Exploring the Active Gel Model for Cell Migration

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BIG PROBLEM

To describe cell migration

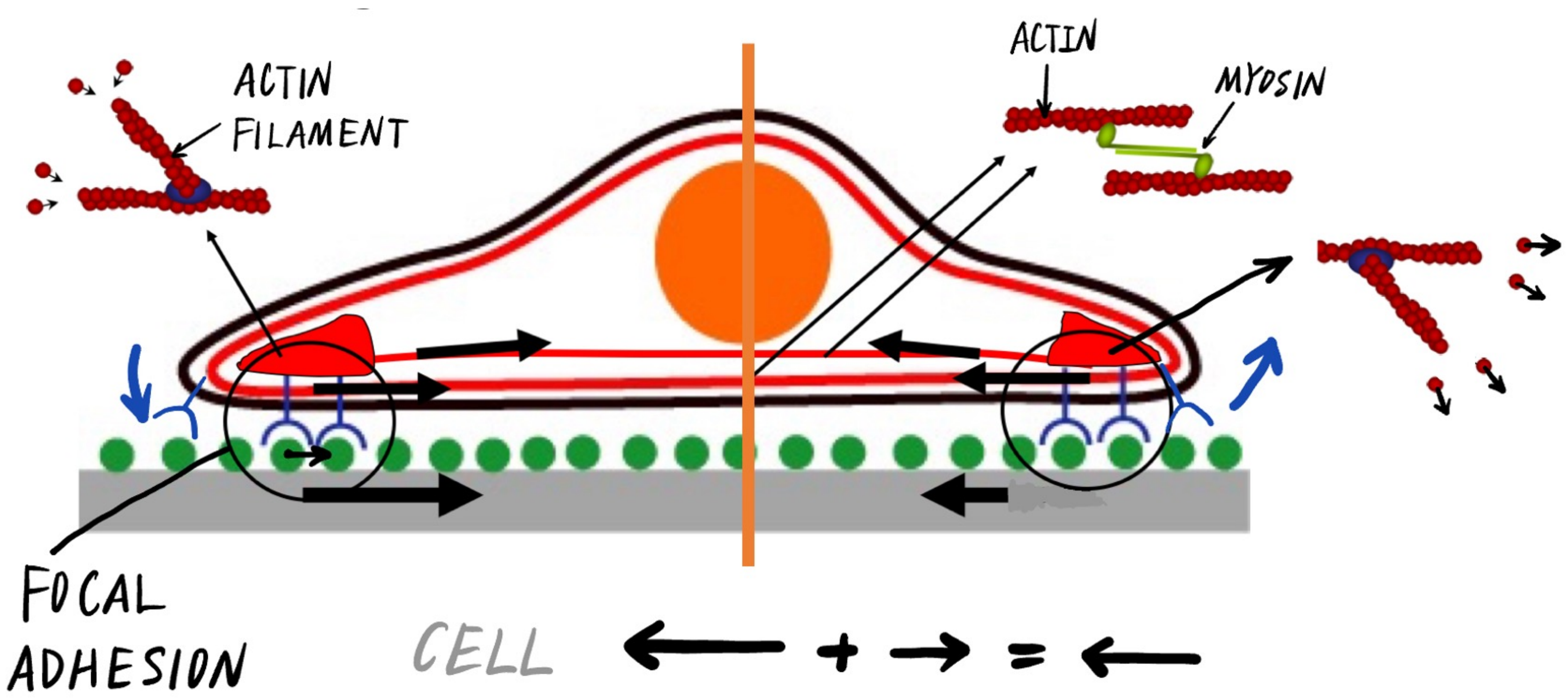
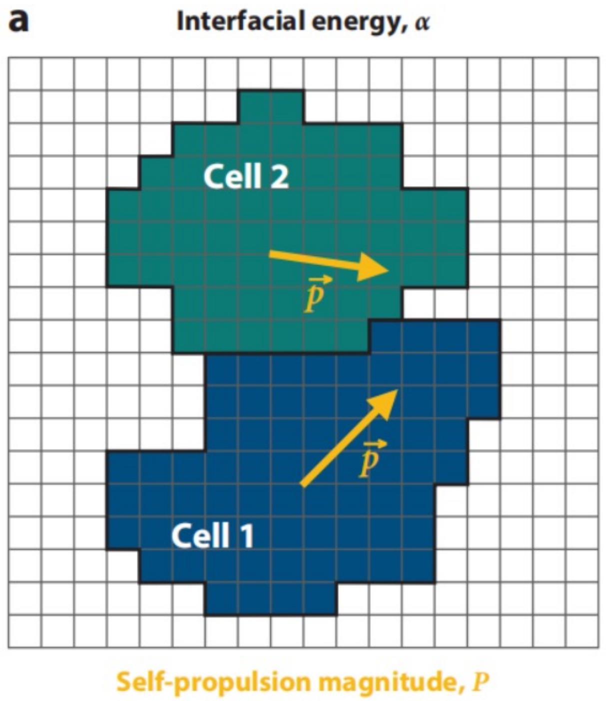
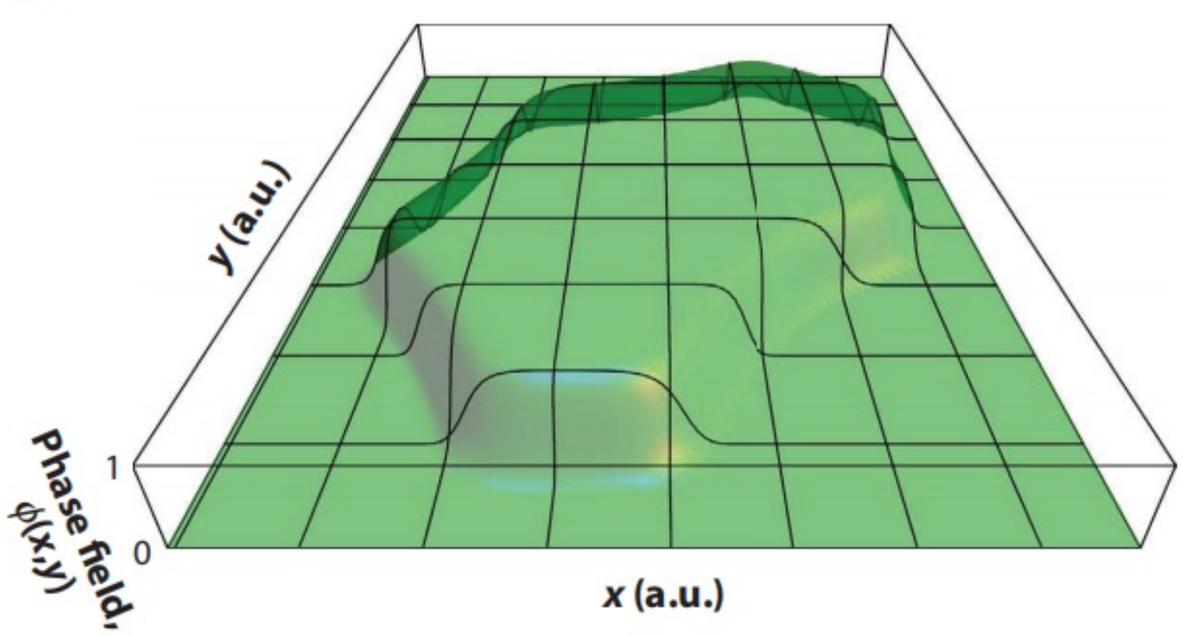


Image credict: https://www.thphys.uni-heidelberg.de/~biophys/

Physical models for cell migration: review





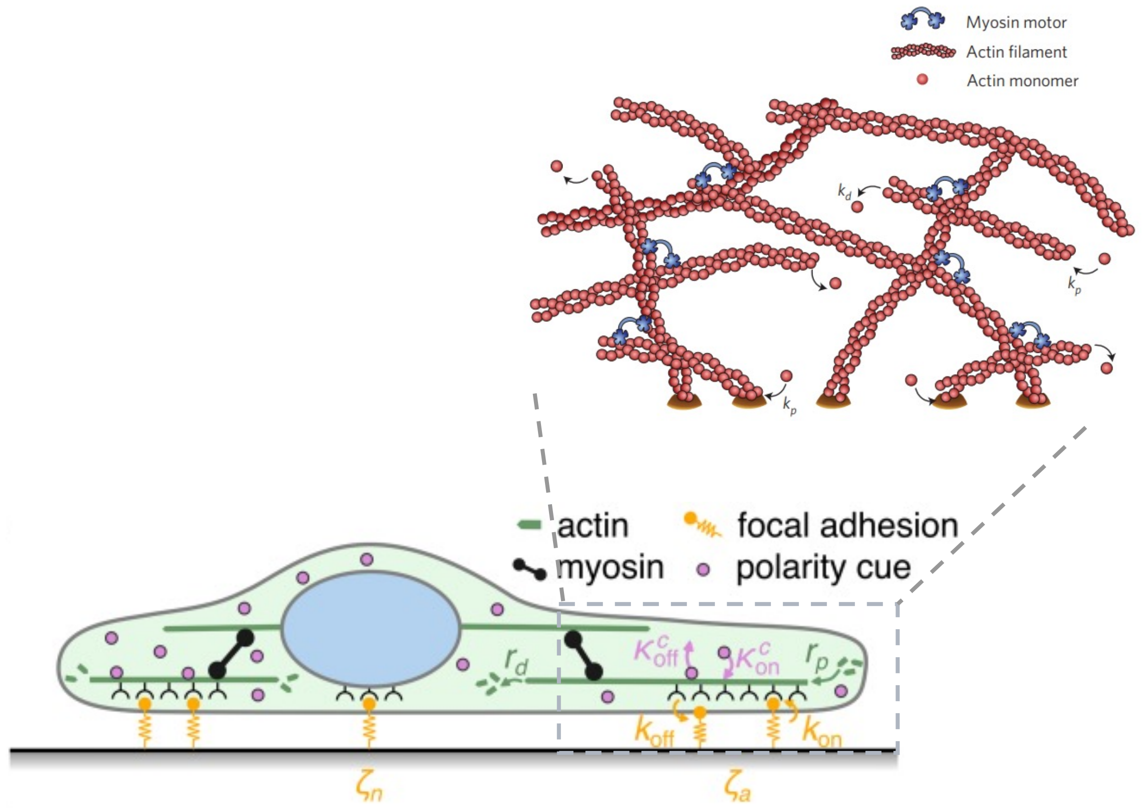
$$\mathcal{H} = \sum_{\langle i,j \rangle} J(\sigma_i, \sigma_j) + \lambda \sum_{\sigma=1}^{m-1} (A_\sigma - A_0)^2 - P \sum_{\sigma=1}^{m-1} \vec{R}_\sigma \cdot \vec{p}_\sigma .$$

$$\partial_t \phi_i + \vec{v}_i \cdot \vec{\nabla} \phi_i = -\frac{\delta \mathcal{F}}{\delta \phi_i}.$$

Alert and Trepat, Annual Review of Condensed Matter Physics, 2020

Physical models for cell migration: review

Active gel theory: including more mechanobiology mechanism



The constitutive relation for the stress associated with an active gel in the long-time limit is

$$\sigma_{ij} = \sigma^p_{ij} + \sigma^a_{ij} \tag{1}$$

where σ_{ij} is the total stress tensor, σ^p_{ij} is that of the passive system and σ^a_{ij} is the new active part, which is

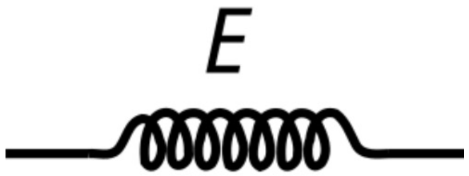
$$\sigma^a_{ij} = \zeta Q_{ij} + \bar{\zeta}\delta_{ij} \tag{2}$$

$$\frac{\partial \rho_f}{\partial t} + \partial_k J^f_k = k_p \rho_m - k_d \rho_f$$

$$\frac{\partial \rho_m}{\partial t} + \partial_k J^m_k = -k_p \rho_m + k_d \rho_f$$

Alert and Trepat, Annual Review of Condensed Matter Physics, 2020

An elastic spring



a purely elastic spring

$$F = kx$$

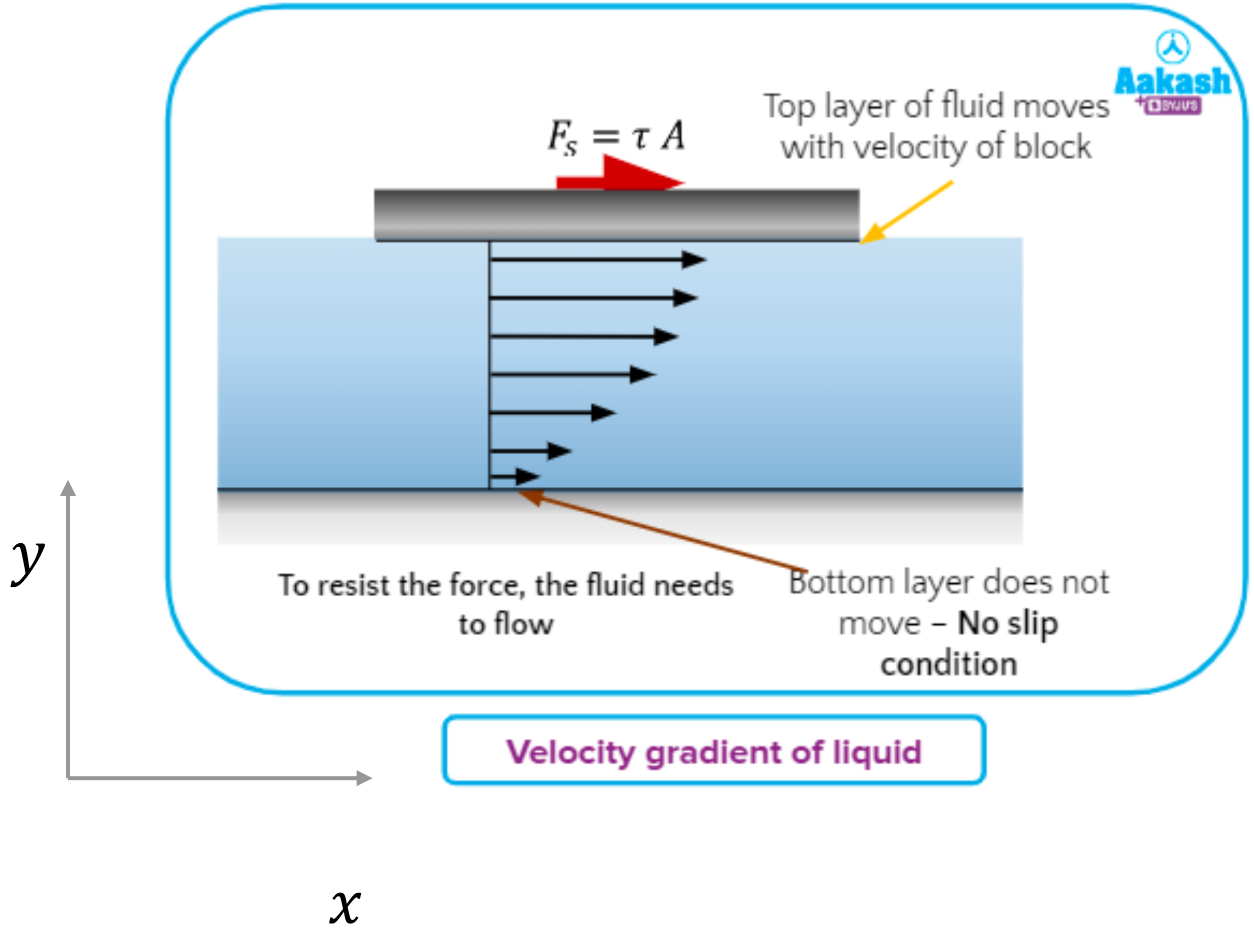
$$\sigma = E\varepsilon$$

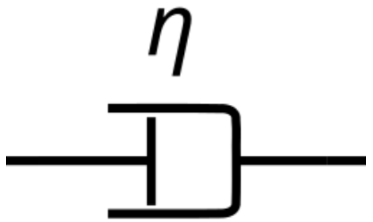
F: Force in units of [newton]
k: Spring constant in units of [force / length]
x: [Length]

σ: Stree in units of [newton / area]
E: Young's modulus in units of [newton / area]
ε: Strain (relative deformation)

Image credits: Wikipedia

A viscous fluid





a purely viscous fluid (damper)

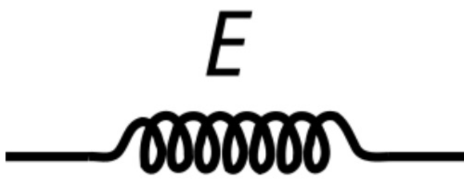
$$\frac{F}{A} = \mu \frac{\partial u}{\partial y}$$

$$\sigma = \eta \dot{\varepsilon}$$

σ: Stree in units of [newton / area]
η: Material viscocity
ε: Strain (relative deformation)

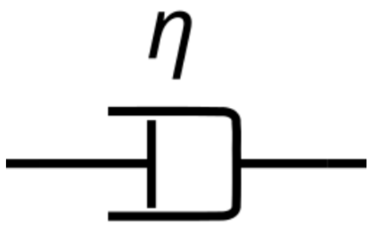
Image credits: https://www.aakash.ac.in/important-concepts/chemistry/coefficient-of-viscosity
Wikipedia

Maxwell model



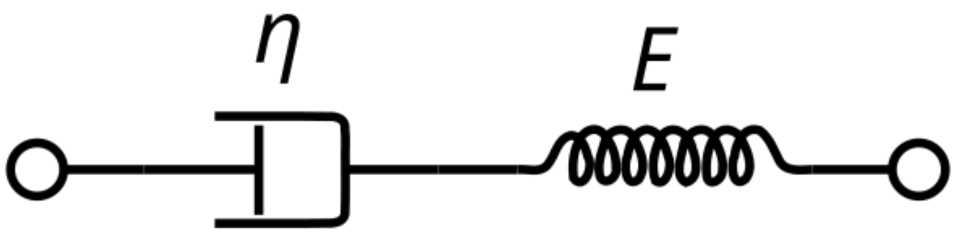
a purely elastic spring

$$\sigma = E\varepsilon$$



a damper

$$\sigma = \eta\dot{\varepsilon}$$



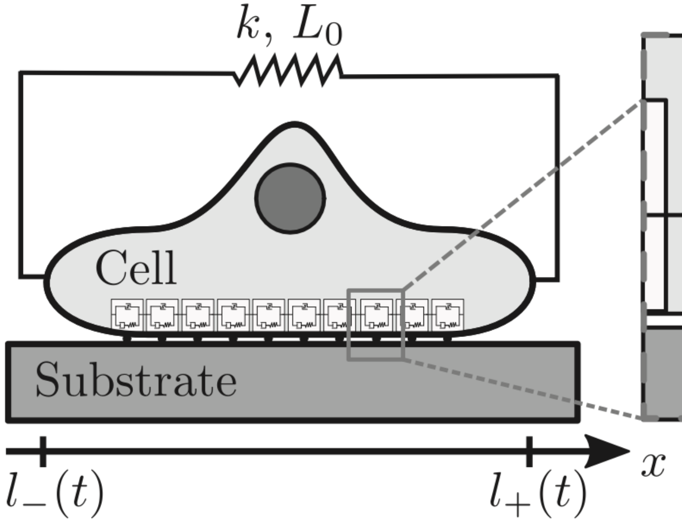
$$\sigma_{Total} = \sigma_{Spring} = \sigma_{Damper}$$

$$\varepsilon_{Total} = \varepsilon_{Spring} + \varepsilon_{Damper}$$

$$\frac{d\varepsilon_{total}}{dt} = \frac{d\varepsilon_D}{dt} + \frac{d\varepsilon_S}{dt} = \frac{\sigma}{\eta} + \frac{1}{E}\frac{d\sigma}{dt}$$

Image credits: Wikipedia

A Physical model for cell migration



$$\sigma(x+dx)-\sigma(x)=\xi v(x)dx$$

$$\boxed{\frac{\partial\sigma}{\partial x}=\xi v}$$

$$\frac{d\varepsilon_{total}}{dt}=\frac{d\varepsilon_D}{dt}+\frac{d\varepsilon_S}{dt}=\frac{\sigma}{\eta}+\frac{1}{E}\frac{d\sigma}{dt}$$

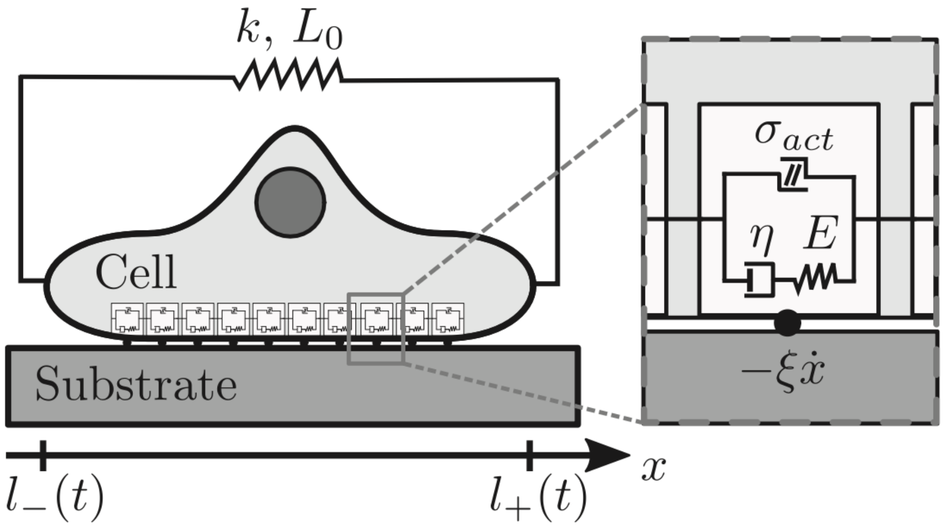
$$\frac{d\sigma(x,t)}{dt}=\frac{\partial\sigma}{\partial x}\frac{\partial x}{\partial t}+\frac{\partial\sigma}{\partial t}=v\frac{\partial\sigma}{\partial x}+\frac{\partial\sigma}{\partial t}$$

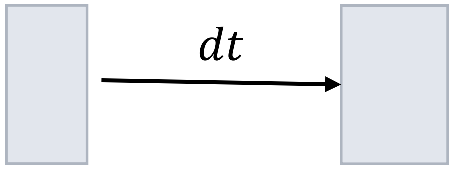
$$\boxed{\eta\frac{\partial\varepsilon}{\partial t}=[1+\frac{\eta}{E}\frac{\partial}{\partial t}+\tau v\frac{\partial}{\partial x}](\sigma-\sigma_{active})}$$

the constitutive relation

O. M. Drozdowski, et al., Phys. Rev. E 104, 024406 (2021)

A Physical model for cell migration





dx $\quad dx + \left(\frac{\partial v}{\partial x} dx\right) dt$

$$d\varepsilon = \frac{dx + \left(\frac{\partial v}{\partial x} dx\right) dt - dx}{dx} = \left(\frac{\partial v}{\partial x}\right) dt$$

$$\frac{\partial \varepsilon}{\partial t} = \frac{\partial v}{\partial x}$$

$$\boxed{\frac{\partial \sigma}{\partial x} = \xi v}$$

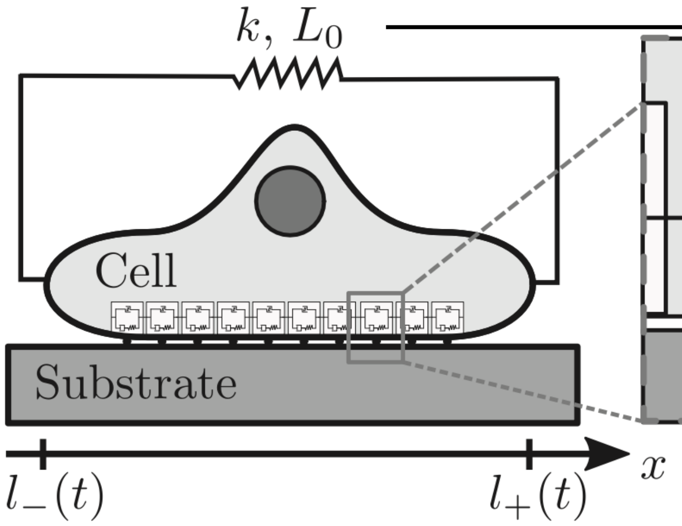
$$\boxed{\eta \frac{\partial \varepsilon}{\partial t} = [1 + \frac{\eta}{E}\frac{\partial}{\partial t} + \tau v \frac{\partial}{\partial x}](\sigma - \sigma_{active})}$$

$$\boxed{\frac{\eta}{\xi}\frac{\partial \sigma}{\partial x^2} = [1 + \frac{\eta}{E}\frac{\partial}{\partial t} + \tau v \frac{\partial}{\partial x}](\sigma - \sigma_{active})}$$

the constitutive relation

O. M. Drozdowski, et al., Phys. Rev. E 104, 024406 (2021)

A Physical model for cell migration



$$\sigma(l_\pm(t), t) = -k\,\frac{L(t) - L_0}{L_0}$$

$$\mathcal{L} = \sqrt{\eta/(\xi L_0^2)}$$

$$\mathcal{T} = (k\tau)/(\xi L_0^2) = (k\eta)/(\xi E L_0^2)$$

$$\boxed{\frac{\partial\sigma}{\partial x} = \xi v}$$

$$\mathcal{L}^2\partial_x^2\sigma - \mathcal{T}\partial_t\sigma - \mathcal{T}(\partial_x\sigma)^2 - \sigma = -\sigma_{\mathrm{act}},$$

$$\sigma(l_\pm(t), t) = -[L(t) - 1],$$

$$\dot{l}_\pm = \partial_x\sigma(l_\pm(t), t).$$

$$\boxed{\frac{\eta}{\xi}\frac{\partial\sigma}{\partial x^2} = [1 + \frac{\eta}{E}\frac{\partial}{\partial t} + \tau v\frac{\partial}{\partial x}]\,(\sigma - \sigma_{active})}$$

O. M. Drozdowski, et al., Phys. Rev. E 104, 024406 (2021)

Steady-state solutions

$$\mathcal{L}^2\partial_x^2\sigma - \mathcal{T}\partial_t\sigma - \mathcal{T}(\partial_x\sigma)^2 - \sigma = -\sigma_{\text{act}},$$
$$\sigma(l_\pm(t),t) = -[L(t)-1],$$
$$\dot{l}_\pm = \partial_x\sigma(l_\pm(t),t),$$

To simplify the boundary conditions:

$$u = (x - l_-)/L \qquad s(u,t) = \sigma(u,t) + (L(t)-1)$$

The steady-state solution:

$$\frac{\mathcal{L}^2}{L^2}\partial_u^2 s + \mathcal{T}\frac{V}{L}\partial_u s - \frac{\mathcal{T}}{L^2}(\partial_u s)^2 - s + (L-1) = -\sigma_{\text{act}},$$
$$s(u_\pm) = 0, \quad \partial_u s(u_\pm) = VL,$$

with $u_- = 0$ and $u_+ = 1$.

For V=0, the nonmotile solutions:

$$\hat{L} = 1 - \sigma_{\text{act}}.$$

V≠0, motile solutions:

$$y_1(u) = (L/\mathcal{L})s(u) \qquad y_2(u) = \partial_u s(u) - VL$$

$$\partial_u y_2 = +\frac{\mathcal{T}}{\mathcal{L}^2}(VL)y_2 + \frac{\mathcal{T}}{\mathcal{L}^2}(y_2)^2 + \frac{L}{\mathcal{L}}y_1 - \frac{L^2}{\mathcal{L}^2}(L-1) - \frac{L^2}{\mathcal{L}^2}\sigma_{\text{act}},$$
$$\partial_u y_1 = \frac{L}{\mathcal{L}}y_2 + \frac{L}{\mathcal{L}}VL.$$

$$V(y_1,y_2) = -\frac{\mathcal{T}}{\mathcal{L}^2}(VL)\frac{1}{2}(y_2)^2 - \frac{\mathcal{T}}{\mathcal{L}^2}\frac{1}{3}(y_2)^3 - \frac{L}{\mathcal{L}}y_1y_2 - \frac{L}{\mathcal{L}}(VL)y_1 + \frac{L^2}{\mathcal{L}^2}[(L-1)+\sigma_{\text{act}}]y_2$$

No steady state!

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Purely viscous case

$$\mathcal{L}^2\partial_x^2\sigma - \mathcal{T}\partial_t\sigma - \mathcal{T}(\partial_x\sigma)^2 - \sigma = -\sigma_{\text{act}},$$
$$\sigma(l_\pm(t),t) = -[L(t)-1],$$
$$\dot{l}_\pm = \partial_x\sigma(l_\pm(t),t),$$

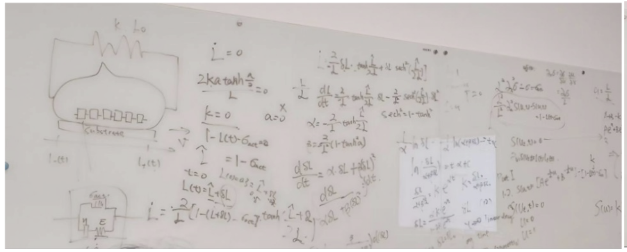
Purely viscous case:

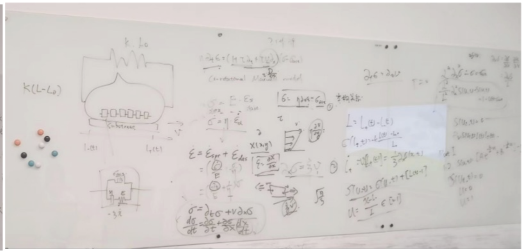
$$\mathcal{T} = 0$$

A simplification so that we can solve the equation analytically:

$$\frac{\mathcal{L}^2}{L^2}\partial_u^2 s(u,t) - s(u,t) = 1 - L(t) - \sigma_{\text{act}},$$
$$s(u_\pm,t) = 0,$$
$$\partial_u s(u_\pm,t) = L(t)\dot{l}_\pm(t).$$

After a few math:





We have:

$$s(u,t) = [\sigma_{\text{act}} + (L-1)]\left\{1 - \frac{\cosh\left(\frac{L}{\mathcal{L}}(u-1/2)\right)}{\cosh(L/2\mathcal{L})}\right\}$$

$$\dot{L} = \frac{2}{\mathcal{L}}(1 - L - \sigma_{\text{act}})\tanh(L/2\mathcal{L})$$

$$\delta L(t) = \frac{\alpha\,\delta L_0\,\exp(\alpha t)}{\alpha - \beta\,\delta L_0\,[\exp(\alpha t)-1]}$$

$$\alpha = -\frac{2}{\mathcal{L}}\tanh(\hat{L}/2\mathcal{L}), \quad \beta = -\frac{1}{\mathcal{L}^2}[1-\tanh^2(\hat{L}/2\mathcal{L})]$$

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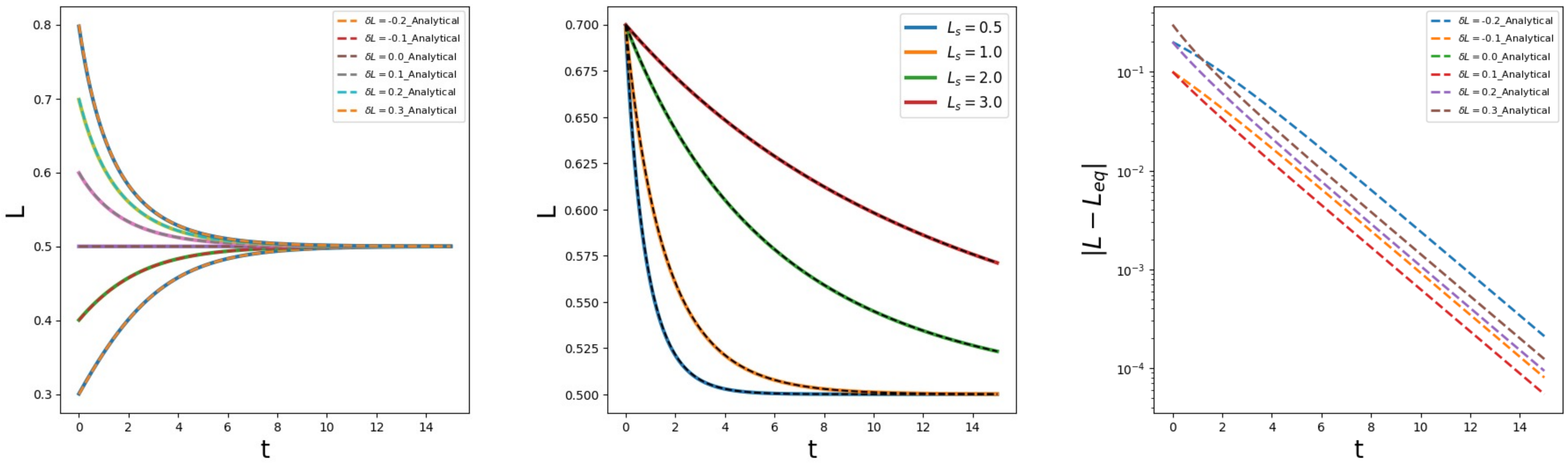
Numerical results

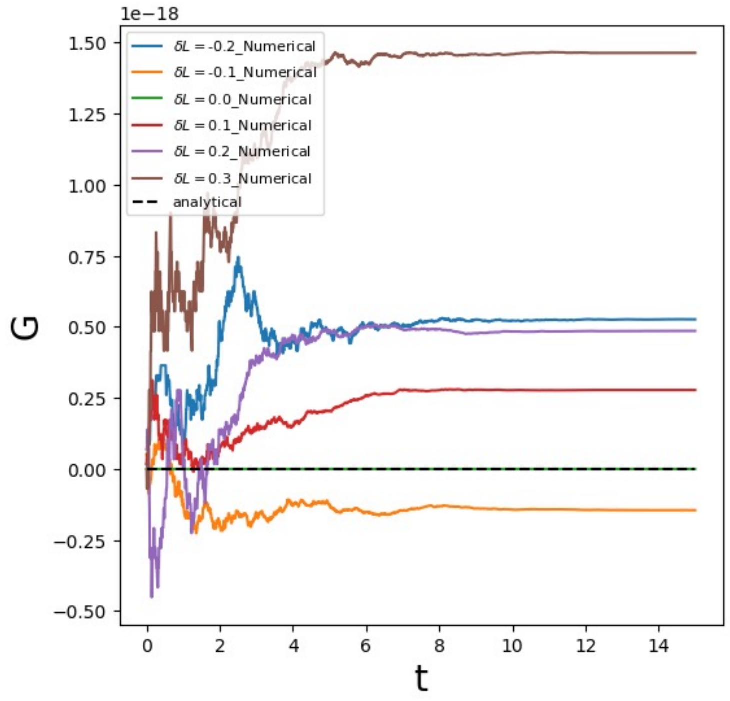


Length relaxes to steady state length

Larger L_s leads to slower decay

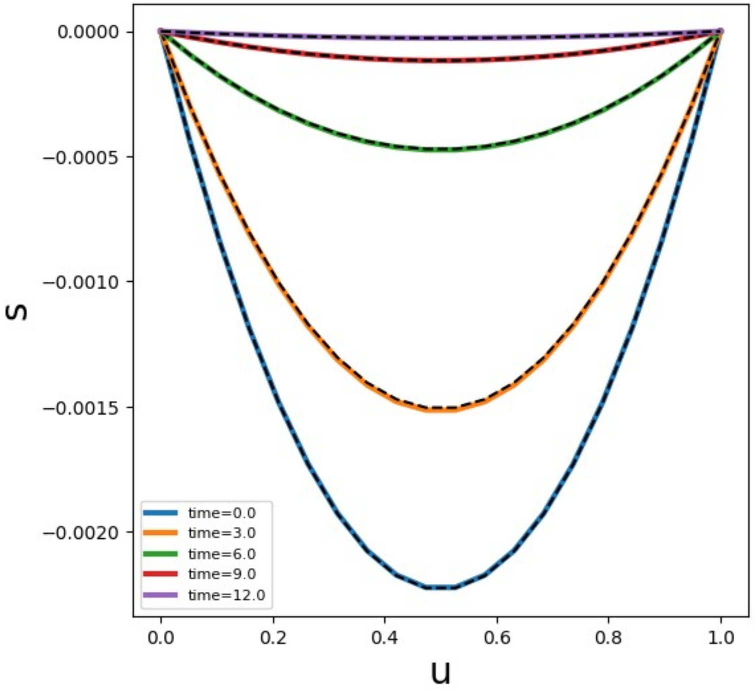
Long-time exponential relaxation

Numerical results

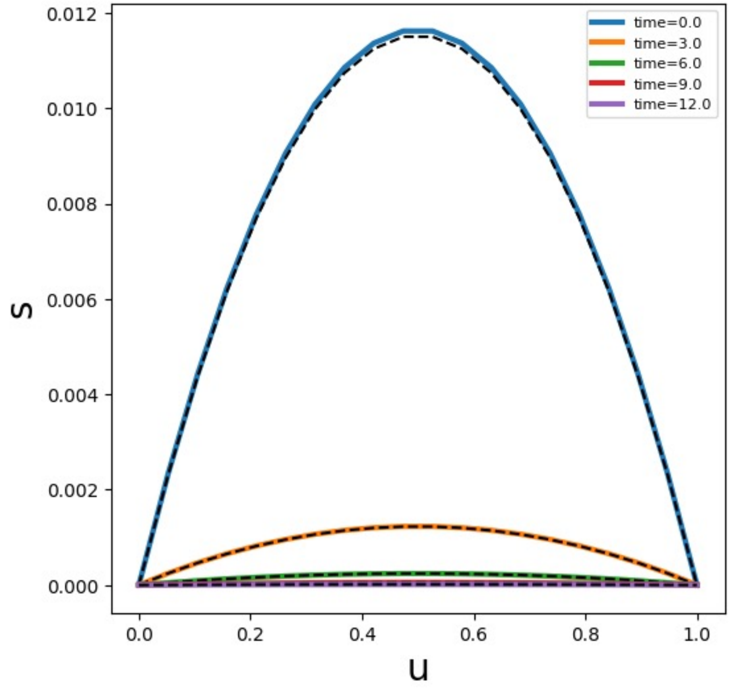


COM not moving

$\delta L = -0.2$



$\delta L = 0.2$



Adding polymerization

Actin polymerization on the left and right cell edge;
Triggered by activation of signaling proteins like
Rac1 or Cdc42

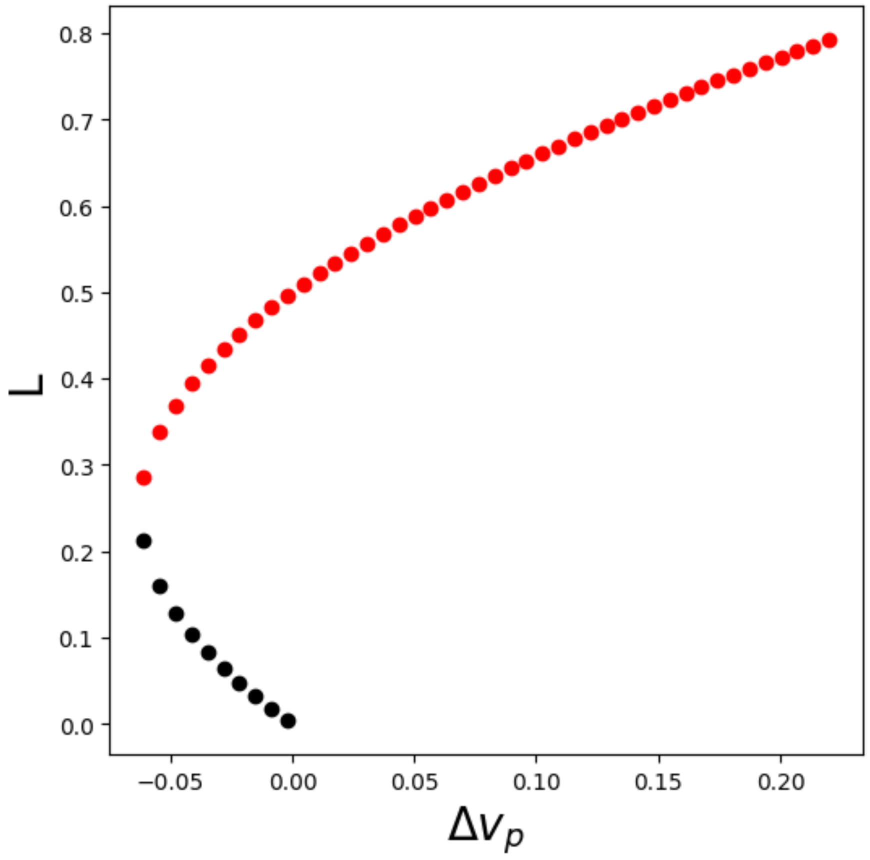
Increasing edge length due to edge velocity:

$$\dot{l}_{\pm} = \frac{1}{\xi}\partial_x \sigma(l_{\pm}(t), t) + v_p^{\pm}$$

$$\dot{L} = -\frac{1}{\mathcal{L}}[2\sigma_{\text{act}} + 2(L-1) \quad]\tanh(L/2\mathcal{L}) + \Delta v_p$$

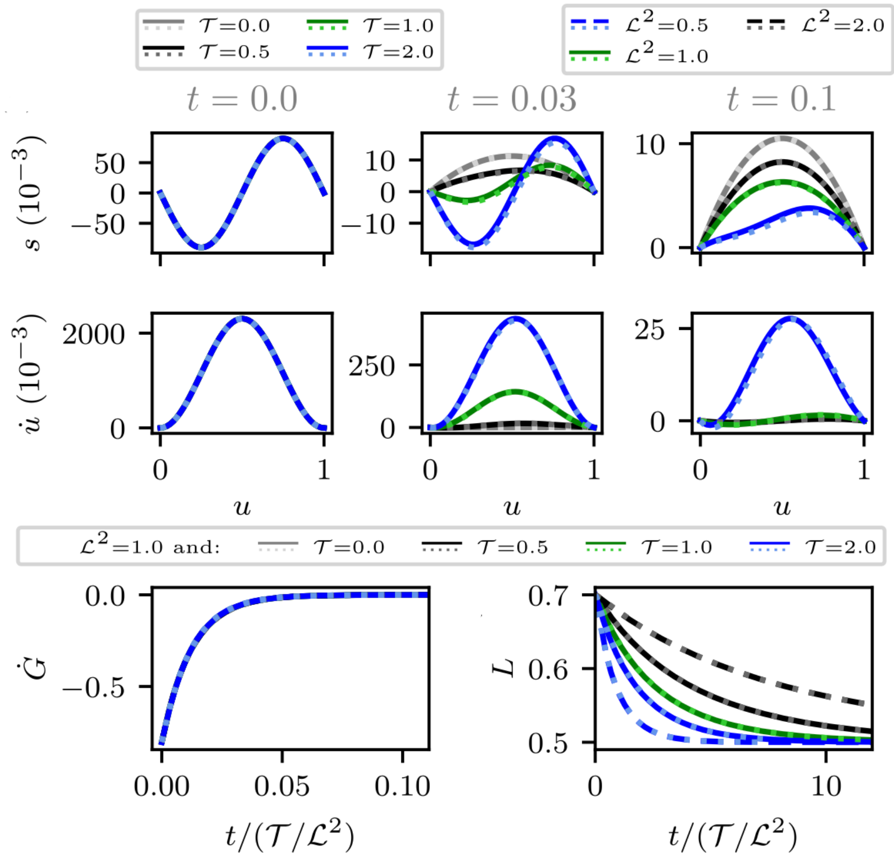
$$\dot{G} = \frac{v_p^+ + v_p^-}{2}$$

Steady state soultion

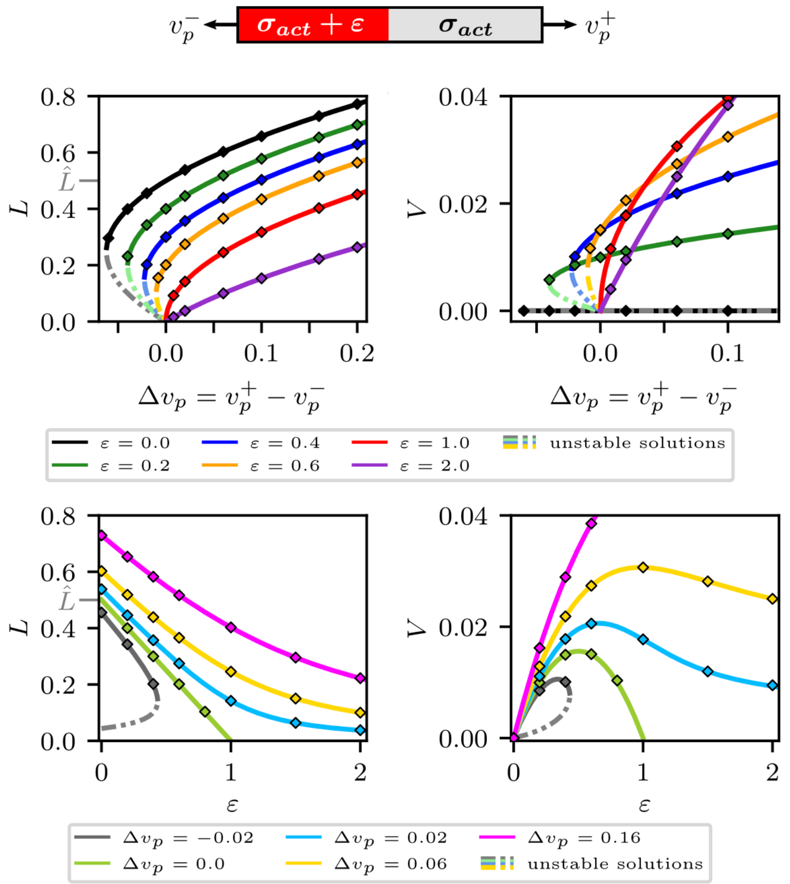


Complicated cases

Complex analytically, yet numerically feasible.



Viscoelastic case



symmetrically spreading cell
with optogenetic activation

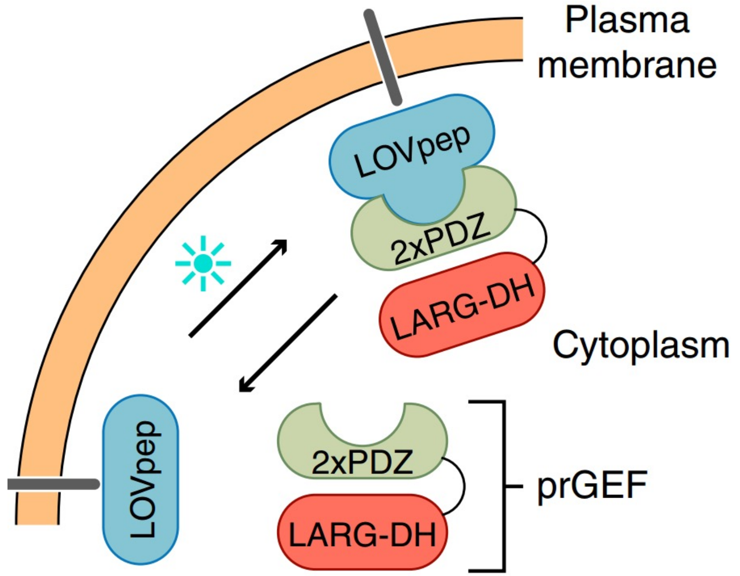
O. M. Drozdowski, et al., Phys. Rev. E 104, 024406 (2021)

Application

Rac1 → actin protrusions

RhoA ⇒ actomyosin contraction

Optogenetics



$$\sigma_{\rm act} \to \sigma_{\rm act} + \sigma_{\rm opt} \qquad \sigma_{\rm opt} = \varepsilon\, \Xi(x,t)$$

$$\mathcal{L}^2\partial_x^2\sigma - \mathcal{T}\partial_t\sigma - \mathcal{T}(\partial_x\sigma)^2 - \sigma = -\sigma_{\rm act}$$

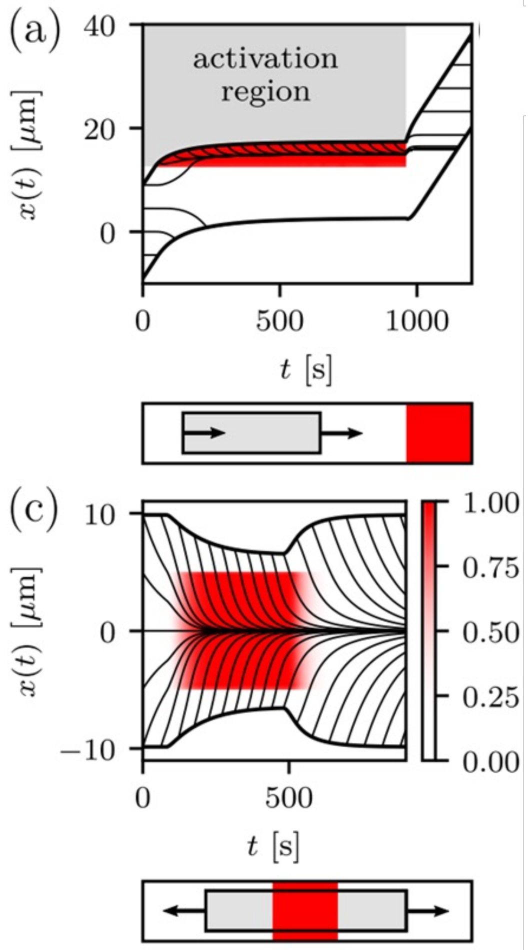
⇓

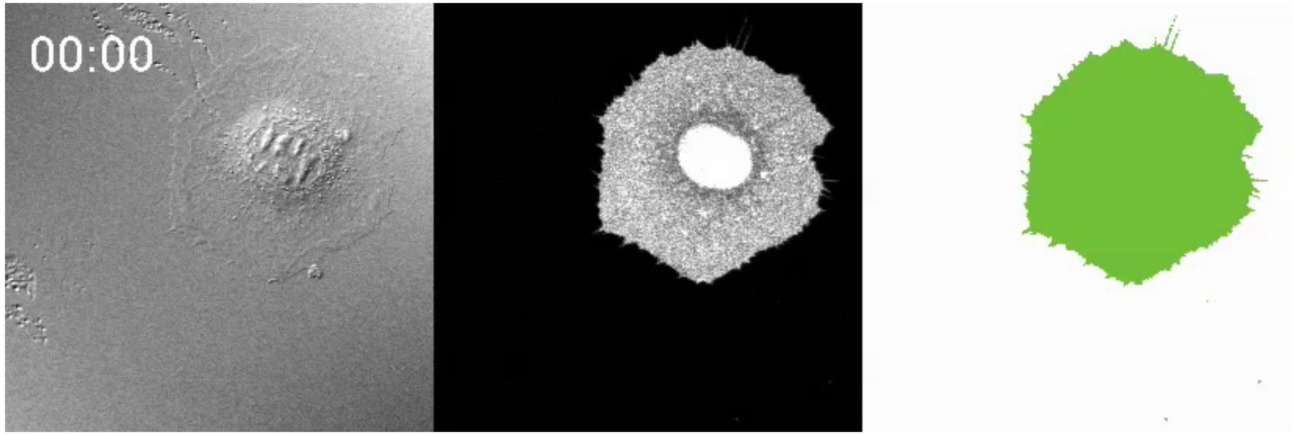
$$\mathcal{L}^2\partial_x^2\sigma - \mathcal{T}\partial_t\sigma - \mathcal{T}(\partial_x\sigma)^2 - \sigma = -\sigma_{\rm act} - \varepsilon\,\Xi - \varepsilon\mathcal{T}\partial_t\Xi - \varepsilon\mathcal{T}(\partial_x\sigma)(\partial_x\Xi)$$

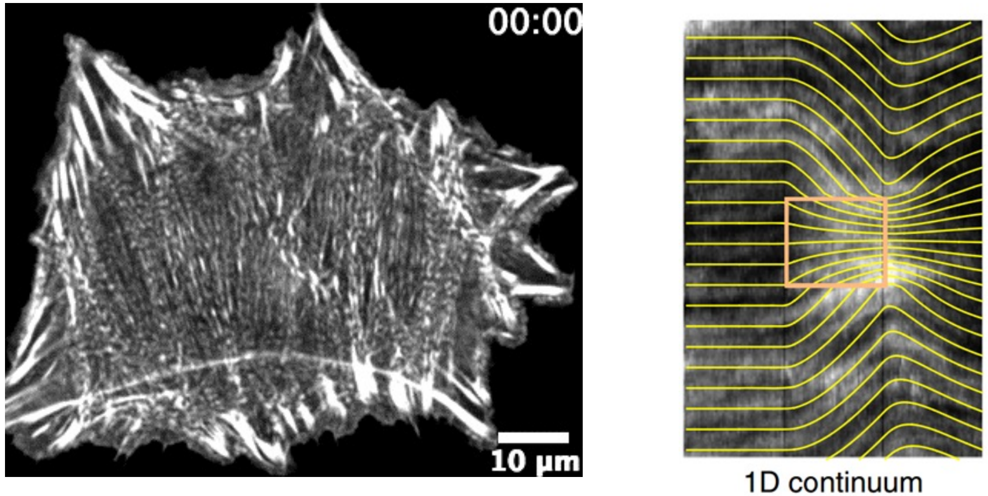
O. M. Drozdowski, et al., Phys. Rev. E 104, 024406 (2021)
P. W. Oakes, et al., Nat. Commun. 8, 15817 (2017).

Application

Y. I. Wu, et al., Nature 461, 104 (2009)







O. M. Drozdowski, et al., Phys. Rev. E 104, 024406 (2021)

P. W. Oakes, et al., Nat. Commun. 8, 15817 (2017).

Take home message

- Cell migration is essential in many biological processes, yet the underlying mechanism is not well understood,

- Active gel model provides a framework for understanding cell migration,

- Analytical methods can be applied to simpler cases, offering valuable insights. For more complex scenarios, numerical methods are essential to address intricate behaviors,

- All models are wrong, but active gel model is (sometimes) useful!

Thank you for your attention!