Multiple Scales in Molecular Motor Models.

John Fricks

Dept of Statistics
Penn State University
University Park, PA

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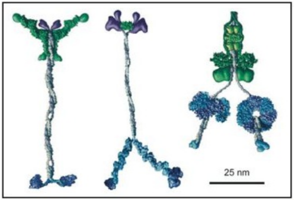
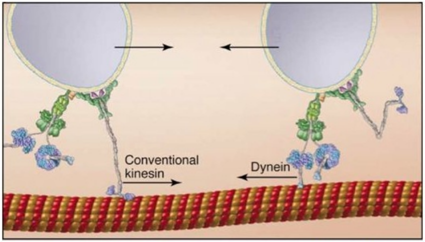
Overview.

- The Biology.
- Nanoscale Models
  - Common Models.
  - Our Model(s).
  - Biological Results.
- Mesoscale Models and Multiple Motors
  - Common Models.
  - A Simple Model.
  - Averaging and Asymptotics.
  - Biological Results.

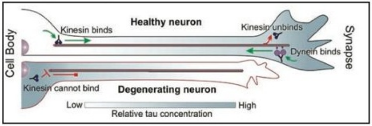
Molecular Motors.



A Kolomeisky, M Fisher, Ann Rev Phys Chem, '07



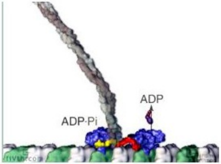
R Vale, Cell, '03



R Dixit, Science, '09

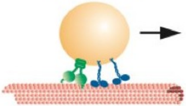
Scales.

Nanoscale
8 - 10 nm: individual kinesin-1 or dynein step size.
5 nm: diameter of kinesin head



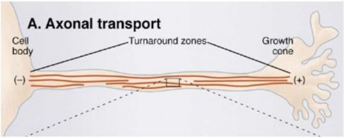
Vale lab, web video

Mesoscale
100 nm
Typical runlength of cargo/motors complex



S Gross, Phys. Biol., '04

Macroscale
> 1 micron
On the order of cells.

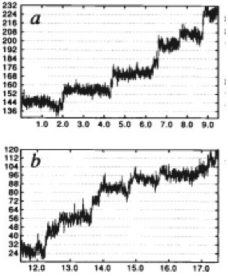


Who Cares?

- When an axon is severed from a dendrite, it must be regenerated.
- The microtubules near the regeneration site realign in a mixed polarity.
- Why do they do this?
- What effect does this have on kinesin transport?
- How is this regulated? At the nanoscale?

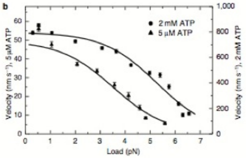
Examples of Data.

Nanoscale



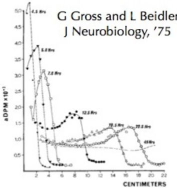
K Svoboda, Nature, '93

Mesoscale



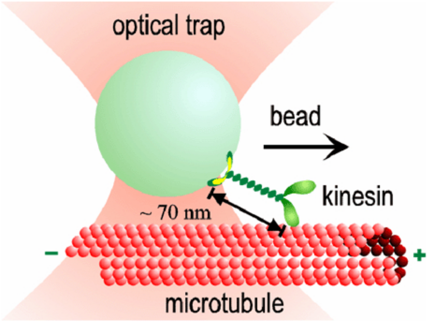
M Schnitzer et al, Nature Cell Biology, '00

>Microscale



G Gross and L Beidler
J Neurobiology, '75

An Artist's Rendering of Experiment.

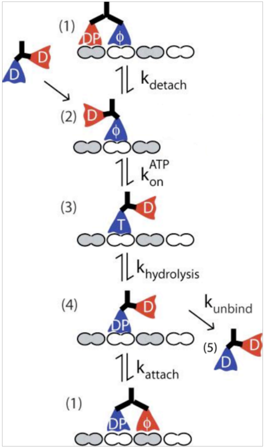


Block Lab:http://www.stanford.edu/group/blocklab/kinesin/kinesin.html

The Important Biological Points.

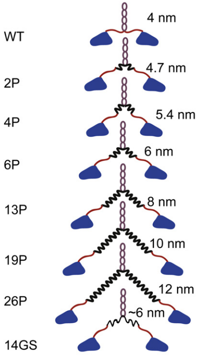
- "Hand over hand" stepping mechanism.
- 8 nanometer steps with 1 ATP per step.
- Length of step determined by the physical structure of microtubule.
- Back steps are rare.
- Kinetics + Constrained Diffusion.
  - Free head detachment.
  - ATP binding.
  - ATP hydrolysis.
  - Free head attachment.

The Kinesin Cartoon.

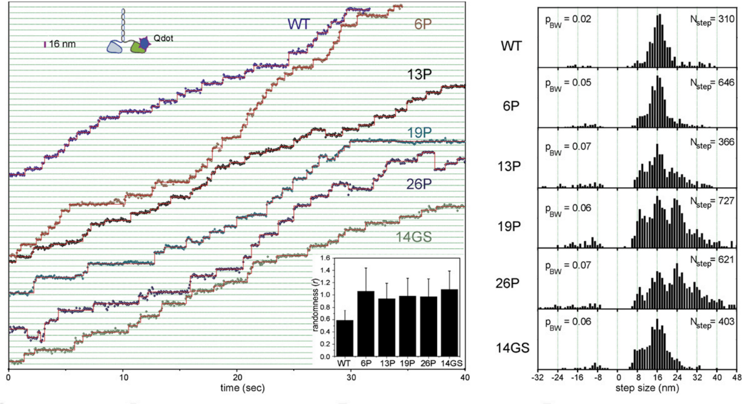


Engineered Motors.

- 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.



Necklinker Extension.



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

Intramolecular Strain Coordinates Kinesin Stepping Behavior along Microtubules.

Important 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**

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

  or the quantity which ensures

$$\frac{X(t) - V_a t}{\sqrt{2D_{eff} t}}$$

  converges to a standard normal.

- **Randomness Parameter**

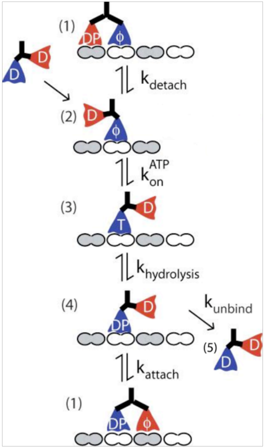
$$R = \frac{2D_{eff}}{LV_a}$$

- **Processivity**
  ν the number of random steps taken before detachment.

The Models.

Pure kinetics model–a discrete space Markov chain.

- Fails to account for the physical movement of heads.



The Models.

Stochastic Differential Equation Model

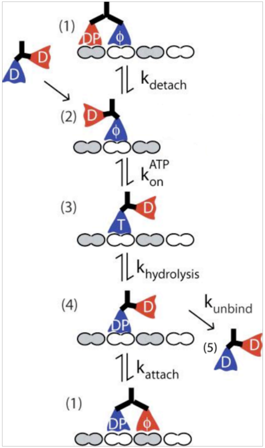
- Brownian particle in a periodic potential.
- $dX(t) = a(X(t))dt + \sigma dB(t)$
- Fails to account for two individual heads.
- Fails to coordinate physical movement and chemical kinetics.

The Models.

Flashing Ratchet

- $dX(t) = a_{K(t)}(X(t))dt + \sigma dB(t)$
- Accounts for both chemical and physical states.
- How can these be coordinated?

The Kinesin Cartoon.



Our Model.

- What about incorporating diffusion of the free head into the model?
- State 1 corresponds to having both heads bound.
- State 2 corresponds to the head having become free
  Tethered diffusion with a negative or neutral bias.
- State 3 and state 4 mean ATP has been bound
  A conformational change causes there to be a forward bias and less compliant spring.

Our Model.

- The position of the free motor head is governed by the following equation.
$$Y(t) = y + \int_0^t a_{K(s)}(Y(s))ds + \sigma B(s)$$
where $K(t)$ is the process corresponding to state events.
- Associate with each binding site a binding process
$$N_j\left(\int_0^t g_j\left(Y(s)\right)ds\right)$$
where the N_j are independent standard Poisson processes (independent of B also).
- The time until we return to (chemical) state one (τ) would then be the time for one of these clocks to fire.
- We define $Y(\tau)$ to be the location of the binding site associated with the binding process which fires first.

Renewal-Reward Processes.

- $Z_i, \ i = 1, 2, \ldots$ with mean μ_z and variance σ_z^2.

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

where $N(t)$ is a renewal process.

- $N(t) = \max\{n : \sum_{i=1}^{n} \tau_i \leq t\}$
- Time between events are independent and identically distributed, $\tau_i, \ i = 1, 2, \ldots$. $(\tau_0 = 0)$.
- The τ_i have finite mean (μ_τ) and variance (σ_τ^2).

Limits for Renewal-Reward Process.

For motor with backwards/forward steps,

- $$V_a = \lim_{t \to \infty} \frac{LX(t)}{t} = \frac{L\mu_z}{\mu_\tau}$$
- $$D_{eff} = \lim_{t \to \infty} \frac{L^2 Var[X(t)]}{2t} = \frac{L^2}{2} \left(\frac{\sigma_Z^2}{\mu_\tau} + \frac{\mu_z^2 \sigma_\tau^2}{\mu_\tau^3} \right)$$

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

$$\Sigma = \begin{pmatrix} \sigma_Z^2 & 0 \\ 0 & \sigma_\tau^2 \end{pmatrix}$$

FCLT for Renewal-Reward.

- 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 Theorem 13.7.3 from Whitt; we obtain

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

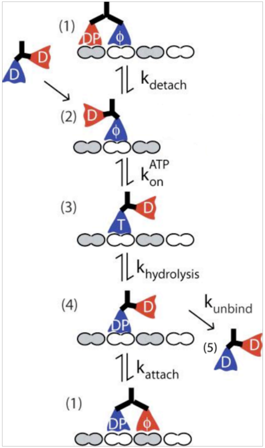
- This is equivalent in law to

$$X_n(t) = n^{-1/2}\left(X(nt) - \frac{\mu_z}{\mu_T}nt\right) \Rightarrow \sqrt{\frac{\sigma_Z^2}{\mu_T} + \frac{\mu_z^2\sigma_T^2}{\mu_T^3}}B(t)$$

-

$$X(nt) \approx \frac{\mu_z}{\mu_T}nt + n^{1/2}\sqrt{\frac{\sigma_Z^2}{\mu_T} + \frac{\mu_z^2\sigma_T^2}{\mu_T^3}}B(t)$$

The Kinesin Cartoon.



Kinetic Model.

Relabel the states. Negative means front head became detached first.

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

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

and

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

Aggregated States of Markov Chains.

- 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

Including Diffusivity of the Free Head.

- Use the matrix for the kinetic model as a block structure.
- Within the blocks, use a tridiagonal matrix to use a discrete space random walk approximation for the free head.
- Find the moments of Z_i and τ_i.

Necklinker Models (Drifts).

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

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

- **WLC**

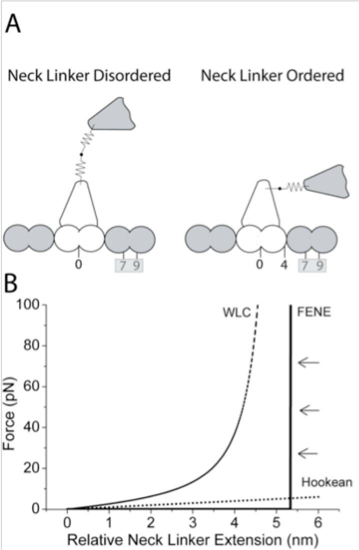
$$a_k(y) = \kappa \left(\frac{1}{4} \left(1 - \frac{y}{L_c} \right)^{-2} - \frac{1}{4} + \frac{y}{L_c} \right)$$

- **FENE**

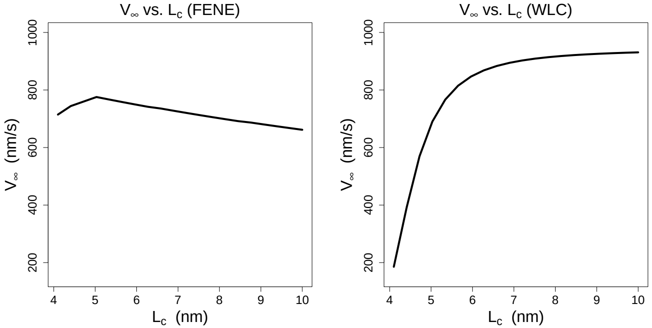
$$a_k(y) = -\kappa(y - c)$$

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

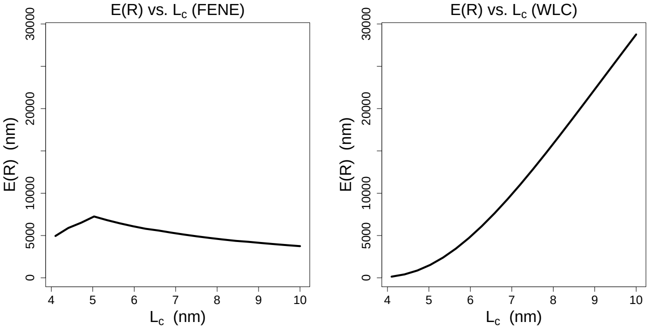
Necklinker Models (Drifts).



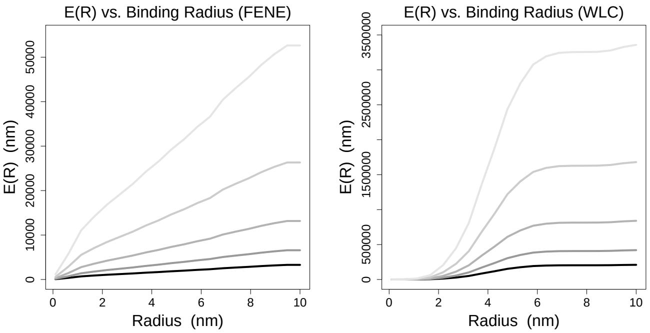
Velocity.


V_∞ vs. L_c (FENE)
V_∞ (nm/s)
200
400
600
800
1000
4
5
6
7
8
9
10
L_c (nm)
V_∞ vs. L_c (WLC)
V_∞ (nm/s)
200
400
600
800
1000
4
5
6
7
8
9
10
L_c (nm)

Run Length.


E(R) vs. L_c (FENE)
E(R) (nm)
L_c (nm)
0
5000
10000
20000
30000
4
5
6
7
8
9
10
E(R) vs. L_c (WLC)
E(R) (nm)
L_c (nm)
0
5000
10000
20000
30000
4
5
6
7
8
9
10

Binding Radius and Attachment Rate.

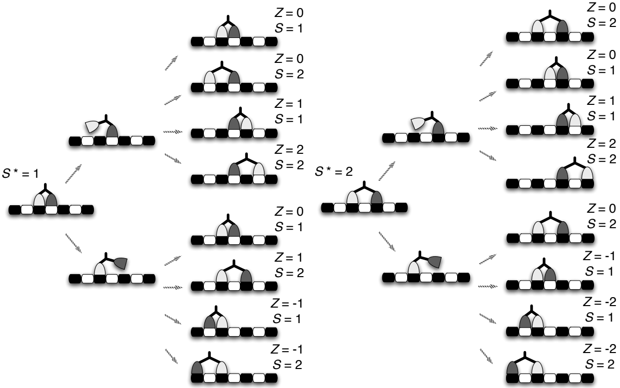


Summary for Different Spring Models.

- WLC.
    - When allowed to extend to approximately 4nm, binding constant must be very high.
    - As neck linker is extended, velocity AND processivity increase.
- FENE.
    - Binding constant is reasonable.
    - As neck linker is extended, velocity and processivity decrease as expected.
- Possible Resolutions.
    - Projection is the problem.
    - Weak binding.
    - Mis-specficiation of neck linker.

Multiple Step Model.

- Heads are not necessarily one binding site away at the beginning of each cycle.
- Return to double binding changes initial conditions of next cycle.



Multiple Step Model.

The following forms a Markov chain

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

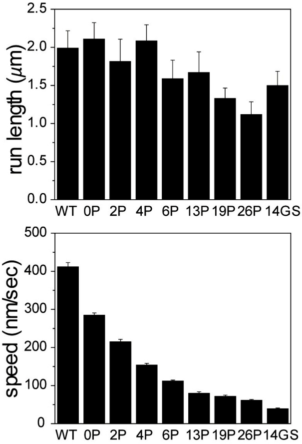
- S_i is a Markov chain describing the distance between heads after previous cycle.
- The position of the front head after a full cycle

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

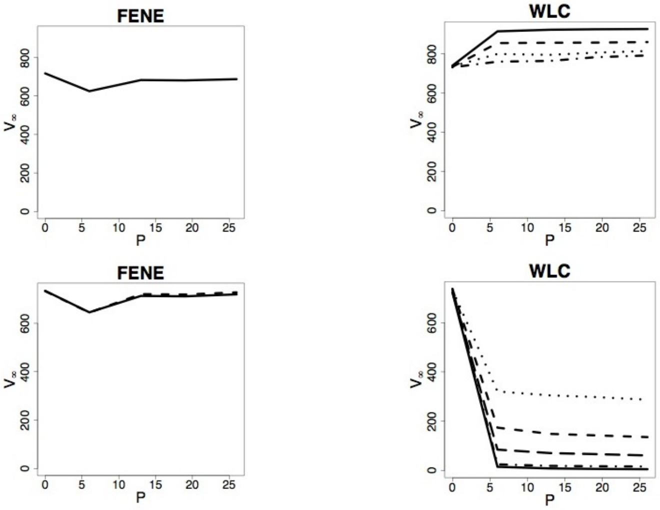
Multiple Step Model.

- Take advantage of the simplified structure; Z_i and τ_i depend on the last value of S.
- Calculate the stationary distribution of S_i using the matrix approximation.
- Can calculate the other moments based only on the conditional means and variances given S_{i-1}.
- Central Limit Theorem for stationary Markov chains will lead to FCLT for sums–the result is a bivariate Brownian motion
- We can still use Whitt to give us the correct FCLT.

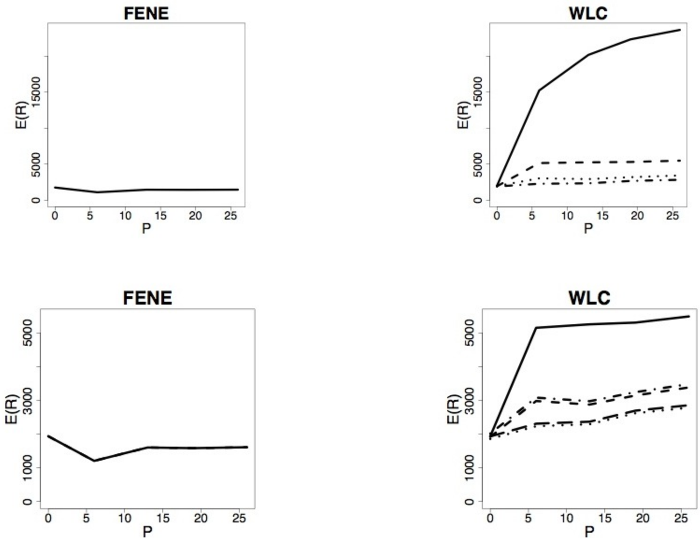
Recall the Yildiz Data.



Velocity Tension vs No Tension.



Expected Runlength Tension vs No Tension.

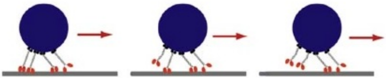


Nanoscale Kinesin: Conclusions

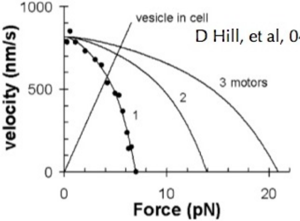
- By using a renewal-reward framework, link a nanoscale diffusive model to stepping.
- If only single steps are permitted, this seems to eliminate WLC as a neck linker model.
- By modifying the framework, we allow for multiple steps.
- By also including intra-head tension when both are bound, WLC model scales with data.

Identical Motors and Cargo with External Load

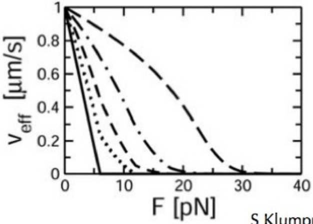
External force vs. average velocity curves



R Lipowsky, et al Phys E, 10



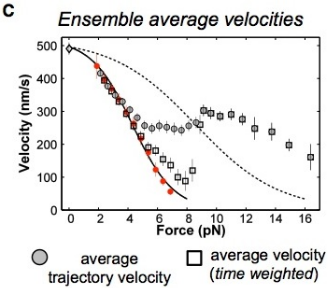
D Hill, et al, 04



S Klumpp

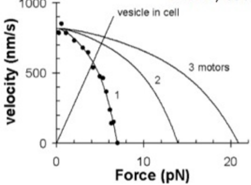
Identical Motors and Cargo with External Load

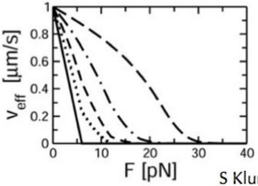
External force vs. average velocity curves



Diehl Lab, Biophys J.2010

D Hill, et al, 04





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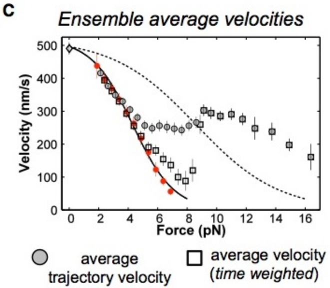
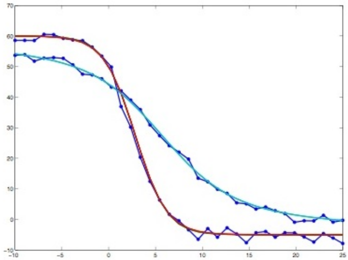
Identical Motors and Cargo with External Load

External force vs. average velocity curves



Diehl Lab, Biophys J.2010



SAMSI working group

red: one motor, cargo.

cyan: two motors, cargo.

An Alternative Model

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

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

- v average velocity of unconstrained motor $\sim 50nm/s$
- F_* stall force $\sim 7pN$
- θ optical track force $\sim 0 \; to \; 10pN$
- $F(\cdot)$ 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 $\sim 500nm/s$

Motors with Cargo and Applied Force

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

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

- $\epsilon = \frac{v\gamma}{\sqrt{2k_B T\kappa}}$ 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 of Two Motors

- $M(t) = \frac{1}{2}\left(\bar{X}_1 + \bar{X}_2\right) \qquad R(t) = \frac{1}{2}\left(\bar{X}_1 - \bar{X}_2\right)$
-

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

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

-

$$G(\xi) = \sqrt{\frac{2}{\pi}}\int_{\mathbb{R}} g(-sy)\exp\left(-2(y - \xi/2)^2\right)dy$$

-

$$\pi_{\tilde{\theta}}(r) = C_R \exp\left[-\frac{1}{\rho}\int_0^r \left(G(r' - \tilde{\theta}) - G(-r' - \tilde{\theta})\right)\mathrm{d}r'\right]$$

Law of Large Numbers

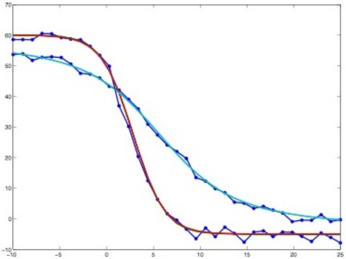
- Stationarity of R allows us to find limit of $\frac{M(t)}{t}$ i.e. asymptotic velocity.

$$\frac{M(t)}{t} \to \frac{1}{2} \int_{\mathbb{R}} \left[G(r - \tilde{\theta}) + G(-r - \tilde{\theta}) \right] d\pi_{\tilde{\theta}}(r)$$

- $G(\cdot)$ is derived from the force-velocity relationship.
- Similar methods allow for a CLT.

Prediction vs Simulation

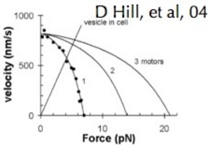
External force vs. average velocity curves

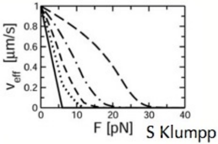


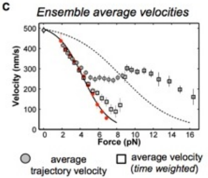
SAMSI working group

red: one motor, cargo.

cyan: two motors, cargo.







Diehl, 10

Conclusions on Multiple Motors

- Cargo is the fast variable.
- Two motors can be slower than one.
- Under what conditions on the original force-velocity curve will yield two motors being slower than one.
- Can we use this framework to explain data?

Where are we going?

- Many motors interacting with the random geometry of the microtubules.
- Linking all three scale explicitly.

Bibliography

- Scott McKinley, Avanti Athreya, John Fricks, and Peter Kramer (2011). Cooperative Dynamics of Kinesin and Dynein Molecular Motors. *Preprint.*
- John Hughes, William O. Hancock, and John Fricks (2011). Kinesins with Extended Neck Linkers: A Chemomechanical Model for Variable-Length Stepping. Submitted to *Bulletin of Mathematical Biology* on January 6, 2011.
- 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.
- 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.