RICE UNIVERSITY

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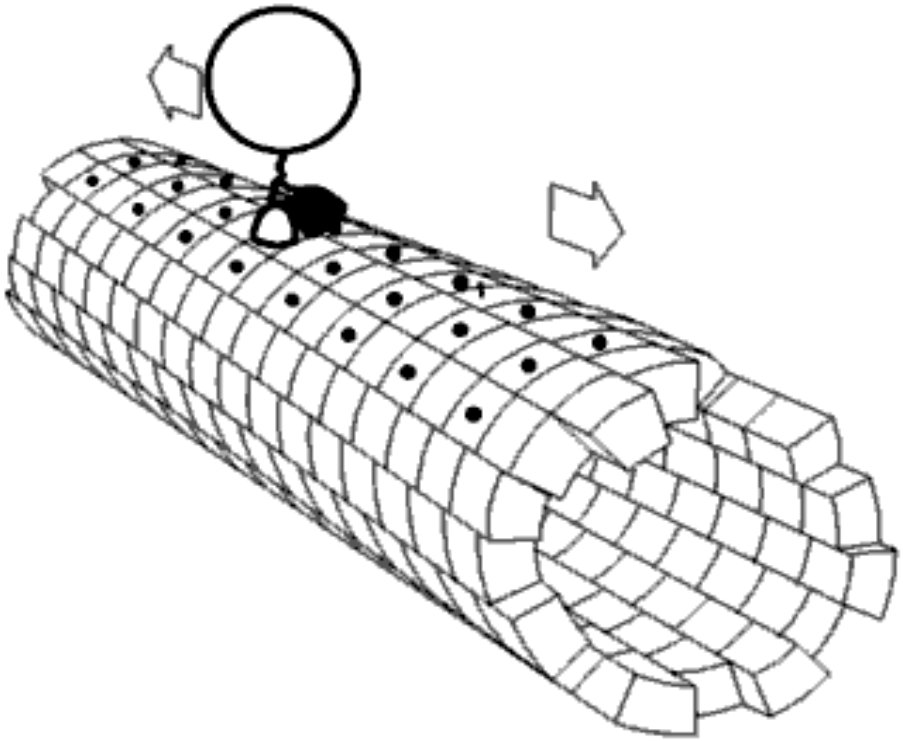
Center for Theoretical Biological Physics

COLLECTIVE DYNAMICS OF INTERACTING MOLECULAR MOTORS

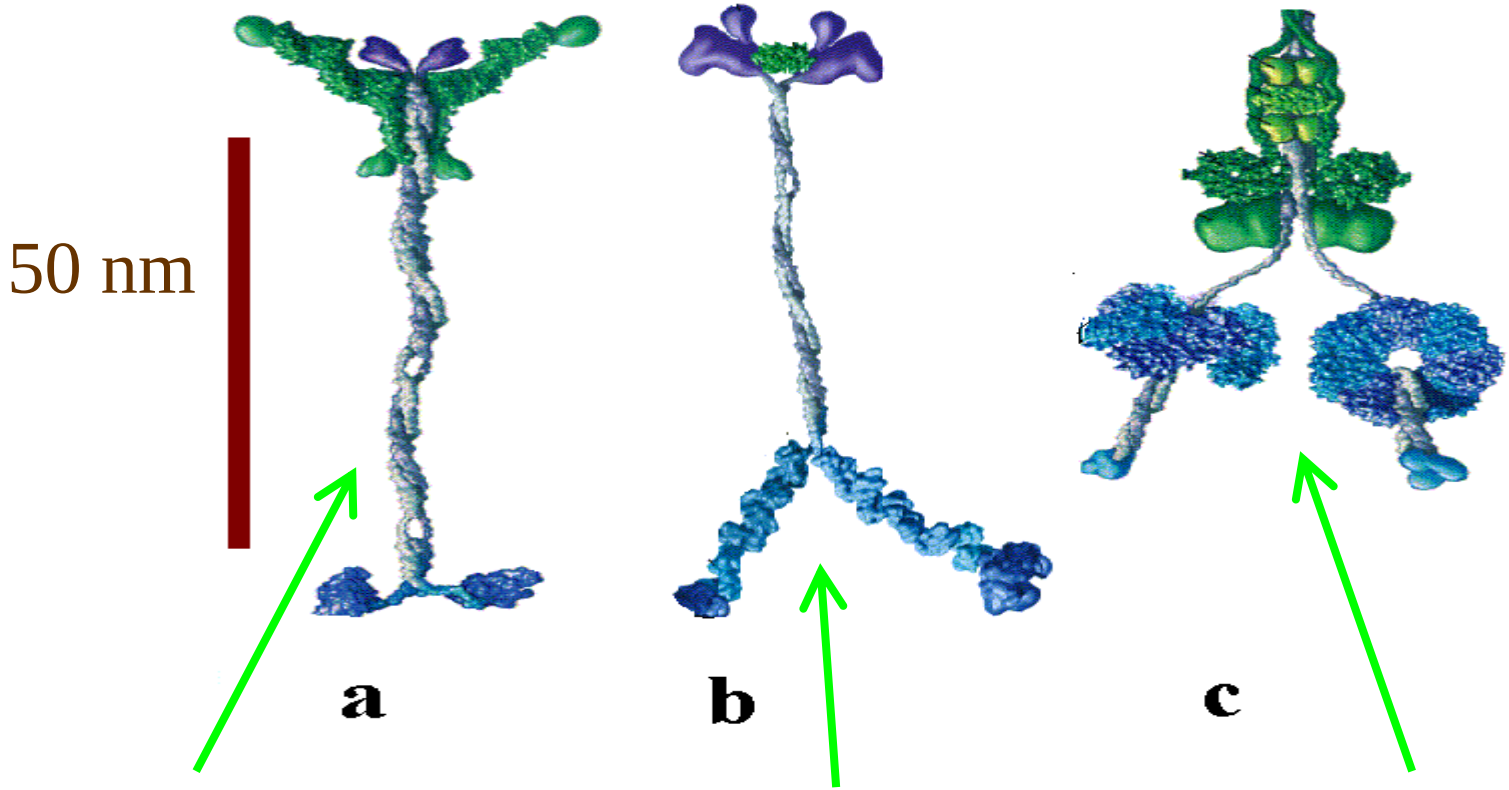
Motor Proteins

Enzymes that convert the chemical energy into mechanical work

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



Motor Proteins: Structure

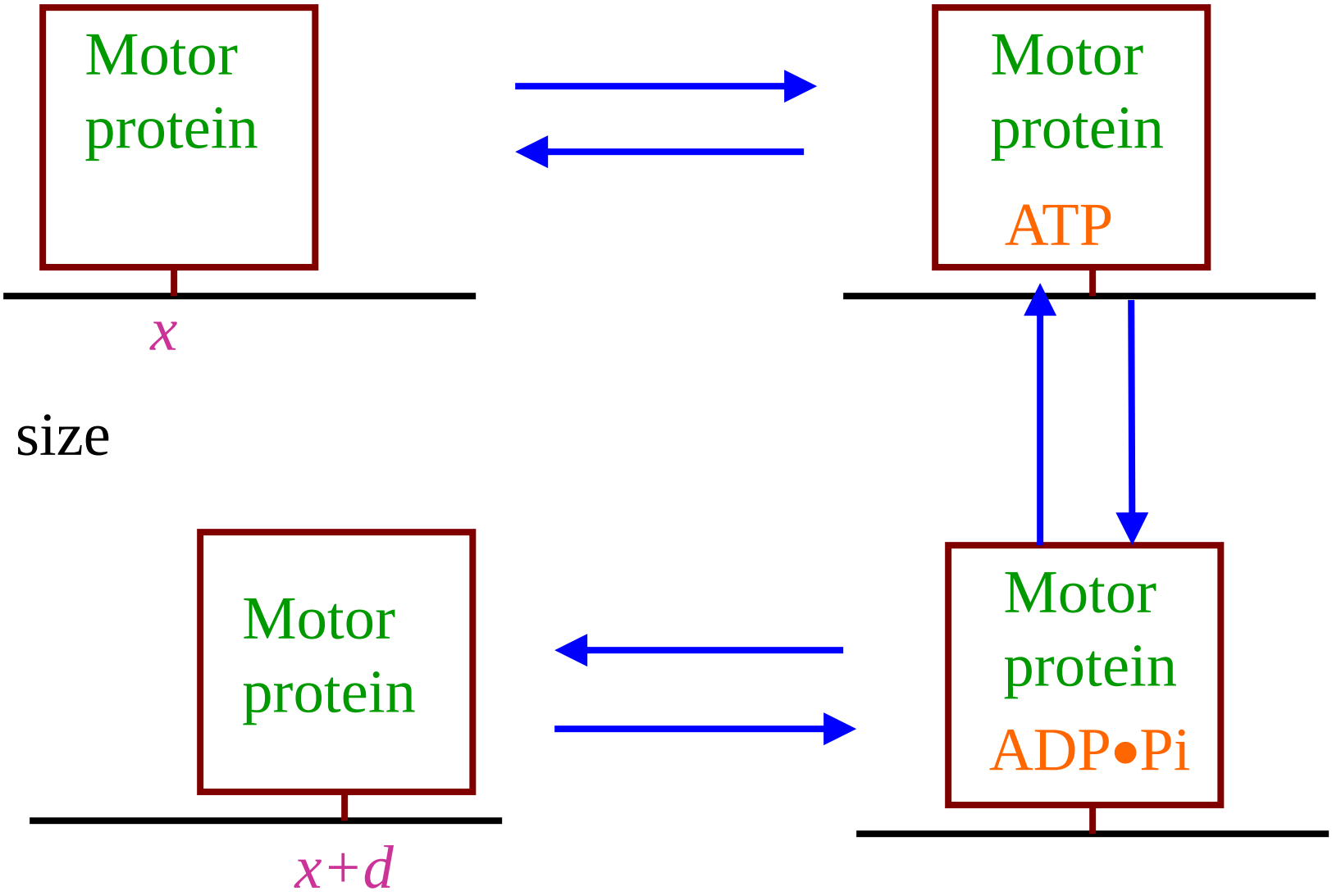


conventional kinesin

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 of DNA, RNA, protein synthesis

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

Directionality; Diversity

Motor Proteins. Properties

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

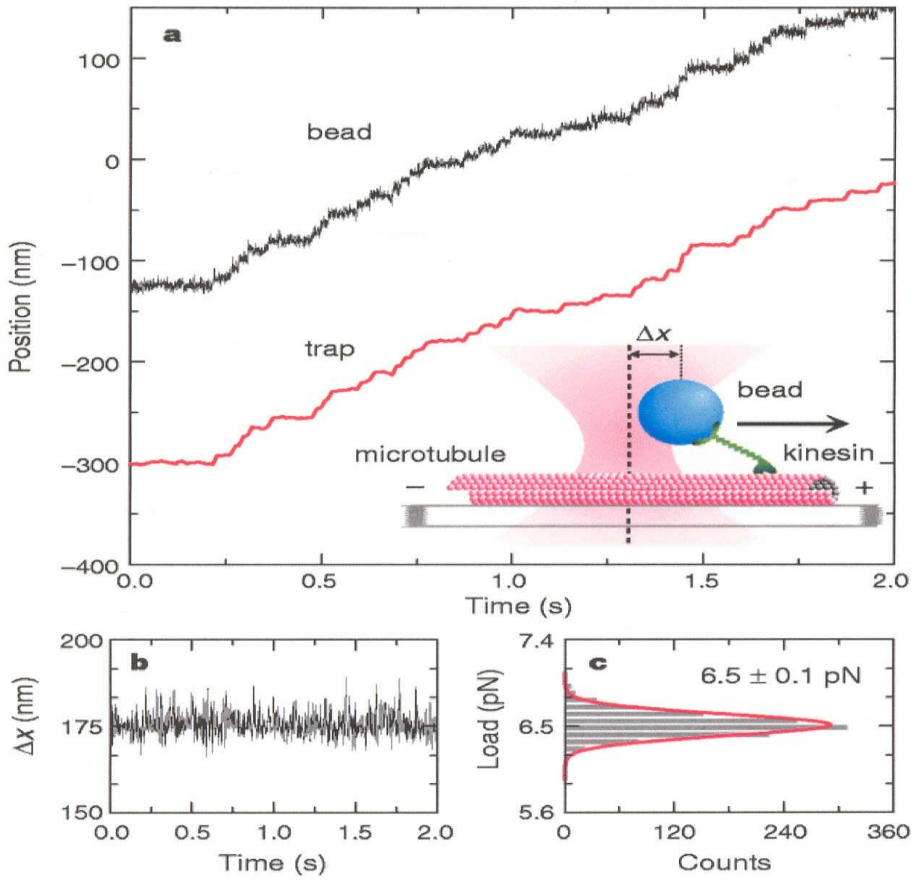
Directionality; Diversity

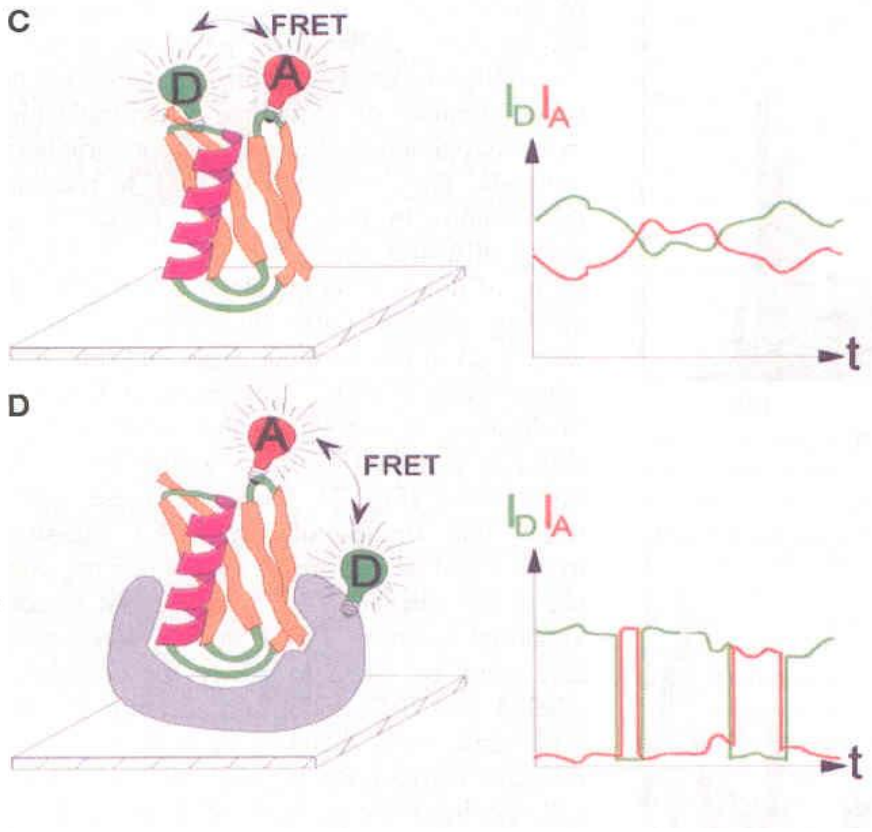
Honda Accord:

Efficiency of engine ~10%

Motor Proteins. Experiments

Single-Molecule Experiments:





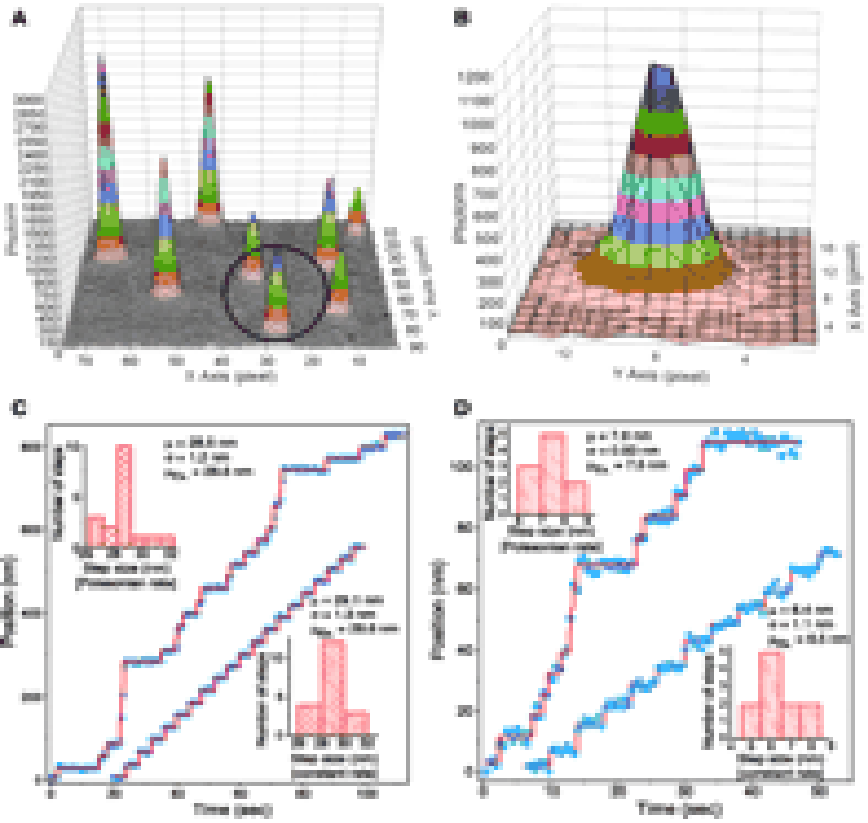
Optical-trap spectrometry

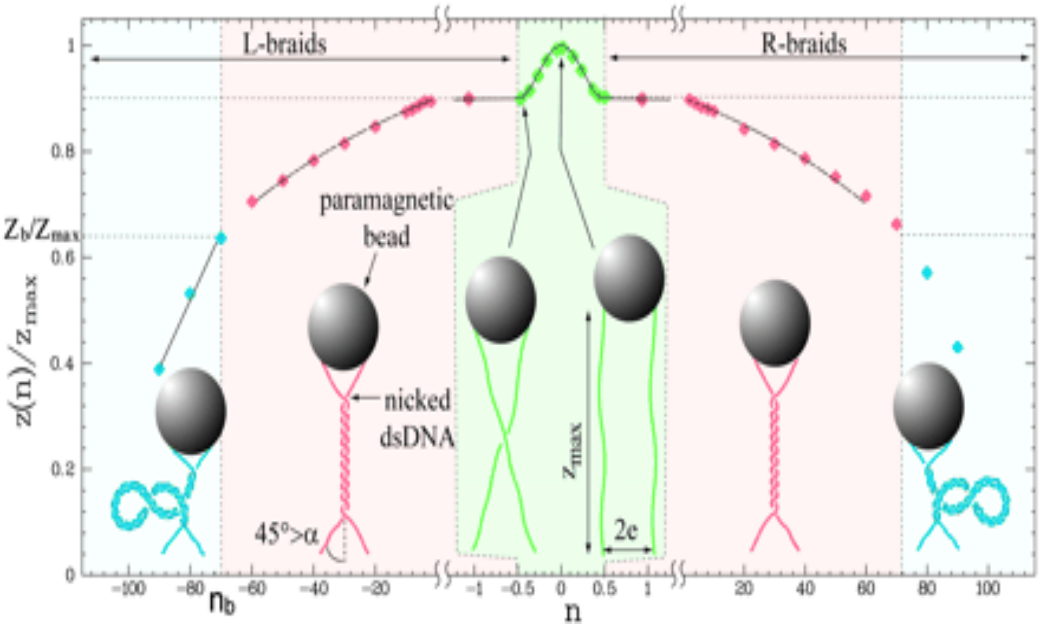
FRET – fluorescence resonance energy transfer

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

Motor Proteins. Experiments

Single-Molecule Experiments:





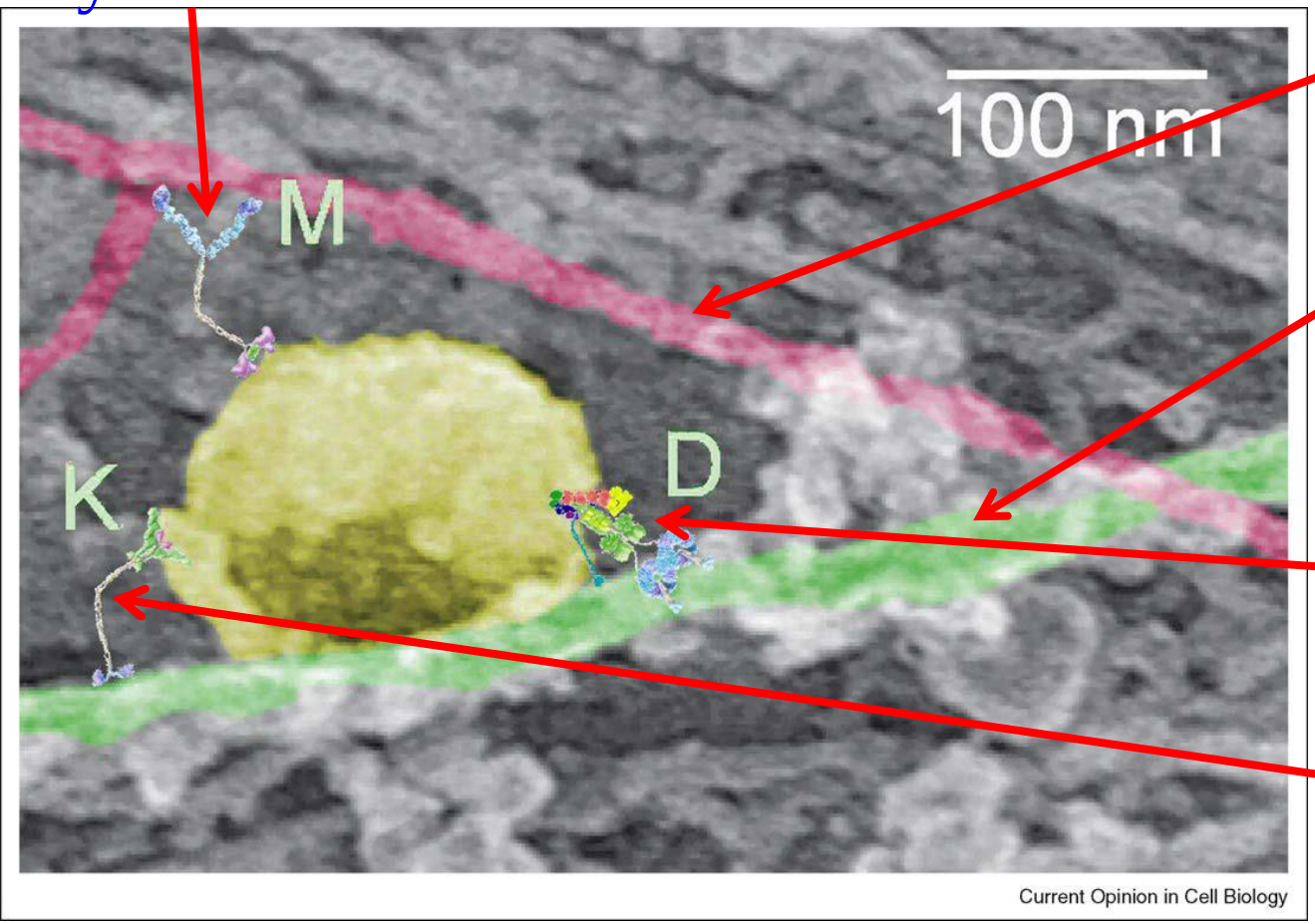
FIONA-fluorescent imaging with one-nanometer accuracy

Magnetic tweezers spectroscopy

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

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

myosin-V



actin

microtubule

dynein

kinesin

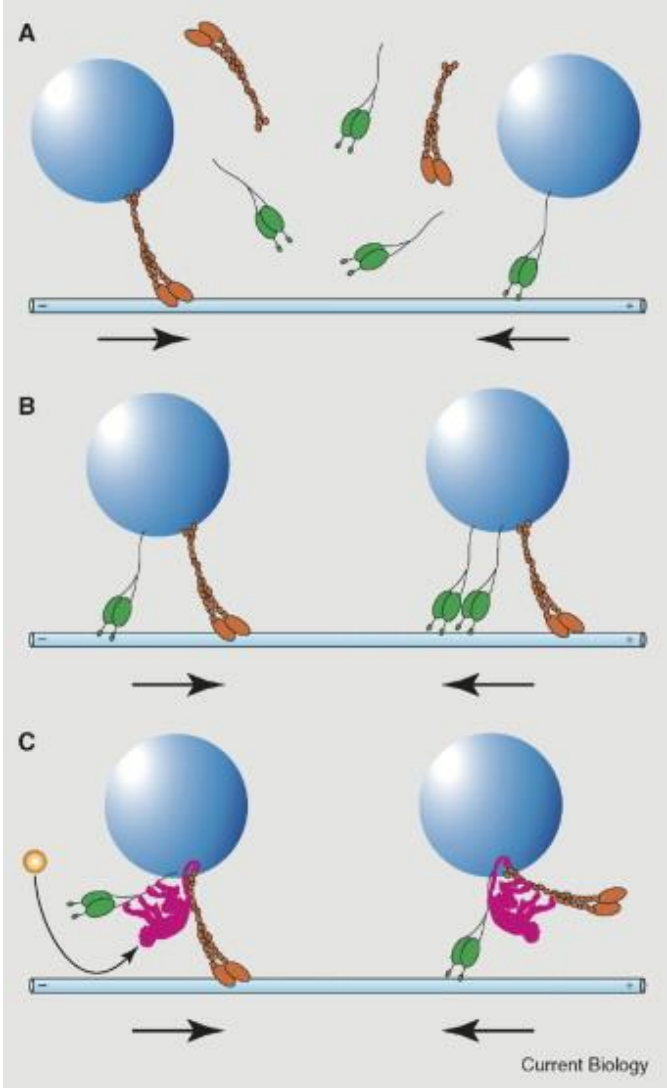
Motor proteins typically work in groups

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

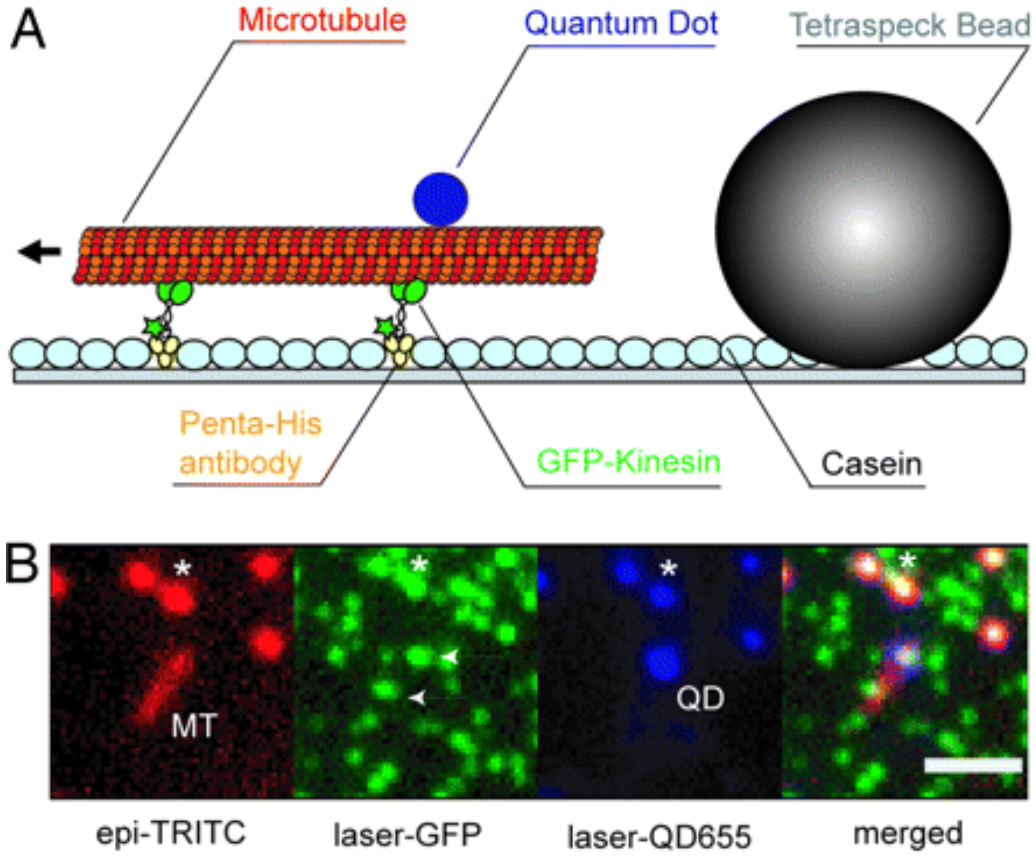
Collective Motion of Motor Proteins

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) ….



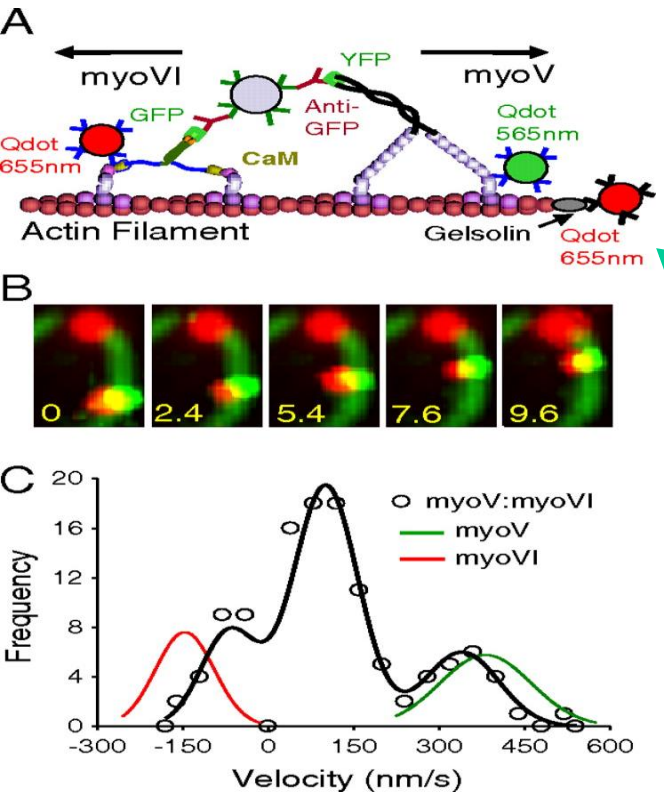
Experiments on Motor Proteins Assemblies



***In vitro* gliding motility assays**

C. Leduc et al., *PNAS* 2007, **104**, 10847-10852

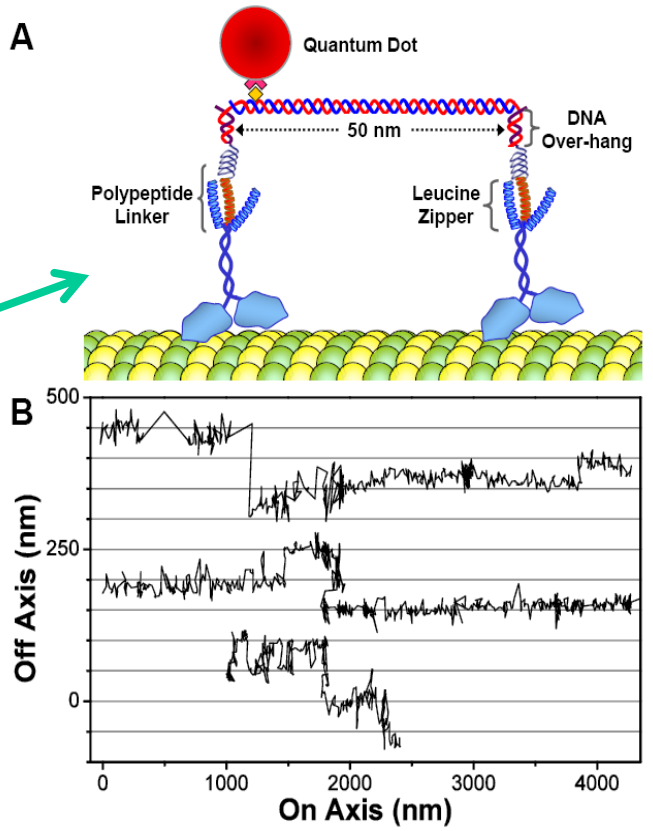
Experiments on Motor Proteins Assemblies



M.Y. Ali et al., *PNAS*, **108**, E545 (2011)

Complex of myosin V and myosin VI on actin filaments

High-quality experimental studies of dynamics of motor protein complexes

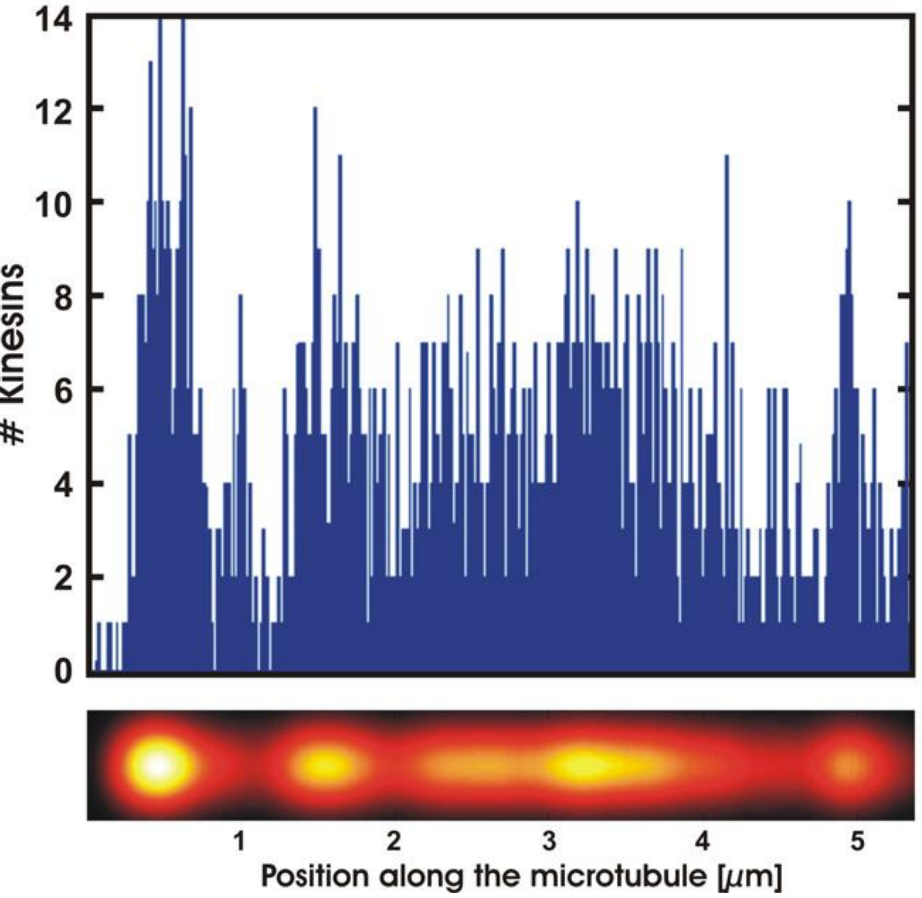


Rogers, et al., *PCCP*, **11**, 4882 (2009)

Complex of 2 coupled kinesins motors on microtubules

Intermolecular Interactions

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



Dynamic clustering of kinesin molecules on microtubules (no ATP)

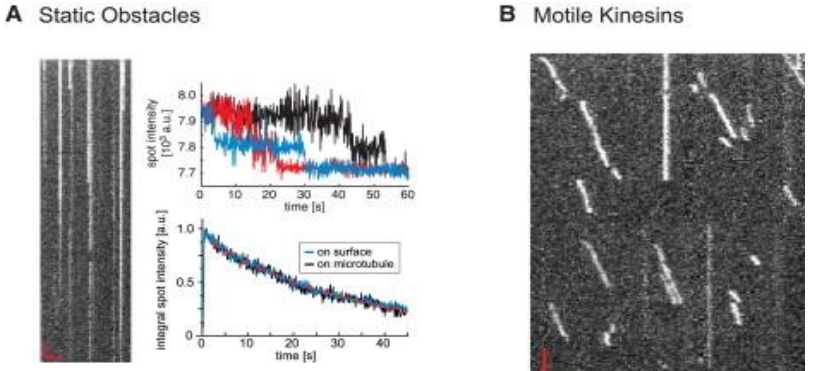
Interactions between 2 neighboring kinesin motors:

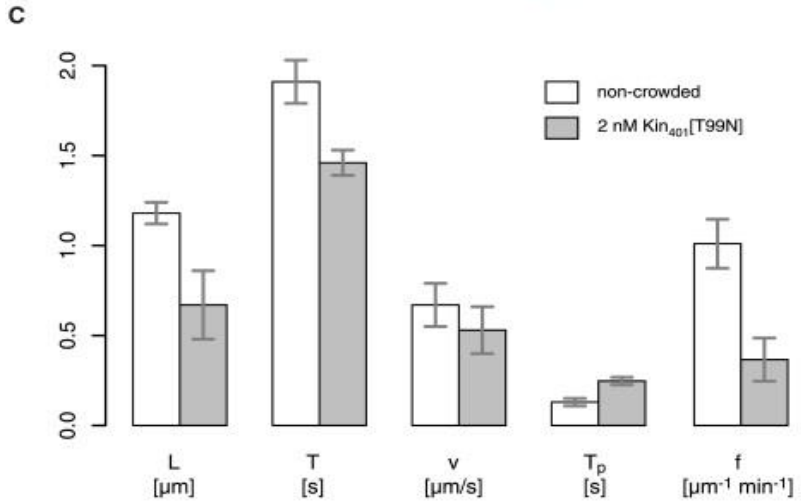
E_{int} ~1.6 k_BT – weak attraction

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

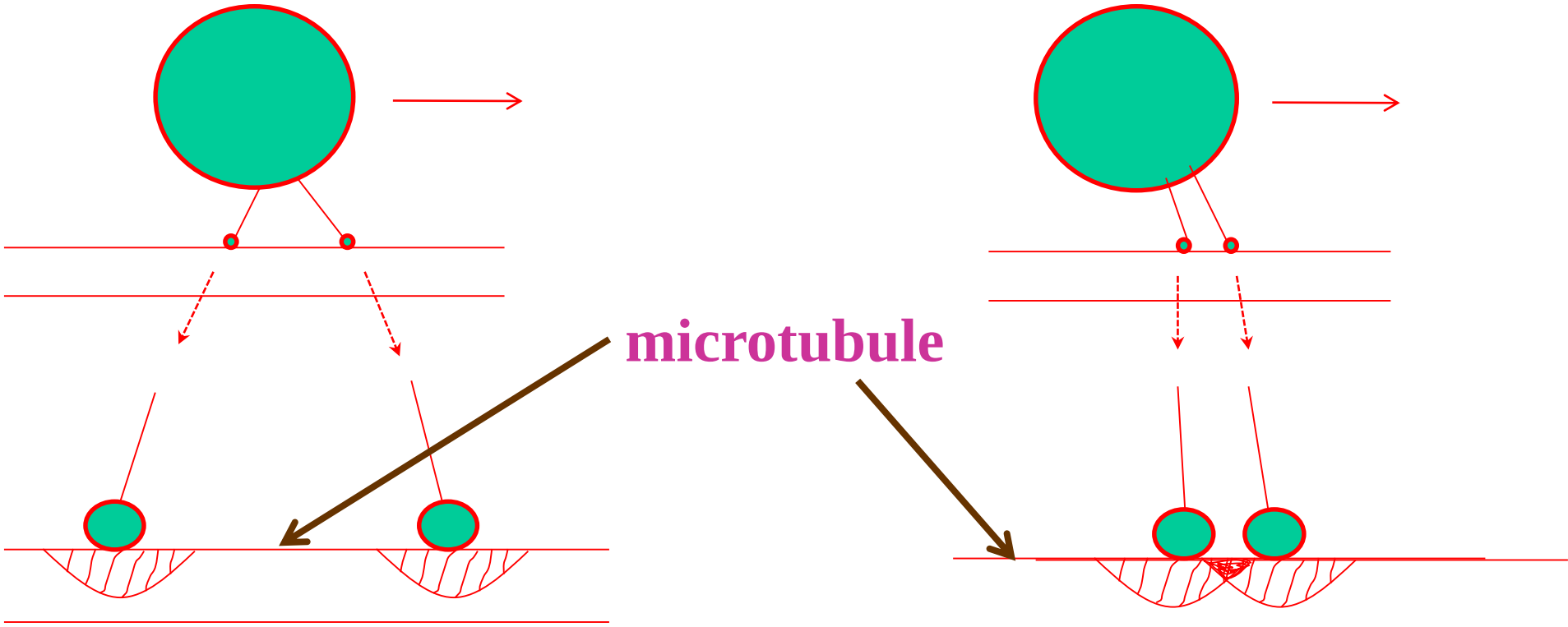
obstacle	landing (µm min)$^{-1}$	accessibility	event probability / step: detach	pause	stop
none	1.01 [0.14]	100%	0.6%	0.4%	0.04%
T99N	0.32 [0.11]	32%	1.0%	1.0%	0.18%
wt	0.34 [0.03]	34%	1.8%	0.9%	0.13%

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

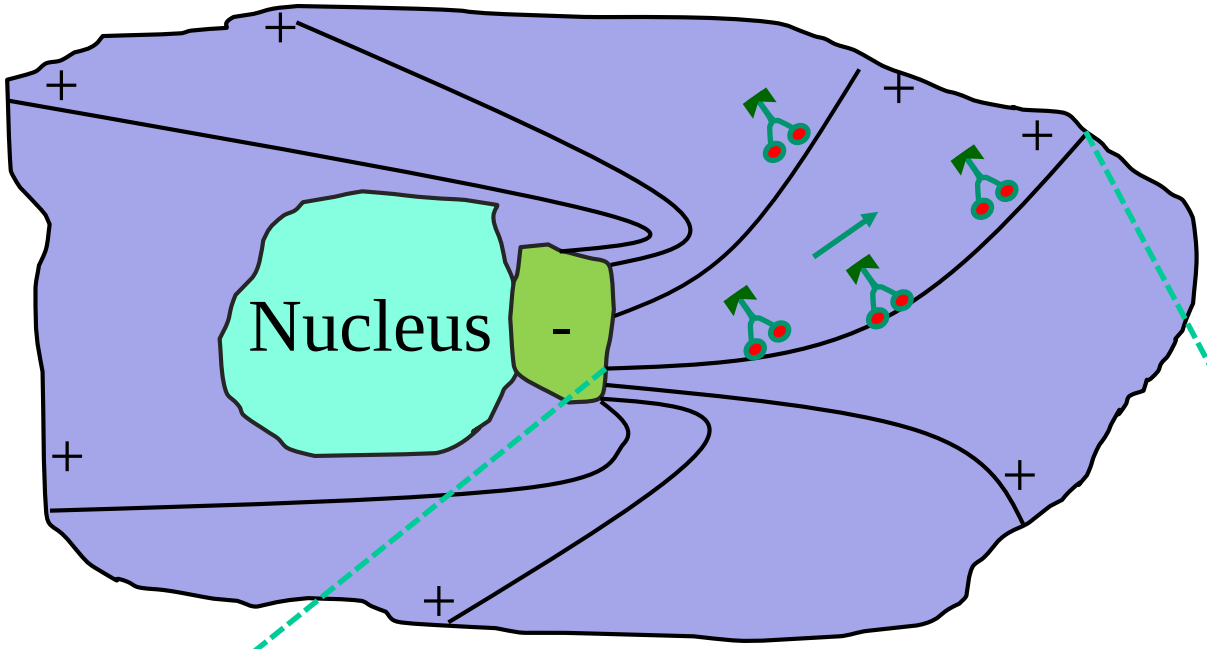
Local interactions due to the overlap of strain areas affected by microtubule-kinesin bindings

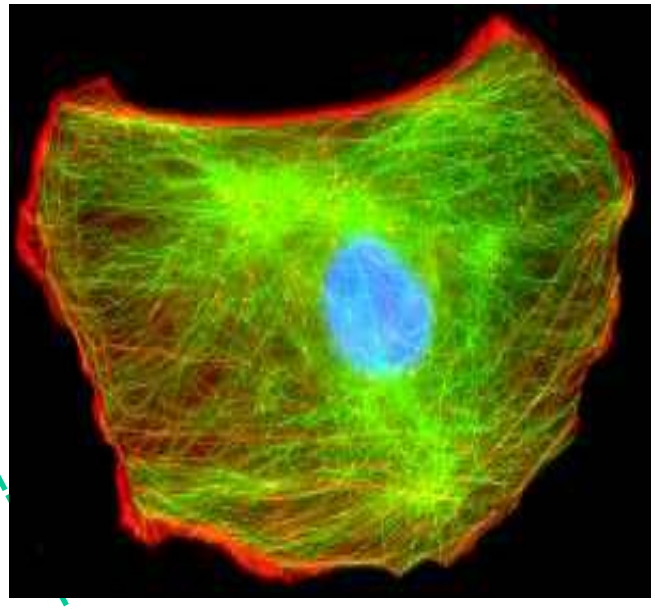
Theoretical Model

Intracellular Transport – quasi 1D

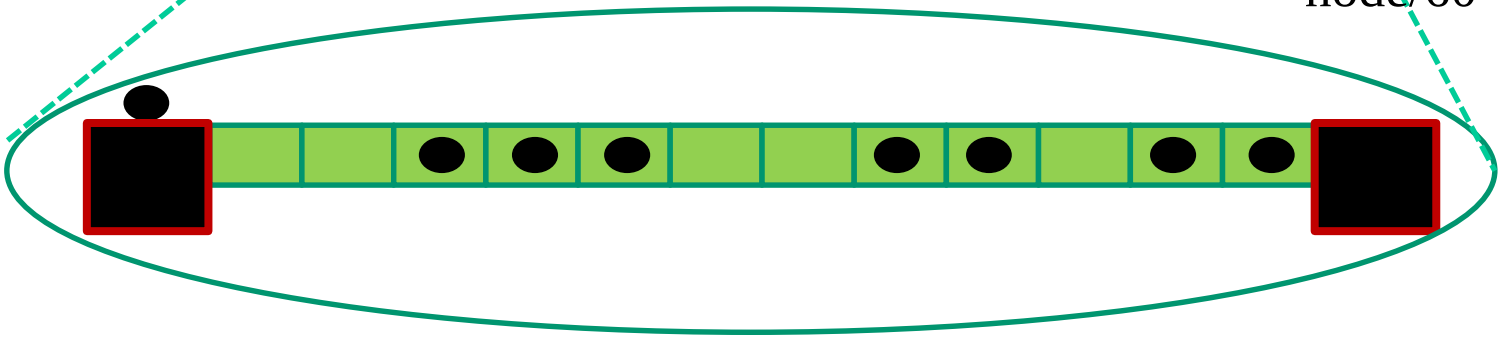
microtubule network

Eukaryotic cell





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

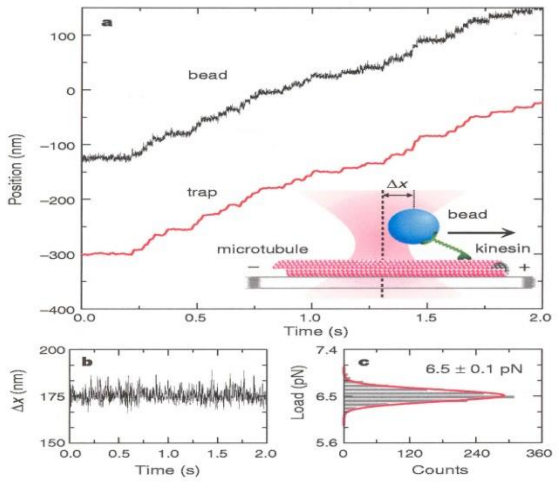


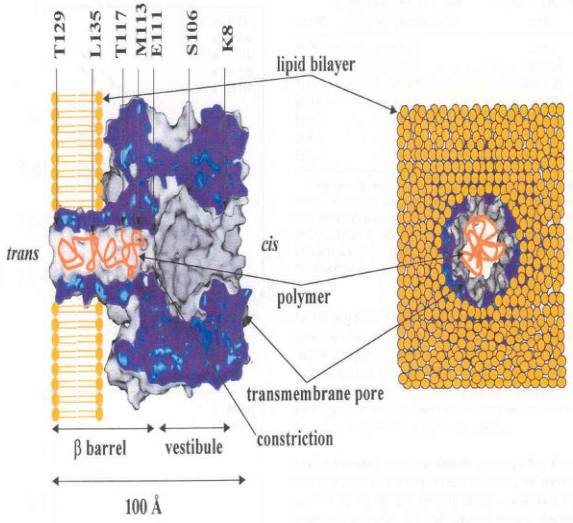
Asymmetric Simple Exclusion Processes

Applications:

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

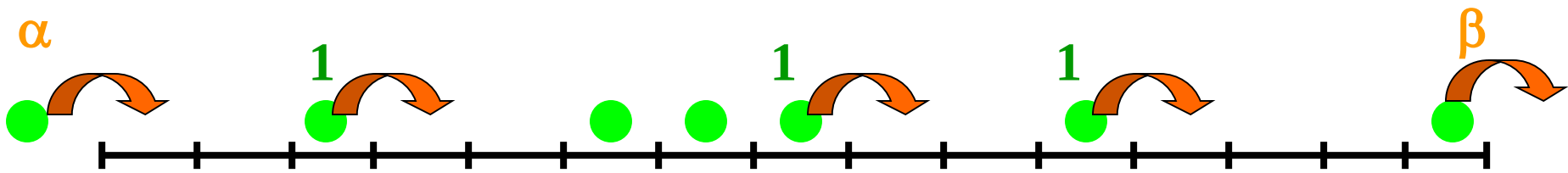
Biological transport, polymerization, protein synthesis	Gel electrophoresis, traffic problems, animal behavior, interface growth	Diffusion through biological channels, polymer dynamics





Asymmetric Simple Exclusion Processes

1D Lattice Gas Models with Hard-Core Exclusions

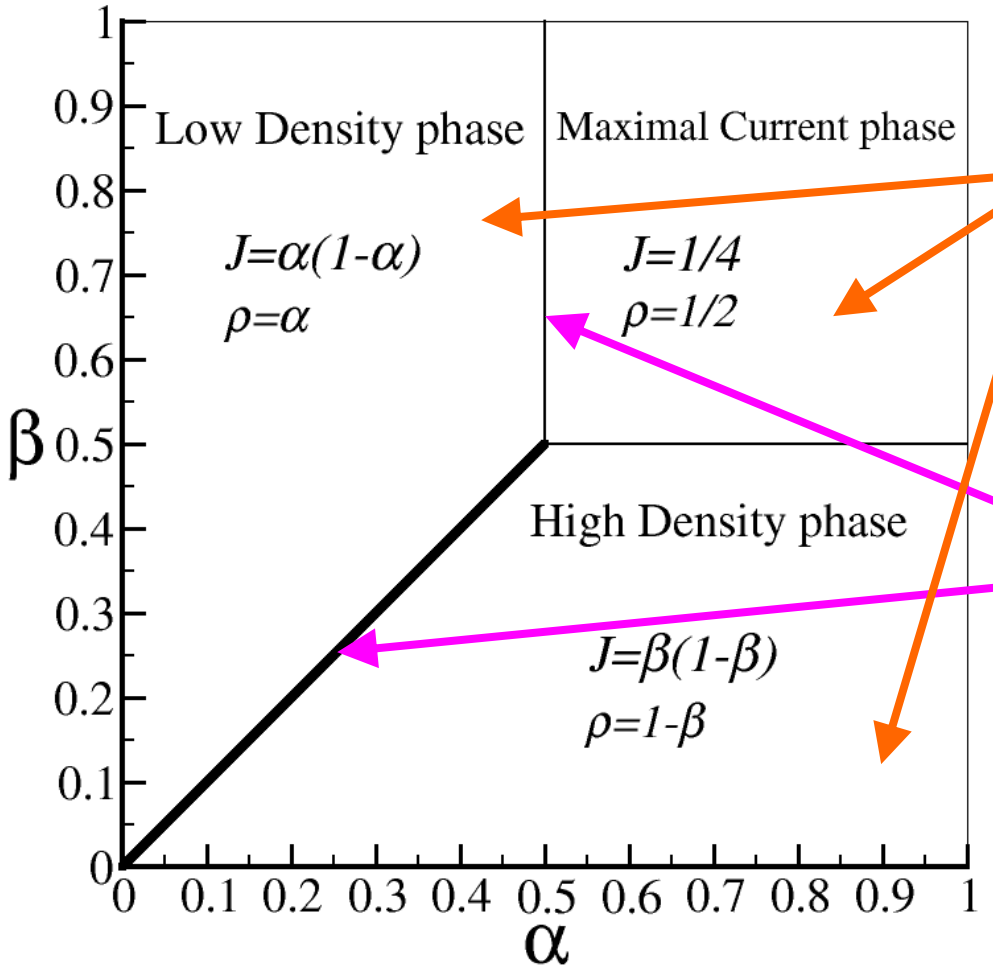


The simplest model: **Totally Asymmetric Simple Exclusion Process (TASEP)**

- 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 $0 \le \beta \le 1$

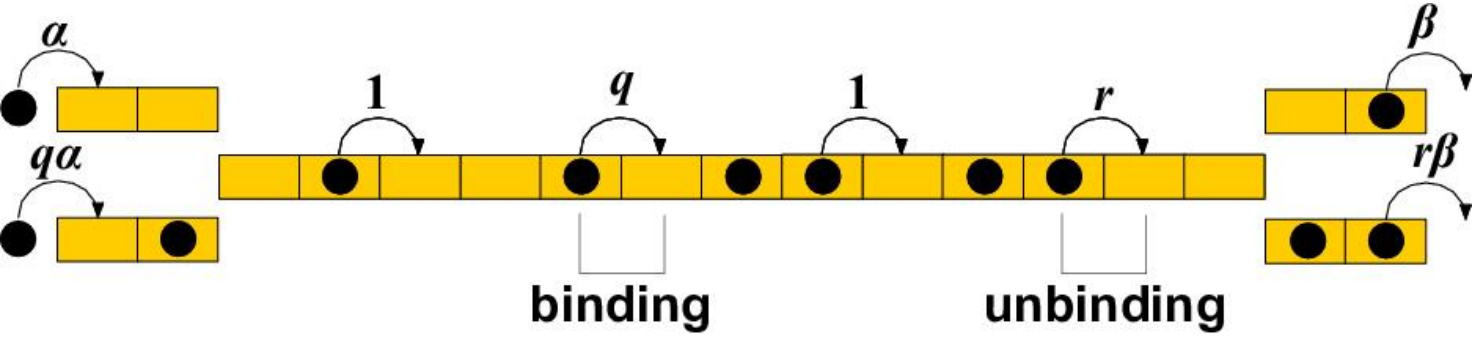
Exact Solutions of TASEP

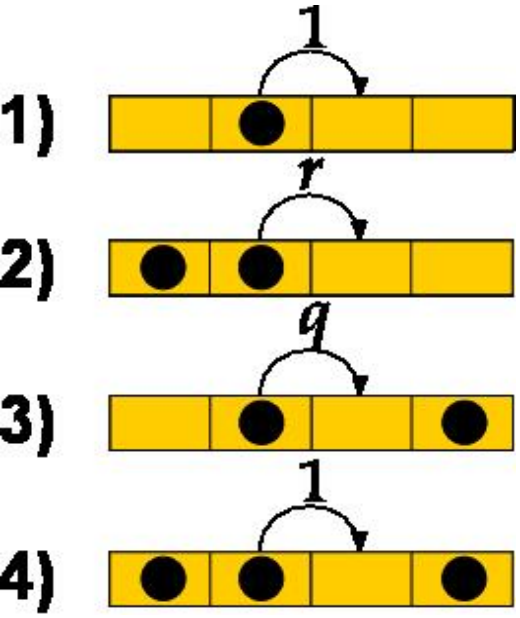
Derrida *et al.*, *J. Phys. A: Math Gen.* **26** 1493 (1993), G. Schutz et al., *J. Stat. Phys*. (1992)



- **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

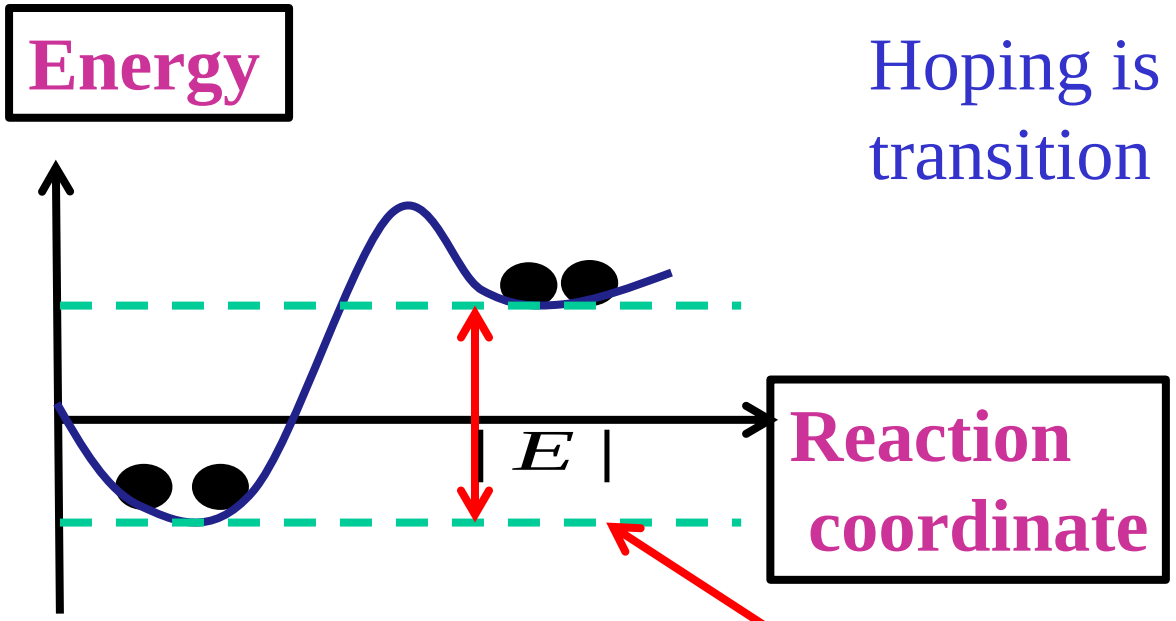
Our Model: TASEP with Interactions



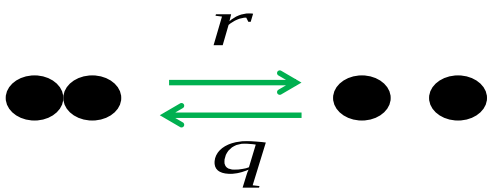


1) Transport of motor proteins is viewed as a motion of multiple particles on a lattice;
2) Short-range interactions between neighboring motor proteins in addition to exclusion
3) Thermodynamically consistent rates of transitions

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

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

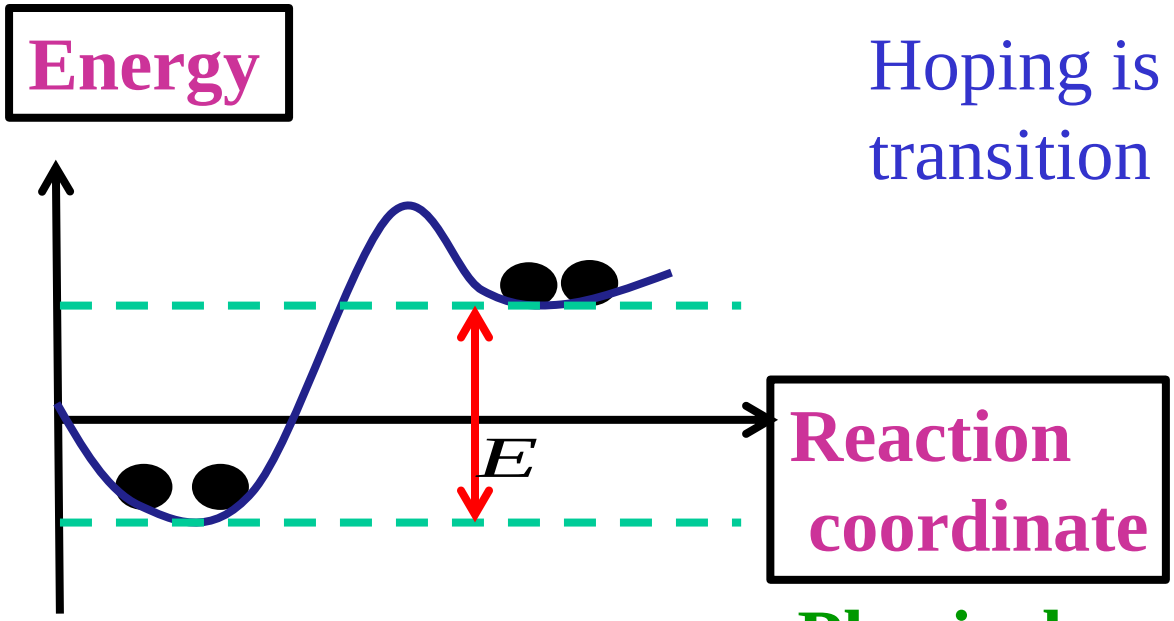
E>0 **Attraction**

E<0 **Repulsion**

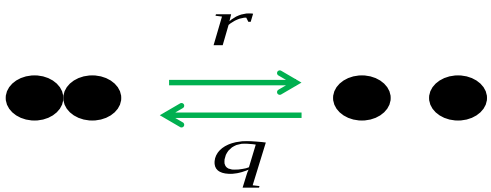
$E=0$, $q=r=1$ normal TASEP

$0<\theta<1$- 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)

'Everything should be made as simple as it can be, but not simpler!' (ascribed to) A. Einstein

SMF approach neglects all correlations in the system

Occupation number

$$\tau_i = \begin{cases} 1 \\ 0 \end{cases}$$

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

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

SMF is successful for describing TASEP without interactions

Methods: Simple Mean Field (SMF)

Occupation number

$$\tau_i = \begin{cases} 1 & \bullet \\ 0 & \square \end{cases}$$

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

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

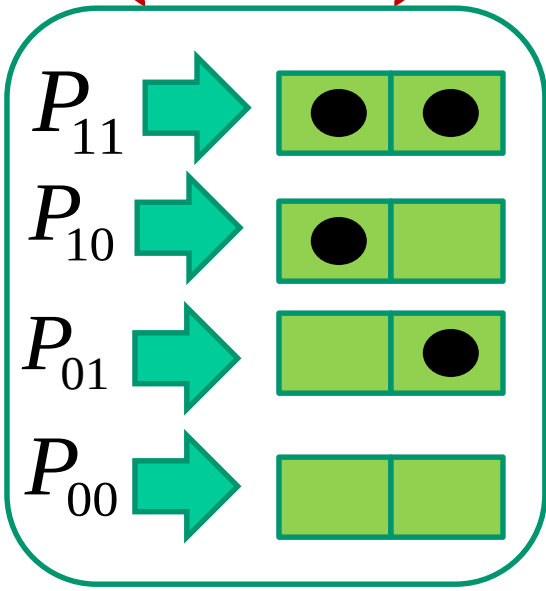
All properties can be calculated analytically, but there are problems:

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

Flux in the maximal-current phase at very large attractions or repulsions is diverging – **unphysical!** Zero or finite currents are expected!!!

Methods: 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: Cluster mean field (CMF)

$$\frac{dP_{01}}{dt} = P_{10}[P_{10}P_{01} + P_{00}^2 + P_{00}P_{01} + P_{00}P_{10}] + rP_{10}[P_{11}P_{00} + P_{01}^2 + P_{00}P_{01} + P_{01}P_{11}]$$
$$+P_{10}[P_{10}P_{11} + P_{11}^2 + P_{11}P_{01} + P_{01}P_{10}] + qP_{10}[P_{00}P_{10} + P_{10}^2 + P_{11}P_{10} + P_{00}P_{11}]$$
$$-P_{01}[qP_{00}P_{01} + P_{00}^2 + P_{00}P_{10} + qP_{10}P_{01} + P_{00}P_{01} + qP_{01}^2 + P_{00}P_{11} + qP_{11}P_{01}]$$
$$-P_{01}[qP_{11}P_{01} + P_{11}^2 + P_{11}P_{10} + qP_{10}P_{01} + qP_{01}^2 + P_{00}P_{11} + P_{11}P_{01} + qP_{00}P_{01}]$$

1) Mathematically very involved method which allows only numerical solutions!
2) Not a very good agreement with computer simulations;
3) Not practical for extending to more realistic situations (more complex models) for partially-asymmetric models and for coupling with Langmuir kinetics

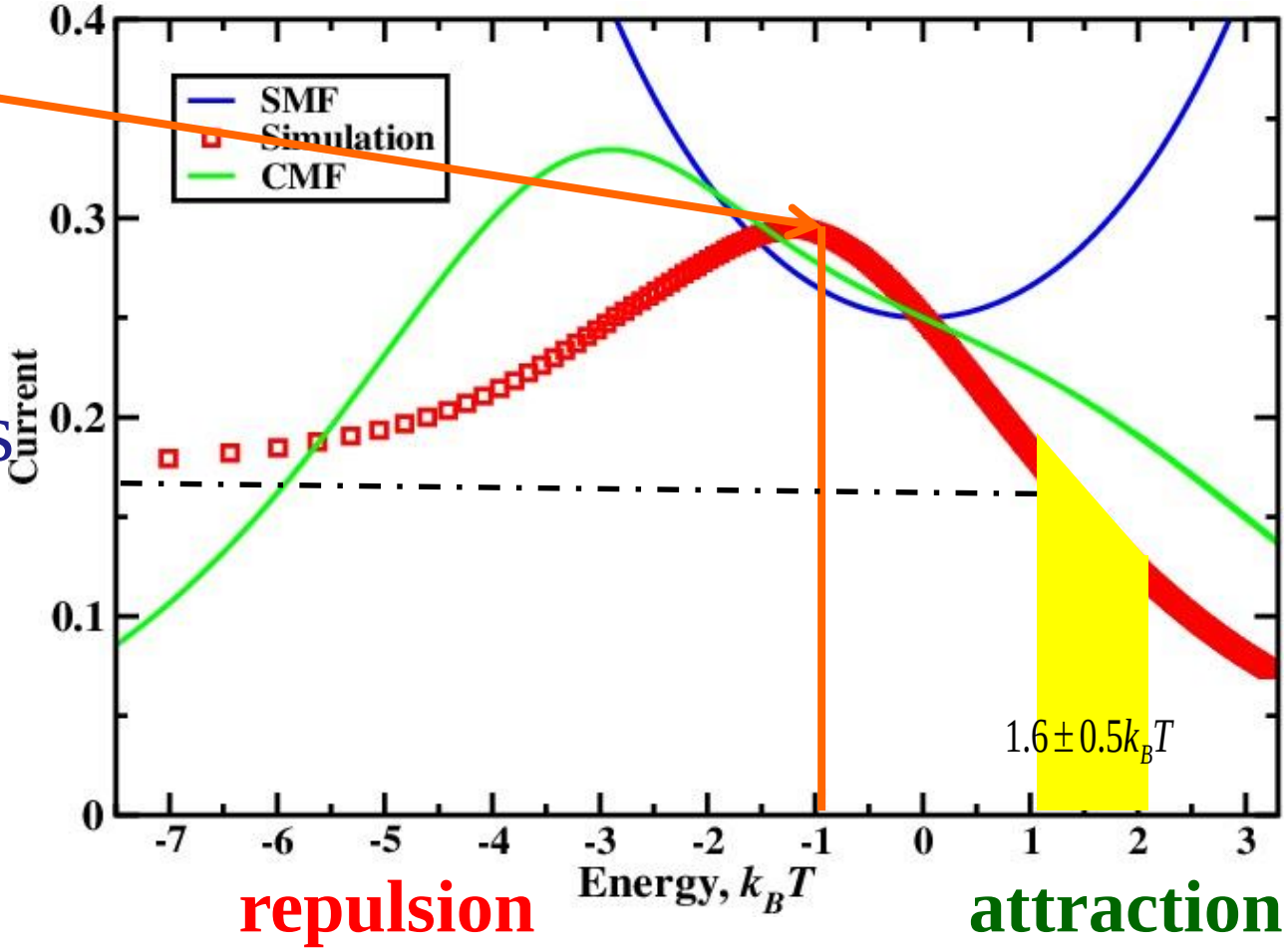
Results: Current Versus Energy

SMF theory is unphysical

Weak repulsion lead to maximal current

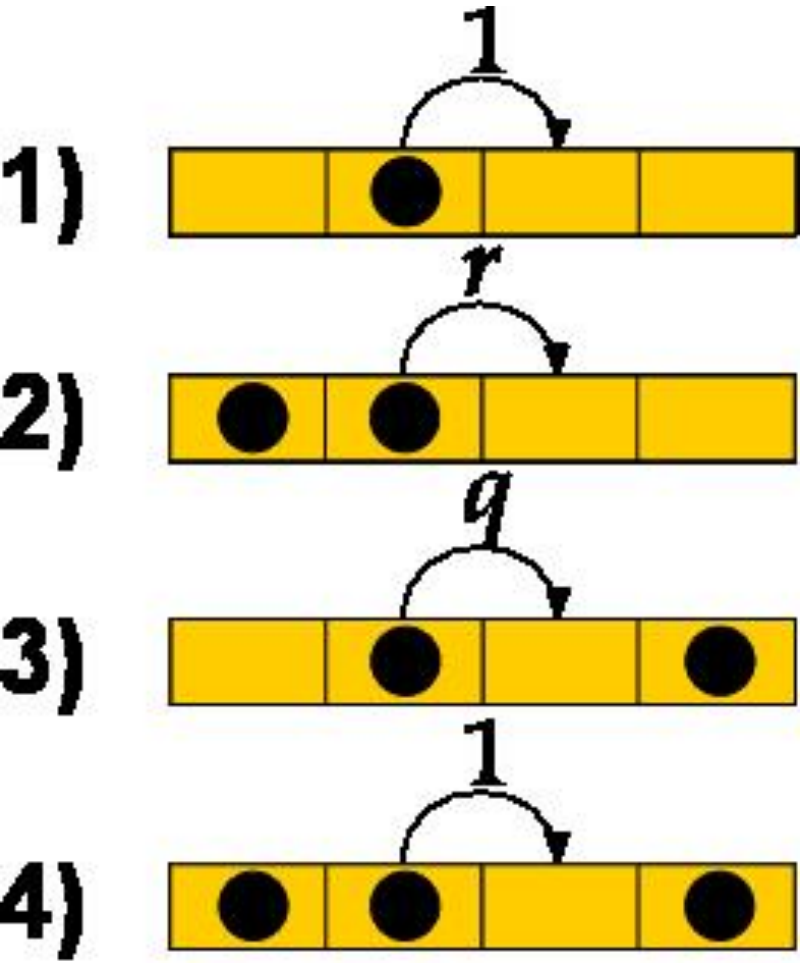
Effect of interactions on particle dynamics is not symmetric

CMF – only qualitative agreement



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

Methods: Modified Cluster Mean-Field (MCMF)



$J=J_1+J_2+J_3+J_4$ ← Total flux through the system

$$J_1 = \gamma P_{10}\left(\frac{P_{00}}{P_{01}+P_{00}}\right)$$

$$\gamma = \frac{1}{1+e^{\beta E}}$$

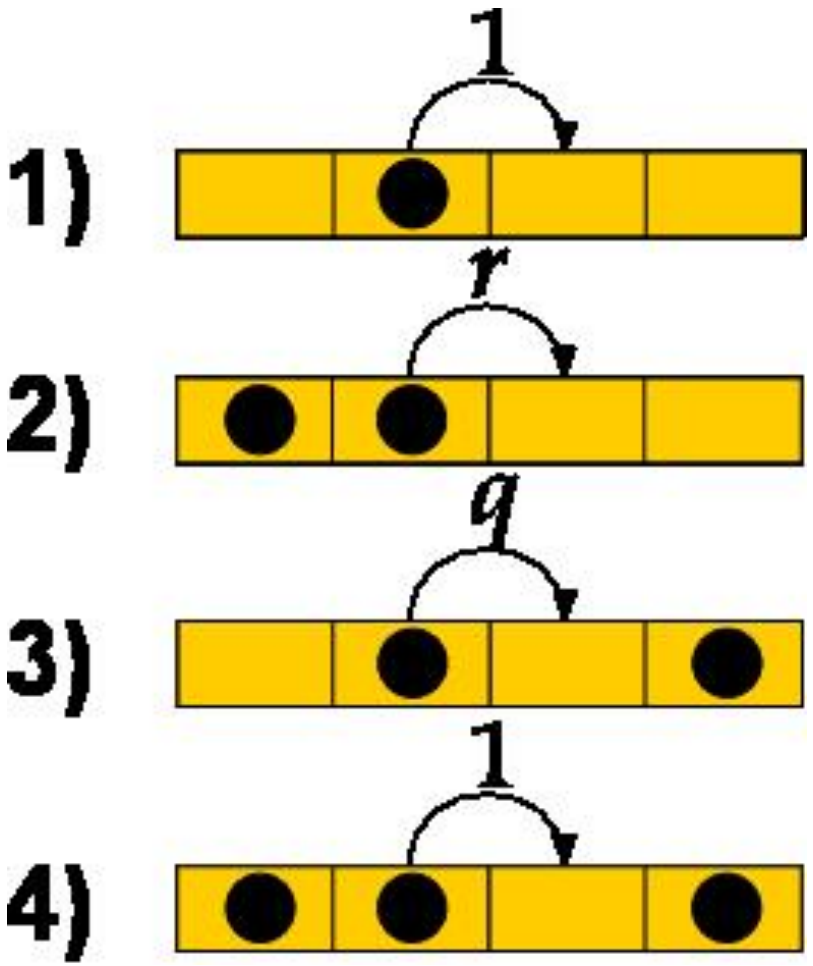
Probability to have the first site empty – Boltzmann's factor

P_{10}-probability to have the configuration (1,0) in the middle

$\left(\frac{P_{00}}{P_{01}+P_{00}}\right)$ Probability to have the last site empty given that there is a configuration (1,0) before

Methods: Modified Cluster Mean-Field (MCMF)

$J=J_1+J_2+J_3+J_4$ ← Total flux through the system



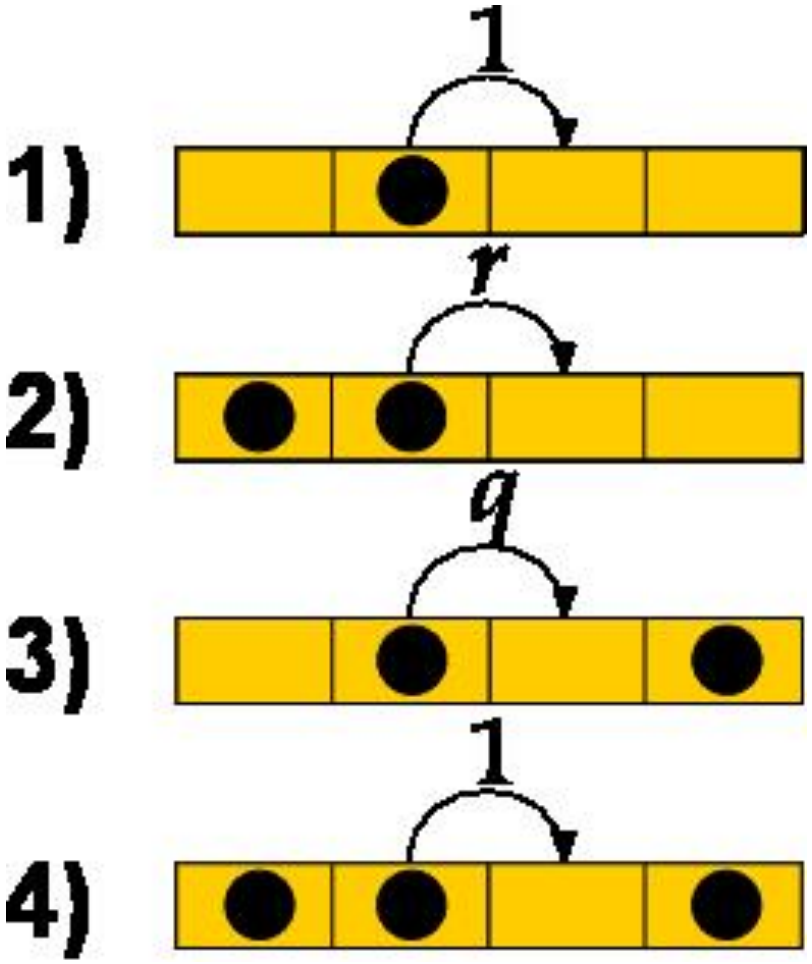
$$J_1 = \gamma P_{10}\left(\frac{P_{00}}{P_{01}+P_{00}}\right)$$

$$J_2 = (1-\gamma) r P_{10}\left(\frac{P_{00}}{P_{01}+P_{00}}\right)$$

$$J_3 = \gamma q P_{10}\left(\frac{P_{01}}{P_{01}+P_{00}}\right)$$

$$J_4 = (1-\gamma) P_{10}\left(\frac{P_{01}}{P_{01}+P_{00}}\right)$$

Methods: Modified Cluster Mean-Field (MCMF)



Additional approximation:

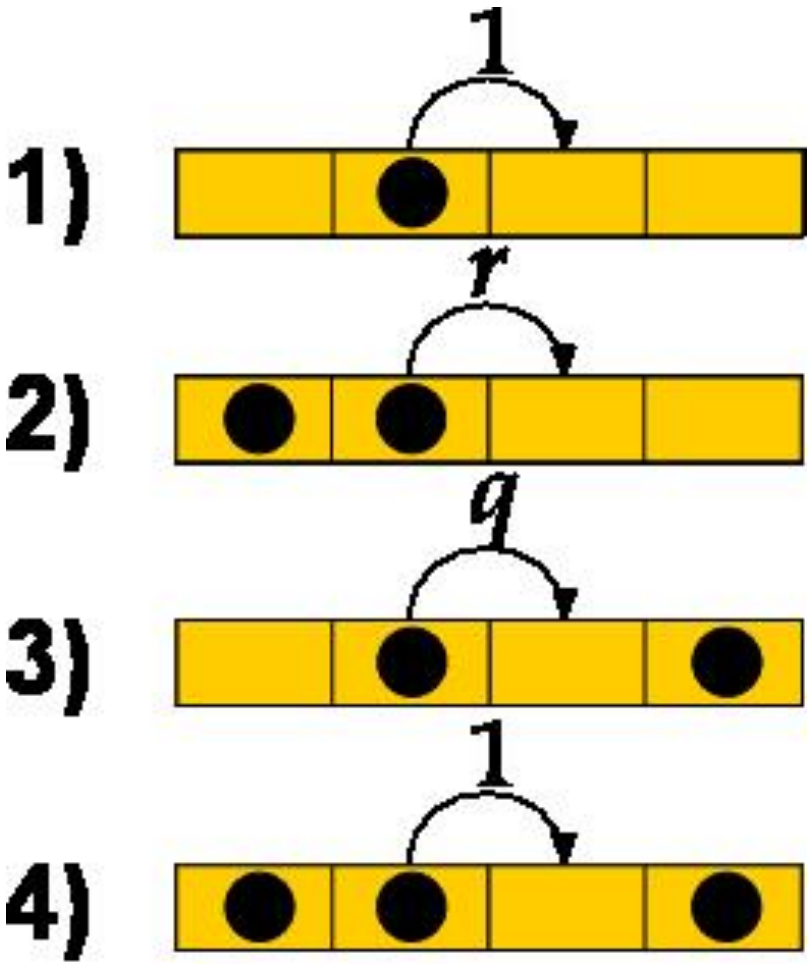
$$P_{10} = \frac{\rho(1-\rho)}{1-\rho+\rho e^{\beta E}}$$

Physical meaning:

ρ is the probability to have the first site occupied

$\frac{(1-\rho)}{1-\rho+\rho e^{\beta E}}$ - probability that the second site is empty given that the first one is not

Methods: Modified Cluster Mean-Field (MCMF)

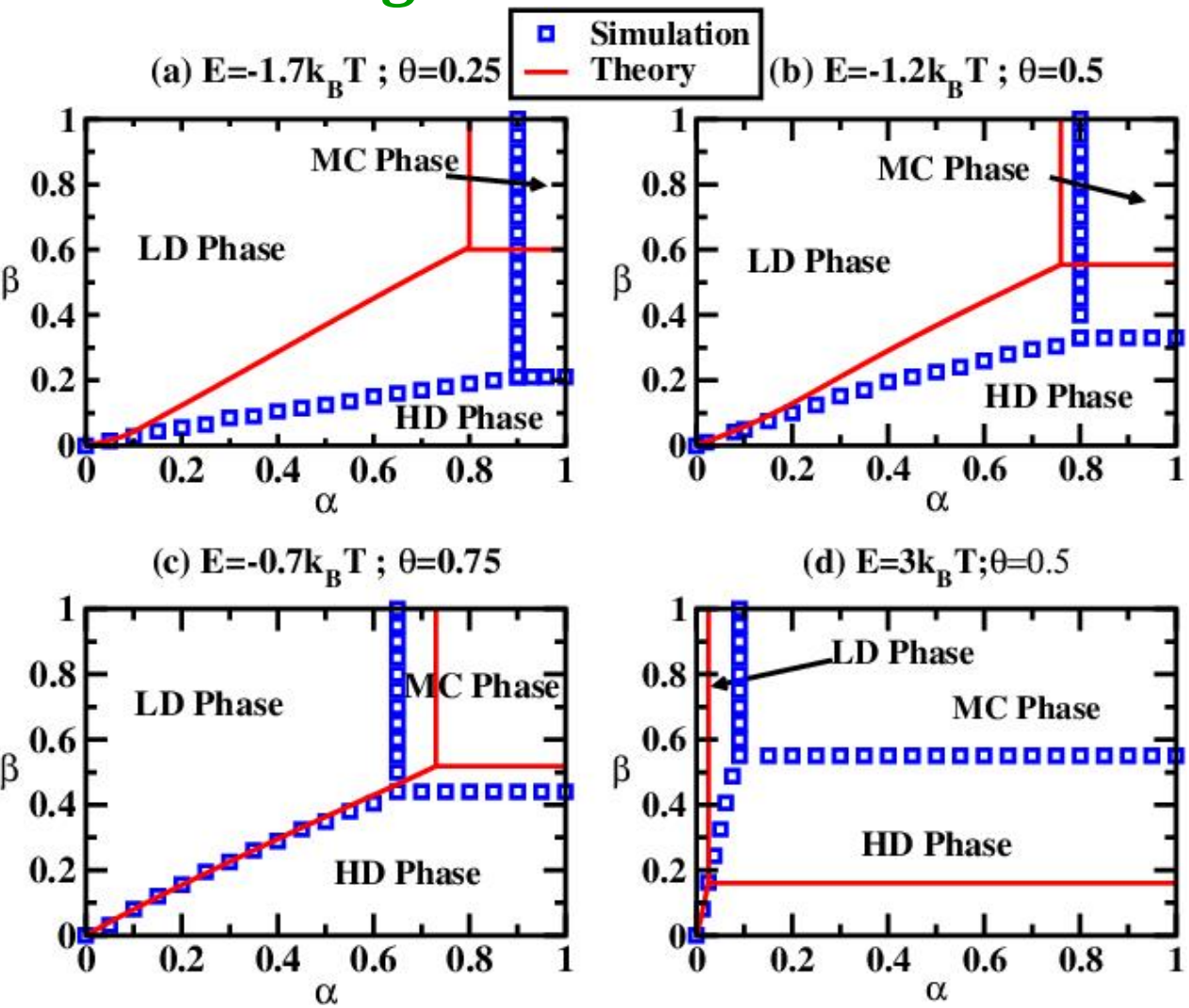


1) Our approach takes into account correlations (nearest-neighbor);
2) All results are analytical;
3) Correct predictions in limiting cases;
4) Can be easily extended to more complex systems

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

Results:

Phase diagrams:

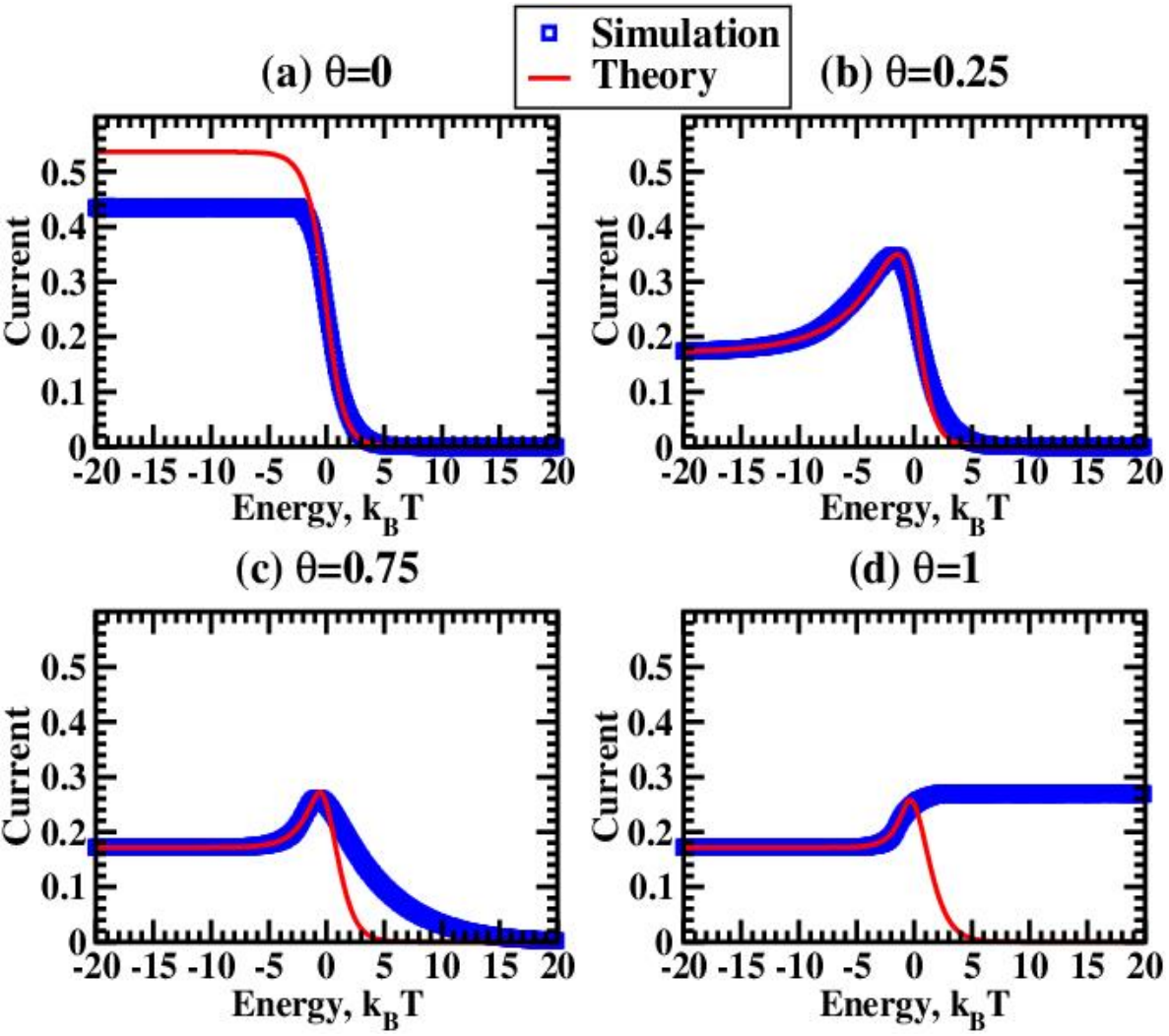


1) Similarly to TASEP without interactions 3 steady-state phases are observed: MC, HD and LD
2) Theoretical predictions agree semi-quantitatively

LD phase dominates for repulsions, HD phase dominates for attractions

Results:

Maximal particle fluxes:



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

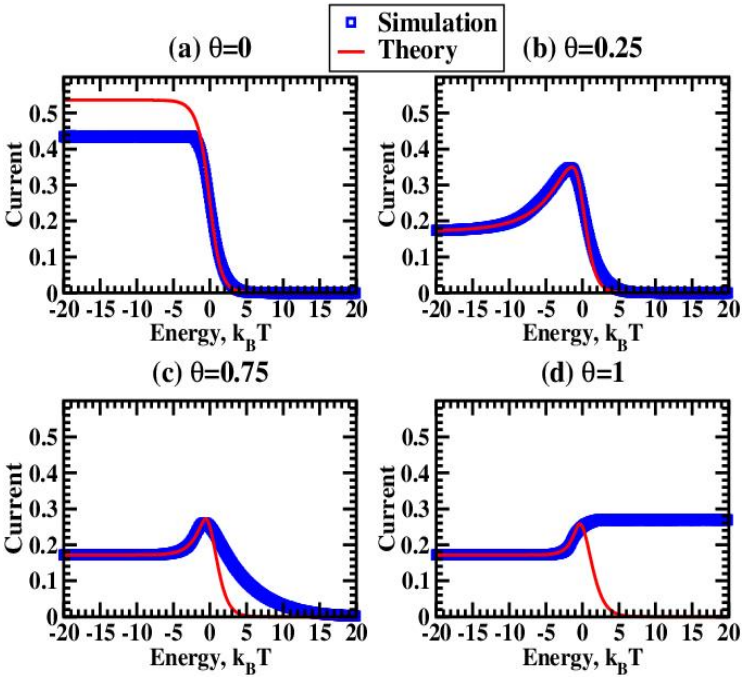
Correlations are important!

Results:

To understand dynamics we introduce a correlation function C:

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

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

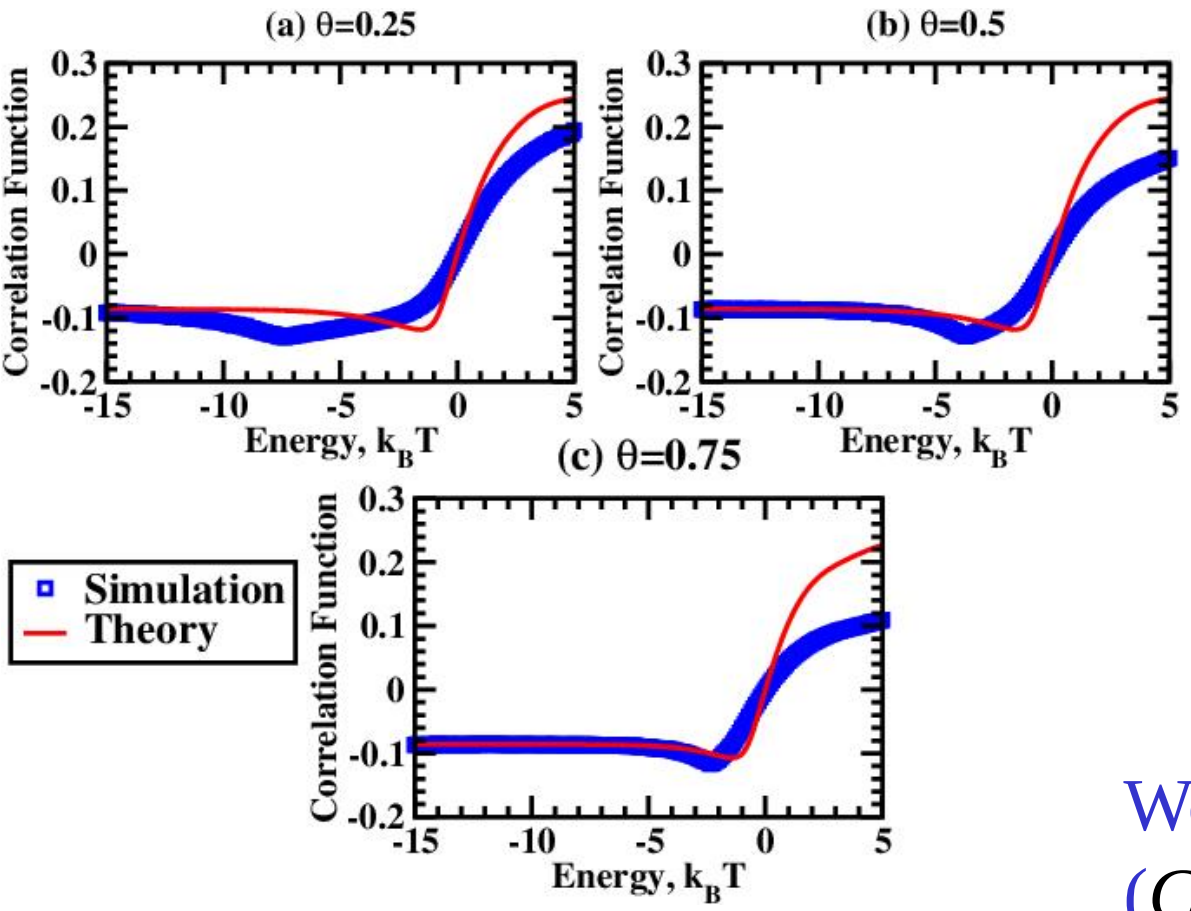


Physical meaning of C- how the presence of particle at the site i affects the occupation at the site $i+1$.

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

Results:

Correlation function



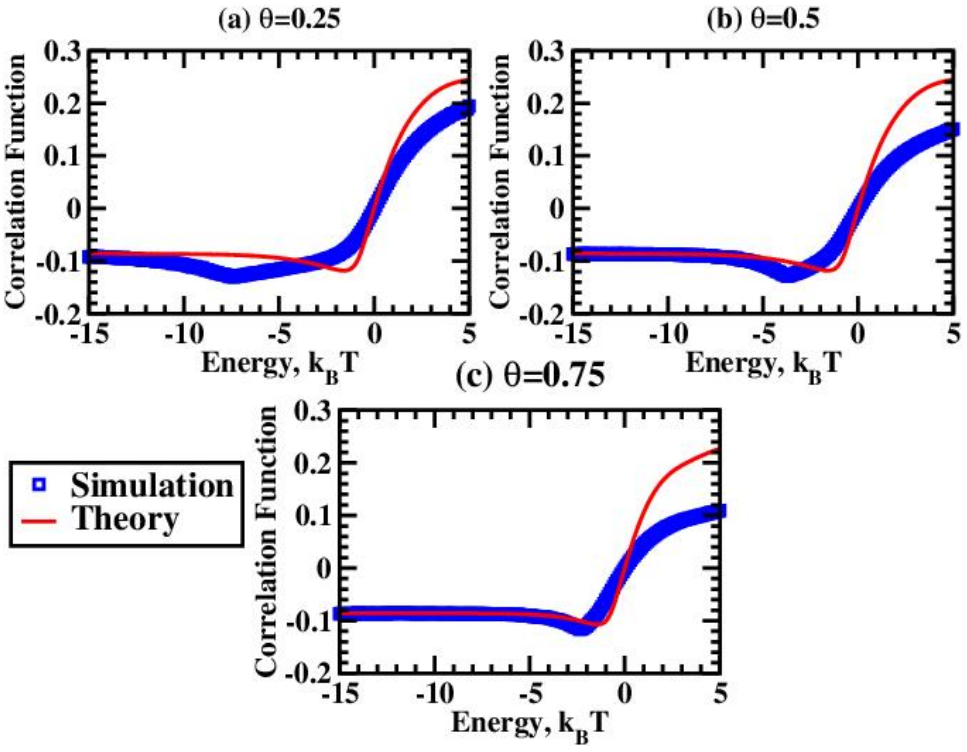
Physical meaning of C- how the presence of particle at the site i affects the occupation at the site i+1.

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

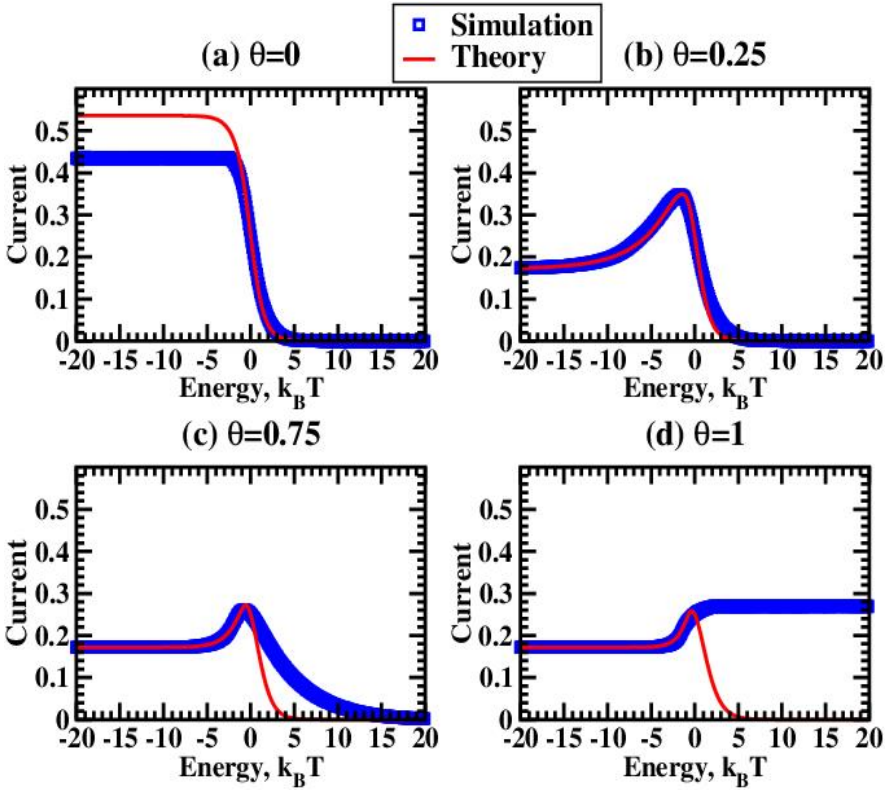
$$C(E) = \frac{\rho^2(1-\rho)[e^{\beta E}-1]}{1+\rho[e^{\beta E}-1]}$$

Results:

Correlation function

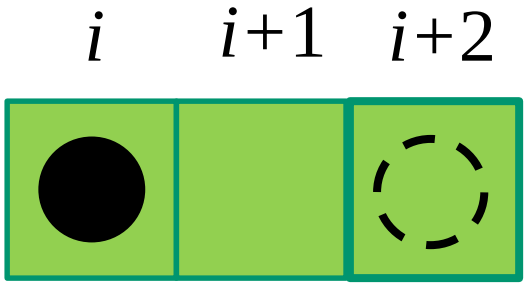


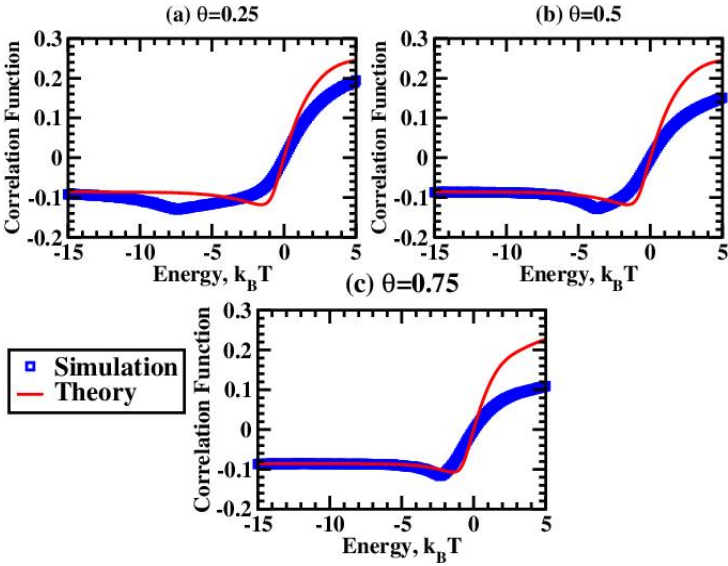
Maximal particle fluxes:



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

Results:

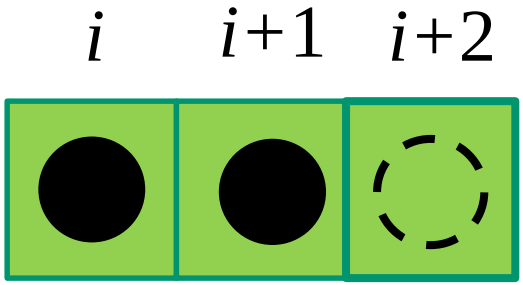


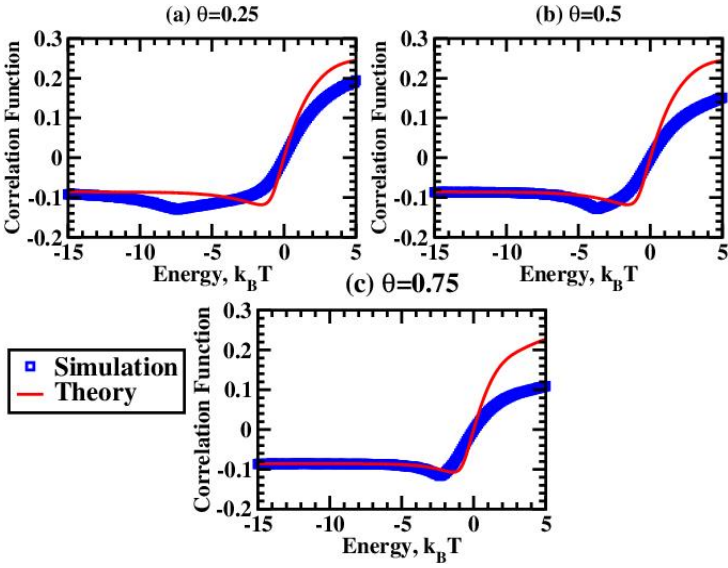


Repulsions: the presence of the particle at the site *i* leads to lower probability of finding the particle at the site *i*+1. Then the occupancy of the site *i*+2 is independent of the occupancy of the site *i*

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

Results:

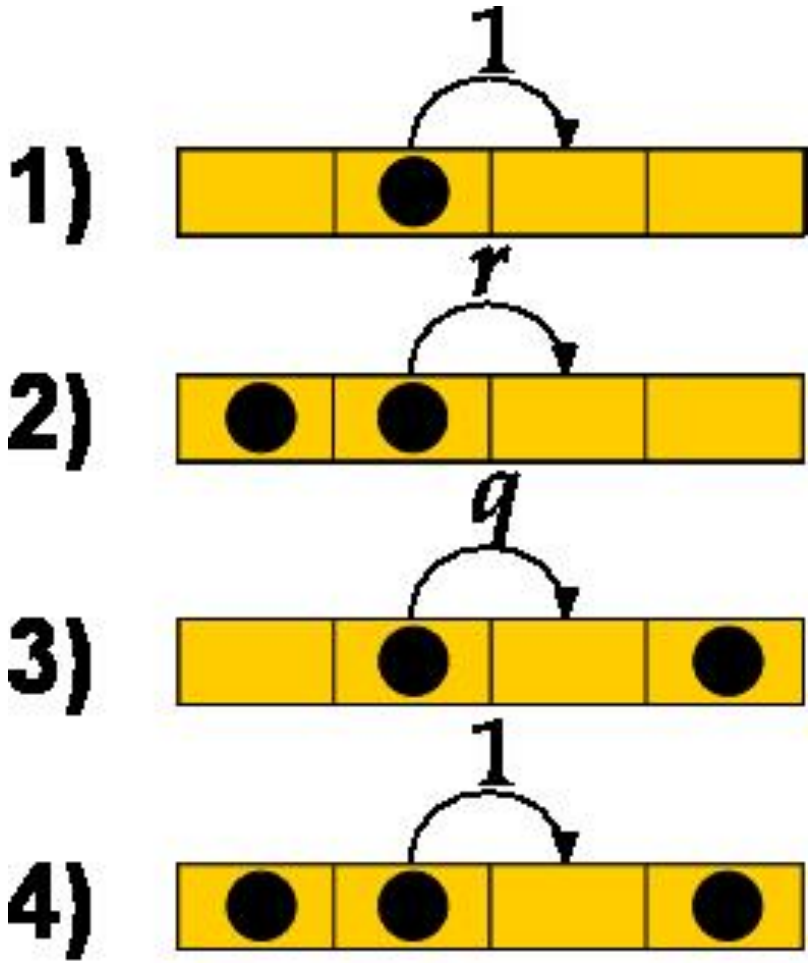


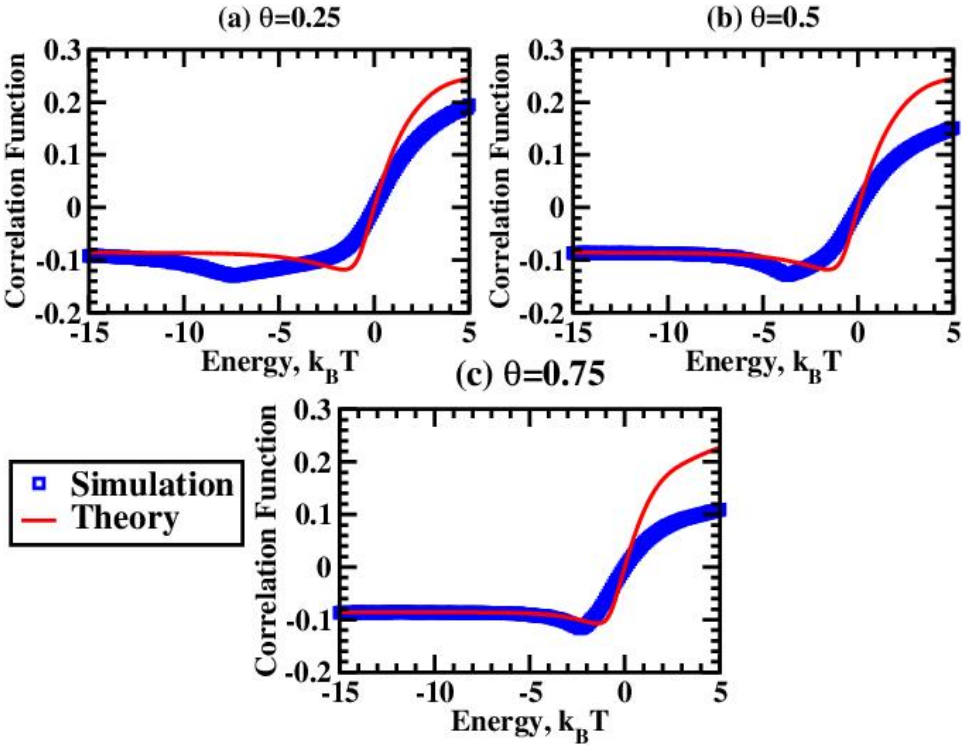


Attractions: the presence of the particle at the site *i* leads to a higher probability of finding the particle at the site *i*+1. Then the occupancy of the site *i*+2 depends on the occupancy of the site *i*

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

Results:



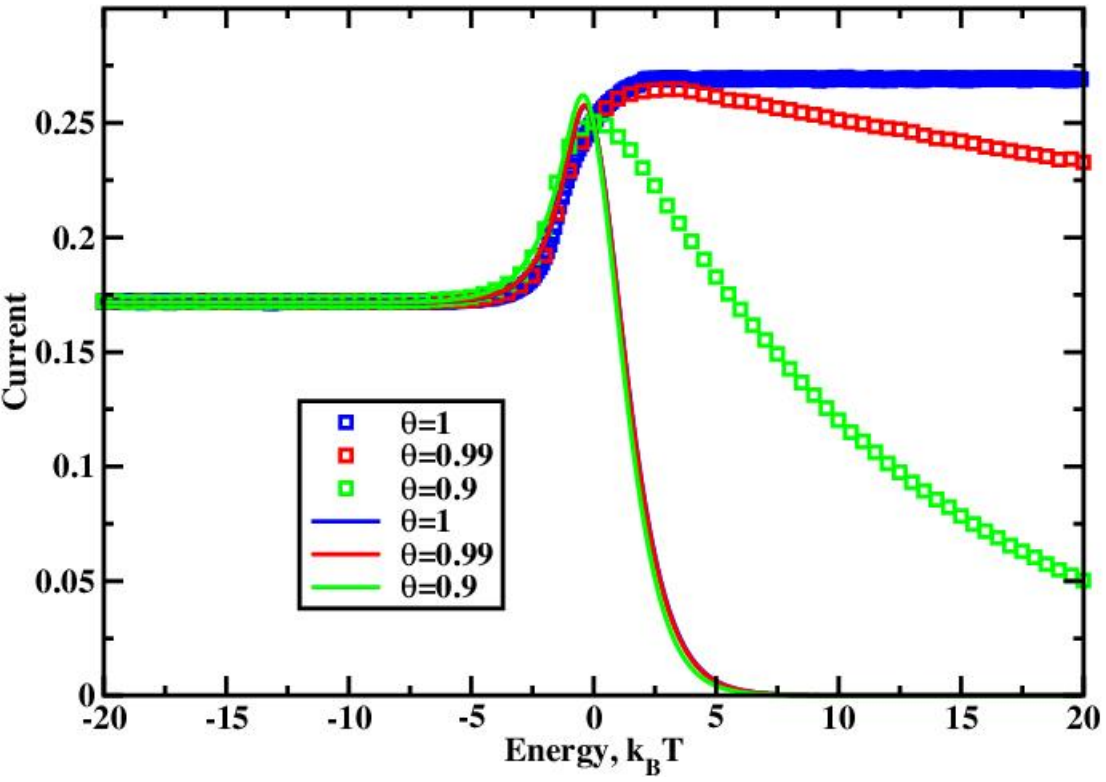


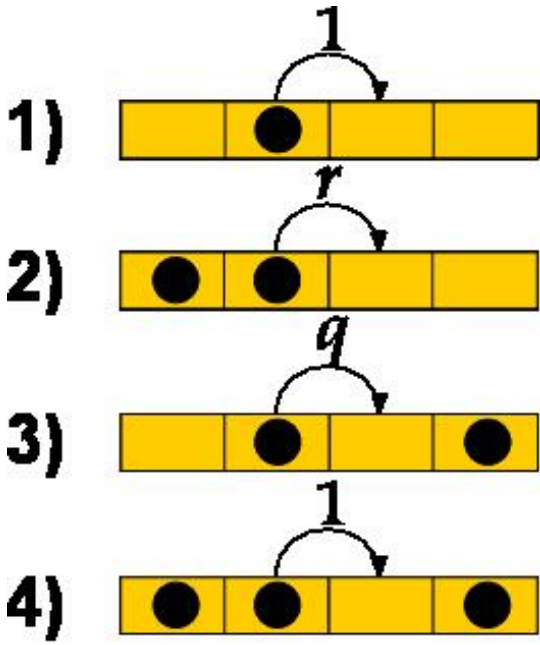
Our theory takes into account only short-range (2 sites) correlations, which are relevant for repulsions, but are less important for attractions

Results:

Maximal particle fluxes for different θ

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

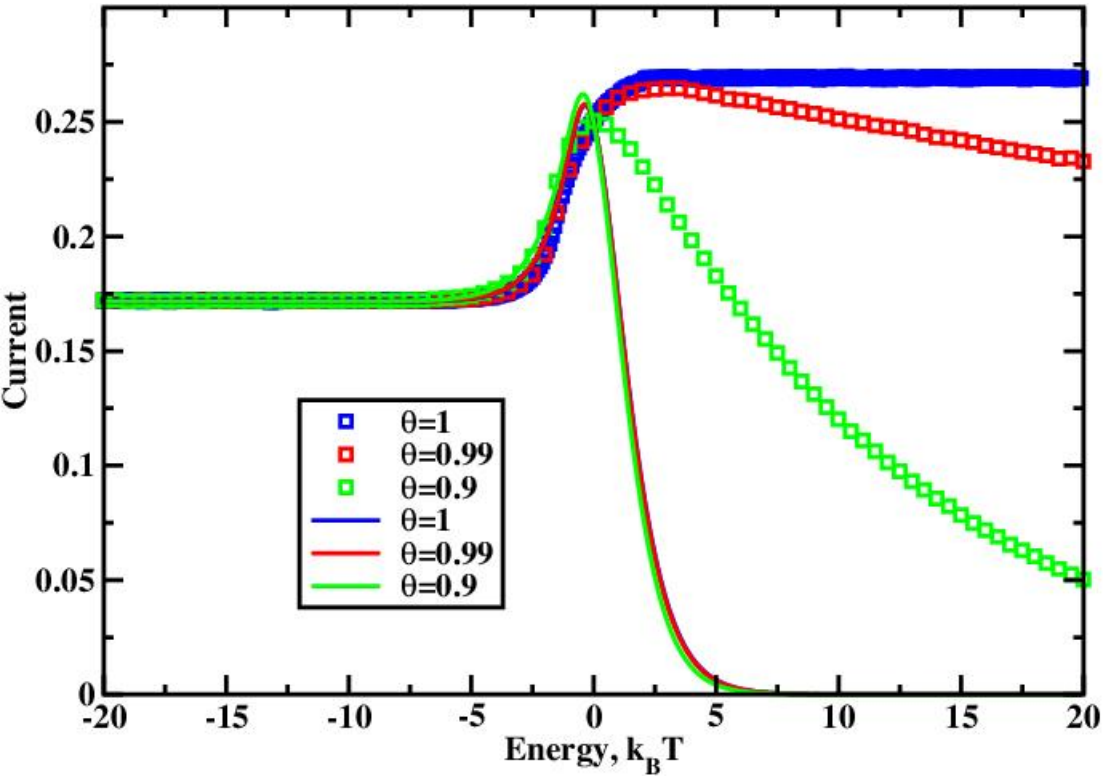




Dynamics of interacting molecular motors depends on how the interaction is split between the formation and breaking the clusters (symmetry of interactions)

Results:

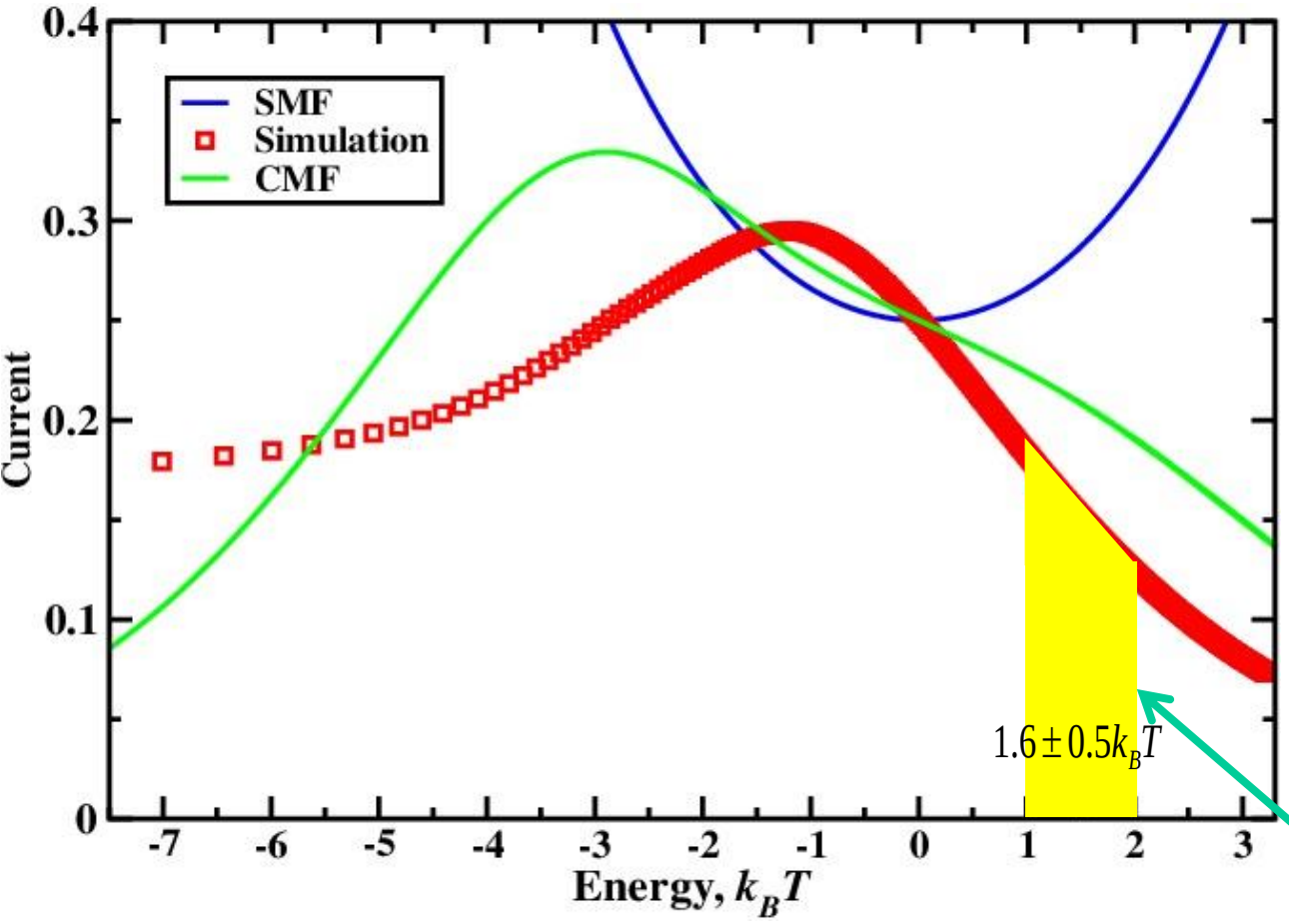
Maximal particle fluxes for different θ

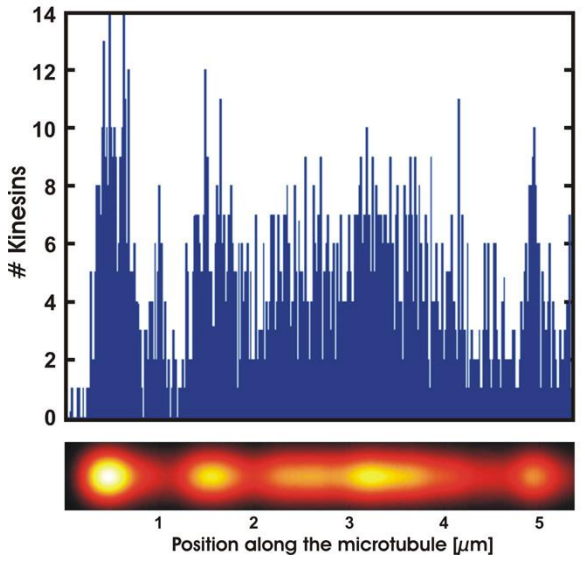


For $0<\theta<0.9$ the most optimal fluxes are achieved for weak repulsions (E~-1 kT).
For $0.9<\theta<1$ the most optimal fluxes are achieved for attractions!

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

Relevance for Real Motor Proteins?



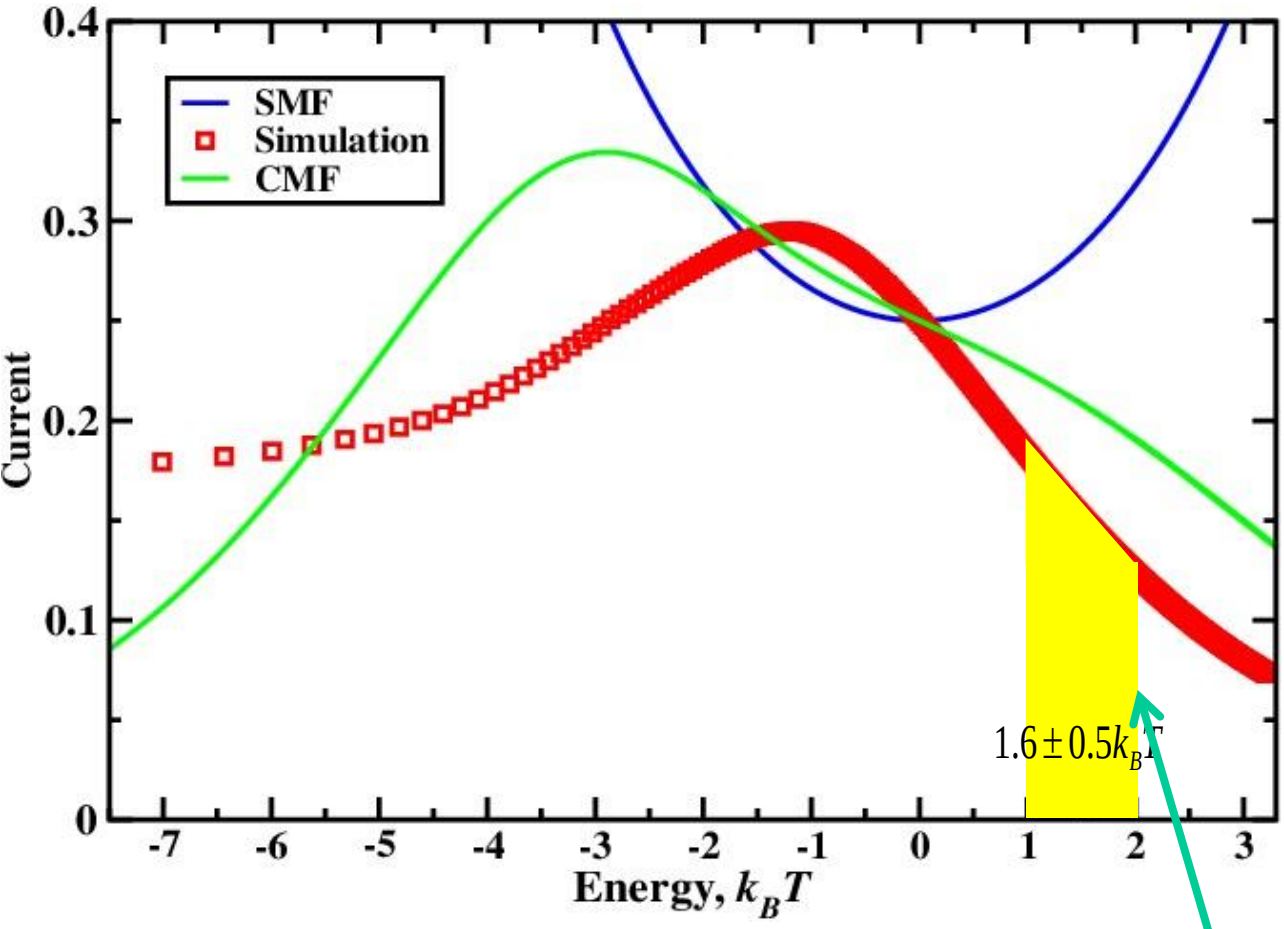


θ=0.5

Weak attractions for kinesins – but maybe repulsions?

What does it mean for transport of multiple kinesin motor proteins?

Relevance for Real Motor Proteins?

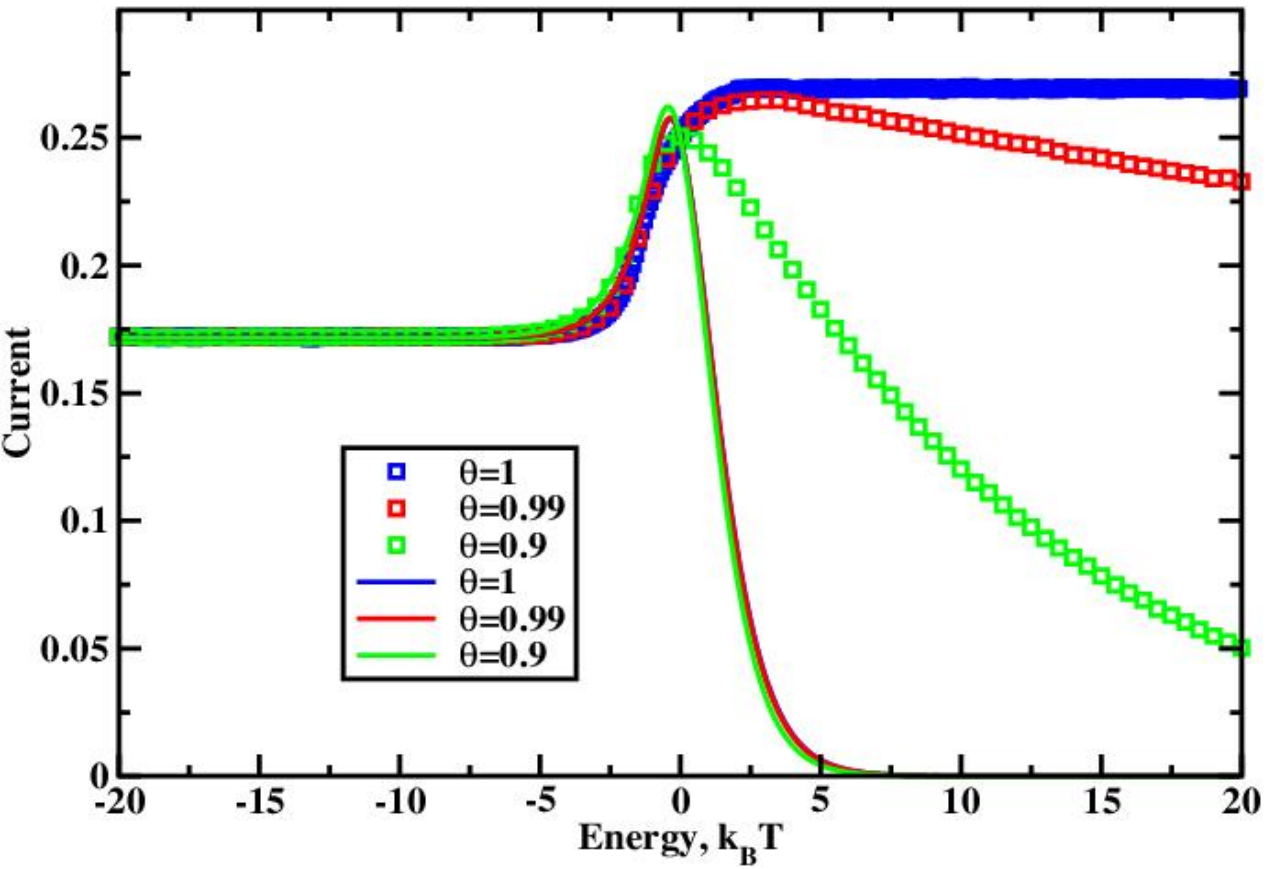


Option #1 for $\theta<0.9$:

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?

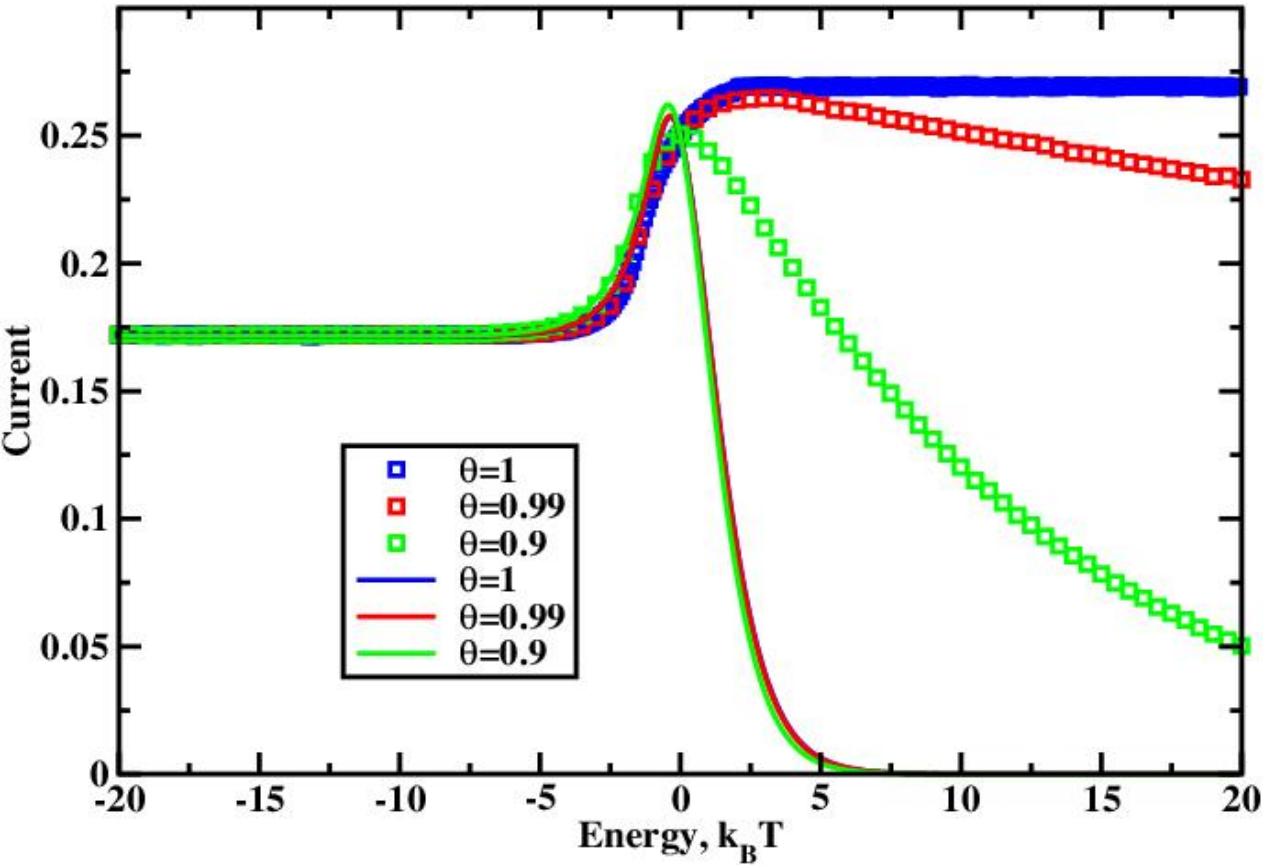


Option #2 for 0.9 <θ<1:

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

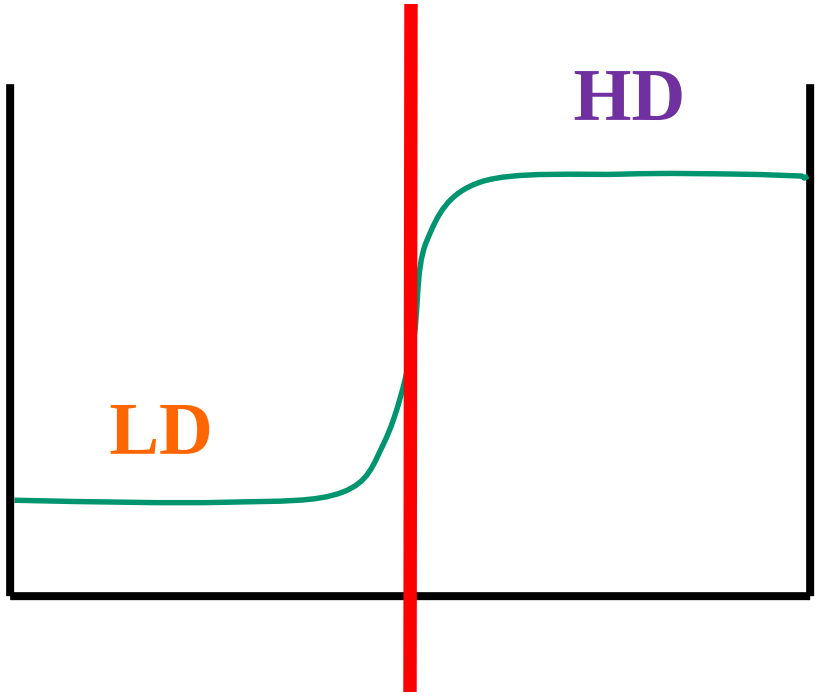
We use the idea of domain wall (DW) as an object that separates different domains

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

DW velocity

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

DW diffusion constant

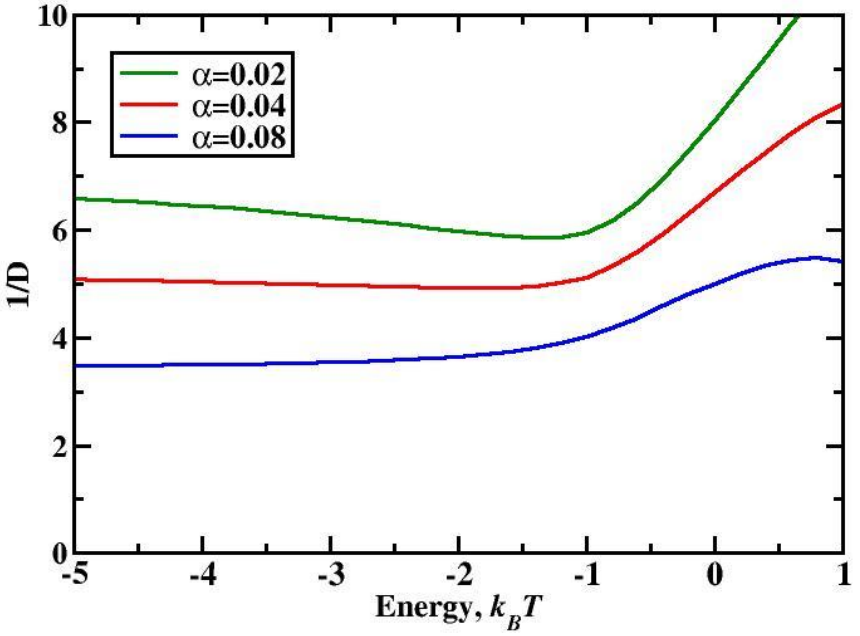


Domain Wall

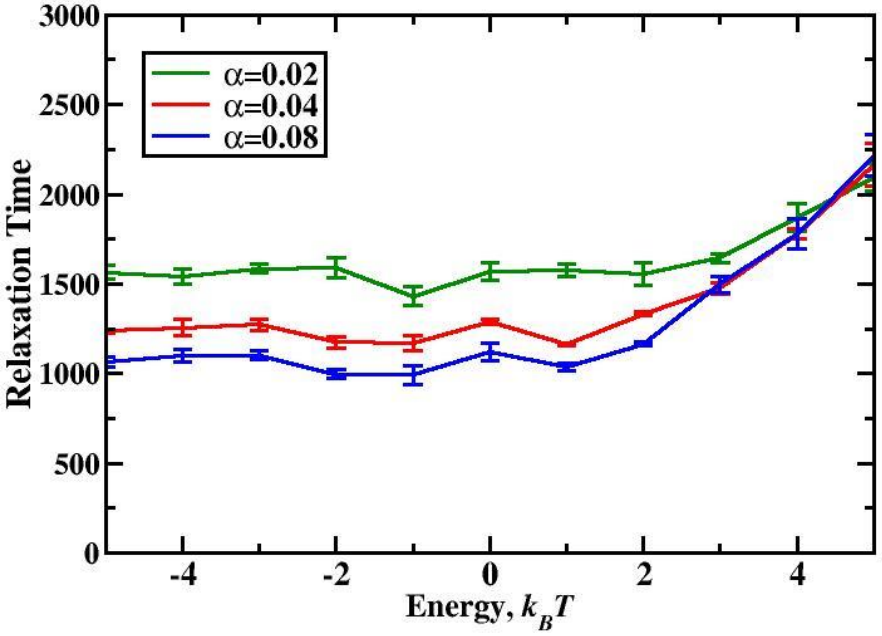
Relaxation time to the stationary state ***T~1/D***

Are Motor Proteins at the Stationary State?

theory



Computer simulations



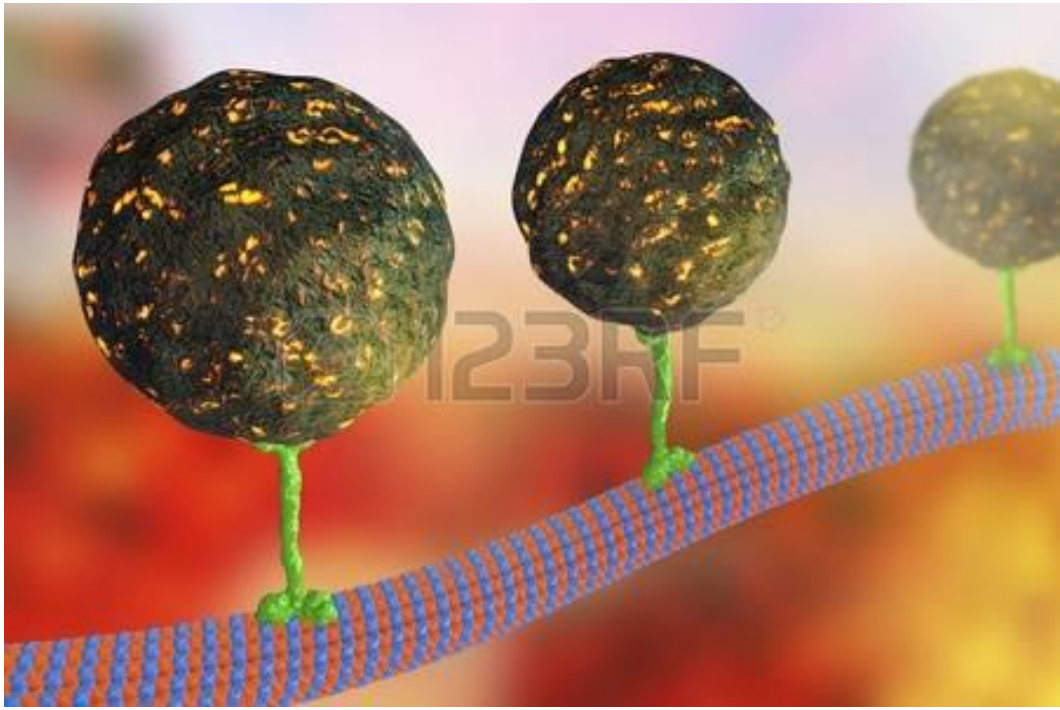
For repulsions molecular motors relax faster to the stationary state than for attractions

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



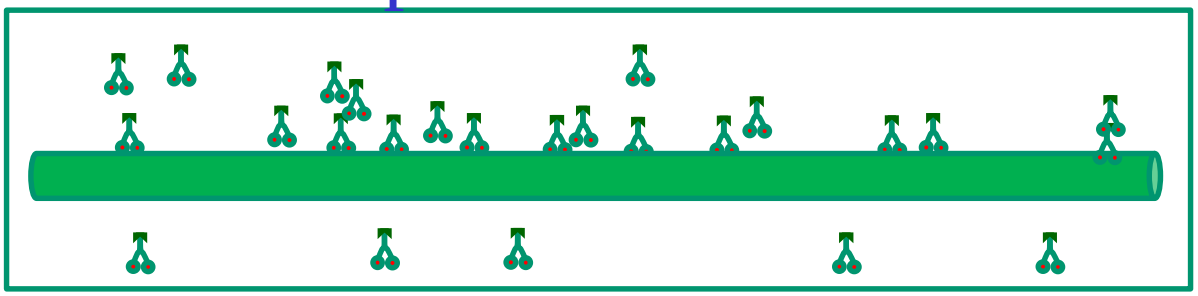
CONCLUSIONS

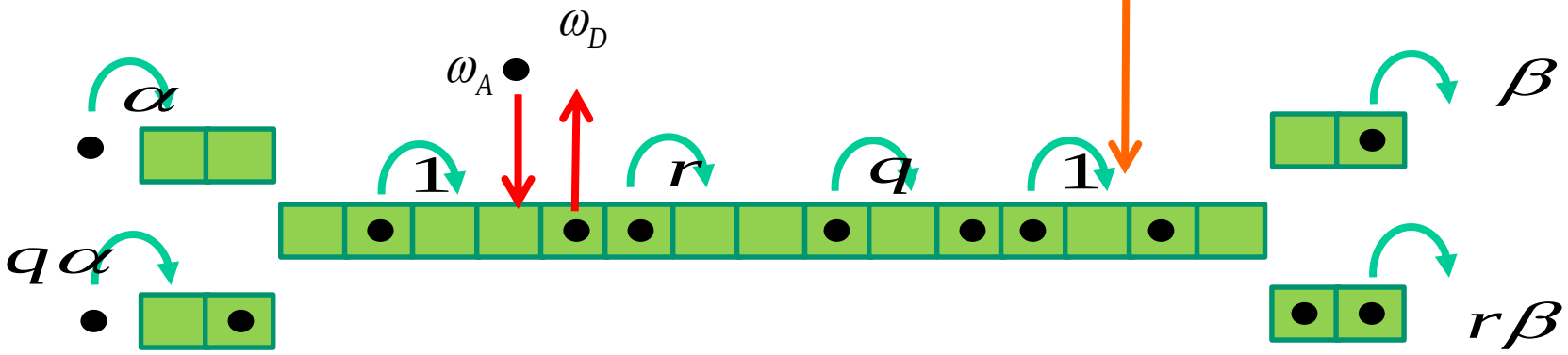
1) Developed a new theoretical approach for analyzing multi-particle dynamics of interacting molecular motors
2) Investigated TASEP with interactions where transition rates are taken into account using proper thermodynamic arguments
3) Interactions induce correlations in the system. For repulsions correlations are weaker, while for attractions they are stronger and more long-range
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

Future Directions

More realistic description of biological transport must include the backward steps, binding/unbinding transitions and the transport along the parallel protofilaments.

Note also better cluster methods developed by Arvind Kumar Gupta and coworkers





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Publications:

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

2) *J. Stat. Mech*. **15** (2015) P04013

Collaborators:

Prof. Arvind Kumar Gupta and his coworkers from IIT Ropar