Two Tails of Motility in Cells

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Self-Assembly-Driven Motility

Neutrophil chasing Staphylococcus aurea

David Rogers, Vanderbilt Univ, 1959
http://www.chem.uic.edu/fenteany/research/cell_migration/neutrophil.html

Xenopus keratocytes

How does self-assembly of actin into branched networks lead to motion?

Kun-Chun Lee, Ed Banigan
Disassembly-Driven Motility

Caulobacter crescentus

How does the chromosome move across the cell during chromosomal segregation in certain asymmetric bacteria?

Ed Banigan, Zemer Gitai, Ned Wingreen

Courtesy of C. W. Shebelut, J. M. Guberman, Z. Gitai
Actin Polymerization and Depolymerization

- A 3µm long filament turns over in 1 min in vivo
- ATP hydrolysis provides polarity to filament growth

Molecular Cell Biology, Lodish et al

How are Growing Ends Localized at Leading Edge?


- Arp2/3 complex binds to F-actin and nucleates new branches
Dendritic Nucleation Model: Participating Proteins

1. Extracellular stimuli
2. Produce active GTPases and PIP₂
3. Activate WASP/Scar
4. Activate Arp2/3 complex to initiate new filaments
5. Barbed ends elongate
6. Growing filaments push membrane forward
7. Capping protein terminates elongation
8. Ageing
9. ADF/cofilin severs and depolymerizes ADP-actin filaments
10. Profilin catalyses exchange of ADP for ATP
11. Pool of ATP-actin bound to profilin

Activated GTPases and PIP₂
WASP/Scar
ADF/cofilin
ATP-actin
ADP-actin
Profilin
Capping protein
Arp2/3 complex

Actin and Listeria Motility

Life cycle of Listeria monocytogenes

Uses actin polymerization to move!
Same physics as cell crawling
How Listeria Spreads from Cell to Cell

Without proteins that generate comet tail, Listeria can...
In vitro Realizations


Actin comet tail has branchy structure similar to that of lamellipodium.

Minimal Ingredients for Motility

“All” you need is

- Actin and buffer w/ ATP
- Arp2/3 makes new growing ends
- Capping protein kills them off
- ADF/cofilin severs filaments
- Profilin converts ADP-G-actin to ATP-G-actin
- Bead coated with ActA,VCA, activates arp2/3

How does self-assembly into a branched structure lead to motility?

Brownian Dynamics Simulations

\[ \eta \frac{dX}{dt} = -\nabla \Phi_H - \nabla \Phi_S - \nabla \Phi_B + F_R \]

\[ F_R = \text{Random Force} \]
\[ \langle F_R \rangle = 0 \]
\[ \langle F_R(t)F_R(t') \rangle = 6k_B T \eta \delta(t - t') \]

\[ \Phi_H = \text{Hardcore interaction} \]
\[ \Phi_H = \frac{1}{2} K_h (R - R_0)^2, \quad R < R_0 \]

\[ \Phi_S = \text{Bond Stretch interaction} \]
\[ \Phi_S = \frac{1}{2} K_s (D - D_0)^2 \]

\[ \Phi_B = \text{Bending interaction} \]
\[ \Phi_B = \frac{1}{2} K_b (\cos(\Theta) - \cos(\Theta_0))^2 \]

- Polymerization at + end (\(k_+\))
- Depolymerization at - end (\(k_-\))
- Branching (\(k_a\))
- Debranching (\(k_d\))
- Capping

We See Motility!

2D projection of 3D simulation
Motion allowed in ±z direction, only

Newton’s Third Law

\[ \vec{F}_{tail} = -\vec{F}_{disk} \]

\[ \zeta_{tail} \vec{v}_{tail} = -\zeta_{disk} \vec{v}_{disk} \]

\[ \vec{v}_{disk} = -\frac{\zeta_{tail}}{\zeta_{disk}} \vec{v}_{tail} \]

>1

Center of drag is stationary

Center of mass can move
Problem with Accepted Mechanism


- Stiff/flexible: 60+%/
  5% of force from tips
- At low viscosity, speed is independent of filament stiffness!
- Mechanism cannot depend on whether force comes from tips

\[ l_p \sim 150 \text{ nm} \]
\[ l_p \sim 20 \text{ nm} \]
Origin of Motility

- Disk activates Arp2/3, which recruits F-actin

- Concentration of F-actin high behind the disk compared to average

- If disk repels actin, then disk will move forwards to avoid F-actin

- In real system, concentration gradient is

BUT: Tail is Attached to Disk

- N-WASP/ActA contain binding sites for actin
  
  Same protein that activates Arp2/3 also binds actin to surface

Include Filament Binding to Disk

• Some sites on disk have attraction \( \varepsilon \) to filament tips

\[
V(r, \psi) = \varepsilon \left( \frac{\sigma^{14}}{r^{14}} - \frac{\sigma^{12}}{r^{12}} \right) \cos^4 \psi
\]

Specific binding of filaments to the disk does not destroy motility.
New Proposed Mechanism for Actin Motility

Why do bagpipe players always walk while they play?

To get away from the noise.

Chromosomal Segregation in Caulobacter
courtesy of C. W. Shebelut, J. M. Guberman, Z. Gitai
Caulobacter crescentus
Asymmetric Cell Division

- Most cells divide symmetrically
  - Caulobacter crescentus and Vibrio cholerae divide asymmetrically

- What is the mechanism for chromosomal motility?
Chromosomal Segregation in *C. crescentus* and *V.*

We are interested in the 4th stage of the process. How does the chromosome (ori) scoot across the cell?

*Courtesy of C. W. Shebelut, J. M. Guberman, Z. Gitai*

*Caulobacter crescentus*
Vibrio cholerae

Courtesy of Popular Logistics

A Closer Look at Process

- Origin is decorated with ParB which binds to and hydrolyzes ParA
- ParA filament structure depolymerizes and drags ParB along
- Origin and terminus switch places

- ParB on origin attaches to ParA
- ParA disassembles and ori moves

- Origin is decorated with ParB which binds to and hydrolyzes ParA
- ParA filament structure depolymerizes and drags ParB along
Simulation Model

Brownian motion
\[ \eta \partial_t \vec{r} = -\nabla U_{\text{repel}} - \nabla U_{\text{bond}} - \nabla U_{\text{angle}} - \nabla U_{\text{crosslink}} - \nabla U_{\text{bind}} + F_r \]
\[ \langle F_r \rangle = 0 \]
\[ \langle F_r(t) F_r(t') \rangle = 6k_B T \delta(t - t') \]

Biochemistry
1. ParB binds to ParA
2. ParA hydrolyzes at rate \( k_h \).
3. Hydrolyzed ParA depolymerizes at rate \( k_d \).

Interaction potentials
\[ U_{\text{repel}} \propto (\vec{r} - \vec{r}_0)^2 \]
\[ U_{\text{bond}} \propto (\vec{r} - \vec{r}_0)^2 \]
\[ U_{\text{angle}} \propto (\cos \theta - \cos \theta_0)^2 \]
\[ U_{\text{crosslink}} \propto (\vec{r} - \vec{r}_0)^2 \]
\[ U_{\text{bind}} = \epsilon \left( \frac{\sigma_{14}}{r_{14}} - \frac{\sigma_{12}}{r_{12}} \right) \cos^2 \psi_1 \cos^2 \psi_2 \cos^2 \psi_3 \]
We See Translocation
How Robust is This Mechanism?

- Speed given by $v = a k_d^{\text{eff}}$ where $a$ is size of ParA monomer and $k_d^{\text{eff}}$ is net depolymerization rate.

- But if $k_d^{\text{eff}}$ is too high, chromosome falls off.

- For robust motility, need $k_d^{\text{eff}} < \tau_{\text{relax}}^{-1}$ (relaxation time of chromosome).
Concentration Gradient Drives Motion

- System uses depolymerization to create steady-state
Diffusiophoresis

Particle interacts with the concentration field and moves up the gradient if it is repelled or down the gradient if it is attracted.

- Actin-polymerization-driven motility arises from repulsions between “particle” (Listeria bacterium) and A (actin).
- ParA/ParB-driven-chromosomal segregation arises from attraction between “particle” (ParB) and A (ParA).

Self-Diffusiophoresis

- But there is no externally-imposed gradient of actin or ParA!
- In Listeria, bacterium activates actin polymerization to create its own actin concentration gradient
- In ParA case, ParB-decorated chromosome in Caulobacter uses ParA depolymerization to create its own ParA gradient
Self-Diffusiophoresis is Very General


- Coat Janus colloids with Pt and put in $H_2O_2$ solution

$$H_2O_2 \rightarrow H_2O + \frac{1}{2} O_2$$


$$D_{\text{eff}} = D + \frac{1}{4} V^2 \tau_R$$

- Diffusion enhanced by propulsion velocity $V$
Self-diffusiophoresis occurs in a fluid. Motion involves a balance between diffusion and advection.

\[ \text{Pe} = \frac{\text{advection}}{\text{diffusion}} = \frac{Ua}{D} \]

- **Diffusion dominated**
- **Advection dominated**


Courtesy of Julie Theriot
http://cmgm.stanford.edu/theriot/movies.htm
Simple Model

- spherical particle, radius $a$
- single solute species, concentration $c$
- reaction occurs in a patch
- surface interaction $V$, range $\delta \ll a$
- assume steady state motion

Rest frame of the particle
Boundary Layer

- Solute is pushed away from surface by interaction
- It carries fluid with it
- More fluid is pushed away where there is more solute
- This gives rise to flow at the boundary layer $\rightarrow$ slip velocity
- This slip velocity propels particle

$U = \frac{-1}{4\pi(a + \delta)^2} \int_{r=a+\delta} u^{\text{slip}}$

Self-diffusiophoresis at high and low Peclet number

\[ U \sim \frac{m^D \bar{\alpha}}{D} \sin^2(\theta_p) \quad \text{Pe} \ll 1 \]

\[ U \sim \left( \frac{m^A \bar{\alpha}}{\delta \ln \left( \frac{a}{\delta} \right)} \right)^{1/2} \sin^3 \left( \frac{1}{2} \theta_p \right) \quad \text{Pe} \gg 1 \]

**Four scenarios**

- Repulsive producer: \( V > 0 \), \( \alpha > 0 \)
- Repulsive consumer: \( V > 0 \), \( \alpha < 0 \)
- Attractive producer: \( V < 0 \), \( \alpha > 0 \)
- Attractive consumer: \( V < 0 \), \( \alpha < 0 \)
Summary

• Physical mechanism underlying actin-polymerization-driven motility and chromosomal translocation in Caulobacter is self-diffusiophoresis.

• But since branched actin network and ParA bundle do not diffuse; this is a new regime of self-diffusiophoresis, dominated by advection, not diffusion.

• This affects the resulting motion profoundly.

• Only two steady-state scenarios:
  - repulsive producer (actin-driven motility)
  - attractive consumer (ParAB-driven motility)
Final Remarks

- Self-diffusiophoresis is the simplest form of chemotaxis
  - Maybe it isn’t surprising that it is exploited in cells

- Physicists tend to think mostly about systems in equilibrium
  - Most many-body phenomena in the world occur far from equilibrium
  - Simple, undiscovered, far-from-equilibrium mechanisms still abound!

  Kun-Chun Lee, Ed Banigan, Gareth Alexander,
  Zemer Gitai, Ned Wingreen
Main ingredient is competition between compressive (forwards) stresses and tensile (backwards) stresses

Compressive stresses put in by hand

Actin comet tail is assumed to be elastic medium

F-v relation from dep. of polymerization rate on stress

BUT

Motility is observed even in absence of crosslinkers
Comparison with Previous Simulations

e.g. Alberts & Odell, PLOS Biology, 2, 2054 (2004).

- Realistic rates
- Realistic numbers of filaments
- BUT
  - Monomers only exist when they are in filaments; artificial mass transfer gives rise to motility as an artifact
  - Artificial forces used to avoid

Our work
- Physically-consistent model
- Don’t violate important physical principles
- BUT
  - Depolymerization rate is too high
  - [G-actin] is too high
  - Filament stiffness is too low
Simulation Model

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