Chapter 1

Introduction to morphogenetic theories in living matter

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Morphogenesis is the ensemble of the coordinates processes which lead to the formation of shapes and structures in living organisms. From a biomechanical point of view,

together with growth and remodeling, morphogenesis is one of the main processes underlying biological development. As defined by Taber in a seminal biomechanical review [11], growth can be defined as the change of mass in a material. It can occur by change of volume or by surface deposition, the former is called *volumetric growth*, the latter is defined as *surface growth*. Remodeling is considered as an alteration of the microstructure in the tissue. Material properties such as stiffness, orientation of fibers, density, strength can change in response of some external stimuli such as stress, pressure, chemical concentration. If changes in the microstructure of the tissue occur without involving variation of mass, they are referred to as *remodeling processes*.
Therefore, morphogenesis includes growth and remodeling, but it is a much more complex phenomenon. First of all, it is the result of a chain of developmental events which are not independent one from another. Second, it is a multi-scale process involving aspects from the molecular, cellular and tissue levels. Third, it is a four-dimensional problem (three-dimensional in space and dependent of time). This first Chapter aims to provide an historical overview on the morphogenetic theories in living matter which built our current knowledge on this fascinating branch of research. First, the main discoveries and ideas behind them will be presented following a chronological order. Then, the modern biomechanical approaches to morphogenesis will be presented, with particular attention on the link between mechanical stimuli and generation of form.

1.1 Early mechanistic vision

The first speculations on morphogenesis date back to ancient Greece time. In order to explain how shapes and structures originate in living organisms, in his book Historia Animalium, **Aristotle** introduced the *epigenetic hypothesis*. Although his approach was mainly philosophical, it was based on the idea that structures and shapes gradually develop and are not pre-existent from the beginning. By contrast, this latter vision called *preformationism*, became predominant in the years when theology was having a strong influence on the society and persisted until the 17th Century. **Malpighi** even claimed that a miniature of the human body (a *homunculus*) was present in the head of each sperm, completely avoiding the problem of generation of shapes in developing organisms. Besides these very early attempts, mostly based on intuition and theological preconceptions, the first approach to morphogenesis based on mechanical and geometrical arguments came from **Galileo Galilei**. After having started his studies in medicine, Galileo followed his

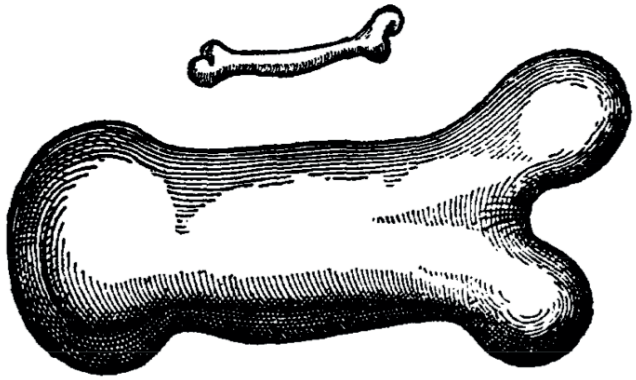


Figure 1.1: Galileo sketch of bones for a small animal (top) and a large animal (down) based on allometric arguments, taken from [1]. The natural length of the small bone has been increased three times and the thickness multiplied until, for a correspondingly large animal, the large bone would have the same strength of the small one.

passion for mathematics and physics and he devoted his entire life to investigate mechanical problems. His method was based on the idea that "*mathematics is the best way of supplying physics with the finest rules of logics*" [1]. The wide interests of Galileo covered some aspects of biomechanics such as allometric studies on vertebrates. He showed that most organisms change their shape in function of the loads that they have to hold, according to a scaling law in the form:

$$y = a_0 x^{\alpha}$$

where a_0 is a constant depending on the organism, α is the scaling exponent, x the reference variable and y is the dependent variable. If an animal increases its length l, then its mass M, being proportional to the volume, would increase by a power $\alpha = 3$ and its strength S, being proportional to the area, by $\alpha = 2$. Therefore, in the case of isometric growth, its mass would have increased more than its strength and thus the animal would have been subjected to a higher load while having a lower strength to support it. Thus, Galileo proved that the changes in size are actually governed by allometric scaling (see Figure 1.1).

The 19th century was the era of Darwinism and evolutionary theories, but also of the discovery of the cell and of the birth of experimental embryology. In particular, a

school of thought which established itself in the second half of the 19th century was the *Recapitulation theory* of Ernst Haeckel [12]. Supported by Darwinism, he claimed that steps of embryonic development of a species correspond to adult stages of their ancestors. Haeckel's school was very influential in the scientific community of the time and every attempt to show that the theory was unfounded and not able to provide a through description of morphogenesis was brutally suppressed.

1.1.1 Wilhelm His and the "constrained expansion" model

The recapitulation theory was particularly rejected by the German scientist **Wilhelm His**. He rather supported a mechanical causation behind embryonic development. He performed several experiments to prove the **constrained expansion principle**, i.e. expansion of a spherical or cylindrical tissue surrounded by inelastic tissue [13]. He performed several experiments on rubber tubes under constrained compression and tension, in order to model the gut tube, the brain formation and other changes of shape during embryogenesis. Among the most relevant results, His showed that the gut tube morphogenesis could be modeled by a rubber tube under tension. In Figure 1.2 a sketch of His's mechanical explanation for gut shaping is depicted. Because of Haeckel scientific influence, His's work had to wait some decades to be diffused. The input came right from one of Haeckel's students, Wilhelm Roux.

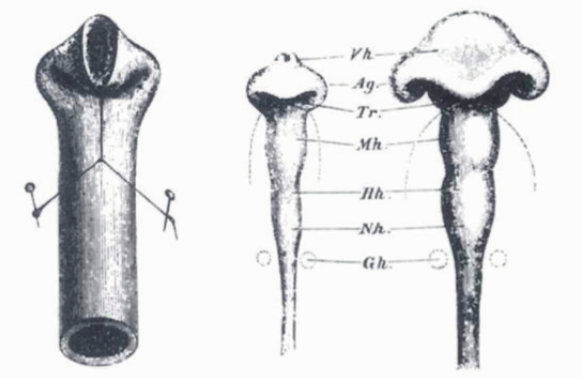


Figure 1.2: Sketch of His's model for gut tube morphogenesis, adapted from [2].

1.1.2 Wilhelm Roux and developmental mechanics

At the end of the 19th century, **Wilhelm Roux** shifted the attention from evolution (final purpose) to mechanisms (cause) in developmental biology. As well as being a promoter of His's work, he was interested into two aspects of development: first, the role of *self-differentiation* and second, the role of *dependent-differentiation*. He investigated self-differentiation by performing a lot of experiments on embryos, which eventually opened the way to the discovery of regulation and induction. *Regulation* is the property by which the embryo develops normally even if a part of it is removed. *Induction* is the ability of a cell or a tissue to influence the development of another.
The experiments to test the role of self-differentiation in the embryo where based on the analysis of the first cleavage of the embryo. Roux separated the two blastomeres which resulted after the first cleavage, killing one of the two, and he observed that from the surviving blastomere, a half-embryo still developed. He erroneously explained the result in the context of the *mosaic theory*, first introduced by **August Weismann** in the 1880s [3]. According to Weismann's theory, the nucleus of the egg contains a number of factors which determinate the cell fate, as shown in Figure 1.3. During cleavage these determinants are asymmetrically distributed between the daughter cells in the embryo. As cleavage proceeds, the potentiality of each daughter cell decreases while the cells become more and more specialized. Roux thought that killing one of the two blastomeres corresponded to remove part of the cell determinants, which resulted in the development of a half-embryo.

Some years later, **Hans Driesch**, another of Haeckel's students, explained Roux's

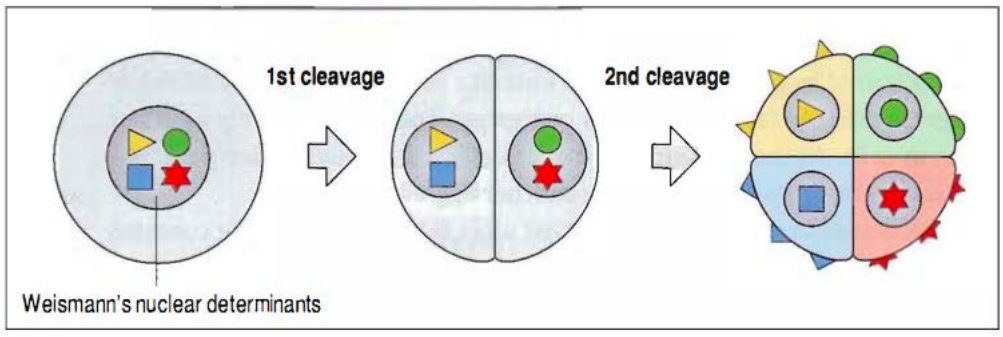


Figure 1.3: Mosaic theory: during cell division, the cell fate determinants are unequally distributed among the daughter cells, adapted from [3].

results with the discovery of regulation. Driesch repeated the experiment done by Roux using frog embryos. Unlike in Roux's experiment, after having killed one of the two blastomeres, he removed the killed cell. As a result, he observed that a whole, but smaller embryo developed from the one-cell fertilized egg because the killed cell didn't prevent the other cell from regulating and forming a complete embryo [14].

The discovery of induction had to wait some more years. Following the methodic experimental approach of Roux, in 1924 **Spemann** and **Mangold** transplanted part of the embryonic tissue from a amphibian into an embryo of a different amphibian species [15]. They observed that a partial second embryo developed from the transplanted tissue: the hosting tissue induced the development of the hosted tissue.

Roux is also remembered for establishing the concept of *functional adaptation* as a principle for dependent-differentiation: cells and tissues respond to change in external conditions in order to preserve their global organization and functions. He applied the principle of functional adaptation to the study of development of bone, cartilage and muscle. Pauwels [16] summarized Roux principle of functional adaptation as follows:

> *The formation of the different types of tissue should be considered as an adaptation of the formative tissue to the function demanded of it.*

According to Roux, the bone would be built with the minimum amount of tissue, in order to support the stresses which it undergoes. Moreover, it would adapt under the action of external forces, through growth in width in order to preserve the lightness.

1.2 The 20th century

The 20th century has been a century rich in crucial discoveries and scientific contributions to the understanding of morphogenesis. This period can be split into two phases. The first half of the century was characterized by the statical point of view of D'Arcy Thompson on the relation between physical forces and generation of shapes. The second half was the era of genetics and molecular biology which shifted the focus to the dynamical aspects of morphogenesis.

1.2.1 D'Arcy Thompson: a first mathematical approach to morphogenesis

In 1917, **D'Arcy Thompson** published his only scientific book, entitled "On growth and form" [17]. While other contemporary scientists focused on experimental analysis, D'Arcy Thompson's investigations were based on a mathematical approach. As Wilhelm His, D'Arcy Thompson was skeptical about evolution theories and natural selection, which were dominant during the 19th century. His idea of morphogenesis was based on the role of physical forces in shaping organisms. Therefore, the book has a purely mechanical approach where living organisms are treated as material bodies subjected to physical forces, obeying to simple physical and geometrical laws. An example of D'Arcy Thompson's approach can be found in the second chapter of his book, where he focused on the effect of external forces on animals of different sizes. He stated that big animals are subjected to inertial forces while small animals are subjected to surface tension. It follows that big animals have strong and heavy structures in order to support the gravitational force, while small animals need lighter structures in response to the weaker surface tension.

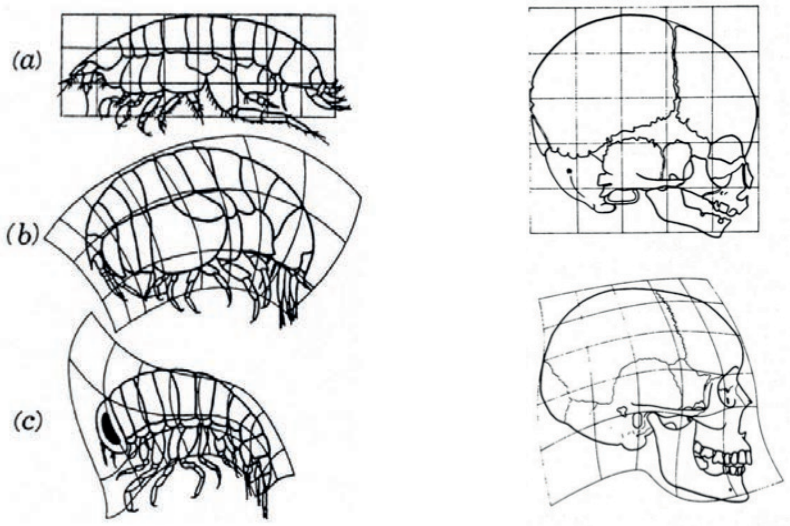


Figure 1.4: Left: Transformation grid applied to the transformation of the shape of a small amphiopod (a) *Harpinia Plumosa* into the shapes of two other genera belonging to the same family (b) *Stegocephalus Inflatus*, and (c) *Hyperia Galba*), adapted from [4]. Right: Transformation grid applied to the growth of a skull in human foetus. In both examples the transformation is achieved by applying physical forces on the considered structure, during evolution and growth respectively.

Furthermore, he proposed a grid transformation method, aimed at showing that physical forces can shape a living organism during growth and even evolution, see Figure 1.4. As highlighted by Ulett [18], "On growth and form" had a great influence on modern biomechanics and is still read and published in reduced and revised versions. D'Arcy Thompson's book inspired the work of Julian Huxley on allometric growth [19] and of Gould in his attempt to deal with such a mechanistic theory of shape in evolutionary theories [20].

1.2.2 Genetics

The origins of genetics date back to the second half of the 19th Century when **Gregor Mendel** discovered the inheritance of biological traits [3]. His theory was based on the idea that the hereditary package is transmitted from parents to offspring through a set of discrete hereditary factors. Each factor is a potential expression of a biological trait. For any biological feature, a child receives one factor from the mother and one from the father. The effective expression of a biological trait is given by the combined action of the two related factors. When the two factors combine, they are not affected by each other, but they just influence the potentiality of the fertilized egg. Mendel proved his theory by performing experiments on pea plants, but his results remained mostly unappreciated until the first half of the 20th century. One of the main problems of Mendel's theory was that it couldn't give a concrete description of the nature of these factors. At that time, genetics was considered the study of transmission of heredity properties in the embryo, while embryology was seen as the science investigating how the organisms develop. But there wasn't any link between the two disciplines, which finally merged only in the second half of the 20th Century. The main steps leading to the fusion of the two fields are basically the discovery that the DNA carries the genetic information and that genes encode proteins. The properties of a cell are determined by the proteins they contain, genes control and act on proteins in order to drive the cell fate and consequently, the development of the embryo. Right after these discoveries, a lot of experiments focused on finding the genes responsible for several morphogenetic events in the embryo. The strategy adopted was to introduce changes in the molecular organization of the DNA in order to observe abnormal changes in a final structure. In this way, it has been possible to identify which genes play an active role in the formation of an emerging pattern.

1.2.3 Pattern Formation

The fast development of genetics in the years following the 50s also promoted an increasing attention to the chemical and molecular mechanisms which might underpin morphogenetic processes. The concept of pattern formation in morphogenesis originated from that period. *Pattern formation* can be defined as the emergence of organized structures in space and time. The main contributions to the development of this concept were given by Alan Turing and Lewis Wolpert.

1.2.3.1 Alan Turing: chemical basis of morphogenesis

In 1952 **Alan Turing**, published his paper on the chemical bases of morphogenesis, which later became another milestone in biomathematics [21]. This was his only contribution on morphogenesis, but it represents the first reaction-diffusion model for pattern formation. The main ingredients of Turing's model are:

- The presence of at least two chemical species which undergo chemical reaction. Turing called them *morphogens*, in order to underline their role in generating a new pattern. The concentration of the two morphogens in the cell drives the cell activity. (In this sense genes can be considered indirectly as morphogens).

- In absence of diffusion, the system is in a stable state, defined by homogeneous concentrations of the two reactants. Under certain conditions, diffusion can destabilize the homogeneous state and a new non-homogenous pattern arises. This is counter-intuitive because generally diffusion would rather be thought to introduce chaos in a system, instead of generating an organized pattern [22].

Turing's model predicted the existence of six possible steady-states as shown in Figure 1.5. The *uniform* stationary (I) and oscillatory (II) states, the *short wavelengths* stationary (III) and oscillatory (IV) states and the *finite wavelength* stationary (V) and oscillatory (VI) states. Of particular interest is the Case VI, which occurs when the diffusion coefficients of the two morphogens differ substantially and initiate the so-called *short range activation long range inhibition* [23] mechanism. The two morphogens are seen as an activator and an inhibitor, respectively, which can act on themselves as well as on the other. A small perturbation in the homogeneous concentration can induce an increase in the activator concentration and initiate the feedback which lead to the formation of one of the Turing's patterns in Figure 1.5 (b).

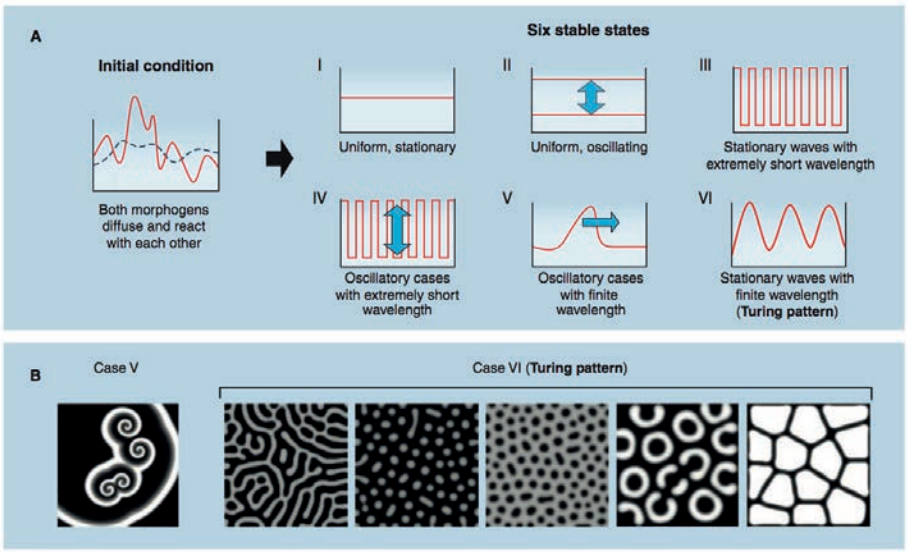


Figure 1.5: Turing's reaction-diffusion model: (a) Examples of the six stable states solutions of Turing's model. (b) The so-called Turing's pattern is depicted as the Case VI where a stationary wave of finite wavelength develops, adapted from [5].

Turing's model has later been largely employed for modeling the emergence of several patterns in vertebrates such as the stripes in the zebra-fish pigmentation [24], the branching pattern in feathers [25], but also the fabulous seashell patterns [26] and the mechanism of plant phyllotaxis, i.e. the arrangement of leaves on a plant stem [27].

1.2.3.2 Positional Information: molecular basis of morphogenesis

In the years right after its publication, Turing's work didn't receive a great attention. The problem of emergence of organized cellular patterns in the tissue was brought back to the attention of developmental biologists some years later in the 70s. In fact, **Lewis Wolpert** introduced the concept of *Positional Information* (PI) in order to explain how complex patterns could arise from initial asymmetries in the tissue [28]. The main idea of Wolpert is that the position of a cell in the tissue specifies the information about the molecular changes the cell will undergo. The key elements of Wolpert's theory can be summarized in the definition of:

- A mechanism which specifies the *polarity* in the tissue. Polarity is the direction in which PI is specified and is defined with respect to one or more reference points.
- A mechanism for specifying the different responses of the cell.

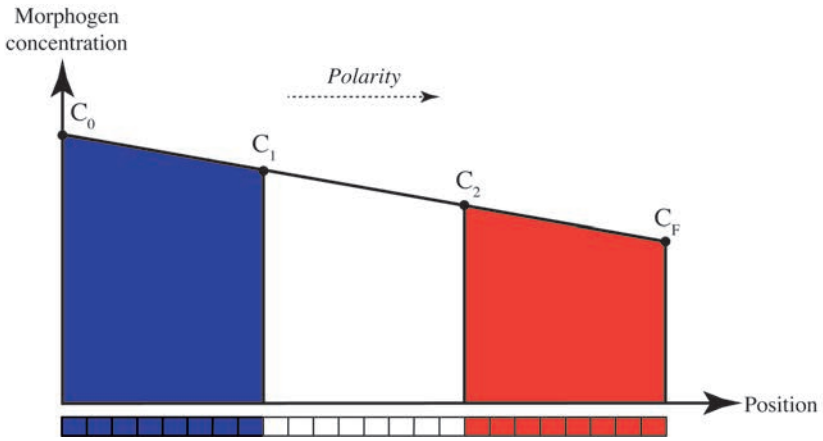


Figure 1.6: The french flag model: positional information is specified by the gradient of a morphogen concentration, the dotted line identifies the direction of the polarity.

PI can be specified by a quantitative variation of some factor such as the concentration, or a qualitative variation of some cell parameters such as a combination of genes or enzymes. A set of cells which have their PI specified with respect to the same reference points constitutes a field. *Interpretation* of PI is the process by which PI specifies the cell state and *conversion* is the mechanism by which PI is translated in a particular cellular activity. Furthermore, PI is universal in organisms and size invariant, meaning that if a part of the tissue is removed, the tissue is still able to pattern and interpret the PI.
The concept of positional information is well clarified in the French Flag Model depicted in Figure 1.6. In this example, the mechanism which specifies polarity is the monotonic variation of the morphogen concentration C, in respect to the reference values C_0 and C_F. The thresholds C_1 and C_2 identify the mechanism for the differential response of the cells. The interpretation acts according to the following rule: cells with position in the region where $C_0 < C < C_1$ express the blue pigment, a cell in the region where $C_1 < C < C_2$ expresses the white pigment and cells in the region where $C_2 < C < C_F$ express the red pigment. The molecular patterning in the early Drosophila embryo has been explained using positional information [29].

The models proposed by Turing and Wolpert offer two different points of view on pattern formation. A first difference comes from the fact that Turing aimed at modeling spontaneous formation of a pattern, while Wolpert asked how a more complex pattern can arise from an asymmetry (polarity) in the tissue. Furthermore, in Turing's model the concentration of morphogens is directly related to the spatial pattern, in this sense

it is a "pre-pattern". Conversely, Wolpert introduced an interpretation step where the cell activity is specified by the concentration gradient. On the other hand, in their recent paper Green and Sharpe have proposed a different mechanism through which the two models can cooperate in pattern formation [30]. For example, in the mouse limb bud a periodic pattern develops with different wavelengths depending on the position along a polarity gradient.

1.3 Modern approaches to morphogenesis

In the previous sections, the main discoveries and theories which have contributed to our current understanding of morphogenesis have been presented. The research field rapidly expanded in the last decades. In particular, modern approaches focused on the effect of external stimuli, such as mechanical, chemical, molecular on the generation of patterns and on the structural organization in living organisms.
In the following, the modern approaches to morphogenesis from a biomechanical viewpoint will be summarized.

1.3.1 Volumetric Growth and Remodeling

At the beginning of the 80s, Skalak and coworkers gave the first analytical description of finite volumetric and surface growth [31,32] in a continuum mechanics framework. They introduced the idea that growth can induce incompatibilities in the geometry of a body. According to the authors, the growing body can pass from an unloaded stress-free configuration to a pre-stressed reference configuration arising due to incompatibilities in the growth process. Conversely, if the growth strains are *compatible*, then no internal stresses will be generated in the tissue.
The seminal work of Skalak opened the door to a number of experimental studies which aimed at characterizing the residual stress distribution in biological tissues. Residual stresses have been found in blood vessels (arteries [10, 33] and veins [34]), heart [35], airways [36]. On the theoretical side, Skalak's formulation of volumetric growth prepared the ground for the paper of Rodriguez and colleagues [37] in which they formalized, in an elegant mathematical formulation, the relation between growth and remodeling on one side and residual stresses on the other side. In their fundamental contribution, they use the *multiplicative decomposition* of the deformation gradient associated to the growth/remodeling process, into a purely growth/remodeling and an elastic component.

The growth/remodeling deformation introduces the incompatibility in the tissue and the elastic deformation restores the compatibility, while residual stresses arise. As highlighted by Ambrosi et al. [38], the main advantage of this type of representation is that it allows to account for the effects of growth and remodeling. On the other hand, the mechanisms underlying these processes are neglected.
The multiplicative decomposition was first introduced in the theory of elasto-plasticity by Kröner [39] and Lee [40] in order to split the inelastic and the elastic components and it has been widely employed in continuum mechanics models. In this framework, the growth and remodeling processes are basically modeled as deformations from a stress-free configuration to a residually stressed state, where the body has grown or remodeled and changed its natural state. The relation between the variation of mass and changes in shapes is given by a volumetric growth. For remodeling, the micro-structural reorganization of the tissue can be linked for example to the changes in density, stiffness, orientation of fibers. Therefore, the thermo-mechanics of open systems has been used to describe the evolution of growth or remodeling parameters in time, as well as the constitutive relations for the material.

1.3.1.1 Extended theories and applications

In the years following Skalak's and Rodriguez's papers, a lot of work has been done both at the theoretical level and for experimental purposes. From the theoretical viewpoint, the attention has been pointed to develop constitutive theories for growth and remodeling. Accounting for mass volumetric sources and fluxes, Epstein and Maugin derived constitutive and evolution laws using the thermomechanical principles [41]. Ganghoffer et al. developed a constitutive framework for volumetric and surface growth involving the Eshelby stress [42]. Following the work of Di Carlo and Quiligotti [43] where accretive forces for growth are included in the system, Ambrosi and Guana derived the evolution laws for mass production which involves a direct link between stress and growth [44].
In parallel, another part of the biomechanical community has focussed on the application of the growth and remodeling theory to determine the onset of pattern formation after an elastic instability. This branch is called *morpho-elasticity*. A number of studies have employed the growth theory of Skalak and of Rodriguez et al. in order to model the emergence of geometrical patterns in tissues as an elastic instability due to excessive accumulation of residual stresses in the tissue. Among the main contributions, Ben Amar and Goriely studied the stability of elastic growing shells of different geometries [45], Li

et al. modeled the formation of mucosal pattern in the oesophagus of pigs [46], Moulton and Goriely modeled the mucosal folding mechanism in growing airways [47].

1.3.2 Mixture theory

The approaches described so far consider the growing tissue as an open system of a single constituent with an internal source of mass. Soft tissues are composed by several constituents such as collagen, elastin, ground substance. In *mixture theory*, the tissue is considered as a sum of different constituents. Each of them obeys some constitutive laws, and it exchanges mass with the other constituents. The mixture theory allows for a more realistic growth considered as exchange of mass between constituents. But, on the other hand, it introduces some controversial issues, such as the constitutive modeling of the partial stresses which act on each constituent and the definition of their physical meaningful boundary conditions.

From a theoretical viewpoint, one of the early contributions came at the end of the 70s from Bowen. He proposed a thermo-mechanical theory for mixtures, which gave the bases for modeling diffusing mixtures of elastic materials [48]. Later in the 90s, Cowin proposed *poroelasticity*, i.e the theory of interactions between deformation and fluid flow in a porous medium, as theoretical framework to study the bone [49]. Humphrey and Rajagopal proposed one of the first mixture models [50] for living materials. The main idea in their model was that each constituent has its own natural configuration. Therefore, the state of stress of each constituent might not be compatible with that of the surrounding tissue and residual stresses arise.
Loret and Simòes developed a theoretical framework for growth within mixture theory [51]. They considered a biphasic tissue composed by a solid and a liquid phase. Using the multiplicative decomposition on the solid phase they split the growth and the elastic effects and they derived the constitutive laws for growth from the second law of thermodynamics. A similar approach has been applied by Garikipati et al. to the growth of artificial tendon [52] and by Baek et al. for modeling aneurysm in brain [53].

Ambrosi et al. used the mixture theory in order to investigate the emergence of residual stresses during growth and remodeling of soft tissues [54]. The mixture framework has also been used for modeling tumor growth. Byrne and Preziosi modeled the tumor as a multicellular spheroid constituted by cells, considered as an elastic fluid, and extracellular space filled by the organic liquid [55]. Such a biphasic model was later extended by Ambrosi and Preziosi to a triphasic mixture which also accounted for the effect of the

extracellular matrix [56]. Finally, Athesian modeled growth and remodeling of a reactive mixture including electrical charged solid and fluid constituents which are typical of cartilage tissue [57].

1.3.3 Morphomechanics: hyper-restoration principle

Another modern approach to morphogenesis comes from the work of Lev Beloussov. During the 70s he performed several experiments on embryos in order to investigate the effects of mechanical stresses on early morphogenetic events [58, 59]. Beloussov in-

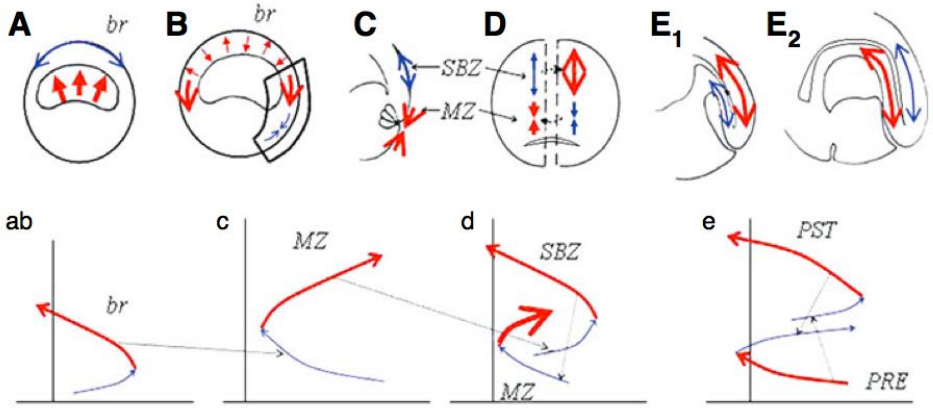


Figure 1.7: Hyper-restoration principle: Beloussov's illustration of the mechanical feedbacks acting in the embryo during gastrulation, adapted from [6]. Active stresses (red curves) overshoot passive ones (blue curves). Horizontal and vertical axes represent stress and time, respectively.

troduced the idea that the changes in shape during gastrulation occur according to a *hyper-restoration principle* [6, 60]. Cells tend to restore the original stress distribution in the embryo by responding to the external forces with generation of active forces inside the embryo and which overshoot the original stress. Therefore, gastrulation is seen as a chain of events driven by mechanical feedbacks. In Figure 1.7, a graphical interpretation of Beloussov's results is depicted. For example, during the early stages of gastrulation (A and B) the passive stretching of the roof of the blastocoel induces an active increase of the blastocoel internal pressure (red curve in Figure 1.7ab), which in turn affects the stress distribution in the neighboring marginal zone (MZ).

1.3.4 Mechanotransduction

The generation of shapes can be initiated by the chemical response of the tissue to some mechanical stimulus. Models which account for this mechanism belong to the class of *mechanotransduction models*. Mechanical stimuli are sensed by the cell through mechanotransducers, such as transmembrane proteins (e.g. cadherins and integrins). They respond to a mechanical stimulus by generating a transduction current which in turn changes the membrane potential and activates a cascade of processes. For example during embryogenesis, changes in the membrane potential induce the contraction of the actomyosin in order to maintain tensional homeostasis in the cell. This process is called mechanoreciprocity and is fundamental during embryogenesis, when the stiffness of the external environment of the cell is translated into contraction forces which in turn drive morphogenetic movements in the embryo [61]. Furthermore, the conversion of physical forces into biochemical information has been demonstrated to play a crucial role in the formation of left-right asymmetry in mammal embryos [62] and during the embryonic development of the heart [63], where the mechanical stimulus is represented by the blood flow.
Mechanotransductors can directly act on gene activation and inhibition, or indirectly, altering morphogen gradients [64]. During tumor growth for example, the stiffness increase of the extra-cellular matrix induces an increase in the cytoskeletal tension which in turn activates the expression of a malignant phenotype through regulation of integrins [65]. Ciarletta et al. recently proposed an analytical mechano-transduction model of avascular tumor growth [66]. Paszek et al. develop a numerical model to investigate how a cluster of integrin responds to chemical and mechanical changes in the extra-cellular matrix [67]. In their review, Mitchell and King provide examples of both experimental and computational methods to model and predict how cancer cells respond to fluid shear forces [68].

1.4 Summary and conclusions

In the first part of this chapter, an historical overview on the evolution of the concept of morphogenesis from ancient to modern times has been presented. Our actual knowledge on morphogenesis has been built over the centuries through the work of many scientists which contributed on several levels and fields. The early mechanistic vision of Galileo, who showed that most organisms change their shape in function of the loads that they have to hold, later inspired D'Arcy Thompson in developing a first mathematical approach to morphogenesis. The methodic experimental approach of Roux to the investigation of the

early steps of embryogenesis opened the way to understand the fascinating properties of the embryo and of the cells. The evolutionary theories developed during the 19th Century gave the basis for the development of the modern genetics.
Since the research field has rapidly expanded in the last decades, in the second part of the chapter the focus has been pointed to the modern theories which consider the effect of external stimuli, such as mechanical, chemical, molecular on the generation of forms in living organisms. In particular, this thesis is based on the recent theory of volumetric growth and remodeling which have been proposed at the end of the 90s. The next chapter is intended to give a comprehensive description of the method adopted in this work to model morphogenesis in tubular organs.