Molecular motors driven by rotation-translation coupling:

A hybrid powerstroke Brownian motor

Brian Geislinger and Ryoichi Kawai
University of Alabama at Birmingham

Les Houches, May 2006

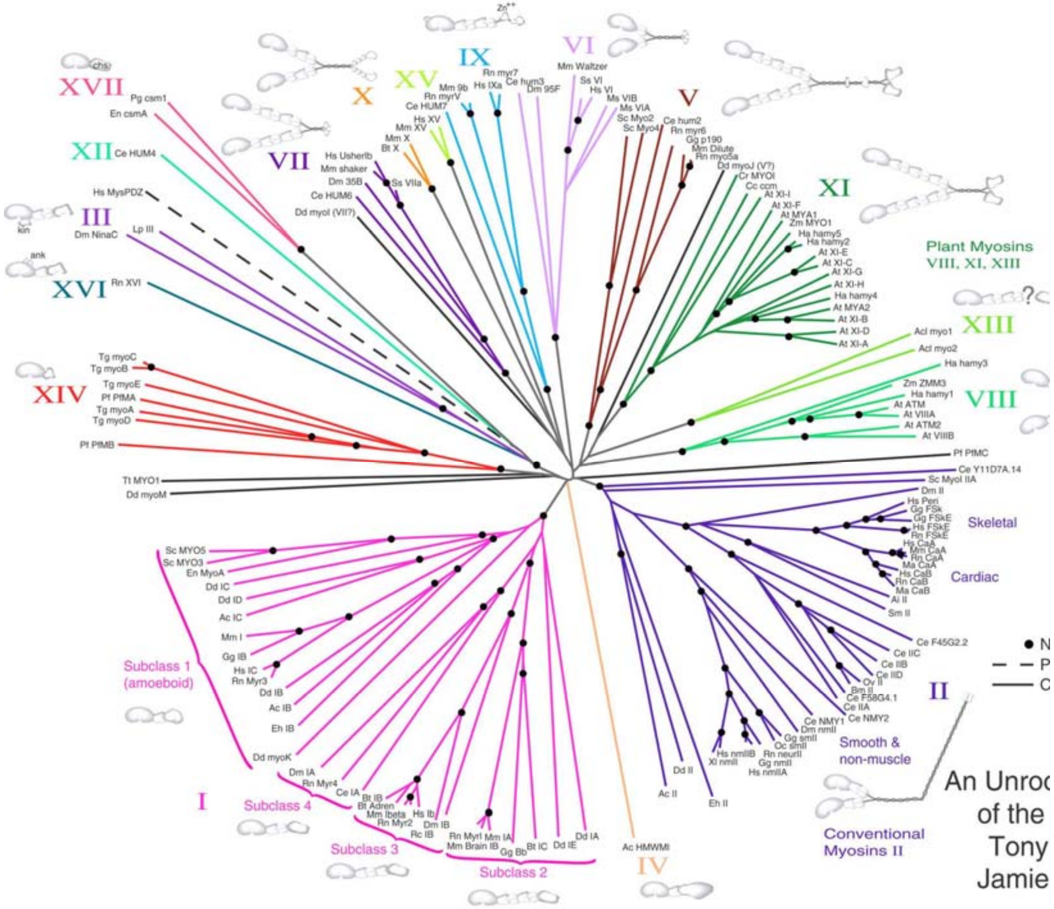
THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Overview

1. Introduction: Powerstroke versus Brownian Motor
2. Modeling a single myosin motor domain
    - Rotation-Translation coupling
    - Two-state monomer
    - Three-state hybrid (the best of both worlds)
3. Dimer motor protein (Myosin V and VI)
4. Collective motion (muscle, Myosin II) [poster]
5. Conclusions

Basic myosin superfamily

- Same motor domain
- Debate over how they move
- Expect motor domains of different subtypes to operate in similar manner
- Different models for different myosin types
- GOAL: Try to explain by first modeling single motor domain, then extend model to different myosin types

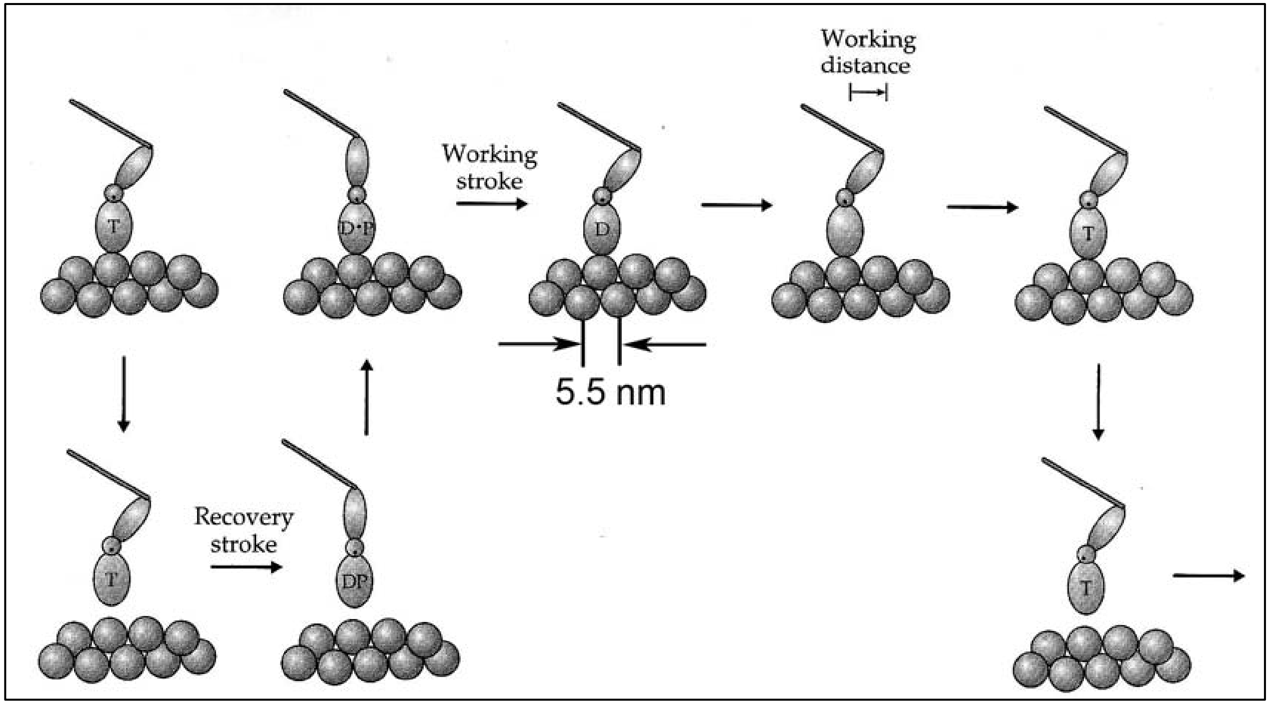


Introduction

- Ongoing debate between powerstroke and Brownian motor models for motor proteins
- Generally agreed upon:
  - ATP hydrolysis leads to cycling between a series of bound and unbound states that motor protein uses to convert chemical energy to mechanical work
  - Series of conformational changes in protein structure
- How do motor proteins put the elements of motion together mechanically? Are they a Brownian ratchet? Or a mechanical engine?

Powerstroke

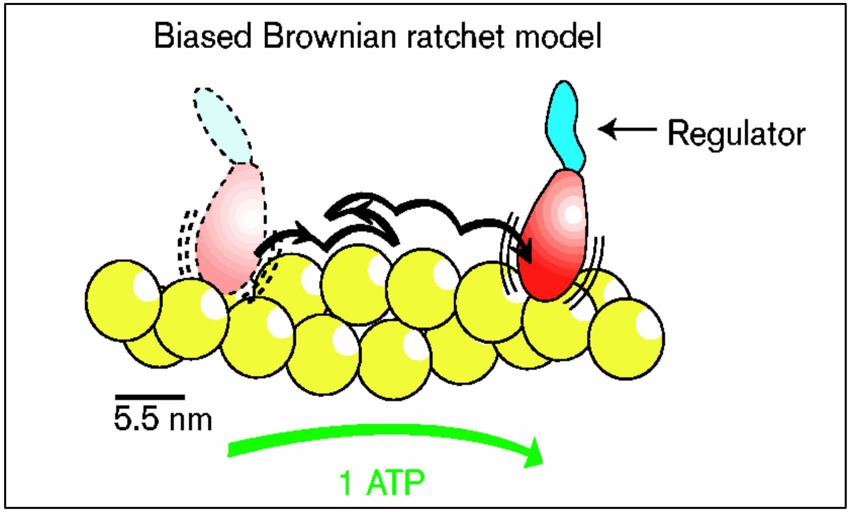
- Conformational change in neck shifts protein forward in deterministic fashion
- Recovery stroke resets protein for the next binding cycle
- Motion arises from the protein continuing to make one step per cycle



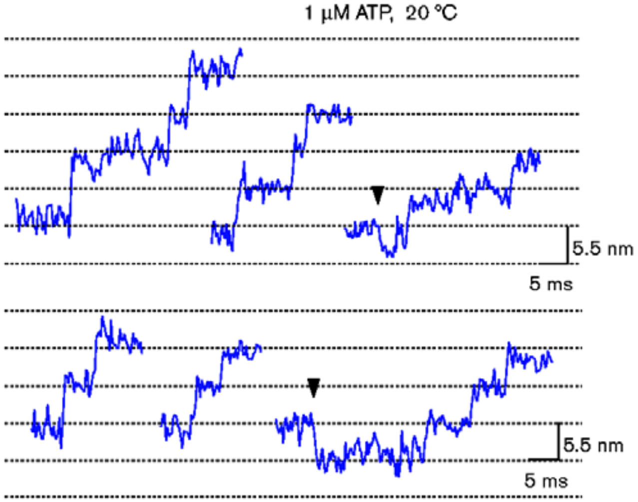
Howard (2001)

Brownian Motor

- General mechanism for rectifying thermal fluctuations
- Some experimental evidence that doesn't work with a powerstroke model
  - Multiple steps per ATP hydrolysis?
  - Backward steps?
  - Steps too large to be explained with a powerstroke
  - In some experiments, step size does not depend on neck length



Yanagida (2002)



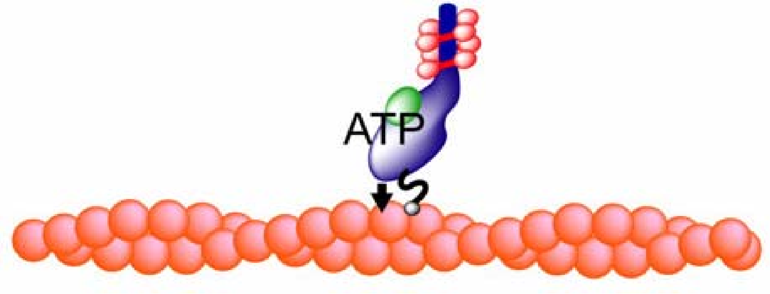
Kitamura (1999)

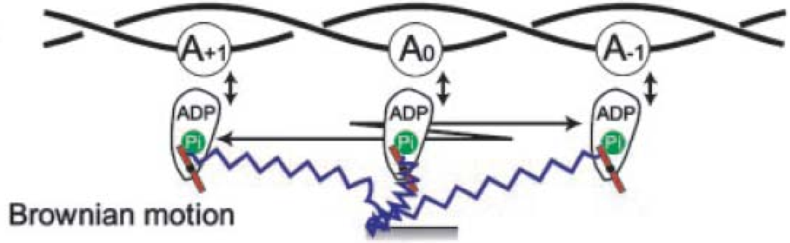
Monomeric motor proteins in experiments

- Myosin II single motor domain
  - *Kitamura, et al.* (1999)

- Myosin IXb
  - *Inoue, et al.* (2002): a single-headed, processive motor
  - *Kambara, et al.* (2005): Unique insert keeps motor tethered to actin

- Myosin V single motor domain
  - *Watanabe, et al.* (2004): single domain still processive





Model:
Rotation-translation Coupling

- Two degrees of freedom, x and θ
- Bound state potential $V(x_P, \theta) = U_{rot}(\theta) + U_{trans}(x_P)$

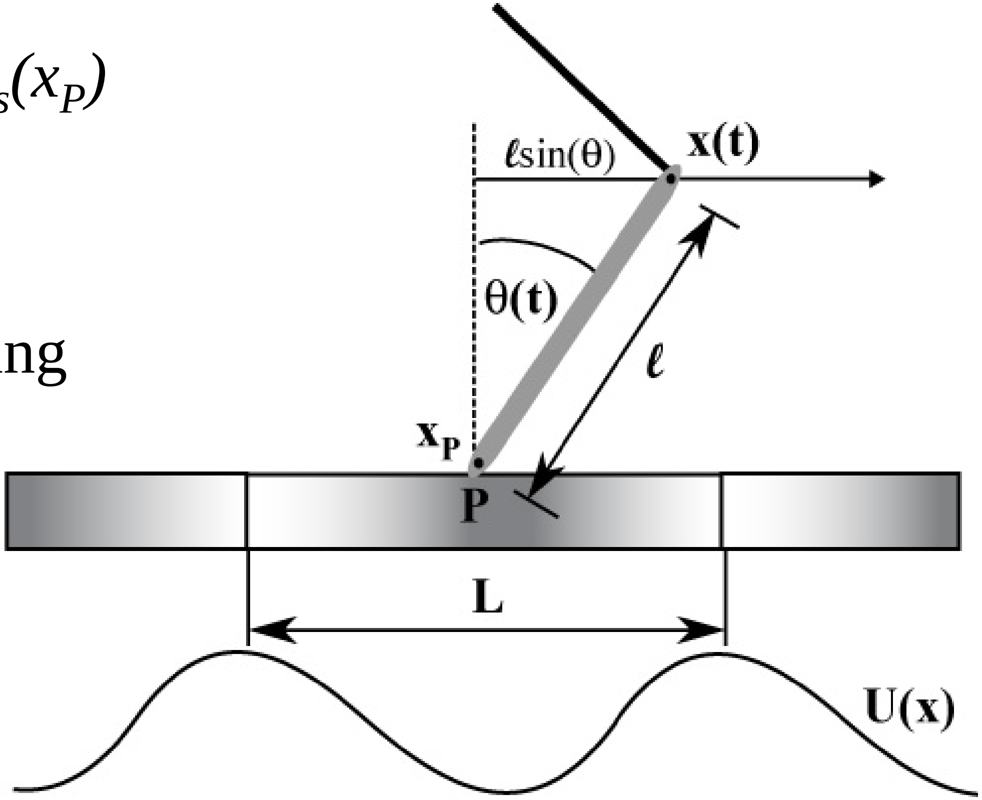
- Only requirement for $U_{trans}(x_P)$

$$U_{trans}(x_P) = U_{trans}(x_P + L)$$

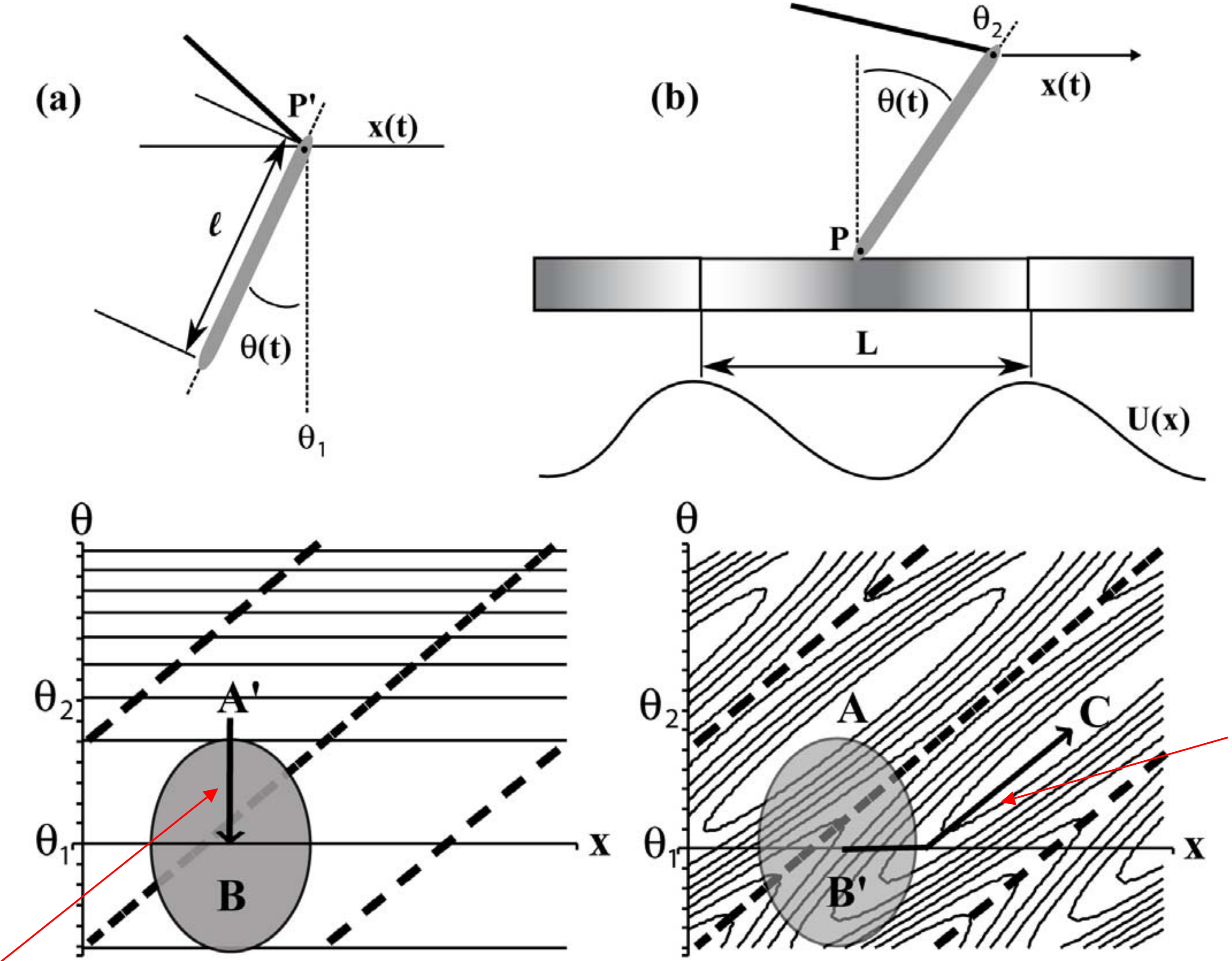
- Rotation-translation coupling

$$x_P = x - \ell \sin\theta \approx x - \ell\theta$$

$$U_{trans}(x_P) = U_{trans}(x - \ell\theta)$$



Two state Brownian motor with powerstroke



$$\Delta\theta = \theta_2 - \theta_1$$

Forward stroke

Recovery stroke

$$V_1(x,\theta) = U_{rot}(\theta)$$

$$V_2(x,\theta) = U_{rot}(\theta) + U_{trans}(x - \ell\theta)$$

Mathematical Model: Overdamped Langevin equations

$$\dot{x} = -\frac{\partial V(x,\theta,t)}{\partial x} + \sqrt{2D}\,\xi_x + F$$

$$\dot{\theta} = -\alpha\frac{\partial V(x,\theta,t)}{\partial \theta} + \sqrt{2\alpha D}\,\xi_\theta$$

F = External Load

$$V(x,\theta,t) = V_1(x,\theta)[1-\sigma(t)] + V_2(x,\theta)\sigma(t)$$

$$\sigma(t) = \begin{cases} 0, & \textit{unbound} \\ 1, & \textit{bound} \end{cases}$$

$$\alpha = \frac{\ell^2\gamma_x}{\gamma_\theta} \qquad D = \frac{kT}{U_0}$$

$$\left\langle \xi_i(t)\xi_j(t') \right\rangle = \delta_{ij}\delta(t-t') \qquad i, j \in (x,\theta)$$

$$V_i(x,\theta) = U_{rot}(\theta) + U_{trans}(x-\ell\theta)$$

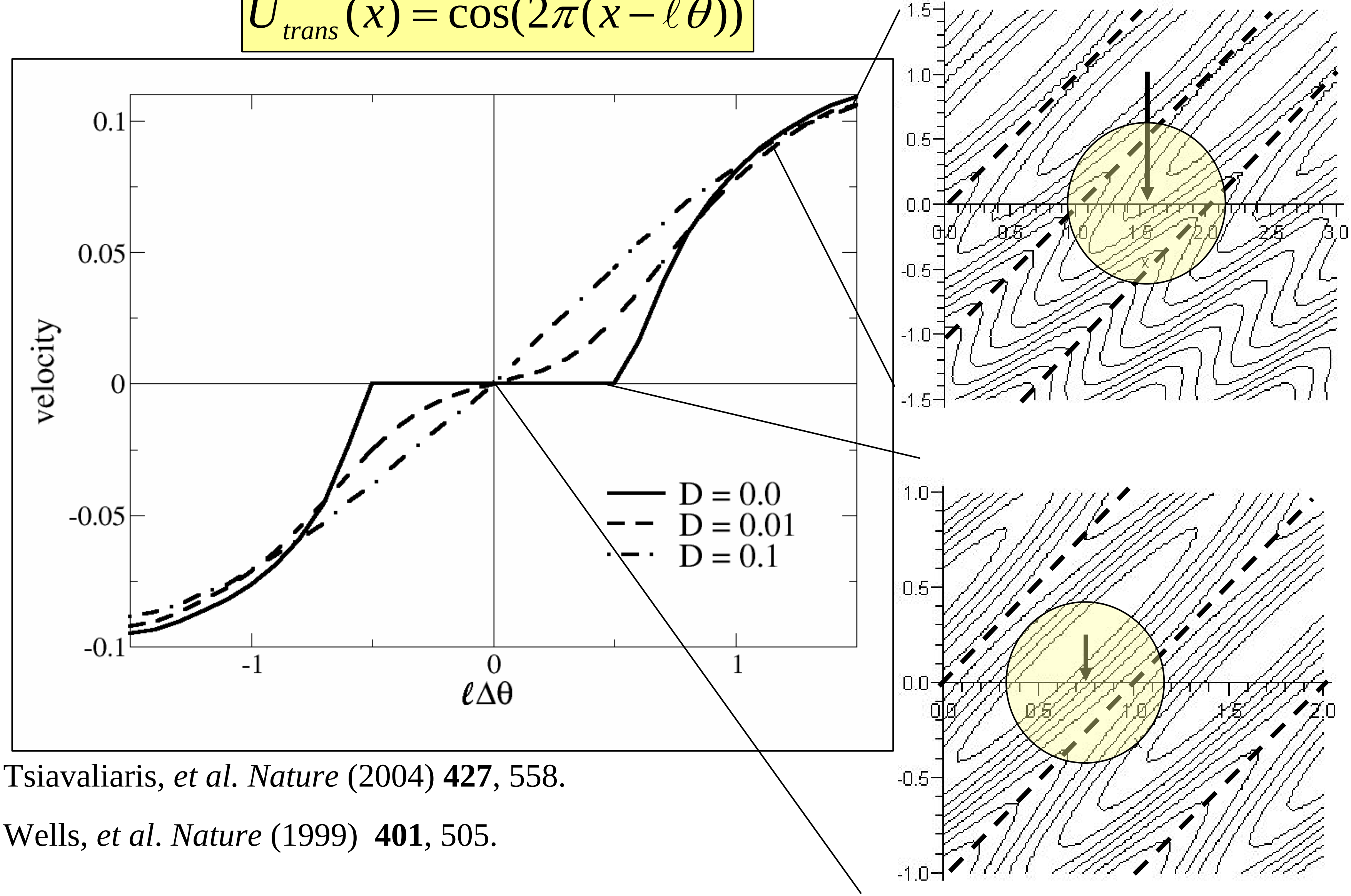
$$U_{rot}(\theta) = \tfrac{K}{2}(\theta-\theta_i)^2$$

$$U_{trans}(x) = U_{trans}(x+L)$$

Length, time and energy have been normalized

Conformational change (*ℓ*Δθ) vs. Velocity

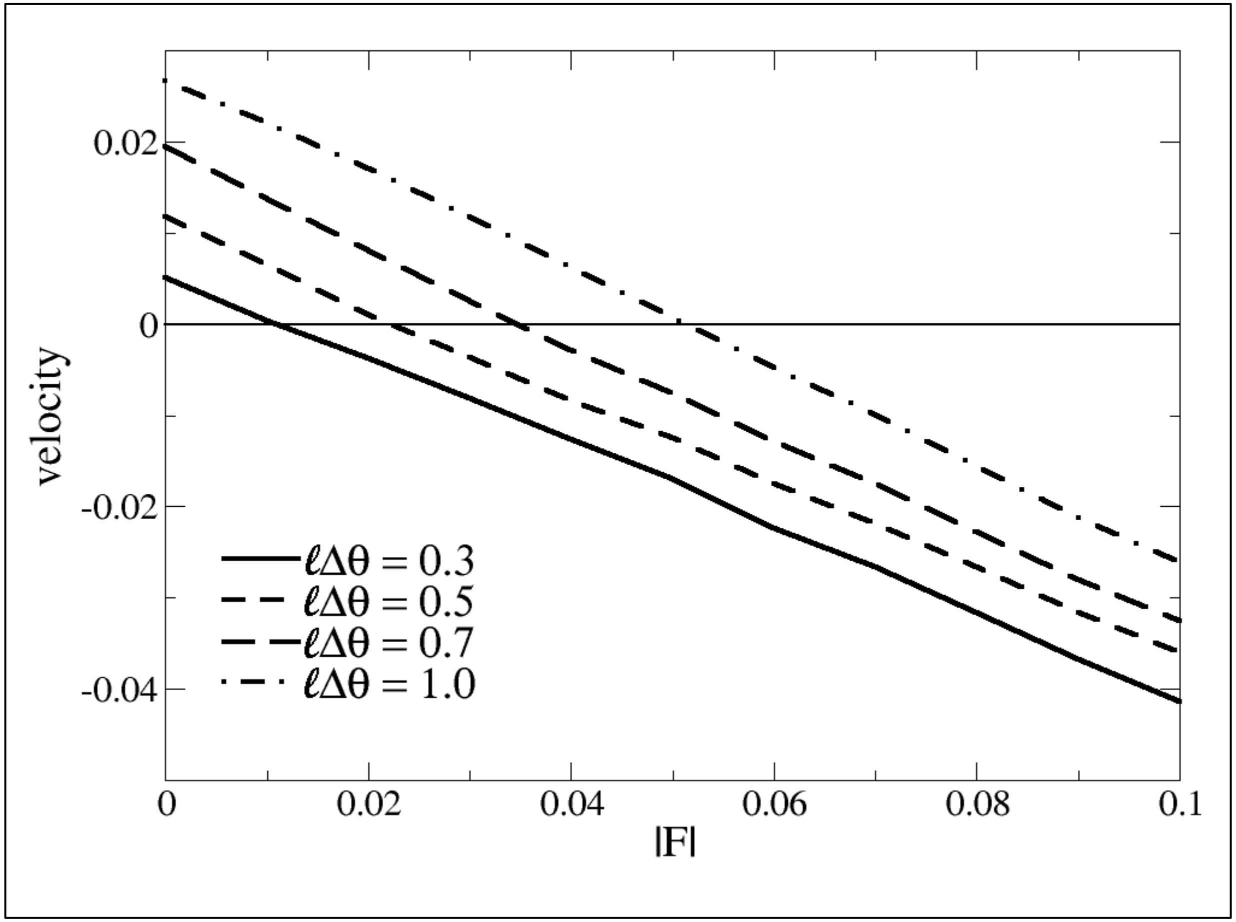
$$U_{trans}(x) = \cos(2\pi(x - \ell\theta))$$



Tsiavaliaris, *et al*. *Nature* (2004) **427**, 558.

Wells, *et al*. *Nature* (1999) **401**, 505.

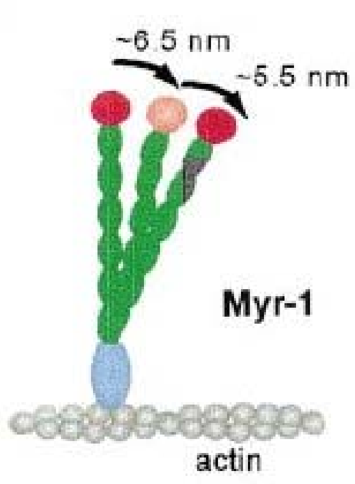
Velocity vs. Applied load



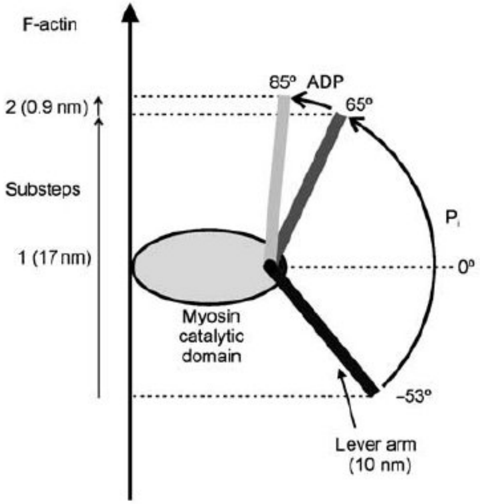
- Linear response in velocity to applied load
- Increasing contribution of powerstroke increases F_{stall}
- Doesn’t amount to much force ($F < 1.0\ pN$)

Three conformational states

- Motor protein working strokes resolved into multiple sub-steps
- Protein structure data
- At least three distinct protein conformations observed based on status of bound nucleotide

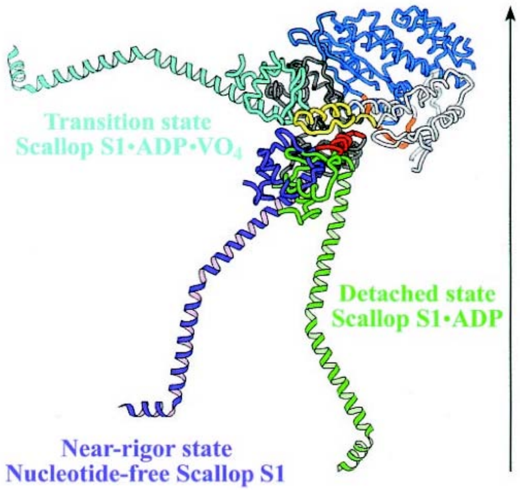


Veigel (1999)



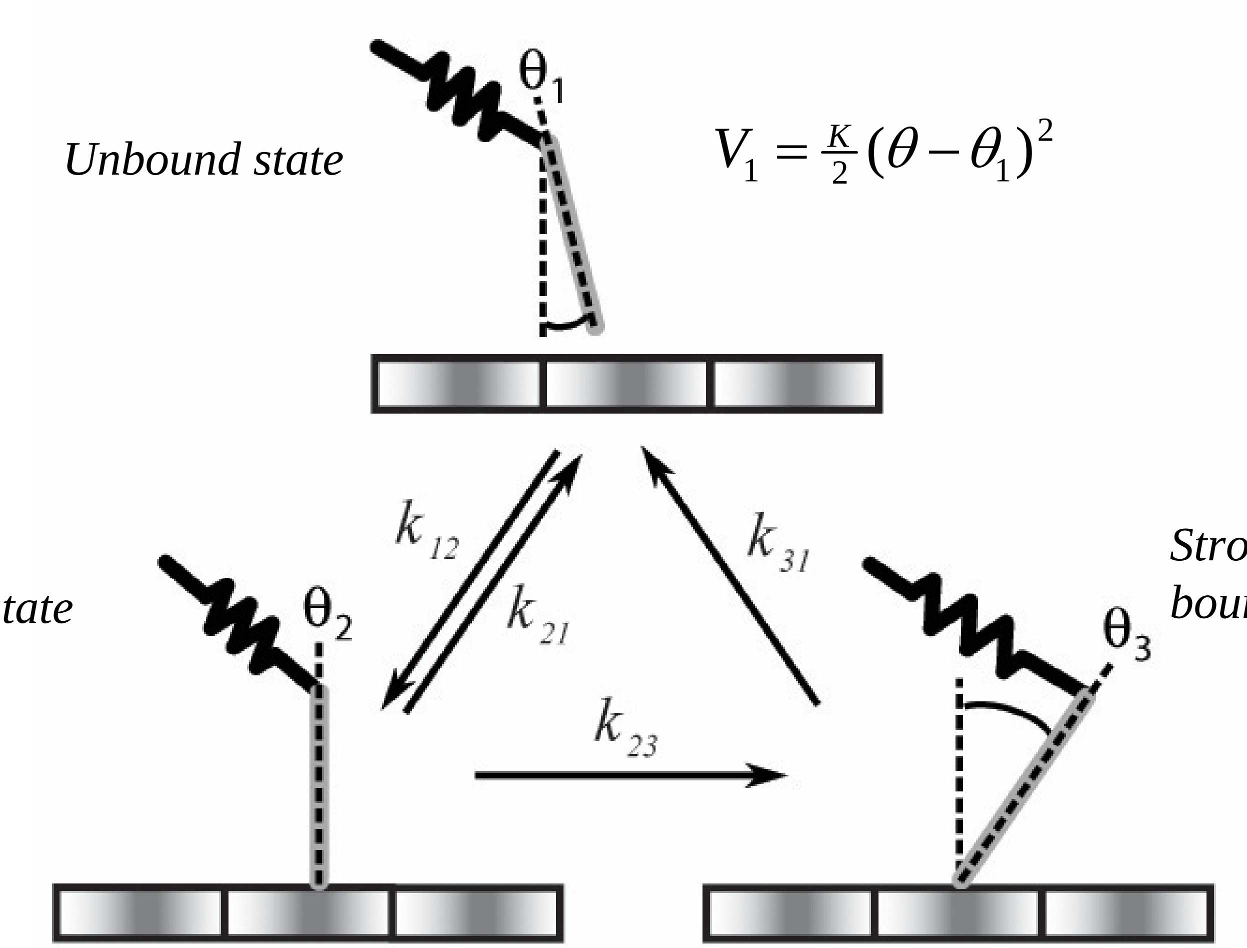
Lister (2004)

Three distinct conformational states of scallop S1



Houdousse (2000)

Three states



Unbound state

$$V_1 = \tfrac{K}{2}(\theta - \theta_1)^2$$

Weakly bound state

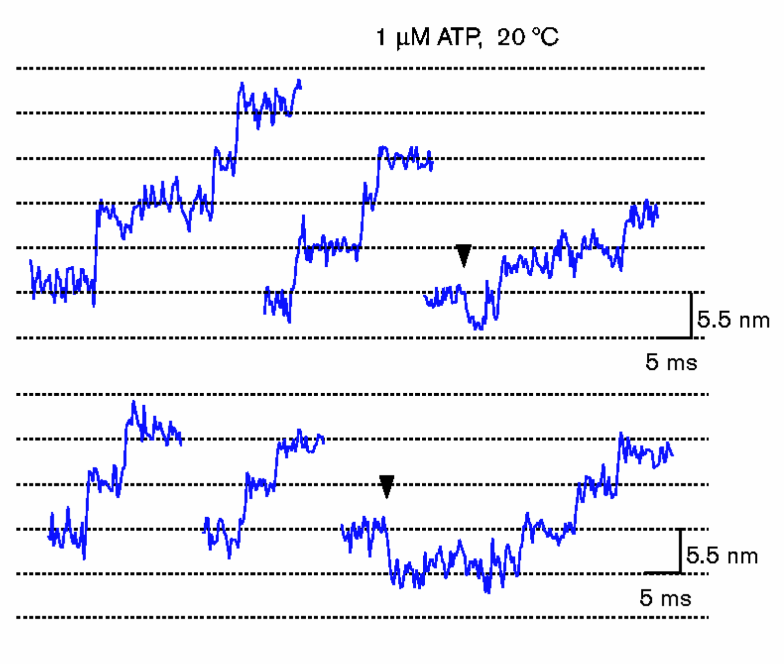
Strongly bound state

$$V_2 = \tfrac{K}{2}(\theta - \theta_2)^2 + U_2 \cos(2\pi(x - \ell\theta))$$

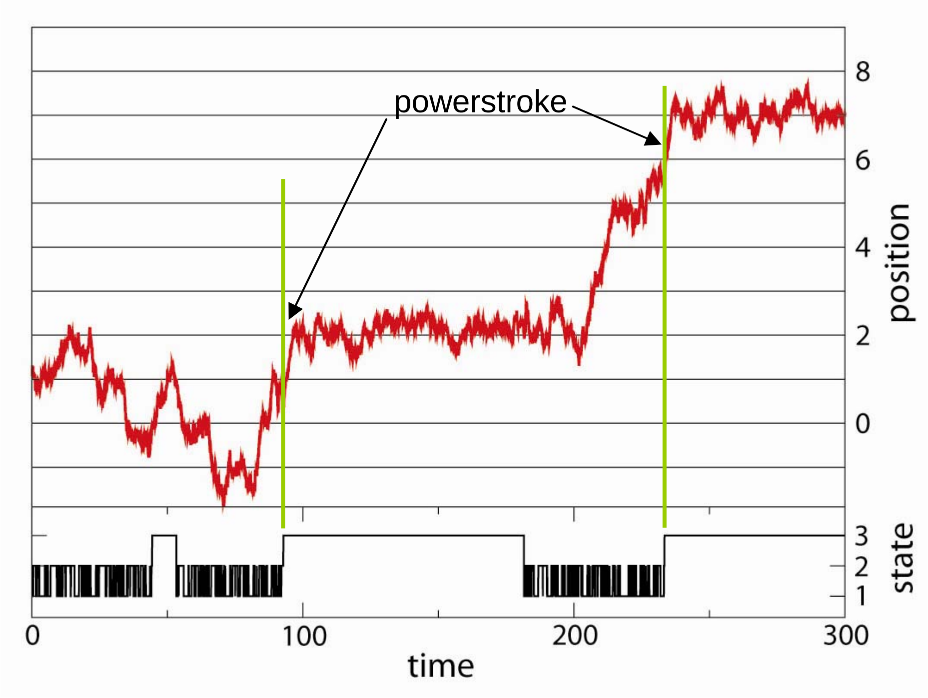
$$V_3 = \tfrac{K}{2}(\theta - \theta_3)^2 + U_3 \cos(2\pi(x - \ell\theta))$$

Trajectory for three state model

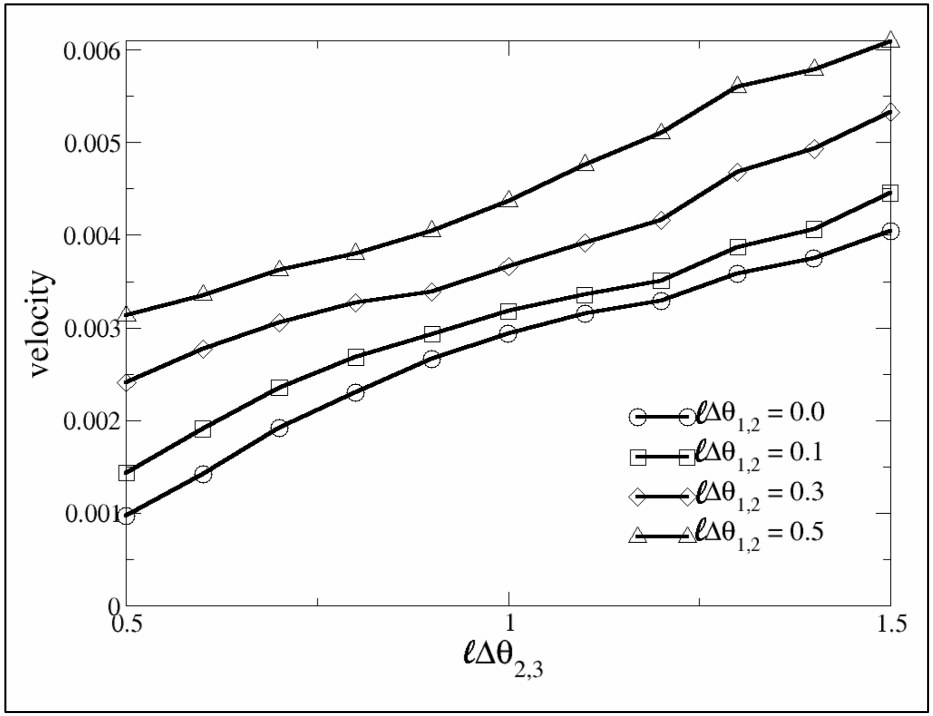
- Transition between state 2 and 3 (powerstroke) moves one potential period
- Simulation steps multiple periods per cycle
- Occasionally takes backward steps



Kitamura (1999)

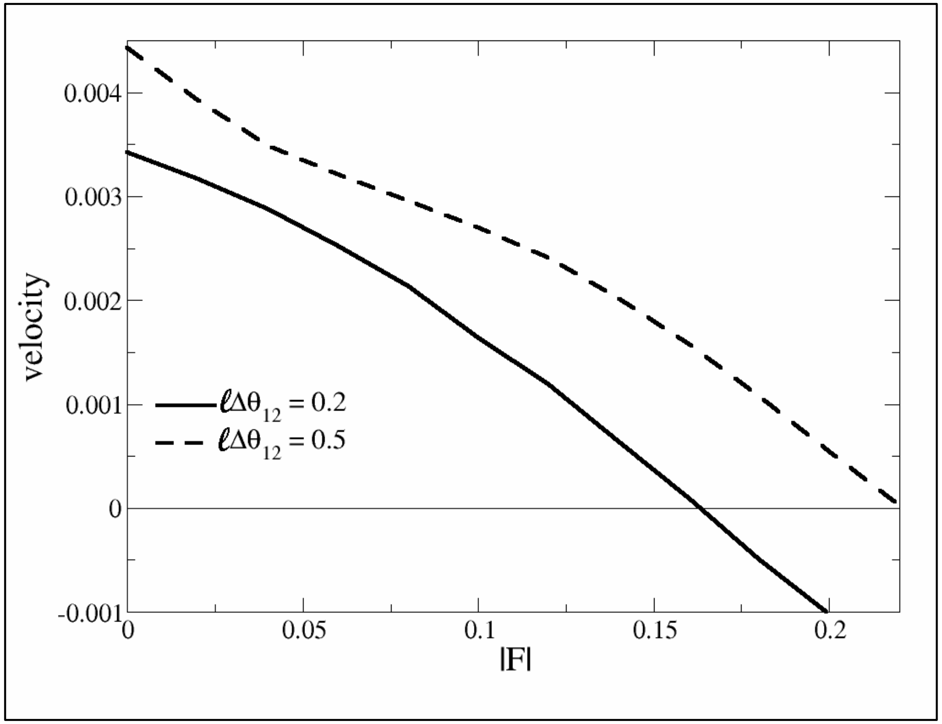


Three State System: Results



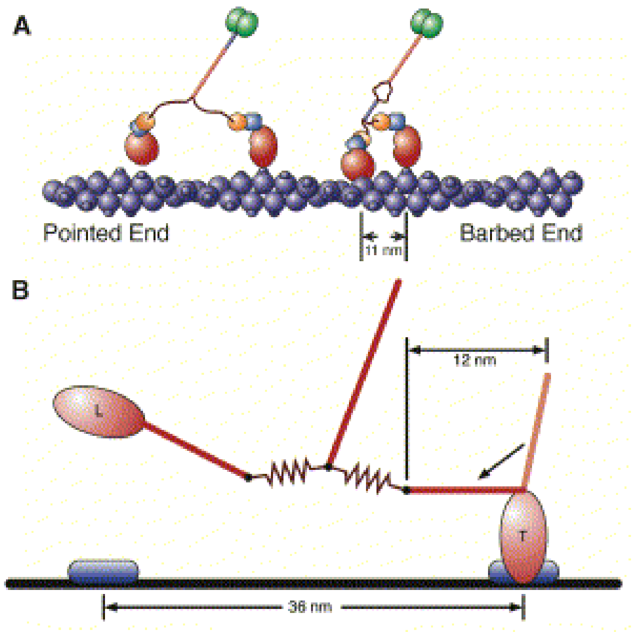
- Increasing contribution of Brownian mechanism
- Maximum contribution of Brownian phase ($\ell\Delta\theta_{12}$=0.5) nearly triples motor speed
- Motor takes approximately two additional steps per ATP cycle

- Linear response to load
- Motor capacity against applied load considerably (F_{stall} = 2.0 *pN*) increased over the two state system (F_{stall} < 1.0 *pN*)

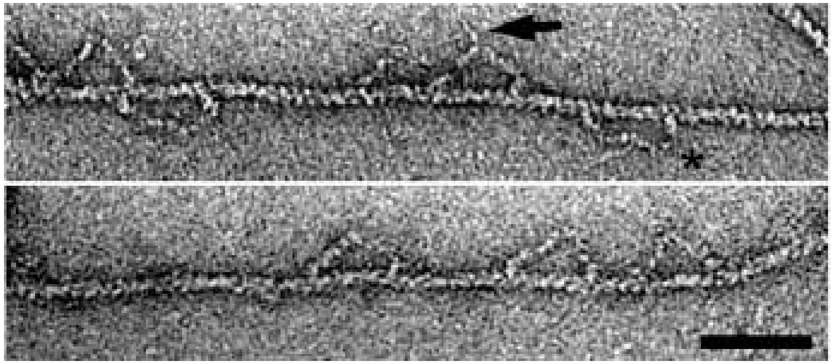


Dimeric processive motors

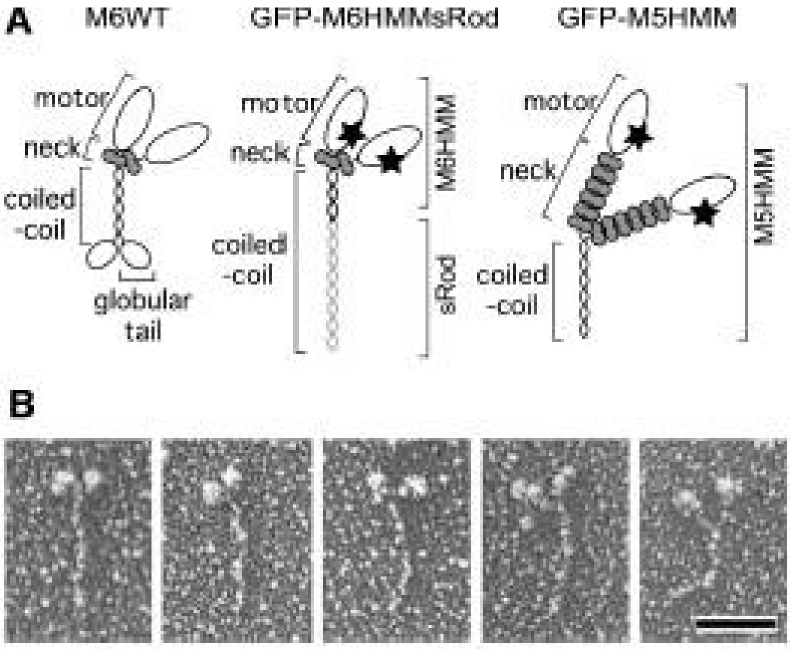
Rock (2005)



- Myosin V
  - Long neck length, long step size
  - Hand-over-hand motion
- Myosin VI
  - Much shorter neck than V
  - Same stepping distance (36 *nm*)
  - Flexible proximal tail



Walker (2000)

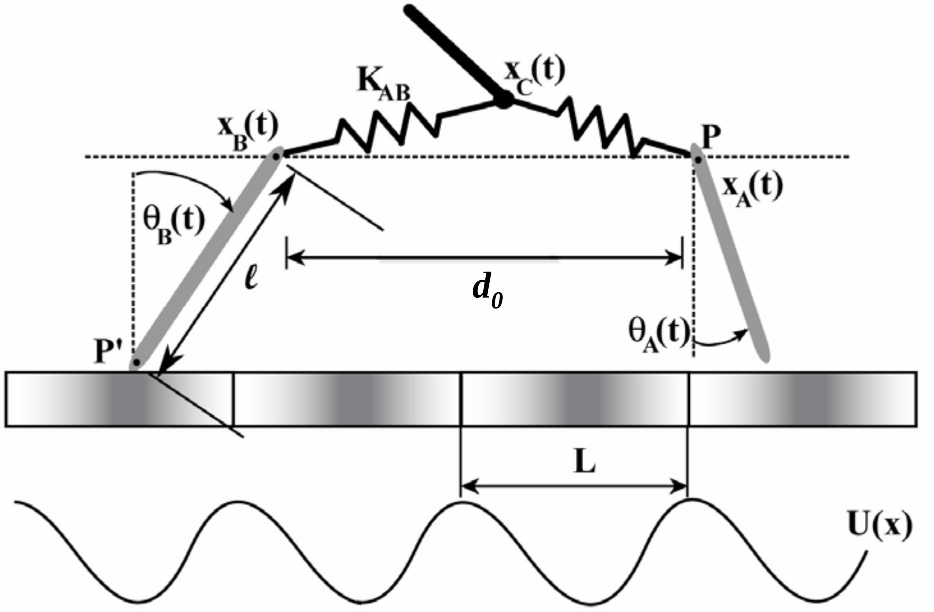


Dimer Model

- Each motor domain described by three-state model
- Motors connected by springs
- Force dependent reaction rates stemming from intra-molecular strain
  - Forward pull increases ADP release
  - Backward force decreases ADP release

  [*Purcell, et al. (2005); Veigel, et al. (2005)*]
- Switch mechanism based on strain

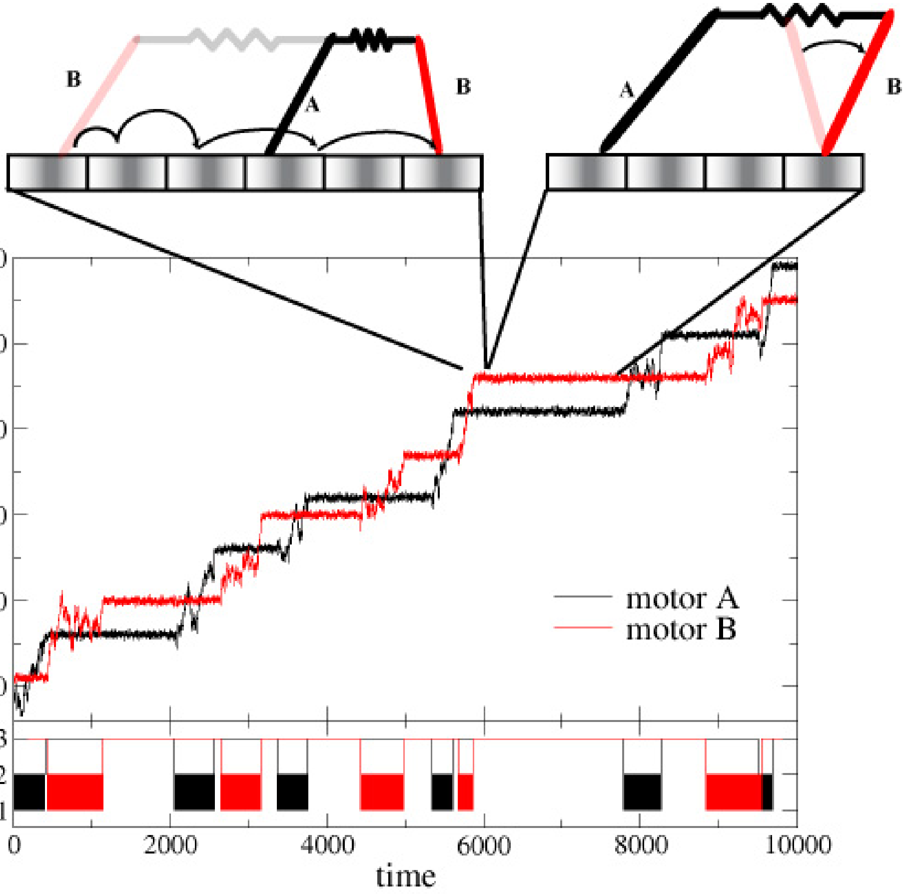
$$k'_{31} = k_{31}\left(1 + \tanh\left(\frac{|x_a - x_b| - d_0}{\Delta d}\right)\right)$$

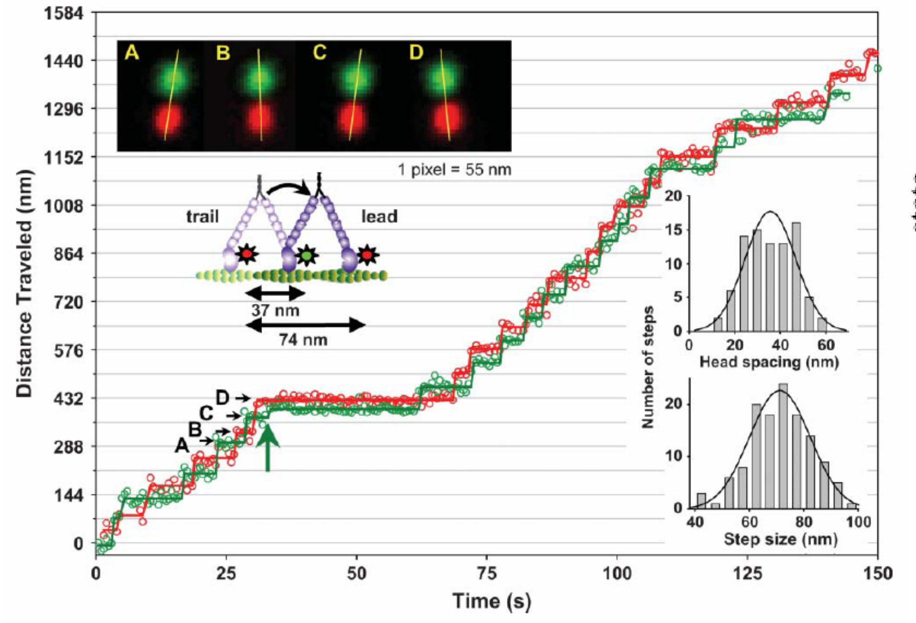


Myosin V	**Myosin VI**
Large ***ℓ***	Small ***ℓ***
Small d_0	Large d_0
Large K_{AB} Tight coupling	Small K_{AB} Weak coupling

Myosin VI

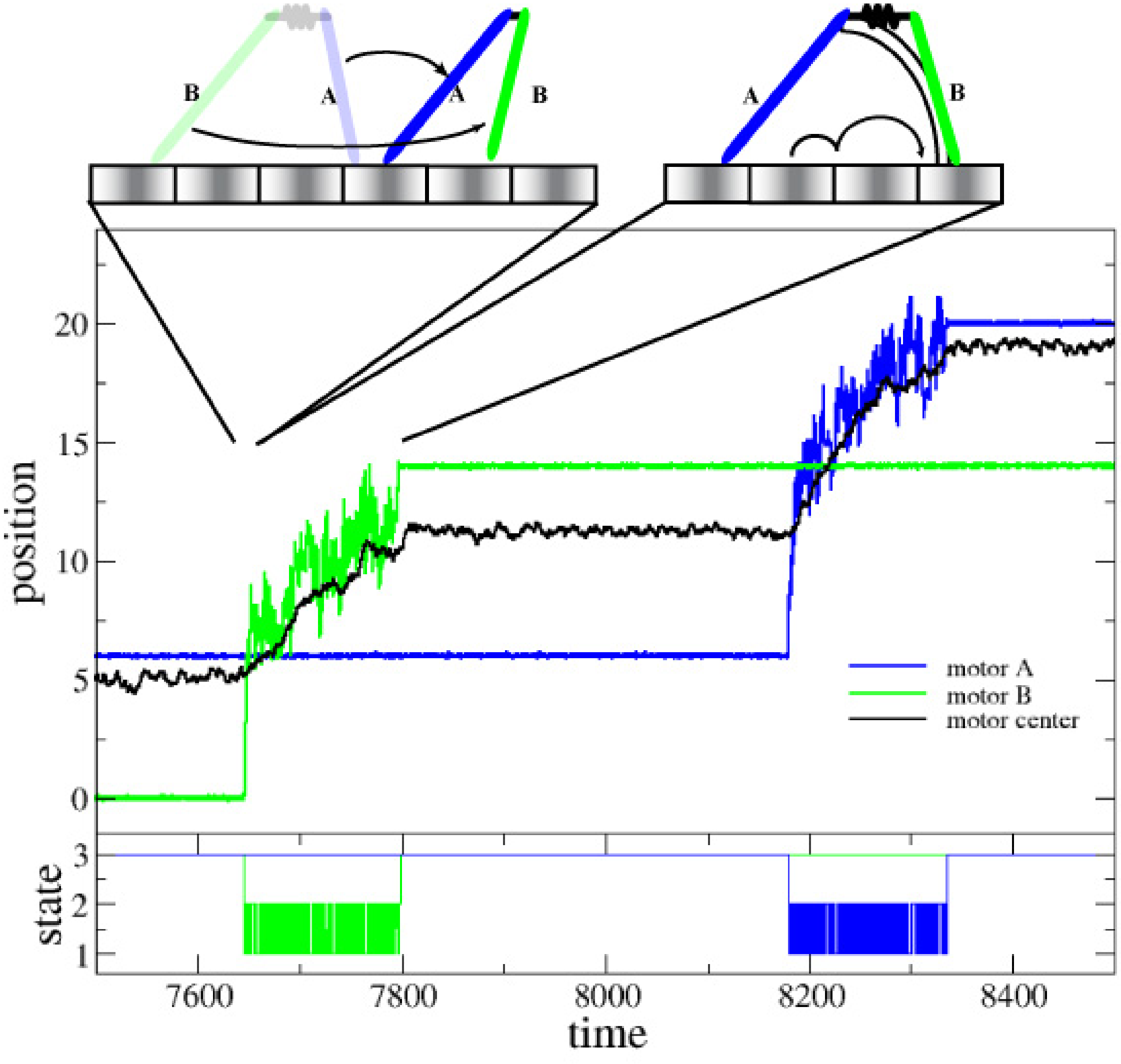
- Hand-over-hand motion
- Reasonable model for Myosin VI
  - Strongly bound state anchors dimer
  - Most motion due to diffusive process





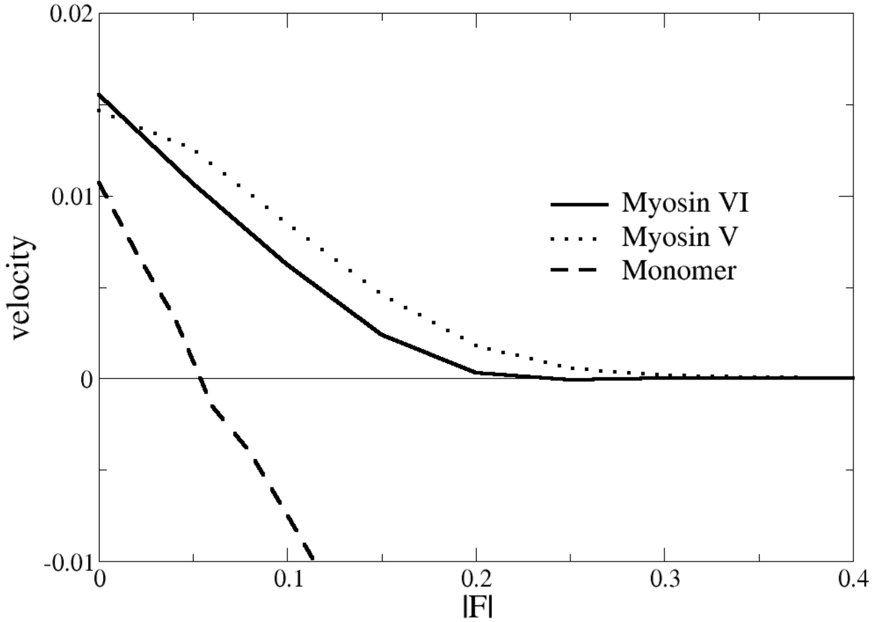
Warshaw (2005)

Myosin V



- Tight spring
- Long neck length
- *Veigel, et al. (2002)*: Myosin V 36-*nm* step length is made of a 25-*nm* powerstroke plus 11-*nm* diffusive step
- Combination powerstroke and Brownian motion
- Telemark-stance

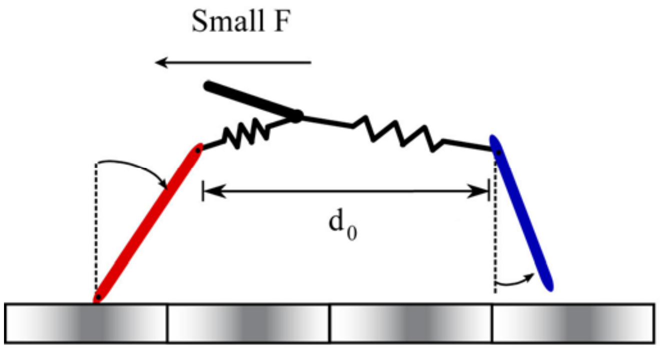
Dimer:
Velocity vs. Applied load

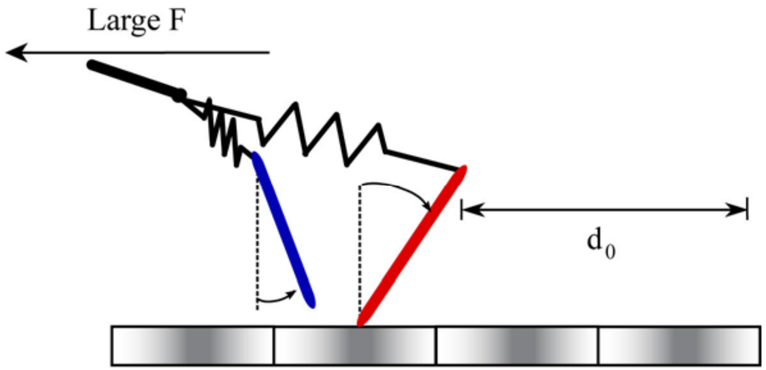


- More than twice the stall load compared with monomer
  [Watanabe, *et al.* PNAS (2004)]
- Monotonic approach to F_{stall} due to force dependent kinetics

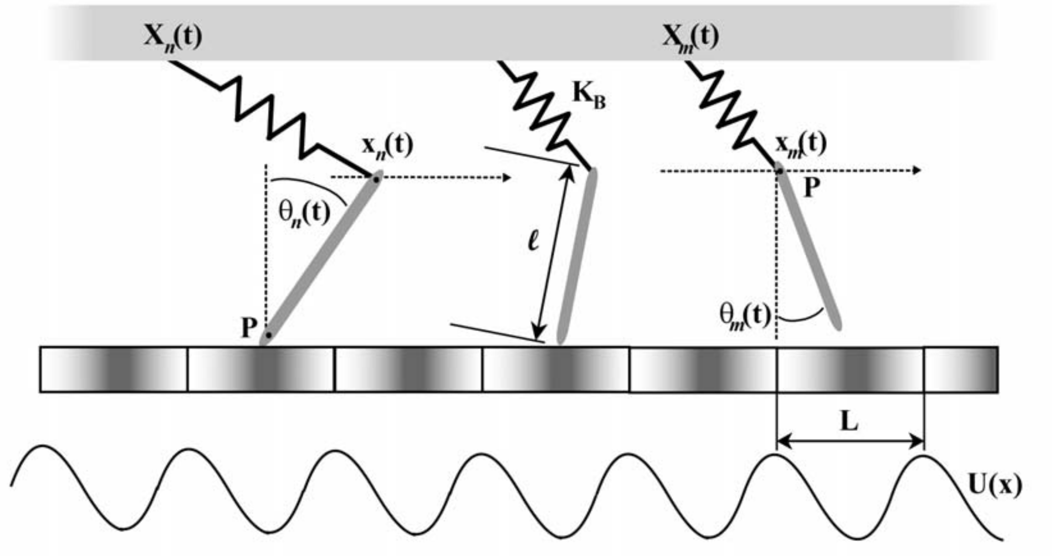
$$F_{stall} \approx 0.9\ pN \quad \text{(monomer)}$$

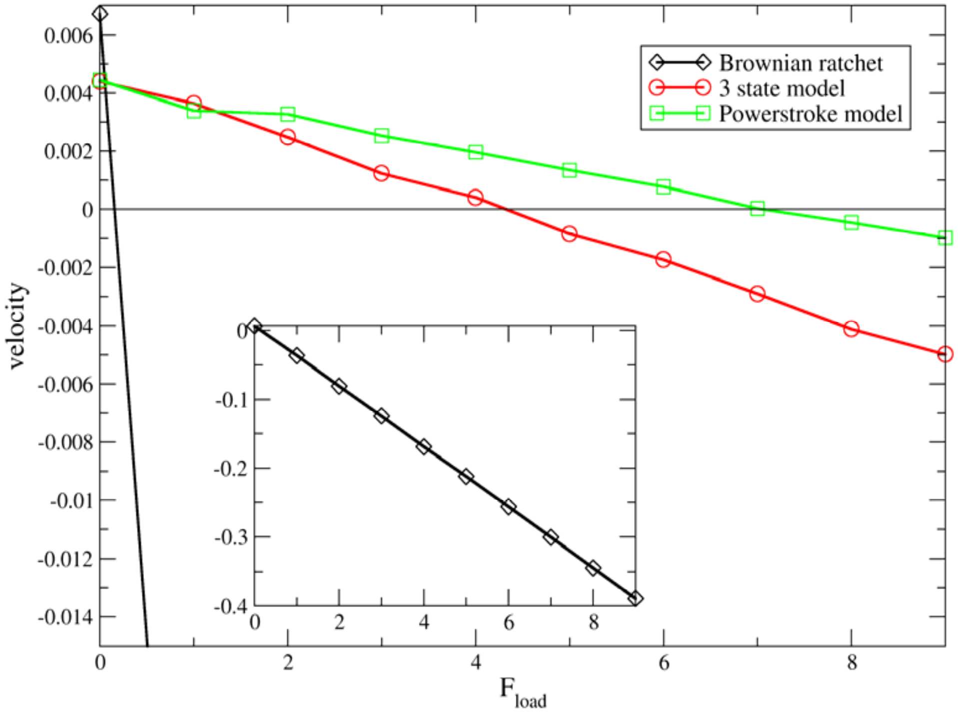
$$F_{stall} \approx 3\ pN \quad \text{(dimer)}$$





Collective motion [poster]





- Monomers coupled to backbone via spring
- Why are single molecule Myosin II experiments different from muscle fiber experiments?
- Hybrid monomers behave more like powerstroke monomers

Conclusions

- Unified system with both powerstroke and Brownian motor mechanisms for single motor domain
- Angular conformational change incorporated into model
- Directionality determined by conformational change
- Asymmetry in U_{trans} not necessary for Brownian motor
- Dimer:
  - Brownian motion plays large role in Myosin VI
  - Combination powerstroke and brownian motion in Myosin V

Thanks to: Kimberly Farris, Erin Darnell, NSF GK-12 Award No. 0139108