Regularity and synchrony for motor proteins

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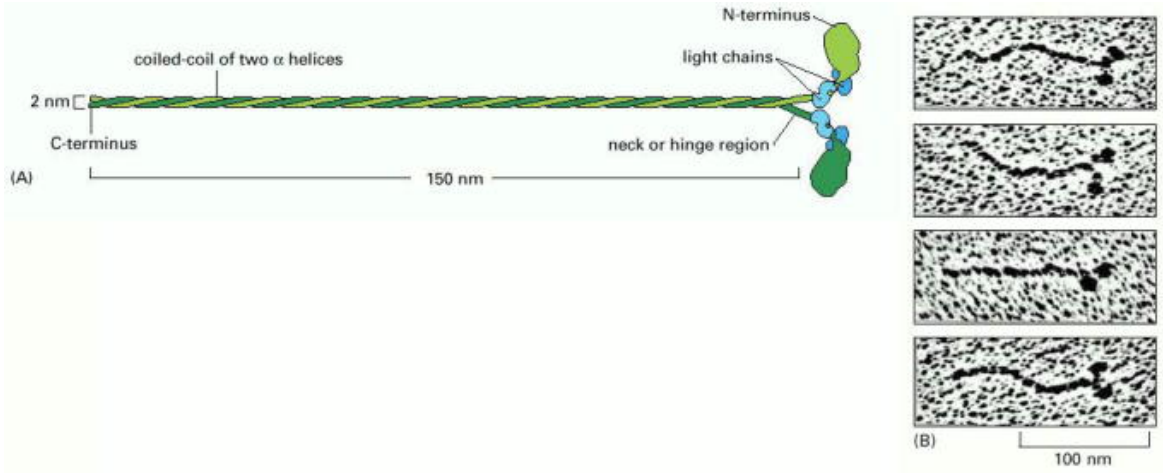
Overview of ideas

- Can noise have a constructive influence in a complicated system?

- Stochastic resonance (and related effects)
  - Well-known and much-studied in physics & biological literature
  - When matched with multiscale dynamics, can be surprisingly regular

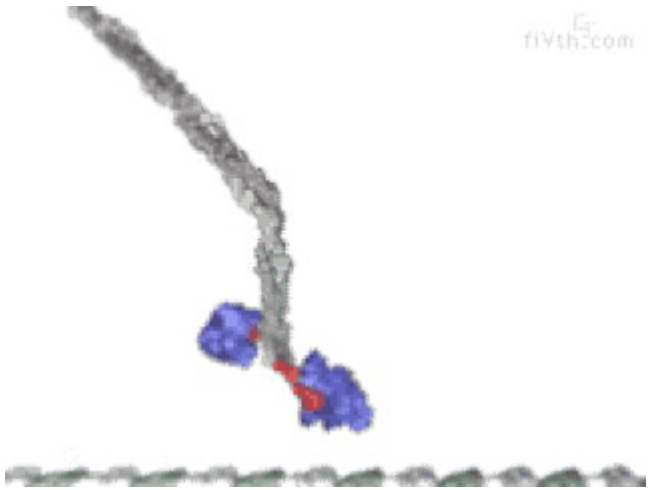
- Motor proteins
  - Analysis predicts regularity and synchrony
    - Regularity for single (or few) proteins
    - Synchrony for large populations
  - Details of mathematical proof speak to real physical behavior!
  - Finally (!), what can we say about motor protein dynamics?

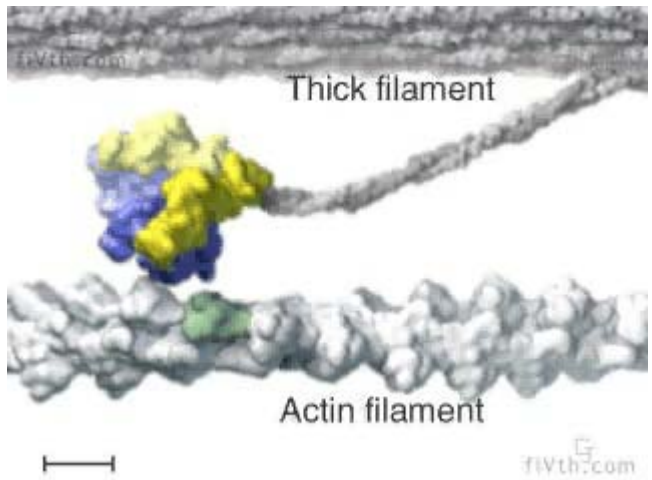
Structure, function of motor proteins



Kinesin – vesicle transport

Myosin II – muscle contraction





Vale, R.D., Milligan, R.A. ***Science 288:*** *88-95* (2000)

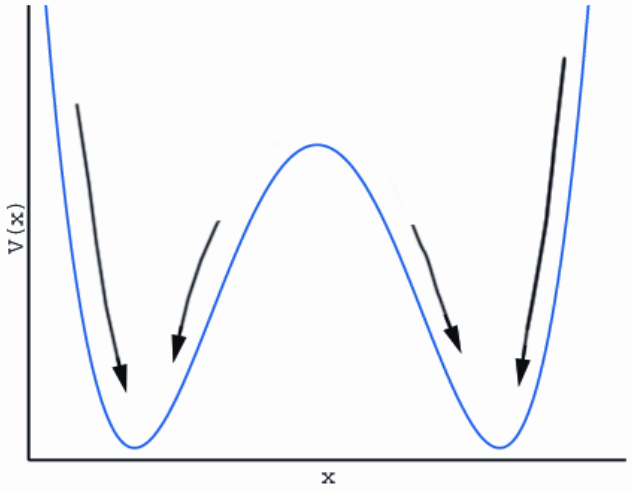
Properties of models

- thermally-driven, single molecule --> stochastic model
- large-scale motion, induced by small-scale reaction
  - This suggests memoryless statistics
- Wide variety of models:
  - diffusion in complex potential: MD or at least fine structure
    - Oster, Peskin (94); Peskin, Elston (00); Atzberger, Peskin (06); Wang, Oster (02, 04); Jülicher, Prost (1995); many more
  - empirically-determined coarse-grained models
    - Huxley (57), Kolomeisky, Fisher (98,99,01,03); Kafri, Lubensky, Nelson (04)
  - ratchet models
    - Reimann (02), Riemann & Hanggi (98,…), Peskin, Oster, Odell (95), many more
- adding a cargo to the molecular motor model creates regularity
    - Schilstra, Martin (06)
    - Crucial component: elastic tether!
- Families of motors: useful in muscle contraction
    - Howard (97); Duke (99, 00); many more

Large deviation / Rare events

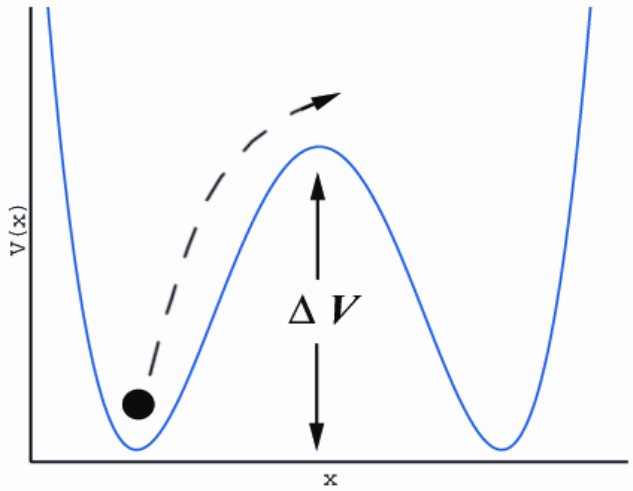
$$V(x) = (1 - x^2)^2$$

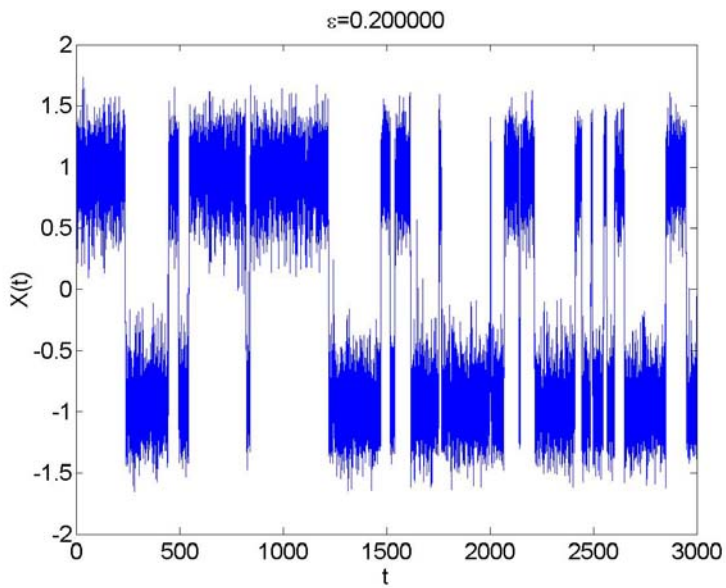
$$\frac{dx}{dt} = -V'(x)$$

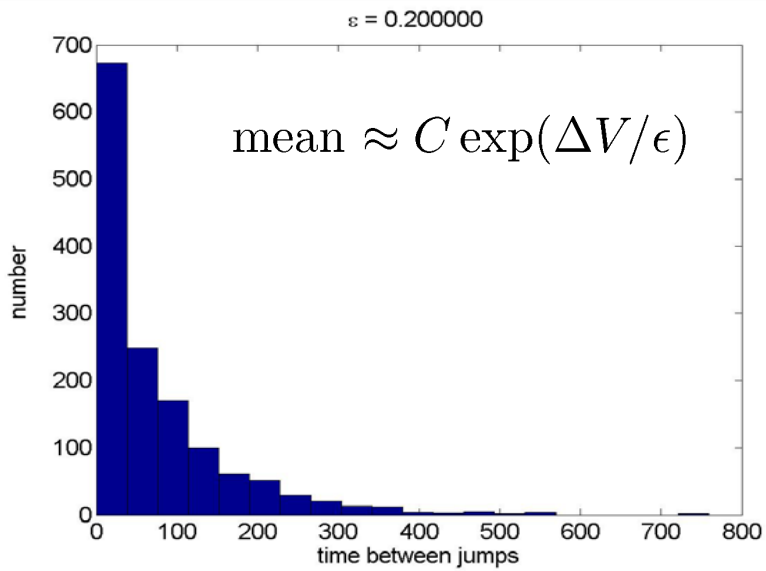


add noise

$$dx = -V'(x)\,dt + \sqrt{2\epsilon}\,dW$$

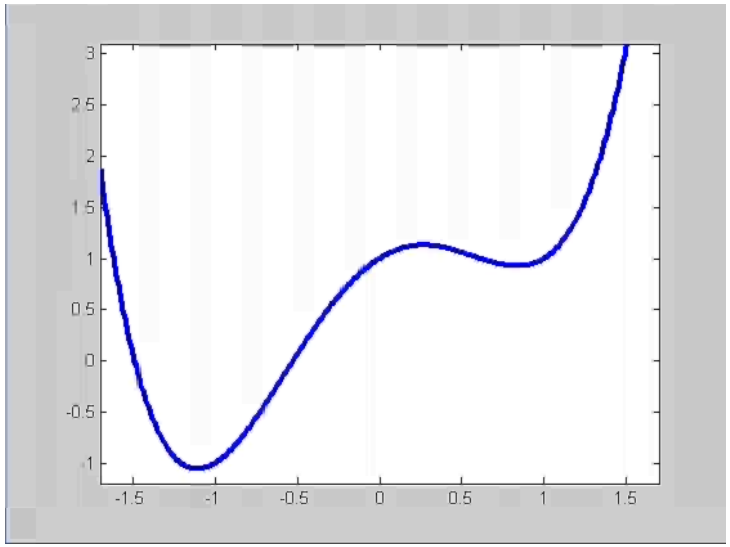


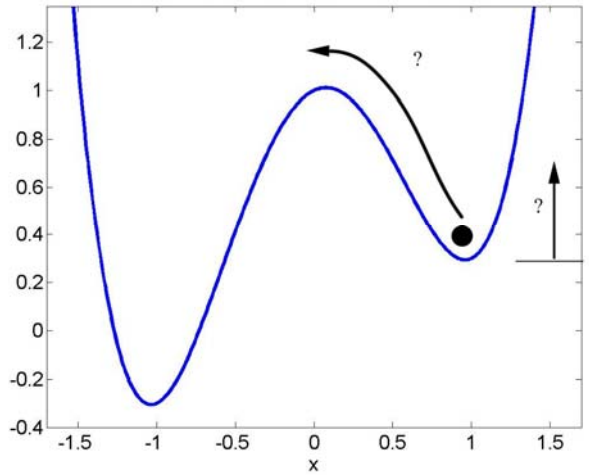




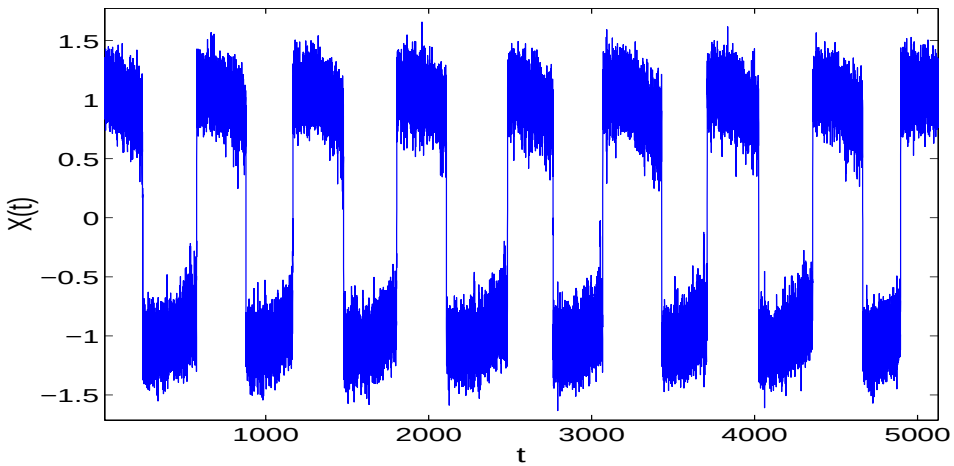
Stochastic Resonance

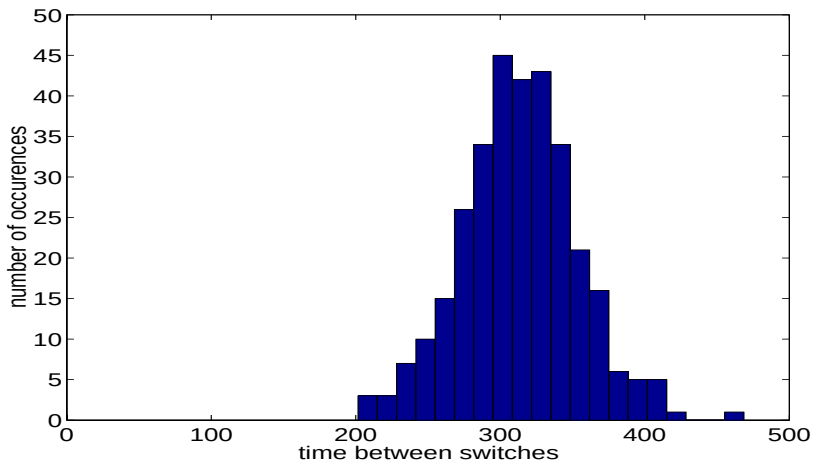
$$V(x) \mapsto V(x) + \cos(\omega t)x, \qquad dx = -(V'(x) + \cos(\omega t))\,dt + \sqrt{2\epsilon}\,dW$$



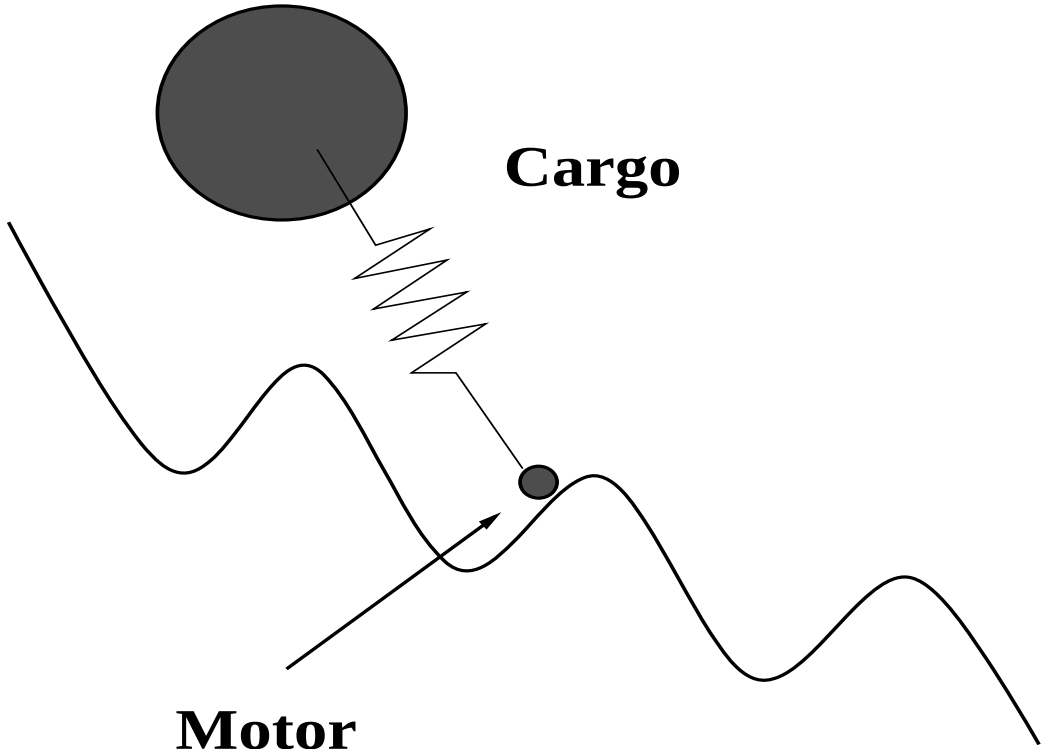


ε = .02, ω = .01





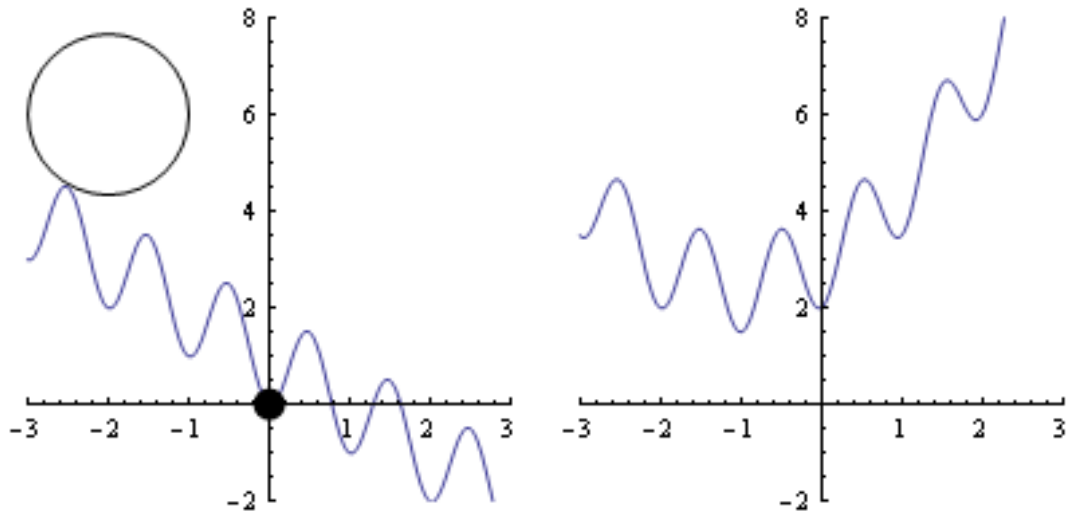
Tilted-potential models



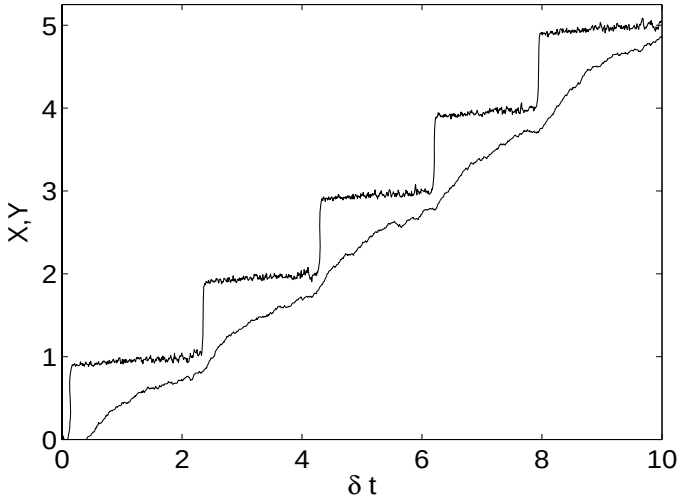
$$dx = \frac{D_M}{k_B T}(-\nabla V(x) + S'(x,y))\,dt + \sqrt{2D_M}\,dW_x,$$

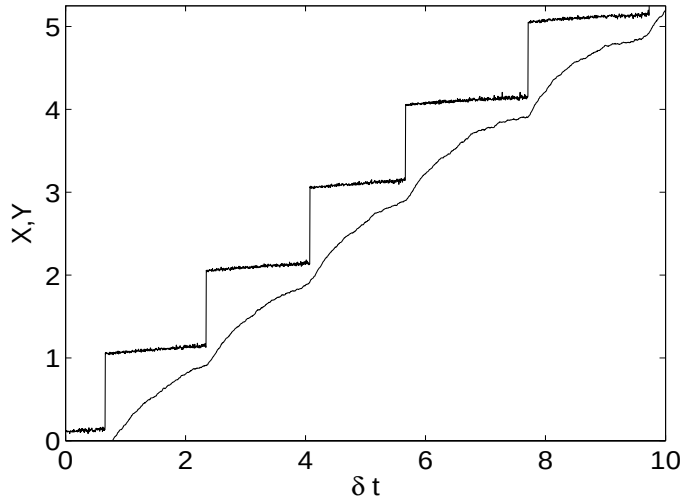
$$dy = \frac{D_C}{k_B T}(-S'(x,y))\,dt + \sqrt{2D_C}\,dW_y.$$

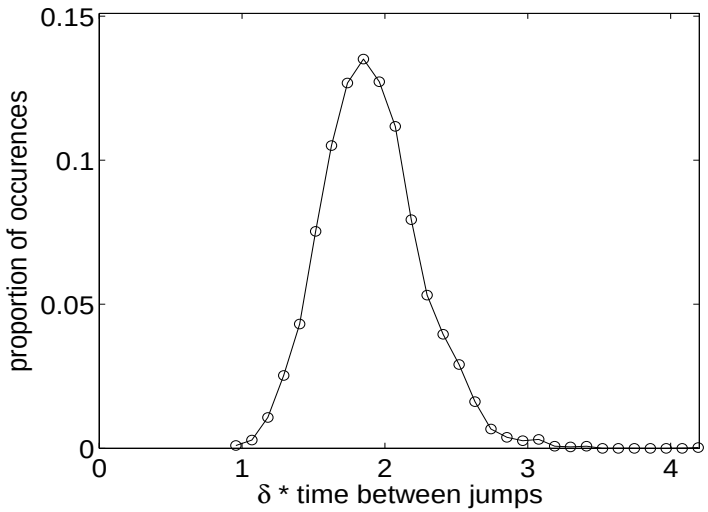
Effective potential with and w/out cargo

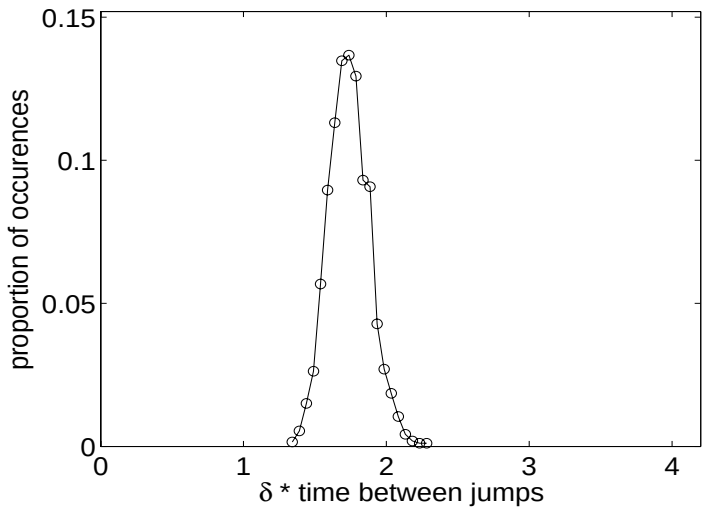


Numerical simulations – Tilted potential









Theorem (Tilted potential)

- Theorem. (D., Vanden-Eijnden, Comm. Math. Sci. '07) Let V(x) be periodic + decreasing shift, S(x,y) = S(x-y) be convex with S(0) = S'(0) = 0. Also assume that S''(0) is sufficiently small. Consider the SDE system

$$dx = \frac{D_M}{k_B T}(-V'(x) + S'(x,y))\,dt + \sqrt{2D_M}\,dW_x,$$
$$dy = \frac{D_C}{k_B T}(-S'(x,y))\,dt + \sqrt{2D_C}\,dW_y.$$

- Define the nondimensional parameters

$$\epsilon = \frac{k_B T}{S''(0)D^2}, \quad \delta = \frac{D_C}{D_M}$$

- In the limit

$$\epsilon \to 0, \quad \delta \to 0, \quad \epsilon \log \delta^{-1} \to \beta \in I \subset \mathbb{R}$$

- the jump times become regular (variance goes to 0) and their mean depends only on β.

Theorem p.2 (TP – more precise)

There is a map $\tau: I \to \mathbb{R}^+$ with the following property:

Let $X_t^\epsilon, Y_t^\epsilon$ be any realization of the system above. Define $\tilde{X}_t^\epsilon = k$ if X_t^ϵ is "in the basin of attraction of the local minimum near $x = k$". Define $\xi(t) = \lfloor t/\tau(\beta) \rfloor$, then there is some $t_0 > 0$ such that for all $T > 0, h > 0$,

$$\lim_{\epsilon \to 0} \mathbb{P}\left(\sup_{t \in \mathcal{T}_h} \left| \tilde{X}_t^\epsilon - \xi(t + t_0) \right| > h \right) = 0,$$

where we define

$$\mathcal{T}_h = [0, T] \setminus \bigcup_{k=0}^{\infty} (k\tau(\beta) - h, k\tau(\beta) + h).$$

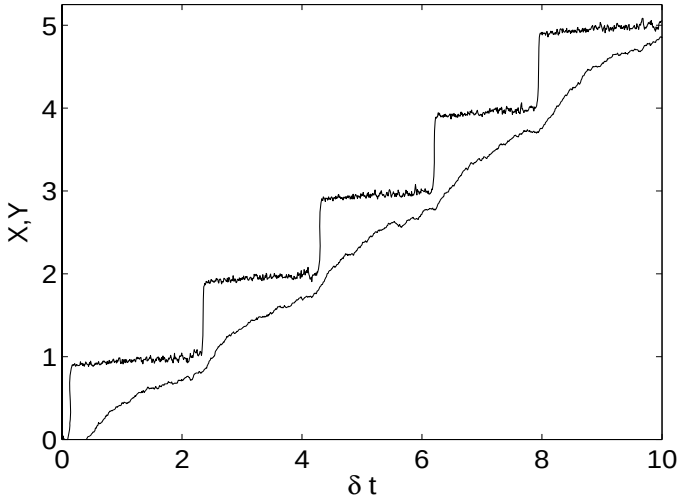
However (!), it is not true that X_t^ϵ converges pathwise uniformly to $\xi(t)$, the best we can do is

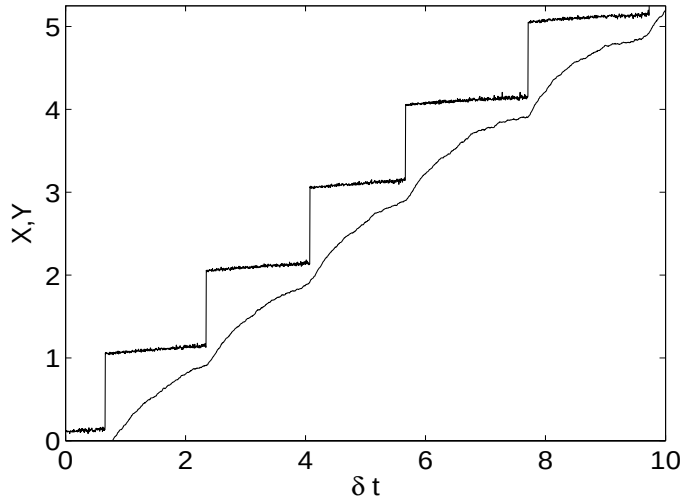
$$\lim_{\epsilon \to 0} \mathbb{P}\left(\int_0^T |X_t^\epsilon - \xi(t + t_0)|^2 \, dt > h \right) = 0.$$

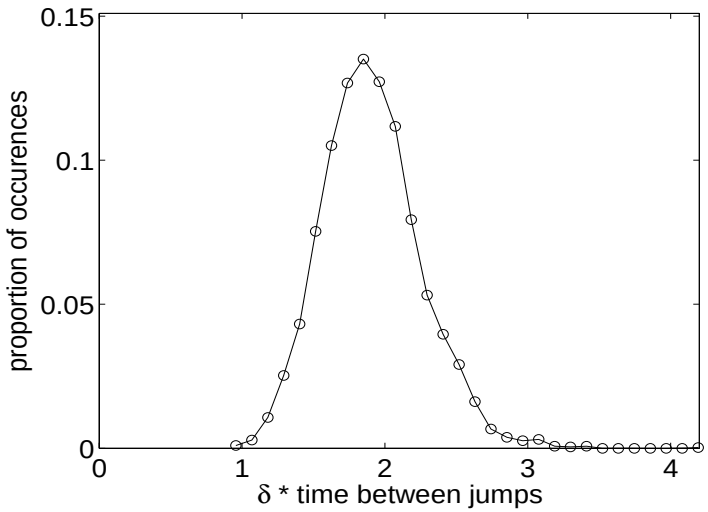
Asymptotics

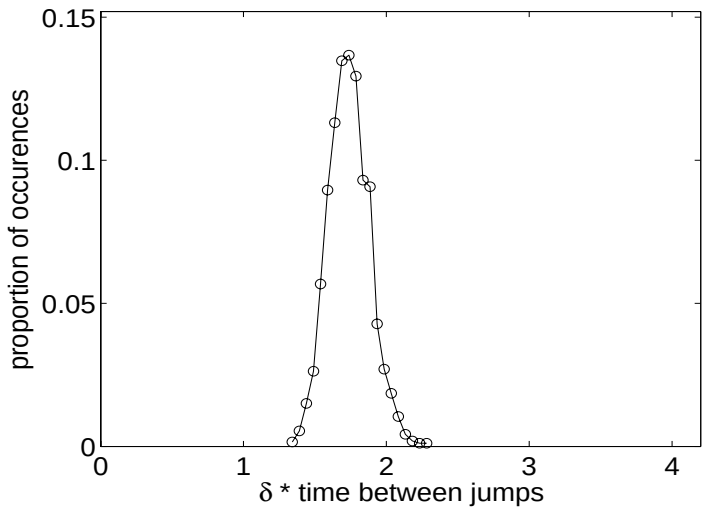
Let τ_n be the first passage time to $(n + 1/2)D$
Let $t_n = \tau_n - \tau_{n-1}$ (the time between crossings).
Then all moments of t_n are $O(\epsilon)$.
Interesting asymptotics:
formula for nth moment of t_n involves $\zeta(n)$!!

Numerical simulations – Tilted potential



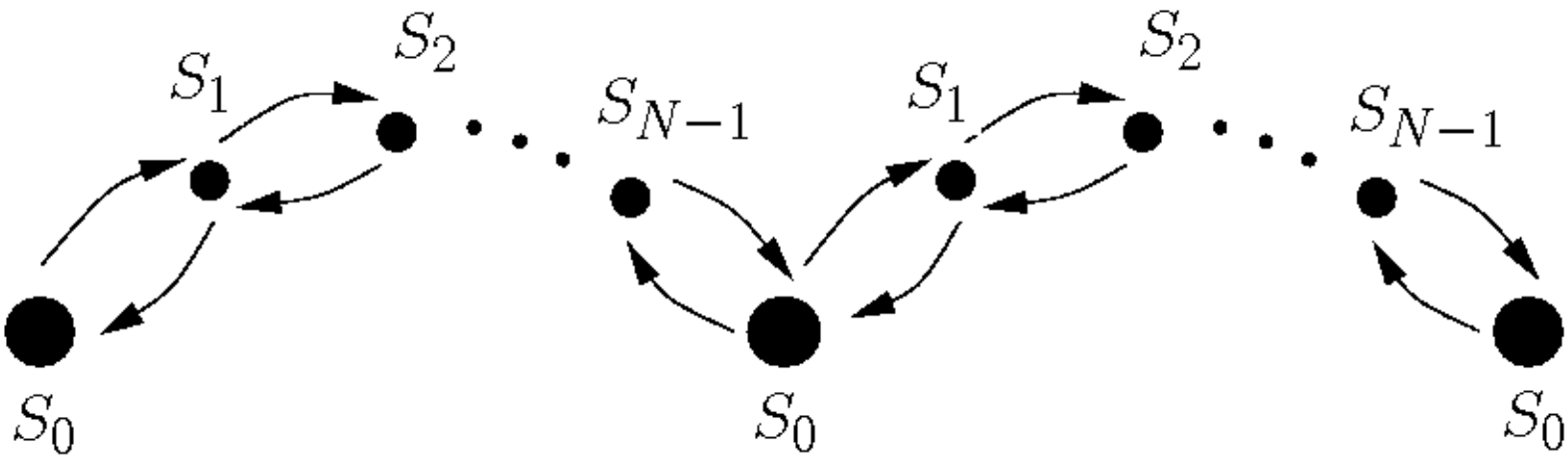






Fisher-Kolomeisky models

- Fisher & Kolomeisky (97,99,01,03)
  - Each step forward involves N intermediate biochemical transitions
  - Each step is reversible, occurs with constant rate
  - Strength of F-K model: determining transition rates
    - in particular, dependence on external forcing
  - For *constant force*, these reproduce empirical data very well
    - N = 2 --- myosin V
    - N = 4 --- kinesin



Fisher-Kolomeisky model (Myosin V, N=2)

- Motor can have both heads, or one head, attached
  - With both attached, either front or back can detach
  - With one attached, loose head can reattach forward or backward
- Each of these steps are governed by chemical kinetics, thus modeled by Poisson process
  - Associate an intensity λ to any event, then in small interval dt the probability of the event is λ dt

Define: y – position of cargo, x – position of motor

$$\text{pick up back foot: } u_0 = k_0^+ [\text{ATP}] \exp\left(-\theta_0^+ \frac{D}{k_B T} F\right),$$

$$\text{pick up front foot: } w_0 = k_0^- [\text{ATP}] \exp\left(\theta_0^- \frac{D}{k_B T} F\right),$$

$$\text{loose foot steps forward: } u_1 = k_1^+ \exp\left(-\theta_1^+ \frac{D}{k_B T} F\right),$$

$$\text{loose foot steps back: } w_1 = k_1^- \exp\left(\theta_1^- \frac{D}{k_B T} F\right).$$

$$\text{motion of cargo: } \dot{y} = -\gamma^{-1} F + \sqrt{2\gamma^{-1} k_B T}\dot{W}.$$

$$\text{force: } F = F(x - y).$$

Experimentally-determined constants (myosin-V)

(all within 5% tolerances, some better)

Constants set by motor:

$$k_0^+ = 7 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}, k_0^- = 5 \text{ M}^{-1} \text{ s}^{-1},$$
$$k_1^+ = 12 \text{ s}^{-1}, \quad k_1^- = 6 \times 10^{-6} \text{ s}^{-1},$$
$$\theta_0^+ = 0.135, \quad \theta_0^- = 0.750,$$
$$\theta_1^+ = 0.035, \quad \theta_1^- = 0.080,$$
$$k_B T = 4 \times 10^{-21} \text{J}, \quad D = 36\text{nm},$$

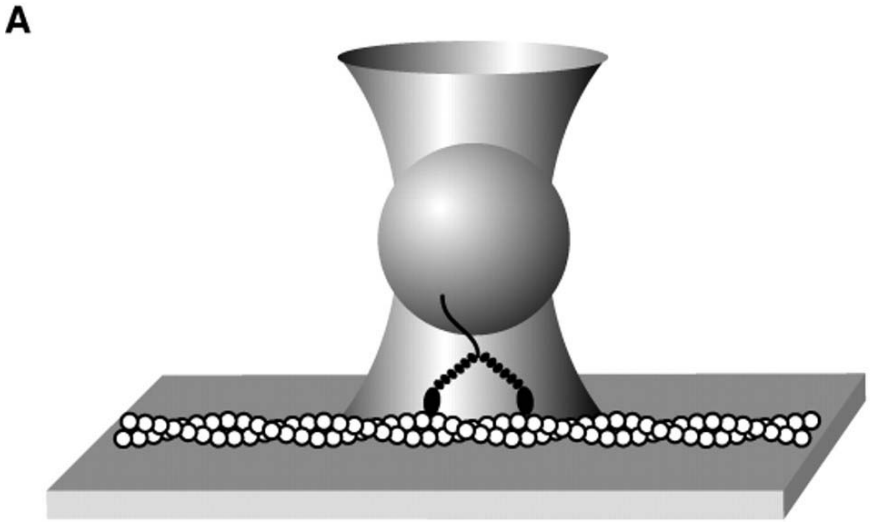
Elastic profile of the tether:

$$F = \kappa d + (bd)^{10},$$
$$\kappa = 5 \times 10^{-2} \text{pN nm}^{-1}, \quad b = 1.6 \times 10^{-2} \text{pN}^{1/10} \text{nm}^{-1}.$$

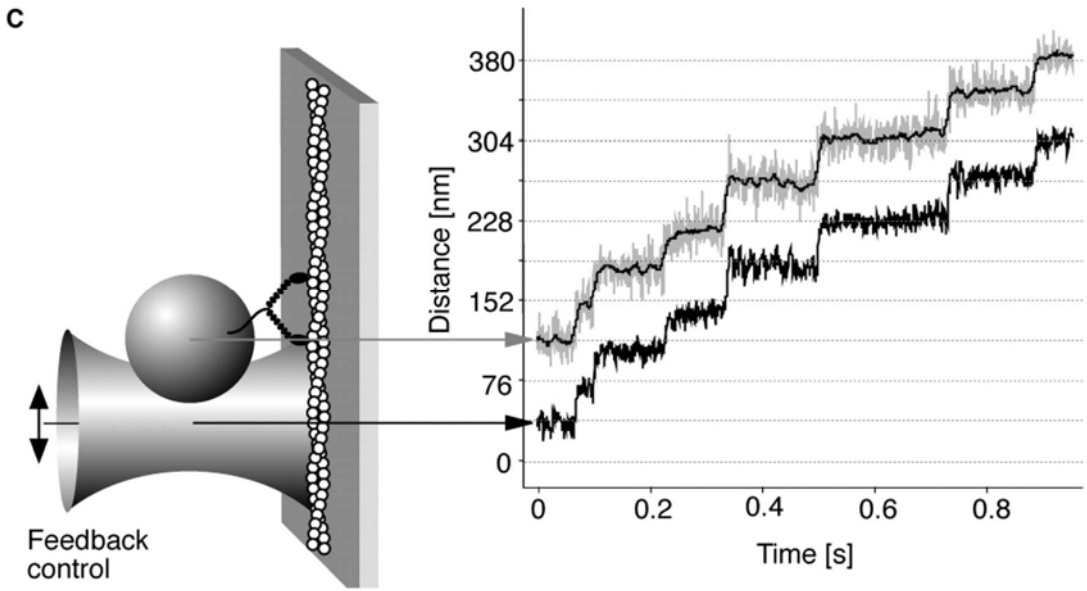
One choice of experimentally-controllable constants:

$$[\text{ATP}] = 2 \times 10^{-3} \text{ M}, \quad \gamma = 1 \times 10^{-4} \text{kg s}^{-1}.$$

Experimental procedures to determine constants



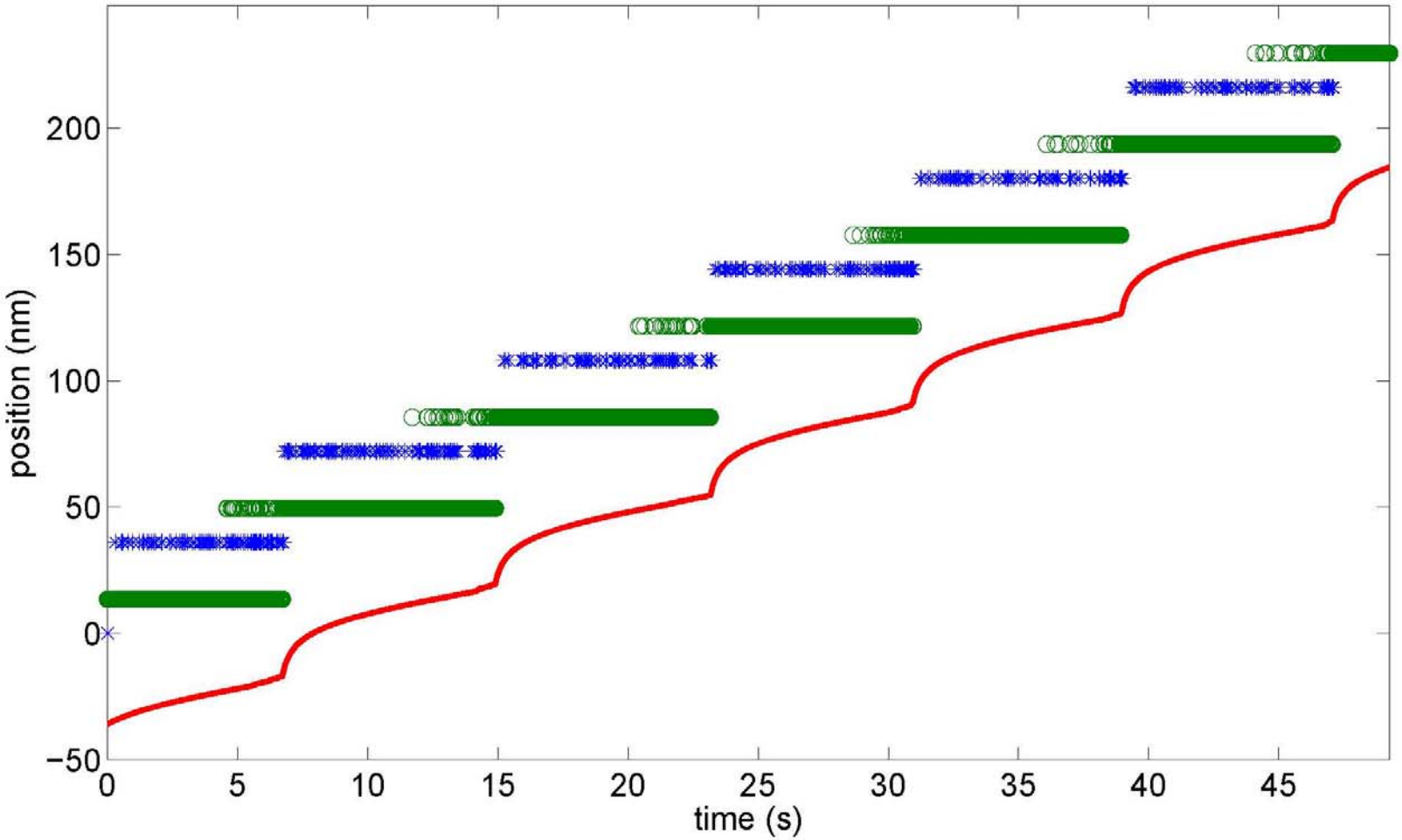
Laser trap



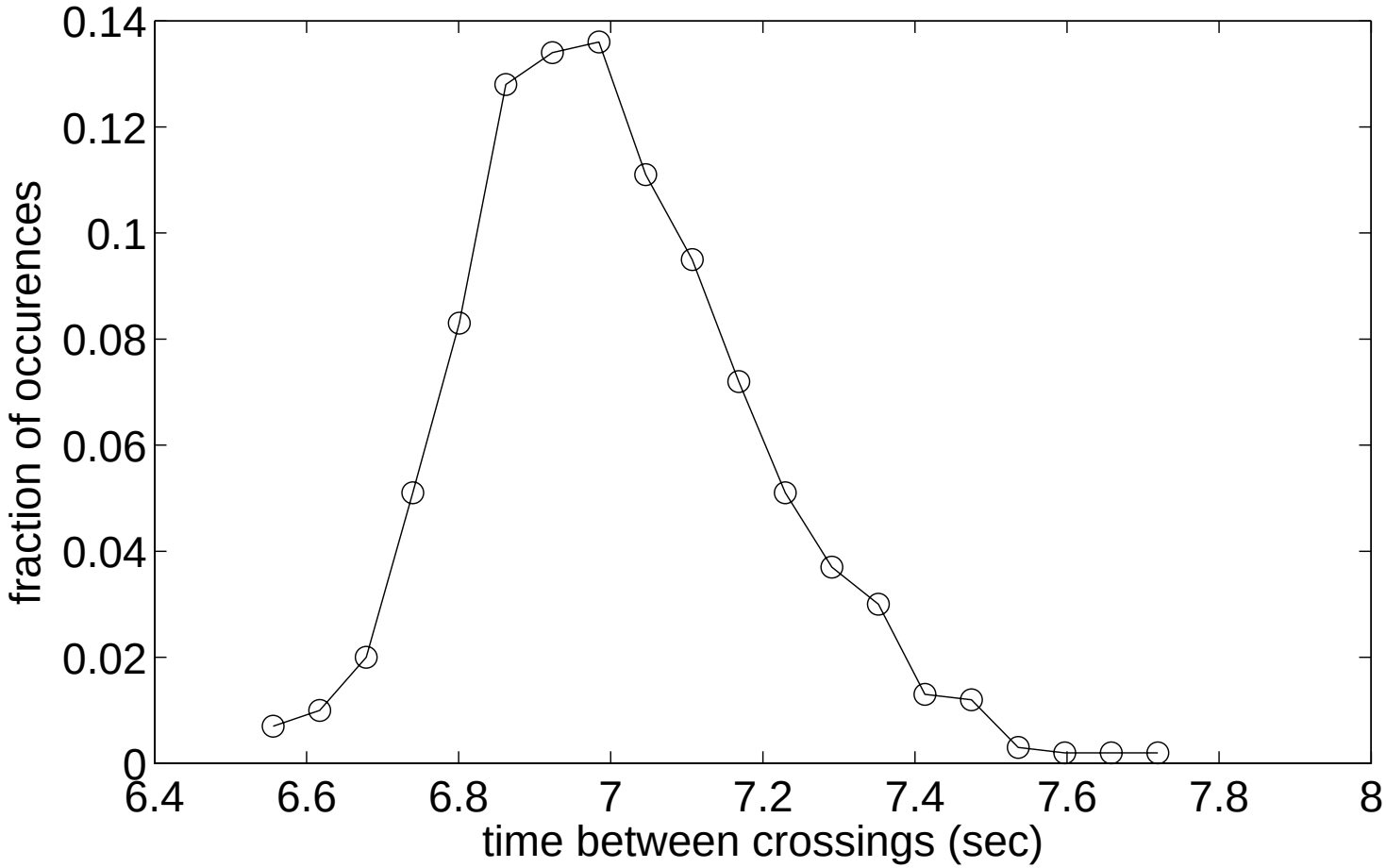
Feedback control

Rief M, Rock RS, Mehta AD, Mooseker MS, Cheney RE, Spudich JA, PNAS 97 (17): 9482-9486 AUG 15 2000

Numerical simulations – KF model for myosin V



Histogram, $\gamma = 10^{-4}$ kg/sec, [ATP]=2mM



- CV is about 3%!!

Theorem (K-F with only forward stepping allowed N = 1)

- Theorem. (D., Vanden-Eijnden, Bull. Math. Bio. '07) Let X be the position of the motor (integer multiple of D) and Y the position of the load (real). Let f(·) be any function which is monotone increasing and

$$\lambda(X,Y) = \exp(f(X-Y)/\epsilon)$$

- Let τ(x,y) be a random variable with CDF

$$\mathbf{P}(\tau(x,y) < T) = 1 - \exp\left(-\int_0^T \lambda(x,\phi(x,y,t))\,dt\right).$$

where ϕ(x,y,t) is the flow of the equation

$$\frac{d\eta}{dt} = \gamma^{-1} f(x-\eta), \quad \eta(0) = y.$$

- Define the jump times of the motor to be τ_0=0, and

$$\tau_{n+1} - \tau_n = \tau(X(\tau_n), Y(\tau_n)).$$

Theorem p.2

- Define X(t) by X→ X+1 at each τ_n and constant otherwise, and between jumps let Y evolve by Y′ = f(X-Y)

- Consider the limit where

$$\epsilon \to 0, \quad \gamma \to \infty, \quad \epsilon \log \gamma \to \beta$$

(thus constraining $\gamma = \gamma(\varepsilon)$) and consider the rescaled jump times

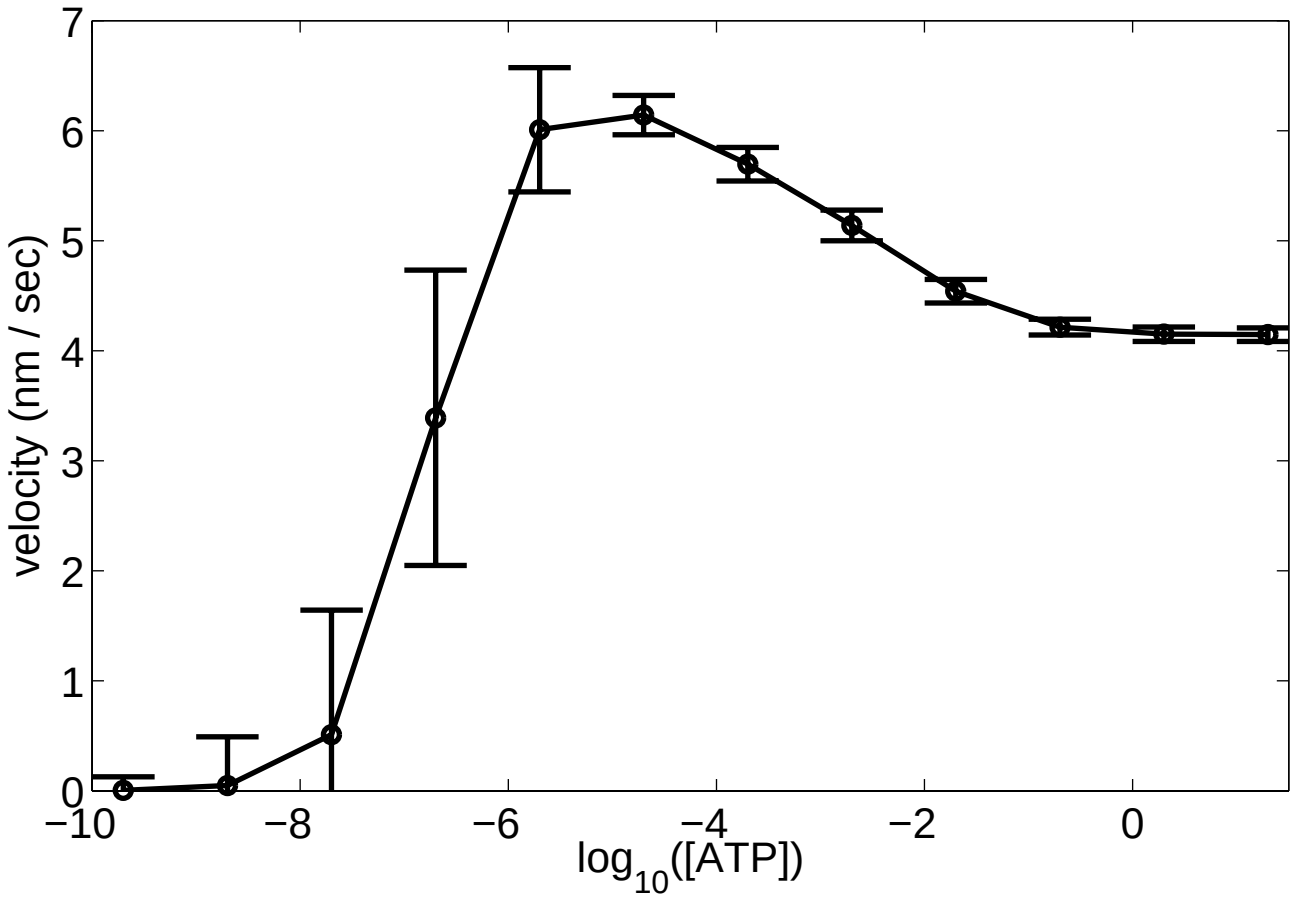
- $$\tilde{\tau}_n = \tau_n / \gamma(\epsilon)$$

- Then there exist a period T>0, and j^* a positive integer, such that for any integer n and h>0,

$$\lim_{\epsilon \to 0} \mathbf{P} \left(\sup_{j^* \le j \le j^*+n} |\tilde{\tau}_{n+1} - (\tilde{\tau}_n + T)| > h \right) = 0.$$

- **NB**: Similar (but much harder to state!!!) theorems if we allow multi-step motors, allow backward stepping, and for populations of motors.

Velocity vs. ATP, $\gamma = 10^{-4}$ kg/s



Clearly: nontrivial dependence on [ATP]

More exciting: in the correct region!!

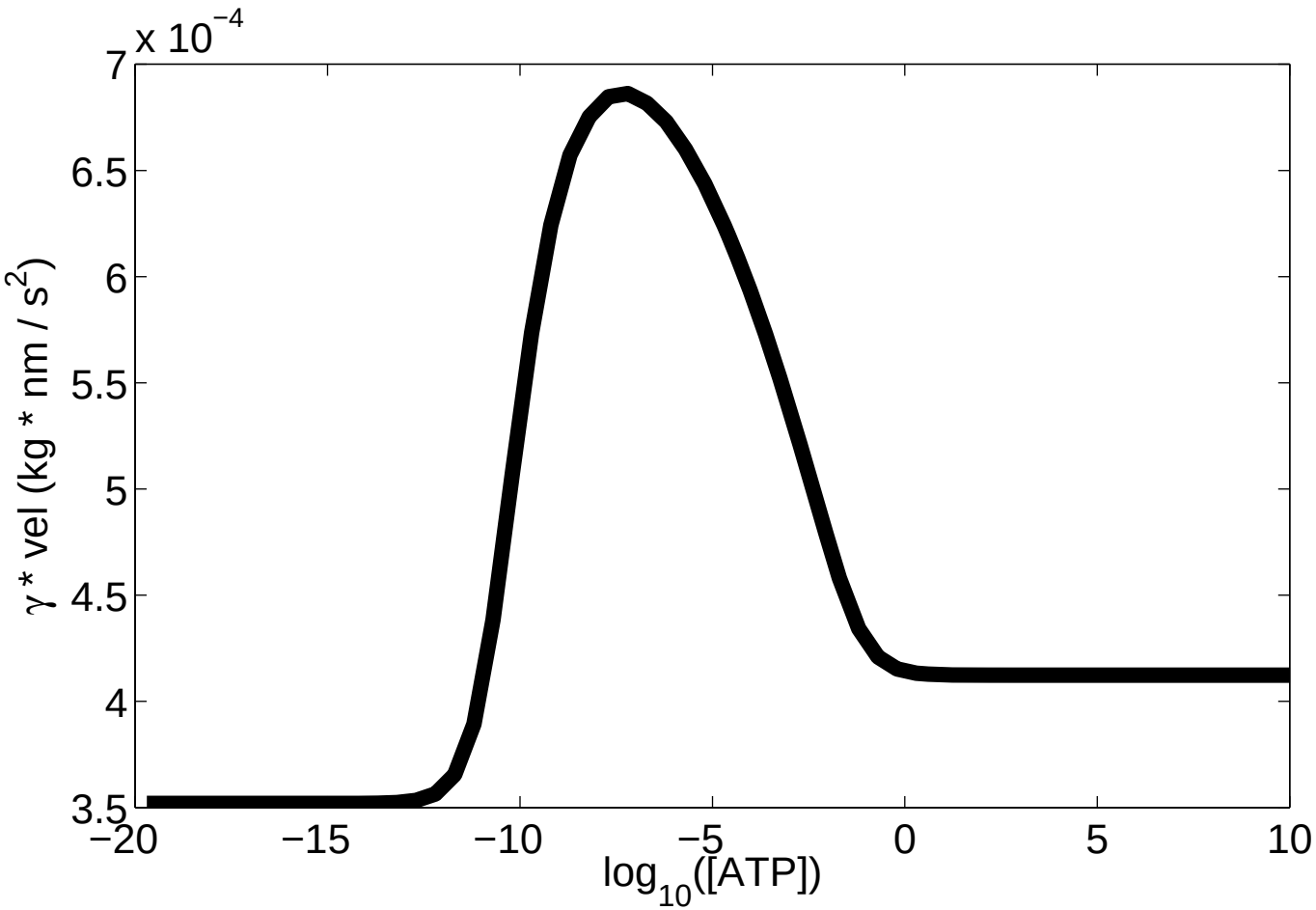
Dependence of mean observables on params

- Main question: how do we use this model to predict observables?
  - E.g. velocity, distance between motor and cargo
  - Mostly means, but higher moments as well

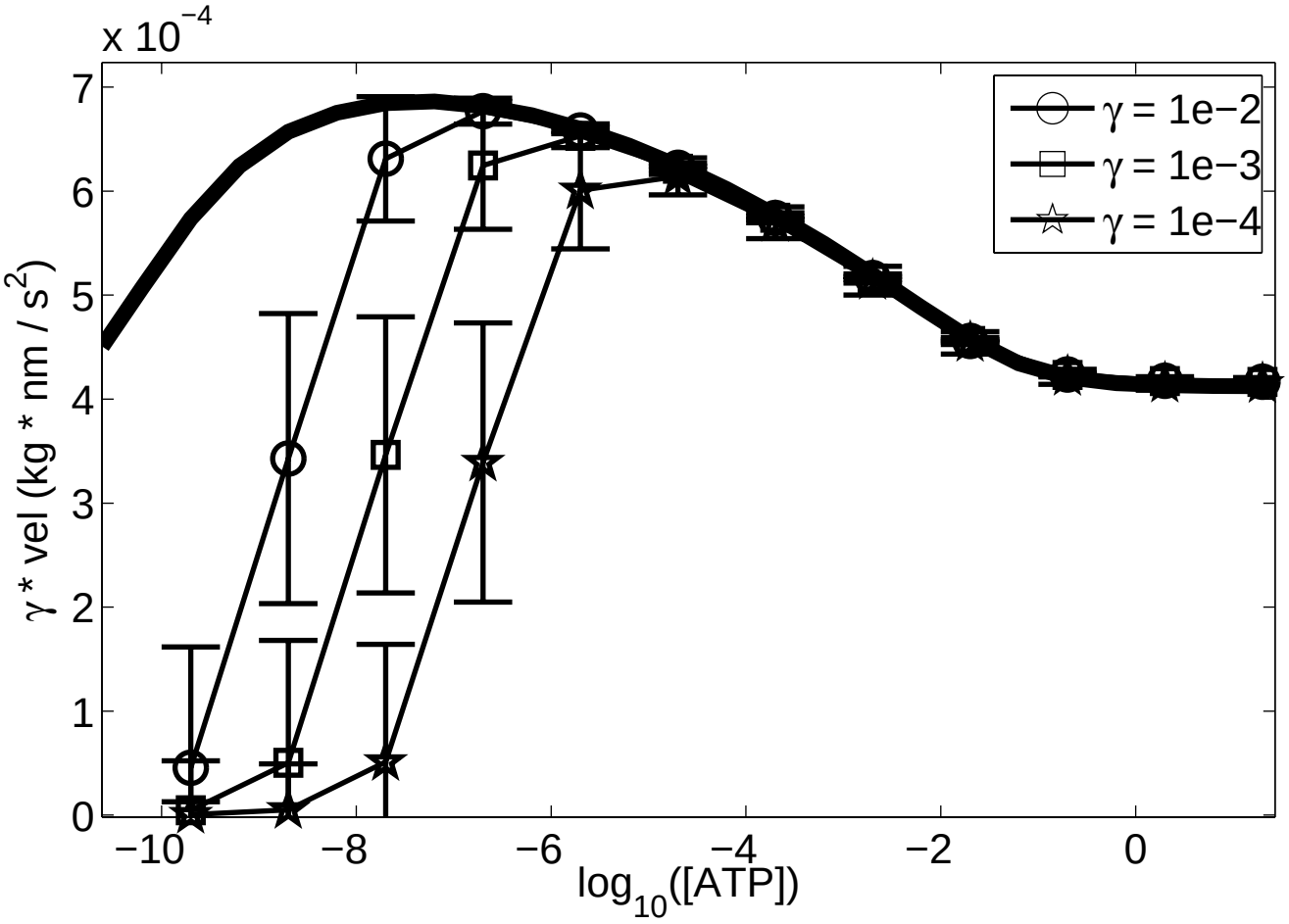
- Idea: in the $\gamma \to \infty$ limit, for each position of the cargo we get a "steady-state" for the position of the motor

- So do asymptotics in neighborhood of ∞

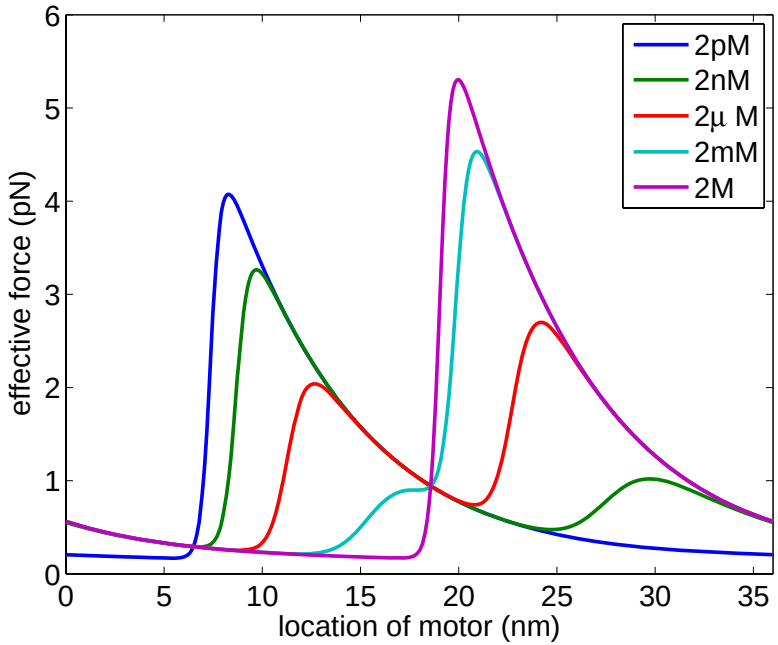
$\gamma \to \infty$ limit

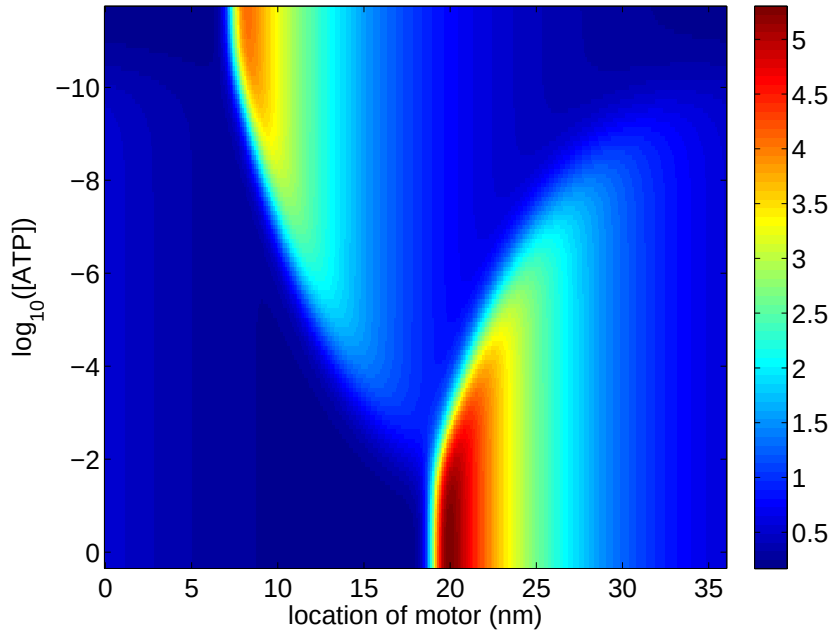


$\gamma \to \infty$ limit + data



$\gamma \to \infty$ limit





- Combination of nonlinearity in elastic tail and rare events
- Intermediate [ATP] gives two “gain regions”

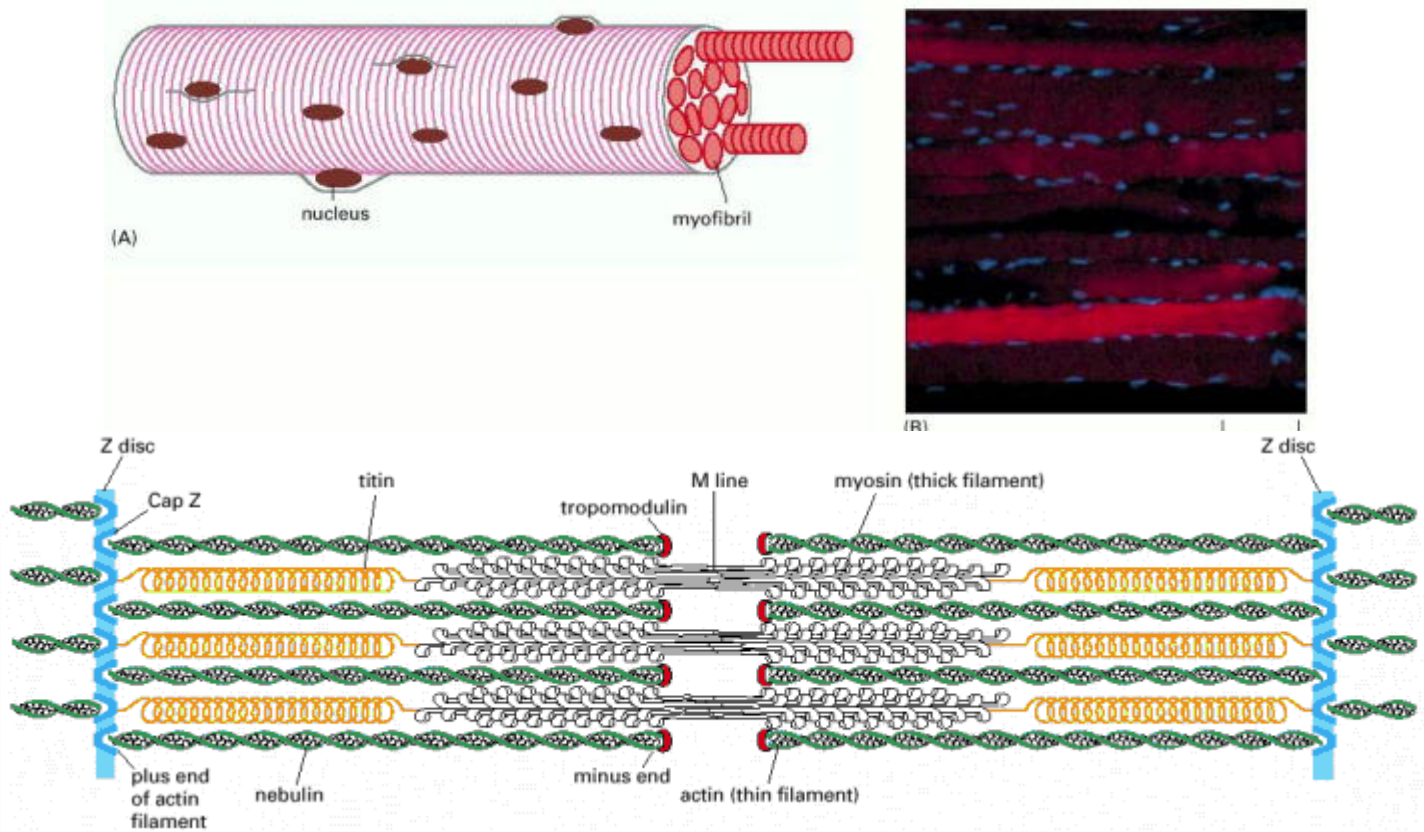
Connection to stochastic resonance

- Typical properties of motor – cargo complex:
  - motor steps are "barrier-crossing" events
    - state-dependent activation energy *I(s)*
  - ε -- nondimensional temperature is small
    - (ratio of $k_B T$ to activation energy)
  - when cargo approaches motor, becomes easier to jump
  - cargo much larger than motor, thus moves relatively slowly

- Conclusions:
  - Timescale of motor stepping should be something like $\exp(I(s)/\epsilon)$
  - This looks like jumping events from SR example above
  - Similar timescale matching works

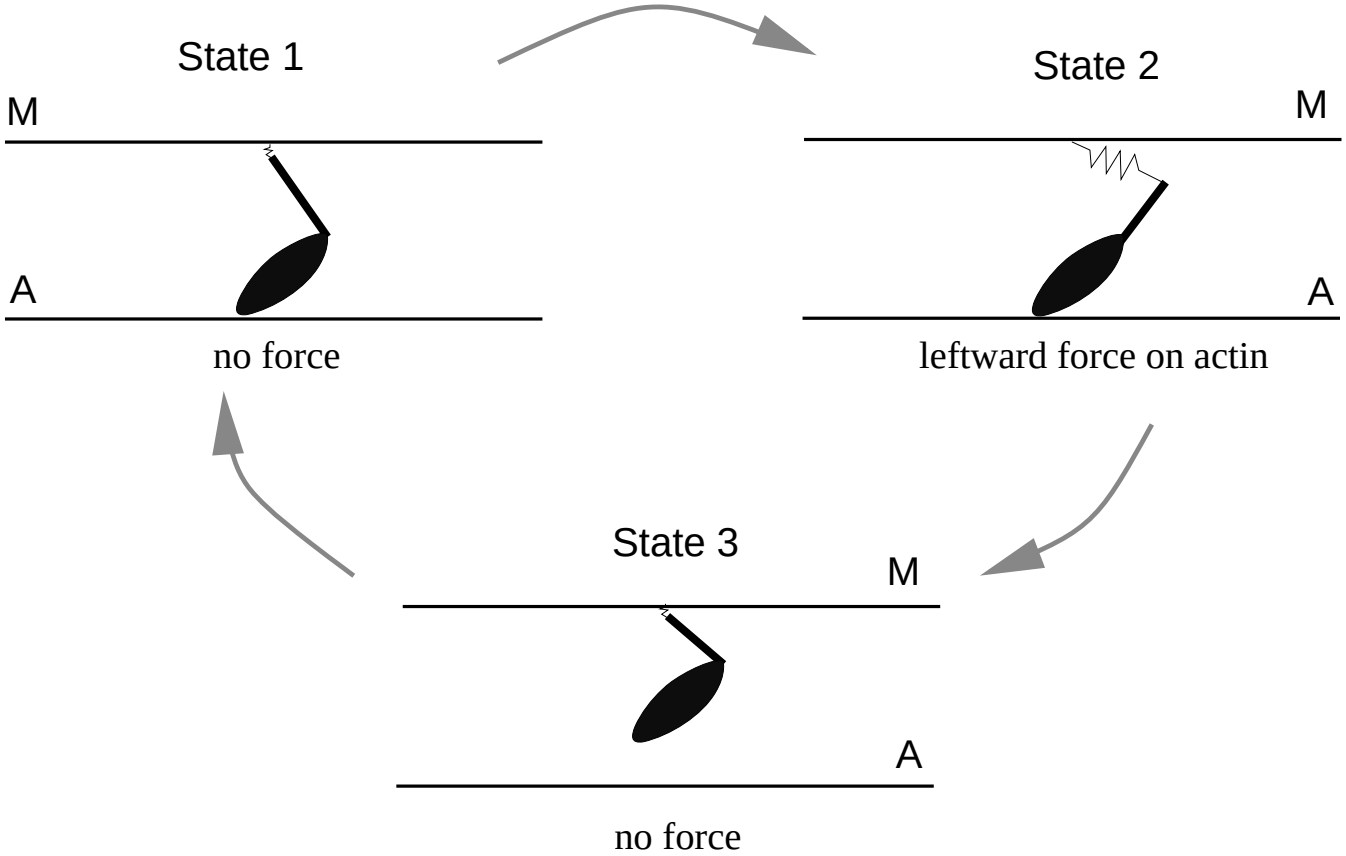
Large populations of motors

- Relevant (at least!) for muscle contration
- Muscle cells are made of myofibrils in parallel
- Myofibrils are serially-stacked sarcomeres
- Sarcomeres contract when motors pull filaments past each other



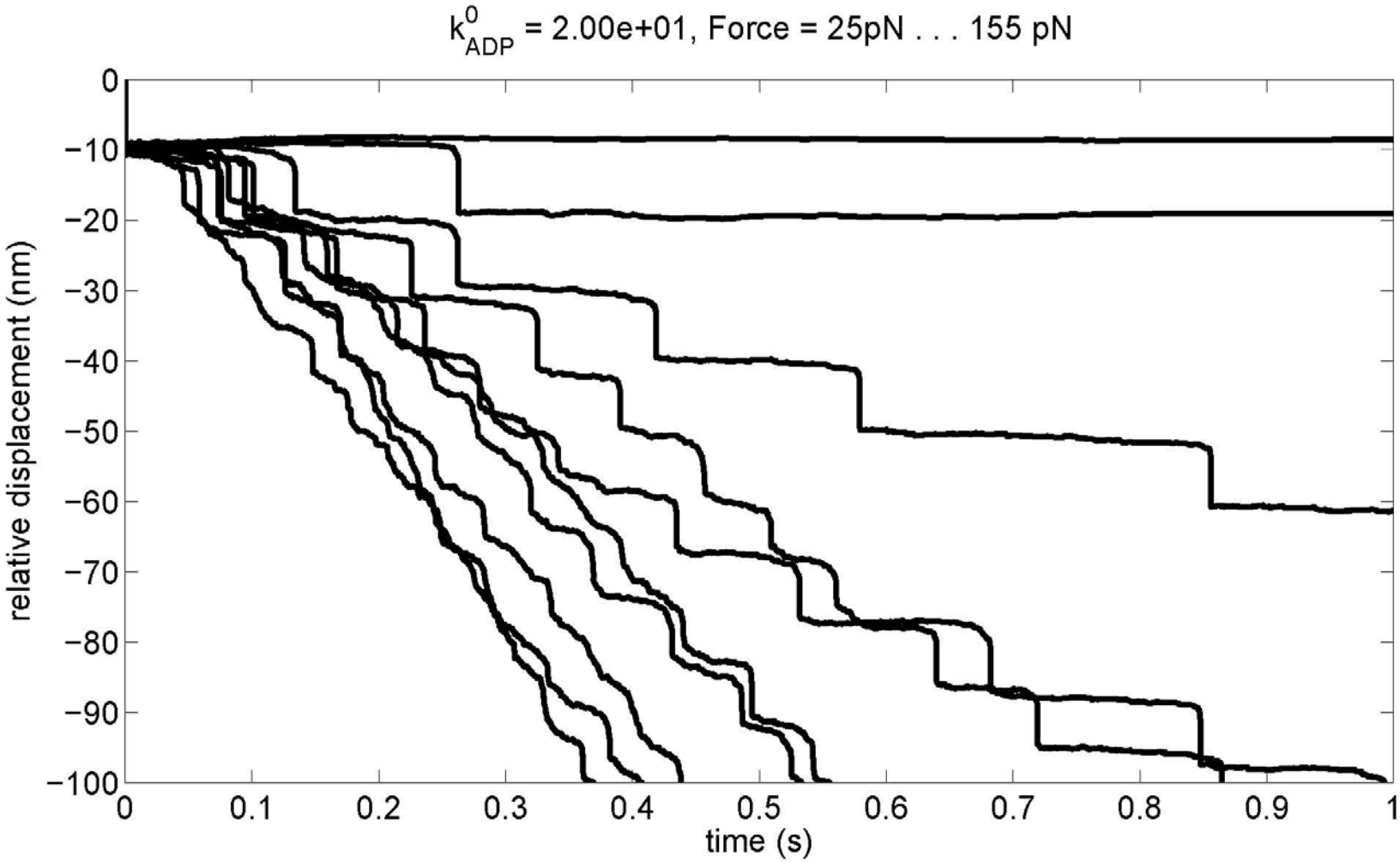
Alberts et al., text, Mol. Biol. Cell., 2004

3 states of activation for myosin head



$$\lambda_1 = \exp(-(\Delta G_{\text{stroke}} + \kappa d(2x+d)/k_B T)),$$
$$\lambda_2 = k^0_{ADP} \exp(-\kappa\delta(x+d)/2k_B T),$$
$$\lambda_3 = k_{bind}$$

Displacement v. time for various forces



Conclusions

- Regularity under load
  - Apply SR-type arguments
  - Why is this good for a motor? The cell is a crowded place!

- Synchrony in large populations
  - SR + auto-catalyzation effect
  - Could be related to macroscopic phenomena!

- This suggests new experimental regimen
  - Consider all parameters set by motor except γ and [ATP];
  - Our theory predicts various behaviors in different parameter regimes
    - E.g. mean and standard deviation of velocity
  - Nonmonotonicity vs. [ATP]
    - Can be checked experimentally

- Genericity:

Genericity

- Genericity -- all we need is:
  - Motor's ability to move is force-dependent
  - Motor's local timescale to move is exponential in force
  - "nondimensional temperature" is small
    - Ratio of k_BT to work done in one step is small enough

- Small enough: e.g. if work is 8 k_BT, $\varepsilon = 1/8$, and $e^8 \approx 3000$!
  - NB: motor can choose work, but k_BT is fixed!

- Many motor proteins are in the $5k_BT \rightarrow 15\ k_BT$ range
  - Thus work is small enough so that events occur
  - But large enough so that regularity is possible!

Context and future directions

- Related biological processes
  - more complicated motor protein models
  - Chromosome transport

- Other places we've applied similar techniques:
  - ODE – bifurcation theory – Fitzhugh-Nagumo (PRE '05 – with Muratov)
  - Chemical kinetics problems (JCP '06 – also with Muratov)
  - Rigorous nontrivial limits for multiscale Markov chains (JSP '06)
  - Spatiotemporal wavetrains in SPDE (Nonlinearity '06)

- Moral of the story: In a wide variety of contexts, there are parameter regimes in which noise induces dynamics, but does so in a regular way.