Diffusion Ratchets and Molecular Motors

A Pathwise Approach

Overview of the Talk

- *The Biology--Molecular Motors*
- *A Suggested Model--The Brownian/Diffusion Ratchet*
    - *A Particle Description of a Ratchet*
    - *Definition of Continuous Ratchet and Weak Convergence Result*
    - *Some Asymptotic Results*
    - *Numerical Methods*
- *A Motor with Cargo*
    - *A Two-dimensional Process*
    - *An Asymptotic Result*
    - *Numerical Methods*
    - *Non-linear Filtering*
- *Future Work*

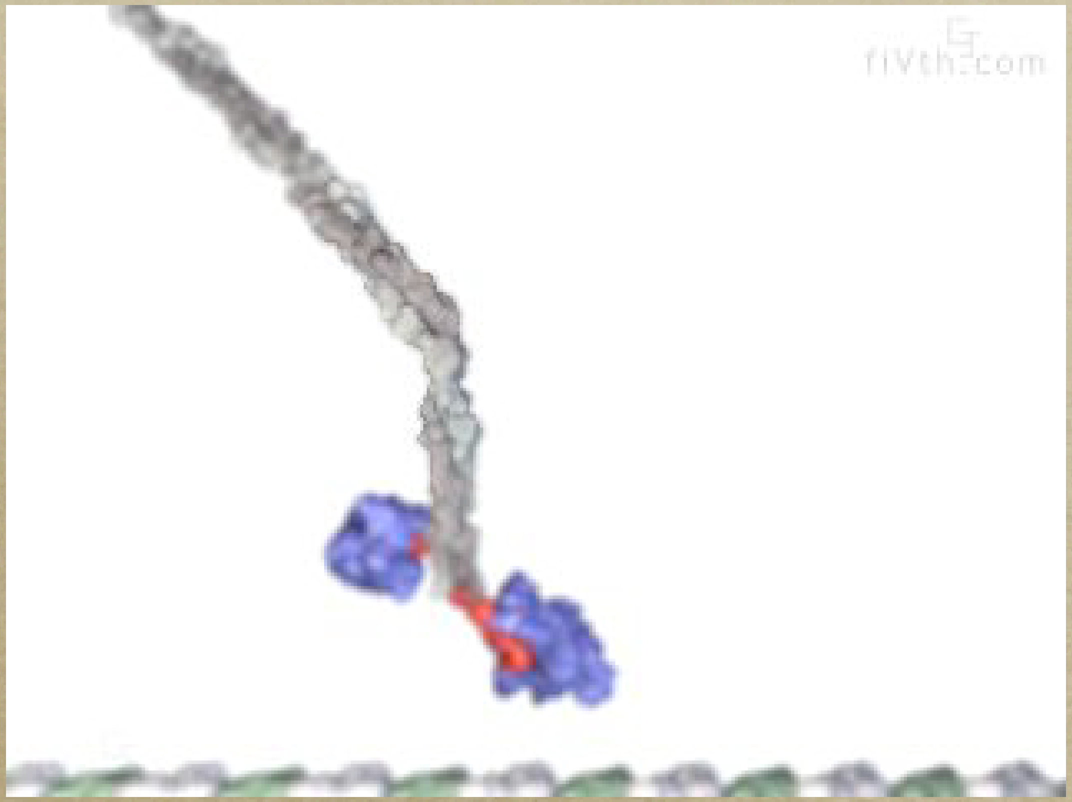
Molecular Motors

- *Large, complex proteins that convert chemical energy into mechanical energy.*
- *Examples--dynein, kinesin, myosin, the flagella rotor.*
- *Kinesin and dynein often have two heads and “walk” along microtubules.*

Microtubules

- *Microtubules form a skeletal network throughout the cell.*
- *Since the microtubules are relatively straight, models for a motor are most often given via a one-dimensional dynamical system.*
- *Microtubules also have a structurally periodic structure.*

Kinesin



Movie from R Milligan's web page at the Scripps Institute

Models for Molecular Motors

- *Continuous time, Markov jump processes. Stepping from one period to the next, but which may consist of a number of intermediate chemical step.*

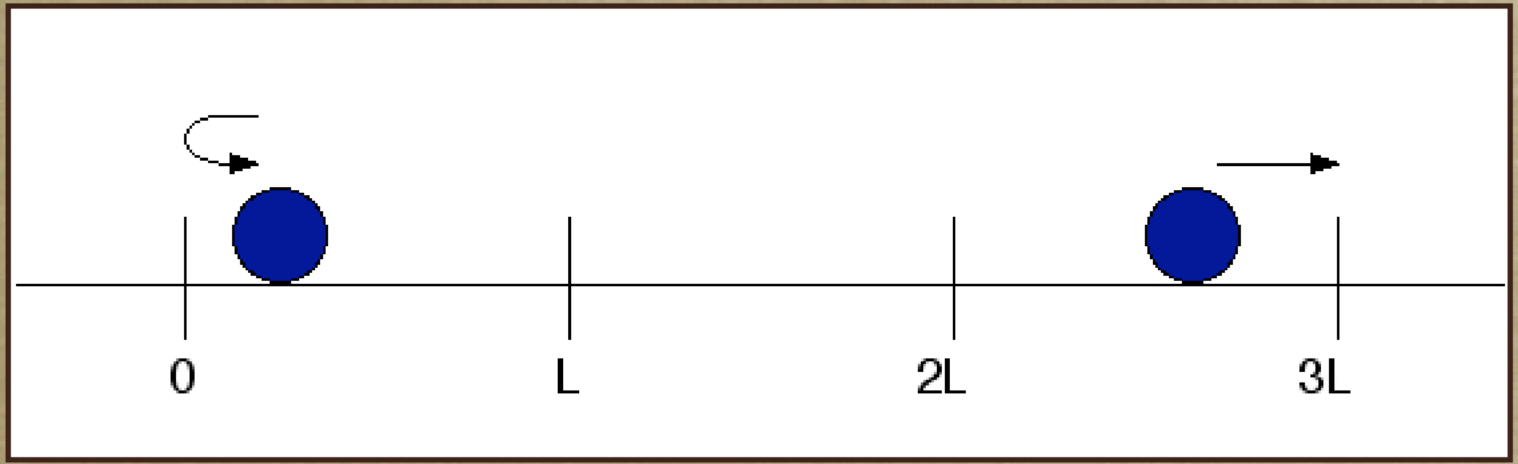
- *Continuous state space models.*
  - *Tilted Periodic Potential* $X(t) = x + \int_0^t (cos(X(s)) + \mu) ds + \sigma W(s)$
  - *Brownian/Diffusion Ratchet*

- *Mixed Approach--Flashing (Correlation) Ratchet*

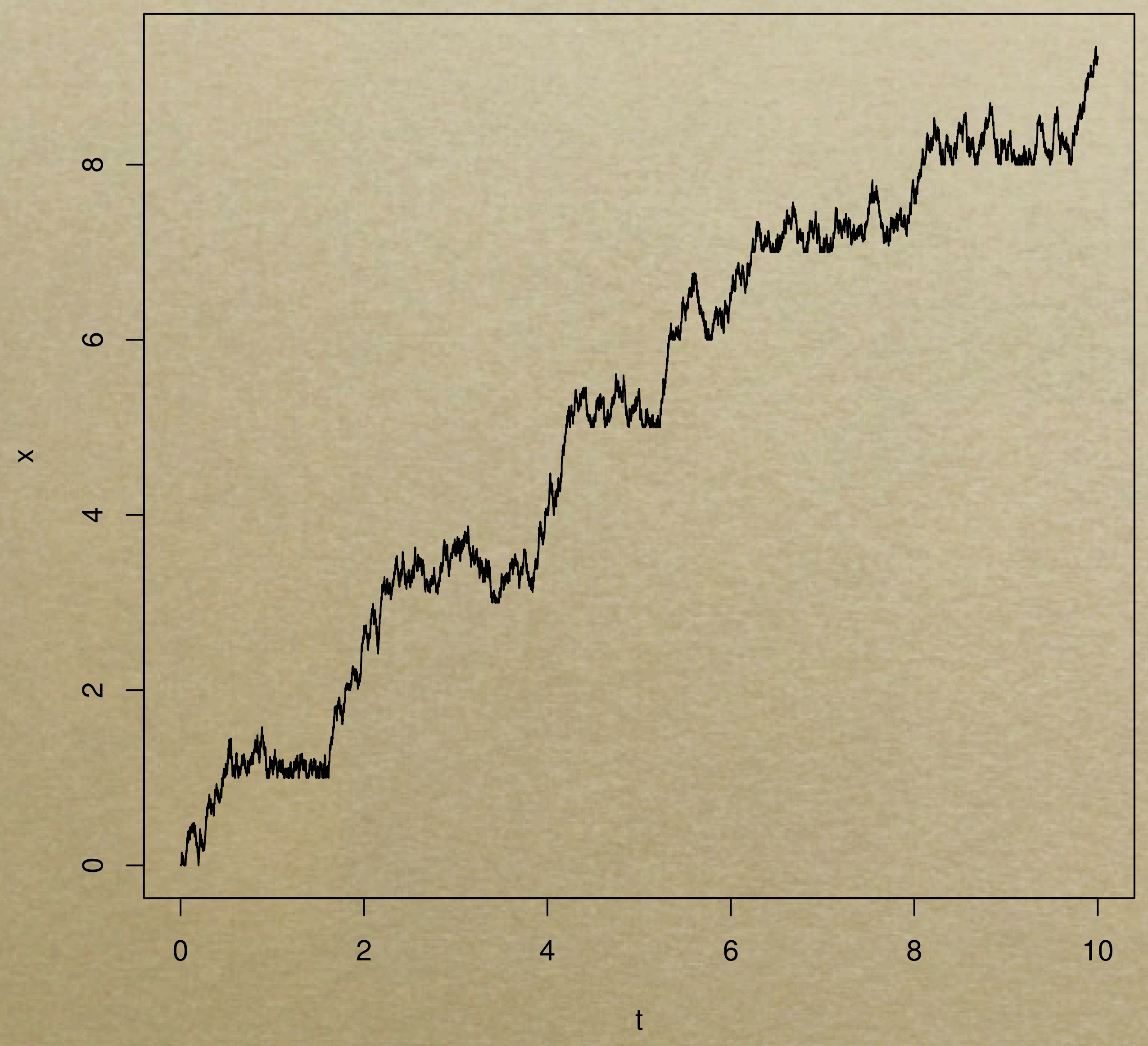
$$dX^{(1)}(t) = b_1(X^{(1)}(t))dt + a_1(X^{(1)}(t))dW^{(1)}(t)$$
$$dX^{(2)}(t) = b_2(X^{(2)}(t))dt + a_2(X^{(2)}(t))dW^{(2)}(t)$$

Brownian/Diffusion Ratchet

- *There are “ratchet sites” located at a fixed period, L, in the state space of the process (0, L, 2L,...)*
- *Away from these barriers, the process follows a given diffusion process.*
- *When a particle reaches a ratchet site from the left, it cannot pass through the barrier and is immediately reflected back.*
- *The ratchet site has no effect on the particle as it approaches from the right.*



Brownian/Diffusion Ratchet



An Intuitive Discrete Space Model

Let $X_n(t)$ *be the location of the motor at time t.*

$X_n(t)$ *is a pure jump process on a lattice with states at a distance of* $\frac{1}{n}$ *with n in*

$$N' = \{n \in R : n = \frac{m}{L}, m \in N\}$$

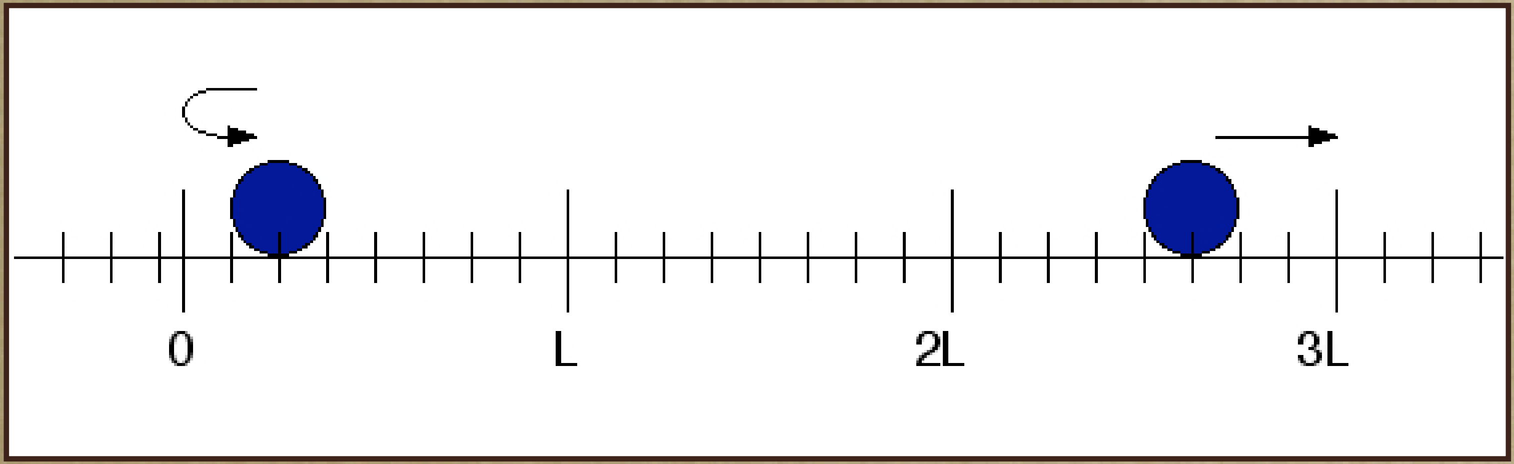
Given that $X_n(t) = x$*, the rate of jump left (or at a ratchet site remaining at x) is*

$$\lambda_n(x)(1 - p_n(x)) = n^2\left(\alpha(x) + \frac{b_2(x)}{n}\right)$$

The rate of jump right is

$$\lambda_n(x)p_n(x) = n^2\left(\alpha(x) + \frac{b_1(x)}{n}\right)$$

As n increases, the jumps get smaller and more often. Away from the barriers, one expects a convergence to a diffusion behavior as $n \longrightarrow \infty$.



Reflected Diffusion

- *Skorokhod Problem and Reflection Map*

Let $x(\cdot) \in D([0,\infty) : R)$. We say that a pair of trajectories
$z(\cdot), l(\cdot) \in D([0,\infty) : R_+)$ solve the Skorokhod Problem for $x(\cdot)$ if
1. $z(t) = x(t) + l(t)$ for all $t \in [0,\infty)$.
2. $l(0) = 0$.
3. $l(t)$ is increasing and increases only when $z(t) = 0$, i.e $l(t) = \int_{[0,t]} 1_{\{z(s)=0\}} dl(s)$.

We also write $Z(t) = \Gamma(X(\cdot))(t)$ *where* Γ *is called the Skorokhod Map or Reflection Map.*

Also, $Z(t) = X(t) - \inf_{0 \le s \le t} X(s)$

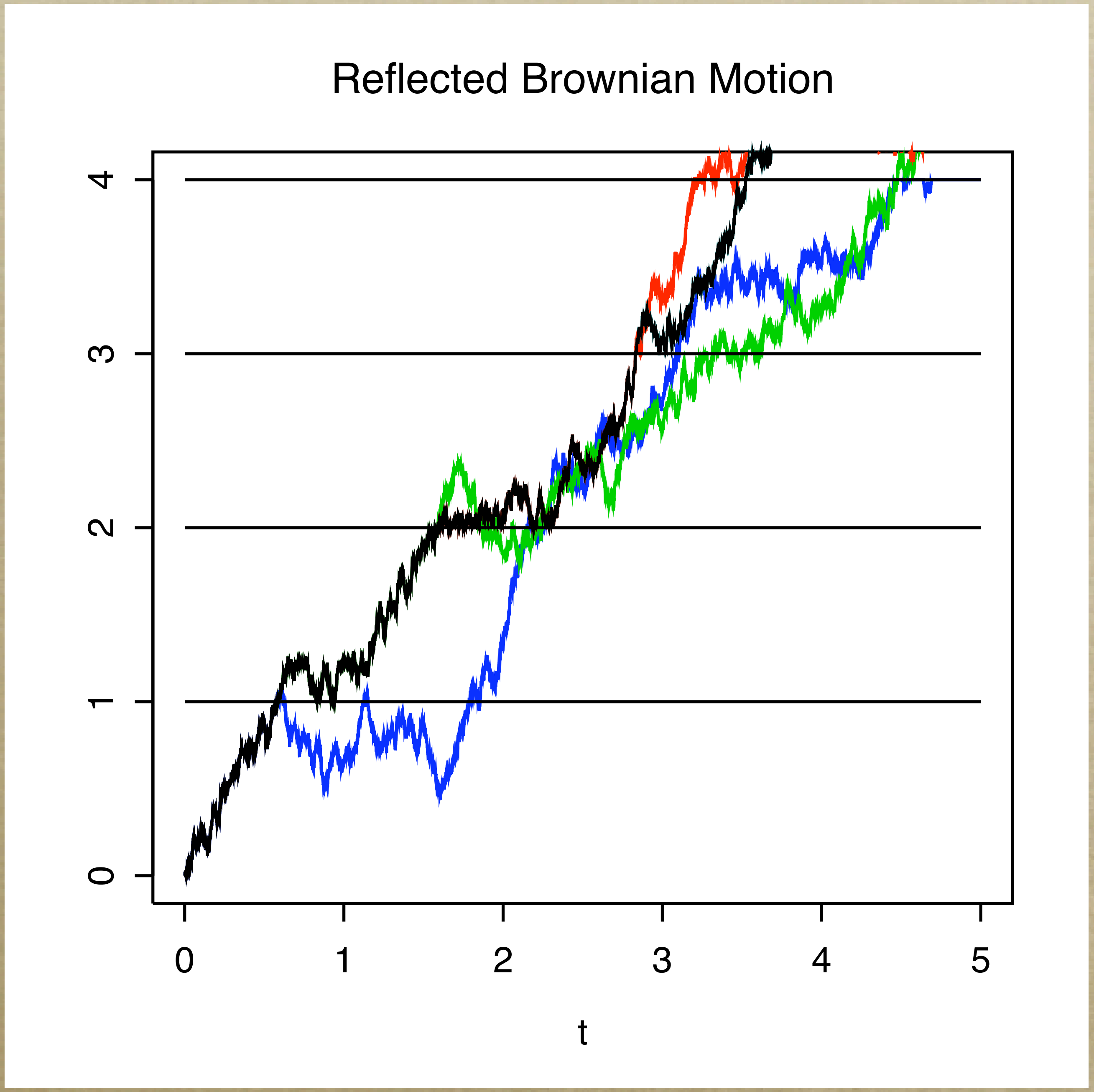
Reflected Diffusion

- *Let $W(t)$ be a standard Brownian motion.*
- $Z(t) = \Gamma(W(\cdot))(t) = W(t) - \inf_{0 \le s \le t} W(s)$ *is called a Reflected Brownian Motion.*
- $X(t) = \Gamma\left(x_0 + \int_0^{\cdot} b(X(s))ds + \int_0^{\cdot} \sigma(X(s))dW(s)\right)(t)$ *is a Reflected Diffusion process, where* $b(\cdot)$ *and* $\sigma(\cdot)$ *are Lipschitz continuous and of linear growth.*

Definition of a Diffusion Ratchet

- *The ratchet sites are at* 0, L, 2L,... *in the state space.*
- *An infinite system of reflected diffusion process.*
- *The ith process is reflected at the ith barrier. (With an associated reflection map we denote by* $\Gamma_i(\cdot)$*).*
- *Reflected diffusions are patched together using stopping times. This "patching" map is continuous to the space of continuous functions.*

Definition of a Diffusion Ratchet



Definition of a Diffusion Ratchet

$$X^{(i)}(t) = \Gamma_i \left(iL + \int_0^{\cdot} b(X^{(i)}(s))ds + \int_0^{\cdot} a(X^{(i)}(s))dW^{(i)}(s) \right)(t),\ t \in [0,\infty)$$

$$\tau^{(i)} = \inf\{t : X^{(i)}(t) \geq (i+1)L\}$$

$$\sigma^{(i)} = \tau^{(i-1)} + \sigma^{(i-1)}$$

$$X(t) = X^{(i)}(t - \sigma^{(i)});\ \ t \in [\sigma^{(i)}, \sigma^{(i+1)}),\ \ i \in Z_+$$

Weak Convergence Theorem

Theorem $X_n(\cdot)$ converges to $X(\cdot)$ in $D([0,\infty):\mathbb{R}_+)$ as $n \to \infty$ with

$$b(x) = b_1(x) - b_2(x) \text{ and } \alpha(x) = \frac{a^2(x)}{2}$$

Sketch of Weak Convergence Proof

Step 1: Let $\mathcal{X}_0 \doteq \mathcal{D}([0,\infty):\mathbb{R}_+) \times [0,\infty]$. Then $Z \doteq \{(X^{(i)},\tau^{(i)})\}_{i\in\mathbb{N}_0}$ is a $\mathcal{X}_0^{\otimes\infty} \doteq \mathcal{X}$ valued random variable and $X(\cdot) = \Psi(Z)$. By "chopping" $X_n(\cdot)$ suitably obtain $Z_n \doteq \{(\tilde{X}_n^{(i)},\tau_n^{(i)})\}_{i\in\mathbb{N}_0}$ s.t. $X_n(\cdot) = \Psi(Z_n)$.

Step 2: Show that $\exists\tilde{\mathcal{X}} \subseteq \mathcal{X}$ s.t. $P[Z(\cdot) \in \tilde{\mathcal{X}}] = 1$ and Ψ is continuous for all $z \in \mathcal{X}$.

Step 3: Show $\tilde{X}_n^{(i)}(\cdot) \Rightarrow X^{(i)}$ for all i.

Step 4: For $\varphi \in \mathcal{D}([0,\infty):\mathbb{R}_+)$, let $\tau(\varphi(\cdot)) \doteq \inf\{t : \varphi(t) \geq L\}$. Then there is a Borel set A s.t. τ is continuous for all $\phi \in A$ and $P[X^{(i)} \in A] = 1$, for all i.

Step 5: Step 3 and Step 4 imply $Z_n \doteq \{(\tilde{X}_n^{(i)},\tau_n^{(i)})\}_{i\in\mathbb{N}_0} \Rightarrow Z \doteq \{(X^{(i)},\tau^{(i)})\}_{i\in\mathbb{N}_0}$.

Step 6: Step 1, Step 2, and Step 5 imply $X_n(\cdot) \Rightarrow X(\cdot)$.

Asymptotic Velocity

$$\lim_{t\to\infty} \frac{X(t)}{t}$$

Theorem Assuming periodicity, $\frac{X(t)}{t} \to \frac{L}{E\tau_0}$ almost surely.
Sketch of proof

$$\begin{aligned}\frac{X(t)}{t} &= \frac{\sum_{i=0}^{n_t-1} X^{(i)}(\tau^{(i)}) + \varepsilon_t}{t} \\ &= \frac{n_t L}{t} + \frac{\varepsilon_t}{t}\end{aligned}$$

where $n_t = \inf\{m : \sum_{i=0}^{m-1} \tau^{(i)} \geq t\}$ is a renewal process, and ε_t is bounded.

Effective Diffusivity

Functional Central Limit Theorem

$$\sqrt{n}\left(\frac{X(n\cdot)}{n} - \frac{L}{\mu}\cdot\right) \Rightarrow \frac{\sigma L}{\mu^{3/2}} W(\cdot)$$

$$\mu = E\tau_0 \qquad \sigma = \sqrt{Var(\tau_0)}$$

$\frac{\sigma^2 L^2}{\mu^3}$ *is called the Effective Diffusivity.*

Alternate Definition (used by experimentalist)

$$\lim_{t\to\infty} \frac{Var(X(t))}{t}$$

Randomness Parameter (asymptotic SNR)

$$\lim_{t\to\infty} \frac{Var(X(t))}{EX(t)L} = \frac{\sigma^2}{\mu^2}$$

Numerical Methods

- *Approximation of hitting times with linear programming. (Helmes, Rohl, and Stockbridge)*
- *Markov chain approximation method. (Kushner/Dupuis,Wang/Elston/Peskin).*
- *Monte Carlo*

Linear Programming

$$X^{(i)}(t) = \int_0^t b(X^{(0)}(s))ds + \int_0^t a(X^{(0)}(s))dW^{(0)}(s) + \ell(t)$$

Ito's formula gives

$$f(X^{(0)}(t\wedge\tau^{(0)})) = f(x_0) + \int_0^{t\wedge\tau^{(0)}} Af(X^{(0)}(s))ds + \int_0^{t\wedge\tau^{(0)}} f'(X^{(0)}(s))dW(s) + f'(0)\ell(t\wedge\tau^{(0)})$$

where

$$Af(x) = \frac{1}{2}a^2(x)\frac{\partial^2 f}{\partial x^2} + b(x)\frac{\partial f}{\partial x}.$$

Taking expections and letting $t \to \infty$

$$f(L) = Ef(X^{(0)}(\tau^{(0)})) = f(x_0) + E\int_0^{\tau^{(0)}} Af(X^{(0)}(s))ds + f'(0)E\ell(\tau)$$

which gives...

Linear Programming

$$\int_{[0,L]} Af(x)\mu_0(dx) + f(x) - f(L) + f'(0)\vartheta = 0.$$

where

$$\mu_0(B) = E\left[\int_0^{\tau^{(0)}} I_B(X^{(0)}(s))ds\right],\ \ B \in B(\mathbb{R}_+), \vartheta = E\ell(t)$$

Take $f(\cdot)$ to be the monomials and we have linear constraints

$$\sum_{i=0}^{n} c_i m_i + \vartheta\, d + \kappa = 0 \text{ where } m_k = \int x^k \mu_0(dx).$$

$E\tau^{(0)}$ is m_0. In addition, Hausdorff moment conditions are used. Then, we minimize and maximize m_0 to get bounds.

Markov Chain Approximation

- *In general, discretize the process in time and space. Used for many types of problems.*
- *One adaptaion (by Wang et al) was designed to calculate asymptotic velocity and effective diffusivity for a one-dimensional motor processes.*
- *The state space is discretized, and one considers the equilibrium distribution of the motor modulo the step size.*
- *Extended method to include cargo. (Joint work with T Elston)*

Numerical Results

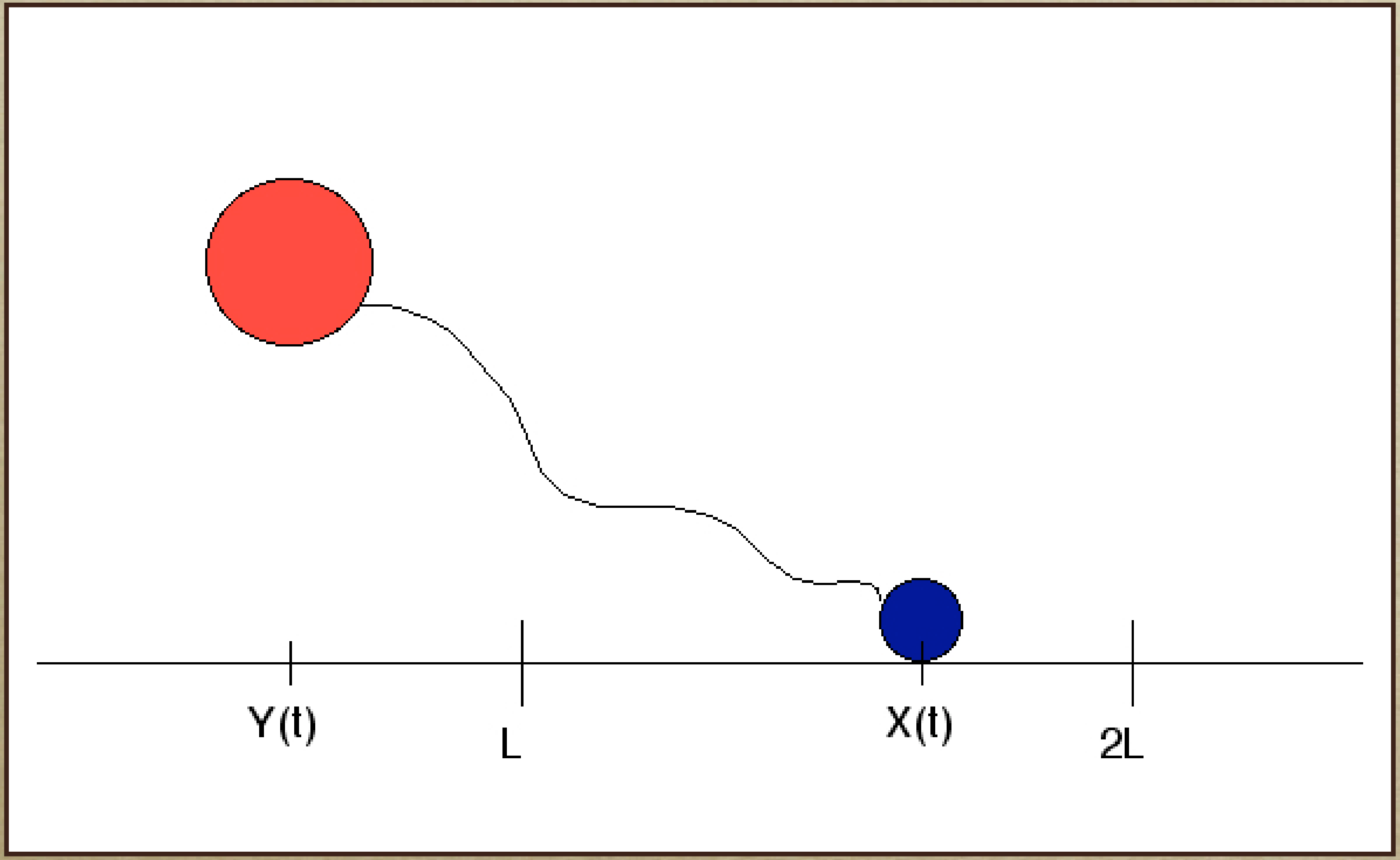
$$X(t) = \mu t + \sigma W(t) + \ell(t)$$

σ	μ	$E\tau_0$	Monte Carlo	Markov Chain	Lin Prog Lower	Lin Prog Upper
1	0	4	4.4302	3.9596	4	4
1	2	0.8750	0.9104	0.8647	0.8749	0.8751
1	-1	24.7991	29.7683	22.749	24.7990	24.7992
2	1	0.7357	0.8270	0.7267	0.7357	0.7357
2	-1	1.4366	1.7643	1.4091	1.4366	1.4366

Motor Pulling a Cargo

- *A motor moves along a microtubule and has a long tail to which a cargo may be attached.*
- *The cargo is usually many times the mass of the motor.*
- *Using laser traps, one may indirectly "observe" the motor by attaching a bead as a cargo and observing this bead.*

Motor and Cargo



Dynamics of the Coupled System

- *Y(t) is the location of cargo at time t*
- *X(t) is the location of motor at time t*

$$
\begin{cases}
Y(t) = & y_0 + \int_0^t b_1(X(s),Y(s))ds + \int_0^t a_1(X(s),Y(s))dB(s), \\
X^{(i)}(t) = & \Gamma_i\left(iL + \int_0^{\cdot} b_2(X^{(i)}(s),Y(s+\sigma^{(i)}))ds + \int_0^{\cdot} a_2(X^{(i)}(s),Y(s+\sigma^{(i)}))dW^{(i)}(s)\right)(t), \\
\tau^{(i)} = & \inf\{t : X^{(i)}(t) = (i+1)L\}, \\
\sigma^{(i)} = & \tau^{(i-1)} + \sigma^{(i-1)} \\
X(t) = & X^{(i)}(t-\sigma^{(i)});\ \ t \in [\sigma^{(i)},\sigma^{(i+1)}),\ \ i \in N_0,
\end{cases}
$$

A Special Case: Linear Spring

$$Y(t) = y_0 + K_1 \int_0^t (X(s) - Y(s))ds + \sigma_1 W_1(t)$$

$$X(t) = x_0 + K_2 \int_0^t (Y(s) - X(s))ds + \sigma_2 W_2(t) + L(t)$$

This represents a motor and cargo connected by a linear spring.

Theorem

As $t \to \infty$, $\dfrac{X(t)}{t}$ converges in probability.

Sketch of Proof

Notice

$$\frac{X(t)}{t} = \frac{Y(t)}{t} - \frac{Y(t) - X(t)}{t} = \frac{Y(t)}{t} - \frac{Z(t)}{t}$$

where $Z(t) = Y(t) - X(t)$.

Recall

$$\frac{Y(t)}{t} = \frac{y_0}{t} + \frac{K_1}{t}\int_0^t Z(s)ds + \sigma_1 \frac{W_1(t)}{t}.$$

Define $\varphi(t) = (Z(t), \lfloor \frac{X(t)}{L} \rfloor L)$.

One can show that $\varphi(t)$ is a Feller-Markov process with values in $(\mathbb{R}, [0, L])$.

Define $\mu_T(\cdot) = \frac{1}{T}\int_0^T P[Z(t) \in \cdot]dt$.
Show that $\{\mu_T : T \geq 0\}$ is a tight family of measures.

Sketch of Proof

From the above tightness and the Feller property, it follows that $\varphi(t)$ has an invariant distribution.

Use the non-degeneracy of the diffusion to show that the invariant distribution is unique. Denote the invariant measure by $\mu(dz, dx)$, and thus

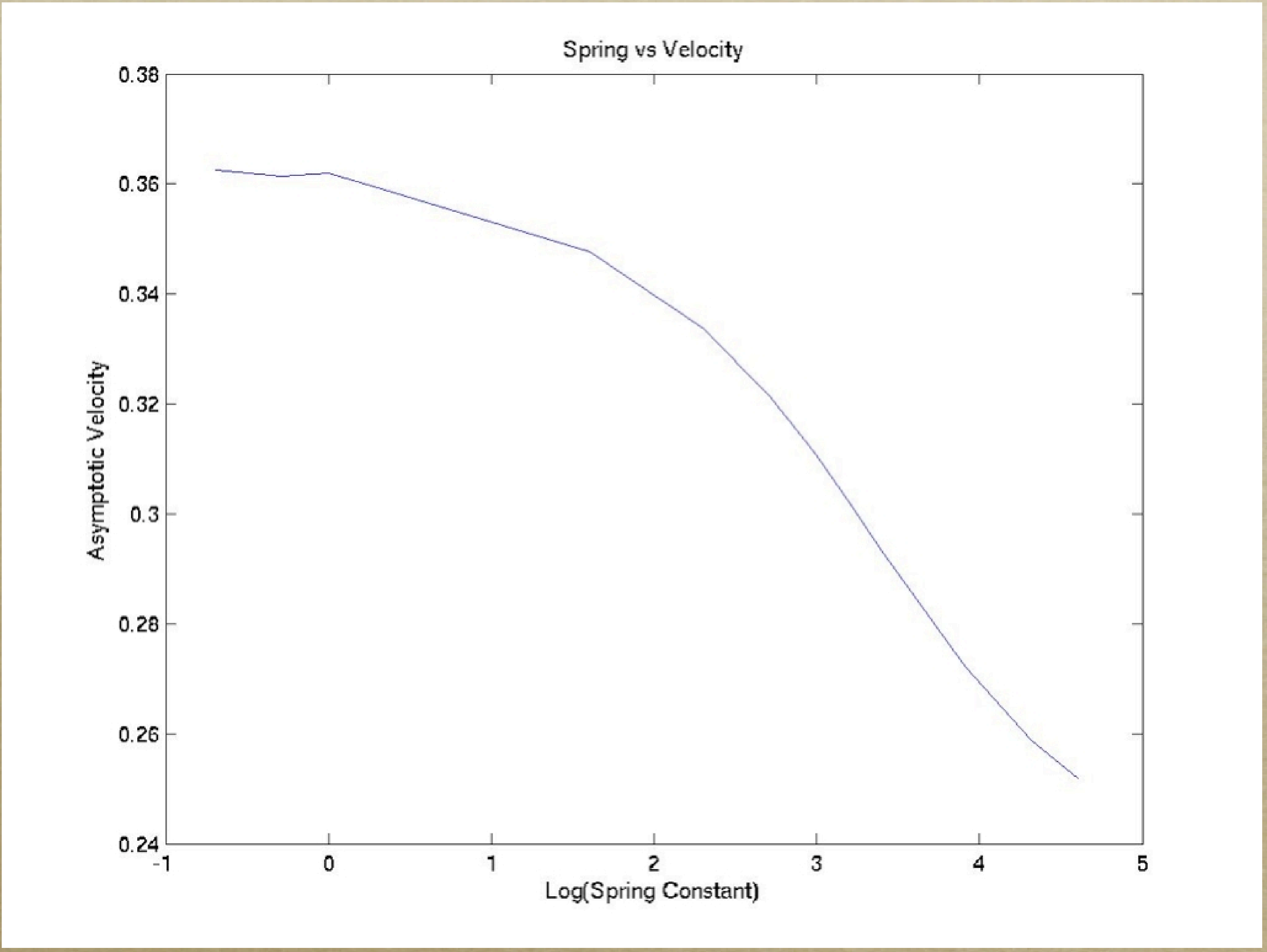
$$\frac{1}{t}\int_0^t Z_s ds \to \int_R z d\mu(dz, dx)$$

Can also show $\frac{Z(t)}{t} \to 0$ in probability. The result follows, and the constant is

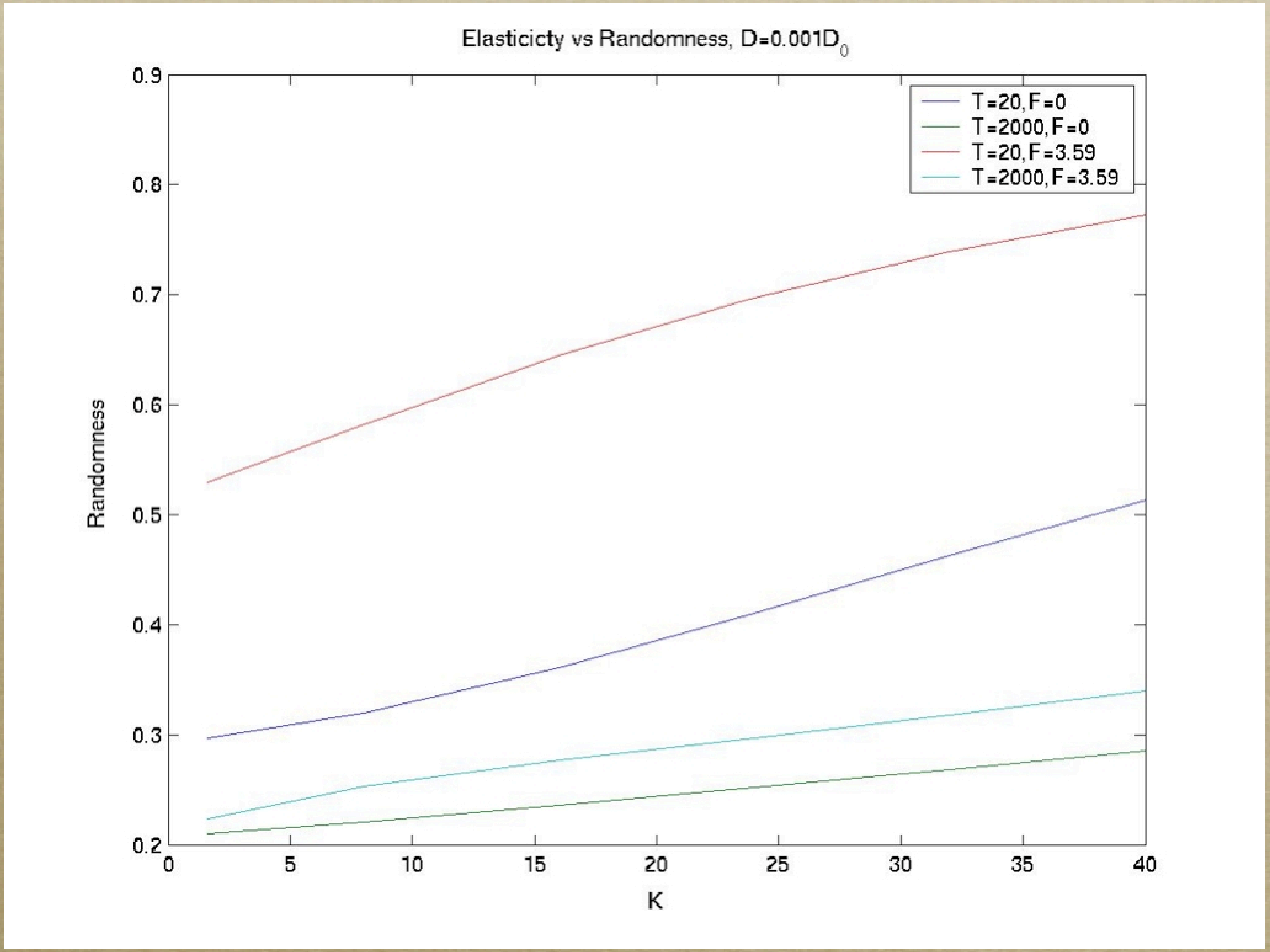
$$\lim_{t\to\infty} \frac{X(t)}{t} = K_1 \int z d\mu(dz, dx)$$

.

Numerical Method



Numerical Method



A Non-Linear Filtering Problem

- *Optical traps allow dynamic measurement and manipulation of microscopic objects of certain sizes.*
- *The cargo can be observed dynamically --the motor cannot.*
- *The observation noise is not independent of the signal. There is feedback of the observation process back into the signal dynamics*

A Non-Linear Filtering Problem

Discretize the model:

$$Y_{k+1} = Y_k + K_1(X_{k+1} - Y_{k+1})\Delta + \sigma_1\sqrt{\Delta}\xi_{k+1}$$

$$X_{k+1} = \Big(X_k + K_2(Y_k - X_k)\Delta + \sigma_2\sqrt{\Delta}\eta_{k+1})\Big) \wedge \left(\lfloor\frac{X_k}{L}\rfloor L\right)$$

$\{\xi_k\}, \{\eta_k\}$ are i.i.d. $N(0,1)$.

$\zeta_k = (X_k, Y_k)$ is a Markov chain.

Δ is the discretization parameter.

Recursion Formula

Transition law of the Markov chain allows us to write a recursive formula for the non-linear filter, i.e. $F_k(dz)$*, the distribution of* X_k *given* $Y_1, \ldots, Y_k$.

$$F_k(dz) = p(Y_k|Y_{k-1}, x_k) \int_{x_{k-1}} Q(dz|x_{k-1}, Y_{k-1}) F_{k-1}(dx_{k-1})$$

$p(y_k|y_{k-1}, x_k)$ is the transition density for Y_k given Y_{k-1}, X_k.

$Q(x_k|x_{k-1}, y_{k-1})$ is the transition distribution for X_k given X_{k-1}, Y_{k-1}.

Approximation of Non-Linear Filter: Numerical Integration

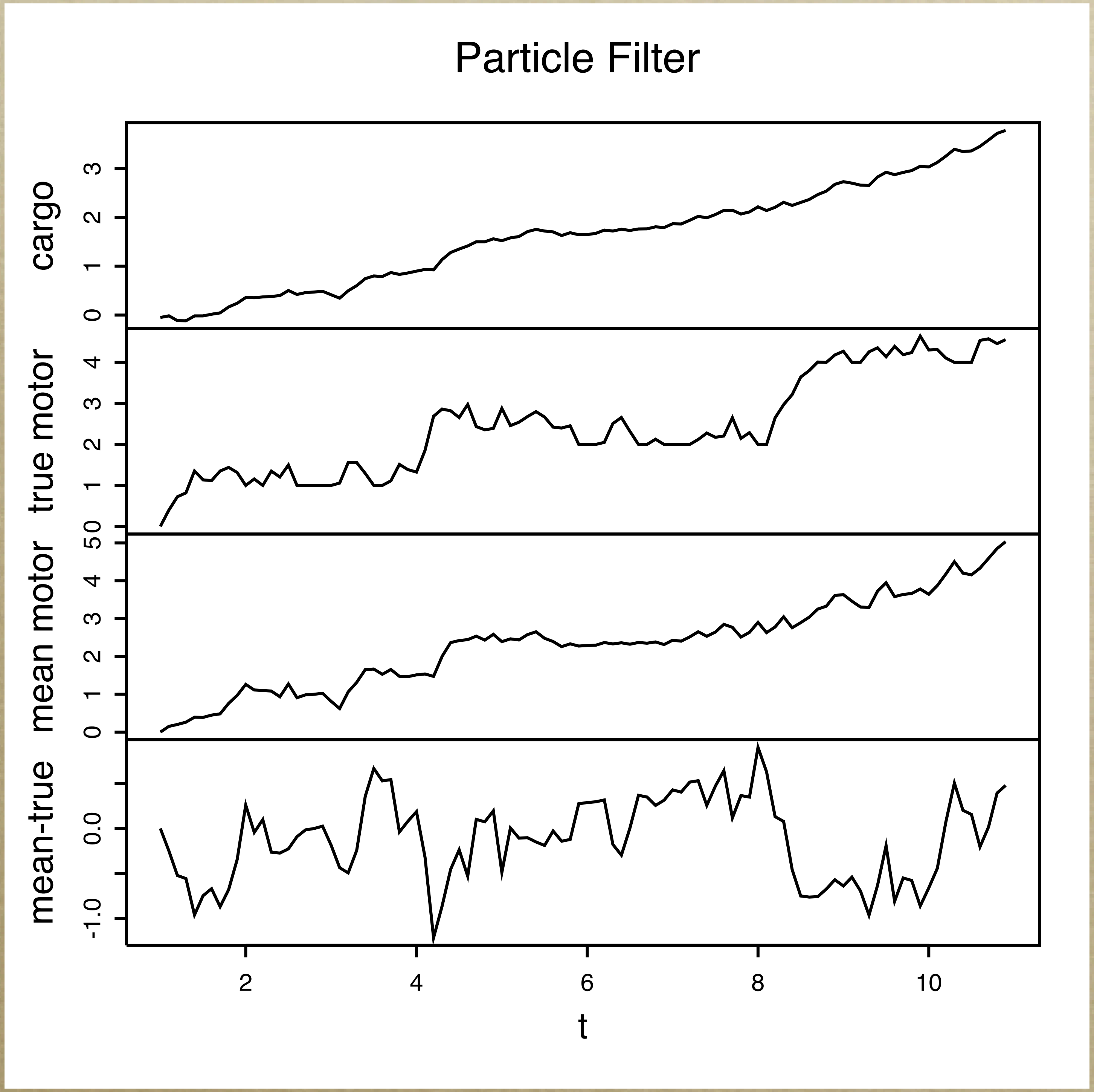
$$F_k(dz) = p(Y_k|Y_{k-1}, x_k) \int_{x_{k-1}} Q(dz|x_{k-1}, Y_{k-1}) F_{k-1}(dx_{k-1})$$

- *Must discretize in space in some type of fixed grid.*
- *Must adapt the grid deterministically.*
- *Can be computationally intensive.*

Approximation of Non-Linear Filter: Particle Filter

- *Algorithm*
  - *Initialize--take an iid sample for n=0* $\{X_0^{(i)}, i = 1 \ldots n\}$
  - *Evolve, sample* $X_k^{(i)}$ from $Q(dz|X_{k-1}^{(i)}, Y_{k-1})$
  - *Weight* $X_k^{(i)}$ with $w_k = p(Y_k|X_k^{(i)}, Y_{k-1})w_{k-1}$
  - *Resample (not at every time step)*
  - *Return to Evolve*
- *The filter estimate at time k is* $\hat{F}_k(z) = \sum_{i=1}^{n} w_k I_{\{X_k^{(i)} \leq z\}}$
- *Inherent adaptivity which fits this application well.*

Filtering Result



Parameter Estimation under Partial Observation

- *Bayesian Approach--Include the parameter as another "hidden" variable of the stochastic system.*
- *Stochastic Maximum Likelihood*
- *Stochastic EM (Expectation Maximization) algorithm*
- *Smoothing can better facilitate these approaches.*

Future Work

- *Fast Motor Limit, i.e Very Small Motor/ Very Large Cargo*
- *Connection between Flashing Ratchet, Imperfect Ratchet, and Diffusion Ratchet*
- *Soft/Weak spring limits via FCLT*
- *More information can be found at:www.unc.edu/~fricks/*