Cell Motility and Migration

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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

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

Kun-Chun Lee, Ed Banigan

Courtesy of T. M. Svitkina, G.G. Borisy

Xenopus keratocytes
Disassembly-Driven Motility

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

Caulobacter crescentus

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

Ed Banigan, Zemer Gitai, Ned Wingreen
Actin Polymerization and Depolymerization

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

G-actin

F-actin

Molecular Cell Biology, Lodish et al

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

Speeded up x900  

Speeded up x150


Without proteins that generate comet tail, Listeria can
How are growing ends localized behind Listeria?


• Arp2/3 complex binds to F-actin to nucleate new branches
• Arp2/3 is activated at back end of Listeria


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

x60

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

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

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

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

\[ \frac{\zeta_{\text{disk}}}{\zeta_{\text{disk}}} > 1 \]

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 Filaments are Bound 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.

E. Banigan
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?
A Closer Look at Process

ParB on origin attaches to ParA

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

ParA disassembles and ori moves

origin and terminus switch places

We See Translocation
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, 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$_2$O$_2$ 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

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

Diffusion dominated

Advection dominated


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

G. Alexander
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)
Cell Migration

How do white blood cells migrate in response to infection?

Neutrophil chasing Staphylococcus aurea

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

CD8+ T cells hunting Toxoplasma gondii

Tajie Harris, David Christian, Chris Hunter
• T cells enter brain in response to infection

• CD8+ T cells hunt down and kill Toxoplasma gondii

• What are their migration statistics?
For ordinary Brownian random walks, mean-squared displacement is **diffusive**

For T cells (control), mean-squared displacement is **superdiffusive**
Correlations are long-lived

- Correlations of displacements $r$ during time interval $t$, separated by time $\tau$

  \[ K(t, \tau) = \frac{\langle r(0, t) \cdot r(\tau, \tau + t) \rangle}{\langle r^2(0, 0) \rangle} \]

- For Brownian walkers, correlations decay exponentially

- For T cells, correlations decay
Displacement Distribution

- For Brownian walkers, displacement distribution is always \textbf{Gaussian} with scale factor $\varsigma$ that increases with time $t^{1/2}$
- T cell distributions show scaling collapse
  - But not onto a \textbf{Gaussian}
  - $\varsigma \sim t^{0.63}$
Lévy walks

- Lévy walks have steps drawn from power-law distribution

\[ P_\mu(x) \sim x^{-\mu} \]

- Such walks
  - are superdiffusive
  - have long-time correlations
  - exhibit scaling collapse of displacement distributions
  - Scaling distribution is wider than Gaussian

T cells execute generalized Lévy walks

- Probability density, \( P(r(t)) \)
- Displacement, \( r(t) \) (\( \mu m \))
- Time, \( \tau \) (min)
- Correlation function, \( K(\tau, t) \)
- Mean squared displacement (MSD), \( \mu m^2 \)

Graphs show the probability density, displacement, correlation function, and mean squared displacement over time.
Generalized Lévy walks

- Our model: cells run a Lévy-distributed distance ($\mu_{\text{run}}=2.15$) and then pause a Lévy-distributed time ($\mu_{\text{pause}}=1.7$)
Search and Capture

- Generalized Lévy searches are more efficient than Brownian searches

\[ \eta = \frac{\text{targets found}}{\text{total distance traveled}} \]
Final Remarks

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

• CD8$^+$ T cells hunt T. gondii much as predators hunt prey
  - Is this due to factors internal or external to the cell?
  - Do other cells of our immune system have migration statistics adapted to their function?

• 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 phenomena still
Thanks to

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Curie Model

- 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