Spatial Stochastic Models for Molecular Motors Attaching and Detaching from Microtubules

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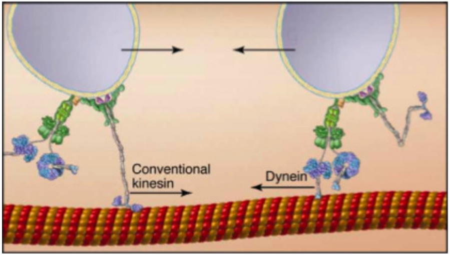
Molecular Motors

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.



R. Vale, *Cell* 2003

Physics of Molecular Motors

Scales $\sim 10^2$ nm:

- friction-dominated
- thermal fluctuations important

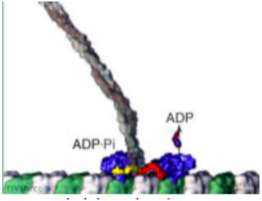
In fact the functioning of the molecular motor relies on effectively random thermal fluctuations

- 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 and organelles in cells) along microtubules.

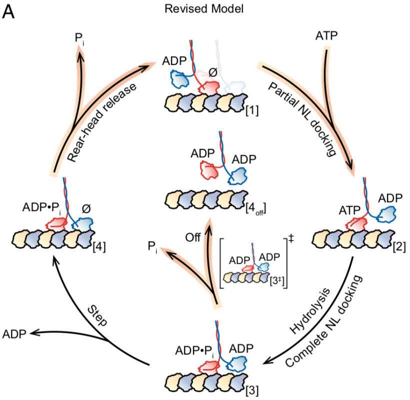
Molecular Scale View

Mechanochemistry of stepping process of motors; video available at `http://valelab.ucsf.edu`;



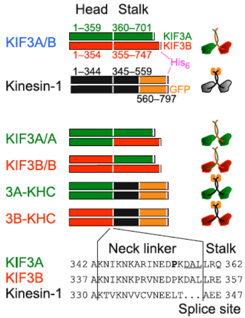
Length scale $10 - 10^2$ nm.
Goal: relate effective mechanical motion of motors to their governing chemomechanical cycle and physical characteristics.

Gating of Mechanochemical Cycle



(Milic, Andreasson, Hancock, and Block, *PNAS* 2015)

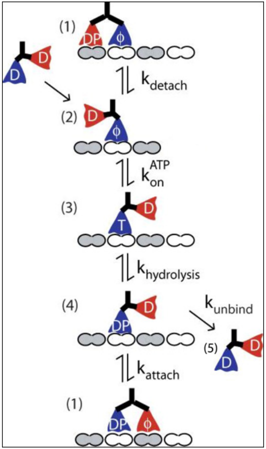
Reason for Differences in Motor Properties



(Andreasson, Shastry, Hancock, Block *Current Biology* 2015)

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; represent some transitions via stopping times related to a (flashing ratchet) stochastic differential equation for a head coordinate $X(t)$:

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

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.

Inference of Parameters of Stepping Models

Such models can be used to infer parameters from experimental observations:

- kinetic parameters of reaction network (Maes and van Wieren 2003, Keller, Berger, Liepelt, Lipowsky 2013)
- Investigation of force-law hypotheses for neck-linker component; WLC seems most plausible (Hughes, Hancock, Fricks 2012). See also Bates & Jia 2010.

Effective Transport Properties

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

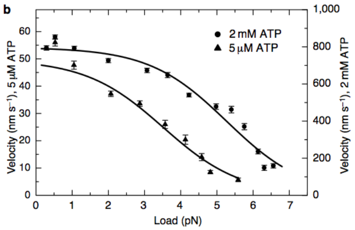
- drift
$$V = \lim_{t\to\infty} \frac{\langle X(t)\rangle}{t},$$
- diffusion
$$D = \lim_{t\to\infty} \frac{\left\langle (X(t) - \langle X(t)\rangle)^2 \right\rangle}{2t}.$$

Force-Velocity and Force-Diffusivity Relations

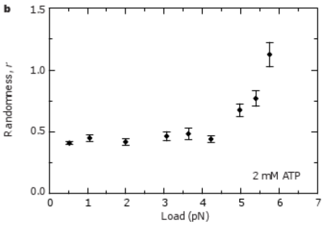
For a given motor, these are usefully expressed in terms of load force F through:

- 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)

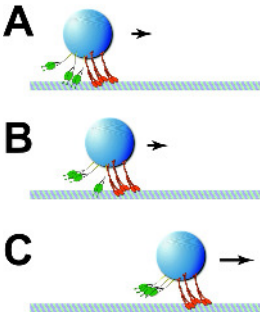
Methods to Derive Effective Transport Properties

- Homogenization theory (Pavliotis 2005, Blanchet, Dolbeault, Kowalcyk 2008)
- Method of Wang, Peskin, Elston (2003) (WPE) based on spatial discretization preserving detailed balance
- Analysis of kinesin stepping model via intermediate (reward)-renewal process framework (Hughes, Hancock, Fricks 2011)

These approaches have generally treated applied force as constant (slowly varying), but especially in context of multiple motors, stochastic force fluctuations should probably be averaged over (Hendricks, Epureanu, Meyhöfer 2009)

Cargo Scale View

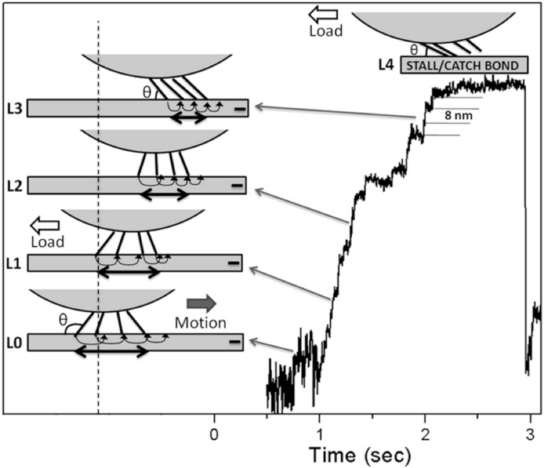
Interaction of cargo with molecular motors and microtubules



Welte & Gross, *HFSP J* 2008

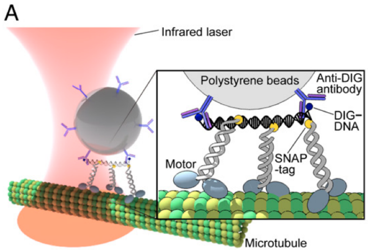
Length scale: $10^2 - 10^3$ nm
Goal: Relate the effective dynamics of multiple interacting molecular motors to the properties of the individual motors and microtubule(s).

Collective Force Generation by Teams of Motors

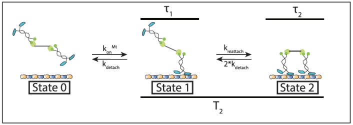


(Rai, Rai, et al, *Cell* 2013)

Engineered Constructs of Motor Groups

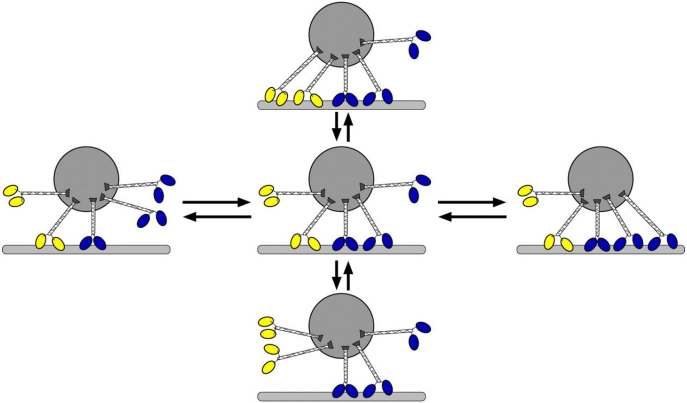


(Furuta, Furuta, *PNAS* 2013)



(Feng, Mickolajczyk, Chen, and Hancock, *Biophysical Journal* 2018)

Force-balance (mean field) Markov Chain Model (Müller, Klumpp & Lipowsky)



Müller, Klumpp & Lipowsky, *PNAS* 2008

Some Other Cargo Scale Modeling Approaches

One-dimensional models with stochastic spatial fluctuations of individual motors

- Lattice stepping models (Wang & Li 2009, Posta, D'Orsogna & Chou 2009); some with steric interference (Klumpp & Lipowsky 2005, Goldman 2010)
- Continuous-space model, coarse-graining over steps (Kunwar *et al* 2008, McKinley, Athreya, *et al* 2012)

Three-dimensional models, including spatial resolution of cargo and cargo-tether binding sites (Korn, Klumpp, *et al* 2009, Jamison, Driver, et al 2010)

- explored primarily through numerical simulations

Confront Models and Experiments

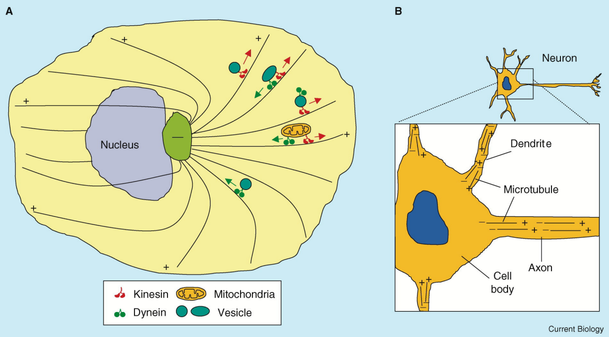
Statistical inference of model parameters

- motor-coupling properties and reattachment rates from *in vitro* N-motor cargo assemblies (Jamison *et al* 2010, Keller *et al* 2013)

Purely mechanical model for tug-of-war scenarios appear incomplete *in vivo* (Kunwar, Tripathy,. . . , Mogilner, Gross 2011; Hancock 2014)

- what other regulatory factors?

Cellular Scale View



Mallik & Gross, *Current Biology* 2004

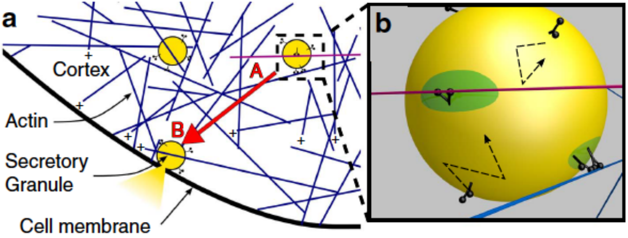
Length scale μm - cm

Goal: Explain mechanistically how molecular motors moving on a microtubule architecture achieve goals of intracellular transport, including targeting cargo delivery and responding to regulatory cues.

Some Key Questions About Cellular Transport

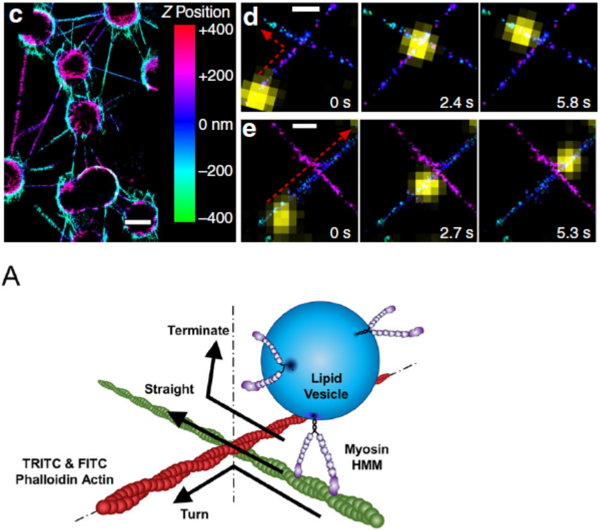
- How is cargo delivered to appropriate destination, i.e., synapses along dendrites or axon of neuron?
- How can cell dynamically regulate cargo transport goals, i.e., melanosomes ?
- What role does microtubule architecture and polarity have in large-scale transport, esp. in neurons?

Navigating Complex Filament Network



(Lombardo, Nelson, et al, *Nature Communications* 2017)

Experimental Exploration of Intersections



(Lombardo, Nelson, et al, *Nature Communications* 2017)

Cellular Scale Modeling Approaches

Kinetic theories for attaching/detaching to microtubule network at various orientations:

$$\frac{\partial p_{\mathrm{on}}(\mathbf{r},\theta,t)}{\partial t} = -\boldsymbol{\nabla}\cdot(\mathbf{V}(\mathbf{r},\theta)p_{\mathrm{on}}) + \boldsymbol{\nabla}\boldsymbol{\nabla} : (D_{\mathrm{on}}(\mathbf{r},\theta)p_{\mathrm{on}}) + k_{\mathrm{on}}(\mathbf{r},\theta)p_{\mathrm{off}} - k_{\mathrm{off}}(\mathbf{r},\theta)p_{\mathrm{on}},$$

$$\frac{\partial p_{\mathrm{off}}(\mathbf{r},t)}{\partial t} = D_{\mathrm{off}}\Delta p_{\mathrm{off}} - p_{\mathrm{off}}\int_0^{2\pi} k_{\mathrm{on}}(\mathbf{r},\theta)\,\mathrm{d}\theta + \int_0^{2\pi} k_{\mathrm{off}}(\mathbf{r},\theta)p_{\mathrm{on}}\,\mathrm{d}\theta$$

- Popovic, McKinley, & Reed 2011: parallel network in axon
- Bressloff & Xu (2015): cell polarization
- Lawley, Tufts, & Brooks (2015): virus trafficking
- Ciocanel, Mowry, Sandstede (2017): mRNA transport

Newby & Bressloff, "Stochastic Models of Intracellular Transport" (2013) review (also target search models with environmental cues (e.g., microtubule associated proteins))

Collective Dynamics of Molecular Motors: Motivation

What is the purpose of the diversity of kinesin and other processive motor types?

- Probably for different cargo types in different environments, etc.

But then why would two different motor types be used simultaneously for the same cargo?

- kinesin-1 and kinesin-2 for synaptotagmin-rich axonal vesicles (Hendricks, Perlson, et al 2010)

kinesin-1 and kinesin-2

Relative to kinesin-1, kinesin-2 is (Andreasson, Shastry, Hancock, Block 2015; Feng, Mickolajczyk, Chen, and Hancock 2018):

- half as fast at low load
- detach from microtubule more readily under load
- reattaches to microtubule four times as rapidly

Moreover, (Feng, Mickolajczyk, Chen, and Hancock 2018) observe that kin1-kin2 pairs:

- covered longer distance ($2.18 \pm 0.39 \mu m$) than kin1-kin1 pairs ($1.62 \pm 0.23 \mu m$)
- almost as long as kin2-kin2 pairs ($2.38 \pm 0.26 \mu m$)
- speed?

One might have expected the partnering of dissimilar motors to be more disruptive.

Collective Dynamics of Molecular Motors: Approach

We are building on previous model which neglects attachment/detachment.

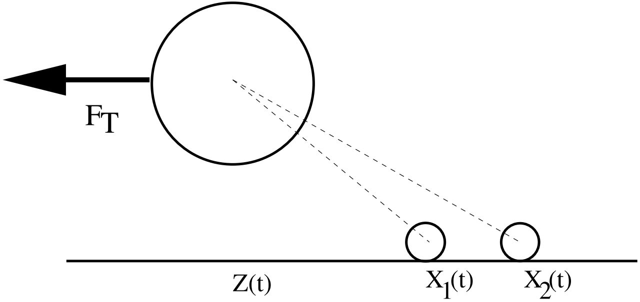
- S. McKinley, A. Athreya, J. Fricks, P. Kramer, "Asymptotic Analysis of Microtubule-Based Transport by Multiple Identical Molecular Motors," *J. Theor. Bio.* **305** (2012): 54-69.

We want to maintain following features:

- we don't assume load force shared equally among bound motors, and track the fluctuating positions and forces experienced by the motors
- we use coupled stochastic differential equation models
- we pursue analytical procedures to describe collective behavior rather than only numerical simulations

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 molecular scale model

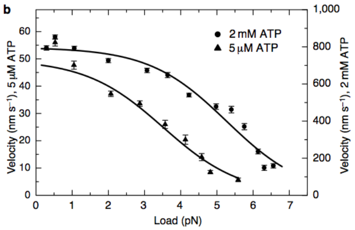


Force-Velocity and Force-Diffusivity Relations

For a given motor i, effective transport properties are usefully expressed in terms of load force F through:

- Force-velocity relation $V = g_i(F)$
- Force-diffusivity relation $D = h_i(F)$ (we take constant)

These are one way in which experimental measurements are presented:



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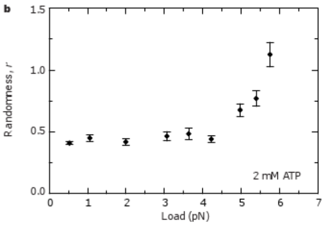


(Visscher *et al*, *Nature*, 1999)

Attachment/Detachment Model

Dynamical elements:

- t: time
- $B_i(t)$: state of motor i ($= 1$ if attached; $= 0$ if detached from microtubule)
- $X_i(t)$: position of ith motor
- $Z(t)$: position of cargo

Transition Rates

- Motor attachment rate a_i for each detached motor,
- Motor detachment rate $d_i \Upsilon_i \left(|F)| / F_i^d \right)$ for each attached motor i
  - $d_i =$ detachment rate at zero force $(\Upsilon(0) = 1)$
  - $F_i^d =$ force scale of detachment rate function
  - functional form Υ_i often modeled as asymmetric double exponential

Model Equation for Cargo

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

- $k_B T$: Boltzmann's constant $\times$ temperature
- γ: friction constant of cargo ($\propto \eta$ (solvent viscosity))
- κ_i: spring constant (linear regime) of motor i
- $W_z(t)$: Gaussian white noise

Model Equations for Motors

Attached state ($B_i = 1$):

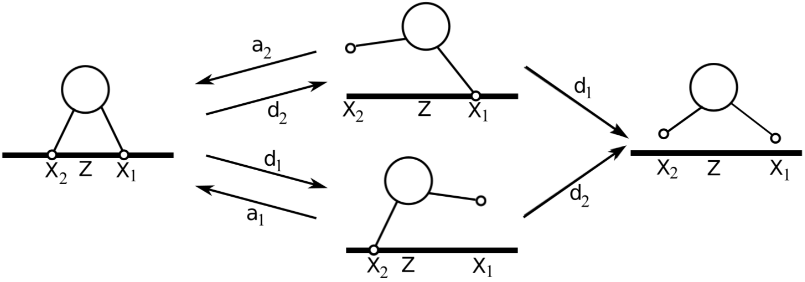
$$\mathrm{d}X_i(t) = v_i g_i\left(\kappa_i(X_i(t) - Z(t))/F_i^s\right)\mathrm{d}t + \sigma_i\,\mathrm{d}W_i(t)$$

Detached state ($B_i = 0$):

$$\gamma_{m,i}\mathrm{d}X_i(t) = -\kappa_i(X_i(t) - Z(t))\,\mathrm{d}t + \sqrt{2k_B T\gamma_{m,i}}\,\mathrm{d}W_i(t).$$

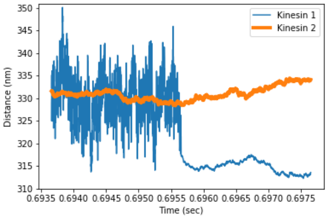
- v_i: unencumbered motor speed
- $\frac{1}{2}\sigma_i^2$: bound motor diffusivity
- g_i: nondimensional force-velocity relation
- F_i^s: stall force
- $\gamma_{m,i}$: friction constant of motor ($\propto \eta$ (solvent viscosity))
- $W_i(t)$: independent Gaussian white noise

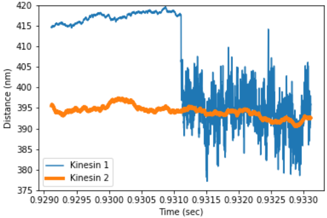
Switched Diffusion Model Schematic



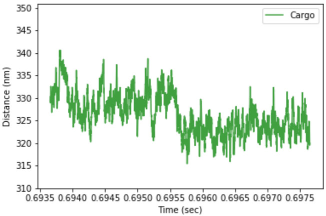
Sample Trajectories

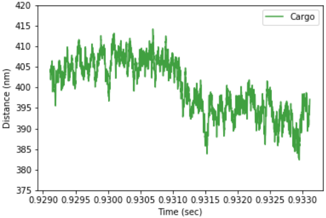
Motors





Cargo





Some Model Shortcomings

- Point particle representation of cargo moving in one dimension
  - no distinction between longitudinal and transverse forces on motors
  - no distinction between fluid and solid cargo
- No steric effects of motors or cargo
- Linear spring model is too crude
  - Can be generalized to nonlinear case
- Mechanistic models may not be adequate for representing *in vivo* behavior (Kunwar, Tripathy, et al 2011)

Nondimensionalization

Nondimensionalize system with respect to:

- length scale $\sqrt{k_B T/\bar{\kappa}}$ of thermal tail fluctuations
- time scale $\gamma/\bar{\kappa}$ of cargo-tail response

where $\bar{\kappa} = \frac{\kappa_1+\kappa_2}{2}$.

Nondimensional parameters:

- $\epsilon_i \equiv \frac{v_i \gamma}{\sqrt{2k_B T \kappa_i}} \sim 3 \times 10^{-3}$
- $s_i \equiv \frac{\sqrt{2k_B T \kappa_i}}{F_i^s} \sim 0.2$
- $u_i \equiv \frac{\sqrt{2k_B T \kappa}}{F_i^u} \sim 1$
- $\tilde{\kappa}_i = \kappa_i/\bar{\kappa}$
- $\tilde{F} \equiv \frac{F_T \sqrt{\kappa_i}}{\sqrt{2k_B T}} \sim 1 - 10$
- $\sigma^2_{\mathrm{m/c,i}} \equiv \frac{\sigma_i^2 \gamma}{2k_B T} \sim 6 \times 10^{-3}$,
- $\tilde{a}_i = a_i \gamma/\kappa \sim 10^{-4}$
- $\tilde{d} = d_i \gamma/\kappa \sim 10^{-4}$
- $\Gamma = \gamma_m/\gamma \sim 10^{-1}$

Set $\sigma_{\mathrm{m/c,i}} = \sqrt{\epsilon \rho_i}$ to prepare asymptotic analysis with $\tilde{a}, \tilde{d} \ll \epsilon \ll 1 \ll \Gamma^{-1}$ and $s_i, u_i, \tilde{F}, \rho_i \sim \mathrm{ord}\,(1)$.

Nondimensionalization

Equation for motors switch between bound state ($B_i = 1$):

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

and unbound state ($B_i = 0$):

$$\mathrm{d}\tilde{X}_i(\tilde{t}) = -\Gamma^{-1}(\tilde{X}_i(t) - \tilde{Z}_i(t))\, \mathrm{d}\tilde{t} + \sqrt{\Gamma^{-1}}\, \mathrm{d}W_i(t).$$

Attachment ($B_i = 0 \to 1$) rate $\tilde{a}_i$ and detachment ($B_i = 1 \to 0$) rate $\tilde{d}_i(u_i \left[\tilde{X}_i - \tilde{Z} \right])$.

Cargo equation always:

$$\mathrm{d}\tilde{Z}(\tilde{t}) = \left[\sum_{i=1}^{2} \left(\tilde{X}_i(\tilde{t}) - \tilde{Z}(\tilde{t}) \right) - \tilde{F} \right] \mathrm{d}\tilde{t} + \mathrm{d}W_z(\tilde{t}).$$

Note the separation of dynamical time scales, from fastest to slowest ($\Gamma, \epsilon \ll 1$):

- unbound motor $\ll$ cargo $\ll$ bound motor $\ll$ attachment/detachment rates

Asymptotic Reformulation

Detached motors treated as always in stationary distribution w.r.t. cargo position:

$$\tilde{X}_i \sim N\left(\tilde{Z}(\tilde{t}), \frac{1}{2}\right) \text{ when } B_i = 0.$$

When $B_1(t) = 1$ and/or $B_2(t) = 1$, cargo treated as always in stationary distribution w.r.t. positions of attached motors:

$$\tilde{Z} \sim N\left(\frac{\sum_{i=1}^{2} b_i \tilde{X}_i}{b_1 + b_2} - \frac{\tilde{F}}{b_1 + b_2}, \frac{1}{2(b_1 + b_2)}\right)$$

- Unbound motors do not affect cargo dynamics to leading order

Coarse-Grained Dynamics

On $O(1/\bar{\epsilon})$ nondimensional time scale ($\bar{\epsilon} = (\epsilon_1 + \epsilon_2)/2$), attached motor dynamics (while $B_i(t) = 1$):

$$\mathrm{d}\bar{X}_i(t) = \bar{g}_i(\bar{X}_1(t), \bar{X}_2(t), B_1(t), B_2(t))\,\mathrm{d}t + \sqrt{\rho_i}\,\mathrm{d}W_i(t),$$

with averaged drift:

$$\bar{g}_i(x_1, x_2, b_1, b_2) = \frac{\epsilon_i}{\bar{\epsilon}} \int_{\mathbb{R}} g_i\left(s_i(x_i - z)\right) p_{\tilde{Z}|\tilde{X},B}(z|(x_1, x_2); (b_1, b_2))\,\mathrm{d}z$$

Each attached motor detaches with rate

$$\bar{d}_i(x_1, x_2, b_1, b_2) = \tilde{d}_i \int_{\mathbb{R}} \Upsilon_i\left(u_i(x_i - z)\right) p_{\tilde{Z}|\tilde{X},B}(z|(x_1, x_2); (b_1, b_2))\,\mathrm{d}z.$$

If only motor 1 detached, it reattaches at rate $\tilde{a}_1$, and does so at a random position

$$\tilde{X}|\tilde{Z} \sim N\left(\tilde{Z}, \frac{1}{2}\right), \qquad \tilde{Z} \sim N\left(\tilde{X}_2 - \tilde{F}, \frac{1}{2}\right);$$

similarly if only motor 2 detached.

Central Coordinate

In experiments, the cargo position is typically observed, but the rapid fluctuations of $\tilde{Z}(t)$ make it awkward to use as the observed variable.

Instead we will examine statistics of the mean cargo position under the istationary distribution given the attached motor configuration:

$$M(t) = \mathbb{E}(\tilde{Z}|\tilde{X}_1(t), \tilde{X}_2(t), B_1(t), B_2(t)) = \frac{\sum_{i=1}^{2} B_i(t)\tilde{\kappa}_i \tilde{X}_i(t) - \tilde{F}}{\sum_{i=1}^{2} B_i(t)\tilde{\kappa}_i}$$

which will evolve more smoothly (on $O(1)$ time scale), so long as at least one motor attached.

Other relevant variables will be considered “internal” variables.

- Internal variables affect central coordinate $M(t)$ but not vice versa.

Central/Internal Variable Dynamics with One Attached Motor

When $B_1(t) = 1, B_2(t) = 0$:

- no internal variable
- Central coordinate undergoes constant coefficient drift-diffusion

$$\mathrm{d}M(t) = \bar{V}^{(1)}\,\mathrm{d}t + \sqrt{2\bar{D}^{(1)}}\mathrm{d}W(t),$$

- Detachment of motor 1 at constant rate $\bar{d}_1^{(1)}$
- Attachment of second motor at constant rate $\tilde{a}_2$ at position

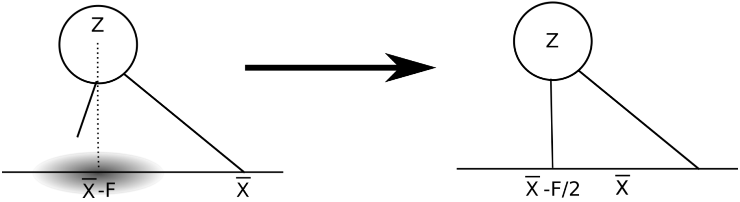
$$\bar{X}_2 = \bar{X}_1 + \Xi^{(1\to 2)}$$

with $\Xi^{(1\to 2)} \sim N(-\tilde{F}/\tilde{\kappa}_1, 1/(\tilde{\kappa}_1\tilde{\kappa}_2))$.

  - Central coordinate $M(t)$ jumps by $\frac{1}{2}(\tilde{\kappa}_2\Xi^{(1\to 2)} + \tilde{\kappa}_1\tilde{F})$

Similarly for $B_1(t) = 0, B_2(t) = 1$

Attachment Jump to Two-Motor-Attached State



Central/Internal Variable Dynamics for Two Attached Motors

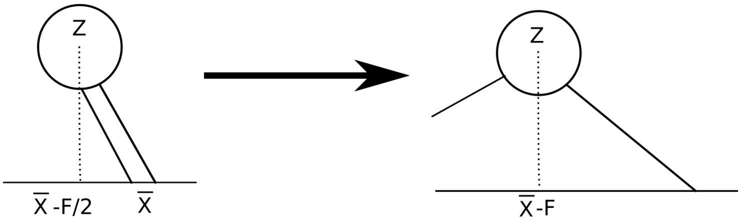
When $B_1(t) = B_2(t) = 1$ (both motors attached), internal variable $R(t) = \bar{X}_1(t) - \bar{X}_2(t)$ and central coordinate $M(t) = \frac{1}{2}(\bar{X}_1(t) + \bar{X}_2(t) - \tilde{F})$ obey SDEs of form:

$$\mathrm{d}\begin{bmatrix} M(t) \\ R(t) \end{bmatrix} = \mathbf{G}(R(t))\,\mathrm{d}t + \Sigma\,\mathrm{d}W(t)$$

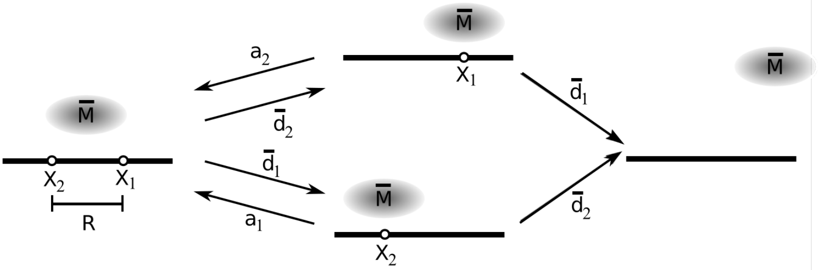
with constant noise matrix Σ.

- Detachment of motor 1 at effective rate $\bar{d}_1^{(1,2)}(R(t))$
  - Central coordinate $M(t)$ jumps by $\frac{\tilde{\kappa}_1}{2}\left[-\frac{\tilde{F}}{\tilde{\kappa}_2} - R(t)\right]$
- Detachment of motor 2 at effective rate $\bar{d}_2^{(1,2)}(R(t))$, formulas mutatis mutandi.

Detachment Jump from Two-Motor-Attached State



Switched Diffusion Model Schematic



Slow Switching Approximation

Under the approximation of slow attachment/detachment ($\tilde{a}_i, \tilde{d}_i \ll \epsilon$), we can at least nominally homogenize over the internal coordinate $R(t)$:

- time spent in each attachment/detachment phase is long compared to time scale of relaxation of $R(t)$ to (explicit) stationary distribution
- in practice, need that the effective detachment rates are also small when enhanced by typical force fluctuation
- gives homogenized constant-coefficient drift-diffusion in 2-motor attached state:

$$\mathrm{d}M(t) = \bar{V}^{*(1,2)}\,\mathrm{d}t + \sqrt{2\bar{D}^{*(1,2)}}\mathrm{d}W(t)$$

- constant effective detachment rate $\bar{d}_i^{*(1,2)}$ of motor i
  - motor separation on detachment $\tilde{R}$ weighted by detachment rate:

$$p_{\tilde{R}}(r) = \tilde{C}_R p_R(r)(\bar{d}_1^{(1,2)}(r) + \bar{d}_2^{(1,2)}(r))$$

Coarse-Grained Markov Chain Model

The slow switching dynamics can be viewed as a 4-state Markov chain parameterized by attachment state $((b_1, b_2) \in \{0,1\} \times \{0,1\})$ with:

- absorption at fully detached state $(b_1, b_2) = (0, 0)$
- random increments $\Delta M_{b_1,b_2}$ for the tracking variable

Starting from the 2-motor attached state $(b_1, b_2) = (1, 1)$, go through N_c cycles (either $(1,1) \to (1,0) \to (1,1)$ or $(1,1) \to (0,1) \to (1,1)$) before complete detachment.

- N_c is geometrically distributed with mean $\frac{1-p_0}{p_0}$, with

$$p_0 = p_1^d \frac{\bar{d}_1^{(1)}}{a_2 + \bar{d}_1^{(1)}} + p_2^d \frac{\bar{d}_2^{(1)}}{a_2 + \bar{d}_2^{(1)}}$$

- probability motor i detaches first (indicator $I_{\mathrm{d}i}$)

$$p_i^d = P(I_{\mathrm{d}i}) = \frac{\bar{d}_i^{*(1,2)}}{\bar{d}_1^{*(1,2)} + \bar{d}_2^{*(1,2)}}.$$

Attachment/Detachment Cycle Statistics

In each of these attachment/detachment cycles, time advances by a random increment

$$\Delta T_{\mathrm{c}} = \Delta T_{\mathrm{a}} + \Delta T_{\mathrm{d},2} I_{\mathrm{d}1} + \Delta T_{\mathrm{d},1} I_{\mathrm{d}2}$$

with:

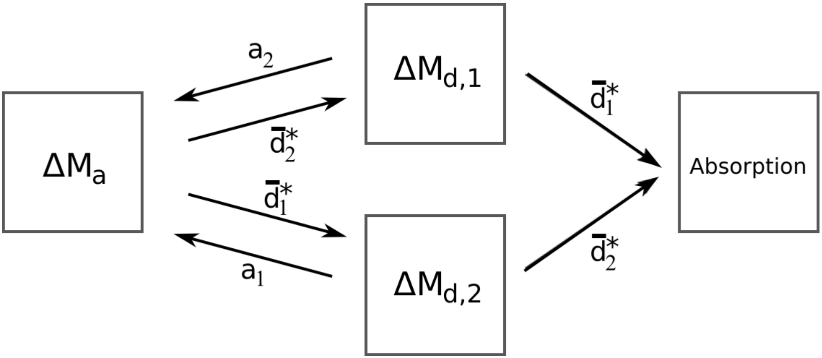
- $\Delta T_{\mathrm{a}} \sim \mathrm{Exp}((\bar{d}_1^{*(1,2)} + \bar{d}_2^{*(1,2)})^{-1})$ is the time spent in the 2-motor attached state,
- $\Delta T_{\mathrm{d},i} \sim \mathrm{Exp}((\tilde{a}_{i'} + \bar{d}_i^{(1)})^{-1})$ is the time spent with just motor i attached

The tracking variable will advance by a random increment

$$\Delta M_{\mathrm{c}} = \Delta M_{\mathrm{a}} + \Delta M_{\mathrm{d},2} I_{\mathrm{d}1} + \Delta M_{\mathrm{d},1} I_{\mathrm{d}2}$$

with parallel interpretation of the terms.

Switched Diffusion Model Schematic



Tracking Increment Statistics: Two-Motor-Attached Phase

Increment while both motors attached

$$\Delta M_{\mathrm{a}} = \bar{V}^{*(1,2)} \Delta T_{\mathrm{a}} + \sqrt{2\bar{D}^{*(1,2)}}\, \Delta W(\Delta T_{\mathrm{a}})$$

so

$$\mathbb{E}\Delta M_{\mathrm{a}} = \frac{\bar{V}^{*(1,2)}}{\bar{d}_1^{*(1,2)} + \bar{d}_2^{*(1,2)}},$$

$$\operatorname{Var} \Delta M_{\mathrm{a}} = \left(\frac{\bar{V}^{*(1,2)}}{\bar{d}_1^{*(1,2)} + \bar{d}_2^{*(1,2)}} \right)^2 + \frac{2\bar{D}^{*(1,2)}\, \bar{V}^{*(1,2)}}{\bar{d}_1^{*(1,2)} + \bar{d}_2^{*(1,2)}}.$$

Tracking Increment Statistics during Attachment/Detachment

Tracking variable increment when motor 1 detaches and reattaches is sum of detachment jump, motion in motor-2 attached state, reattachment jump:

$$\Delta M_{\mathrm{d},2} = \Delta M_{\mathrm{a}\to\mathrm{d},1} + \bar{V}^{(2)} \Delta T_{\mathrm{d},2} + \sqrt{2\bar{D}^{(2)}}\, \Delta W(\Delta T_{\mathrm{d},2}) + \Delta M_{\mathrm{d}\to\mathrm{a},1}$$

$$\mathbb{E}\Delta M_{\mathrm{d},2} = \frac{\tilde{\kappa}_1}{2}\left(-\mathbb{E}\tilde{R} - \frac{\tilde{F}}{\tilde{\kappa}_2}\right) + \frac{\bar{V}^{(2)}}{\tilde{a}_1 + \bar{d}_2^{(1)}},$$

$$\operatorname{Var}\Delta M_{\mathrm{d},2} = \frac{\tilde{\kappa}_1^2}{2}\operatorname{Var}\tilde{R} + \frac{(\bar{V}^{(2)})^2}{(\tilde{a}_1 + \bar{d}_2^{(1)})^2} + \frac{2\bar{D}^{(2)}}{\tilde{a}_1 + \bar{d}_2^{(1)}} + \frac{\tilde{\kappa}_2}{4\tilde{\kappa}_1}.$$

Similarly for when motor 2 detaches and reattaches.

Run Length and Time Statistics

Mean time T until complete detachment

$$\mathbb{E}T = (1 + \mathbb{E}N_{\mathrm{c}})(\mathbb{E}\Delta T_{\mathrm{c}}) = \left(p_1^d \frac{\bar{d}_1^{(1)}}{a_2 + \bar{d}_1^{(1)}} + p_2^d \frac{\bar{d}_2^{(1)}}{a_2 + \bar{d}_2^{(1)}} \right)^{-1}$$
$$\times \frac{1}{\bar{d}_1^{*(1,2)} + \bar{d}_2^{*(1,2)}} \left(1 + \frac{\bar{d}_1^{*(1,2)}}{\bar{d}_2^{(1)} + a_1} + \frac{\bar{d}_2^{*(1,2)}}{\bar{d}_1^{(1)} + a_2} \right)$$

Distance $M(T)$ until complete detachment has mean

$$\mathbb{E}M(T) = (1 + \mathbb{E}N_{\mathrm{c}})(\mathbb{E}\Delta M_{\mathrm{c}}) - \dots$$

and variance

$$\mathrm{Var}\, M(T) = (\mathrm{Var}\, N_{\mathrm{c}})(\mathbb{E}\Delta M_{\mathrm{c}}) + (1 + \mathbb{E}N_{\mathrm{c}})(\mathrm{Var}\, \Delta M_{\mathrm{c}}) - \dots$$

with correction terms to exclude the final reattachment adjustment.

Summary of Cooperative Motor Dynamic Model

Relate properties of two dissimilar but cooperative motors to their effective transport working together

- can show existence of parameter regimes where team of two dissimilar motors go faster than either team of two identical motors
- integrate stochastic spatial fluctuations with attachment/detachment dynamics
- exploit separation fo time scales for explicit effective transport formulas

Comparison with kin1-kin2 experimental results in progress. . .

For $N > 2$ cooperative motors, or for $N = 2$ without slow switching, need to numerically homogenize cargo-averaged dynamics.

Averaging of detachment rates has limited validity

- more delicate coarse-graining of detachment surely required for antagonistic motors

Attachment Dynamics of Molecular Motors: Motivation

For transport by multiple motors along a microtubule:

- understand how motors detached from microtubule reattach
- how affected by cargo properties and the attached motors (Furuta, Furuta et al 2013)
  - or other anchoring mechanisms like dynactin (Smith and McKinley 2018)
- attempt to improve on spherical search arguments (Feng, Mickolajczyk, Chen, and Hancock 2018)

For transport through microtubule network:

- need probabilities and rates of cargo switching to different microtubule filaments.
- bridge cargo-scale description to cellular-scale
- explore parametric validity of slow attachment rate approximations for network transport theories such as (Bressloff and Xu 2015)

Attachment Dynamics of Molecular Motors: Approach

Model spatial dynamics of (re)-attachment of molecular motors to microtubules

- Quantitatively represent the spatial search time scale through dynamical model
- Estimate probability to reattach to same or different microtubule
- Track spatial "memory" of motor-cargo complex as it detaches and reattaches
- As complement to simulations, aiming for analytical/asymptotic procedures to relate model parameters to effective transport properties of the motor.

Cargo represented by a sphere with finite radius and a fixed attachment point of tether on surface.

Physical Model

Molecular motor

- while attached, point particle moving in one direction (longitudinally) with effective velocity, diffusivity, detachment rate
- while detached, overdamped dynamics in three dimensions with friction constant γ_m. Reattach upon spatial contact with microtubule (with reactivity K_a)

Cargo

- rigid sphere of radius ρ_c, with overdamped dynamics with translational (rotational) friction coefficient γ_c (γ_r)

Motor-cargo tether

- spring (linear approximation for now) connecting motor particle to fixed attachment point on cargo surface

Microtubule network

- periodic array of parallel cylinders with radius ρ_{MT} and period spacing ℓ_{MT}

Attached Phase

The dynamics of a motor with cargo while attached to a microtubule is well-studied (Elston & Peskin 2000); we subcontract this analysis to previous work which coarse-grains the properties of motor, cargo, and tether to effective dynamics of motor position $X_1(t)$ along microtubule to:

$$\mathrm{d}X_1(t) = v_a \,\mathrm{d}t + \sqrt{2D_a}\mathrm{d}W(t)$$

with:

- effective velocity v_a,
- effective diffusivity D_a ($= 0$ for now).

Also assume effective constant detachment rate k_d (through, i.e., stochastic averaging as in previous part).

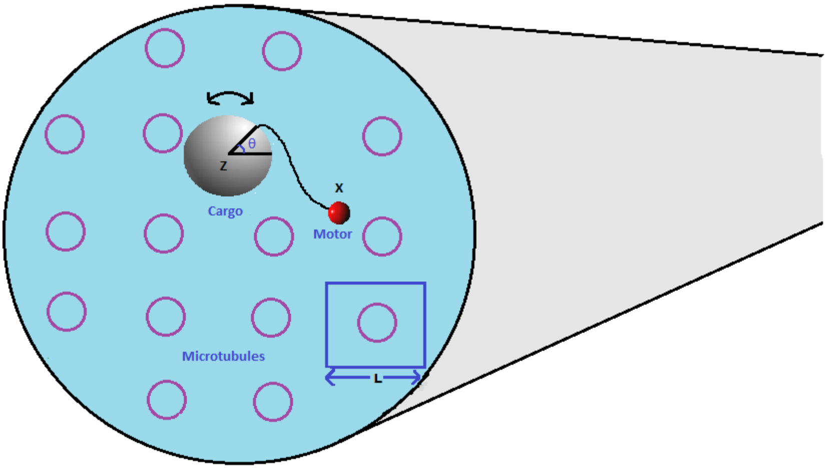
Two-Dimensionalization in Detached Phase

To develop the methodology without the complexities of three-dimensional rotational dynamics, we currently project the detached dynamics onto two-dimensional planes

- first passage time problem in plane transverse to the microtubules
- transport along longitudinal plane through cargo center at detachment and microtubule

This is not a controlled approximation, and will partially relax it later.

Detached Transverse Dynamics



Detached Transverse Dynamics

Motor:

$$\gamma_m \mathrm{d}\mathbf{X}^{\perp}(t) = -\kappa(\mathbf{X}^{\perp}(t) - (\mathbf{Z}^{\perp}(t) + \rho_c \hat{\mathbf{R}}^{\perp}(t)))\,\mathrm{d}t + \sqrt{2k_B T \gamma_m}\,\mathrm{d}\mathbf{W}^{x,\perp}(t).$$

Cargo:

$$\gamma_c \mathrm{d}\mathbf{Z}^{\perp}(t) = -\kappa(\mathbf{Z}^{\perp}(t) + \rho_c \hat{\mathbf{R}}^{\perp}(t) - \mathbf{X}^{\perp}(t))\,\mathrm{d}t + \sqrt{2k_B T \gamma_c}\,\mathrm{d}\mathbf{W}^{z,\perp}(t),$$

$$\gamma_r \mathrm{d}\hat{\mathbf{R}}^{\perp}(t) = -\kappa\rho_c(\mathbf{Z}^{\perp}(t) + \rho_c \hat{\mathbf{R}}^{\perp}(t) - \mathbf{X}^{\perp}(t)) \cdot \hat{\mathbf{\Theta}}^{\perp}(t)\hat{\mathbf{\Theta}}^{\perp}(t)\,\mathrm{d}t + \sqrt{2k_B T \gamma_r}\,\mathrm{d}\mathbf{W}^{\theta,\perp}(t)$$

where $\hat{\mathbf{R}}^{\perp}(t) = \left[\cos\Theta^{\perp}(t), \sin\Theta^{\perp}(t)\right]^T$,
$\hat{\mathbf{\Theta}}^{\perp}(t) = \left[-\sin\Theta^{\perp}(t), \cos\Theta^{\perp}(t)\right]^T$.
Attach when $\mathbf{X}^{\perp}(t) \equiv \mathbf{x}' \pmod{\ell_{\mathrm{MT}}}$ for some $|\mathbf{x}'| \leq \ell_{\mathrm{MT}}$.
No steric interactions at this point...

First Passage Time Problem

We attempt a simplification by taking $\epsilon \equiv \rho_{\mathrm{MT}}/\ell_{\mathrm{MT}} \ll 1$.

- Small target problem (Ward & Keller, Bressloff, Lawley, Isaacson, Schuss, Holcman, ...)
  - asymptotic analysis of 5-dimensional PDE for mean first passage time (MFPT) $\bar{T}_a = \langle T_a \rangle$
  - logarithms arise as in 2-dimensional PDE because target is "small" in two directions and large in three
- Exponential distribution (if not starting close)

Leading Order Asymptotics

If motor starts at distance ℓ_d from microtubule center then MFPT

$$\bar{T}_a \sim \frac{\ell_{\mathrm{MT}}^2}{2\pi D_m}\left[\ln\left(\frac{\ell_d}{\rho_{\mathrm{MT}}}\right) + \frac{1}{K_a}\right]\left[1 + O\left(1/\ln\left(\frac{1}{\epsilon}\right)\right)\right].$$

- No dependence on presence of cargo in this asymptotic limit.

Probability to Reattach on Same Microtubule

Once motor distance from microtubule ℓ_d is more than a few microtubule radii $\ell_d \gg \rho_{\mathrm{MT}}$ away from the nearest microtubule, well-mixed and likely to attach to different microtubule in the vicinity.

But if detachment of motor at small distance $\ell_d \lesssim O(\rho_{\mathrm{MT}})$ from microtubule, probability to reattach to the same microtubule is enhanced by factor

$$1 - \frac{\ln(\ell_d/\rho_{\mathrm{MT}})}{\ln(\ell_{\mathrm{MT}}/\rho_{\mathrm{MT}})}.$$

Better to have a more realistic model of motor dynamics just after detachment, modeling escape from weak binding potential (Smith and McKinley 2018)

Cargo Effects

The thin microtubule approximation implicitly assumes the motor search time scale is long compared to cargo time scale

- so cargo reaches uniform stationary distribution before motor attachment

A complementary frozen cargo approximation:

- thin microtubule approximation, but cargo time scale to move $\frac{k_B T}{\kappa D_c}$ longer than motor search time from current location
  - so in general valid only for cargo near enough to microtubule

Frozen Cargo Approximation

With the attachment point $\mathbf{z}^\perp + \rho_c \hat{\mathbf{r}}^\perp = \mathbf{y}$ fixed, the mean time to attachment is:

$$T^\circ(\mathbf{y}) \sim \frac{\ell_{\mathrm{MT}}^2}{2\pi D_m}\left[\ln\left(\frac{\ell_d}{\rho_{\mathrm{MT}}}\right) + \frac{1}{K_a}\right]\exp\left(\frac{\kappa|\mathbf{y}|^2}{k_B T}\right)$$

if microtubule centered at $\mathbf{0}$ is closest.

Much longer search time if the microtubules are far from attachment point, relative to root-mean-square tether length $\sqrt{k_B T/\kappa}$.

Formally valid for attachment point near enough to microtubule

$$|\mathbf{y}| \ll \sqrt{\frac{k_B T}{\kappa}}\left\{\ln\left[\frac{\gamma_c}{\gamma_m}\frac{k_B T}{\kappa \ell_{\mathrm{MT}}^2}\right] + \ln\ln\left[\left(\frac{\ell_d}{\rho_{\mathrm{MT}}}\right) + \frac{1}{K_a}\right]\right\}$$

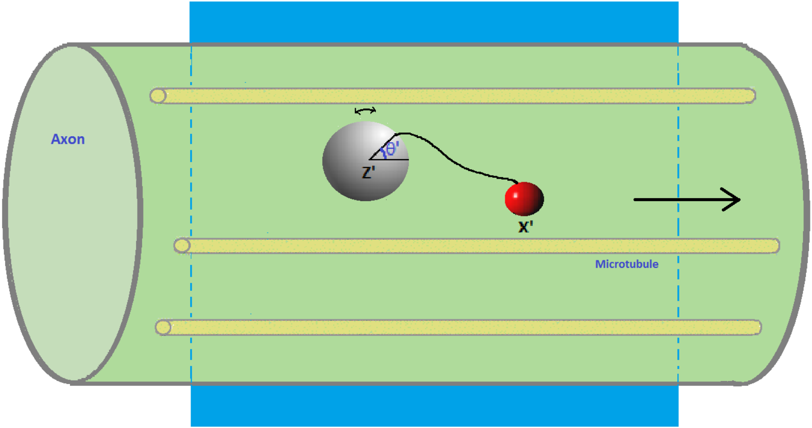
Cargo-Aware Thin Microtubule Approximation

For other starting locations:

- express mean time to attachment T° under frozen cargo approximation as function of attachment point location $\mathbf{y}(\mathbf{z}^\perp, \theta^\perp)$
- determine region $D^\circ = \{(\mathbf{z}^\perp, \theta^\perp) \in D \times [0, 2\pi) : T^\circ(\mathbf{y}(\mathbf{z}^\perp, \theta^\perp)) \leq \frac{k_B T}{\kappa D_c}\}$ where frozen cargo approximation is good
- compute mean time for $(\mathbf{Z}^\perp(t), \Theta^\perp(t))$ to reach D° under motor-averaged dynamics (roughly $\ell_{\mathrm{MT}}^2 / D_c$)
- transition zone between domains of validity thin

Simpler version of self-induced stochastic resonance work by DeVille and Vanden-Eijnden 2007.

Detached Longitudinal Dynamics



Longitudinal Transverse Dynamics

Motor:

$$\gamma_m \mathrm{d}\mathbf{X}^{\parallel}(t) = -\kappa(\mathbf{X}^{\parallel}(t) - (\mathbf{Z}^{\parallel}(t) + \rho_c \hat{\mathbf{R}}^{\parallel}(t)))\,\mathrm{d}t + \sqrt{2k_B T \gamma_m}\,\mathrm{d}\mathbf{W}^{x,\parallel}(t).$$

Cargo:

$$\gamma_c \mathrm{d}\mathbf{Z}^{\parallel}(t) = -\kappa(\mathbf{Z}^{\parallel}(t) + \rho_c \hat{\mathbf{R}}^{\parallel}(t) - \mathbf{X}^{\parallel}(t))\,\mathrm{d}t + \sqrt{2k_B T \gamma_c}\,\mathrm{d}\mathbf{W}^{z,\parallel}(t),$$

$$\gamma_r \mathrm{d}\hat{\mathbf{R}}^{\parallel}(t) = -\kappa\rho_c(\mathbf{Z}^{\parallel}(t) + \rho_c \hat{\mathbf{R}}^{\parallel}(t) - \mathbf{X}^{\parallel}(t)) \cdot \hat{\mathbf{\Theta}}^{\parallel}(t)\hat{\mathbf{\Theta}}^{\parallel}(t)\,\mathrm{d}t + \sqrt{2k_B T \gamma_r}\,\mathrm{d}\mathbf{W}^{\theta,\parallel}(t)$$

where $\hat{\mathbf{R}}^{\parallel}(t) = \left[\cos\Theta^{\parallel}(t), \sin\Theta^{\parallel}(t)\right]^T$,
$\hat{\mathbf{\Theta}}^{\parallel}(t) = \left[-\sin\Theta^{\parallel}(t), \cos\Theta^{\parallel}(t)\right]^T$.

Longitudinal Displacements During Detached Phase and Transitions

Uniform approximation for longitudinal displacement during detached phase based on fast detached motor relative to slow cargo:

- assume motor-cargo configuration $(\mathbf{Z}^{\parallel} - X_1^{\parallel}\hat{e}_1, \Theta^{\parallel})$ in stationary distribution upon conclusion of attached phase (neglecting attached diffusivity D_a)

$$p^{(a)}(\mathbf{y}, \theta) = C \exp\left\{-\frac{\kappa}{k_B T}\left[\frac{(y_1 + \rho_c \cos\theta)^2 + (y_2 + \rho_c \sin\theta)^2}{2}\right] - \frac{\gamma_c v_a}{k_B T} y_1\right\}$$

- frozen cargo for short detachment durations
- stochastically averaged motor for long detachment durations

Longitudinal Displacements During Detached Phase and Transitions

$$
\begin{aligned}
&\mathbb{E}[X_1^{\|}(t) - X_1^{\|}(0)] \\
&\qquad = \mathbb{E}_{p^{(a)}}[Y_1 + \rho_c \mathrm{e}^{-D_r t} \cos(\Theta^{\|})](1 - \mathrm{e}^{-\frac{\kappa}{\gamma m} t}), \\
&\mathrm{Var}[X_1^{\|}(t) - X_1^{\|}(0)] \\
&\qquad = (1 - \mathrm{e}^{-\frac{\kappa}{\gamma m} t})^2 \, \mathrm{Var}_{p^{(a)}}[Y_1 + \rho_c \mathrm{e}^{-D_r t} \cos \Theta^{\|}] + 2 D_c t \\
&\qquad + \frac{k_B T}{\kappa} (1 - \mathrm{e}^{-2 \frac{\kappa}{\gamma m} t}) \\
&\qquad + \left(\frac{1 - \mathrm{e}^{-4 D_r t}}{2} + (\mathrm{e}^{-4 D_r t} - \mathrm{e}^{-2 D_r t}) \mathbb{E}_{p^{(a)}}[\cos^2 \Theta^{\|}] \right)
\end{aligned}
$$

Renewal-Reward Framework

View motor attachment/detachment as renewal process starting at detachment time, with motor displacement along microtubule (whether attached/detached) as 'reward"

- reward while detached $\Delta_d X_1(T_a)$
- reward while attached given by $v_a T_d + \sqrt{2D_a} W(T_d)$ where D_a is effective diffusivity of attached motor, and T_d is exponentially distributed attachment time

Can compute effective drift and diffusivity of motor (and therefore cargo), both longitudinally and transversely.

- adapt calculation of (Hughes, Hancock, Fricks 2011) from other molecular motor models
- see also (Miles, Lawley, Keener 2017)

Summary of Motor Attachment Model

Analytically computable framework for representing motor attachment to microtubule

- spatial search; similar to search of motor head for binding site in (Hughes, Hancock, Fricks 2011)
- thin microtubule asymptotics to approximate solution to complicated PDE for first passage time
- couple to renewal-reward framework to track impact on longitudinal transport
- Quasi-two-dimensional approximations can be relaxed straightforwardly in the transverse direction.
- Main deficit is absence of steric effects on cargo

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See also:

- J. Newby & P. Bressloff, "Stochastic Models of Intracellular Transport" *Rev. Mod. Phys.*, (2013)
- Lipowsky, Beeg, et al, "Active Bio-Systems: From Single Motor Molecules to Cooperative Cargo Transport," *Biophysical Reviews and Letters* (2013)
- D. Chowdhury, "Stochastic mechano-chemical kinetics of molecular motors: A multidisciplinary enterprise from a physicist's perspective" in *Physics Reports*, (2013)