Active-gel theory for multicellular migration of polar cells in the extra-cellular matrix

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Abstract

We formulate an active-gel theory for multicellular migration in the extra-cellular matrix (ECM). The cells are modeled as an active, polar solvent, and the ECM as a viscoelastic solid. Our theory enables to analyze the dynamic reciprocity between the migrating cells and their environment in terms of distinct relative forces and alignment mechanisms. We analyze the linear stability of polar cells migrating homogeneously in the ECM. Our theory predicts that, as a consequence of cell–matrix alignment, contractile cells migrate homogeneously for small wave vectors, while sufficiently extensile cells migrate in domains. Homogeneous cell migration of both extensile and contractile cells may be unstable for larger wave vectors, due to active forces and the alignment of cells with their concentration gradient. These mechanisms are stabilized by cellular alignment to the migration flow and matrix stiffness. They are expected to be suppressed entirely for rigid matrices with elastic moduli of order 10 kPa. Our theory should be useful in analyzing multicellular migration and ECM patterning at the mesoscopic scale.

1. Introduction

Multicellular migration plays a key role during development, wound healing and metastasis [1–3]. A basic distinction can be made between solid-like and fluid-like migration, which differ in the strength and duration of cell–cell adhesions. Fluid-like migration is referred to as ‘multicellular streaming’ [4, 5] and is the main motivation for this paper. The exact migration mode depends on the properties of the cells and their environment, including polarization. Polarization is important for cell migration in both the single-cell and multicellular levels. Intuitively, cells with a well-defined direction migrate in this direction. The constant crosstalk between migrating cells and their environment is also gaining increasing attention as an essential factor for multicellular migration [5–8]. This is referred to as ‘dynamic reciprocity’ [7] or ‘mechanoreciprocity’ [8].

We focus on migration that takes place in the extra-cellular matrix (ECM), which consists mostly of collagen I. It was shown that anisotropic ECM organization with aligned collagen fibres promotes cancer-cell migration in collagen tracks [5, 9]. Cells are able to remodel the fibres and change their environment, either mechanically or chemically. For example, interactions between ECM fibers and fibroblasts tune ECM properties and can account for variations in matrix isotropy, density, and homogeneity found across different tissues [10].

While several mathematical models have been proposed for multicellular migration in the ECM in different contexts [11–16], a physical understanding of cell-ECM interaction at the mesoscopic scale and in three dimensions is still missing. Here, we propose to describe the ECM together with the migrating cells as...
an active, permeating, polar gel. Such systems were studied in the past in different contexts [17–23]. We rely on our recent work [23], which explored permeation instabilities in active polar gels. This theory was formulated as a two-fluid model, with a clear distinction between forces that act on the network and solvent separately and relative forces between them.

In this work, we formulate a solid–fluid model for cells in a viscoelastic solid and take into account cell division and strain-polarization alignment. We analyze the linear stability of a homogeneous flow of polarized cells. Instabilities infer transient and possibly long-lived, migrating cell collections. Our key findings are:

(a) Cell-matrix interactions can be classified within a thermodynamic framework, according to their characteristic spatial order, dynamics, activity, reversibility, and elasticity.
(b) Active stresses can destabilize soft matrices.
(c) Matrix stiffness stabilizes the ECM and suppresses alignment-driven instabilities.
(d) ECM stability for small wave vectors is determined by the active nematic stress; it is stable for contractile cells and unstable for sufficiently extensible cells.
(e) Alignment of polarization to concentration gradients can either stabilize or destabilize the ECM, while alignment to the migration current stabilizes it. The former can change the transient domain size by orders of magnitude.

The outline of the paper is as follows: in section 2, we derive our theory for multicellular migration in the ECM, in terms of an active, polar fluid permeating in a viscoelastic solid. Next, we highlight in section 3 the different matrix-cell interactions that arise naturally from our theory. In section 4 we derive the linearized equations that determine the linear stability of the system. The analysis is performed in the isotropic case and in the rigid-matrix limit in sections 5 and 6, respectively. We analyze the stability in the general case in section 7 and clarify the stabilizing or destabilizing role of cell-matrix alignment mechanisms. We conclude in section 8 by discussing possible extensions of our theory and how it relates to biologically-relevant scenarios.

2. Theory

We consider a two-component gel, composed of active, polar cells (c) and a viscoelastic matrix (m). The cells are considered to be close to the fully-polarized state, where the polarization field is given by the unit vector \( \mathbf{u} \). The matrix is modeled as a viscoelastic solid (Kelvin–Voigt model). Its deviation from the reference state is given by the displacement vector \( \mathbf{u} \). The matrix has a volume fraction \( \phi \), and the cells \( 1 - \phi \). The gel is assumed to be incompressible.

The free energy of the gel is considered as

\[
F = \int \mathrm{d}^3r \left[ k_B T a^{-3} (1 - \phi) \ln (1 - \phi) + \phi (1 - \phi) \left[ \chi_0 + \psi \right. \left. \mathbf{Tr} (Q \mathbf{e}) \right] + \kappa (\nabla \phi)^2 \right. \\
+ K \left. \left( \frac{1}{2} (\nabla \mathbf{p})^2 - l_p^{-2} \mathbf{p} \cdot \nabla \phi \right) - \frac{1}{2} \epsilon_0 \mathbf{p}^2 + \frac{\phi}{\phi_0} \left( G \mathbf{Tr} (\epsilon^2) + \frac{1}{2} Be^2 \right) \right] .
\] (1)

The first line is the Flory–Huggins free energy of a binary mixture in the limit of long polymer chains, where \( k_B T \) is the thermal energy and \( a \) is a microscopic length related to the cell size. The \( \chi_0 \) term accounts for short-range interactions, and \( \psi \) to an aligning interaction [see, e.g., 22, 24–26], that can be related to three-dimensional ‘contact guidance’ in biological contexts. It is written in terms of \( Q_{\alpha \beta} = p_{\alpha \beta} p_\beta - 1/3 \delta_{\alpha \beta} \) and linearized strain tensor \( \epsilon_{\alpha \beta} = (\partial_\alpha u_\beta + \partial_\beta u_\alpha) / 2 \). The tensor \( Q \) coincides with the nematic order parameter close to the fully polarized state. The \( \psi \) coupling results in a shear elastic stress in the reference state, which aligns the matrix parallel or normal to the polarization axis (\( \psi < 0 \) or \( \psi > 0 \), respectively). The reference state \( \epsilon = 0 \) is considered as the stress-free state for \( \psi = 0 \). The \( \kappa \) term accounts for the interfacial tension that suppresses large concentration gradients.

The first part of the second line accounts for variations of the polarization field from the homogeneously polarized state [27, 28], where \( K \) is the Frank constant in the one-constant approximation.

It is generally a function of the cellular volume fraction, but this dependence does not play any role in our linear analysis and is disregarded hereafter. The second term accounts for alignment with respect to concentration gradients in terms of the parameter \( l_p \) that has units of length. This describes, for example, cellular alignment at cluster interfaces, similarly to anchoring at droplet interfaces [29]. We refer hereafter to
this mechanism as ‘concentration alignment’. Note that this term can equivalently be written in terms of the divergence $\phi \nabla \cdot p$ (see, e.g., references [23, 28]), using integration by parts. The $h_1$ term is a Lagrange multiplier to ensure that $\dot{p}^2 = 1$.

The final contribution is the elastic free energy. For simplicity, we restrict ourselves to linear elasticity, where $G$ and $B$ are the shear and bulk moduli for $\phi = \phi_0$, respectively. We decompose the strain into the scalar $\epsilon = \epsilon_{\alpha\alpha}$ and the traceless tensor, $\tilde{\epsilon}_{\alpha\beta} = \epsilon_{\alpha\beta} - \epsilon/3\delta_{\alpha\beta}$.

We describe the dynamics of the concentration, polarization, and displacement fields within a thermodynamic framework. The matrix moves with a velocity $v^m = \partial u/\partial t$ and the cells with a velocity $v^c$, corresponding to a center-of-mass (COM) velocity, $v = \phi v^m + (1 - \phi) v^c$, and a relative current, $j = \phi (1 - \phi) (v^m - v^c)$. We assume the same specific mass for both components.

Living cells are active. They are constantly driven out of equilibrium by the input of an energy $\Delta \mu$ that corresponds, for example, to the chemical potential difference between ATP and its hydrolysis products [17, 30]. In particular, the cells divide and die, while the mass of the matrix is conserved, i.e.,

$$\partial_t \phi + \nabla \cdot (\phi v^m) = 0, \quad \partial_t (1 - \phi) + \nabla \cdot [(1 - \phi) v^c] = (1 - \phi) k \approx k_\psi (\phi - \phi_0).$$

The cellular growth rate, $k_1$ is generally a function of the pressure [31, 32]. We linearize the right-hand side around the homeostatic pressure or, equivalently, around the volume fraction $\phi_0$, where cell division and death balance each other, in terms of the rate $k_\psi > 0$.

In equation (2), cell division and death are related only to the cell component. A more detailed description would include a third solvent component that exchanges mass with the cells as part of these processes. Coarse-graining over the solvent neglects cell-solvent friction. This is reasonable because the cells are much more viscous than the solvent, making cell-matrix friction more important. This description also neglects active matrix deposition and degradation by the cells, which can be especially important for fibroblasts. The study of this effect is reserved for future work. Note that the incompressibility condition is affected by the active growth rate and is given by $\nabla \cdot v = k_\psi (\phi - \phi_0)$.

For the polarization, we derive in appendix A the following constitutive equation:

$$(\partial_t + v^c \cdot \nabla) p = h_1 p + p \cdot \nabla v^c + D_p \nabla^2 p + D_p l_p^{-1} \nabla \phi + \lambda j + \phi (1 - \phi) \bar{\psi} \epsilon \cdot p.$$  

The first term on the right-hand side is $h_1 = h_{||}/\gamma_1$, where $\gamma_1$ is the rotational viscosity. $h_1$ is a Lagrange multiplier to ensure that $\dot{p}^2 = 1$.

The next term accounts for the shear alignment of the cells as if they were solid rods (shear-alignment parameter of $-1$) and $D_p = K/\gamma_1$ is the angular diffusion constant. The final three terms in equation (3) describe polarization alignment due to cell-matrix interaction. The first describes alignment to concentration gradients, while $\lambda$ is the permeation-alignment constant [23] that describes how the cells align to their migration current in the matrix. Finally, $\bar{\psi}$ describes cell-matrix alignment due to the $\psi$ term in equation (1) and possible active mechanisms. We focus on passive alignment, for which $\bar{\psi} = -2\psi/\gamma_1$ (see appendix A). These alignment mechanisms are illustrated in figure 1.

Equations (2) and (3) describe the dynamics of the cellular concentration and orientation. They depend on the cell velocity and matrix displacement, which can be determined from force balance equations. We
make use of a solid–fluid model, similar to the fluid–fluid model of reference [23]. Force-balance equations are written separately for the matrix and cells as

\[ f^m - \phi \nabla \delta P = f^{rel}, \quad f^c - (1 - \phi) \nabla \delta P = -f^{rel}, \]

where \( f^m \) and \( f^c \) are the forces acting on the matrix and cells, respectively, \( \delta P \) is a pressure difference that enforces global incompressibility, and \( f^{rel} \) is the relative force between the two components. The forces in equation (4) are derived in appendix A from phenomenological constitutive equations that relate forces and fluxes in the entropy production rate of the system. These equations include leading-order terms in a gradient expansion and satisfy polar symmetry.

The forces acting on each of the components are

\[ f^m_{\alpha} = \partial_\beta \left[ \sigma^\text{rel}_{\alpha \beta} + \frac{\phi}{\phi_0} \left( 2G\tau \partial_\gamma \epsilon_{\alpha \beta} + B\tau \epsilon \delta_{\alpha \beta} \right) \right] - \phi \partial_\beta \tilde{\mu}, \]

\[ f^c_{\alpha} = \partial_\beta \left[ -h_{\beta \gamma} p_{\gamma} + (1 - \phi) \left( \zeta \delta_{\alpha \beta} + \zeta Q_{\alpha \beta} \right) \right] - h_{\beta \gamma} \partial_\beta p_{\gamma}, \]

where the summation convention was used. The terms in the square brackets constitute the deviatoric stress, while the final terms of the two equations originate from the Ericksen stress that generalizes the osmotic pressure for anisotropic systems. As they originate from the surface of each unit volume of the gel, they include derivatives. Here, \( \sigma^\text{rel}_{\alpha \beta} = \delta F/\delta \epsilon_{\alpha \beta} \) is the elastic stress and the next two terms describe the viscoelastic shear and compressional stresses, in terms of the shear and compressional retardation times, \( \tau \) and \( \tau' \), respectively (Kelvin–Voigt model). The last term is the osmotic pressure gradient, with the relative chemical potential \( \tilde{\mu} = \delta F/\delta \phi \).

In equation (6), the first term is the stress due to shear alignment, where \( h = -\delta F/\delta p \) is the orientational field. Next is the active cellular stress that consists of an isotropic contribution \( \sim \zeta \) and a traceless contribution \( \sim \zeta \), proportional to the nematic tensor, \( Q \). The stresses \( \zeta \) and \( \zeta \) are considered as constants, neglecting the possible dependence on matrix properties [33]. The last term in equation (6) originates in the Ericksen stress and vanishes to linear order around a polarized state. The cellular viscous dissipation has been neglected; it is negligible compared to the relative friction force on length scales larger than the matrix mesh size, which are relevant to our hydrodynamic framework.

The cell-matrix relative force is given by

\[ f^{rel} = \frac{1}{\gamma} j - \phi (1 - \phi) \left( \lambda h + \nu p + \nu' \epsilon \cdot p \right). \]

The first term is the friction force, where \( \gamma \) is the mobility. The term \( \sim \lambda \) is the reactive force associated with permeation alignment [23]. The last two terms are active forces that are the main contributors to cell motility in the polar case. The \( \nu' \) term can also be related to anisotropic friction due to matrix strain, as is explained in appendix B.

### 3. Description of cell-matrix interaction

Our framework is convenient for analyzing the crosstalk between cells and their environment and classifying its underlying mechanisms. First, the matrix and cells influence each other indirectly, because they are constrained by global force balance (sum of the two lines in equation (4)). At the same time, each component undergoes convection according to its own velocity, which is also determined from the force-balance equations. More interestingly, we can identify and classify mechanisms of direct interaction between the cells and the matrix. These include the friction force and active relative forces, as well as permeation alignment, concentration alignment, and strain-polarization alignment. The three alignment mechanisms are illustrated in figure 1.

The interaction terms require a combination of matrix and cells and vanish in pure phases (\( \phi = 0, 1 \)). They are especially important in the case of multicellular streaming and small matrix mesh size, where cells can flow and mix with the matrix on a mesoscopic scale. This mixing yields bulk interaction terms and relative forces that exist between the cells and matrix within each volume element, rather than surface terms that exist only between clearly separated phases.

The thermodynamic framework allows to classify these mechanisms according to five categories (and see table 1); dynamics—requires cell migration (dynamic) or not (static). Reversibility—produces entropy (dissipative) or not (reactive). Activity—requires ATP hydrolysis (active) or not (passive). Symmetry—requires polar order, nematic order, or no order (isotropic). Elasticity—requires elasticity or not. As is evident from table 1, each mechanism is unique according to this classification. This demonstrates
that the different terms of our theory have distinguishable properties and can be inferred from sufficient experimental data.

4. Linear stability analysis

The system has a homogeneous steady state at the homeostatic concentration $\phi = \phi_0$ and is in a fully polarized state that we set as $p^0 = \hat{x}$. The active relative force drives a homogeneous steady-state current $j^0 = j, p^0$ (see appendix B). This effect is purely active and polar. As the concentration and polarization are homogeneous, the active cellular stress and matrix alignment stress are constant, and the matrix displacement is determined by the boundary conditions. We consider the case where the matrix is in its equilibrium configuration, meaning that the stress on the boundaries matches the active stress. The steady-state strain is then given by $\epsilon = -\psi \phi_0 (1 - \phi_0) Q/2G$. As cells are mostly known to align parallel to matrix segments, the sign $\psi < 0$ is chosen.

We analyze the linear stability of the steady state with respect to perturbations with a growth rate $s$ and wave vector $q$, of the form $x = x_0 + x_1 \exp(st + iq \cdot r)$, where $x = (\phi, p, u)$. For simplicity, we focus on wave vectors perpendicular to the steady-state polarization, $q_x = 0$, assuming that heterogeneity is most notable normal to the direction of migration. As the matrix is elastic, its concentration changes only via strain, according to $\phi^1/\phi_0 = -\epsilon^1$. This relates the normal components of the displacement, $u^1$ and $u^2$, to $\phi^1$. In addition, $\phi^1$ is affected only by the divergence of the polarization, $iq \cdot p = p^1_d$. This is reasonable because, around the polarized state and to linear order, this is the only scalar obtained from $p^1$. These arguments reduce the dimensions of the linear stability analysis to three, corresponding to $\phi^1, p^1_d$, and $u^1$.

We find $u^1$ as a function of the concentration and polarization and obtain the following linearized equations (see appendix B):

\begin{align}
\dot{\phi}^1 &= - \left[ \dot{k}_0 + (D_0 + \tilde{L}_p s) q^2 \right]\phi^1 - \left[ j_0 + j_u u + p \left( \tilde{L}_p^{-1} - \lambda \right) \left( \tilde{L}_1 s - \phi^2 \right) \right] p^1_d, \\
\dot{p}^1_d &= - \left[ (\bar{\psi} - \gamma \phi) u + p \left( 1 + \lambda \left( \tilde{L}_p^{-1} \right) \tilde{L}_1 \right) \phi^2 \right] p^1_d + \left[ \left( D_0 + \tilde{L}_p s \right) - \tilde{L}_p^{-1} \tilde{L}_1 \right] q^2 \phi^1.
\end{align}

The parameters that appear in equations (8) and (9) are listed in table 2. In equation (8), the first term describes the concentration relaxation due to active cell division and death. The terms quadratic in $q$ account for osmotic diffusion, where $D_0$ is the effective diffusion coefficient in the presence of elasticity, permeation alignment and active cellular stress (see appendix B). $l_i = \sqrt{(1 - \phi_0) / \gamma (4Gr/3 + Br)} / \phi_0$ is a screening length that arises from the interplay between transient matrix viscosity and cell-matrix friction.

The second part of equation (8) accounts for the relative force in the direction of $p^1$. The first two terms relate to the active relative current. $j_0$ is the steady-state current, while $j_u = \gamma (2\lambda \phi_0 (1 - \phi_0) \psi - \nu^1)$ describes a correction due to the network strain. The term $u_p$ is a function of the dimensionless rate $\tau s$ and is related to the network displacement in the $x$-direction, due to strain-polarization coupling (see section 6 and appendix B). The relative force quadratic in $q$ originates from concentration-polarization alignment, with $l_1 = \sqrt{\gamma(1 - \phi_0) / \gamma \phi_0}$ being a screening length due to the interplay between rotational viscosity and friction.

In equation (9), the first term describes a $q^0$ polarization rate resulting from network-strain coupling (see section 7.1). The term quadratic in $q$ is the effective angular diffusion constant. Alignment to concentration gradients and flow may render it negative. The second line of equation (9) describes the two mechanisms of polarization rotation due to concentration gradients; one is dynamic (permeation alignment $\sim \lambda$) and the second is static (concentration alignment $\sim \tilde{L}_p^{-1}$). The two mechanisms either add up or compete with each other.

This linear set of equation can be written as $M \cdot x = 0$, where $x = (\phi^1, p^1_d)^T$. The dispersion relation $s(q)$ is found by solving $\det M = 0$. The system is stable if $Re s < 0$ for all the eigenvalues of the linear

| Mechanism                          | Dynamics  | Reversibility | Activity | Symmetry | Elasticity |
|------------------------------------|-----------|---------------|----------|----------|------------|
| Friction                           | Dynamic   | Dissipative   | Passive  | Isotropic| None       |
| Active relative force              | Dynamic   | Reactive      | Active   | Polar    | None/elastic|
| Permeation alignment               | Dynamic   | Reactive      | Passive  | Polar    | None       |
| Concentration alignment            | Static    | Dissipative   | Passive  | Polar    | None       |
| Strain-polarization alignment      | Static    | Dissipative   | Passive/active | Nematic  | Elastic |

**Table 1.** Classification of cell-matrix interaction terms.
system. The stability analysis is involved, due to the large number of mechanisms that take place. Therefore, we focus first on two limiting cases of isotropic cells and a rigid matrix. Then, we analyze separately the different alignment mechanisms and their effect on stability.

5. Isotropic case: active stresses may destabilize a soft ECM

Cells are often isotropic. In this case, the polar and nematic phases cannot form and the polarization terms drop out of the equations. The dispersion relation is then found from equation (8) as

\[ s = -\left(\kappa_0 + D_0 q^2\right) / \left(1 + l_0 q^2\right). \]

This situation was explored by Murray et al. [11, 12] in their works on mesenchymal morphogenesis, which similarly describe cell migration as fluid flow in a viscoelastic solid.

The stability is determined by the sign of the osmotic diffusion constant. It is given in the isotropic case by

\[ D_0 = D_2 \left(1 + l_0 q^2\right) + \frac{1 - \phi_0}{\phi_0} \left(\frac{4}{3} G + B\right) - \gamma \phi_0 \zeta = D_1 + D_2 \left(l_0 q^2\right)^2. \]

Here \( D_2 = \gamma \phi_0 \left(1 - \phi_0\right) \chi^{-1} \) is the co-operative diffusion constant due to mixing, given in terms of the inverse osmotic susceptibility \( \chi^{-1} = -\frac{\partial \mu}{\partial \phi} \). \( l_0 = \sqrt{2 K \chi} \) is the correlation length due to the interfacial tension, i.e., the width of interfaces in the simple binary-mixture case [29]. The \( D_2 l_0 q^2 \) term ensures stability for large wave vectors.

The second term accounts for elasticity that drives diffusion in order to relax stresses and network strain [34]. The last term in equation (10) results from the active solvent stress and can make the diffusion coefficient negative. This is the case for a contractile stress, \( \zeta > 0 \). The network is then further contracted in cell-rich regions, where it should extend. The \( \zeta \) term is equivalent to an active relative force proportional to \( \partial_\phi \phi \) (see appendix B), which shifts the osmotic susceptibility and can result in a negative diffusion constant. This is the mechanism described by Murray et al. [11, 12]. Our theory in the isotropic case differs from their work mainly because of the global incompressibility that relates the osmotic diffusion constant to elasticity.

Note that the cooperative osmotic diffusion constant is different from the cell self-diffusion constant. The latter describes correlations in the single-cell velocity, while the former describes correlations in the relative current that depends also on concentration. Alternatively, these diffusion constants are different because the random motion of cells does not necessarily result in concentration changes.

The question is whether the osmotic diffusion constant can become negative for reasonable values of the physical parameters of the cells in the ECM. We examine the different contributions to \( D_1 \) for \( q = 0 \). They are all proportional to the mobility, multiplied by different energy-density scales: \( \chi^{-1} \), \( G \) and \( B \), and the active stress \( \zeta \). We estimate (see appendix D) \( \chi^{-1} \) and the active stresses to be of order 0.1 kPa. The elastic moduli of the ECM, on the other hand, can range between 0.1 and 10 kPa [35, 36]. This means that \( D_1 < 0 \) is possible only for soft matrices with moduli of the order of 0.1 kPa. Note that in the polar case, even for \( D_1 < 0 \), other mechanisms can stabilize the system (see section 7).

6. Rigid case: matrix stiffness always stabilizes the ECM, while strain-polarization alignment may destabilize it

The osmotic diffusion coefficient depends on the elastic moduli. For large moduli, it scales as \( \sim \gamma G, \gamma B \) and suppresses concentration gradients. This infers stability in the isotropic case, but not necessarily in the polar case. We verify whether alignment mechanisms can destabilize the system in this limit or not.

In the rigid limit, one solution to the dispersion relation is simply \( s = -D_0 l_0^{-1} \) (see appendix C). This corresponds to stable concentration fluctuations with a decay rate that is comparable with the largest of \( \tau \) and \( \tau^\ast \). The other solutions solve

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| Symbol | Description | Symbol | Description |
|--------|-------------|--------|-------------|
| \( D_0 \) | Effective osmotic diffusion constant | \( l_0 \) | Interfacial correlation length |
| \( k_0 \) | Effective cellular division rate | \( D_\tau \) | Angular diffusion constant |
| \( l_0 \) | Screening length due to matrix viscosity | \( l_1 \) | Screening length due to rotational viscosity |
| \( \psi \) | Strain-polarization alignment rate | \( u_\nu \) | Measure of polarization-induced network \( x \)-displacement |
| \( j_0 \) | Steady-state relative current | \( j_\nu \) | \( j_\nu \) is the strain-induced relative current |
| \( l_p \) | Concentration-alignment coupling (length) | \( \lambda \) | Permeation-alignment coupling (inverse length) |

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Table 2. Parameters of the theory. Estimations of the parameters are found in appendix D.
\[
0 = (\tau s)^2 + \left[ 1 + \tau \left( \lambda \phi_0 + D_p q^2 - \frac{1}{2} \phi_0 (1 - \phi_0)^2 \frac{\psi}{G} \right) \right] \tau s + \tau \left( \lambda \phi_0 + D_p q^2 + \psi u_p(0) \right) \tag{11}
\]

The system is unstable if either the constant term or the linear coefficient of the quadratic equation is negative.

We examine the signs of the different contributions in equation (11). The \(\lambda \phi_0\) term is expected to be positive. The steady-state current \(j_0 < 0\) for cells that move in the direction of their polarization, and \(\lambda < 0\) for cells that align with their direction of motion. The angular diffusion term \(D_p q^2\) is also positive. As we consider passive alignment with \(\bar{\psi} = -2\psi/\gamma_1\), the last term is positive as well. All together, this yields a positive linear coefficient.

The remaining term is \(\psi u_p(0)\) in the constant term, where \(u_p(0)\) describes network displacement in the \(x\)-direction due to polarization changes. It is purely active and is given by (see appendix B)

\[
u_p(0) = \frac{1}{2} \phi_0 (1 - \phi_0) \frac{(1 - \phi_0) \zeta + \gamma_1 \lambda \phi_0}{G}.
\]

These terms are active components of the shear stress. The first stems from the active solvent nematic stress and the latter from the convective polarization stress (shear alignment) in the presence of permeation-alignment and an active current. In the rigid limit of large \(G\), \(u_p(0)\) is negligible. This means that the constant term is positive as well, and the system is stable.

The strain-polarization coupling can still have an effect in the rigid limit, as long as \(\psi/G\) is of finite magnitude. This is possible, for example, for nematic elastomers, where \(\psi/G\) can be related to a typical angle between segments, while \(G\) is related to the number of crosslinks [24]. As this ratio is at most of order unity within linear elasticity, we use hereafter the value \(\phi_0 (1 - \phi) \psi \approx -0.1 G\). According to equation (12), \(u_p(0) > 0\), unless the cells are sufficiently extensile (\(\zeta < 0\)). While active cellular stresses are partially contractile (\(\zeta > 0\)) due to the stresses in the cytoskeleton, they can still be overall extensile, as a result of anisotropic cell division [32] and intercellular interactions [37]. For reasonable values of the active stress and migration velocity (see appendix D), \(u_p(0)\) can become negative only for sufficiently small values of the permeation-alignment coupling \(|\lambda| < 2 \times 10^{-2}/\mu\text{m} \). Furthermore, in order for the constant term in equation (11) to become negative, the permeation alignment should be even smaller \(|\lambda| < 2 \times 10^{-3}/\mu\text{m}\). In this case, the instability occurs for small wave vectors up until it is stabilized by angular diffusion.

The ECM, therefore, is expected to be stable in the rigid limit, unless three conditions are fulfilled: (a) cells are sufficiently extensile; (b) the strain-polarization coupling is of the same order of magnitude as the matrix stiffness; (c) the permeation-alignment parameter is small in absolute value. Note that the third alignment mechanism, concentration alignment, is negligible in this limit, because concentration gradients are suppressed by the large osmotic diffusion coefficient.

We estimate the relaxation time in the stable case. The retardation time for collagen gels that mimic the ECM are of order of minutes [38]. The polarization rates that appear in equation (11) are of order of \(h^{-1}\) (see appendix D). This allows to expand equation (11) to find \(s \approx -1/\tau\) and \(s \approx - (\lambda \phi_0 + D_p q^2 + \psi u_p(0))\). Together with the pure concentration mode, this means that two modes decay on the scale of minutes, and a third mode that is related to the polarization on the scale of hours.

### 7. Analysis in the general case

We analyze the stability in the general case and focus on the stability-instability crossover with zero frequency, \(s = 0\), which is adequate for our hydrodynamic theory. This analysis is independent of the retardation times, which enter the theory via terms linear in \(s\). As any rheological model of a viscoelastic solid reduces to an elastic solid for \(s = 0\), this analysis is universal and holds beyond the Kelvin–Voigt model.

The determinant of the linear system in equations (8) and (9) is then given by a quadratic equation, \(s^2 + 2B(q)s + C(q) = 0\). The instability threshold is defined by setting \(C = 0\). Explicitly, this condition is given by

\[
\frac{P}{D_2 D_p} \left( \bar{\psi} - \lambda \phi_0 \right) u_p(0) + ax + bx^2 + x^3 = 0,
\]

where \(x = P/q^2\). The system is unstable when the left-hand side is negative. The coefficients are given by
\[
\begin{align*}
    a &= \frac{\ell_p^2 k_0}{D_p} \left[ 1 + \lambda \left( \lambda - 1 \right) \ell_p + \frac{D_p}{\ell_p} \frac{\bar{\psi} u_p(0) + \lambda j_0}{k_0} - \left( 1 + \lambda^2 \ell_p^2 \right) j_0 + \left( j_0 + \lambda \ell_p^2 \bar{\psi} \right) u_p(0) \right], \\
    b &= \frac{\ell_p^2}{D_p} \left( \bar{\psi} u_p(0) + \lambda j_0 \right) + \frac{D_1 - \ell_p^2 D_p}{D_2}, \quad (14)
\end{align*}
\]

Here we have defined \( D_2 = D_1 + D_3 q^2 - \lambda_\psi \ell_p D_p \). \( D_1 \) is given by the \( q^0 \) terms in equation (10), with slight modifications due to the strain-polarization coupling (see appendix B). Note that the \( x^3 \) interfacial-tension term stabilizes the system for large wave vectors.

### 7.1. Strain-polarization coupling stabilizes (destabilizes) contractile (extensile) cells in the ECM for small wave vectors

The stability for small wave vectors is determined by the sign of the constant term in equation (13) \( \sim k_0 \left( \bar{\psi} - \lambda j_0 \right) u_p(0) \). This term is active. It occurs because both the concentration and polarization are not pure hydrodynamic modes and have a finite relaxation rate for \( q = 0 \). The concentration, which is a conserved quantity in passive systems, has a finite relaxation rate due to cell division. The polarization, which is usually a soft mode, is coupled to the strain and has a finite relaxation/growth rate due to active shear stresses that polarization rotation imposes on the network. We emphasize that this term vanishes in the absence of cell division.

The question is whether this constant term stabilizes the ECM or destabilizes it. As was shown above, cells that align with matrix segments yield \( \bar{\psi} > 0 \). Contractile cells have \( u_p(0) > 0 \), while sufficiently extensile cells have \( u_p(0) < 0 \). The remaining term to examine is the strain-induced relative current, \( j_0 = \gamma \left( 2 \lambda \phi_0 \left( 1 - \phi_0 \right) \psi - \nu' \right) \). The first term is positive for parallel cell-network alignment (\( \psi < 0 \)) and cells that align with their direction of motion (\( \lambda < 0 \)). The \( \nu' \) term is expected to be negative, similarly to \( \nu \), such that the cells flow in their direction of polarization. This can also be attributed to a strain-dependent friction coefficient (see appendix B). This yields \( j_0 > 0 \).

Overall, the constant term has the same sign as \( u_p(0) \). This means that the net effect of cell division and several alignment mechanisms depends mostly on the sign of the active stress. For contractile cells and weakly extensile cells, the combined effects facilitate a homogeneous, steady flow. For sufficiently extensile cells, an instability can occur, during which large domains of different concentrations and polarizations form. A similar version of this instability was described in reference [22] for active, uniaxial, elastomeric gels.

The mechanism behind this instability is nematic in nature. It can be understood heuristically by considering a fluctuation in the orientation of active nematic cells (figure 2). As the cells rotate, the matrix mesh deforms elastically in order to balance the cellular active stress. Extensile cells deform the mesh in a way that aligns it parallel with the cells. This drives the rotation of additional cells, because of the aligning interaction. Such a positive feedback infers an instability. Contractile cells, on the other hand, deform the mesh in a way that aligns it perpendicularly to the cells. This drives alignment in the normal direction and relaxes the fluctuation.

The scaling of the domain size in the unstable case depends on other system parameters. In the simple case where \( a > 0 \), the most unstable mode is \( q = 0 \) and system-size domains form for sufficiently large systems. For a negligible permeation-alignment coupling (\( \lambda = 0 \)), the critical system size is \( L_c = l_p / \sqrt{-\phi_0 (1 - \phi_0) \psi / G} \), where \( l_p = 2 \pi \sqrt{\ell_p / \ell_0} \) is the active length. A similar scaling appears in the more general analysis below (see section 7.4), as well as other active flow instabilities in nematic cells [39]. Reasonable values of the physical parameters (see appendix D) yield \( L_c \) of the order of 100 \( \mu \text{m} \). The growth rate is found from the \( q = 0 \) limit of equation (9). It can be approximated as \( \phi_0 \left( 1 - \phi_0 \right) \psi \sqrt{\ell_p / G \ell_0} \). Our estimates (see appendix D) yield a growth time of approximately 100 h. It is shorter for extensile active stresses that are larger than 0.1 kPa or more negative values of \( \phi \left( 1 - \phi \right) \psi / G < -0.1 \). The latter limit infers strains of order 1 and a quantitative treatment of it would require a framework of nonlinear elasticity.

Extensile cells can induce an instability also via the term \( \bar{\psi} u_p(0) D_1 / D_p \) in a. This requires large \( D_1 / D_p \) values and was described as part of the rigid-limit analysis in section 6. Below, we focus on the contractile case.

### 7.2. Concentration alignment can stabilize or destabilize the ECM

We now analyze equation (13) for arbitrary \( q \) values. The system is unstable when the left-hand side is negative. As \( x > 0 \), this requires either \( a < 0 \) or \( b < 0 \). Reviewing equation (14), we find that the only possible source of instability, aside from \( D_1 < 0 \) that was discussed in section 5, is concentration alignment.

Concentration alignment can destabilize the system via three mechanisms. The first mechanism is the term \( \lambda (\lambda - 1) \ell_p^2 \) in \( a \) that originates from the effective angular diffusion coefficient, \( \left[ 1 + \lambda (\lambda - 1) \ell_p^2 \right] D_p \). The permeation-alignment parameter is negative (\( \lambda < 0 \)) for cells that align with...
their migration velocity (see figure 1). For sufficiently negative \( l_p^{-1} \), where the cells align towards higher cellular concentrations, the angular diffusion coefficient becomes negative. While this is a passive mechanism, it has an effect only in the active case where \( k_p > 0 \). Otherwise, it is compensated by osmotic diffusion.

The second mechanism is the term \( \sim l_p^{-1} (\lambda - l_p^{-1}) \) in \( b \). This is a known passive instability mechanism, where the concentration-alignment coupling favors gradients in concentration and polarization \([28, 40, 41]\) over a homogeneous state. It depends on \( l_p^{-2} \) and not on the sign of \( l_p \).

The third mechanism is described by the last terms in \( a \) in equation (14). The \( j_0 \) term is responsible for the active instability reported in reference \([23]\). Consider a concentration fluctuation. The sign of \( l_p \) determines whether cells orient into or out of cell-rich regions \( (l_p < 0 \text{ or } l_p > 0) \), respectively, and see figure 1). Cells with \( l_p < 0 \) actively flow in the direction of their polarization, resulting in an instability.

The \( l_p > 0 \) case may also become unstable due to the strain-induced current, \( j_0 > 0 \). For sufficiently large \( j_0 \), cells would move in the \( pz \) plane oppositely to how they re-orient. However, for reasonable physical values (see appendix D), the \( j_0 \) term is negligible compared with the \( j_0 \) term. Overall, \( l_p < 0 \) is expected to be destabilizing, while \( l_p > 0 \) is expected to be stabilizing, except for when \( D_p E_l l_p^{-2} > D_1 \).

### 7.3. Stability diagrams

So far we have identified destabilizing terms. We now precise the instability condition. Equation (13) is a cubic equation with positive zeroth-order and cubic coefficients. For it to become negative, it must have a minimum point for some \( x_0 = (q_0 l_0)^2 > 0 \) that has a negative value, as is illustrated in figure 4(a).

Equating \( C'(q_0) = 0 \) yields \( x_0 = -b/3 \pm \sqrt{(b/3)^2 - a/3} \), where we further require its value to be negative, i.e., \( C(q_0) < 0 \).

These conditions enable to determine the stability of the system. We focus on soft matrices, such that an instability is possible, and substitute reasonable physical values for cells in the ECM. An important variable to take into account is the mobility \( \gamma \) that appears in most of the terms in equations (13) and (14). It is related to the matrix architecture and is expected to scale as the second power of the typical matrix mesh size \( \gamma \sim \xi^2 \). Namely, the active alignment mechanism \( \sim j_0/l_p \) in the \( a \) term of equation (14) is more important for smaller \( \xi \) values. As \( \xi \) becomes larger, its contribution becomes negligible with respect to osmotic diffusion and permeation alignment.

Our results are presented in figure 3 using stability diagrams in the \( (\lambda l_0, l_0/l_p) \) parameter space. We define \( D_1 = \gamma G K l_0^2 \) and draw three different diagrams for three values of the dimensionless \( \tilde{G} \). Each diagram illustrates stable (white) and unstable (colored) regions for two different mesh sizes, \( \xi/l_0 = 1, 5 \).

Figures 3(a) and (b) show that the system is generally unstable for a negative osmotic diffusion constant. The system may still be stable for sufficiently large \( l_p^{-1} \) and negative \( \lambda \) values. This is thanks to the stabilizing couplings to the active relative current and the large effective angular diffusion coefficient. The system is harder to stabilize for more negative \( \tilde{G} \) values and larger \( \xi \) values, which yield a more negative osmotic diffusion constant. The region in the top right corner of figure 3(b), which is marked with an asterisk sign, is unstable due to the passive concentration-alignment mechanism that occurs for \( D_p E_l l_p^{-2} > D_1 \). This region remains unstable for \( \tilde{G} < 0.3 \). Figure 3(c) demonstrates that the system is relatively stable for \( \tilde{G} > 0 \). The system is more susceptible for instabilities for \( \xi = l_0 \), where the stabilizing osmotic diffusion coefficient is smaller. The instability is the active concentration-alignment instability of section 7.2. Note that it occurs for small \( \lambda \) values in absolute values. For more negative \( \lambda \) values, the permeation-alignment mechanism stabilizes the system.

### 7.4. Critical wave vector

As the system is stable for both vanishing and large wave vectors, all the aforementioned instabilities occur at finite wave vectors. At the critical system parameters, there is only one marginally stable, critical wave
Figure 3. Stability diagrams for $\xi = l_\phi$ (blue) and $\xi = 5l_\phi$ (light orange) and different osmotic diffusion constants $\sim \tilde{G}$. Colored regions are unstable. The values $D_p = 2.52 k_\phi$, $\bar{\psi} = 0.25k_\phi$, $j_0 = -10l_\phi k_\phi$, and $j_0 = (10l_\phi - 0.25\lambda^C)k_\phi$ are used, in accordance with the estimates of appendix D. The asterisk sign in figure. (b) Marks the region where the passive concentration-alignment instability takes place. The other regions correspond to active instabilities.

Figure 4. (a) $C(q)$ in arbitrary units. The system is unstable for $C < 0$. The wave vector $q_c$ is found as a negative, minimal point, while the critical wave vector $q_c$ is a degenerate root. (b) Critical wave vector as a function of $l_p$ in the case $a > 0$ for $\tilde{G} = -1$. The result in the isotropic case ($l_p = 0$) is marked by a dashed line. (c) Critical wave vector as a function of $l_p$ in the case $a < 0$ for $\tilde{G} = 1$. The same values as those of figure 3 are used with $\xi = l_\phi$.

vector $q_c$. This is illustrated in figure 4(a). The critical wave vector is found from $C(q_c) = C'(q_c) = 0$, where $C(q)$ is the polynomial in equation (13).

We find $q_c$ in the reasonable limit where the constant term of equation (13) is small, i.e.,

$$0 < \frac{n}{k_\phi^2} k_\phi \left( \bar{\psi} - \lambda j_0 \right) u_p(0) \ll 1.$$ 

The solution depends on the sign of $a$ that is defined in equation (14). It is given by

$$q_c l_\phi = a^{1/4} \quad a > 0,$$

$$q_c l_\phi = \left( -2 \frac{k_\phi}{D_p} \left( \bar{\psi} - \lambda j_0 \right) u_p(0) \right)^{1/2} \quad a < 0.$$ 

In the isotropic limit, $a = l_\phi k_\phi / D_2$, where $l_\phi$ is the correlation length, $k_\phi$ is the rate associated with cell division and death, and $D_2$ is the co-operative diffusion constant due to mixing. Our result then reduces to that of Oster et al [11, 12]. This is a generic scaling for phase separation of reproducing entities (see also reference [42] for pattern formation in bacteria). In the polar case, while the scaling $q \sim \left( k_\phi / D_2 \right)^{1/4}$ still holds, the prefactor can change substantially due to alignment mechanisms. This is illustrated in figure 4(b) as a function of $l_p$ for $\lambda = 0$. $a$ decreases as $l_p$ becomes more negative and, consequently, the critical wave vector decreases as well. It becomes infinitesimally small as $a$ approaches zero.

The second line in equation (15) arises due to the active concentration-alignment mechanism. We focus on the $\lambda = 0$ case and plot the critical wave vector for different $l_p$ values in figure 4(c). It is possible to estimate it in the limit where $-j_0 / \left( l_p k_\phi \right)$ is the dominant contribution to $a$. This yields the scaling

$$q_c l_\phi \sim \sqrt{\frac{\bar{\psi} k_\phi}{G j_0}}.$$ 

(16)
Namely, the critical wavelength is proportional to the active length \( l_p = 2\pi \frac{1}{\lambda \left| \lambda \right|} \) and its magnitude depends on the level of cell-matrix alignment, the migration velocity, and the cell division rate. The critical wave vector is expected to be small in this limit, as is evident from figure 4(c).

In addition to the critical wave vector, there is also a fastest growing mode with wave vector \( q_s \), for which \( s \) is maximal. This infers the formation of transient periodic domains of size \( \sim 1/q_s \) with continuous flow patterns between the domains. This may correspond to the formation of clusters or strands of cells that migrate in localized collections. In standard binary systems, these domains grow into macroscopic phase-separated regions. However, any coarsening dynamics is arrested by cell division and death [42], which does not allow stable macroscopic domains with a concentration that is different from the homeostatic one \( \phi \neq \phi_0 \).

8. Discussion

In this paper, we have formulated an active-gel theory to describe multicellular migration in the ECM as an active, polar solvent permeating in a viscoelastic solid. The theory accounts naturally for dynamic reciprocity and classifies clearly different cell-matrix interactions. Namely, we highlight three alignment mechanisms that relate the polarization with the strain (\( \sim \psi \)), permeation current (\( \sim \lambda \)) and concentration gradients (\( \sim l_p^{-1} \)). The three are distinguishable; the \( \psi \) coupling, unlike the other two, occurs also for nematic cells and in the absence of concentration gradients and current. It is possible to separate between the permeation- and concentration-alignment mechanisms by studying cells with different motilities and in different setups (e.g., in the bulk of a cell collection, compared to an invading cell front).

A main conclusion of our work regards the effect of cell-matrix alignment on the stability of homogeneous multicellular migration for small wave vectors. Confluent cell monolayers can be extensile or contractile depending on the cell type and the regulation of cell–cell adhesions [37]. Our results indicate that cells with different values of the active stress would migrate in qualitatively different manners within a three-dimensional matrix. Contractile and weakly extensile cells flow homogeneously, while sufficiently extensile cells form domains. This simple distinction is remarkable, given the large number of forces and alignment mechanisms that take place. We note that cell-cell interactions in polarized cells that migrate in a fluid-like manner are generally weaker than those in confluent monolayers.

In addition to this strain-driven instability in the extensile case, our analysis suggests two possible origins for instability in the contractile case: a negative, effective diffusion constant, due to active forces, or a negative \( l_p < 0 \) that aligns cells towards larger cellular concentrations. The value of \( l_p \) tunes the critical wave vector of the instability.

While this work focuses on the linear stability of homogeneous polarized cells, our framework could be equally useful in other relevant situations. It could describe, for example, the flow of cell fronts during invasion or an isotropic-polar transition of cells in the ECM. The combination of alignment mechanisms is expected to polarize cells. Namely, cells would flow mainly parallel to network segments, due to anisotropy of the friction coefficient, while the polarization and migration speed are expected to feedback via the permeation-alignment mechanism, resulting in polarized, flowing cells. The isotropic-polar transition requires further treatment of \( |\rho| \)-dependent terms in the polarization free-energy and transport coefficients (see, e.g., references [43, 44]).

Another interesting example is cells migrating in tracks of aligned collagen fibers [5, 9]. Concentration gradients are expected to be small in this case, and the flow in the normal direction to the polarization is expected to be negligible. Most of the effects discussed in this work should not be relevant then. This is evident by taking the limit of vanishing mobility. Rather, the cells could be described in this case as a fluid flowing in a confined geometry, similarly to the theoretical description of \textit{in vitro} migration experiments in channels (see, e.g. [39]). As cell-matrix friction becomes a boundary effect, the cellular viscous stresses become important in this setup.

Several extensions of our theory can be considered. It is possible to add components to the current two-component description that coarse-grains the solvent and cells together. This overlooks solvent-cell friction, which is reasonable, because the cells are almost ten orders of magnitude more viscous than water and thus dominate the dissipative processes. The description becomes problematic, however, when the cellular concentration is inhomogeneous across the solvent. For example, when contractile cells are added to a pre-existing gel, they contract it and squeeze out some of the solvent. This can be described in our two-component theory only in an indirect way, by varying the value of the active stresses. Second, this framework overlooks diverse cell species, such as cancer cells vs fibroblasts. Fibroblasts are especially interesting because they are abundant in the ECM and are able to remodel it.

The theory can also be adapted for more complicated rheological descriptions of the ECM. While the ECM is usually considered as an elastic solid, it can exhibit several viscoelastic properties [45, 46], including...
plasticity, long-time stress relaxation and non-linearities. A treatment of the latter two in a general physical context and within a similar framework can be found in [23]. Our current work, together with reference [23], can be used to study cell migration in both viscoelastic fluids and solids (Maxwell and Kelvin–Voigt models, respectively), which are both relevant to different tissues and engineered gels [45, 46]. The main difference between the two cases is the role of strain. In a viscoelastic solid, the matrix deforms only via elastic deformations, and matrix anisotropy is described by the strain. In a viscoelastic fluid, the strain can decouple from the spatial order due to relaxation. Relaxation allows for additional alignment mechanisms, including network deformation by the relative current (‘permeation deformation’ [23]). Stress relaxation and permeation deformation should be considered together with active matrix remodeling by cells. We reserve the further study of these effects to a future work.

In conclusion, this work could open an avenue for studying cell-migration modes, ECM patterning, and cell-ECM interactions in three dimensions and at the mesoscopic scale. Thanks to the generic framework, it can be used to study other physical systems, such as bacteria and active colloids in viscoelastic media. It would be interesting to apply our theory to three-dimensional migration experiments that measure cellular concentration, alignment and velocity in the ECM or engineered gels. We suggest to compare between the migration of extensile and contractile cells and to verify whether domains form for sufficiently extensible cells. In addition, measuring and deducing typical values of \( \dot{l}_p \) for different cell types should be important in characterizing their migration modes.

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Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

Appendix A. Derivation of the polarization-rate and force-balance equations

In this section we derive the polarization-rate equation (equation (3) in the main text) and force-balance equations (equations (4)–(7) in the main text) from the general framework of linear, close-to-equilibrium thermodynamics [47]. We consider that the matrix is a linear, viscoelastic solid, whose velocity is given by \( \bar{v}_m = \bar{\partial}_t u_m \), where \( u_m \) is the network displacement vector. A similar derivation in the case of a non-linear viscoelastic fluid can be found in the supplemental material of reference [23].

A.1. Derivation of a generic, active, polar solid–fluid model

The total entropy production rate is found from the time derivative of the free energy and is given by (see similar cases in [18, 21])

\[
\dot{F} = - \int \! \! \! \! \! d\bar{r} \left[ v_{\alpha \beta} \sigma_{\alpha \beta}^d + h_a \frac{D}{Dt} p_a + \sigma_{\alpha \beta}^{el} \partial_\alpha \epsilon_{\alpha \beta} - j_a \partial_\alpha \mu + \Delta \mu r \right],
\]

(A.1)

where \( v_{\alpha \beta} = ( \partial_\alpha v_\beta + \partial_\beta v_\alpha ) / 2 \) is the COM strain rate and \( \sigma_{\alpha \beta}^d \) is the symmetric, deviatoric stress tensor, defined below. The cellular orientational field is \( h_a = -\delta F / \delta p_a \), while the co-rotational derivative of the polarization is given by \( \dot{D} p_a / \dot{D} t = ( \dot{\partial}_a + v_\alpha \partial_\alpha ) p_a + \omega_{a \beta} p_\beta, \) with \( \omega_{a \beta} = ( \dot{\partial}_a v_\beta - \dot{\partial}_\beta v_\alpha ) / 2 \) being the COM vorticity tensor. The elastic stress in the matrix is \( \sigma_{\alpha \beta}^{el} = \delta F / \delta \epsilon_{\alpha \beta}, \) where \( \epsilon_{\alpha \beta} = ( \partial_a u_\beta + \partial_\beta u_a ) / 2 \) is the linearized strain tensor. The relative current between the two components is \( j_a = \phi (1 - \phi) (v^m_a - v^c_a), \) while the relative chemical potential is \( \mu = \delta F / \delta \phi. \) Finally, \( r \) is the rate associated with the active consumption of the energy \( \Delta \mu. \)

The deviatoric stress tensor is related to the total stress tensor, \( \sigma_{\alpha \beta}, \) by

\[
\sigma_{\alpha \beta}^d = \sigma_{\alpha \beta} - \sigma_{\alpha \beta}^{el} + \rho v_\alpha v_\beta - \sigma_{\alpha \beta}^{Er,s},
\]

(A.2)

where \( \sigma_{\alpha \beta}^{Er,s} = ( p_a h_\beta - p_\beta h_a ) / 2 \) is the antisymmetric part of the total stress and \( \rho v_\alpha v_\beta \) is the momentum transfer with \( \rho \) being the total mass density.

We neglect this term hereafter. The last term in the equation
above is the symmetric part of the Ericksen stress. The Ericksen stress tensor, \( \sigma_{\alpha\beta}^{\text{Er}} \), is given by [17]

\[
\sigma_{\alpha\beta}^{\text{Er}} = (f - n_c \mu_c - n_m \mu_m) \delta_{\alpha\beta} - \frac{\partial f}{\partial (\partial_\alpha p_\gamma)} \partial_\alpha n_c - \frac{\partial f}{\partial (\partial_\alpha n_m)} \partial_\alpha n_m,
\]

where \( n_m \) and \( n_c \) are the matrix and cellular densities, respectively, and \( \mu_m \) and \( \mu_c \) are their chemical potentials.

As part of a solid–fluid or two-fluid model, we consider that each component is convected with its own velocity [48, 49]. We, therefore, rewrite the free-energy production rate of equation (A.1) in terms of a cellular convected derivative, \( L_t^c \), as

\[
L_t^c p_\alpha = (\partial_t + v_c^c \partial_\beta) p_\alpha + \omega_{\alpha\beta}^c p_\beta + \nu v_{\alpha\beta}^c p_\beta,
\]

where \( \omega_{\alpha\beta}^c \) is the cellular vorticity tensor and \( v_{\alpha\beta}^c \) is the cellular strain-rate tensor. The term \( \nu \) is the cellular shear-alignment parameter. For simplicity, we set \( \nu = -1 \) hereafter, corresponding to cells that rotate as rigid rods. This yields

\[
L_t^c p_\alpha = (\partial_t + v_c^c \partial_\beta) p_\alpha - p_\beta \partial_\beta v_c^c.
\]

The convected derivative \( L_t^c \) thus reduces to a vector Lie derivative [50].

Inserting the convected derivative and using integration by parts, equation (A.1) transforms into

\[
\dot{F} = - \int d\mathbf{r} \left[ v_{\alpha\beta} \delta \sigma_{\alpha\beta} + h_n L_t^c p_\alpha + \Delta \mu r + j_a \left( \frac{1}{\phi} (\partial_\beta \sigma_{\alpha\beta}^\text{el} - \phi \partial_\alpha \mu) + \frac{1}{1-\phi} \left[ h_m \delta \sigma_{\alpha\beta} - \partial_\beta \left( h_a p_{\beta} \right) \right] \right) \right].
\]

In equation (A.6), we have defined the stress

\[
\delta \sigma_{\alpha\beta} = \sigma_{\alpha\beta} + \rho v_{\alpha\beta} - \sigma_{\alpha\beta}^{\text{Er}} + h_m \delta \sigma_{\alpha\beta} + h_n \sigma_{\alpha\beta}^\text{el}.
\]

Note that \(-h_m p_{\beta}\) is the reactive stress associated with polarization rotations, given the convective derivative \( L_t^c \). It includes the antisymmetric part of the stress.

The stress \( \delta \sigma_{\alpha\beta} \) includes additional contributions to the deviatoric stress and, namely, the dissipative and active stress. In the spirit of a solid–fluid model, we assume that stress can be decomposed into a stress that arises from the cells \( \delta \sigma^c \) and a stress that arises from the matrix \( \delta \sigma^m \). As each component is advected by its own velocity, each stress depends only on its own strain rate. Furthermore, as only the cells are considered as active, we relate the activity to the cellular stress alone, i.e.,

\[
\delta \sigma_{\alpha\beta} = \delta \sigma_{\alpha\beta}^c (v_{\alpha\beta}^c, \Delta \mu) + \delta \sigma_{\alpha\beta}^m (v_{\alpha\beta}^m).
\]

Substituting in equation (A.6) yields

\[
\dot{F} = - \int d\mathbf{r} \left[ v_{\alpha\beta}^c \delta \sigma_{\alpha\beta}^c (v_{\alpha\beta}^c, \Delta \mu) + v_{\alpha\beta}^m \delta \sigma_{\alpha\beta}^m (v_{\alpha\beta}^m) + h_n L_t^c p_\alpha + j_a \frac{f_{\alpha}}{\phi (1-\phi)} + \Delta \mu r \right],
\]

where we have defined the relative, matrix, and cellular forces

\[
f_{\alpha} = (1 - \phi) f_{\alpha}^m - \partial_\alpha \mu,
\]

\[
f_{\alpha}^m = \partial_\beta \left( \sigma_{\alpha\beta}^m + \delta \sigma_{\alpha\beta}^m \right) - \phi \partial_\alpha \mu,
\]

\[
f_{\alpha}^c = \partial_\beta \left( -h_m p_{\beta} + \delta \sigma_{\alpha\beta}^c \right) - h_n \partial_\beta p_{\beta}.
\]

In order to clarify the definitions above, we examine the force originating from the Ericksen stress

\[
\partial_\beta \sigma_{\alpha\beta}^{\text{Er}} = -n_c \partial_\alpha \mu_c - n_m \partial_\alpha \mu_m - h_m \partial_\alpha p_{\beta} - \phi \partial_\alpha \mu - h_n \partial_\alpha p_{\beta} - \partial_\alpha \delta P.
\]
Here we have defined $\bar{\mu} = \rho (\mu_m - \mu_c) / m$, where $m$ is the molecular mass (assumed equal for both components) and $\delta P = \rho \mu_c$. It is now clear that $f^m_m - \phi \partial_\alpha \delta P$ and $f^c_c - (1 - \phi) \partial_\alpha \delta P$ describe the total surface forces acting on the matrix and cells, respectively. A linear combination of the equations yields the force balance equations (equation (4)),

$$f^m_m - \phi \nabla \delta P = f^{\text{rel}}, \quad f^c_c - (1 - \phi) \nabla \delta P = - f^{\text{rel}}. \quad (A.14)$$

The force-balance equations and polarization-rate equation are obtained by writing phenomenological constitutive equations for $L^c_p \rho_f f^{\text{rel}}, \delta \sigma^c_{\alpha \beta},$ and $\delta \sigma^m_{\alpha \beta}$.

### A.2. Constitutive equations

The free-energy production rate of equation (A.9) is written as an integral over pairs of forces and conjugate fluxes. In each pair, we consider the first variable as the force, and the second as the flux. Our aim is to derive constitutive equations between forces and fluxes in a linear theory, close to equilibrium. Fluxes are related to forces with the same signature under time-reversal as their conjugate force, by dissipative couplings, and to forces with opposite signatures by reactive couplings. Reciprocal dissipative couplings are equal and have a positive contribution to the total entropy production, while reciprocal reactive couplings have opposite signs and do not contribute to the entropy production [47]. We consider for the constitutive equations only the leading, zeroth-order terms in a gradient expansion. The constitutive equation for the reaction rate $r$ does not affect the dynamics and will not be addressed.

The constitutive equation for the polarization rate reads

$$L^c_p \rho_f = \frac{1}{\gamma_1} \dot{h}_f + \lambda j_f + \phi (1 - \phi) \psi' \Delta \mu \epsilon_{\alpha \beta} p_{\beta}. \quad (A.15)$$

The right-hand side accounts for dissipative couplings, while the reactive couplings are already incorporated in the convective derivative (equation (A.5)). The coupling to the orientational field $h_\parallel = - \partial \Phi / \partial P_\parallel$ is given in terms of the rotational viscosity $\gamma_1$. The coupling to the relative current $j_\alpha$ is referred to as the permeation-alignment coupling. The coupling to activity $\Delta \mu$ includes the strain (a term $\sim \Delta \mu p_\parallel$ simply renormalizes the parallel field, $h_\parallel$) and is proportional to $\phi (1 - \phi)$, because it involves interaction with the matrix.

The orientational field is given by

$$h_\parallel = h_\parallel p_\alpha + K \left( \partial_\beta \partial_\beta p_\alpha + L_p^{\text{rel}} \partial_\alpha \phi \right) - 2 \phi (1 - \phi) \psi \epsilon_{\alpha \beta} p_{\beta}. \quad (A.16)$$

Substituting in equation (A.15) yields equation (3) with $h_\parallel = h_\parallel / \gamma_1$, $D_p = K / \gamma_1$, and $\psi = \psi' \Delta \mu - 2 \psi / \gamma_1$.

We consider hereafter $\psi' = 0$, such that strain-polarization alignment is driven by the passive free-energy coupling, $\psi = - 2 \psi / \gamma_1$.

We consider as the relative force

$$f^{\text{rel}} = \frac{1}{\gamma} - (1 - \phi) \left( \lambda h + \nu \Delta \mu p + \nu' \Delta \mu \epsilon \cdot p \right). \quad (A.17)$$

The first term on the right-hand-side is the dissipative coupling to the relative current, written in terms of the mobility $\gamma$. Dissipation due to the cell and matrix strain rates is not considered as a relative force and is included in $\delta \sigma_{\alpha \beta}$. The next term is the permeation-alignment coupling that appears as a reciprocal term to the coupling in equation (A.15). Finally, the last two terms are couplings to the activity $\Delta \mu$. For brevity, we omit the $\Delta \mu$ hereafter. For the matrix and cellular stresses we consider

$$\delta \sigma^{m}_{\alpha \beta} = \frac{\phi}{\phi_0} \left( 2 G r \partial_\alpha \epsilon_{\alpha \beta} + B r \partial_\alpha \partial_\beta \epsilon_\delta_{\alpha \beta} \right), \quad (A.18)$$

$$\delta \sigma^{c}_{\alpha \beta} = (1 - \phi) \left( \zeta \delta_{\alpha \beta} + \zeta Q_{\alpha \beta} \right), \quad (A.19)$$

where $\epsilon = \epsilon_{\alpha \alpha}$ and $\epsilon_{\alpha \beta} = \epsilon_{\alpha \beta} - \epsilon / 3 \delta_{\alpha \beta}$. The matrix stress includes the viscoelastic shear and compressional stresses, in terms of the shear and compressional retardation times, $\tau$ and $\bar{\tau}$, respectively (Kelvin–Voigt model). The cellular viscosity is neglected. The cellular stress is active, consisting of an isotropic contribution $\sim \zeta$ and a traceless contribution $\sim \zeta$, proportional to the nematic tensor,

$$Q = \left( p_\alpha p_\beta - \delta_{\alpha \beta} / 3 \right).$$

The stresses are proportional to the cellular concentration $\sim 1 - \phi$. Other than that, $\zeta$ and $\zeta$ are considered as constants, neglecting the possible dependence on matrix properties [33]. These constitutive equations together with equations (A.11) and (A.12), yield equations (5) and (6) in the main text.
Appendix B. Linearization of the dynamic equations

In this appendix we derive the linearized version of the equations, which is used for the linear stability analysis. We first write the equations in full form, including explicit expressions for the fields that are derived from the free energy. Then, we solve the steady-state equations, and linearize around the steady-state solution.

B.1. Matrix forces

The dynamic equations include force-balance equations, written in terms of the cell and matrix forces. The matrix force is given in equation (5). It includes the divergence of the elastic stress,

\[ \sigma_{\alpha\beta}^{el} = \frac{\delta F}{\delta \epsilon_{\alpha\beta}} = \frac{\phi}{\phi_0} (2G\epsilon_{\alpha\beta} + Be\delta_{\alpha\beta}) + \phi (1 - \phi) \psi Q_{\alpha\beta}, \]  

(B.1)

where \( \epsilon_{\alpha\beta} = \left( \partial_\alpha u_\beta + \partial_\beta u_\alpha \right) / 2 \) is the elastic strain. In addition, it includes the force that results from osmotic pressure gradients, \(-\phi \partial_\alpha \mu\). The relative chemical potential is given by

\[ \bar{\mu} = \frac{\delta F}{\delta \phi} = -k_B Ta^{-3} (1 + \ln (1 - \phi)) + (1 - 2\phi) \left( \chi_0 + \psi Q_{\alpha\beta} \epsilon_{\alpha\beta} \right) \]

\[ + G\epsilon^2 + \frac{1}{2} Be^2 + K_p^{-1} \partial_\alpha p - 2 \kappa \partial_\alpha \partial_\alpha \phi. \]  

(B.2)

B.2. Steady state

We consider a homogeneous, polar, steady-state, as is described in section 4. For a homogeneous system, the forces acting on the cells and matrix (equations (5) and (6)) vanish. Force balance then requires that the relative force vanishes as well, i.e.,

\[ \frac{1}{\gamma}\phi = \phi_0 (1 - \phi_0) \left( \lambda \phi_0^2 + \left[ \nu - \nu' \frac{\psi}{3G} \phi_0 (1 - \phi_0) \right] p_0^0 \right). \]  

(B.3)

The steady-state molecular field results from the active relative current and is given by

\[ k_0 = -\gamma_1 \lambda \phi_0^0. \]  

(B.4)

Inserting this result in the previous equation yields the relative current at steady state,

\[ p_0 = \frac{\gamma}{1 + \lambda^2 \gamma_1} \phi_0 (1 - \phi_0) \left[ \nu - \nu' \frac{\psi}{3G} \phi_0 (1 - \phi_0) \right] p_0^0, \]  

(B.5)

where \( \lambda_1 = \sqrt{\phi_0 (1 - \phi_0) \gamma_1} \) is a screening length due to the interplay between friction and rotational viscosity. We consider \( \nu, \nu' < 0 \), such that the cells migrate in the direction of their polarization. The role of \( \nu' \) at steady state is to renormalize the motility. The permeation-alignment mechanism effectively increases the friction.

B.3. Linearized equations

The stability is studied by introducing a small perturbation in the fields at point \( \mathbf{r}_B \) and time \( t \) with a wave vector \( \mathbf{q}_B \), and growth rate \( s \),

\[ (\phi, p_0, u_0) \approx (\phi_0, p_0^0, u_0^0) + (\phi^1, p_1, u_1^0) \exp (i \mathbf{q}_B \mathbf{r}_B + st). \]  

(B.6)

For simplicity, we consider \( q_1 = 0 \). Also, in order to maintain the modulus of the polarization, \( p_1^1 = 0 \). It is possible to integrate over the displacement variable and to analyze the stability in terms of \( \phi^1 \) and \( p_1^1 = i \mathbf{q}_B p_1^1 \).

The linearized continuity equation (equation (2)) is given by

\[ s \phi^1 = -i \mathbf{q}_B \phi^1 - k_0 \phi^1. \]  

(B.7)
The linearized equation for the polarization (divergence of equation (3)) reads
\[ sp_d^{i} = h_1 p_d^{i} - D_0 q^{i2} p_d^{i} - D_1 q^{-1} q^{i2} \phi^i + \lambda i q_{ij} \gamma^i + \phi_0 (1 - \phi_0) \psi i q_{j} (\epsilon_{i\alpha\beta} p_{\beta})^i. \] (B.8)

The parallel field can be found from the polarization-rate equation at steady state, 
\[ h_{ij} = -\lambda f_0 + \frac{1}{2} \phi_0^2 (1 - \phi_0)^2 \psi \psi / G. \] 
The \( \bar{q} \) term in equation (B.8) is given by
\[ \bar{q}^{-1} = \frac{1}{2} q^{j2} u_s^j + \frac{\psi}{6 G} \phi_0 (1 - \phi_0) p_d^{j}. \] (B.9)

The displacement in the \( x \)-direction is found from the force balance on the entire gel (sum of the two lines in equation (4)) in the \( x \)-direction. As \( q_x = 0 \), only the total shear stress of the system contributes to this force. We find that
\[ u_x^i = \frac{1}{G (1 + \tau_s) q^2} [(1 - \phi_0) \zeta + \phi_0 (1 - \phi_0) \psi - h_{ij}^0 p_d^j]. \] (B.10)

This demonstrates how the network is strained by active stresses (\( \zeta \) term) and alignment mechanisms (\( h_{ij}^0 \) term), as well as the stress due to passive alignment (\( \psi \) term).

We find that
\[ i q_{\alpha \beta} (\epsilon_{i \alpha \beta})^i = -\frac{1}{\phi_0 (1 - \phi_0)} \left( u_p + \frac{1}{3} \phi_0^2 (1 - \phi_0)^2 \psi / G \right) p_d^j, \] (B.11)
where \( u_p \) is given by
\[ u_p = u_p (0) - \frac{\tau_s}{1 + \tau_s} \left( u_p (0) + \frac{1}{2} \phi_0^2 (1 - \phi_0)^2 \psi / G \right), \]
\[ u_p (0) = \frac{\phi_0 (1 - \phi_0)}{2G} [(1 - \phi_0) \zeta - h_{ij}^0]. \] (B.12)

This yields overall
\[ sp_d^{i} = -\left( \lambda f_0 + \bar{q} u_p + D_0 q^{2} \right) p_d^{i} - D_1 q^{-1} q^{i2} \phi^i + \lambda i q_{ij} \gamma^i. \] (B.13)

It remains to find the divergence of the relative current. We take a linear combination of the two force balance equations in equation (4) of the main text, and find that
\[ \frac{1}{\gamma} iq_{\alpha i} = iq_{\alpha} \left( \phi_0 (1 - \phi_0) \left[ \lambda h_{ij}^{i} + \nu p_{\alpha}^{i} + \nu' (\epsilon_{i \alpha \beta})^i \right] + (1 - \phi_0) f_{\alpha}^{inl} - \phi_0 f_{\alpha}^{nl} \right). \] (B.14)

Before resuming the calculation, we note that the active relative force \( \sim \nu' \) plays, in part, a similar role to an anisotropic friction coefficient. To see this, consider a friction coefficient \( \gamma_{i\alpha} = \gamma_0 \gamma^{-1} \delta_{i\alpha} + \gamma^{-1} \epsilon_{i\alpha}. \) Then, expanding the friction force would yield
\[ \left( \gamma_{i\alpha}^{-1} \right)^i = \left[ \gamma_0^{-1} \delta_{i\alpha} - \frac{\psi}{2 G} \phi_0 (1 - \phi_0) Q_{i\alpha}^{0} \gamma^{-1} \right] j_{\gamma}^i + \gamma_0^{-1} j_{\delta}^i \epsilon_{i\alpha}. \] (B.15)

It is evident that the correction \( \sim \epsilon_{i\alpha} \) appears in a similar way either due to \( \gamma^{-1} \) or \( \nu' \). Explicitly this yields the relation \( \nu' = -\gamma^{-1} j_0. \) For \( j_0 < 0 \) and considering that the friction is expected to decrease due to network alignment, we conclude that \( \nu' \) is indeed expected to be negative, as was mentioned above.

We return to the calculation of the divergence of the relative current and examine each contribution separately. For the orientational field, we find that
\[ iq_{\alpha} h_{\alpha}^{i} = -K \left( q^{i2} p_d^{i} + f_{\alpha}^{-1} q^{i2} \phi^i \right) + h_{ij}^0 p_d^j - 2 \phi_0 (1 - \phi_0) \psi i q_{\beta} (\epsilon_{i \alpha \beta} p_{\beta})^i. \] (B.16)

The last contribution appears also in the \( \nu' \) term. Summing the two contributions leads to
\[ j_{\alpha} (u_p + \frac{1}{2} \phi_0^2 (1 - \phi_0)^2 \psi / 6 G) p_d^j, \] where \( j_{\alpha} / \gamma = -\nu' + 2 \lambda \phi_0 (1 - \phi_0) \psi \) describes the two contributions to the strain-dependent relative forces: the active relative force \( \sim \nu' \) and the permeation-alignment mechanism \( \sim \lambda \), which includes polarization alignment to the strain. We further simplify using the steady-state equation for the current,
\[
\frac{1}{3} \phi_0^3 (1 - \phi)^2 \frac{\psi}{G} j_u + \gamma \phi_0 (1 - \phi_0) \left( \lambda h_{||} + \nu \right) = j_u. \tag{B.17}
\]

For the matrix force, we calculate separately the contributions of the elastic stress and osmotic pressure. The elastic contribution is
\[
- q_\alpha q_\beta \sigma_{\alpha\beta}^{el} = - q_\alpha q_\beta \left[ 2 G e_{\alpha\beta} + B e^i \delta_{\alpha\beta} + 2 \phi_0 (1 - \phi_0) \psi \phi_0 p_{\alpha\beta}^0 + (1 - 2 \phi_0) \psi \phi_0 Q_0^{el} \phi_1 + 2 \phi_0^2 G e_{\alpha\beta} \right]
\]
\[
= \left[ \frac{1}{\phi_0} \left( \frac{4 \gamma}{3} G + B \right) - \frac{1}{3} \phi_0 \psi \right] q^2 \phi_1,
\tag{B.18}
\]
where we have made use of the fact that \( \epsilon^1 = - \phi^1 / \phi_0 \) and \( q_x = 0 \). The contribution from the osmotic pressure is
\[
\phi_0 q^2 \bar{\Pi}^1 = \phi_0 q^2 \left[ \frac{k_B T}{a^3} \frac{1}{1 - \phi_0} - 2 \chi_0 + \frac{2 \psi^2}{3 G} \phi_0 (1 - \phi_0) - \frac{1}{3} \psi + 2 \kappa q^2 \right] \phi^1 + \phi_0 K \phi_0 q^2 \phi^1. \tag{B.19}
\]
Together this yields
\[
 i q_\alpha f_\alpha^{11} = \left[ \frac{1}{\phi_0} \left( \frac{4 \gamma}{3} G (1 + \tau s) + B (1 + \tau s) \right) + \phi_0 \chi^{-1} \left( (1 + \phi_0^2 q^2) \right) \right] q^2 \phi_1 + \phi_0 K \phi_0 q^2 \phi^1. \tag{B.20}
\]
where we have defined the effective inverse susceptibility
\[
\chi^{-1} = \frac{k_B T}{a^3} \frac{1}{1 - \phi_0} - 2 \left( \chi_0 + \frac{\psi^2}{3} \right) + \frac{2 \psi^2}{3 G} \phi_0 (1 - \phi_0), \tag{B.21}
\]
and the interfacial correlation length \( l_0 = \sqrt{2 \kappa \chi} \). Note that parallel cell-strain alignment \( (\psi < 0) \) has a positive contribution.

For the cellular force, we find that
\[
 i q_\alpha f_\alpha^{cl} = \left( \frac{\phi_0}{3} \right) q^2 \phi_1. \tag{B.22}
\]
Note that the isotropic \( \zeta \) stress does not affect the total stress, due to incompressibility. It simply renormalizes the pressure \( \delta P \). Its only role is in the equation for the relative current (equation (B.14)) and it can be interpreted as an active, relative force \( \sim \partial_\phi \psi \).

Inserting back in the equation for the current yields overall
\[
 i q_\alpha f_\alpha = \left( D_0 + \ell_p^2 \right) q^2 \phi_1 + \left[ \left( \ell_p^{-1} - \lambda \right) \ell_p^2 D_1 q^2 + j_u + j_u \ell_p \right] P \phi_1. \tag{B.23}
\]
Here we have defined the effective osmotic diffusion constant as \( D_0 = D_1 + D_2 \ell_p^2 q^2 - \lambda \ell_p^{-1} \ell_p D_1 \) with
\[
D_1 = \gamma \phi_0 (1 - \phi_0) \chi^{-1} + \frac{1}{\phi_0} \frac{1 - \phi_0}{\phi_0} \left( \frac{4 \gamma}{3} G + B \right) + \gamma \phi_0 \left( \frac{1}{3} \zeta - \zeta \right),
\]
\[
D_2 = \gamma \phi_0 (1 - \phi_0) \chi^{-1}, \tag{B.24}
\]
as well as \( l_0 = \sqrt{\frac{\gamma (1 - \phi_0)}{\phi_0} \left( \frac{4 \gamma}{3} G (1 + B) \right)} \), a screening length due to the interplay between friction and transient matrix viscosity. This diffusion constant differs from that in the isotropic case (equation (10)) in two ways: its inverse susceptibility has contributions \( \sim \psi \) (equation (B.21)), and it includes the nematic active stress \( \sim \zeta \).

Inserting equation (B.23) in equations (B.7) and (B.13) yields the linearized dynamic equations, equations (8) and (9).

**Appendix C. Linear stability in the rigid limit**

In the rigid matrix limit, concentration fluctuations generate a large free-energetic cost, and \( D_0 \) becomes very large. For a finite retardation time, \( \ell_p^2 \) becomes very large as well. We consider a finite system size \( L \) and
a minimal wave vector \( q_m = 2\pi / L \), such that \( l^2 \eta m^2 \gg 1 \) and \( D_0 l^2 q_m^2 \gg k_B T \). In this approximation, equations (8) and (9) reduce to

\[
0 = (D_0 + \xi q^2) \phi^3 + [(l_p^2 - \lambda) \xi, D_0 q^2 + j_0 + j_u u_p] p^2_d
\]

\[
0 = [s + (\psi - \lambda j_d) u_p + (1 + \lambda (l_p^2 - \lambda)) \xi, D_0 q^2 - \lambda (D_0 + \xi q^2) q^2 \phi^1].
\]

(C.1)

One solution is \( s = -D_0/\xi l^2 \) and \( p_d^2 = 0 \) which corresponds to stable concentration fluctuations. The other two possible solutions are found from the remaining factor in the determinant

\[
0 = s + (\psi - \lambda j_d) u_p + (1 + \lambda (l_p^2 - \lambda)) \xi, D_0 q^2 + \lambda [(l_p^2 - \lambda) \xi, D_0 q^2 + j_0 + j_u u_p]
\]

\[
s + \psi u_p + \lambda j_0 + D_0 q^2.
\]

(C.2)

Substituting \( u_p \) (equation (B.12)) leads to equation (11).

### Appendix D. Estimations of parameters

The basic time scale of the theory is \( 1/k_0 \). We estimate it as \( 1/k_0 = 24 \text{ h} \) for a typical division time of one day. The basic length scale of the theory is the correlation length \( l_0 \). For simplicity, we choose a small length of order of the cell size \( a \) that we set as \( l_0 = a = 10 \mu m \). This is the lowest value that we consider for length scales, including \( \lambda^{-1} \), \( l_p \), and \( \xi \). Next, we estimate the remaining parameters of our theory. The estimations are summarized in table 2.

### Osmotic diffusion constant

The diffusion constant \( D_1 \) includes terms of the form \( \gamma G_1, \gamma \zeta, \gamma \chi^{-1} \) (equation (B.24)). The mobility can be related to the cellular shear viscosity \( \eta \) as \( \eta \approx \xi^2 / \lambda \), where \( \xi \) is a typical mesh size. The viscosity of epithelial monolayers is of order \( \eta \approx 10^{-3} - 10^{-4} \text{ Pa s} \) [51]. As our theory coarse grains the cells and solvent together, we consider the value of \( \eta = 1 \text{ kPa s} \). This value can be regarded as an upper bound of the viscosity. The ECM and collagen gels in general can have a large range of stiffness values in the range \( 0.1 < G < 10 \text{ kPa} \) [35, 36]. For the active stress that originates from acto-myosin contractility, we consider a 2D myosin contractility of \( \zeta_{2D} \approx 1 \text{ kPa} \mu m^{-1} \) [52]. Dividing by a typical cell size of \( a = 10 \mu m \), the cells are expected to exert a stress of order 0.1 kPa. We use this order of magnitude as well for extensile active stresses. For the inverse susceptibility, we make a scaling argument, taking \( 1/k_0 \) as the basic timescale of the system. We write the corresponding term in the diffusion constant as \( D_2 = \gamma \phi_0 (1 - \phi_0) \chi^{-1} \approx F k_0 \), where \( L \) is a lengthscale. The minimal possible \( l \) is \( l = a \). For a fixed \( \chi \), this is obtained for the minimal mobility \( \gamma = a^2 / \eta \). This yields \( \gamma \approx k_0 \) and, consequently, \( \chi^{-1} \approx \eta k_0 \approx 0.1 \text{ kPa} \).

### Relative current and strain-polarization coupling

The steady-state relative current is estimated by a typical migration velocity [36] \( j_0 = 5 \mu m \text{ h}^{-1} \). We also consider the contribution of the strain-induced current around the steady state, \( (\xi \phi_a + \lambda \xi \psi) u_p \) (0). We have \( j_0 + \lambda \xi \psi = -\gamma \nu \). The strain-dependent, active, relative force is estimated as \( \nu = -\gamma \nu j_0 \), assuming that it has a similar effect as a strain-dependent friction coefficient (appendix B). For simplicity, we consider \( \gamma_\nu = -\gamma \). This yields \( j_0 + \lambda \xi \psi = -j_0 \). The polarization-induced strain parameter is given by \( u_p (0) = \phi_0 (1 - \phi_0) [1 + \xi (1 - \phi_0)] / (2G) \). For a small modulus \( G = 0.1 \text{ kPa} \), we find that \( u_p (0) \approx 0.1 (1 - 5\lambda l_0) \). The strain \( u_p (0) \) often appears next to the strain-polarization rate \( \psi = -2\psi / \gamma_\psi \). For the strain-polarization coupling \( \psi \), we consider the value \( \phi_0 (1 - \phi_0) \psi = -0.1G \). The sign signifies that the cells align parallel to network segments and the order of magnitude is the largest possible within the framework of linear elasticity. The product \( \psi u_p (0) \) is then given by \( 0.25 (1 - 5\lambda l_0) k_0 \), where we have set the rotational viscosity as the shear viscosity, \( \gamma_\psi = \eta \).

### Angular diffusion constant

The angular diffusion constant is \( D_\psi = K / \gamma_\psi \). The Frank constant in two dimensions \( K_{2D} \) can be estimated from experiments that measure the active lengthscale.
\[ l_a = 2\pi \sqrt{K_{2D}/|\zeta_{2D}|} \], where \( \zeta_{2D} \) is the two-dimensional active, nematic stress. Experiments on cell monolayers have measured a length of order \( l_a \approx 50 \, \mu m \) [39]. Considering again a 2D myosin contractility of order kPa \( \mu m \), we find that \( K_{2D} \approx 100 \, kPa \mu m^3 \). Dividing by the cell size yields \( K_{2D} \approx 10 \, kPa \mu m^2 \) and \( D_p \approx 10 \, \mu m^2 \, h^{-1} \) (table D1).

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