RICE UNIVERSITY

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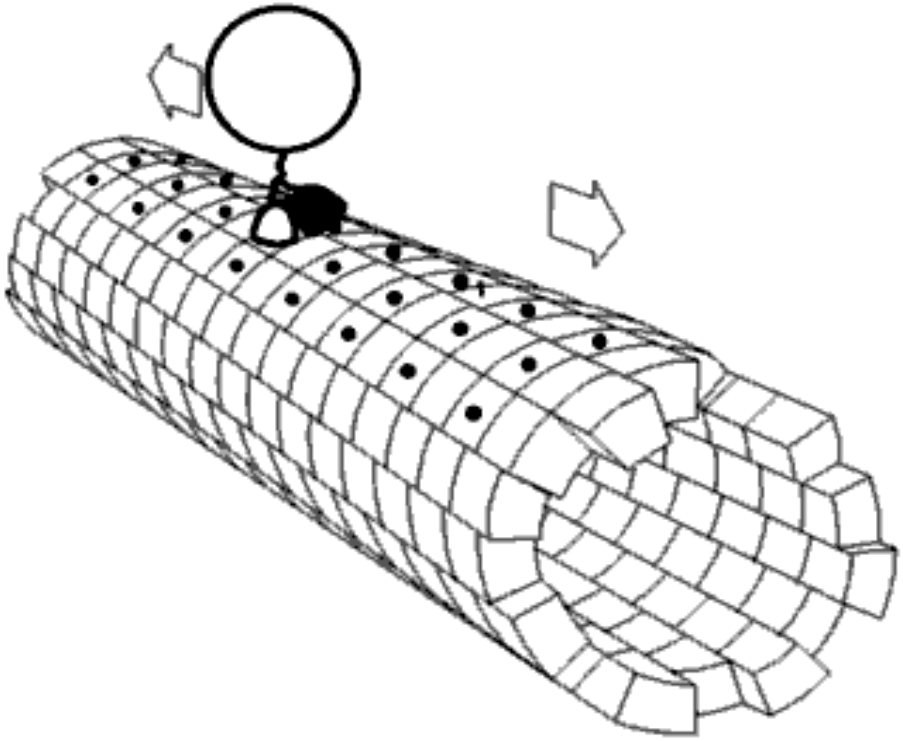
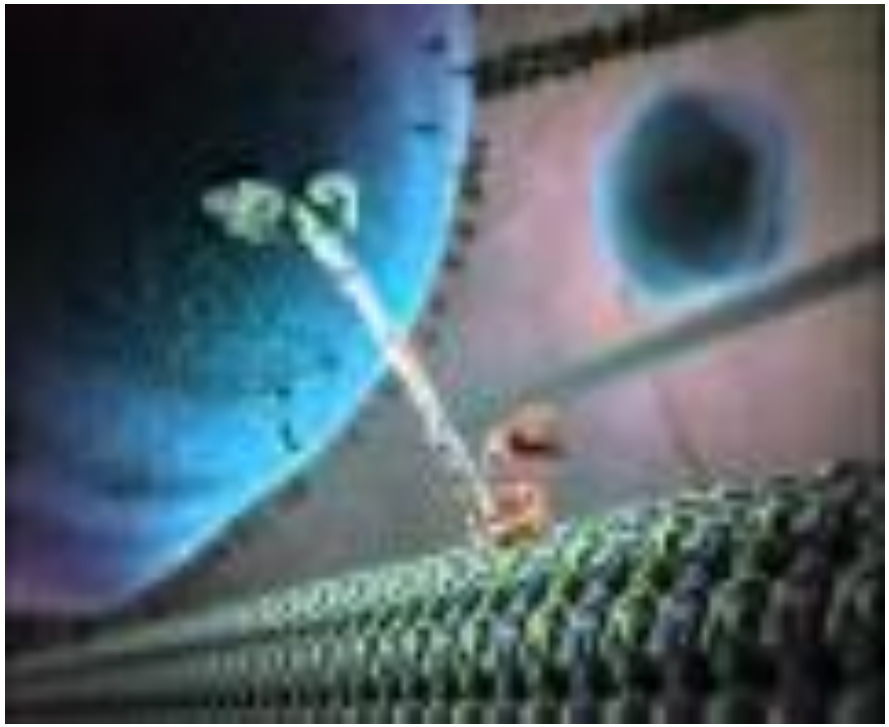
COLLECTIVE DYNAMICS OF INTERACTING MOLECULAR MOTORS

Motor Proteins

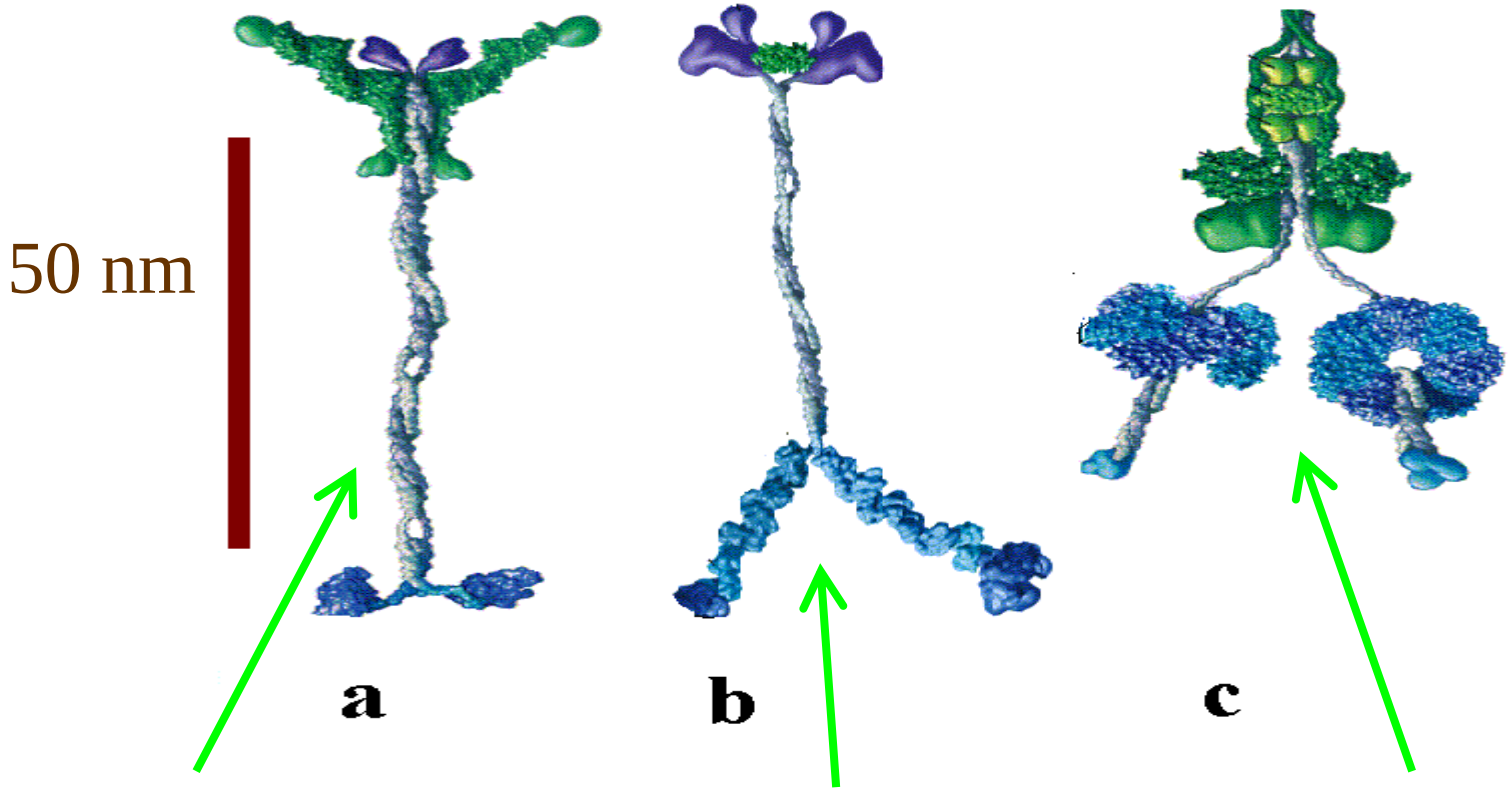
Enzymes that convert the chemical energy into mechanical work

Functions: cell motility, cellular transport, cell division and growth, muscles, …





Motor Proteins: Structure

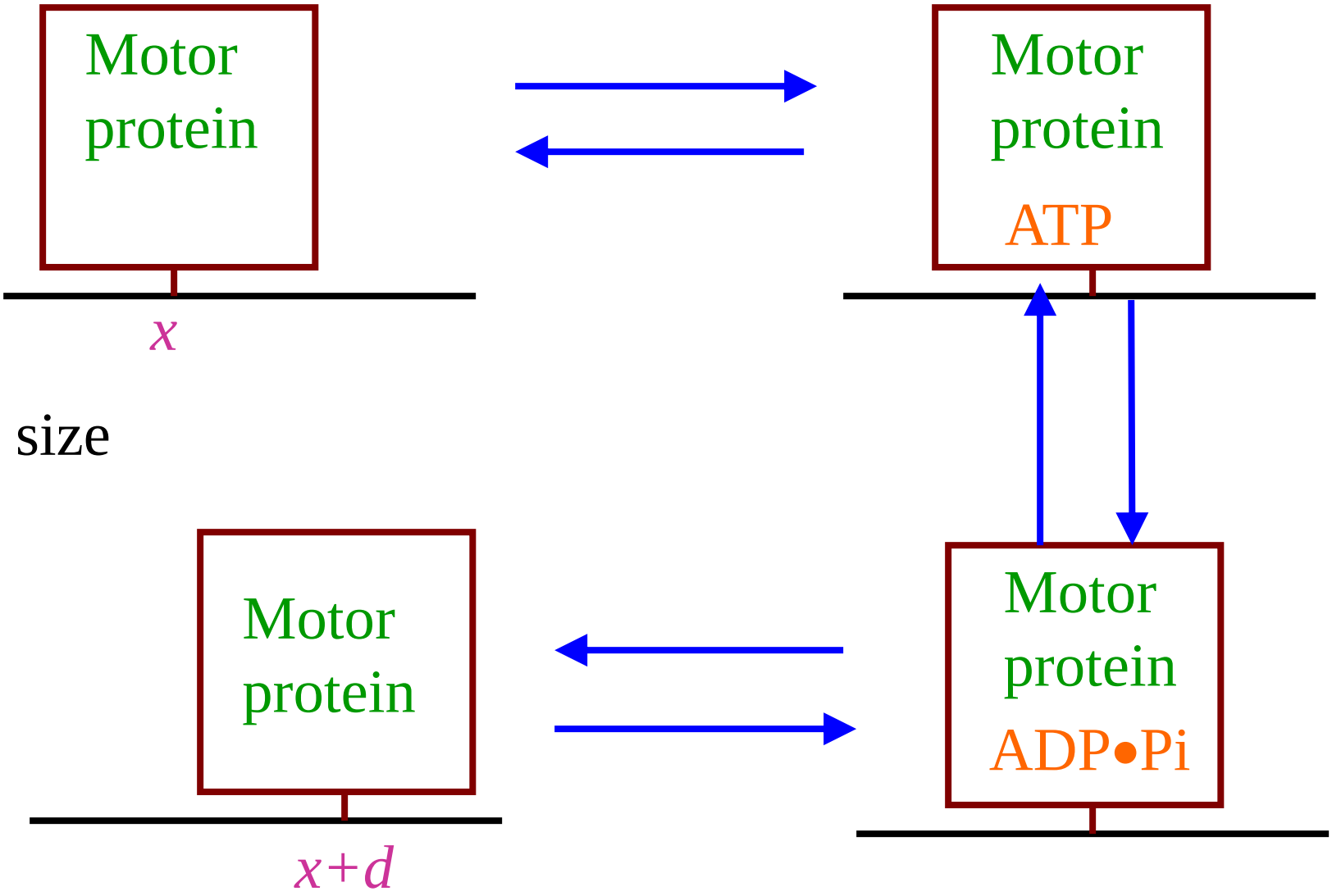


conventional kinesin

myosin V

cytoplasmic dynein

Motor Proteins: Chemistry



Motor Proteins. Properties

Non-equilibrium systems

Velocities: 0.01-100 μm/s (for linear processive)

Step Sizes: 0.3-40 nm; Forces: 1-60 pN

Fuel: hydrolysis of ATP, polymerization

Efficiency: 50-100% (!!!); Power – like jet engine

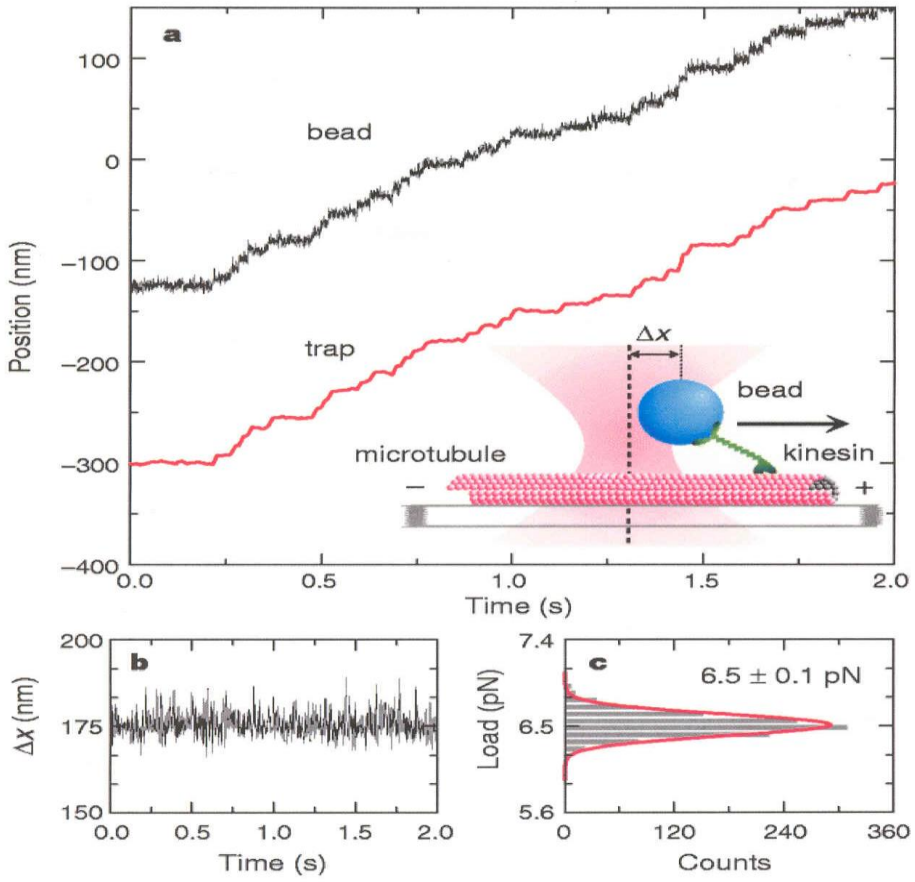
Directionality; Diversity

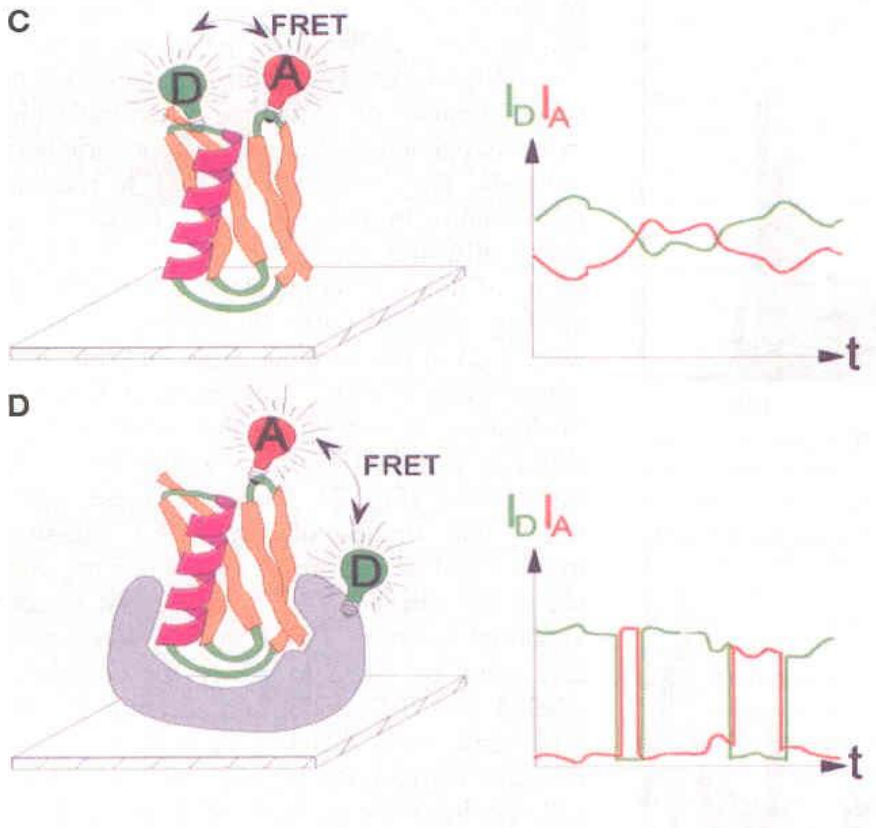
Honda Accord:

Efficiency of engine ~10%

Single Motor Proteins. Experiments

Single-Molecule Experiments:





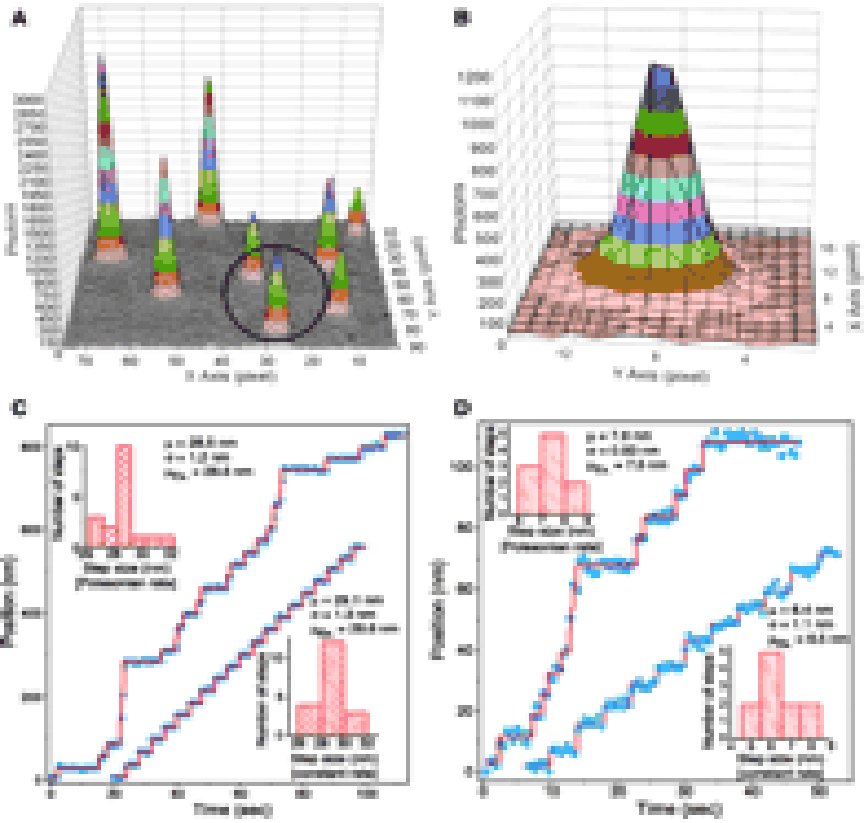
Optical-trap spectrometry

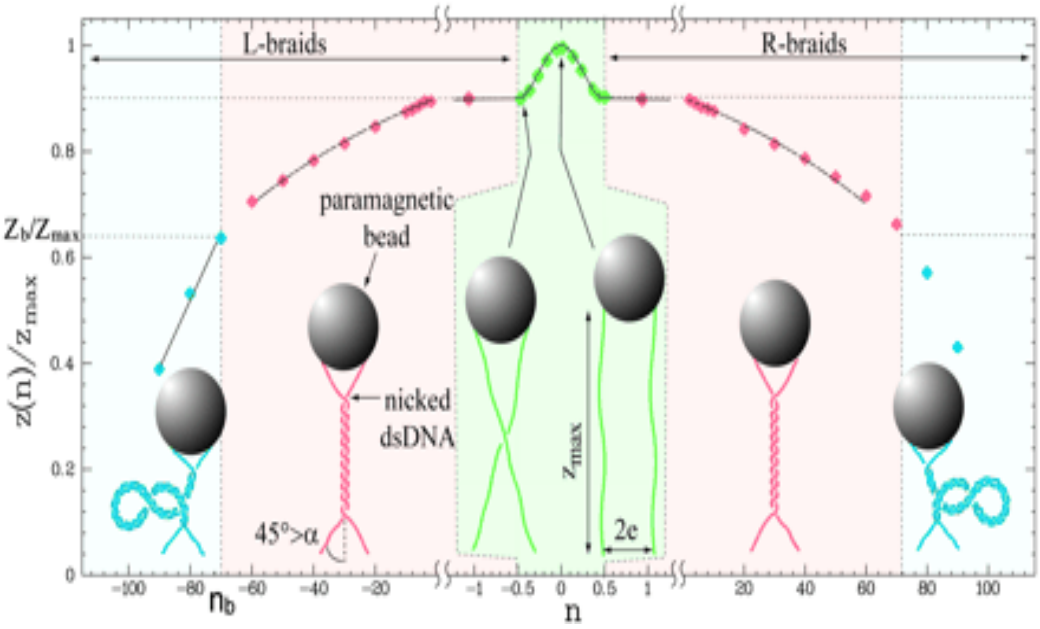
FRET – fluorescence resonance energy transfer

S. Block, S. Xie, J. Spudich, S. Weiss, C. Bustamante, S. Gross…

Motor Proteins. Experiments

Single-Molecule Experiments:





FIONA-fluorescent imaging with one-nanometer accuracy

Magnetic tweezers spectroscopy

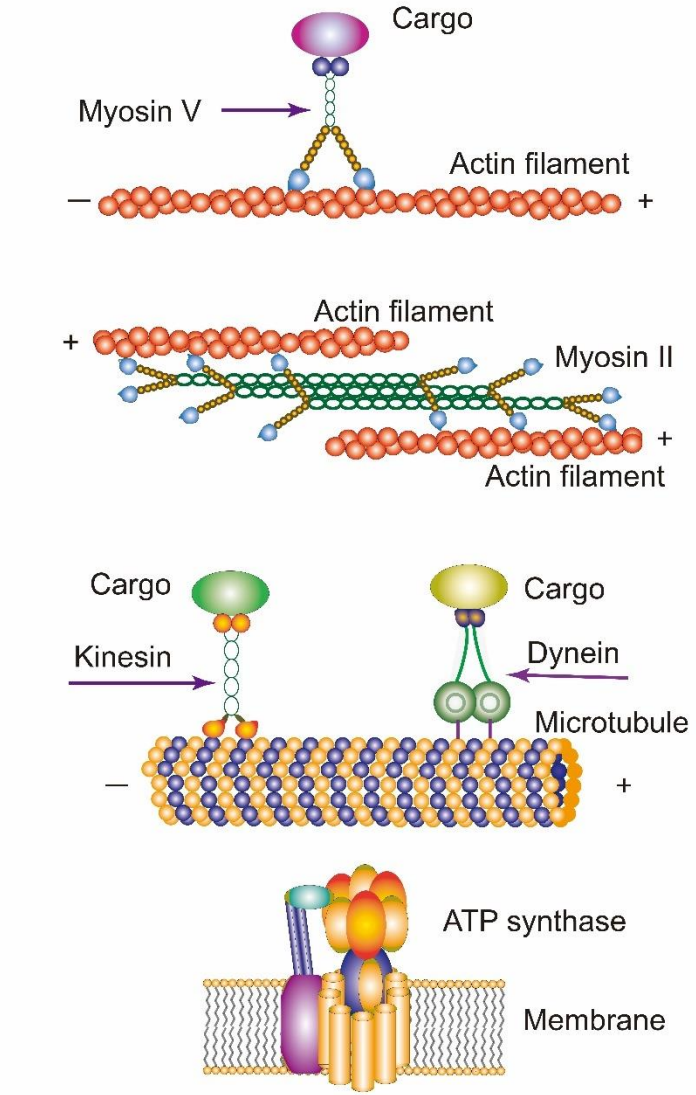
P. Selvin, W.E. Morner, N. Sherer, D. Bensimon,…

Theories for Single Motor Proteins

The main goal of theoretical models is to provide a quantitative link between biochemical and mechanical/dynamic properties of molecular motors.

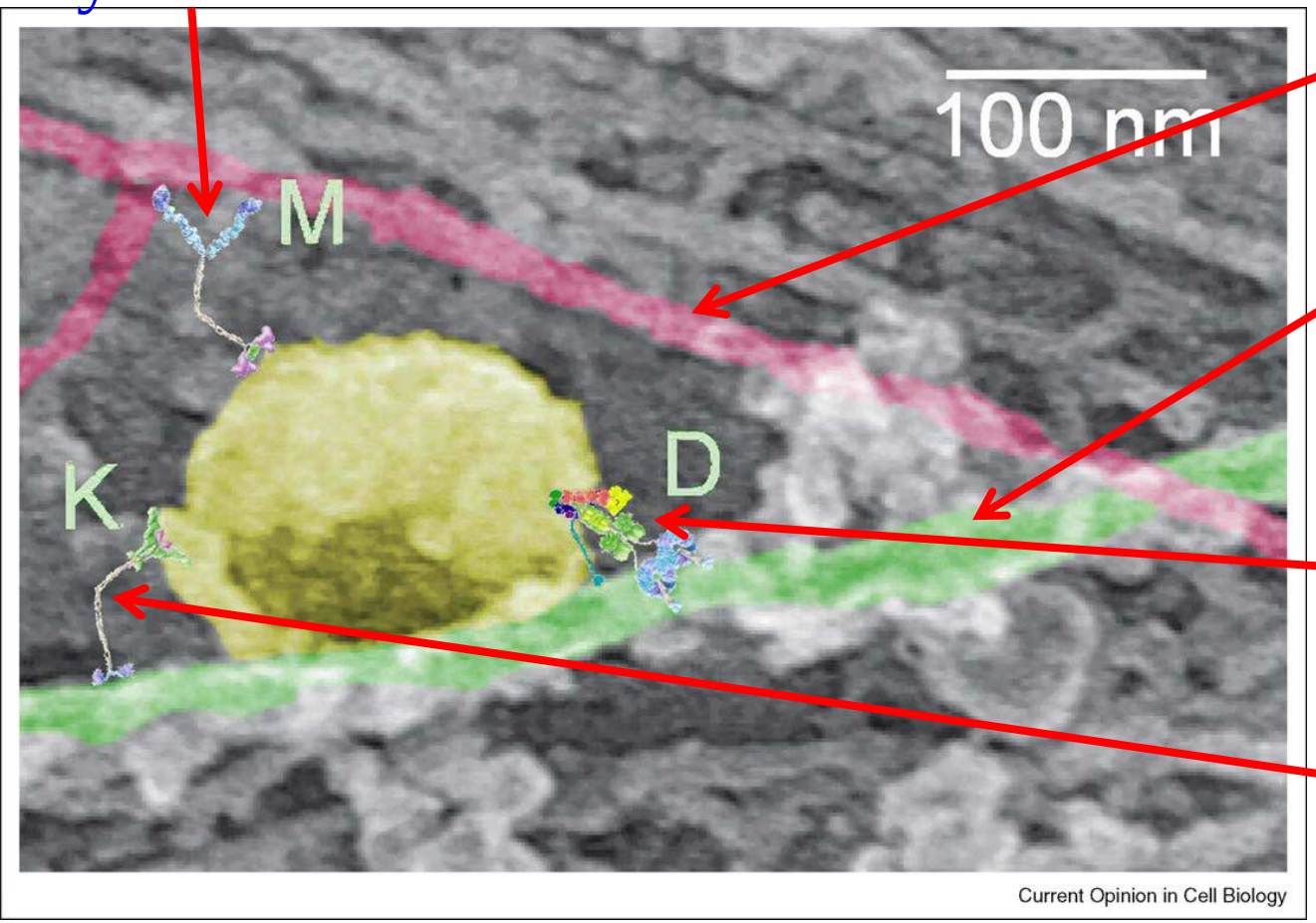
2 main theoretical approaches:

1) Continuum Ratchets;
2) Discrete-State Stochastic Models



Cellular Cargos Transport by Teams of Similar and/or Dissimilar Motor Proteins

myosin-V



actin

microtubule

dynein

kinesin

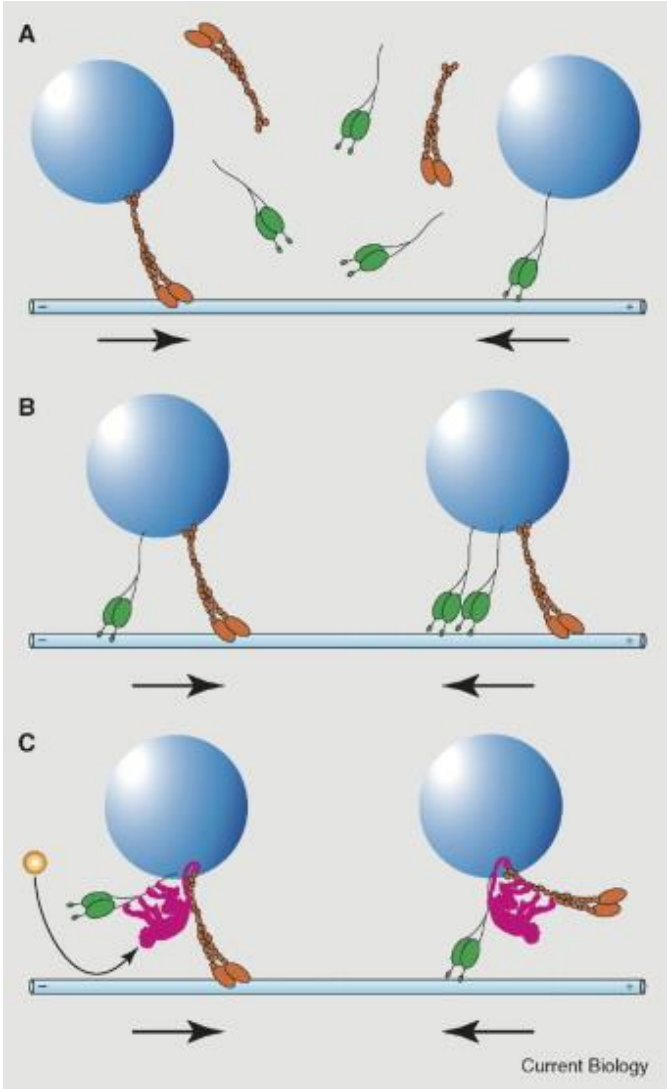
Motor proteins typically work in groups

E. Holzbaur and Y. Goldman, *Curr. Opin. Cell Biol*. 2010, **22**, 4-13

Collective Motion of Motor Proteins

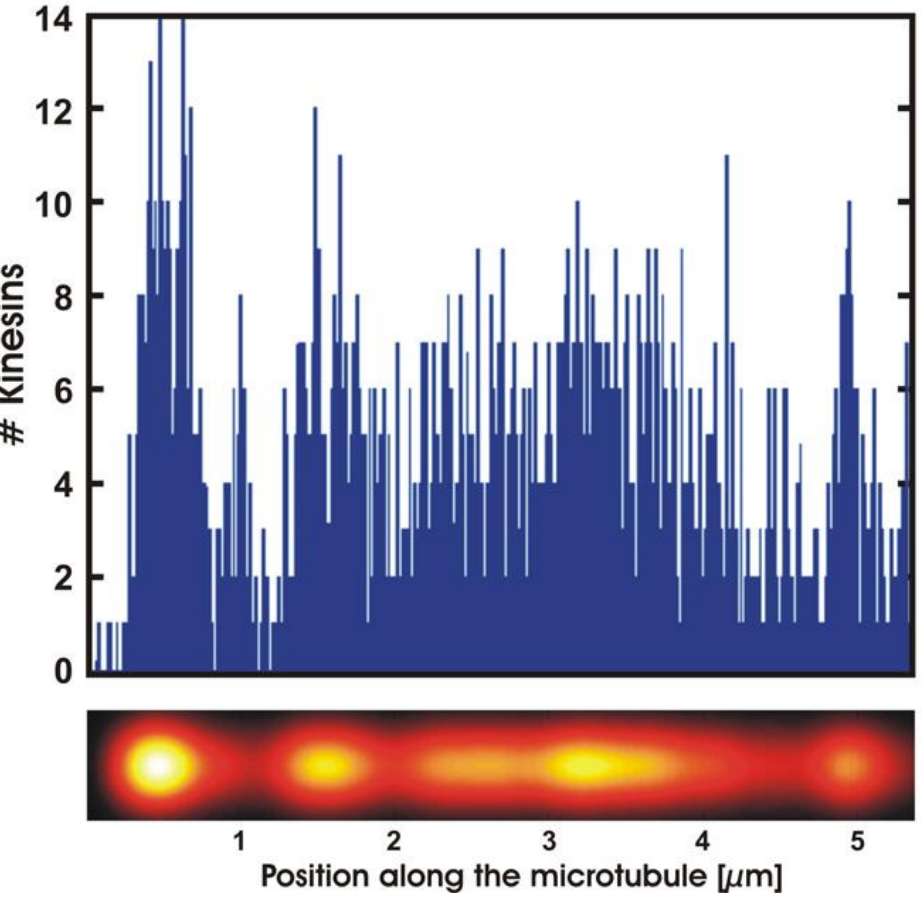
Not much is known about collective motion of motor proteins:

1) Do motor proteins compete or collaborate?
2) What are the mechanisms of cooperative behavior?
3) How interactions between molecular motors affect their dynamics?
4) ….



Intermolecular Interactions

W.H. Roos et al., *Phys. Biol*. 2008, **5**, 046004



Dynamic clustering of kinesin molecules on microtubules (no ATP)

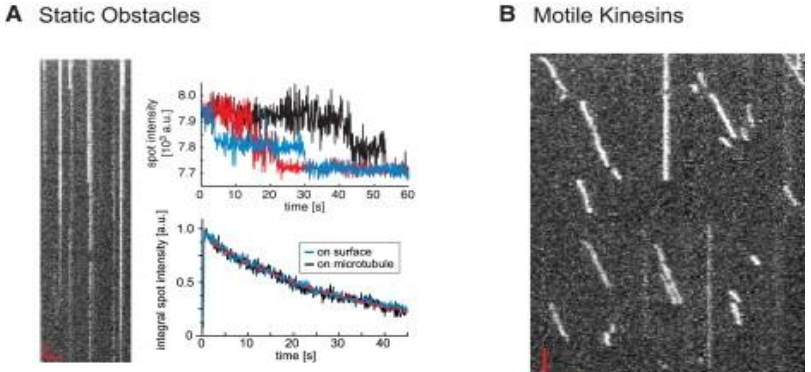
Interactions between 2 neighboring kinesin motors:

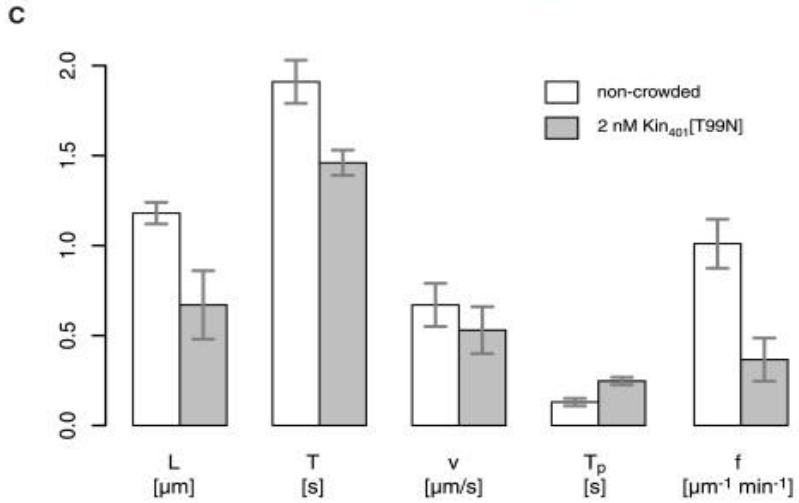
$E_{int} \sim 1.6\ k_B T$ – weak attraction

See also: A. Vilfan et al., *J. Mol. Biol*. 2001, **312**, 1011-1026

Intermolecular Interactions

I.A. Telly et al., *Biophys. J.* 2009, **96**, 3341





D

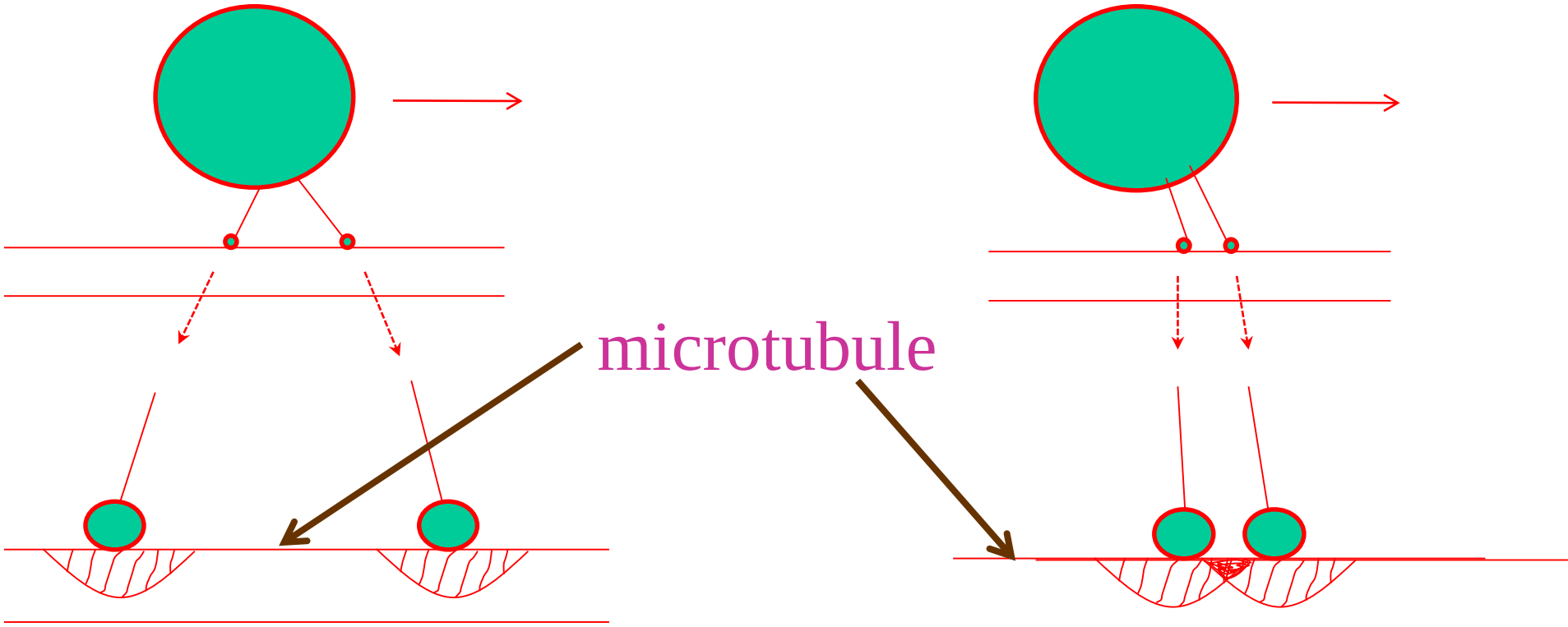
obstacle	landing (µm min)$^{-1}$	accessibility	event probability / step: detach	pause	stop
none	1.01 [0.14]	100%	0.6%	0.4%	0.04%
T99N	0.32 [0.11]	32%	1.0%	1.0%	0.18%
wt	0.34 [0.03]	34%	1.8%	0.9%	0.13%

Single-Molecule imaging of kinesins motion in the presence of obstacles (other mutated kinesins)

Interactions between 2 neighboring kinesin motors: weak repulsion

Sign of interactions – controversial!

Molecular Origin of Intermolecular Interactions (possible)



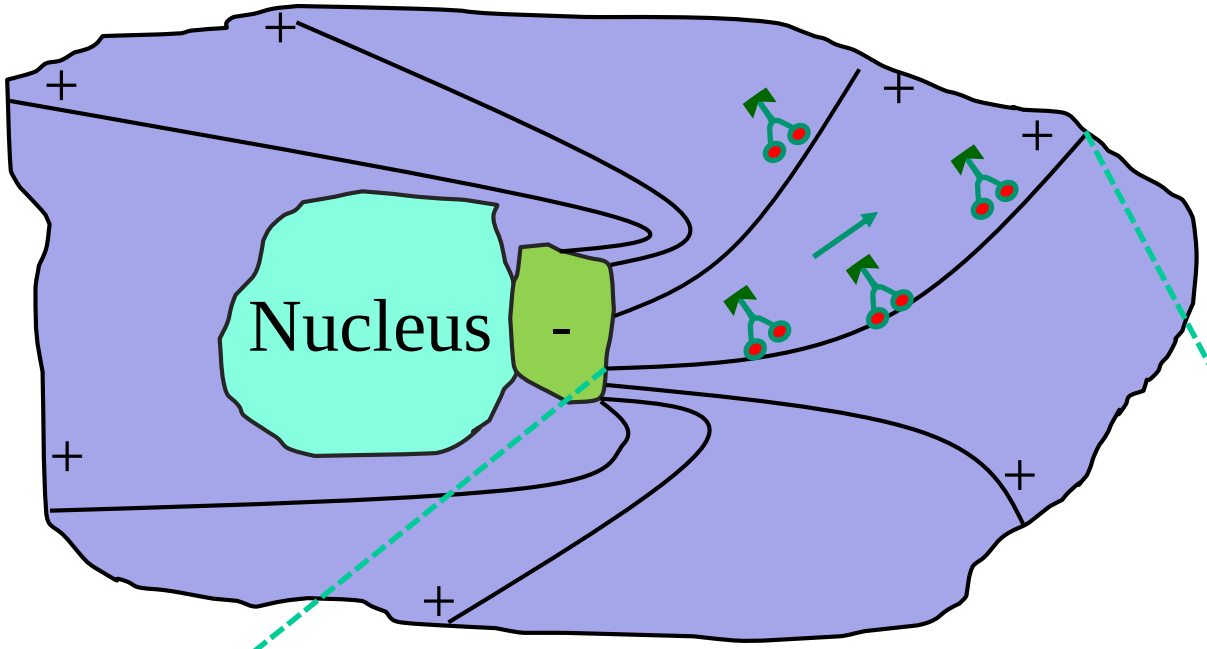
no interactions

Local interactions due to the overlap of strain areas affected by microtubule-kinesin bindings

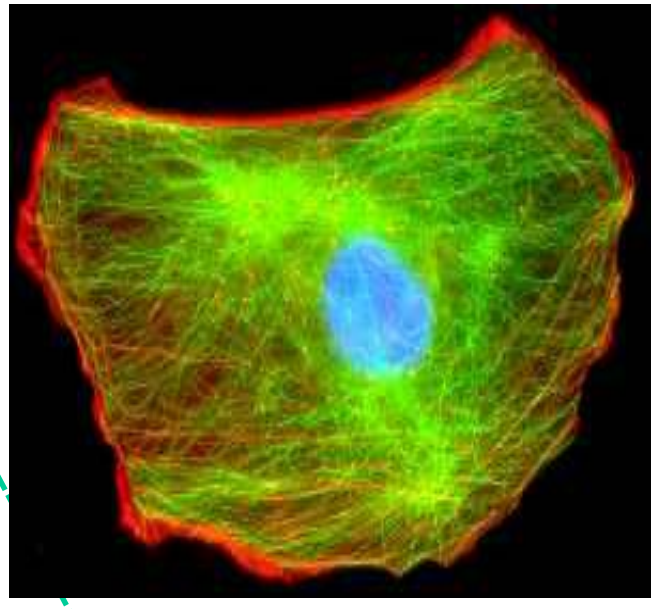
Theoretical Model

Intracellular Transport – quasi 1D

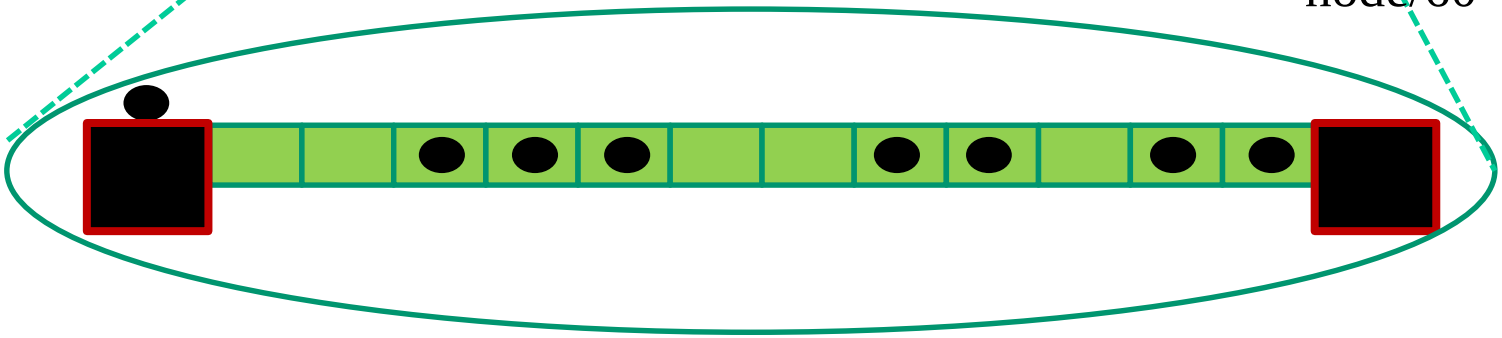
Eukaryotic cell



microtubule network



http://bsp.med.harvard.edu/?q=node/60

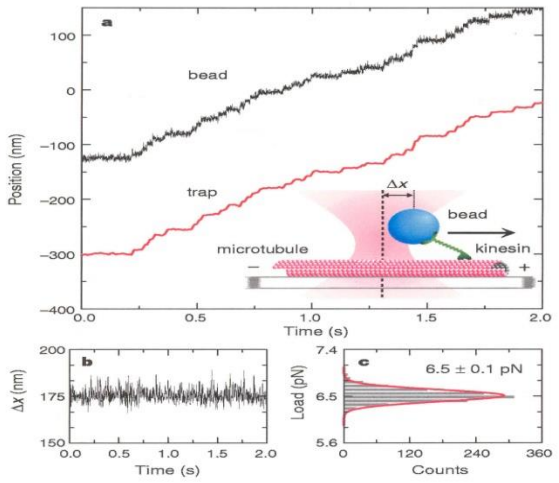


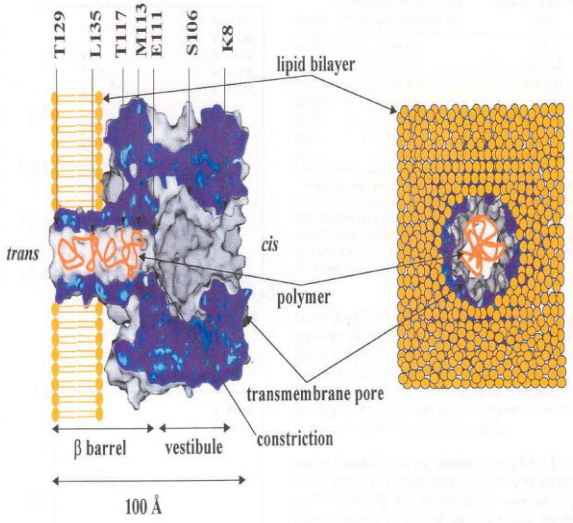
Asymmetric Simple Exclusion Processes

Applications:

To investigate 1D multi-particle, cooperative phenomena in chemistry, physics and biology

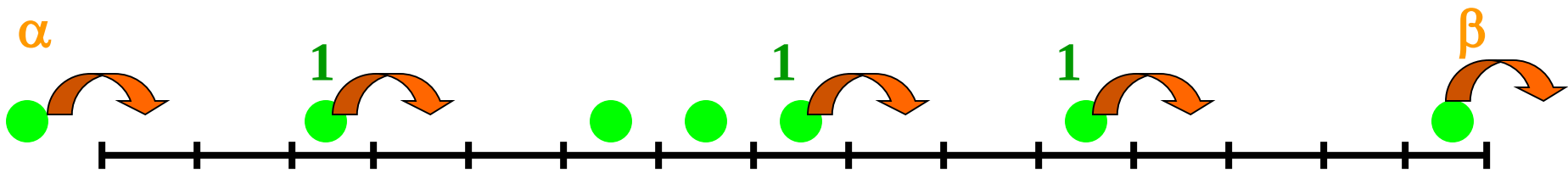
Biological transport, polymerization, protein synthesis	Gel electrophoresis, traffic problems, animal behavior, interface growth	Diffusion through biological channels, polymer dynamics





Asymmetric Simple Exclusion Processes

1D Lattice Gas Models with Hard-Core Exclusions

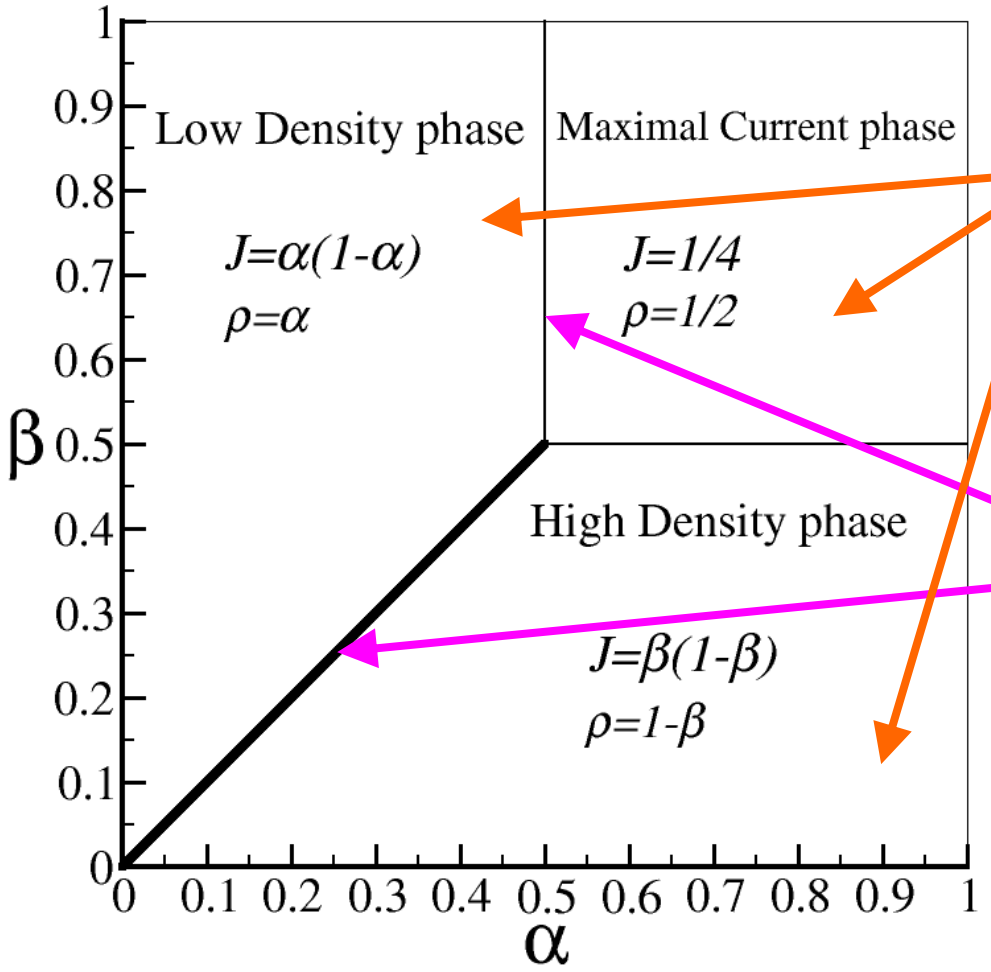


The simplest model: **Totally Asymmetric Simple Exclusion Process (TASEP)**

- Non-equilibrium process
- Particles enter from the left with rate $0 \le \alpha \le 1$ if the first site is unoccupied
- Inside the lattice particles hop to the next site with rate 1 if there is no particle at this site – hard-core exclusion
- Particles leave from to the right with rate $0 \le \beta \le 1$

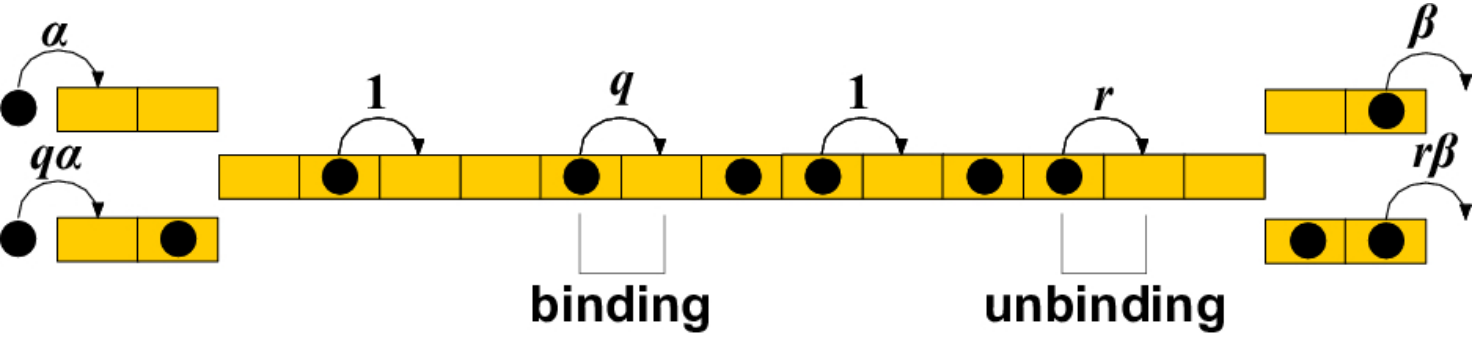
Exact Solutions of TASEP

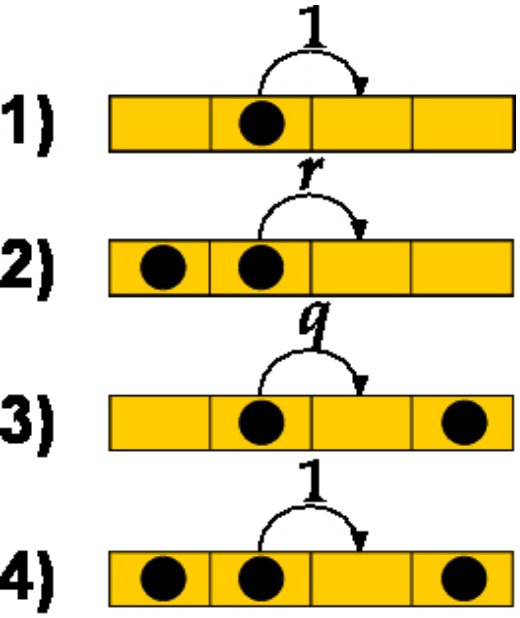
Derrida *et al.*, *J. Phys. A: Math Gen.* **26** 1493 (1993), G. Schutz et al., *J. Stat. Phys*. (1992)



- **Non-equilibrium process**
- Three stationary states each with its own particle current (J) and bulk density(ρ)
- Two types of phase transitions
- Boundary-induced phase transitions

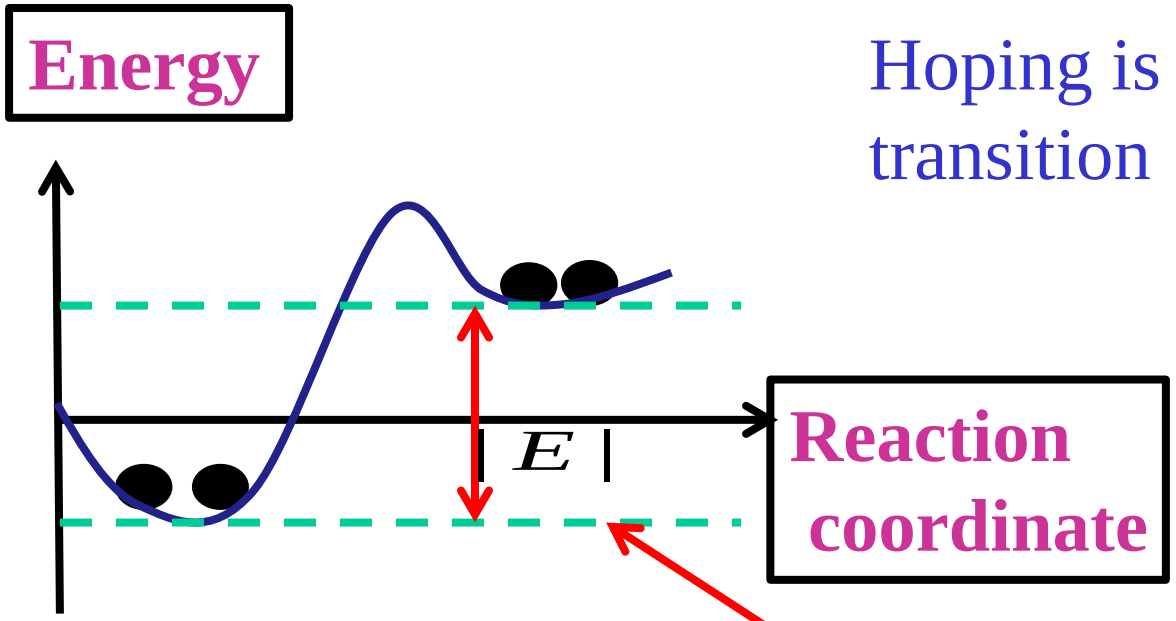
Our Model: TASEP with Interactions



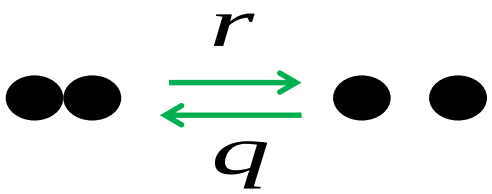


1) Transport of motor proteins is viewed as a motion of multiple particles on a lattice;
2) Short-range interactions between neighboring motor proteins in addition to exclusion
3) Thermodynamically consistent rates of transitions

Our Model: TASEP with Interactions



Hoping is viewed as a chemical transition



We can use detailed-balance like arguments to describe all rates in the system

$$\frac{P(\bullet\bullet)}{P(\bullet\ \bullet)} = \exp\left(\frac{E}{k_B T}\right) = \frac{q}{r} = \frac{\exp\left(\frac{\theta E}{k_B T}\right)}{\exp\left(\frac{(\theta-1)E}{k_B T}\right)}$$

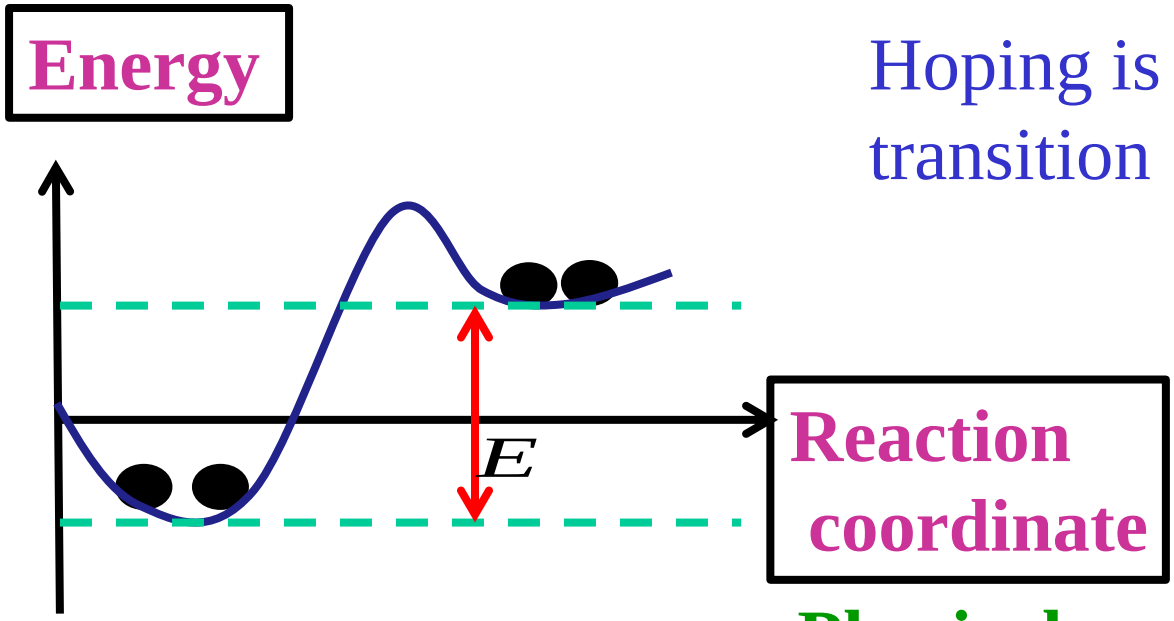
E>0 **Attraction**

E<0 **Repulsion**

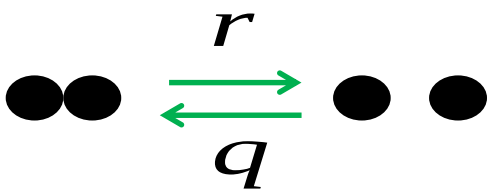
$E=0$, $q=r=1$ normal TASEP

$0<\theta<1$- specifies how energy is distributed between forward and backward transitions

Our Model: TASEP with Interactions



Hoping is viewed as a chemical transition



$$q = e^{\beta\theta E}, r = e^{\beta(\theta-1)E}$$

Physical meaning:
for **E>0** (attraction) it is faster to create the cluster of particles (**q>1, r<1**), while for **E<0** (repulsion) it is faster to break the cluster (**q<1, r>1**)

$0<\theta<1$- specifies how energy is distributed between forward and backward transitions

Methods: Simple Mean Field (SMF)

Occupation number

$\tau_i =$ { **1** ● **0** □

$$< \tau_i \tau_{i+1} > = < \tau_i > < \tau_{i+1} >$$

$$\mathbf{P}(\tau_i\ \tau_{i+1}) \sim \mathbf{P}(\tau_i) \times \mathbf{P}(\tau_{i+1})$$

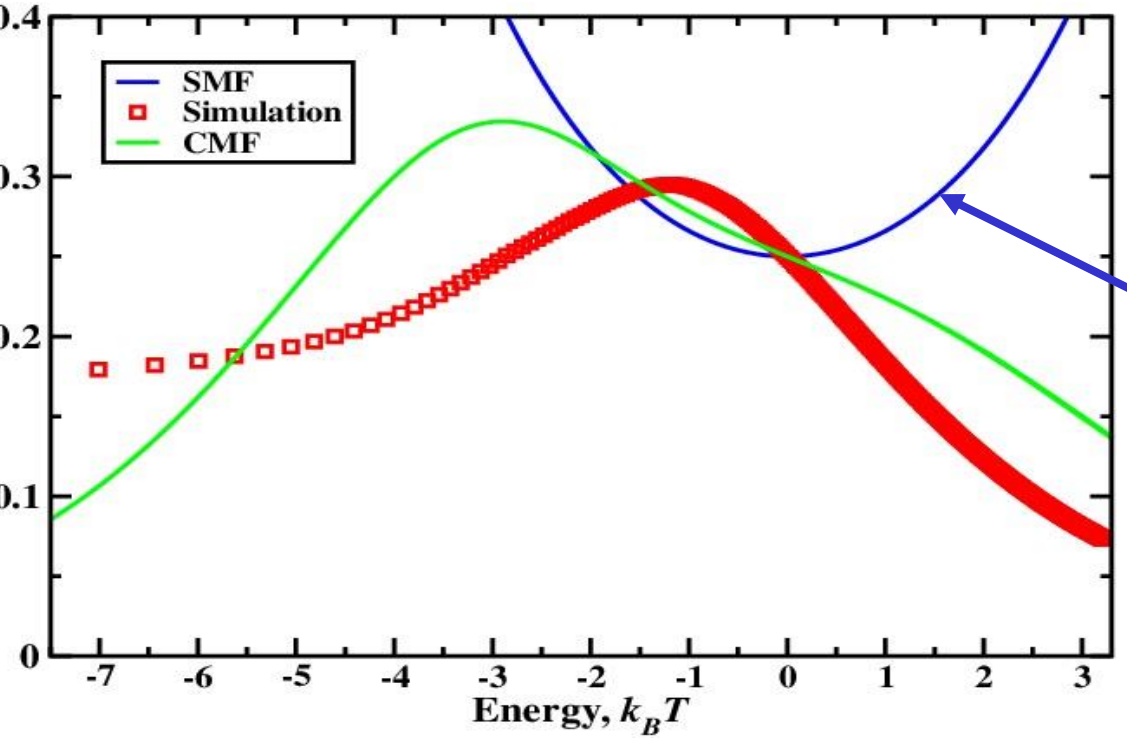
All properties can be calculated analytically, but there are problems:

$$J_{MC} = \frac{1}{8} + \frac{r+q}{16} = \frac{1}{8} + \frac{e^{\beta\theta E} + e^{\beta(\theta-1)E}}{16}$$

Flux in the maximal-current phase at very large attractions or repulsions is diverging – **unphysical!**

Zero or finite currents are expected!!!

Methods: Simple Mean Field (SMF)



Fluxes in the MC phase.

Simple Mean Field

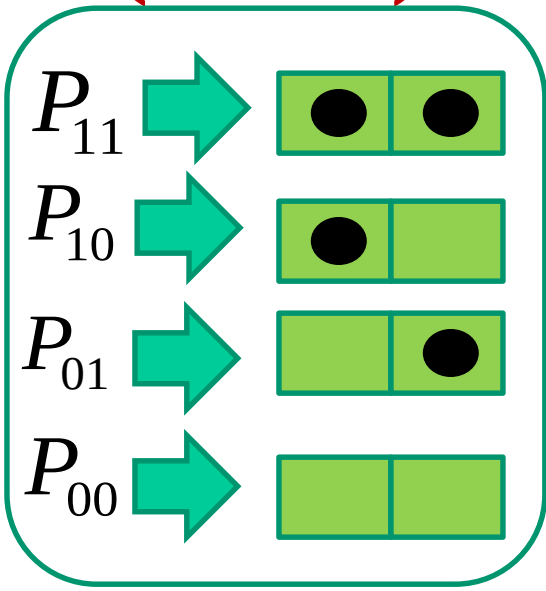
$$J_{MC}=\frac{1}{8}+\frac{r+q}{16}=\frac{1}{8}+\frac{e^{\beta\theta E}+e^{\beta(\theta-1)E}}{16}$$

Flux in the maximal-current phase at very large attractions or repulsions is diverging – **unphysical!**

Zero or finite currents are expected!!!

Methods: Cluster Mean Field (CMF)

CMF approach partially takes correlations into account

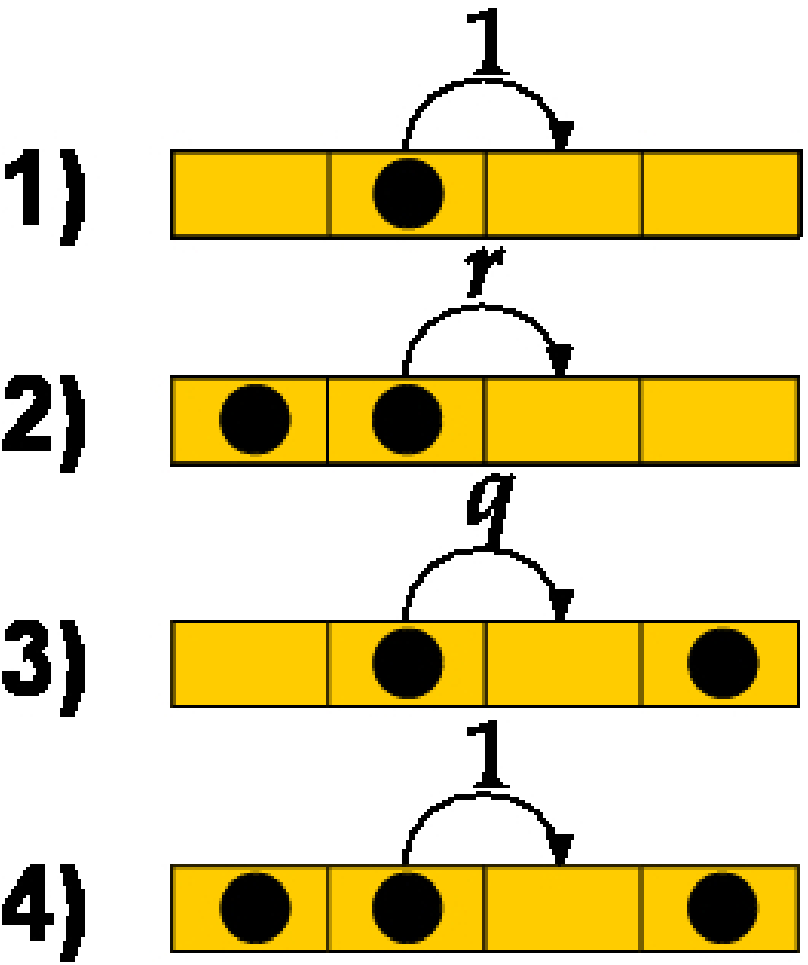


CMF utilizes clusters with 2 lattice sites

$$< \tau_i \tau_{i+1} > \neq < \tau_i > < \tau_{i+1} >$$

CMF neglects correlations between different clusters:

Methods: Two-Cluster Mean-Field



1) Our approach takes into account correlations (nearest-neighbor);
2) All results are analytical;
3) Correct predictions in limiting cases;
4) Can be easily extended to more complex systems

Note that for very strong repulsions ($E \to -\infty$) our system is identical to TASEP of non-interacting dimers

Methods: Two-Cluster Mean-Field

The probability of the sequence of ***m*** sites in the bulk is factorized into the product of two-site clusters probabilities normalized by single-site probabilities

$$P(\tau_i, \tau_{i+1}, \dots, \tau_{i+m-1}) = \frac{P(\tau_i,\tau_{i+1})P(\tau_{i+1},\tau_{i+2})\dots P(\tau_{i+m-2},\tau_{i+m-1})}{P(\tau_{i+1})P(\tau_{i+2})\dots P(\tau_{i+m-2})}$$

Example:

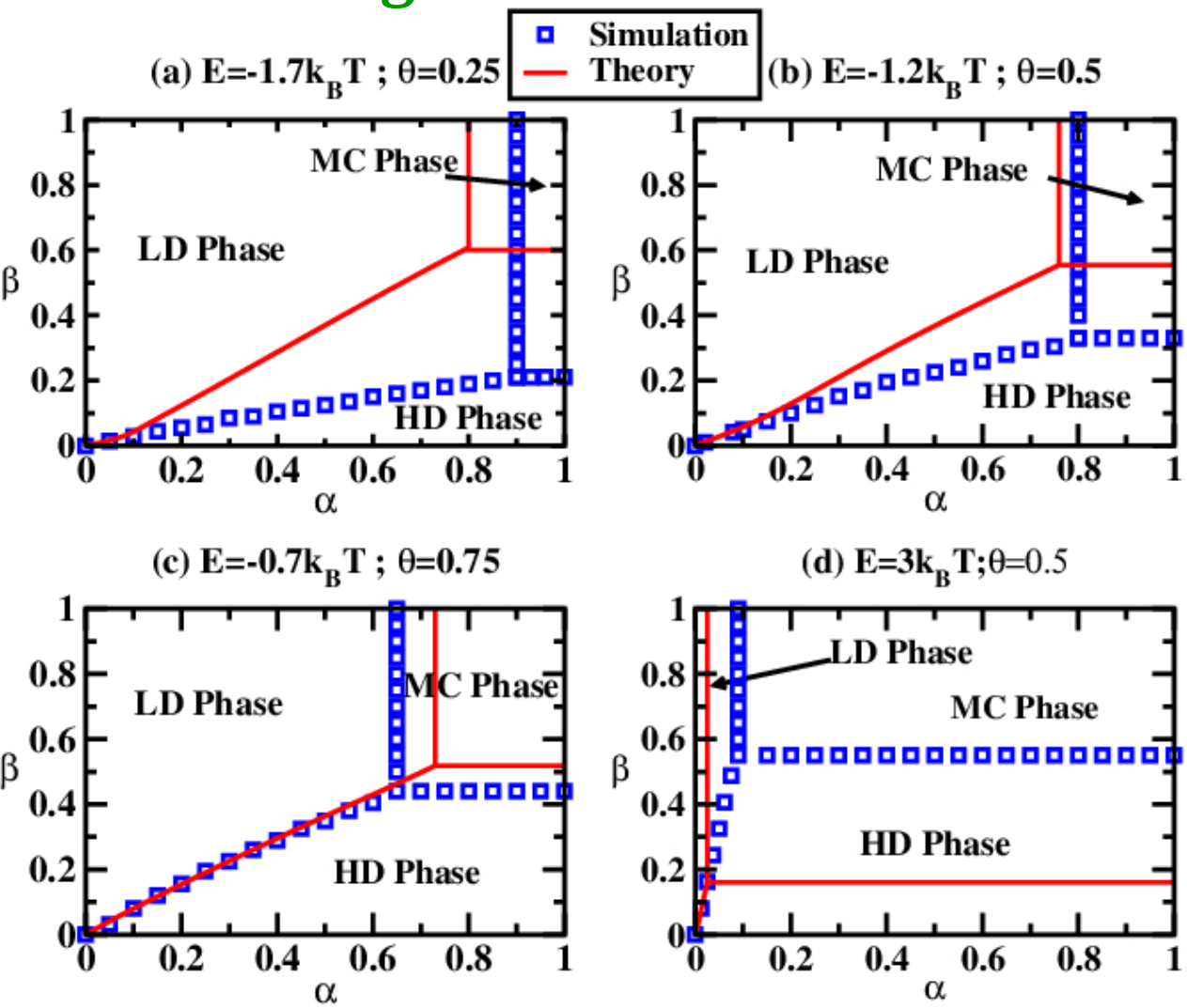
$$P(0,1,1,0) = \frac{P(0,1)P(1,1)P(1,0)}{P(1)P(1)}$$

Two-site and single-site probabilities are related:

$$P(1,0) + P(1,1) = P(1); P(0,0) + P(0,1) = P(0)$$

Results:

Phase diagrams:

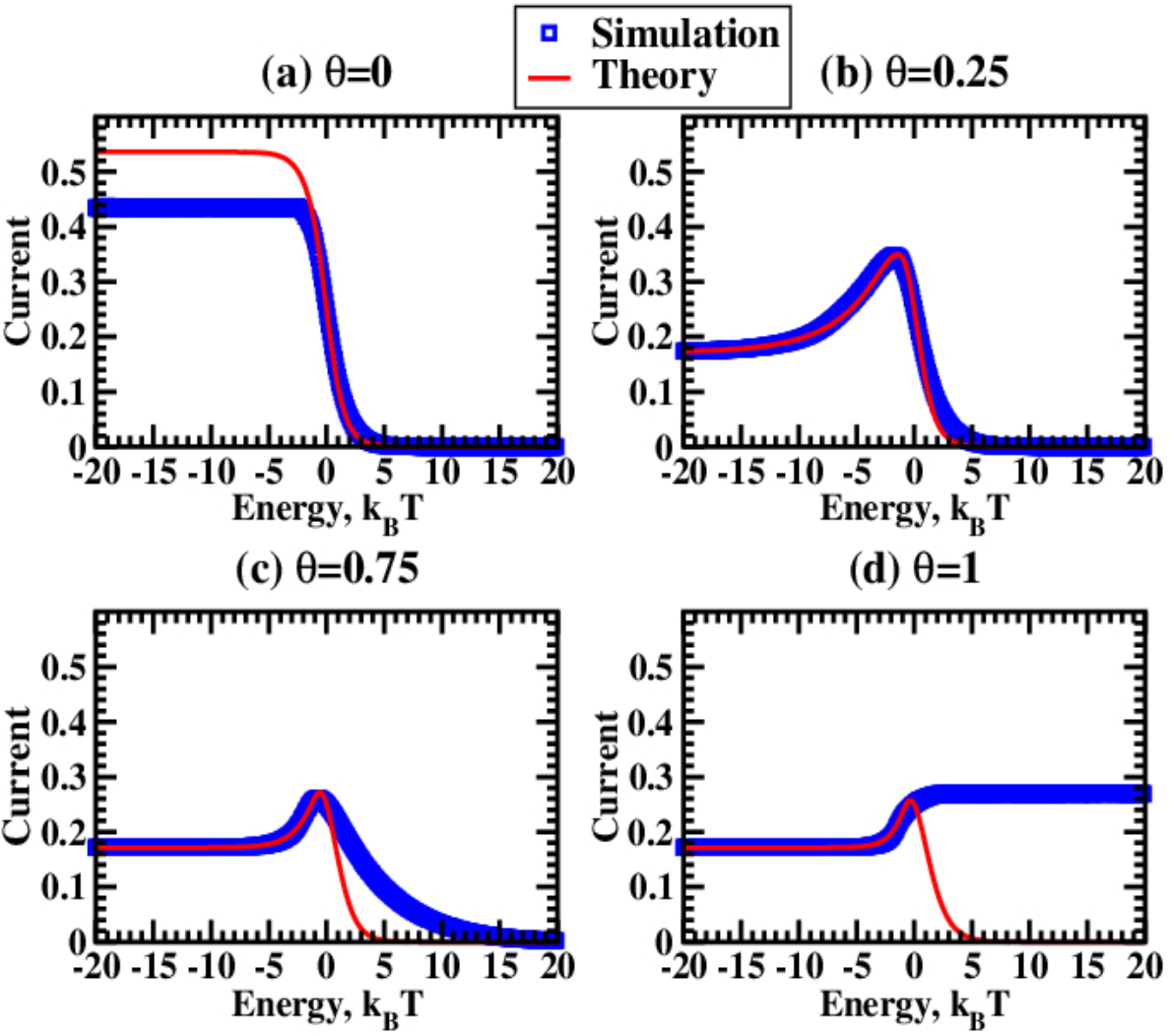


1) Similarly to TASEP without interactions, 3 phases: MC, HD and LD
2) Theoretical predictions agree semi-quantitatively

LD phase dominates for repulsions, HD phase dominates for attractions

Results:

Maximal particle fluxes:



Correlations are important!

1) Excellent agreement with theory for repulsions for $\theta>0$

2) Excellent agreement for attractions for $\theta<0.25$, and after that a reasonable qualitative agreement

3) $\theta=0$ and $\theta=1$ are special cases

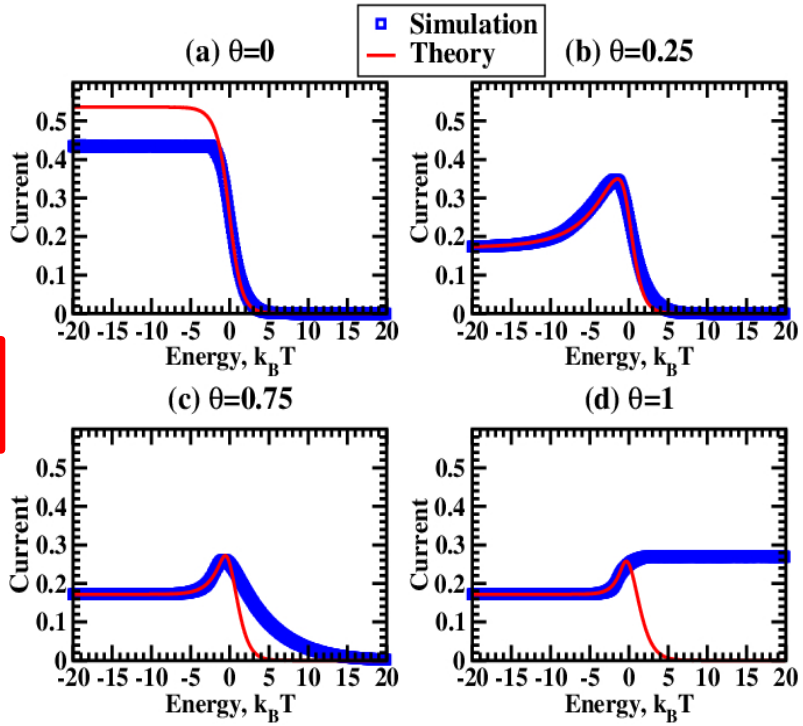
Results:

To understand dynamics, we introduce a correlation function C:

$$C = < \tau_i \tau_{i+1} > - < \tau_i > < \tau_{i+1} >$$

$$C(E) = \frac{\rho^2(1-\rho)[e^{\beta E} - 1]}{1 + \rho[e^{\beta E} - 1]}$$

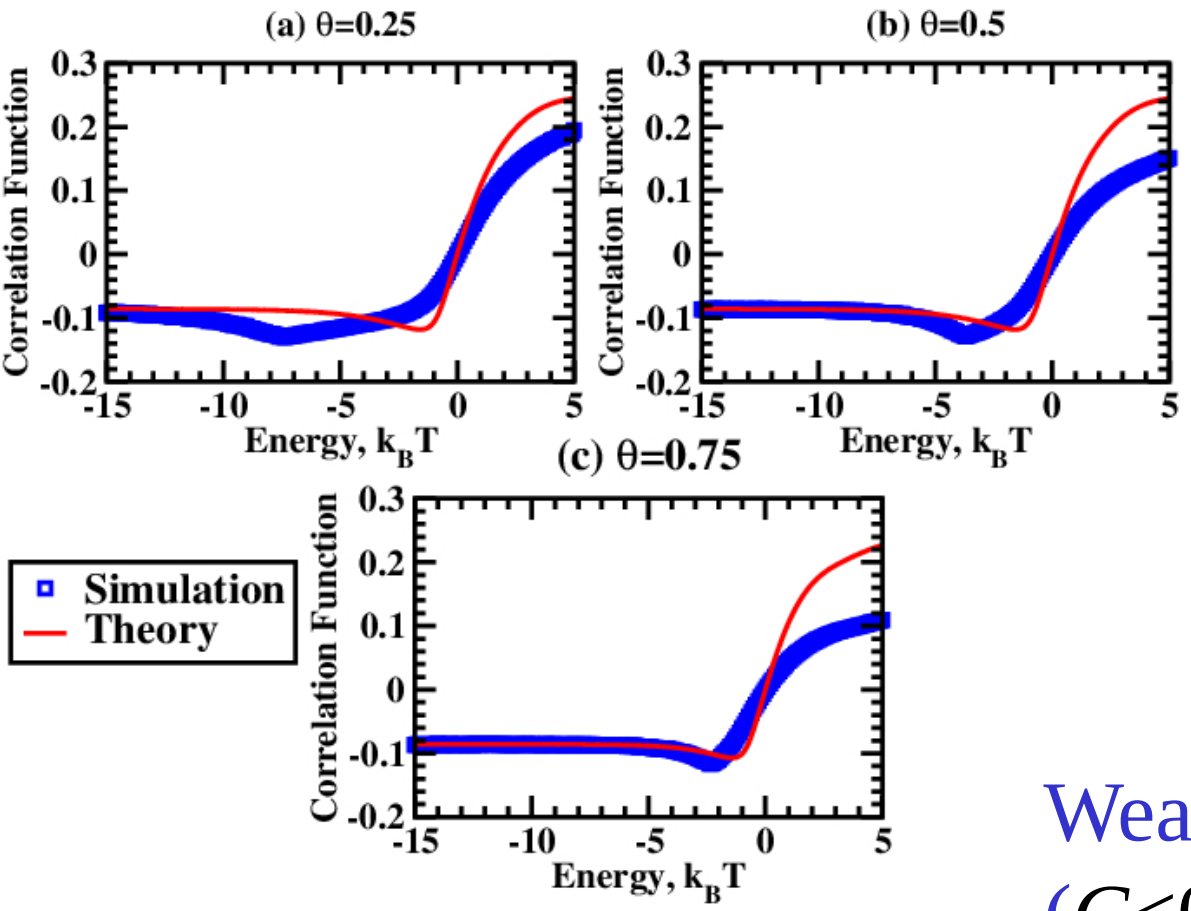
For E=0, we obtain C=0 – no correlations, simple mean-field works



Physical meaning of C- how the presence of particle at the site i affects the occupation at the site $i+1$.

Results:

Correlation functions



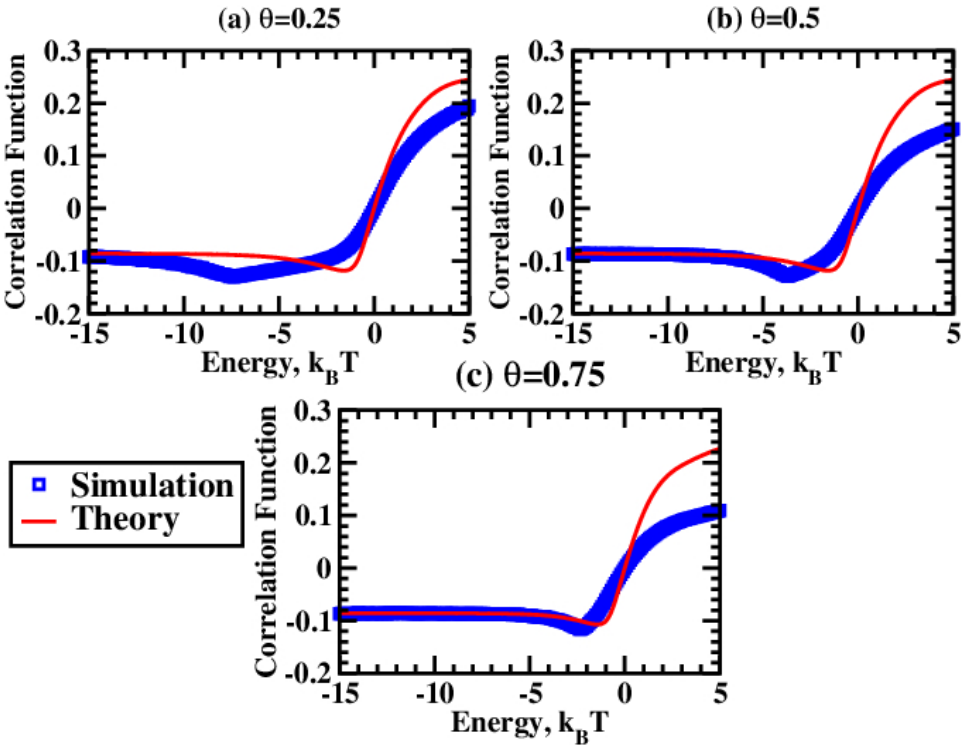
Physical meaning of C- how the presence of particle at the site i affects the occupation at the site $i+1$.

Weak anti-correlations ($C<0$) for repulsions, and stronger positive correlations ($C>0$) for attractions

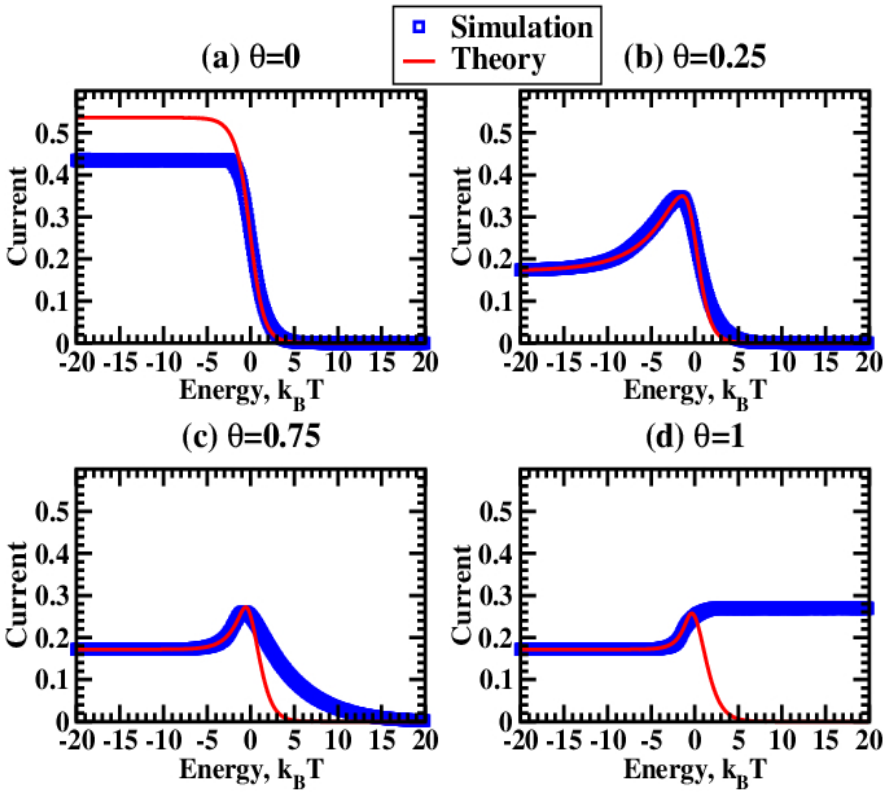
$$C(E) = \frac{\rho^2(1-\rho)[e^{\beta E}-1]}{1+\rho[e^{\beta E}-1]}$$

Results:

Correlation functions

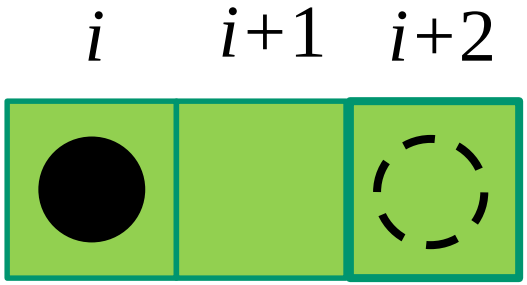


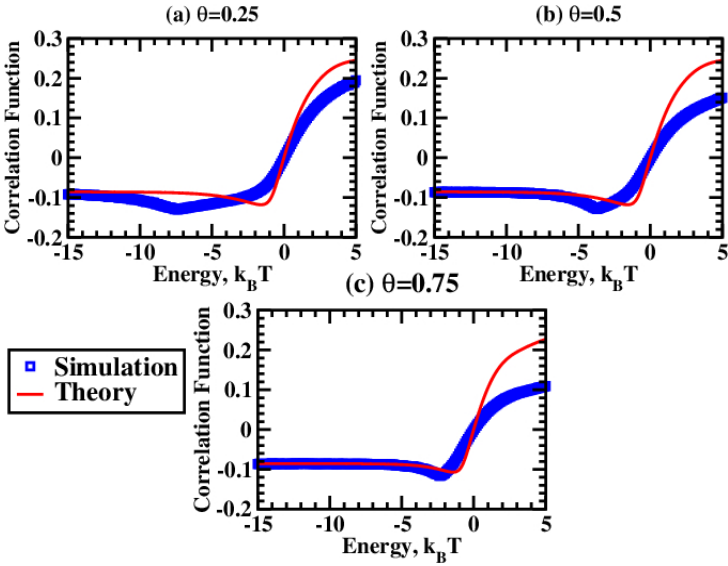
Maximal particle fluxes:



Question: why our theoretical approach, that takes into account some correlations, is successful only for repulsions and weak attractions?

Results:



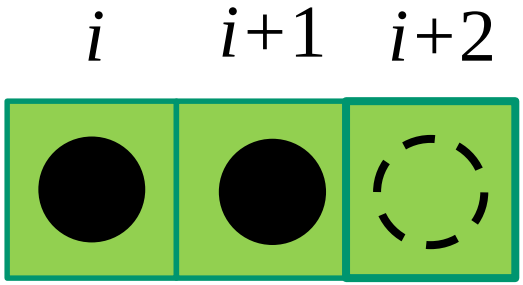


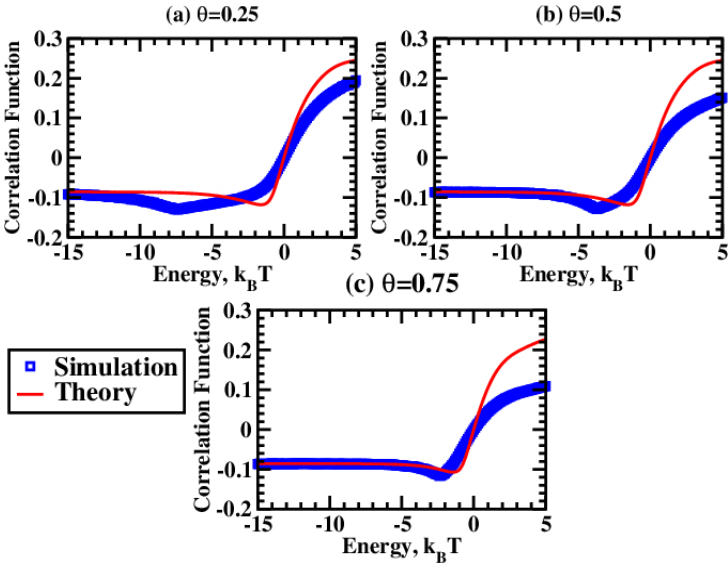
Repulsions: the presence of the particle at the site *i* leads to lower probability of finding the particle at the site *i*+1.

Then the occupancy of the site *i*+2 is independent of the occupancy of the site *i*

Correlations for E<0 are short-range and relatively weak!

Results:





Attractions: the presence of the particle at the site *i* leads to a higher probability of finding the particle at the site *i*+1.

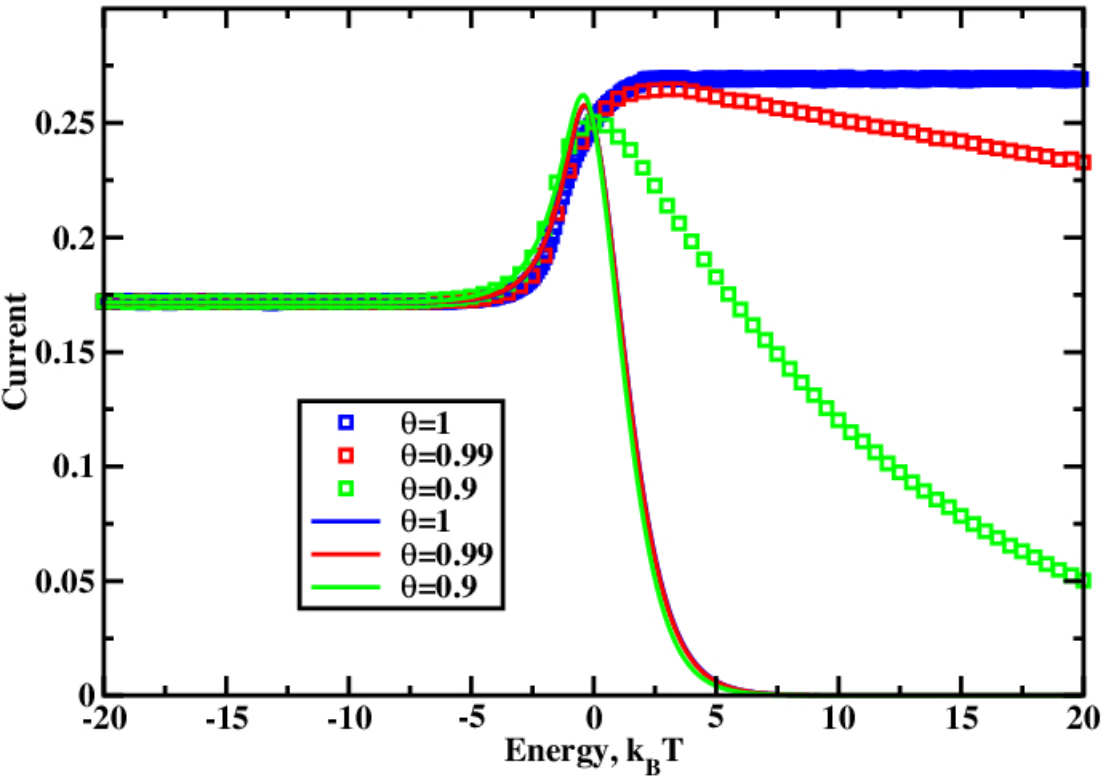
Then the occupancy of the site *i*+2 depends on the occupancy of the site *i*

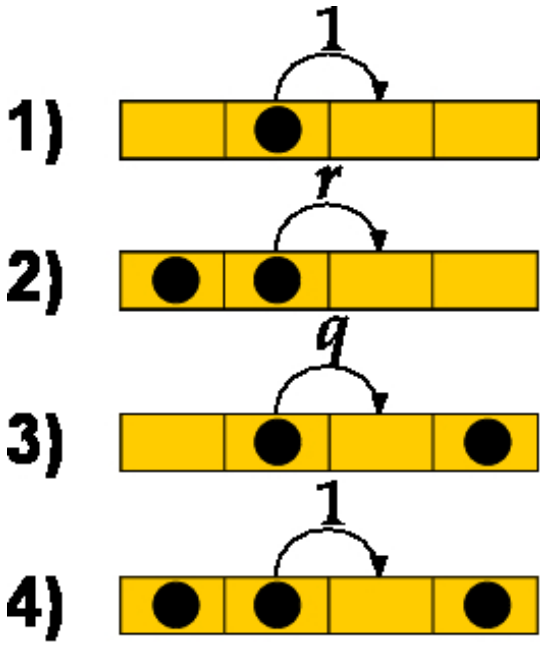
Correlations for E>0 are long-range and strong!

Results:

Maximal particle fluxes for different θ

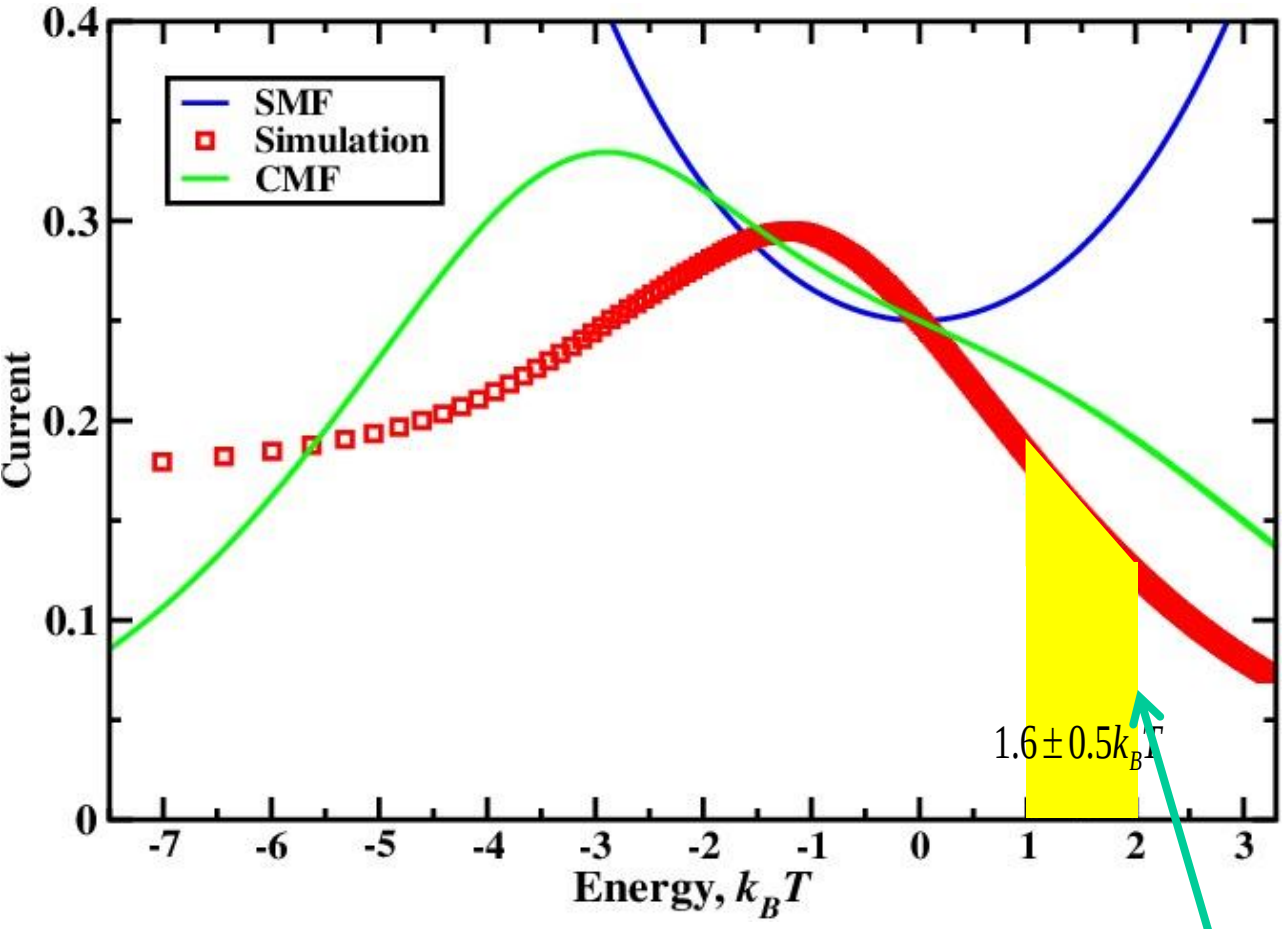
$$\exp\left(\frac{E}{k_B T}\right) = \frac{q}{r} = \frac{\exp\left(\frac{\theta E}{k_B T}\right)}{\exp\left(\frac{(\theta - 1)E}{k_B T}\right)}$$





Dynamics of interacting molecular motors depends on how the interaction is split between the formation and breaking the clusters (symmetry of interactions)

Relevance for Real Motor Proteins?

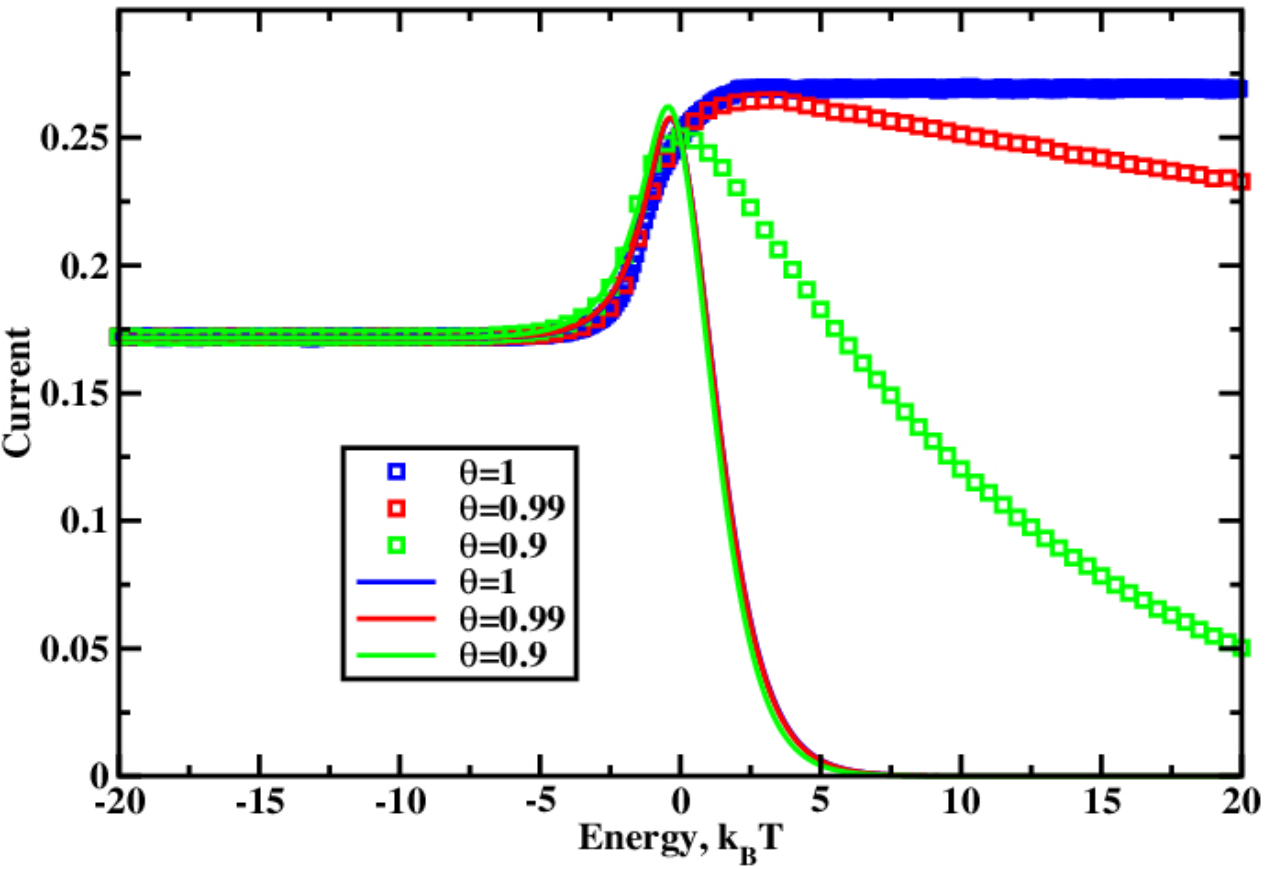


Option #1 for $\theta<0.9$:

Kinesin is not optimized for the maximal flux but maybe for maximal sensitivity if attractions dominate?

Weak attractions for kinesins

Relevance for Real Motor Proteins?

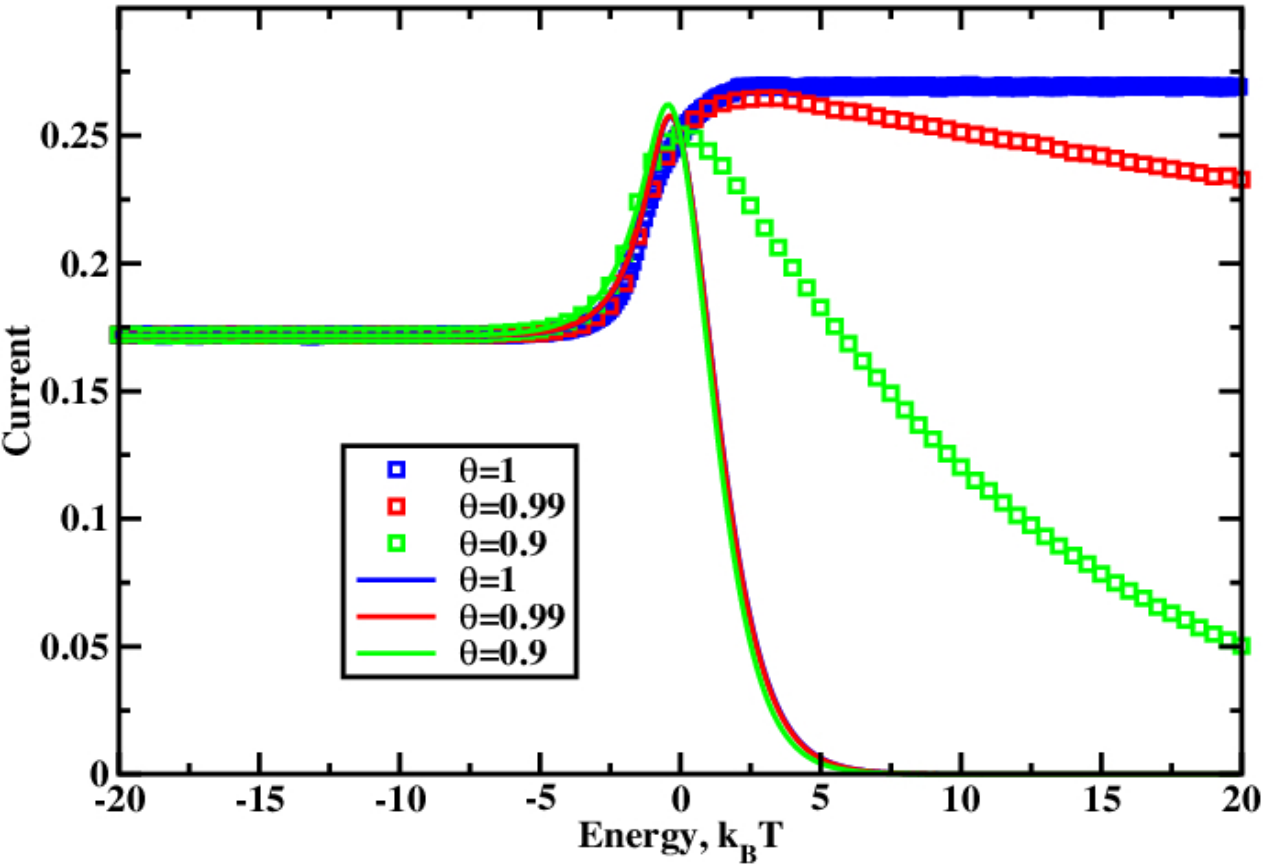


Option #2 for 0.9 <θ<1:

Kinesin might be optimized for the maximal flux if attractions dominate

Critical role of the parameter θ (symmetry of interactions)– must be determined from more microscopic measurements!

Relevance for Real Motor Proteins?



Option #3 for $\theta<0.9$:

Kinesin might be optimized for the maximal flux if they repel

The sign of interactions affects dynamics of motor proteins

Are Motor Proteins at the Stationary State?

Dynamics of relaxation to the stationary state for interacting molecular motors

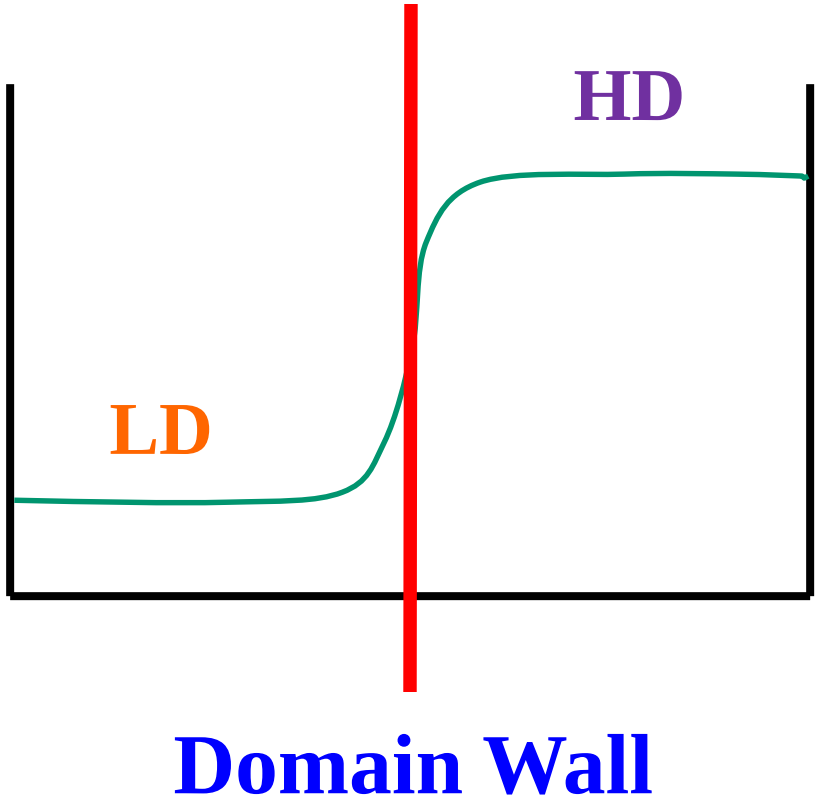
We use the idea of domain wall (DW) as an object that separates different domains

$$V = \frac{J_{HD} - J_{LD}}{\rho_{HD} - \rho_{LD}}$$

DW velocity

$$D = \frac{J_{HD} + J_{LD}}{2(\rho_{HD} - \rho_{LD})}$$

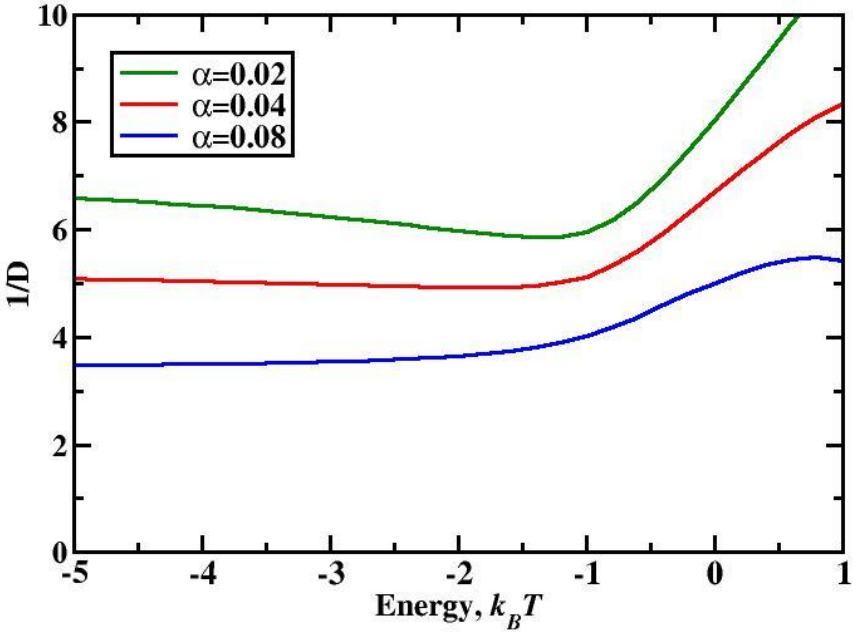
DW diffusion constant



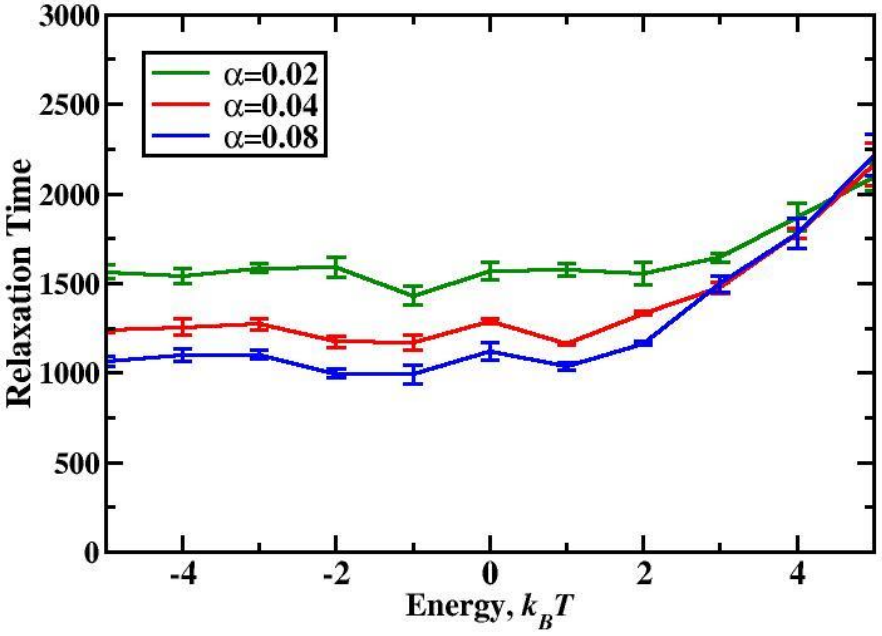
Relaxation time to the stationary state ***T~1/D***

Are Motor Proteins at the Stationary State?

theory

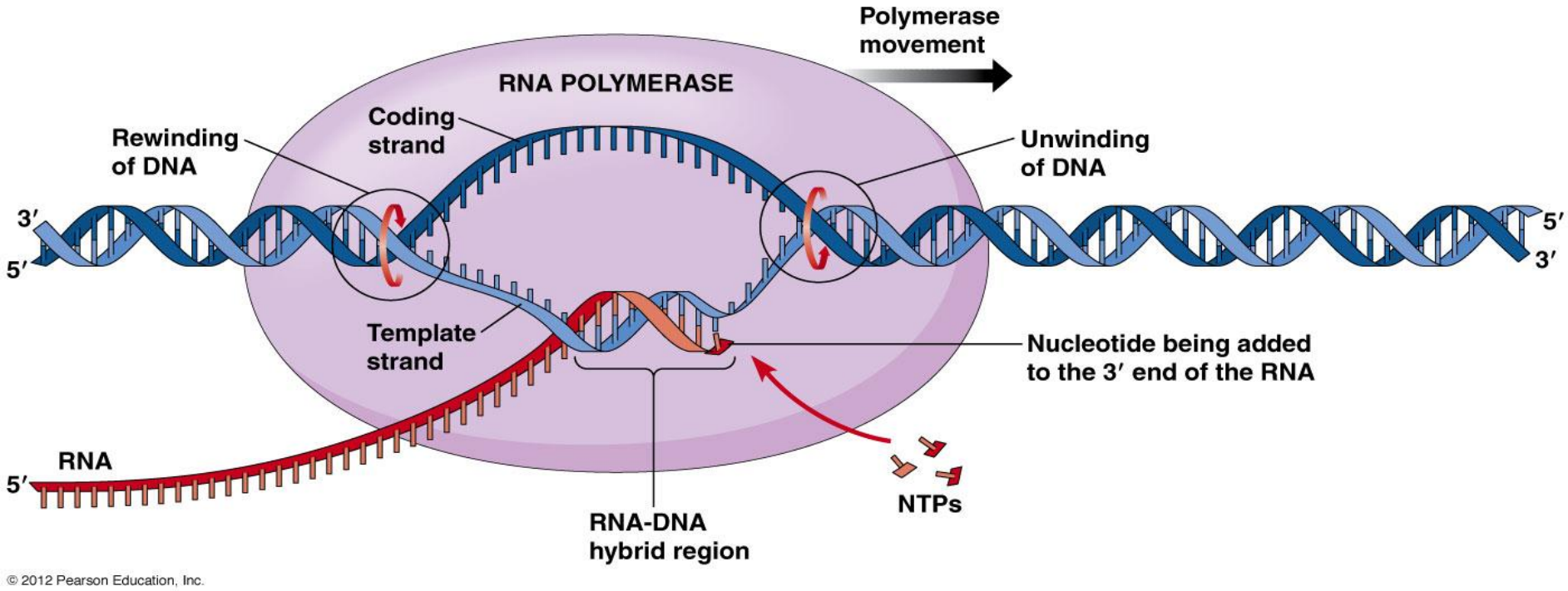


Computer simulations



For repulsions molecular motors relax faster to the stationary state than for attractions

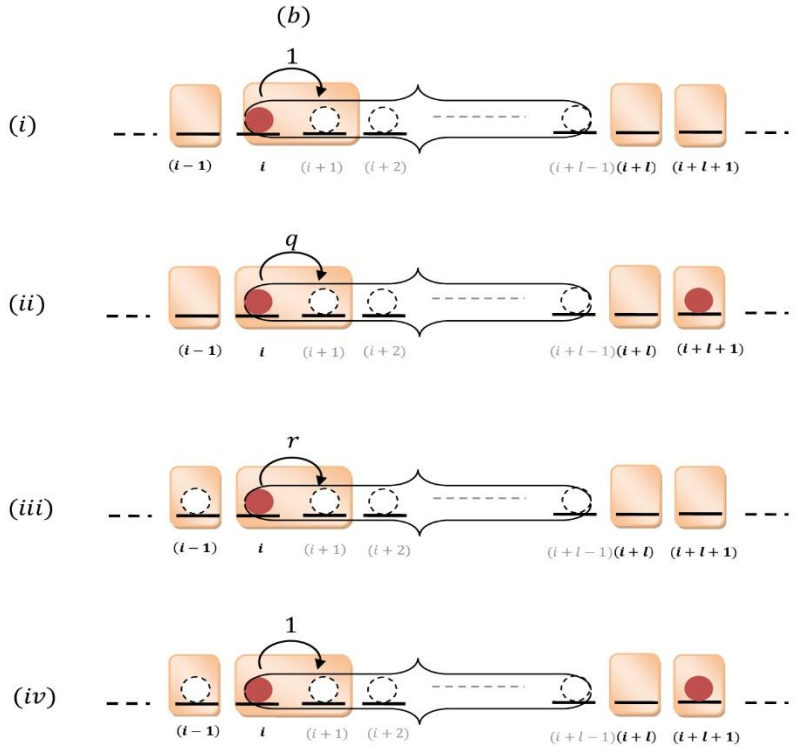
TASEP FOR INTERACTING OLIGOMERS



More realistic description of motor proteins transport: motors can be viewed as oligomers occupying several sites on the lattice

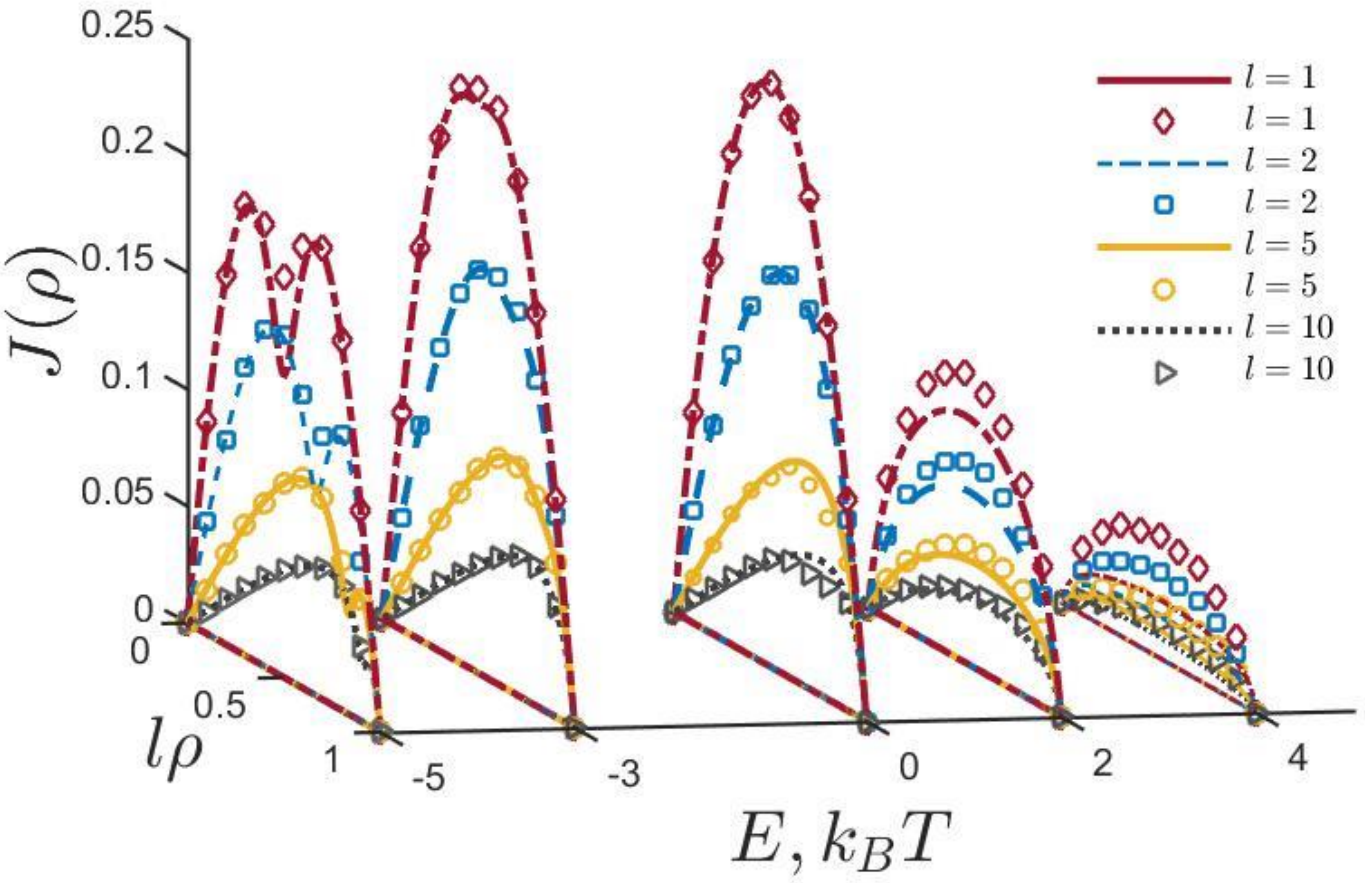
TASEP FOR INTERACTING OLIGOMERS

Motor proteins are viewed as interacting particles of size ***l***>1.
4 possible types of transitions.
Analysis using two-cluster mean-field can be done.



$$q = e^{\beta\theta E}, r = e^{\beta(\theta-1)E}$$

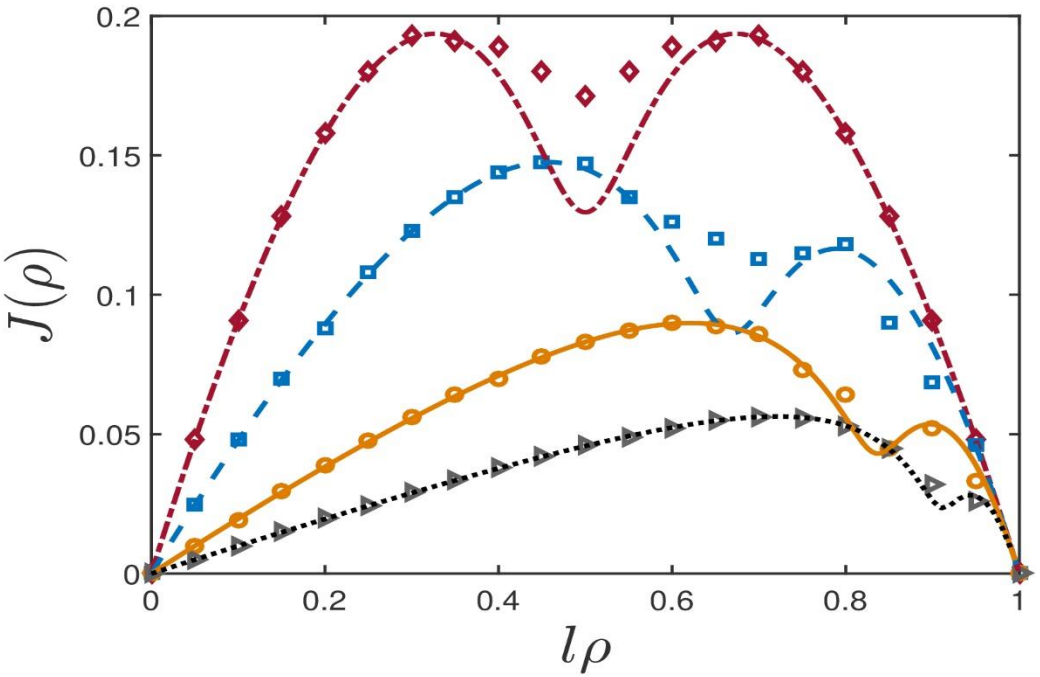
TASEP FOR INTERACTING OLIGOMERS



Periodic boundary conditions with θ=0.5

Fundamental diagram changes its behavior for different interactions.

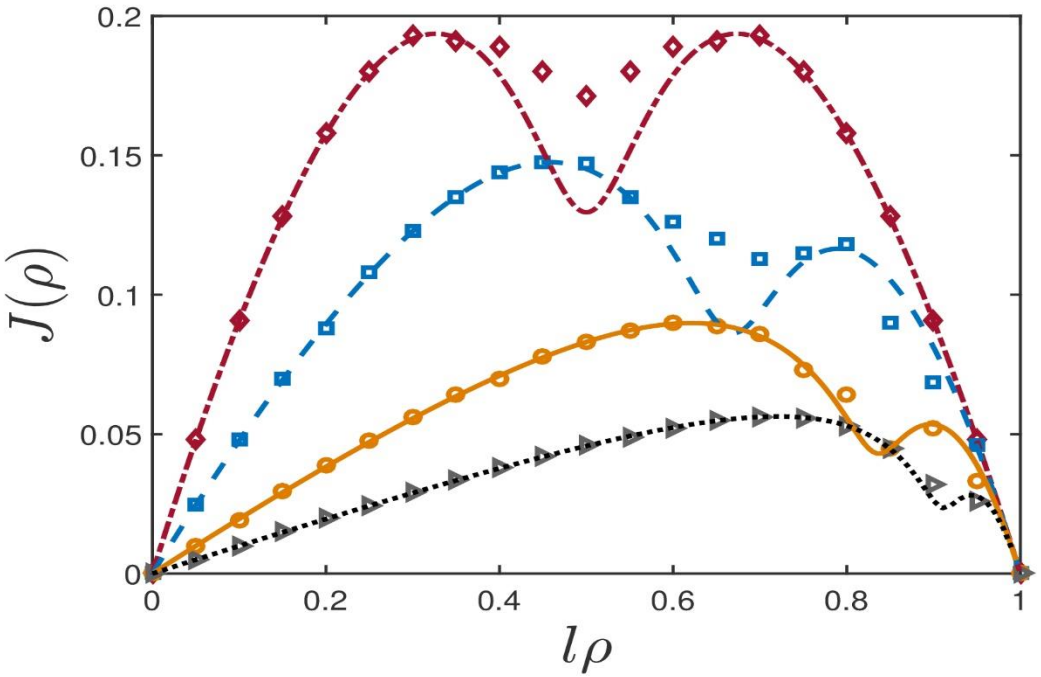
TASEP FOR INTERACTING OLIGOMERS



Periodic boundary conditions with E=-5 kT and θ=0.5

Symmetry arguments: at large repulsions the oligomers if size ***l*** with interactions behave like oligomers of size ***l+1*** without interactions

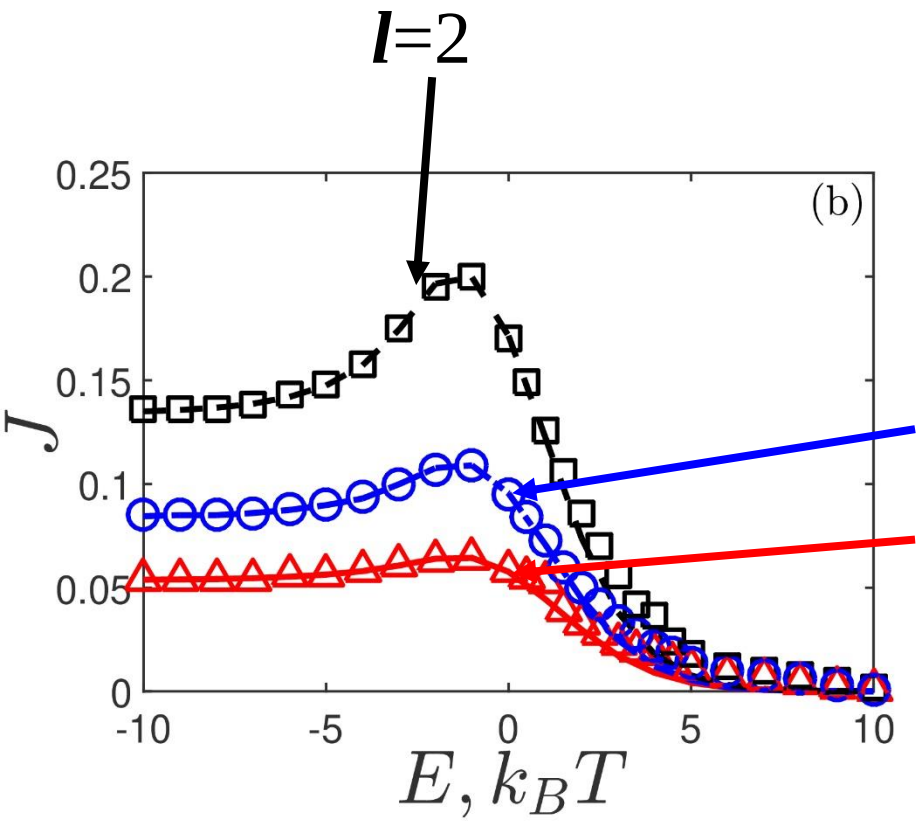
TASEP FOR INTERACTING OLIGOMERS



Periodic boundary conditions with E=-5 kT and θ=0.5

Motion of particles of size l in one direction can be viewed as a motion of "holes" of size 1 in opposite direction

TASEP FOR INTERACTING OLIGOMERS



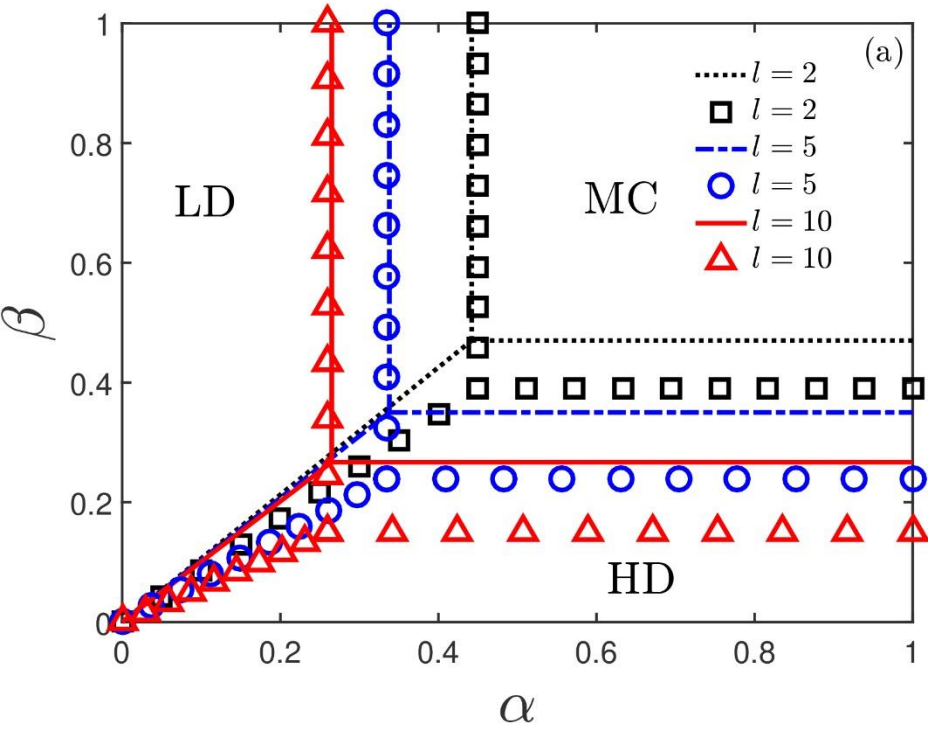
Maximal current in the system with open boundary conditions and θ=0.5

l=5

l=10

Flux decreases with the size l, but the maximal current still observed at weak repulsions

TASEP FOR INTERACTING OLIGOMERS

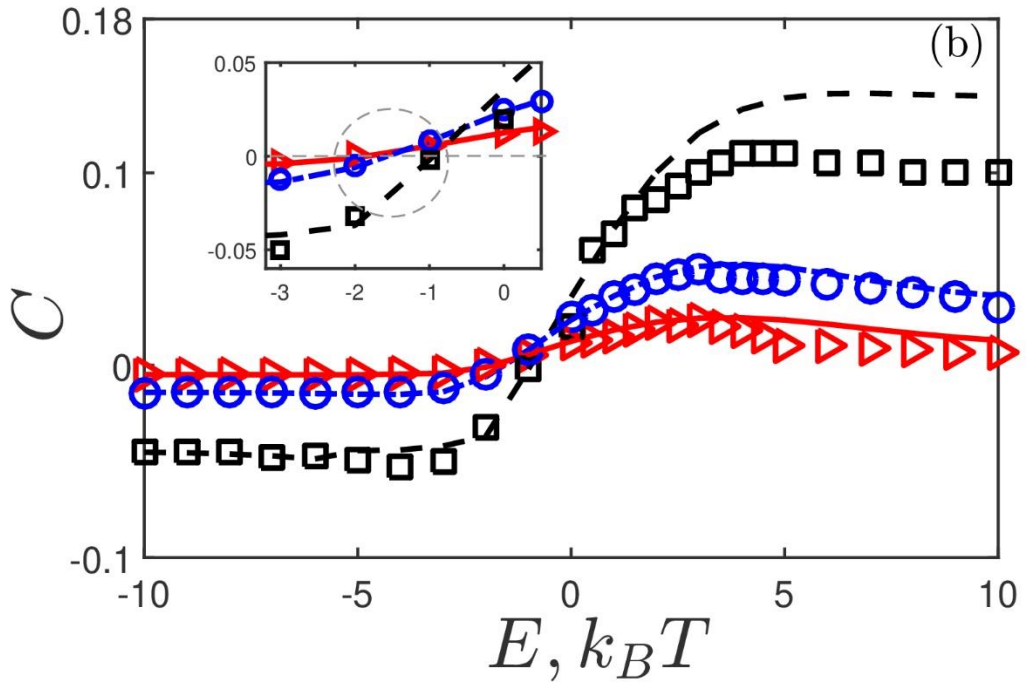


Phase diagram for E=-5 kT and θ=0.5

3 phases (MC, LD and HD) are observed, and the range for MC increases with increasing size of oligomers.

Observation: two-cluster mean-field theory works better for larger l.

TASEP FOR INTERACTING OLIGOMERS



Correlation functions for θ=0.5

l=2

l=5

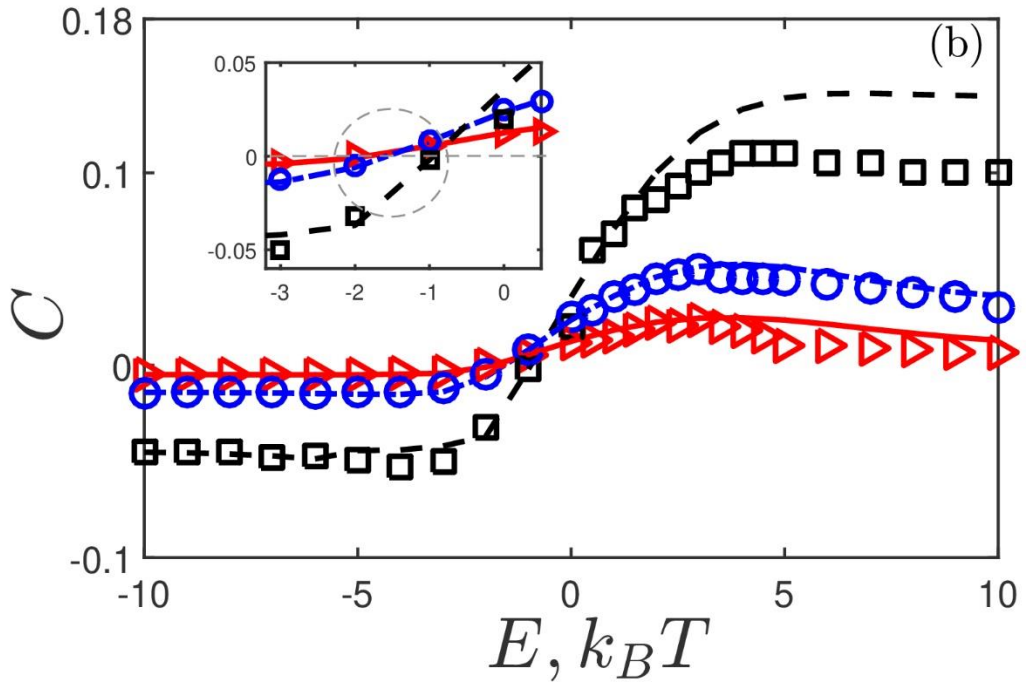
l=10

Two-cluster theory works better for larger l because correlations decrease with l

TASEP FOR INTERACTING OLIGOMERS

Correlation function for ***E=0 kT***

$$C = \frac{\sqrt{l} - 1}{l(\sqrt{l} + 1)^2}$$



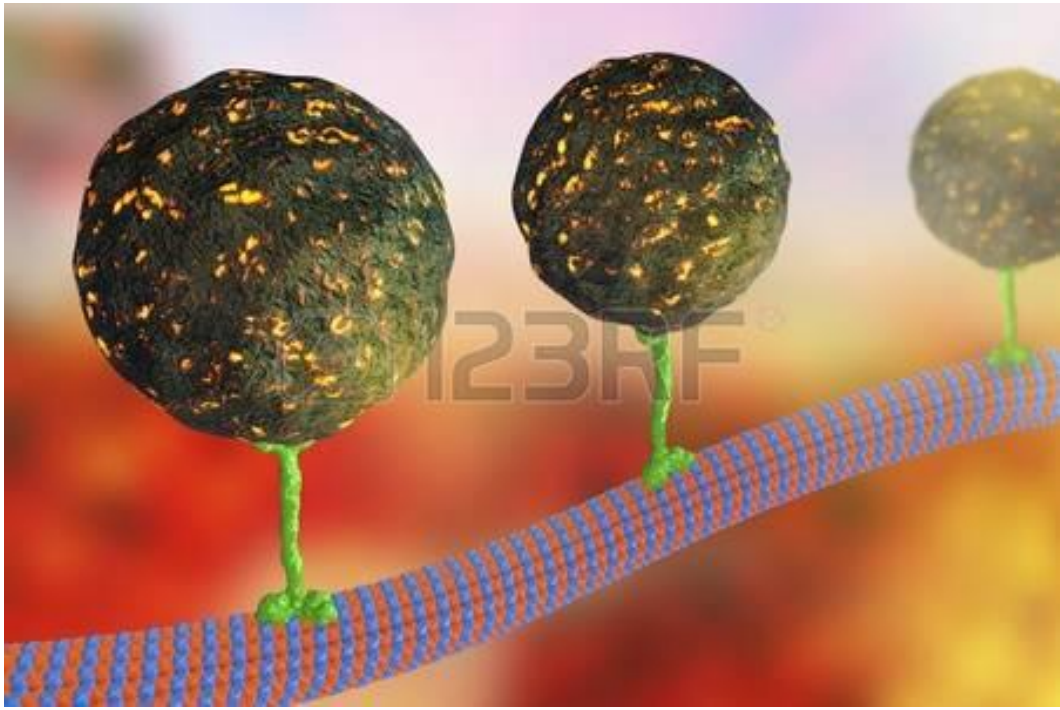
In contrast to interacting monomers (***l***=1), correlations are not zero for oligomers. ***C=0*** for weak repulsions

What is Better for Motor Proteins Supported Cellular Transport?

We speculate that weak repulsive short-range are beneficial for collective behavior of motor proteins:

1) Transport is faster;

2) Robustness – reaching faster the stationary state



CONCLUSIONS

1) Developed a new theoretical approach for analyzing multi-particle dynamics of interacting molecular motors
2) Investigated TASEP with interactions where transition rates are taken into account using proper thermodynamic arguments
3) Interactions induce correlations in the system. For repulsions correlations are weaker, while for attractions they are stronger and more long-ranged
4) Symmetry of interactions also influences dynamics
5) Relaxation to stationary states is faster for repulsive molecular motors.
6) The implications for the transport by motor proteins are discussed

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PUBLICATIONS:

1) *J. Phys A.: Math. Theor*, **48**, 065001 (2015);

2) *J. Stat. Mech*. P04013 (2015);

3) *J. Stat. Mech*. P043205 (2018);

4) *J. Stat. Mech*. P053209 (2018);

5) *J. Phys A.: Math. Theor*, **52**, 365001 (2019);

6) *J. Stat. Mech*. P083202 (2019);