RICE UNIVERSITY

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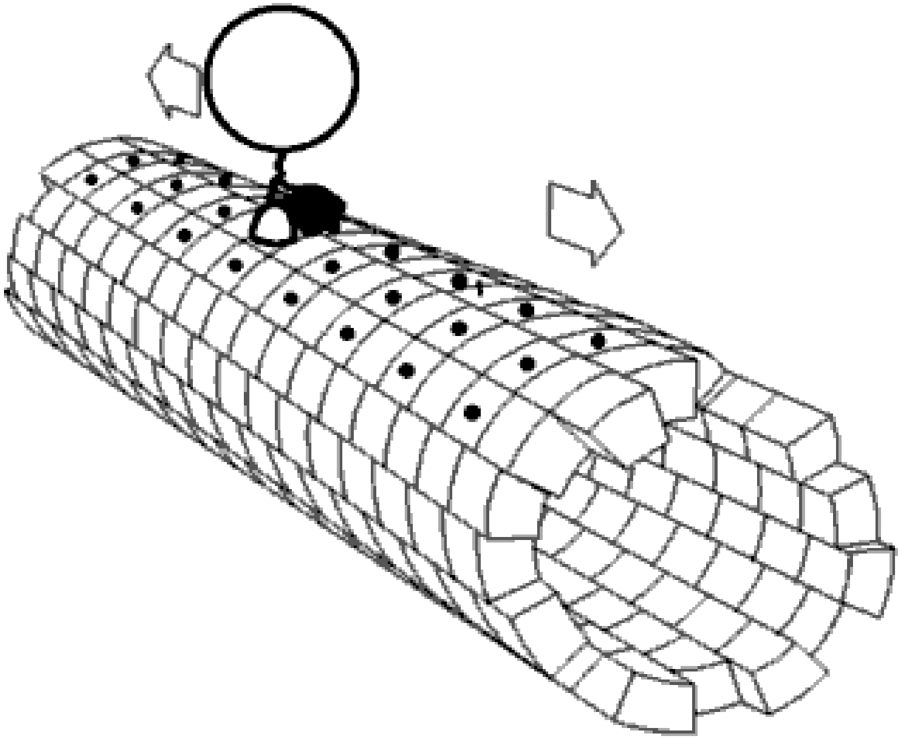
SPATIAL FLUCTUATIONS AFFECT DYNAMICS OF MOTOR PROTEINS

Motor Proteins

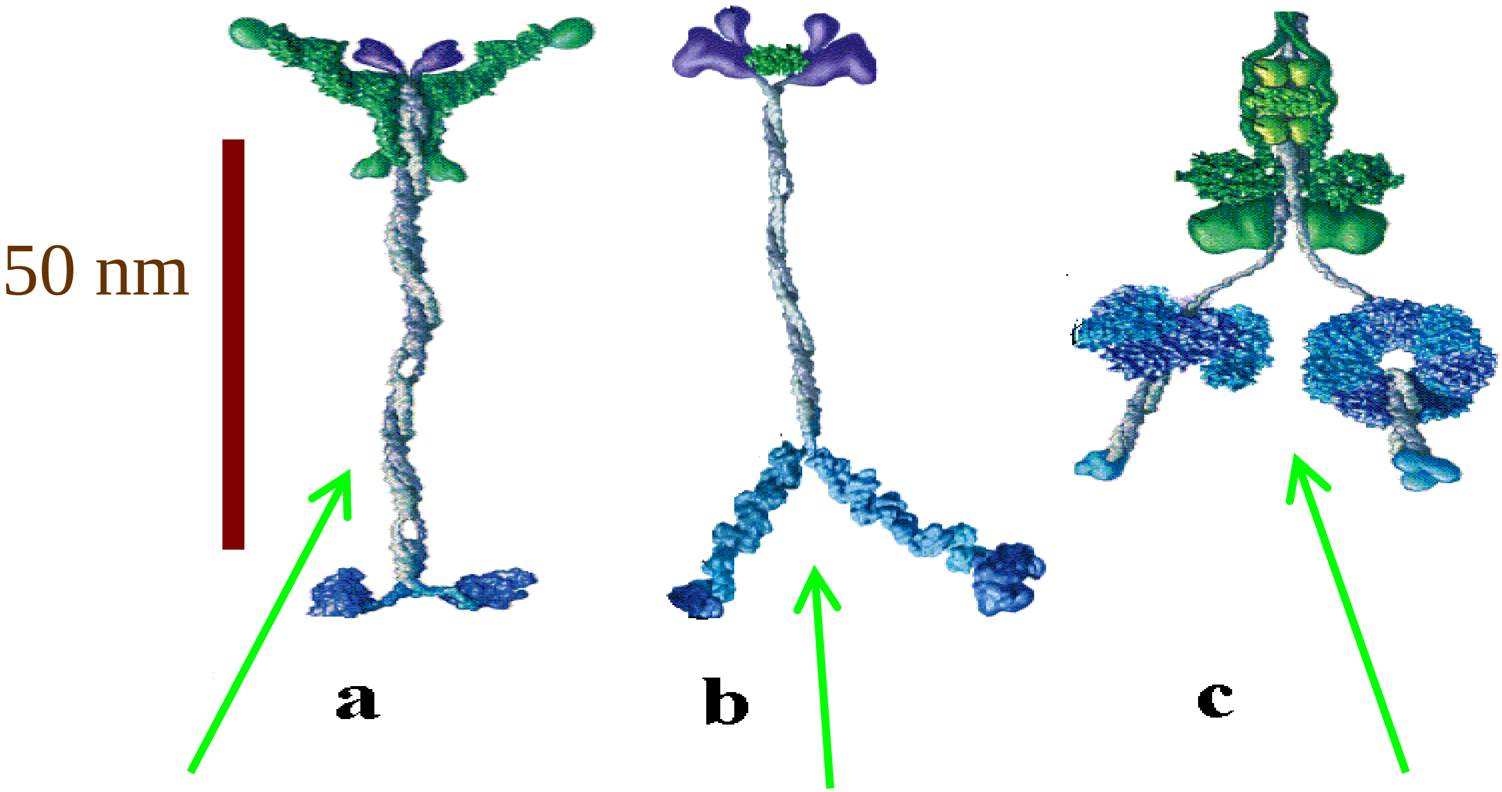
Enzymes that convert the chemical energy into mechanical work

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



Courtesy of Marie Curie Research Institute, Molecular Motor Group

Motor Proteins: Structure



conventional kinesin

myosin V

cytoplasmic dynein

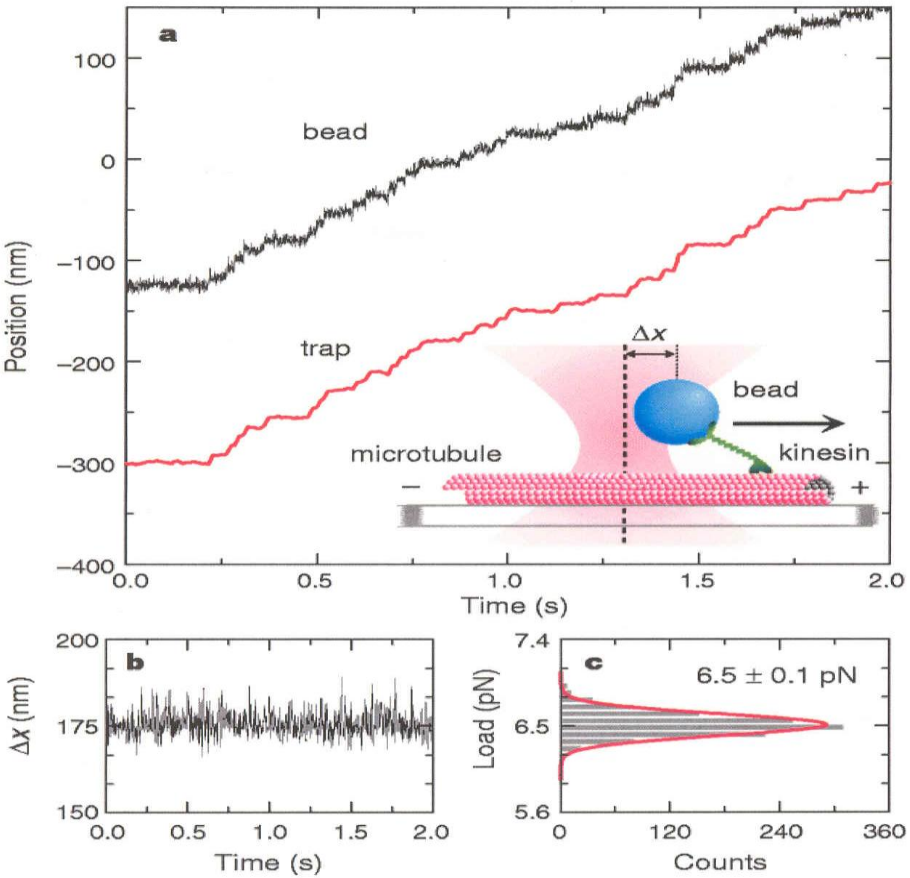
Motor Proteins

Fundamental Problems:

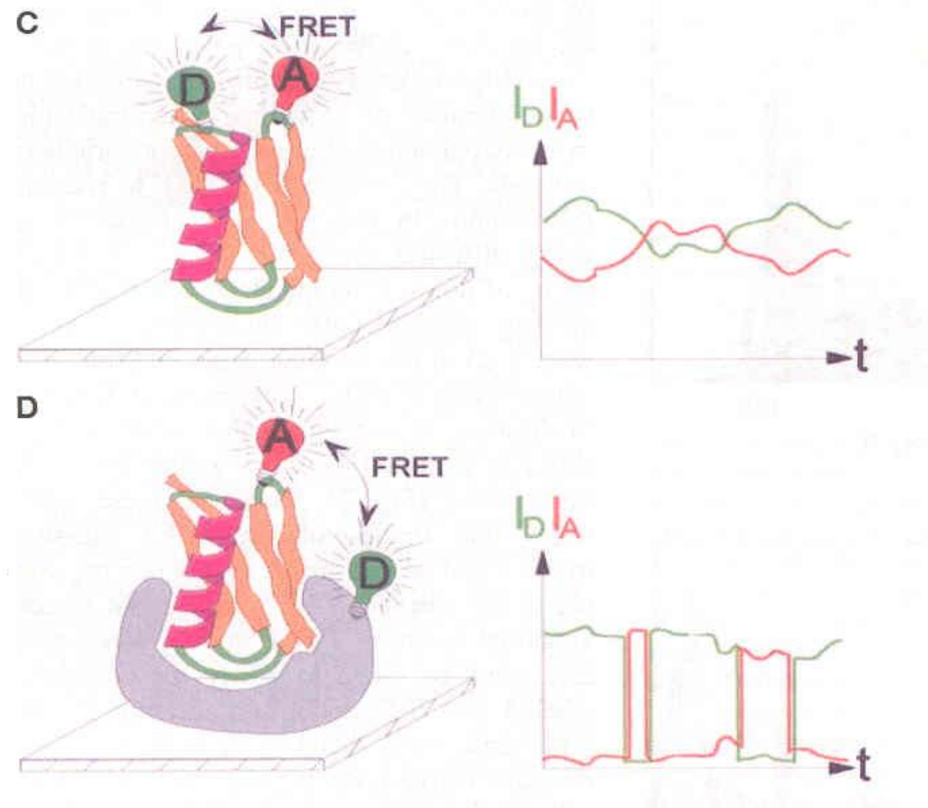
1) How the chemical energy is transformed into the mechanical motion?
2) How many different mechanisms of motor proteins motion? Universality, "Physicists *versus* biologists"
3) How spatial fluctuations might influence the overall dynamics of motor proteins?
4) Why many motor proteins are complexes of already functional subunits?
5) Interactions with linear tracks (microtubules, etc.)

Motor Proteins. Experiments

Single-Molecule Experiments:

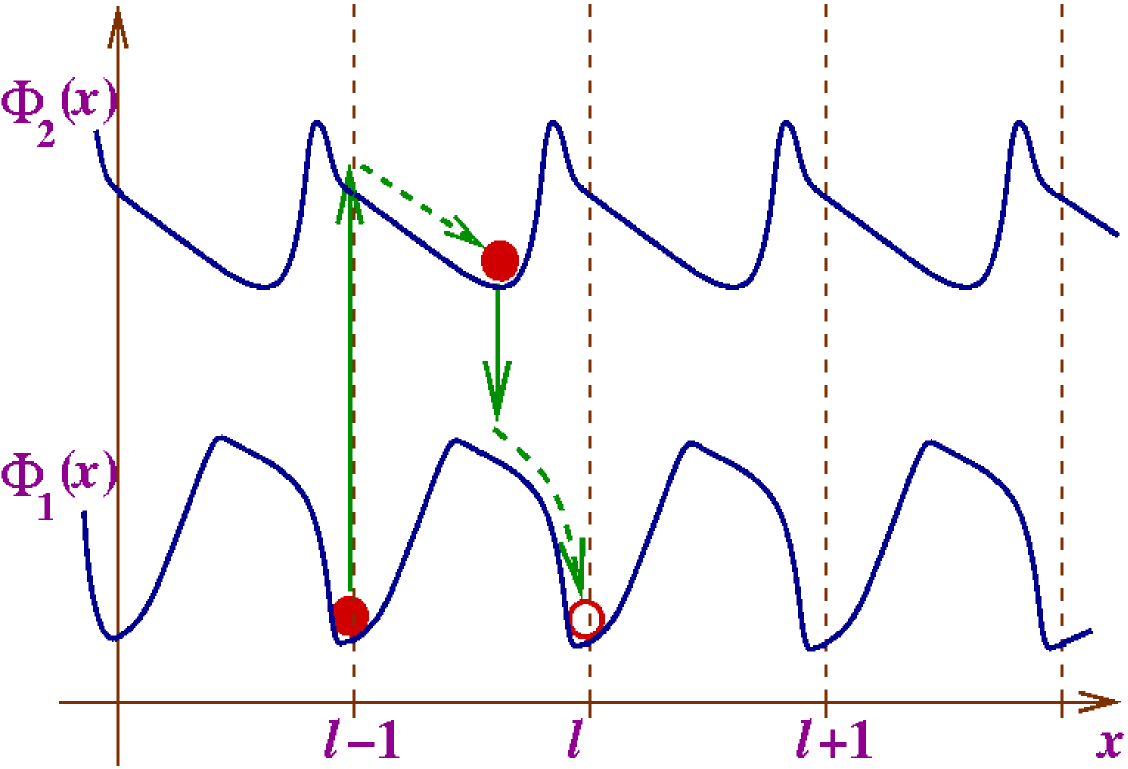


Optical-trap spectrometry



FRET – fluorescence resonance energy transfer

Thermal Ratchet Models



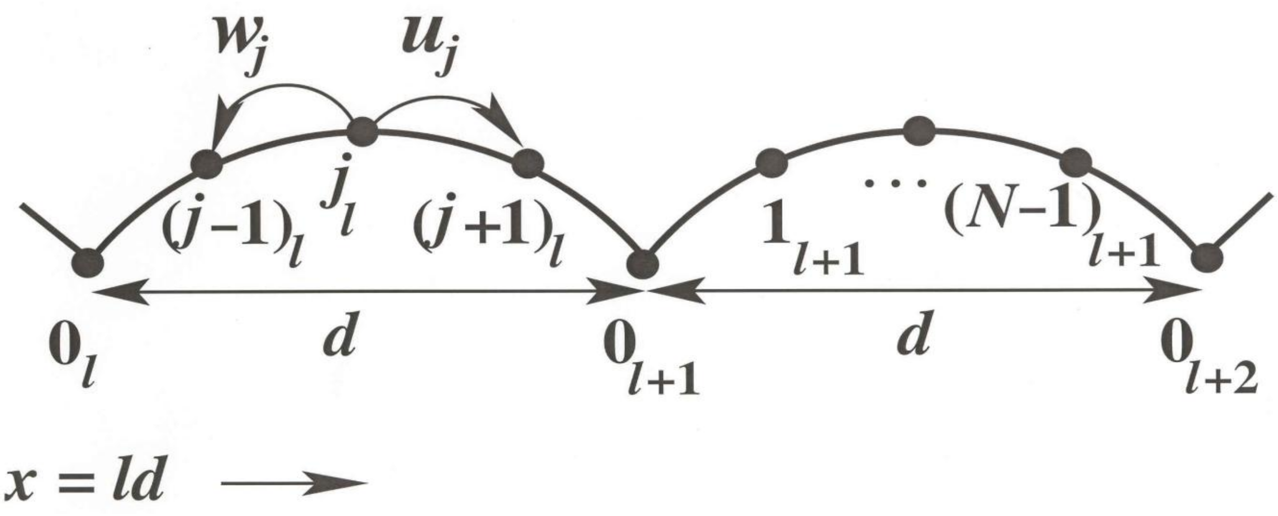
System evolves according to a set of Fokker-Planck equations

Chemically-driven ratchets-

Markov-Fokker-Planck Models

J. Prost, G. Oster, F. Julicher, S. Sean, A. Mogilner, T. Elston
and many others contributed

DISCRETE STOCHASTIC MODELS



Fisher and ABK and coworkers, Hong Qian, R. Lipowsky, etc.

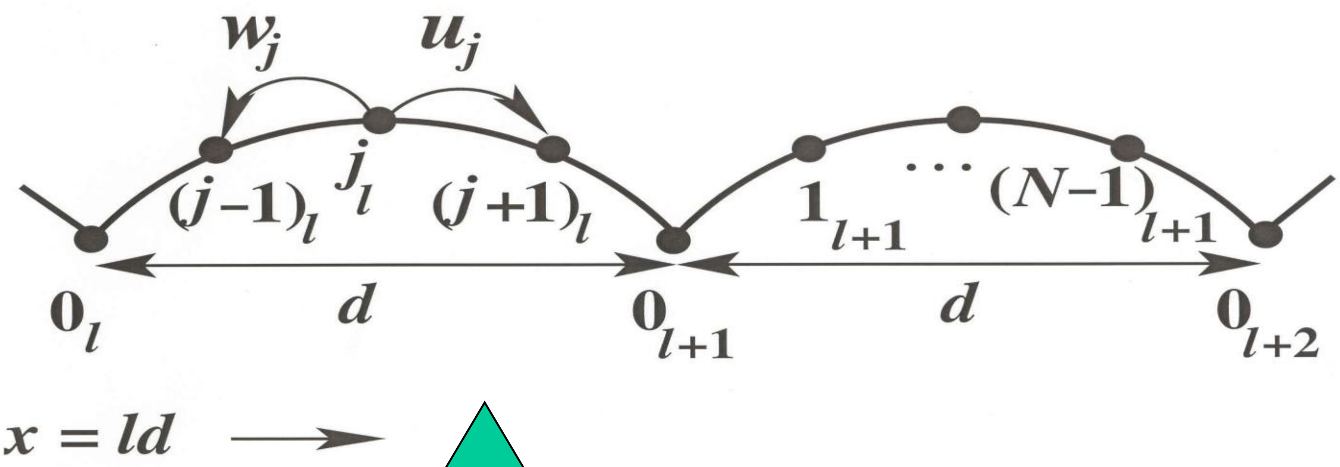
j=0,1,2,…,N-1 – intermediate biochemical states

N=4 model

kinesin/ microtubule ⟷ kinesin/ microtubule/ ATP ⟷ kinesin/ microtubule/ ADP/Pi ⟷ kinesin/ microtubule/ ADP ⟷

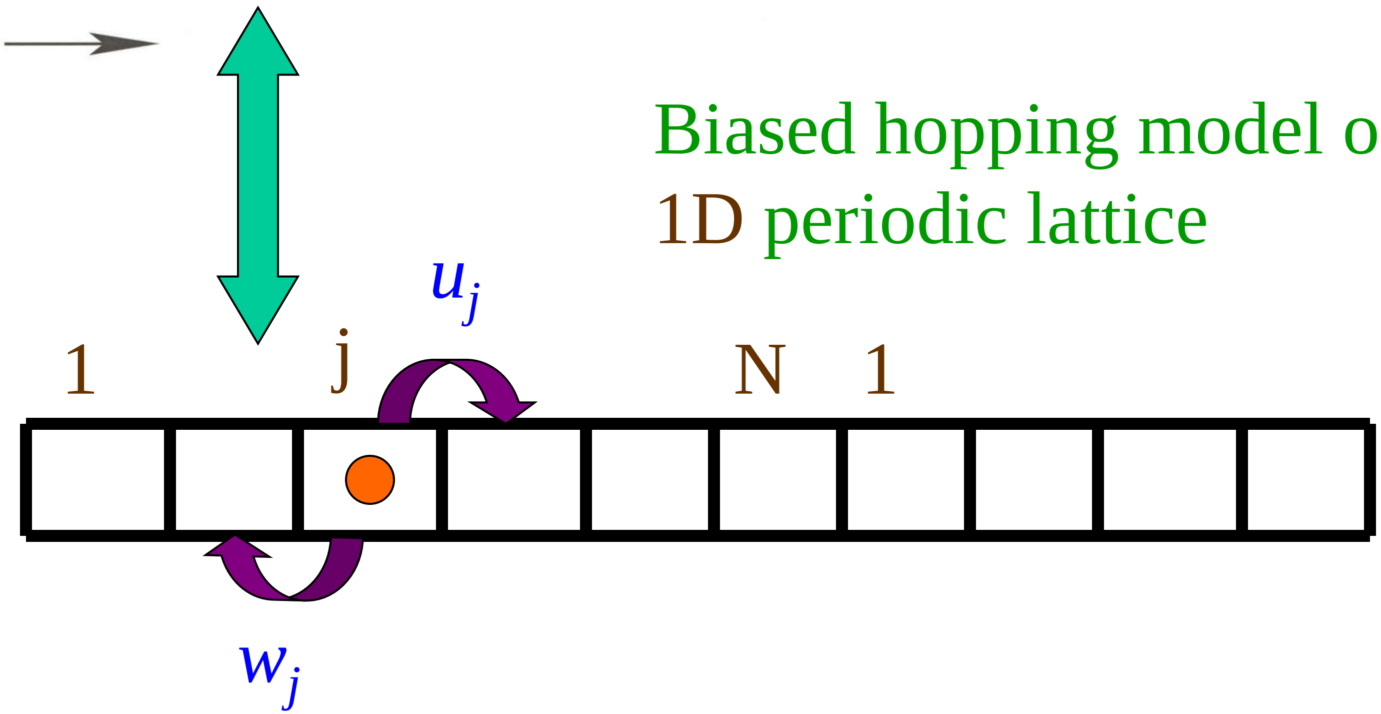
OUR THEORETICAL APPROACH

Multi-State Chemical Kinetic (Stochastic) Models



step size d is assumed to be constant

Biased hopping model on 1D periodic lattice



OUR THEORETICAL APPROACH

our model → periodic hopping model on 1D lattice

↓

exact expressions for asymptotic (long-time) properties

for any N! in terms of the rate constants

Derrida, J. Stat. Phys. **31** (1983) 433-450

drift velocity
$$V = V(\{u_j, w_j\}) = \lim_{t \to \infty} \frac{d}{dt} \langle x(t) \rangle,$$

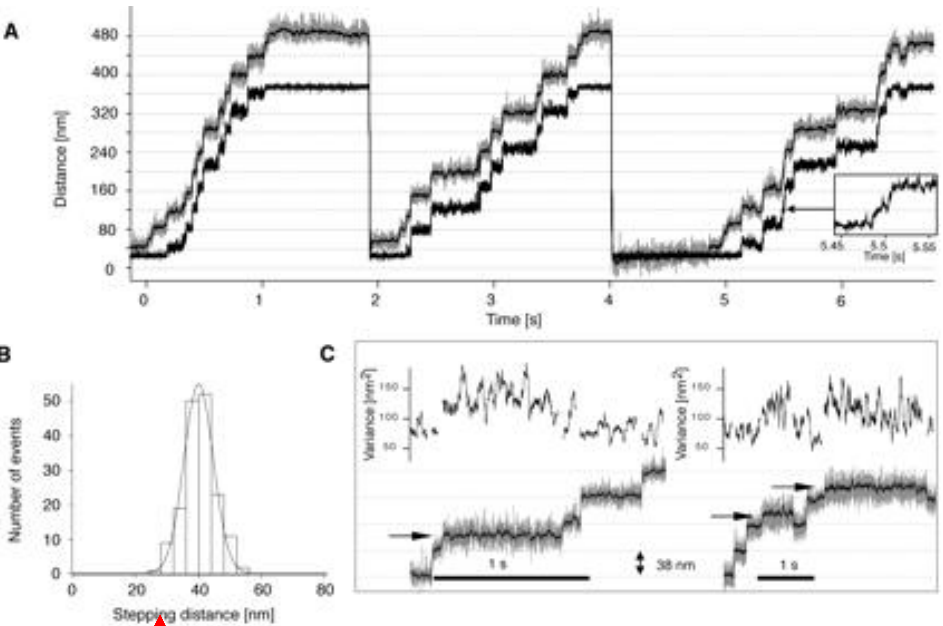
dispersion
$$D = D(\{u_j, w_j\}) = \frac{1}{2} \lim_{t \to \infty} \frac{d}{dt} \left[\langle x^2(t) \rangle - \langle x(t) \rangle^2 \right]$$

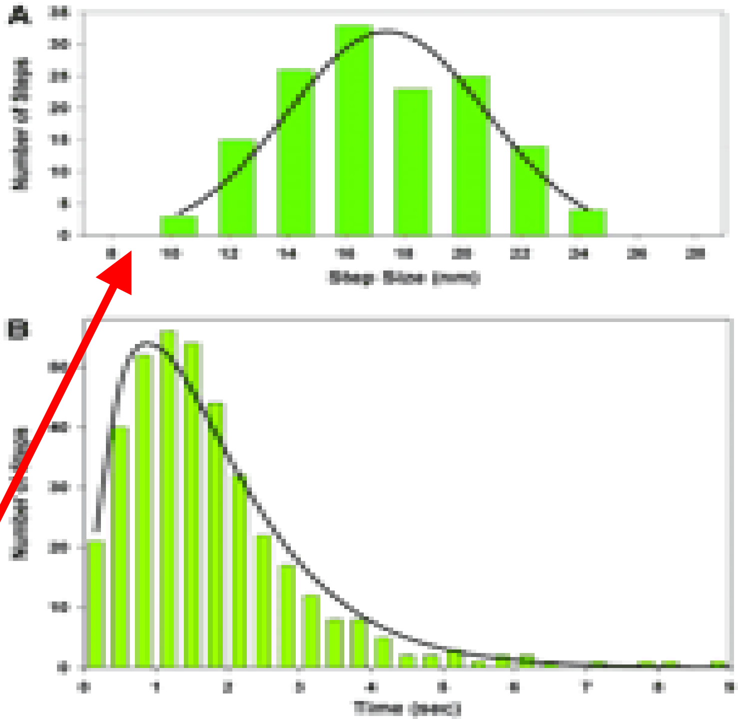
x(t) – spatial displacement along the motor track

Rate constants – can be obtained from independent chemical kinetic bulk experiments

Single-Molecule Experiments:

Large variability and fluctuations in dynamic properties of motor proteins





Step-size distributions for myosins-V

PNAS 2000, **97**, 9482

Step sizes of individual heads for kinesin dimers

Science, 2004, **303**, 676

Spatial Fluctuations

Fluctuations are real – larger than spatial precision of measurments.

Contain important biochemical and biophysical information

Valuable tool for understanding mechanisms of motor proteins

However, very few theoretical efforts:

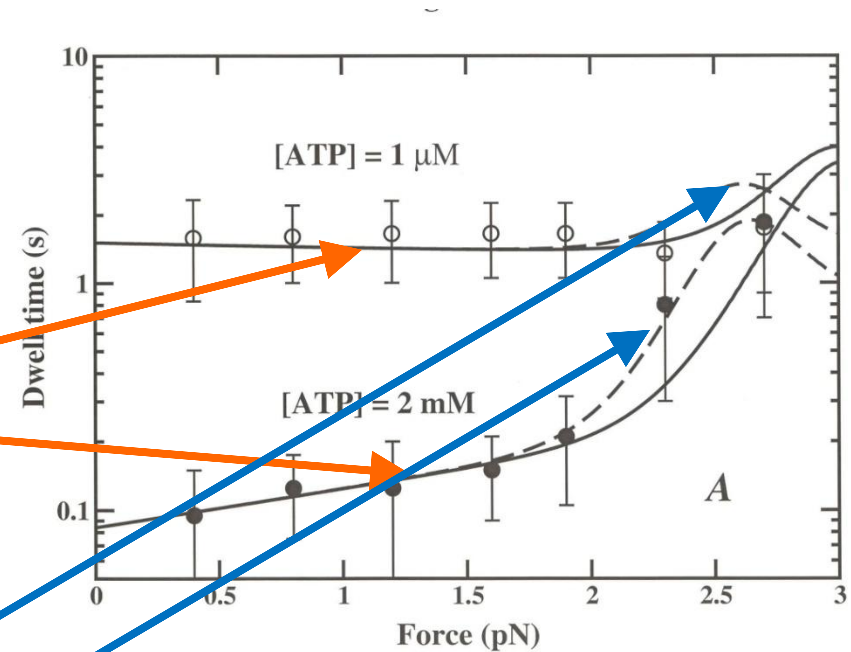
1) ABK and M.E. Fisher, *Biophys. J*. 2003, **84**, 1642;
2) J.W. Shaevitz, S.M. Block and M.J. Schnitzer, *Biophys. J*., 2005, **89**, 2277;
3) A. Vilfan, *Biophys. J*., 2005, **88**, 3792;
4) G. Lan and S.X. Sun, *Biophys. J*., 2005, **88,** 999.

Previous Theoretical Efforts:

ABK and M.E. Fisher,
Biophys. J. 2003, **84**, 1642

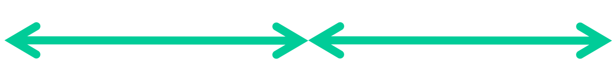
N=2 model with fixed step size d_0=36 nm

model with alternating 50% steps of d_+=41.5 nm and 50% steps of d_-=30.5 nm – equivalent to *N*=4 model with d=72 nm



Dwell-time distributions for myosin-V

d_0=36 nm d_0=36 nm

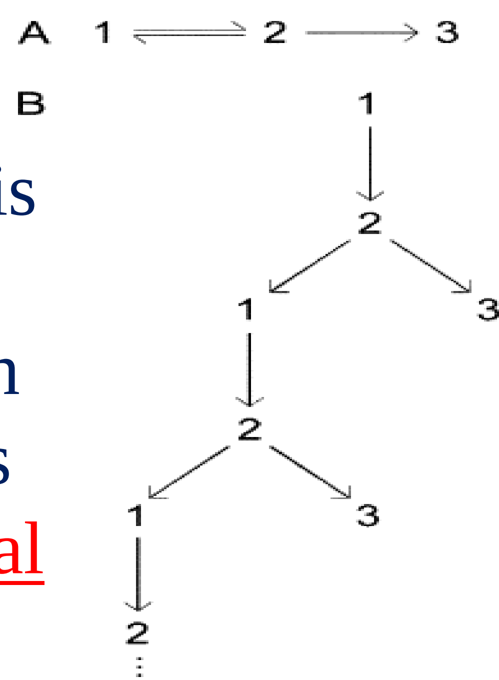


d_- d_+

Previous Theoretical Efforts

J.W. Shaevitz, S.M. Block and M.J. Schnitzer, *Biophys. J*., 2005, **89**, 2277;

Moment-generating functions method



$$r = \frac{2D}{dV}$$

$$r = r_{stepsizes} + r_{steptimes}$$

$$r_{stepsizes} = \frac{\langle d^2 \rangle - \langle d \rangle^2}{\langle d \rangle^2}$$

$$r_{steptimes} = \frac{\langle \tau^2 \rangle - \langle \tau \rangle^2}{\langle \tau \rangle^2}$$

It is argued that this is a general result for the system with spatial fluctuations

It means that spatial fluctuations are independent from stochastic

randomness-dimensionless measure of fluctuations

Problems: irreversibility in biochemical transitions

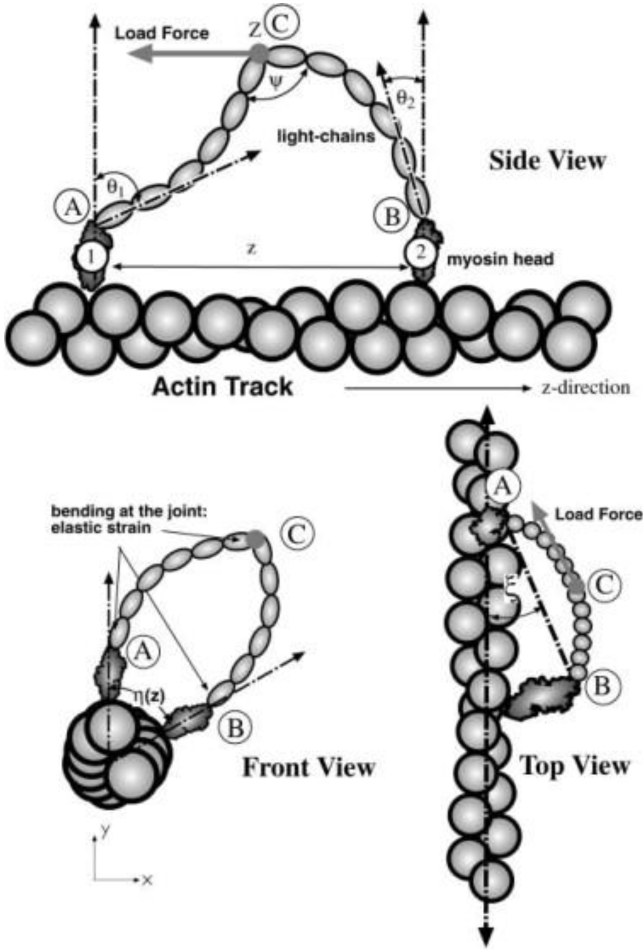
Previous Theoretical Efforts

V A. Vilfan, *Biophys. J.*, 2005, **88**, 3792;
G. Lan and S.X. Sun, *Biophys. J.*, 2005, **88,** 999

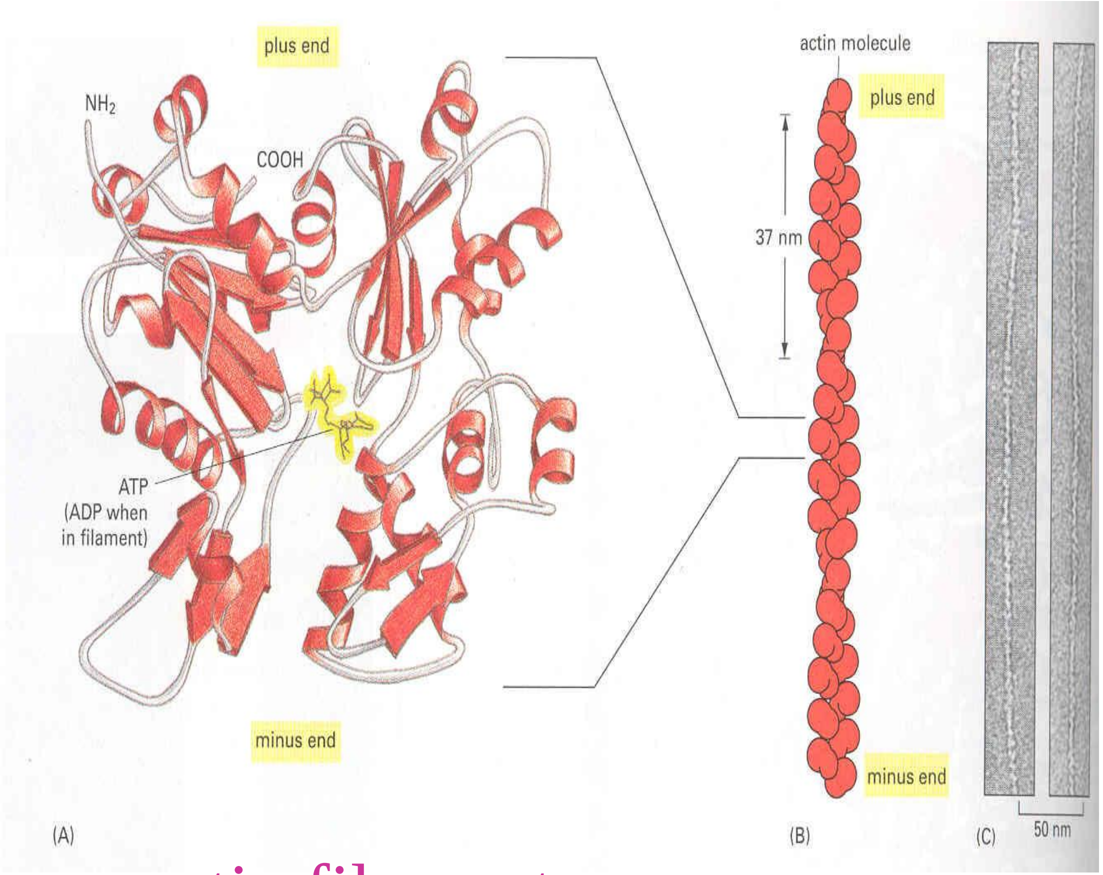
Mechanical models: combine mechanical properties of motor proteins with ATP hydrolysis kinetics

Problems:

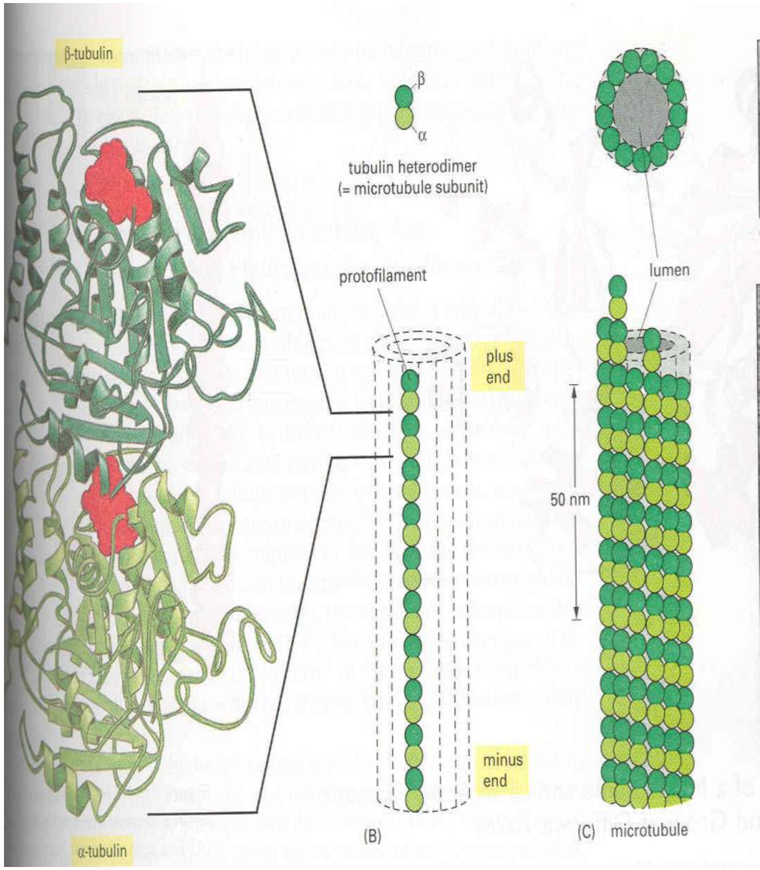
1) depend on potentials of interactions and on choice of mechanical parameters
2) Requires numerical solutions and/or Monte Carlo simulations



Our Approach



actin filaments



microtubules

Spectrum of step sizes for motor proteins most probably discrete!

Our Approach

It is assumed that fluctuations are discrete and symmetric;

3 possible step sizes:

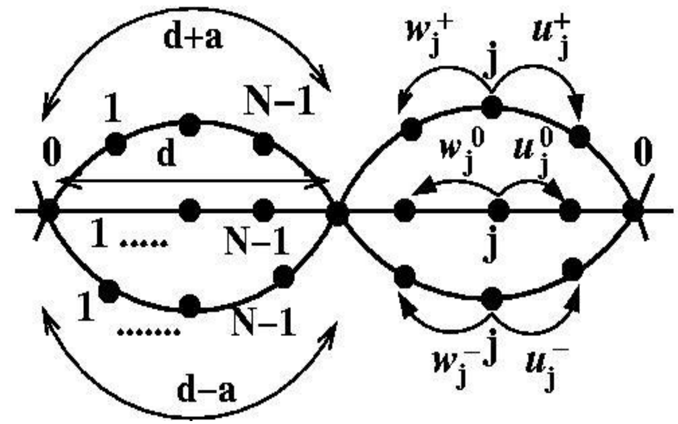
$d_- = d - a$ – with probability p

$d_0 = d$ –with probability $(1-2p)$

$d_+ = d + a$ – with probability p

d- average step size (36 nm for myosin-V)

a-amplitude of spatial fluctuations (5.5 nm for myosin-V



General schematic picture for discrete-state stochastic model with 3 step sizes

Parallel-chain kinetic models – can be solved by Derrida's method

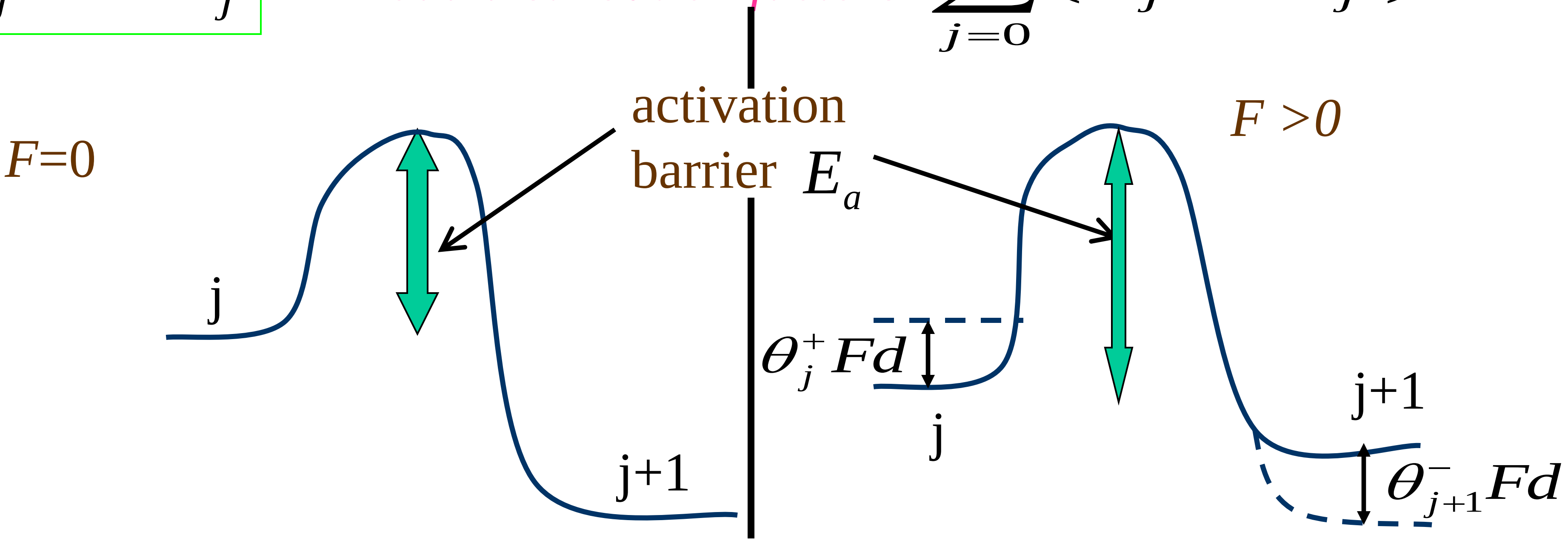
A.B. Kolomeisky, *J. Chem. Phys.* 2001, **115**, 7253

OUR APPROACH

Effect of an external load F:

$$u_j \Rightarrow u_j(F) = u_j(0)e^{-\theta_j^+ Fd/k_B T}, \quad w_j \Rightarrow w_j(F) = w_j(0)e^{+\theta_j^- Fd/k_B T}$$

θ_j^+ and θ_j^- ⇐ *load distribution factors* $\sum_{j=0}^{N-1}(\theta_j^+ + \theta_j^-) = 1$



$$u_j \cong e^{-E_a/k_B T}$$

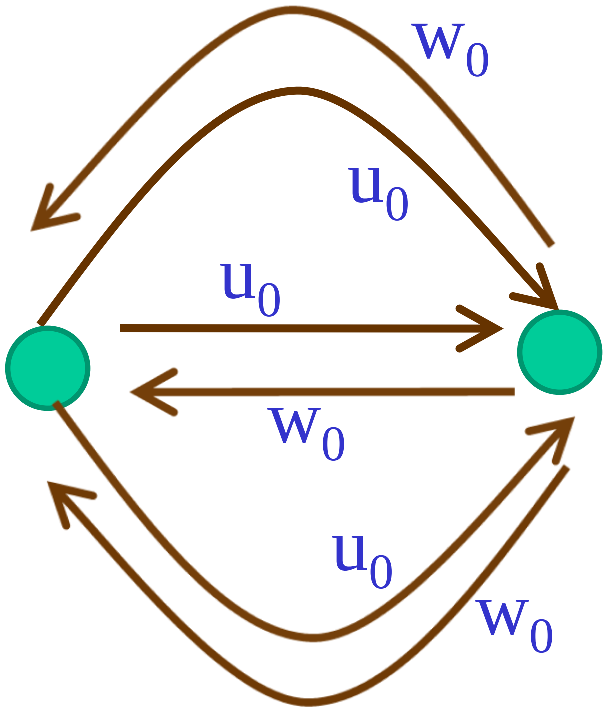
Our Approach

Illustrative Example: ***N*** **=1 model**

$$V = d_0 (u_0 - w_0)$$

Velocity- independent of spatial fluctuations

$$D = \frac{d_0^2}{2}(u_0 + w_0) + pa^2 (u_0 + w_0)$$



Spatial fluctuations strongly affect dispersion

p –probability to fluctuatuate, reflects different energies of binding sites

Our Approach

Illustrative Example: *N*=1 model

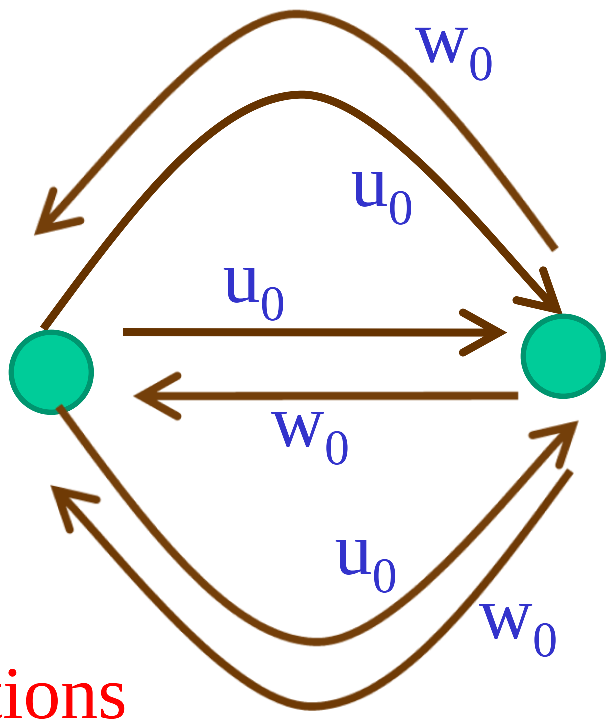
randomness parameter

$$r = \frac{u_0 + w_0}{u_0 - w_0} + 2p\left(\frac{a}{d}\right)^2 + 4p\left(\frac{a}{d}\right)^2 \frac{w_0}{u_0 - w_0}$$

stochastic fluctuations in transition rates

Step-size variations

correlations between different pathways



$$r = r_{steptimes} + r_{stepsizes} + r_{corr}$$

In contrast to predictions from J.W. Shaevitz, S.M. Block and M.J. Schnitzer, *Biophys. J.*, 2005, **89**, 2277;

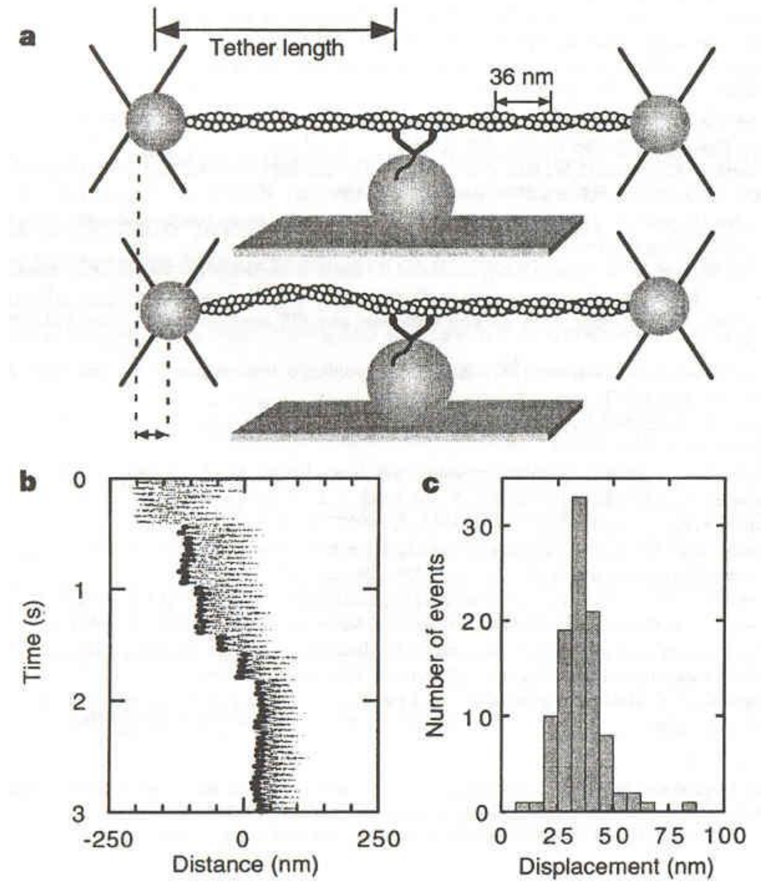
Analysis of Myosin-V Dynamics

We utilize N=2 model from ABK and M.E. Fisher, *Biophys. J.* 2003, **84**, 1642;

with d_0=36 nm, a=5.5 nm, p=0.3

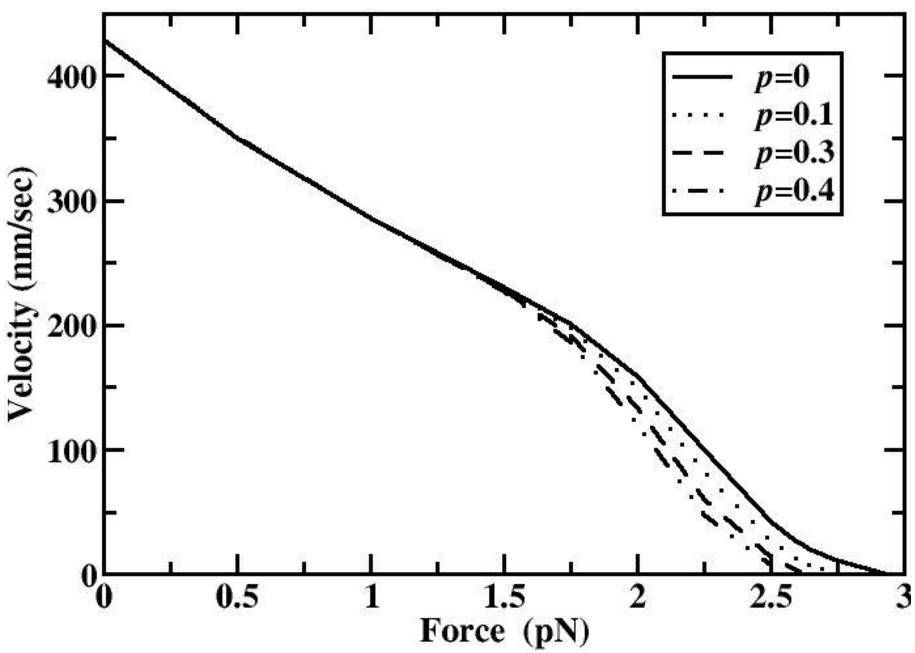
Also assumed:

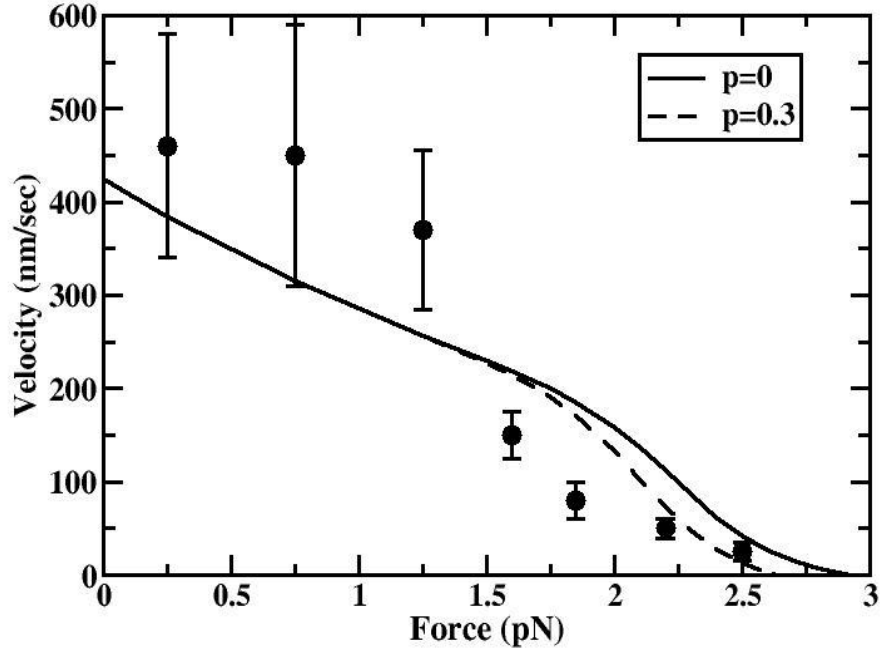
1) Fluctuations are symmetric
2) Kinetic rates are independent from the pathways



Analysis of Myosin-V Dynamics

Force-velocity curves





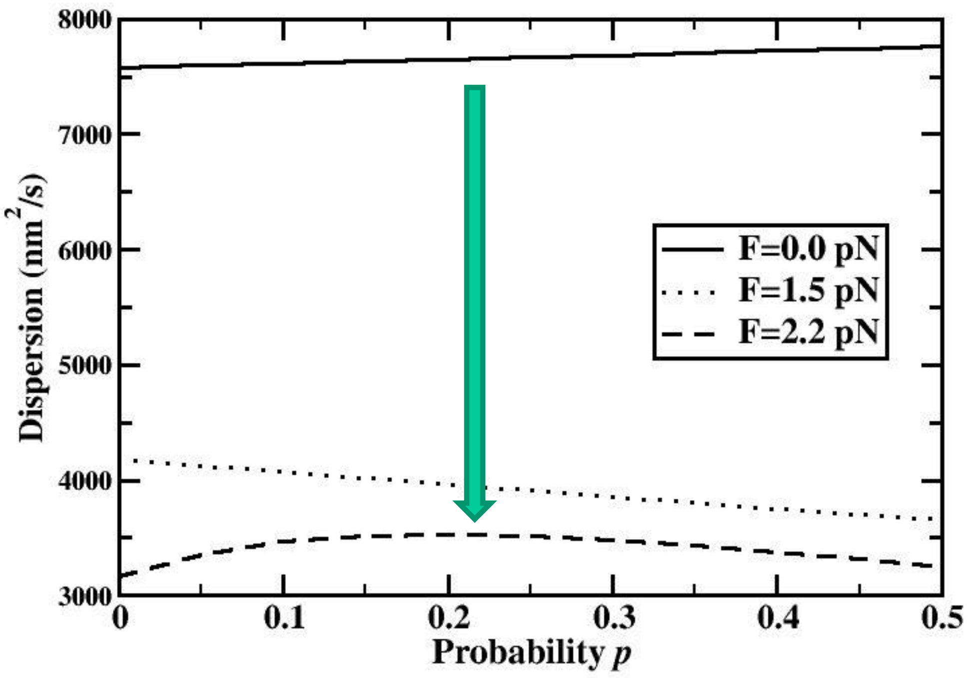
Step-size fluctuations affect the velocity only close to stall forces

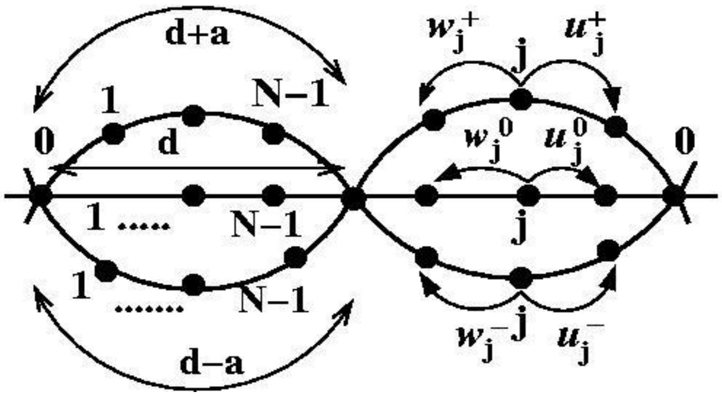
Theoretical fit obtained for *PNAS*, 2000, **97**, 9482; and compared with another exp. results from *Nature Struct. Mol. Biol.*, 2004, **9**, 877

Theoretical Predictions

Increasing the resistance force lowers the dispersion: Stochasticity in each pathway is reduced by decreasing the forward rates stronger than increasing the backward

dispersion



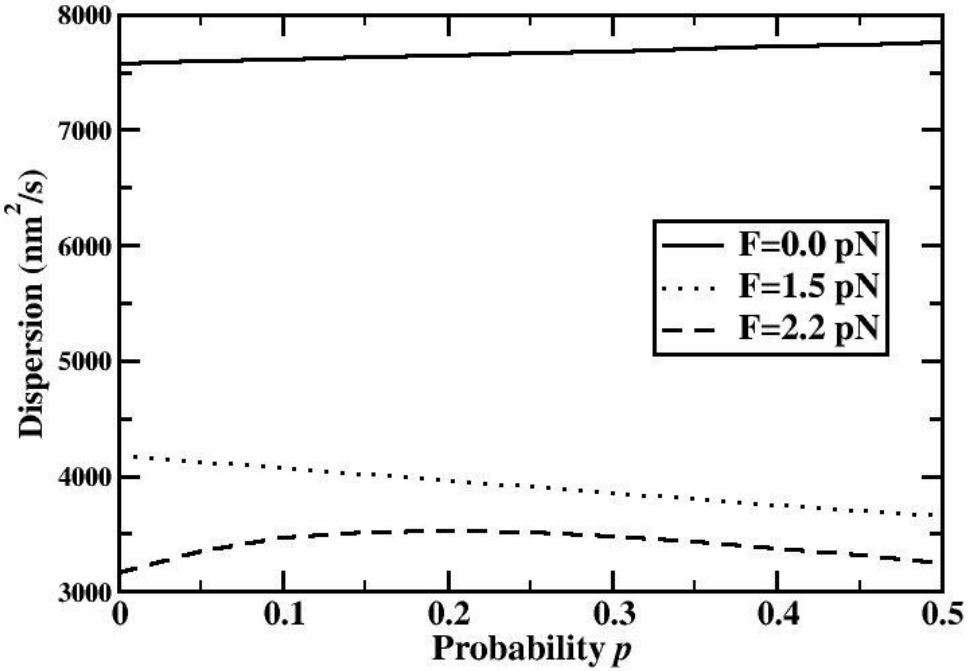


Theoretical Predictions

For *F*=0 dispersion is increasing function of *p* – more channels lead to more fluctuations

For *F*=1.5 pN dispersion is decreasing function – because increase in *p* leads to the particle motion in the channel with lower stochasticity

dispersion



Non-monotonous behavior for *F*=2.2 pN:

Increasing *p* opens new pathways and it increases fluctuations

For larger *p* the particle mostly in the pathways with lower stochasticity, and it lowers *D*

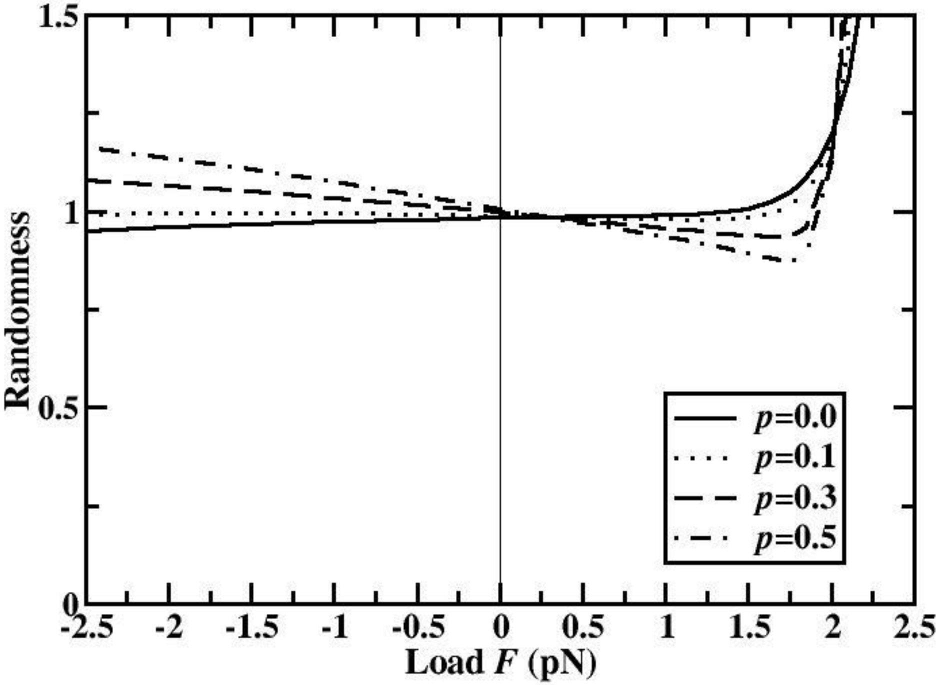
Theoretical Predictions

For small *p* randomness is the increasing function of *F*

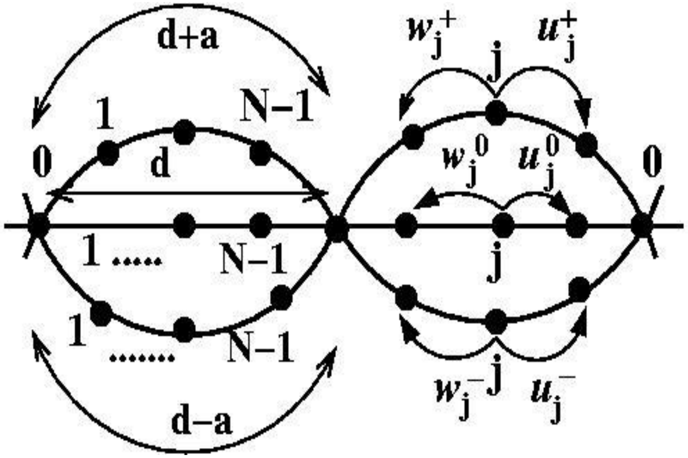
Surprising behavior at larger *p*:
a minimum close *F*=2 pN

$$r = \frac{2D}{dV}$$

randomness



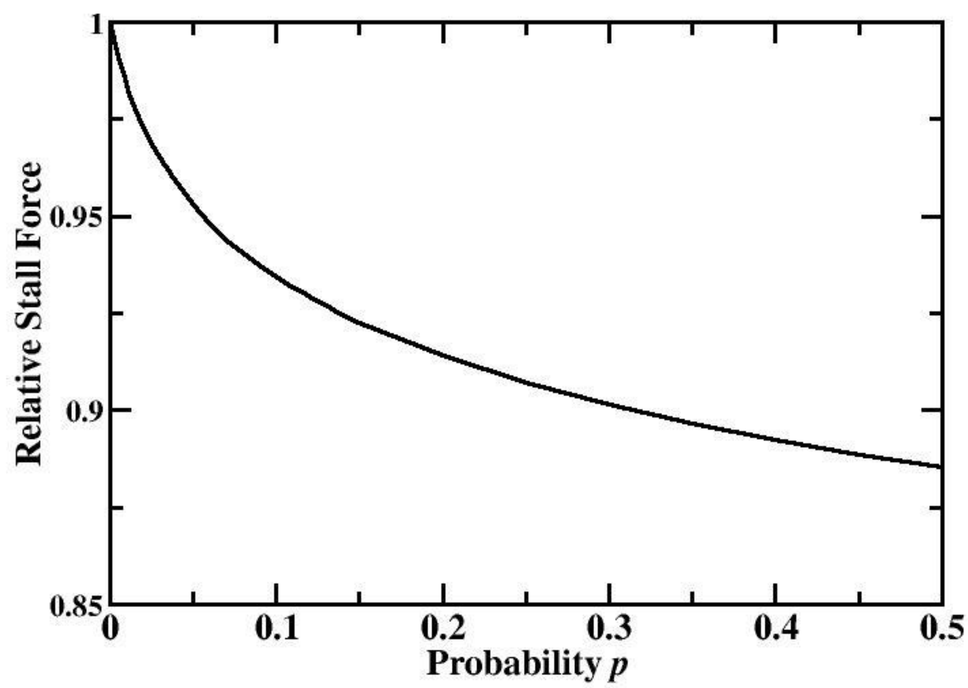
Theoretical Predictions



$$V = V_+ + V_0 + V_-$$

For $p>0$ F_S is a dynamic quantity

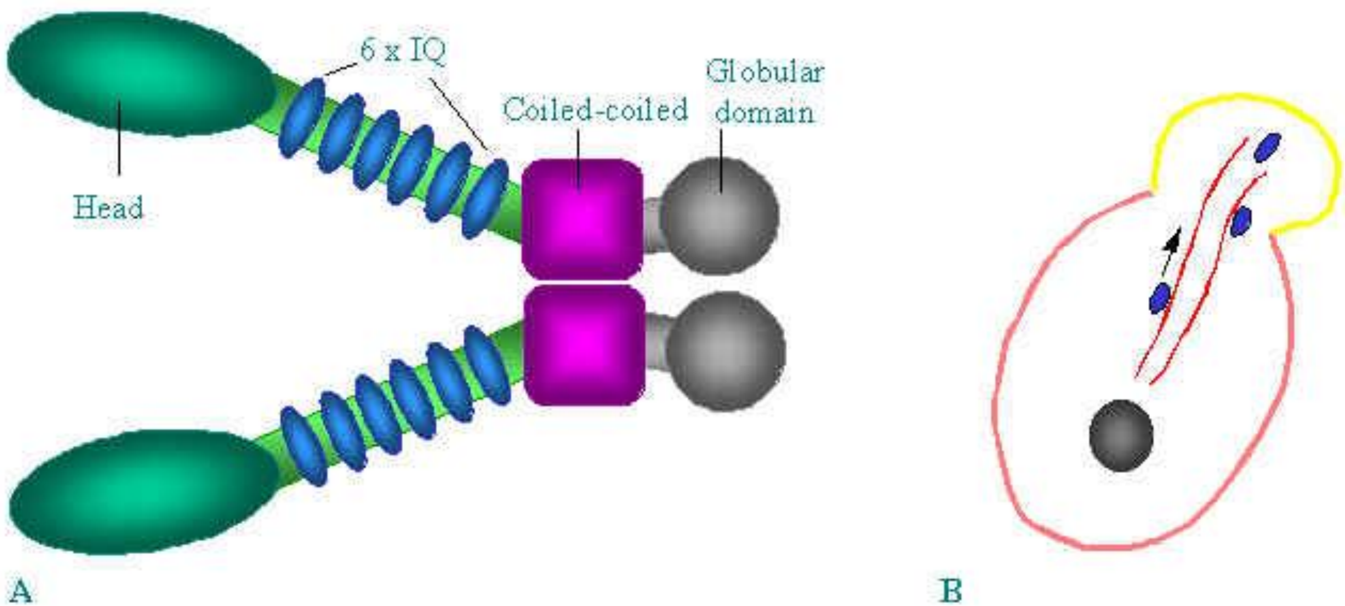
relative stall force



Spatial fluctuations decrease stall forces

Degree of Fluctuations

Myosin-V structure



p- degree of spatial fluctuations;

Can be modified by changing the number of IQ motifs in the lever arm regions

CONCLUSIONS

- **A theoretical approach that allows to estimate the effect of spatial fluctuations on dynamics of motor proteins is developed**
- **For $F=0$ symmetric spatial fluctuations do not change the velocity, but strongly influence the dispersion**
- **Theory is applied for analyzing dynamics of myosins-V**
- **With external forces spatial fluctuations start to affect the velocity only near stall forces, complex behavior for the dispersion**
- **Non-monotonous behavior of randomness**
- **Spatial and stochastic fluctuates are coupled!**
- **Spatial fluctuations decrease the effective stall force**

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R.K. Das and A.B.Kolomeisky, *J. Phys. Chem. B* 2008, **112**, 11112