Estimating velocity from time traces of molecular motors.

Mathematical and Statistical Challenges in Bridging Model Development, Parameter Identification and Model Selection in the Biological Sciences.
BIRS
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https://en.wikipedia.org/wiki/Tardigrade

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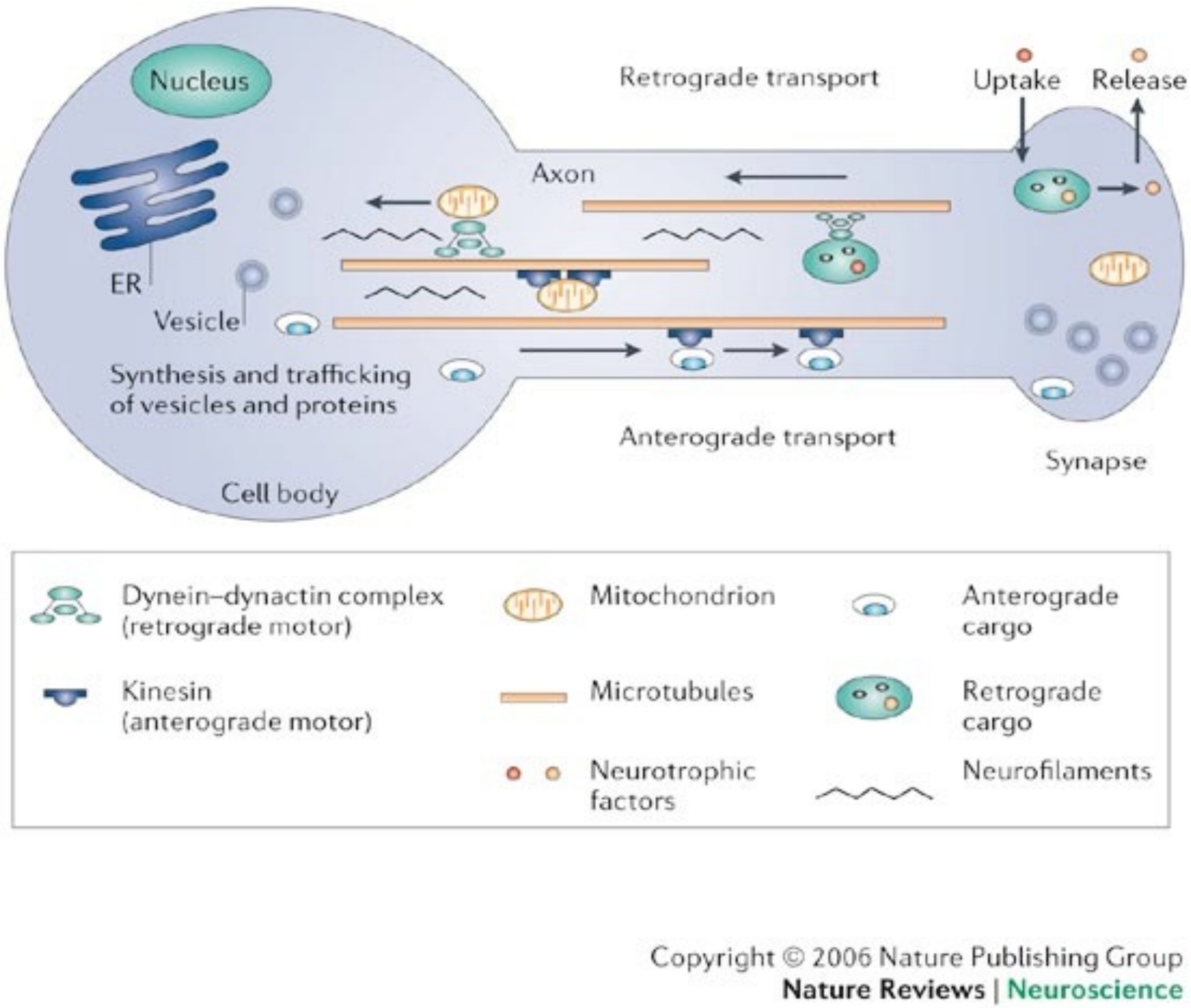
Overview

- Brief introduction to motor-based transport.
- Stochastic models and renewal-reward framework.
- Empirical asymptotic velocity.
- Current-future work.

Kinesin

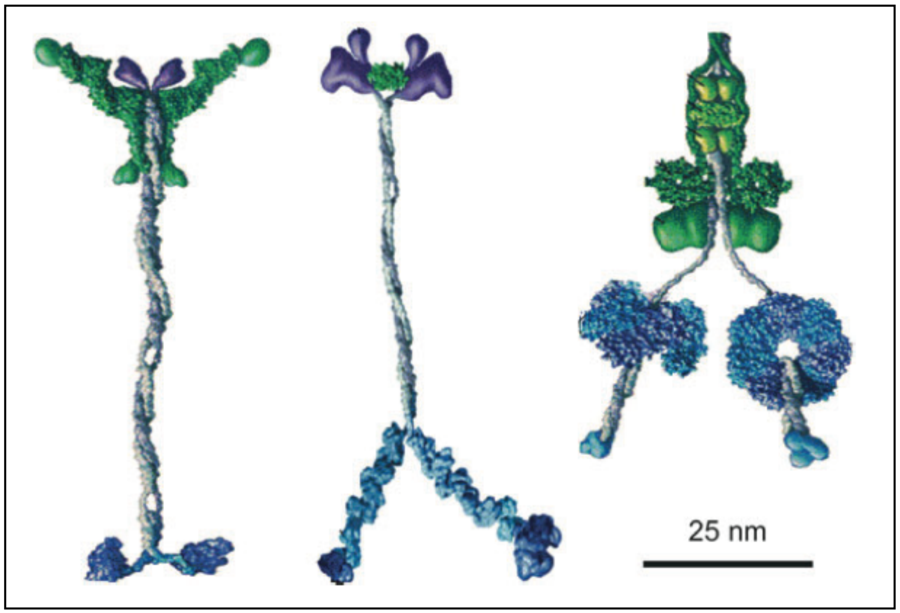
- What does the molecular motor Kinesin do?
- Stepping is the interaction of diffusion and kinetics.
- What type of data can be obtained from what type of experiment?
- What are some of the quantities of interest and basic models?

Motor-based Neuronal Transport

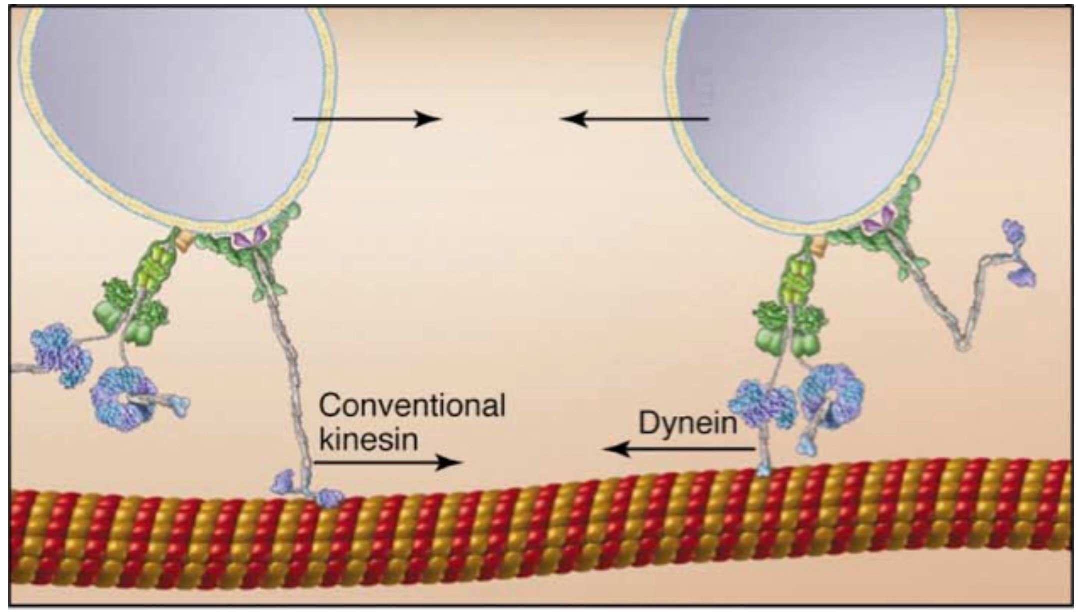


Pasinelli and Brown *Nature Reviews Neuroscience* **7**, 710–723 (September 2006) | doi: 10.1038/nrn1971

Kinesin, Myosin, and Dynein

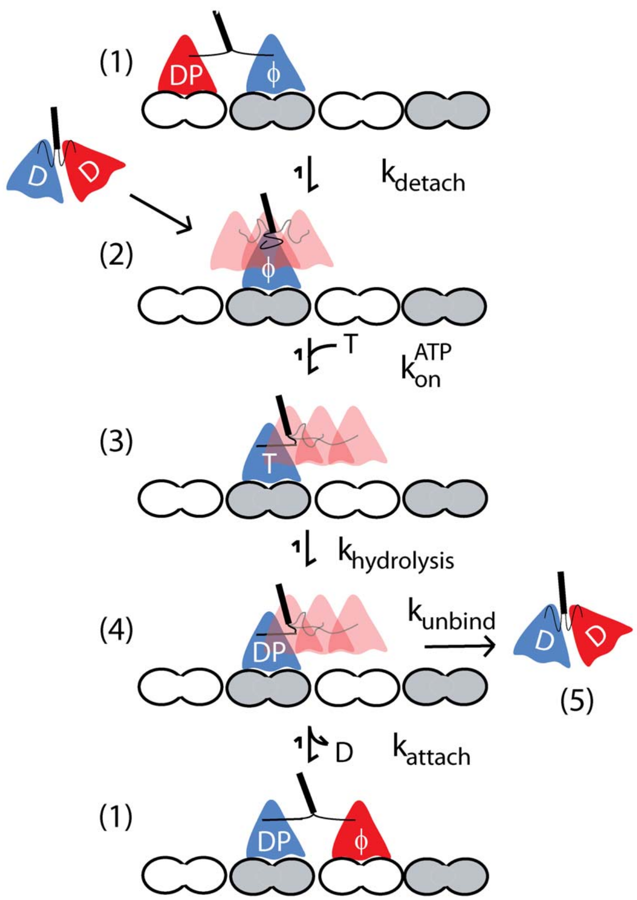


A Kolomeisky, M Fisher, Ann Rev Phys Chem, 2007



R Vale, Cell, 2003

Kinesin


(1)
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k_{attach}
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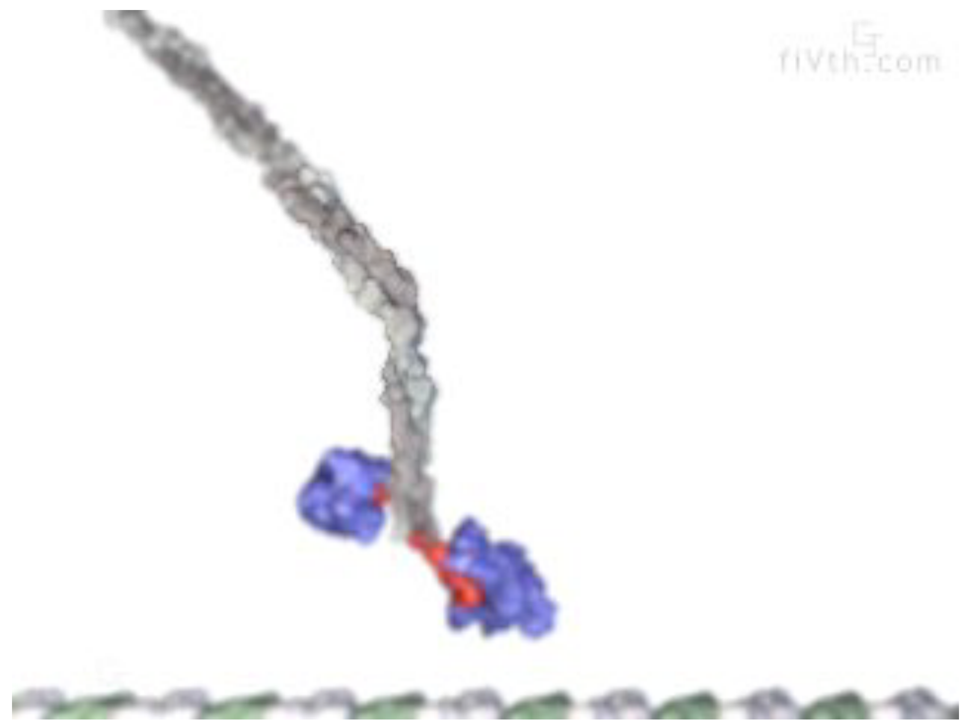
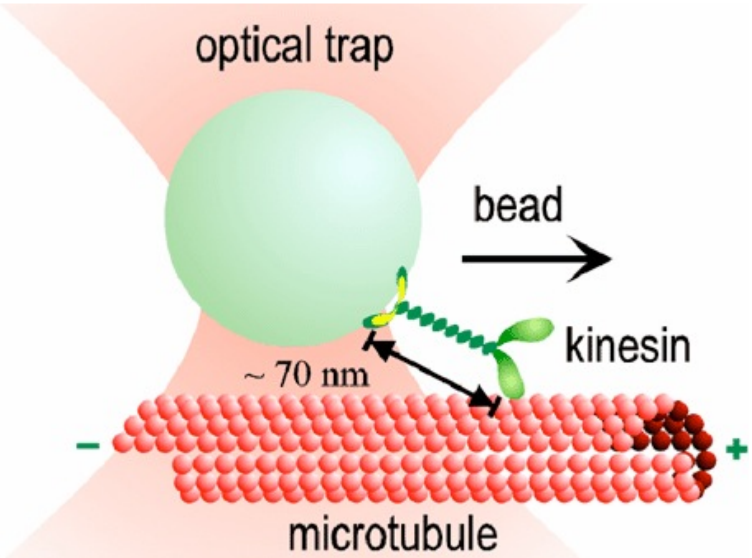
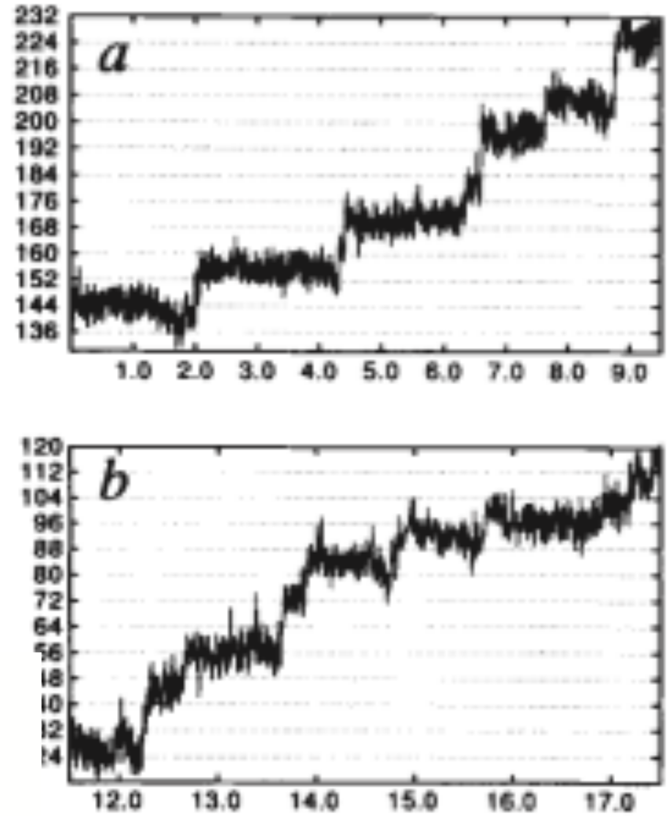


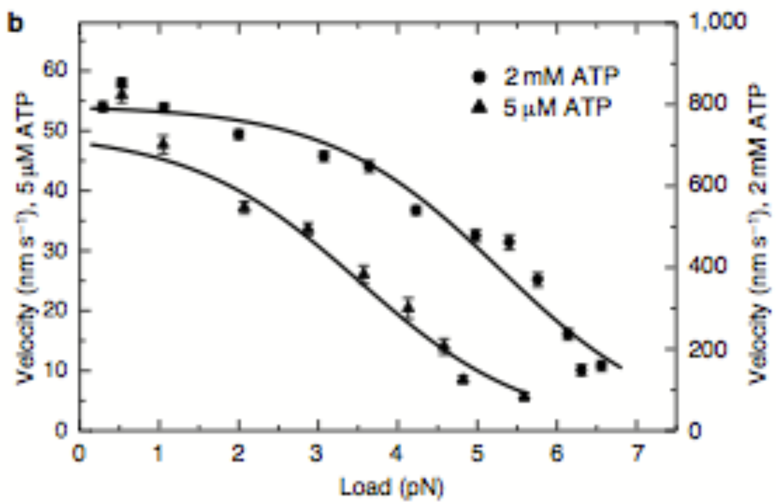
Single Motor Experiments



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

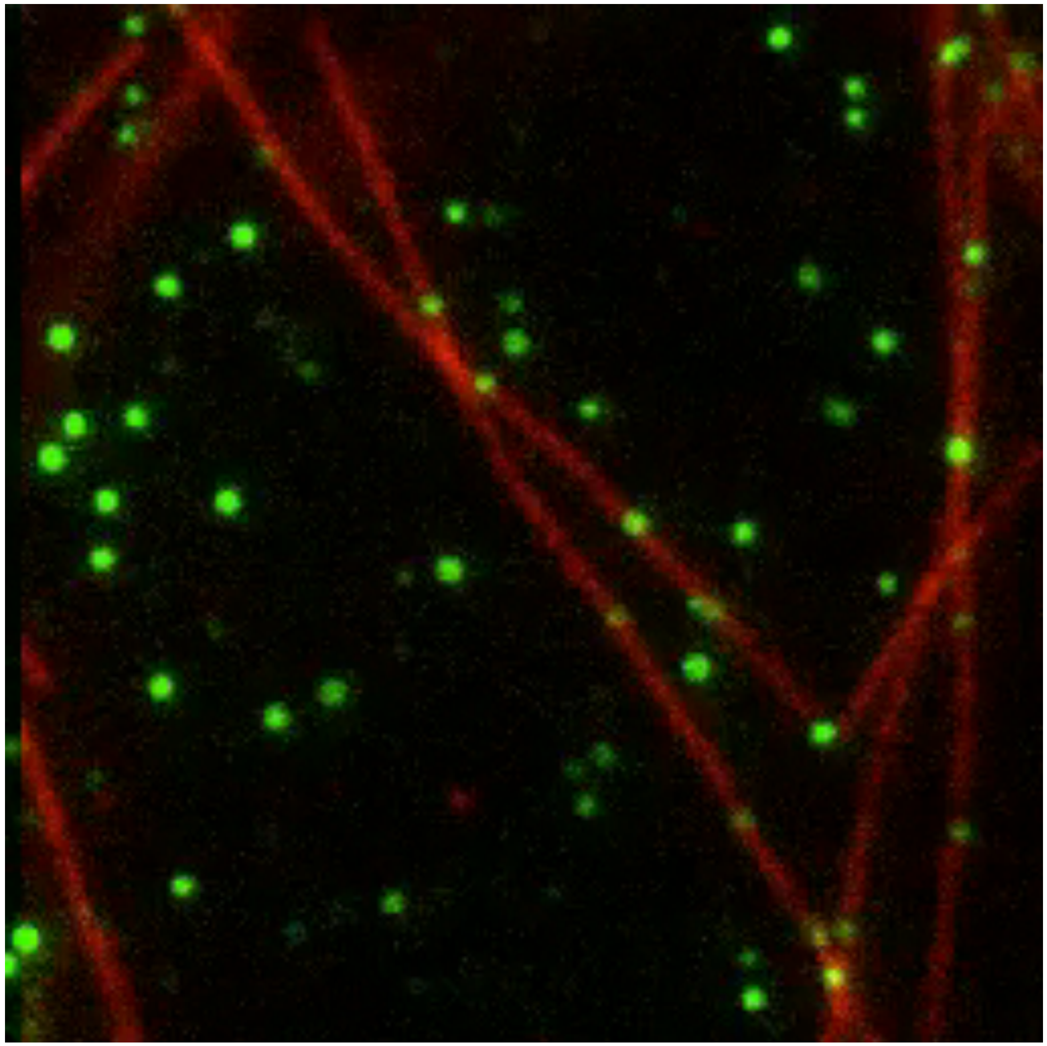


Svoboda et al, Nature, 1993



M Schnitzer et al, Nature Cell Biology, 2000

Single Motor Experiments



Quantities of Interest

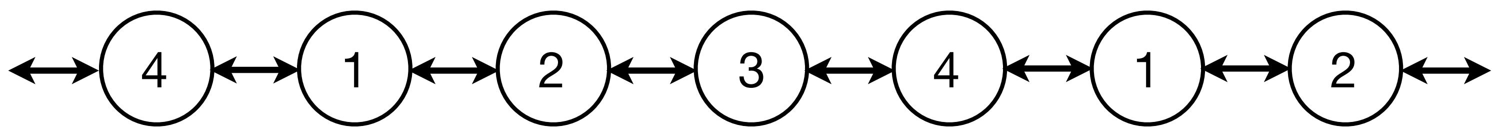
Asymptotic Velocity $V_a = \lim_{t \to \infty} \frac{E[X(t)]}{t}$ *or* $V_a = \lim_{t \to \infty} \frac{X(t)}{t}$

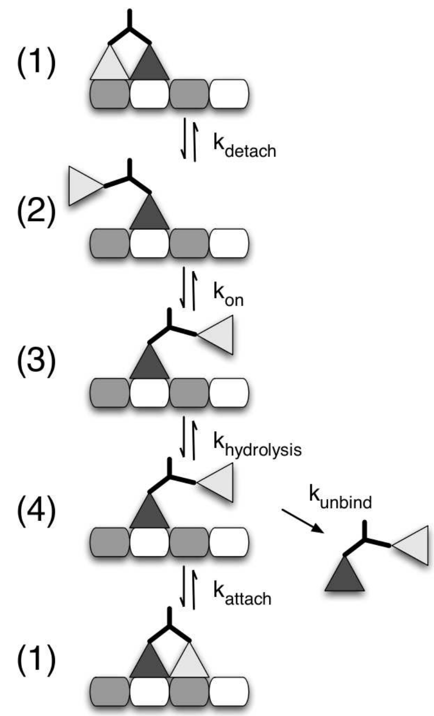
Effective Diffusion $D_{eff} = \lim_{t \to \infty} \frac{Var[X(t)]}{2t}$

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

Processivity: expected
number of steps before
detachment.

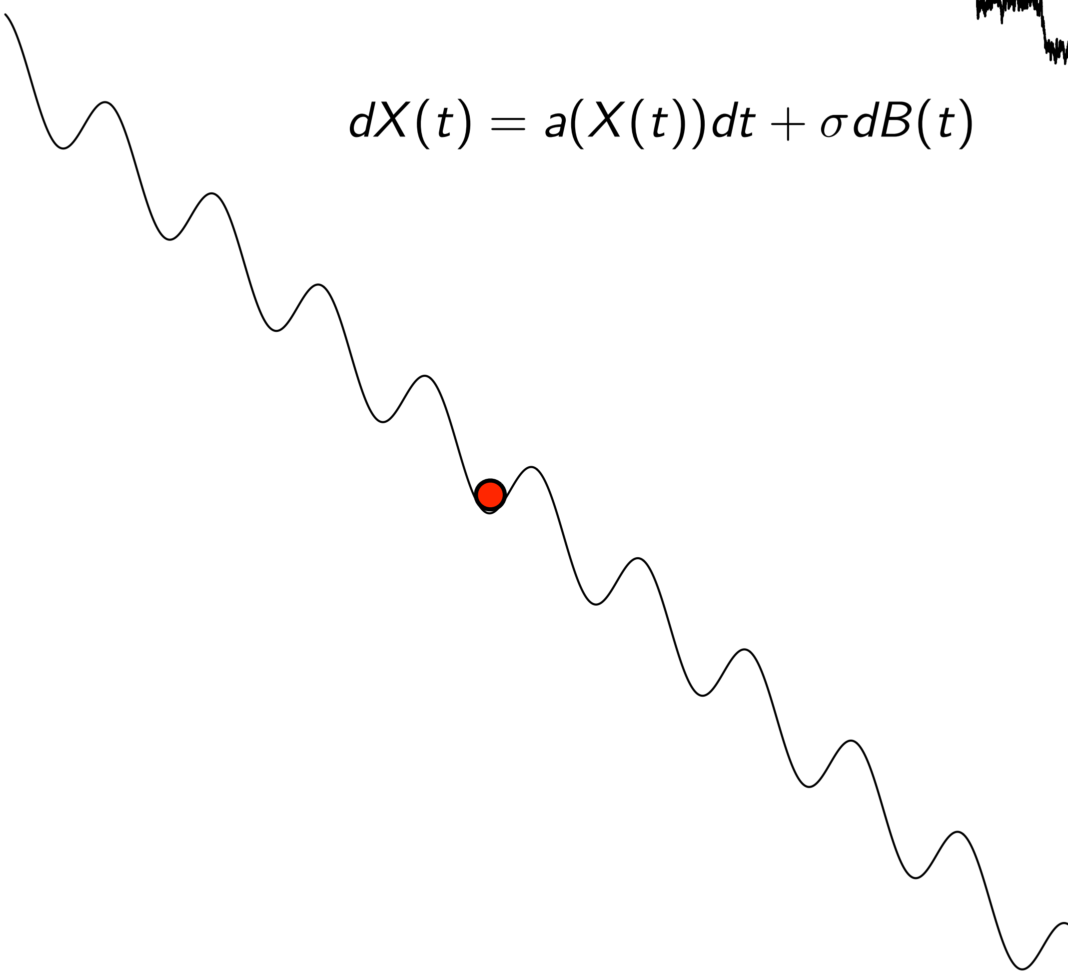
Periodic Discrete Space Markov Process

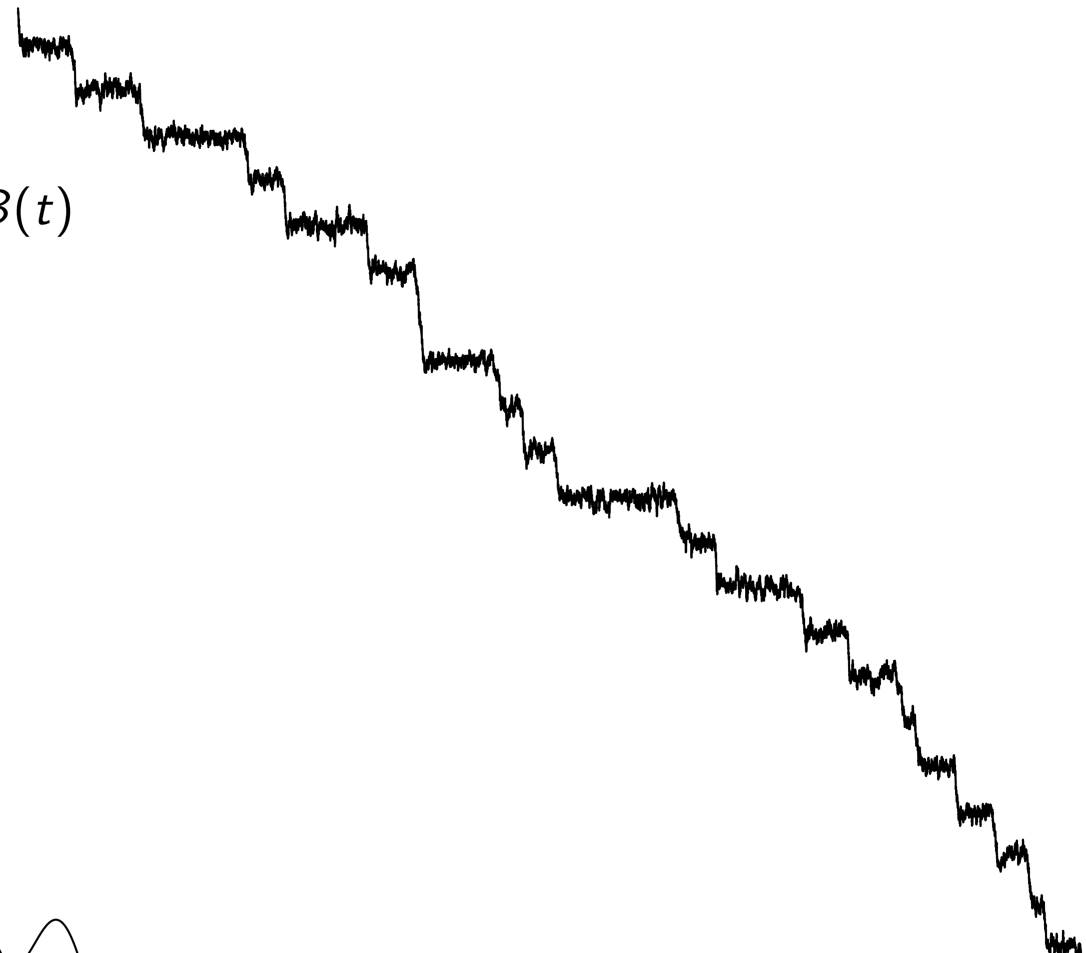




Diffusion in a Tilted Periodic Potential

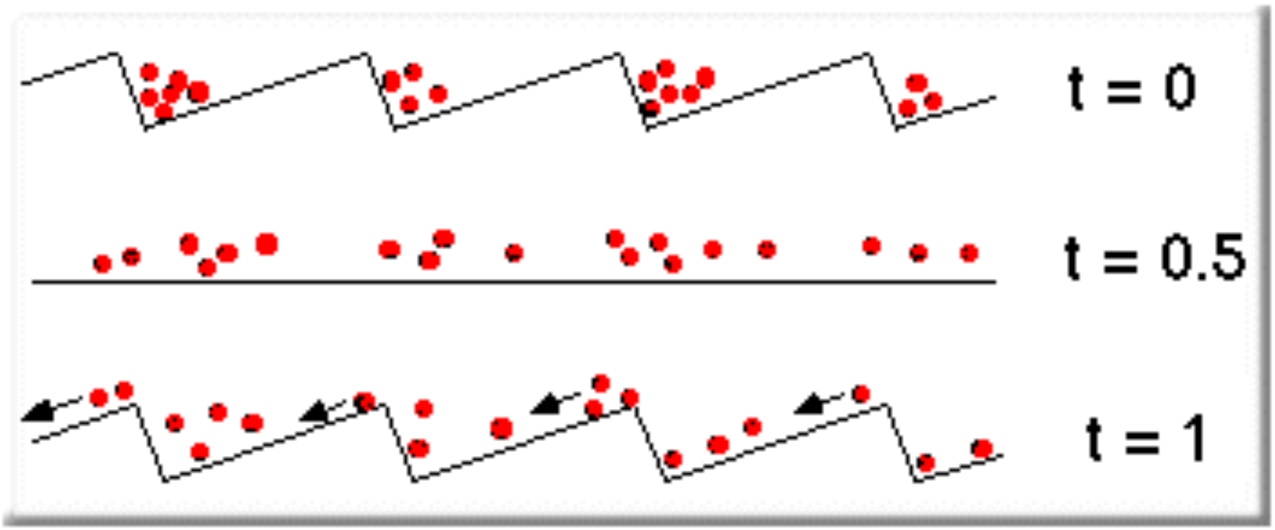
$$dX(t) = a(X(t))dt + \sigma dB(t)$$





Flashing Ratchet

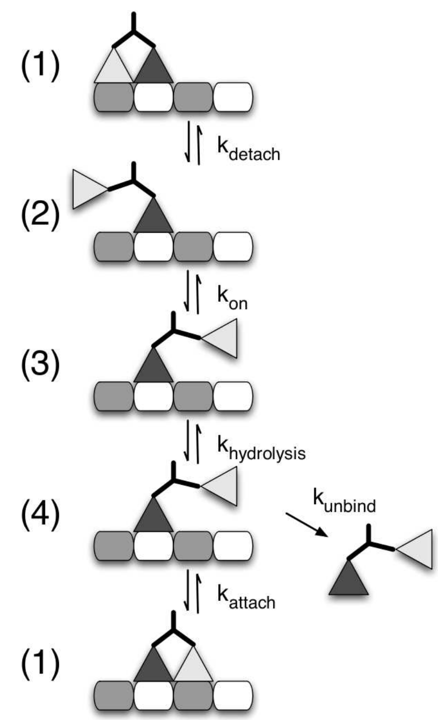
$$dX(t) = a_{K(t)}(X(t))dt + \sigma dB(t)$$

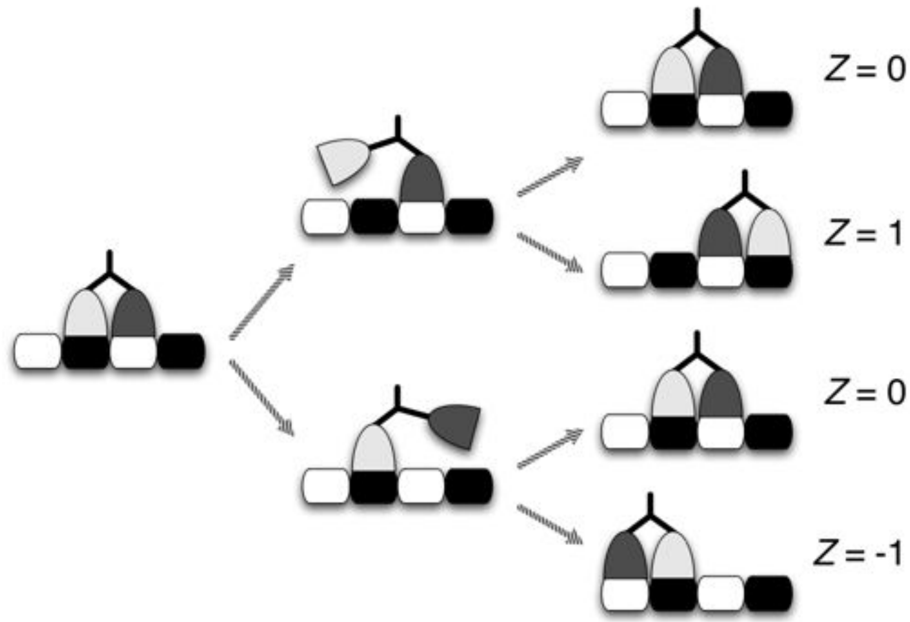


Heiner Linke (http://www.phys.unsw.edu.au/STAFF/RESEARCH/linke.html)

Role of diffusion in the hydrolysis cycle

- The kinetics of the hydrolysis cycle is important, but what about the movement through space of the free head?
- How does an applied force affect the stepping speed?

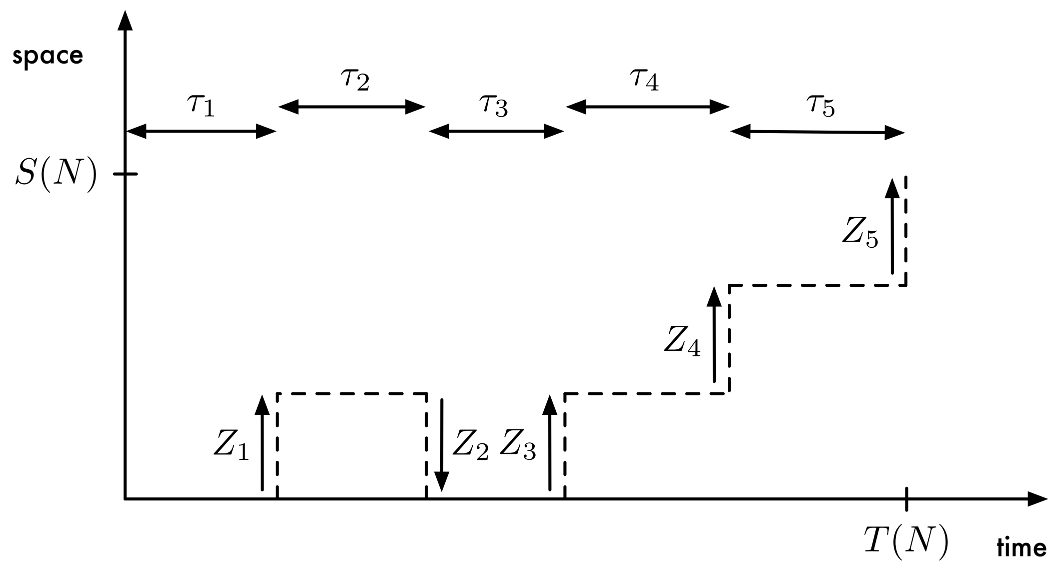




Z = 0
Z = 1
Z = 0
Z = -1

Renewal-Reward Framework

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



Note: work of Arjun Krishnan (Utah)

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

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

Functional Central Limit Theorem

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

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

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

Standard Quantities

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

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

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

- In the modeling community, processivity (distance/time traveled) has been under-emphasized.
- One type of data obtainable from each type of experiment is distance/time till detachment.
- How can we connect randomly-detached motor data to our models?

Random Stopping and Asymptotic Velocity

Asymptotic distribution of empirical velocity

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

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

Pearson VII distribution

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

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

John Hughes, Shankar Sastry, William O. Hancock, and John Fricks (2013). Estimating Velocity for Processive Motor Proteins with Random Detachment. Journal of Agricultural, Biological, and Environmental Statistics. 18, No. 2, 204-217.

Also, see;
Vu, Huong T., et al. "Discrete step sizes of molecular motors lead to bimodal non-Gaussian velocity distributions under force." *arXiv preprint arXiv:1604.00226* (2016).

How?

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

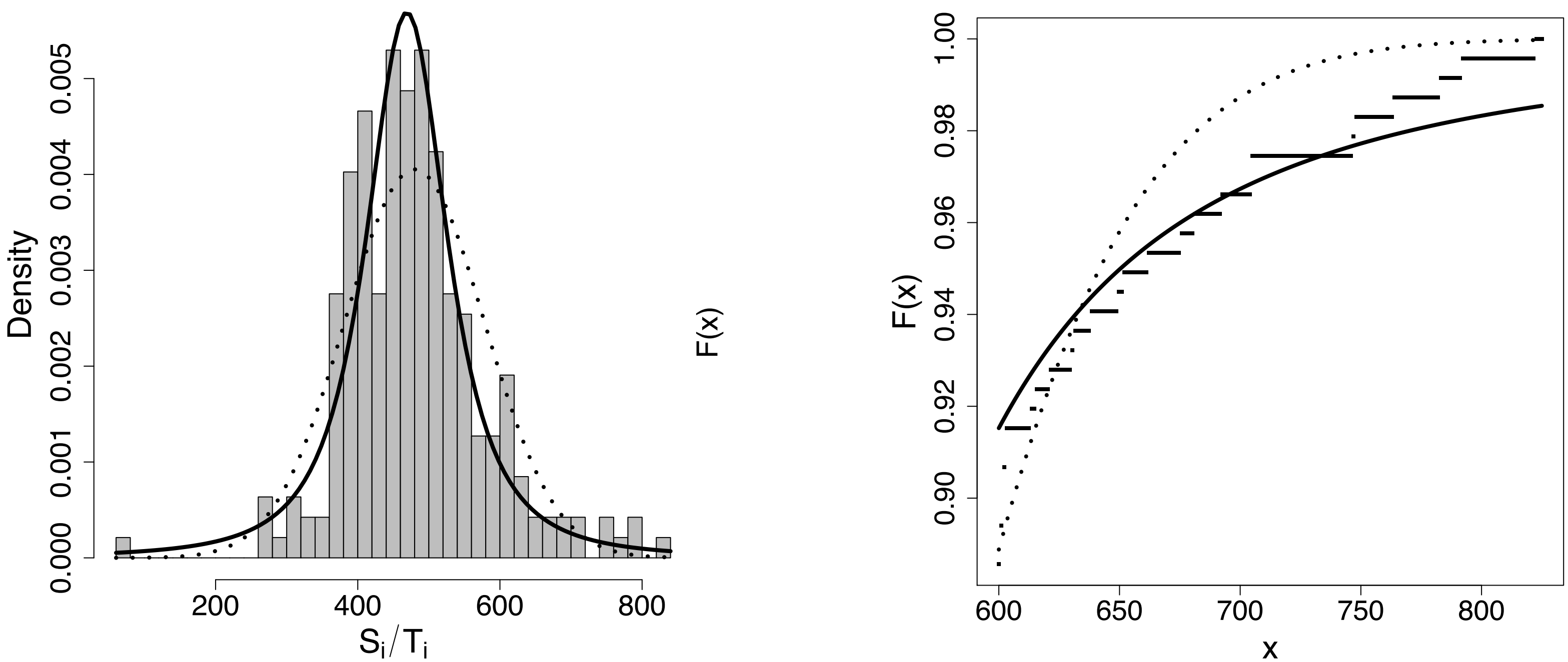
$$\eta_n = \frac{1}{n} T(N) \Rightarrow \eta = \mu_\tau \varepsilon$$

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

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

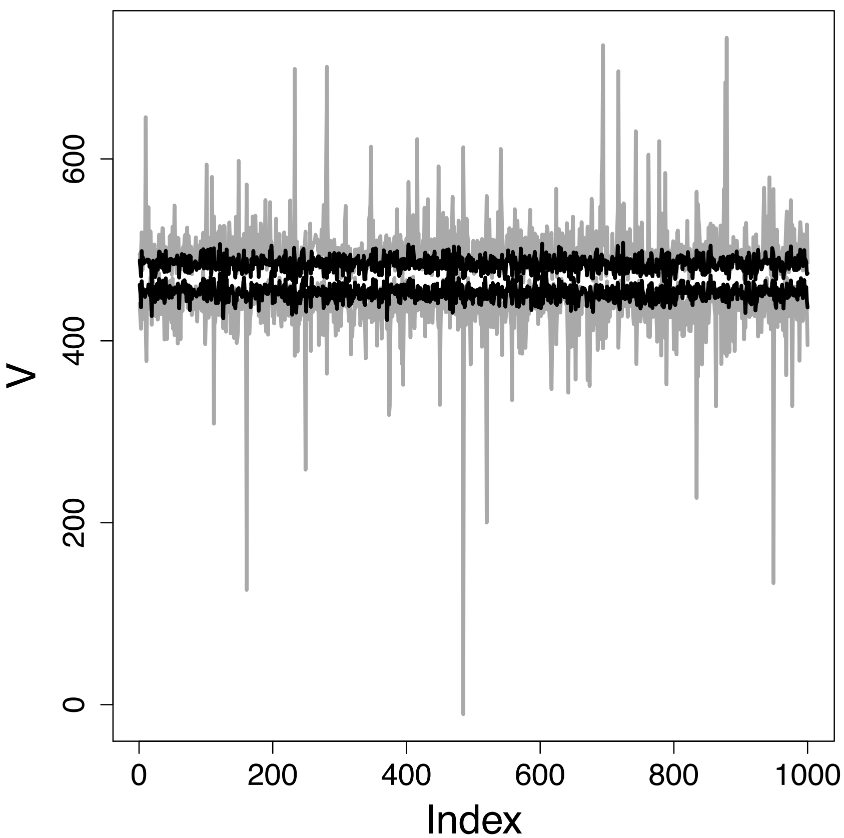
$$n^{-1/2} \left(\frac{S(N)}{T(N)} - \frac{\mu_Z}{\mu_\tau} \right) \Rightarrow \sqrt{2D} \frac{B(\eta)}{\eta}$$

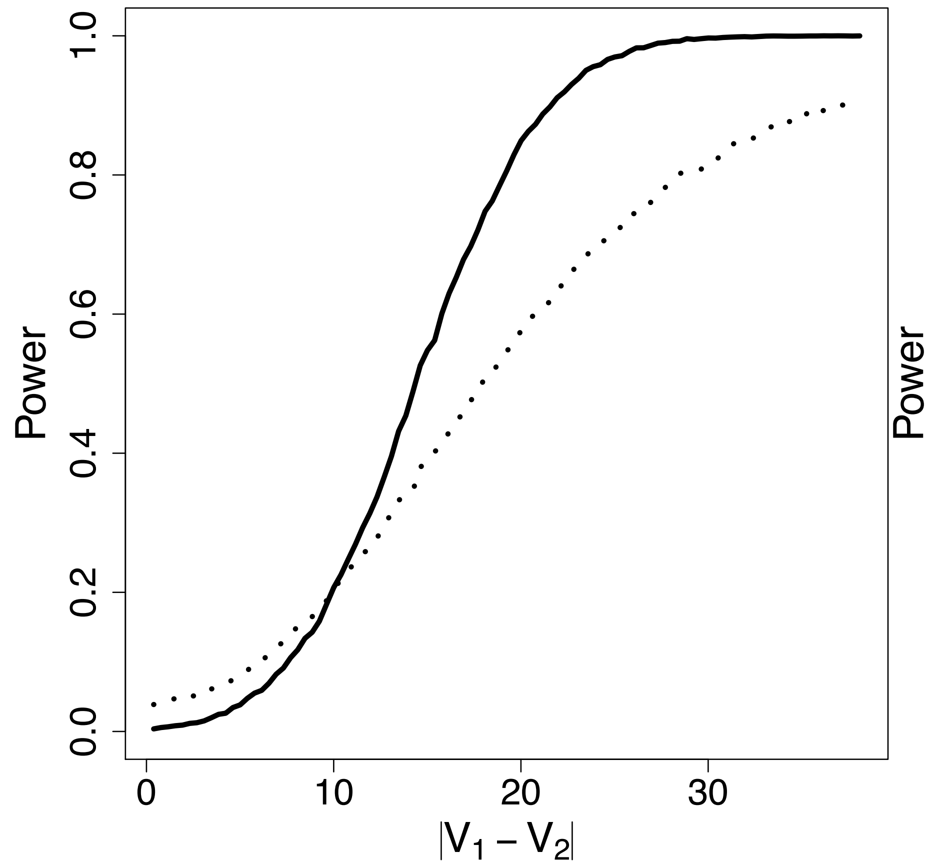
Does the data match the Pearson VII?



Using K-S test, reject the null hypothesis of a normal distribution with p-value 0.0468.
Fail to reject the null hypothesis of a Pearson-VII with p-value 0.618.

MLE for Pearson VII





An alternative approach

$$\hat{V}_c = \frac{\sum_{j=1}^m S_j(N_j)}{\sum_{j=1}^m T_j(N_j)}$$

Note that

$$\sqrt{m}\left(\begin{pmatrix} \frac{1}{m}\sum_{j=1}^m S_j(N_j) \\ \frac{1}{m}\sum_{j=1}^m T_j(N_j) \end{pmatrix} - \begin{pmatrix} \frac{1}{p}\mu_Z \\ \frac{1}{p}\mu_\tau \end{pmatrix}\right)$$

converges to multivariate normal with zero mean and covariance

$$\begin{pmatrix} \frac{1}{p}\sigma_Z^2 + \frac{1-p}{p^2}\mu_Z^2 & \frac{1}{p}\sigma_{Z,\tau} + \frac{1-p}{p^2}\mu_Z\mu_\tau \\ \frac{1}{p}\sigma_{Z,\tau} + \frac{1-p}{p^2}\mu_Z\mu_\tau & \frac{1}{p}\sigma_\tau^2 + \frac{1-p}{p^2}\mu_\tau^2 \end{pmatrix}$$

Now, we apply the delta method

$$\sqrt{m}\left(\frac{\sum_{j=1}^{m} S_j(N_j)}{\sum_{j=1}^{m} T_j(N_j)} - \frac{\mu_Z}{\mu_\tau}\right)$$

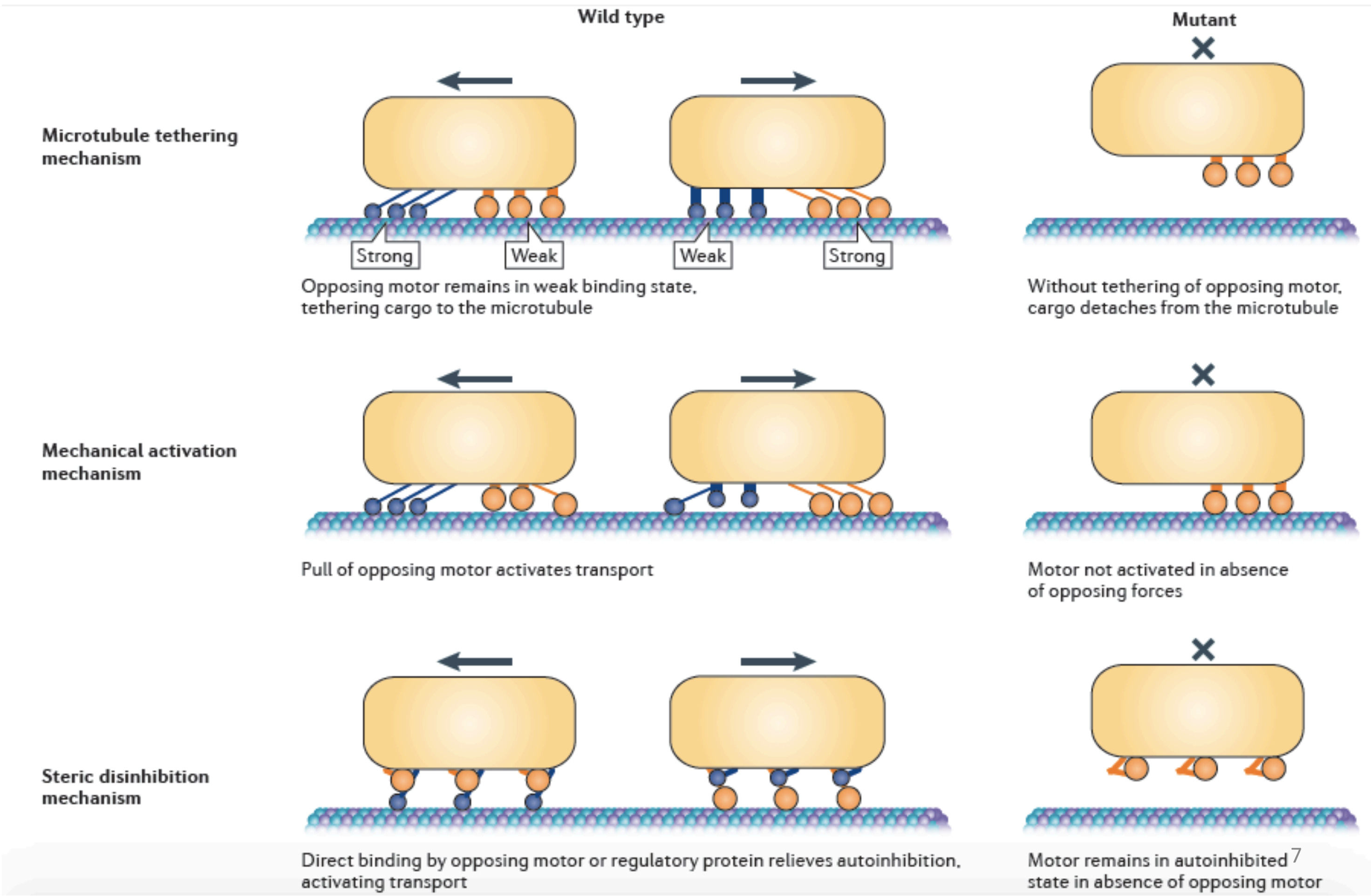
converges in distribution to a zero-mean normal distribution with variance

$$\begin{pmatrix} \frac{1}{\frac{1}{p}\mu_\tau} & \frac{-\mu_Z}{\frac{1}{p}\mu_\tau^2} \end{pmatrix} \begin{pmatrix} \frac{1}{p}\sigma_Z^2 + \frac{1-p}{p^2}\mu_Z^2 & \frac{1}{p}\sigma_{Z,\tau} + \frac{1-p}{p^2}\mu_Z\mu_\tau \\ \frac{1}{p}\sigma_{Z,\tau} + \frac{1-p}{p^2}\mu_Z\mu_\tau & \frac{1}{p}\sigma_\tau^2 + \frac{1-p}{p^2}\mu_\tau^2 \end{pmatrix} \begin{pmatrix} \frac{1}{\frac{1}{p}\mu_\tau} \\ \frac{-\mu_Z}{\frac{1}{p}\mu_\tau^2} \end{pmatrix}$$

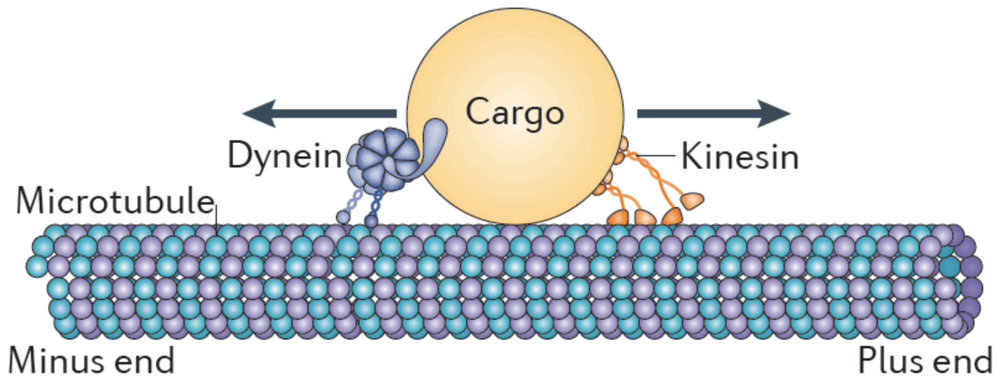
or

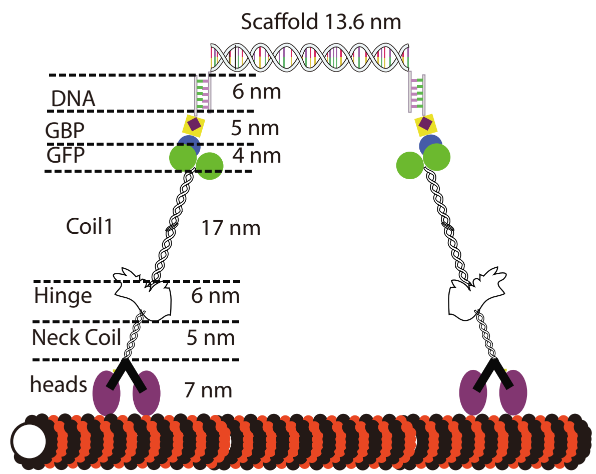
$$\frac{1}{\frac{1}{p}\mu_\tau}\left(\frac{\sigma_Z^2}{\mu_\tau} - 2\frac{\mu_Z\sigma_{Z,\tau}}{\mu_\tau^2} + \frac{\sigma_\tau^2\mu_Z^2}{\mu_\tau^3}\right)$$

Alternative Models to ToW



[7]


Cargo
Dynein
Kinesin
Microtubule
Minus end
Plus end


Scaffold 13.6 nm
DNA
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GBP
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GFP
4 nm
Coil1
17 nm
Hinge
6 nm
Neck Coil
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heads
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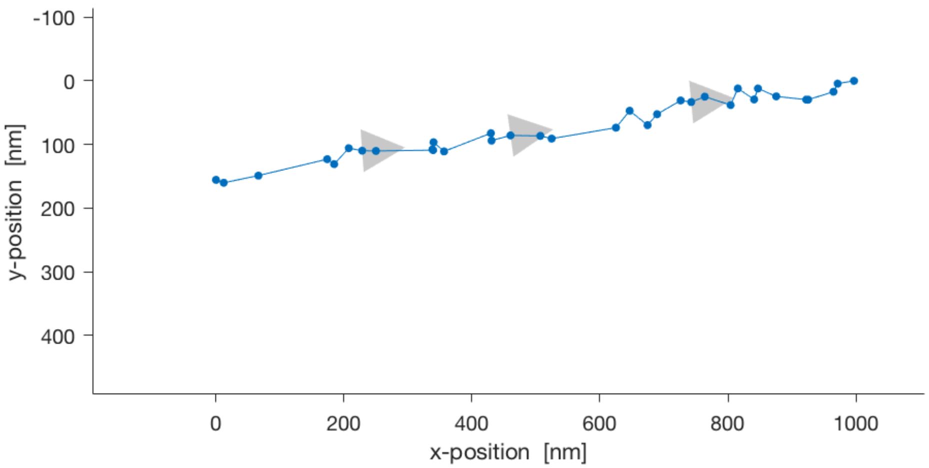
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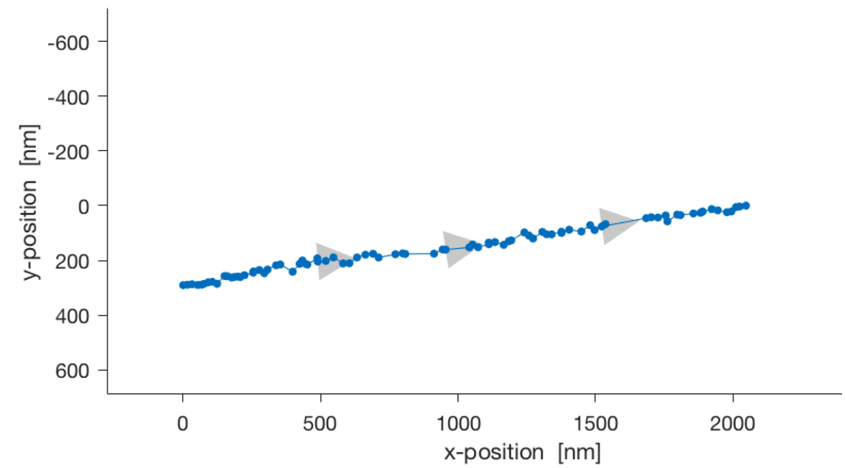
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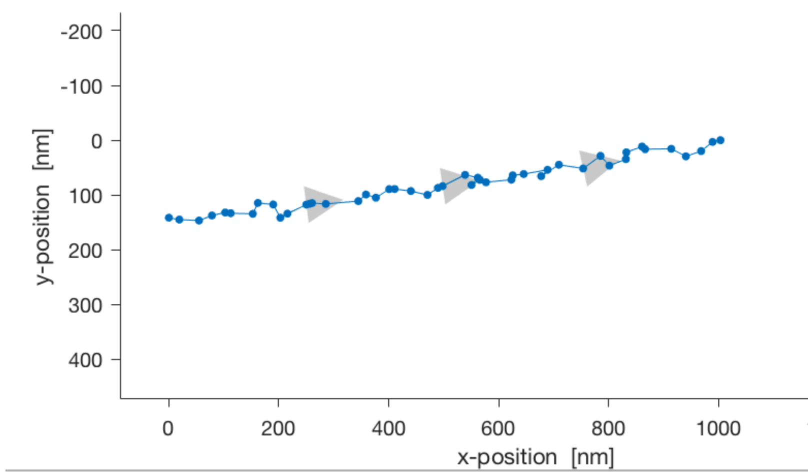
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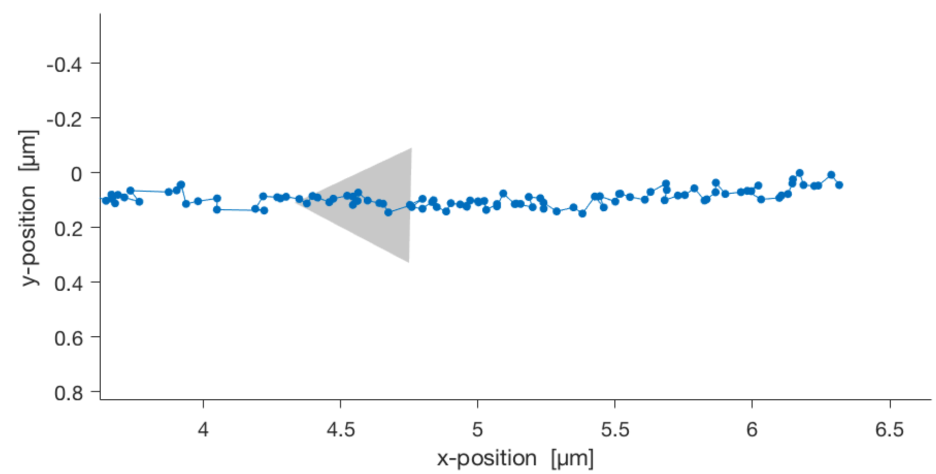
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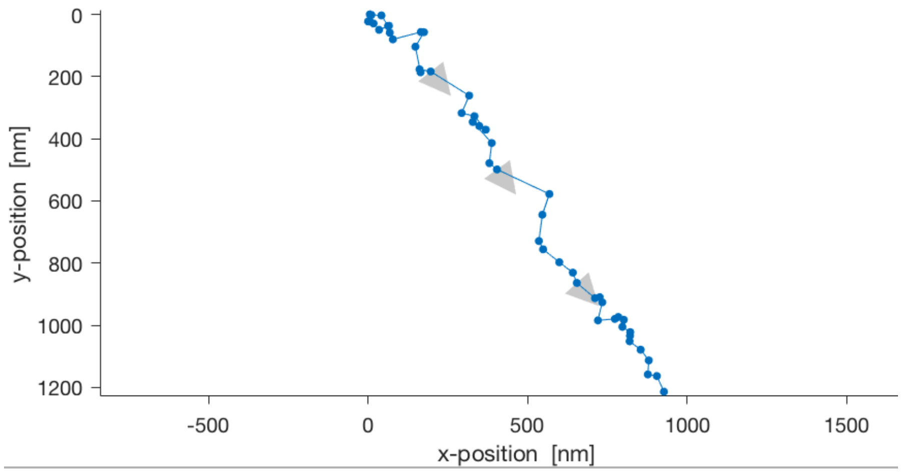
x-position [µm]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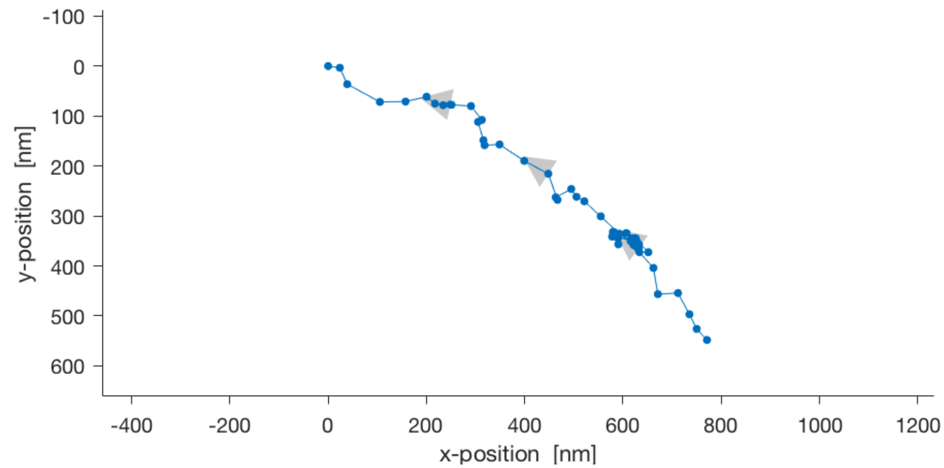
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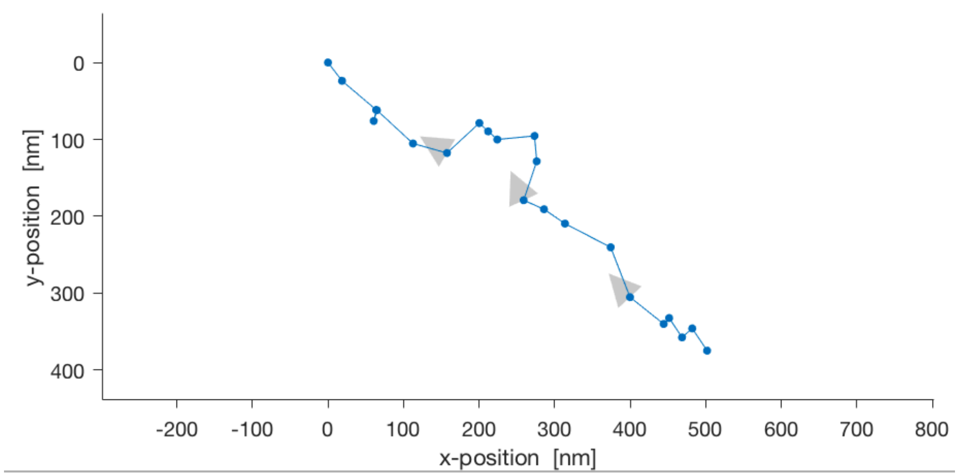
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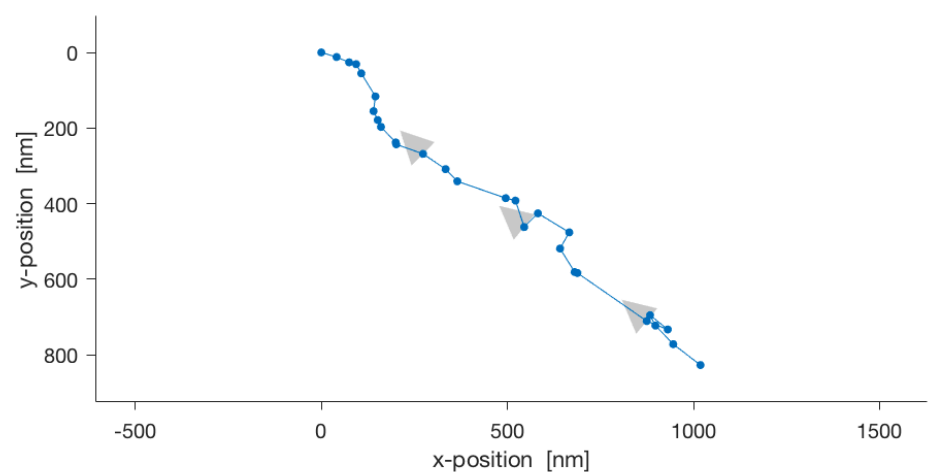
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Thanks.