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Diffuse interface models for tumour growth within a non-isothermal Cahn-Hilliard theory for phase separation: thermodynamics, chemotaxis and stability

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Alla mia famiglia

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Abstract

In this thesis we provide a scheme for phase separation by accounting for diffusion, dynamic equations and consistency with thermodynamics. The constituents are two compressible fluids and, for the non-simple character of the mixture, an extra energy flux is allowed to occur. Since also thermal effects are included, the result is a whole set of evolution equations for the concentration, the velocity and the temperature which describes a non-isothermal Navier-Stokes-Cahn-Hilliard model for phase separation in a binary mixture with extra fluxes and within the Fourier heat theory. Alternative heat theories may be proposed for this Navier-Stokes-Cahn-Hilliard theory. Meanwhile the mixing problem is described graphically. Moreover the model may be generalized including a source term, and this doesn't affect the thermodynamic scheme.

Then we describe and then compare two mathematical models for chemotactic processes: the pioneeristic Keller-Segel model and the hydrodynamic model by Chavanis and Sire. The first one is able to describe clusters or peaks, the second one involves inertial effects together with a friction force and leads to network patterns or filaments that are in good agreement with the experimental results.

We analyze the linear stability of an infinite, stationary and homogeneous distribution of cells for determining the critical thresholds above which chemotactic collapse is allowed and cellular aggregation is reproduced.

Then we discuss the differences between the two models, moreover we show the analogy between the instability criterion for biological populations and

the Jeans instability criterion in an astrophysical setting.

Finally we propose a different approach for the derivation of new diffuse interface models for tumour growth (with chemotaxis and active transport) based on the Cahn-Hilliard theory, combined with the (stationary) Darcy momentum equation.

Key words: phase field model, Cahn-Hilliard equation, thermal effects, chemotaxis, tumour growth, stability

Introduction

The mechanism by which a mixture of two or more components can spontaneously separate into distinct regions (or phases) with different chemical compositions and physical properties is usually named spinoidal decomposition or phase separation.
The spinoidal decomposition has been investigated primarily from a metallurgic point of view, and the most common experimental examples occur in metallic alloys and glassy mixture. It has also been extended to binary fluid mixtures, where the separation is often described in the framework of phase-field modelings.
In order to distinguish one phase from the other, it is necessary to select a quantity which differs in the two phases; since Landau, this quantity is called the order parameter and assume different values in the bulk phases away from the interfacial regions over which it varies smoothly.
Cahn and Hilliard interpreted the order parameter as the concentration of one of the two metallic components of the binary alloy and introduced the so-called Cahn-Hilliard equation which describes the evolution of the concentration field in a binary alloy.
Then, the phenomenon of phase separation has been widely studied within the phase-field approach; in that the interface between the two pure phases is not sharp and it is replaced by a narrow diffuse layer across which the fluids may mix.
Tipically, the phenomenon of phase separation takes place when a mixture of two different species, forming a single and homogeneous phase, is quickly

cooled below a critical value of the temperature where the mixture can no longer exist in equilibrium in its homogeneous state. In the result the instability leads to phase separation.

Recently, many new diffuse interface models for tumour growth, based on Cahn-Hilliard theory, have been developed.

One of them has been proposed by Garcke et alt. in [15], the model takes into account transport mechanisms, such as chemotaxis and active transport. The coupled system of partial differential equations models a tumour growing in the presence of a nutrient species and surrounded by healthy tissue.

The purpose of this thesis is to provide a scheme for phase separation and shear-induced mixing by accounting for diffusion, dynamic equations and consistency with thermodynamics; the model developed is a Cahn-Hilliard model for phase separation which has recently been used for modeling tumour growth taking into account main transport mechanism as chemotaxis. Thus, in the first chapter, we derive a non-isothermal Navier-Stokes-Cahn-Hilliard model for phase separation within a Fourier background for heat conduction.

Following [3], in order to keep the model as simple as possible, we account for the evolution of concentration, but look at the balance of energy and entropy as for a single constituent. However, due to the internal structure of the mixture, we allow for an extra energy flux, in addition to the heat flux and an extra entropy flux. We also account for motion and diffusion effects by letting the stress in the mixture have additive viscous terms. Thus, we get a whole set of evolutions equations for the concentration, the velocity and the temperature through the balance of mass, linear momentum and energy. Finally, we show that an appropriate free-energy potential allows for a thermally-induced phase separation and describe the role of the critical temperature in mixing and demixing.

In the second chapter, we describe the pioneerstic model for chemotaxis by Keller and Segel. It consists of a system of two coupled parabolic equations, for the time variation of the organism density and of the chemical concentra-

tion. The former is a drift-diffusion equation; the diffusion term models the erratic motion of the particles whereas the drift term is responsible of a systematic motion along the gradient of concentration of the secreted chemical. The latter is an evolution equation for the diffusion of the secreted chemical which involves source and degradation terms. Then we study the instability conditions of the homogeneous steady state.
The parabolic model leads to the formation of Dirac peaks; however, recent experiments of in vitro formation of blood vessels show that cells randomly spread on a gel matrix autonomously organize to form a connected vascular network, which can be interpreted as the beginning of a vasculature. These networks cannot be explained by parabolic models, but they can be recovered by hyperbolic models.
We, then, describe a hydrodynamic (hyperbolic) model by Chavanis and Sire (see e.g. [7]) which takes into account inertia effects, together with a friction force. This model is able to reproduce the formation of filaments that are interpreted as the beginning of a vasculature. This phenomenon is responsible for angiogenesis, a major actor in the growth of tumours.
We underline the similarities between this model and the Euler-Poisson system used to describe the dynamics in self-gravitating particles. Indeed, there are several analogies between the chemotactic collapse in biology and the gravitational collapse in astrophysics.
Finally, in the third chapter, we describe a new diffuse interface model for tumour growth by Garcke et alt. in [15], which is based on the Cahn-Hilliard theory. We also perform a brief description of the derivation of the model by comparison with the model provided in the first chapter.

Introduzione

Il meccanismo tramite il quale una miscela di due o più componenti può spontaneamente separarsi in regioni distinte (o fasi) con differenti composizioni chimiche e proprietà fisiche è solitamente chiamata decomposozione spinodale o transizione di fase.
La decomposizione spinodale è stata prima studiata da un punto di vista della metallurgia, e i più comuni esempi sperimentali riguardano leghe metalliche e miscela vetrosa. E' stata anche estesa ad una miscela di due fluidi, dove la separazione è spesso descritta tramite la struttura di modellazione di fase.
Per distinguere una fase dall'altra, è necessario scegliere una quantità che differisce nelle due fasi; a partire da Landau, questa quantità è stata chiamata parametro d'ordine e assume differenti valori nelle regioni di massa lontane da regioni di interfaccia dove invece varia lentamenete.
Cahn e Hilliard hanno interpretato il parametro d'ordine come la concentrazione di una delle due componenti metalliche della lega e hanno introdotto la cosiddetta equazione di Cahn-Hilliard che descive l'evoluzione della concentrazione in una lega di due componenti metalliche.
In seguito, il fenomeno della transizione di fase è stato largamente studiato tramite l'approccio di modellazione di fase; qui l'interfaccia tra due fasi separate non è netta ma è sostituita da uno stretto (quasi continuo) spessore di diffusione attraverso il quale i due fluidi possono mescolarsi.
Tipicamete, il fenomeno di transizione di fase ha luogo quando una miscela di due differenti specie, che formano un'unica fase omogenea, è rapidamente raffreddata sotto un valore critico di temperatura dove la miscela non può

più esistere all'equilibrio nel suo stato omogeneo. Come risultato, l'instabilità porta alla separazione di fase.

Recentemente, sono stati sviluppati molti nuovi modelli di diffusione tramite interfaccia per la crescita di tumori, basati sulla teoria di Cahn-Hilliard.

Uno di questi è stato proposto da Garcke et altri in [15], il modello tiene conto di meccanismi di trasporto quali chemiotassi e trasporto attivo. Il sistema di equazioni alle derivate parziali accopiate modella la crescita dei tumori in presenza di un nutriente e circondata da tessuto sano.

L'obiettivo di questa tesi è di presentare un modello per la separazione di fase che è stato recentemente usato nella crescita dei tumori che tiene conto di meccanismi di trasporto come la chemiotassi.

Nel primo capitolo, deriviamo un modello non isotermo di Navier-Stokes-Cahn-Hilliard per la separazione di fase, preservando la teoria di Fourier per la conduzione del calore.

Seguendo [3], per mantenere il modello il più semplice possibile, spieghiamo l'evoluzione della concentrazione ma guardiamo il bilancio dell'energia e dell'entropia per un singolo costituente. Comunque, a causa della struttura interna della miscela, teniamo conto di un flusso di energia extra, in aggiunta al flusso di calore, e di un flusso di entropia extra. Teniamo conto, inoltre, di effetti di moto e diffusione lasciando che il termine di stress nella miscela abbia termini additivi di viscosità. In questo modo, otteniamo un intero insieme di equazioni evolutive per la concentrazione, la velocità, la temperatura attraverso il bilancio della massa, del momento lineare e dell'energia. Infine, mostriamo che una scelta accurata del potenziale di energia libera porta ad una transizione di fase indotta dalla temperatura e descive il ruolo della temperatura critica nel mescolamento e demiscelazione.

Nel secondo capitolo, descriviamo il modello pioneristisco per la chemiotassi di Keller e Segel. Consiste in un sistema di due equazioni paraboliche accoppiate, per la variazione temporale della densità dell'organismo e della concentrazione chimica. Il primo è un'equazione di diffusione-trasporto; il termine di diffusione modella il movimento caotico delle particelle, mentre il termine

di trasporto è responsabile del movimento sistematico lungo il gradiente di concentrazione della sostanza chimica secreta. La seconda è un'equazione evolutiva per la diffusione della sostanza chimica secreta che include termini di produzione e diffusione. In seguito, studiamo le condizioni di equilibrio di uno stato di equilibrio omogeneo.
Il modello parabolico porta a picchi di Dirac. Comunque, recenti esperimenti della formazione in vitro di vasi sanguigni mostrano che cellule sparse casualmemte su una matrice di gel si organizzano autonomamente per formare una rete vascolare connessa che viene interpretata come l'inizio di una vascolarizzazione. Queste reti non possono essere spiegate da modelli parabolici, ma possono essere giustificate da modelli iperbolici.
Quindi, studiamo il modello idrodinamico (iperbolico) di Chavanis e Sire (vedi [7]) che tiene conto di effetti inerziali. Questo modello è in grado di riprodurre la formazione di filamenti che sono interpretati come l'inizio di una vascolarizzazione.
Questo fenomeno è responsabile per l'angiogenesi, uno degli attori principali nella crescita dei tumori.
In seguito analizziamo le somiglianze tra questo modello e il sistema di Eulero-Poisson usato per descrivere le dinamiche di particelle auto-gravitanti. In effetti, ci sono molte analogie tra il collasso chemiotattico e quello gravitazionale in astrofisica.
Infine, nel terzo capitolo, seguendo Garcke et altri [15], descriviamo un nuovo modello di diffusione per la crescita dei tumori tramite interfaccia, che è basato sulla teoria di Cahn-Hilliard. Inoltre, forniamo una breve derivazione termodinamica di tale modello comparandola con quella sviluppata nel primo capitolo.

Chapter 1

Derivation of a Phase Field Model of non-isothermal Cahn-Hilliard Fluids with Extra Fluxes

1.1 Preliminaries and termodynamic scheme

In this section we focus on the behavior of a (binary) mixture of two complex materials, in particular two non-reacting constituents occupying a region Ω which is a generally time-dependent bounded region of $\mathbb{R}^3$, with boundary $\partial\Omega$ sufficiently smooth to allow applications of the divergence theorem.
We here address the following two possibilities: both components are compressible fluids or only one is compressible.
We indicate the mass densities of the two constituents as ρ_1 and ρ_2, so that we can define the total mass density of the mixture as $\rho = \rho_1 + \rho_2$.
We also define the concentration of the first constituent (or the mass fraction) as $c = \rho_1/\rho$; physically the concentration is meaningful in $[0, 1]$.
The mass densities ρ, ρ_1, ρ_2 and the concentrations $c, 1 - c$ are all functions of the position $\vec{x} \in \Omega$ and time $t \geq 0$.

In this thesis, we are not interested in modeling quasi-incompressible fluids, where both densities are constant, but the total density of the mixture may depend on $(\vec{x}, t)$, via c.

We have that ρ_1 and ρ_2 are constants in the special case of incompressible constituents, even if ρ may depend on $\vec{x}$ and t, unless $\rho_1 = \rho_2$.
The mass densities ρ_1 and ρ_2 are related to ρ and c as follows:

$$\rho_1 = \rho c \quad \rho_2 = \rho(1-c)$$

This is the reason why we can choose to describe the mixture either by ρ_1 and ρ_2 or by ρ and c, via a unified phase-field approach. To account for diffusion it is suitable to consider ρ and c as independent variables.
Let M_1 and M_2 be the masses of each species in Ω, so that we have:

$$M_1 = \int_\Omega \rho(\vec{x}, t)c(\vec{x}, t)d\nu \quad M_2 = \int_\Omega (1 - c(\vec{x}, t))\rho(\vec{x}, t)d\nu \tag{1.1}$$

Denoting $\vec{v_1}$ and $\vec{v_2}$ the velocities of the two fluids, the mass-averaged fluid velocity (or barycentric velocity) $\vec{v}$ is defined by:

$$\vec{v} = c\,\vec{v_1} + (1-c)\,\vec{v_2}$$

1.1.1 Balance equations

In this section we enunciate the local forms of the balance equations. In order to introduce the basic notations and notions about balance and constitutive equations we refer to [1] so, thinking of a general scalar quantity $\widetilde{\psi}$, sufficiently smooth, we indicate by $\vec{J_{\widetilde{\psi}}}$ and $r_{\widetilde{\psi}}$ its flux vector and supply respectively; the couple $(\vec{J_{\widetilde{\psi}}}, r_{\widetilde{\psi}})$ is usually referred to as the inflow associated to $\widetilde{\psi}$, as in [1]. In particular the local expressions for the (total) mass conservation (in divergence or convective form) read:

$$\frac{\partial}{\partial t}\rho + \nabla \cdot (\rho\,\vec{v}) = 0 \tag{1.2}$$

$$\dot{\rho} + \rho\nabla\cdot\,\vec{v} = 0$$

where we indicate with $\dot{} = \frac{\partial}{\partial t} + \vec{v} \cdot \nabla$ the convective time (also called material time derivative). We now introduce the diffusion/drift velocity $\vec{u}$ and the mass flux $\vec{J}$ as

$$\vec{u} = \vec{v_1} - \vec{v} \quad \vec{J} = \rho c \, \vec{u}$$

Then, the balance of the first constituent, in a non-reacting mixture, reads:

$$\rho \dot{c} = -\nabla \cdot \vec{J} \, . \tag{1.3}$$

As a consequence of (1.1) and through the Transport Theorem, we have:

$$0 = \frac{d}{dt} \int_\Omega \rho c \quad d\nu = \int_\Omega \rho \dot{c} \quad d\nu$$

By (1.3), integration Ω and the use of the divergence theorem yields:

$$\int_\Omega \rho \dot{c} \quad d\nu = - \int_\Omega \nabla \cdot \vec{J} \quad d\nu = - \int_{\partial\Omega} \vec{J} \cdot \vec{n} \, da$$

So we obtain:

$$\int_{\partial\Omega} \vec{J} \cdot \vec{n} \, da = 0 \tag{1.4}$$

where $\vec{n}$ is the outward normal to the boundary $\partial\Omega$ of Ω. For definiteness we account for (1.4), by letting the homogeneous Neumann boundary condition

$$\vec{J} \cdot \vec{n} = 0 \quad on \quad \partial\Omega$$

Next, for sake of simplicity, from now on we will consider $\vec{J}$ as a constitutive flux vector, subject to the thermodynamic restrictions; hence we focus on the C.H. equation as the local balance law (1.3) accounting for advection and diffusion terms, but without sources.

The balance of linear momentum for the mixture as a whole is written in the standard form:

$$\rho \dot{\vec{v}} = \nabla \cdot T + \rho \, \vec{f} \tag{1.5}$$

where T is the (Cauchy) stress tensor and $\vec{f}$ the body force density. T is taken to be symmetric, as it follows from the balance of angular momentum,

and needs a constitutive equation.

In order to introduce the local balance equation of energy we have to observe that in addition to the classical thermal and mechanical inflows, as in the standard context, we have to introduce an extra-flux vector, because of the non-local nature of the material under study. The thermal inflow is given by the (constitutive) heat flux vector and the heat supply (per unit mass), due to external sources such as radiation, respectively:

$$(\vec{q}\ (\vec{x},t), \rho r(\vec{x},t))$$

The mechanical inflow is formed by the power of superficial and external forces, respectively:

$$(-T\ \vec{v}, \rho\ \vec{f}\cdot\vec{v})$$

So, by comparison with the general local Balance Law, we have $\widetilde{\psi} = \rho(e+\frac{v^2}{2})$ and the (total) energy inflows read

$$\vec{J}_{\widetilde{\psi}} = \vec{q}\ (\vec{x},t) - T\ \vec{v}$$
$$r_{\widetilde{\psi}} = \rho r(\vec{x},t) + \rho\ \vec{f}\cdot\vec{v}$$

to which we have to add an extra energy-flux vector (see e.g. [3]), henceforth indicated by $\vec{w}$. We observe that an analogous extra-flux vector, with the physical meaning of an interstitial working, was introduced by Dunn and Serrin in [10] to describe the behaviour of complex fluids of Korteweg type. Indeed it is just this term, making these materials compatible with the Continuum Theory of Thermodynamics.

Thus, from the First Law of Thermodynamics we locally get

$$\rho(e+\frac{v^2}{2})^{\cdot} = \nabla\cdot(T\ \vec{v} - \vec{q}) - \nabla\cdot\vec{w} + \rho\ \vec{f}\cdot\vec{v} + \rho r$$

where e is the energy density (internal energy density). Also, its interlacement with the local form of the kinetic energy theorem

$$\rho(\frac{v^2}{2})^{\cdot} = \nabla\cdot(T\ \vec{v}) - T\cdot\nabla\ \vec{v} + \rho\ \vec{f}\cdot\vec{v}$$

leads to the local equation of the caloric energy (local balance of energy):

$$\rho\dot{e} = T \cdot L - \nabla\cdot \vec{q} - \nabla\cdot \vec{w} + \rho r \tag{1.6}$$

where $L = \nabla \vec{v}$ is the velocity gradient. For the Second Law of Thermodynamics we introduce the entropy density η and the entropy flux $\vec{J_\eta}$ which is just given by $\frac{\vec{q}}{\theta}$, $\frac{1}{\theta}$ being the coldness.
Keeping in mind that the entropy supply consists of two (external and internal) contributions:

$$r = r^{ext} + r^{int} \quad with \quad r^{ext} = \frac{\rho r}{\theta} \quad and \quad r^{int} \geq 0$$

the second law is taken as the statement that the entropy density η satisfies the inequality:

$$\rho\dot{\eta} \geq -\nabla \cdot \frac{\vec{q}}{\theta} + \frac{\rho r}{\theta}$$

for every thermodynamic process compatible with all the previous balance equations.
In this way the new theory doesn't modify the Thermodynamic structure of the entropy inequality. Finally, the introduction of the Helmholtz free energy $\psi = e - \theta\eta$, together with the substitution of $\rho r - \nabla\cdot \vec{q}$ from (1.6) easily provide the Clausius-Duhem form of the entropy inequality, modified due to the presence of $\vec{w}$:

$$-\rho(\dot{\psi} + \eta\dot{\theta}) + T \cdot L - \frac{1}{\theta} \vec{q} \cdot\nabla\theta - \nabla\cdot \vec{w} \geq 0 \tag{1.7}$$

1.2 Thermodynamic developments: restrictions on the constitutive responses and evolution equations

1.2.1 Thermodynamic restrictions

In this section we are primarily interested in deriving the restrictions placed upon the constitutive functions by the Second Law of Thermodynamics, as

expressed by (1.7). In order to provide our constitutive theory, within this Thermodynamic framework, we let $\Gamma = (\theta, \rho, c, \nabla\theta, \nabla c, D)$ be the set of essential independent state variables, even if for a more complex setting possible higher-order gradients of θ, ρ, c may be introduced.
To begin, we will assume that $\vec{J}, T, \eta$ and $\vec{w}$ are continuously differentiable functions of Γ. Also, the free energy $\psi = e - \theta\eta$ is assumed to be a C^2 function of $\Gamma = (\theta, \rho, c, \nabla c, D, \nabla\theta)$. After substituting in (1.7) and making use of the chain rule, we obtain:

$$-\rho\left[(\psi_\theta + \eta)\,\dot{\theta} + \psi_\rho\dot{\rho} + \psi_c\dot{c} + \psi_{\nabla c}\cdot(\nabla c)^{\cdot} + \psi_{\nabla\theta}\cdot(\nabla\theta)^{\cdot} + \psi_D\cdot\dot{D}\right] + T\cdot L - \frac{1}{\theta}\,\vec{q}\cdot\nabla\theta - \nabla\cdot\vec{w} \geq 0 \tag{1.8}$$

By employing classical Thermodynamics arguments, the arbitrariness of $\dot{\theta}, \dot{\nabla\theta}$ $\dot{D}$ implies that:

$$\eta = -\psi_\theta, \quad \psi_{\nabla\theta} = 0, \quad \psi_D = 0$$

that is to say that ψ can only depend on $\theta, \rho, c, \nabla c$.
Now we have to use the identity:

$$(\nabla c)^{\cdot} = \nabla\dot{c} - L^T\nabla c \tag{1.9}$$

This relation may be proven via the definition of the convective time derivative together with some standard vectorial identities.
In order to prove it, we focus on the right hand side and the left one separately:

$$\begin{aligned} L.H.S: \quad & (\nabla c)^{\cdot} = \partial_t(\nabla c) + \nabla(\nabla c)\,\vec{v} \\ R.H.S: \quad & \nabla\dot{c} - L^T\nabla c = \nabla(\partial_t c + (\nabla c\cdot\vec{v})) - L^T\nabla c = \\ & = \partial_t\nabla c + (\nabla(\nabla c))^T\,\vec{v} + (\nabla v)^T\nabla c - (\nabla v)^T\nabla c = \\ & = \partial_t\nabla c + (\nabla(\nabla c))^T\,\vec{v} \end{aligned}$$

where $(\nabla(\nabla c))^T = (\nabla(\nabla c))$, being a symmetric tensor.
Using this identity together with the continuity equation, we can easily

rewrite the L.H.S. of (1.8) as follows

$$-\rho\left[\psi_\rho(-\rho\nabla\cdot\vec{v})+\psi_c\dot{c}+\psi_{\nabla c}\cdot(\nabla\dot{c}-L^T\nabla c)\right]+T\cdot L-\frac{1}{\theta}\vec{q}\cdot\nabla\theta-\nabla\cdot\vec{w}=$$
$$\left[T+\rho^2\psi_\rho\mathbf{1}+\rho\nabla c\otimes\psi_{\nabla c}\right]\cdot L-\rho\psi_c\dot{c}-\rho\psi_{\nabla c}\cdot\nabla\dot{c}-\frac{1}{\theta}\vec{q}\cdot\nabla\theta-\nabla\cdot\vec{w}$$

where we have employed the identity (see e.g. [6]):

$$\psi_{\nabla c}\cdot L^T\nabla c=L\cdot\nabla c\otimes\psi_{\nabla c} \tag{1.10}$$

In this way the Clausius-Duhem inequality (1.8) reads:

$$\left[T+\rho^2\psi_\rho\mathbf{1}+\rho\nabla c\otimes\psi_{\nabla c}\right]\cdot L-\rho\psi_c\dot{c}-\rho\psi_{\nabla c}\cdot\nabla\dot{c}-\frac{1}{\theta}\vec{q}\cdot\nabla\theta-\nabla\cdot\vec{w}\geq 0 \tag{1.11}$$

In order to describe the suitable Thermodynamic restrictions on our constitutive setting, it is convenient the introduction of the notation, see [3]

$$\delta_c\psi:=\psi_c-\frac{1}{\rho}\nabla\cdot(\rho\psi_{\nabla c})$$

so that (1.11) may be rewritten as follows:

$$\left[T+\rho^2\psi_\rho\mathbf{1}+\rho\nabla c\otimes\psi_{\nabla c}\right]\cdot L-\rho\delta_c\psi\dot{c}-\nabla\cdot(\vec{w}+\rho\psi_{\nabla c}\dot{c})-\frac{1}{\theta}\vec{q}\cdot\nabla\theta\geq 0 \tag{1.12}$$

making use of the identity

$$\dot{c}\nabla\cdot(\rho\psi_{\nabla c})+\rho\psi_{\nabla c}\cdot\nabla\dot{c}=\nabla\cdot(\dot{c}\rho\psi_{\nabla c}).$$

To begin, we have to specify the possible dependence of T on Γ. Let

$$T=T_0+2\nu\langle D\rangle+\sigma(\nabla\cdot\vec{v})\mathbf{1} \tag{1.13}$$

where $\langle\quad\rangle$ denotes the deviatoric part of a tensor and T_0 represents an extra stress tensor associated with non local capillary effects and is supposed to be independent of D; $2\nu\langle D\rangle+\sigma(\nabla\cdot\vec{v})\mathbf{1}$ describes the viscous stress tensor, within the classical Navier-Stokes theory and hence ν and σ are the shear and bulk viscosity parameters.

Letting

$$T_0=-p\mathbf{1}+\langle T_0\rangle$$

where p plays the role of the modified pressure, due to non-local effects and using the standard tensor product in Lin $A \cdot B = tr(AB^T)$, as defined in [6], we get:

$$T \cdot L = -p\nabla\cdot \vec{v} + \langle T_0\rangle \cdot \langle L\rangle + 2\nu \langle D\rangle \cdot \langle D\rangle + \sigma(\nabla\cdot \vec{v})^2$$

Also setting

$$\mu := \delta_c\psi$$

in view of (1.2) and (1.3) and substituting in (1.12), after some simple rearrangements, we obtain

$$(\langle T_0\rangle + \rho \langle \nabla c \otimes \psi_{\nabla c}\rangle) \cdot \langle L\rangle + (-p + \rho^2\psi_\rho + \frac{1}{3}\rho\nabla c \cdot \psi_{\nabla c})\nabla\cdot \vec{v} + 2\nu \langle D\rangle \cdot \langle D\rangle + \sigma(\nabla\cdot \vec{v})^2 \tag{1.14}$$
$$+\mu\nabla\cdot \vec{J} - \nabla\cdot(\vec{w} + \rho\psi_{\nabla c}\dot{c}) - \frac{1}{\theta}\vec{q}\cdot\nabla\theta \geq 0$$

Since

$$\mu\nabla\cdot \vec{J} - \nabla\cdot(\vec{w} + \rho\psi_{\nabla c}\dot{c}) = -\vec{J}\cdot\nabla\mu - \nabla\cdot(\vec{w} + \rho\psi_{\nabla c}\dot{c} - \mu\vec{J})$$

we note that (1.14) holds if, see e.g. [3]

$$T_0 = -\rho^2\psi_\rho \mathbf{1} - \rho\nabla c \otimes \psi_{\nabla c} \quad \nu, \sigma \geq 0 \tag{1.15}$$
$$\vec{w} = \psi_{\nabla c}\nabla\cdot \vec{J} + \mu \vec{J}$$
$$\frac{1}{\theta}\vec{q}\cdot\nabla\theta + \vec{J}\cdot\nabla\mu \leq 0$$

Moreover, owing to the symmetry of T (and hence T_0), ψ is required to satisfy the condition:

$$\nabla c \otimes \psi_{\nabla c} = \psi_{\nabla c} \otimes \nabla c$$

In this way it follows that $\psi_{\nabla c}$ is parallel to ∇c:

$$\psi_{\nabla c} = \chi(\theta, \rho, c, |\nabla c|)\nabla c$$

This occurs when ψ is dependent on ∇c, via $|\nabla c|$. This is the reason why, when χ is independent of $|\nabla c|$, ψ takes the simplified quadratic form

$$\psi = \psi_0(\theta, \rho, c) + \frac{1}{2}\chi(\theta, \rho, c)\,|\nabla c|^2$$

Both (thermal and chemical) fluxes $\vec{q}$ and $\vec{J}$ are involved in (1.15). For simplicity, but also customarily, we require both the terms to be non-positive, namely we can write the following (stationary) constitutive relations of gradient-flux type:

$$\vec{J} = -\kappa \nabla \mu \qquad \vec{q} = -k \nabla \theta \tag{1.16}$$

where κ and k are positive-valued functions of Γ; in a simplified picture κ and k may be non negative constants. In particular κ represents the chemical mobility and k denotes the thermal conductivity; in this way the classical Fourier theory of heat conduction will not be modified, even if we may perform a Cahn-Hilliard theory within a non Fourier thermal background, allowing for temperature to travel as a wave rather than simply by diffusion and dealing either the heat flux vector as an extra state variable (to be inserted in Γ) or an internal variable.
In both cases the equation relating $\vec{q}$ and $\nabla\theta$ assumes the form of a generalized Maxwell-Cattaneo rate-type equation which includes a thermal relaxation time, see e.g. [17] and [13] for a more detailed discussion.

1.2.2 Evolution equations

In this section we focus on the derivation of equations governing the non-isothermal Navier-Stokes-Fourier-Cahn-Hilliard model for phase-separation in a binary mixture.
In the light of previous results, in order to furnish an easy understanding of the transition between phase separation and mixing, we confine our attention to free energy potentials of the following form

$$\psi(\theta, \rho, c, \nabla c) = \Psi(\theta, \rho) + \theta G(c) + \Theta F(c) + \frac{1}{2}\chi(\theta, \rho, c)\,|\nabla c|^2 \tag{1.17}$$

where $\Psi(\theta, \rho)$ represents the standard equilibrium contribution and Θ is a positive constant, corresponding to a critical temperature of the ambient. We note that $G(c)$ and $F(c)$ are suitable smooth functions depending only

on c. A typical choice of these functions may be polynomial

$$F(c) = \frac{1}{4}(2c-1)^2[((2c-1)^2) - 2]$$
$$G(c) = \frac{1}{2}(2c-1)^2$$

corresponding to the double-well type potential. However, it is worth to point out that a (singular) logarithmic choice may be more physically relevant, see e.g. [19]. By gathering previous relations, in view of the special free energy (1.17), we obtain the following forms for the chemical potential μ and the stress tensor T:

$$\mu = \delta_c \psi = \Theta(F_c + \frac{\theta}{\Theta} G_c) - \frac{1}{\rho}\nabla \cdot (\chi \rho \nabla c) + \frac{1}{2}\chi_c \left|\nabla c\right|^2$$

$$T = -P1 - \rho\chi \nabla c \otimes \nabla c + 2\nu \left\langle D \right\rangle + \sigma(\nabla \cdot \vec{v})1$$

where

$$P = \rho^2 \Psi_\rho + \frac{1}{2}\rho^2 \chi_\rho \left|\nabla c\right|^2$$

represents the modified pressure, due to non-local capillary effects. On the other hand the entropy reads:

$$\eta = -\Psi_\theta - G - \frac{1}{2}\chi_\theta \left|\nabla c\right|^2 \tag{1.18}$$

so the internal energy e becomes:

$$\begin{aligned} e &= \psi + \theta\eta = \\ &= \Psi - \theta\Psi_\theta + \Theta F + \frac{1}{2}(\chi - \theta\chi_\theta)\left|\nabla c\right|^2 \end{aligned} \tag{1.19}$$

and the (non negative) specific heat is now given by:

$$\begin{aligned} e_\theta &= \Psi_\theta - \Psi_\theta - \theta\Psi_{\theta\theta} - \frac{1}{2}\theta\chi_{\theta\theta}\left|\nabla c\right|^2 \\ &= -\theta\Psi_{\theta\theta} - \frac{1}{2}\theta\chi_{\theta\theta}\left|\nabla c\right|^2 \end{aligned} \tag{1.20}$$

It is worth to note that the specific heat reduces to the classical part $-\theta\Psi_{\theta\theta}$, whenever $\chi_{\theta\theta} = 0$; indeed a special simplified setting is just recovered whenever χ is a constant parameter.

Now we are able to set up the evolution equations for $\rho, c, \vec{v}, \theta$ governing the non-isothermal Navier-Stokes-Cahn-Hilliard model for binary phase transitions. We are primarily interested in deriving the heat equation of the new theory. We start from (1.19) within the simplified frame $\chi = \theta\chi_0$, where χ_0 is a positive constant. By (1.19) it follows that

$$e = \Psi(\theta, \rho) - \theta\Psi_\theta(\theta, \rho) + \Theta F(c)$$

so the non-classical dependence on ∇c is lost. Hence we find

$$\rho\dot{e} = -\rho\theta\Psi_{\theta\theta}\dot{\theta} - \rho^2(\Psi_\rho - \theta\Psi_{\theta\rho})\nabla\cdot\vec{v} - \Theta F_c\nabla\cdot\vec{J} \tag{1.21}$$

Also, we have

$$\rho\mu = \rho\Theta F_c + \rho\theta G_c - \nabla\cdot(\chi_0\rho\theta\nabla c) = \rho W'_\Theta(c,\theta) - \nabla\cdot(\chi_0\rho\theta\nabla c) \tag{1.22}$$

since χ_0 is a positive constant.
Finally from (1.13), we get

$$T\cdot L = -\rho^2\Psi_\rho\nabla\cdot\vec{v} - \rho\theta\chi_0\nabla c\cdot D\nabla c + \hat{\mathcal{D}} \tag{1.23}$$

where

$$\hat{\mathcal{D}} = 2\nu\langle D\rangle\cdot\langle D\rangle + \sigma(\nabla\cdot\vec{v})^2$$

represents the standard (non negative) viscous dissipation. Hence, taking into account (1.15), (1.21), (1.23) into the energy balance equation (1.6), we recover the following special heat equation:

$$\begin{aligned} -\rho\theta\Psi_{\theta\theta}\dot{\theta} = {} & -\rho^2\theta\Psi_{\theta\rho}\nabla\cdot\vec{v} + \Theta F_c\nabla\cdot\vec{J} - \rho\theta\chi_0\nabla c\cdot D\nabla c + \hat{\mathcal{D}} \\ & -\nabla\cdot(\mu\vec{J}) - \nabla\cdot\vec{q} + \rho r - \nabla\cdot[\theta\chi_0(\nabla\cdot\vec{J})\nabla c] \end{aligned} \tag{1.24}$$

where the fluxes $\vec{q}$ and $\vec{J}$ are just given by (1.16).
In view of our constitutive setting, the heat equation reads

$$\begin{aligned} -\rho\theta\Psi_{\theta\theta}\dot{\theta} = {} & -\rho^2\theta\Psi_{\theta\rho}\nabla\cdot\vec{v} - \Theta F_c\nabla\cdot(\kappa\nabla\mu) - \rho\theta\chi_0\nabla c\cdot D\nabla c + \hat{\mathcal{D}} \\ & +\nabla\cdot(\mu\kappa\nabla\mu) + \nabla\cdot\{\theta\chi_0[\nabla\cdot(\kappa\nabla\mu)]\nabla c\} + \nabla\cdot(k\nabla\theta) + \rho r \end{aligned} \tag{1.25}$$

Also, it is worth to remark that even if the Fourier theory of heat conduction will not be here modified, alternative heat theories accounting for memory effects may be proposed for the Cahn-Hilliard theory, as in [17]. We are still concentrated on the heat equation (1.24). Using the vectorial identity:

$$\begin{aligned}\nabla \cdot (\mu \overrightarrow{J}) &= \nabla\mu \cdot \overrightarrow{J} + \mu\nabla \cdot \overrightarrow{J} \\ &= -\kappa\nabla\mu \cdot \nabla\mu + \mu\nabla \cdot \overrightarrow{J}\end{aligned}$$

where we have substituted $(1.16)_1$, and taking into account (1.3), and (1.22) we have:

$$\begin{aligned}\nabla \cdot \overrightarrow{J}\,(\Theta F_c - \mu) &= \nabla \cdot \overrightarrow{J}\,(-\theta G_c + \frac{1}{\rho}\nabla \cdot (\chi_0\rho\theta\nabla c)) \\ &= -\rho\dot{c}(-\theta G_c + \frac{1}{\rho}\nabla \cdot (\chi_0\rho\theta\nabla c)) \\ &= \rho\theta\dot{G(c)} - \dot{c}\nabla \cdot (\chi_0\rho\theta\nabla c)\end{aligned} \tag{1.26}$$

This term (1.26) appears in (1.25) which in turn could be rewritten as follows:

$$\begin{aligned}-\rho\theta\Psi_{\theta\theta}\dot{\theta} = -\rho^2\theta\Psi_{\theta\rho}\nabla \cdot \overrightarrow{v} + \rho\theta\dot{G(c)} - \dot{c}\nabla \cdot (\chi_0\rho\theta\nabla c) + k\nabla\mu \cdot \nabla\mu + \nabla \cdot (k\nabla\theta) + \rho r \\ - \rho\theta\chi_0\nabla c \cdot D\nabla c + \hat{\mathcal{D}} + \nabla \cdot (\theta\chi_0\rho\dot{c}\nabla c)\end{aligned}$$

From the vectorial identity

$$\nabla \cdot (\theta\chi_0\rho\dot{c}\nabla c) = \dot{c}\nabla \cdot (\chi_0\rho\theta\nabla c) + \nabla\dot{c} \cdot \chi_0\rho\theta\nabla c$$

and using (1.9) we obtain

$$\begin{aligned}-\rho\theta\Psi_{\theta\theta}\dot{\theta} = -\rho^2\theta\Psi_{\theta\rho}\nabla \cdot \overrightarrow{v} + \rho\theta\dot{G(c)} + k\nabla\mu \cdot \nabla\mu + \nabla \cdot (k\nabla\theta) + \rho r \\ + \hat{\mathcal{D}} + \chi_0\rho\theta\nabla c \cdot (\dot{\nabla c})\end{aligned}$$

By summarizing, the whole system of equations reads as follows:

$$\begin{cases}\dot{\rho} + \rho\nabla \cdot \overrightarrow{v} = 0 \\ \rho\dot{\overrightarrow{v}} = -\nabla P - \nabla \cdot (\rho\theta\chi_0\nabla c \otimes \nabla c) + \nabla \cdot [2\nu \langle D \rangle] + \nabla[\sigma\nabla \cdot \overrightarrow{v}] + \rho \overrightarrow{f} \\ -\rho\theta\Psi_{\theta\theta}\dot{\theta} = -\rho^2\theta\Psi_{\theta\rho}\nabla \cdot \overrightarrow{v} + \rho\theta\dot{G(c)} + k\nabla\mu \cdot \nabla\mu + \nabla \cdot (k\nabla\theta) + \rho r \\ +\hat{\mathcal{D}} + \chi_0\rho\theta\nabla c \cdot (\dot{\nabla c}) \\ \rho\dot{c} = \nabla \cdot (\kappa\nabla\mu)\end{cases} \tag{1.27}$$

where
$P = P(\rho, \theta) = \rho^2 \Psi_\rho$ and $\mu = \Theta F_c + \theta G_c - \frac{1}{\rho} \nabla \cdot (\chi_0 \rho \theta \nabla c)$.
It is natural to name this system as the compressible non-isothermal Navier-Stokes-Fourier-Cahn-Hilliard system, based on the names of Navier, Stokes, Fourier, Cahn and Hilliard.
Such system in the unknowns $\rho, \vec{v}, \theta, c$ may be then equipped with the homogeneous boundary conditions:

$$\nabla \mu \cdot n = 0, \quad \nabla c \cdot n = 0, \vec{v} = 0 \quad on \quad \partial\Omega \times \{t \geq 0\}$$

and with prescribed initial conditions on $\rho, \vec{v}, \theta, c$, to yield the boundary initial value problem P, to be further investigated.
It is important to note that, because of the possibility of the components to be compressible, $\nabla \cdot \vec{v}$ is not necessarly zero, unlike the incompressible case.

1.3 Transition temperature and double-well potential

For definiteness, we now give an example of a free-energy function which allows an easy understanding of the transition between phase separation and phase mixing, see e.g. [3].
Following the polynomial choices of the functions $F(c)$ and $G(c)$, introduced in the previous section, we have:

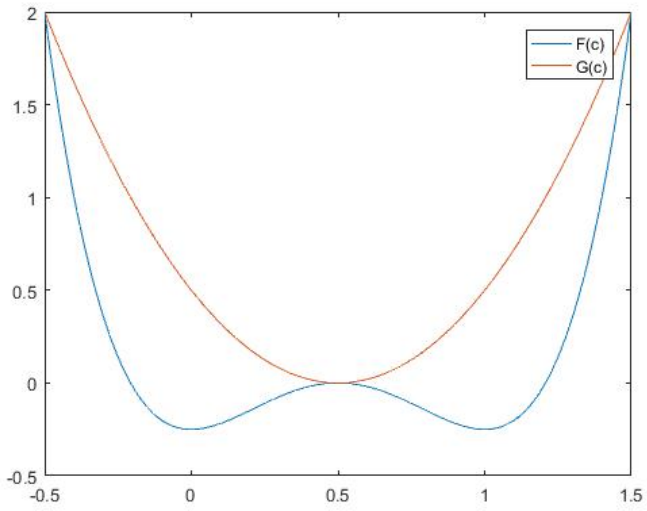

Figure 1.1

We can also plot the function $F(c) + \frac{\theta}{\Theta}G(c)$ with $\frac{\theta}{\Theta} = 0.05, 0.6, 1, 1.4$:

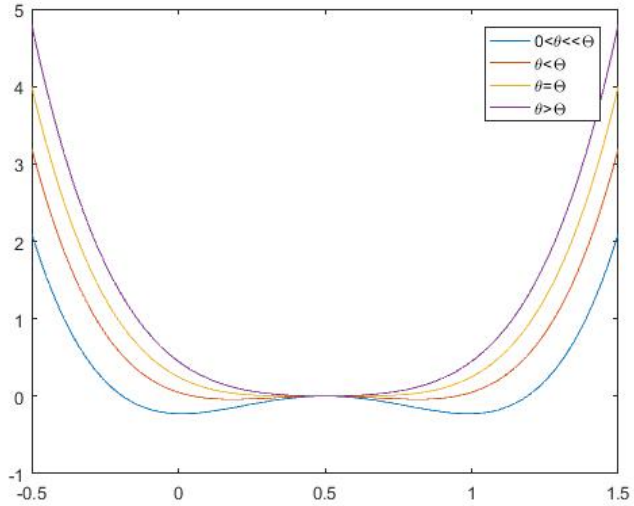

Figure 1.2

The mixture has two phases, one with a single solution (uniform concen-

tration) c_*, the other with a double solution, named c_-, c_+. The transition is characterized as the passage between the two phases. In order to do this, we focus our attention on the stationary points of ψ, with respect to c. Accordingly we examine the vanishing of $\mu = \delta_c \psi$. We restrict our attention to homogeneous regions and let the continuum be in stationary conditions; we then let $\nabla \mu = \vec{0}$ and, in particular, $\nabla c = \nabla \theta = \vec{0}$.
By the C.H. equation, $\dot{c} = 0$ implies $\nabla \cdot \vec{J} = 0$ and this in turn yields that the extra energy flux vanishes if $\mu = 0$. Under these hypotheses, the chemical potential reduces to

$$\mu = F_c + \frac{\theta}{\Theta} G_c = W'_\Theta(c; \theta)$$

where

$$F_c = 8c(2c-1)(c-1) = 16c^3 - 24c^2 + 8c$$
$$G_c = 2(2c-1)$$

and θ is supposed to have fixed values; without any misunderstanding the high apex denotes differentiation with respect to c. Separation of phases is induced by changes in the convexity/concavity of ψ and such changes are related to the passage from maxima to minima (or viceversa). When the mixture is completely melt, the potential ψ attains only one stationary point which is a minimum, corresponding to a stable centre topologically speaking, i.e. the mixed phase is stable. On the contrary if there are two separate substances, the potential presents two minima and a maximum, namely two stable centres and a saddle type unstable point; thus, we have the so called double-well potential and the mixed phase is unstable.
Hence the qualitative analysis of stationary/equilibrium points of ψ is really relevant for an easy understanding of the mixing problem.
We require $\mu = 0$ and get:

$$8c(2c-1)(c-1) + \frac{\theta}{\Theta} 2(2c-1) = 0$$

From this we obtain:

$$2(2c-1)(4c(c-1)+\frac{\theta}{\Theta})=0$$

We have

$$c_*=\frac{1}{2} \quad or \quad (4c(c-1)+\frac{\theta}{\Theta})=0 \tag{1.28}$$

The second equation of (1.28) has $\frac{\Delta}{4}=4(1-\frac{\theta}{\Theta})$. We have two interesting cases:

- if $\theta > \Theta$ no additional solutions occur, the function has a (unique) minimum and the two components are completely mixing.
- if $\theta < \Theta$ we have also $c_-=\frac{1-\sqrt{1-\frac{\theta}{\Theta}}}{2}$ and $c_+=\frac{1+\sqrt{1-\frac{\theta}{\Theta}}}{2}$; they are two minima and the solution $c=\frac{1}{2}$ become a maximum, the two components being separated.

It is worth to observe that at the transition $\mu=0$, $\theta=\Theta$, the energy ψ has a point of inflection at $c=c_*$, as it is shown by figure 1.2.
So Θ can be viewed as the transition temperature: beyond a certain critical temperature the two components become a whole, on the other hand, under that critical temperature the two are quite separated.

Chapter 2

Mathematical models for chemotaxis: from the pioneeristic Keller Segel model to the Hydrodynamic model by Chavanis and Sire

2.1 Derivation of the model

In this section we derive the Keller-Segel model for chemotactic movement due to Keller and Segel in '70s.
Chemotaxis is the influence of chemical substances in the environment on the movement of mobile species. The movement towards a higher concentration of the chemical substance is termed positive chemotaxis and the movement towards region of lower chemical concentration is called negative chemotactic movement.
In biology, many microscopic organisms as bacteria, amoebae, endothelial cells or even social insects like ants interact through the phenomenon of chemotaxis.

The KS model is composed of two parabolic PDEs, henceforth we refer to it as the parabolic-parabolic model.

This model was proposed by E.F.Keller and L.A.Segel as a simplified formulation of the original Keller-Segel model of four strongly coupled equations to a model that is as simple as possible. In fact, their motto was: '*it is useful for the sake of clarity to employ the simplest reasonable model*'. Its success was just a consequence of its intuitive simplicity, analytical tractability and capacity of replicate the key behaviors of chemotactic populations. We have two quantities at disposal: the first one represents the density $\rho(\vec{x}, t)$ of the healthy cell, the second one is the concentration $c(\vec{x}, t)$ of a chemical substance, also called the chemical. Hence, we state two local balance laws for the two constituents: we denote the inflows of ρ and c by $(\vec{J_\rho}, r_\rho)$ and $(\vec{J_c}, r_c)$ respectively. As usual $\vec{J_\rho}, \vec{J_c}$ are the (constitutive) fluxes of the healthy cell and the chemical, instead r_ρ, r_c represent the supplies of the healthy cell and the chemical: from now on we work in fixed (in time) $3D$ domains. Thus, the local balance equations can be written as follows:

$$\begin{aligned} \frac{\partial}{\partial t}\rho &= -\nabla\cdot \vec{J_\rho} + r_\rho \\ \frac{\partial}{\partial t}c &= -\nabla\cdot \vec{J_c} + r_c \end{aligned} \tag{2.1}$$

Both fluxes are then supposed to be diffusive-type fluxes, namely we consider the following flux gradient type constitutive relations:

$$\begin{aligned} \vec{J_\rho} &= -D_\rho \nabla\rho + D_k \nabla c \\ \vec{J_c} &= -D_c \nabla c \end{aligned} \tag{2.2}$$

The density and chemical mobilities D_ρ and D_c are here supposed to be non-negative constants, even if they could depend also on the quantities ρ and c. Also the chemotactic mobility D_k could depend on both ρ and c, but an interesting special form is $D_k = \chi_0\rho$, where χ_0 is called the *chemotactic sensitivity* and is here supposed to be positive, in order to describe attraction effects. It is worth to observe that χ_0 is negative when the chemical acts as a poison, in this case we would have repulsion. In the pioneeristic version of

the KS model the density supply is neglected, whereas the chemical supply takes the usual form:

$$r_c = -\Lambda c + h\rho$$

where Λ and h are non negative functions: in this way Λc and $h\rho$ represent degradation and source rates respectively. We finally can write the system of the two coupled (quasi linear) parabolic equations, governing the KS model:

$$\begin{cases} \frac{\partial}{\partial t}\rho = \nabla \cdot (D_\rho \nabla \rho) - \nabla \cdot (D_k \nabla c) \\ \frac{\partial}{\partial t} c = \nabla \cdot (D_c \nabla c) - \Lambda c + h\rho \end{cases} \tag{2.3}$$

The first equation is a **diffusion-drift** equation: in addition to their diffusive motion, the cells move preferentially along the concentration gradient (leading to a chemotactic flux), the cells diffuse with a diffusion coefficient D_ρ and also move in the direction of the gradient of c (attraction of healthy cells). The term $\nabla \cdot (D_\rho \nabla \rho)$ is the standard diffusion term, $-\nabla \cdot (D_k \nabla c)$ is the so called drift term.
The second equation describes the evolution of the chemical and is a **reaction-diffusion** equation, accounting for degradation and source terms.

2.1.1 The KS chemotactic instability

In order to analyze the KS chemotactic instability we divide the description into steps.
First step: we consider an homogeneous and stationary equilibrium state $s_0 = (\rho_0, c_0)$, where the two quantities ρ_0 and c_0 are reciprocally related by:

$$\Lambda c_0 = h\rho_0, \quad namely \quad c_0 = \frac{h}{\Lambda}\rho_0 \tag{2.4}$$

Second step: we consider a 'small' instantaneous perturbation δs to s_0:

$$s_0 + \delta s(\vec{x}, t), \quad with \quad \delta s(\vec{x}, t) = (\delta\rho(\vec{x}, t), \delta c(\vec{x}, t))$$

of the Fourier modes type:

$$0 \neq \delta s = s_1 e^{i(\vec{k} \cdot \vec{x} - \omega t)}$$

where s_1 is the (non null) amplitude, $\vec{k}$ is the real wave number vector ($k^2 > 0$), and ω is the (real or complex) frequency.
An additional useful notation may be given by the stability parameter (also called the growth rate parameter), defined as:

$$\sigma = -i\omega \tag{2.5}$$

Third step: we consider this linearized perturbation system for $(\delta\rho, \delta c)$:

$$\begin{cases} \delta\rho_t = \nabla \cdot (D_\rho(0)\nabla\delta\rho) - \nabla \cdot (\chi_0\rho_0\nabla\delta c) \\ \delta c_t = \nabla \cdot (D_c(0)\nabla\delta c) - \Lambda(0)\delta c + h(0)\delta\rho \end{cases} \tag{2.6}$$

Dividing by $D_c(0)$ ($D_c(0) >> 1$ empirically) the second equation, we obtain

$$\frac{1}{D_c(0)}\delta c_t = \Delta\delta c - \frac{\Lambda(0)}{D_c(0)}\delta c + \frac{h(0)}{D_c(0)}\delta\rho$$

where

$$D_\rho(0) = D_\rho(\rho_0, c_0), \quad D_c(0) = D_c(\rho_0, c_0)$$
$$\Lambda(0) = \Lambda(\rho_0, c_0), \quad h(0) = h(\rho_0, c_0)$$

It is worth to note that $\frac{1}{D_c(0)}$ denotes a chemical relaxation time for the model.
Fourth step (dispersive Cramer system): we obtain the dispersive system for ρ_1 and c_1:

$$\begin{cases} -i\omega\rho_1 = -D_\rho(0)k^2\rho_1 + \chi_0\rho_0k^2c_1 \\ -i\omega c_1 = -D_c(0)k^2c_1 - \Lambda c_1 + h(0)\rho_1 \end{cases} \tag{2.7}$$

This can also be written in the matricial form:

$$Ds_1 = 0, \quad s_1 = (\rho_1, c_1)^T$$

where the matrix D is defined as follows

$$D = \begin{pmatrix} \sigma + D_\rho(0)k^2 & -\chi_0\rho_0k^2 \\ -h(0) & \sigma + D_c(0)k^2 + \Lambda \end{pmatrix} \tag{2.8}$$

Fifth step (The Cramer theorem and the related dispersion equation): In view of the Cramer Theorem, the necessary and sufficient condition for $s_1 \neq \vec{0}$ (namely $detD = 0$) can be written as an algebraic dispersive equation in σ:

$$\sigma^2 + \sigma((D_\rho(0) + D_c(0))k^2 + \Lambda) + D_\rho(0)k^2(D_c(0)k^2 + \Lambda) - h\chi_0\rho_0 k^2 = 0 \quad (2.9)$$

It is worth to point out that the stability/instability of the equilibrium state $s_0 = (\rho_0, c_0)$ is strictly connected to the sign of the known term. Indicating as σ_1, σ_2 the two solutions of (2.9), we have:

$$\sigma_1\sigma_2 = D_\rho(0)k^2((D_c(0)k^2 + \Lambda)) - h\rho_0\chi_0 k^2 =$$
$$k^2(D_\rho(0)D_c(0)(k^2 - (\frac{h(0)\rho_0\chi_0}{D_\rho(0)D_c(0)} - \frac{\Lambda}{D_c(0)}))$$

In this way the critical threshold for the onset of the Chemotactic Collapse may be defined as:

$$\tilde{k}^2_{KS} := k^2_{KS} - \frac{\Lambda}{D_c(0)} < k^2_{KS}$$

where

$$k^2_{KS} := \frac{h(0)\rho_0\chi_0}{D_\rho(0)D_c(0)}$$

Thus the sufficient condition for the Chemotactic Instability reads:

$$k^2 < \tilde{k}^2_{KS}$$

which, keeping in mind the definition of the wavelength $\lambda = \frac{2\pi}{k}$, may also become:

$$\lambda > \tilde{\lambda}_{KS}$$

where

$$\tilde{\lambda}_{KS} := \frac{2\pi}{\tilde{k}_{KS}} > \frac{2\pi}{k_{KS}} =: \lambda_{KS}$$

By all means, the equilibrium state is asymptotically (exponentially) stable if $k^2 > \tilde{k}^2_{KS}$.

2.2 The Chavanis Sire model

The KS model, as seen before, is generally a quasi linear parabolic model consisting in two coupled PDEs of parabolic type. This model ignores inertial effects and assumes that the drift velocity of the organisms is directly induced by a chemotactic force which is proportional to the concentration gradient of the chemical.
The KS model can predict the formation of clusters by chemotactic collapse, however it is not able to reproduce the formation of network patterns (filaments). These filaments have been observed in experiments of capillary blood vessels formation. These structures are due to the spontaneous self-organization of endothelial cells during vasculogenesis, a process involved in embryologic development and very important in tumour growth.
In order to overcome this fact and describe these patterns, more general mathematical models of chemotaxis have been developed.
They are generally hydrodynamic (hyperbolic) models, taking into account inertial effects, and are able to reproduce the formation of filaments, which are interpreted as the beginning of a vasculature. This phenomenon is responsible of angiogenesis, a major actor in the growth of tumors.
One of this is the recent hydrodynamic model with a friction force, introduced by Chavanis and Sire in 2007, within a unified approach. When the friction term is negligible, we obtain an hydrodynamic model for chemotaxis which is quite similar to the Euler-Poisson system describing self-gravitating barotropic fluids in an astrophysical setting, by a suitable managing of notations.
This unified model by Chavanis and Sire is described by the following system:

$$\begin{aligned} \frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \, \vec{v}) &= 0 \\ \frac{\partial \, \vec{v}}{\partial t} + (\vec{v} \cdot \nabla) \, \vec{v} &= -\frac{1}{\rho} \nabla p + \nabla c - \xi \, \vec{v} \\ \frac{\partial}{\partial t} c &= D_c \Delta c - \widehat{\Lambda} c + \widehat{h} \rho \end{aligned} \tag{2.10}$$

where ρ is the cellular density, $\vec{v}$ is the cellular velocity distribution and $-\xi\ \vec{v}$ is just the friction force, with $\xi > 0$.

The last equation for the chemical cell c is just the same reaction-diffusion equation as in the KS model, but D_c, $\widehat{\Lambda}$ and $\widehat{h}$ are now constant. Interestingly, the system (2.10) may be compared to the model of self-gravitating Langevin fluids described by the damped Euler-Poisson system:

$$\begin{aligned} &\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho\ \vec{v}) = 0 \qquad (2.11)\\ &\frac{\partial\ \vec{v}}{\partial t} + (\vec{v}\ \cdot\nabla)\ \vec{v} = -\frac{1}{\rho}\nabla p + \nabla\Phi - \xi\ \vec{v}\\ &\Delta\Phi - \Lambda\Phi + 4\pi G\rho = 0 \end{aligned}$$

where $\Lambda > 0$ represents the cosmological constant and G is the gravitational constant. We observe that the concentration c plays the same role as the gravitational potential Φ. However, biological interactions are mediated by a material substance (the secreted chemical), while the physical interpretation of the gravitational potential in astrophysics is more abstract.

The main difference between (2.10) and (2.11) is the third equation: in astrophysics, the gravitational potential is generally determined instantaneously from the mass density, through the Poisson equation $(2.11)_3$, when $\Lambda = 0$; in biology, $(2.10)_3$ determines the evolution of the chemical: it is more complex and involves memory terms.

Backing to $(2.10)_3$, the chemical diffuses with a mobility D_c, it is produced by the organisms at a rate $\widehat{h}$ and it is also degraded at a rate $\widehat{\Lambda}$. In the momentum equation $(2.10)_2$ the friction/reaction term $-\xi\ \vec{v}$ can be interpreted as a Darcy porous effect. The Darcy Law is an experimental law which can be written as follows, see e.g. [12]:

$$\frac{\mu_D}{k}\ \vec{v}_D = -\nabla p + \rho\ \vec{f} \qquad (2.12)$$

where μ_D is the dynamic viscosity, k is the permeability and $\vec{v}_D$ is the Darcy/seepage velocity; $\vec{v}_D$ is related to the intrinsic/averaged velocity $\vec{v}$ of the pore by the equation:

$$\vec{v}_D = \epsilon\ \vec{v}$$

where $0 < \epsilon < 1$ is the mean porosity. Using only intrinsic quantities (2.12) becomes:

$$\frac{\mu_D}{k}\epsilon \vec{v} = -\nabla p + \rho \vec{f}$$

Following Nield and Bejan's notation in [11] we set: $R = \frac{\epsilon}{k}$ (which is called the (positive) retardability parameter) to obtain:

$$\mu_D R \vec{v} = -\nabla p + \rho \vec{f}$$

where the porosity doesn't appear explicitly, but is included in the definition of R.

So, in agreement with the Nield strategy, we can write the friction term $-\xi \vec{v}$ in $(2.10)_2$ in terms of the intrinsic velocity of the fluid, namely $-\nu_D R \vec{v}$ where ν_D is the kinematical viscosity.

2.2.1 The Hydrodynamic model instability analysis

In this section, we focus our attention on the hydrodynamic model described in (2.10). Following the observations made by Chavanis and Sire in [7], we shall consider a simplified setting, where $\frac{\partial c}{\partial t}$ can be neglected.

We may introduce the chemical relaxation time $\tau_c = \frac{1}{D_c} << 1$ and first consider the case without degradation of the chemical($\Lambda = 0$). Then, setting:

$$\Lambda = \frac{\widehat{\Lambda}}{D_c} \quad and \quad h = \frac{\widehat{h}}{D_c} \tag{2.13}$$

and taking the limit $D_c \to +\infty$, we reduce to

$$\Delta c + h\rho = 0 \tag{2.14}$$

which, in turn, may be further modified, replacing ρ with $\rho - \rho_0$, in order to overcome the so-called 'Jeans swindle', see e.g. [14]. In this case, the concentration of the chemical is just given by a stationary Poisson equation: this model is referred to as the 'Newtonian model'.

Then, we consider the case of a finite degradation rate. In the previous setting (2.13) and taking the limit $D_c \to +\infty$, we now obtain:

$$\Delta c - \Lambda c + h\rho = 0 \tag{2.15}$$

This equation is similar to the elliptic equation $(2.11)_3$ on an expanding universe approach, where $c(\vec{x},t)$ plays the role of $\Phi(\vec{x},t)$ and h plays the role of the constant $4\pi G$. Equation (2.15) has been derived for $\Lambda > 0$; this implies that the interaction is shielded on a typical distance Λ^{-1}. We shall refer to this model as the 'Yukawa model', from the Yukawa shielding in nuclear physics.

The stability analysis of an infinite and homogeneous distribution of cells against the chemotactic collapse is just similar to the classical Jeans stability analysis for the barotropic Euler-Poisson system in the presence of a self-gravity potential. Indeed the 'chemotactic collapse' of biological populations is similar to the 'chemotactic collapse' in an astrophysical setting (Jeans instability).

There are, however, two main differences between the two; the first one is the presence of the friction force $-\xi\ \vec{v}$ in the Euler equation. However, this term doesn't change the onset of the instability, but affects the evolution of the perturbation, by damping effects.

The second one may be due to the nature of the field equations $(2.10)_3$ and $(2.11)_3$, without Λ. In gravitational dynamics, in fact, an infinite and homogeneous distribution of matter with $\rho_0 = const$ and $\vec{v}_0 = 0$ is not a stationary solution of the barotropic Euler-Poisson system (2.11) because it is not possible to satisfy simultaneously the condition of hydrostatic equilibrium $\nabla p(\rho_0) - \rho_0 \nabla\Phi_0 = 0$ reducing to $\nabla\Phi_0 = 0$ and the Poisson equation $\Delta\Phi_0 = 4\pi G\rho_0$, unless $\rho_0 = 0$. This fact leads to a mathematical inconsistency in the study of the linear (dynamical) stability of such a distribution: this drawback is called the 'Jeans swindle', see e.g. [14].

On the contrary, there is no 'Jeans swindle' in the chemotactic problem.

Indeed, an infinite and homogeneous distribution of cells is a quiescent steady and homogeneous solution of (2.10), which satisfies the link $\widehat{\Lambda} c_0 = \widehat{h}\rho_0$ and $\vec{v}_0 = \vec{0}$.

In the modified 'Newtonian model' (2.14), the previous condition would become $\rho = \rho_0$ and for the 'Yukawa model' we need the relation $\Lambda c_0 = h\rho_0$.

We focus our stability analysis on the simplified equations (2.14) and (2.15). In the 'Newtonian model', the only difference with the Jeans analysis is the presence of the friction force ξ. In the 'Yukawa model' the differences are both in the friction term and in the shielding length Λ^{-1}, generated by the degradation of the chemical.

In [7] Chavanis and Sire show that the system is always stable for

$$c_s \geq (c_s)_{crit} \equiv (\frac{h\rho_0}{\Lambda})^{\frac{1}{2}}$$

where $c_s \equiv (\frac{dp}{d\rho})^{\frac{1}{2}}$ is the constant sound velocity in the medium.

Therefore, the system is always stable if c_s is above a certain critical threshold fixed by the shielding length Λ^{-1}. On the contrary, in the case $c_s < (c_s)_{crit}$, the sufficient condition for the onset of the Chemotactic Collapse reads

$$k^2 < \widetilde{k}^2_{CS}$$

where $\widetilde{k}^2_{CS} := k^2_{CS} - \Lambda$, with $k^2_{CS} := \frac{h\rho_0}{c_s^2}$.

It is worth to remark that the critical threshold $k^2_{CS} := \frac{h\rho_0}{c_s^2}$ may be compared with the critical Jeans wave number $k^2_J := \frac{4\pi G\rho_0}{c_s^2}$, within the gravitational instability analysis, see e.g. [14]. In the 'Newtonian model', the condition $\Lambda = 0$ implies $(c_s)_{crit} = +\infty$ so the system is always unstable to perturbations with sufficiently large wavelengths ($k < k_J$). These results do not depend on ξ; indeed the friction term only affects the evolution of the perturbation.

If $k < k_m(\Lambda)$ the perturbation grows exponentially rapidly; it can been defined a friction-dependent wavenumber k_c such that if $k_m(\Lambda) < k < k_c(\xi, \Lambda)$, the perturbation is damped exponentially rapidly without oscillating and for $k > k_c(\xi, \Lambda)$ it presents damped oscillations. Indeed the unstable modes present a growth rate dependent only on the shielding length, instead the stable modes present damping rate and growing oscillations depending on both Λ and ξ.

Owing to the above mentioned analogy between chemotaxis and gravity, our stability analysis also applies to self-gravitating Langevin particles provided that we make use of the 'Jeans swindle', when $\Lambda = 0$.

Chapter 3

A special Cahn-Hilliard-Darcy model for tumour growth

3.1 A description of the model

The complexity of oncology has attracted an increasing interest among mathematicians, with the purpose to find the appropriate PDEs to provide additional insights to best fit certain aspects of tumour growth.
In this section we'll give a brief introduction on new diffuse interface models for tumour growth (with chemotaxis and active transport effects), recently proposed in [15] and based on the Cahn-Hilliard theory.
In this thesis we are not primarily interested in well-posedness results, whereas we aim in recovering novel mathematical models for tumour growth, even in the light of what we have discussed in the previous two Chapters.
Referring to [15], in order to obtain a realistic and mathematically tractable system of partial differential equations, we will neglect some effects and, hence from a medical point of view, we will make the following assumptions:

- Tumour cells only die by apoptosis; therefore we neglect the process of tumour necrosis, where we would have to consider negative effects of chemical species from the former intracellular space on the surrounding tumour cells.

- The tissue around the tumour does not react to the tumour cells in any active way. More precisely, we do not take into account any response of the immune system to the tumour tissue.
- Larger tumour entities are actually enforcing blood vessel growth toward themselves, by secreting vessel growth factors. This phenomenon could be the object for further studies.
- We postulate the presence of an unspecified chemical species acting as a nutrient for tumour cells.

Therefore, the model proposed by Garcke et altri in [15] addresses a binary mixture comprised by tumour and healthy cells, described by a Cahn-Hilliard-Darcy system coupled to a convection-diffusion-reaction equation for the nutrient.
We now consider a (time dependent) bounded domain $\Omega \subset \mathbb{R}^3$ with smooth boundary $\partial\Omega$, for any time $t \geq 0$. Hence, within a unified scheme, the governing evolution system reads:

$$\begin{cases} \nabla \cdot \vec{v} = \alpha\Gamma \\ \vec{v} = -K(\nabla p - \mu\nabla\varphi - \chi_\varphi \sigma \nabla\varphi) \\ \frac{\partial\varphi}{\partial t} + \nabla \cdot (\varphi\ \vec{v}) = \nabla \cdot (m(\varphi)\nabla\mu) + \overline{\rho}_s\Gamma \\ \mu = \frac{\beta}{\epsilon}\psi'(\varphi) - \beta\epsilon\Delta\varphi - \chi_\varphi\sigma \\ \frac{\partial\sigma}{\partial t} + \nabla \cdot (\sigma\ \vec{v}) = \nabla \cdot (n(\varphi)(\chi_\sigma\nabla\sigma - \chi_\varphi\nabla\varphi)) - C\sigma h(\varphi) \\ \Gamma = (P\sigma - A)h(\varphi) \end{cases} \tag{3.1}$$

Here, $\vec{v}$ denotes the volume-averaged velocity of the mixture, p indicates the pressure and σ represents the concentration of an unspecified chemical species that serves as a nutrient for the tumour.
The scalar quantity φ denotes the difference in volume fraction and has the same role as c in chapter 1 and μ still denotes the chemical potential; it is worth to observe that the momentum equation $(3.1)_2$ may be rewritten as

$$\frac{1}{K}\ \vec{v} = -(\nabla p - \mu\nabla\varphi - \chi_\varphi\sigma\nabla\varphi).$$

In the first chapter $c \in [0,1]$, whereas in this approach $\varphi \in [-1,1]$; $\{\varphi = 1\}$ represents the unmixed tumour tissue and $\{\varphi = -1\}$ the surrounding healthy tissue.

The positive constants K, β, P, A and C represent permeability, surface tension, proliferation rate, apoptosis rate and consumption rate, respectively. The constants $\overline{\rho}_s$ and α are related to the densities of the two components: in particular, we have $\alpha = 0$ in the case of matched densities.

Moreover $m(\varphi)$ and $n(\varphi)$ are non-negative mobilities for φ and σ respectively, ψ is a potential with two equal minima at ± 1. The function h is chosen as an interpolation function with $h(-1) = 0$ and $h(1) = 1$. A simple choice of h could be $h(\varphi) = \frac{1}{2}(1 + \varphi)$.

The term $\chi_\sigma \geq 0$ denotes the diffusivity of the nutrient and $\chi_\varphi \geq 0$ can be seen as a parameter for transport mechanisms, such as chemotaxis and active transport. Finally, the parameter ϵ is related to the small thickness of the interfacial layers present in phase field systems.

In equation $(3.1)_1$ the quantity $\alpha\Gamma$ represents a source term which can be also included in a generalized Cahn-Hilliard model (in chapter 1 we have described the derivation of the C.H. model without source terms, but for compressible fluids).

Equation $(3.1)_2$ represents the local momentum balance equation using the Darcy-type approximation which neglects the acceleration (inertia) terms, in the presence of chemotactic forces; in $(3.1)_3$ the quantity/order parameter φ is governed by a (reaction-diffusion) Cahn-Hilliard equation in a divergence form, with the additional source term $\overline{\rho}_s\Gamma$; the chemical potential includes a dependence on the nutrient cell σ.

Mass transition from healthy cells to tumour components and vice versa is described by condition $(3.1)_6$, where the term $P\sigma h(\varphi)$ represents tumour growth and proliferation whereas $Ah(\varphi)$ models the process of apoptosis.

Finally, $(3.1)_5$ is a convection-reaction-diffusion equation for σ where the additional term $C\sigma h(\varphi)$ indicates consumption of the nutrient only in the presence of the tumour cells: it may be viewed as a generalization to time

dependent $3D$ domains of the first equation by Keller and Segel with the additional term $C\sigma h(\varphi)$. In this way σ and φ play the same roles of ρ and c in the KS model.

The particular choices proposed in [15] for modeling proliferation, apoptosis, chemotaxis and mass transition in (3.1) are justified by the following considerations:

- In $(3.1)_6$, we obtain that $\Gamma = P\sigma - A$ holds in the tumour region $\varphi = 1$. The implicit assumption that the tumour growth is proportional to the nutrient supply follows by the fact that malign tumours have the common genetic feature that certain growth inhibiting proteins have been switched off by mutations. Hence, we can consider that while in the healthy cells the mitotic cycle is rather than strictly inhibited, tumour cells often show unregulated growth behaviour, which is only limited by the supply of the nutrients. Moreover, it is implicitly assumed that the tumour proliferation rate is more significant than that of the healthy tissue in the choice of zero mass transition $\Gamma = 0$ in the healthy region $\varphi = -1$.

- In $(3.1)_3$ and $(3.1)_5$ the fluxes for φ and σ are expressed as follows:

$$\vec{q}_\varphi := -m(\varphi)\nabla\mu = -m(\varphi)\nabla(\frac{\beta}{\epsilon}\psi'(\varphi) - \beta\epsilon\Delta\varphi - \chi_\varphi\sigma)$$
$$\vec{q}_\sigma := -n(\varphi)\nabla(\chi_\sigma\sigma - \chi_\varphi\varphi)$$

  It has also been pointed out by Roussous, Condeelis and Patsialou in [16] that the undersupply of the nutrient induces chemotaxis in certain tumour entities. This is reflected in the new term $m(\varphi)\nabla(\chi_\varphi\sigma)$ of $\vec{q}_\varphi$, which drives the cells in regions of high nutrient.

  The term $n(\varphi)\nabla(\chi_\varphi\varphi)$ in $\vec{q}_\sigma$, instead, drives the nutrient to regions of high φ, namely to the tumour cells, which indicates that the nutrient is actively moving towards the tumour cells. This allows the interpretation that the term $n(\varphi)\nabla(\chi_\varphi\varphi)$ represents active transport mechanisms which move the nutrient into the tumour colony and generalizes the drift term in the first equation by Keller and Segel. In the

same paper, the authors specify that the term 'active transport' is used in a biological sense, in order to enhance that some kind of mechanism is needed to maintain the transport (in contrast to passive transporters which are driven only by the concentration gradient of the substance).

3.2 Model derivation

In this section, even if we are not primarily interested in the Thermodynamic derivation of the model (3.1), in the light of the results established in Chapter 1, in order to provide a comparison between two different approaches, we just want to give a brief review of the key steps of the construction of (3.1) and refer to [15] for the detailed derivation of it.
As already mentioned, we address a binary mixture consisting of tumour and healthy cells (in a time dependent bounded domain $\Omega \subset \mathbb{R}^3$). The two components denote healthy and tumour tissues.
We indicate by ρ_1 and ρ_2 the actual masses of the components matter per volume in the mixture, and by $\overline{\rho_1}$ and $\overline{\rho_2}$ the mass densities of the pure components.
Then, $\rho = \rho_1 + \rho_2$ denotes the total mixture density (which is not necessarily constant) and we define the volume fraction of each component as:

$$u_1 = \frac{\rho_1}{\overline{\rho_1}} \quad and \quad u_2 = \frac{\rho_2}{\overline{\rho_2}} \tag{3.2}$$

We expect that physically $\rho_i \in [0, \overline{\rho_i}]$ and thus $u_i \in [0, 1]$ for $i = 1, 2,$.
In addition to the considerations of the previous section, we make the following modeling assumptions:

- There is no external volume compartment besides the two components, i.e.

$$u_1 + u_2 = 1$$

- We allow for mass exchange between the two components. Growth of the tumour is represented by mass transfer from component 1 (healthy

tissue) to component 2 (tumour tissue), while tumour cells are converted back into the surrounding healthy tissues when they die.

- We choose the mixture (mean volume) velocity to be:

$$\vec{v} = u_1 \vec{v_1} + u_2 \vec{v_2}$$

where $\vec{v_1}$ and $\vec{v_2}$ are the individual velocities of the two components; it is worth to note that $\vec{v}$ is different from the barycentric velocity.

- We model a general chemical species which is treated as a nutrient for the tumour tissues. Its concentration is denoted by σ and it is transported by the volume-averaged mixture velocity and a flux $\vec{J_\sigma}$.

3.2.1 Balance Laws

The local balance laws for mass of each component in a divergence form read:

$$\frac{\partial \rho_1}{\partial t} + \nabla \cdot (\rho_1 \vec{v_1}) = \Gamma_1 \tag{3.3}$$

$$\frac{\partial \rho_2}{\partial t} + \nabla \cdot (\rho_2 \vec{v_2}) = \Gamma_2 \tag{3.4}$$

Using (3.2) we can rewrite (3.3)-(3.4) in the following way: for $i = 1, 2$

$$\frac{\partial u_i}{\partial t} + \nabla \cdot (u_i \vec{v_i}) = \frac{\Gamma_i}{\overline{\rho}_i}$$

Thus we obtain

$$\nabla \cdot \vec{v} = \nabla \cdot (u_1 \vec{v_1}) + \nabla \cdot (u_2 \vec{v_2}) = \frac{\Gamma_1}{\overline{\rho}_1} + \frac{\Gamma_2}{\overline{\rho}_2} =: \Gamma_{\vec{v}} \tag{3.5}$$

which reduces to the solenoidality constraint $\nabla \cdot \vec{v} = 0$ iff $\Gamma_{\vec{v}} = 0$.
We now introduce the fluxes

$$\vec{J_i} := \rho_i(\vec{v_i} - \vec{v}), \quad \vec{J} := -\frac{1}{\overline{\rho}_1} \vec{J_1} + \frac{1}{\overline{\rho}_2} \vec{J_2} \tag{3.6}$$

Then, we have

$$\vec{J_1} + \vec{J_2} + \rho \vec{v} = \rho_1 \vec{v_1} + \rho_2 \vec{v_2}$$

So, adding equations (3.3)-(3.4), we obtain the equation for the mixture density:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho_1 \vec{v_1} + \rho_2 \vec{v_2}) = \frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \vec{v} + \vec{J_1} + \vec{J_2}) = \Gamma_1 + \Gamma_2$$

Following the notations by Garcke et altri, we now define the order parameter φ as the difference in volume fractions

$$\varphi := u_2 - u_1$$

then, by subtracting the equation for u_1 from the equation from u_2, and using (3.6), we obtain the evolution equation for φ:

$$\frac{\partial \varphi}{\partial t} + \nabla \cdot (\varphi \vec{v}) + \nabla \cdot \vec{J} = \frac{\Gamma_2}{\overline{\rho}_2} - \frac{\Gamma_1}{\overline{\rho}_1} =: \Gamma_\varphi \tag{3.7}$$

It is worth to note that, taking into account the constraint $u_1 + u_2 = 1$, we find

$$u_1 = \frac{1-\varphi}{2} \quad u_2 = \frac{1+\varphi}{2}$$

In this way, as already cited, the regions of the tumour and healthy tissues are represented by $\left\{\vec{x} \in \Omega : \quad \varphi = 1\right\}$ and $\left\{\vec{x} \in \Omega : \quad \varphi = -1\right\}$ respectively. Moreover, the mixture density ρ can be expressed as

$$\rho = \rho_1 + \rho_2 = \overline{\rho}_1 u_1 + \overline{\rho}_2 u_2 = \frac{\overline{\rho}_1 + \overline{\rho}_2}{2} + \varphi \frac{\overline{\rho}_2 - \overline{\rho}_1}{2} \tag{3.8}$$

For the nutrient, we postulate the following balance law:

$$\frac{\partial \sigma}{\partial t} + \nabla \cdot (\sigma \vec{v}) + \nabla \cdot \vec{J}_\sigma = -S \tag{3.9}$$

where S denotes a source/sink term for the nutrient.
In addition, $\sigma \vec{v}$ models the transport by the volume-averaged velocity and $\vec{J}_\sigma$ models other transport mechanisms, like diffusion and chemotaxis.

3.2.2 Thermodynamic developments and energy inequality

Following [15], we postulate a general energy density of the form:

$$e(\varphi, \nabla\varphi, \sigma) = f(\varphi, \nabla\varphi) + N(\varphi, \sigma)$$

Here, we neglect inertia effects, so the kinetic energy does not appear in e. The first term f accounts for the interfacial energy and unmixing tendencies, while the second term N describes the chemical energy of the nutrient and energy contributions resulting from the interactions between the tumour tissues and the nutrient.
The latter will, for example, lead to chemotatic effects which are of particular interest as they result in the tumour tissue growing towards regions with high nutrient concentration.
We now consider f to be of Ginzburg-Landau type: hence, we choose

$$f(\varphi, \nabla\varphi) := A\psi(\varphi) + \frac{B}{2}|\nabla\varphi|^2$$

where A and B are two positive constants and ψ is now a potential with two equal minima at ± 1.
We refer to [18] for a detailed discussion of the situation with source terms. By adjusting the thermodynamic strategy of Chapter 1, the second law of thermodynamics in an isothermal setting requires that, for all volumes $V(t) \subset \Omega$ which are trasported with the fluid velocity, the following inequality has to hold:

$$\frac{d}{dt}\int_{V(t)} e \quad dv \leq -\int_{\partial V(t)} \vec{J_e} \cdot \vec{n} \quad d\sigma + \int_{V(t)} c_\varphi \Gamma_\varphi + c_{\vec{v}} \Gamma_{\vec{v}} + c_s(-S) \quad dv$$

where $\vec{J_e}$ is the energy flux, and $\vec{n}$ is the outer unit normal to $\partial V(t)$. Following [18], we postulate that the source terms Γ_φ, $\Gamma_{\vec{v}}$ and the nutrient supply S carry with them a supply of energy described by:

$$\int_{V(t)} c_\varphi \Gamma_\varphi + c_{\vec{v}} \Gamma_{\vec{v}} + c_s(-S) \quad dv$$

for some $c_\varphi, c_{\vec{v}}$ and c_s yet to be determined.
Using the transport theorem and the divergence theorem, we obtain the following local form:

$$\frac{\partial}{\partial t}e + \nabla \cdot (e\ \vec{v}) + \nabla\cdot\ \vec{J}_e - c_{\vec{v}}\Gamma_{\vec{v}} - c_\varphi\Gamma_\varphi + c_s S \leq 0.$$

Then, we employ the Lagrange multiplier method of Liu and Muller, see e.g. [5]: let $\lambda_{\vec{v}}$, λ_σ, λ_φ denote the Lagrange multipliers for equations (3.5), (3.9), (3.7) respectively.
We require that the following inequality holds for an arbitrary Thermodynamic process:

$$\begin{aligned} -D :=& \frac{\partial e}{\partial t} + \nabla \cdot (e\ \vec{v}) + \nabla\cdot\ \vec{J}_e - c_{\vec{v}}\Gamma_{\vec{v}} - c_\varphi\Gamma_\varphi + c_s S \\ & - \lambda_{\vec{v}}(\nabla\cdot\ \vec{v} - \Gamma_{\vec{v}}) \\ & - \lambda_\sigma(\dot{\sigma} + \sigma\nabla\cdot\ \vec{v} + \nabla\cdot\ \vec{J}_\sigma + S) \\ & - \lambda_\varphi(\dot{\varphi} + \varphi\nabla\cdot\ \vec{v} + \nabla\cdot\ \vec{J} - \Gamma_\varphi) \leq 0 \end{aligned}$$

Employing some standard identities already seen in Chapter 1 and after some further rearrangements (see e.g. [15]), we recover the form:

$$\begin{aligned} -D =& \nabla \cdot (\vec{J}_e - \lambda_\varphi\ \vec{J} - \lambda_\sigma\ \vec{J}_\sigma + B\frac{\partial\varphi}{\partial t}\nabla\varphi + (e - \lambda_\varphi\varphi - \lambda_\sigma\sigma - \lambda_{\vec{v}})\ \vec{v}) \\ & + (\mu - \lambda_\varphi)\dot{\varphi} + S(c_s - \lambda_\sigma) + \Gamma_{\vec{v}}(\lambda_{\vec{v}} - c_{\vec{v}}) + \Gamma_\varphi(\lambda_\varphi - c_\varphi) + (N_{,\sigma} - \lambda_\sigma)\dot{\sigma} \\ & - \vec{v}\cdot(\nabla(e - \lambda_\varphi\varphi - \lambda_\sigma\sigma - \lambda_{\vec{v}} - \frac{B}{2}|\nabla\varphi|^2) - B\Delta\varphi\nabla\varphi) + \nabla\lambda_\varphi\cdot\ \vec{J} + \nabla\lambda_\sigma\cdot\ \vec{J}_\sigma\ . \end{aligned} \tag{3.10}$$

where we have used the notations:

$$N_{,\sigma} := \frac{\partial N}{\partial\sigma}, \quad N_{,\varphi} := \frac{\partial N}{\partial\varphi}, \quad \mu := A\psi'(\varphi) + N_{,\varphi} - B\Delta\varphi$$

3.2.3 Constitutive assumptions and the general model

We are now seeking for a model fulfilling the second law of thermodynamics in the version of a dissipation inequality, stated in the previous section.

As in [15] we make the following assumptions which take the most relevant effects into account:

$$\begin{aligned}
&\vec{J}_e = \lambda_\varphi \vec{J} + \lambda_\sigma \vec{J}_\sigma - B\frac{\partial \varphi}{\partial t}\nabla\varphi - (e - \lambda_\varphi\varphi - \lambda_\sigma\sigma - \lambda_{\vec{v}})\vec{v} \qquad (3.11)\\
&c_S = \lambda_\sigma = N_{,\sigma} \quad c_\varphi = \lambda_\varphi = \mu, \quad c_{\vec{v}} = \lambda_{\vec{v}}\\
&\vec{J}_\sigma = -n(\varphi)\nabla N_{,\sigma} \quad \vec{J} = -m(\varphi)\nabla\mu
\end{aligned}$$

where $n(\varphi)$ and $m(\varphi)$ are non-negative mobilities.
We introduce a pressure-like function p and choose:

$$\lambda_{\vec{v}} = p - A\psi(\varphi) - \frac{B}{2}|\nabla\varphi|^2 + e - \mu\varphi - N_{,\sigma}\sigma, \qquad (3.12)$$

and for a positive constant K,

$$\begin{aligned}
\vec{v} &= K(\nabla(e - \mu\varphi - N_{,\sigma}\sigma - \lambda_{\vec{v}} - \frac{B}{2}|\nabla\varphi|^2) - B\Delta\varphi\nabla\varphi) \qquad (3.13)\\
&= K(\nabla(-p + A\psi(\varphi)) - B\Delta\varphi\nabla\varphi)\\
&= -K(\nabla p - (\mu - N_{,\varphi})\nabla\varphi).
\end{aligned}$$

Equation $(3.11)_1$ makes a constitutive assumption for the energy flux $\vec{J}_e$ which guarantees that the divergence term in (3.10) vanishes.
Meanwhile, $(3.11)_2$, $(3.11)_3$, (3.12), (3.13) are just taken in order that the right hand side of (3.10) is non-positive for arbitrary values of $(\varphi, \sigma, \vec{v}, \Gamma_{\vec{v}}, \Gamma_\varphi, S, \dot{\varphi}, \dot{\sigma})$.
We mention that (3.13) is just the Darcy equation with force $(\mu - N_{,\varphi})\nabla\varphi$.
Thus, our general model for tumour growth is described by the following system of PDEs:

$$\begin{cases}
\nabla\cdot\vec{v} = \Gamma_{\vec{v}}\\
\vec{v} = -K(\nabla p - \mu\nabla\varphi + N_{,\varphi}\nabla\varphi)\\
\frac{\partial\varphi}{\partial t} + \nabla\cdot(\varphi\vec{v}) = \nabla\cdot(m(\varphi)\nabla\mu) + \Gamma_\varphi\\
\mu = A\psi'(\varphi) - B\Delta\varphi + N_{,\varphi}\\
\frac{\partial\sigma}{\partial t} + \nabla\cdot(\sigma\vec{v}) = \nabla\cdot(n(\varphi)\nabla N_{,\sigma}) - S
\end{cases} \qquad (3.14)$$

and we associate to it the homogeneous Neumann boundary conditions:

$$\nabla\varphi\cdot\vec{n} = \nabla\mu\cdot\vec{n} = 0 \quad on \quad \partial\Omega \qquad (3.15)$$

Finally, let $P, A, C, \chi_\sigma, \chi_\varphi$ be non-negative constants; for physically relevant values of the model variables, i.e. $\varphi \in [-1, 1]$ and $\sigma \geq 0$, we choose

$$\begin{aligned} \Gamma &= (P\sigma - A)h(\varphi) \\ N(\varphi, \sigma) &= \frac{\chi_\sigma}{2} |\sigma|^2 + \chi_\varphi \sigma(1 - \varphi) \\ S &= C\sigma h(\varphi) \end{aligned}$$

where $h(\varphi)$ is an interpolation function with $h(-1) = 0$ and $h(1) = 0$.
We have already stressed on the physical motivations for the particular forms of Γ and S in the description of the model.
For the choice of $N(\varphi, \sigma)$, if both χ_φ and χ_σ are positive constants, then for physically relevant parameter values:

$$N_{,\sigma} = \chi_\sigma \sigma + \chi_\varphi(1 - \varphi) \geq 0$$

Thus, this choice of the flux $\nabla N_{,\sigma}$ provides two transport mechanisms for the nutrient σ.
The first term $\chi_\sigma \nabla\sigma$ results in a diffusion process along negative gradients of σ, while the second term $-\chi_\varphi \nabla\varphi$ is a chemotactic term that drives the nutrient towards the tumour cell regions.
In particular, in the tumour cell regions $\{\varphi = +1\}$, the nutrient will only experience diffusion, while in the healthy cell regions $\{\varphi = -1\}$, the nutrient will experience diffusion and active transport to the tumour.

3.3 Specific models

3.3.1 Zero excess of total mass

Setting $\Gamma_2 = -\Gamma_1 =: \Gamma$, so that there is no excess of total mass, and letting

$$\alpha := \frac{1}{\overline{\rho}_2} - \frac{1}{\overline{\rho}_1}, \quad \overline{\rho}_S := \frac{1}{\overline{\rho}_2} + \frac{1}{\overline{\rho}_1}$$

so that

$$\Gamma_{\vec{v}} = \alpha\Gamma, \quad \Gamma_\varphi = \overline{\rho}_S \Gamma,$$

then, the governing system reduces to the form:

$$\begin{cases} \nabla\cdot \vec{v} = \alpha\Gamma \\ \vec{v} = -K(\nabla p - \mu\nabla\varphi + N_{,\varphi}\nabla\varphi) \\ \frac{\partial\varphi}{\partial t} + \nabla\cdot(\varphi\ \vec{v}) = \nabla\cdot(m(\varphi)\nabla\mu) + \overline{\rho}_S\Gamma \\ \mu = A\psi'(\varphi) - B\Delta\varphi + N_{,\varphi} \\ \frac{\partial\sigma}{\partial t} + \nabla\cdot(\sigma\ \vec{v}) = \nabla\cdot(n(\varphi)\nabla N_{,\sigma}) - S \end{cases} \tag{3.16}$$

In particular, in the case of equal densities, i.e. $\overline{\rho}_1 = \overline{\rho}_2 = \overline{\rho}$, then, $\alpha = 0$ and $\overline{\rho}_S = \frac{2}{\overline{\rho}}$; thus, the model is described by:

$$\begin{cases} \nabla\cdot \vec{v} = 0 \\ \vec{v} = -K(\nabla p - \mu\nabla\varphi + N_{,\varphi}\nabla\varphi) \\ \frac{\partial\varphi}{\partial t} + \nabla\cdot(\varphi\ \vec{v}) = \nabla\cdot(m(\varphi)\nabla\mu) + \frac{2}{\overline{\rho}}\Gamma \\ \mu = A\psi'(\varphi) - B\Delta\varphi + N_{,\varphi} \\ \frac{\partial\sigma}{\partial t} + \nabla\cdot(\sigma\ \vec{v}) = \nabla\cdot(n(\varphi)\nabla N_{,\sigma}) - S \end{cases} \tag{3.17}$$

3.3.2 Absence of the nutrient

Setting $\sigma = N(\sigma, \varphi) = 0$, then the model simplifies to:

$$\begin{cases} \nabla\cdot \vec{v} = \Gamma_{\vec{v}} \\ \vec{v} = -K(\nabla p - \mu\nabla\varphi) \\ \frac{\partial\varphi}{\partial t} + \nabla\cdot(\varphi\ \vec{v}) = \nabla\cdot(m(\varphi)\nabla\mu) + \Gamma_\varphi \\ \mu = A\psi'(\varphi) - B\Delta\varphi \end{cases} \tag{3.18}$$

3.3.3 Zero velocity, zero excess of mass and equal densities

We suppose the volume-averaged mixture velocity $\vec{v}$ is zero, the excess of mass $\Gamma_1 + \Gamma_2$ is zero and the densities are equal. Also neglecting the Darcy

equation, we find:

$$\begin{cases} \frac{\partial \varphi}{\partial t} = \nabla \cdot (m(\varphi)\nabla \mu) + \frac{2}{\bar{\rho}}\Gamma \\ \mu = A\psi'(\varphi) - B\Delta\varphi + N_{,\varphi} \\ \frac{\partial \sigma}{\partial t} = \nabla \cdot (n(\varphi)\nabla N_{,\sigma}) - S \end{cases} \tag{3.19}$$

Following the same strategy as in Chapter 2, we may now perform a linear stability analysis to investigate the roles of the new terms.
We conclude by remarking the importance of a numerical approach to analyze the influence of these new terms for specific growth scenarios.

Chapter 4

Conclusions

In this thesis, we have derived a non-isothermal Cahn-Hilliard model for phase-separation in a binary mixture. We have firstly focused our attention to balance equations and constitutive restrictions placed upon the constitutive functions by the second law of thermodynamics.
We've described the evolution of the concentration by the standard equation for mixture, but the balance of energy and entropy of the mixture have been stated as for a single constituent. Moreover, due to the non-standard nature of the materials involved, we have allowed for an extra-energy flux $\vec{w}$ in addition to the heat flux $\vec{q}$. We've also considered motion and diffusion effects by letting the stress in the mixture have additive viscous terms. Thus, we have obtained a set of evolution equations for the concentration, the velocity and the temperature through the balance of mass, linear momentum and energy. The main feature is that the constituents have been allowed to be compressible fluids; the transition is induced by temperature: above the critical temperature Θ, the uniform concentration of the mixture prevails, below Θ, the two fluids separate. In the end of the first chapter we've underlined this phenomenon by giving an example of energy function which allows an easy understanding on the transition between phase separation and phase mixing.
In the second chapter, we have described two models for chemotaxis: the

pioneeristic model by Keller and Segel and the hydrodynamic model by Chavanis and Sire.
The former is a parabolic-parabolic model of two coupled PDEs describing the motion of microorganisms and chemicals in interaction.
We've also performed a linear stability analysis (spectral analysis) and found the sufficient condition for instability.
The latter is an hydrodynamic (hyperbolic) model which, besides the presence of the chemotactic force, takes into account inertial effects together with a friction force, via the parameter ξ. We've also examined the analogies between this model and the Euler-Poisson system for self-gravitating bodies in astrophysics.
Further, we have performed a brief stability analysis as before and discussed the instability conditions for two simplified model: the 'Newtonian' model and the 'Yukawa' model.
A generalization of this model could be provided by the introduction of visco-elastic properties: in fact, this model may be easily generalized to include the viscous properties of Navier-Stokes type described in Chapter 1. On the other hand, by experimental observations, it has been seen the blood in microtubes to have both viscous and elastic properties acting together; thus, it may be more appropriate to consider it like a visco-elastic material by the introduction of a relexation/delay time, typical of visco-elastic settings.
In the third chapter, we've focused our attention on the continuum thermodynamically consistent new diffuse interface model for tumour growth, introduced in [15].
After performing a brief description of the model and the medical reasons which justify the choices of the authors, we've succinctly described the main steps of the model derivation, by a comparison with the thermodynamic strategy developed in chapter 1.
Some of the main features of this model are that it takes into account the presence of sources terms in the Cahn-Hilliard theory (this generalizes the model obtained in the first chapter) and introduce an additional equation for

σ, which represents the concentration of an unspecified chemical species that serves as a nutrient for the tumour. This equation could be interpreted as a generalization of the first equation by Keller-Segel.
The work may be further completed by employing numerical simulations (see e.g. [15]). Moreover the model could also be generalized taking into account inertia effects, which are neglected in this model, towards a generalized Chavanis-Sire model, including the presence of visco/visco-elastic effects and within an advection-reaction-diffusion C.H. equation, replacing the chemical equation.
Indeed a suitable and realistic combination of the continuum mathematical models for chemotactic processes in angiogenesis, discussed within this thesis, could become an interesting research issue for future papers.

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