



# Mechanical Model of Fiber Morphogenesis in the Liver

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**Abstract.** We give a description of fibroblast cell diffusion in a soft tissue, paying special attention to the coupling of force, matter and microforce balance laws through a suitable dissipation principle. To this end we cast our framework into a multi-level schematics, comprising both kinematics and kinetics, which is based on a characterization of the free energy. This way we lay down first a force balance law, where force and stress fields are defined as power conjugate quantities to velocity fields and their gradients, then we give a species molar balance law, with chemical potential test fields, as power conjugate quantities to the rate of change of species concentration, and finally a microforce balance law. The main feature of this framework is the constitutive expression for the chemical potential which turns out to be split in a natural way into a term derived from the homogeneous convex part of the free energy and an *active* external chemical potential giving rise to the spinodal decomposition. The active part of the chemical potential is given an expression depending on the cell density and resembling the one defined in [29], where it is meant to characterize an upward cell diffusion induced by cell motility.

**Keywords:** Pattern formation · Cell aggregation · Motility induced phase separation

## 1 Introduction

Our ultimate goal is to construct the simplest possible biomechanical model accounting for the fibrosis pattern formation in the liver.

Fibrosis consists in collagen fiber deposition of fibroblasts migrating in the liver tissue. These fibers turn out to be arranged in regular patterns evolving with the disease progression.

As a first step we plan to extend a basic diffusion model [33] for describing *active cell diffusion*, i.e. an *uphill diffusion* driven by *cell motility*, and cast such a description into a Cahn-Hilliard equation framework.

Pattern formations in *biological systems* and *materials science* is a wide research area, comprising both the general framework setting and the evolution analysis, where both analytical methods and numerical simulations are used for characterizing time evolutions and pattern instabilities.

Starting from the work of Cahn [1, 5, 7, 8, 24], *nucleation*, *solidification*, and *phase separation*, from topics in *materials science*, have been extended over the following years to the general framework of *phase-field* methods [3, 19], comprising a wide range of microstructural evolutions. A *reaction-diffusion* theory for pattern formation in *biological systems* was proposed in 1952 by Turing in his work on morphogenesis [35], consisting in the description of the concurrent diffusion of two competing species. In 1972 Meinhardt and Gierer introduced the notions of *activating* and *inhibiting* chemicals to model pattern formation during a developmental process [21, 26]. A mechano-chemical theory of pattern formation was developed by Murray and Oster [28] based on cell adhesion to a substrate or to the extra cellular matrix as a mechanism for pattern formation in biological systems [29].

Recently a growing interest in *motility induced phase separation* has been motivated by studies on active matter, such as bacterial biofilm formation or tumor cell migration, or more generally on the dynamics of self-propelled particles [11, 12, 31, 34, 36].

The main feature of the framework outlined here is the derivation of the constitutive expression for the chemical potential. It turns out to be split in a natural way into a term derived from the homogeneous convex part of the free energy and an *active* external chemical potential giving rise to the spinodal decomposition. The active part of the chemical potential is given an expression depending on the cell density and resembling the one defined in [29], where it is meant to characterize an upward cell diffusion induced by cell motility.

## 2 Species Diffusion in a Crystal Lattice

We outline here the basic setting for describing cell diffusion in a tissue referring to the atomic diffusion in a crystal lattice [23], as a prototype.

### 2.1 Kinematics, Kinetics and Species Power Balance

Let us denote by

$$\chi : \mathcal{R}_o \rightarrow \mathcal{R}, \quad (1)$$

a time dependent deformation of a crystal lattice from the reference shape to the current shape. Describing the *intercalation distortion* of a crystal lattice [25] as a spherical tensor field

$$\mathbf{G} = \beta^{\frac{1}{3}} \mathbf{I}, \quad (2)$$

with  $\det \mathbf{G} = \beta$ , and ruling out any plastic distortion, the accompanying *elastic distortion*  $\mathbf{F}$  is defined by the deformation gradient decomposition

$$\mathbf{F}_o \equiv \nabla \chi = \mathbf{F} \mathbf{G}. \tag{3}$$

It is convenient to describe the amount of intercalated **b**-atoms by the *concentration*

$$c = \frac{\rho_{\mathbf{b}}}{\rho_o} = \frac{\langle \text{molar density of species } \mathbf{b} \text{ per unit reference volume} \rangle}{\langle \text{molar density of lattice sites per unit reference volume} \rangle}, \tag{4}$$

and make the assumption that it is related to the lattice volume change through

$$\beta = 1 + \alpha (c - c_o), \tag{5}$$

where  $\alpha$  is a stoichiometric positive constant coefficient and  $c_o$  is a reference concentration.

If we denote by  $\rho$  the molar density of lattice sites *per unit current volume*, then by (4) the product  $c\rho$  is the molar density of species **b** per unit current volume. For any regular subset  $\mathcal{P} \subset \mathcal{R}$  which is *convected* from a reference subset  $\mathcal{P}_o \subset \mathcal{R}_o$  by the same deformation (1) the rate of change of the amount of species **b** will be

$$\frac{d}{dt} \int_{\mathcal{P}} c\rho dV = \frac{d}{dt} \int_{\mathcal{P}_o} c\rho \det \mathbf{F}_o dV = \frac{d}{dt} \int_{\mathcal{P}_o} c\rho_o dV = \int_{\mathcal{P}_o} \dot{c}\rho_o dV = \int_{\mathcal{P}} \dot{c}\rho dV. \tag{6}$$

Denoting by  $\mathbf{h}$  the *molar flux* per unit current area, and by  $h$  a *supply* density per unit current volume, the species **b** *molar balance law* reads

$$\int_{\mathcal{P}} \dot{c}\rho dV = - \int_{\partial \mathcal{P}} \mathbf{h} \cdot \mathbf{n} dA + \int_{\mathcal{P}} h dV, \tag{7}$$

and localizes to

$$\dot{c}\rho = - \operatorname{div} \mathbf{h} + h. \tag{8}$$

Let us set now a scalar field  $\underline{\mu}$ , power conjugate to the kinetic descriptor  $\dot{c}\rho$ , transforming the *molar balance law* (8) into a *power balance law*

$$\int_{\mathcal{P}} \underline{\mu} \dot{c}\rho dV = - \int_{\mathcal{P}} \underline{\mu} \operatorname{div} \mathbf{h} dV + \int_{\mathcal{P}} \underline{\mu} h dV \quad \forall \underline{\mu}. \tag{9}$$

Since

$$\operatorname{div}(\underline{\mu} \mathbf{h}) = \underline{\mu} \operatorname{div} \mathbf{h} + \mathbf{h} \cdot \nabla \underline{\mu}, \tag{10}$$

we get finally the *molar balance law* (7) replaced by the *species power balance law*

$$\int_{\mathcal{P}} \underline{\mu} \dot{c}\rho dV = - \int_{\partial \mathcal{P}} \underline{\mu} \mathbf{h} \cdot \mathbf{n} dA + \int_{\mathcal{P}} \mathbf{h} \cdot \nabla \underline{\mu} dV + \int_{\mathcal{P}} \underline{\mu} h dV \quad \forall \underline{\mu}. \tag{11}$$

Notice that  $\underline{\mu}$  (*energy per mole*) is a *chemical potential*, acting here just as a test field.<sup>1</sup> It is worth noting that equation (11) can be interpreted as the balance of an *energy transport* [23].

<sup>1</sup> Throughout the paper we will consistently denote *test* fields by underlying the corresponding symbol.

### 2.2 Power Balance Laws

We can move the species power balance (11) back to the reference shape, and get  $\forall \mathcal{P}_o \subset \mathcal{R}_o$

$$\int_{\mathcal{P}_o} \underline{\mu} \dot{c} \rho_o dV = - \int_{\partial \mathcal{P}_o} \underline{\mu} \mathbf{h}_o \cdot \mathbf{n}_o dA + \int_{\mathcal{P}_o} \mathbf{h}_o \cdot \nabla_o \underline{\mu} dV + \int_{\mathcal{P}_o} \underline{\mu} h_o dV \quad \forall \underline{\mu}, \quad (12)$$

using first the identity relating the reference and the current gradient of the scalar field  $\mu$ , which we get from

$$\forall \mathbf{e} \quad (\nabla_o \mu) \cdot \mathbf{e} = (\nabla \mu) \cdot \mathbf{F}_o \mathbf{e} \quad \Rightarrow \quad \nabla_o \mu = \mathbf{F}_o^T \nabla \mu, \quad (13)$$

then replacing the current flux with the reference flux, according to the relation

$$\mathbf{h}_o = (\det \mathbf{F}_o) \mathbf{F}_o^{-1} \mathbf{h}, \quad (14)$$

$$h_o = (\det \mathbf{F}_o) h. \quad (15)$$

The *force power balance law*,  $\forall \mathcal{P}_o \subset \mathcal{R}_o$  reads

$$\int_{\mathcal{P}_o} \mathbf{b}_o \cdot \underline{\mathbf{v}} dV + \int_{\partial \mathcal{P}_o} \mathbf{t}_o \cdot \underline{\mathbf{v}} dA = \int_{\mathcal{P}_o} \mathbf{S}_o \cdot \nabla_o \underline{\mathbf{v}} dV \quad \forall \underline{\mathbf{v}}, \quad (16)$$

where  $\mathbf{b}_o$  and  $\mathbf{t}_o$  stand for the reference bulk force density and the reference boundary traction. The reference Piola stress  $\mathbf{S}_o$ , the Cauchy stress  $\mathbf{T}$  and the intermediate Piola stress  $\mathbf{S}$  turn out to be related one another by

$$\mathbf{S}_o = (\det \mathbf{F}_o) \mathbf{T} \mathbf{F}_o^{-T} = \beta (\det \mathbf{F}) \mathbf{T} \mathbf{F}_o^{-T} = \beta^{\frac{2}{3}} (\det \mathbf{F}) \mathbf{T} \mathbf{F}^{-T} = \beta^{\frac{2}{3}} \mathbf{S}, \quad (17)$$

while the current gradient of the vector field  $\mathbf{v}$  is related to the reference one by the identity

$$\nabla_o \mathbf{v} = (\nabla \mathbf{v}) \mathbf{F}_o. \quad (18)$$

The standard *frame-invariance* argument, stating that  $\mathbf{T} \cdot \nabla \underline{\mathbf{v}} = 0$  for any rigid test velocity field, leads to the symmetry property of tensor  $\mathbf{T}$ .

### 2.3 Free Energy Imbalance

Let us consider now any evolution of the model we are defining, i.e. any *constitutive process*, and the corresponding force power balance

$$\underbrace{\int_{\mathcal{P}_o} \mathbf{b}_o \cdot \mathbf{v} dV + \int_{\partial \mathcal{P}_o} \mathbf{t}_o \cdot \mathbf{v} dA}_{(exchanged) \text{ external power}} = \int_{\mathcal{P}_o} \mathbf{S}_o \cdot \dot{\mathbf{F}}_o dV, \quad (19)$$

together with the species power balance

$$\int_{\mathcal{P}_o} \mu \dot{c} \rho_o dV = - \underbrace{\int_{\partial \mathcal{P}_o} \mu \mathbf{h}_o \cdot \mathbf{n}_o dA + \int_{\mathcal{P}_o} \mu h_o dV}_{(exchanged) \text{ external power}} + \int_{\mathcal{P}_o} \mathbf{h}_o \cdot \nabla_o \mu dV. \quad (20)$$

Comparing the power exchanged between the matter inside any  $\mathcal{P}_o$  and the outside with the rate of change of a free energy density per unit reference volume  $\psi$ , we state the *energy imbalance* or *dissipation inequality* [14,23]

$$\mathbf{S}_o \cdot \dot{\mathbf{F}}_o + \mu \rho_o \dot{c} - \mathbf{h}_o \cdot \nabla_o \mu - \frac{d}{dt} \psi \geq 0. \quad (21)$$

By (17), (3) and (5), the stress power term in (21) can be given the expression

$$\mathbf{S}_o \cdot \dot{\mathbf{F}}_o = \beta \mathbf{S} \cdot \dot{\mathbf{F}} + \frac{1}{3} \mathbf{S} \cdot \mathbf{F} \alpha \dot{c}, \quad (22)$$

which, since

$$\mathbf{S} \cdot \mathbf{F} = (\det \mathbf{F}) \mathbf{T} \mathbf{F}^{-\top} \cdot \mathbf{F} = (\det \mathbf{F}) \mathbf{T} \cdot \mathbf{I} = (\det \mathbf{F}) \operatorname{tr} \mathbf{T}, \quad (23)$$

simplifies to

$$\mathbf{S}_o \cdot \dot{\mathbf{F}}_o = \beta \mathbf{S} \cdot \dot{\mathbf{F}} - J p \alpha \dot{c}, \quad (24)$$

with

$$J := \det \mathbf{F}, \quad p := -\frac{1}{3} \operatorname{tr} \mathbf{T}. \quad (25)$$

Therefore the inequality (21) can be rewritten as

$$\beta \mathbf{S} \cdot \dot{\mathbf{F}} + (\mu \rho_o - J p \alpha) \dot{c} - \mathbf{h}_o \cdot \nabla_o \mu - \frac{d}{dt} \psi \geq 0. \quad (26)$$

## 2.4 Free Energy Expression and Constitutive Characterization

Looking at (26) let us choose a free energy expression like the one given in [4,16,37]

$$\psi = \hat{\psi}(\mathbf{F}, c) = \varphi_{ch}(c) + \beta \varphi_e(\mathbf{F}), \quad (27)$$

which is the sum of a *chemical energy* density per unit reference volume, and a *strain energy* density per unit intermediate volume. Defining the response functions  $\hat{\mu}$  and  $\hat{\mathbf{S}}$  such that

$$\rho_o \hat{\mu}(c) \dot{c} = \frac{d}{dt} \varphi_{ch}(c), \quad (28)$$

$$\hat{\mathbf{S}}(\mathbf{F}) \cdot \dot{\mathbf{F}} = \frac{d}{dt} \varphi_e(\mathbf{F}), \quad (29)$$

the rate of change of the free energy, because of the decomposition (3) and the assumption (5), turns out to be

$$\frac{d}{dt} \hat{\psi}(\mathbf{F}, c) = \beta \hat{\mathbf{S}}(\mathbf{F}) \cdot \dot{\mathbf{F}} + (\rho_o \hat{\mu}(c) + \alpha \varphi_e(\mathbf{F})) \dot{c}. \quad (30)$$

If we finally substitute (30) into (26) we get

$$\beta \underbrace{(\mathbf{S} - \hat{\mathbf{S}}(\mathbf{F}))}_{\mathbf{S}^+} \cdot \dot{\mathbf{F}} + \underbrace{(\rho_o (\mu - \hat{\mu}(c)) - \alpha (J p + \varphi_e(\mathbf{F})))}_{\rho_o \mu^+} \dot{c} - \mathbf{h}_o \cdot \nabla_o \mu \geq 0. \quad (31)$$

In order for the inequality (31) to hold for any constitutive process the following conditions must be fulfilled

$$\mu = \hat{\mu}(c) + \frac{\alpha}{\rho_o} (Jp + \varphi_e(\mathbf{F})) + \mu^+, \quad \mu^+ \dot{c} \geq 0, \tag{32}$$

$$\mathbf{S} = \hat{\mathbf{S}}(\mathbf{F}) + \mathbf{S}^+, \quad \mathbf{S}^+ \cdot \dot{\mathbf{F}} \geq 0, \tag{33}$$

$$- \mathbf{h}_o \cdot \nabla_o \mu \geq 0, \tag{34}$$

with  $\mathbf{S}^+$  and  $\mu^+$  possibly describing dissipative mechanisms.

Notice how the coupling between diffusion and stress is described by the expression (32) characterizing the chemical potential through the spherical part of the Eshelby tensor [18,37]

$$\mathbf{E} = -\mathbf{F}^T \mathbf{S} + \varphi_e(\mathbf{F}) \mathbf{I}. \tag{35}$$

### 2.5 Fick’s Law

The last condition (34) holds true if

$$\mathbf{h}_o = -\mathbf{M}_o \nabla_o \mu, \tag{36}$$

with  $\mathbf{M}_o$  a positive semi-definite tensor. Expression (36) is the reference form of *Fick’s law*. By (13) and (14) the reference flux and the reference chemical potential gradient can be transformed into the corresponding current quantities, leading to the new expression of *Fick’s law*

$$\mathbf{h} = -\mathbf{M} \nabla \mu, \tag{37}$$

where the reference and the current *mobility* tensors are related by

$$\mathbf{M}_o = (\det \mathbf{F}_o) \mathbf{F}_o^{-1} \mathbf{M} \mathbf{F}_o^{-T} \tag{38}$$

## 3 Cahn-Hilliard Equation

The following derivation of the Cahn-Hilliard equation is based on [22]. Similar derivations can be found in [2,13,17,30].

### 3.1 Free Energy

According to [7], let us consider the diffusion of a single species with the free energy (27) modified by an additional term

$$\psi = \hat{\psi}_g(\mathbf{F}, c, \nabla_o c) = \varphi_{ch}(c) + \beta \varphi_e(\mathbf{F}) + \varphi_g(\nabla_o c), \tag{39}$$

with

$$\varphi_g(\nabla_o c) = \frac{1}{2} k_g \|\nabla_o c\|^2. \tag{40}$$

This term is called the *gradient energy* or the *interfacial free energy* [7].

### 3.2 Microforce Balance Law

The rate of change of the free energy turns out to be

$$\frac{d}{dt} \hat{\psi}_g(\mathbf{F}, c, \nabla_o c) = \beta \hat{\mathbf{S}}(\mathbf{F}) \cdot \dot{\mathbf{F}} + (\rho_o \hat{\mu}(c) + \alpha \varphi_\epsilon(\mathbf{F})) \dot{c} + k_g \nabla_o c \cdot \nabla_o \dot{c}, \quad (41)$$

where again the decomposition (3) together with the assumption (5) have been used.

Since the expression above differs from (30) by the last term, we wonder what additional term could possibly complement the power expenditure in (21). Looking at the last term of (41), we guess that additional term taking the expression

$$\rho_o \check{s} \dot{c} + \check{\mathbf{g}}_o \cdot \nabla_o \dot{c}, \quad (42)$$

Recalling that (21) is based on the balance laws (19) and (20), in the same spirit we should consider balancing (42) by some external power and introduce the *microforce balance law*

$$\forall \mathcal{P}_o \subset \mathcal{R}_o \quad \int_{\mathcal{P}_o} \rho_o \check{s} \dot{c} dV + \int_{\mathcal{P}_o} \check{\mathbf{g}}_o \cdot \nabla_o \dot{c} dV = \int_{\partial \mathcal{P}_o} \tau_o \dot{c} dA + \int_{\mathcal{P}_o} \rho_o s \dot{c} dV \quad \forall \dot{c}. \quad (43)$$

By using the identity

$$\operatorname{div}_o(\dot{c} \check{\mathbf{g}}_o) = \dot{c} \operatorname{div}_o \check{\mathbf{g}}_o + \check{\mathbf{g}}_o \cdot \nabla_o \dot{c} \quad (44)$$

we get (43) transformed into

$$\int_{\mathcal{P}_o} \rho_o \check{s} \dot{c} dV + \int_{\partial \mathcal{P}_o} \dot{c} \check{\mathbf{g}}_o \cdot \mathbf{n}_o dA = \int_{\partial \mathcal{P}_o} \tau_o \dot{c} dA + \int_{\mathcal{P}_o} (\operatorname{div}_o \check{\mathbf{g}}_o + \rho_o s) \dot{c} dV, \quad (45)$$

from which we derive the local form

$$\operatorname{div}_o \check{\mathbf{g}}_o + \rho_o (s - \check{s}) = 0 \quad \text{on } \forall \mathcal{P}_o, \quad (46)$$

$$\check{\mathbf{g}}_o \cdot \mathbf{n}_o = \tau_o \quad \text{on } \partial \mathcal{P}_o. \quad (47)$$

### 3.3 Dissipation Inequality

The dissipation inequality (21) with the additional expression (42) will change to

$$\mathbf{S}_o \cdot \dot{\mathbf{F}}_o + \mu \rho_o \dot{c} - \mathbf{h}_o \cdot \nabla_o \mu + \rho_o \check{s} \dot{c} + \check{\mathbf{g}}_o \cdot \nabla_o \dot{c} - \frac{d}{dt} \psi \geq 0. \quad (48)$$

Correspondingly, the inequality (26) will be replaced by

$$\beta \mathbf{S} \cdot \dot{\mathbf{F}} + (\rho_o (\mu + \check{s}) - J p \alpha) \dot{c} - \mathbf{h}_o \cdot \nabla_o \mu + \check{\mathbf{g}}_o \cdot \nabla_o \dot{c} - \frac{d}{dt} \psi \geq 0. \quad (49)$$

If we finally substitute (41) into (49) we get

$$\beta \left( \underbrace{\mathbf{S} - \hat{\mathbf{S}}(\mathbf{F})}_{\mathbf{s}^+} \cdot \dot{\mathbf{F}} + \underbrace{\left( \rho_o (\mu + \check{s} - \hat{\mu}(c)) - \alpha (J p + \varphi_e(\mathbf{F})) \right)}_{\rho_o s^+} \right) \dot{c} + (\check{\mathbf{g}}_o - k_g \nabla_o c) \cdot \nabla_o \dot{c} - \mathbf{h}_o \cdot \nabla_o \mu \geq 0. \tag{50}$$

In order to get this inequality fulfilled for any constitutive process, we update (32) to

$$\mu + \check{s} = \hat{\mu}(c) + \frac{\alpha}{\rho_o} (J p + \varphi_e(\mathbf{F})) + s^+, \quad s^+ \dot{c} \geq 0, \tag{51}$$

keep conditions (33) and (34) unchanged, and make the additional constitutive assumption

$$\check{\mathbf{g}}_o = k_g \nabla_o c. \tag{52}$$

We can define also  $\check{\mathbf{g}}$  by

$$\int_{\mathcal{P}} \check{\mathbf{g}} \cdot \nabla \dot{c} dV = \int_{\mathcal{P}_o} \check{\mathbf{g}}_o \cdot \nabla_o \dot{c} dV, \tag{53}$$

and get, as in (14),

$$\check{\mathbf{g}}_o = (\det \mathbf{F}_o) \mathbf{F}_o^{-1} \check{\mathbf{g}}. \tag{54}$$

### 3.4 Balance Law Summary

Summarizing, the current framework is characterized by the *force balance law* (16)

$$\int_{\mathcal{P}_o} \mathbf{b}_o \cdot \underline{\mathbf{v}} dV + \int_{\partial \mathcal{P}_o} \mathbf{t}_o \cdot \underline{\mathbf{v}} dA = \int_{\mathcal{P}_o} \mathbf{S}_o \cdot \nabla_o \underline{\mathbf{v}} dV \quad \forall \underline{\mathbf{v}},$$

the *species power balance law* (12)

$$\int_{\mathcal{P}_o} \underline{\mu} \dot{c} \rho_o dV = - \int_{\partial \mathcal{P}_o} \underline{\mu} \mathbf{h}_o \cdot \mathbf{n}_o dA + \int_{\mathcal{P}_o} \mathbf{h}_o \cdot \nabla_o \underline{\mu} dV + \int_{\mathcal{P}_o} \underline{\mu} h_o dV \quad \forall \underline{\mu},$$

and the *microforce balance law* (43)

$$\int_{\mathcal{P}_o} \rho_o \check{s} \dot{c} dV + \int_{\mathcal{P}_o} \check{\mathbf{g}}_o \cdot \nabla_o \dot{c} dV = \int_{\partial \mathcal{P}_o} \tau_o \dot{c} dA + \int_{\mathcal{P}_o} \rho_o s \dot{c} dV \quad \forall \dot{c},$$

supplemented by constitutive prescriptions about  $\mathbf{S}$ ,  $\mathbf{h}_o$ ,  $\mu$ ,  $\check{s}$ ,  $\check{\mathbf{g}}_o$ , consistent with the assumptions (33) and (34), possibly through Fick’s law (36), as well as (51) and (52).

It is interesting to look at the local form of the balance laws above. Let us note first that the local form (46) of the *microforce balance law*, after substituting the constitutive expression (52), can be written as

$$\rho_o \check{s} = k_g \Delta_o c + \rho_o s. \tag{55}$$

Then let us derive the local form of the *species power balance law* (12)

$$\dot{c} \rho_o = -\operatorname{div}_o \mathbf{h}_o + h_o, \tag{56}$$

and get, by replacing Fick’s law (36),

$$\dot{c} \rho_o = \operatorname{div}_o(\mathbf{M}_o \nabla_o \mu) + h_o. \tag{57}$$

It is worth noting that equations (55) and (57) turn out to be coupled through  $\check{s}$  by the chemical potential constitutive expression (51).

To make this coupling explicit we substitute the expression for  $\check{s}$  from (51) into (55) and get

$$\mu = \hat{\mu}(c) - s + \frac{\alpha}{\rho_o} (J p + \varphi_e(\mathbf{F})) - \frac{k_g}{\rho_o} \Delta_o c + s^+, \quad s^+ \dot{c} \geq 0, \tag{58}$$

to be eventually replaced in (57).

Here we make the assumptions, as in [22],

$$s = 0, \tag{59}$$

$$s^+ = 0, \tag{60}$$

on the whole shape  $\mathcal{R}_o$ .

We further assume  $\tau_o = 0$  on the outermost boundary  $\partial \mathcal{R}_o$ , which is equivalent, by (52) and (47), to the condition  $\nabla_o c \cdot \mathbf{n}_o = 0$  on  $\partial \mathcal{R}_o$  (as in [7], where because of a small strain assumption there is no difference between  $\nabla_o c \cdot \mathbf{n}_o$  and  $\nabla c \cdot \mathbf{n}$ ).

## 4 Allen-Cahn Equation

The following derivation of the Allen-Cahn equation is based again on [22], where it is referred to also as the Ginzburg-Landau equation.

Let us keep the energy expression in Sect. 3.1 and the microforce balance law in Sect. 3.2 unchanged. Let us remove instead the species power balance law (12) completely.

### 4.1 Dissipation Inequality

As a consequence of removing the species power balance law, we should remove the corresponding power expenditure from the dissipation inequality (21). Hence we get (48) changed to

$$\mathbf{S}_o \cdot \dot{\mathbf{F}}_o + \rho_o \check{s} \dot{c} + \check{\mathbf{g}}_o \cdot \nabla_o \dot{c} - \frac{d}{dt} \psi \geq 0. \tag{61}$$

Correspondingly, the inequality (49) will be replaced by

$$\beta \mathbf{S} \cdot \dot{\mathbf{F}} + (\rho_o \check{s} - J p \alpha) \dot{c} + \check{\mathbf{g}}_o \cdot \nabla_o \dot{c} - \frac{d}{dt} \psi \geq 0. \tag{62}$$

If we finally substitute (41) into (62) we get

$$\beta \underbrace{(\mathbf{S} - \hat{\mathbf{S}}(\mathbf{F}))}_{\mathbf{s}^+} \cdot \dot{\mathbf{F}} + \underbrace{(\rho_o (\check{s} - \hat{\mu}(c)) - \alpha (Jp + \varphi_e(\mathbf{F})))}_{\rho_o s^+} \dot{c} + (\check{\mathbf{g}}_o - k_g \nabla_o c) \cdot \nabla_o \dot{c} \geq 0. \tag{63}$$

In order to get this inequality fulfilled for any constitutive process, we replace (51) with

$$\check{s} = \hat{\mu}(c) + \frac{\alpha}{\rho_o} (Jp + \varphi_e(\mathbf{F})) + s^+, \quad s^+ \dot{c} \geq 0, \tag{64}$$

and leave conditions (33) and (52) unchanged, while removing (34).

### 4.2 Balance Law Summary

Summarizing, the current framework is characterized by the *force balance law* (16)

$$\int_{\mathcal{P}_o} \mathbf{b}_o \cdot \underline{\mathbf{v}} dV + \int_{\partial \mathcal{P}_o} \mathbf{t}_o \cdot \underline{\mathbf{v}} dA = \int_{\mathcal{P}_o} \mathbf{S}_o \cdot \nabla_o \underline{\mathbf{v}} dV \quad \forall \underline{\mathbf{v}},$$

and the *microforce balance law* (43)

$$\int_{\mathcal{P}_o} \rho_o \check{s} \dot{c} dV + \int_{\mathcal{P}_o} \check{\mathbf{g}}_o \cdot \nabla_o \dot{c} dV = \int_{\partial \mathcal{P}_o} \tau_o \dot{c} dA + \int_{\mathcal{P}_o} \rho_o s \dot{c} dV \quad \forall \dot{c},$$

supplemented by constitutive prescriptions about  $\mathbf{S}$ ,  $\check{\mathbf{g}}_o$ ,  $\check{s}$ , consistent with the assumption (33), as well as (52) and (64).

Let us consider again the local form (46) of the *microforce balance law*, changed into (55) by substituting the constitutive expression (52), and further replace  $\check{s}$  with the expression (64) leading to

$$\rho_o s^+ = -\rho_o \hat{\mu}(c) - \alpha (Jp + \varphi_e(\mathbf{F})) + k_g \Delta_o c + \rho_o s, \quad s^+ \dot{c} \geq 0. \tag{65}$$

If we make again the assumption (59) on the whole shape  $\mathcal{R}_o$ , while characterizing instead the dissipative term by

$$s^+ = \eta \dot{c}, \quad \eta \geq 0 \tag{66}$$

we finally get

$$\eta \dot{c} = \frac{k_g}{\rho_o} \Delta_o c - \hat{\mu}(c) - \frac{\alpha}{\rho_o} (Jp + \varphi_e(\mathbf{F})). \tag{67}$$

## 5 Active Species Diffusion

### 5.1 Uphill Diffusion and Aggregation

Fick's law (36) can be transformed into

$$\mathbf{h}_o = -\mathbf{M}_o \nabla_o \mu = -\frac{\partial \mu}{\partial c} \mathbf{M}_o \nabla_o c = -\mathbf{D}_o \nabla_o c, \tag{68}$$

where the mobility  $\mathbf{M}_o$ , by (34), is a positive semi-definite tensor, while the *diffusivity*  $\mathbf{D}_o$  is a positive or negative semi-definite tensor, depending on whether  $\partial\mu/\partial c$  is positive or negative.

The expression *uphill diffusion* [6] refers to the latter case where

$$\mathbf{h}_o \cdot \nabla_o c = -\mathbf{D}_o \cdot \nabla_o c \cdot \nabla_o c \geq 0. \tag{69}$$

In [29] an uphill diffusion model relies on a motility mechanism based on *haptotaxis*, whereby cells tend to move up a gradient of “increasing substrate adhesion” [9,10].

A different point of view relates an uphill diffusion to a motility mechanism based on the *differential adhesion hypothesis* [20,32], whereby cell-cell adhesion is stronger for same type cells and weaker for dissimilar cells.

We rely on the differential adhesion mechanism in making the assumption that the uphill diffusion is driven by the gradient of an *active chemical potential* depending on cell density. In doing so the expression we found convenient turns out to be very similar to expression (7) in [27] describing a *cell traction* due to the interaction with the extracellular matrix.

### 5.2 Active Chemical Potential Constitutive Characterization

Let us consider the derivation of the Cahn-Hilliard equation in Sect. 3 and look at the constitutive expression for the chemical potential (58). Besides the assumptions (59) and (60), we should use, as in [7], the *regular solution model* for the free energy term  $\varphi_{ch}$  and get an expression for  $\hat{\mu}$  from (28).

Quoting from [7], p. 258: “Several different meanings are associated with the term regular solution. We will use it to denote a solution having an ideal configurational entropy and an enthalpy of mixing which varies parabolically with composition.”

We will assume instead that the free energy  $\varphi_{ch}$  is given by

$$\varphi_{ch}(c) = \frac{1}{2} \rho_o k_{ch} c_{max} (\bar{c} \log(\bar{c}) + (1 - \bar{c}) \log(1 - \bar{c})), \tag{70}$$

with  $\bar{c} = c/c_{max}$ , which is just the (convex) *entropic energy* in the regular solution model, leading through (28) to the chemical potential term

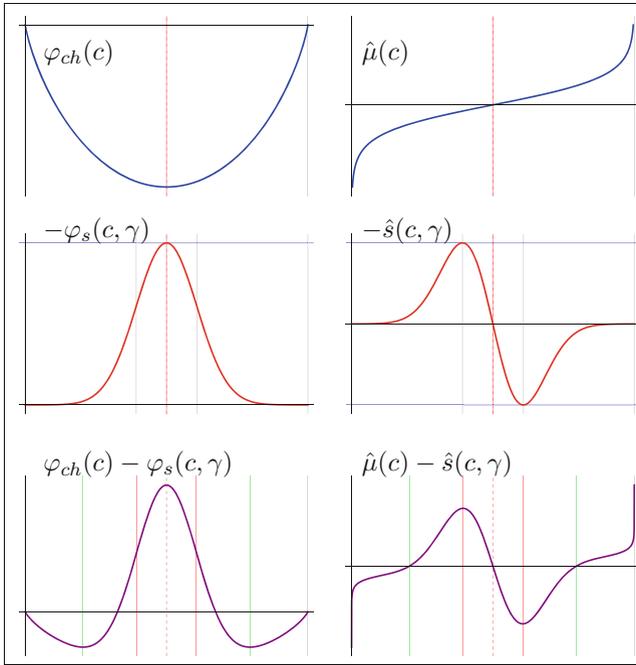
$$\hat{\mu}(c) = \frac{1}{\rho_o} \frac{d}{dc} \varphi_{ch}(c) = -k_{ch} \operatorname{arctanh}(1 - 2\bar{c}). \tag{71}$$

Further, we replace the assumption (59) with

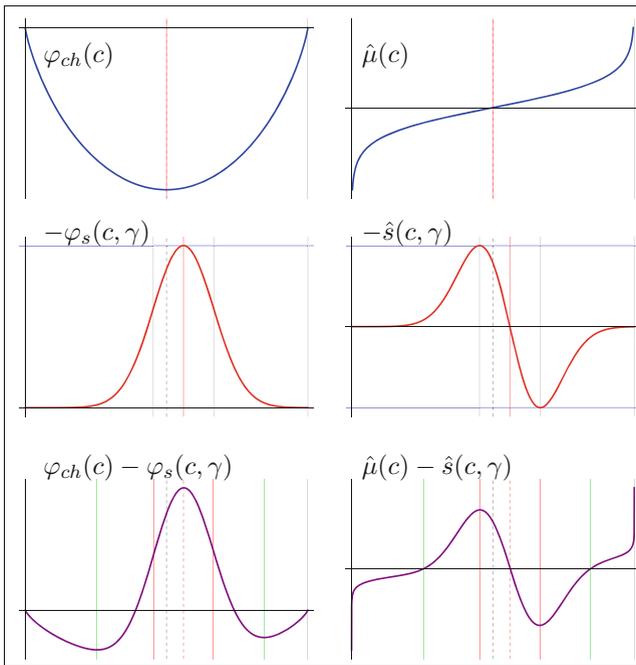
$$s = \hat{s}(c, \gamma) = k_s \frac{\gamma (c - c_s)}{\exp(\lambda (c - c_s)^2)}, \tag{72}$$

characterizing an *active chemical potential*, with  $\gamma$  an *activity control parameter*.

Figures 1 and 2 show how the composition of (71) and (72) generates a *spinodal interval* for the cell density. Some properties of (72) are worth noting. Namely: the derivative at  $c_s$  is  $k_s \gamma$ ; the spinodal interval is defined by  $c_s \pm 1/\sqrt{2\lambda}$ .



**Fig. 1.** Active chemical potential and double well free energy.



**Fig. 2.** Active chemical potential with shifted spinodal and double well free energy.

## 6 Numerical Simulations

We performed some numerical simulations on a toy model in the shape of a hollow cylinder in a rigid container, leaving the end faces and the interior cylindrical boundary free to deform, with no applied forces other than the reaction from the container. We used COMSOL Multiphysics<sup>®</sup> software [15] to get a finite element solution by implementing directly in their original form the expressions for:

- *the force power balance law (16),*
- *the species power balance law (12),*
- *the microforce power balance law (43).*

The strain energy  $\varphi_e$  in (27) has been chosen to characterize the tissue as an almost incompressible neo-Hookean material.

We didn't bother to choose any value for the material parameters as appropriate to the bio-physical problem we would like to address. Nevertheless our aim was to get some insights about the behavior of the mechanical model arising from the framework outlined above, and devised to describe cell diffusion and aggregation in a biological tissue.

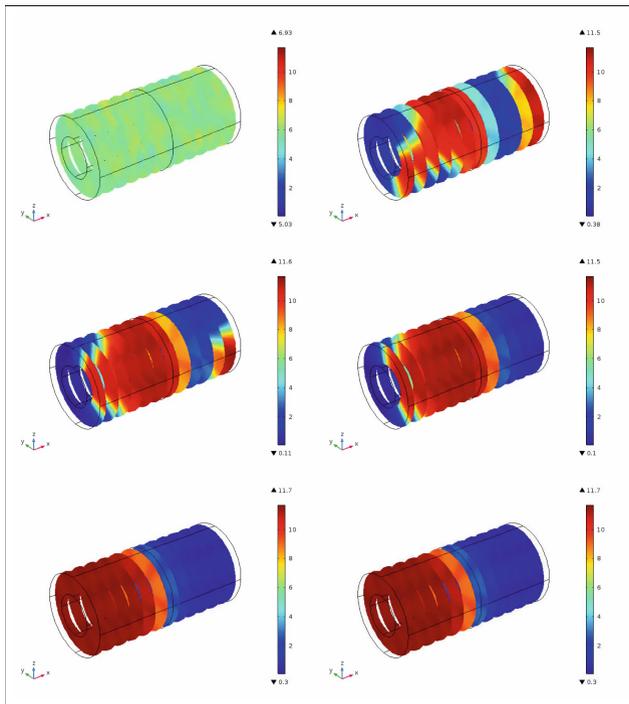


Fig. 3. Cell density on cross sections (A).

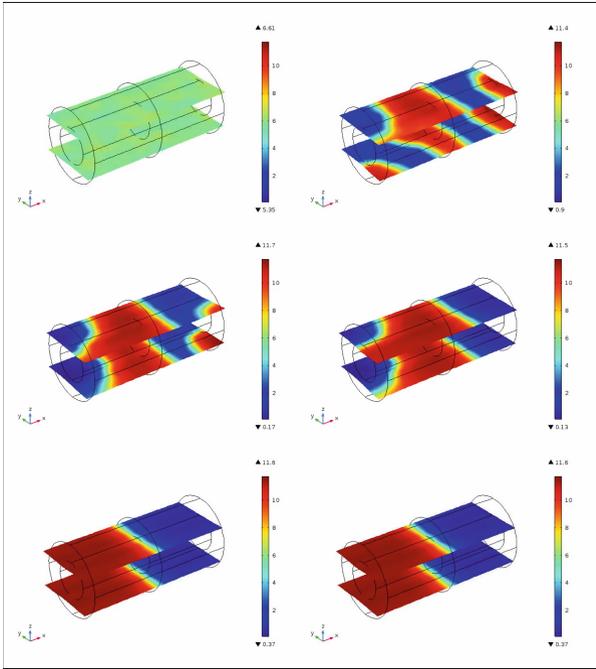


Fig. 4. Cell density on longitudinal sections (A).

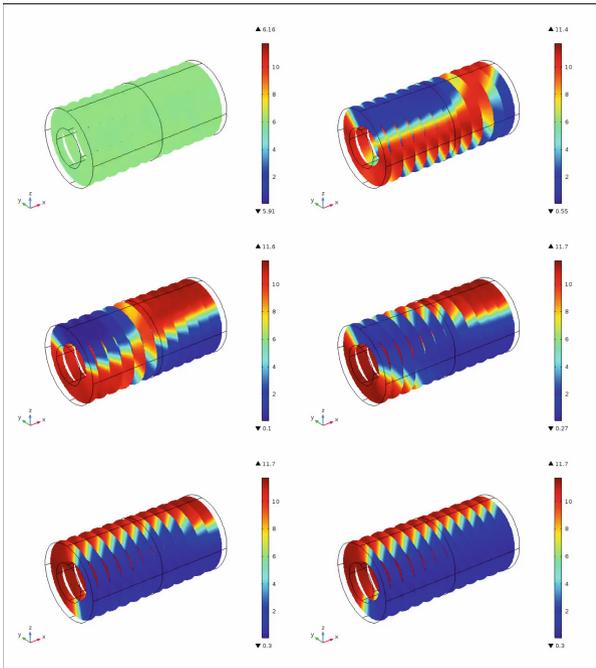
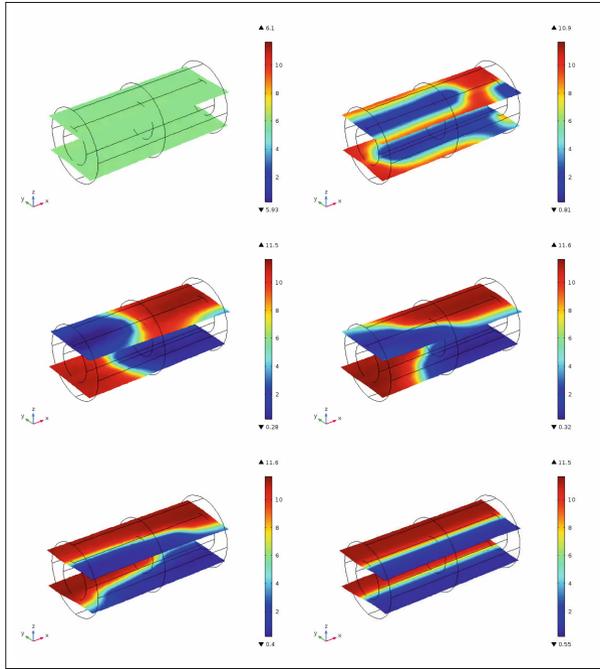
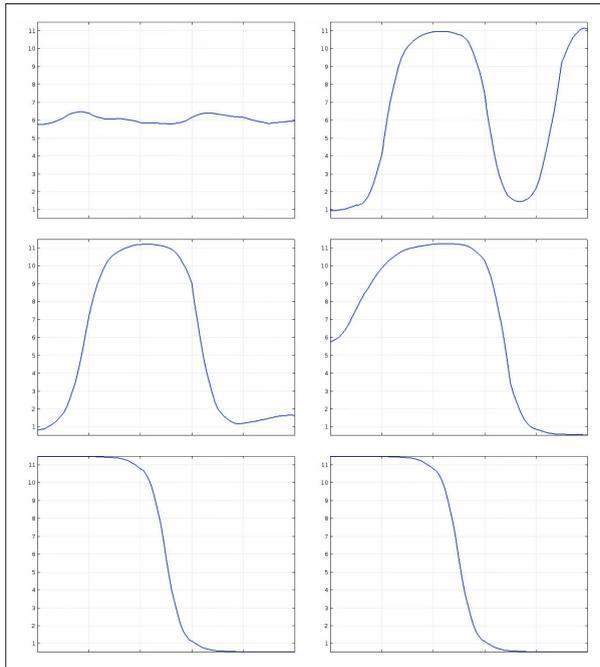


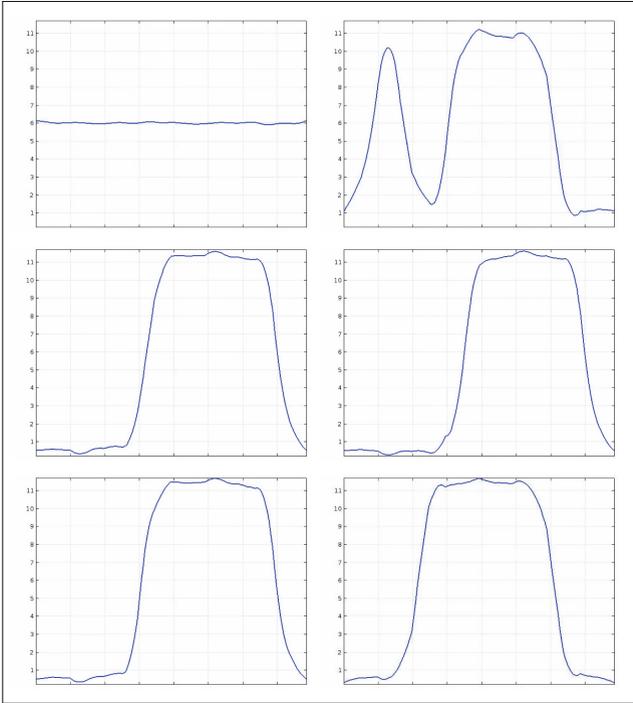
Fig. 5. Cell density on cross sections (B).



**Fig. 6.** Cell density on longitudinal sections (B).



**Fig. 7.** Cell density on the top longitudinal line (A).



**Fig. 8.** Cell density on the middle cross section boundary (B).

The simulation consists in starting from an initial uniform cell density, corresponding to  $c_m = 6$ , and let the cells migrate inside the tissue according to the Cahn-Hilliard equation. The concentration value  $c_s = c_m$  marks the onset of the spinodal decomposition, characterized by the parameters  $\gamma$  and  $\lambda$  in (72), besides the constants  $k_{ch}$  and  $k_s$ , as well as by  $\rho_o$  in (4) and  $\alpha$  in (5), while the coarsening evolution will depend on  $k_g$  in (40). During the phase separation and aggregation process the concentration cannot exceed  $c_{max} = 12$ .

The pictures and graphs in Figs. 3, 4, 5, 6, 7 and 8 show two kinds of evolutions, corresponding to two quite similar data sets, denoted by (A) and (B), which differ only by an axial or circumferential modulation for  $\gamma$  and for the initial perturbation of  $c$  triggering the spinodal decomposition.

The time-frames in Figs. 3 and 4, and Figs. 5 and 6 are ordered from top-left to bottom-right, and describe by colors the density on cross-sections and on sections parallel to the cylinder axis, respectively. These two evolutions are exemplary since they lead to quite different stationary solutions, as the pictures show. The graphs in Figs. 7 and 8 describe, with the same time ordering, the evolution of the interface along a line parallel to the axis or along the boundary of the middle cross section, respectively.

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