Minimal Models of Actin-based Cell Motility

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Introduction

Motile cells have two states: stationary and moving. Stationary modes are characterized by symmetric forces on the cell. In order to achieve movement, a cell must break symmetry [1]. When symmetry is broken, the forces exerted on the cell become unbalanced, which causes the cell to move. We aim to model how symmetry is broken in motile cells.

Our minimal model, originally proposed by A. Mogilner (NYU) [1], considers three factors that influence cell movement: actin flow, myosin concentration, and the membrane. Using a mathematical model, we show that a cell can achieve various modes of motion by altering parameters such as actin polymerization, initial myosin concentration, and the viscosity of the actin network.

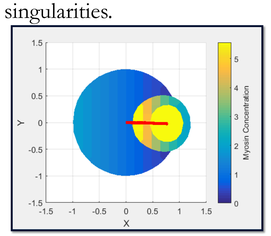
We show that the mechanisms included in the model are enough to break symmetry in the cell and initiate movement. By simulating cells with various parameters, we discover which characteristics must change to break symmetry.

Objectives

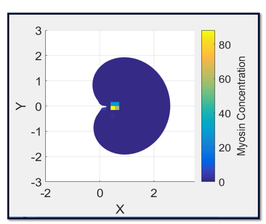
1. Mathematically assess how changing parameter sets leads to transitions between moving and non-moving states.
2. Predict how changes in a cell's internal structure lead to transitions in modes of motility.

Model

The original equations are revised because they yield nonphysical states: collapsing cells and cells that develop singularities.



Collapsing: cell area decreases to zero



Singularity: all myosin collects at one point in the cell, and actin velocities become infinite there

In simulations, the cell initially has a circular shape, a slight linear myosin gradient, and no actin flow. These initial conditions, "favoring" a stationary state, were chosen to probe its stability with respect to transition to motion.

Methods

Governing Equations (Nondimensionalized)

	Original	Revised
Myosin Concentration	$\frac{\partial m}{\partial t} = \nabla \cdot \nabla m - \nabla \cdot (\boldsymbol{u} m)$	$\frac{\partial m}{\partial t} = \nabla \cdot \left[\left(1 - \frac{m}{m_{md}}\right)\nabla m\right] - \nabla \cdot \left[\left(1 - \frac{m}{m_{ma}}\right)(\boldsymbol{u} m)\right]$
Actin Flow	$\frac{\partial \boldsymbol{u}}{\partial t} = \alpha\, \Delta \boldsymbol{u} + \beta \nabla \cdot (m\boldsymbol{I}) - \boldsymbol{u} = \boldsymbol{0}$	$\alpha\, \Delta \boldsymbol{u} + \beta \nabla \cdot (m\boldsymbol{I}) - \boldsymbol{u} = \boldsymbol{0}$
Membrane Velocity	$\boldsymbol{n} \cdot (\boldsymbol{v_f} - \boldsymbol{u}) = v_p$	$\boldsymbol{n} \cdot (\boldsymbol{v_f} - \boldsymbol{u}) = v_p$

Variables:
m: myosin concentration
$\boldsymbol{u}$: actin flow
$\boldsymbol{v_f}$: membrane velocity

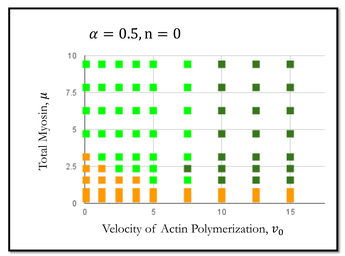
Parameters:
α: viscosity
β: force per unit myosin
v_0: velocity of polymerization
k: membrane tension
A_0: initial area of cell
A: area of cell
m_{md}: diffusion threshold
m_{ma}: advection threshold

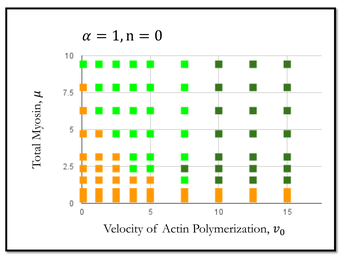
Two Boundary Conditions: Two Models

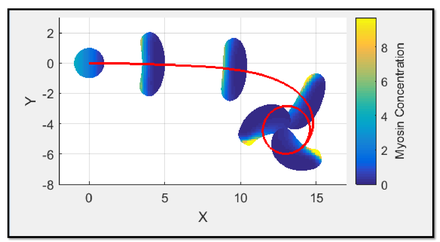
	Boundary Condition	Original Membrane Kinematics	Revised Membrane Kinematics
"Zero-Velocity" Model	$\boldsymbol{n} \cdot \boldsymbol{u}\vert_{\partial\Omega} = 0$	$v_p = \frac{v_0}{1 + m\vert_{\partial\omega}} - kA$	$v_p = \frac{v_0}{1 + m\vert_{\partial A}}\left(\frac{A_0}{A}\right) - k\left(A - A_0\left(\frac{A_0}{A}\right)^n\right)$
"Zero-Stress" Model	$\boldsymbol{n} \cdot (\alpha \nabla \boldsymbol{u} + \beta m \boldsymbol{I})\vert_{\partial\Omega} = 0$	$v_p = v_0 - kA$	$v_p = v_0\left(\frac{A_0}{A}\right) - k\left(A - A_0\left(\frac{A_0}{A}\right)^n\right)$

Results

"Zero-Velocity"



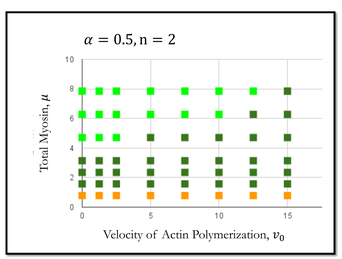


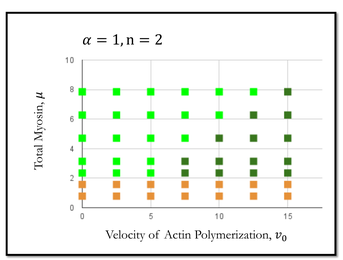


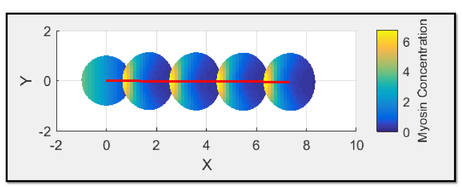
Simulation of cell rotating in "Zero-Velocity" Model
$\alpha = 1$, $v_0 = 12.5$, $\mu = 6.28$

Stationary Moving (Rotating) Moving (Straight)

"Zero-Stress"





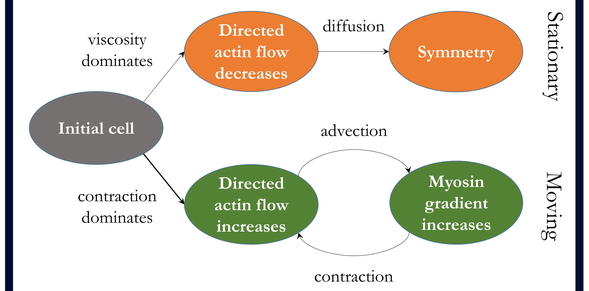


Simulation of cell moving straight in "Zero-Velocity" Model
$\alpha = 1$, $v_0 = 2.5$, $\mu = 6.28$

Discussion

For a cell to move, membrane velocity must be asymmetric. A positive feedback loop—the gradient of myosin bound to actin speeds up the actin flow which in turn reinforces the gradient of myosin—leads to a steady state of asymmetry in distributions of myosin and actin velocity fields, if the total myosin is sufficiently large.

- "Zero-Velocity" Model: differences in myosin concentration cause movement
- "Zero-Stress" Model: differences in actin velocity cause movement



The cell's shape determines the type of movement.

- If a cell's rear becomes concave, myosin concentrates in the two corners of the cell. Each provides a contractile force on the actin network until one becomes stronger than the other, and the cell begins to rotate.
- If a cell's rear remains convex, myosin concentrates in the back. This is the sole locus of force on the actin network, so stable forward motion occurs.

Conclusion

Even though the model only considers actin velocity, myosin and the membrane, characteristic features of cell movement are preserved. Changes in total myosin, viscosity, and actin polymerization are sufficient to prevent, initiate, or change the type of movement. The two models give insight to the role of adhesions of actin to the membrane.

References

[1] E. Barnhart et al. (2015). PNAS 112(16):5045-5050.

Acknowledgements

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