Physics of multicellular systems

From cell to tissue mechanics

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March 20, 2023

Contents

Chapter 1

Continuous models of tissues - dissipation and nematic order

In this chapter, that will be the subject of two lessons, we will discuss continuous descriptions of tissues. During embryonic development or organ formation, morphogenesis relies on the collective motion of thousands of cells that deform, rearrange, divide,, die and flow to establish the shape of a tissue. At large scales, one may expect the emergence of collective behaviors and features that are independent of the microscopic details of cellular organization. Continuum approaches require the existence of an intermediate length scale, larger than a typical cell size, but smaller than the spatial extension of the tissue.

1.1 Preliminary: continuum mechanics, a minimal introduction

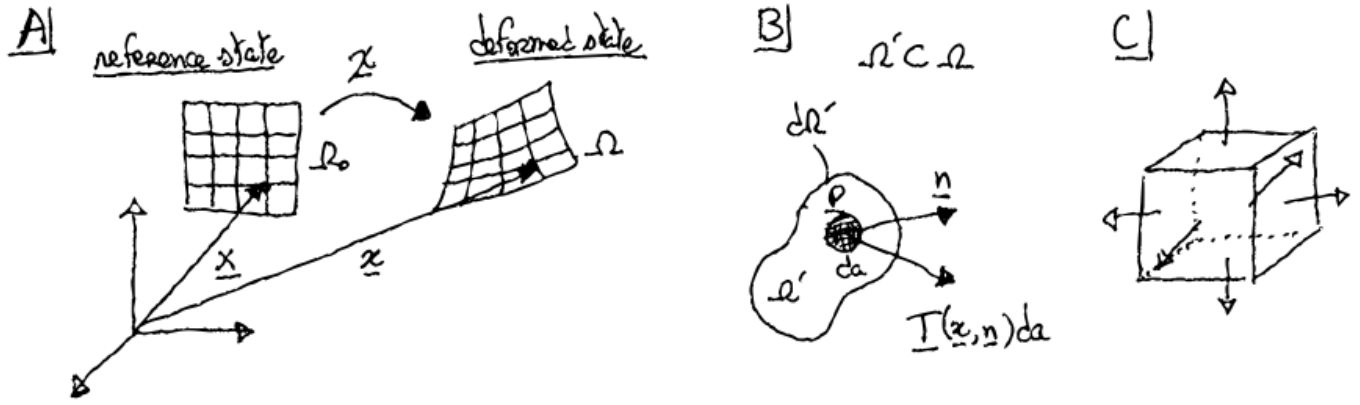

Figure 1.1: (A) Schematics of the mapping $\boldsymbol{\chi}$ between the reference and deformed states of the material. (B) Traction force $\boldsymbol{T}(\boldsymbol{s},\boldsymbol{n})da$ exerted along the normal $\boldsymbol{n}$ at a point P of a subset $\Omega' \subset \Omega$ of the material. (C) Elementary cubic subset of the material with traction forces depicted at each interface.

Deformation

The continuous material occupies a space Ω_0 in the reference state and Ω in the current or deformed state, as represented on Fig. 1.1. Each material point in the reference state is parametrized by a vector $\boldsymbol{X}$ and correspondingly by a vector $\boldsymbol{x}$ in the deformed state. The material deformation is described by a (invertible) mapping $\boldsymbol{\chi}$, which unambiguously relates $\boldsymbol{x}$ and $\boldsymbol{X}$ at time t

$$\Omega_0,\, [0,+\infty[\xrightarrow{\boldsymbol{\chi}} \Omega \tag{1.1}$$

$$\boldsymbol{X},\, t \longmapsto \boldsymbol{x} = \boldsymbol{\chi}(\boldsymbol{X},t) \tag{1.2}$$

The velocity of a material (or Lagrangian) point can be defined as

$$\boldsymbol{v} = \frac{d\boldsymbol{x}}{dt} = \left.\frac{\partial \boldsymbol{\chi}(\boldsymbol{X}, t)}{\partial t}\right|_{\boldsymbol{X}} \tag{1.3}$$

Deformations may be defined as $\boldsymbol{u}(\boldsymbol{X}) \equiv \boldsymbol{x} - \boldsymbol{X}$, but it is usually useful to define a deformation gradient tensor

$$\underline{\underline{F}} = \frac{\partial \boldsymbol{x}}{\boldsymbol{X}} = \frac{\partial \boldsymbol{\chi}}{\boldsymbol{X}} \tag{1.4}$$

or in cartesian coordinates $F_{ij} = \frac{\partial x_i}{\partial X_j}$. The deformation gradient tensor describes the transport of a material point $\boldsymbol{V}$ in the reference state: $\boldsymbol{v} = \underline{\underline{F}} \cdot \boldsymbol{V}$.

From the deformation tensor we can measure the change in a scalar product between two material vectors defined as $\boldsymbol{V}$ and $\boldsymbol{W}$ (so dilatations) in the reference state by

$$\boldsymbol{v}(t) \cdot \boldsymbol{w}(t) = \boldsymbol{V} \cdot \underline{\underline{C}} \cdot \boldsymbol{W} \tag{1.5}$$

where $\underline{\underline{C}} = \underline{\underline{F}}^T \cdot \underline{\underline{F}}$ is called the dilatation tensor.

Finally, the important measures that one may wish to relate to stress are strains, which measure the variation of scalar products between the reference and current configurations. The strain is quantified in general using the *Green Lagrange strain tensor*

$$\underline{\underline{\epsilon}} \equiv \frac{1}{2}\left(\underline{\underline{C}} - \underline{\underline{\mathbb{1}}}\right) = \frac{1}{2}\left(\underline{\underline{F}}^T \cdot \underline{\underline{F}} - \underline{\underline{\mathbb{1}}}\right) \tag{1.6}$$

The material movement is rigid if and only if this tensor vanishes at any point of Ω_0.

Traction and stress

We consider a subdomain $\Omega' \subset \Omega$ of the material at the current state as represented on Fig. 1.1. The elementary force exerted on the point P at $\boldsymbol{x}$ of the boundary $\partial\Omega'$ of the subdomain reads

$$d\boldsymbol{f} = \boldsymbol{T}\big(\boldsymbol{x}, \boldsymbol{n}(\boldsymbol{x})\big) da \tag{1.7}$$

where $\boldsymbol{T}$ is called the traction and is a density of contact forces, $\boldsymbol{n}(\boldsymbol{x}, t)$ is the normal of the boundary at $\boldsymbol{x}$ and da is the elementary area around the point P.

The Cauchy theorem states that the traction at an interface $\boldsymbol{T}\big(\boldsymbol{x}, \boldsymbol{n}(\boldsymbol{x})$ is a linear form of the normal of this interface $\boldsymbol{n}$[1]. This defines the **Cauchy stress tensor**

$$\boldsymbol{T}\big(\boldsymbol{x}, \boldsymbol{n}(\boldsymbol{x})\big) = \underline{\underline{\sigma}}(\boldsymbol{x}, t) \cdot \boldsymbol{n}(\boldsymbol{x}, t) \tag{1.8}$$

In cartesian coordinates, this reads $T_i = \sigma_{ij} n_j$ and leads to the elementary traction force expression

$$df_i = \sigma_{ij} n_j da$$

.

If now we consider an elementary cubic material domain as shown on Fig. 1.1, we can write down the traction force on each interface and takes the limit of infinitely small domain. This leads to the equation for the mechanical equilibrium of the cube[2]

$$\boldsymbol{\nabla} \cdot \underline{\underline{\sigma}} = \boldsymbol{0}$$

or in cartesian coordinates $\partial_i \sigma_{ij} = 0$

[1] The Cauchy theorem can be demonstrated by writing momentum balance on an elementary tetrahedron and taking the limit of infinitely small volume.

[2] Here we don't consider external bulk forces on the domain nor acceleration.

Finally, by writing similarly torque balance (conservation of angular momentum) on the elementary cube in the same limit, one can easily prove that the Cauchy stress tensor shall be symmetric

$$\underline{\underline{\sigma}}^t = \underline{\underline{\sigma}} \iff \sigma_{ij} = \sigma_{ji}$$

.

Conservation equations
There are generally two major conservation equations associated to continuum descriptions: mass conservation and momentum conservation.

Mass conservation reads in all generality

$$\frac{\partial \rho}{\partial t} + \boldsymbol{\nabla} \cdot (\rho \boldsymbol{v}) = s, \tag{1.9}$$

where ρ is the mass density (or mass per unit area in 2D), $\boldsymbol{v}$ is the material velocity and s represents material source or sink terms, which in the context of tissue growth and homeostasis, will be linked later to cell growth and apoptosis.

The conservation of momentum reads generally

$$\rho \boldsymbol{a}(\boldsymbol{x}, t) = \boldsymbol{\nabla} \cdot \sigma(\boldsymbol{x}, t) + \boldsymbol{f}(\boldsymbol{x}, t).$$

and relates the acceleration $\boldsymbol{a} = \frac{\partial \boldsymbol{v}}{\partial t} + (\boldsymbol{v} \cdot \boldsymbol{\nabla})\, \boldsymbol{v}$ to the Cauchy stress tensor σ and external forces $\boldsymbol{f}$. In tissues, the inertial term is most generally negligible (overdamped equation), when compared to the divergence of stress, and in the following it will be dropped[3], leading to

$$\boldsymbol{\nabla} \cdot \sigma(\boldsymbol{x}, t) + \boldsymbol{f}(\boldsymbol{x}, t) = \boldsymbol{0}. \tag{1.10}$$

Note that in comparison to the mechanical equilibrium derived in the previous paragraph,, we have considered here possible bulk forces $\boldsymbol{f}(\boldsymbol{x}, t)$ on the domain.

1.2 Tissues as active fluids

1.2.1 Active gel theory

In this section we will present a systematic method to derive hydrodynamic equations for a system weakly out-of-equilibrium, relying on Onsager relations [1]. This approach is the one that was used to derive active polar (and nematic) gel theories [2], which generalize hydrodynamic equations for polar (or nematic) liquid crystals to active materials.

Hydrodynamic variables and conservation laws
Hydrodynamic descriptions suppose that there exist variables (called *hydrodynamic* variables), which are degrees of freedom varying 'slowly' in space and time for the system [3]. They are generally of three types: conserved variables, soft modes (associated to broken continuous symmetries of the system) and critical variables. In this specific context, we don't consider systems close to critical points, and we will only work with conserved variables and variables associated to soft modes. The only originality of the approach below is that it applies to an open system, sustained in an out-of-equilibrium state by constant input of (bio)chemical energy. We will suppose that the deviation from equilibrium remains weak in the following.

[3]The validity of this approximation may be checked in specific examples by relevant dimensionless numbers, such as the *Reynolds number* $\mathcal{R} = \frac{\rho v L}{\eta}$ for a purely viscous material of viscosity η, or the *Mach number* $\mathcal{M} = \frac{v}{\sqrt{E/\rho}} = \frac{v}{c}$ for a purely elastic material (with E the Young modulus, and $c = \sqrt{E/\rho}$ the speed of sound in the material.

Below we describe the tissue as a single phase, made of a single constituent that are the cells themselves. More complex descriptions may account for the extracellular matrix that lies between cells in certain tissues, and couple this additional constituent considering its own rheological model as well [4].

One first obvious candidate for conserved variables is the number density $\rho = \frac{n}{V}$ (with n the number of cells in a tissue), that is associated to the conservation equation[4]:

$$\frac{\partial \rho}{\partial t} + \boldsymbol{\nabla} \cdot \boldsymbol{j} = \mathbf{0}. \tag{1.11}$$

Defining the velocity $\boldsymbol{v} = \frac{d\boldsymbol{x}}{dt}$ of the tissue, which characterizes the flow that transport cells, the current in our context for the density is simply the convective term $\boldsymbol{j} = \rho \boldsymbol{v}$.

Another conserved variable is the impulsion $\boldsymbol{g} = \rho m \boldsymbol{v}$ (where m is the effective mass of cells), for which one can write a similar conservation equation in the form

$$\frac{\partial \boldsymbol{g}}{\partial t} + \boldsymbol{\nabla} \cdot \underline{\underline{\Pi}} = \mathbf{0} \tag{1.12}$$

where the momentum flux in the system is $\underline{\underline{\Pi}} = -\underline{\underline{\sigma}}^t + \rho m \boldsymbol{v} \times \boldsymbol{v}$. σ^t is the total stress in the system and the second term is called the Reynolds tensor[5] and accounts for the inertial transport of the impulsion by the velocity[6].

The last hydrodynamic variable we will consider is associated with a broken continuous symmetry and describes the polarity of cells. We consider indeed that cells may have a preferred orientation, either linked with their shape, or with an intrinsic polarity (biochemical for instance). For instance, in epithelia cells can spontaneously polarize in the apical plane, through interactions between polarity proteins across cellular interfaces. This is called planar-polarity and leads generally to a tendency of neighbouring cells to align with each others, giving rise to large-scale polarity patterns. We therefore introduce a polarization vector $\boldsymbol{p}(\boldsymbol{x}, t)$ as hydrodynamic variable to describe cell polarity.

To summarize, we have identified three hydrodynamic variables to describe the state of the tissue: the density $\rho(\boldsymbol{x}, t)$, the velocity $\boldsymbol{v}(\boldsymbol{x}, t)$ and the polarization $\boldsymbol{p}(\boldsymbol{x}, t)$.

Entropy production and variation of the free energy

To derive generalized hydrodynamic equations coupling the hydrodynamic variables, we need to write the rate of entropy production *à la* de Groot and Mazur[1] and to identify the generalized fluxes and forces.

We consider the tissue maintained at the temperature T, that means that it is in contact to a heat bath of temperature T, with which it can exchange heat Q and work W[7]. The first principle of thermodynamics reads

$$\dot{U} = \dot{Q} + \dot{W} \tag{1.13}$$

where the superimposed dot stands denotes the time derivative.

The entropy balance may be written

$$\dot{S} = \frac{\dot{Q}}{T} + \dot{\mathcal{S}}_{\text{irr}} \tag{1.14}$$

[4]Note that if sink and source terms are added on the right side of equation (1.11) (to model proliferation and apoptosis for instance), ρ will not be conserved anymore in a strict sense, and to be rigorous the derivation below would need to be changed to account explicitly for the thermodynamics of the exchange with a reservoir of cells. In practice this is however rarely done.

[5]This term appears frequently in turbulence and may be found by averaging the Navier-Stokes equation with a fluctuating velocity [5].

[6]For most active gels, it can be neglected as well as the time derivative of the impulsion (acceleration) because the deformation of tissues is inertialess. This leads to the momentum conservation equation $\nabla \cdot \underline{\underline{\sigma}}^t = \mathbf{0}$. In fact, since mass does not play any role in the following, we will use $\boldsymbol{v}(\boldsymbol{x}, t)$ as second independent hydrodynamic variable instead of the impulsion.

[7]In all generality we would have to consider that the system is open as cells gets their nutrients - and therefore their energy - from the bath and we would add a contribution U_e of exchanged energy with a bath. In a similar manner if the number of cells is not constant, an additional energy is required.

where $S(t)$ is the entropy of the tissue, $\dot{\mathcal{S}}_{\rm irr}$ is the irreversible entropy production rate of the system. The second principle states that the irreversible entropy production rate is positive $\dot{\mathcal{S}}_{\rm irr} \geq 0$.

Introducing the Helmholtz free energy $F = U - TS$ for the tissue, we can combine the two principles above and we can express the dissipation from the entropy production rate[8]

$$\mathcal{D} \equiv T\dot{\mathcal{S}}_{\rm irr} = \dot{W} - \dot{F} \geq 0. \tag{1.15}$$

The constitutive equations of the system have to satisfy this fundamental inequality.

For a passive gel at rest, the free energy density f of the system is a function of the two intensive variables, the density ρ and the polarization $\boldsymbol{p}$ and its differential is $df = \mu d\rho - \boldsymbol{h} \cdot d\boldsymbol{p}$. The field conjugate to the density is the chemical potential μ, and the field conjugate to the polarization is the orientational field $\boldsymbol{h}$ [6]. For a passive system moving at a velocity $\boldsymbol{v}$, the density of kinetic energy $\frac{1}{2}\boldsymbol{g}\cdot\boldsymbol{v} = \frac{1}{2}\rho m \boldsymbol{v}^2$ must furthermore be added to the free energy.

For an active gel, one must also take into account the fact that energy is constantly injected into the gel locally. A simple and intuitive way to introduce the energy injection is to assume that it is due to a non-equilibrium chemical reaction such as the consumption of ATP (Adenosine TriPhosphate), the unit of energy in a cell. We denote $\Delta\mu$ the chemical potential associated to the hydrolysis of one ATP molecule into ADP (adenosine diphosphate) and an inorganic phosphate. It corresponds to the energy gain per ATP molecule of the hydrolysis of the reaction, whose rate of advancement (number of ATP consumed per unit time and unit volume) is noted r. The associate rate of change of the free energy per unit volume is calculated as $-r\Delta\mu$. Taking all contributions,the time variation of the free energy reads

$$\frac{dF}{dt} = \int_V d\boldsymbol{r} \left\{ \mu \frac{\partial \rho}{\partial t} - \boldsymbol{h} \cdot \frac{\partial \boldsymbol{p}}{\partial t} + \frac{\partial}{\partial t}\left(\frac{1}{2}\boldsymbol{g}\cdot\boldsymbol{v}\right) - r\Delta\mu \right\} \tag{1.16}$$

To make explicit the expression of orientational field $\boldsymbol{h} = -\frac{\delta F_p}{\delta \boldsymbol{p}}$, we need to define a polarization free energy F_p The polarization energy in 3 dimensions is a functional of the three components of the polarization vector $\boldsymbol{p}$. However, if the system is not in the vicinity of a critical point, there are only two soft modes associated with rotations of the polarization: the modulus of the polarization is not a hydrodynamic variable and is taken to be constant. Without loss of generality, we can consider it as a unit vector. One common choice for a polarization free energy is to take the Frank energy of a nematic liquid crystal[6]:

$$F_p = \int_V d\boldsymbol{r} \left\{ \frac{K_1}{2}\big(\boldsymbol{\nabla}\cdot\boldsymbol{p}\big)^2 + \frac{K_2}{2}\big(\boldsymbol{p}\cdot(\boldsymbol{\nabla}\times\boldsymbol{p})\big)^2 + \frac{K_3}{2}\big(\boldsymbol{p}\times(\boldsymbol{\nabla}\times\boldsymbol{p})\big)^2 - \frac{1}{2}h_\parallel^0\left(\boldsymbol{p}^2 - 1\right) \right\} \tag{1.17}$$

This energy was obtained by Frank using symmetry arguments and developing the energy up to the second order in $\boldsymbol{\nabla p}$[9]. The three first terms correspond to the energies associated to splay, twist and bend deformations (see Fig. 1.2), where the Frank constants K_i are considered positive. $h_\parallel^0$ is a Lagrange multiplier to ensure that $\boldsymbol{p}$ is a unit vector[10]. In general it is useful to decompose the orientational field as $\boldsymbol{h} = -\frac{\delta F_p}{\delta \boldsymbol{p}} = h_\parallel \boldsymbol{p} + \boldsymbol{h}_\perp$, where the first term $h_\parallel = \boldsymbol{h}\cdot\boldsymbol{p}$ is parallel to the polarization and the second term $\boldsymbol{h}_\perp = \big(\boldsymbol{h} - (\boldsymbol{h}\cdot\boldsymbol{p})\,\boldsymbol{p}\big)$ is perpendicular to the polarization. $\boldsymbol{h}_\perp$ may be seen as a driving force density, which tends to minimize gradients of polarization.

[8] Considering explicitly exchanges, one would have to consider an additional positive free energy term $F_e = U_e - TS_e$ in the dissipation.

[9] Here we did not consider terms linear in $\boldsymbol{p}$, because we suppose the system essentially nematic, that is following the symmetry $\boldsymbol{p} \to -\boldsymbol{p}$. For a polar system an additional term $k\boldsymbol{\nabla}\cdot\boldsymbol{p}$ shall be added to the Frank energy, and leads to a surface contribution only if $k =$ cte by the Green-Ostrogradski theorem.

[10] This constraint of unit vector is an approximation, and means that we neglect fluctuations in our mesoscopic volume, by supposing that the polarization of each cell in this volume is exactly $\boldsymbol{p}$.

In the next we consider the simplifying case where all Frank constants are equal $K_1 = K_2 = K_3 = K$, which simplifies the energy into

$$F_p = \frac{1}{2}\int_V d\boldsymbol{r}\left\{K\left|\left|\boldsymbol{\nabla p}\right|\right|^2 - h_{\parallel}^0\left(\boldsymbol{p}^2-1\right)\right\} = \frac{1}{2}\int_V d\boldsymbol{r}\left\{K\left[\left(\boldsymbol{\nabla}\cdot\boldsymbol{p}\right)^2 + \left|\nabla\times\boldsymbol{n}\right|^2\right] - h_{\parallel}^0\left(\boldsymbol{p}^2-1\right)\right\} \tag{1.18}$$

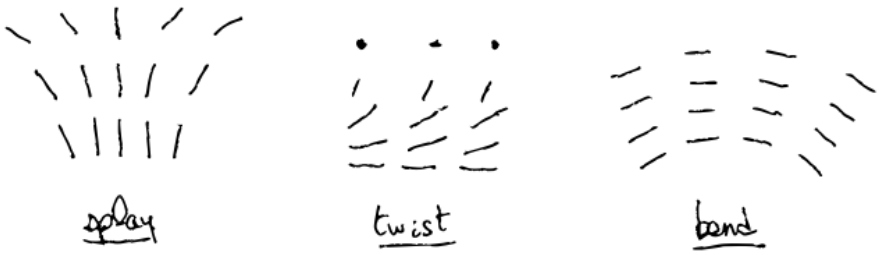

Figure 1.2: Deformations in nematics: splay, bend and twist.

In the simple case of a 2-dimensional system, the polarization is simply characterized by its polar angle θ ($\boldsymbol{p}\cdot\boldsymbol{e}_x = \cos\theta$) and the Frank energy reads then

$$F_p^{\mathrm{2D}} = \frac{1}{2}K\int_A d\boldsymbol{r}\left(\boldsymbol{\nabla}\theta\right)^2 =$$

. The perpendicular part of the orientational field becomes then simply $h_\perp = K\nabla^2\theta$, which means that the equilibrium with respect to polarization is obtained for $\nabla^2\theta = 0$.

In a non-isotropic medium, such as nematic tissues, the total stress is not symmetric anymore. There is an antisymmetric component of the stress associated to torques in the medium. This anti-symmetric component can be calculated from the conservation of momentum and is equal to[11]

$$\sigma^{\mathrm{A}} = \frac{1}{2}\left(h_\alpha p_\beta - p_\alpha h_\beta\right)$$

Considering a pressure P to ensure the incompressibility constraint in the gel, the total stress $\underline{\underline{\sigma}}^t$ may be decomposed as follows

$$\sigma^t_{\alpha\beta} = \sigma_{\alpha\beta} + \sigma^{\mathrm{A}}_{\alpha\beta} - P\delta_{\alpha\beta} \tag{1.19}$$

The component $\sigma_{\alpha\beta}$ is symmetric and is called the deviatoric stress tensor.

Fluxes, forces and time-reversal

According to Onsager theory entropy production (or dissipation) is the sum of terms that are products of generalized hydrodynamic fluxes and hydrodynamic forces. Close to thermodynamic equilibrium, the generalized fluxes entering in the dissipation can be written as a linear combination (with some symmetries on the kinetic coefficients) of the generalized forces[1]. Below, we will therefore start from (minus) the rate of change of the free energy to deduce the entropy production.

[11] If the system is chiral, the antisymmetric par of the stress takes a different form, and needs to be calculated in details, see [7].

We use conservation laws and perform an integration by parts of minus the time derivative of the free energy:

$$\begin{aligned}
-\frac{dF}{dt} = & -\int_V d\boldsymbol{r}\left\{\mu\frac{\partial\rho}{\partial t} - \boldsymbol{h}\cdot\frac{\partial\boldsymbol{p}}{\partial t} + \frac{\partial}{\partial t}\left(\frac{1}{2}\rho m\boldsymbol{v}^2\right) - r\Delta\mu\right\} \\
= & \int d\boldsymbol{r}\left\{\mu\boldsymbol{\nabla}\cdot(\rho\boldsymbol{v}) + \boldsymbol{h}\cdot\frac{\partial\boldsymbol{p}}{\partial t} + \left(\boldsymbol{\nabla}\cdot\underline{\underline{\Pi}}\right)\cdot\boldsymbol{v} + r\Delta\mu\right\} \\
& \text{where we used the two conservation laws for } \boldsymbol{g} \text{ and } \rho \\
= & \int d\boldsymbol{r}\left\{\mu\partial_\alpha(\rho v_\alpha) + h_\alpha\frac{\partial p_\alpha}{\partial t} - \partial_\alpha\sigma^t_{\alpha\beta}v_\beta + r\Delta\mu\right\} \\
& \text{where we used the definition } \Pi_{\alpha\beta} = -\sigma^t_{\alpha\beta} + \rho m v_\alpha v_\beta \text{ and dropped inertial terms.} \\
= & \int d\boldsymbol{r}\left\{-\rho v_\alpha\partial_\alpha\mu + h_\alpha\frac{\partial p_\alpha}{\partial t} + \sigma^t_{\alpha\beta}\partial_\alpha v_\beta + r\Delta\mu\right\} \\
& \text{where we performed integrations by parts.}
\end{aligned}$$

At this point, we need an additional relation between the density and the pressure in the fluid. This is the Gibbs-Duhem relation, which for a nematic fluid [6] reads[12]

$$dP - \frac{S}{V}dT = \rho d\mu + \boldsymbol{h}\cdot d\boldsymbol{p} \tag{1.20}$$

where $dT = 0$ because the tissue is in contact with a thermal bath. Replacing in minus the rate of change of the free energy above leads to

$$\begin{aligned}
-\frac{dF}{dt} = & \int d\boldsymbol{r}\left\{-v_\alpha\left(\partial_\alpha P - h_\beta\partial_\alpha p_\beta\right) + h_\alpha\frac{\partial p_\alpha}{\partial t} + \sigma^t_{\alpha\beta}\partial_\alpha v_\beta + r\Delta\mu\right\} \\
= & \int d\boldsymbol{r}\left\{P\delta_{\alpha\beta}\partial_\alpha v_\beta + h_\beta v_\alpha\partial_\alpha p_\beta + h_\alpha\frac{\partial p_\alpha}{\partial t} + \sigma_{\alpha\beta}\partial_\alpha v_\beta + \frac{1}{2}\left(h_\alpha p_\beta - p_\alpha h_\beta\right)\partial_\alpha v_\beta - P\delta_{\alpha\beta}\partial_\alpha v_\beta + r\Delta\mu\right\} \\
& \text{where we integrated by part and used the definition of } \sigma^t_{\alpha\beta} \\
= & \int d\boldsymbol{r}\left\{\sigma_{\alpha\beta}\partial_\alpha v_\beta + h_\alpha\left(\frac{\partial p_\alpha}{\partial t} + v_\beta\partial_\beta p_\alpha + \frac{1}{2}\left(p_\beta\partial_\alpha v_\beta - p_\beta\partial_\beta v_\alpha\right)\right) + r\Delta\mu\right\} \\
= & \int d\boldsymbol{r}\left\{\sigma_{\alpha\beta}v_{\alpha\beta} + h_\alpha P_\alpha + r\Delta\mu\right\}
\end{aligned} \tag{1.21}$$

where we introduced the convected corotational time derivative of the polarization

$$P_\alpha \equiv \frac{Dp_\alpha}{Dt} = \frac{\partial p_\alpha}{\partial t} + v_\beta\partial_\beta p_\alpha + \omega_{\alpha\beta}p_\beta \tag{1.22}$$

the vorticity (antisymmetric) tensor

$$\underline{\underline{\omega}} = \frac{1}{2}\boldsymbol{\nabla}\times\boldsymbol{v} \leftrightarrow \omega_{\alpha\beta} = \frac{1}{2}\left(\partial_\alpha v_\beta - \partial_\beta v_\alpha\right) \tag{1.23}$$

and the (symmetric) strain rate tensor (because $\sigma_{\alpha\beta}$ is symmetric)

$$v_{\alpha\beta} = \frac{1}{2}\left(\partial_\alpha v_\beta + \partial_\beta v_\alpha\right) \tag{1.24}$$

[12]The relation of Gibbs-Duhem ensures the extensivity of the variables ρ and $\boldsymbol{h}$.

This form of free energy (1.21) may be read by identifying pairs of conjugate generalized fluxes and forces

$$\text{flux} \leftrightarrow \text{force} \tag{1.25}$$
$$\sigma_{\alpha\beta} \leftrightarrow v_{\alpha\beta} \tag{1.26}$$
$$P_\alpha \leftrightarrow h_\alpha \tag{1.27}$$
$$r \leftrightarrow \Delta\mu \tag{1.28}$$
$$\tag{1.29}$$

The rate of change of the free energy (1.21) can be divided into an irreversible part $\dot{F} = \dot{F}_{\text{rev}} + \dot{F}_{\text{irr}} = \dot{W} - T\dot{\mathcal{S}}$ (see (1.15)). We therefore decompose the fluxes into reactive and dissipative parts as well. They are characterized by their different signature with respect to time-reversal, and will depend on the - well-defined - signature of generalized forces under time-reversal: $v_{\alpha\beta}$ has a signature -1 (because the velocity has a signature -1), while h_α and $\Delta\mu$ have a signature $+1$. We write

$$\sigma_{\alpha\beta} = \sigma^r_{\alpha\beta} + \sigma^d_{\alpha\beta} \tag{1.30}$$
$$P_\alpha = P^r_\alpha + P^d_\alpha \tag{1.31}$$
$$r = r^r + r^d \tag{1.32}$$

To satisfy the second principle of thermodynamics $T\dot{\mathcal{S}} \geq 0$, the dissipative fluxes have the same signature under time reversal as their conjugate forces, while reactive fluxes have the opposite signature. Therefore, $\sigma^d_{\alpha\beta}$ has a signature -1, and r^d and P^d_α have a signature $+1$. Reactive parts have correspondingly opposite signatures.

The rate of entropy production $T\dot{\mathcal{S}} = -\dot{F}_{\text{irr}}$ reads therefore

$$T\dot{\mathcal{S}} = \int d\boldsymbol{r} \left\{ \sigma_{\alpha\beta} v^d_{\alpha\beta} + h_\alpha P^d_\alpha + r^d \Delta\mu \right\} \tag{1.33}$$

Now we can write down the Onsager relations, that is all the possible linear relations between forces and fluxes, as far as they respect the symmetry of the system and have either the same time-reversal signature for dissipative fluxes or opposite time-reversal signature for reactive fluxes. Respecting symmetries of the system means that vectors can be constructed only with vectors and gradients, but gradients are supposed subdominant (slowly varying hydrodynamic variables), and tensors can be constructed with $\delta_{\alpha\beta}$ or $q_{\alpha\beta} = p_\alpha p_\beta - \frac{1}{3}\delta_{\alpha\beta}$.

By convenience, we split all tensors into diagonal and traceless parts: $\sigma_{\alpha\beta} = \sigma\delta_{\alpha\beta} + \tilde{\sigma}_{\alpha\beta}$, with $\sigma = \frac{1}{3}\sigma_{\alpha\alpha}$ and $\tilde{\sigma}_{\alpha\alpha} = 0$. Similarly, we write $v_{\alpha\beta} = \frac{\bar{v}}{3}\delta_{\alpha\beta} + \tilde{v}_{\alpha\beta} = \frac{\bar{v}}{3}\delta_{\alpha\beta}$.

Dissipative fluxes. Only fluxes and forces with the same time-reversal signature are coupled. For the stress tensor, this leads to

$$\sigma^d = \bar{\eta}\frac{\bar{v}}{3} \tag{1.34a}$$
$$\tilde{\sigma}^d_{\alpha\beta} = 2\eta\tilde{v}_{\alpha\beta} \tag{1.34b}$$

where $\bar{\eta}$ is the longitudinal viscosity while η is called the shear viscosity[13]

The two other fluxes are coupled and the corresponding constitutive equations read

$$P^d_\alpha = \frac{h_\alpha}{\gamma} + \lambda p_\alpha \Delta\mu \tag{1.35}$$

[13] In all generality, the most generic linear combination between the stress and strain is tensors is described by a viscosity tensor or rank 4 $\tilde{\sigma}^d_{\alpha\beta} = \eta^{\gamma\delta}_{\alpha\beta}\tilde{v}_{\alpha\beta}$

and

$$r^d = \Lambda\Delta\mu + \lambda p_\alpha h_\alpha \tag{1.36}$$

because h_α and $\Delta\mu$ have the same signature +1. Note that the coefficient λ is the same because the matrix of coefficients shall be symmetric (Onsager relations).

Reactive fluxes. The reactive Onsager matrix is antisymmetric and couples fluxes and forces of opposite time reversal signatures:

$$\sigma^r = -\bar{\zeta}\Delta\mu + \bar{\nu} p_\alpha h_\alpha \tag{1.37a}$$

$$\tilde{\sigma}^r_{\alpha\beta} = -\zeta\Delta\mu q_{\alpha\beta} + \frac{\nu}{2}\left(p_\alpha h_\beta + p_\beta h_\alpha - \frac{2}{3} p_\gamma h_\gamma \delta_{\alpha\beta}\right) \tag{1.37b}$$

$$P^r_\alpha = -\bar{\nu} p_\alpha \frac{\bar{v}}{3} - \nu_1 p_\beta \tilde{v}_{\alpha\beta} \tag{1.37c}$$

$$r^r = \bar{\zeta}\frac{\bar{v}}{3} + \zeta q_{\alpha\beta}\tilde{v}_{\alpha\beta} \tag{1.37d}$$

In the following, we will consider an incompressible tissue, such that $\bar{v} = \boldsymbol{\nabla}\cdot\boldsymbol{v} = 0$. In this case, the diagonal component of the stress can be included in the pressure, which is a Lagrange multiplier ensuring incompressiblity and one can set $\bar{\zeta} = \bar{\nu} = \bar{\eta} = 0$

Summary of the active tissue model

In summary, the hydrodynamic equations for an incompressible one-component active tissue of nematic symmetry are given by

$$m\rho\big(\partial_t + \boldsymbol{v}\cdot\nabla\big)\boldsymbol{v} = -\boldsymbol{\nabla}P + \boldsymbol{\nabla}\cdot\underline{\underline{\sigma}}^t \tag{1.38a}$$

$$\big(\partial_t + v_\beta\partial_\beta\big)p_\alpha + \omega_{\alpha\beta}p_\beta = -\nu v_{\alpha\beta}p_\beta + \frac{1}{\gamma}h_\alpha + \lambda\Delta\mu p_\alpha \tag{1.38b}$$

to be supplemented with the incompressibility condition $\boldsymbol{\nabla}\cdot\boldsymbol{v} = 0$, the expression of the molecular field (for the approximation of one Frank constant)

$$h_\alpha = K\nabla^2 p_\alpha + h^0_\parallel p_\alpha \tag{1.39}$$

where $h^0_\parallel$ is a Lagrange multiplier to be determined from the constraint $|\boldsymbol{p}| = 1$. Finally the total stress tensor is the sum of deviatoric and trace parts of the dissipative and reactive components plus the anti-symmetric component, and may be conveniently separated into passive and active parts $\sigma^t_{\alpha\beta} = \sigma^p_{\alpha\beta} + \sigma^a_{\alpha\beta}$ where

$$\sigma^p_{\alpha\beta} = 2\eta\tilde{v}_{\alpha\beta} + \frac{\nu}{2}\left(p_\alpha h_\beta + p_\beta h_\alpha - \frac{2}{3}p_\gamma h_\gamma\delta_{\alpha\beta}\right) - \frac{1}{2}\big(p_\alpha h_\beta - h_\alpha p_\beta\big), \tag{1.40a}$$

$$\sigma^a_{\alpha\beta} = -\zeta\Delta\mu q_{\alpha\beta} \tag{1.40b}$$

1.2.2 Application: spontaneous flow in a confined epithelium

Here we present an instability which has been observed in tissues cultured *in vitro* in a confined situation [8].

As sketched on Fig. 1.3, we consider a 2-dimensional epithelium confined between two flat boundaries separated by a distance L along the direction x. The tissue is supposed long enough in the y-direction to suppose invariance by translation along y. To quantify the elongation of cells, we introduce $r(\theta)$ the position

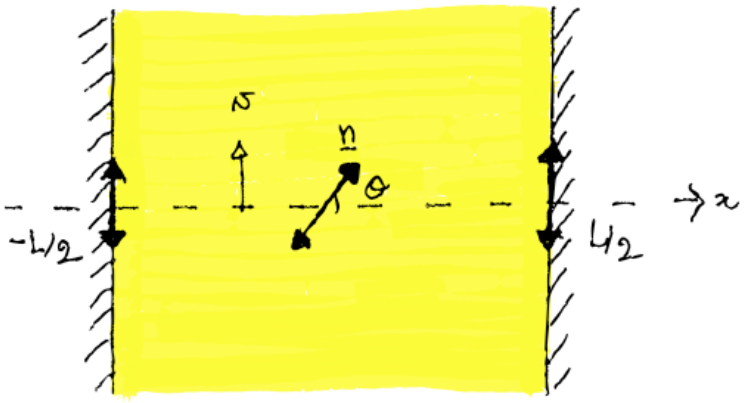

Figure 1.3: Sketch of the 2-dimensional tissue in confinement between two plates, separated by a length L and supposed invariant along y. $\boldsymbol{n}$ is the director field and the velocity field is denoted by $\boldsymbol{v}$

of the contour of a cell in polar coordinates away from the cell center, with θ the angle made with the basis vector $\boldsymbol{e}_x$. One could, in principle, introduce a polarization vector of cells

$$\boldsymbol{p}^{\text{cell}} = \frac{1}{2\pi R}\begin{pmatrix} \int_0^{2\pi} d\theta\, r(\theta)\cos\theta \\ \int_0^{2\pi} d\theta\, r(\theta)\sin\theta \end{pmatrix} \tag{1.41}$$

where we introduced $R = \frac{1}{2\pi}\int_0^{2\pi} d\theta\, r(\theta)$ the average radius of cells. Nevertheless, the shape of cells is better characterized by a nematic order parameter, which does not include a notion of polarity

$$\underline{\underline{Q}}^{\text{cell}} = \frac{1}{2\pi R}\begin{pmatrix} \int_0^{2\pi} d\theta\, r(\theta)\cos(2\theta) & \int_0^{2\pi} d\theta\, r(\theta)\sin(2\theta) \\ \int_0^{2\pi} d\theta\, r(\theta)\sin(2\theta) & -\int_0^{2\pi} d\theta\, r(\theta)\cos(2\theta) \end{pmatrix} \tag{1.42}$$

which is a symmetric and traceless tensor. We can rewrite this tensor as follows

$$\underline{\underline{Q}}^{\text{cell}} = 2S\begin{pmatrix} n_x^2 - \frac{1}{2} & n_x n_y \\ n_x n_y & n_y^2 - \frac{1}{2} \end{pmatrix} \tag{1.43}$$

with $S \equiv \sqrt{(Q_{xx}^{\text{cell}})^2 + (Q_{yy}^{\text{cell}})^2}$ and we introduced a normalized nematic director $\boldsymbol{n}$ such that $\boldsymbol{n}^2 = 1$. Both $\boldsymbol{n}$ and $-\boldsymbol{n}$ lead to the same tensor $\underline{\underline{Q}}^{\text{cell}}$, as required by the fact that the nematic order parameter shall not vary by a rotation of π.

In the next, we will consider a mean local cell elongation tensor, averaged over a certain mesoscopic area containing a sufficient number of cells α

$$\underline{\underline{Q}} = \left\langle \underline{\underline{Q}}^{\text{cell}} \right\rangle = \frac{\sum_\alpha A_\alpha \underline{\underline{Q}}_\alpha}{\sum_\alpha A_\alpha} \tag{1.44}$$

This definition gives less weight to cells that occupy a smaller area in the 2-dimensional tissue.

The director $\boldsymbol{n} = (\cos\theta, \sin\theta)$ allows us to precise the boundary conditions of the cell elongation in this system $\theta\left(\frac{-L}{2}\right) = \theta\left(\frac{L}{2}\right) = \frac{\pi}{2}$. Furthermore, the tissue is free to slide along boundaries, such that $\sigma_{xy}\left(-\frac{L}{2}\right) = \sigma_{xy}\left(\frac{L}{2}\right) = 0$

We assume that the tissue is described by active viscous nematic hydrodynamic equations, as derived in the previous subsection:

$$\sigma_{ij}^t = -P\delta_{ij} + 2\eta\tilde{v}_{ij} + \zeta\Delta\mu\left[n_i n_j - \frac{1}{2}\delta_{ij}\right] + \frac{\nu}{2}\left(n_i h_j + n_j h_i - \frac{1}{2}n_k h_k \delta_{ij}\right) - \frac{1}{2}\left(n_i h_j - n_j h_i\right) \tag{1.45}$$

$$\partial_t n_i + v_j \partial_j n_i + \omega_{ij} n_j = \frac{1}{\gamma} h_i - \nu \tilde{v}_{ij} n_j \tag{1.46}$$

where we have included the pressure into the total stress. In absence of inertia, momentum conservation is given here simply by

$$\partial_i \sigma^t_{ij} = 0$$

We further assume the tissue incompressible $\partial_i v_j = 0$, and the pressure$P$ is the Lagrange multiplier enforcing this constraint. The molecular field derives from the Frank energy

$$\mathcal{F}_F = \int_S d^2\boldsymbol{r} \left[\frac{K}{2} \big(\boldsymbol{\nabla n}\big)^2 + \frac{\lambda}{2} \big(\boldsymbol{n}^2 - 1\big) \right] \tag{1.47}$$

where λ is the Lagrange multiplier enforcing $\boldsymbol{n}^2 = 1$, and reads

$$h_i = -\frac{\partial \mathcal{F}}{\partial n_i} = K \Delta n_i - \lambda n_i \tag{1.48}$$

In 2 dimensions, it can be rewritten

$$h_x = -\big[K(\partial_x \theta)^2 + \lambda\big] \cos\theta - K\big(\partial_x^2 \theta\big) \sin\theta \tag{1.49a}$$
$$h_y = -\big[K(\partial_x \theta)^2 + \lambda\big] \sin\theta + K\big(\partial_x^2 \theta\big) \cos\theta \tag{1.49b}$$

We introduce $h_\parallel = n_x h_x + n_y h_y$ and $h_\perp = n_y h_x - n_x h_y$, the components of $\boldsymbol{h}$ parallel and perpendicular to $\boldsymbol{n}$:

$$h_\parallel = -\big[K(\partial_x \theta)^2 + \lambda\big] \tag{1.50a}$$
$$h_\perp = -K(\partial_x^2 \theta) \tag{1.50b}$$

In absence of flow, at steady-state, the above equations lead to $\boldsymbol{h} = K\Delta\boldsymbol{n} - \lambda\boldsymbol{n} = \boldsymbol{0}$. To satisfy the boundary conditions, the only possible solution is $\theta = \frac{\pi}{2}$.

The goal now is to study the stability of this solution. In the case where the solution is unstable, a distorsion in the cell elongation pattern and a spontaneous flow can emerge in the 2D tissue. To study the stability of the system, we perturb the equilibrium solution $\theta = \frac{\pi}{2} + \delta\theta$, where $\delta\theta \ll 1$.

The incompressibility condition implies $\partial_x v_x + \partial_y v_y = \partial_x v_x = 0$, and v_x shall vanish at the walls, such that $v_x = 0$. The polarity dynamics gives

$$\partial_t n_x + \frac{1}{2}(\partial_x v_y) n_y = \frac{1}{\gamma} h_x - \frac{\nu}{2}(\partial_x v_y) n_y \tag{1.51a}$$
$$\partial_t n_y - \frac{1}{2}(\partial_x v_y) n_x = \frac{1}{\gamma} h_y - \frac{\nu}{2}(\partial_x v_y) n_x \tag{1.51b}$$

where we have used $\omega_{xy} = \frac{1}{2}\partial_x v_y$ and $\omega_{yx} = -\frac{1}{2}\partial_x v_y$. Noting the identity

$$\partial_t \theta = n_x(\partial_t n_y) - n_y(\partial_t n_x)$$

and the (1.50b), we get

$$\partial_t \theta = \frac{K}{\gamma} \partial_x^2 \theta - \frac{\partial_x v_y}{2} \big(-1 + \nu \cos(2\theta) \big) \tag{1.52}$$

which, in the limit $\delta\theta \ll 1$, becomes

$$\partial_t \theta = \frac{K}{\gamma} \partial_x^2 \delta\theta + \frac{1+\nu}{2} \partial_x v_y \tag{1.53}$$

To determine the solution for the flow profile v_y, we write the force balance taking into account of the invariance along y:

$$\partial_x \sigma_{xx} = 0, \qquad \partial_x \sigma_{xy} = 0.$$

Since $\sigma_{xy} = 0$ at the boundaries, we have uniformly $\sigma_{xy} = 0$ in the tissue, which reads

$$\eta \partial_x v_y + \nu \cos\theta \sin\theta h_\parallel + \frac{\nu}{2}\big(\sin^2\theta - \cos^2\theta\big) h_\perp + \frac{1}{2} h_\perp + \zeta \Delta\mu \cos\theta \sin\theta = 0 \tag{1.54}$$

where we used the fact that

$$\begin{aligned} n_x h_y + n_y h_x &= \cos\theta\big(h_\parallel \sin\theta - h_\perp \cos\theta\big) + \sin\theta\big(h_\parallel + h_\perp \sin\theta\big) \\ &= 2 h_\parallel \cos\theta \sin\theta + \big(\sin^2\theta - \cos^2\theta\big) h_\perp \end{aligned} \tag{1.55}$$

Moreover, since $\boldsymbol{n} = 1$, we have the relation

$$0 = \boldsymbol{n} \cdot \partial_t \boldsymbol{n} = n_x(\partial_t n_x) + n_y(\partial_t n_y) = \frac{h_\parallel}{\gamma} - \nu(\partial_x v_y) n_x n_y,$$

which yields

$$h_\parallel = \nu\gamma(\partial_x v_y) n_x n_y \tag{1.56}$$

Using the expressions for $h_\parallel$ and $h_\perp$, (1.54) reads

$$\big(\eta + \nu^2 \gamma \cos^2\theta \sin^2\theta\big)\partial_x v_y - \frac{K}{2}\partial_x^2\theta\big(1 - \nu\cos(2\theta)\big) + \zeta\Delta\mu\cos\theta\sin\theta = 0 \tag{1.57}$$

which becomes, in the limit $\delta\theta \ll 1$

$$\partial_x v_y = \frac{K}{2\eta}(1+\nu)\partial_x^2\delta\theta + \frac{\zeta\Delta\mu}{\eta}\delta\theta \tag{1.58}$$

Combining (1.53) and (1.58), we obtain a differential equation for the orientation of the angular field $\delta\theta$

$$\partial_t \delta\theta = K\left(\frac{1}{\gamma} + \frac{(1+\nu)^2}{4\eta}\right)\partial_x^2\delta\theta + \frac{\zeta\Delta\mu(1+\nu)}{2\eta}\delta\theta \tag{1.59}$$

Using an ansatz $\delta\theta = \epsilon(t)\cos\left(\frac{\pi x}{L}\right)$ for the solution, we get

$$\partial_t \epsilon = \left[\frac{\zeta\Delta\mu(1+\nu)}{2\eta} - K\left(\frac{1}{\gamma} + \frac{(1+\nu)^2}{4\eta}\right)\frac{\pi^2}{L^2}\right]\epsilon \tag{1.60}$$

which exhibits an instability (exponentially growing solution when

$$\frac{\zeta\Delta\mu(1+\nu)}{2\eta K} > \left(\frac{1}{\gamma} + \frac{(1+\nu)^2}{4\eta}\right)\frac{\pi^2}{L^2}$$

which defines a critical length L_c above which the tissue becomes unstable

$$L > L_c \equiv \pi\sqrt{\frac{K}{\zeta\Delta\mu}}\sqrt{\frac{2\eta}{\gamma(1+\nu)} + \frac{1+\nu}{2}} \tag{1.61}$$

The tissue becomes therefore unstable for a **contractile** tissue $\zeta\Delta\mu > 0$ and for large enough confinement length L. If the length of confinement is too small, distorsions in the nematic orientation become energetically too costly and the instability does not develop.

Experimentally, this instability is indeed observed (Fig. 1.4) above a well-defined critical length of length, as shown on Fig. 1.5.

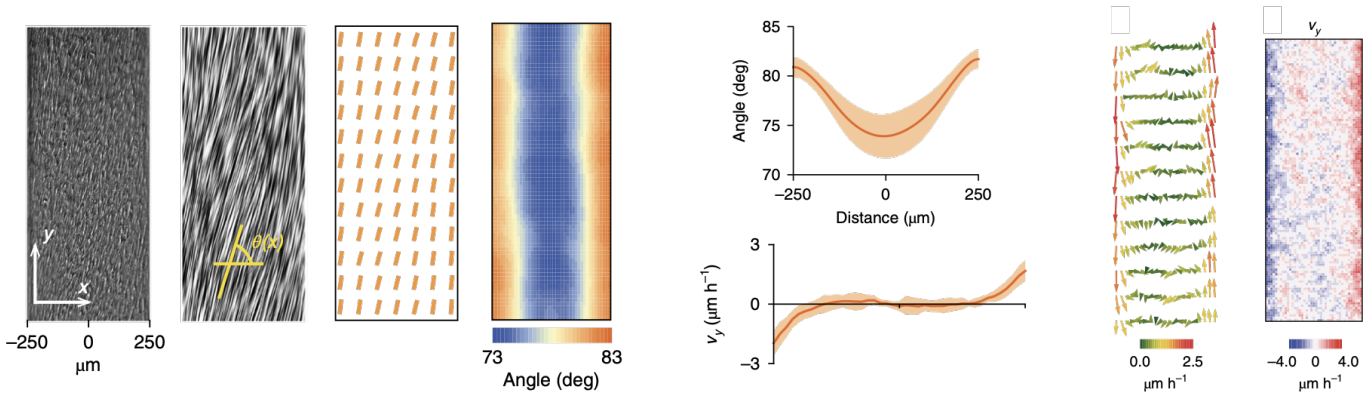

Figure 1.4: Spontaneous flow profile and angle profile in a confined 2-dimensional tissue made of RPE1 cells [8].

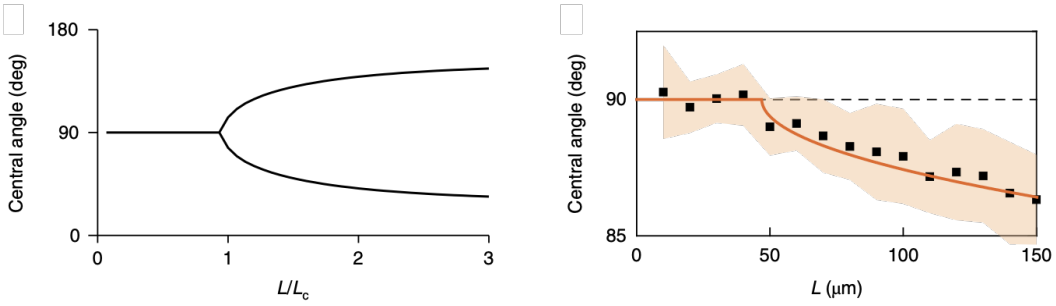

Figure 1.5: Bifurcation diagrams predicted theoretically (left) and found experimentally (right) in [8].

1.2.3 Topological defects

We consider a 2-dimensional nematic tissue, and suppose that the distortion of its director field $\boldsymbol{n} = (\cos\phi, \sin\phi)$ is controlled by the Frank-Oseen energy $\mathcal{F} = \int_S d^2\boldsymbol{r}\frac{K}{2}(\partial_i \boldsymbol{n})^2 = \int_S d^2\boldsymbol{r}\frac{K}{2}(\partial_i\phi)^2$. The angles ϕ and $\phi + \pi$ refer to the same nematic state. Minimizing this energy with respect to θ, yields a Poisson equation $\Delta\phi = 0$, where $\Delta = \partial_x^2 + \partial_y^2$ is the Laplacian operator.

Cellular elongation patterns of tissues, like for nematic liquid crystals, can exhibit topological defects. A defect is a point where the nematic angle is not defined. These defects can be classified according to their topological charge, which is defined by

$$m = \frac{1}{2\pi}\oint_{\mathcal{C}} d\ell_i \partial_i \phi \tag{1.62}$$

where $\mathcal{C}$ is a curve of positive orientation that encloses the charge.

The topological charges quantifies how much the director field rotates along the curve and does not depend on the precise shape of the curve $\mathcal{C}$: a full rotation in the clockwise direction corresponds to a charge $+1$, and in the anticlockwise direction to a charge -1.

One can find the nematic orientation profile around a defect using the polar expression of the Laplacian operator $\Delta = \partial_r^2 + \frac{1}{r}\partial_r + \frac{1}{r^2}\partial_\theta^2$. A solution that does not depend on r leads to

$$\phi(\theta) = m\theta + \phi_0 \tag{1.63}$$

where m is the nematic charge of the defect.

Since the direction of $\boldsymbol{n}$ must be well-defined at each point, one has the constraint

$$\oint_\theta d\phi = 2\pi m = k\pi \tag{1.64}$$

where $k \in \mathbb{Z}$ For nematic defect, m must be a multiple of $1/2$ to ensure periodicity and nematic symmetry ($\phi \leftrightarrow \phi + \pi$). The constant angle ϕ_0 corresponds simply to a solid rotation of the defect.

Inserting (1.63) into the Frank energy, the distortion energy associated with a defect of charge m can be calculated as $\mathcal{F}_m = \pi K m^2 \log \frac{R}{r_c}$, where R and r_c are upper and lower cutoff radii around the defect. Hence, a defect with a lower topological charge has a smaller energy and is favored.

On Fig.1.6, we show the corresponding solutions for the lowest-charge defects $m = +1/2$ and $m = -1/2$.

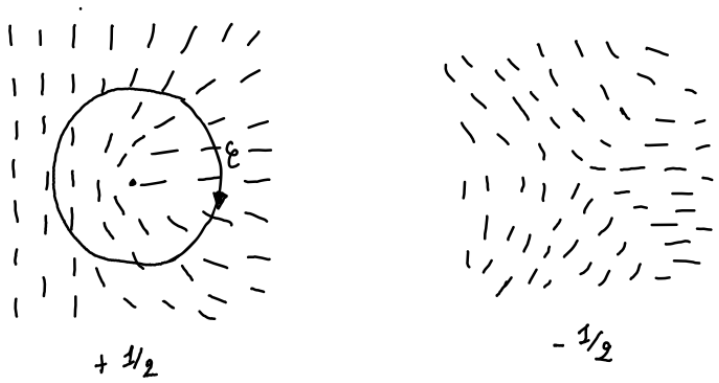

Figure 1.6: Topological defects and nematic orientation profiles for charge defects $m = \frac{1}{2}$ and $m = -\frac{1}{2}$.

One should note that the two $\pm 1/2$ defects have different symmetries: the $+1/2$ defect has a preferred direction (left to right here), while the $-1/2$ has a 3-fold rotational symmetry, and it cannot acquire a velocity.

Experimentally, Duclos et al. [9] have observed patterns of elongated cells cultured *in vitro* (NIH 3T3 mouse embryo fibroblasts) grown on circular discs. The cells tend to orient their axis of elongation parallel to the external interface, as often observed both *in vitro* and *in vivo*. On a disc this enforces a total topological charge of $+1$; therefore defects must arise within the tissue. The number of visible nematic defects decrease over time as the tissue dynamically rearranges and defects of opposite charge annihilate. Eventually the system converges to an organization with only two $+1/2$ defects which form at a reliable distance within the disc. This is consistent with the effective energy argument: the system prefers to choose defect with low charges. In fact, even the final position of defects is also predicted by minimizing the effective distortion energy.

Bibliography

[1] Sybren Ruurds De Groot and Peter Mazur. *Non-equilibrium thermodynamics*. Courier Corporation, 2013.

[2] Karsten Kruse, Jean-Francois Joanny, Frank Jülicher, Jacques Prost, and Ken Sekimoto. Generic theory of active polar gels: a paradigm for cytoskeletal dynamics. *The European Physical Journal E*, 16(1): 5–16, 2005.

[3] Paul M Chaikin, Tom C Lubensky, and Thomas A Witten. *Principles of condensed matter physics*, volume 10. Cambridge university press Cambridge, 1995.

[4] Vikram Deshpande, Antonio DeSimone, Robert McMeeking, and Pierre Recho. Chemo-mechanical model of a cell as a stochastic active gel. *Journal of the Mechanics and Physics of Solids*, 151:104381, 2021.

[5] P Yo Chou. On velocity correlations and the solutions of the equations of turbulent fluctuation. *Quarterly of applied mathematics*, 3(1):38–54, 1945.

[6] Pierre-Gilles De Gennes and Jacques Prost. *The physics of liquid crystals*. Number 83. Oxford university press, 1993.

[7] S Fürthauer, M Strempel, Stephan W Grill, and Frank Jülicher. Active chiral fluids. *The European physical journal E*, 35(9):1–13, 2012.

[8] G Duclos, C Blanch-Mercader, V Yashunsky, G Salbreux, J-F Joanny, J Prost, and Pascal Silberzan. Spontaneous shear flow in confined cellular nematics. *Nature physics*, 14(7):728–732, 2018.

[9] Guillaume Duclos, Christoph Erlenkämper, Jean-François Joanny, and Pascal Silberzan. Topological defects in confined populations of spindle-shaped cells. *Nature Physics*, 13(1):58–62, 2017.