The Brownian Ratchet Revisited: Multiple Filamentous Bundle Growth

Christine Lind Cole & Hong Qian

Department of Applied Mathematics, University of Washington

clind@amath.washington.edu *qian@amath.washington.edu*

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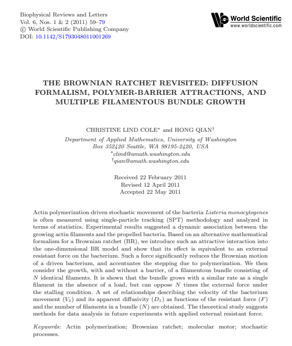
Brownian Ratchet (BR)

Main Reference:



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THE BROWNIAN RATCHET REVISITED: DIFFUSION FORMALISM, POLYMER-BARRIER ATTRACTIONS, AND MULTIPLE FILAMENTOUS BUNDLE GROWTH

CHRISTINE LIND COLE* and HONG QIAN†
Department of Applied Mathematics, University of Washington
Box 352420 Seattle, WA 98195-2420, USA
*clind@amath.washington.edu
†qian@amath.washington.edu

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Actin polymerization driven stochastic movement of the bacteria *Listeria monocytogenes* is often measured using single-particle tracking (SPT) methodology and analyzed in terms of statistics. Experimental results suggested a dynamic association between the growing actin filaments and the propelled bacteria. Based on an alternative mathematical formalism for a Brownian ratchet (BR), we introduce such an attractive interaction into the one-dimensional BR model and show that its effect is equivalent to an external resistant force on the bacterium. Such a force significantly reduces the Brownian motion of a driven bacterium, and accentuates the stepping due to polymerization. We then consider the growth, with and without a barrier, of a filamentous bundle consisting of N identical filaments. It is shown that the bundle grows with a similar rate as a single filament in the absence of a load, but can oppose N times the external force under the stalling condition. A set of relationships describing the velocity of the bacterium movement (V_z) and its apparent diffusivity (D_z) as functions of the resistant force (F) and the number of filaments in a bundle (N) are obtained. The theoretical study suggests methods for data analysis in future experiments with applied external resistant force.

Keywords: Actin polymerization; Brownian ratchet; molecular motor; stochastic processes.

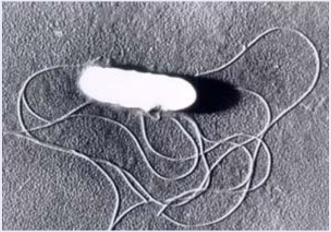
[Cole and Qian, 2011]

Presentation Outline:

1. Introduction
   - Motivation: Actin-Based Motility of *Listeria*
   - BR Model for Simplest Case: Single Polymer & Fluctuating Barrier
2. *N* Polymer Ratchet Model
   - “Pattern” Arises
   - (Something *Nonlinear*)
3. Summary/Acknowledgments
   - Additional References

Motivation: Actin-Based Motility

Listeria Monocytogenes:



http://textbookofbacteriology.net/Listeria_2.html

Bacteria that Causes *Listeriosis*
Usually Only Flu-Like Symptoms,

Fall 2011 Outbreak:

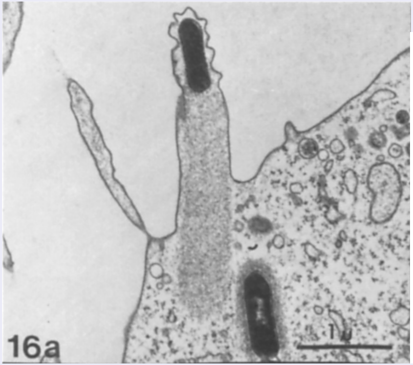
- 146 Cases Reported
- 30 Deaths, 1 Miscarriage

http://www.cdc.gov/listeria/outbreaks/cantaloupes-jensen-farms/index.html

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

Motivation: Actin-Based Motility

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



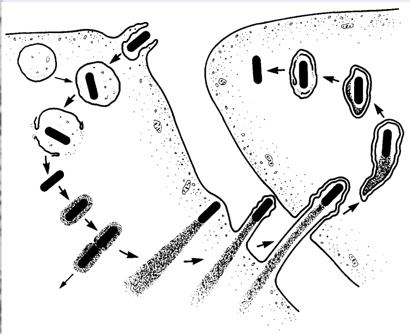


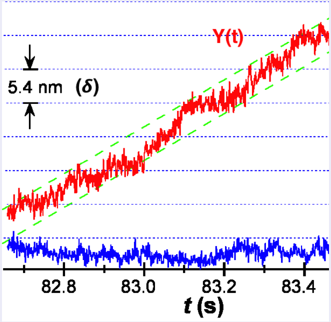
Image Source: Tilney & Portnoy 1989, *J Cell Biol* 109:1597-1608

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

Motivation: Actin-Based Motility of *Listeria*

Experimental Observations: Single Particle Tracking

Kuo & McGrath Measured *Listeria* Trajectory (Red)



1. "Stepping" Behavior
   - Suggesting: Coordinated Growth of Actin Polymers
2. MSD Smaller than Expected
   - (Decreased Fluctuation)

Image Source: [Kuo and McGrath, 2000]

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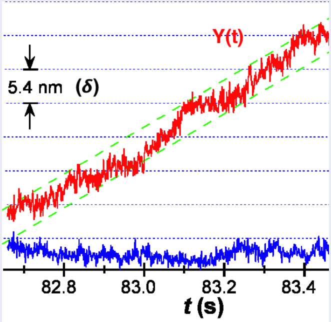

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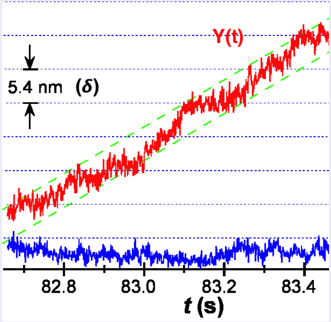

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Motivation: Actin-Based Motility

Actin-Based Motility of *Listeria*

Motivates Study of:

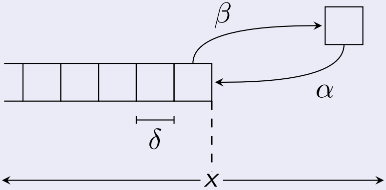
- Polymerization-Driven Motion of a Fluctuating Barrier

Mathematical Framework:

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

Single Polymer Ratchet

What is a Single Polymer Ratchet?



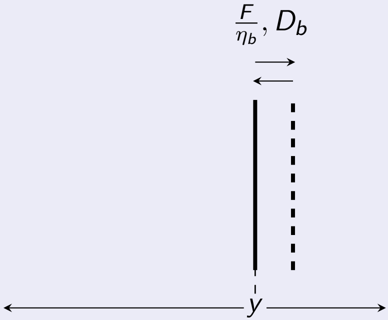
Component 1:

Polymer

- α, β: Adding/Subtracting Rates
- δ: Monomer Length
- $\alpha > \beta$: Polymer Grows (On Average)

Single Polymer Ratchet

What is a Single Polymer Ratchet?



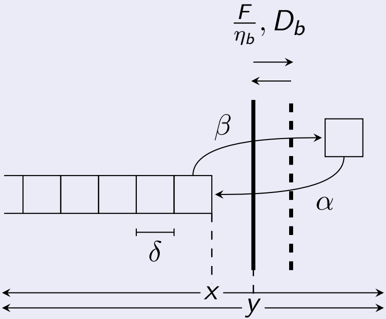
Component 2:

Fluctuating Barrier

- Biased Brownian Motion
- D_b: Fluctuation
- $-\frac{F}{\eta_b}$: Drift

Single Polymer Ratchet

What is a Single Polymer Ratchet?

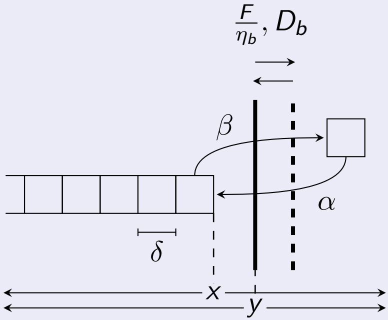


When Components Interact:

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

Single Polymer Ratchet

What is a Single Polymer Ratchet?



When Components Interact:

If Polymerization is Fast:

- Barrier Moves Far Enough
- Polymer *Immediately* Grows
- Blocking Backward Fluctuation of Barrier

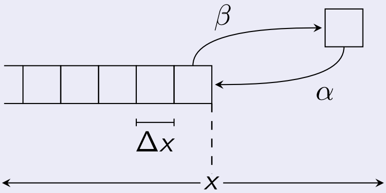
Barrier is "Ratcheted" Forward

Single Polymer (No Barrier)

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

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

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



Biased Random Walk Model

- $P_{\mathbf{X}}(x,t) = \mathrm{Prob}\{\mathbf{X}(t) = x\}$
- (Spatially Discrete)

Spatially Continuous Model:

- Taylor Expand in x . . .

Single Polymer (No Barrier)

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

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

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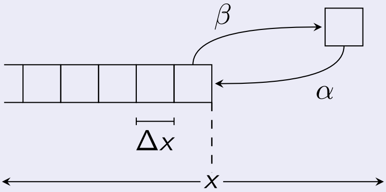


Biased Brownian Motion Model

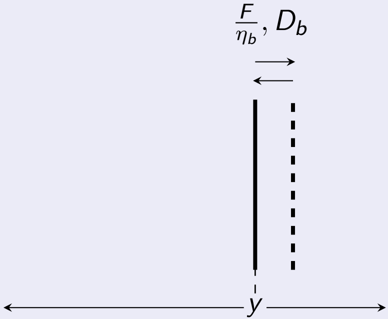
- $P_{\mathbf{X}}(x,t) = \mathrm{Prob}\{x < \mathbf{X}(t) \le x + dx\}$
- (Spatially Continuous) *Diffusion with Drift*

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

Barrier (No Polymer)

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

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



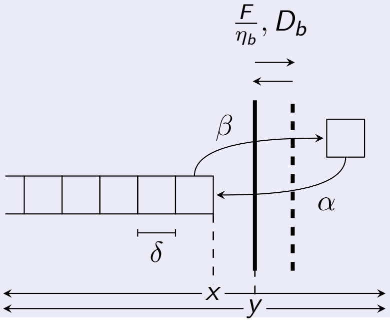
Biased Brownian Motion Model

- $P_{\mathbf{Y}}(y,t) = \mathrm{Prob}\{y < \mathbf{Y}(t) \leq y + dy\}$
- (Spatially Continuous) *Diffusion with Drift*

Single Polymer Ratchet

Diffusion Formalism Model: [Qian, 2004]

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



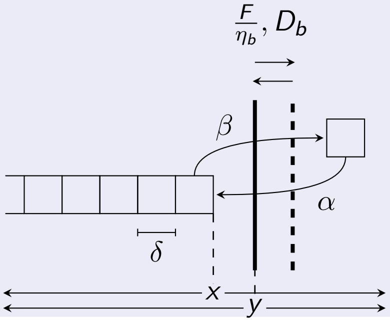
Joint pdf:

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

Single Polymer Ratchet

Diffusion Formalism Model: [Qian, 2004]

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



Strategy: Decouple System

Introduce:

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

Change of Variables:

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

Single Polymer Ratchet

Diffusion Formalism Model: [Qian, 2004]

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

$$\frac{\partial P_{\mathbf{\Delta}}(\Delta,t)}{\partial t} = D_\delta \frac{\partial^2 P_{\mathbf{\Delta}}}{\partial \Delta^2} + V_\delta \frac{\partial P_{\mathbf{\Delta}}}{\partial \Delta}, \quad \Delta \geq 0 \qquad (2a)$$

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

$$D_\delta = D_b + D_a, \; V_\delta = V_a + F/\eta_b$$

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

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

Single Polymer Ratchet

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

Single Polymer Ratchet: Average Position

Avg. Position: Diffusion with Drift (Biased Brownian Motion)

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

$$P_{\mathbf{Z}}(z,0) = \delta(z)$$

Solution:

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

With:

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

Normal Distribution

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

Single Polymer Ratchet

Diffusion Formalism Model: [Qian, 2004]

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

$$\frac{\partial P_{\boldsymbol{\Delta}}(\Delta,t)}{\partial t} = D_\delta \frac{\partial^2 P_{\boldsymbol{\Delta}}}{\partial \Delta^2} + V_\delta \frac{\partial P_{\boldsymbol{\Delta}}}{\partial \Delta}, \quad \Delta \geq 0 \qquad (2a)$$

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

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

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

Single Polymer Ratchet: Gap Distance

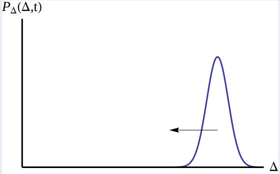
Gap Distance → Steady State (Qualitative Argument):

$$\frac{\partial P_{\boldsymbol{\Delta}}(\Delta, t)}{\partial t} = D_\delta \frac{\partial^2 P_{\boldsymbol{\Delta}}}{\partial \Delta^2} + V_\delta \frac{\partial P_{\boldsymbol{\Delta}}}{\partial \Delta}, \quad \Delta \geq 0$$

Subject to:

- No-Flux B.C. at $\Delta = 0$
- Vanishing C.'s at $\Delta = \infty$

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



Gap → Steady State!

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Gap Distance → Steady State (Qualitative Argument):

$$\frac{\partial P_{\boldsymbol{\Delta}}(\Delta, t)}{\partial t} = D_{\delta} \frac{\partial^2 P_{\boldsymbol{\Delta}}}{\partial \Delta^2} + V_{\delta} \frac{\partial P_{\boldsymbol{\Delta}}}{\partial \Delta}, \quad \Delta \geq 0$$

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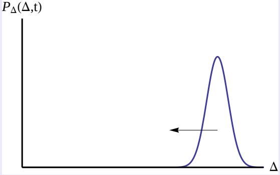

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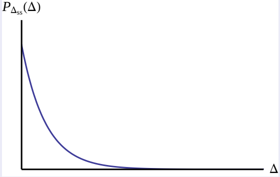

Gap → Steady State!

Single Polymer Ratchet: Gap Distance

Full Time-Dependent Gap Distance Solution:

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

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

New Unified Transform Method of Fokas [Fokas, 2002], [Cole, 2011]:

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

$$+ e^{-\frac{V_\delta \Delta}{2D_\delta}} e^{-\left(\frac{V_\delta}{D_\delta}\right)^2 \frac{t}{4D_\delta}} \int_0^\infty \frac{k e^{-\frac{k^2 t}{4D_\delta}} \left(k \cos(k\Delta/2) - \frac{V_\delta}{D_\delta} \sin(k\Delta/2)\right) dk}{\pi \left(\left(\frac{V_\delta}{D_\delta}\right)^2 + k^2\right)}$$

Single Polymer Ratchet: Gap Distance

Full Time-Dependent Gap Distance Solution:

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

- $\frac{\partial P_{\mathbf{\Delta}}(\Delta,t)}{\partial t} = D_\delta \frac{\partial^2 P_{\mathbf{\Delta}}}{\partial \Delta^2} + V_\delta \frac{\partial P_{\mathbf{\Delta}}}{\partial \Delta}$
- $P_{\mathbf{\Delta}}(\Delta, 0) = \delta(\Delta)$
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- $\lim_{\Delta\to\infty} P_{\mathbf{\Delta}}(\Delta, t) = 0$
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Single Polymer Ratchet: Gap Distance

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

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

- $D_\delta = (D_a + D_b)$
- $V_\delta = \left(V_a + \frac{F}{\eta_b}\right)$

Steady State Distribution

- Exponential

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

Single Polymer Ratchet

Single Polymer Ratchet Summary

Average Position, $\mathbf{Z}(t) \rightarrow$ Biased Brownian Motion

- Normal Distribution
- $\mu = V_z t$
- $\sigma^2 = 2D_z t$

Gap Distance, $\mathbf{\Delta}(t) \rightarrow$ Steady State:

- Exponential Distribution
- $\mu = \frac{D_\delta}{V_\delta} = \frac{D_b + D_a}{V_a + F/\eta_b}$

Single Polymer Ratchet

Single Polymer Ratchet Summary

Average Position, $\mathbf{Z}(t) \rightarrow$ Bia

- Normal Distribution
- $\mu = V_z t$
- $\sigma^2 = 2D_z t$

Gap Distance, $\mathbf{\Delta}(t) \rightarrow$ Steady

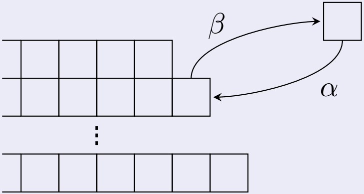
- Exponential Distribution
- $\mu = \frac{D_\delta}{V_\delta} = \frac{D_b + D_a}{V_a + F/\eta_b}$

N Polymer Model:

- More Realistic. Recall:
  - *Listeria* is Propelled by *Network* of Actin Filaments
- Model Will Predict Observed Behavior:
  - Coordinated Polymer Growth (with barrier present)
  - Decreased Fluctuation (D_z deacreases with N)

N Polymer Ratchet

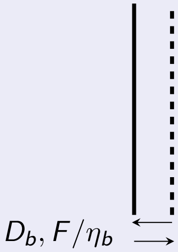
What is an N Polymer Ratchet?



Component 1:
Bundle of
N Identical Polymers

N Polymer Ratchet

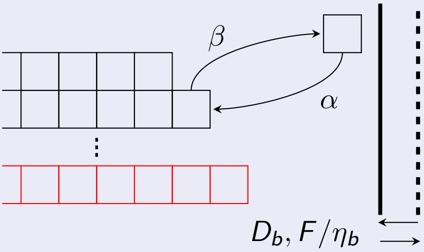
What is an N Polymer Ratchet?



Component 2:
Barrier

N Polymer Ratchet

What is an N Polymer Ratchet?



When Components Interact:

Ratchet:

Longest Polymer

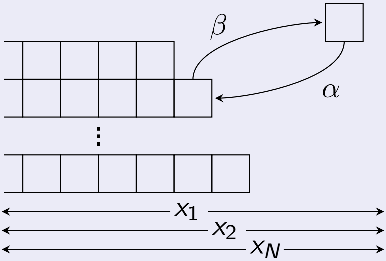
+

Barrier

N Polymer Bundle (No Barrier)

$\mathbf{X}_i(t)$: Position of i^{th} Polymer Tip at Time t

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



Each *Individual* Polymer:

- Normal Distribution
  $\mu = V_a t,\ \sigma^2 = 2D_a t$
- *pdf*:
  $P_{\mathbf{X}_i}(x,t) =$
  $f_{\mathbf{X}}(x,t) = \frac{1}{\sqrt{4\pi D_a t}} e^{-\frac{(x-V_a t)^2}{4D_a t}}$
- *cdf*:
  $F_{\mathbf{X}}(x,t) = \int_{-\infty}^{x} f_{\mathbf{X}}(x,t)dx$

N Polymer Bundle (No Barrier)

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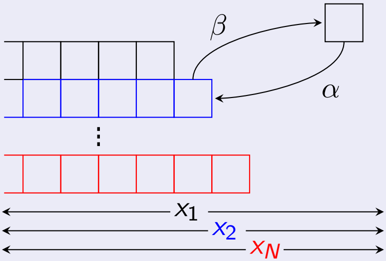

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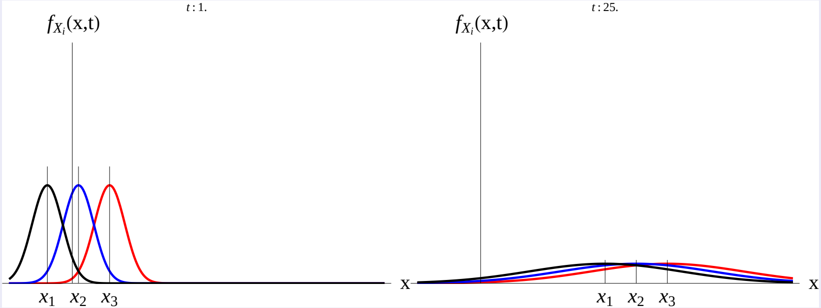
  $F_{\mathbf{X}}(x,t) = \int_{-\infty}^{x} f_{\mathbf{X}}(x,t)dx$

N Polymer Bundle (No Barrier)

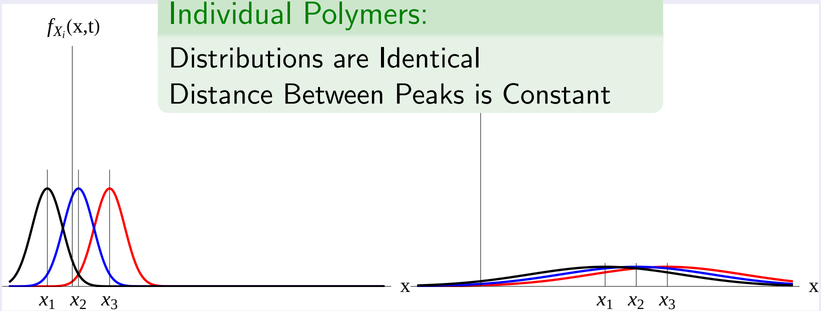
Example: 3 Polymers Starting Out Separated:



(Click for Movie)

N Polymer Bundle (No Barrier)

Example: 3 Polymers Starting Out Separated:



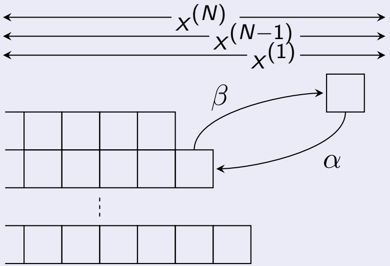
Individual Polymers:

Distributions are Identical
Distance Between Peaks is Constant

(Click for Movie)

N Polymer Bundle (No Barrier)

$\mathbf{X}^{(k)}(t)$: Position of k^{th} Longest Polymer Tip at Time t



Instead of Tracking *Individual* Polymers

- Order Them By Length
- Define: $\mathbf{X}^{(k)}(t)$: Position of k^{th} *Longest* Polymer:

$$\mathbf{X}^{(1)}(t) \geq \mathbf{X}^{(2)}(t) \geq ... \geq \mathbf{X}^{(k-1)}(t) \geq \mathbf{X}^{(k)}(t) \geq \mathbf{X}^{(k+1)}(t) \geq ... \geq \mathbf{X}^{(N-1)}(t) \geq \mathbf{X}^{(N)}(t)$$

N Polymer Bundle (No Barrier)

$\mathbf{X}^{(k)}(t)$: Position of k^{th} Longest Polymer Tip at Time t

$$\mathbf{X}^{(1)}(t) \geq \mathbf{X}^{(2)}(t) \geq ... \geq \mathbf{X}^{(k-1)}(t) \geq \mathbf{X}^{(k)}(t) \geq \mathbf{X}^{(k+1)}(t) \geq ... \geq \mathbf{X}^{(N-1)}(t) \geq \mathbf{X}^{(N)}(t)$$

$\mathbf{X}^{(k)}(t)$: k^{th} *Longest* Polymer:

Order Statistics:

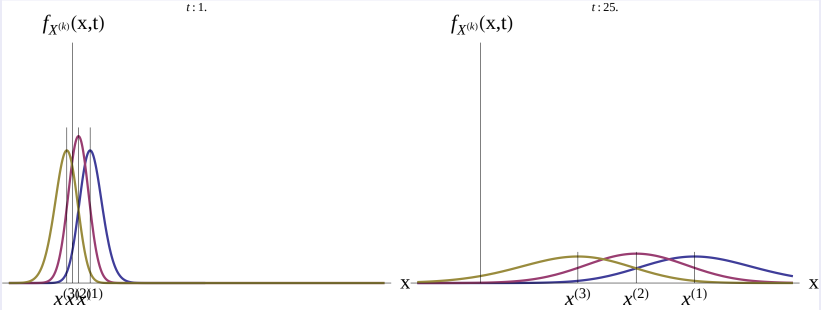
- *pdf* :
  $$f_{\mathbf{X}^{(k)}}(x,t) = \frac{N!}{(k-1)!(N-k)!} F_{\mathbf{X}}(x,t)^{N-k} \left[1 - F_{\mathbf{X}}(x,t)\right]^{k-1} f_{\mathbf{X}}(x,t)$$

Qualitatively "Biased-Diffusion-Like:"

- Single Traveling Peak
- Increasing Width

N Polymer Bundle (No Barrier)

Example: 3 Polymers Starting Out Even (Same Length)



(Click for Movie)

N Polymer Bundle (No Barrier)

Polymers Ordered by Length:

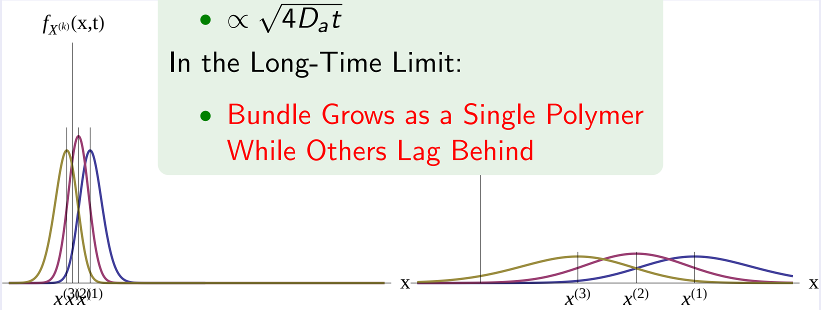
Distance Between Peaks Increases:

- $\propto \sqrt{4D_a t}$

In the Long-Time Limit:

- Bundle Grows as a Single Polymer While Others Lag Behind

Example: 3 ... ngth)



(Click for Movie)

N Polymer Bundle (No Barrier)

Longest Polymer, $\mathbf{X}^{(1)}(t)$

We Can Show:

- *cdf* Satisfies a Nonlinear Diffusion Equation:

$$\frac{\partial F_{\mathbf{X}^{(1)}}(x,t)}{\partial t} = D_a \frac{\partial^2 F_{\mathbf{X}^{(1)}}(x,t)}{\partial x^2} - q(x,t)\frac{\partial F_{\mathbf{X}^{(1)}}(x,t)}{\partial x}$$

- "Drift" Rate:

$$q(x,t) = V_a + \frac{D_a(N-1)}{N F_{\mathbf{X}^{(1)}}(x,t)} \frac{\partial F_{\mathbf{X}^{(1)}}(x,t)}{\partial x}$$

N Polymer Bundle (No Barrier)

As Promised:
Something Nonlinear ✓

Longest Polymer, $\mathbf{X}^{(1)}(t)$

We Can Show:

- *cdf* Satisfies a Nonlinear Diffusion Equation:

$$\frac{\partial F_{\mathbf{X}^{(1)}}(x,t)}{\partial t} = D_a \frac{\partial^2 F_{\mathbf{X}^{(1)}}(x,t)}{\partial x^2} - q(x,t) \frac{\partial F_{\mathbf{X}^{(1)}}(x,t)}{\partial x}$$

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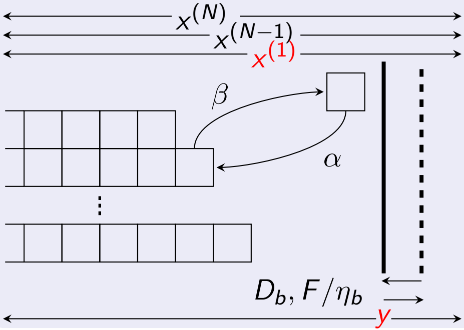
N Polymer Ratchet

Bundle Ratchet:

Fluctuating Barrier Interacts with Longest Polymer, $\mathbf{X}^{(1)}(t)$:

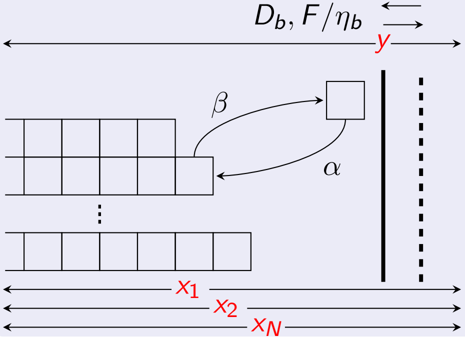


- Joint *pdf* for $\mathbf{X}^{(1)}(t)$, $\mathbf{Y}(t)$ (MESSY!)
- Joint *pdf* for all $\{\mathbf{X}_i(t)\}$, $\mathbf{Y}(t)$ (EASIER!)

N Polymer Ratchet

Bundle Ratchet:

Fluctuating Barrier Interacts with Longest Polymer, $\mathbf{X}^{(1)}(t)$:

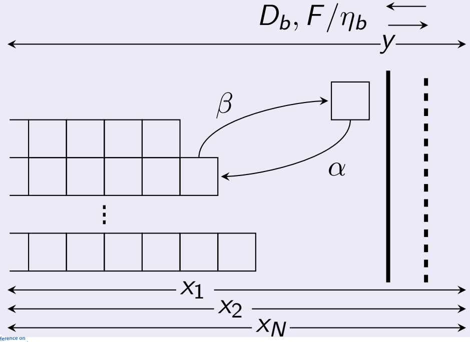


- Joint *pdf* for $\mathbf{X}^{(1)}(t)$, $\mathbf{Y}(t)$ (MESSY!)
- Joint *pdf* for all $\{\mathbf{X}_i(t)\}$, $\mathbf{Y}(t)$ (EASIER!)

N Polymer Ratchet

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

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



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 $\{\boldsymbol{\Delta}_i(t)\}$, $\mathbf{Z}(t)$: $f(\{\xi_i\}, z, t)$

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

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

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

$f(\{x_i\}, y, t) = f(\{\xi_i\}, z, t)$
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

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

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

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$f(\{x_i\}, y, t) = f(\{\xi_i\}, z, t)$

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: Average Position

Avg. Position: Diffusion with Drift (Biased Brownian Motion)

$$\begin{aligned} \frac{\partial P_{\mathbf{Z}}(z,t)}{\partial t} &= D_{z_N}\frac{\partial^2 P_{\mathbf{Z}}}{\partial z^2} - V_{z_N}\frac{\partial P_{\mathbf{Z}}}{\partial z}, \quad -\infty < z < \infty, \\ P_{\mathbf{Z}}(z,0) &= \delta(z) \end{aligned}$$

Solution:

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

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:
  $\sigma^2 = 2 D_{z_N} t$

N Polymer Ratchet

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

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

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

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

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

Can We Find Time-Dependent Solution?

$$\frac{\partial \phi(\{\xi_i\}, t)}{\partial t} = \sum_{i,j}^{N} (D_a \delta_{ij} + D_b) \frac{\partial^2 \phi}{\partial \xi_i \partial \xi_j} + \left(V_a + \frac{F}{\eta_b} \right) \sum_{i=1}^{N} \frac{\partial \phi}{\partial \xi_i}, \quad \{\xi_i\} \geq 0,$$

Not Separable → Not Yet

Subject to:

- No-Flux B.C. at each $\xi_i = 0$
- Vanishing C.'s at $\{\xi_i\} = \infty$

Diffusion,
"+": Drift → Boundaries
Conditions: Can't "Leak Out"

Gap Distances → Steady State

N Polymer Ratchet: Gap Distance

Can We Find Time-Dependent Solution?

$$\frac{\partial \phi(\{\xi_i\},t)}{\partial t} = \sum_{i,j}^{N} (D_a \delta_{ij} + D_b) \frac{\partial^2 \phi}{\partial \xi_i \partial \xi_j} + \left(V_a + \frac{F}{\eta_b}\right) \sum_{i=1}^{N} \frac{\partial \phi}{\partial \xi_i}, \quad \{\xi_i\} \geq 0,$$

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Diffusion,
"+": Drift → Boundaries
Conditions: Can't "Leak Out"

Gap Distances → Steady State

N Polymer Ratchet: Gap Distance

Gap Distances Steady State:

$$0 = \sum_{i,j}^{N} (D_a \delta_{ij} + D_b) \frac{\partial^2 \phi_{ss}}{\partial \xi_i \partial \xi_j} + \left(V_a + \frac{F}{\eta_b} \right) \sum_{i=1}^{N} \frac{\partial \phi_{ss}}{\partial \xi_i}, \quad \{\xi_i\} \geq 0,$$

$$\phi_{ss}(\{\xi_i\}) = \epsilon^N \exp\left(-\epsilon \sum_{i=1}^{N} \xi_i \right), \qquad \epsilon = \frac{V_a + F/\eta_b}{N D_b + D_a}, \qquad P_{\Delta_{(1)}}(x) = N\epsilon e^{-N\epsilon x}$$

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

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

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

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

N Polymer Ratchet: Gap Distance

Gap Distances Steady State:

$$0 = \sum_{i,j}^{N} (D_a \delta_{ij} + D_b) \frac{\partial^2 \phi_{ss}}{\partial \xi_i \partial \xi_j} + \left(V_a + \frac{F}{\eta_b} \right) \sum_{i=1}^{N} \frac{\partial \phi_{ss}}{\partial \xi_i}, \quad \{\xi_i\} \geq 0,$$

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

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

N Polymer Ratchet: Gap Distance

Steady State:

Gaps are Identical

$\Rightarrow$ Coordinated Growth of Polymers ✓

$\boldsymbol{\Delta}_{(1)}$, Smallest Gap

- Gap Between *Bundle* and Barrier!

Gap Di

0 … 0,

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

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

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

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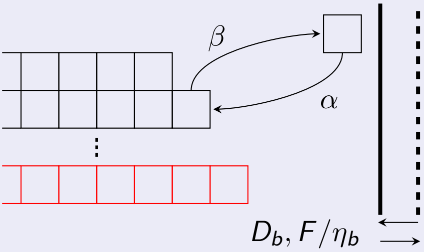
- $\mu_{(1)} = \frac{1}{N\epsilon} = \frac{D_b + D_a/N}{V_a + F/\eta_b}$

N Polymer Ratchet

What is an N Polymer Ratchet?



Characterized By:

Either:

- *Longest* Polymer
- Barrier
- $\mathbf{X}^{(1)}(t)$, $\mathbf{Y}(t)$

Or:

- *Smallest* Gap Distance
- Average Position
- $\mathbf{\Delta}_{(1)}(t)$, $\mathbf{Z}(t)$

N Polymer Ratchet

N Polymer Ratchet Pattern:

Average Position, $\mathbf{Z}(t) \rightarrow$ Biased Brownian Motion

- Normal Distribution
- $\mu = V_{z_N} t$
- $\sigma^2 = 2D_{z_N} t$

Min. Gap Distance, $\boldsymbol{\Delta}_{(1)}(t) \rightarrow$ Steady State:

- Exponential Distribution
- $\mu_{(1)} = \frac{D_b + (D_a/N)}{V_a + F/\eta_b}$

N Polymer Ratchet

N Polymer Ratchet Pattern:

Average Position, $\mathbf{Z}(t) \rightarrow$ Bias

- Normal Distribution
- $\mu = V_{z_N} t$
- $\sigma^2 = 2 D_{z_N} t$

Min. Gap Distance, $\mathbf{\Delta}_{(1)}(t) \rightarrow$

- Exponential Distribution
- $\mu_{(1)} = \frac{D_b + (D_a/N)}{V_a + F/\eta_b}$

N Polymer Ratchet Summary:

With Multiple Polymer Filaments:

$$D_{z_N} = \frac{D_b (D_a/N)}{D_b + (D_a/N)}$$

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

- Interaction with Barrier
  $\rightarrow$ Polymers Grow Together ✓

Increasing N:

- Decreases Mean Gap Distance
- Increases V_z (Drift)
- Decreases D_z (Fluctuation) ✓

Results From the Brownian Ratchet Model

By Incorporating N Identical Polymers:

Can Predict Observed *Listeria* Behavior:

- Coordinated Actin Polymerization
- Decreased Fluctuation of the Bacterium (Barrier)

Not *just* a Model for *Listeria*. Also:

- Other Actin-Based Motility Scenarios
- Molecular Motor "Pushing" a Barrier (Load) Along its Track

Acknowledgments

Thank You:

- Co-Author & Ph.D. Advisor:
  - Hong Qian, University of Washington
- Method of Fokas:
  - Katie Oliveras, Seattle University
  - Bernard Deconinck, University of Washington
- Comments and Suggestions on [Cole and Qian, 2011]:
  - Alex Mogilner, Mathematics, UC Davis
  - Anatoly Kolomeisky, Chemistry, Rice University
- Organizers of Mini-Symposium:
  - David J. Wollkind & Bonni Kealy, Washington State University
- Funding:
  - NSF VIGRE Grant (DMS9810726)

Questions?

Thank You:

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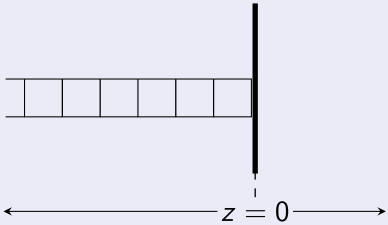
Single Polymer Ratchet

Initial State of System:

Polymer Touching Barrier, Define Coordinates

$t = 0$:



Initial Conditions:

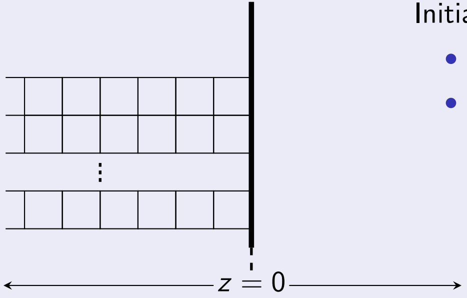
- Gap Distance is Zero: $P_{\mathbf{\Delta}}(\Delta, 0) = \delta(\Delta)$
- Average Position is Zero: $P_{\mathbf{Z}}(z, 0) = \delta(z)$

N Polymer Ratchet

Initial State of System:

Each Polymer Touching Barrier, Define Coordinates

$t = 0$:



Initial Conditions:

- Gap Distances are Zero
- Average Position is Zero: $P_{\mathbf{Z}}(z, 0) = \delta(z)$

N Polymer Ratchet: Average Position

Define Stalling Force, F_N^*:

Value of the Force that "Stalls" the Drift:

$$V_{z_N} = \frac{ND_b V_a - D_a F/\eta_b}{ND_b + D_a}$$

- $F_N^* = N\eta_b D_b \frac{V_a}{D_a}$

Qualitatively:

- $F < F_N^*$: Polymer Bundle Pushes Barrier

N Polymer Ratchet: Average Position

F_N^* Scales with N:

Bundle can Oppose
N times External Force
of a Single Polymer! ✓

Define Stalling Force, F_N^*:

Value of the Force that "Stalls" the Drift:

$$V_{z_N} = \frac{ND_b V_a - D_a F/\eta_b}{ND_b + D_a}$$

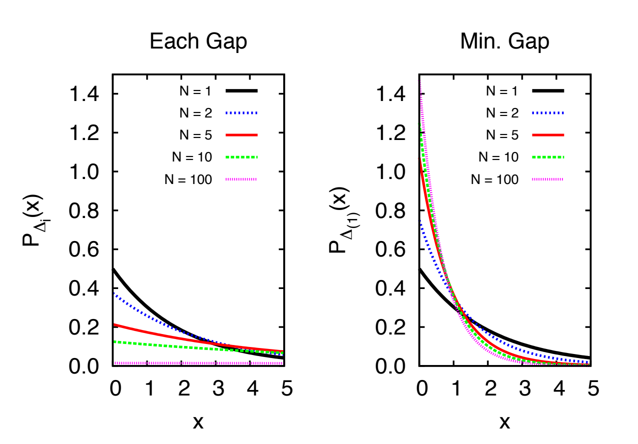
- $F_N^* = N\eta_b D_b \frac{V_a}{D_a}$

Qualitatively:

- $F < F_N^*$:
  Polymer Bundle
  Pushes Barrier

N Polymer Ratchet: Gap Distance

$D_a = 4, \quad V_a = 2, \quad D_b = 2, \quad F/\eta_b = 1$

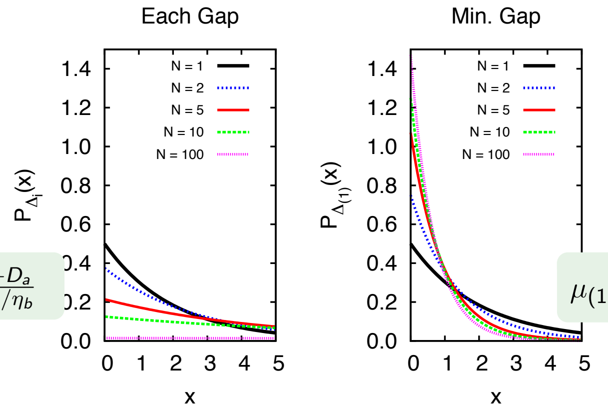


Observations:

Adding Polymers to the Bundle:

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

D_a



$$\mu_i = \frac{ND_b + D_a}{V_a + F/\eta_b}$$

$$\mu_{(1)} = \frac{D_b + D_a/N}{V_a + F/\eta_b}$$

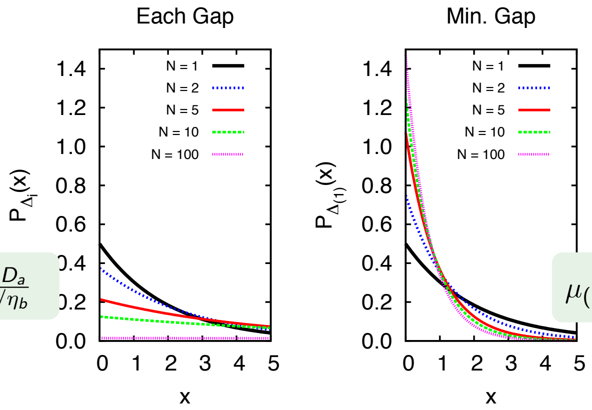
D_a

Observations:

In Other Words,

Adding Polymers to the Bundle:

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



$$\mu_i = \frac{ND_b + D_a}{V_a + F/\eta_b}$$

$$\mu_{(1)} = \frac{D_b + D_a/N}{V_a + F/\eta_b}$$

N Polymer Ratchet: Gap Distance

Example: 2 Polymer Case

$$\frac{\partial \phi(\xi_1, \xi_2, t)}{\partial t} = (D_a + D_b)\left(\frac{\partial^2 \phi}{\partial \xi_1 \partial \xi_1} + \frac{\partial^2 \phi}{\partial \xi_2 \partial \xi_2}\right) + 2D_b \frac{\partial^2 \phi}{\partial \xi_1 \partial \xi_2} + \left(V_a + \frac{F}{\eta_b}\right)\left(\frac{\partial \phi}{\partial \xi_1} + \frac{\partial \phi}{\partial \xi_2}\right), \quad \{\xi_1, \xi_2\} \geq 0,$$

$$= -\nabla \cdot J(\xi_1, \xi_2, t)$$

"No-Flux" B.C.'s:

$$-J = -\begin{pmatrix} J_1 \\ J_2 \end{pmatrix} = \begin{pmatrix} (D_a + D_b)\frac{\partial \phi}{\partial \xi_1} + D_b \frac{\partial \phi}{\partial \xi_2} + \left(V_a + \frac{F}{\eta_b}\right)\phi \\ (D_a + D_b)\frac{\partial \phi}{\partial \xi_2} + D_b \frac{\partial \phi}{\partial \xi_1} + \left(V_a + \frac{F}{\eta_b}\right)\phi \end{pmatrix}, \quad \begin{matrix} J_1(0, \xi_2, t) = 0 \\ J_2(\xi_1, 0, t) = 0 \end{matrix}$$