Modelling cell migration with active gel theory

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Introduction

A minimal model for cells migrating on a substrate has to account for the following:

- cells are an active material with active stress throughout
- the cytoskeleton can flow, so it is mainly viscous
- intracellular flows are balanced by substrate friction
- cells tend to keep a typical size/volume

Active gel theory provides a thermodynamically consistent framework to incorporate activity into continuum mechanics, where it can be described as an active stress contribution σ_{act}. Here, we want to consider an one-dimensional limit with the spatial dimension along the cells direction of motion. This model was introduced and investigated by Drozdowski et al. [1], which is the paper we want to follow here. It can be considered to be a reduced version of the model by Recho et al. [2], which also included a field for myosin concentration. Later Drozdowski et al. followed up on their optogenetics 2021 paper with the analysis of an active gel model including myosin concentration and non-linear diffusion [3].

Please make yourself familiar with the beginning of the Drozdowski 2021 paper (we do not need the later parts on optogenetics). In section IIA, the model is derived, where equation (1) gives the constitutive relation for the bulk, relating stress and strain. Here, we only consider the purely viscous case, such that it reduces to

$$\eta \partial_x v(u,t) = \sigma - \sigma_{\text{act}},$$

with effective viscosity η, velocity $v = \dot{x}$ of the intracellular flow and stress σ. Equation (2) describes the substrate friction, which allows the cell to transmit forces onto the substrate and is essential to convert intracellular forces into movement. Equation (4) states an elastic stress boundary condition (BC), which provides us with a reference length L_0 and accounts for the typical size. Equation (5) is a kinematic BC, which determines how the cell edges $l_\pm(t)$ move. It is assumed that they flow with the gel, i.e. $\dot{l}_\pm(t) = v(l_\pm(t))$.

Overall, the problem is defined as a bulk PDE (or, in the purely viscous case, as an ODE) with suitable BCs to close the problem. To reduce the effective number of parameters, like e.g. the viscosity η, one usually non-dimensionalizes all the physical quantities, here stress σ, position x and time t, and formulates a dimensionless problem with new parameters. The full boundary value problem (BVP) in dimensionless form is given in equation (6), where we consider, as stated above, the purely viscous case, i.e. $\mathcal{T} = 0$. To simplify the analysis, we map the spatial domain to the unit interval by changing into the internal coordinate $u = (x - l_-)/L$. Additionally, we introduce an auxiliary stress field $s(u,t) = \sigma(u,t) + L(t) - 1$, which then has homogeneous Dirichlet BCs $s(u_\pm) = 0$.

The final equations we want to analyse are

$$\frac{\mathcal{L}^2}{L^2}\partial_u^2 s(u,t) - s(u,t) = 1 - L(t) - \sigma_{\text{act}}, \tag{1}$$

$$s(u_\pm, t) = 0, \tag{2}$$

$$\partial_u s(u_\pm, t) = L(t)\dot{l}_\pm(t). \tag{3}$$

Therefore, the stress is describe by a linear, second order, inhomogeneous ODE in space with homogeneous Dirichlet BCs and an implicit time evolution due to the dependence on the length as a dynamic quantity. Here, we want to solve this problem analytically and numerically and reproduce the results from figure 2 in [1] together with equation (12).

Part I: Deriving an analytical solution via a second order approximation

As a first part, we want to derive an analytical solution for the auxiliary stress s and the cell length L. The following steps will guide you. Equations (10)-(12) in [1] provide the solutions and the corresponding explanations might help if you are stuck.

1. Find the general solution $s^{hom}(u,t)$ for the homogeneous part of equation (1), i.e. for RHS=0. You should have two unspecified prefactors.

2. Guess a particular solution $s^{par}(u,t)$ fulfilling equation (1), which is here quite easy, since the inhomogeneity is constant in space.

3. Evaluate the full solution $s(u,t) = s^{hom}(u,t) + s^{par}(u,t)$ at the boundaries $u_\pm$ and determine the prefactors, such that they fulfill the BCs (2).

4. Evaluate the derivative $\partial_u s(u,t)$ at the boundaries and determine the edge velocities $\dot{l}_\pm(t)$ via (3). With that, derive expressions for the change in the cell's length $\dot{L} = \dot{l}_+ - \dot{l}_-$ and the center position $\dot{G} = (\dot{l}_+ + \dot{l}_-)/2$.

5. The equation for $\dot{L}$ cannot be solved explicitly (cf. equation (11) in [1]). However, it only allows one steady state length $\hat{L}$, such that $\dot{L} = 0$.

Determine this steady state. To solve the equation in the vicinity of this steady state, we consider small perturbations $\delta L(t)$, such that $L(t) = \hat{L} + \delta L(t)$. Expand the equation up to second order in δL and define α and β as in [1].

6. The resulting expression is a nonlinear ODE (Bernoulli's equation) in δL, which has an analytical solution. To derive it by hand, you can use e.g. separation of variables ($\mathrm{d}(\delta L)$ and $\mathrm{d}t$). Subsequent partial fraction decomposition makes the integration much easier (or just use Mathematica). Considering $\delta L(t_0) \equiv \delta L_0$ for $t_0 = 0$, you should recover equation (12) in [1]. What kind of behavior do you expect from this result? How is the length evolution reflected in the stress profile?

Part II: Numerical integration via a BVP solver and explicit Euler stepping

In this second part, we want to solve the problem (1)-(3) numerically and compare it to our approximated solution from the first part. To solve a general BVP described by a PDE and suitable BCs, one typically needs a solver which can handle a discretization in space and time. However, here we deal with an ODE for the stress and only implicit time dependence through $L(t)$. Therefore, we can solve this problem with the BVP solver of the python package "scipy" (`https://docs.scipy.org/doc/scipy/reference/generated/scipy.integrate.solve_bvp.html`) and an explicit Euler stepping to update the changes in length (and position). If you want to use another solver, feel free to do so.

The following steps and the documentation of the BVP solver (link above) guide you to implement the necessary code in a jupyter notebook. If you want additional help, you start from the provided file *ExerciseHints.ipynb*.

1. We have two parameters in this problem, $\mathcal{L}$ and σ_{act}. Choose their values as in [1] and store them e.g. in a dictionary.

2. The documentation states in which form you have to provide the ODE and the BCs for the solver. You have to convert the second order ODE into a system of two first order ODEs. Implement a function $stress\_ODE$ returning the ODE and a function $stress\_BC$ returning the corresponding Dirichlet BCs.

3. Define the spatial domain as an array, on which the ODE will be solved.

4. We have to provide initial guesses for all variables in our ODE system. We know the trivial solution $s(u,t) = 0$ for $L = \hat{L}$. For L not to far away from $\hat{L}$, $s = 0$ will work.

At this point, you might wanna test if your solver converges for a given L and if the solution looks reasonable, e.g. check the behavior for L closer or

further away from $\hat{L}$. If everything looks fine, you can proceed as follows to implement the explicit Euler stepping

$$L(t_{n+1}) = L(t_n) + \dot{L}(t_n) \cdot \Delta t. \tag{4}$$

5. Choose initial values for L and G and store them each in a list. If you want to safe the stress profiles s as well, create another list. Define an initial and final time and your step size Δt.

6. Define a loop which iterates over time until the final time is reached. In this loop, you solve the BVP for the given length. From this solution, you can derive $\dot{l}_\pm$, with which you then can update L and G. Append all the desired solutions to your lists and update the current time. In the next iteration, the BVP should be solved with the updated length.

After your loop is complete, plot L and G as functions of time. You should see similar results as in figure 2 in [1].

Finally, implement the analytical solution for s and L derived in the previous section and check how well the approximation captures the full dynamics by changing initial conditions and/or parameters values. You can also check at which δL_0 the second order in our expansion in δL is actually necessary. Interpret the sign of s depending on the initial value of L with respect to $\hat{L}$.

Part III: Adding polymerization

Following section IV "Effect of Polymerization" in [1], we now extend the above model by adding edge polymerization. In motile cells, one typically observes an increased actin polymerization at the leading edge, while reduced or even depolymerization at the trailing edge. Due to the mechanical resistance of the cell membrane, this protrusion is partially converted into retrograde flow. In nonmotile yet spreading cells, both protrusive activity and retrograde flow are symmetric, occurring along the whole cell periphery. To complement our analysis by these important features, we now consider polymerization at the boundaries by introducing the constant polymerization velocities $v_p^\pm$ for the right and the left edge, respectively. This changes our kinematic BC (3) to

$$\partial_u s(u_\pm) = L\dot{l}_\pm - L v_p^\pm, \tag{5}$$

such that the polymerization offsets actin flow and edge movement.

1. How does this change the equations for $\dot{L}$ and $\dot{G}$? Under which condition does the cell persistently migrate?

2. What is the new steady state? Can you determine it analytically? If not, use numerical methods.

3. Try different values for $\Delta v_p = v_p^+ - v_p^-$ and plot it against $\hat{L}$ (cf. Figure 9(a) in [1]).

References

[1] Oliver M. Drozdowski, Falko Ziebert, and Ulrich S. Schwarz. Optogenetic control of intracellular flows and cell migration: A comprehensive mathematical analysis with a minimal active gel model. Physical Review E, 104(2):024406, August 2021. Publisher: American Physical Society.

[2] P. Recho, T. Putelat, and L. Truskinovsky. Contraction-Driven Cell Motility. Physical Review Letters, 111(10):108102, September 2013.

[3] Oliver M. Drozdowski, Falko Ziebert, and Ulrich S. Schwarz. Optogenetic control of migration of contractile cells predicted by an active gel model. Communications Physics, 6(1):1–12, June 2023. Publisher: Nature Publishing Group.