* **269**, No. 1, 181-194.

Standard Quantities

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

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

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

CLT

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

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

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

and we apply a continuous mapping theorem.

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

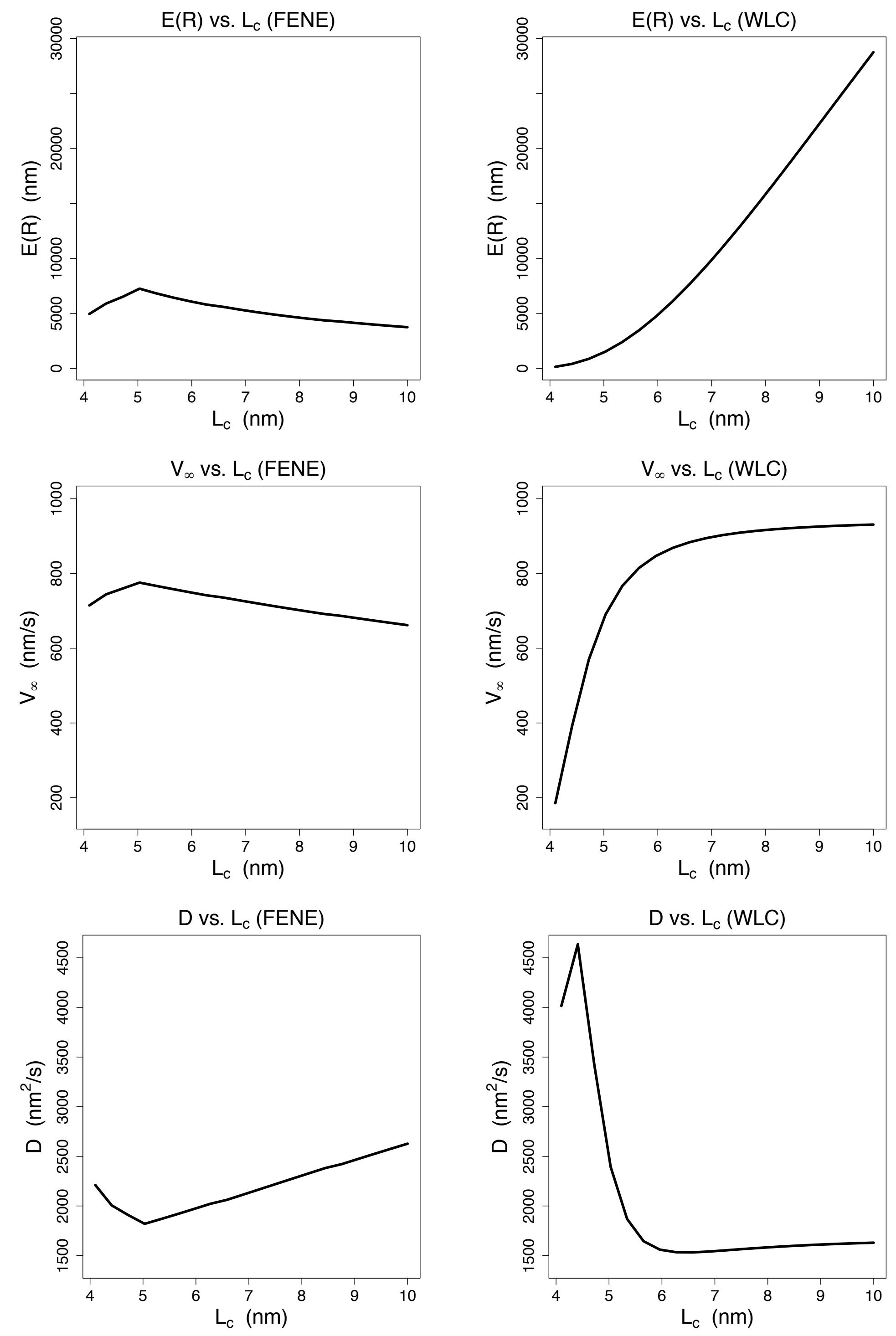
Or

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

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

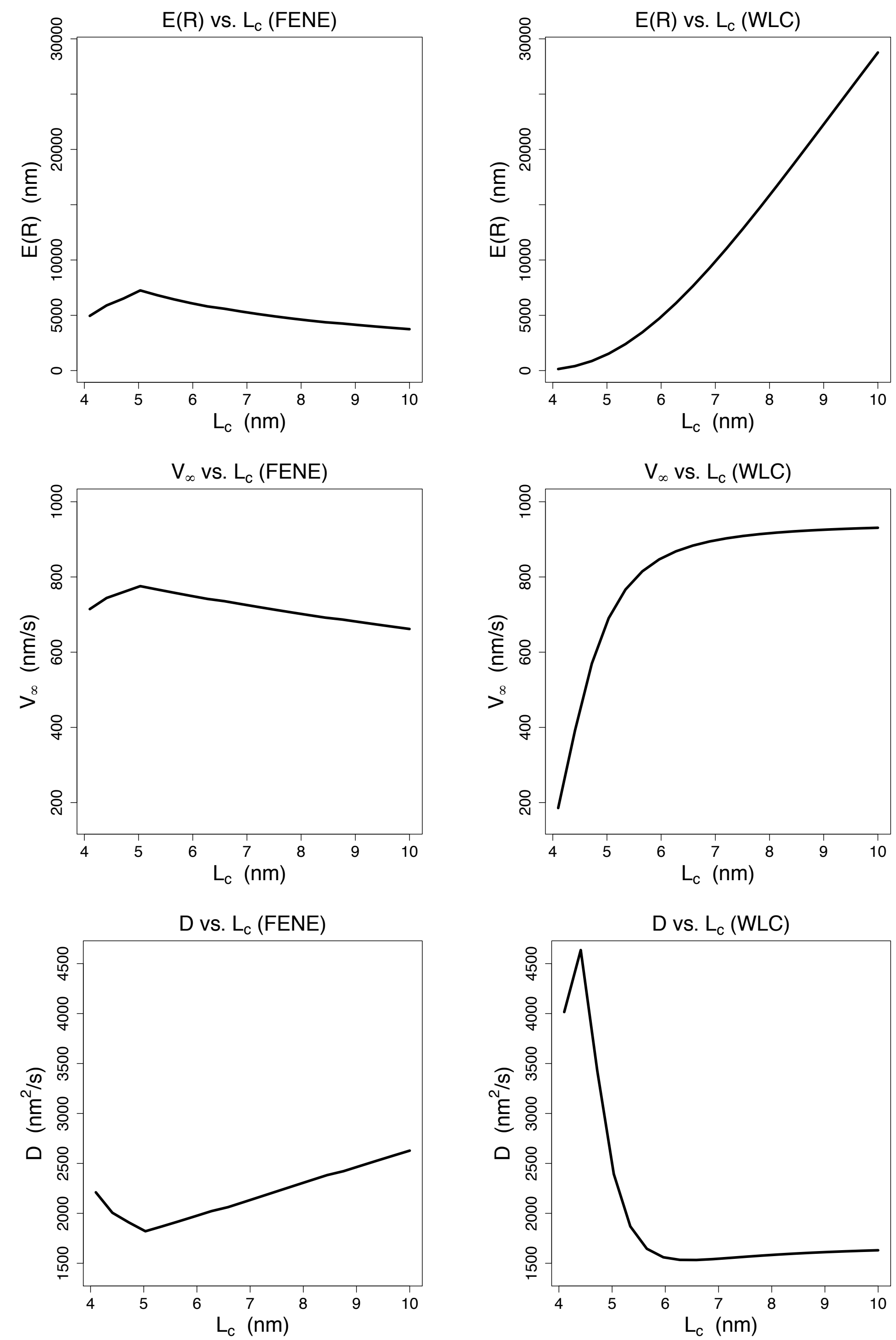
Results for First Try

- Run length is unaffected/reduced in experiments.
- Run length decreases mildly in FENE
- Run length increases rapidly for WLC.

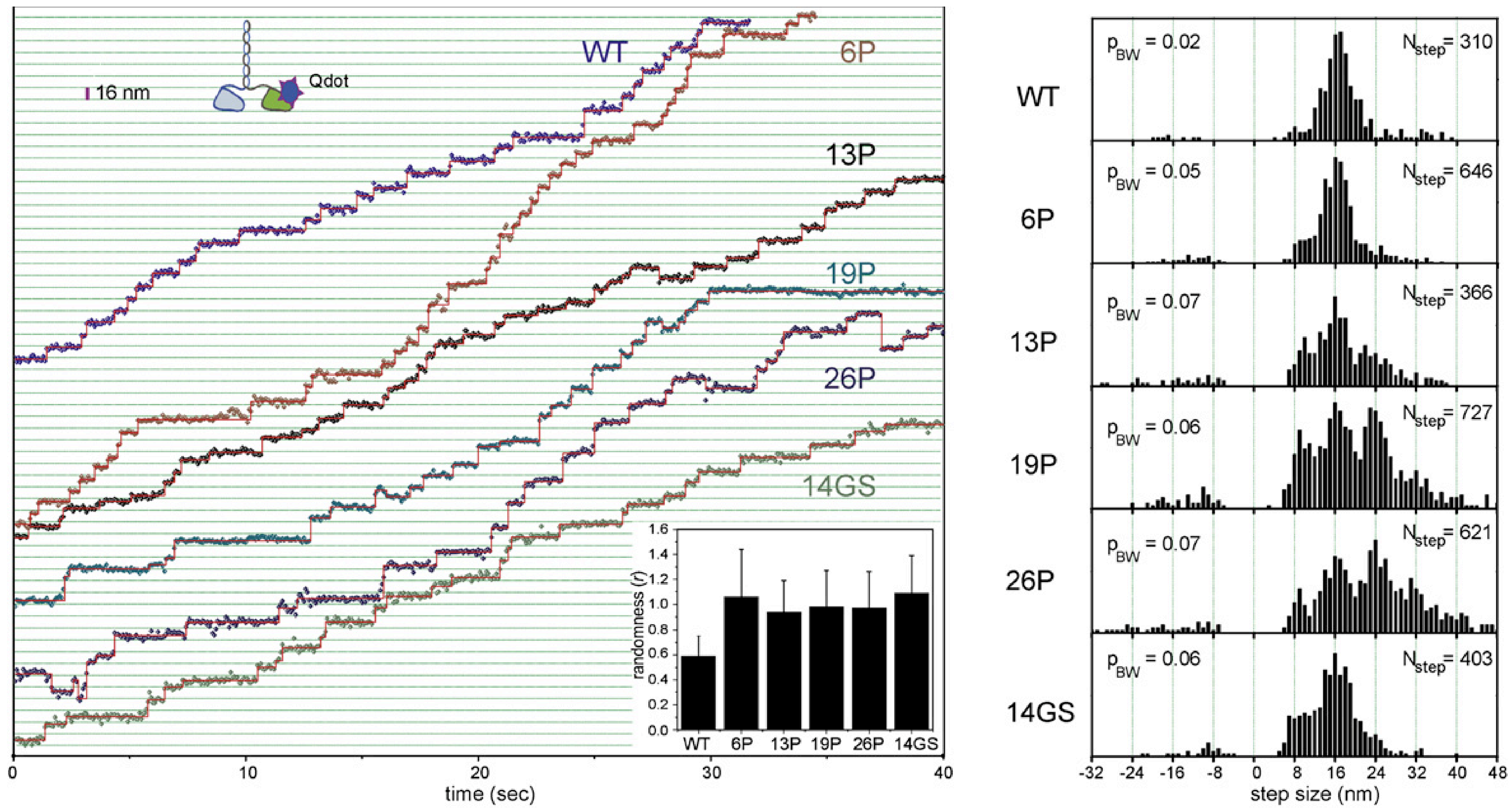


Results for First Try

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

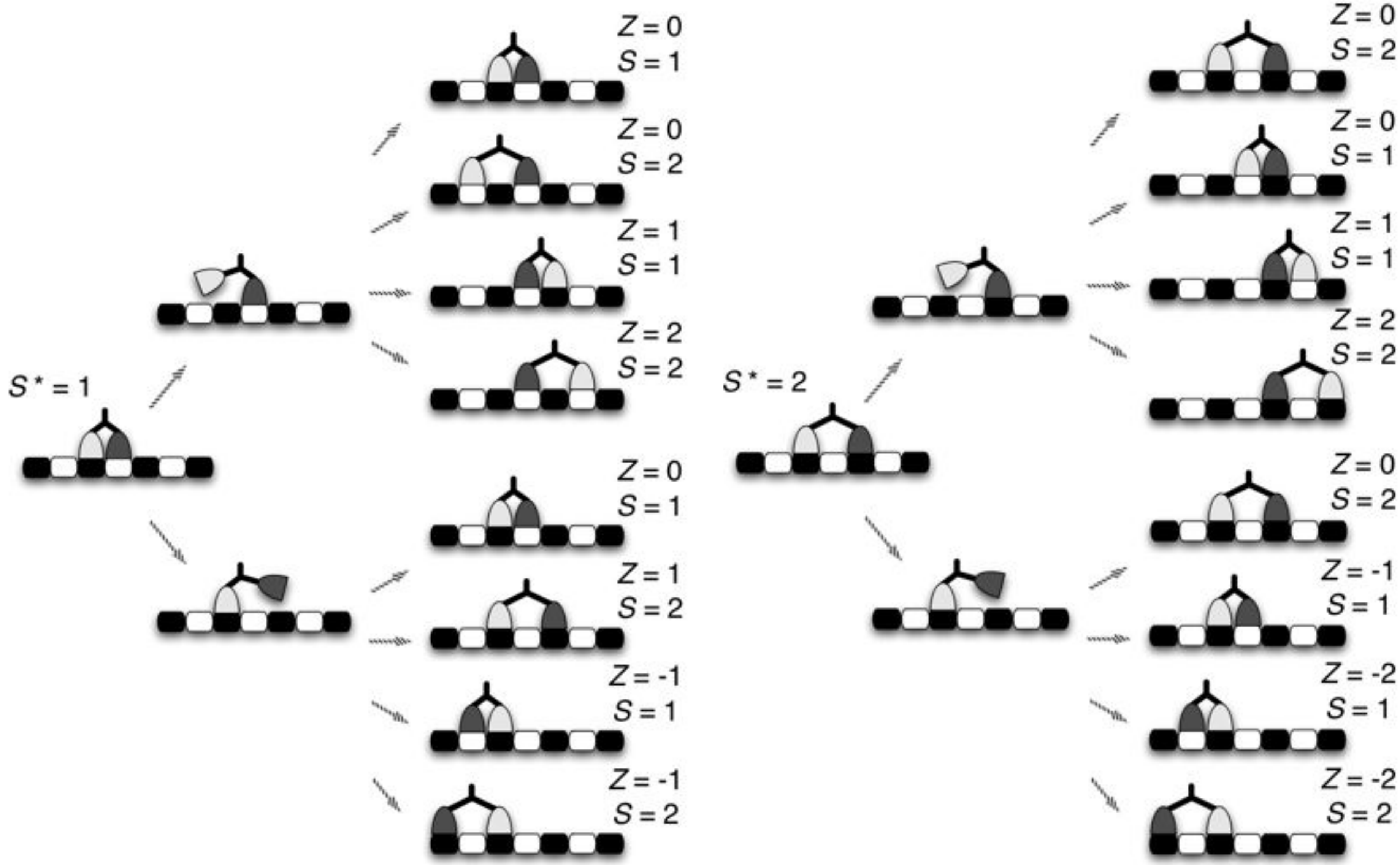


Yildiz et al.



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

Mathematical Model–Second Try



John Hughes, William O. Hancock, and John Fricks (2011). Kinesins with Extended Neck Linkers: A Chemomechanical Model for Variable-Length Stepping. To appear in *Bulletin of Mathematical Biology*.

Mathematical Model–Second Try

- 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 Try

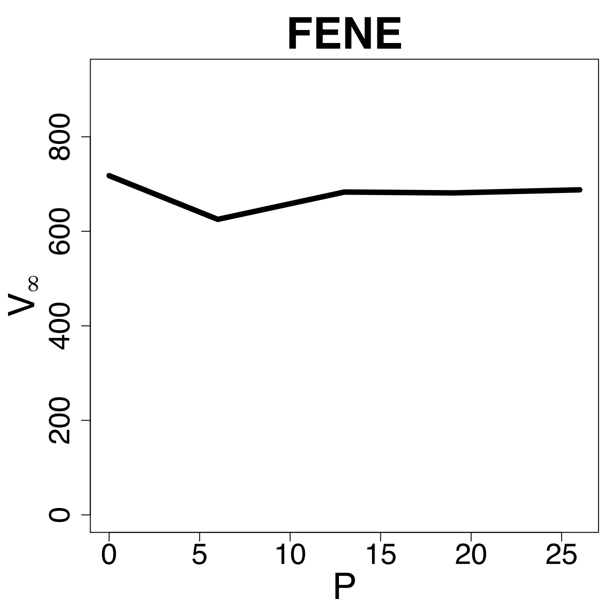
$$\begin{pmatrix} Z_i \\ \tau_i \\ S_i \end{pmatrix}$$

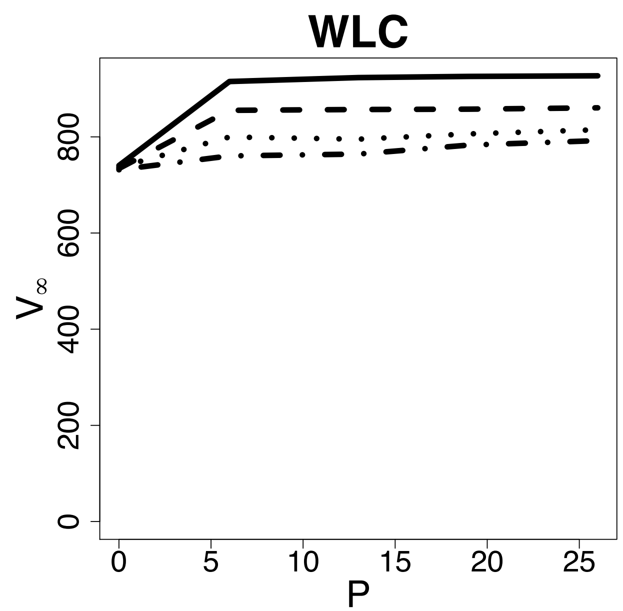
S_i is a Markov chain describing the distance between heads after previous cycle.

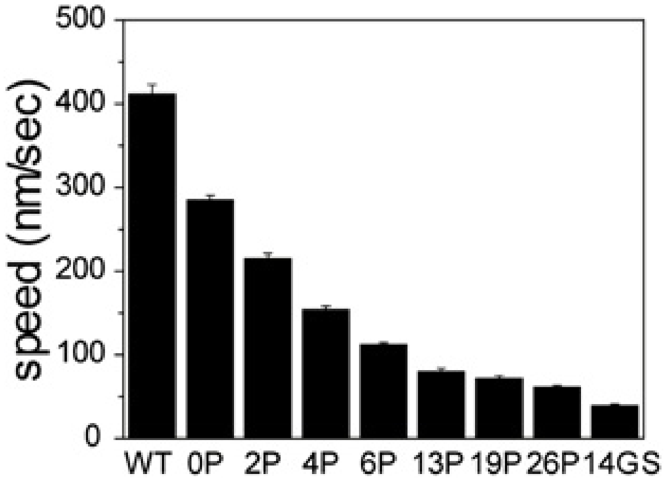
The position of the front head after a full cycle

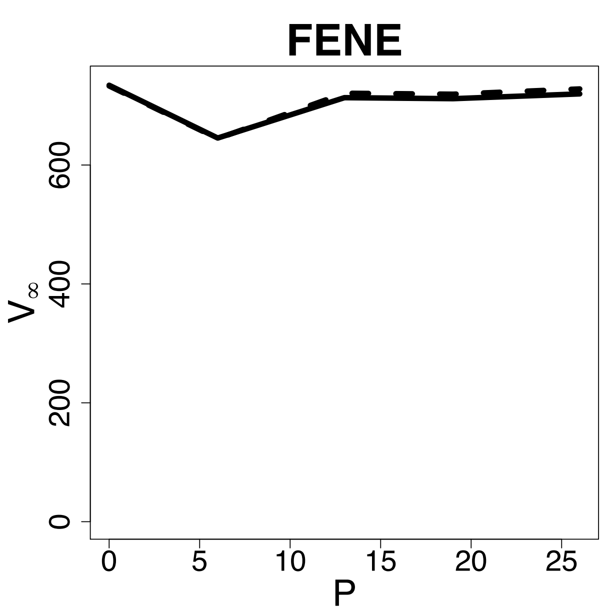
$$X(t) = \sum_{i=1}^{N(t)} Z_i$$

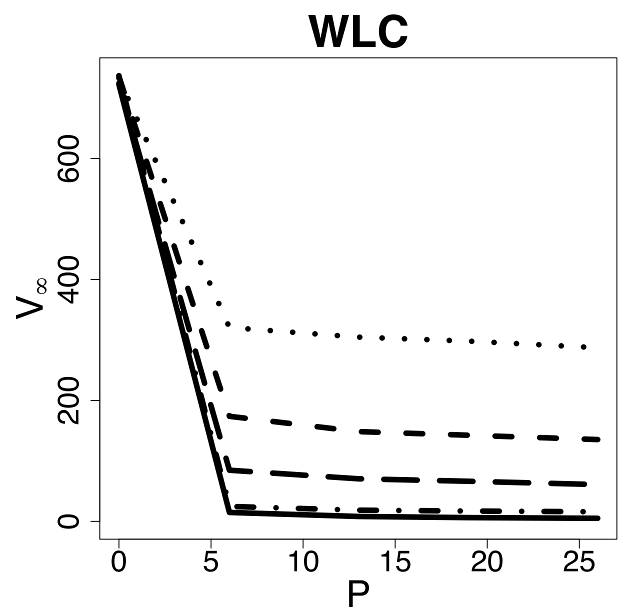
Results for Second Try



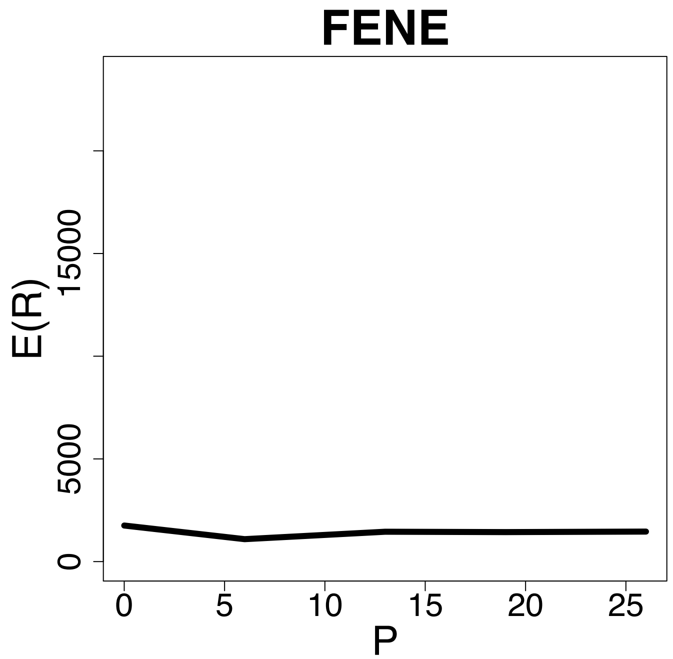


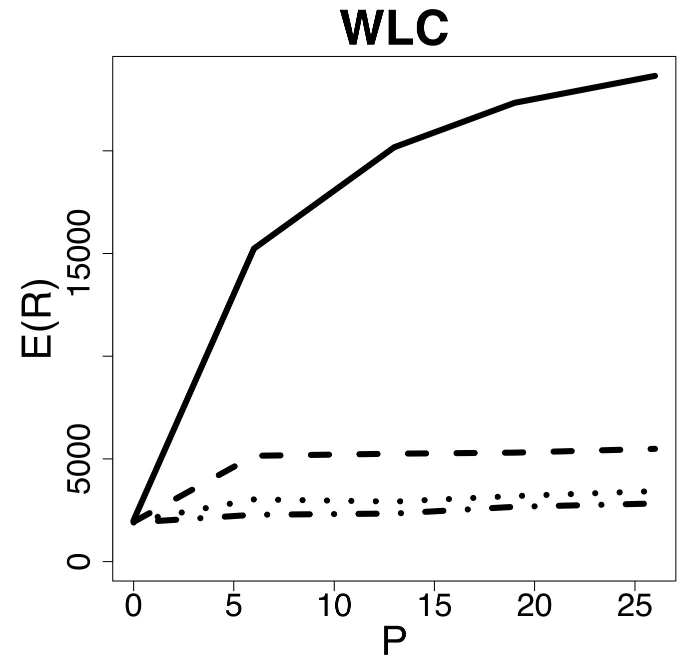


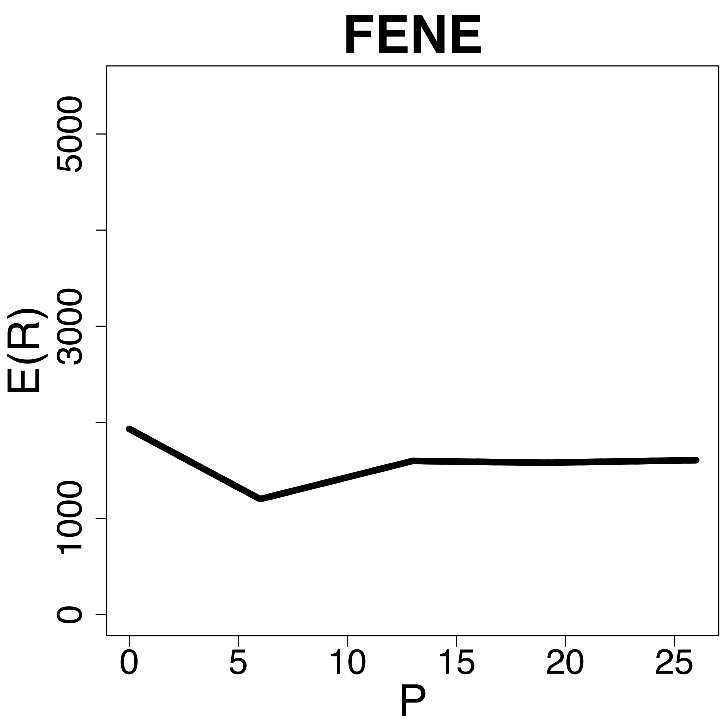


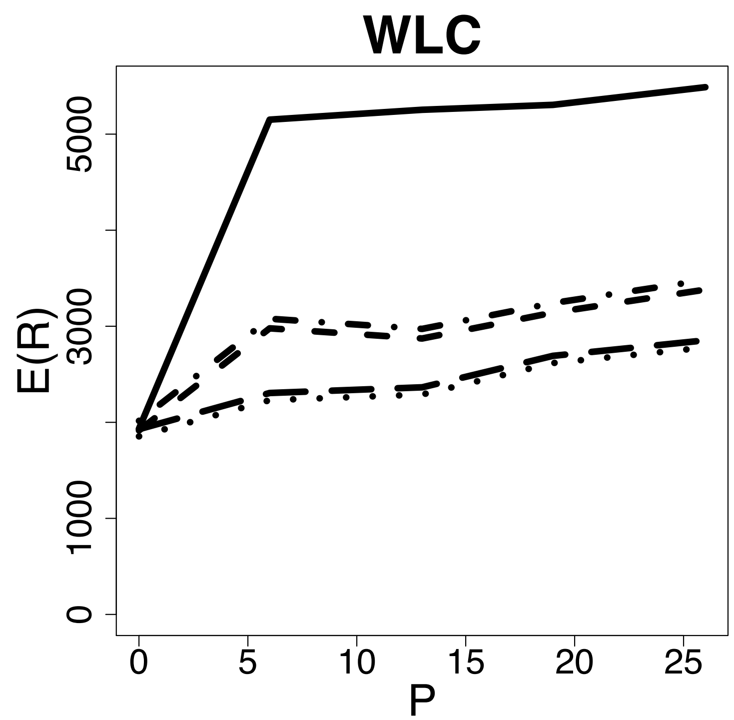


Results for Second Try









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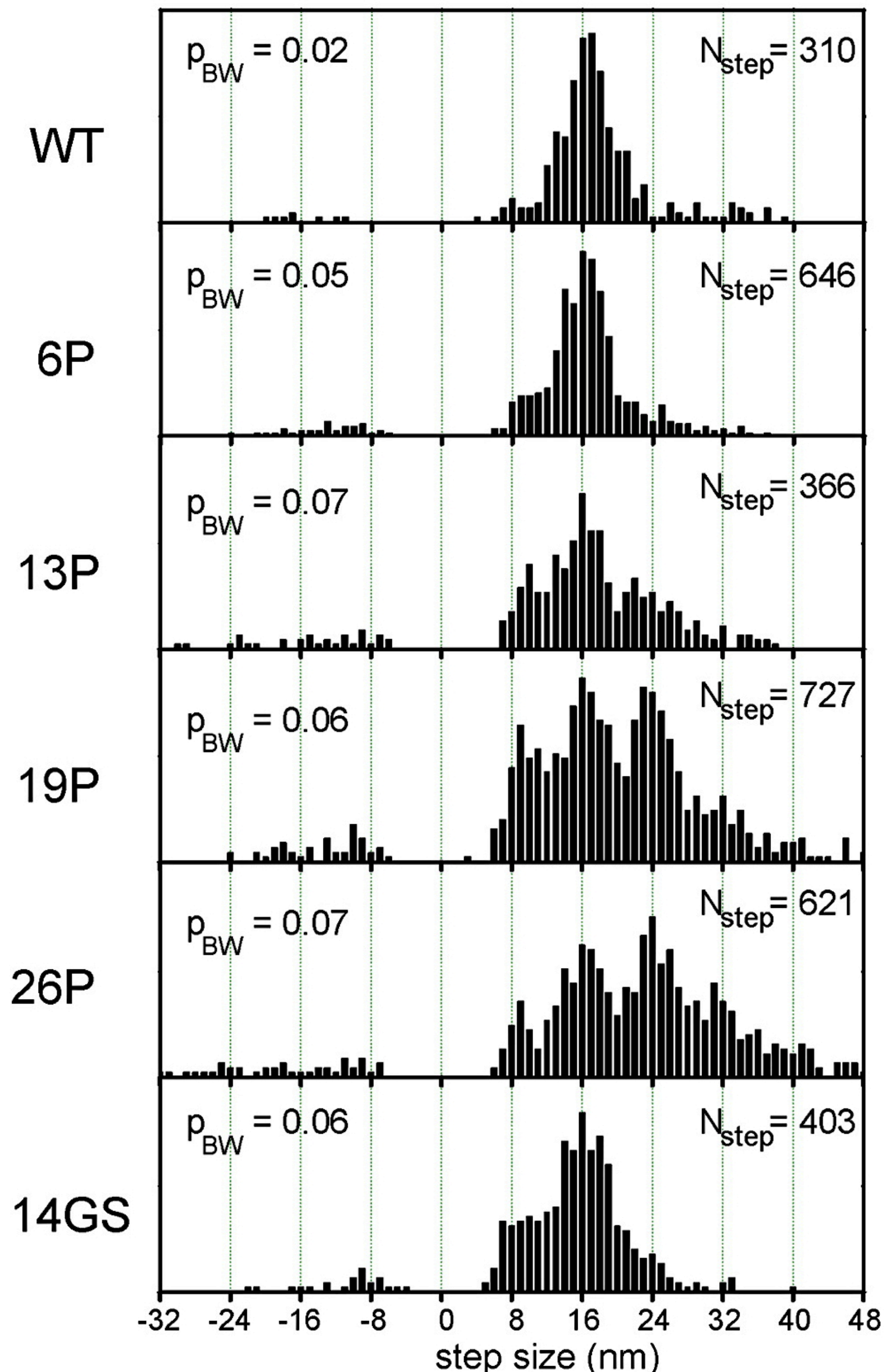
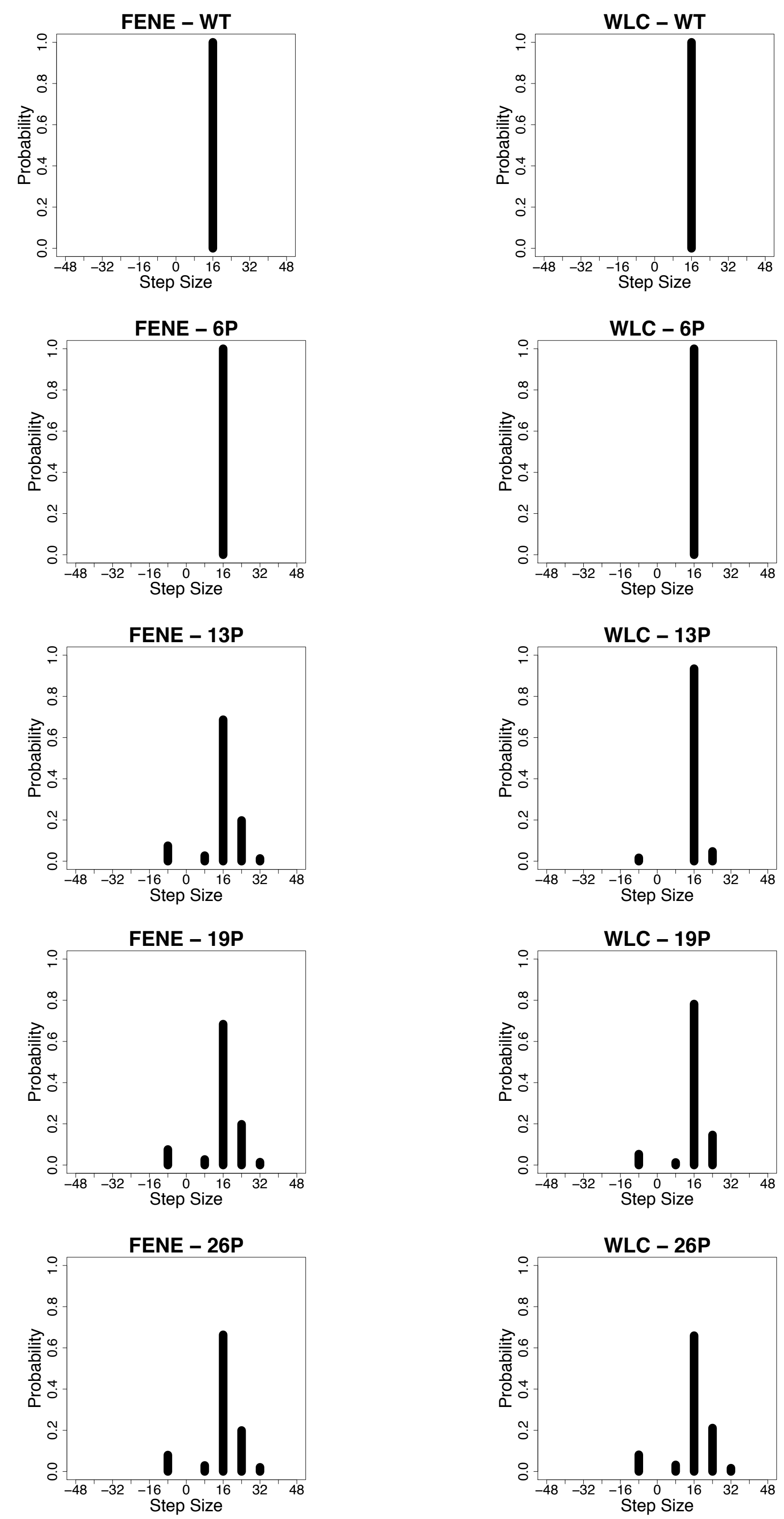




Random Stopping

- By using the renewal-reward framework, we can find the 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

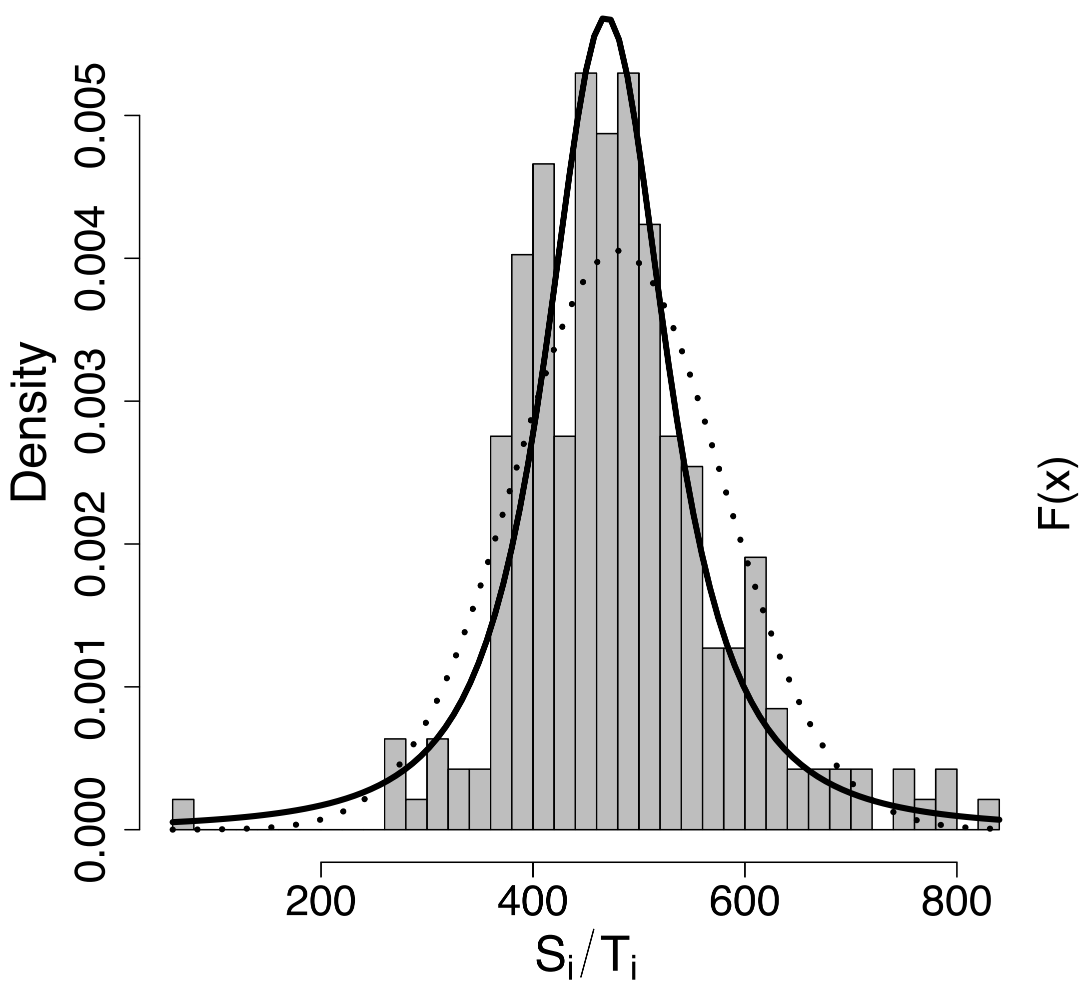
- The Pearson VII distribution

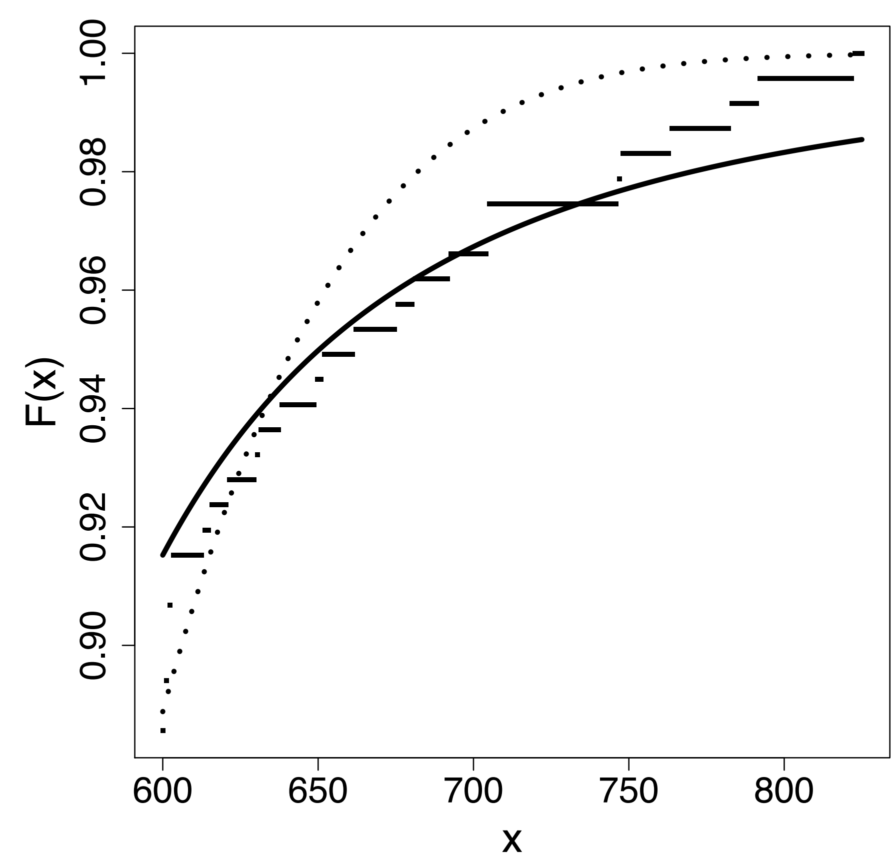
$$f(x) = \frac{1}{\sigma\beta\left(\alpha - \frac{1}{2}, \frac{1}{2}\right)} \left(1 + \left(\frac{x-\mu}{\sigma}\right)^2\right)^{-\alpha}$$

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

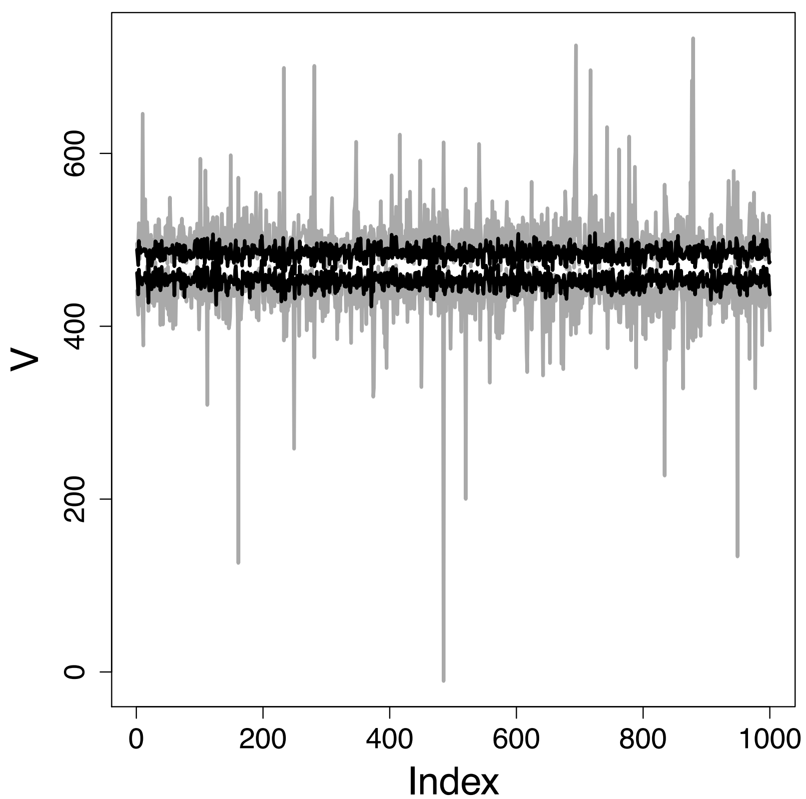
Pearson VII

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

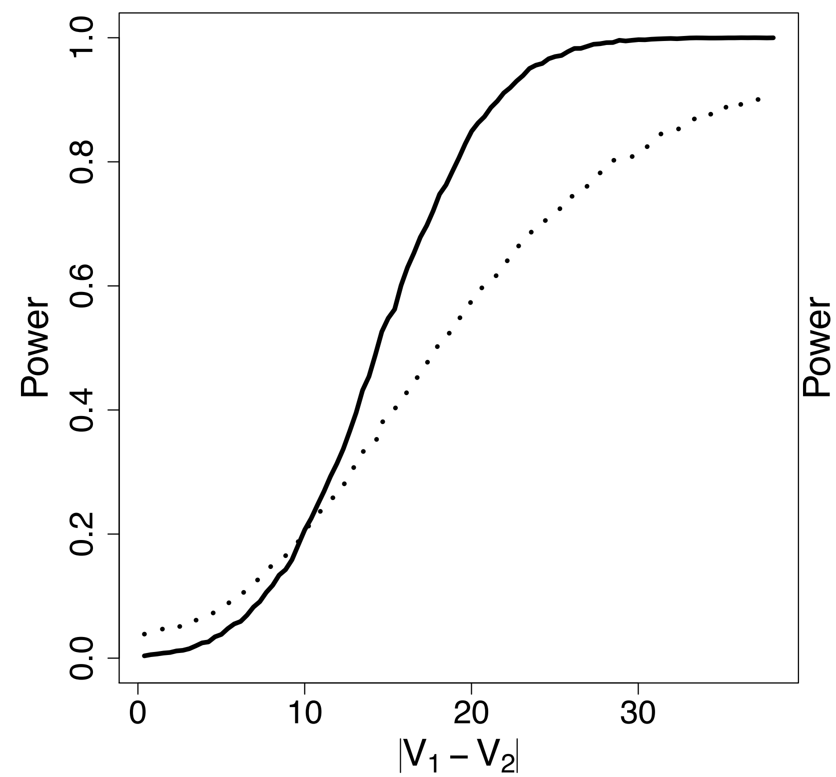




Pearson VII



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



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

Conclusions Nanoscale to Mesoscale

- The WLC model gives qualitatively similar behavior to experiments.

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

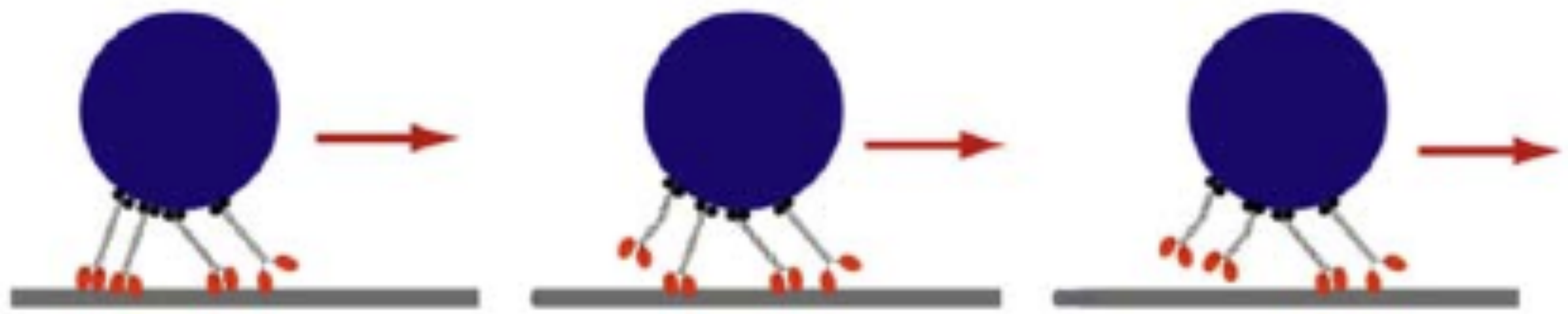
- A general Semi-Markov structure allows for concrete statistical models.

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-First Try



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

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

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 $\sim 500nm/s$

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