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Effects of microgravity on cell motility

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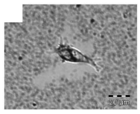
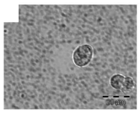
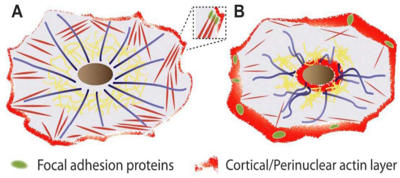
Introduction

- the immune system of astronauts is severely impaired after return from space flight [1]
- *in vitro* experiments during space flight show disruptions of the actin cytoskeleton of immune cells [2]
- such severe microgravity-induced cytoskeletal alternations have been shown to impact cell shape and motility [3]
- microgravity leads to changes of, e.g., cortical thickness and distribution of focal adhesion proteins [3,4]

Question: What are the effects of such microgravity-induced changes on the ability of the cell to migrate, polarize, and deform?

	1g cell	***µ*-g cell**
in vitro experiments [3]:	 wide migration tracks, typical elongated shape of a migrating cell	 short migration tracks, contracted morphology
presumed cytoskeletal changes [5]:		

Key terms

- The **cell cortex** is a thin layer of actin filaments on the inner face of the cell membrane. It is an important part of the cell's cytoskeleton.
- **Actin** is a filamenteous protein which dynamically polymerizes and depolymerizes. Actin **polymerization** creates membrane protrusions which are essential for cell migration.
- **Focal adhesion proteins** link the cortex to the extracellular environment, transmitting forces which allow for migration.

Two-dimensional model for the cell

- cortex is described as a closed, one-dimensional contour of compressible viscous fluid which forms the cell surface
- cortex force includes membrane tension and cell area conservation

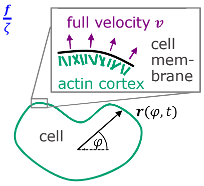
$$\boldsymbol{f} = -\left[\gamma\frac{p_{\max}-p_0}{p_{\max}-p}H + \frac{2\kappa}{A_0}(A-A_0)\right]\hat{\boldsymbol{n}}$$

surface tension γ, maximum perimeter $p_{\max}$, reference perimeter $p_0 = 2\pi R_0$, radius of circular reference cell shape R_0, curvature of contour $H(\varphi,t)$, area modulus κ, cell area $A(t)$, reference area A_0, unit normal vector $\hat{\boldsymbol{n}}(\varphi,t)$

- cortex velocity (cortex deformation rate) $\boldsymbol{v}_c = \frac{\boldsymbol{f}}{\zeta}$
  drag coefficient ζ
- polymerization velocity (filament growth) depends on actin concentration $c(\varphi,t)$ [6]

$$\boldsymbol{v_p} = Ve^{\frac{-c}{c_r}}\hat{\boldsymbol{n}}$$

polymerization speed V, reference concentration c_r



- full velocity $\boldsymbol{v} = \boldsymbol{v}_c + \boldsymbol{v_p}$ describes motion of filament end points and cell shape evolution
- time-evolution of actin concentration due to filament advection, diffusion, and restoration (due to, e.g., depolymerization) [7,8]

$$\dot{c} = -\boldsymbol{\nabla}^l \cdot (\boldsymbol{v}c) + D\Delta^l c + \beta(c_0 - c)$$

contour Laplace operator $\Delta^l = \boldsymbol{\nabla}^l \cdot \boldsymbol{\nabla}^l$, homeostatic actin concentration c_0, diffusion coefficient D, restoration rate β

Spontaneous onset of motility

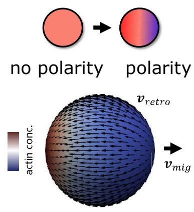
Non-motile base state: circular cell (radius R_0) with homogeneous actin concentration c_0 along the cortex

Linear stability analysis:

- first circular harmonic: No cell shape changes
- stationary instability for polymerization speeds above

$$V_1^{crit} = \frac{c_r}{c_0}e^{\frac{c_0}{c_r}}\left[\frac{D}{R_0} - R_0\beta\right]$$

- spontaneous onset of cell polarity and motility: Retrograde flow of cortex from cell front to rear
- see also three-dimensional case [9]

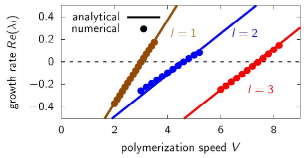


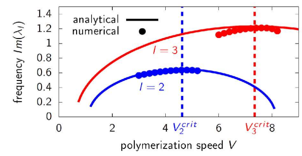
Shape dynamics

Linear stability analysis:

- higher-order harmonics: Shape changes
- consider small perturbations $\delta R(t)$, $\delta c(t)$ of circular cell shape and homeostatic concentration
- coupled dynamics of shape and concentration
- complex growth rate λ_l of perturbation
- oscillatory instability (Hopf bifurcation) for polymerization speeds above

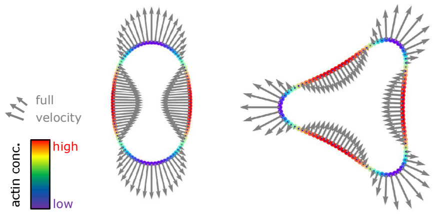
$$V_l^{crit} = \frac{c_r}{c_0}e^{\frac{c_0}{c_r}}\left[(l^2-1)\frac{\gamma}{R_0\zeta} + l^2\frac{D}{R_0} - R_0\beta\right]$$

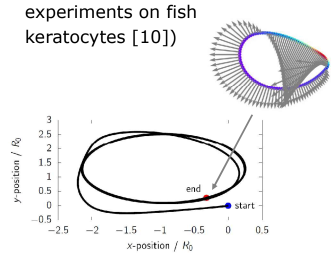




Numerical simulations:

- Second harmonic ($l = 2$)
- Third harmonic ($l = 3$)
- Circular trajectories (see also experiments on fish keratocytes [10])





Conclusion

Summary:

- the developed physical model for a cell allows to study the effects of microgravity on cell migration
- linear stability analysis reveals spontaneous symmetry breaking, leading to cell polarization, motility, and dynamic shape changes
- numerical simulations allow investigation of large cell deformations

Outlook:

- include anisotropic diffusion of cortical filaments to account for microgravity-induced disruptions of cortex
- study effects of external forces on cell migration
- include coupling of the cortex to extracellular environment using a focal adhesion model

References

[1] M. ElGindi *et al.*, Cells **10**, 1941 (2021).
[2] K. Paulsen *et al.*, Acta Astronaut. **94**, 277 (2014).
[3] M. A. Meloni *et al.*, Cytoskeleton **68**, 125 (2011).
[4] N. Nabavi, A. Khandani, A. Camirand, and R. E. Harrison, Bone **49**, 965 (2011).
[5] D. Vorselen *et al.*, FASEB J. **28**, 536 (2014).
[6] A. Farutin, J. Étienne, C. Misbah, and P. Recho, Phys. Rev. Lett. **123**, 118101 (2019).
[7] A. Colin *et al.*, EMBO J. **42**, 9 (2023).
[8] A. Mietke, F. Jülicher, and I. F. Sbalzarini, Proc. Natl. Acad. Sci. **116**, 29 (2019).
[9] W. Schmidt, W. Zimmermann, C. Misbah, and A. Farutin, under review (2024).
[10] G. M. Allen *et al.*, Cell Syst. **11**, 286 (2020).