Mathematical Models for Molecular Motors: The Polymerization Ratchet

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SEATTLE UNIVERSITY

APPLIED MATHEMATICS
UNIVERSITY *of* WASHINGTON

About Me

Ph.D. in Applied Mathematics

University of Washington, Seattle, WA, 2011

- Dissertation:
  - Mathematical Models for Facilitated Diffusion and the Brownian Ratchet
- Advisor:
  - Hong Qian

Undergraduate Degree:

- Macalester College, St. Paul, MN
- Math & Physics Major

From Tacoma, WA

Outline

Introduction

Molecular Motors

Motivation for the Polymerization Ratchet Model

Polymerization Model

Model System & Simulations

Analysis of the Mathematical Model

Polymerization Ratchet Model

Single Polymer Ratchet

N Polymer Bundle Ratchet

Conclusions

Summary

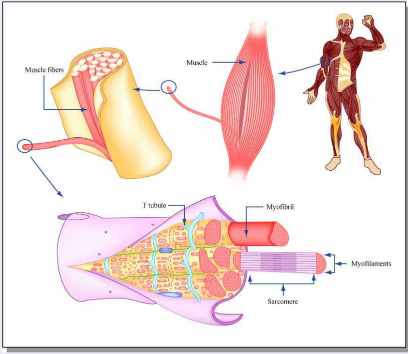
What are Molecular Motors?
In General Terms:

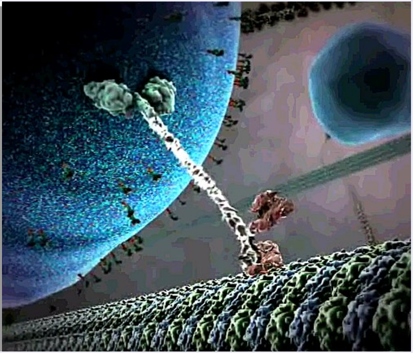
Protein Molecules in the Cell that:

- Generate Forces
- Cause the Transport of Material

What are Molecular Motors?

Two Specific Examples:





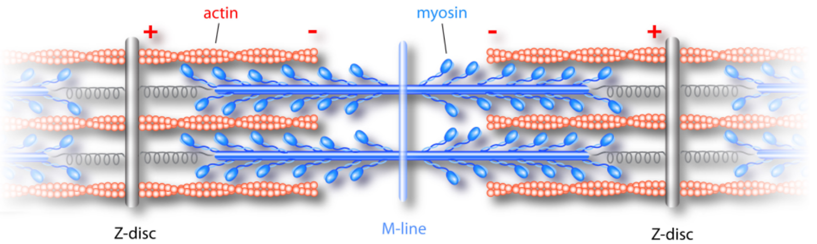
Muscle: http://www.bio.davidson.edu/people/midorcas/animalphysiology/websites/2011/Miller/Background.html

Kinesin: http://multimedia.mcb.harvard.edu/media.html

Conventional Molecular Motors

Myosin

Muscle Contraction



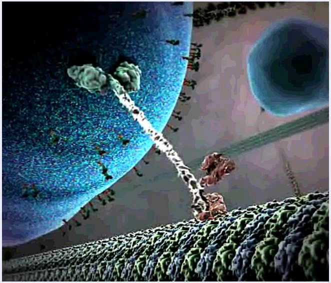
http://www.embl.de/∼guenther/project_muscleoscillations.html

Conventional Molecular Motors

Kinesin

Intracellular Transport

Short Video Excerpt: Inner Life of the Cell



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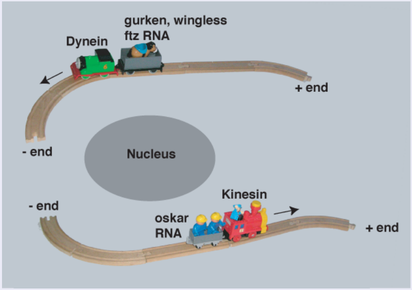
Conventional Molecular Motors

Conventional Molecular Motors



Move Along Polymer Tracks

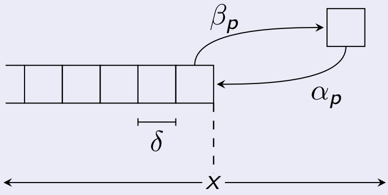
- myosin - actin microfilaments
- kinesin - tubulin microtubules

http://www.bioch.ox.ac.uk/aspsite/index.asp?pageid=573

Polymerization

Another Way to Cause Motion/Transport

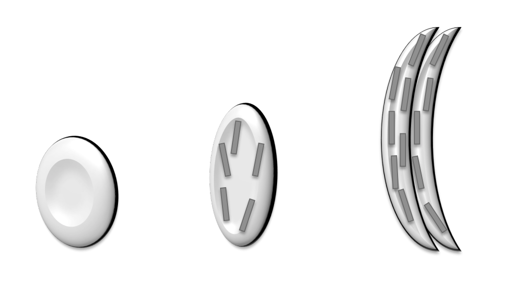
Change the Length of the Polymers Themselves!



- Polymerization: Adding Subunits
- Depolymerization: Subtracting Subunits
- (Subunits = Monomers)

Polymerization Causing Cell Membrane Deformation

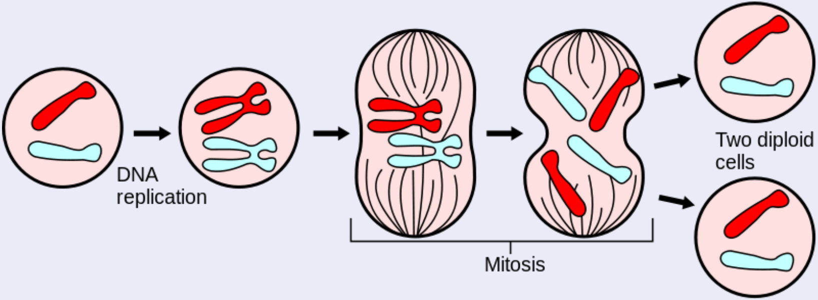
Sickle Cell Anemia: Sickle Hemoglobin Polymerization



Left: http://www.hopkinsmedicine.org/Medicine/sickle/patient/index.html Right: (My Dissertation)

Depolymerization During Cell Division

Mitosis:
Depolymerization of Spindle Pulls Sister Chromatids Apart



http://www.ncbi.nlm.nih.gov/About/primer/genetics_cell.html

Why Do We Care About Molecular Motors?

Molecular Motors are Special Because:

- Chemical Energy $\Rightarrow$ Mechanical Energy
  - DIRECTLY! (Not Via Heat or Electrical Energy)
- Highly Efficient:
  - 6 Times More Efficient than a Car
- Models for Molecular Motors
  $\Rightarrow$ Theoretical Foundations for Nano-Engineering
  - Nano-mechano-chemical Machines
  - Tiny Robots!

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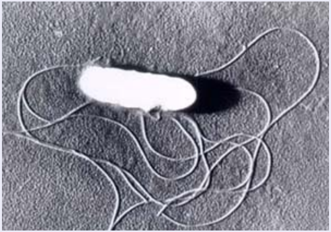
Motivation: Actin-Based Motility

Listeria monocytogenes:



http://textbookofbacteriology.net/Listeria_2.html

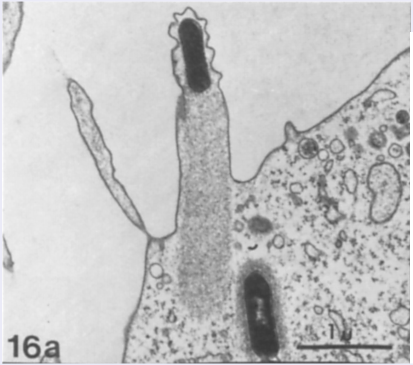
Bacteria that Causes *Listeriosis*
Usually Only Flu-Like Symptoms,
CDC Estimates that in the U.S.

- 1,600 People per Year Become Seriously Ill due to Listeriosis
- Out of Those, 260 Die

At body temperature:
Listeria is propelled by polymerization of actin filaments.

Motivation: Actin-Based Motility

Actin-Based Motility of *Listeria* (Click for Movie)



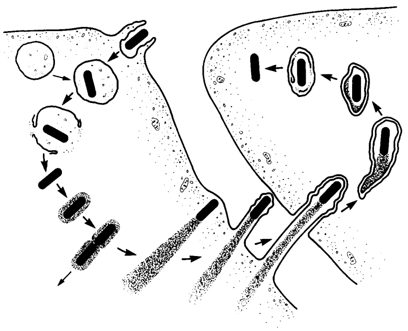


Image Source: Tilney & Portnoy 1989, *J Cell Biol* 109:1597-1608

Movie Source: Theriot & Portnoy: http://cmgm.stanford.edu/theriot/movies.htm

Motivation: Actin-Based Motility

Actin-Based Motility of *Listeria*

Motivates Study of:

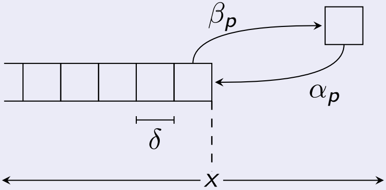
- Polymerization-Driven Motion of a Fluctuating Barrier

Mathematical Framework:

- Diffusion Formalism Brownian Ratchet Model
- Building On Simplest Case:
  Single Polymer Ratchet

Single Polymer Ratchet Model

What is a Single Polymer Ratchet?



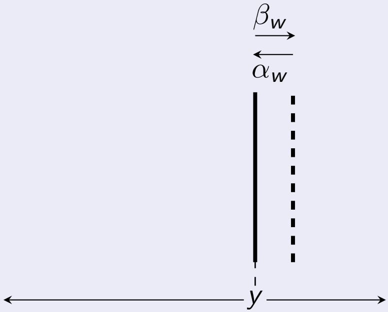
Component 1:

Polymer

- α_p, β_p: Adding/Subtracting Rates
- δ: Monomer Width
- $\alpha_p > \beta_p$: Polymer Grows (On Average)

Single Polymer Ratchet Model

What is a Single Polymer Ratchet?



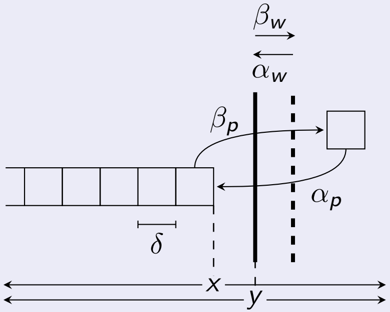
Component 2:

Fluctuating Barrier (Wall)

- α_w
  "Left" Rate
- β_w:
  "Right" Rate
- $\alpha_w > \beta_w$:
  Barrier Moves "Left"

Single Polymer Ratchet Model

What is a Single Polymer Ratchet?

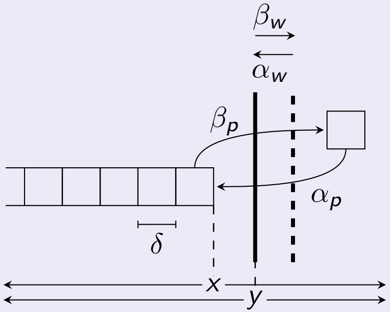


When Components Interact:

- Barrier Motion "blocked" by Polymer
- Polymer Growth "blocked" by Barrier

Single Polymer Ratchet Model

What is a Single Polymer Ratchet?



When Components Interact:

If Polymerization is "Fast:"

- Barrier Moves Away
- Polymer *Immediately* Grows
- Blocking Backward Fluctuation of Barrier

Barrier is "Ratcheted" Forward

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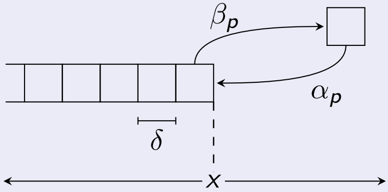
Basic Polymerization Model System

How does Polymerization Work?



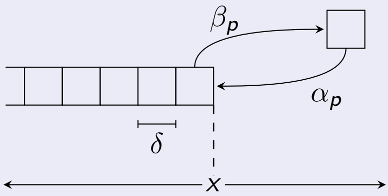
- x: position of the end of the polymer

Rate Constants:

- α_p: adding a monomer (growth rate)
- β_p: subtracting a monomer (shrinking rate)

Basic Polymerization Model System

How does Polymerization Work?



Deterministic Model:

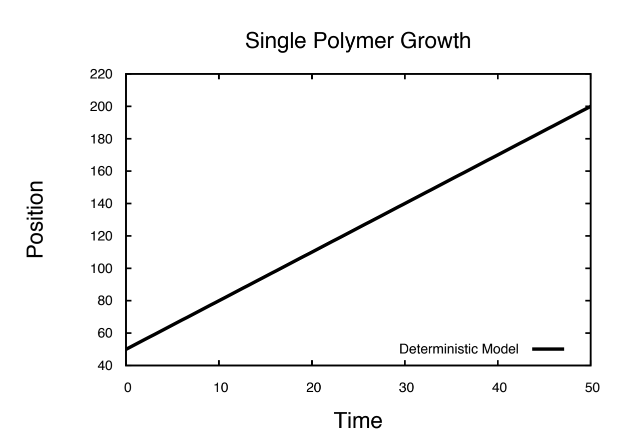
- $\frac{dx}{dt} = (\alpha_p - \beta_p)\delta$
- x_0: initial position

$\Rightarrow$

$$x(t) = x_0 + (\alpha_p - \beta_p)\delta t$$

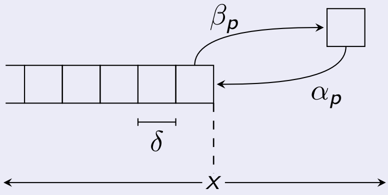
Polymer Position -vs- Time: Deterministic Model

$$x(t) = x_0 + (\alpha_p - \beta_p)\delta t, \quad \alpha_p = 4, \quad \beta_p = 1, \quad x_0 = 50$$



Basic Polymerization Model

How does Polymerization Work?



Deterministic System:

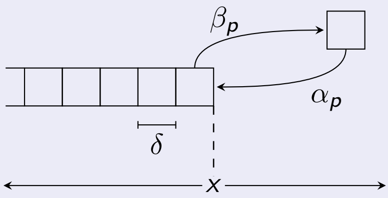
- Motion is continuous in Space, Time
- Initial Condition
  $\Rightarrow$ one possible trajectory

Stochastic System:

- Direction of motion
  Time motion occurs
  Random
- Initial Condition
  $\Rightarrow$ *many* possible trajectories

Basic Polymerization Model

How does Polymerization Work?



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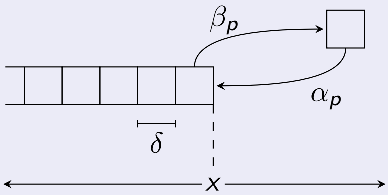
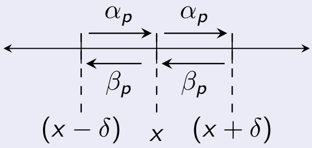
Stochastic Polymerization Model

Continuous-Time 1-D Biased Random Walk



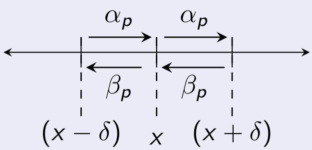


Generate Exact Stochastic Simulations $\Rightarrow$ Gillespie Algorithm

[Gillespie, 2007]

Simulation: Gillespie Algorithm

Basic Simulation Scheme:

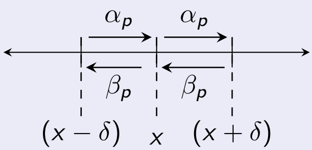


Start: $t = t_0$, $x = x_0$.

- Wait dt for an "Event" to Occur.
  Set $t = t_0 + dt$.
  - If "Adding Event"
    Set $x = x_0 + \delta$.
  - If "Subtracting Event"
    Set $x = x_0 - \delta$.
- Repeat Until $t = t_{max}$.

Simulation: Gillespie Algorithm

Basic Simulation Scheme:



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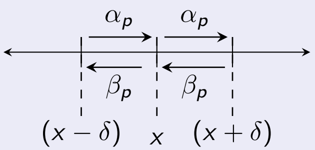
Simulation: Gillespie Algorithm

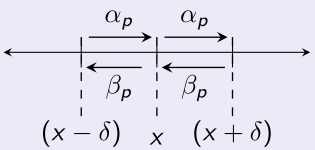
Wait dt for an "Event" to Occur.



- Number of Events: *Poisson Process* with rate $\lambda = \alpha_p + \beta_p$.
- $\Rightarrow$ dt is a random number from *Exponential Distribution*, rate λ.
- If u is a random number from a *Uniform(0,1) Distribution*, $dt = -\frac{1}{\lambda}\log u$

Simulation: Gillespie Algorithm

Basic Simulation Scheme:



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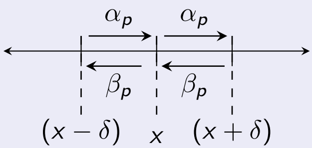
Simulation: Gillespie Algorithm

Decide which "Event" Occurs.



Probability of Subtracting or Adding:

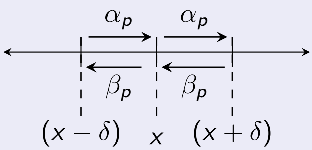
- $P(-) = \frac{\beta_p}{\alpha_p+\beta_p} = \frac{\beta_p}{\lambda}$
- $P(+) = \frac{\alpha_p}{\alpha_p+\beta_p} = \frac{\alpha_p}{\lambda}$
- Note: $P(-) + P(+) = 1$.

Generate a *Uniform(0,1)* random number, u.

- If $0 \leq u < P(-)$, Subtract
- If $P(-) \leq u \leq 1$, Add

Simulation: Gillespie Algorithm

Basic Simulation Scheme:



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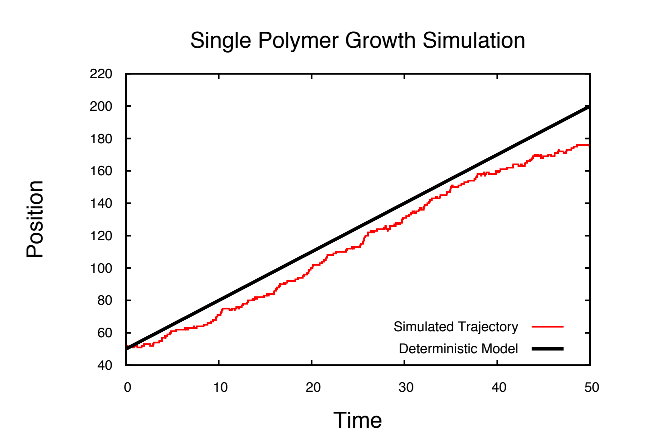
Polymer Position -vs- Time: Simulated Data

$$x(t) = x_0 + (\alpha_p - \beta_p)\delta t, \quad \alpha_p = 4, \quad \beta_p = 1, \quad x_0 = 50$$



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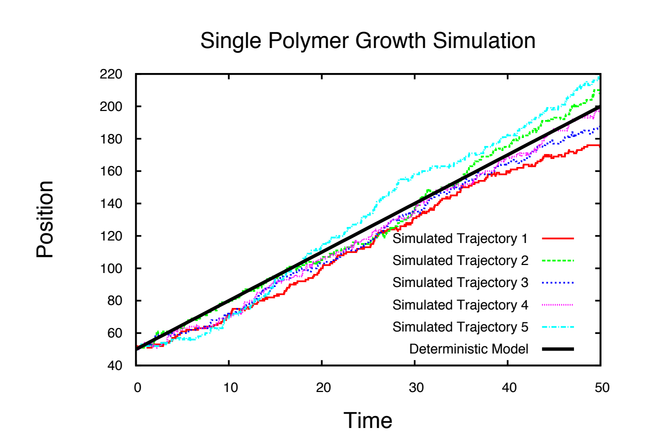

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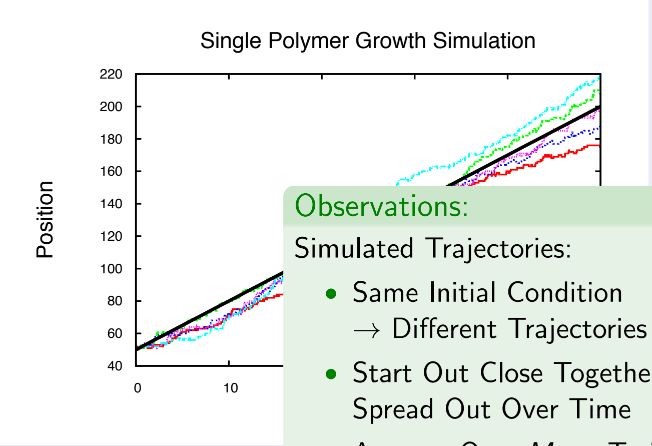

Observations:

Simulated Trajectories:

- Same Initial Condition $\rightarrow$ Different Trajectories
- Start Out Close Together, Spread Out Over Time
- Average Over *Many* Trajectories $\rightarrow$ Deterministic Trajectory

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Stochastic Polymerization Model

Formulating the Mathematical Model:

Random Variable $\mathbf{X}(t)$: Position of Polymer Tip

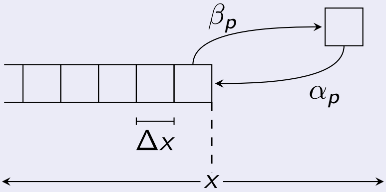
- *Discrete Space* Model
  - $P_{\mathbf{X}}(x,t) = \mathrm{Prob}\{\mathbf{X}(t) = x\}$
  - Biased Random Walk
- *Continuous Space* Model
  - $P_{\mathbf{X}}(x,t) = \mathrm{Prob}\{x < \mathbf{X}(t) \leq x + dx\}$
  - Biased Brownian Motion

Single Polymer (No Barrier)

Random Variable $\mathbf{X}(t)$: Position of Polymer Tip

$$\frac{\partial P_{\mathbf{X}}(x,t)}{\partial t} = \alpha_p P_{\mathbf{X}}(x-\Delta x, t) + \beta_p P_{\mathbf{X}}(x+\Delta x, t) - (\alpha_p + \beta_p) P_{\mathbf{X}}(x, t)$$

$$\frac{\partial P_{\mathbf{X}}(x,t)}{\partial t} = D_a \frac{\partial^2 P_{\mathbf{X}}(x,t)}{\partial x^2} - V_a \frac{\partial P_{\mathbf{X}}(x,t)}{\partial x}$$



Discrete Space Model:

- $P_{\mathbf{X}}(x,t) = \mathrm{Prob}\{\mathbf{X}(t) = x\}$
- Biased Random Walk

To Obtain *Continuous Space* Model:

- Taylor Expand in $x \ldots$

Single Polymer (No Barrier)

Random Variable $\mathbf{X}(t)$: Position of Polymer Tip

$$\frac{\partial P_{\mathbf{X}}(x,t)}{\partial t} = \alpha_p P_{\mathbf{X}}(x-\Delta x, t) + \beta_p P_{\mathbf{X}}(x+\Delta x, t) - (\alpha_p + \beta_p) P_{\mathbf{X}}(x, t)$$

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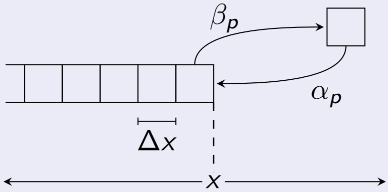


Continuous Space Model:

- $P_{\mathbf{X}}(x,t) = \mathrm{Prob}\{x < \mathbf{X}(t) \leq x + dx\}$
- Biased Brownian Motion (Diffusion with Drift)

$$D_a = \lim_{\Delta x \to 0} (\alpha_p + \beta_p) \frac{\Delta x^2}{2}, \qquad V_a = \lim_{\Delta x \to 0} (\alpha_p - \beta_p) \Delta x$$

Mathematical Model

Continuous Space Polymer Length Model

Partial Differential Equation for Diffusion with Drift

- $\frac{\partial P_{\mathbf{X}}(x,t)}{\partial t} = D_a \frac{\partial^2 P_{\mathbf{X}}(x,t)}{\partial x^2} - V_a \frac{\partial P_{\mathbf{X}}(x,t)}{\partial x}$

$$D_a = \lim_{\Delta x \to 0} (\alpha_p + \beta_p) \frac{\Delta x^2}{2}, \qquad V_a = \lim_{\Delta x \to 0} (\alpha_p - \beta_p) \Delta x$$

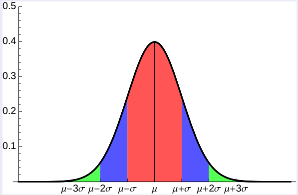
Solution:

- $P_{\mathbf{X}}(x,t) = \frac{1}{\sqrt{4\pi D_a t}} \exp\left(-\frac{(x - V_a t)^2}{4 D_a t}\right)$

(Brownian Motion)

Mathematical Model

Continuous Space Polymer Length Model (Click for Movie)



68.26%
95.44%
99.74%

Solution:

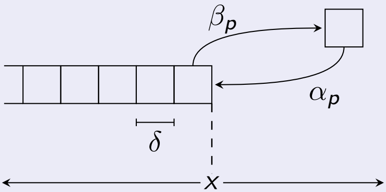
- $P_{\mathbf{X}}(x,t) = \frac{1}{\sqrt{4\pi D_a t}} \exp\left(-\frac{(x-V_a t)^2}{4D_a t}\right)$

Gaussian (Normal) Distribution:

- $P_{\mathbf{X}}(x,t) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right)$
- $\mu = V_a t$
- $\sigma^2 = 2D_a t$

Basic Polymerization Model

How does Polymerization Work?



Deterministic System:

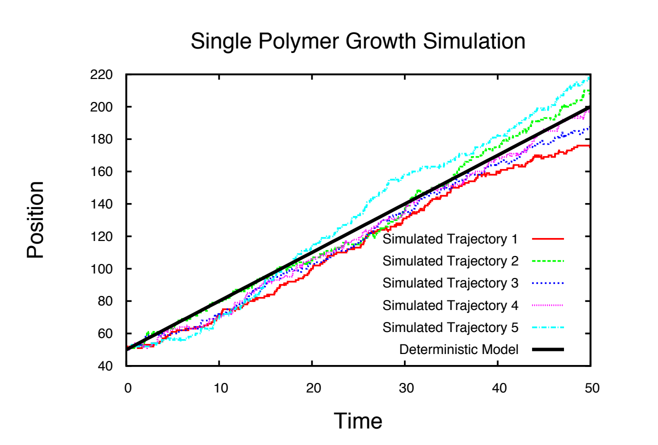
- Polymer Length: $x(t) = V_a t$

Stochastic System:

- Polymer Length Distribution:
  $P_{\mathbf{X}}(x,t) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right),$
  $\mu = V_a t, \quad \sigma^2 = 2D_a t$

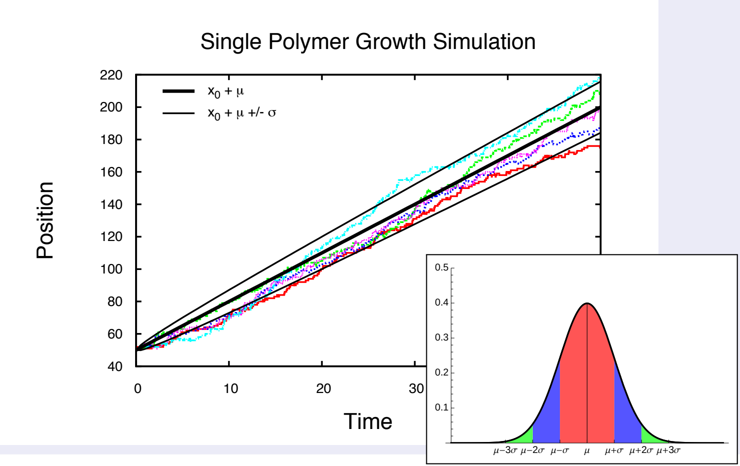
Compare Simulated Data to Theoretical Results

$$\mu = V_a t, \quad \sigma^2 = 2D_a t, \quad V_a = 3, \quad D_a = 5/2, \quad x_0 = 50$$



Compare Simulated Data to Theoretical Results

$$\mu = V_a t, \quad \sigma^2 = 2D_a t, \quad V_a = 3, \quad D_a = 5/2, \quad x_0 = 50$$



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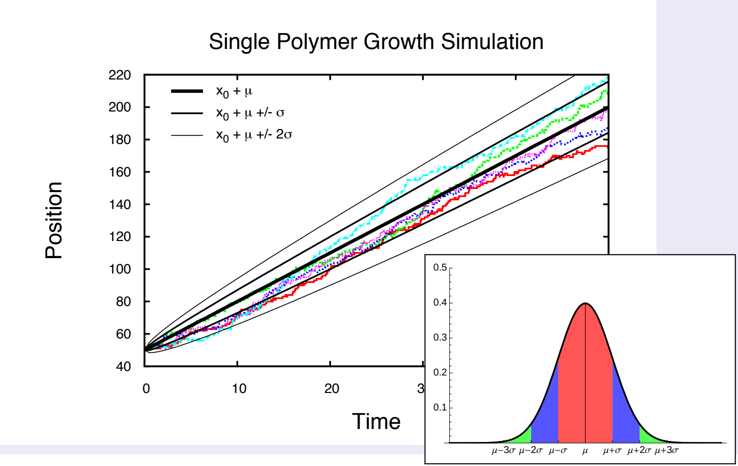

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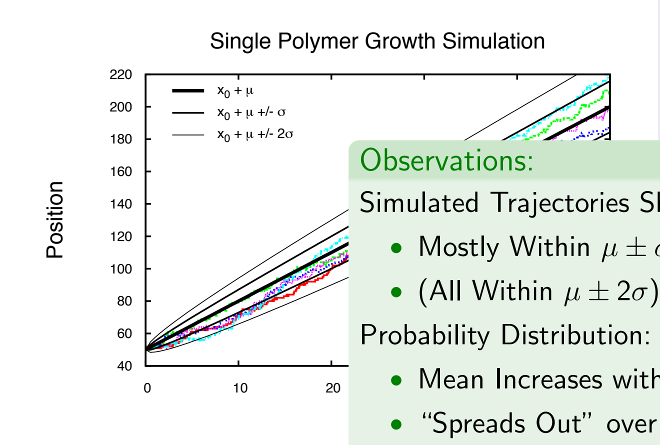

Observations:

Simulated Trajectories Shown:

- Mostly Within $\mu \pm \sigma$
- (All Within $\mu \pm 2\sigma$)

Probability Distribution:

- Mean Increases with Time
- "Spreads Out" over Time

Excellent Agreement!

Stochastic Polymerization Model Summary

Position of the End of a Single Polymer

- Simulation Scheme
  (Spatially Discrete Model)
- Analytical Result:
  Formula for Probability Distribution
  (Spatially Continuous Model)

$\Rightarrow$ Build On These to Formulate a
Model for the Polymerization Ratchet!

Introduction
Molecular Motors
Motivation for the Polymerization Ratchet Model

Polymerization Model
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Polymerization Ratchet Model
Single Polymer Ratchet
N Polymer Bundle Ratchet

Conclusions
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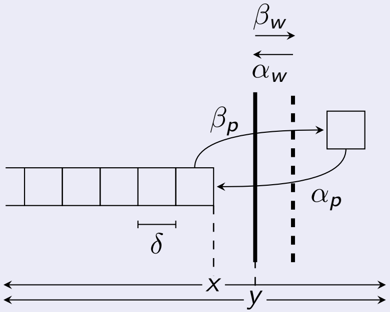
Single Polymer Ratchet Model

What is a Single Polymer Ratchet?



When Components Interact:

If Polymerization is "Fast:"

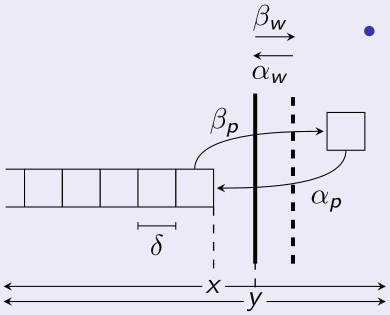
- Barrier Moves Away
- Polymer *Immediately* Grows
- Blocking Backward Fluctuation of Barrier

Barrier is "Ratcheted" Forward

Simulation: Gillespie Algorithm

Basic Simulation Idea

$\lambda = \alpha_p + \beta_p + \alpha_w + \beta_w$



Start: $t = t_0$, $x = x_0$, $y = y_0$.

- Wait dt for an "Event" to Occur. Set $t = t_0 + dt$.
  - If "Polymer Adding Event" Set $x = x_0 + \delta$.
  - If "Polymer Subtracting Event" Set $x = x_0 - \delta$.
  - If "Wall Moves Right Event" Set $y = y_0 + \delta$.
  - If "Wall Moves Left Event" Set $y = y_0 - \delta$.

Geometric Constraint: Polymer/Wall Can "Block" Events

Simulation: Gillespie Algorithm

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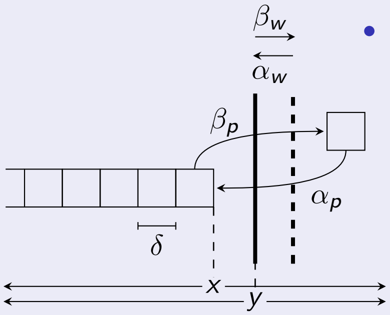

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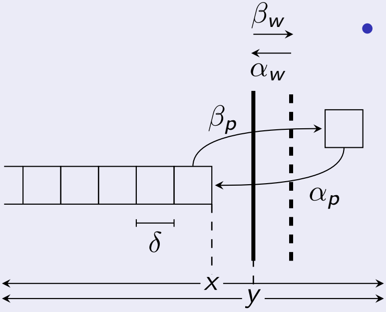

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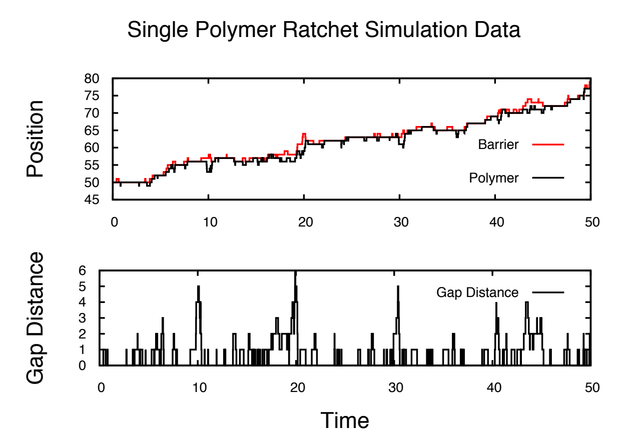
Geometric Constraint: Polymer/Wall Can “Block” Events

Single Polymer Ratchet Simulated Data

$\alpha_p = 4, \quad \beta_p = 1, \quad \alpha_w = 2, \quad \beta_w = 1, \quad x_0 = y_0 = 50$



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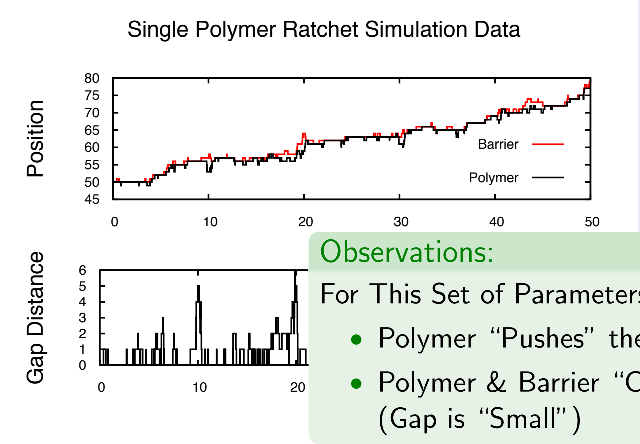


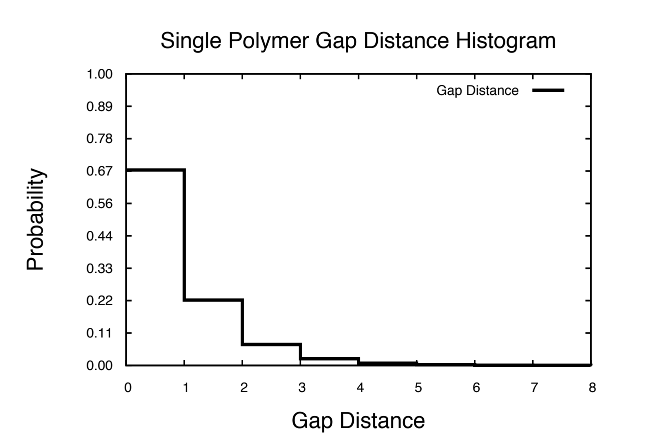
Observations:

For This Set of Parameters:

- Polymer "Pushes" the Barrier
- Polymer & Barrier "Close" (Gap is "Small")

Single Polymer Ratchet Simulated Data

$\alpha_p = 4, \quad \beta_p = 1, \quad \alpha_w = 2, \quad \beta_w = 1, \quad t_{max} = 10,000$



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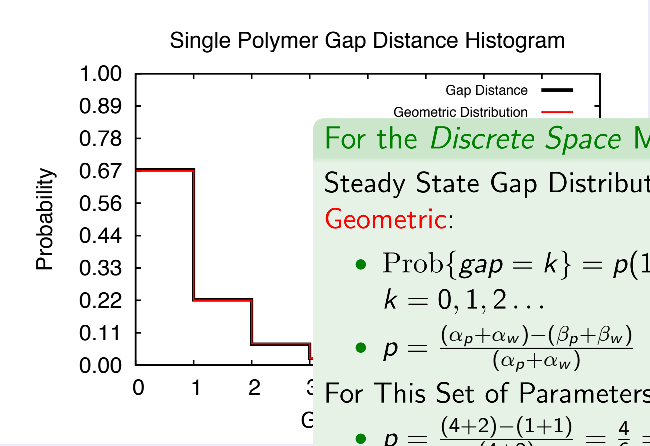


For the *Discrete Space* Model:

Steady State Gap Distribution is Geometric:

- $\mathrm{Prob}\{gap = k\} = p(1-p)^k$
  $k = 0, 1, 2 \ldots$
- $p = \frac{(\alpha_p+\alpha_w)-(\beta_p+\beta_w)}{(\alpha_p+\alpha_w)}$

For This Set of Parameters:

- $p = \frac{(4+2)-(1+1)}{(4+2)} = \frac{4}{6} = \frac{2}{3}.$

Single Polymer Ratchet Model

Formulating the Mathematical Model:

Can Formulate both:

- *Discrete Space* Model
- *Continuous Space* Model

Focus on the *Continuous Space* Model Because:

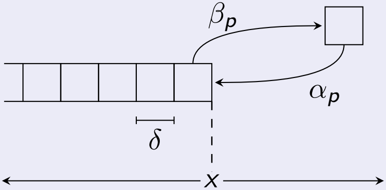
- Analytical Results can be (More) Easily Obtained
- Easier to Incorporate Additional Features:
  - Attraction Between Polymer and Barrier
  - N Polymer Ratchet

Single Polymer (No Barrier)

Random Variable $\mathbf{X}(t)$: Position of Polymer Tip

Recall:

$$\frac{\partial P_{\mathbf{X}}(x,t)}{\partial t} = D_a \frac{\partial^2 P_{\mathbf{X}}(x,t)}{\partial x^2} - V_a \frac{\partial P_{\mathbf{X}}(x,t)}{\partial x}$$



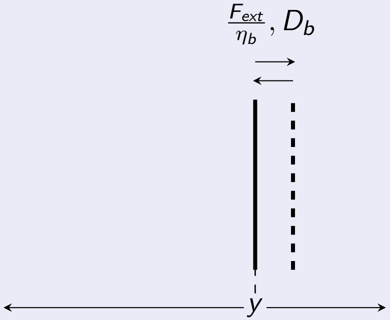
Continuous Space Model:

- $P_{\mathbf{X}}(x,t) = \mathrm{Prob}\{x < \mathbf{X}(t) \le x + dx\}$
- Biased Brownian Motion (Diffusion with Drift)

Barrier (No Polymer)

Random Variable $\mathbf{Y}(t)$: Position of Barrier

$$\frac{\partial P_{\mathbf{Y}}(y,t)}{\partial t} = D_b \frac{\partial^2 P_{\mathbf{Y}}(y,t)}{\partial y^2} + \frac{F_{ext}}{\eta_b} \frac{\partial P_{\mathbf{Y}}(y,t)}{\partial y}$$



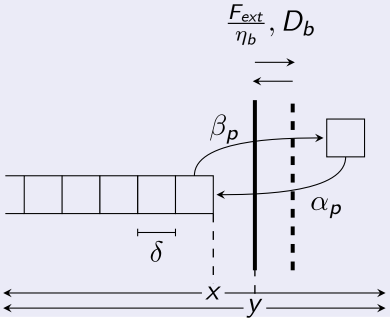
Continuous Space Model:

- $P_{\mathbf{Y}}(y,t) = \mathrm{Prob}\{y < \mathbf{Y}(t) \leq y + dy\}$
- Biased Brownian Motion (Diffusion with Drift)

Single Polymer Ratchet

Diffusion Formalism Model: [Qian, 2004]

$$\frac{\partial P_{\mathbf{XY}}(x,y,t)}{\partial t} = D_a \frac{\partial^2 P_{\mathbf{XY}}}{\partial x^2} + D_b \frac{\partial^2 P_{\mathbf{XY}}}{\partial y^2} - V_a \frac{\partial P_{\mathbf{XY}}}{\partial x} + \frac{F_{ext}}{\eta_b} \frac{\partial P_{\mathbf{XY}}}{\partial y} \tag{1}$$

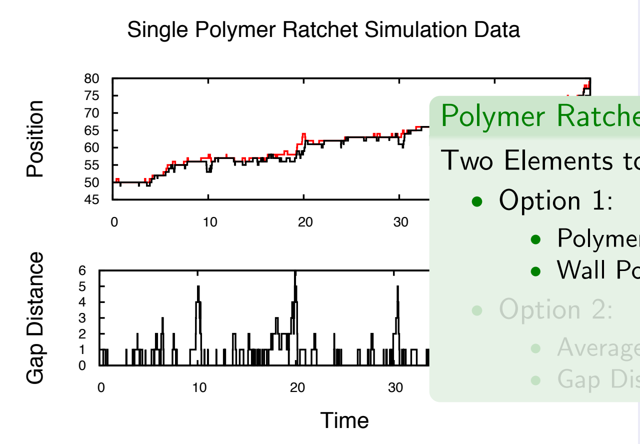


Joint pdf:

- $P_{\mathbf{XY}}(x,t) =$ $\mathrm{Prob}\{x < \mathbf{X}(t) \leq x + dx,$ $y < \mathbf{Y}(t) \leq y + dy\}$
- $\mathbf{X}(t), \mathbf{Y}(t)$ Coupled by Geometric Constraint: $\mathbf{X}(t) \leq \mathbf{Y}(t)$

Single Polymer Ratchet Simulated Data

$\alpha_p = 4, \quad \beta_p = 1, \quad \alpha_w = 2, \quad \beta_w = 1, \quad x_0 = y_0 = 50$



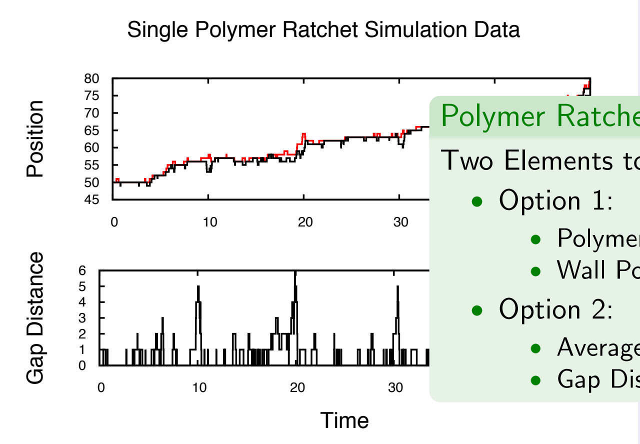
Polymer Ratchet Model:

Two Elements to Track.

- Option 1:
  - Polymer Position
  - Wall Position
- Option 2:
  - Average Position
  - Gap Distance

Single Polymer Ratchet Simulated Data

$\alpha_p = 4, \quad \beta_p = 1, \quad \alpha_w = 2, \quad \beta_w = 1, \quad x_0 = y_0 = 50$



Polymer Ratchet Model:

Two Elements to Track.

- Option 1:
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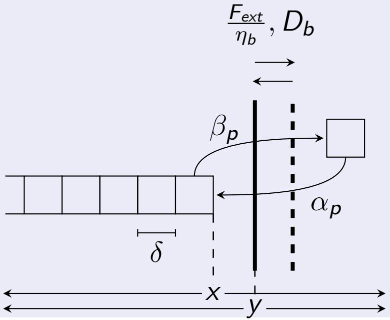
  - Wall Position
- Option 2:
  - Average Position
  - Gap Distance

Single Polymer Ratchet

Diffusion Formalism Model: [Qian, 2004]

$$\frac{\partial P_{\mathbf{XY}}(x,y,t)}{\partial t} = D_a \frac{\partial^2 P_{\mathbf{XY}}}{\partial x^2} + D_b \frac{\partial^2 P_{\mathbf{XY}}}{\partial y^2} - V_a \frac{\partial P_{\mathbf{XY}}}{\partial x} + \frac{F_{ext}}{\eta_b} \frac{\partial P_{\mathbf{XY}}}{\partial y} \tag{1}$$



Strategy: Decouple System

Introduce:

- $\boldsymbol{\Delta}(t)$: Gap Distance
- $\mathbf{Z}(t)$: Average Position

Change of Variables:

- $\boldsymbol{\Delta} = \mathbf{Y} - \mathbf{X}$, $\mathbf{Z} = \frac{D_b \mathbf{X} + D_a \mathbf{Y}}{D_b + D_a}$

Single Polymer Ratchet

Diffusion Formalism Model: [Qian, 2004]

$$\frac{\partial P_{\mathbf{XY}}(x,y,t)}{\partial t} = D_a \frac{\partial^2 P_{\mathbf{XY}}}{\partial x^2} + D_b \frac{\partial^2 P_{\mathbf{XY}}}{\partial y^2} - V_a \frac{\partial P_{\mathbf{XY}}}{\partial x} + \frac{F_{ext}}{\eta_b} \frac{\partial P_{\mathbf{XY}}}{\partial y} \qquad (1)$$

$$\frac{\partial P_{\mathbf{\Delta}}(\Delta,t)}{\partial t} = (D_a + D_b) \frac{\partial^2 P_{\mathbf{\Delta}}}{\partial \Delta^2} + \left(V_a + \frac{F_{ext}}{\eta_b}\right) \frac{\partial P_{\mathbf{\Delta}}}{\partial \Delta}, \quad (\Delta \geq 0) \qquad (2a)$$

$$\frac{\partial P_{\mathbf{Z}}(z,t)}{\partial t} = D_z \frac{\partial^2 P_{\mathbf{Z}}}{\partial z^2} - V_z \frac{\partial P_{\mathbf{Z}}}{\partial z}, \quad -\infty < z < +\infty \qquad (2b)$$

$$D_a = (\alpha+\beta)\tfrac{\delta^2}{2},\; V_a = (\alpha-\beta)\delta$$
$$D_z = \tfrac{D_a D_b}{D_b + D_a},\; V_z = \tfrac{D_b V_a - D_a F_{ext}/\eta_b}{D_b + D_a}$$

- (1) Constraint: $\mathbf{X}(t) \leq \mathbf{Y}(t)$
- (2a) Constraint: $\mathbf{\Delta}(t) \geq 0$

Single Polymer Ratchet: Gap Distance

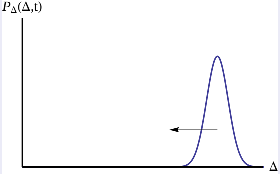
Gap Distance Approaches a Steady State:

$$\frac{\partial P_{\boldsymbol{\Delta}}(\Delta,t)}{\partial t} = (D_a + D_b)\frac{\partial^2 P_{\boldsymbol{\Delta}}}{\partial \Delta^2} + \left(V_a + \frac{F_{ext}}{\eta_b}\right)\frac{\partial P_{\boldsymbol{\Delta}}}{\partial \Delta}, \quad \Delta \geq 0$$

Subject to:

- No-Flux B.C. at $\Delta = 0$
- Normalization Condition

"+": Diffusion → Boundary
Conditions: Can't "Leak Out"



Gap → Steady State!

Single Polymer Ratchet: Gap Distance

Gap Distance Approaches a Steady State:

$$\frac{\partial P_{\boldsymbol{\Delta}}(\Delta, t)}{\partial t} = (D_a + D_b)\frac{\partial^2 P_{\boldsymbol{\Delta}}}{\partial \Delta^2} + \left(V_a + \frac{F_{ext}}{\eta_b}\right)\frac{\partial P_{\boldsymbol{\Delta}}}{\partial \Delta}, \quad \Delta \geq 0$$

Subject to:

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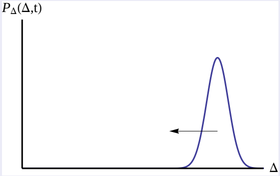

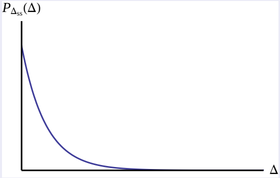

Gap → Steady State!

Single Polymer Ratchet: Gap Distance

$P_{\mathbf{\Delta}_{ss}}(\Delta)$: Steady State Gap Distance

$$0 = D_\delta \frac{d^2 P_{\mathbf{\Delta}_{ss}}}{d\Delta^2} + V_\delta \frac{dP_{\mathbf{\Delta}_{ss}}}{d\Delta}, \qquad \Delta \geq 0$$

- $D_\delta = (D_a + D_b)$
- $V_\delta = \left(V_a + \frac{F_{ext}}{\eta_b}\right)$
- No-Flux B.C. at $\Delta = 0$
- Normalization Condition

Steady State Distribution

- Exponential

$$\boxed{P_{\mathbf{\Delta}_{ss}}(\Delta) = \frac{V_\delta}{D_\delta} e^{-\frac{V_\delta \Delta}{D_\delta}}}$$

Single Polymer Ratchet: Average Position

Average Position: Diffusion with Drift

$$\frac{\partial P_{\mathbf{z}}(z,t)}{\partial t} = D_z \frac{\partial^2 P_{\mathbf{z}}}{\partial z^2} - V_z \frac{\partial P_{\mathbf{z}}}{\partial z}, \qquad -\infty < z < \infty$$

Solution:

- $\boxed{P_{\mathbf{z}}(z,t) = \frac{1}{\sqrt{4\pi D_z t}} e^{-\frac{(z-V_z t)^2}{4D_z t}}}$

With:

- $D_z = \frac{D_a D_b}{D_b + D_a}$, $V_z = \frac{D_b V_a - D_a F_{ext}/\eta_b}{D_b + D_a}$

Normal Distribution

- Mean: $\mu = V_z t$
- Variance: $\sigma^2 = 2D_z t$

Single Polymer Ratchet: Average Position

Average Position: Diffusion with Drift

$$\frac{\partial P_{\mathbf{z}}(z,t)}{\partial t} = D_z \frac{\partial^2 P_{\mathbf{z}}}{\partial z^2} - V_z \frac{\partial P_{\mathbf{z}}}{\partial z}, \qquad -\infty < z < \infty$$

Solution:

- $\boxed{P_{\mathbf{z}}(z,t) = \frac{1}{\sqrt{4\pi D_z t}} e^{-\frac{(z-V_z t)^2}{4D_z t}}}$

With:

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Normal Distribution

- Mean: $\mu = V_z t$
- Variance: $\sigma^2 = 2D_z t$

Stochastic Polymerization Ratchet Model

Summary of Single Polymer Ratchet Results

- Gap Distance Reaches a Steady State
- Average Position Follows Biased Brownian Motion
  $\mu = V_z t$ (Average of Drift Rates for Polymer and Barrier)

$\Rightarrow$ Build On These Results to Formulate a
Model for the N Polymer Ratchet!
(Hint at a Few Results)

Introduction
- Molecular Motors
- Motivation for the Polymerization Ratchet Model

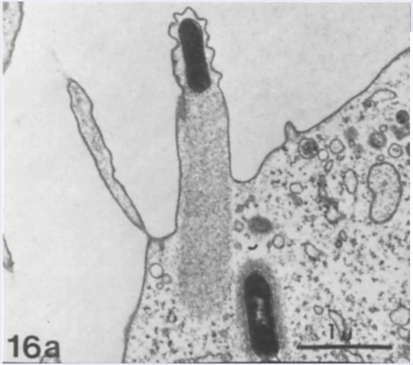
Polymerization Model
- Model System & Simulations
- Analysis of the Mathematical Model

Polymerization Ratchet Model
- Single Polymer Ratchet
- N Polymer Bundle Ratchet

Conclusions
- Summary

Motivation: Actin-Based Motility

Actin-Based Motility of *Listeria* (Click for Movie)



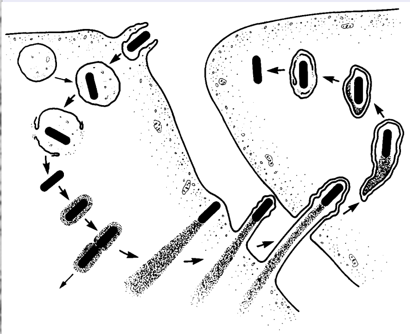
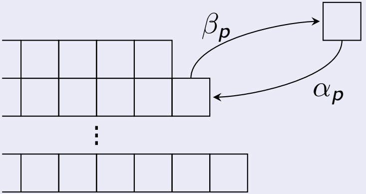


Image Source: Tilney & Portnoy 1989, *J Cell Biol* 109:1597-1608

Movie Source: Theriot & Portnoy: http://cmgm.stanford.edu/theriot/movies.htm

N Polymer Ratchet

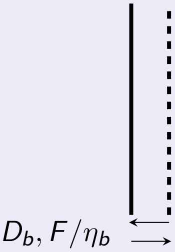
What is an N Polymer Ratchet?



Component 1:
Bundle of
N Identical Polymers

N Polymer Ratchet

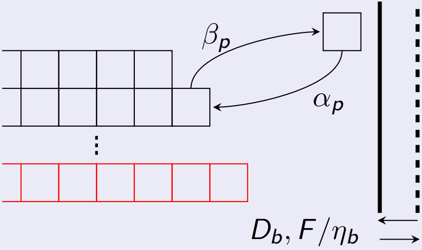
What is an N Polymer Ratchet?



Component 2:
Barrier

N Polymer Ratchet

What is an N Polymer Ratchet?



When Components Interact:

Ratchet:

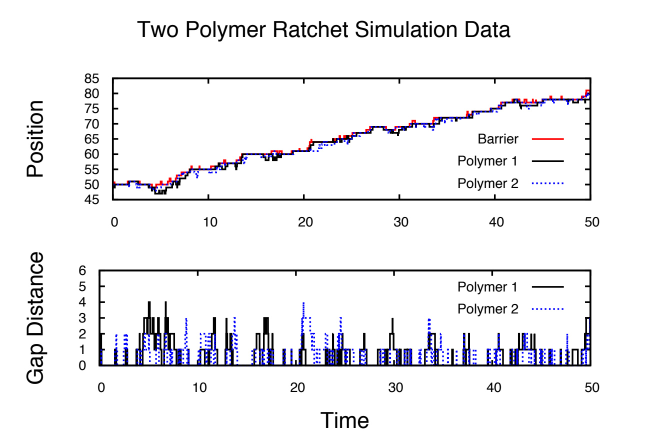
Longest Polymer

$+$

Barrier

Two Polymer Ratchet Simulated Data

$\alpha_p = 4, \quad \beta_p = 1, \quad \alpha_w = 2, \quad \beta_w = 1, \quad t_{max} = 10,000$



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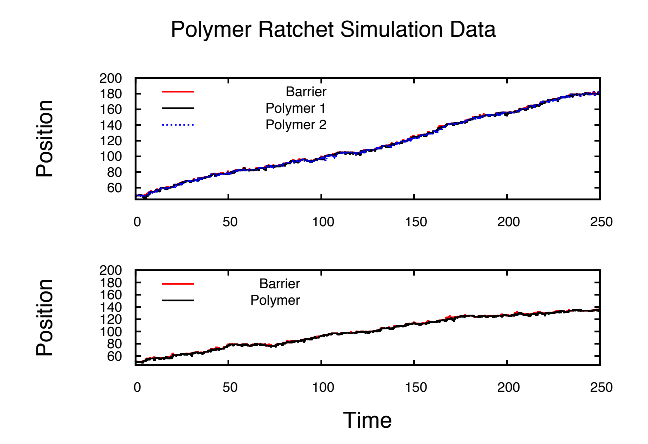

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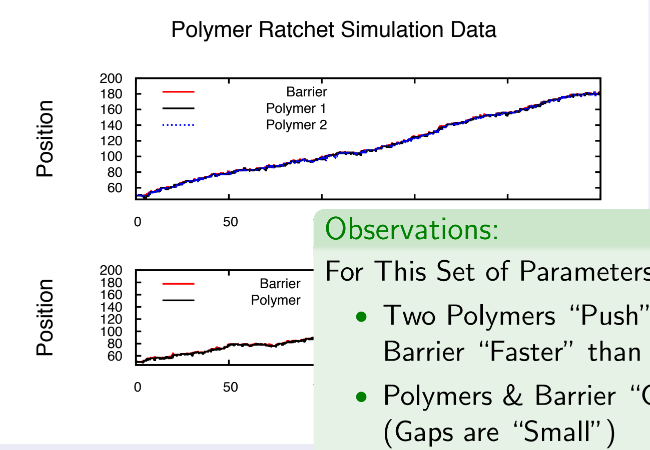


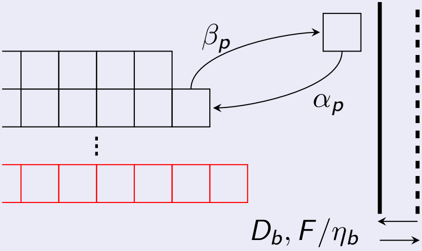
Observations:

For This Set of Parameters:

- Two Polymers "Push" the Barrier "Faster" than One
- Polymers & Barrier "Close" (Gaps are "Small")

N Polymer Ratchet

What is an N Polymer Ratchet?



N Polymer Ratchet:

Interaction Between:

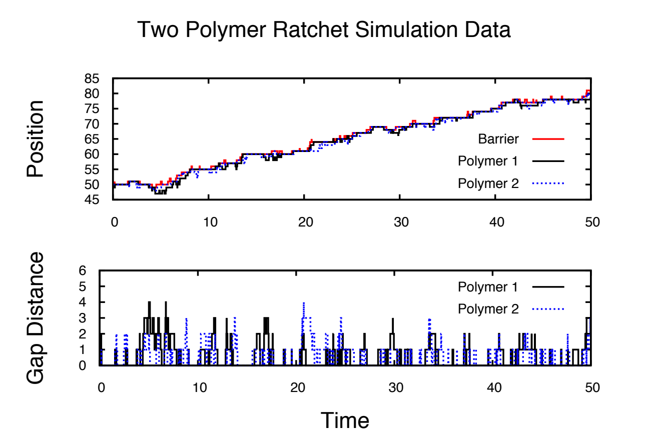
- *Longest* Polymer
- Barrier

Corresponds to:

- *Shortest* Gap Distance

Two Polymer Ratchet Simulated Data

$\alpha_p = 4, \quad \beta_p = 1, \quad \alpha_w = 2, \quad \beta_w = 1, \quad t_{max} = 10,000$



N Polymer Ratchet Simulated Data

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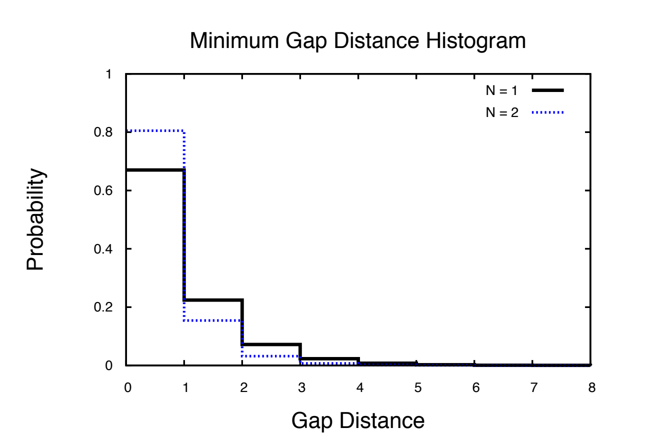
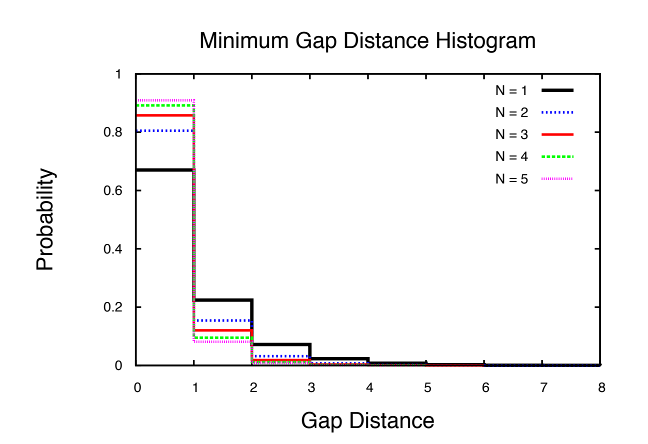


N Polymer Ratchet Simulated Data

$\alpha_p = 4, \quad \beta_p = 1, \quad \alpha_w = 2, \quad \beta_w = 1, \quad t_{max} = 10,000$

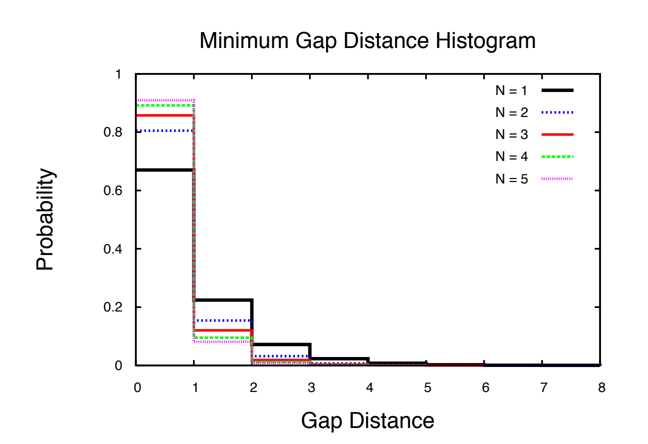


Observations:

Adding Polymers to the Bundle:

- *Decreases* Mean Gap Distance for the *Shortest* Gap

α_p



Stochastic Polymerization Ratchet Model

Summary of N Polymer Ratchet Results

Observations from Simulated Data:

Increasing Number of Polymers in the Bundle

- Allows Bundle to "Push Faster"
- Decreases the Mean Gap Distance Between *Bundle* and the Barrier

Supported by Analysis of N-Polymer Ratchet Model, [Cole and Qian, 2011]

Introduction
Molecular Motors
Motivation for the Polymerization Ratchet Model

Polymerization Model
Model System & Simulations
Analysis of the Mathematical Model

Polymerization Ratchet Model
Single Polymer Ratchet
N Polymer Bundle Ratchet

Conclusions
Summary

Conclusions

Summary

In This Talk:

1. Single Polymer Growth Model (No Barrier)
    - Stochastic Simulations (Gillespie Algorithm)
    - Continuous Space Mathematical Model Results:
        - Polymer Position $\sim$ Biased Brownian Motion (Diffusion with Drift)
2. Single Polymer Ratchet Model
3. N Polymer Bundle Ratchet Model

Conclusions

Summary

In This Talk:

1. Single Polymer Growth Model (No Barrier)
2. Single Polymer Ratchet Model
    - Stochastic Simulations (Gillespie Algorithm)
    - Continuous Space Mathematical Model Results:
        - Average (Ratchet) Position $\sim$ Biased Brownian Motion (Diffusion with Drift)
        - Gap Distance $\rightarrow$ Steady State, Exponential Distribution
3. N Polymer Bundle Ratchet Model

Conclusions

Summary

In This Talk:

1. Single Polymer Growth Model (No Barrier)
2. Single Polymer Ratchet Model
3. N Polymer Bundle Ratchet Model
   - Stochastic Simulations (Gillespie Algorithm)
   - Increasing Number of Polymers in the Bundle:
     - Allows Bundle to “Push Faster”
     - Decreases the Mean Gap Distance between Bundle and Barrier
   - For More Information: [Cole and Qian, 2011]

Selected References

Cole, C. L. and Qian, H. (2011).
The brownian ratchet revisited: Diffusion formalism, polymer-barrier attractions, and multiple filamentous bundle growth.
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Gillespie, D. T. (2007).
Stochastic simulation of chemical kinetics.
Annu Rev Phys Chem, 58:35–55.

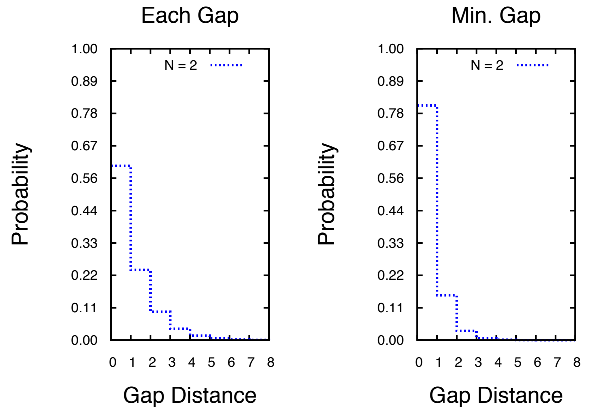
Qian, H. (2004).
A stochastic analysis of a brownian ratchet model for actin-based motility and integrate-and-firing neurons.
MCB: Mol. & Cell. Biomech., 1:267–278.

Thank You!

- Advisor at UW: Hong Qian
- Organizers of the Colloquium
- Audience

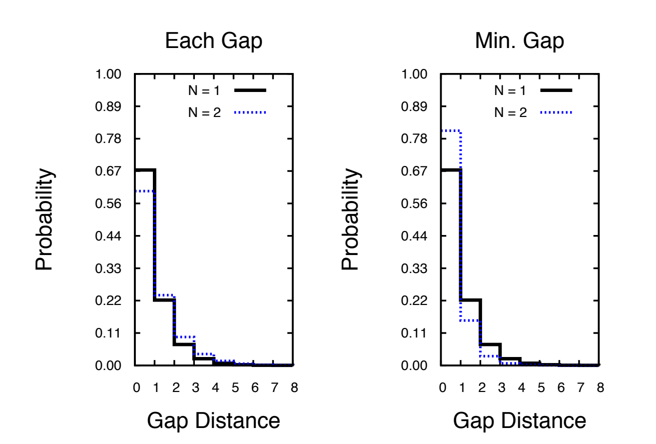
N Polymer Ratchet Simulated Data

$\alpha_p = 4, \quad \beta_p = 1, \quad \alpha_w = 2, \quad \beta_w = 1, \quad t_{max} = 10,000$



N Polymer Ratchet Simulated Data

$\alpha_p = 4, \quad \beta_p = 1, \quad \alpha_w = 2, \quad \beta_w = 1, \quad t_{max} = 10,000$

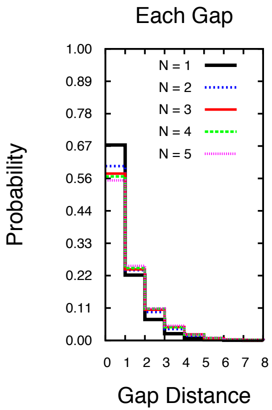


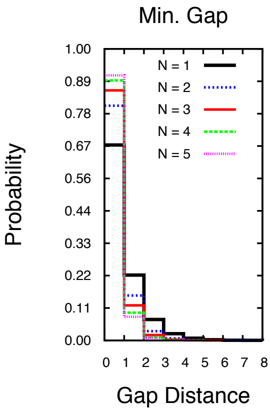
Observations:

Adding Polymers to the Bundle:

- *Increases* Mean Gap Distance for *Each* Gap
- *Decreases* Mean Gap Distance for the *Minimum* Gap

α_p





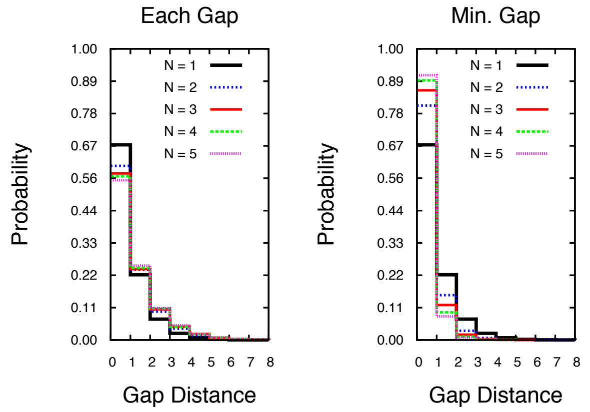
α_p

Observations:

In Other Words,

Adding Polymers to the Bundle:

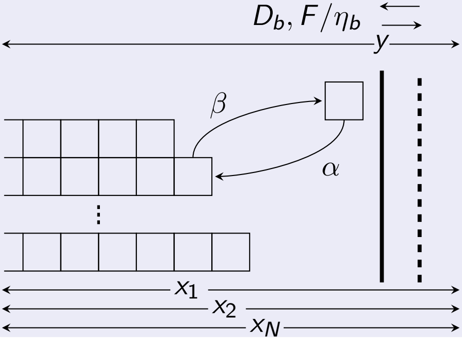
- *Decreases* Mean Gap Between *Bundle* and the Barrier



N Polymer Ratchet

Joint *pdf* for all $\{\mathbf{X}_i(t)\}$, $\mathbf{Y}(t)$: $f(\{x_i\}, y, t)$

$$\frac{\partial f(\{x_i\}, y, t)}{\partial t} = \sum_{k=1}^{N} \left(D_a \frac{\partial^2 f}{\partial x_k^2} - V_a \frac{\partial f}{\partial x_k} \right) + D_b \frac{\partial^2 f}{\partial^2 y} + \frac{F}{\eta_b} \frac{\partial f}{\partial y} \tag{3}$$



Strategy: Decouple via Change of Variables:

- $\mathbf{\Delta}_i = \mathbf{Y} - \mathbf{X}_i$,
  $\mathbf{Z} = \frac{D_b \sum_{j=1}^{N} \mathbf{X}_j + D_a \mathbf{Y}}{N D_b + D_a}$

N Polymer Ratchet

Joint *pdf* for all $\{\boldsymbol{\Delta}_i(t)\}$, $\mathbf{Y}(t)$: $f(\{\xi_i\}, z, t)$

$$\frac{\partial f(\{x_i\}, y, t)}{\partial t} = \sum_{k=1}^{N} \left(D_a \frac{\partial^2 f}{\partial x_k^2} - V_a \frac{\partial f}{\partial x_k} \right) + D_b \frac{\partial^2 f}{\partial^2 y} + \frac{F}{\eta_b} \frac{\partial f}{\partial y} \tag{3}$$

$$\frac{\partial \phi(\{\xi_i\}, t)}{\partial t} = \sum_{i,j}^{N} (D_a \delta_{ij} + D_b) \frac{\partial^2 \phi}{\partial \xi_i \partial \xi_j} + \left(V_a + \frac{F}{\eta_b} \right) \sum_{i=1}^{N} \frac{\partial \phi}{\partial \xi_i} \tag{4a}$$

$$\frac{\partial P_{\mathbf{Z}}(z, t)}{\partial t} = \frac{D_b D_a}{N D_b + D_a} \frac{\partial^2 P_{\mathbf{Z}}}{\partial z^2} - \left(\frac{N D_b V_a - D_a F / \eta_b}{N D_b + D_a} \right) \frac{\partial P_{\mathbf{Z}}}{\partial z} \tag{4b}$$

$f(\{x_i\}, y, t) = f(\{\xi_i\}, z, t)$
Decoupled:
$= \phi(\{\xi_i\}, t) P_{\mathbf{Z}}(z, t)$

Geometric Constraints:

- For (3): $\mathbf{X}_i(t) \leq \mathbf{Y}(t)$
- For (4a): $\boldsymbol{\Delta}_i(t) \geq 0$

N Polymer Ratchet: Gap Distance

Gap Distances Approach Steady State:

$$\phi(\{\xi_i\}) = \epsilon^N \exp\left(-\epsilon \sum_{i=1}^{N} \xi_i\right), \qquad \epsilon = \frac{V_a + F/\eta_b}{ND_b + D_a}, \qquad P_{\boldsymbol{\Delta}_{(1)}}(x) = N\epsilon e^{-N\epsilon x}$$

$\{\boldsymbol{\Delta}_i\}$: Gaps are Identical, Exponentially Distributed

- $\mu = \frac{1}{\epsilon} = \frac{ND_b + D_a}{V_a + F/\eta_b}$

$\boldsymbol{\Delta}_{(1)} = \min\{\boldsymbol{\Delta}_i\}$ Exponentially Distributed

- $\mu = \frac{1}{N\epsilon} = \frac{D_b + D_a/N}{V_a + F/\eta_b}$

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N Polymer Ratchet: Gap Distance

Gap Distances Approach Steady State:

$$\phi(\{\xi_i\}) = \epsilon^N \exp\left(-\epsilon \sum_{i=1}^{N} \xi_i\right), \qquad \epsilon = \frac{V_a + F/\eta_b}{ND_b + D_a}, \qquad P_{\mathbf{\Delta}_{(1)}}(x) = N\epsilon e^{-N\epsilon x}$$

$\{\mathbf{\Delta}_i\}$: Gaps are Identical, Exponentially Distributed

- $\mu = \frac{1}{\epsilon} = \frac{ND_b + D_a}{V_a + F/\eta_b}$

$\mathbf{\Delta}_{(1)} = \min\{\mathbf{\Delta}_i\}$ Exponentially Distributed

- $\mu = \frac{1}{N\epsilon} = \frac{D_b + D_a/N}{V_a + F/\eta_b}$

N Polymer Ratchet: Average Position

Average Position: Diffusion with Drift

$$\frac{\partial P_{\mathbf{z}}(z,t)}{\partial t} = D_{z_N}\frac{\partial^2 P_{\mathbf{z}}}{\partial z^2} - V_{z_N}\frac{\partial P_{\mathbf{z}}}{\partial z}$$

Solution:

- $\boxed{P_{\mathbf{z}}(z,t) = \frac{1}{\sqrt{4\pi D_{z_N} t}} e^{-\frac{(z - V_{z_N} t)^2}{4 D_{z_N} t}}}$

With:

- $D_{z_N} = \frac{D_a D_b}{N D_b + D_a}$,
  $V_{z_N} = \frac{N D_b V_a - D_a F/\eta_b}{N D_b + D_a}$

Normal Distribution

- Mean:
  $\mu = V_{z_N} t$
- Variance:
  $\sigma^2 = 2 D_{z_N} t$

Diffusion Formalism: Single Polymer Ratchet
Full Time-Dependent Gap Distance Solution

Initial Boundary Value Problem for ($x \geq 0$, $t > 0$):

- $\frac{\partial P_{\mathbf{\Delta}}(x,t)}{\partial t} = D_\delta \frac{\partial^2 P_{\mathbf{\Delta}}}{\partial x^2} + V_\delta \frac{\partial P_{\mathbf{\Delta}}}{\partial x}$
- $P_{\mathbf{\Delta}}(x, 0) = \delta(x)$
- $D_\delta \frac{\partial P_{\mathbf{\Delta}}(0,t)}{\partial x} + V_\delta P_{\mathbf{\Delta}}(0, t) = 0$
- $\lim_{x \to \infty} P_{\mathbf{\Delta}}(x, t) = 0$
  $\lim_{x \to \infty} \frac{\partial P_{\mathbf{\Delta}}(x,t)}{\partial x} = 0$

Solution Via New Transform Method of Fokas

$$P_{\mathbf{\Delta}}(x,t) = \frac{V_\delta}{D_\delta} e^{-\frac{V_\delta x}{D_\delta}}$$

$$+ e^{-\frac{V_\delta x}{2D_\delta}} e^{-\left(\frac{V_\delta}{D_\delta}\right)^2 \frac{t}{4D_\delta}} \int_0^\infty \frac{z e^{-\frac{z^2 t}{4D_\delta}} \left(z \cos(zx/2) - \frac{V_\delta}{D_\delta} \sin(zx/2)\right) dz}{\pi \left(\left(\frac{V_\delta}{D_\delta}\right)^2 + z^2\right)}$$