Cooperative effects in motor-driven cargo transport

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Vortrag zur Bachelorarbeit, 2016

Overview

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1. Introduction
   - Motivation
   - The mean-field model by Li et al.
   - Discussion
2. The explicit model
   - Adjustments and comparison to the mean-field model
   - Analysis of the transport process
3. Summary

Intracellular Cargo Transport

- Cells need to be able to rearrange or move cargos in its interior (e.g. nutrients, organelles)
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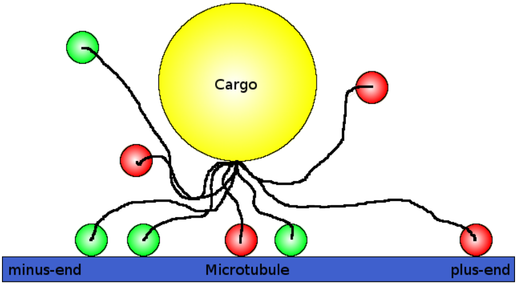

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- Different attempts of modeling these kinds of transport
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- One slow and one fast team of kinesins pulling the cargo
- N_f and N_s motors available, n_f and n_s numbers of bound motors
- Force independent binding rates π_{0s} and π_{0f}
- Force dependent unbinding rates

$$\epsilon(F) = \epsilon_0 exp\left(\frac{F}{F_d}\right)$$

- Force dependent velocities

$$\begin{aligned} V_s(F) &= v_s(1 - F/F_{ss}) && \text{for} \quad F \leq 0 < F_{ss} \\ V_f(F) &= v_f(1 - F/F_{sf}) && \text{for} \quad 0 \leq F < F_{sf}, \end{aligned}$$

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$$n_f F_+ = -n_s F_- \equiv F(n_f, n_s),$$

- Assumption of equal velocities of all motors

$$V_s(F_-) = V_f(F_+) = v(n_f, n_s),$$

- These lead to the transport velocity

$$v(n_f, n_s) = \frac{v_s v_f}{\left(1 - \frac{n_f}{n}\right) v_f + \frac{n_f}{n} v_s},$$

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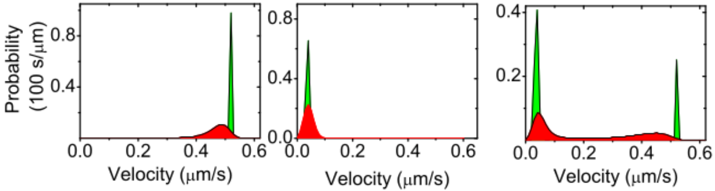
Results

- By using different sets of motor parameters Li *et al.* find three distinct motility regimes



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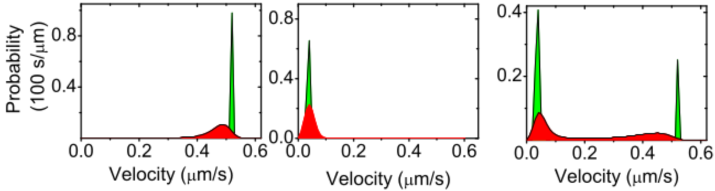

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Idea

- Introducing a new model which takes the explicit motor positions into account
- Comparing the results of this explicit model to the results of the mean-field model

Overview

Adjustments

- Stalks of the motors modeled as cable-like Hookean springs: slack up to a length of L_0 and linear force relation beyond L_0. The force of the i-th motor on the cargo reads

$$F_i = \begin{cases} \alpha\left(x_i(t) - x_C(t) + L_0\right), & x_i(t) - x_C(t) < -L_0, \\ 0, & |x_i(t) - x_C(t)| < L_0, \\ \alpha\left(x_i(t) - x_C(t) - L_0\right), & x_i(t) - x_C(t) > L_0. \end{cases}$$

- Stepping rates for each motor

$$s_s(F_i) = \begin{cases} \frac{v_s}{d}, & F_i < 0, \\ \frac{v_s}{d}\left[1 - \frac{F_i}{F_{ss}}\right], & 0 \leq F_i \leq F_{ss}, \\ \frac{v_s^B}{d}, & F_i > F_{ss} \end{cases}$$

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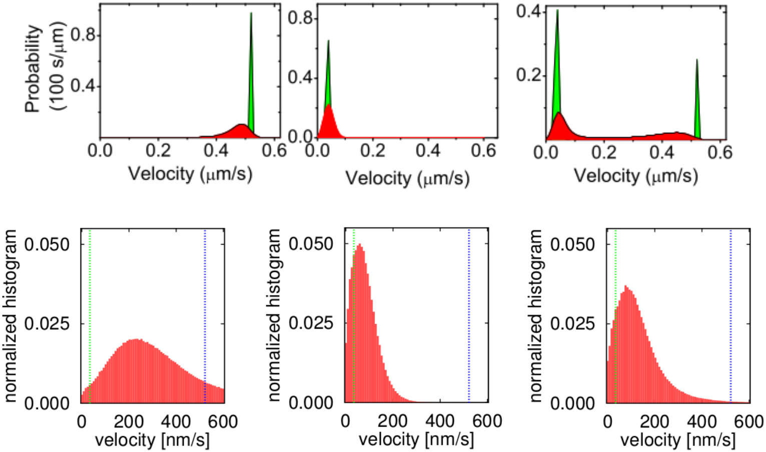
Comparison to results of Li *et al.*



- Different results for same sets of parameters!

Bimodal velocity distributions?

- Are bimodal velocity distributions possible in the explicit model?
- Yes they are, but with different sets of parameters!

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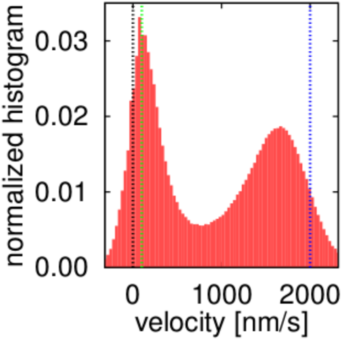

Overview

A closer look at the motor parameters

- In order to understand the underlying effects, which lead to the shown bimodal velocity distribution, changes to the following parameters have been examined:
  - Slow and fast velocities v_s and v_f
  - Attachment rate κ_a
  - Stall forces F_{ss} and F_{sf}
  - Force free detachment rate κ_a^0
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Velocities, attachment rate and stall forces

- Bimodal velocities: $v_s = 100\,\frac{\text{nm}}{\text{s}}$, $v_f = 2000\,\frac{\text{nm}}{\text{s}}$
  Increasing the velocity of slow motors leads to a vanishing distinctness of the bimodal velocity distribution
- Bimodal attachment rate: $\kappa_a = 5\,\text{s}^{-1}$
  For very low attachment rates ($< 0.1\,\text{s}^{-1}$) transport is stalling most of the time and is carried out by only one attached motor at a time.
  Very high attachment rates ($> 100\,\text{s}^{-1}$) lead to unimodal velocity distributions, as all motors are involved into transport.
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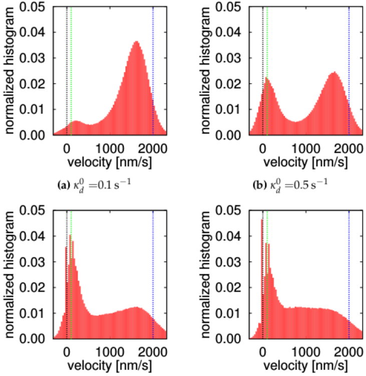
Force free detachment rate

- Bimodal force free detachment rate: $\kappa_d^0 = 1\,\mathrm{s}^{-1}$
- Reminder: $\kappa_d(F_i) = \kappa_d^0 exp\left(\frac{|F_i|}{F_d}\right)$

- Bimodal for roughly $0.1\,\mathrm{s}^{-1} \leq \kappa_d^0 \leq 5\,\mathrm{s}^{-1}$



(a) $\kappa_d^0 = 0.1\,\mathrm{s}^{-1}$ (b) $\kappa_d^0 = 0.5\,\mathrm{s}^{-1}$ (c) $\kappa_d^0 = 5\,\mathrm{s}^{-1}$ (d) $\kappa_d^0 = 10\,\mathrm{s}^{-1}$

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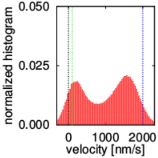
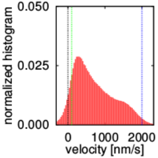
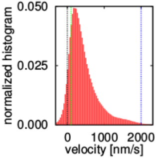


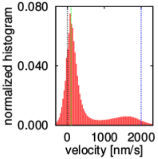
(a) $F_{ds} = F_{df} = 1.5\,\text{pN}$



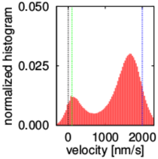
(b) $F_{ds} = F_{df} = 3\,\text{pN}$



(c) $F_{ds} = F_{df} = 5\,\text{pN}$



(d) $F_{ds} = 1\,\text{pN}$, $F_{df} = 0.8\,\text{pN}$



(e) $F_{ds} = 1\,\text{pN}$, $F_{df} = 1.2\,\text{pN}$

Summary of the parameter analysis

In order to obtain bimodal velocity distribution one needs:

- $F_{sf} > F_d$
- Only few motors must participate in cargo transport simultaneously
- Detachment forces of fast and slow motors need to be “close”
- A considerable gap between slow and fast motor’s velocities

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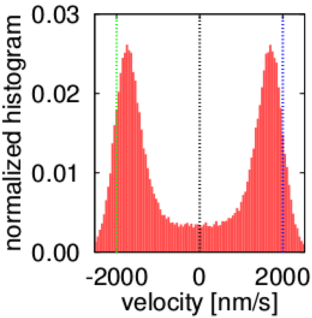
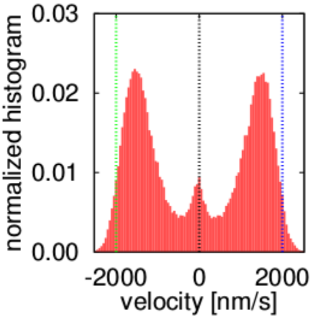
Extension on bidirectional case

- Bi- and even trimodal velocity distributions obtainable for symmetric motors.





Summary

- Bimodal motility states have been obtained by Li *et al.* using the mean field model.
- These bimodal states cannot be reproduced by an explicit model for the same set of parameters but for different sets of parameters.
- The explicit model can be extended on the bidirectional case and, there, leads to bimodal and even trimodal motility states.

- Further improvements:
  - A different modeling approach for the detachment rate could be examined, as the exponential modeling heavily effects the motility state.

Thank you for your attention!

References I

X. Li, R. Lipowsky, and J. Kierfeld.
Bifurcation of Velocity Distributions in Cooperative Transport of Filaments by Fast and Slow Motors.
Biophysical Journal, vol. 104, pp. 666–676, 2013.

Li *et al.* parameters

Parameters used by Li *et al.* for the three different motility regimes

	Larson *et al.* [2]	Pan *et al.* [4]	Bieling *et al.* [3]
	Fast motors		
	Wild kinesin-I	OSM-3	Xklp1
	Slow motors		
Parameter	Mutant kinesin-I	Kinesin-II	Xkid
Binding rate, fast π_{0f}	$5\,s^{-1}$	$5\,s^{-1}$	$5\,s^{-1}$
Binding rate, slow π_{0s}	$5\,s^{-1}$	$5\,s^{-1}$	$5\,s^{-1}$
Unbinding rate, fast ϵ_{0f}	$1\,s^{-1}$	$1\,s^{-1}$	$1\,s^{-1}$
Unbinding rate, slow ϵ_{0s}	$1\,s^{-1}$	$1\,s^{-1}$	$1\,s^{-1}$
Detachment force, fast F_{df}	3 pN	6 pN*	6 pN*
Detachment force ratio $\eta \equiv \frac{F_{ds}}{F_{df}}$	0.45	3.3*	1.9*
Stall force, fast F_{sf}	6 pN	6 pN	6 pN
Stall force, slow F_{ss}	6 pN	6 pN	6 pN
Zero load velocity, fast v_f	$0.522\,\mu m\,s^{-1}$	$1.09\,\mu m\,s^{-1}$	$1.0\,\mu m\,s^{-1}$
Zero load velocity, slow v_s	$0.034\,\mu m\,s^{-1}$	$0.34\,\mu m\,s^{-1}$	$0.1\,\mu m\,s^{-1}$
$\hat{\pi} \equiv \frac{\pi_{0f}}{\epsilon_{0f}} = \frac{\pi_{0s}}{\epsilon_{0s}}$	5	5	5
$\hat{F} \equiv \frac{F_s}{F_{df}}$	2	1	1
$\hat{v} \equiv \frac{v_s}{v_f}$	0.065	0.31	0.1

Parameters used for the explicit model simulation for the bistable motility regime

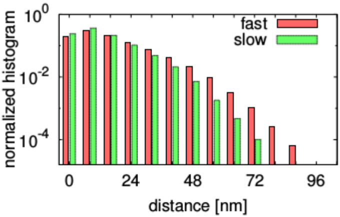
System parameters	
Simulation time t_{end}	100 000 s
Velocity measurement interval Δt	0.1 s

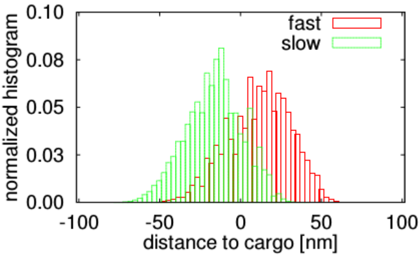
Motor parameters		
Parameter	Slow	Fast
Number of available motors N	8	2
Stalk length L_0 (*)	10 nm	10 nm
Stepsize d (*)	8 nm	8 nm
Stiffness constant α (*)	$10^{-4}\,\frac{kg}{s^2}$	$10^{-4}\,\frac{kg}{s^2}$
Detachment force F_d	1.35 pN	3 pN
Stall force F_s	6 pN	6 pN
Force free detachment rate κ_d^0	$1\,s^{-1}$	$1\,s^{-1}$
Attachment rate κ_a	$5\,s^{-1}$	$5\,s^{-1}$
Velocity forward v^F	$34\,\frac{nm}{s}$	$522\,\frac{nm}{s}$
Velocity backward v^B (*)	$6\,\frac{nm}{s}$	$6\,\frac{nm}{s}$

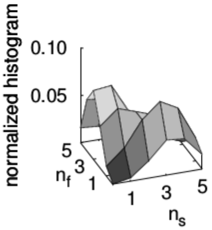
Changes to parameters to obtain bimodal velocity distribution

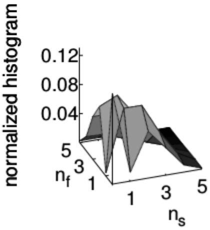
Motor parameters		
Parameter	Slow	Fast
Number of available motors N	5	5
Detachment force F_d	1 pN	1 pN
Stall force F_s	5 pN	5 pN
Velocity forward v^F	$100\,\frac{\text{nm}}{\text{s}}$	$2000\,\frac{\text{nm}}{\text{s}}$

Different transport characteristics to the shown bimodal case

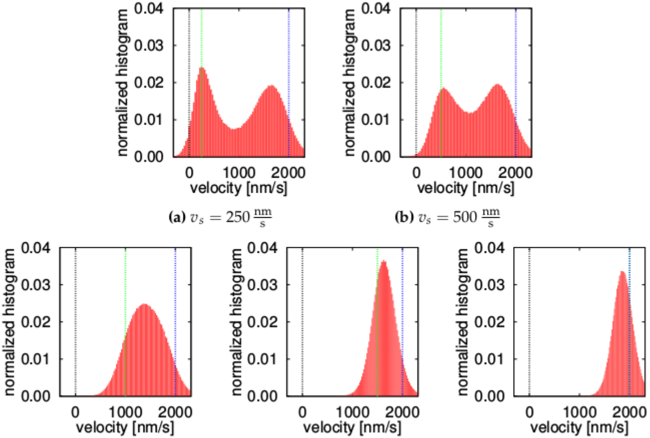








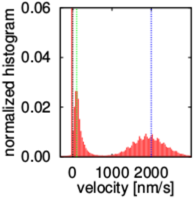
Simulations for differing slow motor velocities



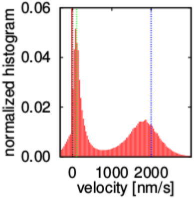
(a) $v_s = 250\,\frac{\mathrm{nm}}{\mathrm{s}}$ (b) $v_s = 500\,\frac{\mathrm{nm}}{\mathrm{s}}$

(c) $v_s = 1000\,\frac{\mathrm{nm}}{\mathrm{s}}$ (d) $v_s = 1500\,\frac{\mathrm{nm}}{\mathrm{s}}$ (e) $v_s = 2000\,\frac{\mathrm{nm}}{\mathrm{s}}$

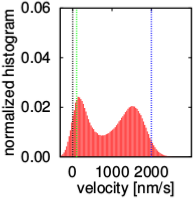
Simulations for differing attachment rates



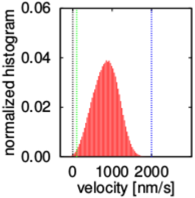
(a) $\kappa_a = 0.1\,\mathrm{s}^{-1}$



(b) $\kappa_a = 1.0\,\mathrm{s}^{-1}$

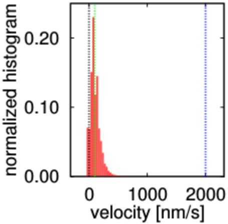


(c) $\kappa_a = 10.0\,\mathrm{s}^{-1}$

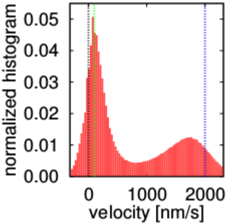


(d) $\kappa_a = 100.0\,\mathrm{s}^{-1}$

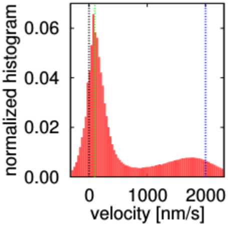
Simulations for differing stall forces of fast motors



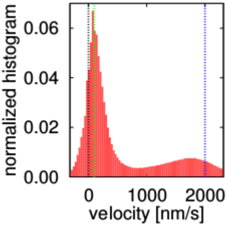
(a) F_{sf} =0.1 pN and F_{ss} =5 pN



(b) F_{sf} =10 pN and F_{ss} =5 pN



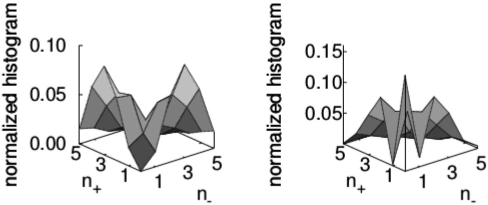
(c) F_{sf} =100 pN and F_{ss} =5 pN



(d) F_{sf} =1000 pN and F_{ss} =5 pN

Motor distributions in the bidirectional case

Bidirectional bimodal velocitiy distribution: motors attached, motors with $|F| > 0$



Bidirectional trimodal velocitiy distribution: motors attached, motors with $|F| > 0$