Dissertation Defense: Mathematical Models for Facilitated Diffusion and the Brownian Ratchet

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APPLIED MATHEMATICS
UNIVERSITY *of* WASHINGTON

Mathematical Models

Facilitated Diffusion

物理化学学报(*Wuli Huaxue Xuebao*)
November *Acta Phys. -Chim. Sin.*, **2010, 26**(11):2857–2864 2857

[Invited Article] www.whxb.pku.edu.cn

Simple Chemical Model for Facilitated Transport with an Application to Wyman-Murray Facilitated Diffusion

COLE Christine Lind* QIAN Hong*
(*Department of Applied Mathematics, University of Washington, Seattle, WA 98195, USA*)

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Key Words: Facilitated diffusion; Transport; Chemical kinetic model; Grand canonical ensemble

[Cole and Qian, 2010]

Brownian Ratchet (BR)

Biophysical Reviews and Letters
Vol. 6, Nos. 1 & 2 (2011) 59–79
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DOI: 10.1142/S1793048011001269

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

CHRISTINE LIND COLE* and HONG QIAN†
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[Cole and Qian, 2011]

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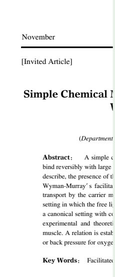
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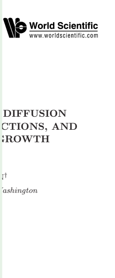
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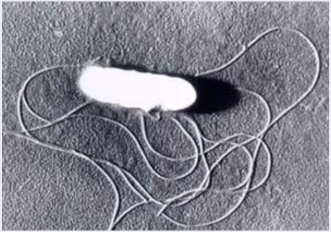
Qian, 2011]

Presentation Abstract:

1. Introduction
   - Motivation:
     Actin-Based Motility of *Listeria*
   - BR Model Applied to the Simplest Case:
     Single Polymer and Fluctuating Barrier
2. Realistic Feature 1: Attractive Force
   - Attractive Force $\sim$ Resistant Force
3. Realistic Feature 2: *N* Polymer Bundle
   - Without Barrier:
     Bundle Grows as Single Polymer
   - With Barrier:
     Bundle can Oppose *N* times External Force
     (Compared to Single Polymer)

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)

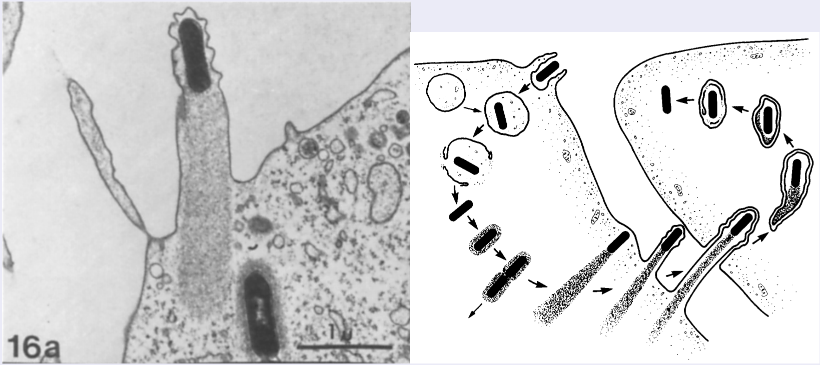


Image Source: Tilney & Portnoy 1989, *J Cell Biol* 109:1597-1608

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

Motivation: Actin-Based Motility of *Listeria*

Experimental Observations: Single Particle Tracking

Kuo & McGrath Measured *Listeria* Trajectory (Red)

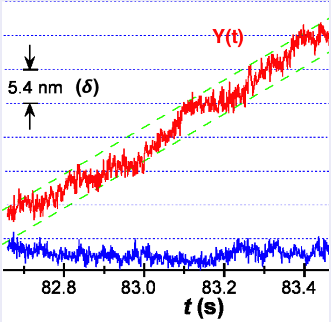


Image Source: [Kuo and McGrath, 2000]

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

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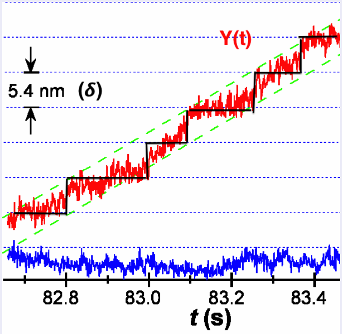

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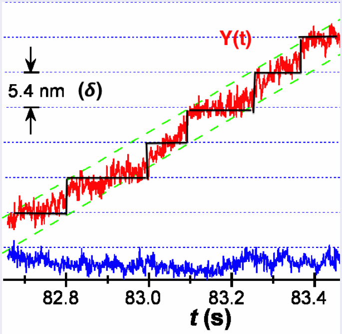

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1. "Stepping" Behavior
   - Step Size: δ (Monomer Width)
   - Suggesting: Coordinated Growth of Actin Polymers
2. MSD Smaller than Expected
   - (Decreased Fluctuation)

Suggest Possible Explanation:

"Binding" between *Listeria* and Actin Cloud

Image Source: [Kuo and McGrath, 2000]

Motivation: Actin-Based Motility

Actin-Based Motility of *Listeria*

Motivates Study of:

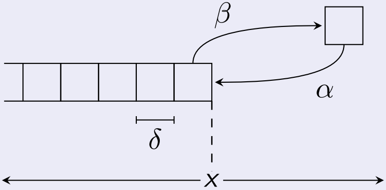
- Polymerization-Driven Motion of a Fluctuating Barrier

Mathematical Framework:

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

Single Polymer Ratchet

What is a Single Polymer Ratchet?



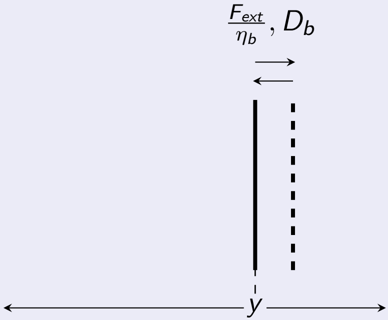
Component 1:

Polymer

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

Single Polymer Ratchet

What is a Single Polymer Ratchet?



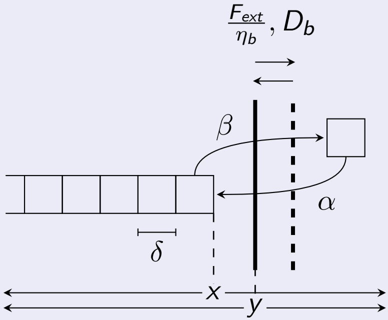
Component 2:

Fluctuating Barrier

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

Single Polymer Ratchet

What is a Single Polymer Ratchet?

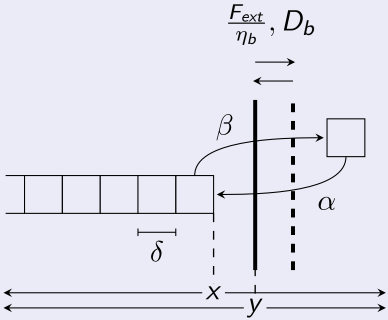


When Components Interact:

- 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

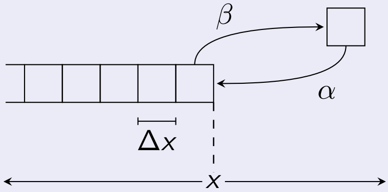
Barrier is "Ratcheted" Forward

Single Polymer (No Barrier)

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

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

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



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 . . .

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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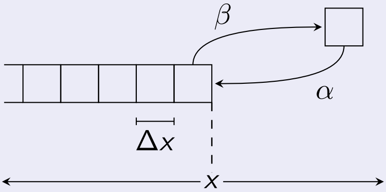


Continuous Space Model:

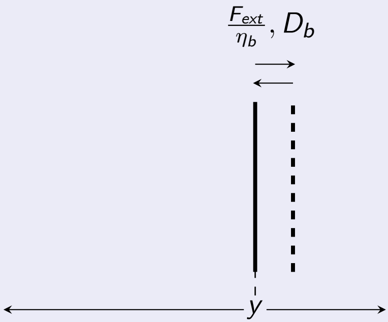
- $P_{\mathbf{X}}(x,t) = \mathrm{Prob}\{x < \mathbf{X}(t) \leq x + dx\}$
- Biased Brownian Motion (Diffusion with Drift)

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

Barrier (No Polymer)

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

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



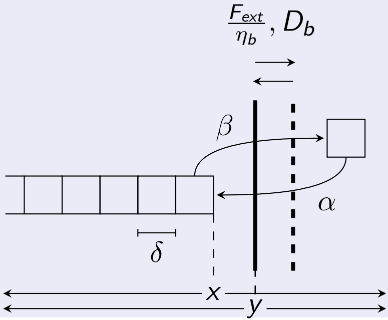
Continuous Space Model:

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

Single Polymer Ratchet

Diffusion Formalism Model: [Qian, 2004]

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



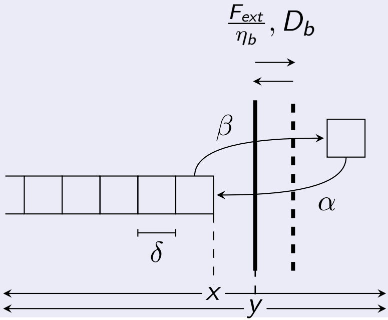
Joint pdf:

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

Single Polymer Ratchet

Diffusion Formalism Model: [Qian, 2004]

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



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]

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

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

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

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

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

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Single Polymer Ratchet: Gap Distance

Gap Distance Approaches a Steady State:

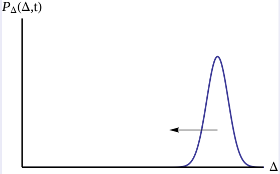
$$\frac{\partial P_{\mathbf{\Delta}}(\Delta,t)}{\partial t} = (D_a + D_b)\frac{\partial^2 P_{\mathbf{\Delta}}}{\partial \Delta^2} + \left(V_a + \frac{F_{ext}}{\eta_b}\right)\frac{\partial P_{\mathbf{\Delta}}}{\partial \Delta}, \quad \Delta \geq 0$$

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

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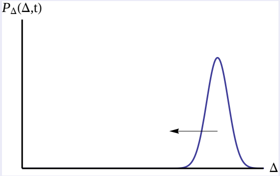

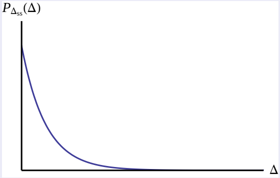

Gap → Steady State!

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

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

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:

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

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

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

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Normal Distribution

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

Single Polymer Ratchet: Stalling Force

Define the Stalling Force, F^*:

Value of the External Force that "Stalls" the Drift:

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

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

Qualitatively:

- $F_{ext} < F^*$: Polymer Pushes Barrier

Single Polymer Ratchet: Stalling Force

Define the Stalling Force, F^*:

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

Qualitatively:

- $F_{ext} < F^*$:
  Polymer Pushes Barrier

Single Polymer Ratchet

Single Polymer Ratchet Summary

Gap Distance → Steady State:

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

Average Position → Biased Diffusion

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

Stalling Force:

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

Single Polymer Ratchet

Single Polymer Ratchet Summary

Gap Distance → Steady State:

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

Average Position → Biased

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

Stalling Force:

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

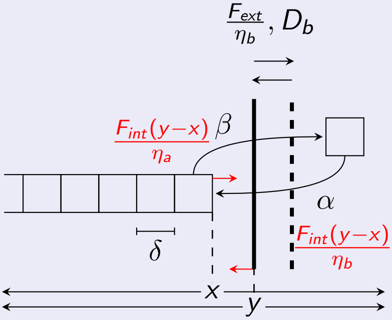
Incorporate Two Realistic Features:

1. Attraction Force
   Between Polymer and Barrier
   - Suggested by Kuo & McGrath
2. Multiple Polymer Filaments
   - *Listeria* is Propelled by *Network* of Actin Filaments

Internal Attraction Force

Internal Attraction Force, $F_{int}(y-x)$

To Represent "Binding" of Polymer to Barrier, Define $F_{int}(y-x)$:



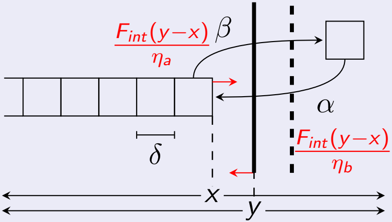
- Acts on *both* Polymer and Barrier
- Function of Gap Distance: $\Delta = y - x$
- Appears in Model: $\rightarrow$ Drift Terms

Internal Attraction Force

Internal Attraction Force, $F_{int}(y-x)$

$$\frac{\partial P_{\mathbf{XY}}(x,y,t)}{\partial t} = D_a \frac{\partial^2 P_{\mathbf{XY}}}{\partial x^2} + D_b \frac{\partial^2 P_{\mathbf{XY}}}{\partial y^2}$$

$$-\frac{\partial}{\partial x}\left[\left(V_a + \frac{F_{int}(y-x)}{\eta_a}\right) P_{\mathbf{XY}}\right] + \frac{\partial}{\partial y}\left[\frac{(F_{ext} + F_{int}(y-x))}{\eta_b} P_{\mathbf{XY}}\right] \qquad (3)$$



Strategy: Decouple via Change of Variables:

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

Internal Attraction Force

Internal Attraction Force, $F_{int}(\Delta)$

$$\frac{\partial P_{\mathbf{XY}}(x,y,t)}{\partial t} = D_a \frac{\partial^2 P_{\mathbf{XY}}}{\partial x^2} + D_b \frac{\partial^2 P_{\mathbf{XY}}}{\partial y^2} - \frac{\partial}{\partial x}\left[\left(V_a + \frac{F_{int}(y-x)}{\eta_a}\right) P_{\mathbf{XY}}\right] + \frac{\partial}{\partial y}\left[\frac{(F_{ext} + F_{int}(y-x))}{\eta_b} P_{\mathbf{XY}}\right] \quad (3)$$

$$\frac{\partial P_{\mathbf{\Delta Z}}(\Delta,z,t)}{\partial t} = D_\delta \frac{\partial^2 P_{\mathbf{\Delta Z}}}{\partial \Delta^2} + D_z \frac{\partial^2 P_{\mathbf{\Delta Z}}}{\partial z^2} + \frac{\partial}{\partial \Delta}\left(V_1(\Delta) P_{\mathbf{\Delta Z}}\right) - \frac{\partial}{\partial z}\left(V_2(\Delta) P_{\mathbf{\Delta Z}}\right) \quad (4)$$

- (3) Constraint: $\mathbf{X}(t) \leq \mathbf{Y}(t)$
- (4) Constraint: $\mathbf{\Delta}(t) \geq 0$

Internal Attraction Force

Internal Attraction Force, $F_{int}(\Delta)$

$$\frac{\partial P_{\mathbf{XY}}(x,y,t)}{\partial t} = D_a \frac{\partial^2 P_{\mathbf{XY}}}{\partial x^2} + D_b \frac{\partial^2 P_{\mathbf{XY}}}{\partial y^2} - \frac{\partial}{\partial x}\left[\left(V_a + \frac{F_{int}(y-x)}{\eta_a}\right) P_{\mathbf{XY}}\right] + \frac{\partial}{\partial y}\left[\frac{(F_{ext} + F_{int}(y-x))}{\eta_b} P_{\mathbf{XY}}\right] \quad (3)$$

$$\frac{\partial P_{\mathbf{\Delta Z}}(\Delta,z,t)}{\partial t} = D_\delta \frac{\partial^2 P_{\mathbf{\Delta Z}}}{\partial \Delta^2} + D_z \frac{\partial^2 P_{\mathbf{\Delta Z}}}{\partial z^2} + \frac{\partial}{\partial \Delta}\left(V_1(\Delta) P_{\mathbf{\Delta Z}}\right) - \frac{\partial}{\partial z}\left(V_2(\Delta) P_{\mathbf{\Delta Z}}\right) \quad (4)$$

- (3) Constraint: $\mathbf{X}(t) \le \mathbf{Y}(t)$
- (4) Constraint: $\mathbf{\Delta}(t) \ge 0$

Gap Dynamics

- Do Not Depend **Z**
- Gap $\rightarrow$ Steady State

Internal Attraction Force: Gap Distance

Steady-State Gap Distribution, $P_{\mathbf{\Delta}_{ss}}(\Delta)$

$$0 = D_\delta \frac{d^2 P_{\mathbf{\Delta}_{ss}}(\Delta)}{d\Delta^2} + \frac{d}{d\Delta}\left(V_1(\Delta) P_{\mathbf{\Delta}_{ss}}(\Delta)\right), \qquad \Delta \geq 0,$$

No-Flux B.C. at $x = 0$

$$V_1(\Delta) = V_\delta + \left(\frac{1}{\eta_a} + \frac{1}{\eta_b}\right) F_{int}(\Delta)$$

$D_\delta = (D_a + D_b)$

$V_\delta = (V_a + F_{ext}/\eta_b)$

$\mathcal{N}$: Normalization Factor

$F_{int}(\Delta) = -\frac{dU_{int}(\Delta)}{d\Delta}$

Solution:

$$P_{\mathbf{\Delta}_{ss}}(\Delta) = \mathcal{N} \exp\left[-\frac{V_\delta \Delta - (1/\eta_a + 1/\eta_b) U_{int}(\Delta)}{D_\delta}\right]$$

Internal Attraction Force: Average Position

After the Gap Reaches the Steady State, Average Position:

$$\int_0^\infty P_{\boldsymbol{\Delta}_{ss}}(\Delta)\frac{\partial P_{\mathbf{z}}(z,t)}{dt}d\Delta = \int_0^\infty \left(P_{\boldsymbol{\Delta}_{ss}}(\Delta)\left(D_z\frac{\partial^2 P_{\mathbf{z}}}{\partial z^2} - \frac{\partial}{\partial z}\left(V_2(\Delta)P_{\mathbf{z}}\right)\right)\right)d\Delta$$

$$\frac{\partial P_{\mathbf{z}}(z,t)}{dt} = D_z\frac{\partial^2 P_{\mathbf{z}}}{\partial z^2} - V_z\frac{\partial P_{\mathbf{z}}}{\partial z} - \frac{\left(\frac{D_b}{\eta_a} - \frac{D_a}{\eta_b}\right)}{D_a + D_b}\frac{\partial P_{\mathbf{z}}}{\partial z}\int_0^\infty F_{int}(\Delta)P_{\boldsymbol{\Delta}_{ss}}(\Delta)d\Delta$$

Expected Value of the Internal Attraction Force

Internal Attraction Force: Average Position

After the Gap Reaches the Steady State, Average Position:

$$\int_0^\infty P_{\Delta_{ss}}(\Delta)\frac{\partial P_z(z,t)}{dt}d\Delta = \int_0^\infty \left(P_{\Delta_{ss}}(\Delta)\left(D_z\frac{\partial^2 P_z}{\partial z^2} - \frac{\partial}{\partial z}\left(V_2(\Delta)P_z\right)\right)\right)d\Delta$$

$$\frac{\partial P_z(z,t)}{dt} = D_z\frac{\partial^2 P_z}{\partial z^2} - V_z\frac{\partial P_z}{\partial z} - \frac{\left(\frac{D_b}{\eta_a} - \frac{D_a}{\eta_b}\right)}{D_a + D_b}\frac{\partial P_z}{\partial z}\int_0^\infty F_{int}(\Delta)P_{\Delta_{ss}}(\Delta)d\Delta$$

Expected Value of the Internal Attraction Force

Internal Attraction Force: Average Position

Define Mean Internal Force, $\overline{F}_{int}$

$$\overline{F}_{int} = \int_0^\infty F_{int}(\Delta) P_{\mathbf{\Delta}_{ss}}(\Delta) d\Delta$$

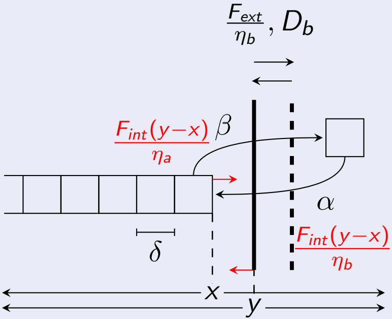
Then:

$$\frac{\partial P_{\mathbf{z}}(z,t)}{dt} = D_z \frac{\partial^2 P_{\mathbf{z}}}{\partial z^2} - V_z \frac{\partial P_{\mathbf{z}}}{\partial z} - \frac{\left(\frac{D_b}{\eta_a} - \frac{D_a}{\eta_b}\right) \overline{F}_{int}}{D_a + D_b} \frac{\partial P_{\mathbf{z}}}{\partial z}$$

Internal Attraction Force: Average Position

Rigid Polymer Structure:

For *Listeria*'s Actin Tail, the Polymer Structure is "Rigid," $\eta_a \gg \eta_b$



- Must Apply a Much Greater Force to Generate Drift
- $\Rightarrow \frac{F_{int}(y-x)}{\eta_a} \ll \frac{F_{int}(y-x)}{\eta_b}$ (Neglect Effect of Attraction Force on Polymer Drift)

Internal Attraction Force: Average Position

Rigid Polymer Structure:

$$\frac{\partial P_{\mathbf{z}}(z,t)}{dt} = D_z \frac{\partial^2 P_{\mathbf{z}}}{\partial z^2} - V_z \frac{\partial P_{\mathbf{z}}}{\partial z} - \frac{\left(\frac{D_b}{\eta_a} - \frac{D_a}{\eta_b}\right)\overline{F}_{int}}{D_a + D_b} \frac{\partial P_{\mathbf{z}}}{\partial z}$$

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

If the Polymer Structure is Rigid, $\eta_a >> \eta_b$, $\frac{\overline{F}_{int}}{\eta_a} \ll \frac{\overline{F}_{int}}{\eta_b}$

$$\frac{\partial P_{\mathbf{z}}(z,t)}{dt} = D_z \frac{\partial^2 P_{\mathbf{z}}}{\partial z^2} - \frac{\left(D_b V_a - D_a \left(F_{ext} + \overline{F}_{int}\right)/\eta_b\right)}{D_a + D_b} \frac{\partial P_{\mathbf{z}}}{\partial z}$$

Internal Attraction Force: Average Position

Rigid Polymer Structure:

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Internal Attraction Force $\sim$ Additional External Resistant Force:

- $\boxed{F = F_{ext} + \overline{F}_{int}}$

For the Rest of This Talk!

Internal Attraction Force: Average Position

Rigid Polymer Structure:

If the Polymer Structure is Rigid, $\eta_a >> \eta_b$, $\frac{\overline{F}_{int}}{\eta_a} \ll \frac{\overline{F}_{int}}{\eta_b}$

$$\frac{\partial P_{\mathbf{z}}(z,t)}{dt} = D_z \frac{\partial^2 P_{\mathbf{z}}}{\partial z^2} - \frac{\left(D_b V_a - D_a \left(F_{ext} + \overline{F}_{int}\right)/\eta_b\right)}{D_a + D_b} \frac{\partial P_{\mathbf{z}}}{\partial z}$$

Internal Attraction Fo

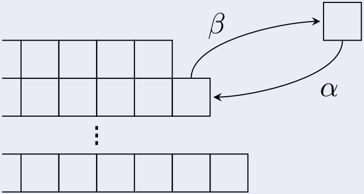
- $\boxed{F = F_{ext} + \overline{F}_{int}}$

First Realistic Feature Results:

1. Attraction Force
   Between Polymer and Barrier
   - Effectively Decreases V_z (Drift)
   - No Direct Effect on D_z (Fluctuation)

N Polymer Ratchet

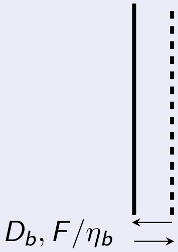
What is an N Polymer Ratchet?



Component 1:
Bundle of
N Identical Polymers

N Polymer Ratchet

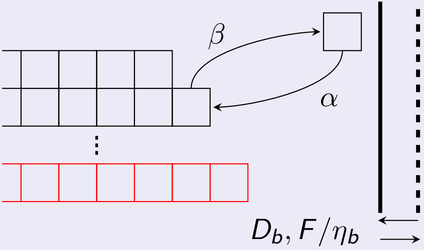
What is an N Polymer Ratchet?



Component 2:
Barrier

N Polymer Ratchet

What is an N Polymer Ratchet?



When Components Interact:

Ratchet:

Longest Polymer

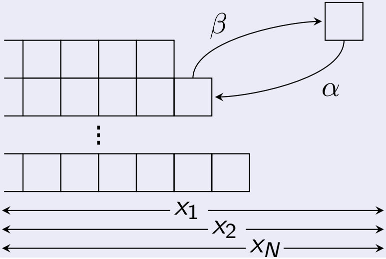
+

Barrier

N Polymer Bundle (No Barrier)

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

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



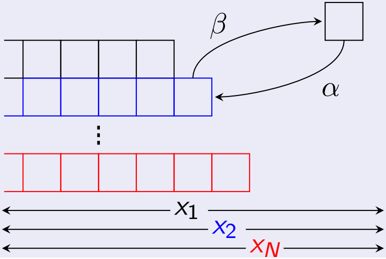
Each *Individual* Polymer:

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

N Polymer Bundle (No Barrier)

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

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



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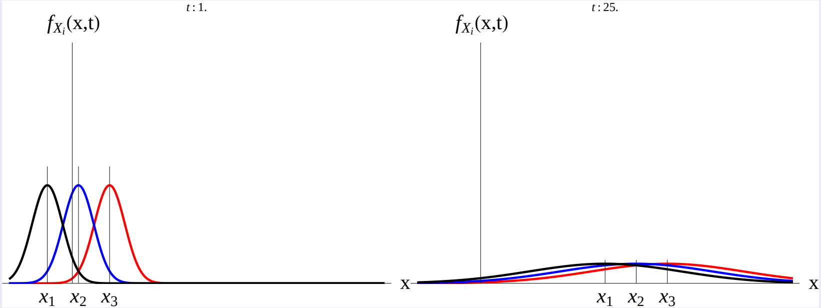
- *cdf*:
  $$F_{\mathbf{X}}(x,t) = \int_{-\infty}^{x} f_{\mathbf{X}}(x,t)dx$$

N Polymer Bundle (No Barrier)

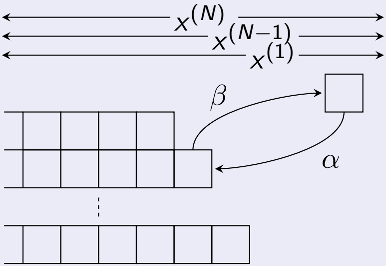
Example: 3 Polymers Starting Out Separated:



(Click for Movie)

N Polymer Bundle (No Barrier)

$\mathbf{X}^{(k)}(t)$: 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:

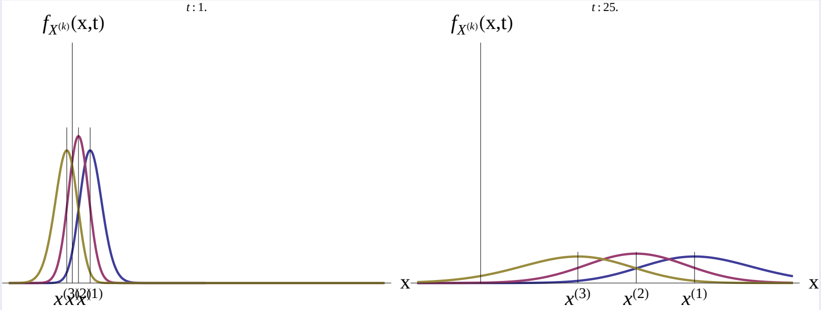
- *pdf*:
  $$f_{\mathbf{X}^{(k)}}(x,t) = \frac{N!}{(k-1)!(N-k)!} F_{\mathbf{X}}(x,t)^{N-k} \left[1 - F_{\mathbf{X}}(x,t)\right]^{k-1} f_{\mathbf{X}}(x,t)$$

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)

N Identical Polymers

In the Absence of a Barrier, Bundle "Spreads Out:"

- Distance Between Peaks Increases:
  - $\propto \sqrt{2D_a t}$

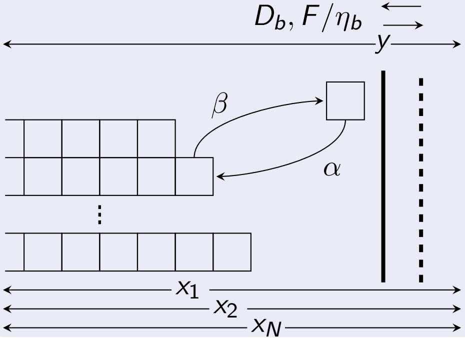
In the Long-Time Limit:

Bundle Grows as a Single Polymer While Others Lag Behind

N Polymer Ratchet

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

$$\frac{\partial f(\{x_i\}, y, t)}{\partial t} = \sum_{k=1}^{N} \left(D_a \frac{\partial^2 f}{\partial x_k^2} - V_a \frac{\partial f}{\partial x_k} \right) + D_b \frac{\partial^2 f}{\partial^2 y} + \frac{F}{\eta_b} \frac{\partial f}{\partial y} \quad (5)$$



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

$$\frac{\partial f(\{x_i\}, y, t)}{\partial t} = \sum_{k=1}^{N} \left(D_a \frac{\partial^2 f}{\partial x_k^2} - V_a \frac{\partial f}{\partial x_k} \right) + D_b \frac{\partial^2 f}{\partial^2 y} + \frac{F}{\eta_b} \frac{\partial f}{\partial y} \tag{5}$$

$$\frac{\partial \phi(\{\xi_i\}, t)}{\partial t} = \sum_{i,j}^{N} (D_a \delta_{ij} + D_b) \frac{\partial^2 \phi}{\partial \xi_i \partial \xi_j} + \left(V_a + \frac{F}{\eta_b} \right) \sum_{i=1}^{N} \frac{\partial \phi}{\partial \xi_i} \tag{6a}$$

$$\frac{\partial P_{\mathbf{Z}}(z, t)}{\partial t} = \frac{D_b D_a}{N D_b + D_a} \frac{\partial^2 P_{\mathbf{Z}}}{\partial z^2} - \left(\frac{N D_b V_a - D_a F/\eta_b}{N D_b + D_a} \right) \frac{\partial P_{\mathbf{Z}}}{\partial z} \tag{6b}$$

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

Geometric Constraints:

- For (5): $\mathbf{X}_i(t) \leq \mathbf{Y}(t)$
- For (6a): $\boldsymbol{\Delta}_i(t) \geq 0$

N Polymer Ratchet: Gap Distance

Gap Distances Approach Steady State:

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

$\{\boldsymbol{\Delta}_i\}$: 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

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

N Polymer Ratchet: Gap Distance

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

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:

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

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: Average Position

Recall 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

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

N Polymer Ratchet: Average Position

Recall Stalling Force, F_N^*:

Value of the Force that "Stalls" the Drift:

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Qualitatively:

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N Polymer Ratchet

N Polymer Ratchet Summary

Min. Gap Distance → Steady State:

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

Average Position → Biased Diffusion

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

Stalling Force:

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

N Polymer Ratchet

N Polymer Ratchet

Min. Gap Distance –

- Exponential Dist
- $\mu = \frac{D_b + (D_a/N)}{V_a + F/\eta_b}$

Average Position → E

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

Stalling Force:

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

Second Realistic Feature Results:

2. Multiple Polymer Filaments:

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

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

- Stalling Force Scales with N
- Interaction with Barrier → 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 Realistic Features:

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

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Future Work

Incorporate More Realistic Features

- Explicit Incorporation of Hydrolysis Cycle
- Interactions Between Filaments in a Bundle
- Capture Discrete "Stepping" Events

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- Reading Committee:
  Bernard Deconinck, Eric Shea-Brown, & Hong Qian
- GSR: Hong Shen, Chemical Engineering
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  - Dr. Alex Mogilner, Mathematics, UC Davis
  - Dr. Anatoly Kolomeisky, Chemistry, Rice University

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- TA, Math Department
- Instructor, Applied Math (AMATH 351 & 383)
- NSF GK-12 Fellow
  (Emerson Elementary School, 3rd & 4th Grade)

Questions?

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

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

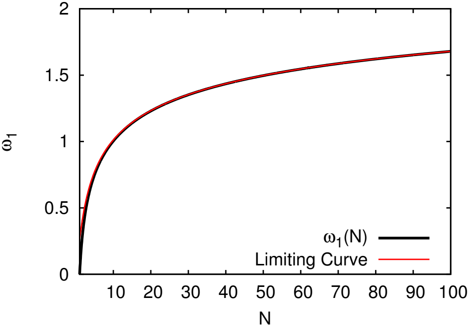
- $\frac{\partial P_{\mathbf{\Delta}}(x,t)}{\partial t} = D_\delta \frac{\partial^2 P_{\mathbf{\Delta}}}{\partial x^2} + V_\delta \frac{\partial P_{\mathbf{\Delta}}}{\partial x}$
- $P_{\mathbf{\Delta}}(x, 0) = \delta(x)$
- $D_\delta \frac{\partial P_{\mathbf{\Delta}}(0,t)}{\partial x} + V_\delta P_{\mathbf{\Delta}}(0,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

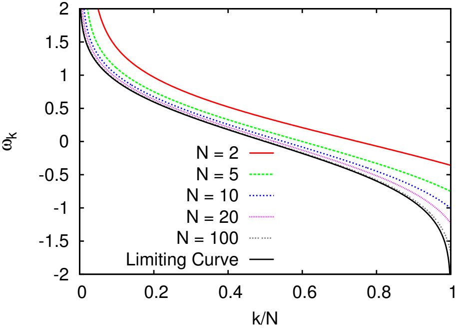
Solution Via New Transform Method of Fokas [Fokas, 2002]

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

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

$$k = 1 + \frac{1-\mathrm{erf}(\omega_k)}{2}\left[N - 1 - \sqrt{\pi}\omega_k[1+\mathrm{erf}(\omega_k)]e^{\omega_k^2}\right]$$





- For $\omega_1 > 1,\ N \approx 2\sqrt{\pi}\omega_1 e^{\omega_1^2}$
- For Large N, ω_1 grows as $\sqrt{\ln N}$

- $\omega_k > \omega_{k+1}$ (monotonically decreasing)
- $\lim_{N\to\infty} \frac{k}{N} = \frac{1-\mathrm{erf}(\omega_k)}{2}$

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