Study of Emergent Transport Properties of Molecular Motor Ensemble

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Intracellular Transport

- Kinesin takes single step by hydrolysis of single ATP molecule
  - \[ M + ATP \overset{k_{ON}}{\rightleftharpoons} M\text{ATP} \overset{k_{CAT}}{\rightarrow} M + ADP + p_i + \Delta E \]
  - \[ k_{OFF} \]
- **Coordinated Transport**: Motors are known to work in teams
- High resolution instrumentation needed for probing

*Video taken from the TED talk of Drew Barry: Animations of unseeable biology.*
High Resolution Probing

- Multiple motors carry cargo
- Statistics on the motion can be obtained under controlled forces on
  - Step-size distribution
  - Run-length
  - Attachment probabilities
  - Detachment probabilities
  - Number of motors


Single Kinesin Model

- **Stepping Probability**
  \[ P_S(F) = \frac{K_{cat}[ATP]}{[ATP] + \frac{k_{cat} + k_{off}(F)}{k_{on}}} \eta(F), \]
  where \( \eta(F) = \begin{cases} 1 & , \quad F = 0 \\ 1 - \left( \frac{F}{F_S} \right)^2 & , \quad 0 < F < F_S \\ 0 & , \quad \text{otherwise} \end{cases} \)

- **Detachment Probability**
  \[ P_D(F) = \begin{cases} \frac{[ATP] + B(1+A)e^{-F\delta_i K_b T}}{[ATP] A e^{-F\delta_i K_b T}} P_S(F), \quad F < F_S \\ P_{back}, \quad F \geq F_S \end{cases} \]

- **Attachment probability**
  \( P_A \approx 5/\text{sec} \)

- **Probability distribution of cargo position** \( Z_{eq} \)
  \[ \Theta(z) = (e^{z^2/\sigma_t^2})/(\int_0^{z} e^{z^2/\sigma_t^2} dz) \]

- **Stalling Force**
  \( F_S \)

- **Condition**
  If \( F \approx F_S \) then \( P_S(F) \approx 0 \)

Model
How Several Motors of Multiple Types Coordinate to Transport Common Cargo
Master Equation For Absolute Configuration

- Infinite Dimensional Model: Master Equation
  \[ \frac{\delta}{\delta t} P_{\Omega}(\Omega, t) = -P_{\Omega}(\Omega, t) \sum_{\Omega' \in A} \nu_{\Omega}(\Omega', \Omega) + \sum_{\Omega' \in A} \nu_{\Omega}(\Omega, \Omega') P_{\Omega}(\Omega', t) \]

- Transition rates can be determined from single motor model for step, detach, attach
  \[ P_{\Omega}(\Omega', t + \Delta t | \Omega, t) = \nu_{\Omega}(\Omega', \Omega) \Delta t \]

- Relative separation with respect to rearguard motor

- Projection Operator \( \Upsilon \) maps \( \Omega \) to \( \Upsilon(\Omega) \)
Relative Configurations

- **Separation between Vanguard and Rearguard motor is bounded**
  - Given an ensemble of $M$ molecular motors attached to a common cargo subjected to load force $F_{load}$, the distance between the rearguard and vanguard motors is bound by,

    \[ n = \max\left\{ \left( M + 1 \right) \max\left( F_s, \bar{F}_s \right) - F_{load} \frac{K_e}{d}, \frac{F_{load} K_e}{d} \right\} + 2L_0 \]

- **Number of Relative Configurations is finite**

- **Transition Rates between Relative Configurations can be determined from transition rates between Absolute Configurations**
  - The transition rates between relative configurations $\vartheta$ and $\vartheta'$ is given by,

    \[ v_{\vartheta}(\vartheta', \vartheta) = \sum_{0 \leq \beta \leq \frac{m}{d}} v_{\vartheta} \left( \tau^\beta \Omega, \Omega \right) \]

where $\Omega$ and $\Omega'$ are any absolute configurations that satisfy $Y(\Omega) = \vartheta$ and $Y(\Omega') = \vartheta'$ respectively, $(\tau^\beta \Omega')$ is an absolute configuration obtained by linearly shifting $\Omega'$ by $\beta$ locations to right, $d$ is dimension of single microtubule dimer
Master Equation for Relative Configuration

- It can be shown that the probability \( P_\vartheta(\vartheta, t) \) of being in relative configuration \( \vartheta \) at time \( t \) satisfies the Master Equation:

\[
\frac{\delta}{\delta t} P_\vartheta(\vartheta, t) = -P_\vartheta(\vartheta, t) \sum_{\vartheta' \in H} \nu_\vartheta(\vartheta', \vartheta) + \sum_{\vartheta' \in H} \nu_\vartheta(\vartheta, \vartheta') P_\vartheta(\vartheta', t)
\]

where \( H \) is the finite set of all relative configurations

- Given: \( \vartheta_1, \ldots, \vartheta_N \) are the set of finite relative configurations, \( P(t) = [P_1(t), \ldots, P_N(t)]^T \) is the vector denoting probabilities of being in these configurations,

Then, solution to the Master Equation provides:

\[
\frac{d}{dt} P(t) = \Gamma P(t), \quad P(t) = e^{\Gamma(t-t_0)} P(t_0)
\]

where \( \Gamma \in \mathcal{R}^{N \times N} \) is completely defined by transition rates \( \nu_\vartheta(\vartheta', \vartheta) \)
Obtaining Biologically Relevant Quantities from Semi-Analytical Solution

- **Average Number of Engaged Motors**
  - Wild type: \( < m_h(t) > = \sum_{i=0}^{N} m_h(\theta_i)P_i(t) \)
  - Mutant: \( < m_d(t) > = \sum_{i=0}^{N} m_d(\theta_i)P_i(t) \)

- **Average Velocity of Cargo**
  \[
  v(t) = \sum_{\theta \in H} \sum_{\theta' \in H} d_{avg}(\theta', \theta) v_{\theta}(\theta', \theta) P_{\theta}(\theta, t)
  \]

  where \( d_{avg}(\theta', \theta) \) is expected change in cargo position when initial and final configurations are restricted to \( \theta \) at \( t \) and \( \theta \) at \( t + \Delta t \)

- **Average Runlength**
  
  \[
  \text{Average Runlength} = \int_{0}^{+\infty} v(t) \, dt
  \]
Effect of Phosphorylation of Kinesin Motor-Domain

- Phosphorylation of a mammal Kinesin motor domain by kinase JNK3 enzyme at a conserved serine residue.
  - Implicated in Huntington’s disease
  - Mechanisms affected are not well understood

- Recent Study*
  - Phosphorylation of kinesin motor domain effects only the stalling force of the motor

<table>
<thead>
<tr>
<th>Stalling Forces</th>
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<tbody>
<tr>
<td>Wild Type: $F_S = 6 \text{ pN}$</td>
</tr>
<tr>
<td>Phosphorylated Mutant: $\bar{F}_S = 5.5 \text{ pN}$</td>
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</tbody>
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*Selvin et.al. Motor Domain Phosphorylation modulates Kinesin-I Transport, Journal of Biological Chemistry
Study of Phosphorylation Mutation In Ensemble: Observations

**Average Run-length** dictated by stalling force

$F_{\text{load}}$ approaches $F_s = 6pN$ and $\bar{F}_s = 5.5pN$

- **2 motor ensemble**
  - Load force on the cargo in pN
  - Average Runs
  - $F_{\text{load}}$ approaches $F_s = 6pN$ and $\bar{F}_s = 5.5pN$

- **3 motor ensemble**
  - Load force on the cargo in pN
  - Average Runs
  - $F_{\text{load}}$ approaches $F_s = 6pN$ and $\bar{F}_s = 5.5pN$

**Average Velocity** can increase with increasing load

- **12 pN**
  - Average Velocity
  - Increase with increasing load

- **High Load favors clustering of motors**
  - Load force on the cargo in pN
  - Average Velocity

- **Low Load favors spreading of motors**
  - Load force on the cargo in pN
  - Average Velocity
Effect of ATP on Coordinated Transport

- Average runlength increases with reducing ATP concentration for ensembles with >1 motor.

- For load forces away from multiples of $F_s$ and $F_s'$, effect of ATP concentration is unaltered by presence of mutant motor in the ensemble.

- Experimentally observed for $WW$ ensemble.*

*Jing Xu, *Tuning multiple motor travel via single motor velocity*, *Traffic*
1. As load force on cargo approaches stalling force or its multiple, motor do not step forward and moors the cargo. Thus $P_S$ reduces, $P_D$ reduces and detachment event is unlikely.

2. Other disengaged motor gets more time on average to reattach to microtubule.

3. Increase in average velocity and runlength at these load forces.

4. More the mooring motors, more runlength
Contributions

1. Novel, semi-analytic methodology developed to allow exact computation of biologically relevant quantities

2. Unlike Monte-Carlo based approaches, efficiency independent of number of iterations and computationally less extensive

3. Investigation rare events possible

4. Possible to study effects due to alterations of other single motor parameters
Thank You!