MATERIAL AND GEOMETRIC PHASE TRANSITIONS IN BIOLOGICAL MEMBRANES

Giuseppe Zurlo

Tutori:

Prof. Luca Deseri
Prof. Salvatore Marzano
Prof. Roberto Paroni
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CHAPTER 1

Introduction
1. Phase transitions in phospholipid bilayers.

This thesis concerns the study of phase transitions in phospholipid bilayers, which are the major structural elements of all biological membranes. For this reason phospholipid bilayers can be considered as the basic bricks of life on earth.

![Figure 1. Schematic representation of a cell membrane.](image1)

Phospholipid molecules are structurally characterized by a hydrophilic, phosphate-containing polar head, which is attracted to water, and a hydrophobic, non-polar hydrocarbon chain, which repels water. The occurrence of both these features endows phospholipid molecules in water solutions of self-organizing properties, so that they tend to organize themselves into a rich variety of structures, such as, for examples, lipid bilayers.

![Figure 2. The structure of an amphiphilic molecule](image2)

Biological membranes may contain hundreds of different constituents. In order to understand the basic features of these structures, experiments are performed on simplified model bilayer membranes, artificially created in laboratory by self-organization in water solution of two or three different kinds of lipid molecules into closed structures, called liposomes. It has been observed that artificially created membranes made of three constituents mixtures of saturated and unsaturated lipid molecules and cholesterol molecules describe quite accurately the crucial properties of biological membranes. These model bilayers are closed spheroidal structures, with a thickness...
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of a few nanometers, and a diameter which can range from 50\text{nm} up to tens of micrometers; larger liposomes are generally referred to as "Giant Unilamellar Vesicles" (GUV).

**Figure 3.** Schematic representation of a liposome.

There is nowadays a strong experimental evidence that rather than being uniformly distributed on the surface, the membrane constituents undergo a phase separation phenomena, as shown by the coexistence of domains characterized by different chemical compositions, configurational properties of the hydrocarbon chains of the lipid molecules, and elastic properties.

**Figure 4.** Phase separation of "rafts", that is domains characterized by different chemical compositions and mechanical properties on the membrane surface.

The elastic properties of lipid membranes play a crucial role in determining the equilibrium configurations assumed by liposomes in water solution: advanced high-resolution fluorescence imaging tools have recently revealed the existence of a rich variety of composition-domain patterns and equilibrium shapes in ternary GUVs, for various values of the liposome composition, of the external temperature and osmotic pressure. It is believed that these exotic equilibrium configurations can be explained on the basis of a still unclear coupling between the chemical and the mechanical properties of lipid bilayers.

It is commonly recognized that the phase separation phenomena on cell membranes are closely associated with cell functionality: lipid phase coexistence is expected to modulate the fundamental transport processes between the organelles contained in
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Figure 5. Images experimentally obtained by Baumgart, Hess & Webb [7], which clearly show how phase separation is strictly related to the equilibrium shapes of GUV in water solution. In red and blue respectively liquid-disordered and liquid-ordered phases. Scale bars 5µm.

the cell and its environment, and it has been shown that deviations from the natural lipid composition and domain distribution may lead to severe health problems.

On the other hand, in recent years a growing interest on the properties of liposomes has been driven by their strong potential in pharmacological applications, in particular for their use as deliverers of anticancer agents or drugs against cardiovascular diseases, or for their use in bio-engineering applications, gene therapy, medical diagnostics and much more. As well as in cell functionality, phase separation is here expected to play a crucial role since closely related to the transport of drugs across the membrane.

Both theoretical studies on human cells and industrial applications of liposomes need mathematical models on the chemo-mechanical behavior of lipid bilayers. Up to now, a huge number of partial model exists, each of which focuses on limited aspects of the whole problem: there are works mainly concerned with the chemical and structural properties of lipid molecules within the bilayer (see for example [1],[35],[43],[57],[62]), works which ignore the question of chemical composition and consider the membrane as a homogenous, elastic, two-dimensional shell under various boundary and loading conditions (see for example [6],[5],[50],[51],[52]) and models which attempt to establish more or less heuristic couplings between chemical and mechanical properties (see for example [34],[32],[33],[53],[60]), but a complete model on the chemo-mechanical behavior of lipid bilayers seems nowadays still un-reached.

The aim of this thesis is to propose a new phenomenologically grounded model which, on the basis of the tools of Thermo-Chemo-Mechanics, can explain how chemistry and mechanics interact in shaping lipid bilayers. In the thesis it is developed a model which fully describes the phase separation phenomena and the observed equilibrium shapes, on the basis of elementary information on the liposome nature and composition, pressure and temperature, ruling out arbitrary assumptions on the phase separation process. We will also stay away from heuristic constitutive couplings between chemical and geometrical variables, which are usually finely tuned in order to produce the desired solutions. On the basis of the Bragg-Williams and Flory-Huggins
theories of solutions and of a procedure of dimension reduction for fluid, elastic bodies, justified by the fact that multilayered liposomes might be of future interest, we derive a new expression of the elastic energy density for lipid bilayers. In the final part of the work we set up the variational formulation of the equilibrium problem, and we present some partial results concerning the stress-free purely membranal case, as a first qualitative discussion on the solution of the complete problem, which is still under investigation.

The structure of this thesis can be summarized as follows: Chapter 2 collects all the needed preliminary mathematical notions regarding differential geometry and surface deformations; Chapter 3 contains a review of the solution theory, both within the classical deformation-free context, and within the Continuum Thermodynamics approach, in order to give a self-contained presentation of the theories at the basis of the chemical properties of lipid bilayers; Chapter 4 contains a short review of the state of the art on the argument; in Chapter 5 we provide our new phenomenological derivation of the energy density for a lipid bilayer, on the basis of the physical evidence of non-local elastic response of the considered material, and of phenomenological coupling between chemical and mechanical effects; Chapter 6 concerns a procedure of 3D-2D dimension reduction which yields a new expression of the elastic energy density for a very thin, fluid membrane; finally, in Chapter 7 the complete variational problem of the equilibrium it set up, and we present some partial results.
CHAPTER 2

Preliminary Notions
1. Mathematical preliminaries.

In this section we recall some basic facts about differential geometry. Point-wise dependence will be omitted when clear from the context, and stressed just when necessary.

1.1. Notation. We denote scalars with light-face, italic letters: \( a, n, A, N, \ldots \); vectors with bold-face italic letters, \( a, n, A, N, \ldots \); ordinary second-order tensors with bold-face majuscules, \( A, B, C, \ldots \); superficial second-order tensors with bold-face, sans-serif majuscules, \( \mathbf{A}, \mathbf{B}, \mathbf{C}, \ldots \). We will refer to \( \mathbb{R}^3 \) as the three dimensional Euclidian space, endowed with a Cartesian orthonormal frame \( \{ \mathbf{E}_1, \mathbf{E}_2, \mathbf{E}_3 \} \). We use the summation convention with the agreement that Latin and Greek indices have the ranges \( \{1, 2, 3\} \) and \( \{1, 2\} \), respectively.

1.2. Surfaces, surface differential operators, fundamental forms. Let \( \Omega \) be an open, bounded set in \( \mathbb{R}^2 \). Any given vector \( \mathbf{z} \in \Omega \) admits the representation

\[
\mathbf{z} = z_\alpha \mathbf{E}_\alpha = [(z - 0) \cdot \mathbf{E}_\alpha] \mathbf{E}_\alpha.
\]

The scalars \( z_\alpha \) will be called the cartesian components of the position vector \( \mathbf{z} \). A surface \( S \) of the 3D point space \( \mathbb{R}^3 \) is defined as follows\(^1\)

\[
S := \{ X \in \mathbb{R}^3 | X = p(z) = p(z_1, z_2), \ \forall z \in \Omega \}
\]

being the parametrization \( p \) a diffeomorphism from \( \Omega \) to \( S \subset \mathbb{R}^3 \)(see [13], pg.74). A natural base\(^2\) of the tangent space at each point of \( S \) can be defined as follows

\[
A_\alpha = \frac{\partial p}{\partial z_\alpha}.
\]

Such a basis needs not to be orthonormal, and it defines the local tangent space to \( S \)

\[
T_S := \text{Span}\{A_1, A_2\}.
\]

On the same local tangent plane \( T_S \) it is possible to define the reciprocal base

\[
\{ \mathbf{A}^1, \mathbf{A}^2 \}
\]

such that \( A_\alpha \cdot A^\beta = \delta^\beta_\alpha \)

which forms an alternative base for the space \( T_S \). Any vector \( \mathbf{t} \in T_S \) can thus be expressed in terms of its natural or reciprocal components

\[
T_S \ni \mathbf{t} = \begin{cases} \ t^\alpha A_\alpha = (\mathbf{t} \cdot A^\alpha) A_\alpha & \text{(natural components)} \\ t_\alpha A^\alpha = (\mathbf{t} \cdot A_\alpha) A^\alpha & \text{(reciprocal components)} \end{cases}
\]

\(^1\)For a precise definition see Do Carmo,[13] pg.73.

\(^2\)We use the convention to adopt majuscules for vector fields defined on the surface \( S \); this convention will be useful in the following, where majuscules will be used for vectors of the reference surface and minuscules will be used for vectors defined on the current surface.
The unit normal vector at each point of the surface $S$ can be defined in terms of natural as well reciprocal basis
\[ N := \frac{A_1 \times A_2}{|A_1 \times A_2|} = \frac{A^1 \times A^2}{|A^1 \times A^2|}. \]

Letting
\[ \{A_1, A_2, A_3\} := \{A_1, A_2, N\} \]
\[ \{A^1, A^2, A^3\} := \{A^1, A^2, N\} \]
we have that
\[ A^i \cdot A^j = \delta^j_i. \]

Let us now define the following fundamental linear operators, according to the definitions given in Gurtin & Murdoch [21].

**Identity Operators:** $I \in \text{Lin}(\mathbb{R}^3, \mathbb{R}^3)$ and $I_S \in \text{Lin}(T_S, T_S)$;

**Perpendicular Projector:** $P_S$ is the operator in $\text{Lin}(\mathbb{R}^3, T_S)$ that projects vectors $v \in \mathbb{R}^3$ on the surface $T_S$;

**Inclusion Map:** $I_S$ is the operator in $\text{Lin}(T_S, \mathbb{R}^3)$ that embeds any vector $\tau \in T_S$ in the space $\mathbb{R}^3$.

Consider the natural basis $\{A_1, A_2, N\}$ and reciprocal basis $\{A^1, A^2, N\}$ for the space $\mathbb{R}^3$ and the natural basis $\{G_1, G_2\}$ and reciprocal basis $\{G^1, G^2\}$ for $T_S$. Then it results
\[ I = A_\alpha \otimes A^\alpha + N \otimes N = A^\alpha \otimes A_\alpha + N \otimes N \in \text{Lin}(\mathbb{R}^3, \mathbb{R}^3) \]
\[ I_S = G_\alpha \otimes G^\alpha = G^\alpha \otimes G_\alpha \in \text{Lin}(T_S, T_S) \]
\[ I_S = A_\alpha \otimes G^\alpha = A^\alpha \otimes G_\alpha \in \text{Lin}(T_S, \mathbb{R}^3) \]
\[ P_S = G_\alpha \otimes A^\alpha = G^\alpha \otimes A_\alpha \in \text{Lin}(\mathbb{R}^3, T_S). \]

When clear from the context and there is not danger of misinterpretations, we will occasionally confuse vectors $A_\alpha$ with $G_\alpha$ and $A^\alpha$ with $G^\alpha$.

It is easy to check the validity of the following properties

1. $I_S^T \equiv P_S$;
2. $P_S P_S^T = I_S^T I_S = P_S I_S = I_S \in \text{Lin}(T_S, T_S)$;
3. $I_S P_S = I - N \otimes N \in \text{Lin}(\mathbb{R}^3, \mathbb{R}^3)$.

Let us now introduce the concept of **surface gradient** of the smooth vector field defined on the surface $S$, namely a **surface vector field**
\[ v : S \subset \mathbb{R}^3 \longrightarrow \mathbb{R}^3. \]
Let us consider a smooth extension $\tilde{v}$ of the function $v$ to a 3D neighborhood of a point $X \in S$, so that $v$ coincides with the restriction of $\tilde{v}$ to the function having $S$ as domain, that is

$$v(X) \equiv \tilde{v}(\tilde{X})|_{X_3=0} \quad \forall X \in S$$

being

$$\tilde{X} = X + X_3 A_3$$

with $X \in S$ and $X_3 = (\tilde{X} - 0) \cdot A_3$ the cartesian component of the position vector $\tilde{X}$ in direction $A_3 \perp A_\alpha$. The three-dimensional gradient of $\tilde{v}$ reads as usual

$$\nabla \tilde{v}.$$ 

The surface gradient of $\tilde{v}$ at any point of $S$ is defined restricting the domain of $\nabla \tilde{v}$ to the local tangent space of $S$ at every point $X \in S$, that is

$$\nabla_S \tilde{v} := (\nabla \tilde{v})|_{T_S} = (\nabla \tilde{v})[A_\alpha] \otimes G^\alpha \in \operatorname{Lin}(T_S, \mathbb{R}^3).$$

Since actually the surface vector field $v$ and its extension $\tilde{v}$ coincide when evaluated on the surface $S$, we can define the gradient of $v$ as the surface gradient of its extension $\tilde{v}$, that is

$$\nabla_S v := (\nabla \tilde{v})|_{T_S}.$$ 

Worth noting, $\nabla_S v$ is a $3 \times 2$ matrix. In particular, on the basis of property (4) enunciated in the previous page

$$I = T_S P_S + N \otimes N,$$

we can recast $\nabla \tilde{v}$ when evaluated at points of the surface $S$ as

$$\nabla \tilde{v} = (\nabla \tilde{v})|_{T_S} = \nabla \tilde{v}|_{T_S} P_S + N \otimes N = (\nabla_S \tilde{v})|_{T_S} P_S + \frac{\partial \tilde{v}}{\partial X_3} \otimes N$$

In similar fashion it is possible to show that, letting $\varphi$ a scalar surface field defined on a surface $S \subset \mathbb{R}^3$, and $\tilde{\varphi}$ its extension to a three-dimensional neighborhood of such functions, the following definition is well posed

$$\nabla_S \varphi := P_S (\nabla \tilde{\varphi}) \in T_S.$$ 

From now on, we will drop the notation $^\sim$ in order to distinguish between the surface field and its smooth extension to the space.

Let now $p : \Omega \subset \mathbb{R}^2 \to S \subset \mathbb{R}^3$ be a parametrization of the surface $S$, then the gradient of $p$ can be unambiguously defined as

$$P := \nabla p$$

and it is clear that

$$\nabla p \equiv (\nabla p)|_{T_S} := \nabla_\Omega p,$$

hence in general $P \in \operatorname{Lin}(\Omega, \mathbb{R}^3)$. Nevertheless, it is evident that

$$\operatorname{Codom}(P) \equiv T_S,$$
as it is easy to check considering that
\[
P = \nabla p = (\nabla p)_S = \nabla p(E_\alpha \otimes E_\alpha) = \frac{\partial p}{\partial z_\alpha} \otimes E_\alpha = A_\alpha \otimes E_\alpha \in \text{Lin}(\mathbb{R}^2, \mathbb{R}^3)
\]

Nevertheless, since evidently in this case it does not lead to confusion the substitution of \( A_\alpha \) with \( G_\alpha \), we can recast the gradient of \( p \) as
\[
P := G_\alpha \otimes E_\alpha
\]
which shows that indeed the tensor \( P \) belongs to the space \( \text{Lin}(\mathbb{R}^2, T_S) \). Without fear of misunderstandings, where possible the vectors \( A_\alpha, A^\alpha \) and \( G_\alpha, G^\alpha \) will always be confused.

Given any vector \( u = u_\alpha E_\alpha \in \Omega \), its image under the parametrization \( p \) is represented by the vector
\[
t = Pu = P[u_\alpha E_\alpha] = u_\alpha P[E_\alpha] = u_\alpha A_\alpha = t^\alpha A_\alpha \in T_S
\]
which incidentally shows that the cartesian components of the vector \( u \) coincide with the components of its image \( t \) under the parametrization \( p \) in the natural basis \( \{A_1, A_2\} \), that is
\[
u_\alpha \equiv t^\alpha.
\]

A vector field \( f \) defined on a surface \( S \) is called **tangential** if \( f \in T_S \) at every point of \( S \); a tensor field \( L \) is called **superficial** if \( LN = 0 \) at every point of \( S \) and in particular **tangential** and **normal** if for any vector \( a \) and any point on \( S \), respectively \( La \in T_S \) and \( La \in T_S^\perp \).

The **surface divergence** of a surface vector field \( f : S \rightarrow \mathbb{R}^3 \) is the field
\[
\text{div}_S f := \text{tr}(\nabla_S f) = (\nabla_S f) \cdot I_S : S \rightarrow \mathbb{R}
\]
Let \( f^\parallel = \Pi_S f \) and \( f^\perp = f \cdot N \) with \( N \perp T_S \), then since
\[
f = f^\parallel + f^\perp N
\]
it results
\[
\nabla_S f = \nabla_S f^\parallel + \nabla_S (f^\perp N) = \nabla_S f^\parallel + N \otimes \nabla_S f^\perp + f^\perp \nabla_S N
\]
hence, taking the trace we get
\[
\text{div}_S f = \text{div}_S f^\parallel + f^\perp \text{div}_S N.
\]
The **surface divergence theorem** asserts that given a tangential field \( f^\parallel \) it results
\[
\int_S \text{div}_S f^\parallel dA = \int_{\partial S} f^\parallel \cdot \nu dL
\]
with \( \nu \) the unit normal to \( \partial S \) contained in the tangent plane \( T_S \); it further results that
\[
\int_S \text{div}_S f dA = \int_{\partial S} f^\parallel \cdot \nu dL + \int_S f^\perp \text{div}_S N dA.
\]
If \( L \) is superficial tensor field on \( S \), then its **surface divergence** is the field defined by

\[
a \cdot \text{div}_S L := \text{div}_S (L^T a)
\]

for every constant vector \( a \) in \( \mathbb{R}^3 \). Furthermore, since it results that \( LN = 0 \) we deduce that

\[
\int_S \text{div}_S L \, dA = \int_{\partial S} L \nu \, dL.
\]

It is possible to show that all metric properties of a smooth surface \( S \) parameterized by \( p \) (such as measures of lengths, angles, areas with respect to those of the domain \( \Omega \)) can be locally expressed in terms of the **metric tensor** of the surface, namely

\[
A = P^T P = (A_\alpha \cdot A_\beta)(E_\alpha \otimes E_\beta) = A_{\alpha\beta}(E_\alpha \otimes E_\beta) \in \text{PSym}(\Omega, \Omega).
\]

For example, given a vector \( t = Pu \in T_S \) with \( u \in \Omega \) a vector of modulus \( |u| = u \), its length can be calculated as follows:

\[
|t| = [t \cdot t]^{1/2} = [Pu \cdot Pu]^{1/2} = [Au \cdot u]^{1/2} = [A_{\alpha\beta}u_\alpha u_\beta]^{1/2},
\]

and, since \( t^\alpha = u_\alpha \), we obtain the expression of the so called **First Fundamental Form** of the surface

\[
|t| = [A_{\alpha\beta}t_\alpha t_\beta]^{1/2}.
\]

In particular, the **local area measure** can be expressed as follows

\[
dA = |A_1 \times A_2| = |PE_1 \times PE_2| = |\det(P^T P)|^{1/2} = |\det A|^{1/2}.
\]

Let us now define a regular curve \( \Gamma \) on the surface \( S \), introducing the parametrization:

\[
\lambda \in [0, 1] \in \mathbb{R} \longrightarrow z = c(\lambda) \in \Omega \longrightarrow X = p(c(\lambda)) = \bar{p}(\lambda) \in \Gamma \subset S.
\]

with

\[
\bar{p} := p \circ c.
\]

The following set of definitions can now be given (see [?], pg...):

\[
\ell(\lambda) = \int_0^\lambda \left| \frac{dp}{d\lambda} \right| \, d\lambda = \int_0^\lambda \left| \frac{dp}{d\lambda} \right| \, d\lambda \quad (\text{Curvilinear Abscissa or Arc Length})
\]

\[
T = \frac{dp}{d\ell} / \left| \frac{dp}{d\ell} \right| = \frac{dp}{d\ell} = \frac{dp}{d\lambda} / d\ell = \frac{\bar{p}'}{|\bar{p}'|} \quad (\text{Unitary Tangent Vector to } \Gamma)
\]

\[
M = \frac{dT}{d\ell} / \left| \frac{dT}{d\ell} \right| = \frac{dT}{d\ell} / \kappa_M \quad (\text{Unitary Normal Vector to } \Gamma)
\]

where we denoted with \((\cdot)' = d(\cdot)/d\lambda\) and used the fact that, by definition of arc length, \( |d\bar{p}/d\ell| = 1 \); we further introduced \( \kappa_M \), the **curvature of** \( \Gamma \) in the plane \( \pi(T, M) \) spanned by the vectors \( T \) and \( M \). The projection of the vector \( dT/d\ell \) on the normal unitary vector \( N \) to the surface \( S \), and on the tangent plane \( T_S \), allows
respectively the definition of the so called **normal curvature** of the surface $S$ and **geodesic curvature** of the curve $\Gamma$ on the surface $S$:

**Normal Curvature:** $\kappa = \kappa(T) = \frac{d T}{d\ell} \cdot N = \kappa_M M \cdot N = \kappa_M \cos \theta(N, M)$

**Geodesic Curvature:** $k_g = k_g(\Gamma, N) = |\mathbb{P}_S \frac{d T}{d\ell}| = \kappa_M |\mathbb{P}_S M|$

being $\mathbb{P}_S = \mathbb{I}_S$ the perpendicular projector on $T_S$. As a remark, notice that in general $M \neq N$ and thus the normal curvature generally differs from the curvature $\kappa_M$ of the curve $\Gamma$ in the plane $\pi(T, M)$. Curves on the surface with identically equal to zero geodesic curvature are called **geodesics**.

Since it results that $N \perp T$ for each point of $S$, thus in particular for each point of $\Gamma$, differentiating the relation $T \cdot N = 0$ with respect of $\lambda$, we obtain that

$$T' \cdot N = -T \cdot N'$$

where it results

$$N' = \frac{d N(\bar{p}(\lambda))}{d\lambda}, \quad T' = \frac{d T(\bar{p}(\lambda))}{d\lambda}.$$ 

This allows to express the normal curvature as follows

$$\kappa = \frac{d T}{d\ell} \cdot N = \frac{d\lambda}{d\ell} T' \cdot N = -\frac{d\lambda}{d\ell} T \cdot N' = -\frac{T \cdot N'}{|\bar{p}'|} = -\frac{\bar{p}' \cdot N'}{|\bar{p}'|^2}.$$ 

Since the vector $\bar{p}' = |\bar{p}'| T$ belongs to the tangent plane $T_S$, it results that $\bar{p}' = \mathbb{P}_S \bar{p}'$, hence

$$N' = \frac{d N(\bar{p}(\lambda))}{d\lambda} = (\nabla \bar{N}) \bar{p}' = (\nabla \bar{N}) \mathbb{P}_S \bar{p}' = (\nabla S N) \bar{p}' = -L \bar{p}'$$

where - analogously to what has been previously done - we have let $\bar{N}$ the 3D extension of $N$, and where the **curvature tensor** $L := -(\nabla S N)$ has been introduced. Substituting this relation in the expression obtained before for $\kappa$ we obtain for the **normal curvature** of the surface in direction of the unitary tangent $T$:

$$\kappa := \frac{L \bar{p}' \cdot \bar{p}'}{|\bar{p}'|^2} = L \cdot (T \otimes T).$$

This last relation takes the name of **Second Fundamental Form** of the surface $S$. The curvature tensor is symmetric and tangential, that is

$$\left\{ \begin{array}{l} L = L^T \\ L^T N = 0. \end{array} \right.$$ 

The proof of these properties can be elegantly given\(^3\) considering the surface $S$ as implicitly defined as the zero level of the function $\Phi$, that is

$$S := \{ X \in \mathbb{R}^3 | \Phi(X) = 0, \Phi : \mathbb{R}^3 \rightarrow \mathbb{R}, \text{ such that } a = |\nabla \Phi| \neq 0 \}. $$

\(^3\)The proof here reported is the one given in **Gurtin**, [25], pg.96.
With this position the unitary normal vector to $S$ reads as

$$N := \frac{\nabla \Phi}{|\nabla \Phi|} = \frac{\nabla \Phi}{a}$$

where the operator $\nabla$ represents here the three-dimensional gradient. Taking the gradient of the relation $a^2 = (\nabla \Phi) \cdot (\nabla \Phi)$ we obtain

$$2a(\nabla a) = 2 \nabla (\nabla \Phi)^T (\nabla \Phi)$$

hence, considering that $\nabla (\nabla \Phi)$ is indeed a symmetric tensor, we obtain that

$$\nabla a = (\nabla \nabla \Phi) N.$$

Furthermore, taking the gradient of the relation $aN = \nabla \Phi$ and using the last relation we get

$$a \nabla N = P_S(\nabla \nabla \Phi)$$

thus

$$L = -\nabla S N = -a^{-1} P_S(\nabla \nabla \Phi) P_S$$

which shows at the same time that $L$ is tangential and it belongs to the space $\text{Sym}(T_S, T_S)$. Being $L \in \text{Sym}(T_S, T_S)$, the Cayley-Hamilton theorem ensures the existence of its real eigenvalues, the so called principal curvatures $k_1$ and $k_2$, and the relative perpendicular eigenvectors, the principal directions of curvature of $S$. The Mean and Gaussian Curvatures are defined by

$$H = \frac{1}{2}(k_1 + k_2) = \frac{1}{2} \text{tr} L$$

$$K = k_1 k_2 = \det L.$$

With these positions for the 2 invariants of the two-dimensional tensor $L$, the Cayley-Hamilton theorem yields

$$L^2 - 2HL + KI_S = 0$$

which is a very useful relation to calculate the inverse of $L$, indeed

$$L - 2H I_S + KL^{-1} = 0 \implies KL^{-1} = 2H I_S - L.$$

Note that the normal curvature of a surface in direction of the unit vector $t$ is

$$\kappa(t) = Lt \cdot t.$$

After introducing the vector $u \in \Omega$ such that $t = Pu$, we can express the normal curvature as

$$\kappa = P^T LP : (u \otimes u) = L \cdot (u \otimes u) \text{ with } L = P^T LP$$

where the tensor $L \in \text{Sym}(\Omega, \Omega)$ is actually the pull-back tensor of $L$ on $\Omega$. Since, as we have shown previously, $t^\alpha = u_\alpha$, this last relation can be expanded as follows

$$\kappa = L \cdot (t^\alpha E_\alpha \otimes t^\beta E_\beta) = L_{\alpha \beta} t^\alpha t^\beta.$$
Taking the determinant of the relation $\mathcal{L} = \mathbf{P}^T \mathbf{L} \mathbf{P}$ we obtain that (see for example Do Carmo[13], pg.155, eq (4))

$$K = \frac{\det \mathcal{L}}{\det \mathbf{A}} = \frac{\mathcal{L}_{11} \mathcal{L}_{22} - \mathcal{L}_{12}^2}{A_{11} A_{22} - A_{12}^2}.$$ 

It would be easy to check (see Do Carmo, [13], pg.232) that the cartesian components $\mathcal{L}_{\alpha \beta}$ of the tensor $\mathcal{L}$ are expressible in terms of the cartesian components $A_{\alpha \beta}$ of the metric tensor $\mathbf{A}$, which can roughly be summarized saying that

$$K = \hat{K}(A_{\alpha \beta}).$$

This fact leads to one of the major theorems in differential geometry, which will be presented in section 1.4.
1.3. Surface deformations, polar decomposition theorem. In what follows we introduce the concept of deformation of a surface. Let $S$ and $s$ be two surfaces parameterized as follows

$$S := \{ X \in \mathbb{R}^3 \mid X = p(z), z \in \Omega \subset \mathbb{R}^2 \}$$

$$s := \{ x \in \mathbb{R}^3 \mid x = g(z), z \in \Omega \subset \mathbb{R}^2 \}$$

with $p$ and $g$ two diffeomorphism on $\Omega$. As done in the previous section, it is possible to define on $S$ and $s$ the natural basis spanning the respective tangent planes $T_S$ and $T_s$

$$\{ A_1, A_2, A_3 \} \quad \text{with} \quad A_\alpha = \frac{\partial p}{\partial z_\alpha} \in T_S, \quad A_3 = N = \frac{A_1 \times A_2}{|A_1 \times A_2|},$$

$$\{ a_1, a_2, a_3 \} \quad \text{with} \quad a_\alpha = \frac{\partial g}{\partial z_\alpha} \in T_s, \quad a_3 = n = \frac{a_1 \times a_2}{|a_1 \times a_2|}.$$  

The reciprocal basis on $S$ and $s$ can be defined as

$$\{ A^1, A^2, A^3 \} \quad \text{with} \quad A^\alpha \in T_S, \quad A_1 \cdot A^j = \delta^j_i \text{ (hence } A_3 = A^3 = N)$$

$$\{ a^1, a^2, a^3 \} \quad \text{with} \quad a^\alpha \in T_s, \quad a_1 \cdot a^j = \delta^j_i \text{ (hence } a_3 = a^3 = n)$$

The surface gradients of the parameterizations $p$ and $g$ read, accordingly to the previous section, as follows

$$P = (\nabla p) = A_\alpha \otimes E_\alpha \in \text{Lin}(\Omega, T_S)$$

$$G = (\nabla g) = a_\alpha \otimes E_\alpha \in \text{Lin}(\Omega, T_s).$$

Let now $A$ and $B$ be two vector spaces with

$$\text{dim } A \neq \text{dim } B,$$

then the following tensor spaces can be introduced (see Gurtin & Murdoch, [21])

$$\text{Sym}(A) := \{ S \in \text{Lin}(A) \mid S^T = S \},$$

$$\text{PSym}(A) := \{ S \in \text{Sym}(A) \mid S \text{ is positive definite} \},$$

$$\text{Orth}(A, B) := \{ Q \in \text{Lin}(A, B) \mid (Q^T Q) = I_A, \quad (QQ^T) = I_B \}$$

$$\text{Rot}(A, B) := \{ Q \in \text{Orth}(A, B) \mid \det Q = +1 \}$$

$$\text{InvLin}(A, B) : \{ S \in \text{Lin}(A, B) \mid \exists S^{-1} \in \text{Lin}(B, A) \text{ such that } \left\{ \begin{array}{l} S^{-1}S = I_A \\ SS^{-1} = I_B \end{array} \right\} \}. $$

The tensor $S$ is called as the inverse of $S$, and the set InvLin represents the set of all invertible, linear operators between the two vector spaces $A$ and $B$. When $\text{dim } A \neq \text{dim } B$ then InvLin($A, B$) is empty.

It is now possible to define by construction the inverse tensors of $P$ and $G$

$$P^{-1} := E_\alpha \otimes A^\alpha \text{ where } \left\{ \begin{array}{l} P^{-1}P = (E_\alpha \otimes E_\alpha) = I_\Omega \\
P P^{-1} = (A_\alpha \otimes A^\alpha) = I_S \end{array} \right\}$$

$$G^{-1} := E_\alpha \otimes a^\alpha \text{ where } \left\{ \begin{array}{l} G^{-1}G = (E_\alpha \otimes E_\alpha) = I_\Omega \\
G G^{-1} = (a_\alpha \otimes a^\alpha) = I_S \end{array} \right\}$$
with \( \mathbb{I}_\Omega, \mathbb{I}_S \) and \( \mathbb{I}_s \) the identity operators on the spaces \( \Omega, T_S \) and \( T_s \) respectively.

Let now \( f \) be a smooth function mapping points of \( S \) in points of \( s \), such that

\[
g = f \circ p.
\]

We can think of \( S \) as the reference configuration and \( s \) as the current configuration of \( S \) under the deformation \( f \), that is

\[
s = f(S).
\]

By taking the gradient of the aforementioned relation \( g = f \circ p \), the chain rule yields

\[
\nabla g = (\nabla f)(\nabla p) \implies G = (\nabla f)P \implies (\nabla f) := GP^{-1}.
\]

Standing on this expression, we infer that \( (\nabla f) \) so defined actually belongs to the space \( \text{Lin}(T_S, T_s) \), since as already noticed it results that \( G \in \text{Lin}(\Omega, T_s) \) and \( P \in \text{Lin}(\Omega, T_S) \). Substituting the expressions obtained before for \( G \) and \( P^{-1} \), we deduce the following explicit expression for \( (\nabla f) \)

\[
(\nabla f) = GP^{-1} = (a_\alpha \otimes E_\alpha)(E_\beta \otimes A^\beta) = a_\alpha \otimes A^\alpha \in \text{Lin}(T_S, T_s),
\]

whose inverse is rapidly checked to be

\[
(\nabla f)^{-1} = A_\alpha \otimes a^\alpha \in \text{Lin}(T_s, T_S).
\]

On the other side, it is evident that \( (\nabla f) \) can be identified with the surface gradient of \( f \); indeed since the surface gradient is defined as

\[
F := (\nabla_S f) = (\nabla f)I_S = (a_\alpha \otimes A^\alpha)(A_\beta \otimes G^\beta) = (a_\alpha \otimes G^\alpha)
\]

hence it is evident that \( F \equiv (\nabla f) \in \text{InvLin}(T_S, T_s) \). In some following parts of the thesis, we will extend the domain of the surface gradient \( F \) by post-composition with the projector, that is

\[
\bar{F} := FP \in \text{Lin}(\mathbb{R}^3, T_s).
\]

Very useful for the developments of this thesis is the following slightly generalized version of the polar decomposition theorem \([21]\):

**Theorem 1 (Polar Decomposition Theorem).** Each \( F \in \text{InvLin}(T_S, T_s) \), admits the unique decomposition

\[
F = RU
\]

being \( R \in \text{Rot}(T_S, T_s) \), and \( U \in \text{PSym}(T_S, T_S) \). Moreover,

\[
U^2 = F^TF = C, \quad R = FU^{-1}.
\]

Analogously to the metric tensors \( P^TP \) and \( G^TG \) of the surfaces \( S \) and \( s \), it would be possible to show that the changes of all metric properties between \( S \) and \( s = f(S) \) can be expressed in terms of the Green-Cauchy tensor \( C = F^TF \), which can be explicitly calculated as

\[
C = F^TF = (A^\alpha \otimes a_\alpha)(a_\beta \otimes A^\beta) = (a_\alpha \cdot a_\beta)(A^\alpha \otimes A^\beta) = C_{\alpha\beta}(A^\alpha \otimes A^\beta).
\]
In particular, the local area variation of a neighborhood of a point $X$ in $S$ can be shown to be equal

$$J(X) = \frac{da(f(X))}{dA(X)} = [\det C]^{1/2}$$

where $dA$ and $da$ represent the area measures of infinitesimal neighborhoods of $X \in S$ and of its image $x = f(X) \in s$, and where the Jacobian $J$ here represents the so-called areal stretch.

### 1.4. Some fundamental facts from differential geometry.

As first thing, let us give some fundamental definitions. Let $S \subset \mathbb{R}^3$ be a surface. We say\(^4\) that a point $X \in \mathbb{R}^3$ is a limit point of $S$ if every neighborhood of $X$ in $\mathbb{R}^3$ contains a point of $S$ distinct from $X$. $S$ is said to be closed if it contains all its limit points. $S$ is bounded if it is contained in some ball of $\mathbb{R}^3$. If $S$ is closed and bounded, it is called compact. A surface $S$ is said to be connected if any two of its points can be joined by a continuous curve in $S$.

Surface deformations that leave unaltered all the metric properties of a surface are called isometries.

**Definition 1 (Isometries\(^5\)).** A surface deformation $f : S \rightarrow s$ is an isometry if for all $X \in S$ and all pairs of vectors $(u_1, u_2)$ in $T_S(X)$ we have

$$u_1 \cdot u_2 = Fu_1 \cdot Fu_2.$$

It is evident that, within the context of classical continuum mechanics, we can rephrase the definition of isometry saying that a deformation $f$ of a surface $S$ is an isometry if

$$C = F^T F \equiv I_S \quad \forall X \in S,$$

which substantially implies that $F \equiv R = \text{Rot}(F)$ at every point of the surface. Such a deformation can be interpreted as pure bending of the surface $S$, where the length of all its fibers and the angles between any couple of its fibers remain locally unaltered. In particular, we trivially see that if $f$ is an isometry then $J = 1$.

One of the major theorems in the differential geometry stands on the concept of isometries. Indeed, as already announced, the Gaussian curvature of a surface can always be expressed as a function of its metric properties. Indeed we have

**Theorem 2 (”EGREGIUM” - Gauss).** The Gaussian curvature $K$ of a surface is invariant by local isometries.

We shall now recall the Gauss-Bonnet theorem, which is ’probably the deepest theorem in the differential geometry of surfaces’ [Do Carmo].

---

\(^4\)See [13], pg.112

\(^5\)See [13], pg.218.
**Theorem 3 (Gauss-Bonnet)**. Let $R \subset S$ be a region of an oriented surface $S$, with a closed regular boundary $\partial R$. Then

$$
\int_R K \, dA = 2\pi \chi(R) - \int_{\partial R} k_g \, dl,
$$

where $K$ the Gaussian curvature, $k_g$ the geodesic curvature of the curve $\partial R$ on the surface $S$, and the number $\chi(R)$ the "Euler-Poincaré" characteristic of the region $R$.

The Euler-Poincaré characteristic of a regular region $R \subset S$ can be determined through the following rule

$$
\chi(R) = F - E + V
$$

where $F, E$ and $V$ respectively represent the number of triangles (Faces), sides (Edges) and Vertices of a triangulation of the surface $R$, which can be defined as follows

**Definition 2 (Triangulation of a surface)**. A triangulation of a surface $R \subset S$ is a finite family $\mathcal{S}$ of triangles $T_i$, with $i = 1, ..., n$ such that

1. $\bigcup_{i=1}^n T_i = R$.
2. If $T_i \cap T_j \neq \emptyset$, then $T_i \cap T_j$ is either a common edge of $T_i$ and $T_j$ or a common vertex of $T_i$ and $T_j$.

It would be possible to show (see [13], pg.273) that the number $\chi(R)$ for a compact, connected surface is indeed related to the genus of the surface, that is the number of handles of the surface, through the relation

$$
g = \frac{2 - \chi(R)}{2}.
$$

As a conclusive remark, let us recall the following theorem of global differential geometry, which will be useful in this thesis.

**Theorem 4**. Let $S$ be a regular, compact and connected surface with Gaussian curvature $K > 0$ and mean curvature $H$ constant. Then $S$ is a sphere.

**1.5. How to reconcile with the classical notation.** Let us now give a brief review of the classical index notation in order to compare it with the absolute notation adopted here.

Given the following parametrization for the surface $S$

$$
p : z = (z_1, z_2) \in \Omega \subset \mathbb{R}^2 \implies X(p) \in S \subset \mathbb{R}^3,
$$

---

6See [13], pg.274, for a generalized version of this theorem to surfaces endowed of a non regular boundary.

7See [13], pg. 271.
the following notation is classical for the derivative of \( p \) with respect to the cartesian coordinate \( z_\alpha \)
\[
p_{,\alpha} \equiv \frac{\partial p}{\partial z_\alpha}
\]
hence the **natural basis** on a neighborhood of \( S \) reads as
\[
A_\alpha = p_{,\alpha} = P E_\alpha,
\]
where the tensor \( P : \Omega \rightarrow T_S \) has been previously introduced. Let now \( v \) be a smooth vector field defined on \( S = p(\Omega) \).
Letting \( \hat{v} = v \circ p \) and omitting as usual point-wise dependence, the following derivative of \( \hat{v} \) w.r. to \( z_\alpha \)
\[
\hat{v}_{,\alpha} := \frac{\partial \hat{v}}{\partial z_\alpha}.
\]
might be expanded, within the formalism adopted in this thesis, as follows
\[
\hat{v}_{,\alpha} = (\nabla v) p_{,\alpha} = (\nabla v) A_\alpha = (\nabla v) I_S A_\alpha = (\nabla_S v) A_\alpha.
\]
Aside the natural basis \( A_\alpha \) it is convenient to introduce a **reciprocal basis** \( A^\alpha \), spanning the same tangent plane \( T_S \), with the following property:
\[
A_\alpha \cdot A^\beta = \delta^\beta_\alpha.
\]
Any given vector \( v \in T_S \) is expressible in both basis:
\[
v = v^\alpha A_\alpha = v_\alpha A^\alpha
\]
and its natural and reciprocal components are found according to
\[
v^\alpha = v \cdot A^\alpha, \quad v_\alpha = v \cdot A_\alpha.
\]
The surface gradient of \( p \) has been explicitly calculated as
\[
P = A_\alpha \otimes E_\alpha.
\]
The components of the metric tensor \( A = P^T P = (A_\alpha \cdot A_\beta)(E_\alpha \otimes E_\beta) \) are usually denoted by
\[
A_{\alpha\beta} = A_\alpha \cdot A_\beta
\]
and the relative determinant \( J^2 = \det C \) is usually called
\[
A = \det(A_{\alpha\beta}).
\]
Given a vector \( u = u_\alpha E_\alpha \in \Omega \), its image \( t \) under the parametrization \( p(z) \) has norm defined by the **first fundamental form**:
\[
|t|^2 = A_{\alpha\beta} u_\alpha u_\beta.
\]
The inverse of the metric tensor \( A \) can be computed as
\[
A^{-1} = (P^T P)^{-1} = P^{-1}P^{-T} = (E_\alpha \otimes A^\alpha)(A^\beta \otimes E_\beta) = (A^\alpha \cdot A^\beta)(E_\alpha \otimes E_\beta) = A^{\alpha\beta}(E_\alpha \otimes E_\beta).
\]
where the cartesian components \( A^{\alpha\beta} \) of the inverse of the metric tensor are called its the **reciprocal** components, thus from
\[
A^{-1} A = I_\Omega,
\]
we have that

\[ A^\alpha_\gamma A^\gamma_\beta = \delta^\alpha_\beta. \]

This last relation relates the vectors of the natural and the reciprocal basis as follows

\[ A^\alpha = A^\alpha_\beta A_\beta. \]

The directed normal \( N \) to the surface \( S \) is given by:

\[ N = \frac{A_1 \times A_2}{|A_1 \times A_2|} = \frac{A_1 \times A_2}{J}. \]

The components of the vectors \( A_\alpha \) defined on the surface \( S \)

\[ A_{\alpha, \beta} = \frac{\partial A_\alpha}{\partial z_\beta}, \]

are expressible in our formalism as

\[ A_{\alpha, \beta} = (\nabla_S A_\alpha) A_\beta; \]

the components of this vector in the tangent plane \( T_S \) are usually denoted by the Christoffel symbols

\[ \Gamma^\gamma_{\alpha\beta} = \Gamma^\gamma_{\beta\alpha} := A_{\alpha, \beta} \cdot A^\gamma = (\nabla_S A_\alpha) A_\beta \cdot A^\gamma, \]

whereas the out-of-plane component is given by

\[ A_{\alpha, \beta} \cdot N = (\nabla_S A_\alpha) A_\beta \cdot N. \]

The curvature tensor of the surface \( S \) is defined as the surface gradient of the directed unit normal to \( S \), with reversed sign, that is \( L = -(\nabla_S N) \in \text{Sym}(T_S, T_S) \).

The reciprocal components \( L_{\alpha\beta} \) of \( L \) are thus

\[ L_{\alpha\beta} = L \cdot (A_\alpha \otimes A_\beta) = -(\nabla_S N) A_\alpha \cdot A_\beta = -N_{,\alpha} \cdot A_\beta, \]

so that

\[ L = L_{\alpha\beta}(A_\alpha \otimes A_\beta). \]

Differentiating the relation \( N \cdot A_\alpha = 0 \) with respect to \( z_\beta \) we obtain:

\[ (N \cdot A_\alpha)_{,\beta} = N_{,\beta} \cdot A_\alpha + N \cdot A_{\alpha, \beta} = (\nabla_S N) A_\beta \cdot A_\alpha + (\nabla_S A_\alpha) A_\beta \cdot N = 0 \]

thus the components of the curvature tensor can be written as

\[ L_{\alpha\beta} = (\nabla_S A_\alpha) A_\beta \cdot N = N \cdot A_{\alpha, \beta} \]

hence the derivative of the vector \( A_\alpha \) with respect to \( z_\beta \) can be written in the following form

\[ A_{\alpha, \beta} = \Gamma^\gamma_{\alpha\beta} A_\gamma + L_{\alpha\beta} N. \]

The Mean and Gaussian curvatures can now be expressed as follows:

\[ H = \frac{1}{2} \text{tr} L = \frac{1}{2} L \cdot (A_\gamma \otimes A^\gamma) = \frac{1}{2} A^{\alpha\beta} L_{\alpha\beta} \]

\[ K = \det L = \frac{1}{2}[(\text{tr} L)^2 - \text{tr} L^2] = \frac{1}{2} [(A^{\alpha\beta})^2(L_{\alpha\beta})^2 - L_{\gamma\delta} L_{\mu\lambda} A^{\mu\delta} A^{\lambda\gamma}] = \frac{L_{11} L_{22} - L_{12}^2}{A}. \]
where it is easy to check that the last term can be rewritten as

\[ K = \frac{e^{\alpha \beta} e^{\lambda \mu} L_{\alpha \lambda} L_{\beta \mu}}{2A} \]

being the cyclic index such that \( e^{12} = -e^{21} = 1 \) and \( e^{11} = e^{22} = 0 \).

Let us consider a surface vector field \( v = v(x) = v^\alpha A_\alpha \). The derivative of \( v \) with respect to \( z^\alpha \) is:

\[ v_{,\alpha} = (v^\beta A_\beta)_{,\alpha} = v^\beta_{,\alpha} A_\beta + v^\beta A_{\beta,\alpha} = [v^\beta_{,\alpha} + v^\gamma \Gamma^\beta_{\alpha \gamma}] A_\beta + v^\beta L_{\alpha \beta} N = v^\beta_{,\alpha} A_\beta + v^\beta L_{\alpha \beta} N. \]

As it is immediate to check, letting \( P_S = I - N \otimes N = (A_\gamma \otimes A_\gamma) \) to be the local perpendicular projector, it results

\[ P_S v_{,\alpha} = (A_\gamma \otimes A_\gamma) v_{,\alpha} = v^\gamma_{,\alpha} A_\gamma \]

which means that the term \( v^\gamma_{,\alpha} A_\gamma \) (usually referred to as the the covariant derivative of the vector field \( v \)), is the projection of \( v_{,\alpha} \) on the local tangent plane. In the literature sometimes the following notation for the components of the covariant derivative is adopted

\[ v^\gamma_{,\alpha} = v^\gamma_{|\alpha} \]

depending on the choice of the domain where the field \( v \) is defined.

Let us finally introduce the concept of surface divergence of a superficial vector field \( v \), that is simply the trace of the surface gradient of \( v \)

\[ \text{div}_S v = \nabla_S v \cdot I_S = \nabla_S v \cdot (A_\gamma \otimes A_\gamma) = v^\gamma_{,\gamma}. \]
1.6. Notes of calculus of variations. We here recall some facts relative to the variational derivative of functionals which will be useful in the thesis.

a) Let $\Omega$ be an open domain in $\mathbb{R}^N$ and let $u(x)$ be a generic vector valued mapping of $\Omega$ in $\mathbb{R}^N$. The most important necessary condition to be satisfied by any minimizer of a variational integral

$$F(u) = \int_{\Omega} F(x, u(x), Du(x), D^2 u(x), ..., D^m u(x)) \, d\Omega$$

with prescribed values of $u$ on the boundary, is the vanishing of its first variation

$$\delta F(u, \varphi) := \left[ \lim_{\varepsilon \to 0} \frac{F(u + \varepsilon \varphi) - F(u)}{\varepsilon} \right]_{\varepsilon=0},$$

for all perturbations $\varphi$ of $u$ which do not change its boundary value. By means of the fundamental lemma of the calculus of variations, the vanishing of the first variation yields the differential Euler-Lagrange equations for $u$ as necessary conditions to be satisfied by minimizers of $F$ which are of class $C^m$.

$C^m$-solutions $u$ of the equation $\delta F(u, \varphi) = 0$ are called weak extremals. If such solutions are even of class $C^{2m}$, an integration by parts will lead to Euler’s equation, the solution of which are called extremals.

The so-called null Lagrangians are some kind of degenerate variational integrands $F$ for which the corresponding Euler equations are satisfied by any smooth function $u$ with compact support. As an example, the integral

$$\int_{\Omega} \text{div} \, u \, dx$$

depends, via the Gauss-Green theorem, only on the assigned boundary values of $u$ on $\partial \Omega$, hence its first variation is vanishing for all perturbations with compact support. Another example of null Lagrangian already encountered in section (1.4) when treating the Gauss-Bonnet theorem, and it is represented by the total curvature of a surface $S$ in the space

$$\int_S K \, dA.$$ 

This integral will indeed play a crucial role for the aim of this thesis.

b) For future use within this thesis, let us consider the following class of variational integrals

$$\mathcal{F}(s, \hat{u}) := \int_s \hat{F}(x, \hat{u}(x), ...) \, da$$

where $\hat{u} : s \to \mathbb{R}^N$ is a generic spatial vector field defined on points of the current surface $s$ of a reference surface $S$ under a deformation $f$, $\hat{F}$ is the variational integrand, and where $da$ represents the surface area measure of a neighborhood of a point
\( x \in s \). Let us show that the \textbf{first variation} of the functional \( \mathcal{F} \) can be written as follows

\[ \delta \mathcal{F} = \int_s [\delta F + \hat{F} \text{div}_s y] \, da. \]

First of all, in order to give a precise definition of the first variation of the functional \( \mathcal{F}(s, \hat{u}) \), which depends, as matter of fact, both on the field \( \hat{u} \) and on the geometry of the surface \( s \), we map the functional on the reference configuration, hence

\[ \mathcal{F}(f, u) := \int_S F(f(X), u(X), ...) \, J(X) \, dA \]

where we have \( F = \hat{F} \circ f \) and \( u = \hat{u} \circ f \) to denote, respectively, the \textit{material} descriptions of the variational integrand \( \hat{F} \) and of the field \( \hat{u} \); \( dA \) here represents the area measure of a neighborhood of a point \( X \in S \) and \( J \) represents the Jacobian of the transformation \( f : S \to s \), defined as

\[ J = [\det C]^{1/2} = [\det(F^T F)]^{1/2} \]

where

\[ F = (\nabla_S f) \]

represents the surface gradient of deformation of \( f \). The functional \( \mathcal{F} \) now depends on two independent fields \( u \) and \( f \), hence it is possible to define its first variation perturbing independently these fields, that is

\[ \delta \mathcal{F} := \left[ \lim_{\varepsilon \to 0} \frac{\mathcal{F}(f + \varepsilon \eta, u + \varepsilon \varphi) - \mathcal{F}(f, u)}{\varepsilon} \right]_{\varepsilon \to 0} \]

where the perturbations \( \eta \) and \( \varphi \) are in general functions in \( C^1_c(S, \mathbb{R}^N) \). Since the reference surface \( S \) is actually independent of \( \varepsilon \), we have

\[ \mathcal{F}(f + \varepsilon \eta, u + \varepsilon \varphi) = \int_S F_\varepsilon J_\varepsilon \, dA \]

where we have called \( F_\varepsilon \) the perturbed variational integrand

\[ F_\varepsilon := F(f + \varepsilon \eta, u + \varepsilon \varphi, ...) \]

and \( J_\varepsilon \) the perturbed Jacobian

\[ J_\varepsilon = [\det C_\varepsilon]^{1/2} = [\det(F^T_\varepsilon F_\varepsilon)]^{1/2}. \]

The perturbed surface deformation gradient reads as

\[ F_\varepsilon = [\nabla_S(f + \varepsilon \eta)] = F + \varepsilon \nabla_S \eta. \]

hence

\[ J_\varepsilon = [\det(F + \varepsilon \nabla_S \eta)^T (F + \varepsilon \nabla_S \eta)]^{1/2}. \]

For \( \varepsilon \to 0 \), the perturbed Jacobian can be expanded in Taylor series around \( \varepsilon = 0 \)

\[ J_\varepsilon = J + \varepsilon \left[ \frac{dJ_\varepsilon}{d\varepsilon} \right]_{\varepsilon=0} + o(\varepsilon), \]
where
\[ \frac{dJ_\varepsilon}{d\varepsilon} = \frac{d}{d\varepsilon} (\det C_\varepsilon)^{1/2} = \frac{1}{2}(\det C_\varepsilon)^{-1/2} d\det C_\varepsilon \cdot \frac{dC_\varepsilon}{d\varepsilon} = \]
\[ = \frac{1}{2} (\det C_\varepsilon)^{-1/2} \left[ (\det C_\varepsilon)C_\varepsilon^{-T} \right] \cdot \left[ F^T(\nabla S \eta) + (\nabla S \eta)^T F + O(\varepsilon) \right] = \]
\[ = \frac{1}{2} J_\varepsilon C_\varepsilon^{-T} \cdot \left[ F^T(\nabla S \eta) + (\nabla S \eta)^T F + O(\varepsilon) \right]. \]

The well known fact that, given any invertible tensor \( A \), it results that \( \nabla_A (\det A) = (\det A) A^{-1} \) has been used (see Gurtin, [22], pg.23). Since given two generic tensors \( A \in \text{Sym} \) and \( B \) it results that
\[ A \cdot B = A \cdot \frac{1}{2} (B + B^T) \implies A \cdot (B + B^T) = 2A \cdot B \]
we have that, since \( C_\varepsilon^{-T} \) is a symmetric tensor\(^8\)
\[ \frac{dJ_\varepsilon}{d\varepsilon} = J_\varepsilon C_\varepsilon^{-T} \cdot \left[ F^T(\nabla S \eta) \right] = J_\varepsilon \left[ F_\varepsilon^{-1} F_\varepsilon^{-T} \right] \cdot \left[ F^T(\nabla S \eta) \right] + O(\varepsilon) \]
which, evaluated at \( \varepsilon = 0 \), using the definition of scalar product and the fact that \( \text{tr}(AB) = \text{tr}(BA) \), yields
\[ \left[ \frac{dJ_\varepsilon}{d\varepsilon} \right]_{\varepsilon=0} = J \left[ F^{-1} F^{-T} \right] \cdot \left[ F^T(\nabla S \eta) \right] = \]
\[ = J \text{tr}[F^{-1} F^{-T} F^T(\nabla S \eta)] = J \text{tr}[F^{-1}(\nabla S \eta)] = J \text{tr}[(\nabla S \eta) F^{-1}]. \]

At this point we introduce the vector function \( y : s \to \mathbb{R}^3 \), which represents the \textit{spatial} description of the perturbation \( \eta \)
\[ y \circ f = \eta. \]

The vector \( y \) can actually be interpreted as a \textit{virtual displacement} of points of the current surface \( s \), indeed letting \( x_\varepsilon \) to denote the position of the point \( x = f(X) \) after the perturbation \( \eta \), we have that
\[ x_\varepsilon = f(X) + \varepsilon \eta(X) = x + \varepsilon y(x) \implies y = [\eta \circ f^{-1}](X) = \lim_{\varepsilon \to 0} \frac{x_\varepsilon - x}{\varepsilon}. \]

Taking the gradient of the relation \( y \circ f = \eta \)
\[ (\nabla y)(\nabla f) = (\nabla \eta) \]
and composing both members with the inclusion map on \( S \), we get
\[ (\nabla y)(\nabla f) I_S = (\nabla \eta) I_S \implies (\nabla y) F = \nabla_S \eta, \]
where we remind that \( F \in \text{Lin}(I_S, I_S) \), hence
\[ FF^{-1} = I_S \]
we finally obtain that
\[ (\nabla y) FF^{-1} = (\nabla y) I_S = (\nabla_S \eta) F^{-1} \implies (\nabla_S y) = (\nabla_S \eta) F^{-1}. \]

\(^8\)By definition \( C_\varepsilon^{-1} = [F_\varepsilon^T F_\varepsilon]^{-1} = F_\varepsilon^{-1} F_\varepsilon^{-T} \) which is symmetric.
On the basis of this last relation, we can further expand the expression of the derivative of the perturbed Jacobian w.r. to $\varepsilon$ as follows

$$
\left[ \frac{d J_\varepsilon}{d\varepsilon} \right]_{\varepsilon=0} = J \text{div}_s y,
$$

where the definition of surface divergence has been used. For the sake of simplicity, we will not stress the fact that the fields $(\nabla_s y)$ and $\text{div}_s y$ appearing in the last relations are actually material descriptions of such fields, hence evaluated at a point $x = f(X)$.

These last developments allow the Taylor expansion of $J_\varepsilon$ to be expressed as follows

$$
J_\varepsilon = J[1 + \varepsilon \text{div}_s y] + o(\varepsilon).
$$

Let us now go back to the expression of the perturbed functional $F_\varepsilon$, which now reads as

$$
F_\varepsilon = \int_S F_\varepsilon [1 + \varepsilon \text{div}_s y] J dA,
$$

thus the first variation of $F$ can be computed as follows

$$
\delta F = \int_S \left[ \lim_{\varepsilon \to 0} \frac{F_\varepsilon [1 + \varepsilon \text{div}_s y] J + o(\varepsilon) - F J}{\varepsilon} \right]_{\varepsilon=0} J dA = \int_S \left[ \lim_{\varepsilon \to 0} \frac{F_\varepsilon - F}{\varepsilon} + \lim_{\varepsilon \to 0} \frac{o(\varepsilon)}{\varepsilon} + F_\varepsilon \text{div}_s y \right] J dA
$$

**In conclusion,** we get the expression of the first variation of a functional defined on a non-fixed surface, expressed both on the reference surface $S$ and on the current surface $s$

$$
\delta F = \int_S [\delta F + F \text{div}_s y] J dA = \int_s [\hat{\delta} F + \hat{F} \text{div}_s y] da
$$

where the first variation of the variational integrand $\delta F$ and its spatial description $\hat{\delta} F$ have been defined as

$$
\delta F = \lim_{\varepsilon \to 0} \frac{F_\varepsilon - F}{\varepsilon}, \quad \hat{\delta} F = (\delta F) \circ f^{-1}.
$$
CHAPTER 3

Solution Theory

The main constituents of lipid bilayers exhibit miscibility under suitable thermo-mechanical conditions. During the mixing process no chemical reaction occurs between the different kinds of components, thus the mass of each one is always conserved. Deviations from ideal mixing (where components are poly-disperse, that is randomly distributed in the bulk), as well from total immiscibility (where components tend to segregate into disjoint domains within the bulk), yield the possibility of coexistence of different material phases - each one characterized by a different chemical composition - within the bilayer; this process is known as lateral phase separation in phospholipid mixtures.

After an introduction to the classical solution theory in absence of deformations, in this section we will explain the physical basis of the occurrence of phase separation phenomena in lipid bilayers. In Chapter 5 these concepts will provide the basis of our new chemo-mechanical model, where deformation effects are accounted.

1.1. Basic definitions. We give in this section a short list of basic definitions.

Molecules. A molecule is the smallest particle in a chemical element or compound that has the chemical properties of that element or compound. Molecules are made up of atoms that are held together by chemical bonds. These bonds form as a result of the sharing or exchange of electrons among atoms.

Mole. The mole is the amount of substance of a system which contains a number of elementary entities equal to the number of atoms in 0.012 kilogram of the isotope $^{12}$C; this number is known as the Avogadro’s number and it is equal to $N_A = 6.022137 \cdot 10^{23}$ elementary entities.

Atomic and Molecular Weight. Improperly referred to as a weight, it is the relative mass of an atom with respect of the unit atomic mass, equal to 1/12 of the mass of the isotope $^{12}$C, that is $u = 1.66054 \cdot 10^{-27}kg$; hence, atomic weight is an a-dimensional number. The molecular weight is obviously the sum of the atomic weights of all the atoms which constitute the molecule.

Concentration. Generally speaking, concentration is the measure of how much a substance is mixed with other substances. There are many different ways to express quantitatively this kind of information, in particular we will deal with the following ones:

- Mole or Molar or Molecular Fraction. The mole fraction (or molar fraction) of a chemical species in a mixture is the ratio between the number of moles of the given species and the total number of moles of the mixture; being the number of moles proportional to the number of molecules through the Avogadro’s number, it is evident that molar fraction and molecular fractions coincide.
1. CLASSICAL SOLUTION THEORY OF FLUID MIXTURES.

- **Mass Fraction.** Obviously, it is the ratio between the mass of a given substance and the mass of the whole mixture. The mass fraction does not coincide with the molar fraction of the species.

### 1.2. Basic thermodynamics - classical approach.

In what follows we will briefly review the basic principles of thermodynamics in the simplified version adopted on elementary books of physics and chemistry (in particular we refer to the book by Silvestroni.[56]). Later on, all these concepts will be embedded in the more general and correct framework of Continuum Thermo-Chemo-Mechanics.

**Thermodynamical System.** It is defined as each perceptible quantity of matter which can be macroscopically observed, usually constituted by a (homo or heterogeneous) set of material bodies. The words perceptible and macroscopic come along together: macroscopic variables, as pressure or temperature, can be defined ($\Leftrightarrow$ measured) for systems which consist of a great amount of elementary particles and are, in this sense, macroscopically perceptible. We intend as material body a region of the space endowed with a continuous distribution of mass. We further define a thermodynamical system to be isolated if there is no energy or mass transport across its boundary, closed if there is energy transport but not mass transport, and open if there are both energy and mass transport.

**State Variables. Extensive and Intensive Quantities.** We mean as state variables the smallest set$^1$ of independent variables which can describe the macrostate$^2$ of a thermodynamical system. We will define as extensive all those state variables which depend upon some extensive properties of the system (for example its total mass or its number of moles, or its extension); extensive variables are always additive. On the other hand, intensive variables are all the remaining (for example pressure, temperature, molar fractions, etc...); intensive variables are not additive.

**First and Second Principle.** The simplified versions of both principles are the following:

\[ \text{i) First Principle: } d\mathcal{E} = d(Q + W),_{\gamma} \ \forall \ \text{processes } \gamma; \]
\[ \text{ii) Second Principle: } dQ,_{\gamma} \leq TdS, \ \forall \ \text{processes } \gamma; \]

Here $\mathcal{E}$ and $S$ are respectively the internal energy and the entropy of the system, $Q$ the heat entering the system during the process $\gamma$, $W$ the mechanical work done on the system during the process $\gamma$ and $T$ the temperature. Both internal energy and entropy are state functions, in the sense that they are path-independent functions and thus can describe the state of a system independently of the path followed to reach it. With $\gamma$ is denoted a generic - reversible or irreversible - process. For $\gamma$

---

$^1$Here we embrace the concept of “minimal state” treated in [12].

$^2$While Classical Thermodynamics is interested in macrostates, Statistical Mechanics studies the microstates, intended as the instantaneous configurations of all the elementary particles which constitute a system. Each macrostate corresponds to an enormous number of possible microstates, all experimentally undistinguishable among each other.
reversible, the equality holds in the second principle, hence the heat entering the system during a reversible process equals
\[ dQ_{\text{Rev}} = T \, dS. \]

For an open system, the expression of \( W \) has to account for both mechanical and for mass diffusion work, \( W = W^M + W^D \). The mechanical work done on a fluid system by the external environment has the form \( dW^M = -pdV \), being \( p \) the pressure. From now on, we will focus our attention on fluid systems.

**State Functions.** Beyond the state functions \( E \) and \( S \), it is possible to introduce the following ones:

- **Enthalpy:** \( H = E + pV \)
  
  [for closed systems, \( dH = dE + pdV + Vdp = d(E - W) + Vdp = (p=\text{cost}) = dQ_p = c_pdT \)]

- **Helmholtz Free Energy:** \( \Psi = E - TS \)
  
  [for open systems, \( d\Psi = dE - TdS - SdT = (T=\text{cost}) = dE - TdS = dW_{\text{Rev}} \)]

- **Gibbs Free Energy [or Free Enthalpy]:** \( G = H - TS \)
  
  [for open systems, \( dG = dE + pdV + Vdp - TdS - SdT = (p=\text{cost}) = dW^D_{\text{Rev}} \)]

These state functions are important in several problems of mechanics with thermal and chemical effects. In particular, as it will be shown later, the Gibbs free energy plays a crucial role during heterogeneous equilibria. The following mnemonic scheme is useful to remember the relations between the different state functions:

\[
\begin{align*}
E & \rightarrow +pV \rightarrow H \\
\downarrow & \quad \downarrow \\
-TS & \quad -TS \\
\downarrow & \quad \downarrow \\
\Psi & \rightarrow +pV \rightarrow G
\end{align*}
\]
1.3. Material and geometric phases. Let us assume that the phenomenon we are observing is completely described by a set $\mathcal{C}$ of independent fields defined on the domain occupied by the body. These fields describe purely geometrical evolutions of the body (that is, its motion) as well as all its non-geometrical evolutions (that is, all kinds of physical and chemical phenomena which intrinsically depend upon some material characteristics of the body); granted the independence of the variables of the list $\mathcal{C}$, it is possible to define unambiguously the both sets of geometrical and material variables as follows:

**Geometrical Variables:** The set $\mathcal{C}^G \subseteq \mathcal{C}$ of all purely geometrical variables.

**Material Variables:** The set $\mathcal{C}^M = \mathcal{C}/\mathcal{C}^G$ of all non-geometrical variables.

Evidently, $\mathcal{C}^G \cap \mathcal{C}^M = \{\emptyset\}$ and $\mathcal{C}^G \cup \mathcal{C}^M = \mathcal{C}$. Since the two sets $\mathcal{C}^G$ and $\mathcal{C}^M$ are disjoint, it is possible to focus our attention separately on each one; if we focus our attention on the evolution of material variables throughout the body, the following definition of Phase might be given:

*A phase is a perceptible portion of matter whose material properties are uniform or at most slowly and smoothly varying within its extension, and endowed at the macroscopical level with a boundary across which such properties have a discontinuity or a continuous and abrupt variation.*

On the other hand, the viewpoint classically adopted in Continuum Mechanics is based on the recognition of geometric fields (such as, for example, the gradient of deformation) as the variables whose discontinuities or abrupt variations define the occurrence of a phase boundary, and thus the definition given above might be rephrased as follows:

*A phase is a region of a body, characterized by uniform or at most slowly and smoothly varying gradient of deformation with respect to a given reference configuration, and which admits discontinuities or continuous and abrupt variations across the phase boundary.*

Since the two viewpoints actually focus on disjoint properties of the material body, precisely material and geometrical, it appears legit to us to label as material phases those recognized through the analysis of material properties, and as geometrical phases those recognized through the analysis of geometrical properties; moreover, the question whether or not the material phases are coupled with geometrical phases, and how this coupling is achieved, is certainly non trivial and is the main topic of this thesis.

Phase Transitions between different phases can be roughly classified as first and second order phase transitions. The first-order phase transitions are those that involve a latent heat. During such a transition, a system either absorbs or releases
a fixed (and typically large) amount of energy. Because energy cannot be instantaneously transferred between the system and its environment, first-order transitions are associated with mixed-phase regimes in which some parts of the system have completed the transition and others have not. Such mixed-phase systems are difficult to study, because their dynamics are violent and hard to control. Many important phase transitions fall in this category, including the solid/liquid/gas transitions and Bose-Einstein condensation.

The so called second-order phase transitions are the continuous phase transitions, mainly characterized by the absence of an associated latent heat. Continuous phase transitions are easier to study than first-order transitions, due to the absence of latent heat, and they have been discovered to have many interesting properties. The phenomena associated with continuous phase transitions are called critical phenomena.
1.4. Heterogeneous equilibrium - The Gibbs phase rule. Let us consider a material body\(^3\) \(\mathcal{B} \subset \mathcal{E}\) in which \(C\) different chemical species coexist in \(P\) different material phases. Such a body is an heterogeneous mixture. Within this simplified treatment of equilibrium of heterogeneous mixtures, we will assume that no boundary layer exists within the different material phases, hence each material phase \(f = 1, \ldots, P\) is assumed to occupy a region \(\mathcal{B}^f \subseteq \mathcal{B}\) such that
\[
\mathcal{B} = \bigcup_{f=1}^{P} \mathcal{B}^f \quad \text{and} \quad \mathcal{B}^f \cap \mathcal{B}^k = \{\varnothing\}, \forall f \neq k.
\]
Each \(\mathcal{B}^f\) is an open thermodynamical system, since the mass of each specie can rearrange in different phases during a process. If we assume that all constituents are non reacting, which means that the mass of each constituent is conserved during all processes, the following system of \(C\) constraints holds:
\[
\sum_{f=1}^{P} n_{i}^f = n_i = \text{const.} \quad \forall i = 1, \ldots, C
\]
where we denoted with \(n_{i}^f\) the number of moles of the constituent \(i\) in the phase \(f\), and with \(n_i\) the total number of moles of the component \(i\) in the mixture.

Chemical Potentials & the Gibbs Phase Rule. The chemical equilibrium of different chemical species coexisting in different phases within a region \(\mathcal{B}\) of the space is analyzed via variational arguments, resembling the method adopted by Gibbs in his work on the equilibrium of heterogeneous substances (Gibbs,[17]).

Let us consider a fluid mixture \(\mathcal{B}\) in which \(C\) different chemical species coexist, and let us make the assumption that the body is under thermal and mechanical equilibrium, that is:

- Mechanical Equilibrium:\( \quad p = \text{const.} \) all over the body;
- Thermal Equilibrium:\( \quad T = \text{const.} \) all over the body.

We now want to investigate the conditions under which the species in the mixture rearrange themselves in different material phases within the body \(\mathcal{B}\), during an isothermal and isobaric process. The classical simplifying hypotesis of chemically homogeneous phases will be assumed, that is each phase is characterized - beyond the same values of pressure and temperature - by uniform values of the molar fractions.

Let us then make the following constitutive assumptions for the total internal energy and entropy of the body \(\mathcal{B}\):
\[
\mathcal{E}(\mathcal{B}) = \hat{\mathcal{E}}(p, T, n_1, \ldots, n_C);
\]
\[
S(\mathcal{B}) = \hat{S}(p, T, n_1, \ldots, n_C).
\]

\(^3\)In this first simple exposition, we are not concerned about the distinction between the body and the region occupied by the body.
Both quantities are extensive and thus additive: this means that, since $B$ is the union of disjoint phase regions $B^f$, it results:

$$
\mathcal{E}(B) = \mathcal{E}\left(\bigcup_{f=1}^{P} B^f\right) = \sum_{f=1}^{P} \mathcal{E}(B^f) = \sum_{f=1}^{P} \mathcal{E}^f(p, T, n_1^f, ..., n_C^f);
$$

$$
\mathcal{S}(B) = \mathcal{S}\left(\bigcup_{f=1}^{P} B^f\right) = \sum_{f=1}^{P} \mathcal{S}(B^f) = \sum_{f=1}^{P} \mathcal{S}^f(p, T, n_1^f, ..., n_C^f).
$$

where we introduced the list of extensive variables of each phase region, $\{p, T, n_1^f, ..., n_C^f\}$, and we contextually admit that each material phase is characterized by its own constitutive equations. The number of moles of each chemical specie is given and thus the following $C$ relations hold:

$$
n_i = \sum_{f=1}^{P} n_i^f \quad \forall \ i = 1, ..., C.
$$

Let us denote - as it is done by Gibbs in his work - all perturbations of the state functions and variables with the symbol $\delta$ (see chapter 2 for further details on variations). As proposed by Gibbs, the equilibrium configurations of a mixture $B$ in contact with a heat bath at constant temperature $T$ can be determined by imposing the vanishing of the total internal energy for all perturbations which leave unaltered the total entropy and the mass of each constituent in the mixture; it will be shown in section 3 of this chapter that this statement is equivalent to look for the solutions of the following constrained variational problem:

$$
\delta \{ \Psi(B) - \mathcal{L}(B) \} = 0
$$

for all perturbations of the independent variables such that

$$
n_i(B) = \check{n}_i(B) = \text{const.} \quad \forall \ i = 1, ..., C.
$$

The potential energy term $\Psi$ represents the so called ballistic free energy (see also Ericksen [15], pg.7), namely in this case the Helmholtz free energy, defined as

$$
\Psi := \mathcal{E} - TS
$$

with $T$ the constant temperature of the surrounding heat bath. The work term $\mathcal{L}(B)$ can be expressed in the usual form $-p \, dV$ valid for fluids; being furthermore $p = \text{const.}$ we have:

$$
\mathcal{L}(B) = \int_{B} -p \, dV = \sum_{f=1}^{P} \int_{B^f} -p \, dV.
$$

The constrained variational problem can now be recast in free form using Lagrange’s multipliers; introducing the list of scalars

$$
\{\mu_1, ..., \mu_C\}.$$
constant all over the domain, we will look for the solutions of the equation

$$\delta F(B) = \delta \left\{ \Psi(B) - \sum_{i=1}^{C} \mu_i [n_i(B) - \bar{n}_i(B)] - L(B) \right\} = 0$$

for all possible perturbations of the variables \( \{n_1^1, \ldots n_1^P, \ldots n_C^1, \ldots, n_C^P\} \). Such perturbations are now free, since the constraint on the conservation of the mass of each constituent has been embedded in the energy functional. Since \( p \) and \( T \) are known constants, and being without constraints \( \Psi(B) = \Psi(P \bigcup_{f=1}^P B^f) = P \bigcup_{f=1}^P \Psi^f, \quad \delta n_i = \sum_{f=1}^P \delta n_i^f, \)

it results

$$\delta F(B) = \delta \Psi(B) + p \sum_{f=1}^P \delta V^f - \sum_{i=1}^{C} \mu_i \delta n_i^f =$$

$$= \sum_{f=1}^P [\delta \Psi(B^f) + p \delta V^f - \sum_{i=1}^{C} \mu_i \delta n_i^f]$$

$$= \sum_{f=1}^P [\delta (\Psi^f + p V^f) - \sum_{i=1}^{C} \mu_i \delta n_i^f] =$$

$$= \sum_{f=1}^P [\delta G^f - \sum_{i=1}^{C} \mu_i \delta n_i^f] = 0.$$  

The state function \( G = \Psi + pV = E - TS + pV \), already defined as the **Gibbs Free Energy**, depends on the state functions \( E \) and \( S \), on the intensive variables \( p \) and \( T \) and on the derived extensive quantity \( V \), hence it is an additive function and it depends on the main set of independent variables \( \{p, T, n_1, \ldots, n_C\} \). According to this constitutive dependence, we can expand the term \( \delta G^f \) as follows:

$$\sum_{f=1}^P \sum_{i=1}^{C} \left[ \frac{\partial G^f}{\partial n_i^f} \right] \delta n_i^f = 0 \quad \forall \text{ variations } \delta n_i^f.$$  

Being the variations \( \delta n_i^f \) linearly independent, it is finally possible to determine the **Euler-Lagrange** equations, which are represented by the following system of conditions:

$$\mu_i = \mu_1^1 = \mu_1^2 = \ldots = \mu_i^P \quad \forall i = 1, \ldots, C.$$  

where we denoted by

$$\mu_i := \frac{\partial G^f}{\partial n_i^f}$$

the **Chemical Potential** of the constituent \( i \) in the phase \( f \). The equilibrium conditions obtained through the Euler-Lagrange equations can be stated as follows
In an heterogeneous mixture of different chemical species, the chemical potential of each species at the equilibrium is the same in all the phases in which the species appears.

**Molar Densities.** Let us now show that the molar densities of all the extensive functions defined on a phase domain $B^f$, as well as the chemical potentials, admit a general constitutive dependence on the following list of intensive variables

$$\{p, T, \chi^f_1, \ldots, \chi^f_{C-1}\}$$

where

$$\chi^f_i = \frac{n^f_i}{n^f} = \frac{n^f_i}{\sum_{i=1}^{C} n^f_i}$$

are the molar fractions of each constituent within the phase $B^f$. By virtue of the hypothesis of chemical homogeneity of each phase of the mixture and by thermo-mechanical equilibrium, we infer that, for any extensive function

$$M = \hat{M}(p, T, n^f_1, \ldots, n^f_C)$$

defined on the phase domain $B^f$ and for any scalar $\alpha > 0$ it results that the function $M$ is 1–homogeneous, that is to say

$$\alpha \hat{M}(p, T, n^f_1, \ldots, n^f_C) = \hat{M}(p, T, \alpha n^f_1, \ldots, \alpha n^f_C).$$

On taking in particular $\alpha = 1/n^f$ with $n^f$ the total number of moles in the phase $B^f$, we get that the molar density of the function $M$ depends solely on the molar fractions, being

$$m := \frac{M}{n^f} = \hat{m} \left( p, T, \frac{n^f_1}{n^f}, \ldots, \frac{n^f_C}{n^f} \right) = \hat{m}(p, T, \chi^f_1, \ldots, \chi^f_{C}),$$

Nevertheless, because of the constraint

$$n^f = \sum_{i=1}^{C} n^f_i \quad \implies \quad 1 = \sum_{i=1}^{C} \chi^f_i$$

we infer that, say, $\chi^f_C$ can be expressed as function of the other $C-1$ molar fractions, hence

$$m = \hat{m}(p, T, \chi^f_1, \ldots, \chi^f_{C-1}).$$

This result shows that molar densities of each phase energy depend solely on the list of independent variables $\{p, T, \chi^f_1, \ldots, \chi^f_{C-1}\}$, such as for example the molar density of the Gibbs free energy of the phase $f$

$$g^f := \frac{G^f}{n^f} = \hat{g}^f(p, T, \chi^f_1, \ldots, \chi^f_{C-1}).$$
Considering the definition of chemical potential of the constituent $i$ in the phase $f$ and being $n_i^f = \chi_i^f n_i^f$ we also get
\[
\mu_i^f = \frac{\partial G^f}{\partial n_i^f} = \frac{\partial (n_i^f g_i^f)}{\partial \chi_i^f} \frac{\partial \chi_i^f}{\partial n_i^f} = n_i^f \frac{\partial g_i^f}{\partial \chi_i^f} \frac{1}{n_i^f} = \frac{\partial g_i^f}{\partial \chi_i^f} = \mu_i^f(p, T, \chi_1^f, ..., \chi_{C-1}^f).
\]

The chemical potential of the pure constituent $i$ in the phase $f$ for given values of the pressure and temperature
\[
\mu_i^{0f} := \mu_i^f(p, T, \delta_{1k}, ..., \delta_{ik}, ..., \delta_{(C-1)k}).
\]
are named standard chemical potentials and express the free energy of formation of a single mole at the given values of pressure and temperature of the considered constituent.

**Variance of a system.** We can now determine the number of independent intensive parameters in a mixture of $C$ heterogeneous constituents in thermal, mechanical and chemical equilibrium in $P$ different phases. The total number of intensive parameters is given by the constant values of pressure and temperature and the $C - 1$ molar fractions for each phase, thus a total number of $2 + P(C - 1)$. On the other side, at equilibrium we have the following relations between the chemical potentials of each constituent in each phase
\[
\mu_1^f = \mu_2^f = ... = \mu_P^f \quad \forall \ i = 1, ..., C
\]
which means a total number of $C(P - 1)$ independent relations. This means the number of independent intensive parameters at equilibrium equals
\[
V = 2 + C - P
\]
and such number is usually referred to as the variance of the system. The definition of the variance of a thermodynamical system defines the **Gibbs’ Law** or the **Phases’ Rule**. For example, in a system in which water coexists in both liquid and vapor phases, the number of independent variables is $V = 2 + 1 - 2 = 1$.

**1.5. Gibbs-Duhem equations - The common tangent rule.** We have already shed evidence on the fact that homogeneity of the Gibbs free energy implies that
\[
G^f(p, T, \alpha n_1^f, ..., \alpha n_C^f) = \alpha G^f(p, T, n_1^f, ..., n_C^f) \quad \forall \alpha > 0.
\]
Differentiating with respect to $\alpha$ and setting $\alpha = 1$ we obtain the following relation:
\[
G^f = \sum_{i=1}^{C} \mu_i^f n_i^f \quad \text{being} \quad \mu_i^f = \frac{\partial G^f}{\partial n_i^f} = \frac{\partial g_i^f}{\partial \chi_i^f}
\]
which, differentiated, yields:
\[
dG^f = \sum_{i=1}^{C} (d\mu_i^f n_i^f + \mu_i^f d n_i^f).
\]
Calculating the total differential of the relation
\[
G^f(p, T, n^f_1, ..., n^f_C) = \mathcal{E}^f + pV^f - TS^f
\]
we obtain
\[
\frac{\partial G^f}{\partial p} \, dp + \frac{\partial G^f}{\partial T} \, dT + \sum_{i=1}^{C} \mu^f_i \, dn^f_i = \, d\mathcal{E} + p \, dV^f - T \, dS^f + V^f \, dp - S^f \, dT = \\
= V^f \, dp - S^f \, dT + dW_{Rev}^{D,f}
\]
where the term \(dW_{rev}^{D,f}\) represents the infinitesimal reversible diffusion work. Independence of the variations \(dp\) and \(dT\) yields that
\[
V^f = \frac{\partial G^f}{\partial p}, \quad S^f = -\frac{\partial G^f}{\partial T}
\]
thus we obtain the following expression for the reversible diffusion work in the phase \(f\)
\[
dW_{Rev}^{D,f} = \sum_{i=1}^{C} \mu^f_i \, dn^f_i.
\]
This allows us to write down the variation of the Gibbs free energy in the form
\[
dG^f = V^f \, dp - S^f \, dT + \sum_{i=1}^{C} \mu^f_i \, dn^f_i
\]
which, combined with the relation obtained before
\[
dG^f = \sum_{i=1}^{C} (d\mu^f_i n^f_i + \mu^f_i dn^f_i).
\]
yields the following **Gibbs-Duhem** relations, valid for each phase
\[
V^f \, dp - S^f \, dT = \sum_{i=1}^{C} n^f_i \, d\mu^f_i \quad \forall \, f = 1, ..., P
\]
which establish a series of \(P\) constraints among the differentials of the intensive variables \(\{p, T, \mu^f_1, ..., \mu^f_C\}\) of the mixture. Dividing for \(n^f\) the expression of \(G^f\) in terms of chemical potentials and mole numbers we obtain that
\[
\frac{G^f}{n^f} = \sum_{i=1}^{C} \mu^f_i \frac{n^f_i}{n^f} \quad \Rightarrow \quad g^f = \sum_{i=1}^{C} \mu^f_i \chi^f_i.
\]
Finally, also the Gibbs-Duhem equations can be rewritten using molar fractions, simply dividing for \(n^f\) the relation obtained before
\[
v^f \, dp - s^f \, dT = \sum_{i=1}^{C} \chi^f_i \, d\mu^f_i \quad \forall \, f = 1, ..., P.
\]
being \(v^f\) molar volume and \(s^f\) molar entropy of the phase \(f\).
Geometrical interpretation of the Gibbs-Duhem equation. Let us consider for simplicity a binary mixture in which the molar fractions of each specie are $\chi_A$ and $\chi_B$, with $\chi_A + \chi_B = 1$. Assuming $\chi = \chi_B$, it results $\chi_A = (1 - \chi)$ and then the molar Gibbs free energy of a certain phase can be expressed, on the bases of what we have shown above, as follows

$$g = \mu_A (1 - \chi) + \mu_B \chi.$$  

Differentiating this relation, and using the Gibbs-Duhem equation, we obtain that  

$$dg = vdp - sdT + (\mu_B - \mu_A)d\chi,$$

which, for an isothermal and isobaric process, yields the following relation:

$$\frac{dg}{d\chi} = (\mu_B - \mu_A).$$

This relation allows to interpret the intercepts of the tangent line in the point $\chi$ to the molar Gibbs free energy $g(\chi)$ with the axis $\chi = 0$ and $\chi = 1$ as the values, respectively, of the chemical potentials $\mu_A$ and $\mu_B$ of both the species at the concentration $\chi$(see figure 1).

![Figure 1. Geometrical meaning of the tangent to the molar Gibbs free energy.](image)

This interpretation can easily be recast for multiple constituents mixtures: for a ternary mixture we will have a tangent plane intersecting axes $\chi_i = 1$ with $i = 1, 2, 3$ at the values of the chemical potentials, and so on.
Equilibrium between different phases: the common tangent rule. Chemical equilibrium among heterogeneous constituents requires chemical potential of each specie to be the same in all the phases in which it appears. On the other hand, we have shown in the previous subsection that the geometrical interpretation of the Gibbs-Duhem equation for a binary mixture (for isothermal and isobaric processes) is that the intercepts of the tangent to the molar Gibbs free energy curve with the axis $\chi = 0$ and $\chi = 1$ respectively represent the values of the chemical potentials for a given value of $\chi$.

More precisely, let a binary mixture of two species $A$ and $B$ be given, and let us assume the coexistence of two phases $\alpha$ and $\beta$ in the mixture. Both the species $A$ and $B$ are characterized through the given values of their chemical potentials in the phases $\alpha$ and $\beta$ at given conditions of pressure and temperature, that is through the knowledge of the functions $\mu_A(p, T, \chi)$ and $\mu_B(p, T, \chi)$ of both phases, since

$$
\begin{align*}
    g^\alpha(\chi^\alpha) &= (1 - \chi^\alpha)\mu_A^\alpha(\chi^\alpha) + \chi^\alpha\mu_B^\alpha(\chi^\alpha) \\
    g^\beta(\chi^\beta) &= (1 - \chi^\beta)\mu_A^\beta(\chi^\beta) + \chi^\beta\mu_B^\beta(\chi^\beta)
\end{align*}
$$

where the variables $p$ and $T$ have been suppressed and we have chosen as independent variable the value of $\chi_B = \chi$. Necessary conditions for both phases $\alpha$ and $\beta$ to coexist within the same mixture are that the concentrations $\chi^\alpha$ and $\chi^\beta$ are such that

$$
\mu_A^\alpha(\chi^\alpha) = \mu_A^\beta(\chi^\beta), \quad \mu_B^\alpha(\chi^\alpha) = \mu_B^\beta(\chi^\beta)
$$

As it is easy to check by virtue of the geometrical interpretation of the Gibbs-Duhem equation, these conditions are geometrically satisfied for values of the concentrations $\chi^\alpha$ and $\chi^\beta$ of the phases $\alpha$ and $\beta$ for which there exist a common tangent line to the curves $g^\alpha$ and $g^\beta$. As depicted in Fig.2, this is actually the case when the values of the concentrations of both phases equal respectively the values $\bar{\chi}^\alpha$ and $\bar{\chi}^\beta$.

In order to better understand how such equilibrium configurations are achieved on the basis of a given value of the total number of moles of both constituents, let us consider a mixture in which $n_A$ and $n_B$ moles of the species $A$ and $B$ coexist in the phases $\alpha$ and $\beta$, and let $n^\alpha = n_A^\alpha + n_B^\alpha$ and $n^\beta = n_A^\beta + n_B^\beta$ be the total number of moles in each phase. The molar fractions will evidently be such that $1 = \chi_A^\alpha + \chi_B^\alpha$ and $1 = \chi_A^\beta + \chi_B^\beta$. The total Gibbs free energy of the mixture can be expressed as:

$$
G^{tot}(n_A, n_B) = G^\alpha(n_A^\alpha, n_B^\alpha) + G^\beta(n_A^\beta, n_B^\beta) = n^\alpha g^\alpha(\chi^\alpha) + n^\beta g^\beta(\chi^\beta).
$$

Dividing for the total number of moles $n = n^\alpha + n^\beta = n_A + n_B$, we obtain the molar Gibbs free energy of the mixture:

$$
g^{tot}(\bar{\chi}) = (1 - f)g^\alpha(\chi^\alpha) + fg^\beta(\chi^\beta)
$$

being $\bar{\chi} = \chi_B / n$ the average composition and $f = f^\beta = n^\beta / n$ the $\beta$-phase fraction in the mixture. Relatively to the curve of figure 2, it is possible to

---

4This is what is customarily done by scientists studying phase separation in metal alloys (see for example Larche-Cahn), and even by analysts who studied problems of chemo-mechanical coupling (see for example Fonseca-Kinderlehrer-Pedregal,[]).
Figure 2. The common tangent construction.

check that the only values of the given average concentration $\bar{\chi}$ such that the two phases can coexist are those belonging to the interval $[\bar{\chi}^{\alpha}, \bar{\chi}^{\beta}]$; for such values of the given average concentration the common tangency condition is fulfilled and an easy calculation allows to determine the value of the $\beta$-phase fraction, since

$$\bar{\chi} = \frac{n_B}{n} = \frac{n_B^{\alpha} + n_B^{\beta}}{n} = \frac{n_B^{\alpha} n^{\alpha}}{n^{\alpha}} + \frac{n_B^{\beta} n^{\beta}}{n^{\beta}} = (1 - f)\bar{\chi}^{\alpha} + f\bar{\chi}^{\beta} \implies f = \frac{\bar{\chi} - \bar{\chi}^{\beta}}{\bar{\chi}^{\beta} - \bar{\chi}^{\alpha}}. $$

The relation now obtained for $f$ represents the so called Lever Rule. The corresponding value of the molar Gibbs free energy attained at $\bar{\chi}$ can finally be calculated as follows:

$$g^{\text{tot}}(\bar{\chi}) = (1 - f)g^{\alpha}(\bar{\chi}^{\alpha}) + fg^{\beta}(\bar{\chi}^{\beta}).$$

Outside of the common tangent interval, the system will be mono-phasic, and its energy will be represented by the lower phase curve. Inside of the common tangency points a mixture of both phases will occur, and the energy of the system will be represented by the common tangent itself. This actually means that the energy of the system is represented by the Convex Envelope of the set of curves which represent the energies of different phases; indeed, this solution can be shown to represent a global minimum of the outlined phases coexistence problem.

Let us now not assume the coexistence of phases in the mixture: in this case, let a single molar Gibbs free energy function be given for the bulk. The common tangent rule shows that necessary condition for phase separation to occur is the Gibbs free energy to be a non convex function in its argument $\chi$. Indeed, as depicted in fig.3, for $G$ non convex there exist values of the concentration - those belonging to
the interval \([\bar{\chi}^\beta, \bar{\chi}^\alpha]\) - for which the tangency condition is satisfied, this allowing the possible coexistence of phases (or the so called "variants") within the same mixture\(^5\).

\[ \begin{array}{c}
\chi = 0 & \bar{\chi}^\beta & \bar{\chi} & \bar{\chi}^\alpha & \chi = 1 \\
\mu^\beta & \mu^\alpha \end{array} \]

\[ \begin{array}{c}
\mu^\alpha = \mu^\beta \\
\mu^a = \mu^a \\
g \end{array} \]

**Figure 3.** The common tangent construction.

As a concluding remark, we observe that the common tangent is usually called, in classic mechanical contexts, the "Maxwell Line".

\(^5\text{As before, this analysis should account for considerations regarding the stability of the solution.}\)
1.6. Ideal solution theory - Raoult’s law. A solution is a "homogeneous dispersion of two or more chemical species". In what follows we will consider liquid solutions. The dissolution of a specie in a liquid solution is considered to happen under isobaric and isothermal conditions; under these conditions, the variation of the Gibbs free energy gives important information about the spontaneity of the process and the equilibrium state. For an isobaric and isothermal mixing, this variation - computed between the very initial state (the collection of pure elements which form the chemical species involved in the mixing process) and the final state (the solution of the chemical species) - reads as follows:

$$
\Delta G_{\text{mix}} = G_{\text{mix}} - G_{\text{elem}} = \Delta H_{\text{mix}} - T \Delta S_{\text{mix}}.
$$

where $G_{\text{mix}}$ represent the final energy of the mixture and $G_{\text{elem}}$ the total initial energy of the pure elements. The arbitrariness of the ground state of the energy allows us to set the energy of the pure elements $G_{\text{elem}}$ equal to zero, so that the free energy $G = G_{\text{mix}}$ of the solution actually equals the $\Delta G_{\text{mix}}$. As matter of fact, this is the procedure to evaluate the Gibbs free energy of a mixture in a given state. Necessary condition for the solution to be a spontaneous process is, as it would be possible to show, that $\Delta G_{\text{mix}} < 0$; if this condition does not occur, each added specie will tend to segregate from others. The variation $\Delta H_{\text{mix}}$ is known as the enthalpy of mixing, and it represents the change in energy due to the establishment of bonds between alike or unlike elementary particles; the variation $\Delta S_{\text{mix}}$ is the entropy of mixing, and it represents at the macroscopical level the variation of the entropy of the system due to the rearrangement of elementary particles in structures characterized by a different microscopic order.

It is important to underline that the terms $\Delta H_{\text{mix}}$ and $\Delta S_{\text{mix}}$ are not completely independent to one another, though they focus on completely different aspects. In fact, on the one hand the microscopic order of an aggregate of different particles does not depend on the eventual interactions between them, but solely on the structures formed at the microscopic level; in general, this order depends in a crucial way on the size of the particles, which means that microscopic order feels the different chemical species through differences in particles sizes. On the other hand, variations of microscopic order can certainly produce changes in the arrangement of inter-particle bonds and thus of the $\Delta H_{\text{mix}}$.

The so called Ideal solution theory is based on the following simplifying assumptions:

- that the enthalpy of mixing vanishes, $\Delta H_{\text{mix}} = 0$, that is the interactions between particles are ignored;
- that the molecules are assumed to be distributed among sites in a random fashion, despite size differences among particles.

$^{6}$In the sense already given for phases, that is with uniform of at most smoothly and slowly varying properties within the extension of the solution.
Later on it will be clear that these approximations actually hold true for a very particular class of aggregates, in which all particles have approximately the same size and energetic interactions between like and unlike particles are equal or vanishing.\footnote{See T. Hill’s book \cite{hill}, pg. 375, pg. 402.}

Within these approximations, the mixing phenomenon is solely governed by entropic effects. Since the solution process occurs spontaneously if $\Delta G_{\text{mix}}^{\text{id}} = -T \Delta S_{\text{mix}} < 0$, that is if $\Delta S_{\text{mix}} > 0$, it is evident that within the hypothesis of ideal solution theory the system will always evolve toward completely poly-dispersed states - that means, at microscopical level, toward configurations characterized by the lowest structural order. Before analyzing the question of equilibrium of several different species in a liquid phase, let us introduce some basic concepts.

**Dalton’s Law.** The ideal gases law ignores completely the chemical nature of particles, thus the pressure in an ideal gas\footnote{Or in a real gases for which the application of ideal gases law holds, vd. \cite{56} pg.134. This kind of approximation of real with ideal gases certainly holds under the hypothesis of ideal solution theory, which ignores relations between particles and does not care of their different chemical nature.} depends solely on the number and not on the kind of particles. If we consider a container of given volume $V$ at a temperature $T$, in which there is a mixture of $M$ different gases, the total pressure can be calculated as follows:

$$P_{\text{tot}} = \frac{n_{\text{tot}}RT}{V} = \left(\sum_{i=1}^{M} n_i\right) \frac{RT}{V} = \sum_{i=1}^{M} \frac{n_iRT}{V} = \sum_{i=1}^{N} p_i.$$  

The pressures $p_i$ are called "partial pressures" of each gas in the mixture, and represent the pressure that each component alone would exert on the container at that given value of temperature. Evidently it results that

$$p_i = \frac{n_i}{n_{\text{tot}}} P_{\text{tot}},$$

which actually represents the so called *Dalton’s Law.*

**Raoult’s Law.** Let us now consider the case of a liquid mixture of different species in equilibrium with its own vapor. The vapor phase will be constituted by the same number of species which constitute the liquid phase, and by Dalton’s law $p_i/P_{\text{tot}} = n_{i}^{\text{vap}}/N_{\text{tot}}^{\text{vap}} = \chi_{i}^{\text{vap}}$. Raoult’s law asserts the following relation between partial pressures of each specie in the vapor phase and the composition of the liquid phase

"For an ideal solution of two or more liquid species at a given temperature, the partial pressure in the vapor phase due to each specie is given by the relation $p_i = \chi_{i}^{\text{liq}} p_i^0$, being $\chi_{i}^{\text{liq}} = n_{i}^{\text{liq}}/n_{\text{tot}}^{\text{liq}}$ the molar fraction of the specie $i$th in the liquid mixture, and $p_i^0$ the pressure that the pure specie $i$th would exert alone on the volume occupied by the whole vapor phase at the same temperature."

\footnote{See T. Hill’s book \cite{hill}, pg. 375, pg. 402.}
As a remark, Raoult’s law establishes a relation between molar fractions of each component in the liquid phase and the vapor phase

\[ \chi_{i,\text{vap}} = \frac{\chi_{i,\text{liq}} p_i^0}{\sum_k M_k \chi_{k,\text{liq}} p_k^0} \]

which shows that a vapor phase is always richer of the most volatile specie with respect to the liquid phase.

We are now in position to compute the \( \Delta G_{\text{mix}}^{\text{id}} \) relative to the phenomenon of solution of \( N \) different chemical species. We intend for initial state the collection of the pure elements, whose combination create all possible chemical species, and for final state the solution itself. Let us consider the following scheme:

- **Step 0.** Set \( G_{i,k} = 0 \) for all pure elements \( k = 1, \ldots, N \) which constitute the specie \( i \);

- **Step 1.** Evaluate the formation free energy \( G_i^0 = \mu_i^0 \) of one unit of the \( i^{th} \) chemical specie from pure elements, that is the standard chemical potential of the pure specie \( i \).

- **Step 2.** Compute the variation of the molar Gibbs free energy \( \Delta G_{i,\text{liq}} \) due to the passage from the pure liquid specie \( i \) to the actual liquid mixture. To accomplish this, consider first that, for a mole of vapor of the specie \( i \) which passes isothermally from a pressure \( p_i^1 \) to a pressure \( p_i^2 \) it is \( dG_i = V dp_i = RT dp_i/p_i \), and then:

\[ \Delta G_{i,\text{vap}} = \int_1^2 dG_i = RT \int_1^2 \frac{dp_i}{p_i} = RT \ln \frac{p_i^2}{p_i^1}. \]

On the basis of this, if a mole of vapor of the specie \( i \) passes from \( p_i^0 \) (pressure of the vapor of the pure liquid \( i \)) to \( p_i \) (partial pressure of the \( i^{th} \) specie in the vapor of the mixture) it results:

\[ \Delta G_{i,\text{vap}} = RT \ln \frac{p_i}{p_i^0}, \]

which, since the framework of ideal solution theory allows the application of Raoult’s law, which can be rewritten as follows:

\[ \Delta G_{i,\text{vap}} = RT \ln \chi_{i,\text{liq}}. \]

Since the conditions for the heterogeneous equilibrium imply that both at the initial stage and at the final stage of the process of solution (that is, pure liquids in equilibrium with their own vapors and mixture in equilibrium with its own vapor), the molar Gibbs free energy has the same value in both liquid and vapor phases, we can finally compute the variation of the Gibbs free energy due to the passage of one mole of the specie \( i \) from its pure liquid phase to the final mixture, being:

\[ \Delta G_{i,\text{liq}} = G_{i,\text{mix,liq}}^0 - G_{i,\text{liq}}^0 = G_{i,\text{mix,vap}}^0 - G_{i,\text{vap}}^0 = \Delta G_{i,\text{vap}} = RT \ln \chi_{i,\text{liq}}. \]
The variation of the Gibbs free energy for one mole of the $i^{th}$ chemical specie from pure elements to the solution is therefore

$$
\Delta G_{id}^i = G_{i}^{mix} = G_i^0 + (G_{i}^{mix} - G_i^0) = G_i^0 + \Delta G_{liq}^i = \mu_i^0 + RT \ln \chi_i^{liq},
$$

thus, the resulting total variation of Gibbs free energy during the solution process of $C$ different species is the sum of the variations for each specie:

$$
\Delta G_{mix}^{id}(n_1, ..., n_C) = \sum_{i=1}^{C} \Delta G_{id}^i = \sum_{i=1}^{C} n_i \mu_i^0 + \sum_{i=1}^{C} n_i RT \ln \chi_i.
$$

Dividing for the total number of moles in the liquid mixture $n = \sum n_i$, yields the molar Gibbs free energy of mixing:

$$
g_{mix}^{id}(\chi_1, ..., \chi_{(C-1)}) = \frac{\Delta G_{mix}^{id}}{n} = \sum_{i=1}^{C} \chi_i \mu_i^0 + RT \sum_{i=1}^{C} \chi_i \ln \chi_i.
$$

Worth noting, since the variation of Gibbs free energy is computed from an initial stage of pure elements, whose energy has been arbitrarily set equal to zero, it actually represents the molar Gibbs free energy of the whole mixture, that is:

$$
g^{id}(\chi_1, ..., \chi_{(C-1)}) = \Delta g_{mix}^{id}(\chi_1, ..., \chi_{(C-1)}) = \sum_{i=1}^{C} \chi_i \mu_i^0 + RT \sum_{i=1}^{C} \chi_i \ln \chi_i.
$$

The function $g^{id}$ is evidently a convex function in each argument $\chi_i$, thus the common tangent rule enunciated before allows to assert that **no phase separation occurs in an ideal mixture**, since there cannot exist common tangent lines (planes, hyperplanes) to more than one point of the curve (see fig. 3).
1.7. Non-ideal solution theory - Bragg-Williams and Flory-Huggins theories. As seen in the previous section, ideal theory of mixtures is based on the strong assumptions that inter-particles bonds and size differences between particles are to be ignored. The removal of these two simplifying assumptions yields two more general theories of solutions, namely the Bragg-Williams and the Flory-Huggins theories, respectively known also as thermal and a-thermal theories of solutions. Both approaches produce deviations from ideal theory - the usually called excess quantities - in the calculation of the Gibbs free energy of the aggregate. In practice, we can summarize the core of both the theories by saying that the accounted excess quantities are

$$\Delta G^e = \Delta H^e - T \Delta S^e = \begin{cases} \text{Bragg-Williams Theory (}\Delta S^e = 0) : & \Delta G^e = \Delta H^e ; \\ \text{Flory-Huggins Theory (}\Delta H^e = 0) : & \Delta G^e = -T \Delta S^e. \end{cases}$$

As it was already put in evidence in the previous section, since the enthalpic and the entropic counterparts of the Gibbs free energy are not completely independent of each other, it is not correct to set $\Delta H^e$ and $\Delta S^e$ alternatively equal to zero. This means that the BW and FH theories are just apparently disjoint and complementary, since a complete and correct treatment should focus contemporarily on both enthalpic and entropic terms and on their connections: this kind of result can be afforded, for example, via a Statistical Mechanical approach.

Bragg-Williams lattice theory. When evaluating the effects of particle interactions, we will first consider the so called ”Lattice Theory of Concentrated Solutions” (Hill, [29], pg. 371), where deformation effects are ignored. After we will introduce in the model deformation effects through the wider framework of ”Cell Theories”.

Let us briefly summarize the basic assumptions of the Bragg-Williams lattice theory:

- the chemical species are fluid like, and the system is treated as a condensed, incompressible solution containing $n_A$ and $n_B$ molecules of the two components $A$ and $B$, which are considered to occupy sites of a regular lattice, with no vacant sites;
- the pair interaction between two particles of different constituents $i$ and $j$ is described by a Lennard-Jones potential of the kind (see[29], Eq. 16-28):

$$\hat{w}_{ij}(r) = \varepsilon_{ij} \left[ \left( \frac{r^*_{ij}}{r} \right)^{12} - 2 \left( \frac{r^*_{ij}}{r} \right)^6 \right],$$

being $r$ the inter-particle distance and $r^*_{ij}$ and $\varepsilon_{ij}$ parameters depending on the particles involved in the interaction. The interaction potentials for the pairs $A - A$ and $B - B$, that is the laws $w_{AA}(r)$, $w_{BB}(r)$ are in general different, as schematically depicted in fig.4; furthermore, relatively to the interaction between $A - B$ particles, $w_{AB}(r)$ is computed - in the absence of
other information - according to the Lennard-Jones potential with parameters (see [29], Eq. 15-53 and pg.383):

$$\varepsilon_{AB} = (\varepsilon_{AA}\varepsilon_{BB})^{1/2}, \quad r_{AB}^* = \frac{r_{AA}^* + r_{BB}^*}{2};$$

Usually the interaction potentials, when evaluated at the nearest-neighbor distances $a$, have negative values.

- the approximation of nearest-neighbor interaction is done, and each site has $c$ nearest-neighbor sites; the lattice is rigid, that is it has a fixed volume per site, hence this model omits all deformation effects. Letting $a$ to be the (fixed) nearest-neighbor distance, we will simply denote by $w_{AA}$, $w_{BB}$ and $w_{AB}$ the functions $\hat{w}_{ij}(r = a)$. Within this theory the $w$’s are considered constants, though one should in general consider dependence on the local molar density (which is the further generalization introduced through Cell Theories) and temperature;

- all molecules have spherical shape and have approximately the same size (which is crucial for interchangeability among sites). This assumption is later on removed through the Flory-Huggins Theory.

Within this theory, all molecules are assumed to be distributed on the lattice in a random fashion, that means that the entropy of mixing is exactly the same as for an ideal solution, i.e. $\Delta s^e = 0$. The excess Gibbs free energy is then completely enthalpic in nature that is $\Delta g^e = \Delta h^e$, and its origin lays on the different interactions between like and unlike particles of the aggregate.

Figure 4. Pair-interaction potentials in the A-B aggregate.
Granted the assumptions stated above it is possible to show that the excess molar enthalpy of the mixture $\Delta h^e$ equals

$$\Delta h^e = -\frac{cw}{2} \chi A \chi B$$

where $w$ represents the interaction parameter (see [29], Eq.20-6)

$$w = w_{AA} + w_{BB} - 2w_{AB}.$$ 

The resulting expression of the molar Gibbs free energy for the binary aggregate is then

$$g(\chi A, \chi B) = g^{id}(\chi A, \chi B) + \Delta g^e$$

$$= \chi A \mu_A^0 + \chi B \mu_B^0 + RT(\chi A \ln \chi A + \chi B \ln \chi B) - \frac{cw}{2} \chi A \chi B,$$

where, letting $\chi = \chi_B$ as usual, and being $\chi_A + \chi_B = 1$, we have:

$$g(\chi) = [(1 - \chi) \mu_A^0 + \chi \mu_B^0] + RT[(1 - \chi) \ln(1 - \chi) + \chi \ln \chi] - \frac{cw}{2} \chi (1 - \chi).$$

As matter of fact, the two terms $g^{id}(\chi)$ and $\Delta g^e(\chi)$ are both convex functions of $\chi$, but their sum can produce, for suitable values of the ratio

$$\frac{cw}{2RT}$$

a non convex function, which is a necessary condition - on the basis of the common tangent rule - for the co-existence of different phases in the mixture.

**Figure 5.** Molar Gibbs free energy according to Bragg-Williams theory.

*Ideal Solution Theory* is recovered for $w = 0$, that is for $w_{AA} + w_{BB} = 2w_{AB}$. In this situation, molecules $A$ and $B$ like their opposite species as their own species; this basically means that all the possible configurations of the same particles are characterized by the same energy;
Bragg-Williams Theory is recovered for \( w \neq 0 \); in this case the Raoult’s law on ideal mixing is corrected by the enthalpic contribution through the so called positive and negative deviations. It would be easy to check that various behaviors of the binary mixture derive from different values attained by the parameter \( cw/2RT \), in particular

**negative deviations from ideality:** are attained whenever the enthalpic contribution is a negative function, hence for \( w > 0 \). In this case - reminding that the \( w_{ij} \)'s have negative values - \( 2w_{AB} \) is more negative than the sum \( w_{AA} + w_{BB} \), hence we have that \( AB \) pairs are energetically favored than \( AA \) and \( BB \) pairs. The Gibbs energy density remains convex all over the range of \( \chi \) hence no phase separation occurs;

**positive deviations from ideality:** are attained whenever the enthalpic contribution is a positive function, that is for \( w < 0 \). Analogously to the case of negative deviations, here it happens that \( w_{AA} + w_{BB} \) is more negative than \( 2w_{AB} \), hence \( AA \) and \( BB \) pairs are energetically favored than \( AB \) pairs. Nevertheless, the Gibbs energy density remains a convex function until

\[
-4 < \frac{cw}{2RT} < 0.
\]

For \( cw/2RT < -4 \), the Gibbs energy density becomes a non-convex function of \( \chi \), hence phase separation occurs in certain ranges of concentration (as discussed with the common tangent argument). In this situation the two components are no longer miscible in all proportions; over part of the composition range we get a separation of the solution in phases with different concentrations. As schematically depicted in Fig.5, for growing negative values of \( cw/2RT \), the Gibbs free energy yields a non convex zone in which a mixture of phases is possible, with both phases weighted according to the lever rule, as shown in the previous sections. This phase separation shows a departure from the homogeneous dispersity of molecules foreseen by ideal solution theory, toward aggregated states in which one or both the chemical species favor, in their neighbor, ”alike” species better than ”unlike” ones.

**Bragg-Williams cell theory.** Lattice Bragg-Williams theory provides a very simple model which predicts correctly some of the most important qualitative features observed experimentally with binary solutions, nevertheless it is affected by serious limitations, in particular it considers the mixture incompressible. This assumption will now be removed, on the basis of the so called Cell Theories of Binary Solutions (see [29], pg. 382).

The main correction introduced with respect to the Lattice Theory is that, granted the assumptions that we have a lattice in which each cell is occupied by molecules \( A \) or \( B \), with \( c \) nearest-neighbors and being \( a \) the nearest-neighbor distance, is that here we consider the \( c \) neighbors of a given molecule smeared uniformly over the surface of a sphere of radius \( a \), consist of \( c\chi_A \) molecules of type \( A \) and of \( c\chi_B \) molecules of
type $B$. Unlike the lattice theory, the volume $V$ is not considered an independent thermodynamic variable, hence letting $v = V/M$ to denote the molecular volume it results

$$a^3 = \gamma v$$

where $\gamma$ is a constant depending on the geometry of the lattice (ordinarily $\gamma = \sqrt{2}$). As it would be possible to show (see Hill, [29], pg. 386), we have for the resulting excess free energy

$$\Delta h^e = RT\left[\chi_A \ln v_f(\chi_A = 1) + \chi_B \ln v_f(\chi_B = 1) - \ln v_f(\chi_A)\right] +$$

$$+ \frac{\varphi(0, \chi_A) - \chi_A\varphi(0, \chi_A = 1) - \chi_B\varphi(0, \chi_B = 1)}{2}$$

where

$$v_f = \hat{v}_f(v, \chi, T)$$

is the averaged free volume per molecule, and being $\varphi = \hat{\varphi}(r)$ the potential energy evaluated on the basis of the Lennard-Jones potentials (for further details we refer to Hill[29], 20-2). The $\varphi$ terms in the expression of the excess free energy are essentially equivalent to the Bragg-William excess term

$$\Delta h^e = -\frac{cw}{2} \chi_A \chi_B.$$ 

Within this theory compressibility effects are considered through the dependence on the specific volume $v$, which constitutively depends on the local values of the pressure, temperature and composition.

We will not treat this theory in further detail; nevertheless, we notice that a further refinement of the present theory is possible including three shells of neighbors instead of only one, as done before.

Further refinements of the compressible Bragg-Williams theory are possible; the so called **Corresponding States Theory**, which instead of using Lennard-Jones functions for pure liquid state (which represents a serious source of error) uses experimental (corresponding states) functions. This approach provides a better model under the quantitative point of view with respect of the Lennard-Jones approach.
Flory-Hugging approximation. The theory which we will briefly present here is a direct generalization of the Bragg-Williams approximation in the lattice model of binary solutions. The BW theory is applicable for all mixtures in which molecules have approximately equal size, so that each cell in the lattice can be occupied by either an A or a B molecule. In all cases in which molecules have non-comparable sizes, the BW approximation shows striking departures from reality.

According to the FH theory, it is believed that non-ideality in mixing arises solely from entropic effects related to the different sizes of molecules, hence the excess contribution to the Gibbs free energy is

$$\Delta g^e = -T\Delta s^e,$$

whereas the enthalpy of mixing is zero, being inter-particles interactions ignored, which agrees with the assumptions of ideal solution theory. The resulting Gibbs free energy of the solution is then

$$g = -T(\Delta s^{id} + \Delta s^e).$$

The FH theory still uses a lattice model and assumes random mixing, but since each molecule occupies different number of cells in the lattice, the mole fractions $\chi_A$ and $\chi_B$ are no more very useful; instead, volume fractions are used. The excess molar free energy for a binary mixture can thus be written as (see Cevc & Marsh, [11]):

$$\Delta g^e = -T\Delta g^e = -RT[\chi_A \ln \frac{\chi_A}{\Phi_A} + \chi_B \ln \frac{\chi_B}{\Phi_B}]$$

where $\Phi_A$ and $\Phi_B$ are the volume fractions of components A and B; a possible way to express these variables is the (see Sackmann, [53], pg. 271, and references there given)

$$\Phi_A = \frac{n_A V_A}{n_A V_A + n_B V_B}; \quad \Phi_B = \frac{n_B V_B}{n_A V_A + n_B V_B};$$

being $n_\alpha$ and $V_\alpha$ the molecular numbers and the molecular volumes, respectively. The resulting Gibbs free energy of the mixture is

$$g = RT[\chi_A \ln \Phi_A + \chi_B \ln \Phi_B],$$

in which, substantially, the molar fractions of the two components are substituted by the volume fractions.

If it is assumed that the two components have different volume fractions (that is a non-random distribution) arising from their mutual interactions, the molar Gibbs free energy might be rewritten as follows:

$$\Delta g^e = -RT[\chi_A \ln(\chi_A + f_{AB}\chi_B) + \chi_B \ln(\chi_B + f_{BA}\chi_A)]$$

where $f_{AB}$ and $f_{BA}$ are the parameters governing the non-random distribution of the species; for a random distribution $f_{AB} = f_{BA} = 0$, and thus the results of ideal solution theory is recovered.

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9See[11], pg 401, and references there given.
1.8. Lipid-lipid and lipid-cholesterol mixtures. Let us now briefly consider the case of biological membranes, which roughly consist of ternary mixtures of saturated and unsaturated lipids\textsuperscript{10} and cholesterol. Strong evidence of the non uniformity in the distribution of the components in biological membranes has been experimentally brought to attention in recent years; this non uniformity is manifested through the formation, on the membrane surface, of domains arising from the so called lateral phase separation, that is the segregation of domains characterized by different values of the concentration of the components.

Preliminary to the understanding of ternary mixtures is the deep knowledge of the behavior of the simpler binary mixtures of lipids (saturated and unsaturated) and of lipids and cholesterol. Let us analyze separately these two cases. In this section we will follow the line sketched in the beautiful article by Komura & others, [35].

**Lipid-Lipid Mixtures.** Let us consider a mixture of saturated and unsaturated lipids, each of which respectively characterized by different transition temperatures $T_s^*$ and $T_u^*$ between the gel (solid) ordered phase and liquid disordered phase. Differences in the transition temperatures arise from different chain lengths, degrees of saturation, or hydrophillic heads. Within the so called ordered phase, the tails of the lipids are straightened and the molecules are arranged on recognizable lattices, with low intra-membrane mobility. On the other hand, within the disordered phase the tails are generally curly and flexible, and the lipids can rearrange with an high intra-membrane mobility. Below the transition temperature, the phase is evidently ordered and above it is disordered. It is assumed that these lipids have the same area per molecule, so that the Bragg-Williams theory of mixtures holds; according to this theory, as already illustrated in the previous section, the molar Gibbs free energy reads as follows:

$$g^\| (\chi) = [(1 - \chi)\mu_s^0 + \chi\mu_u^0] + RT[(1 - \chi)\ln(1 - \chi) + \chi\ln \chi] - \frac{cw}{2}\chi(1 - \chi).$$

where $\chi$ is the molar fraction of the unsaturated lipid, and all other symbols have been previously defined. The negative values attained by the interaction parameter $w$ lead to, as discussed in the previous section, the existence of a region of concentrations in which - at a given temperature - different material phases may coexist.

**Lipid-Cholesterol Mixtures.** Let us now consider the case of binary mixtures of lipids (saturated or unsaturated) and cholesterol. It experimentally results that each cholesterol molecule dimers with a lipid molecule, thus it is possible to think that the mixture is actually formed by two different structural components, namely monomers, consisting of pure lipid molecules, and dimers, consisting of one molecule

\textsuperscript{10}It should be reminded that the difference between saturated and unsaturated fatty acids consists in the respective absence and presence of double bonds within the basic molecule; in unsaturated fatty acids, double bonds between carbon molecules can break up and generate new bonds with hydrogen atoms, whereas this cannot occur in saturated acids - hence the name. Saturation results generally in a higher molecular density, hence saturated acids appear - at common temperatures - as solids (es. butter or all the derived products of milk), in opposition with unsaturated ones which appear as liquids (es. olive’s oil).
of lipid and one of cholesterol. In such case, the volume fractions (or better, since we are dealing with a thin, planar bilayer, the area fractions) are calculated as follows; let be given a mixture of \( n_l \) and \( n_c \) molecules of lipid and cholesterol, which share the same area \( A \) (this further assumption follows from the lattice model adopted), where it results \( \chi_l = 1 - \chi_c \); letting \( n_m \) and \( n_d \) to be the number of monomers and dimers, it is evident that \( n_d = n_c \) and \( n_m = n_l - n_c \), thus it results that \( \chi_m = 1 - 2\chi_c \) and \( \chi_d = \chi_c \). Evidently, it further results that \( A_m = A \) and \( A_d = 2A \), so that the resulting area fractions can be calculated as follows:

\[
\begin{align*}
\Phi_m &= \frac{\chi_m A_m}{\chi_m A_m + \chi_d A_d} = 1 - 2\chi_c; \\
\Phi_d &= \frac{\chi_d A_d}{\chi_m A_m + \chi_d A_d} = 2\chi_c.
\end{align*}
\]

According to the Flory-Huggins theory of solutions, it is finally possible to express the molar Gibbs free energy of a binary lipid-cholesterol mixture as follows:

\[
G_{lc}^{\chi c} = RT[\chi_m \ln \Phi_m + \chi_d \ln \Phi_d] = RT[\chi_c \ln 2\chi_c + (1 - 2\chi_c) \ln(1 - 2\chi_c)].
\]

Worth noting, the assumption of absence of interactions between monomers and dimers has been done, according to the basic assumptions of Flory-Huggins theory.
2. Continuum thermodynamics of solution theory with deformation.

The aim of this section is to introduce, within the framework of classical three-dimensional continuum mechanics, the fields and basic laws of the Theory of Non Reacting Mixtures. We here follow the lines traced by Gurtin [19]-[20]-[23], Gurtin & Vargas [22] and Lowengrub & Truskinovsky [42].

2.1. Preliminary definitions & basic laws. We consider a mixture as a single body $B \subset \mathbb{R}^3$, constituted by $C+1$ constituents (or chemical species). Let $x : B \times \mathbb{R}^+ \rightarrow \mathbb{R}^3$ be a motion of $B$. Let $dv = dv(x)$ be a volume measure of a neighbor of $x$ and $dm_\alpha$ be the mass of the constituent $\alpha$ in such neighbor. The measure of the total mass is then

$$dm = \sum_{\alpha=1}^{C+1} dm_\alpha.$$  

We define the local mass density\(^{11}\) of the constituent $\alpha$ as the spatial field

$$\bar{\rho}_\alpha = \bar{\rho}_\alpha(x, t) := \lim_{dv \to 0} \frac{dm_\alpha}{dv}$$

which roughly speaking represents the mass of the constituent $\alpha$ per unit of current volume, and the local mass fraction of the constituent $\alpha$ as the spatial field

$$c_\alpha = c_\alpha(x, t) := \lim_{dv \to 0} \frac{dm_\alpha}{dm}.$$  

In addition it results

$$\sum_{\alpha=1}^{C+1} c_\alpha = 1, \quad \bar{\rho} = \lim_{dv \to 0} \frac{dm}{dv} = \sum_{\alpha=1}^{C+1} \bar{\rho}_\alpha, \quad \bar{\rho}_\alpha = \bar{\rho} c_\alpha,$$

where $\bar{\rho}$ represents the total mass density at $x$. Let $v_\alpha$ be the velocity of the constituent $\alpha$, and let the averaged velocity of the mixture be defined as

$$v := \frac{1}{\bar{\rho}} \sum_{\alpha=1}^{C+1} \bar{\rho}_\alpha v_\alpha.$$  

The following postulates are common in mixture theory:

**balance of total mass:** the total mass of a part $R \subseteq B$ remains constant during the motion $x$, that is

$$\frac{d}{d\tau} m(R) = \frac{d}{d\tau} \int_R \bar{\rho} dv = 0$$

where we called $r = x(R, \tau)$. Localization of this last relation yields

$$\dot{\bar{\rho}} + \bar{\rho} \text{div} v = 0.$$  

\(^{11}\)We denote with $\hat{\rho}$ the mass surface density, while later on (in Chapter 5) we will label with $\rho$ the local molecular surface density, namely the number of molecules per unit surface.
balance of mass for each constituent: the mass of each single constituent can be varied by a relative mass flux $j_\alpha$ across the boundary of the control volume $r = x(R, t)$, that is

$$
\frac{d}{d\tau} m_\alpha(R) = \frac{d}{d\tau} \int_r \tilde{\rho}_\alpha \, dv = - \int_{\partial r} j_\alpha \cdot n \, da.
$$

Localization of this integral relation, on the basis of the continuity of total mass, yields the local equation

$$
\tilde{\rho} \dot{c}_\alpha + \text{div} j_\alpha = 0.
$$

It should be remarked that in absence of chemical reactions (which is the case of this thesis) there are no further terms accounting for the mass supply due to chemical reactions.

The **First Principle of Thermodynamics**, in presence of mechanical, thermal and compositional effects, asserts that

$$
\frac{d}{dt} E(R) = \frac{d}{dt} \int_r \tilde{\rho} \, e \, dv = P_m(R) + P_d(R) + P_T(R), \quad \forall R \subseteq B
$$

where the state function $e = e(x, t)$ represent the internal energy density, where $P_m$ and $P_T$ respectively represent the classical mechanical and thermal powers provided to the part $R$ during the motion $x$, and where $P_d$ represents the diffusional power, that is the energy inflow [in $r$] due to mass transport (see Efendiev & Miranville [14]). The expression of thermal power is not troublesome for the aims of this thesis, whereas the expressions of both mechanical and diffusional powers actually depend on the constitutive assumptions made on the internal energy density $e$. As done by Gurtin & Fried [26]-[24], Lowengrub & Truskinovsky [42], Efendiev & Miranville [14], let us consider a non-local constitutive equation of Cahn-Hilliard or Ginzburg-Landau type

$$
e = e(c, \text{grad} c),
$$

where for the sake of simplicity we here consider a binary mixture described by one of the two mass concentration fields (the other is uniquely determined by the relation $c_1 + c_2 = 1$) and being ”grad” the spatial gradient. Such constitutive assumption justifies the following expressions of the mechanical and diffusional powers

$$
P_m = \int_{\partial r} (t_c \cdot n) \, \dot{c} \, da, \quad P_d = - \int_{\partial r} \mu \, j \cdot n \, da
$$

where $\mu$ represents the chemical potential, hence being $\mu \, j \cdot n$ the net energy inflow per unit time and area carried by the mass transport, and where the vector $t_c$ represents the reactive extra-stress\(^{12}\) associated with the presence of concentration gradients (the so called ”Ericksen’ Stress”); the vector $t_c$ can be interpreted as a generalized surface force associated with the variation of concentration on the boundary.

\(^{12}\)See Truskinovsky & Lowengrub [42] and Gurtin[23].
The introduction of a *micro-stress* \( t_c \) reflects the need to introduce a system of forces acting on a lower level with respect to *standard forces*: whereas standard forces are associated with macroscopic length scales, the so-called *micro-forces* are associated with microscopic configurations of atoms.

The **Second Principle of Thermodynamics**, in the case of isothermal evolutions and in absence of internal sources of heat (which represents the case studied in this thesis), asserts that

\[
\frac{d}{dt} S(R) = \frac{d}{dt} \int_R \dot{\rho} \eta \, dv \geq \frac{P_T(R)}{T}, \quad \forall R \subseteq B
\]

where the state function \( \eta = \eta(x, t) \) represents the **internal entropy density**, where \( T \) represents the absolute temperature and the ratio \( P_T/T \) represents the *entropy flux induced by heating*.

Defining the **Helmholtz free energy density** as

\[
\psi = e - T \eta
\]

and combining the first and second principle we obtain the **Clausius-Duhem inequality** (or "free energy inequality") for isothermal processes

\[
\frac{d}{d\tau} \int_R \dot{\rho} \psi \, dv \leq P_m(R) + P_d(R), \quad \forall R \subseteq B.
\]

which, on the basis of continuity of the total mass, can be written as

\[
\int_R \dot{\rho} \dot{\psi} \, dv \leq P_m(R) + P_d(R), \quad \forall R \subseteq B.
\]

In order to deduce a fully general form of the indefinite equilibrium equations for a fluid mixture, let us consider the following constitutive assumption for the Helmholtz free energy

\[
\psi = \hat{\psi}(c, \text{grad} c, \hat{J})
\]

with \( \hat{J} \) the spatial description of \( J = \text{det(grad}x) \). Let furthermore the expressions of mechanical and diffusional power be the following

\[
\mathcal{P}_m + \mathcal{P}_d = \int_R b \cdot v \, dv + \int_{\partial R} [Tn \cdot v - \mu j \cdot n + (t_c \cdot n)c] \, da,
\]

with \( T \) the Cauchy stress tensor, such that local stress reads as

\[
t_m(n) = Tn.
\]

Considering that

\[
\text{grad} \dot{c} = \text{grad} c - (\text{grad} v)^T (\text{grad} c), \quad (\hat{J}) = \hat{J}(\text{div} v) = \hat{J} \cdot \text{grad} v,
\]
with \( \mathbf{v} \) the spatial description of the velocity \( \mathbf{x} \), we can develop the term \( \hat{\psi} \) as follows

\[
\frac{d\hat{\psi}}{dt} = \frac{d\hat{\psi}}{dc}\dot{c} + \frac{d\hat{\psi}}{d(\text{grad} \, c)} \cdot \text{grad} \, c + \frac{d\hat{\psi}}{dB}(J) = 
\]

\[
= \psi_1 \dot{c} + \psi_2 \cdot \text{grad} \, \dot{c} + (\text{grad} \, v) \cdot \left[ \psi_3 \dot{J} \mathbf{I} - (\text{grad} \, c) \otimes \psi_2 \right]
\]

where we have set for simplicity

\[
\psi_1 := \frac{d\hat{\psi}}{dc}, \quad \psi_2 := \frac{d\hat{\psi}}{d(\text{grad} \, c)}, \quad \psi_3 := \frac{d\hat{\psi}}{dB}.
\]

Using the Gauss-Green theorem, the mass continuity for each constituent, and localizing the isothermal Clausius-Duhem inequality we get finally the following set of equations:

- **Factors of \( \dot{c} \) on the boundary**: (constitutive equation for the extra-stress)
  \( t_c = \tilde{\rho} \psi_2 \);

- **Factors of grad \( v \) in the bulk**: (constitutive equation for the Cauchy stress)
  \( T = \tilde{\rho} \dot{J} \psi_3 \mathbf{I} - (\text{grad} \, c) \otimes t_c \);

- **Factors of \( v \) in the bulk**: (indefinite equilibrium to translation)
  \( \text{div} T + b = \mathbf{0} \);

- **Factors of \( \dot{c} \) in the bulk**: (constitutive relation for the chemical potential)
  \( \mu = \psi_1 - \frac{1}{\tilde{\rho}} \text{div} t_c \);

Furthermore, we get the following relation between the chemical potential and the mass flux

\( \dot{j} \cdot (\text{grad} \, \mu) \leq 0 \)

which can be interpreted saying that mass flux always occurs in directions where the chemical potential is decreasing.
2. CONTINUUM THERMODYNAMICS OF SOLUTION THEORY WITH DEFORMATION.

2.2. The variational problem for a non-reacting mixture. The problem of finding the equilibrium configurations of an isolated mixture $\mathcal{B}$ of chemically non-reacting constituents can be set following the pioneering ideas of Gibbs [17] on the equilibrium of heterogeneous substances. In more recent times, Larché & Cahn [37], used the approach suggested by Gibbs in order to combine compositional effects with deformation within the context of metal sciences; in particular, the main idea is to investigate the equilibrium configurations of a mixture in contact with a heat bath at constant temperature $T^*$ by imposing the vanishing of the first variation of the so-called ballistic free energy (see Ericksen [15])

$$\Psi = E - T^*S$$

for all perturbations which leave unaltered the total mass of each constituent in the mixture.

In other words, this principle corresponds to impose the vanishing of the potential energy for all perturbations which leave unaltered the total entropy and the total mass of each constituent; for a two component mixture $\mathcal{B}$ in its current configuration $\mathcal{P} = f(\mathcal{B})$ this can be done by solving the following variational problem

$$\delta \left\{ E - \mathcal{L} \right\} = \delta \left[ \int_\mathcal{P} \tilde{\rho} e \, dv - \mathcal{L} \right] = 0$$

for all perturbations which satisfy the following global constraints

$$S = \int_\mathcal{P} \tilde{\rho} \eta \, dv = \bar{S}, \quad M = \int_\mathcal{P} \tilde{\rho} c \, dv = \bar{M}.$$  

We called $\mathcal{L}$ the work done on the body $\mathcal{B}$ by the system of external forces. This constrained variational problem can actually be solved using Lagrange multipliers in order to introduce the global constraints on mass and entropy in the variational integral to be vanished, hence getting rid of the constraints on the perturbations.

Introducing the two multipliers

$$\{\theta; \lambda\}$$

the variational problem can be recast as follows

$$\delta \{ E - \theta [S - \bar{S}] - \lambda [M - \bar{M}] - \mathcal{L} \} = 0.$$  

Expanding this last relation, we obtain that

$$\{ \delta E - \theta \delta S - \lambda \delta M - \delta \mathcal{L} \} - \delta \theta [S - \bar{S}] - \delta \lambda [M - \bar{M}] = 0;$$

since the Lagrange multipliers can be varied independently of each other, the factors of the perturbed multipliers $\{\delta \theta; \delta \lambda\}$ give back the global constraints on total constituents mass and on total entropy, whereas the vanishing of the remaining variational integral can be written as

$$\delta E - \theta \delta S - \lambda \delta M - \delta \mathcal{L} = 0.$$
It would be possible to show that the multipliers $\theta$ and $\lambda$ are respectively interpretable, at equilibrium, as the constant temperature of the heat bath and the chemical potential; in particular, regarding the identification between $T^*$ and $\theta$, it is enough to recall that the following expression relates the absolute temperature with internal energy and entropy (see Ericksen, [15])

$$\theta = \frac{\partial e}{\partial \eta}.$$ 

After assuming the same constitutive assumptions adopted in the previous section for $e$ and $\eta$ in terms of spatial fields

$$e = \hat{e}(c, \text{grad} c, \hat{J}, T), \quad \eta = \hat{\eta}(c, \text{grad} c, \hat{J}, T)$$

it is indeed easy to show that the vanishing of the first variation of the total internal energy with respect to perturbations which leave unaltered the total entropy and the mass of each constituent of the mixture yields, at equilibrium

$$\theta = \frac{\partial e}{\partial T} \frac{\partial \eta}{\partial T},$$

that is

$$\theta \equiv \frac{\partial e}{\partial \eta} \equiv T,$$

where the temperature is in our case constant and equal to $T^*$. Furthermore, it also results that at equilibrium

$$\text{const.} = \lambda = \frac{\partial (e - \theta \eta)}{\partial c} - \tilde{\rho} \text{div} \left[ \tilde{\rho} \frac{\partial (e - \theta \eta)}{\partial (\text{grad} c)} \right],$$

hence with $\theta$ equal to the absolute temperature the identification between the multiplier $\lambda$ and the chemical potential $\mu$ is complete. This allows to set the variational problem for a mixture of two non reacting constituents in a heat bath at constant temperature $T = T^*$ by searching the solutions of the equation

$$\delta[\Psi - \mathcal{L}] - \mu \delta M = 0$$

where

$$\Psi := \int_{\mathcal{P}} \tilde{\rho} \psi \, dv = \int_{\mathcal{P}} (e - T\eta) \, dv$$

being $\psi = e - T\eta$ the Helmholtz free energy density.
CHAPTER 4

State of the Art
1. State of the art.

In this section we illustrate, after a brief review on the pioneering works of the morphology of thin fluid films, some of the approaches proposed within the last 33 years to the argument of the elasticity and phase transitions in lipid membranes. The seminal work of W. Helfrich ([28], 1973) on the elasticity of lipid membranes on one side, and the new experimental tools of image resolution of very small aggregates on the other side, opened the way of the interesting and charming field of phase transitions in cell membranes to speculations of two generations of biologists, physicists and mathematicians. In would be literally impossible to produce a complete list of works on the topic of lipid bilayers. Nevertheless, the aim of this chapter is not merely to present a short list of the most relevant works, up to our scientific tastes and interests, but rather we mean to explain via a critical exposure of such approaches the reasons which motivated us in pursuing a new model to study problems regarding mechanical equilibrium in lipid bilayers, which we think can better capture and explain many of the interesting features experimentally observed in recent years (see Baumgart & others [7], 2003).

1.1. Pioneering works on the morphology of thin fluid films. The problem of determining the equilibrium configurations of fluid films can be traced back to the pioneering ideas of Lagrange, who proposed the problem of minimal surfaces of given boundary. This problem become later famous as the Plateau’s problem, who studied in the first half of 1800 the equilibrium configurations of a soap film attached to a metal ring, without external forces being applied, determining the minimum of the functional

$$F = \sigma \int_s da$$

where $\sigma$ represents the constant surface tension and $s$ the unknown surface shape. He obtained the condition of vanishing mean curvature at equilibrium, that is $H = 0$.

From 1805 and 1806 both Young and Laplace studied soap bubbles under a pressure difference $p$ by taking the minimum of the functional

$$F = \sigma \int_s da + p \int_v dv$$

being $v$ the enclosed volume by the closed surface $s$. Their result represents the famous Laplace’s formula

$$2H\sigma = p,$$

which relates osmotic pressure to mean curvature, which results constant at equilibrium. A remarkable result of the Global Differential Geometry quoted in section 2 further explains the reason for which soap bubbles have to be spheres, since any embedded surface in the space with constant mean curvature has to be a sphere.
In 1812 Poisson considered a shell characterized by an energy functional of the type

\[ \mathcal{F} = \int_s H^2 \, da, \]

whose Euler-Lagrange equation is

\[ \Delta H + 2H(H^2 - K) = 0. \]

Solutions of this differential equation are called Willmore surfaces, and their complete characterization is nowadays a still open problem for people interested in Differential Geometry.

1.2. The model proposed by Helfrich. The model proposed by Helfrich in his seminal work ([28], 1973) is based on several assumptions deriving on experimental observations. In substance, the lipid bilayer is considered as a 2D fluid, whose "...fluidity amounts to a vanishing shear modulus...", and whose lipid molecules deform conserving perpendicularly to the bilayer mid surface. Elasticity of lipid bilayers is seen by Helfrich as "...a special case of the well-established theory of thin elastic shells..." (the author refers to the work of Naghdi on the 'Theory of Plates and Shells') and the deduced curvature strain energy density admits the following expression

\[ w = \frac{k}{2} (c_1 + c_2 - c_o)^2 + \bar{k} c_1 c_2, \]

where \( c_1 \) and \( c_2 \) represent the local principal curvatures of the surface and \( c_1 + c_2 = 2H \) is the double of the mean curvature and \( c_1 c_2 = K \) is the Gaussian curvature, and \( k \) and \( \bar{k} \) are curvature elastic moduli. The term \( c_o \) represents the so called spontaneous curvature of the bilayer, which "...allows for bilayers whose two sides are chemically different".

For closed, smooth vesicles characterized by homogenous values of the bending rigidities, the Gaussian term of the Helfrich energy represents a null Lagrangian for the variational problem of the equilibrium (on the basis of the Gauss-Bonnet Theorem), hence the energy density reduces to

\[ w = \frac{k}{2} (c_1 + c_2 - c_o)^2. \]

1.3. The model proposed by Baesu & others. Within the framework of purely mechanical models which, as well as Helfrich model, ignore issues of phase transitions and any chemical peculiarity of lipid bilayers, it is worth mentioning the energy density deduced in the work by Baesu & others [5]. In substance, according to this model the lipid bilayer is conceived as a surface whose energy density admits the following general constitutive dependence

\[ w = \hat{w}(J, H, K). \]
being $J, H, K$ respectively the areal stretch of the current configuration of the membrane with respect to a certain reference configuration, the mean and Gaussian curvature of the current configurations. The idea of the authors in order to reach a more explicit expression of the energy density is that '...the variable $J$ is dimensionless whereas $H$ and $K$ have dimensions of reciprocal length and squared reciprocal length, respectively; thus there is an inherent local length scale...' and in particular 'the only such scale available is the thickness $t$ of the membrane, typically on the order of the length of the one or two polar molecules, in the case of monolayers or bilayers, respectively, which traverse the wall. This is not an explicit parameter in the theory but it is nevertheless needed to generate physically meaningful explicit forms of the response function.' At this point, an asymptotic expansion of the energy density with respect to the thickness of the bilayer, up to the first order, yields the following expression of the energy density

$$w = f(J) + a(J)H + b(J)H^2 + c(J)K$$

where the functions $f$, $a$, $b$ and $c$ are not specified at this stage: the Helfrich model can actually be recovered by this energy density, suitably tuning the values of such functions.

1.4. The model proposed by Jülicher & Lipowsky. These authors have been interested in several articles (see for example [32], [33]) to both problems of phase transitions in lipid bilayers and the question of their elasticity. Nevertheless, the question of why and how phase separation occurs in lipid membranes is not explicitly afforded, since the authors assume that the two component mixture of lipids which constitute the bilayer is already separated in two phases $\alpha$ and $\beta$. In particular, they consider as a control parameter of their problem the relative domain size

$$x := \frac{A^{(\beta)}}{A^{(\alpha)} + A^{(\beta)}}$$

being $A^{(i)}$ the area occupied by the phase $i$. The authors then make the strong assumption that '... shape changes of of the membrane do not affect the thermodynamics of the binary system...', which, as matter of fact, means that there is not a true coupling between chemical and mechanical behaviors of the membrane. This assumption allows to consider the domain sizes $A^{(i)}$ fixed as data of the problem.

Within the assumption of homogeneous phases $\alpha$ and $\beta$, the elastic energy density that the authors assume for each phase is represented by the Helfrich energy

$$w^{(i)} = \frac{k^{(i)}}{2}(c_1 + c_2) - c_o^{(i)}c_1c_2$$

where $i = \alpha, \beta$; the two material phases mechanically differ for their bending moduli $k^{(i)}$, $k_G^{(i)}$ and the values of the spontaneous curvature $c_o^{(i)}$ (homogeneous throughout each phase). Restricting attention to regular closed surfaces, the functional minimized
in order to investigate the equilibrium configurations is then the following

$$\mathcal{F} = \int_{s(\alpha)} \left[ \frac{k_G^{(\alpha)}}{2} (c_1 + c_2 - c_o^{(\alpha)})^2 + k_G^{(\alpha)} c_1 c_2 \right] da +$$

$$+ \int_{s(\beta)} \left[ \frac{k_G^{(\beta)}}{2} (c_1 + c_2 - c_o^{(\beta)})^2 + k_G^{(\beta)} c_1 c_2 \right] da +$$

$$+ \int_{\gamma} \sigma d\ell + \Sigma^{(\alpha)} A^{(\alpha)} + \Sigma^{(\beta)} A^{(\beta)} + pV$$

where the integral on $\gamma = \partial s^{(\alpha)} \equiv \partial s^{(\beta)}$ represents the interfacial energy across the phase boundary and $\sigma$ represents the so called ”line tension”, where $\Sigma^{(i)}$ represent Lagrange multipliers ensuring the constraint of fixed domain sizes $A^{(i)}$.

The scalar $p$ is interpretable either as the pressure difference between the inside and outside of the membrane (hence being the term $pV$ the work done on the membrane), or as a Lagrange multiplier for the enclosed volume.

The minimization of such functional with given values of the domain sizes, line tension $\sigma$ and pressure difference or enclosed volume $V$ allows to determine the equilibrium shapes of budded domains, modulated varying the control parameter $x$.

Regarding the constraint on the enclosed volume, it should be remarked that the authors consider two possibilities:

1. the water is essentially free of molecules that cannot permeate the bilayer membrane. In this case, on long time scales water permeates the membrane reaching the condition $p = 0$; in such situation, the volume is freely adjustable and there is no volume constraint;

2. there are some molecules within the aqueous solution that cannot permeate the bilayer; in this case the resulting osmotic pressure leads to a constraint on the reduced volume

$$v = \frac{V}{\frac{4}{3} \pi R_o^3}$$

where $R_o$ is defined by the relation $A^{(\alpha)} + A^{(\beta)} = 4 \pi R_o^2$.

In both situations the authors reach interesting results on the possible equilibrium configurations and on the neck conditions at the phase interface for varying values of the domain ratio $x$.

As a remark, a recent theoretical work by Baumgart & others[8], confirms the crucial role of Gaussian curvature, and in particular of the difference in Gaussian modulus $k_G$ between coexisting phases, in order to explain budded equilibrium configurations, as predicted by the theory of Jülicher & Lipowsky.
1.5. The model proposed by Sackmann. Let us now consider a number of models which pay attention to the question of how chemical and mechanical features of lipid membranes actually cooperate in the definition of equilibrium configurations of lipid membranes.

The model proposed by Sackmann in the work \cite{53} is based on the Ginzburg-Landau theory of phase transitions in presence of more than one order parameter; within the work of Sackmann two order parameters accounting separately for material and geometrical characteristics of binary lipid membranes are introduced, namely the deformation of the bilayer mid-surface and the normalized difference $\phi = c_A - c_B$ between the concentrations of the chemical species $A$ and $B$. The coupling of phase separation and curvature is described by an extension of the Cahn-Hilliard mean field theory of spinoidal decomposition. The proposed energy density admits the following additive decomposition

$$w_{\text{tot}} = w_{\text{chem}} + w_{\text{bend}} + w_{\text{coupl}}.$$  

The purely chemical counterpart of the energy density admits a Landau type of chemical energy density

$$w_{\text{chem}} = \left[ \frac{1}{2} A(\sigma,T)\phi^2 + \frac{1}{2} B(\sigma,T)\phi^4 \right] + \left[ \frac{1}{2} C(\sigma,T)|\nabla\phi|^2 \right]$$

where terms in the first square brackets represent a double-well potential in the order parameter $\phi$ whose coefficients $A$ and $B$ depend on the surface tension and temperature, whereas the term in the second square bracket represents a gradient term which is necessary in order to '...introduce a scale factor describing the correlation length of the concentration fluctuations...' which basically is needed in order to penalize configurations in which the material phases are randomly dispersed within the domain.

The only elastic contribution considered by Sackmann is represented by the Helfrich mean curvature term

$$w_{\text{bend}} = \frac{1}{2} k(2H - c_o)^2$$

where as usual $H$ is the mean curvature and $k$ and $c_o$ are respectively the bending rigidity and the spontaneous curvature. Apparently, the model illustrated by Sackmann makes no difference between the bending rigidity and the spontaneous curvature of different phases.

The coupling between chemical and elastic characteristics of the lipid membrane is achieved introducing a first order coupling terms following the rules of the Landau theory, whose lowest order term is represents by

$$w_{\text{coupl}} = \frac{1}{2} \gamma H \phi,$$

being $\gamma$ a coupling constant. The author specifies that higher order coupling terms have been considered in other works (by Andelmann and Leibler).
As a comment to the considered energy functional, obtained integrating the density $w_{\text{tot}}$ on the unknown membrane surface, the author warns that the problem "...is even more complicated than the classical Cahn-Hilliard-Langer theory" which "...up to present has only been solved for the one dimensional case" - (the article is dated to 1995). The author concludes his presentation (pg.285) asserting that "...phase separation and shape transitions of vesicles is a most fascinating albeit complex problem. A more systematic study of these processes is certainly crucial in order to understand many essential cellular processes. However, it is certainly also of great scientific interest to explore the coupling of phase separation and shape and curvature ... fortunately better theories are gradually developed.'

1.6. The model proposed by Taniguchi. The model proposed by Taniguchi & others in two works we have considered here (see [34], [60]) is exactly the same used by Sackmann, seemingly originally developed by Andelmann & Leibler in a series of seminal works on this topic. It is interesting to notice that in studying dynamics of phase transitions in two component vesicles in the work [60], Taniguchi considers a lateral continuity condition for the mobility of the chemical species on the surface, which reads as

$$\frac{\partial \phi}{\partial t} + \text{div} j = 0$$

where $\phi$ is an order parameter for the relative mass concentration and $j$ represents the mass flux of one chemical species on the surface. The spontaneous curvature again arises, according to Taniguchi, from asymmetries in the composition between the two halves of the bilayer. The result obtained by Taniguchi via numerical solution of the dynamical problem yields suggestive configurations of the membrane at each instant of the evolution, which show surprising connections with the experimental observations of Baumgart [7].

![Figure 1. Configurations numerically determined by Taniguchi.](image)

1.7. The model proposed by Ayton & others. In a recent work by Ayton & others ([3],2005) the energy functional used by Taniguchi, with small variations, is proposed in order to study dynamics of phase and shape transitions in lipid membranes. In this work spontaneous curvature is not considered and the coupling between bending elasticity and chemical composition is achieved by considering a term

Figure 2. Equilibrium configurations numerically determined by Ayton & others for a binary mixture. The letters CH and GL stand for Cahn-Hilliard dynamics and Ginzburg-Landau dynamics. The a-dimensional order parameter $\Phi$ is a simple function of the local mass density and the mass densities of both constituents.

\[
w_{\text{coup}} \propto \phi H^2
\]

being the square of the mean curvature considered instead of the linear term considered by Sackmann and Taniguchi & others. A numerical tool called "Smooth Particle Applied Dynamics" (SPAM) is here used in order to solve the time dependent Landau-Ginzburg or Cahn-Hilliard free energy model for the composition dynamics. As well as Taniguchi’s results, the obtained equilibrium configurations are suggestive and again show a strong correlation with the experimental images determined by Baumgart [7].

1.8. The model proposed by Chen & others. Among the models which adopt a more or less heuristic procedure in achieving the coupling between chemical and mechanical characteristics of lipid membranes, it is worth noting the work of Chen & others [9], where the following energy density is considered

\[
w_{\text{tot}} = w_{\text{bend}} + w_{\text{chem}} + w_{\text{coup}} = \\
= \left[ \frac{1}{2}k(2H - c_0)^2 + k_G K \right] + \left[ \frac{1}{2}t\phi^2 \right] + [\gamma \phi K],
\]

where the bending elastic energy is evidently the Helfrich energy, where the purely chemical energy is naively represented by a convex quadratic function and where the coupling between the order parameter and the deformation is achieved through the Gaussian curvature and not through the mean curvature, as done in the works cited above. The coupling constant $\gamma$ is expressed by the authors as

\[
\gamma = k_G' - k_G
\]
where $k'_G$ is the Gaussian rigidity of the minor lipid component.

The heuristic reason of such a novel coupling is that the authors of this article are interested at the theory of fission in two-component membranes, hence they argue that '...since fission involves topological change, the coupling of local lipid composition to Gaussian curvature is believed to be important for a fission transition ... we show that this coupling can destabilize the narrow neck, which is stable in one-component lipid vesicles and show that such a coupling can reduce the Gaussian rigidity, which in turn can enhance fission if the minor component lipids prefer to stay at regions with large positive Gaussian curvature. On the other hand, Gaussian rigidity is enhanced if the minor component lipids prefer to stay at regions with large negative Gaussian curvature.'

**Figure 3.** Configurations whose energy has been compared by Chen & others.

The variational problem is afforded considering the following energy functional

$$F = \int_s w \, da + \sigma A(s) - pV(s) + \mu \int_s \phi \, da$$

where the scalars $\sigma, p, \mu$ represent Lagrange multipliers for the constraint of given total surface area $A(s)$, total enclosed volume $V(s)$ and given composition. As matter of fact the variational problem is not solved, rather the authors claim that '... to investigate the feasibility of a fission transition, we compare the free energy of the two-vesicle state to that of the budded state in which two buds are connected by a narrow neck', as schematically depicted in the figure here reported.

The authors conclude that 'our prediction is consistent with the experimental results ... in which fission was not observed by thermally creating excess surface area. Furthermore, our theory shows that fission can be induced by applying osmotic pressure or increasing the percentage of minor component lipids.'

**1.9. The model proposed by Sens & Safran.** Let us conclude this list of models inspired by the Landau theory of phase transitions - based on a polynomial expansion of the energy with respect to a list of order parameters - with the work of Sens & Safran [54], which introduces a further novelty for the coupling term between the order parameter and the deformation.
In substance, the authors consider a two-dimensional symmetrical bilayer, and focus only on the deformation of one monolayer, assuming that the same deformation occurs symmetrically with respect to the mid-surface in both monolayers. The deformation energy per unit length can be written in the general form (see posted figure for notations)

\[ w = \left[ \frac{1}{2} \kappa \left( c_o(\phi)^2 + u''^2 \right) + \frac{1}{2} k(u - u_\infty)^2 \right] - [\kappa c_o(\phi) u''] \]

where \( u \) is the deviation of the membrane surface from the flat state, \( k \) and \( \kappa \) are the stretching and bending moduli of one monolayer per unit length, and \( c_o(\phi) \) is the spontaneous curvature of the monolayer. Within this uni-dimensional model, the terms in the first square brackets represent the purely elastic energy density, actually constituted of the sum of a bending energy - which accounts for a pre-curvature \( c_o \) of the monolayer which, in its reference configuration, is forced to be flat - and a stretching energy; the term in the second square brackets is the first order coupling term between the local curvature (measured by \( u'' \) for small deformations) and the local spontaneous curvature \( c_o(\phi) \), which depends on the local concentration.

The dependence of the spontaneous curvature is shown to admit the following expression (when it is assumed that interactions between the two components \( A \) and \( B \) of the mixture do not influence the spontaneous curvature)

\[ c_o(\psi + \bar{\phi}) = c_o(\bar{\phi}) + \psi(c_A - c_B) \]

where \( \bar{\phi} \) is the mean value of the order parameter on the membrane, \( \psi \) expresses fluctuations with respect to that value, and \( c_A \) and \( c_B \) are the spontaneous curvatures of pure species \( A \) and \( B \).

1.10. The model proposed by Komura & others. The model proposed by Komura & others ([35], 2004) represents a great element of novelty with respect to all the other models listed in this chapter, since it moves important steps toward a deeper understanding of how phase separation occurs in lipid/lipid or lipid/cholesterol mixtures on the basis of elementary information of their chemical behavior, and
how this phase separation can be influenced by the membranal deformations of the bilayer on the basis of a phenomenological point of view, rather than arbitrarily proceeding via less physically grounded couplings between order parameters and mean or Gaussian curvatures. This model will be more deeply exposed in the following chapter, thus we here just give a taste of its main ideas.

The authors of this article consider that ‘...it is now believed that model membranes containing two phospholipids (saturated and unsaturated) and cholesterol exhibit "rafts" which are liquid-ordered (L_o) domains, coexisting with a surrounding background in a liquid-disordered (L_d) state.’ The authors then separately consider the cases of binary mixtures of saturated lipid and unsaturated lipid (ℓℓ) and of binary mixtures of lipid and cholesterol (ℓc).

Relatively to (ℓℓ) mixtures, the authors consider the following additive decomposition of the energy density

\[ w_{ℓℓ} = w_{ℓℓ}^{chem} + w_{ℓℓ}^{elast} \]

where the purely chemical counterpart of the energy density represents the mixing and binary interactions energy, which can be written within the Bragg-Williams mean field theory (see Chapter 3) as

\[ w_{ℓℓ}^{chem} = kT \left[ \chi \ln \chi + (1 - \chi) \ln (1 - \chi) \right] - \frac{1}{2} J \chi^2 \]

where \( \chi \) here represents the mole fraction of the saturated lipid and \( (1 - \chi) \) the mole fraction of the unsaturated lipid, and \( J > 0 \) is an ‘attractive interaction parameter that enhances demixing’. Regarding the elastic counterpart of the energy density, deformation effects enter the theory in order to describe the chain order/disorder transition of the hydrocarbon tails; a rescaled membrane thickness

\[ \phi = \frac{δ - δ_d}{δ_d} \]

is introduced as order parameter, where \( δ \) is the actual membrane thickness and \( δ_d \) the membrane thickness in the disordered liquid phase \( L_d \). The authors then consider a phenomenological Landau expansion of the ‘transversal stretching’ free energy in powers of the order parameter \( \phi \)

\[ w_{elast}(φ, T) = \frac{a_2}{2}(T - T^*)φ^2 - \frac{a_3}{3}φ^3 + \frac{a_4}{4}φ^4. \]

where the coefficients \( a_i \) are experimentally determined, being \( T \) the current temperature and \( T^* \) a reference temperature which depends on the material. A careful study of this expression, carried on in Chapter 5 - Appendix A, shows that the difference \( (T - T^*) \) deeply influences the behavior of the energy density \( w_{elast} \): whether \( T \) is greater or less than the transition temperature

\[ T_g = T^* + \frac{2a_2^2}{9a_2a_4}. \]
the global minimum of the function \( w_{\text{elast}} \) with respect to the order parameter \( \phi \) falls on the disordered or on the ordered phase (characterized by different values of \( \phi \)). Since pure saturated and pure unsaturated lipids have different transition temperatures\(^1\), it is evident that for a binary mixture the transition temperature has to be a function of the local composition \( \chi \). For convenience, the authors then assume the following linear interpolation between the two pure limits

\[
T^*(\chi) = \chi T^*_s + (1 - \chi) T^*_u.
\]

This assumption achieves, as matter of fact, the desired coupling between purely mechanical and purely chemical aspects of the model: the resulting elastic energy indeed reads as

\[
w_{\text{elast}}(\chi, \phi, T) = \frac{a_2}{2} [T - T^*(\chi)] \phi^2 - \frac{a_3}{3} \phi^3 + \frac{a_4}{4} \phi^4,
\]

where the function \( T^*(\chi) \) linearly depends on \( \chi \). This finally leads to a coupling term between the two order parameters \( \chi \) and \( \phi \) of the kind

\[
w_{\text{coup}} \propto \chi \phi^2,
\]

which derives from a physically grounded reasoning, rather than being an heuristic unclear assumption to be confirmed a posteriori.

Further minimization of the integral of the obtained energy density with respect to the two order parameters \( \chi \) and \( \phi \) allows the authors to determine phase diagrams which agree with the experimental data.

The case of (\( \ell c \)) mixtures is then afforded by the authors. They assume for the energy density of a binary lipid/cholesterol mixture the following additive decomposition

\[
w^{\ell c} = w_{\text{chem}}^{\ell c} + w_{\text{elast}}^{\ell c} + w_{\text{coup}}^{\ell c}.
\]

Since each cholesterol molecule in the membrane dimerizes with a single lipid molecule, the purely chemical counterpart of the energy can be expressed by the Flory-Huggins (see Chapter 3 for details) theory and reads as

\[
w_{\text{chem}}^{\ell c}(\chi_c; T) = kT [\chi_c \ln \chi_c + (1 - 2\chi_c) \ln(1 - 2\chi_c)],
\]

where \( \chi_c \) represents the mole fraction of cholesterol in the mixture. The elastic counterpart of the energy density is still represented by a Landau expansion in terms of the structural order parameter \( \phi \), which maintains the same meaning introduced for lipid/lipid mixtures

\[
w_{\text{elast}}^{\ell c}(\phi, T) = \frac{a_2}{2} [T - T^*_\ell] \phi^2 - \frac{a_3}{3} \phi^3 + \frac{a_4}{4} \phi^4.
\]

Nevertheless, differently than in lipid/lipid mixtures, the transition temperature here is assumed to equal the transition temperature of the pure lipid system, hence \( T^* \equiv T^*_\ell \). The coupling between the two different order parameters is here achieved by the experimental observation that ‘...on one hand, a small amount of cholesterol

\(^1\)hence different reference temperatures \( T^*_s \) and \( T^*_u \); in particular, \( T^*_s > T^*_u \) because unsaturated lipids break up the crystallization tendencies.
destabilizes the gel phase in favor of a liquid-disordered $L_d$ phase. Substantial cholesterol, on the other hand, stabilizes a liquid ordered $L_o$ phase in which the lipid hydrocarbon tails are extended, but maintain lateral mobility. This behavior is achieved by the authors introducing the following coupling energy
\[ w_{\text{coul}}^{\ell c}(\chi_c, \phi) = \Gamma_1 \chi_c \phi - \Gamma_2 \chi_c^2 \phi, \]
where $\Gamma_1 > 0$ and $\Gamma_2 > 0$ are coupling constants. In the words of the authors, the first term '...expresses the fact that a small amount of cholesterol acts as an impurity ... it interferes with the crystalline ordering, and enhances disordered chains (smaller $\phi$)'. The second term '...corresponds to the 'chain rigidifying' effect reflecting the fact that a larger amount of cholesterol favors ordered tail states and hence larger $\phi$'.

Once again the coupling term is grounded on a physical basis, and minimization of the energy functional with suitable constraints yields again phase diagrams which agree with experimental data.
2. Critical comparison among the discussed models.

All models listed in this chapter, with no exception, are affected by serious limitations. Purely mechanical models, such as Helfrich’s and all works in which Helfrich’s energy is considered as only energy density, completely neglect the phenomena of phase separation and how this is coupled to the mechanics of the problem. The approach followed by Jülicher & Lipowsky moves steps forward with respect to Helfrich’s, introducing in the model regions occupied by different material phases, but does not explain how this phase separation occurs; furthermore, it is assumed that once material phase separation occurs the phase domains are ”frozen” and thus there is not a real coupling between chemistry and mechanics. Heuristic models in which a more or less clear physical intuition suggests particular couplings between order parameters and curvatures often give surprising results (Taniguchi, Ayton & others, Chen & others, Sens & Safran and many others which have not been quoted in this chapter) but seem obscure and perfectible, lacking of rigorous motivations for their assumptions. Finally, the model proposed by Komura & others in 2004 really gives an insight to the chemical grounds which motivate phase separation in lipid/lipid and lipid/cholesterol mixtures on the basis of basic material data, via the celebrated theories of Bragg-Williams and Flory-Huggins, and introducing a phenomenologically clear method in order to achieve a coupling between purely chemical factors and purely geometrical factors; nevertheless, the crucial aspect of the curvature elasticity of lipid membranes is completely neglected.

Furthermore, all quoted articles (with the exception of the works by Sens & Safran and Komura & others) consider the membrane as an intrinsically 2-dimensional body, whereas it is in reality a 3-dimensional thin body; even though the articles by Sens & Safran and Komura & others consider the membrane as a 3-dimensional body, they just consider 1-dimensional transversal or planar deformations.

The main motivation of this thesis work lays exactly on the gaps now shed in evidence, as it will be illustrated in the next chapter.
CHAPTER 5

The Proposed Model
1. Phenomenological derivation of a free energy for binary mixtures.

1.1. Introduction and notations. In this section we consider a binary mixture of lipid molecules in aqueous solution, and following the lines traced in Chapter 3 and Chapter 4 regarding the classical solution theory, the Bragg-Williams and Flory-Huggins theories of solutions, we will provide a phenomenological derivation of the Helmholtz free energy which accounts for chemical and mechanical effects.

In the first section of this chapter, the aggregate of saturated and unsaturated lipid molecules in aqueous solution is assumed as an intrinsically 2-dimensional body, in particular an open surface, whose current configuration $S$ can be described via the map

$$p : \Sigma \subset \mathbb{R}^2 \mapsto \mathbb{R}^3, \quad S := p(\Sigma) = \{x \in \mathbb{R}^3 | x = p(\zeta), \forall (\zeta_1, \zeta_2) \in \Sigma\}$$

hence we will assume that the reference configuration of the aggregate consists of a flat surface. The knowledge of the map $p$ allows for calculating the values of the areal stretch $J$ and of the mean and Gaussian curvatures $(H, K)$ at each point $x$ of the current surface; these measures play a crucial role in the definition of the constitutive response of the aggregate. The material nature of the aggregate at each point of the current configuration of the surface $\Sigma$ can be described in terms of the spatial molecular fractions$^1$, which might be defined as

$$\hat{\chi}_i := \hat{\chi}_i(x) = \frac{dN_i(x)}{dN(x)}$$

where $dN_i(x)$ and $dN(x)$ respectively represent measures$^2$ of the number of molecules of the species and the measure of the total number of molecules in a neighbor of the point $x$ of the current configuration. For the sake of generality, here the index $i$ ranges from 1 to $C$, where $C$ the number of different species present in the aggregate. Let us further denote with

$$\chi_i := \hat{\chi}_i \circ p$$

the material description of the molecular fraction field. The spatial description of the molecular density$^3$ of the species $i$ is defined as

$$\hat{\rho}_i := \hat{\rho}_i(x) = \frac{dN_i(x)}{da(x)}$$

---

$^1$The field $\chi$ is then the Radon-Nikodym derivative of the measure of the number of moles of the $i$th species with respect to the measure of the number of total moles.

$^2$The measures $N_i$ and $N$ are assumed to be absolutely continuous with respect to the area-Lebesgue measure.

$^3$We remind that in Section III.2.1 we labelled with $\hat{\rho}$ the mass density per unit of current volume, not to be confused with the molecular densities $\hat{\rho}$ and $\rho$ per unit of current and reference area, respectively.
and it represents the local number of molecules per unit of current area\(^4\); furthermore, the local total molecular concentration is simply defined as
\[
\hat{\rho} := \hat{\rho}(x) = \frac{dN(x)}{da(x)} = \sum_{i=1}^{C} \hat{\rho}_i.
\]

The material descriptions of the spatial fields \(\hat{\rho}\) and \(\hat{\rho}_i\) are defined as
\[
\rho := \hat{\rho} \circ p, \quad \rho_i := \hat{\rho}_i \circ p.
\]

Let finally the molecular density of the reference configuration be defined as
\[
\rho_0 : \Sigma \rightarrow \mathbb{R}^+.
\]

The basic idea in order to provide a phenomenological construction of the Helmholtz energy is to consider, on the basis of the theory of non-reacting mixtures; here the "fundamental" unit is the given molecule and that the molecular energy density at a given point of the membrane consists of the sum of three main terms, each of which regards a broader neighbor of the considered molecule at that point:

1. **point-wise effects**: - they include the molecular formation and the ideal mixing energies; both quantities depend on the local value of the concentrations \(\{\chi_1, \ldots, \chi_{(C-1)}\}\) and completely neglect what happens around that given molecule;

2. **local or nearest-neighbor effects**: - these terms include corrections to the formation and ideal mixing energies deriving from some kinds of interactions with the neighboring particles; under a purely chemical point of view these interactions derive from different interaction potentials between alike and unlike molecules, or from the particular tendency of cholesterol molecules to dimerize with their neighbor lipid molecules. Under a geometrical point of view, locality implies that these dependence solely involves the displacements of neighboring particles, that is the first gradient of deformation \(F := \nabla \Sigma p\) at the given point: local elasticity can be ascribed to this kind of effects;

3. **non-local or medium-to-long-range effects**: - these terms actually introduce in the model the dependence of the Helmholtz energy of the mixture at a given point and at the length scale of the molecules on a broader neighbor of that point at that scale; in particular, under a purely geometrical point of view molecules at a given place 'feels' the displacements of slightly more far molecules.

The consistency of the obtained results with a procedure of 3D-2D dimension reduction will be proved; the still unspecified medium to long range interaction energy

\(^4\)Mathematically speaking, the Radon-Nikodym derivative of \(N_i\) with respect to the area-Lebesgue measure.
term which was introduced before will be recognized as an higher order energy term
deriving from an expansion of the energy density in powers of the membrane thick-
ness. In other words this will be a bending energy term. The results will be achieved
in Chapter 6. In particular, it will be shown that the bending energy density does
not need further constitutive assumptions on the bending stiffness of the lipid bilayer
(as done in a number of works cited in the previous chapter): indeed these informa-
tion are completely determined on the basis of constitutive hypothesis done at the
membranal level.

1.2. Formation and ideal mixing energies. As already pointed out in Section
1.6 - Chapter 3, the material description of the formation energy density per
mole unit of an aggregate of \( C \) components is expressible as follows

\[
\psi^0 = \sum_{i=1}^{C} \chi_i \mu_i^0
\]

where standard chemical potentials \( \mu_i^0 \) represent the formation energies per mole
unit of the pure \( i^{th} \) species. In our model, these quantities are to be considered the
only data of the problem, together with the number of different molecules and the
temperature.

According to Raoult theory of ideal solutions, the ideal energy of mixing per mole
unit can be derived on the basis of purely entropic effects, which means that all kinds
of interactions between particles have to be ignored. On the basis of the results of
Section 1.6 - Chapter 3, this counterpart of the molecular energy density can be
expressed as follows

\[
\psi_{\text{id mix}} = RT \sum_{i=1}^{C} \chi_i \ln \chi_i.
\]

The temperature \( T \) is considered as a constant all over the body: since the lipid
membranes we will consider are endowed with a much smaller heat capacity with
respect of the heat capacity of the surrounding heat bath, such temperature will be
set equal to the controlled temperature of the water solution.

As already pointed previously (see Section 1.6 - Chapter 3), the ideal molecular
energy density

\[
\psi^0 + \psi_{\text{mix}} = \sum_{i=1}^{C} \chi_i \mu_i^0 + RT \sum_{i=1}^{C} \chi_i \ln \chi_i
\]

represents a convex function in its independent arguments \( \{\chi_1, \ldots, \chi_{C-1}\} \), hence it does
not account for phase separation phenomena.

1.3. Nearest-neighbor energy (1): local chemical interactions. We will
separately consider the cases of lipid/lipid and lipid/cholesterol molecules.
Lipid/lipid mixtures. Within the context of binary mixtures of saturated and unsaturated lipid molecules, the correction to the ideal molecular energy density, namely the "excess" term
\[ \psi_{\text{mix}}^{(\text{ex})} \]
arises from the evidence that among alike and unlike molecules there exist different interaction potentials. As already discussed in Section 1.6 - Chapter 3 this term can be calculated on the basis of the Bragg-Williams Cell Theory (see Hill [29], pg.382), considering nearest-neighbor interactions, as follows
\[ \psi_{\text{mix}}^{(\text{ex})} = -cw \frac{\chi(1-\chi)}{2} \]
where \( \chi := \chi_u \) is the local concentration of the unsaturated lipid molecules (and evidently \( \chi_s + \chi_u = 1 \)) and the interaction parameter \( w = \hat{w}(J,T) \) is in our case a function of the temperature and of the local areal stretch
\[ J = \sqrt{\det[F^TF]} \]
where
\[ F := \nabla \Sigma p \]
represents the surface gradient of deformation. An explicit calculation of this excess contribution is possible by considering Lennard-Jones interaction potentials between the different molecules, analogously to what has been done within the context of the Bragg-Williams Lattice Theory in Section 1.7 - Chapter 3; more precise calculations are possible using experimental interaction potentials instead of the Lennard-Jones potentials, via the so called Corresponding States Theory (see Hill [29], pg.387). It should be remarked that for the sake of simplicity in the calculations, the function \( w = \hat{w}(J,T) \) is often set equal to a constant, which is suitably "tuned" in order to produce non-convexities of the final energy density with respect to the argument \( \chi \). This instance was also discussed in Section 1.7 - Chapter 3.

Lipid/cholesterol mixtures. As recognized by several authors in the bio-chemical literature (see Sackmann[53], Komura & others[35]) for solutions of lipid molecules and cholesterol the Flory-Huggins polymer solution theory applies, on the basis of the experimental evidence that each cholesterol molecule "dimerizes" with one lipid molecule. In this sense, each molecule "feels" its neighboring molecules and this effect can be ascribed to the class of nearest-neighbor effects. As already pointed out in Chapter 3 and in Chapter 4, on the basis of the a-thermal Flory-Huggins theory of solutions this effect is accounted for by substituting, in the expression of the ideal energy of mixing, molecular fractions with area fractions of the monomers and dimers formed in the solution, hence obtaining the following energy density
\[ \psi_{\text{mix}}^{(FH)} = RT[\chi_c \ln 2\chi_c + (1 - 2\chi_c) \ln(1 - 2\chi_c)] \]
with \( \chi_c \) the molecular fraction of cholesterol in the mixture. In this model we will further consider the phenomenological observation by Komura & others[35], which
is grounded on the experimental evidence that cholesterol has different roles depending on its concentration in a binary lipid/cholesterol mixture, with respect to its 'chain ordering effect'; since in our model the transition order-disorder is described by a local order parameter, consisting of the local areal stretch \( J \), this phenomenological evidence is evidently ascribable to nearest-neighbor effects. In particular, as already discussed in Section 4.1.10, we will adopt the following expression of the nearest-neighbor energy term for lipid/cholesterol mixtures

\[
\psi_{\text{cholest}}^{(nn)} = \frac{1}{J} [\Gamma_1 \chi_c - \Gamma_2 \chi_c^2],
\]

where \( \Gamma_1 > 0 \) and \( \Gamma_2 > 0 \) are coupling constants. This expression can be explained considering that at small values of \( \chi_c \), an increase of cholesterol acts as an impurity hence it enhances disorder (hence, letting the energy constant, \( \chi \rightarrow \) implies that \( J \rightarrow \) thus disorder is favored), whereas for higher values of \( \chi_c \) an increase of cholesterol implies a 'chain rigidifying' effect, hence order is favored (hence, letting the energy constant, \( \chi \rightarrow \) implies that \( J \rightarrow \) thus order is favored).

### 1.4. Nearest-neighbor energy (2): local elasticity effects.

Nearest-neighbor interactions are taken into account also considering local interactions of a molecule with its neighbor under the elastic point of view. More precisely, within the classical context of local elasticity, we will assume the following constitutive dependence of the molecular nearest-neighbor energy density on the deformation

\[
\psi_{\text{elast}}^{(nn)} = \hat{\psi}_{\text{elast}}^{(nn)} (\chi_1, \ldots, \chi_{(C-1)}, \mathbf{F})
\]

where \( \mathbf{F} := \nabla \Sigma p \) actually defines a local description of the deformation. Higher order derivatives of the deformation \( p \) will be considered later on in order to introduce medium to long range interactions.

Accordingly to the viewpoint adopted by Komura & others [35] discussed in Section 4.1.10, we will focus our attention on the so called main transition in lipid membranes between a liquid-ordered \( L_o \) phase and a liquid-disordered \( L_d \) phase. As already discussed in the previous chapter, the cited authors adopt the rescaled thickness

\[
\phi := \frac{\delta - \delta_d}{\delta_d}
\]

as main geometrical order parameter of their theory, being \( \delta_d \) the membrane thickness in phase \( L_d \) and \( \delta \) the current membrane thickness. Within this framework, for \( \phi = 0 \) the membrane is in phase \( L_d \) and for \( \phi = \delta_o/\delta_d - 1 > 0 \) the membrane is in phase \( L_o \). The "stretching" elastic energy adopted by the cited authors consists of a double-well potential deriving from a Ginzburg-Landau expansion of the energy density with respect to the order parameter \( \phi \), whose wells respectively fall on the values \( \phi_d = 0 \) and \( \phi_o > 0 \) (see Section 4.1.10). See Appendix A for a detailed treatment of the Ginzburg-Landau expansion.
In the present treatment, which is intrinsically 2-dimensional, we prefer to use the areal stretch \( J \) defined above as order parameter, with respect to an arbitrary reference configuration, which we assume to be homogeneous and in the ordered \( L_o \) phase. In this configuration, the areal stretch \( J_o \) equals 1, and for \( J = J_d > 1 \) the membrane is in the disordered \( L_d \) phase. This viewpoint is experimentally justified by the fact that in a wide range of temperatures lipid bilayers can be considered as incompressible bodies, thus in the \( L_o \) phase the lipid molecules have long and straightened hydro-carbon tails, hence small head-group area, whereas in the \( L_d \) phase the hydro-carbon tails are short and curly, hence the head-group area is large. It will be shown in the next chapter that for very thin, incompressible bodies our viewpoint coincides exactly with that adopted by the cited authors.

For reasons which will be better explained in Appendix B, the stretching energy density per unit area adopted in our treatment admits the following expression

\[
\psi_{elast}^{(mn)}(\chi, J; T) := \tilde{\varphi}(J; J_t) = A \left[ \frac{1}{4} (J^4 - J_d^4) - \frac{1}{3} (J^3 - J_d^3)(J_o + J_d + J_t) \right] + A \left[ \frac{1}{2} (J^2 - J_d^2)(J_o J_d + (J_o + J_d) J_t) - (J - J_d) J_o J_d J_t \right],
\]

where:

- \( A > 0 \): is the amplitude of energy density;
- \( J_o, J_d \): respectively, the head-group areas of the the ordered and disordered phase, with \( J_d > J_o \);
- \( J_t \): is the value of \( J \) where the curve \( \tilde{\varphi}(J; J_t) \) attains its relative maximum in the interval \([J_o, J_d]\).

It is worth noting that this function is not consistent with a dimension reduction procedure. The elastic energy density is now "tuned" letting the value \( J_t \) to vary between \( J_o \) and \( J_d \), in such a way to reproduce the desired behavior of a continuous shift between the two situations in which \( J_o \) and \( J_d \) are respectively global minima, passing thought a transition temperature in which both the wells have the same height. This target is achieved choosing the following parametric dependence of \( J_t \) on \( T \) and \( \chi \):

\[
J_t = f(t) \quad \text{with} \quad t := T - T_{Tr}(\chi)
\]

where \( T_{Tr} \) represents the transition temperature which depends on the local concentration, and the function \( f(t) \) has the following properties:

- **i.** \( f(t) \) is strictly decreasing function in \( t \);
- **ii.** \( f(t) = \begin{cases} J_d & \text{for } t = t' < 0; \\ (J_o + J_d)/2 & \text{for } t = 0; \\ J_o & \text{for } t = t'' > 0. \end{cases} \)
where the values of $t'$ and $t''$, inferred by the Ginzburg-Landau expansion adopted by several biophysicists (see for example Goldstein & Leibler [18], Komura & others[35]) are respectively

$$t' = -2 \frac{a_2^2}{9a_2a_4}, \quad t'' = \frac{a_3^2}{36a_2a_4},$$

and where the constants $a_2$, $a_3$ and $a_4$ are experimentally measurable quantities. The elastic energy density will then be defined as follows

$$\psi^{(nm)}(\chi, J; T) = \tilde{\phi}(J; f(\chi, T)),$$

where the amplitude $A$ and the function $f(t)$ can be tuned in such a way to give the best agreement between the energy here proposed with the Ginzburg-Landau expansion adopted by the above mentioned authors. For the sake of simplicity we here omit the details of these calculations, reported in the Appendix B.

In lipid/lipid mixtures, the transition temperature $T_{Tr}$, which realizes the condition of same height of the elastic energy wells, is strongly influenced by the local composition. Indeed, transition temperatures of saturated and unsaturated lipids are different and the most simple choice for describing concentration dependence is to adopt a linear function of the $\chi$. According to the guideline traced by Komura & others, we propose the following linear law

$$T_{Tr}(\chi) = \chi T^*_r + (1 - \chi) T^*_u,$$

being $T^*_r$ and $T^*_u$ the transition temperatures of the pure saturated and unsaturated lipids respectively.

In lipid/cholesterol mixtures it is simply assumed that the transition temperature $T_{Tr}$ coincides with the transition temperature of the lipid molecule.
1.5. Medium to long range interaction energy. The assumption that the energy density at a point of the membrane 'feels' the presence of molecules in broader neighbors than those whose motion is well described by the first gradient of deformation, traduces in the introduction of the further energy term
\[ \psi_{elast}^{(nl)}(\chi_1, ..., \chi_{(C-1)}, F, \nabla\Sigma F) \]
where the index \((nl)\) stands for 'non-local'. Consistently with the procedure of dimension reduction which will be carried on in the next chapter, we assume that the non-local energy term admits the following expression\(^5\)
\[ \psi_{elast}^{(nl)} \equiv \hat{h}_0^2 \hat{\phi}^b(\chi, J, H, K) = \frac{1}{6} \left[ \kappa_1(\chi, J)H^2 + \kappa_2(\chi, J)K \right] + \alpha_o \frac{\left| \nabla S \hat{J} \right|_m^2}{2}, \]
where \(H\) and \(K\) are respectively the material descriptions of the mean and Gaussian curvatures of the current surface \(S\), where \(\left| \nabla S \hat{J} \right|_m\) represents the material description of the surface gradient of the spatial field \(\hat{J} = J \circ p^{-1}\), and where it will be shown that the functions \(\kappa_1, \kappa_2\) and \(\alpha_o\), rather than being postulated on the basis of heuristic assumptions, are completely defined on the basis of the purely membranal constitutive response of the bilayer.

1.6. Final form of the Helmholtz free energy density. In light of what has been shown in the previous sections, we assume the following expressions for the surface energy densities of lipid/lipid and lipid/cholesterol mixtures per unit of reference area:

**lipid-lipid mixtures:**
\[ \psi_{\ell\ell} = \varphi_{\ell\ell}^m + h_0^2 \varphi_{\ell\ell}^b \quad \text{with} \quad \varphi_{\ell\ell}^m = [\rho_0 \psi_0^0 + \rho_0 \psi_{mix}^{(id)} + \rho_0 \psi_{mix}^{(ex)} + \psi_{elast}^{(nm)}]_{\ell\ell} \]

**lipid/cholesterol mixtures:**
\[ \psi_{\ell c} = \varphi_{\ell c}^m + h_0^2 \varphi_{\ell c}^b \quad \text{with} \quad \varphi_{\ell c}^m = [\rho_0 \psi_0^0 + \rho_0 \psi_{mix}^{(FH)} + \rho_0 \psi_{cholest}^{(nm)} + \psi_{elast}^{(nm)}]_{\ell c} \]
where the energy density \(\varphi^m\) collects all purely membranal terms. The final form of the energy density shows that local effects and non-local effects do not act at the same energy level, since these last ones are weighted by the factor \(h_0^2\). Since the membrane thickness is very small, this means that the procedure of dimension reduction accomplishes a hierarchy between local effects, endowed of higher energy levels, and non-local effects.

\(^5\)We labelled \(\chi := \{\chi_1, ..., \chi_{(C-1)}\}\).
2. Appendix A - The Landau expansion of the elastic energy.

The elastic energy usually adopted by chemists and physicists to describe a first order phase transition with respect to a given order parameter \( \phi \) is the Landau expansion:

\[
\varphi(\phi, T) = \frac{a_2}{2} (T - T^*) \phi^2 - \frac{a_3}{3} \phi^3 + \frac{a_4}{4} \phi^4.
\]

Let us now study the solutions of the function \( \psi_{2\ell}(\chi, J) \) for varying values of the parameter \( \tau = (T - T^*) \), and with \( a_2 > 0, a_3 > 0 \) (notice, in the Landau expansion the sign of \( a_3 \) has been reversed) and \( a_4 > 0 \). The zeros of the first derivative of \( \varphi \) with respect to \( \phi \) are:

\[
\frac{\partial \varphi}{\partial \phi} = 0 \implies \begin{cases} 
\phi_1 = 0 \\
\phi_2 = a_3 + \sqrt{a_3^2 - 4a_4a_2 \tau} \\
\phi_3 = a_3 - \sqrt{a_3^2 - 4a_4a_2 \tau}
\end{cases}
\]

Necessary condition for \( \phi_{2/3} \) to be real is that:

\[
\tau = T - T^* \leq \frac{a_3^2}{4a_2a_4}.
\]

Furthermore, the values attained by the function \( \varphi \) in the zeros of the first derivative are:

\[
\varphi(\phi) = \begin{cases} 
\phi = \phi_1 : 0 \\
\phi = \phi_2 : \frac{1}{\sqrt{6}} \left( a_3 + \sqrt{a_3^2 - 4a_4a_2 \tau} \right)^2 \left( -a_3^2 - a_3 \sqrt{a_3^2 - 4a_4a_2 \tau} + 6a_4a_2 \tau \right) \\
\phi = \phi_3 : \frac{1}{\sqrt{6}} \left( a_3 - \sqrt{a_3^2 - 4a_4a_2 \tau} \right)^2 \left( -a_3^2 - a_3 \sqrt{a_3^2 - 4a_4a_2 \tau} + 6a_4a_2 \tau \right)
\end{cases}
\]

The values of the second derivative in the zeros of the first derivative are now:

\[
\frac{\partial^2 \varphi}{\partial \phi^2} = \begin{cases} 
\phi = \phi_1 : a_2 \tau \\
\phi = \phi_2 : \frac{(a_3^2 - 4a_4a_2 \tau) - a_3 \sqrt{a_3^2 - 4a_4a_2 \tau}}{2a_4} \\
\phi = \phi_3 : \frac{(a_3^2 - 4a_4a_2 \tau) + a_3 \sqrt{a_3^2 - 4a_4a_2 \tau}}{2a_4}
\end{cases}
\]

Several instances might occur at this point, for varying values of the parameter \( \tau \):

- \( \tau < 0 \): \( \phi_3 < \phi_1 < \phi_2 \) and \( \frac{\partial^2 \varphi}{\partial \phi^2}(\phi_3) > 0, \frac{\partial^2 \varphi}{\partial \phi^2}(\phi_1) < 0, \frac{\partial^2 \varphi}{\partial \phi^2}(\phi_2) > 0 \);
- \( \tau = 0 \): \( \phi_1 = \phi_3 < \phi_2 \) and \( \frac{\partial^2 \varphi}{\partial \phi^2}(\phi_3) = \frac{\partial^2 \varphi}{\partial \phi^2}(\phi_1) = 0, \frac{\partial^2 \varphi}{\partial \phi^2}(\phi_2) = a_3^2/a_4 > 0 \);
- \( 0 < \tau < a_3^2/4a_2a_4 \): \( \phi_1 < \phi_3 < \phi_2 \) and \( \frac{\partial^2 \varphi}{\partial \phi^2}(\phi_1) > 0, \frac{\partial^2 \varphi}{\partial \phi^2}(\phi_3) < 0, \frac{\partial^2 \varphi}{\partial \phi^2}(\phi_2) > 0 \);
- \( \tau = 2a_3^2/9a_2a_4 \): \( \phi_2 = 2a_3/3a_4 \) and \( \varphi(\phi_2) = 0 \);
- \( \tau = a_3^2/4a_2a_4 \): \( \phi_1 < \phi_3 = \phi_2 = a_3/a_4 \) and \( \frac{\partial^2 \varphi}{\partial \phi^2}(\phi_1) > 0, \frac{\partial^2 \varphi}{\partial \phi^2}(\phi_3) = \frac{\partial^2 \varphi}{\partial \phi^2}(\phi_2) = 0 \);
- \( \tau > a_3^2/4a_2a_4 \): \( \phi_1 = 1, (\phi_2, \phi_3) \) complex roots, and \( \frac{\partial^2 \varphi}{\partial \phi^2}(\phi_1) > 0 \).
The situation is schematically depicted in the following figure, where it is evident the situation corresponding to the reference temperature, \( T = T^* \) (fig.1-b), and to the first order transition temperature, \( T = T_{tr} = T^* + \frac{2a_2^2}{9a_2a_4} \) (fig.1-d). Some

![Figure 2](image_url)

**Figure 2.** Evolutions of the Landau expansion \( \varphi(\cdot, \phi; \tau) = a_2^2 \tau \varphi^2 - \frac{a_3^2}{3} \varphi^3 + \frac{a_4^2}{4} \varphi^4 \) for varying values of the temperature parameter \( \tau \). It results that for every value of \( \tau \), \( \phi_1 = 0 \), whereas both \( \phi_2 \) and \( \phi_3 \) depend on \( \tau \).

Important values given by the Landau’s expansion are the following ones:

- \( \tau = 0 \) (fig. b): \( \phi_2 = \frac{a_3^2}{a_4^2} \) and \( \varphi(\phi_2) = -\frac{1}{12} \frac{a_4^4}{a_3^4} \)
- \( \tau = \frac{2}{9} \frac{a_3^2}{a_2a_4} \) (fig. d): \( \phi_2 = \frac{2}{3} \frac{a_3}{a_4} \), \( \phi_3 = \frac{1}{3} \frac{a_3}{a_4} \) and \( \varphi(\phi_3) = \frac{1}{324} \frac{a_4^4}{a_3^4} \)
- \( \tau = \frac{1}{4} \frac{a_3^2}{a_2a_4} \) (fig. f): \( \phi_2 = \phi_3 = \frac{1}{2} \frac{a_3}{a_4} \) and \( \varphi(\phi_2) = \varphi(\phi_3) = \frac{1}{192} \frac{a_4^4}{a_3^4} \)

The viewpoint of Komura, Shirotori, Olmsted & Andelmann is to adopt the Landau expansion to model the first order phase transition in the binary lipid mixture. For a (lc) mixture, it is assumed that the reference temperature equals the one on the lipid, whereas in a (ll) mixture they assume the following reference temperature:

\[ T^*(\chi) = \chi T^*_s + (1 - \chi) T^*_u, \]

being \( T^*_s \) and \( T^*_u \) the reference temperatures of the pure saturated and unsaturated lipids respectively, and \( \chi = \chi_s \). As shown previously, the transition temperature is related to the reference temperature through the relation:

\[ T_{tr} = T^* + \frac{2a_2^2}{9a_2a_4} \]

where the coefficients \( a_i \) refer to the Landau’s expansion.
3. Appendix B - The elastic energy density \( \varphi(\chi, J; T) \).

3.1. Motivations of the choice. The Landau energy density foresees that for varying values of temperature there is a continuous shift between the two energy wells, attained at different values of the order parameter \( \phi_1 = 0 \) and \( \phi_2 > 0 \); of these values, \( \phi_1 \) does not depend on temperature, while \( \phi_2 \) depends on temperature, passing from the value \( \phi_2 = a_3/a_4 \), attained for \( \tau = 0 \) to \( \phi_2 = a_3/2a_4 \), attained for \( \tau = a_3^2/4a_2a_4 \), which means that it becomes the half of the first value.

Somehow, we believe that temperature should consistently influence either both of the values of the relative minimizers \( \phi_1 \) and \( \phi_2 \), or neither of them. For this reason, it is assumed that the two values \( J_o = 1 \) and \( J_d \) are "frozen" and do not depend on temperature, whose only effect is to shift the height of the energy wells attained in correspondence of \( J_o \) and \( J_d \).

3.2. Tuning \( A \) and \( f(\chi; t) \). The elastic energy density proposed in par 2.1 has the following form:

\[
\varphi(\chi, J; T) = A \left[ \frac{1}{4} (J^4 - J_d^4) - \frac{1}{3} (J^3 - J_d^3)(J_o + J_d + f(\chi; T)) \right] + \\
+ A \left[ \frac{1}{2} (J^2 - J_d^2)(J_oJ_d + (J_o + J_d) f(\chi; T)) - (J - J_d)J_oJ_d f(\chi; T) \right].
\]

In order to tune the amplitude constant \( A \) and the function \( f(\chi; T) \) we make the following assumptions:

**amplitude A:** we assume that the depth of the well of \( \varphi \) when evaluated in correspondence to the limit case \( t = t' = -\frac{2}{9a_2a_4} \) equals the depth of the Landau expansion proposed by the physicists in limit situation \( \tau = 0 \), depicted in fig.5-b, that is:

\[
\tilde{\varphi}(J_o; J_d)|_{J_t=J_d} = -\frac{A}{12} (J_d - J_o)^4 \quad \text{has to be equal to} \quad \varphi_{\text{Landau}}(\phi_2; T^*) = -\frac{1}{12} \frac{a_3^4}{a_4^3},
\]

which allows the following identification of the constant \( A \) with the experimentally evaluated constants:

\[
A = \frac{1}{(J_d - J_o)^4} \frac{a_3^4}{a_4^4}.
\]

**function** \( f(t) = f(\chi; T) \): we assume that the function \( f(\chi; T) \) is the simplest possible satisfying the aforementioned requisites:

\[
i.: \quad f(t) \text{ is strictly decreasing function in } t; \\
\quad f(t) = \begin{cases} 
J_d & \text{for } t = t' < 0; \\
J_m = (J_o + J_d)/2 & \text{for } t = 0; \\
J_o & \text{for } t = t'' > 0.
\end{cases}
\]
Our choice for $f(t)$ is the simplest possible, that is two linear laws between the points $(t', J_d), (0, J_m)$ and $(t'', J_o)$:

\[
\begin{align*}
& t \in [t', 0] : \quad f(t) = J_m + \frac{t}{t'} (J_d - J_m); \\
& t \in [0, t''] : \quad f(t) = J_m - \frac{t}{t''} (J_m - J_o).
\end{align*}
\]

With these positions, the function $\varphi(\chi, J; T)$ is finally determined. The numerical values proposed by Komura & alii for the experimentally measurable quantities are:

\[
\begin{align*}
a_2 &= 174 k; \\
a_3 &= 307 \cdot 260 k \\
a_4 &= 613 \cdot 260 k
\end{align*}
\]

With these values of the constants, the maximum value attained by the order parameter $\phi_2 = (\delta_o - \delta_d)/\delta_d = a_3/a_4$, when $\tau = 0$, equals $307/613 \approx 0.5$; in correspondence of this value, the areal stretch $J_d = A_d/A_o$ equals $1 + 0.5 = 1.5$. Our assumption is that such value remains \textbf{frozen} for varying values of the temperature, being this hypothesis consistent with the fact that also $J_o = 1$ does not vary with temperature. We can now evaluate all the characteristic parameters of the function $\varphi$:

\[
\begin{align*}
A &= 160422.54 k \\
t' &= -51.05 K \\
t'' &= 6.38 K
\end{align*}
\]

A plot of the density energy $\varphi$ with respect to $J$, parameterized by the constant $t = T - T_{tr}$ is given in Figure 3.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{energy_density.png}
\caption{The energy density $\varphi$.}
\end{figure}
CHAPTER 6

Dimension Reduction
1. Constitutive and kinematical assumptions.

1.1. Experimental grounds of the models. In this chapter we consider lipid bilayers as three-dimensional bodies. In particular we are interested in describing the behavior of elastic binary lipid/lipid and lipid/cholesterol mixtures, whose three-dimensional constitutive equation can be expressed as follows

$$\psi = \hat{\psi}(\chi, \mathbf{F})$$

with $\mathbf{F}$ the three-dimensional gradient of deformation and $\chi$ the material description of the molar fraction of one of the two components of the mixture. Examples of lipid bilayers as three-dimensional bodies are multi-welled GUV, or planar multi-bilayers, in which an alternating structure of lipid bilayers trapping interstitial water may be encountered. We will show that a general three-dimensional energy density can be reduced to a simpler lower dimensional energy density, once some physically grounded assumptions concerning the thickness of the membrane and its kinematical behavior are done. An asymptotic equivalence between the fully 3-dimensional energy and the reduced 2-dimensional energy is expected when the parameter which measures the vanishing dimension goes to zero.

We will now focus on the main phenomenological evidences on the basis of which we will formulate the main assumptions of our mechanical model of lipid bilayer.

i. Experimental observation suggest that the thickness of the membrane is small in comparison to its extension in all other directions; this is actually evident from the experimental observations on GUV (Giant Unilamellar Vesicles), which show that the thickness is in the order of magnitude of few nanometers while the diameter is up to tens of micrometers;

ii. Lipid membranes exhibit four main structural phases, basically differing from each other because of the packing structure of the lipid molecules within the membrane; these phases can be summarized as follows (see Sackmann\cite{53}):

$L_\alpha$ - the fluid (also called "smectic A") phase in which the hydrocarbon tails are completely disordered; this phase is actually endowed with an high in-plane mobility of the lipid molecules;

$P_{\beta'}$ - the gel-phase (also called "ripple") phase in which the hydrocarbon chain form a triangular lattice, and the long axes of the chains are tilted with respect to the mid-surface of the membrane by about 30 degrees;

$L_{\beta'}$ - the gel-phase phase with chains forming an orthorhombic lattice, and the chains tilted with respect to the local mid surface of the membrane;

$L_c$ - the solid phase analogous to the $L_{\beta'}$ phase, but with chains perpendicular to the mid surface of the membrane.
The definition of fluid, gel and solid phases is actually reflecting the fact that molecules are endowed with an higher or lower lateral mobility on the surface of the membrane. Within the framework of classical biophysical literature, the fluid-gel $L_\alpha - P_\beta$ transition is referred to as the main transition, the gel-solid $P_\beta - L_\beta$ as the pre-transition and the solid-solid $L_\beta - L_c$ as the sub-transition\(^1\).

Recent experimental evidences have shown that addition of cholesterol in lipid bilayers made of saturated and unsaturated lipids is to “suppress” the fluid-gel main transition below physiologically relevant temperatures, and to favor the coexistence of variants of the liquid phase characterized by different orientational order of the hydrocarbon tails\(^2\); these variants of the $L_\alpha$ phase are are named liquid-ordered $L_o$ and liquid-disordered $L_d$ phases.

The study of phase transitions in lipid membranes is further complicated by the fact that the phases before described differ also in terms of chemical composition. It should be added that the main purpose of this thesis consists in achieving a further ambitious target, that is to produce a model in which phase separation is coupled with the deformation of the membrane, in order to explain the phase separation patterns illustrated in experimental works such as those of Baumgart & others [7]. It thus seems evident that some simplifying assumptions are necessarily needed, in order to derive a manageable model, whose analytical solution is expected to confirm the relevant aspects of the experimentally observed equilibrium configurations.

According to a number of works in the bio-physical literature\(^3\), in our work we focus on the $L_o - L_d$ transition within the liquid $L_\alpha$ phase. As already discussed in Chapter 4, a suitable coarse grained order parameter to describe the order-disorder phase transition can be seen in the bilayer

\(^1\)See Sackmann, [53], pg. 221.
\(^2\)See Komura & others, [35].
\(^3\)See cited works by Sackmann, Komura and Goldstein & Leibler, GL.
1. CONSTITUTIVE AND KINEMATICAL ASSUMPTIONS. thickness, since chain ordering effect produces an increase of the thickness, while the viceversa happens during the chain disordering effect.

This choice, of course, is not the only possible, nevertheless it should be understood that, quoting Goldstein & Leibler [18], \[\ldots\text{no specific assumption about the microscopic state of the lipids is made in choosing [the thickness] as order parameter: it should be seen a an hybrid coarse-grained variable which summarizes changes in various type of degrees of freedom such as tilt and conformational changes of the hydrocarbon chains.}\]

We will further assume that during the membrane deformations, the hydrocarbon chains remain perpendicular to the bilayer mid-surface. The removal of this constraint would certainly allow to achieve finer theories, but, at the same time, it would result into undesired complications of the model.

\[\text{iii. again on the basis of experimental evidence, we will further assume that both the liquid } L_d \text{ and } L_o \text{ phases are indeed characterized by the incapability of supporting in plane-shear stresses; we will refer to this assumption as the characteristic of } \text{in plane fluidity} \text{ of lipid bilayers (see Deseri, Healey & Paroni, to be published).}\]

\[\text{iv. it has been experimentally noticed (see Nagle & Wilkinson [44]) that thermal variations of the molecular volume}^4 \text{ in lipid molecules are negligible over a wide range of temperatures; this instance is for example embraced by Goldstein & Leibler [18], who consider molecular volume of lipids substantially constant, as well as their surrounding water molecules, and on the basis of this assumption they conclude that it may be equally possible to choose, as coarse-grained order parameter, the head-group area } \Sigma \text{ which, in their simplified model, is related to the molecular volume of the lipid } v_l \text{ via the relation }\]

\[
\Sigma \delta = 2v_l = \text{const}.
\]

In our model we will then assume the incompressibility constraint for lipid bilayers; we will show that this constraint allows to recover the choice made in the previous Chapter 5 of the areal stretch as order parameter for the main transition. Furthermore, in the sequel we shall not be concerned about the internal hydrostatic reactive pressure which allows for preserving incompressibility, although this should be considered for a future stress analysis.

\[\text{v. we will assume that chemical composition is constant throughout the thickness of the membrane; this hypothesis actually holds true for each of the two monolayers of which the bilayer is composed, and it ceases to be true when one is interested in modelling the behavior of membranes where the outer}\]

\[^4\text{Namely, the volume per mole unit.}\]
and inner layers have independent concentration fields.

vi. under particular conditions of the inner and outer water environment, such as differences in the PH or in the electric charges, or in case of different chemical concentration of the two monolayers, lipid bilayers are endowed of a spontaneous curvature; we will ignore these effects in our simplified model.

1.2. The ansatz on the shell deformation. Let as usual $\mathbf{E}$ be an orthonormal basis in $\mathbb{R}^3$, and let the the reference configuration of the membrane be defined as follows

$$\Omega_{h_0} := \left\{ \zeta = (\zeta_\alpha, \zeta_3) \in \Sigma \times \left( -\frac{h_0}{2}, \frac{h_0}{2} \right) \right\},$$

that is a cylindrical region of constant thickness $h_0$ developed on the open domain $\Sigma \subset \mathbb{R}^2$. Let $\Omega_1$ be the rescaled domain defined by

$$\Omega_1 := \left\{ z = (z_\alpha, z_3) \in \Sigma \times \left( -\frac{1}{2}, \frac{1}{2} \right) \right\},$$

where points of $\Omega_{h_0}$ and points of $\Omega_1$ are related by the re-parametrization

$$r = z_\alpha \mathbf{E}_\alpha + h_0 z_3 \mathbf{E}_3 : \Omega_1 \rightarrow \Omega_{h_0}$$

that is

$$r : (z_\alpha, z_3) \in \Omega_1 \rightarrow (\zeta_\alpha, \zeta_3) = (z_\alpha, h_0 z_3) \in \Omega_{h_0}.$$  

Let the mapping $p : \Sigma \mapsto \mathbb{R}^3$ be the deformation of the surface $\Sigma$, whose current configuration is represented by the surface

$$S := \{ x \in \mathbb{R}^3 | x = p(\zeta_\alpha), \zeta_\alpha \in \Sigma \}$$

and let the sans-face vector $\mathbf{n} : S \mapsto S^2$ to denote the directed unit normal vector to the surface $S$, and the bold-face vector $\mathbf{n} = \mathbf{n} \circ p$ its description in terms of points of the surface $\Sigma$.

According to the notation established in Section II.1.2, the following tensors will be extensively used within this section$^5$

Identity Operators: $I \in \text{Lin}(\mathbb{R}^3, \mathbb{R}^3)$ and $I \in \text{Lin}(\mathbb{R}^2, \mathbb{R}^2)$;

Perpendicular Projector: $\mathbb{P}$ is the operator in $\text{Lin}(\mathbb{R}^3, \mathbb{R}^2)$ that projects vectors $\mathbf{v} \in \mathbb{R}^3$ on the surface $\mathbb{R}^2$;

Inclusion Map: $\mathcal{I}$ is the operator in $\text{Lin}(\mathbb{R}^2, \mathbb{R}^3)$ that embeds any vector $\mathbf{\tau} \in \mathbb{R}^2$ in the space $\mathbb{R}^3$.

---

$^5$See Gurtin & Murdoch [21].
where we remind that the following properties holds

\[ T^T = P, \quad PP^T = TT^T = I_{\mathbb{R}^2}, \quad I = TP + E_3 \otimes E_3. \]

When not specified the operators \( I, T \) and \( P \) are referred to the plane \( \mathbb{R}^2 \), otherwise surface dependence will be stressed. In particular, consider the orthonormal basis \( \{ E_1, E_2, E_3 \} \) for the space \( \mathbb{R}^3 \) and the orthonormal basis \( \{ e_1, e_2 \} \) for \( \mathbb{R}^2 \). Then the following relations hold true

\[ I = E_i \otimes E_i, \quad I = e_\alpha \otimes e_\alpha, \quad T = E_\alpha \otimes e_\alpha, \quad P = e_\alpha \otimes E_\alpha. \]

When dealing with the local tangent plane \( T_S \) to the surface \( S \), we will denote with \( \{ A_1, A_2, n \} \) and \( \{ A^1, A^2, n \} \) the local natural and reciprocal basis for \( \mathbb{R}^3 \) and with \( \{ a_1, a_2 \} \) and \( \{ a^1, a^2 \} \) the local natural and reciprocal basis for \( T_S \). Furthermore it results

\[ I = A_\alpha \otimes A^\alpha + n \otimes n = A^\alpha \otimes A_\alpha + n \otimes n \in \text{Lin}(\mathbb{R}^3, \mathbb{R}^3) \]
\[ \mathbb{I}_S = a_\alpha \otimes a^\alpha = a^\alpha \otimes a_\alpha \in \text{Lin}(T_S, T_S) \]
\[ T_S = A_\alpha \otimes A^\alpha = A^\alpha \otimes A_\alpha \in \text{Lin}(T_S, \mathbb{R}^3) \]
\[ P_S = a_\alpha \otimes A^\alpha = a^\alpha \otimes A_\alpha \in \text{Lin}(\mathbb{R}^3, T_S). \]

As done in other parts of this thesis, we will occasionally confuse vectors \( E_\alpha \) with \( e_\alpha \), \( A_\alpha \) with \( a_\alpha \) and \( A^\alpha \) with \( a^\alpha \), when this does not lead to misinterpretations.

On the basis of the assumptions done in section 6.1 at point (ii), we assume that the current configuration of the membrane consists of the region

\[ B := f(\Omega_{h_0}) = \left\{ x = f(\zeta) = p(\zeta) + \frac{h(\zeta)}{h_0} n(\zeta) \mid \zeta \in \Omega_{h_0} \right\} \]

with \( h(\zeta) \) the thickness of the current configuration, which is a function of the points of the mid-surface \( \Sigma \). The 3-dimensional deformation gradient from \( \Omega_{h_0} \) to \( B \) then can be calculated as follows

\[ F = \nabla f = \nabla f[TT^T + E_3 \otimes E_3] = (\nabla_{\Sigma} f)^T + \frac{\partial f}{\partial \zeta_3} \otimes E_3 \]

where

\[ (\nabla_{\Sigma} f) := (\nabla f) T \in \text{Lin}(\Sigma, T_S). \]

Substituting to \( f \) the given ansatz, after application of the aforementioned properties we get

\[ F = \tilde{F} + \frac{h}{h_0} n \otimes E_3 + \zeta_3 \left[ \frac{1}{h_0} n \otimes (\nabla_{\Sigma} h) - \frac{h}{h_0} LF \right] \]

where the following tensors have been introduced

\[ \tilde{F} = FP = (\nabla p) T P: \text{ represents the extension to the space Lin}(\mathbb{R}^3, T_S) \text{ of the surface gradient of deformation} \]
\[ F = F(\zeta_3) = (\nabla p) T = \nabla_{\Sigma} p \in \text{Lin}(\Sigma, T_S) \]
1. CONSTITUTIVE AND KINEMATICAL ASSUMPTIONS.

of the surface Σ; as already discussed in Chapter 2, the expression of \( F \) in terms of the vectors of the reference basis \( \{ E_\alpha \} \) on Σ and the natural basis \( \{ A_\alpha \} \) on \( T_S \) is the following

\[
F = A_\alpha \otimes e_\alpha,
\]

hence in particular it results

\[
\bar{F} = F^p = (A_\alpha \otimes e_\alpha)(e_\beta \otimes E_\beta) = A_\alpha \otimes E_\alpha.
\]

\( L = L(\zeta_\alpha) = (\hat{L} \circ p)(\zeta_\alpha) = -(\nabla_S n \circ p)(\zeta_\alpha) \): represents the material description of the curvature tensor of the surface \( S \); the curvature tensor properly derives, in the previous expression of \( F_h \), from the following calculation

\[
\nabla_S n = \nabla_S(n \circ p) = (\nabla n)(\nabla p)I = (\nabla n)F_S F = (\nabla n)I = (\nabla n)L \equiv (\nabla n)T_S F = (\nabla_S n)F,
\]

where we have unambiguously confused \( I_S \) with \( I_S^0 \), on the basis that evidently \( F : \Sigma \rightarrow T_S \). We here recall that

\[
2\hat{H} = 2\hat{H}(x) := \text{tr}L(x), \quad \hat{K} = \hat{\chi} := \det L(x)
\]

where \( \hat{H} \) and \( \hat{K} \) represent the spatial fields of mean and Gaussian curvatures at a point \( x \) of the current surface \( S \).

Important to the following developments is the explicit expression of the local variation of volume, measured by the determinant of the 3-dimensional deformation, which can be calculated from the definition

\[
\det F := (F E_1 \times F E_2) \cdot F E_3.
\]

It results

\[
F E_1 = A_1 - \zeta_3 \frac{h}{h_0} LA_1 + \zeta_3 \frac{1}{h_0} h_1 n,
\]

\[
F E_2 = A_2 - \zeta_3 \frac{h}{h_0} LA_2 + \zeta_3 \frac{1}{h_0} h_2 n,
\]

\[
F E_3 = \frac{h}{h_0} n,
\]

where the vectors \( A_\alpha = \bar{F} E_\alpha \) span the tangent space \( T_S \) to the current mid-surface \( S \) and where we have set \( h_{\alpha} = (\nabla_S h) \cdot E_\alpha \). Since it results

\[
n := A_1 \times A_2 / J, \quad J = |A_1 \times A_2| = [\det(F^T F)]^{1/2}
\]

after substitution we obtain

\[
\det F = (F E_1 \times F E_2) \cdot F E_3 = \frac{h}{h_0} \left[ (A_1 \times A_2) \cdot n - \zeta_3 \frac{h}{h_0} (A_1 \times L A_2 + L A_1 \times A_2) \cdot n + \zeta_3^2 \frac{h^2}{h_0^2} (L A_1 \times L A_2) \cdot n \right].
\]

At this point, from the identity

\[
n \times A_\alpha = \varepsilon_{\alpha \beta} A_\beta
\]
1. CONSTITUTIVE AND KINEMATICAL ASSUMPTIONS.

with \( \varepsilon_{\alpha\beta} \) equal to \((1, -1)\) respectively if \( \alpha\beta = (12, 21) \) and equal to 0 otherwise, we get that

\[
(\mathbf{L} \mathbf{A}_1 \times \mathbf{A}_2) \cdot \mathbf{n} + (\mathbf{A}_1 \times \mathbf{L} \mathbf{A}_2) \cdot \mathbf{n} = \mathbf{L} \cdot (\mathbf{A}^\alpha \otimes \mathbf{A}_\alpha) = \mathbf{L} \cdot \mathbb{I}_S = 2H,
\]

where \( H = \hat{H} \circ \mathbf{p} \) represents the material description of the local mean curvature of the current mid-surface \( S \). Furthermore, from the definition of determinant of a surface tensor

\[
K = \text{det} \mathbf{L} := \frac{(\mathbf{L} \mathbf{A}_1 \times \mathbf{L} \mathbf{A}_2) \cdot \mathbf{n}}{(\mathbf{A}_1 \times \mathbf{A}_2) \cdot \mathbf{n}} = \frac{(\mathbf{L} \mathbf{A}_1 \times \mathbf{L} \mathbf{A}_2) \cdot \mathbf{n}}{J}
\]

being \( K = \hat{K} \circ \mathbf{p} \) the local Gaussian curvature of the surface \( S \), expressed in material form. Hence we finally get

\[
\text{det} \mathbf{F} = \frac{\mathbf{h}}{\mathbf{h}_0} \left[ J - 2\zeta_3 \frac{\mathbf{h}}{\mathbf{h}_0} \mathbf{H} + \zeta_3^2 \frac{\mathbf{h}^2}{\mathbf{h}_0^2} \mathbf{J} \mathbf{K} \right],
\]

which can be recast as follows

\[
\text{det} \mathbf{F} = \beta J - 2\mathbf{h}_0 \zeta_3 \beta^2 \mathbf{H} + \mathbf{h}_0^2 \zeta_3^2 \beta^3 \mathbf{J} \mathbf{K}
\]

where the dimensionless thickness variable

\[
\zeta_3 = \frac{\zeta_3}{\mathbf{h}_0}
\]

has been introduced, with \( \zeta_3 \in (-1/2, 1/2) \), and we have set

\[
\beta = \frac{\mathbf{h}}{\mathbf{h}_0}.
\]

The ratio \( \beta \) will always be a finite quantity in our model, in particular it will result that \( \beta \approx 1 \).

Let us now assume, on the basis of the experimental evidence, volume incompressibility of the lipid bilayer. This assumption places a precise restriction on the deformation law \( \mathbf{f} \), precisely that

\[
\text{det} \mathbf{F}(\zeta) = 1
\]

for all points \( \zeta \in \Omega_{\mathbf{h}_0} \). On the other side, on the basis of the ansatz we have imposed on the deformation, we see that the calculated expression of the determinant of \( \mathbf{F} \) yields that for each point \( \zeta_\alpha \in \Sigma \) the incompressibility condition \( \text{det} \mathbf{F} = 1 \) is satisfied at most in two points, precisely those whose coordinate \( \zeta_3 = \zeta_3 \mathbf{h}_0 \) are the zeroes of the equation

\[
\mathbf{h}_0^2 \zeta_3^2 \beta^3 \mathbf{J} \mathbf{K} - 2\mathbf{h}_0 \zeta_3 \beta^2 \mathbf{H} + \beta J - 1 = 0.
\]

This instance practically means that in general the proposed ansatz cannot deliver the desired incompressibility condition.

Nevertheless, as already pointed out in the previous section, it should be remarked that lipid membranes we are considering are indeed very thin, which means that
2. Asymptotic expansion of the energy density.

$h_0 \ll 1$; standing on this fact we will assume that
\[
\det F = \beta J - 2h_0 z_3 \beta^2 H + h_0^2 z_3^2 \beta^3 J K \approx \beta J.
\]
We thus deduce that the incompressibility constraint for a very thin shell whose kinematics is constrained by the proposed ansatz implies that
\[
\det F \approx \beta J = 1 \implies h_0 = hJ.
\]
This relation shows that, within this model, taking $J$ or $h$ as order parameter is completely equivalent, since $h_0$ is constant; this fact agrees with the viewpoint adopted by Goldstein & Leibler in their work [18].

Taking the surface gradient of this last expression we obtain
\[
0 = \nabla \Sigma (hJ) = h(\nabla \Sigma J) + J(\nabla \Sigma h)
\]
thus we deduce that
\[
\frac{\nabla \Sigma h}{h_0} = -\frac{\nabla \Sigma J}{J^2}.
\]
The final 3-dimensional deformation gradient, on the basis of the assumptions of normal preserving deformations, volume incompressibility and very small thickness, can finally be expressed as follows
\[
F = \bar{F} + \frac{1}{J} n \otimes E_3 - \zeta_3 \left[ n \otimes \frac{\nabla \Sigma J}{J^2} + \frac{1}{J} L \bar{F} \right].
\]

2. Asymptotic expansion of the energy density.

2.1. Surface energy density of a very thin, elastic body. Let us consider the frame-indifferent 3-dimensional constitutive equation
\[
\psi = \hat{\psi}(\chi, C)
\]
where
\[
C = F^T F \in \text{PSym} (\Sigma, \Sigma),
\]
and where the field $\chi$ here represents the material description of the molar fraction field $\hat{\chi}$ of one of the two components at points of the current configuration $\Omega_{h_0}$, that is
\[
\chi = \hat{\chi} \circ f
\]
with $\hat{\chi} : \Omega_{h_0} \rightarrow [0, 1]$. On the basis of the assumption (vi) done in the previous section, it is reasonable to assume that
\[
\hat{\chi}(x + x_3 n(x)) = \hat{\chi}(x) \quad \forall (x, x_3) \in \mathcal{B},
\]
which basically means that the current concentration field does not vary moving along the normal at a fixed point on the current mid-surface $S$; in terms of the material description,
\[
\chi(\zeta_\alpha, \zeta_3) = \chi(\zeta_\alpha) \quad \forall (\zeta_\alpha, \zeta_3) \in \Omega_{h_0}.
\]
We now assume that the 3-dimensional deformation gradient $F$ is exactly the one found in the previous section; after some calculations we get

$$C = C_0 + \zeta_3 C_1 + \zeta_3^2 C_2$$

where

$$C_0 = \bar{F}^T \bar{F} + \frac{1}{J^2} E_3 \otimes E_3,$$

$$C_1 = - \left[ \frac{2}{f} \bar{F}^T \mathbf{L} \bar{F} + \frac{1}{J^3} \left( E_3 \otimes (\nabla_\Sigma J) + (\nabla_\Sigma J) \otimes E_3 \right) \right],$$

$$C_2 = \frac{1}{J^4} (\nabla_\Sigma J) \otimes (\nabla_\Sigma J) + \frac{1}{J^2} \bar{F}^T \mathbf{L}^2 \bar{F}.$$
hence we deduce the expression of the surface energy density derived by 3-dimensional elasticity within the framework of the considered assumptions
\[
\varphi = \varphi^m + h_0^2 \varphi^b = h_0 \hat{\psi}(\chi, C_0) + \frac{h_0^3}{24} [A_1[C_1] \cdot C_1 + 2B \cdot C_2],
\]
where the two terms \(\varphi^m\) and \(\varphi^b\) respectively represent the purely membranal energy density and the bending energy density, as it will be more clear at the end of this chapter.

2.2. The 3D constitutive equation of a very thin, fluid, incompressible elastic material. Let us suppress the dependence on the local concentration for simplicity. As it was shown in an unpublished work by Deseri-Healey-Paroni, the general frame indifferent 3-dimensional constitutive equation
\[
\psi = \hat{\psi}(C)
\]
can be further reduced when requiring its invariance under the group of symmetry transformations defined by ”transversely unimodular tensors”, namely the group
\[
\text{Unim}\{E_3\} := \{H = H + E_3 \otimes E_3 | \det H = 1\}.
\]
Invariance under \(\text{Unim}\{E_3\}\), required as usual imposing that
\[
\hat{\psi}(F^T F) = \hat{\psi}([F H]^T [F H]), \quad \forall H \in \text{Unim}\{E_3\},
\]
was shown to produce the following reduced constitutive dependence of \(\psi\) on \(C\)
\[
\psi = \hat{\psi}(\det C, \det C, C_{33})
\]
where
\[
C := (\nabla_\Sigma f)^T (\nabla_\Sigma f) = [(\nabla f)^T [(\nabla f) I] = T^T [F^T F] I = T^T C I \in \text{PSym}(\Sigma, \Sigma),
\]
with \(I\) the inclusion map on \(\Sigma\). It is important to underline that the tensor \(C\) depends on all the coordinates \({\zeta_\alpha, \zeta_3}\), since it is defined by
\[
C(\zeta) := T^T F^T (\zeta) F(\zeta) I.
\]
When restricting our attention to very thin, incompressible fluid films, whose kinematics is restricted to normal preserving deformations through the ansatz proposed in the pervious section, this 3-dimensional constitutive equation can be further reduced as follows
\[
\psi = \bar{\psi}(\det C),
\]
since the incompressibility constraint implies that \(\det C = 1\) and since, within the approximation of very small thickness, the function
\[
C_{33} = CE_3 \cdot E_3 = \frac{h^2}{h_0^2}
\]
can be derived from the function \((\det C)\) by the relation
\[
h_0 = h(\zeta_\alpha) J(\zeta_\alpha) = h(\zeta_\alpha) \sqrt{\det C(\zeta_\alpha, 0)}.
\]
2.3. Calculation of the tensors B and A. Let us consider some preliminary facts; concentration dependence is suppressed in this section for simplicity of notation, nevertheless such dependence will be reintroduced when necessary.

i. Let be given the following tensors, with \( \mathcal{I} \) the inclusion map on \( \Sigma \);

\[
\mathbf{M} \in \text{PSym}(\mathbb{R}^3, \mathbb{R}^3), \quad \mathbf{M} = \mathcal{I}^T \mathbf{M} \in \text{PSym}(\mathbb{R}^2, \mathbb{R}^2),
\]

and let be given the functions \( \hat{\varphi} : \text{PSym}(\mathbb{R}^3, \mathbb{R}^3) \mapsto \mathbb{R}^+ \) and \( \tilde{\varphi} : \text{PSym}(\mathbb{R}^2, \mathbb{R}^2) \mapsto \mathbb{R}^+ \) such that

\[
\hat{\varphi}(\mathbf{M}) = \tilde{\varphi}((\mathcal{I}^T \mathbf{M}) \mathcal{I}) = \tilde{\varphi}(\mathbf{M}).
\]

Taking the differential of both sides of this last relation with respect to an arbitrary increment \( \mathbf{N} \in \text{PSym}(\mathbb{R}^3, \mathbb{R}^3) \), we obtain for the term at the left side

\[
D\hat{\varphi}(\mathbf{M})[\mathbf{N}] = (\nabla_{\mathbf{M}} \hat{\varphi}) \cdot \mathbf{N},
\]

and for the term at the right side

\[
D\tilde{\varphi}(\mathbf{M})[\mathbf{N}] = D\tilde{\varphi}(\mathbf{M})[D(\mathbf{M})[\mathbf{N}]] = D\tilde{\varphi}(\mathbf{M})[I^T \mathbf{N} \mathcal{I}]
= (\nabla_{\mathbf{M}} \tilde{\varphi}) \cdot I^T \mathbf{N} = \mathcal{I}(\nabla_{\mathbf{M}} \tilde{\varphi})I^T \cdot \mathbf{N}
\]

hence from arbitrariness of the tensor \( \mathbf{N} \) we get

\[
(\nabla_{\mathbf{M}} \hat{\varphi}) = \mathcal{I}(\nabla_{\mathbf{M}} \tilde{\varphi})I^T = \mathcal{I}(\nabla_{\mathbf{M}} \tilde{\varphi})^P,
\]

where the subscripts \( \mathbf{M} \) and \( \mathbf{M} \) are merely reminders of the variable with respect which variable differentiation is done. It is important to underline that

\[
\nabla_{\mathbf{M}} \hat{\varphi} \in \text{Lin}(\mathbb{R}^3, \mathbb{R}^3), \quad \nabla_{\mathbf{M}} \tilde{\varphi} \in \text{Lin}(\mathbb{R}^2, \mathbb{R}^2).
\]

ii. Given \( \mathbf{M} \) and \( \mathbf{M} \) as before, let be given the following tensor functions \( \hat{\mathbf{G}} : \text{PSym}(\mathbb{R}^3, \mathbb{R}^3) \mapsto \text{Lin}(\mathbb{R}^3, \mathbb{R}^3) \) and \( \tilde{\mathbf{G}} : \text{PSym}(\mathbb{R}^2, \mathbb{R}^2) \mapsto \text{Lin}(\mathbb{R}^2, \mathbb{R}^2) \) such that

\[
\hat{\mathbf{G}}(\mathbf{M}) = \mathcal{I} \hat{\mathbf{G}}(\mathbf{M}) I^T \quad \forall \mathbf{M} \in \text{PSym}(\mathbb{R}^3, \mathbb{R}^3).
\]

Differentiating as done in the previous point with respect to a generic tensor \( \mathbf{N} \in \text{PSym}(\mathbb{R}^3, \mathbb{R}^3) \) we obtain for the left hand side

\[
D\hat{\mathbf{G}}(\mathbf{M})[\mathbf{N}] = \{\nabla_{\mathbf{M}} \hat{\mathbf{G}}(\mathbf{M})\}[\mathbf{N}]
\]

and for the right hand side

\[
D\{\mathcal{I} \hat{\mathbf{G}}(\mathbf{M}) I^T\}[\mathbf{N}] = \{I \otimes I\} D\hat{\mathbf{G}}(\mathbf{M})[\mathbf{N}]
= \{I \otimes I\} D\hat{\mathbf{G}}(\mathbf{M})[D(\mathbf{M})[\mathbf{N}]] = \{I \otimes I\} D\hat{\mathbf{G}}(\mathbf{M})[D(I^T \mathbf{M} \mathcal{I})[\mathbf{N}]]
= \{I \otimes I\} D\hat{\mathbf{G}}(\mathbf{M})[I^T \mathbf{N} \mathcal{I}] = \{I \otimes I\} \{\nabla_{\mathbf{M}} \hat{\mathbf{G}}(\mathbf{M})\}[I^T \mathbf{N} \mathcal{I}]
= \{I \otimes I\} \{\nabla_{\mathbf{M}} \hat{\mathbf{G}}(\mathbf{M})\} \{I^T \otimes I^T\}[\mathbf{N}],
\]
2. ASYMPTOTIC EXPANSION OF THE ENERGY DENSITY.

where by the definition of the operator \( \otimes \) it results that given arbitrary tensors \( \mathbf{A}, \mathbf{B}, \mathbf{C} \) it results that
\[
\{ \mathbf{A} \otimes \mathbf{B} \}[\mathbf{C}] = \mathbf{A}\mathbf{C}\mathbf{B}^T.
\]

At this point, arbitrariness of the tensor \( \mathbf{N} \) finally yields
\[
\{ \nabla_{\mathbf{M}} \hat{\mathbf{G}}(\mathbf{M}) \} = \{ \mathbf{I} \otimes \mathbf{I} \} \{ \nabla_{\mathbf{M}} \tilde{\mathbf{G}}(\mathbf{M}) \} \{ \mathbf{P} \otimes \mathbf{P} \}.
\]

\textbf{iii.} Given functions and tensors as before, it is easy to show that
\[
\nabla_{\mathbf{M}} (\det \mathbf{M}) = (\det \mathbf{M}) \mathbf{M}^{-1}.
\]

\textbf{iv.} Given \( \mathbf{M} \) as before, by the definition of inverse,
\[
\mathbf{M}^{-1} \mathbf{M} = I
\]
it results, taking the differential of this relation with respect to an increment \( \mathbf{N} \in \text{PSym}(\mathbb{R}^2, \mathbb{R}^2) \), that
\[
D(\mathbf{M}^{-1} \mathbf{M})[\mathbf{N}] = 0 = D(\mathbf{M}^{-1})[\mathbf{N}] \mathbf{M} + \mathbf{M}^{-1} D(\mathbf{M})[\mathbf{N}]
\]
hence we get
\[
D(\mathbf{M}^{-1})[\mathbf{N}] = -\mathbf{M}^{-1} \mathbf{N} \mathbf{M}^{-1} = -(\mathbf{M}^{-1} \otimes \mathbf{M}^{-1})[\mathbf{N}].
\]

In conclusion, granted the arbitrariness of the tensor \( \mathbf{N} \), we get\(^6\)
\[
\nabla_{\mathbf{M}}(\mathbf{M}^{-1}) = -(\mathbf{M}^{-1} \otimes \mathbf{M}^{-1}).
\]

\textbf{v.} With \( \mathbf{M} \) as before, letting \( \phi = \tilde{\phi}(\mathbf{M}) \) a scalar field and \( \mathbf{G} = \tilde{\mathbf{G}}(\mathbf{M}) \) a tensor field, it is easy to check that
\[
\nabla_{\mathbf{M}}(\phi \mathbf{G}) = \phi \nabla_{\mathbf{M}} \mathbf{G} + \mathbf{G} \otimes \nabla_{\mathbf{M}} \phi.
\]

At this point remind that in the previous section we have shown that the following reduced constitutive equation can be introduced
\[
\psi = \tilde{\psi}(\mathbf{C}) = \hat{\psi}(\det \mathbf{C}), \quad \mathbf{C} = \mathbf{I}^T \mathbf{C} \mathbf{I}
\]
hence standings on the remarks \textbf{i.} - \textbf{v.} we deduce that:

\textbf{1.} it results that
\[
\nabla_{\mathbf{C}} \hat{\psi}(\mathbf{C}) = \mathbf{I} [\nabla_{\mathbf{C}} \tilde{\psi}(\det \mathbf{C})] \mathbf{I}^T = \mathbf{I} [g_1 \mathbf{C}^{-1}] \mathbf{I}^T
\]
where it has been set
\[
g_1 = \tilde{g}_1(\chi, \det \mathbf{C}) := \frac{\partial \tilde{\psi}(\chi, \det \mathbf{C})}{\partial \det \mathbf{C}}(\det \mathbf{C}).
\]

Let us set for later use
\[
\hat{\mathbf{G}}(\mathbf{C}) := \nabla_{\mathbf{C}} \hat{\psi}(\mathbf{C}) = g_1 \mathbf{I} \mathbf{C}^{-1} \mathbf{I}^T := \mathbf{I} \hat{\mathbf{G}}(\mathbf{C}) \mathbf{I}^T.
\]

\(^6\)See Gurtin [22], pg.28, es.2
2. it results that
\[ \nabla_C \nabla_C \dot{\psi}(C) = \nabla_C \dot{G}(C) = \nabla_C \{ \mathcal{I} \dot{G}(C) \mathcal{I}^T \} = \]
\[ = \{ \mathcal{I} \otimes \mathcal{I} \} \{ \nabla_C \dot{G}(C) \} \{ \mathcal{I}^T \otimes \mathcal{I}^T \} = \]
\[ = \{ \mathcal{I} \otimes \mathcal{I} \} \{ \nabla_C (g_1 C^{-1}) \} \{ \mathcal{I}^T \otimes \mathcal{I}^T \} = \]
\[ = \{ \mathcal{I} \otimes \mathcal{I} \} \{ g_1 \nabla_C (C^{-1}) + C^{-1} \otimes (\nabla_C g_1) \} \{ \mathcal{I}^T \otimes \mathcal{I}^T \} = \]
\[ = \{ \mathcal{I} \otimes \mathcal{I} \} \{ -g_1 C^{-1} \otimes C^{-1} + g_2 C^{-1} \otimes C^{-1} \} \{ \mathcal{I}^T \otimes \mathcal{I}^T \}, \]
where it has been set
\[ g_2 := \bar{g}_2(\chi, \det C) = \frac{\partial \bar{g}_1(\chi, \det C)}{\partial \det C} (\det C). \]

In order to compute the deriving expression of the tensors \( B \) and \( A \), we further need to evaluate the tensors \( \nabla_C \dot{\psi}(C) \) and \( \nabla_C \nabla_C \dot{\psi}(C) \) at \( h_0 = 0 \); for such value of \( h_0 \) it results that
\[ \mathbf{F}|_{h_0=0} = \left\{ \mathbf{F} + \frac{1}{J} \mathbf{n} \otimes \mathbf{E}_3 - h_0 z_3 \left[ \mathbf{n} \otimes \frac{\nabla \chi}{J^2} + \frac{1}{J} \mathbf{L} \mathbf{F} \right] \right\}_{h_0=0} = \mathbf{F} + \frac{1}{J} \mathbf{n} \otimes \mathbf{E}_3 \]

hence
\[ \mathbf{C}|_{h_0=0} = \mathcal{I}^T \mathbf{F}^T \mathbf{F}|_{h_0=0} \mathcal{I} = \mathcal{I}^T \mathbf{F}^T \mathbf{F} = \mathcal{I}^T \{ [\mathbf{F} \mathcal{P}]^T \mathbf{F} \mathcal{P} \} \mathcal{I} = \mathcal{I}^T \mathbf{F}^T \mathbf{F} \mathcal{I} = \bar{\mathcal{F}} = \mathbf{C}_0 \in \text{PSym}(\Sigma, \Sigma). \]

Calling \( J^2 = \det(\mathbf{F}^T \mathbf{F}) = \det \mathbf{C}_0 \), it finally results
\[ \mathbf{B} = g_1 \mathcal{I} \mathbf{C}_0^{-1} \mathcal{I}^T, \]
\[ \mathbf{A} = \{ \mathcal{I} \otimes \mathcal{I} \} \{ -g_1 \mathbf{C}_0^{-1} \otimes \mathbf{C}_0^{-1} + g_2 \mathbf{C}_0^{-1} \otimes \mathbf{C}_0^{-1} \} \{ \mathcal{I}^T \otimes \mathcal{I}^T \}, \]
where \( g_1 \) and \( g_2 \) are known functions of the local concentration \( \chi \) and of the mid-surface areal stretch \( J \).

### 2.4. Surface energy density of a very thin, fluid, elastic body.

The general constitutive response for an elastic surface determined in section 2.1 can be further developed in the special case of fluid, elastic surfaces by simply substituting in the general equation
\[ \varphi = \dot{\psi}(\chi, \mathbf{F}, \mathbf{L}) = h_0 \dot{\psi}(\chi, \mathbf{C}_0) + \frac{h_0^3}{24} \{ \mathbf{A}[\mathbf{C}_1] \cdot \mathbf{C}_1 + 2 \mathbf{B} \cdot \mathbf{C}_2 \}, \]
the expressions of the elastic tensors \( \mathbf{A} \) and \( \mathbf{B} \) determined in the previous section, where
\[ \dot{\psi}(\chi, \mathbf{C}_0) \equiv \dot{\psi}(\chi, \det \mathbf{C}_0), \quad \mathbf{C}_0 = \mathbf{F}^T \mathbf{F}. \]
We have
\[ A[C_1] = \{ T \otimes T \} \{ g_1 C_0^{-1} \otimes C_0^{-1} - g_2 C_0^{-1} \otimes C_0^{-1} \} \{ T^T \otimes T^T \} \]
\[ = \frac{2}{J} F^T L F + \frac{1}{J^3} \left[ E_3 \otimes (\nabla \Sigma J) + (\nabla \Sigma J) \otimes E_3 \right] = \]
\[ = \frac{2}{J} \{ T \otimes T \} \{ g_1 C_0^{-1} \otimes C_0^{-1} - g_2 C_0^{-1} \otimes C_0^{-1} \} [F^T L F] = \]
\[ = \frac{2}{J} \{ T \otimes T \} [g_1 C_0^{-1} F^T L F C_0^{-1} - g_2 (F^T L F \cdot C_0^{-1}) C_0^{-1}] = \]
\[ = \frac{2}{J} \{ T \otimes T \} [g_1 F^{-1} F^T F^T L F F^{-1} F^T - g_2 (F^T L F \cdot F^{-1} F^T) F^{-1} F^T] = \]
\[ = \frac{2}{J} \{ T \otimes T \} [g_1 F^{-1} L F^{-T} - g_2 (L \cdot I_S) F^{-1} F^T], \]

where \( I_S \) is the surface projector on the current surface \( S \), and where correctness of this last passage is rapidly checked recalling that for any two tensors \( U \) and \( V \) with \( \text{Domain}(U) = \text{Codomain}(V) \) and \( \text{Domain}(V) = \text{Codomain}(U) \), the trace operator is well defined for the tensors \( UV \) and \( VU \) and furthermore
\[ \text{tr}(UV) = \text{tr}(VU). \]

Standing on this fact we have, being \( F \in \text{Lin}(\Sigma, T_S) \) and \( L \in \text{Sym}(T_S, T_S) \), that
\[ F^T L F \cdot F^{-1} F^{-T} = \text{tr}[F^T L F F^{-1} F^{-T}] = \text{tr}[F^T L F^{-1} F^T] = \text{tr}[L F^{-1} F^T] = \text{tr}L = L \cdot I_S. \]

Proceeding in the previous calculations we find
\[ A[C_1] \cdot [C_1] = \frac{4}{J^2} \{ g_2 (L \cdot I_S) F^{-1} F^T - g_1 F^{-1} L F^{-T} \} \cdot [F^T L F] = \]
\[ = \frac{4}{J^2} \{ g_2 (L \cdot I_S)^2 - g_1 (L^2 \cdot I_S) \}. \]

For the linear term we have
\[ B \cdot C_2 = g_1 T C_0^{-1} T^T \cdot \left[ \frac{1}{J^4} (\nabla \Sigma J) \otimes (\nabla \Sigma J) + \frac{1}{J^2} F^T L^2 F \right] = \frac{g_1}{J^2} (L^2 \cdot I_S) + \frac{g_1}{J^4} \| F^{-T} [\nabla \Sigma J] \|^2. \]

On the basis of the Cayley-Hamilton theorem for the symmetric tensor \( L \), follows that
\[ L^2 - 2H L + K I_S = 0 \quad \Rightarrow \quad L^2 \cdot I_S = 4 H^2 - 2 K, \]
hence the resulting form of the bending part of the elastic energy density is the following
\[ \varphi^b = \varphi^b(\chi, F, L, \nabla \Sigma J) = \frac{1}{6} \left[ \kappa_1 H^2 + \kappa_2 K + \frac{\alpha_0}{2} \| F^{-T} [\nabla \Sigma J] \|^2 \right] \]
where it has been set
\[ \kappa_1 = \bar{k}_1(\chi, J) = \frac{2h_0 (2g_2 - g_1)}{J^2}, \quad \kappa_2 = \bar{k}_2(\chi, J) = \frac{h_0 g_1}{J^2} \quad \alpha_0 := \bar{\alpha}_0(\chi, J) = \frac{\kappa_2}{J^2}. \]
The apparently non invariant term $||F^{-T}[\nabla_S J]||$ is merely the material description of the spatial field $||\nabla_S \hat{J}||$
where $\hat{J}$ represents the spatial description of the areal stretch $J$, that is
$J = \hat{J} \circ p$.

A final refinement is possible by setting
$\varphi^m = \tilde{\varphi}^m(\chi, J) := h_0 \tilde{\psi}(\chi, \det C_o) = h_0 \tilde{\psi}(\chi, J^2)$
hence, after some tedious but simple calculations, it results
$g_1 = \frac{1}{h_0} \left[ \frac{J \partial \varphi^m}{2 \partial J} \right] = \frac{\tilde{\gamma}_1(\chi, J)}{h_0}$,
$g_2 = \frac{1}{h_0} \left[ \frac{J \partial \varphi^m}{4 \partial J} + \frac{J^2 \partial^2 \varphi^m}{4 \partial J^2} \right] = \frac{\tilde{\gamma}_2(\chi, J)}{h_0}$,
thus the bending moduli $\kappa_1, \kappa_2$ and the function $\alpha$ can be recast as follows
$\kappa_1 = \tilde{\kappa}_1(\chi, J) = \frac{2(2\gamma_2 - \gamma_1)}{J^2}$, \hspace{0.5cm} $\kappa_2 = \tilde{\kappa}_2(\chi, J) = \frac{\gamma_1}{J^2}$, \hspace{0.5cm} $\alpha_o = \tilde{\alpha}_o(\chi, J) = \frac{\gamma_1}{J^4}$.

The final form of the membranal-bending energy density per unit of reference area
is then
$\psi = \varphi^m + h_0^2 \varphi^b = \varphi^m(\chi, J) + \frac{h_0^2}{6} \left[ \kappa_1 H^2 + \kappa_2 K + \frac{\alpha_o}{2} ||\nabla_S \hat{J}||^2_\Sigma \right]$,
where with $||\nabla_S \hat{J}||_\Sigma$ we denote the material description of the term $||\nabla_S \hat{J}||$. Introducing the bending moduli $k_1 = \kappa_1/J, k_2 = \kappa_2/J$ and $\alpha := \alpha_o/J$ we can finally recast this expression in terms of energy per unit of current area
$\psi_S = \frac{1}{f}(\psi \circ p^{-1}) = \frac{1}{f} \varphi^m(\hat{\chi}, \hat{J}) + \frac{h_0^2}{6} \left[ k_1 \hat{H}^2 + k_2 \hat{K} + \frac{\alpha}{2} ||\nabla_S \hat{J}||^2_\Sigma \right]$.
CHAPTER 7

The Equilibrium Problem
1. The variational problem.

1.1. Settings and formulation of the problem. According to the general variational principles for non-reacting mixtures discussed in Section III.3.2, the variational formulation of the equilibrium problem for a closed, binary, lipid membrane in aqueous environment at a given temperature, and subject to a given pressure difference, will be afforded following the guideline traced by Gibbs\[17].

The membrane is here seen as a surface whose Helmholtz free energy density is the one determined in Chapter 5. The current unknown surface $S$ occupied by the membrane in the space is, as usual, parameterized as follows

$$S := p(\Sigma) = \{x \in \mathbb{R}^3 | x = p(\zeta_\alpha), \zeta_\alpha \in \Sigma \subset \mathbb{R}^2\}$$

Let $\psi = \psi(x)$ be the Helmholtz energy density per unit of current area, $\chi = \chi(x)$ the molecular fraction of one of the two species in the mixture and $\rho = \rho(x)$ the total molecular density per unit of current area, hence the following integrals can be defined

**Stored Helmholtz Energy:** defined as

$$\Psi(S) := \int_S \psi_S da = \int_\Sigma (\psi_S \circ p) J dA = \int_\Sigma \psi dA,$$

where $\psi = J(\psi_S \circ p)$ and $J$ is the surface Jacobian

$$J := \sqrt{F^T F} = \sqrt{(\nabla \Sigma p)^T (\nabla \Sigma p)}.$$

**Total number of molecules:** defined as

$$N_{tot}(S) := \int_S \hat{\rho} da = \int_\Sigma (\hat{\rho} \circ p) J dA = \int_\Sigma \rho_0 dA,$$

with $\hat{\rho} = \hat{\rho}(x)$ the molecular density per unit of current area and $\rho_0 = \rho_0(\zeta_\alpha)$ the given molecular density per unit of reference area. The requirement of conservation of the molecules number during the motion of any subpart of the body, precisely

$$N_{tot}(p(R)) = N_{tot}(R) \quad \forall R \subseteq \Sigma$$

yields the local form for the continuity of the total number of molecules

$$(\hat{\rho} \circ p) J = \rho_0.$$

Being the reference configuration arbitrary, we here assume that $\rho_0 = \rho_0(\zeta_\alpha)$ is constant all over $\Sigma$. Local form of the conservation of total molecules number implies that the spatial field $\hat{\rho}$ is completely determined once the deformation law is known.
1. THE VARIATIONAL PROBLEM.

Number of molecules of the two chemical species: defined as
\[ N_1(S) := \int_S \hat{\rho} \hat{\chi} \, da = \int_\Sigma (\hat{\rho} \circ p)(\hat{\chi} \circ p) J \, dA = \int_\Sigma \rho_0 \chi \, dA \]
where \( \chi := \hat{\chi} \circ p \) represents the material description of the molecular fraction of one of the two species in the mixture; evidently,
\[ N_2(S) := \int_S \hat{\rho}(1 - \hat{\chi}) \, da = N_{\text{tot}} - N_1(S). \]

The Potential Energy of the membrane is defined as the difference
\[ \Psi - \mathcal{L} \]
where \( \mathcal{L} \) here represents the work done on the surface by external forces. For equilibrium it is required the vanishing of the variation of the potential energy with respect to all perturbations which leave unaltered the number of molecules of each chemical species; this condition can be recast by introducing an unknown Lagrange multiplier \( \mu \) in order to embed the constraint in the energy functional
\[ \delta \mathcal{F} = \delta \left\{ \int_\Sigma \psi \, dA - \mu \left[ \int_\Sigma \rho_0 \chi \, dA - N_1 \right] - \mathcal{L} \right\} = 0, \]
and let the constitutive response be the one defined in Chapter 5, precisely the following
\[ \psi = \hat{\psi}(\chi, J, H, K, ||\nabla_S \hat{J}||_{\Sigma}; T) \]
where we remind that \( H, K \) and \( ||\nabla_S \hat{J}||_{\Sigma} \) are material descriptions of spatial fields \( \hat{H}, \hat{K} \) and \( ||\nabla_S \hat{J}|| \) respectively, and temperature here appears as a parameter. Essentially, under the point of view of the functional dependence,
\[ \mathcal{F} = \hat{\mathcal{F}}(\chi, p) \]
hence for first variation of the functional \( \mathcal{F} \) we mean
\[ \delta \mathcal{F} := \lim_{\varepsilon \to 0} \frac{\hat{\mathcal{F}}(\chi + \varepsilon \xi, p + \varepsilon \eta) - \hat{\mathcal{F}}(\chi, p)}{\varepsilon} \]
where \( \xi : \Sigma \mapsto [0, 1] \) and \( \eta : \Sigma \mapsto \mathbb{R}^3 \) are perturbations of the molecular fraction field and of the surface deformation, respectively. Within the qualitative discussion we are carrying on, these fields are assumed smooth enough. As a remark, once that the constraint on the number of molecules of each chemical species has been embedded in the functional via the Lagrange multiplier \( \mu \), the functions \( \xi \) are completely free.

It can be show that the spatial form of the variation of the work done by the external loads admits the following representation
\[ \delta \mathcal{L} = \int_S \Delta P \, n \cdot y \, da \]
where \( \Delta P \) the imposed pressure difference between the inside and outside of the membrane, \( n = n(x) \) the local unit normal to the current surface and \( y = y(x) \) a virtual displacement of points of the current configuration.
1.2. A strategy for solving the variational problem. We have derived in Chapter 5 the Helmholtz free energy density for unit of reference area for a binary lipid mixture, which was shown to admit the following general expression

\[ \psi = \varphi^m + h_0^2 \varphi^b \]

where we have shown that

**lipid-lipid mixtures:**

\[ \varphi^m = \rho_0 \psi^0 + \rho_0 \psi^{(id)}_{mix} + \rho_0 \psi^{(ex)}_{mix} + \psi^{(nn)}_{elast} \]

**lipid/cholesterol mixtures:**

\[ \varphi^m = \rho_0 \psi^0 + \rho_0 \psi^{(FH)}_{mix} + \rho_0 \psi^{(nn)}_{cholest} + \psi^{(nn)}_{elast} \]

and where the lower order bending term admits the following contribution

\[ \varphi^b = \frac{h_0^2}{6} \left[ \kappa_1 H^2 + \kappa_2 K + \frac{\alpha_o}{2} \left| \nabla S \hat{J} \right| \right] \]

We remind that the bending rigidities \( \kappa_1, \kappa_2 \) as well as the penalizing factor \( \alpha_o \) are expressible as functions of the derivatives of the purely membranal energy term \( \varphi^m \).

The solution of the resulting variational problem, for given values of temperature \( T \), pressure difference \( \Delta \pi \) and number of molecules of the two components \( N_1 \) and \( N_2 \), leads to the determination of the Euler-Lagrange equations for our membrane model which, as we expect, couples all the main features of chemical phase separation, order/disorder transition and curvature elasticity.

Under a qualitative point of view very little can be said regarding the local minimizers of the whole energy functional. Nevertheless, the hierarchy between membranal and bending energy terms suggests that a first insight to the solution of the problem might be obtained neglecting the lower order bending energy term. Indeed at a very first stage the following stress-free problem for an open lipid membrane in aqueous solution may be studied

\[ \min_{(\chi, J)} \left\{ \int_{\Sigma} \varphi^m(\chi, J; T) \, dA \right\} \quad \text{with} \quad \int_{\Sigma} \rho_0 \chi \, dA = N_1 \]

for given values of the temperature and composition, which will be carried out in the following section. A further generalization would consist in studying the same problem in a soft-device, provided by the application of a constant, hydrostatic membranal surface tension \( \sigma \), such that the expression of the work of external loads might trivially be written as

\[ \delta \mathcal{L} = \sigma \int_{\Sigma} \delta J \, dA. \]

Within this stage the constant \( \sigma \) would represent a given data, and would allow us to understand the influence of surface tension on the chemo/structural phase transition.
The solution of the complete purely membranal problem
\[
\min_{(\chi,J)} \left\{ \int_{\Sigma} \varphi^m(\chi,J;T) \, dA - \mathcal{L}(\Delta P) \right\} \quad \text{with} \quad \int_{\Sigma} \rho_0 \chi \, dA = N_1,
\]
describes issues relative to the chemical phase separation and the order/disorder transition, but (as it will be shown in the next section) it is not capable to provide equilibrium shapes different than spheres. One of the aims of this work is also to account for the ”budded domains” which are experimentally observed in lipid membranes: we expect that these equilibrium configurations are found as minimizers of the whole variational problem.


2.1. Introduction. According to the model proposed in Chapter 5 we here deal with the purely membranal, stress free problem for a lipid/lipid membrane, whose energy density was found to be non-convex in both its argument \(\chi\) and \(J\). Here we investigate the occurrence of phase separation and order/disorder transition for varying values of the temperature and composition.

As described in Chapter 5, the so called main transition is described by the order parameter \(J\), which defines the \(L_o\) ordered and \(L_d\) disordered phases. In this section we will further show, in agreement with the results obtained by Komura & others [35], that non convexity of the energy density in \(\chi\) then defines further variants of such phases, distinguished from each other by the composition, that is the \(L^1_o\), \(L^2_o\) and \(L^1_d\), \(L^2_d\) phases.

The results of this procedure are strongly influenced by the temperature, which acts as a shifter of the various energy terms, inducing or cancelling non-convexities in the chemical counterpart of the energy. Some general aspects of the global minimizers of the problem are shed in evidence, although neither local minimizers nor general equilibria are explained.

2.2. Lipid/lipid binary mixtures. We are here interested to the phase separation phenomena temperature driven in a binary membrane of saturated and unsaturated lipids. To do this we specify the given data and we make some assumptions on the reference configuration.

**Given data:** are the mole numbers \(N_s, N_u\) and the order/disorder transition temperatures \(T^{s}_{ts}\) and \(T^{u}_{ts}\) of the saturated and unsaturated lipids; the average molecular fractions are \(\bar{\chi}_s = N_s/N_{tot}\) and \(\bar{\chi}_u = N_u/N_{tot}\). Furthermore it is given the external temperature \(T\). In agreement with Komura & others [35] we here neglect the formation free energy density term \(\psi^0\), hence the data regarding standard chemical potentials \(\mu^0_i\) are not needed;
Reference configuration: according to the formulated model, the structural coarse grained order parameter of this theory is represented by the areal stretch $J$ with respect to an arbitrary reference configuration; more precisely, we assume

- that the membrane is an open, stress free surface in water solution; otherwise we might postulate that the membrane is closed but swollen, but this would require more detailed information regarding the enclosed volume and the membrane permeability, which we are not interested in in this stage of the model;
- that the reference configuration of the membrane coincides with its initial configuration, defined by a reference temperature $T_o$ which is inferior to the lower transition temperature of both the lipids, so that the reference configuration is completely in the $L_o$ phase; in such phase $J = J_o = 1$;
- that the reference configuration has a homogeneous composition, given by the values of the mean molecular fractions $\bar{\chi}_u$ and $\bar{\chi}_s$, and hence a uniform reference molecular density $\rho_0$, which from now on will be considered as a known constant.

As derived in Chapters 5 & 6, the purely membranal counterpart of the stored Helmholtz energy can be written as

$$E^{(m)}(\chi, J) := \int_{\Sigma} \left[ \rho_0 \psi_1^{(id)} + \rho_0 \psi_{mix}^{(ex)} + \rho_0 \psi_{mix}^{(en)} \right] dA = \int_{\Sigma} \left[ \psi_1(J; T) + \psi_2(\chi, J; T) \right] dA,$$

where

$$\begin{align*}
\psi_1(\chi; T) &= kT[\chi \ln \chi + (1 - \chi) \ln(1 - \chi)] - W\chi(1 - \chi), \\
\psi_2(\chi, J; T) &= \psi_{elast}^{(en)}(\chi, J; T)
\end{align*}$$

where $k$ is the Boltzmann’s constant, $T$ the actual given temperature, $W$ the interaction parameter, $\chi$ the molecular fraction of the saturated lipid in the mixture, $\psi_2$ the elastic, non-convex energy density phenomenologically introduced in Chapter 5.

The variational problem can finally be recast as follows

$$\min_{(\chi, J)} E^{(m)}(\chi, J; T) = \min_{(\chi, J)} \left\{ \int_{\Sigma} [\psi_1(\chi; T) + \psi_2(\chi, J; T)] dA \right\} \quad \text{with} \quad \rho_0 \int_{\Sigma} \chi dA = N_1.$$

For simplicity of notation, parametric dependence on the $T$ will be suppressed. We now first will minimize with respect to $J$ and hence the minimization of the resulting functional of $\chi$ will be performed.

### 2.3. Minimization in $J$.

In correspondence of the global minimizer $\bar{J}$ it results that:

$$E^{(m)}(\chi, J) \geq E^{(m)}(\chi, \bar{J}) =: \bar{E}^{(m)}(\chi) \quad \forall J > 0.$$

The minimization in $J$ can be accomplished observing that only the term $\psi_2$ depends on $J$, thus it results that the global minimizer $\bar{J}$ can simply be found minimizing $\psi_2$. 
The global minimization of $\psi_2(\chi, J)$ with respect to $J$ is, at this point, trivial; basically it depends on the local value of the molecular fraction $\chi$ and of the temperature $T$. Recall that in our model the order/disorder transition temperature of the mixture is a function of the local molecular fraction via the linear interpolation between the different transition temperatures of saturated and unsaturated lipids

$$T_{tr}(\chi) = \chi T_{tr}^s + (1 - \chi) T_{tr}^u.$$  

The way the elastic energy density $\psi_2$ is built is such that for $T < T_{tr}$ the global minimum is attained in correspondence of $J = J_o = 1$, and for $T > T_{tr}$ in correspondence of $J = J_d > 1$. Since the experimental evidence suggests that $T_{tr}^s > T_{tr}^u$, the following cases may occur:

- $T < T_{tr}^u$: for all values of the local molecular fraction $\chi$, it results that $T < T_{tr}(\chi)$, thus the system is always in the ordered $L_o$ phase;
- $T = T_{tr}^u$: in all points characterized by a local value of $\chi = 0$ there is local coexistence of $L_o$ and $L_d$ phases, everywhere else the system is in phase $L_o$;
- $T \in (T_{tr}^u, T_{tr}^s)$: there exists a value of the local molecular fraction, equal to:

$$\chi^* = \frac{T - T_{tr}^u}{T_{tr}^s - T_{tr}^u}$$

such that any point in which $\chi < \chi^*$ is in phase $L_d$ (since there $T > T_{tr}$) and any point in which $\chi > \chi^*$ is in phase $L_o$ (since there $T < T_{tr}$). Phases $L_o$ and $L_d$ locally coexist in points where $\chi = \chi^*$;
- $T = T_{tr}^s$: in all points characterized by a local value of $\chi = 1$ there is local coexistence of $L_o$ and $L_d$ phases, everywhere else the system is in phase $L_d$;
- $T > T_{tr}^s$: for any value of the local molecular fraction, the system is completely in the disordered $L_d$ phase.

The minimization of the energy with respect to $J$ yields the minimizer as a function of $\chi$ and $T$, that is $\tilde{J} = \tilde{J}(\chi(\zeta_\alpha))$, where the point-wise dependence has been underlined. The values of the minimizer $\tilde{J}$ for varying values of the local molecular fraction and of the temperature can be summarized in the following table:

<table>
<thead>
<tr>
<th>$T$</th>
<th>$\chi$</th>
<th>Phase</th>
<th>$J$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T &lt; T_{tr}^u$</td>
<td>all</td>
<td>$L_o$</td>
<td>$J = J_o$</td>
</tr>
<tr>
<td>$T \in [T_{tr}^u, T_{tr}^s]$</td>
<td>$\chi &lt; \chi^*$</td>
<td>$L_d$</td>
<td>$J = J_d$</td>
</tr>
<tr>
<td></td>
<td>$\chi = \chi^*$</td>
<td>$L_d &amp; L_o$</td>
<td>$\tilde{J} = J_o &amp; \tilde{J} = J_d$</td>
</tr>
<tr>
<td></td>
<td>$\chi &gt; \chi^*$</td>
<td>$L_o$</td>
<td>$\tilde{J} = J_o$</td>
</tr>
<tr>
<td>$T &gt; T_{tr}^s$</td>
<td>all</td>
<td>$L_d$</td>
<td>$J = J_d$</td>
</tr>
</tbody>
</table>
The situation is depicted in the following **local** phase diagram:

![Figure 1](image)

**Figure 1.** The order-disorder domains for varying values of the molecular fraction and temperature.

**REMARK.** The validity of the proposed energy density $\psi_2$ is actually limited to the range in which the parameter $t$ belongs to the interval $[t', t'']$. As matter of fact, the range of temperatures investigated in this study is broader than such interval, but this does not produce effects on the previous discussion on the values of the energy (see Chapter 5 - Appendix B for details).

### 2.4. Minimization in $\chi$: qualitative discussion.

The minimization in $\chi$ involves the whole energy functional, and it has to fulfill the constraint on the conservation of the given number of molecules

$$
\begin{align*}
\min_{\{\chi\}} \bar{E}^{(m)}(\chi) &= \min_{\{\chi\}} E^{(m)}(\chi, J(\chi)) \\
&= \min_{\{\chi\}} \int_S [\psi_1(\chi) + \psi_2(\chi, J(\chi))] \, dA \\
&\text{with the constraint: } N_1 = \rho_0 \int_{\Sigma} \chi \, dA = \text{const.}
\end{align*}
$$

where:

$$
\psi_1(\chi) = kT[\chi \ln \chi + (1 - \chi) \ln(1 - \chi)] - W\chi(1 - \chi).
$$

Let us now make some general considerations about the constrained variational problem. To simplify the notations, let us denote the specific energy as

$$
\Phi(\chi) := \psi_1(\chi) + \psi_2(\chi, J(\chi)).
$$
We are here seeking the solution of the following problem, for a given value of the external temperature

$$\min_{\chi} \tilde{E}^{(m)}(\chi) = \min_{\chi} \int_{\Sigma} \Phi(\chi) \, dA, \quad \text{with} \quad N_1 = \rho_0 \int_{\Sigma} \chi \, dA,$$

where $N_1$ is the given total mole number of the saturated lipid in the mixture. The minimizer $\bar{\chi} = \bar{\chi}(\zeta_\alpha)$ satisfies the following inequality

$$\tilde{E}^{(m)}(\bar{\chi} + \varepsilon \xi) \geq \tilde{E}^{(m)}(\bar{\chi}), \quad \forall \varepsilon > 0, \forall \xi \quad \text{such that} \int_{\Sigma} \xi \, dA = 0.$$

Granted the regularity of the energy functional, the extremum points of the energy functional can be found as follows

$$\left[ \frac{d}{d\varepsilon} \tilde{E}^{(m)}(\chi + \varepsilon \xi) \right]_{\varepsilon=0} = \int_{\Sigma} \frac{\partial \Phi}{\partial \chi} \xi \, dA = 0, \quad \forall \xi \quad \text{such that} \int_{\Sigma} \xi \, dA = 0.$$

Since it is known that, given any two functions $g$ and $h$, integrable on a domain $\Omega$, it results that

$$\int_{\Omega} gh = 0 \quad \forall h \quad \text{such that} \quad \int_{\Omega} h = 0 \quad \Rightarrow \quad g = \text{const.} \quad \text{on} \ \Omega$$

we can infer that the variational problem formulated before reduces to find the field $\bar{\chi}$ which solves the following differential problem:

$$\frac{\partial \Phi}{\partial \chi} = \rho_0 \mu = \text{const},$$

$$N_1 = \rho_0 \int_{\Sigma} \chi \, dA,$$

where we remind that here the reference molecular density $\rho_0$ is a given constant.

The determination of the unknown constant $\mu$ (namely, the molecular chemical

\[1\]The proof is trivial and does not require other hypothesis but integrability. Indeed let

$$\bar{g} := \frac{1}{|\Omega|} \int_{\Omega} g \, dA \quad \text{and} \quad \delta g := g - \bar{g}$$

then let

$$\Omega_1 := \{ \zeta \in \Omega \mid \delta g(\zeta) \geq 0 \}, \quad \Omega_2 := \{ \zeta \in \Omega \mid \delta g(\zeta) < 0 \}.$$

If $|\Omega_1| = 0$ then all over the domain $\delta g < 0$ thus the value $\bar{g}$ cannot be the average, and this contradicts the hypothesis. Else if $|\Omega_2| = 0$ then all over the domain $\delta g \geq 0$: if $\delta g > 0$ the same argument used before holds, else if $\delta g = 0$ then the thesis is satisfied. Let us now consider the case $|\Omega_1| \neq 0$ and $|\Omega_2| \neq 0$. If it were $g \neq \text{const}$, let $\bar{g}_1$ and $\bar{g}_2$ respectively the different mean values of $g$ on $\Omega_1$ and $\Omega_2$, where evidently $\Omega_1 \cap \Omega_2 = \{ \emptyset \}$ and $\Omega_1 \cup \Omega_2 = \Omega$; hence, chosen $h$ defined by parts as follows:

$$h = \begin{cases} |\Omega_2| & \text{on} \ \Omega_1 \\ -|\Omega_1| & \text{on} \ \Omega_2 \end{cases}$$

it results that:

$$\int_{\Omega} h \, dA = |\Omega_2| \int_{\Omega_1} dA - |\Omega_1| \int_{\Omega_2} dA = |\Omega_2||\Omega_1| - |\Omega_1||\Omega_2| = 0 \quad \Rightarrow \quad \int_{\Omega} gh \, dA = |\Omega_1||\Omega_2|(\bar{g}_1 - \bar{g}_2) = 0$$

which means that the hypothesis $\bar{g}_1 \neq \bar{g}_2$ was absurd, hence $g = \text{const.}$
potential) crucially depends on the form of the energy density and on stability considerations. Let us consider the two main cases regarding the general energy density $\Phi$.

i. $\Phi$ is a strictly convex functional. In this case, for any value of the unknown constant $\mu$ there exists a unique value $\bar{\chi}_\mu = \text{const.}$ for all $\zeta \in \Sigma$ which satisfies the tangency condition. The molecular number constraint implies that

$$N_1 = \rho_0 \int_{\Sigma} \bar{\chi}_\mu dA = \rho_0 \bar{\chi}_\mu \int_{\Sigma} dA = \bar{\chi}_\mu N_{tot} \implies \bar{\chi}_\mu = \frac{N_1}{N_{tot}} = \bar{\chi},$$

where we remind that $\bar{\chi}$ is a given data; this relation means that the field $\chi$ is constant all over the domain and equals at every point the average composition. The value of $\mu$ is then easily determined as

$$\mu = \frac{1}{\rho_0} \frac{\partial \Phi(\bar{\chi})}{\partial \chi}.$$

ii. $\Phi$ is a strictly non-convex functional. In this case, for any given value of the unknown constant $\mu$ there exist in general more than one value of $\chi$ which satisfy the tangency condition. As it was shown in Chapter 5, the energy density we are dealing with is convex in $\chi$ for all values of the given temperature which are inferior to a certain critical temperature, above which $\Phi$ becomes a non-convex, two well energy density. This evidence leads to the conclusion that for any given value of $\mu$ at most two stable values of $\chi$ exist, for which the tangency condition is satisfied. Let $\bar{\chi}_1^\mu$ and $\bar{\chi}_2^\mu$ to be such values, then it results:

$$\rho_0 \mu = \frac{\partial \Phi(\bar{\chi}_1^\mu)}{\partial \chi} = \frac{\partial \Phi(\bar{\chi}_2^\mu)}{\partial \chi} = \text{const.}.$$ 

This means that there exist two sub-domains $\Sigma^1$ and $\Sigma^2$, with $\Sigma^1 \cap \Sigma^2 = \{\emptyset\}$ and $\Sigma^1 \cup \Sigma^2 = \Sigma$, such that $\chi = \bar{\chi}_1^\mu$ in $\Sigma^1$ and $\chi = \bar{\chi}_2^\mu$ in $\Sigma^2$, then the molecular number constraint reads as follows

$$N_1 = \rho_0 \int_{\Sigma} \chi dA = \rho_0 \bar{\chi}_1^\mu \int_{\Sigma^1} dA + \rho_0 \bar{\chi}_2^\mu \int_{\Sigma^2} dA = \bar{\chi}_1^\mu N_{tot}(\Sigma^1) + \bar{\chi}_2^\mu N_{tot}(\Sigma^2).$$

where $N_{tot}(\Omega)$ represents the total number of molecules contained in the domain $\Omega$. If the parameter

$$\lambda := \frac{N_{tot}(\Sigma^1)}{N_{tot}(\Sigma)}$$

represents the ratio between the total number of molecules of the domain $\Sigma^1$ and the total number of molecules on the surface, we can rewrite the previous condition as

---

$^2$Remind that by the definition of $\rho_0$ it is

$$\int_{\Omega} \rho_0 dA = N(\Omega)$$

gives the total number of molecules contained in the domain $\Omega$. 
follows
\[ \bar{\chi} = \bar{\chi}_1^1 \lambda + \bar{\chi}_2^2 (1 - \lambda) \implies \lambda = \frac{\bar{\chi} - \bar{\chi}_2^2}{\bar{\chi}_1^1 - \bar{\chi}_2^2}, \]

and this last relation expresses the so called lever rule. The value of \( \lambda \), determined up to this moment on the basis of an assumed value for the chemical potential, gives a precise information on the relative dimensions of the domains occupied by different material phases characterized by different concentrations \( \bar{\chi}_1 \) and \( \bar{\chi}_2 \).

Furthermore, since the reference molecular density \( \rho_0 \) is constant all over \( \Sigma \), we infer that the ratio \( \lambda \) also represents the ratio
\[ \lambda = \frac{\text{meas}(\Sigma^1)}{\text{meas}(\Sigma)} = \frac{A^1}{A} \]

between the area \( A^1 \) of the reference domain where the molecular fraction equals \( \bar{\chi}_1 \) and the total reference area \( A \). The calculation of the current areas of these domains will be carried out in the next section.

Let us now focus on the determination of the unknown chemical potential \( \mu \). Let now \( \bar{\chi} \) be an extremum point for the energy \( E(\chi) \); standard stability considerations allow us to infer that the convex envelope of the energy density functional represents the locus of the global minima of the minimization problem. The computation of the convex envelope can be done by using the "Maxwell line", that is the common tangent line to the two wells of the energy density functional. Letting \( \bar{\chi}_1^1 \) and \( \bar{\chi}_2^2 \) be the points where the Maxwell line is tangent to the energy density \( \Phi(\chi) \), the convex envelope \( \Phi_c(\chi) \) is defined as follows:
\[ \Phi_c(\chi) = \begin{cases} \Phi(\chi) & \forall \chi < \bar{\chi}_1^1 \text{ and } \chi > \bar{\chi}_2^2; \\ \frac{\bar{\chi}_2^2 - \chi}{\bar{\chi}_2^2 - \bar{\chi}_1^1} \Phi(\bar{\chi}_1^1) + \frac{\chi - \bar{\chi}_1^1}{\bar{\chi}_2^2 - \bar{\chi}_1^1} \Phi(\bar{\chi}_2^2) & \forall \chi \in [\bar{\chi}_1, \bar{\chi}_2^2]. \end{cases} \]

The global minimizers of the variational problem, according to different values taken by the average molecular fraction of the saturated lipid \( \bar{\chi} \), which is a given data:
- \( \bar{\chi} < \bar{\chi}_1^1 \) or \( \bar{\chi} > \bar{\chi}_2^2 \): the mixture is uniformly characterized by the composition \( \bar{\chi} \), and the chemical potential is given by \( \rho_0 \mu = \partial \Phi(\bar{\chi})/\partial \chi \)
- \( \bar{\chi}_c^2 \leq \bar{\chi} \leq \bar{\chi}_c^1 \): in the mixture is made of two disjoint sub-domains \( \Sigma^1 \) and \( \Sigma^2 \) respectively characterized by uniform compositions \( \bar{\chi}_c^1 \) and \( \bar{\chi}_c^2 \); the total number of molecules in the domain \( \Sigma^1 \) is given by \( \lambda N_{tot} \), where \( \lambda = (\bar{\chi} - \bar{\chi}_c^2)/(\bar{\chi}_c^1 - \bar{\chi}_c^2) \); the chemical potential \( \mu \) is trivially the angular coefficient of the Maxwell line, given by \( \rho_0 \mu = (\Phi(\bar{\chi}_c^2) - \Phi(\bar{\chi}_c^1))/(\bar{\chi}_c^2 - \bar{\chi}_c^1) \).

Let us now pass to the particular case we are dealing with. The energy density function to be studied is the following one:
\[ \Phi(\chi) = \psi_1(\chi) + \psi_2(\chi, \bar{J}(\chi)). \]
Let us try to understand qualitatively the behavior of the functional $\psi_2$ with respect to $\chi$ for different values of the fixed temperature. The expression of $\psi_2$ was given in Chapter 5 - Appendix B as a function of the value $J_t \in [J_o, J_d]$ at which the relative maximum for $\psi_2$ is achieved. We do not report the explicit expression of the energy density $\psi_2$ here for reasons of brevity, rather we refer to the above mentioned Appendix B for all the following dissertation.

As first thing, it is easy to check that since $t = T - T_{tr}(\chi) = T - \chi T_{tr}^a - (1 - \chi) T_{tr}^o$, with $T_{tr}^o < T_{tr}^a$, it results from the definitions that $\chi \uparrow \Rightarrow t \downarrow \Rightarrow J_t \uparrow$; furthermore, the behavior of the energy with respect to the molecular fraction $\chi$ is driven by the external temperature as follows

a) $T < T_{tr}^o$: then $t < 0$ for all $\chi$, hence $\tilde{J} = J_o$ so $\psi_2(\chi, J_o) < 0$; moreover if $\chi \uparrow \Rightarrow J_t \uparrow \Rightarrow \psi_2(\chi, J_o) \downarrow$;

b) $T = T_{tr}^o$: $t \leq 0$ if, respectively, $\chi \geq 0$; it results that for $\chi = 0$ the two wells have the same height and the energy is the same, that is $\psi_2(\chi, J_o) = \psi_2(\chi, J_d) = 0$. For $\chi > 0$, the energy behaves like in case a);

c) $T_{tr}^o < T < T_{tr}^s$: $t \geq 0$ if, respectively, $\chi \geq \chi^*$, where $\chi^* = (T - T_{tr}^o)/(T_{tr}^s - T_{tr}^o)$. For $\chi < \chi^*$, it results that $t > 0$, thus $\tilde{J} = J_d$ hence $\psi_2(\chi, J_d) = 0$, and for $\chi = \chi^*$ it is $t = 0$ and again $\psi_2(\chi, J_o) = \psi_2(\chi, J_d) = 0$. For $\chi > \chi^*$ it results that $t < 0$ and the energy behaves like in case a);

d) $T = T_{tr}^s$: $t \geq 0$ if, respectively, $\chi \leq 1$; it results that for $\chi = 1$ the two wells have the same height and the energy is the same, that is $\psi_2(\chi, J_o) = \psi_2(\chi, J_d) = 0$. For $\chi < 1$, $t > 0$ thus $\tilde{J} = J_d$, hence $\psi_2(\chi, J_d) = 0$;

e) $T > T_{tr}^s$: $t > 0$ for all $\chi$, thus $\tilde{J} = J_d$ and $\psi_2(\chi, J_d) = 0$.

To summarize, we deduced that the function

$$\tilde{\psi}_2(\chi) := \psi_2(\chi, \tilde{J}(\chi))$$

has the following behavior with respect to $\chi$

$$\tilde{\psi}_2(\chi; T) = \begin{cases} 
T \leq T_{tr}^o & : A(J_d - J_o)^3(J_m - f(\chi; T))/6; \\
T \in (T_{tr}^o, T_{tr}^s) & : \begin{cases} 
\chi \leq \chi^*: 0; \\
\chi > \chi^*: A(J_d - J_o)^3(J_m - f(\chi; T))/6;
\end{cases}; \\
T \geq T_{tr}^s & : 0;
\end{cases}$$

being $J_m = (J_o + J_d)/2$. A qualitative behavior of the energy $\psi_2$ with $\chi$ for various values of the fixed temperature is depicted in Figure 2.

---

3It has been already remarked (see Appendix C) the existence of a lower bound for the external temperature $T_{inf}$, such that $T \geq T_{inf}$ is a necessary condition for the energy $\psi_2$ proposed to be well defined; for the range of temperature here considered, this threshold value is never attained.
2. Purely Membranal Problem I: Temperature Driven Phase Transitions

The elastic energy \( \tilde{\psi}_2(\chi; T) = \psi_2(\chi, \tilde{J}(\chi); T) \) for varying values of the temperature \( T \). Essentially, it represents the fact that when the membrane is in the \( L_o \) phase, the value of the energy attained in correspondence of the minimizer \( J_o \) decreases as \( \chi \) is increased, while when the membrane is in the \( L_d \) phase the energy attained in correspondence of the minimizer \( J_d \) equals zero for all values of the molecular fraction.

2.5. Minimization in \( \chi \): calculations. Let us now go back to the minimization of the energy functional with respect to \( \chi \), once minimization in \( J \) has already been accomplished. Let us recall that the integral form of the problem is the following:

\[
\min_\chi \left\{ \int_\Sigma \Phi(\chi) \, dA \right\} \quad \text{with } \chi \text{ such that } N_1 = \rho_0 \int_\Sigma \chi \, dA = \text{const.}
\]

where we recall that the energy density \( \Phi \) had been defined, after the minimization in \( J \), as

\[
\Phi(\chi) := \psi_1(\chi) + \psi_2(\chi, \tilde{J}(\chi)) = \psi_1(\chi) + \tilde{\psi}_2(\chi).
\]

We have shown that the problem can be recast in the following form

\[
\rho_0 \mu = \frac{\partial \Phi}{\partial \chi} = \text{const.} \quad \text{with } \chi \text{ such that } N_1 = \rho_0 \int_\Sigma \chi \, dA = \text{const.}
\]

where the chemical potential \( \mu \) is a constant to be determined. Substituting the complete expression of \( \Phi \) we obtain the following differential equation:

\[
\rho_0 \mu = \frac{\partial \Phi}{\partial \chi} = kT[\ln \chi - \ln(1 - \chi)] + W(2\chi - 1) + \frac{\partial \tilde{\psi}_2}{\partial \chi},
\]

where (we refer to Chapter 5 - Appendix B for the complete expressions of the energy \( \psi_2 \))

\[
\frac{\partial \tilde{\psi}_2}{\partial \chi} = \begin{cases} 
0 & \text{for } \chi \leq \chi^*; \\
\frac{A}{6} \frac{\partial f}{\partial \chi}(J_d - J_o)^3(T_{tr}^d - T_{tr}^u) & \text{for } \chi > \chi^*.
\end{cases}
\]

The energy density \( \Phi \) is the sum of three different contributions, namely:
Entropic counterpart: \( kT[\ln \chi + (1 - \chi) \ln(1 - \chi)] \);

Enthalpic counterpart: \( -W \chi(1 - \chi) \);

Elastic counterpart: \( \tilde{\psi}_2(\chi) \),

where each contribution is depicted schematically in Figure 3. If the interplay of the three energy densities is such to determine the occurrence of non-convexities of \( \Phi \) with respect to \( \chi \), then we assist to the eventuality of material variants of the geometric phases \( L_o \) and \( L_d \).

Figure 3. A qualitative behavior of the three addends of the final energy density \( \Phi \) with respect of the molecular fraction \( \chi \).

As already discussed when dealing with the minimization with respect to \( J \), we argued that the elastic energy density \( \psi_2(\chi, J) \), when evaluated in the minimizer \( \tilde{J} \), attains the following values

\[
\tilde{\psi}_2(\chi) = \begin{cases} 
T \leq T_{tr}^u : A(J_d - J_o)^3(J_m - f(\chi; T))/6; \\
T \in (T_{tr}^u, T_{tr}^s) : \chi \leq \chi^* : 0; \\
T \geq T_{tr}^s : \chi > \chi^* : A(J_d - J_o)^3(J_m - f(\chi; T))/6; 
\end{cases}
\]

being \( \chi^* = (T - T_{tr}^u)/(T_{tr}^s - T_{tr}^u) \). As discussed and motivated in Chapter 5 - Appendix B, our choice for the function \( f(t) \) is the simplest possible, that is

\[
\begin{align*}
& \quad \{ t \in [t', 0] \} \text{ (that is, } \chi > \chi^* \}) : f(t) = J_m + \frac{t}{t'}(J_d - J_m); \\
& \quad \{ t \in [0, t''] \} \text{ (that is, } \chi \leq \chi^* \}) : f(t) = J_m - \frac{t}{t'}(J_m - J_o).
\end{align*}
\]
Furthermore, it should be noticed that for \( T < T_{tr}^u \) and \( T > T_{tr}^s \) it results respectively that \( \chi^* < 0 \) (hence \( \chi > \chi^* \) always), and \( \chi^* > 1 \) (hence \( \chi < \chi^* \) always), thus we can give the following simple expression for the energy \( \tilde{\psi}_2(\chi) \):

\[
\tilde{\psi}_2(\chi; T) = \begin{cases} 
\chi \leq \chi^* : 0; \\
\chi > \chi^* : -A \frac{4}{T'} (J_d - J_o)^{\frac{4}{7}};
\end{cases}
\]

where the value \( t' \) was determined on the basis of experimental data relative to the Landau expansion of the energy density, precisely \( t' = -\frac{2}{9} \frac{a^2_3}{a_2 a_4} \).

In Figure 4, using MatLab we carried out some numerical calculations and plots of the whole energy \( \Phi(\chi) \). It is interesting to observe that non-convexities of the resulting energy density arise also when the purely chemical counterpart of the energy density is convex, as depicted in the Figure 4-a.

This shows that the resulting energy density \( \Phi(\chi) \) consists of the sum of the piece-wise constant function \( \tilde{\psi}_2(\chi) \) and of the function \( \psi_1(\chi) \) which can be convex or non-convex according to the ratio \( T/W \).

It is evident that even when \( \psi_1(\chi) \) is convex in \( \chi \), the resulting total energy is certainly non-convex for temperatures in the range \([T_{tr}^u, T_{tr}^s]\), as depicted in Figure 4-a where the interaction parameter is \( W = 0 \).

When the purely chemical energy \( \psi_1(\chi) \) is non-convex, the resulting energy density \( \Phi(\chi) \) will result non-convex for all values of temperature, as depicted in Figure 4-b.
2.6. Final results: temperature driven phase separation. Let us now schematically depict the obtained solutions of the purely membranal, stress-free problem, for varying values of the controlled temperature and average chemical composition $\bar{\chi}$. It results that the following possibilities may occur:

![Diagram](image)

**Figure 5.** The common tangent construction for the energy density $\Phi(\chi; T) = \psi_1(\chi) + \tilde{\psi}_2(\chi)$, represented by the black curve. The $\psi_1$ curve, where not coincident with $\Phi$, is represented by the red curve. Cases a), b) and c) refer to the case $\psi_1(\chi; T)$ convex, whereas cases d), e) and f) refer to $\psi_1(\chi; T)$ non-convex. The isotherms range inside and outside of the interval $[T_{u}\operatorname{tr}, T_{s}\operatorname{tr}]$.

1. $\psi_1(\chi; T)$ is strictly convex: the following sub-cases occur:

   a) $T < T_{u}\operatorname{tr}$: for any given value of the average $\bar{\chi}$, the molecular fraction is uniform all over the membrane and it is equal to $\bar{\chi}$; the membrane is all in the $L_o$ ordered geometric phase hence $J = J_o = 1$. The measure of the current configuration of the membrane is
   $$ a = \int_{S} J_o \, dA = A $$
   hence it equals the surface of the reference configuration $A$;

b) $T_{u}\operatorname{tr} \leq T \leq T_{s}\operatorname{tr}$: three instances might occur:
2. PURELY MEMBRANAL PROBLEM I: TEMPERATURE DRIVEN PHASE TRANSITIONS.

b)-1: \( \bar{\chi} < \bar{\chi}^1 \): the molecular fraction is uniform and equal to \( \bar{\chi} \) all over the membrane, moreover the system is all in the disordered \( L_d \) phase, hence \( J = J_d \); the measure of the current configuration of the membrane is

\[
a = \int_S J_d dA = J_d A > A;
\]

b)-2: \( \bar{\chi}^1 < \bar{\chi} < \bar{\chi}^2 \): the membrane appears in two distinct material phases \( \bar{\chi}^1 \) and \( \bar{\chi}^2 \); the geometric phase is \( L_d \) within the domain where \( \chi = \bar{\chi}^1 \) and \( L_o \) within the domain where \( \chi = \bar{\chi}^2 \). The coefficient:

\[
\lambda = \frac{\bar{\chi} - \bar{\chi}^2}{\bar{\chi}^1 - \bar{\chi}^2}
\]

represents the ratio between area of the domains - measured on the reference configuration - \( \Sigma^1 \) and \( \Sigma \), respectively the domain where the molecular fraction is \( \bar{\chi}^1 \) and the whole reference domain of the membrane; the measure of the current area is:

\[
a = \int_S J dA = \int_{S^1} J_d dA + \int_{S^2} J_o dA = J_d A_1 + A_2 = [\lambda J_d + (1 - \lambda)]A > A;
\]

b)-3: \( \bar{\chi} > \bar{\chi}^2 \): the molecular fraction is uniform and equal to \( \bar{\chi} \) all over the membrane, moreover the system is all in the \( L_o \) phase, hence \( J = J_o \); the measure of the current area is:

\[
a = \int_S J_o dA = A;
\]

c) \( T > T_{s^*} \): for any given value of the average \( \bar{\chi} \), the molecular fraction is uniform all over the membrane and it is equal to \( \bar{\chi} \); the membrane is all in the \( L_d \) geometric phase hence \( J = J_d \); the area of the current surface is:

\[
a = \int_S J_d dA = J_d A > A.
\]

2. \( \psi_1(\chi;T) \) is strictly non-convex: the following cases may occur:

\[\text{d)} \ T < T_{s^*} \]: the system is completely in the \( L_o \) phase, hence the measure of the current surface is always equal to \( A \), the area of the reference surface. Under the material point of view, three instances might occur:

- \( \bar{\chi} < \bar{\chi}^1 \): the molecular fraction is uniform and equal to \( \bar{\chi} \);
• $\bar{\chi}_1 < \bar{\chi} < \bar{\chi}^2$: the membrane appears in two distinct material phases with concentrations $\bar{\chi}^1$ and $\bar{\chi}^2$ respectively; the coefficient:

$$\lambda = \frac{A^1}{A_{tot}} = \frac{\bar{\chi} - \bar{\chi}^2}{\bar{\chi}^1 - \bar{\chi}^2}$$

represents the ratio between the extension of the domains - measured on the reference configuration - $\Sigma^1$ and $\Sigma$

• $\bar{\chi} > \bar{\chi}^2$: the molecular fraction is uniform and equal to $\bar{\chi}$ all over the membrane;

e) $T_{tr}^u \leq T \leq T_{tr}^s$: things go exactly as in case 1.b);

f) $T > T_{tr}^s$: the system is completely in the $L_d$ phase, hence the measure of the current surface is $a = J_d A$. Under the material point of view, things go exactly as in case 2.d).

We will now set up the equilibrium problem for a closed two-constituents membrane, under a given pressure difference $\Delta P$ and at a given temperature $T$. We will show that neglecting higher order energy terms in the thickness $h_0$ of the Helmholtz energy density, which means considering a purely membranal energy density of the form

$$\psi = \psi(\chi, J)$$

imposes that the only possible equilibrium configurations are spheres, which is in contrast with the experimental evidence, where configurations differing from spheres are commonly observed (see Figure 5 in Chapter 1). This suggests that a purely membranal energy, though non-convex in both its arguments $\chi$ and $J$, is incapable to account for the non-spherical equilibrium configurations we are interested at in this Thesis, which leads to the conclusion that the higher order bending term of the Helmholtz energy density might be necessary in order to fulfill the target above.

Consider a closed membrane at a given temperature $T$ and pressure difference $\Delta P$, made of a binary mixture of two constituents of given total number of molecules $N_1$ and $N_2$. Let $p : \Sigma \subset \mathbb{R}^3 \mapsto S \subset \mathbb{R}^3$ the deformation law from the reference configuration $\Sigma$ to the current configuration $S$. We assume that in the reference configuration $\Sigma$ it results $\Delta P = 0$, furthermore the surface molecular density $\rho_0 = \frac{dN_{\text{tot}}}{dA}$ is constant all over the domain, hence $A_0 = \frac{(N_1 + N_2)}{\rho_0}$. We further assume that the reference configuration $\Sigma$ coincides with the natural configuration of the membrane, in particular $\Sigma$ is a sphere, whose radius can be determined by the relation

$$R = \sqrt{\frac{A_0}{4\pi}} = \sqrt{\frac{(M_1 + M_2)}{4\pi \rho_0}}.$$

We will show that the assumption of a spherical reference configuration does not place restrictions of any kind on equilibrium configurations of the membrane under a non-zero pressure difference. We assume that the constitutive response is given by the following molecular\(^4\) energy density

$$\phi = \phi(\chi, J)$$

with $\chi = \hat{\chi} \circ p$ the material description of the order parameter $\hat{\chi} : S \mapsto [0, 1]$ and

$$J := \sqrt{|\det[(\nabla_{\Sigma} p)^T(\nabla_{\Sigma} p)]|}$$

\(^4\)Given the surface energy density $\psi$ (energy per unit of reference area), the molecular energy density $\phi$ is simply defined as

$$\phi(\chi, J) := \frac{\psi(\chi, J)}{\rho_0}$$

The use of $\phi$ in place of $\psi$ makes calculations easier.
the surface Jacobian from $\Sigma$ to $S$. We here restrict our attention to the class of smooth deformations $p$, which means that the surface Jacobian $J$ is well defined at each point.

Consider the potential energy functional already discussed in the previous section, written on the current configuration, that is

$$\hat{F} := \int_S \hat{\rho} \hat{\phi} da - \mu \int_S \hat{\rho} \hat{\chi} da - N_1 - \hat{L}$$

where $\hat{\rho} : S \mapsto \mathbb{R}^+$ is the density of molecules per unit of current area, $\hat{\phi}$ is the spatial description of the molecular Helmholtz energy density, $\mu$ is a constant ensuring the conservation of the number of molecules for each of the two constituents, and $\hat{L}$ the work done by external loads from the reference configuration to the current configuration. Let furthermore the local conservation of the total number of molecules to hold

$$(\hat{\rho} \circ p)J = \rho J = \rho_0$$

where $\rho_0$ represents the molecular density of the reference configuration. Define the material description of the potential energy functional as $F := \hat{F} \circ p$, thus we find Euler-Lagrange equations by vanishing the variation of $F$, to be defined as

$$\delta F := \lim_{\varepsilon \to 0} \frac{\mathcal{F}(p + \varepsilon \eta, \chi + \varepsilon \xi) - \mathcal{F}(p, \chi)}{\varepsilon}$$

where the virtual displacement $\eta : \Sigma \mapsto \mathbb{R}^3$ and the perturbation $\xi : \Sigma \mapsto [0, 1]$ are completely free and smooth enough. The first variation of $\mathcal{F}$ can be calculated as follows

$$\delta \mathcal{F} = \int_{\Sigma} \rho_0 \left[ \frac{\partial \phi}{\partial \chi} \xi + \frac{\partial \phi}{\partial J} \delta J - \mu \xi \right] dA - \delta \mu \left[ \int_{\Sigma} \rho_0 \chi dA - N_1 \right] - \delta \hat{L}$$

where $\delta \mu$ represents a perturbation of the Lagrange’s multiplier $\mu$. Introducing the function $y : S \mapsto \mathbb{R}^3$ defined as follows

$$\eta = y \circ p$$

it is possible to prove that

$$\delta J = J(\text{div}_S y)_m$$

where $(\text{div}_S y)_m = (\text{div}_S y) \circ p$ represents the material description of the field $y$, and $\text{div}_S$ is the surface divergence. Let $\hat{\xi}$ be the spatial description of $\xi$, that is

$$\xi = \hat{\xi} \circ p.$$ 

At this point it is more convenient to recast the variational equation $\delta \mathcal{F} = 0$ on the current configuration

$$\int_S \hat{\rho} \left\{ \left[ \frac{\partial \phi}{\partial \chi} \right]_{S} \hat{\xi} + \left[ \frac{\partial \phi}{\partial J} \right]_{S} J \text{div}_S y - \mu \hat{\xi} \right\} da - \delta \mu \left[ \int_S \hat{\rho} \hat{\chi} da - N_1 \right] - \delta \hat{L} = 0.$$
where it is possible to show that
\[ \delta \hat{L} = \int_S -\Delta P \mathbf{n} \cdot \mathbf{y} \, dA, \]
where \( \mathbf{n} : S \mapsto \mathbb{S}^2 \) is the unit normal to the surface \( S \). Let us here remind that given a vector field \( \mathbf{v} : S \mapsto \mathbb{R}^3 \), the surface divergence theorem asserts that
\[ \int_S \text{div}_S \mathbf{v} \, da = \int_{\partial S} \mathbf{v}^\parallel \cdot \nu \, d\ell - \int_S \mathbf{v}^\perp 2H \, da \]
where \( \nu \perp \partial S \) is the normal unit vector to the boundary \( \partial S \), which belongs to the local tangent plane \( T_S \), \( \mathbf{v}^\parallel := P_S \mathbf{v} \) and \( \mathbf{v}^\perp := \mathbf{v} \cdot \mathbf{n} \) and \( H := -1/2 \text{tr}(\nabla_S \mathbf{n}) \) is the mean curvature of \( S \). Let us label \( \sigma := \hat{\rho} \hat{J} \left[ \frac{\partial \phi}{\partial \chi} \right] \bigg|_{S} = \hat{\rho}_0 \left[ \frac{\partial \phi}{\partial J} \right] \bigg|_{S} = \sigma(\chi, J) \)
where with the notation \([f]_S\) we mean the spatial description of the field \( f \). Since the surface \( S \) is here smooth and closed, it results that \( \partial S \equiv \{ \emptyset \} \), hence the variational equation can be recast as follows
\[
0 = \int_S \left\{ \hat{\rho} \left[ \frac{\partial \phi}{\partial \chi} \right]_{S} \hat{\xi} - \hat{\rho} \mu \hat{\xi} + \sigma \text{div}_S \mathbf{y} \right\} \, da + \int_S \Delta P \mathbf{n} \cdot \mathbf{y} \, da = \\
= \int_S \left\{ \hat{\rho} \left[ \frac{\partial \phi}{\partial \chi} \right]_{S} \hat{\xi} - \hat{\rho} \mu \hat{\xi} - [2H \sigma \mathbf{n} + \nabla_S \sigma - \Delta P \mathbf{n}] \cdot \mathbf{y} \right\} \, da,
\]
thus on the arbitrariness of the perturbations \( \mathbf{y}, \xi \) and \( \Delta \mu \) we infer the following Euler-Lagrange equations

**factors of \( \mathbf{y} \) in the bulk:**
\[ 2H \sigma \mathbf{n} + \nabla_S \sigma - \Delta P \mathbf{n} = 0 \]
which, projected on the local directions \( \mathbf{n} \) and \( \mathbf{n}^\perp \) yields the equations
\[ 2H \sigma - \Delta P = 0, \quad \nabla_S \sigma = 0; \]

**factor of \( \xi \) in the bulk:**
\[ \mu = \left[ \frac{\partial \phi}{\partial \chi} \right]_S \]
where \( \mu \) is an unknown constant;

**factor of \( \delta \mu \):**
\[ N_1 = \int_S \hat{\rho} \hat{\chi} \, da \]
which represents the constraint on the number of molecules.
It is evident at this point that the equilibrium equation projected on the tangent plane

$$\nabla_S \sigma = 0$$

simply means that all over the membrane the tension \( \sigma \) has to attain to a constant value. In turn, on the basis of the equilibrium equation projected on the normal direction

$$2H \sigma - \Delta P = 0$$

we deduce that, at equilibrium, the mean curvature \( H \) has to result constant all over the membrane. On the basis of a theorem in differential geometry recalled in Section II.1.4, we then deduce that

*within a purely membranal theory, where the constitutive response is given in general by the expression*

$$\phi = \phi(\chi; J; T),$$

*the smooth equilibrium configurations of a closed membrane under a given pressure difference \( \Delta p \) are spheres, whose radius is determined by the relation*

$$r := \frac{1}{H} = \frac{2\sigma}{\Delta P}.$$ 

The unknown value of the surface tension \( \sigma \) should be found considering that

$$\sigma = \rho_0 \frac{\partial \phi}{\partial J} = \text{const.}$$

where evidently the value attained by the field \( J \) at equilibrium has to fulfill the condition

$$a = \int_{\Sigma} J \, dA = 4\pi r^2 = \frac{4\pi}{H^2} = 16\pi \frac{\sigma^2}{\Delta P^2}.$$ 

This condition seems not to exclude the possibility of the coexistence of phases characterized by different values of \( \chi \) and \( J \) within the same equilibrium configuration; this last relation also puts in evidence the crucial role played by the pressure difference in modulating the extension of phase domains over the equilibrium configurations. Nevertheless, we have shown that within a purely membranal constitutive response, such equilibrium configurations have to be spheres: this does not agree with experimental evidence, suggesting that higher order energy terms are necessary in order to describe the observed equilibrium configurations.
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