Asymptotic Analysis of Cooperative Molecular Motor System

Peter Kramer[1,2]
Avanti Athreya[1,3], Scott McKinley[1,4], John Fricks[1,5]

[1]Statistical and Applied Mathematical Sciences Institute
[2]Rensselaer Polytechnic Institute
[3]Duke University
[4]University of Florida
[5]Pennsylvania State University

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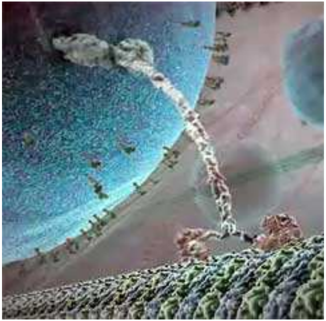
Outline

- Stochastic Models for Individual Molecular Motors
- Mesoscale Model for Collections of Molecular Motors
- Stochastic Asymptotic Techniques

Molecular Motors

Biological engines which catabolize ATP (fuel) to do useful work in a biological cell.

- Molecular pumps.
- Walking motors: Kinesin, Dynein.
- Rowing motors: Myosin
- Polymer Growth.



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Molecular Motors

Scales $\sim 10^2$ nm:

- friction-dominated
- thermal fluctuations important

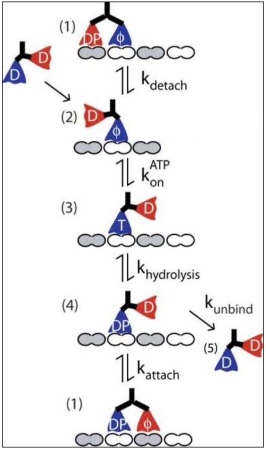
In fact the functioning of the molecular motor relies on effectively random thermal fluctuations

- diffusive transport of ATP (fuel) to activate chemically-driven steps
- physical search for binding sites

We will focus on porter molecules kinesin and dynein which transport cargo (vesicles in cells) along microtubules.

Nanoscale Stepping Model for Kinesin

The dynamics is often characterized by a continuous-time Markov chain $S(t)$ with prescribed rates between allowed transitions (Kolomeisky and Fisher 2007, Wang, Peskin, Elston 2003)



(Kutys, Fricks, Hancock, *PLOS Comp. Bio.*, 2010)

Nanoscale Stepping Model for Kinesin

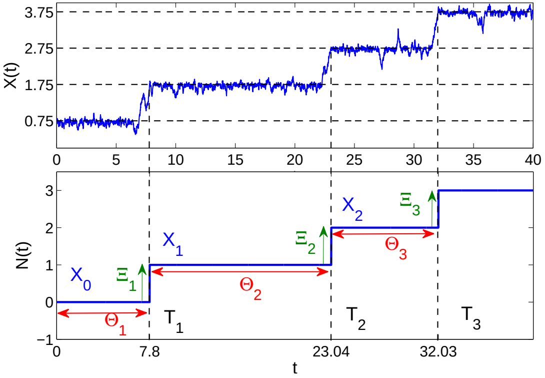
More detailed models (Peskin and Oster 1995, Kutys, Fricks, Hancock 2010; Bates and Jia 2011) represent some transitions via stopping times related to a (flashing ratchet) stochastic differential equation for a head coordinate $X(t)$:

$$\mathrm{d}X(t) = \gamma^{-1}(-F - \phi'_{S(t)}(X(t)))\mathrm{d}t + \sqrt{\frac{2k_B T}{\gamma}}\,\mathrm{d}W(t), \qquad (1)$$

where F is an applied load force, ϕ is potential energy (depending on chemical state $S(t)$), k_B is Boltzmann's constant, T is temperature, γ is friction constant, $W(t)$ is Wiener process.

Coarse-Grained Random Walk Model

For overall transport properties, one may only wish to resolve the times at which the motor cycle restarts at a new spatial location:



Coarse-Grained Random Walk Model

For example:

$$
\begin{aligned}
T_0 &= 0, \\
X_0 &= 0, \\
T_n &= \inf_{t > T_{n-1}} \{X(t) \in \alpha + \mathbb{Z}, X(t) \neq X_{n-1} + \alpha\}, \\
X_n &= X(T_n) - \alpha, \\
N(t) &= X_n \text{ for } T_n \le t < T_{n+1}, n = 0, 1, 2, \ldots
\end{aligned}
$$

- Analysis of diffusive transport in tilted periodic potential (Lindner, Kostur, Schimansky-Geier 2001)
- Analysis of conditions under which Markovian properties of imperfect ratchet models survive this coarse-graining (K, Khan, Latorre 2010)
- Analysis of kinesin stepping model via intermediate (reward)-renewal process framework (Hughes, Hancock, Fricks 2011)

Effective Transport Properties

A further useful coarse-graining exploits the periodicity and central limit theorem arguments (Elston 2000) to characterize the long-time properties of the motor through:

- drift

$$V = \lim_{t \to \infty} \frac{\langle X(t) \rangle}{t},$$

- diffusion

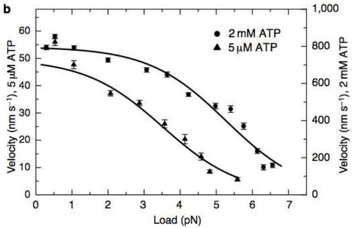
$$D = \lim_{t \to \infty} \frac{\left\langle (X(t) - \langle X(t) \rangle)^2 \right\rangle}{2t}.$$

Force-Velocity and Force-Diffusivity Relations

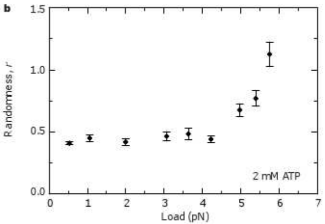
For a given motor, these are usefully expressed in terms of load force F through:

- Force-velocity relation $U = g(F)$
- Force-diffusivity relation $D = h(F)$

These are one way in which experimental measurements are presented:



(Schnitzer *et al*, *Nature Cell Biology*, 2000)



(Visscher *et al*, *Nature*, 1999)

Methods to Derive Effective Transport Properties

- Homogenization theory (Pavliotis 2005, Blanchet, Dolbeault, Kowalcyk 2008)
- Method of Wang, Peskin, Elston (2003) (WPE) based on spatial discretization preserving detailed balance

Equations distinct but derivable from common framework

- choices of discretization and use of infinitesmal generator or its adjoint.

Both methods provide deterministic linear equations (after numerical discretization) for drift and diffusion coefficients

- generalizable to multiple dimensions (Elston and Wang 2007)
- more accurate and efficient than Monte Carlo simulations

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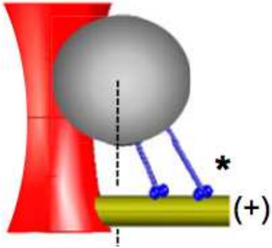
- Mesoscale Model for Collections of Molecular Motors
- Stochastic Asymptotic Techniques

Collective Dynamics of Molecular Motors

Nothing prevents multiple molecular motors (from possibly different microtubules) binding to a common cargo, *in vivo* or *in vitro*.



(from Jamison, *et al*, *Biophys. J.*, 2010)

We'll focus on N cooperative, noninterfering motors (primarily $N = 2$).

Collective Dynamics of Molecular Motors: Who Cares?

- Theoretical study (Müller, Klumpp & Lipowsky 2008) with functional implications: Tug-of-war configurations exhibit rich dynamics which might enable coordination of transport without special regulator (Welte and Gross 2008)
- Experimental inference regarding number of motors actively working against cargo: 1–10? (Jamison *et al* 2010, Gross *et al* 2007)

Collective Dynamics of Molecular Motors: Approach

Our main purpose is to develop a mathematical modeling framework rich enough to incorporate

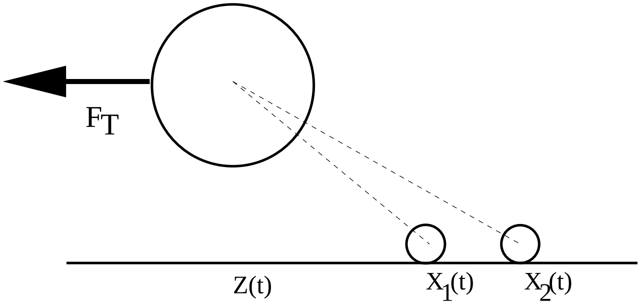
- stochastic fluctuations in spatial distribution of motors and cargo; some aspect of which is often neglected in existing models

yet amenable to analysis through stochastic asymptotic procedures. Relative to existing models,

- we don't assume load force shared equally among bound motors (Müller, Klumpp & Lipowsky 2008, Wang and Li 2009, Newby and Bressloff 2010)
- we use more detailed coupled stochastic differential equation models rather than Markov chains or random walks (Wang and Li 2009, Müller, Klumpp & Lipowsky 2008)
- we pursue analytical procedures to describe collective behavior rather than just numerical simulations (Korn et al 2009, Kunwar et al 2008).

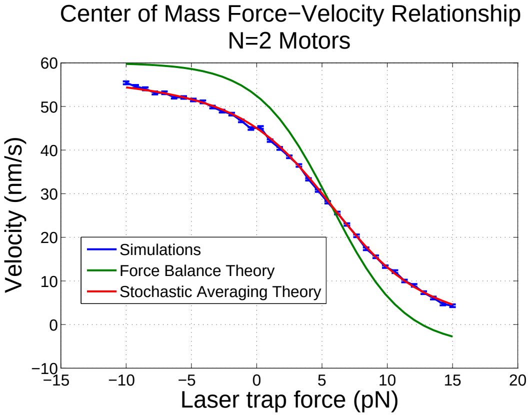
Coarse-Grained Description

- Each motor is coarse-grained to point particle with effective velocity and diffusivity as function of applied force, parameterized in principle by either:
  - Experiment
  - Coarse-graining of nanoscale model



Preview of Conclusions

We will find qualitative differences from force-balance theory, with implications for inferences from experiment (Jamison *et al*, *Biophys. J.*, 2010).



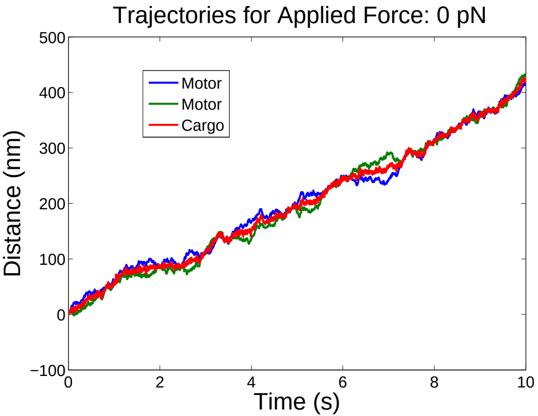
Mesoscale Model Equations

$$\mathrm{d}X_i(t) = vg\left(\kappa(X_i - Z(t))/F_s\right)\,\mathrm{d}t + \sigma\,\mathrm{d}W_x(t)$$

$$\gamma\mathrm{d}Z(t) = -\sum_{j=1}^{N}\kappa(Z(t) - X_j(t))\,\mathrm{d}t - F_T\,\mathrm{d}t + \sqrt{2k_BT\gamma}\,\mathrm{d}W_z(t)$$

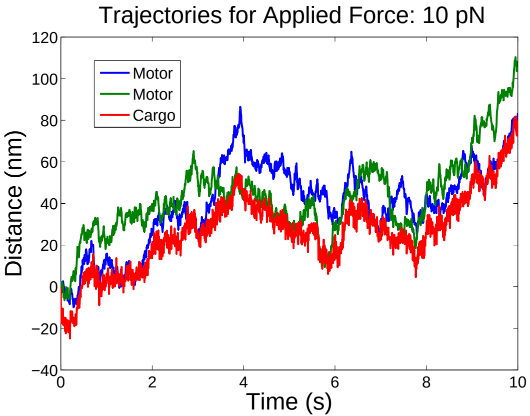
- t: time
- $X_i(t)$: position of ith motor; $Z(t)$: position of cargo
- N: number of motors
- v: unencumbered motor speed
- $\frac{1}{2}\sigma^2$: motor diffusivity
- g: nondimensional force-velocity relation
- F_s: stall force; F_T: force applied by laser trap
- k_BT: Boltzmann's constant $\times$ temperature
- γ: friction coefficient of cargo
- κ: spring constant (linear regime)
- $W_x(t)$, $W_z(t)$: independent Gaussian white noise

Sample Trajectories



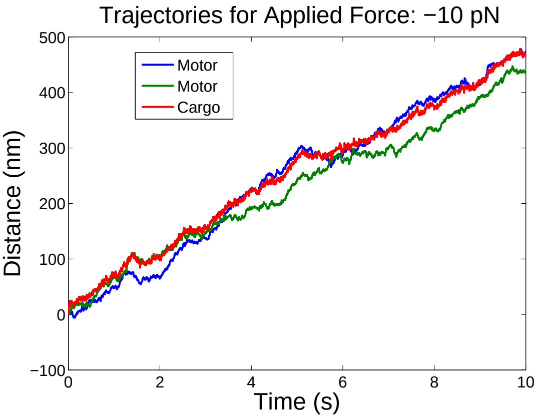
Trajectories without laser trap force

Sample Trajectories



Trajectories with strong laser trap force

Sample Trajectories



Trajectories with assisting laser trap force

Force magnitudes

- Typical spring tension due to thermal fluctuations $F_{\text{sp}} = \sqrt{\kappa k_B T} \sim 1$ pN
- Maximum friction force $F_{\text{fric}} = \gamma v \sim 5 \times 10^{-4}$ pN
- Stall force $F_S \sim 5 - 10$ pN
- Laser trap force $F_T \sim 1 - 10$ pN

Suggests length scale of spring set by thermal fluctuations $\sqrt{k_B T/\kappa} \sim 3$ nm

- nonlinearity of spring possibly important at extensions ~ 5 nm,

Nondimensionalization

Nondimensionalize system with respect to:

- length scale $\sqrt{k_B T/\kappa}$ of thermal spring fluctuations
- time scale γ/κ of cargo-spring response

$$\mathrm{d}\tilde{X}_i(\tilde{t}) = \epsilon g\left(s\left[\tilde{X}_i(\tilde{t}) - \tilde{Z}(\tilde{t})\right]\right)\mathrm{d}\tilde{t} + \sigma_{\mathsf{m/c}}\mathrm{d}W_i(\tilde{t})$$

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

Nondimensional parameters:

- $\epsilon \equiv \frac{v\gamma}{\sqrt{2k_B T\kappa}} = F_{\mathsf{fric}}/F_{\mathsf{sp}} \sim 10^{-4}$
- $s \equiv \frac{\sqrt{2k_B T\kappa}}{F_s} = F_{\mathsf{sp}}/F_S \sim 0.1 - 1$
- $\tilde{F} \equiv \frac{F_T\sqrt{\kappa}}{\sqrt{2k_B T}} = F_T/F_{\mathsf{sp}} \sim 1 - 10$
- $\sigma_{\mathsf{m/c}} \equiv \frac{\sigma\sqrt{\gamma}}{\sqrt{2k_B T}} = \sqrt{\frac{\frac{1}{2}\sigma^2}{k_B T/\gamma}} = \sqrt{D_m/D_c} \sim 10^{-2}$, square root of ratio of diffusivities

Nondimensionalization

Set $\sigma_{\mathsf{m/c}} = \sqrt{\epsilon\rho}$ to prepare asymptotic analysis with $\epsilon \ll 1$ and $s, \tilde{F}, \rho \sim O(1)$.

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

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

With this nondimensionalization, cargo variable $\tilde{Z}$ evolves on fast $\operatorname{ord}(1)$ time scale and motors on slow $\operatorname{ord}(\epsilon^{-1})$ time scale.

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Stochastic Averaging

Helpful to rescale variables to slower time scale

$$X_i^\epsilon(\tilde{t}) = \tilde{X}_i(\tilde{t}/\epsilon), \qquad Z^\epsilon(\tilde{t}) = \tilde{Z}(\tilde{t}/\epsilon)$$

and drop tilde on time variable:

$$\begin{aligned}
\mathrm{d}X_i^\epsilon(t) &= g\left(s\left[X_i^\epsilon(t) - Z^\epsilon(t)\right]\right)\mathrm{d}t + \sqrt{\rho}\,\mathrm{d}W_i(t), \\
\mathrm{d}Z^\epsilon(t) &= \epsilon^{-1}\left[\sum_{i=1}^{N}\left(X_i^\epsilon(t) - Z^\epsilon(t)\right) - \tilde{F}\right]\mathrm{d}t + \epsilon^{-1/2}\mathrm{d}W_z(t)
\end{aligned}$$

This is in two-time-scale form in which we can approximately replace fast cargo variable by its statistical distribution, conditioned on motor positions, in motor equation.

- Averaging theorems for $\epsilon \downarrow 0$ (Khas'minskii 1966, Freidlin & Wentzell 1979,. . .)
- See also Elston & Peskin 2000 for single motor context.

Averaged Motor Equations

$X_i^\epsilon(t) \sim \bar{X}_i(t)$ for $\epsilon \ll 1$:

$$\mathrm{d}\bar{X}_i(t) = \bar{g}_i(\vec{\bar{X}}(t))\,\mathrm{d}t + \rho\,\mathrm{d}W_i(t), \quad i = 1, \cdots, n$$

$$\bar{g}_i(\vec{x}) = \int_{\mathbb{R}} g\left(s(x_i - z)\right) m_{\vec{x},\tilde{F}}(z)\,\mathrm{d}z$$

where

$$m_{\vec{x},\tilde{F}}(z) = \frac{\sqrt{n}}{\sqrt{\pi}} \exp\left[-\frac{\left(z - \left[\frac{\sum_{i=1}^N x_i}{N} - \frac{\tilde{F}}{N}\right]\right)^2}{1/N}\right]$$

is stationary distribution of cargo $Z(t)$ given motor positions $\vec{x}$.

Sense of Averaging Approximation

More precisely, under regularity conditions (to be stated later) on force-velocity relation g, for any fixed time interval $[0, T]$,

- the stochastic processes $\{X_i^\epsilon(t)\}_{i=1}^N$ converge weakly in $C_{[0,T]}(\mathbb{R}^N)$ to $\{\bar{X}_i(t)\}_{i=1}^N$

as $\epsilon \downarrow 0$.

Two-Motor Case

For $N = 2$ motors:

$$\bar{g}_1(\vec{x}) = \bar{G}(x_2 - x_1 - \tilde{F}), \qquad \bar{g}_2(\vec{x}) = \bar{G}(x_1 - x_2 - \tilde{F}),$$

where

$$\bar{G}(r) = \frac{\sqrt{2}}{\sqrt{\pi}} \int_{-\infty}^{\infty} g\left(-sy\right) \exp\left(-2\left[y + \left(\frac{r}{2}\right)\right]^2\right) \mathrm{d}y.$$

Two-Motor Case

Under change of variables:

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

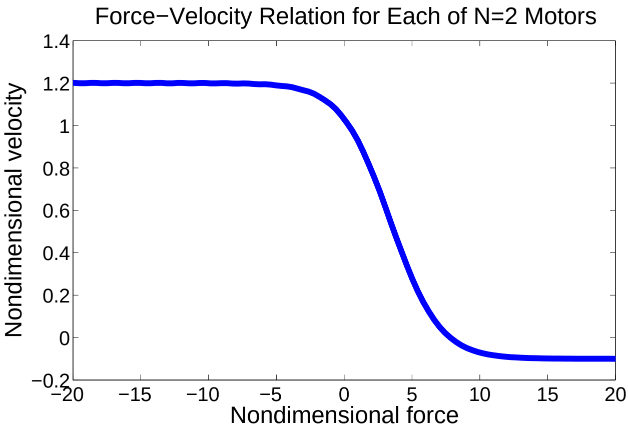
obtain equations for center of mass and difference of motor positions:

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

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

where $W_m(t)$ and $W_r(t)$ are independent standard Brownian motions.

Two-Motor Case



Two-Motor Case

Iterative solution:

$$\bar{M}(t) = \bar{M}(0) + \frac{1}{2}\int_0^t \left(\bar{G}(\bar{R}(t') - \tilde{F}) + \bar{G}(-\bar{R}(t') - \tilde{F})\right) \mathrm{d}t' \\ + \sqrt{\frac{\rho}{2}} W_m(t)$$

and note $\bar{R}(t)$ satisfies a (one-dimensional) stochastically forced gradient flow equation, therefore formally ergodic.

Two-Motor Case

Can define effective drift of the system:

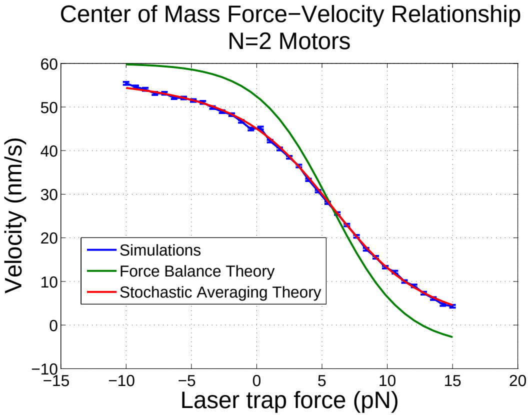
$$
\begin{aligned}
V^{(2)}(\tilde{F}) &\equiv \lim_{t\to\infty} \frac{\bar{M}(t)-\bar{M}(0)}{t} \\
&= \lim_{t\to\infty} \frac{1}{2t}\int_0^t \left(\bar{G}(\bar{R}(t')-\tilde{F}) + \bar{G}(-\bar{R}(t')-\tilde{F})\right)\,\mathrm{d}t' \\
&= \frac{1}{2}\int_{\mathbb{R}} m_{\bar{R},\tilde{F}}(r)\left(\bar{G}(r-\tilde{F}) + \bar{G}(-r-\tilde{F})\right)\,\mathrm{d}r
\end{aligned}
$$

where stationary distribution for $\bar{R}(t)$ is given by:

$$
m_{\bar{R},\tilde{F}}(r) = C_R \exp\left[\frac{-\int_0^r \left(\bar{G}(r'-\tilde{F}) - \bar{G}(-r'-\tilde{F})\right)\,\mathrm{d}r'}{\rho}\right]
$$

where C_R is normalizing constant. Effective diffusivity of center of mass also similarly computable as explicit integral.

Two-Motor Case



Equal-Load-Force Sharing Hypothesis

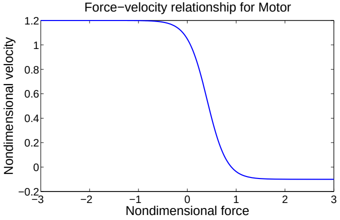
Would result from equilibrium (noiseless) approximation:
$X_i^\epsilon(t) - Z^\epsilon(t) = \tilde{F}/N$ for $i = 1, \ldots, N$.
Average speed of progress $= g(s\tilde{F}/N)$.

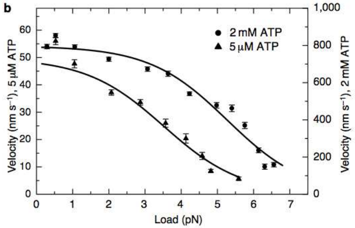
Two Motors vs. One Motor

1. For low applied force $F_T \ll F_S$, the effective velocity of two-motor-cargo system is slower than for single-motor-cargo system.
2. The stall force of two-motor-cargo system is more than twice that of a single-motor-cargo system.

These conclusions result from concavity properties of single-motor force-velocity curve g and would not follow from a force-balance theory.

Force-Velocity Relationship Model

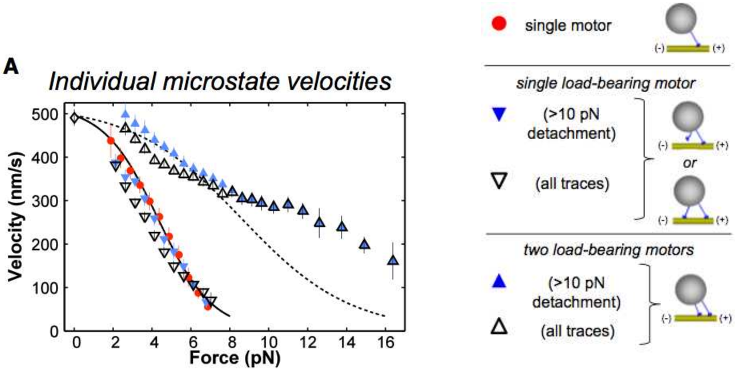




(Schnitzer *et al*, *Nature Cell Biology*, 2000)

Comparison with Experiment

These deviations from force-balance theory are in qualitative agreement with the experimental findings of Jamison *et al*, *Biophys. J.*, 2010:



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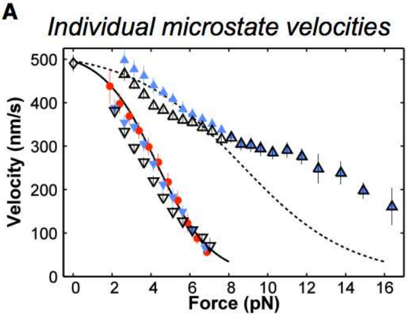
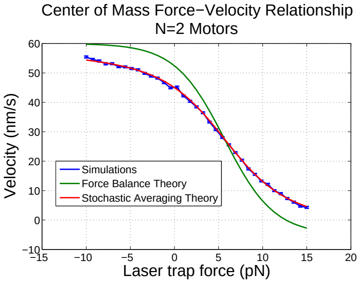




Range of Validity of Mathematical Theory

We can state our conclusions precisely under the assumption that the force-velocity relation obeys the following conditions (overkill):

1. $g(f)$ is normalized so that $g(0) = 1$ and $g(1) = 0$,
2. $g(f)$ is nonincreasing, bounded, and C^2,
3. Concavity conditions:
   - $g''(0) < 0$
   - $g''(1) > 0$
   - $\frac{1}{2}(g(\theta) + g(-\theta))$ is a decreasing function on $\theta \geq 0$,
   - $\frac{1}{2}(g(1+\theta) + g(1-\theta))$ is an increasing function on $\theta \geq 0$.

Formalized Results

Under the previously stated assumptions on the force-velocity curve $g(f)$, there exist constants $f_c > 0$ and $s_c > 0$ so that, provided $0 < s < s_c$,

- $V^{(2)}(\tilde{F}) < V^{(1)}(\tilde{F})$ for $|\tilde{F}| < f_c$
- $V^{(2)}(2\tilde{F}) > V^{(1)}(\tilde{F})$ for $|\tilde{F} - s^{-1}| < f_c$

Key Objects for Analysis

$$V^{(1)}(f) = \frac{1}{2\sqrt{\pi}} \int_{-\infty}^{\infty} g(s(f+r))\mathrm{e}^{-r^2}\,\mathrm{d}r,$$

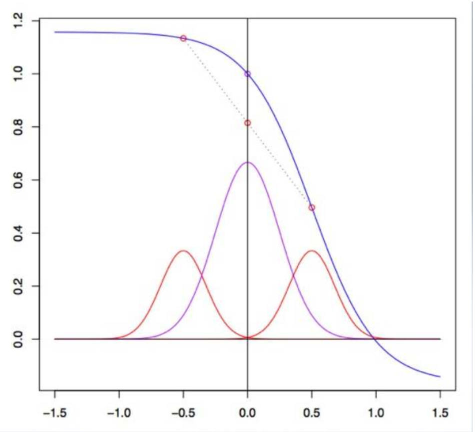
$$V^{(2)}(f) = \frac{1}{2} \int_{-\infty}^{\infty} \left[\bar{G}(r-f) + \bar{G}(-r-f) m_{\bar{R},\tilde{F}}(r)\right],$$

where

$$\bar{G}(r) = \frac{\sqrt{2}}{\sqrt{\pi}} \int_{-\infty}^{\infty} g(-sy) \exp\left(-2\left[y + \left(\frac{r}{2}\right)\right]^2\right)\,\mathrm{d}y,$$

$$m_{\bar{R},\tilde{F}}(r) = C_R \exp\left[\frac{-\int_0^r \left(\bar{G}(r'-\tilde{F}) - \bar{G}(-r'-\tilde{F})\right)\,\mathrm{d}r'}{\rho}\right].$$

Proof in a Picture



Extensions

- Low ATP regime: concavity of force-velocity $g(f)$ relation reversed; so are conclusions
- Multiplicative noise case:

$$\begin{aligned} \mathrm{d}X_i(t) = &\, vg\left(\kappa(X_i - Z(t))/F_s\right)\,\mathrm{d}t \\ &+ \sigma h\left(\kappa(X_i - Z(t))/F_s\right)\,\mathrm{d}W_x(t) \end{aligned}$$

- Nonlinear spring force law between motor and cargo

Extension to Nonlinear Spring Models

$$F_{\mathsf{sp}}(x-z) = \kappa L_c \Phi'\left((x-z)/L_c\right)$$

where L_c is a length scale of spring extension characterizing onset of nonlinear behavior. ($\Phi(\xi) \sim \frac{1}{2}\xi^2 + o(\xi^2)$)

Changes (nondimensional) equation for cargo:

$$\mathrm{d}Z^\epsilon(t) = \epsilon^{-1}\left[\sum_1^n c^{-1}\Phi'\left(c(X_i^\epsilon(t) - \tilde{Z}(t))\right) - \tilde{F}\right]\mathrm{d}t + \epsilon^{-1/2}\mathrm{d}W_z(t)$$

where

$$c \equiv \frac{\sqrt{2k_BT/\kappa}}{L_c} \lesssim 1.$$

This in turn only changes the stationary distribution for $Z(t)$:

$$m_{\vec{x},\tilde{F}}(z) = C_Z \exp\left[-\frac{2\Phi\left(c\left(z-\left[\frac{\sum_1^n x_i}{n} - \frac{\tilde{F}}{n}\right]\right)\right)}{c/n}\right]$$

with normalization constant C_Z.

Future Work

- Three-dimensional cargo
- Tug-of-war configurations
- Binding/unbinding dynamics