AN INTRODUCTION TO BIOMECHANICS AND MECHANOBIOLOGY

Manuel Doblaré
Group of Structural Mechanics and Materials Modelling. Aragón Institute of Engineering Research (I3A). Universidad de Zaragoza, Spain

José Merodio
Department of Continuum Mechanics, Escuela de Caminos Canales y Puertos, Universidad Politécnica de Madrid, Spain

Keywords: Biomechanics, mechanobiology, tissue biomechanics, tissue microstructure, tissue adaptation, bone remodeling, bone healing, tissue engineering.

Contents

1. Biomechanics: concept, scope and history
2. Structure and biomechanical behavior of biological tissues
3. Mechanobiology: concept, scope and applications
4. Tissue Engineering
5. Future trends and open questions
Glossary
Bibliography
Biographical Sketches

Summary

In this chapter we present the concepts of biomechanics and mechanobiology and discuss their current importance in health sciences. First, and very briefly, we review the history, main applications, subdisciplines and current role in Science of biomechanics. Second, and recognizing the impossibility of including all possible aspects of interest in one introductory chapter, we focus in only some of the many possible subdivisions of biomechanics as they are tissue mechanics and tissue engineering. In the first case, we review the main features of the composition and structure of living tissues that give rise to their particular mechanical properties and present some examples where the mechanical behavior of bone and soft tissues is essential. We also discuss the long-term adaptive capacity of living tissues and especially of bone, introducing the Wolff's law as the foundation of the explosive current development of bone remodeling models and applications. Some other aspects as cell-substrate interaction are also commented. The next section deals with tissue engineering, a novel area of regenerative medicine, with the final aim of creating artificial substitutes to treat tissue defects, injuries or even to replace whole organs. The basis of tissue engineering is reviewed, including biomaterials for scaffolds, cell types used, the characteristics and optimal features of cell-scaffold constructs or the importance of bioreactors to culture and prepare those constructs before implantation. Here, again, the control of the mechanical environment is essential, including the initial and evolving stiffness of the scaffold, the fluid velocity and shear stress induced by the perfusing flow, or even the direct application of stresses onto the scaffold. We finish this chapter with a discussion on some of the future trends

of current biomechanics that is progressively becoming a fundamental tool in biology and medicine with influence from protein and DNA behavior and cell processes like proliferation, migration or differentiation, to structural tissue performance or diseases like osteoporosis, malaria or cancer.

1. Biomechanics: Concept, Scope and History

"*Nothing has such power to open our mind as the ability to systematically investigate everything that comes from the observation of life*."
Marcus Aurelius

The enormous progress of Medicine since the mid decades of the twentieth century would have not been possible without the concurrent interaction of advanced technologies that have enabled new solutions to secular problems, making health industry one of the sectors with fastest growth nowadays in world economy. This, combined with its unquestionable social impact, is leading to a growing demand of professionals and research related to the design, manufacturing, testing, certification, marketing and repair of equipment, tools and medical devices. On the other hand, the continuous advances in technology are providing a huge amount of information via improved experimental (e.g. atomic force microscopy, laser tweezers) and clinical (microcatheters, magnetic resonance imaging) capabilities. Consequently, there is an ever-a growing need to expand and properly use these derived databases. Progress in computers and computational methods is also increasing our ability to handle these huge amounts of data and to model and accurately simulate complex biological processes.

Biomedical engineering or bioengineering applies engineering principles and methods to the understanding, definition and problems solving in biology and medicine, incorporating elements of electronics, informatics, materials science, mechanics, communications, chemistry and other engineering disciplines, in addition to those of life sciences. Biomechanics, in particular, is often defined as "mechanics applied to biology" (Fung, 1993). It aims to explain, analyze and predict the mechanics of living beings and their main components, from molecules to whole organisms. It helps, therefore, to understand how living systems move, to characterize the structural behavior of living tissues and organs, to predict the microstructural changes they undergo, the alterations in their mechanical function induced by injuries, diseases or pathologies and to propose methods of artificial intervention for functional recovery.

Biomechanics has a vital role in many applications such as: design of organ substitutes like implants and prostheses for different systems (musculoskeletal, circulatory, vision), improving rehabilitation protocols, promoting faster healing, predicting and preventing failure of bones, aneurysms or ligaments, design of prostheses, implants, ortheses for the disabled and many other mechanical devices like respiratory ventilators or surgical robots, and, more recently, enhancing properties of tissue engineering constructs, and these among thousands of other applications.

In its broadest sense, biomechanics has been with us for millennia. In 2000, German archaeologists discovered a 3,000 years old Egyptian mummy from Thebes with a wooden prosthesis attached to one toe, considered the oldest functional prosthesis known. The most ancient text containing concepts that today could be understood as biomechanics is probably the classic Greek *Parts of Animals* of Aristotle (384-322 BC). Aristotle presented a description of the anatomy and function of internal organs of several animals. However, he made the mistake of considering the heart as a respiratory organ, probably because he never saw blood inside as performing autopsies several days after death on bodies killed in war.

Other more modern scientists have also contributed to particular aspects related to this discipline (Mason, 1962). Leonardo da Vinci (1452-1519) can be considered as the first biomechanical scientist. He addressed topics such as the gait movement. Galileo Galilei (1564-1642), who studied Medicine before becoming a famous physicist, discovered the constancy of the period of the pendulum and used it to measure the blood pulse. He was interested in the strength of bones and suggested that long bones are hollow to achieve maximum strength with minimum weight, establishing, implicitly, the important principle of biological optimization. Galileo Galilei (1564-1642), who studied Medicine before becoming a famous physicist, discovered the constancy of the period of the pendulum and used it to measure the blood pulse. He invented the thermoscope and was also the first to design in 1609 a microscope in the modern sense. He was also interested in the strength of bones and suggested that long bones are hollow to achieve maximum strength with minimum weight, establishing, although implicitly, the important *principle of biological optimization*.

Miguel Servet (1551-1553), the great Spanish researcher, found the pulmonary circulation. It was, however, William Harvey (1578-1658), following the work of Servet, who discovered the systemic blood circulation. In 1628 he published his proof based only on logical reasoning, that is, without the ability to see the blood capillaries. Giovanni Alfonso Borelli (1608-1679), an eminent mathematician and astronomer, clarified the movement of muscles and body dynamics. He studied the flight of birds and swimming of fish and the functioning of the heart and intestines in his posthumous work *De Motu Animalium*. Other great scientists like Robert Boyle (1627-1691), Leonhard Euler (1707-1783), Thomas Young (1773-1829) or Jean Poiseuille (1797-1869) among other worked also in different aspects of biomechanics. Giovanni Alfonso Borelli (1608-1679), an eminent mathematician and astronomer, clarified the movement of muscles and body dynamics. He studied the flight of birds and swimming of fish and the functioning of the heart and intestines in his posthumous work *De Motu Animalium*. Other great scientists were interested in different aspects of Biomechanics. Robert Boyle (1627-1691) studied the lung function and the air dissolved in water due to the fish respiration. Leonhard Euler (1707-1783) wrote the first work on the pulse wave propagation through arteries. Thomas Young (1773-1829) studied the formation of the human voice through vibration, relating it with the elasticity of materials. Jean Poiseuille (1797-1869) determined the pressure-flow relationship in the interior of a tube. His most important contribution was to establish the “non-slip” condition as the most appropriate to model the interaction between a viscous fluid and a solid wall. Its empirical relationship, known as Poiseuille’s law, is still frequently used in cardiology.

Guillaume Wertheim (1815-1861), an outstanding but relatively unknown experimentalist, was the first to measure the mechanical properties of most human tissues including bones, muscles, arteries and nerves, taking into account the dependence of age and sex. In fact, many of the values he obtained are still in medical texts after more than one hundred and fifty years since its publication (Wertheim, 1847). Since then, many other scientists have contributed to the advancement of biomechanics that has been progressively specialized in many branches of application, being virtually impossible to name them all.

Many authors suggest however that modern biomechanics did not truly emerge as a distinct field of study until the mid 1960s when the theoretical frameworks of nonlinear continuum mechanics and, in particular, of finite elasticity, viscoelasticity and mixture theory were settled (Truesdell and Noll, 1965). The parallel development of the early generation of computers and numerical methods as the finite-element method, introduced in 1956, provided the enabling technology that allowed using the whole potential of such theoretical framework. An important milestone was the publication of the book *Biomechanics: Material Properties of Living Tissues* by Y.C. Fung (Fung, 1993), considered the father of modern biomechanics.

It is not coincidental either that the birth of biomechanics came on the heels of the birth of modern biology in the 1950s. This was partly due to the discovery of the structure of some of the most important constituents in the body like the alpha -helix and beta-sheet structures of proteins by L.C. Pauling, that of the double helix structure of DNA by J.D Watson and F.H.C. Crick, as well as the triple-helix structure of collagen by G.N. Ramachandran and G. Kartha and almost simultaneously by A. Rich and F.H.C. Crick, and, finally, of the cross-bridge hypothesis for muscle contraction by A.F. Huxley.

Much has been discovered in biomechanics since then, particularly over the last 35 years. New technologies like sophisticated medical imaging, advanced modeling and simulation techniques, cell manipulation and less invasive *in vivo* testing procedures are revealing fundamental details of the main building blocks of life like genes, proteins and cells, so new hypotheses and theories appear every day upon these new observations.

In this chapter, only some of the myriad of possibilities that could be analyzed like gait and movement of animals and humans, injury analysis, rehabilitation, prostheses, implants and ortheses, tissue behavior, tissue engineering, artificial organs, cell mechanics, mechanobiology, and a long etcetera are addressed. After this introduction and in Section 2, the structure and mechanical behavior of both hard and soft biological tissues is reviewed, considering them as inert structural materials, that is, without taking into account biological effects performed by their living components: the cells. It is well-known that cells react to the specific fluid flow, extracellular deformation or substrate stiffness by moving themselves, proliferating, differentiating, dying both in an apoptotic way or by necrosis and, finally, expressing specific signals or producing tissue components. The study of this interaction between biological effects and mechanical cues is currently known as mechanobiology, and is the object of Section 3. Section 4 deals with a specific clinical therapy where artificial materials and biomechanics have an essential role, as it is tissue engineering. The main components and the effect of mechanical stimulation into tissue engineering constructs is briefly reviewed. The chapter finishes with comments on some of the current hot topics of research. Some of them will be the object of the rest of chapters in this volume.

2. Structure and Biomechanical Behavior of Biological Tissues

"The Science of today is the technology of tomorrow."
Edward Teller

One of the most important branches of biomechanics is related to understanding, mathematically formulating and predicting the behavior of biological tissues as structural materials, i.e., to relate displacements, strains and stresses with the loads and movements to which they are subjected, whether physiological or pathological, and also to predict functional changes induced by diseases or therapies. This is usually named as tissue biomechanics.

In fact, biological tissues are wonderful examples of materials that are manufactured with minimum resources and achieve maximum performance. We can enumerate as the most important properties of these materials: multifunctionality, adaptability, self-repair, biodegradability and recyclability.

Natural and man-made materials often follow different routes to get the required properties (Vincent, 2006). While artificial systems use a wide variety of chemical components for achieving the functions required (for example, a car contains not less than 30 different materials), biological systems consist of a relatively limited number of building blocks that are assembled in highly organized composite structures from the nano- to micro- and macro-scales in a hierarchical manner that ultimately give rise to myriads of different functional materials. A molecule such as collagen type I serves as the building block for a wide variety of tissues in the human body: bone, cartilage, skin, or cornea. Furthermore, in contrast to many artificial materials that are produced by heating and high pressure, "fabrication" of biologically derived materials occurs at ambient conditions, with minimal waste and pollution.

When we speak of biological tissues, it is usual to distinguish between hard and soft. The former include materials such as bone, horns or turtle shells with an important structural function so they are reasonably rigid and resistant. By contrast, soft tissues although resistant to some extent, have other more prevalent functions such as high deformability and viscoelasticity derived from a very different structure and composition. What follows is a brief description of each of them, considered initially as inert materials, i.e., without taking into account the functions of the cells, responsible for growth, maintenance, repair and adaptation. Some of these latter functions are discussed explicitly in Section 3.

2.1. Biomechanical Behavior of Hard Tissues

Most living tissues, both hard and soft, are multiphasic where coexisting at least one solid and one fluid phase, the first being further composed, in general, of organic materials, inorganic crystals and amorphous phases. The essential difference between hard and soft tissues is the existence of inorganic phases in the former. This mineral component provides hard tissues their resistance while the organic components result in high ductility. The interfaces between relatively soft organic and hard inorganic matter are of prime importance in the properties of the compound.

The most striking feature of hard biocomposites is that the organic matrix occupies only 3 to 5% of the volume but results in a considerable improvement in the mechanical properties of the mineral. One of the examples better studied is the shell of the abalone. The abalone shell derives its extraordinary mechanical properties from a highly hierarchically organized structure. The mechanical properties of nacre, the main component of the abalone shell, have been measured by several authors, finding that the nacre has 500 to 3000 times greater toughness than its main inorganic component, chalk, which constitutes 95% of its mass.

Bone is another example of biological material that combines high performance soft organic material (collagen, proteoglycans and non-collagenous proteins) that contribute to its tensile properties, with a mineral (hydroxyapatite) that confers stiffness and resistance to compression (Carter and Beaupre, 2001). As in nacre, the bone structure is organized in various scales, with six or seven levels of hierarchy. At the molecular level, the collagen filaments are joined to form a tropocollagen molecule. Such molecules are arranged in a staggered manner to overlap leaving spaces at each end. A sequence of such molecules forms microfibrils, which in turn are grouped to form larger fibrils. Within the collagen fibrils nanoscopic hydroxyapatite mineral crystals are embedded.

At the macroscopic level, the constitution and structure of bones differ from animal to animal and within the same animal from place to place in order to serve specific functions (Currey, 2002). Furthermore, the structure of bone is not uniform, being a porous heterogeneous material with anisotropic behavior and with different strength and stiffness in tension and compression. In fact, the mechanical behavior of bone is fairly related to its porosity, n. This varies in humans between 5 and 95%, although the most common is finding very high or very low porosities. We distinguish between spongy or trabecular bone ($n = 50 - 95\%$) and compact or cortical bone ($n = 5 - 10\%$). The first is found in cuboidal and flat bones and the ends of long bones, while compact bone is usually on the external layer of long bones surrounding cancellous bone. The combination of both bone types forms a “sandwich” structure, well known in engineering as a highly optimized composition.

Bone is a heterogeneous and anisotropic elastic material with only a small dependency on the strain rate (viscoelasticity) for very high strains rates. To estimate its mechanical properties, and as a first approach, Keller (Keller, 1994) proposed the following expression that allows explaining over 96% of the statistical variation in the mechanical behavior of combined vertebral and femoral data over the range of ash density (0.03 – 1.22 gcm^{-3}):

$$\begin{aligned} E\left(\mathrm{MPa}\right) &= 10500\rho_\alpha^{2.57\pm0.04} \\ \sigma_c\left(\mathrm{MPa}\right) &= 117\rho_\alpha^{1.93\pm0.04} \end{aligned} \tag{1}$$

where ρ_α is the ash density (mass of the mineralized component over the total volume).

The high porosity of trabecular bone and the arrangement of the struts and small beams of trabeculae that compose the cancellous bone make this material to behave as a structure. Load in cancellous bone is transferred by bending moments and compressive loads that may cause the individual trabecula to buckle, which provides a high resilience (ability to store energy under local permanent strains) and resistance to impact loads. This produces mechanical properties of trabecular bone to be mainly determined by the spatial arrangement of the trabeculae or equivalently of voids. Therefore, measuring mechanical properties of cancellous bone is far more difficult than doing for cortical bone. Many experimental correlations have been proposed between void porosity and mechanical properties. For example, Hernández et al. (2001) determined the elastic modulus and compressive strength in terms of the bone volume fraction and ash fraction, with a 97% of correlation:

$$\begin{aligned} E\left(\mathrm{MPa}\right) &= 84370\frac{BV^2}{TV}\cdot 58 \pm 0.02\alpha^{2.74\pm 0.13} \\ \sigma_c\left(\mathrm{MPa}\right) &= 749.33\frac{BV^1}{TV}\cdot 92 \pm 0.02\alpha^{2.79\pm 0.09} \end{aligned} \tag{2}$$

Another important feature of bone is anisotropy. The different directional behavior of this tissue is also a consequence of the microscopic structure that depends on the type of bone. Thus, anisotropy of cortical bone is associated with the orientation of the osteons (Currey, 2002), while in spongy bone it essentially depends on the spatial orientation of the trabeculae. In order to quantify the anisotropy of cancellous bone, Cowin (1979) introduced the concept of *fabric tensor*, defining it as a second-order tensor, positive definite, whose principal axes coincide in average with the principal directions of the trabeculae and whose eigenvalues are proportional to the amount of mass of the trabecular structure associated with each principal direction. Many authors have measured such tensor using different techniques, concluding that all well characterize the anisotropic structure of trabecular bone (Cowin, 2001).

2.2. Biomechanical Behavior of Soft Tissues

Some typical soft tissues are arteries and veins, cartilage, ligaments, tendons, muscles or skin. Generally, they are composite materials formed by an organic matrix, reinforced by highly flexible collagen and elastin fibers with a high content of water (Cowin and Doty, 2009).

The behavior of soft tissue depends again on its composition and structure, with a strong dependence of their properties on the percentage of fibers, their characteristics, directionality and type of grouping. Another typical feature of soft tissues like cartilage, skin, cornea, and particularly of blood vessels is its layered structure.

For example, tensile strength specialized tissues, like tendons or ligaments, are rich in highly oriented fibers that essentially coincide with the direction of stress to which they are subjected and are therefore highly anisotropic. The organization, for example, of tendons shows a hierarchical structure, with the fibers aligned along a preferential direction, as shown in (Fung, 1993) , whereas in veins and arteries, two families exist with fibers helically oriented and rotating in opposite angles. This provides circumferential rigidity to withstand the internal pressure. On the other hand, compressive elastically absorbing tissues, like cartilage, are rich in fibers, distributed in various directions in a highly compliant matrix, being again anisotropic and practically incompressible in a wide range of deformations due to the high content in water.

The tendon (and ligaments), for example, has a multi-unit hierarchical structure composed of collagen molecules, fibrils, fiber bundles, fascicles and tendon units that run parallel to the tendon long axis. The fibril is the smallest tendon structural unit; it consists of rod-like collagen molecules aligned end-to-end in a staggered array. Fibril diameters vary from 10 to 500nm, depending on species, age, and body location. Fibers forming the next level of tendon structure, are bound by endotenons a thin layer of connective tissue that contains blood and lymph vessels and nerves. Fiber bundles form fascicles, and bundles of fascicles are enclosed by the epitenon, which is a fine, loose connective-tissue sheath containing again the vascular, lymphatic, and nerve supply to the tendon. Tendons are finally surrounded by a third layer of connective tissue called the paratenon. This hierarchical structure provides the tendon high tensile strength.

Because of the incredible complexity of both the ultra and microstructures of these materials, and for describing their mechanical behavior, we continue relying primarily on phenomenological models. Hence, although tissues are complex mixture-composites with inelastic behavior, under particular conditions of interest it is usually sufficient to model their behavior within the framework of the theories of elasticity, viscoelasticity or the mixture theory.

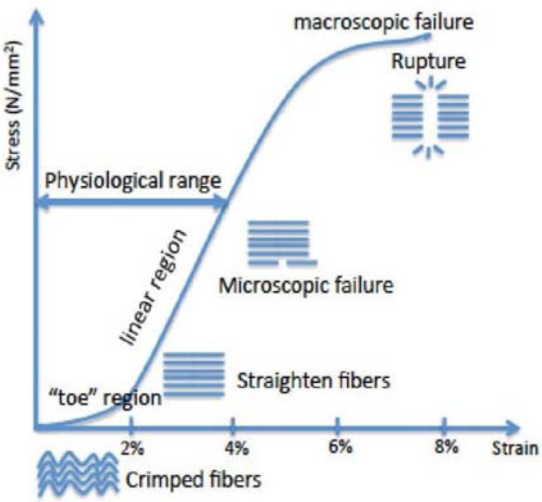

Figure 1. Typical stress-strain curve for tendons and ligaments.

A typical soft tissue stress–strain curve, like the one of a tendon (Figure 1) has an initial toe region, where the tendon is strained up to 2%. This toe region represents the stretching-out of the crimp-pattern of the composing fibers. In the linear region of the stress-strain curve, where the tendon is stretched less than 4%, collagen fibers lose their crimp pattern. The slope of this linear region is referred to as the Young modulus of the tendon. The elastic modulus is of the order of the stresses, so that deformations are in

-

-

-

Bibliography

[1] Carter DR and Beaupre GS. (2001) *Skeletal Function and Form*. Cambridge University Press. [Classical book showing the correlation between shape, both macro and micro, and function of living organs].

[2] Carter DR, Blenman PR and Beaupre GS. (1988) Correlations between mechanical stress history and tissue differentiation in initial fracture healing. *J Orthop Res* **6**:736–748. [Paper where a cell differentiation scheme depending on a specific mechanical stimulus is established].

[3] Carter DR, Beaupre GS, Giori NJ and Helms JA. (1998) Mechanobiology of skeletal regeneration. *Clin Orthop Rel Res* **355**:41–55. [First paper where the term Mechanobiology was introduced].

[4] Claes LE and Heigele CA. (1999) Magnitudes of local stress and strain along bony surfaces predict the course and type of fracture healing. *J Biomech* **32**:255–266. [Paper where a cell differentiation scheme during bone fracture healing depending on a specific mechanical stimulus was established].

[5] Cowin SC. (1979) On the strength anisotropy of bone and wood. *J Appl Mech* **4**:137–147. [Paper where the concept of fabric tensor was introduced to characterize the anisotropy of bone mass distribution and stiffness].

[6] Cowin, SC. (2000) How is a tissue built? *ASME J Biomech Engng* **122**:553-569. [A general description of the fundamental structure of biological tissues and its relation with the particular function].

[7] Cowin SC. (2001) The false premise in Wolff's law. In *Bone Mechanics Handbook* Chapter 31 (Cowin SC, ed.). CRC Press. [An essential handbook in bone tissue mechanics, describing mechanical properties, constitutive behavior, structure, composition, basic biochemistry and biological bone cell behavior including bone long-term adaptation].

[8] Cowin SC and Doty SB. (2009) *Tissue Mechanics*. Springer Verlag, New York A handbook in tissue mechanics, describing mechanical properties, constitutive behavior, structure, composition, basic biochemistry and biological behavior of the most important living tissues].

[9] Currey JD. Bones. (2002) *Structure and mechanics*. Princeton University Press, Princeton, NJ. [A collection of the most important knowledge on bone organs and tissue structure, types, evolution and mechanical properties in different animals].

[10] Doblare M and Garcia-Aznar JM. (2005) On the numerical modeling of growth, differentiation and damage in structural living tissues. *Arch Comput Meth Engng* **11**:1–45. [A review of the most important models and computational approaches to predict mechanobiology of living tissues with main emphasis in bone adaptation and healing].

[11] Fung YC. (1993) *Biomechanics. Mechanical properties of living tissues*. Springer-Verlag, New York. [One of the first and more complete books in tissue biomechanics, including models and

constituive properties for most important living tissues, both solids and fluids].

[12] Garcia-Aznar JM, Ruberg T and Doblare M. (2005) A bone remodeling model coupling microdamage growth and repair by 3D BMU-activity. *Biomech Model Mechanobiol* **4**:147–167. [A continuum model for bone remodeling including most of the physical and biological aspects involved in this process].

[13] Gomez-Benito MJ, Garcia-Aznar JM, Kuiper JH and Doblare M. (2005) Influence of fracture gap size on the pattern of long bone healing: A computational study. *J of Theor Biology* **235**(1):105–119. [A continuum model for bone fracture healing including most of the physical and biological aspects involved in this process].

[14] Hernandez CJ, Beaupre GS, Keller TS and Carter DR. (2001) The influence of bone volume fraction and ash fraction on bone strength and modulus. *Bone* **29**(1):74–78. [It states a relation between bone elastic modulus and Poison ratio and bone solid fraction].

[15] Humphrey JD. (2002) *Cardiovascular solid mechanics: cells, tissues, and organs*. Springer Verlag, New York. [A state of the art review of the biology, physiology and mechanics of cardiovascular solid tissues, including heart and blood vessels, as well as the constitutive behavior, mechanical parameters and computational predictive physico-mathematical models available].

[16] Keller TS. (1994) Predicting the compressive mechanical behavior of bone. *J Biomech* **27**:1159–1168. [It states a relation between bone elastic modulus and Poison ratio and bone solid fraction].

[17] Kuiper JH, Richardson JB and Ashton BA. (1996) Mechanical signals in early fracture callus. In Proc 10th Europ Soc Biomech, page 154 (J. Vander Sloten, G. Lowet, R. Van Audekercke, and G. Van der Perre, eds.). [Work where a cell differentiation scheme depending on a specific mechanical stimulus is established].

[18] Lacroix D and Prendergast PJ. (2002) A mechano-regulation model for tissue differentiation during fracture healing analysis of gap size and loading. *J Biomech* **35**: 1163–1171. [Paper where a cell differentiation scheme depending on a specific mechanical stimulus is established].

[19] Langer R and Vacanti JP. (1993) Tissue engineering. *Science* **260**:920-926. [One the of the key papers in the early development of tissue engineering where the fundamentals and techniques are described].

[20] Mason SF. (1962) *A history of the sciences*. Collier Books, New York. [A classical history of sciences from early civilization to the date of publication].

[21] Moreo P, Garcia-Aznar JM, Doblare M. (2008) Modeling mechanosensing and its effect on the migration and proliferation of adherent cells. *Acta Biomat* **4(3)**:613–621. [A mechanosensing model for single cells onto a specific substrate is established, considering in a continuous approach the most important components of cell involved in mechanosensing].

[22] Mow VC, Hochmuth RM, Guilak F and Trans-Son-Tay R. (1994) *Cell mechanics and cellular engineering*. Springer Verlag, New York. [One of the first books analyzing the mechanics of single cells and interactions in cell populations and between cell and substrate, as well as the effect on cell functions of several engineering approaches].

[23] Murray, CD. (1926) The physiological principle of minimum work. I. The vascular system and the cost of blood volume. *PNAS* **12**:207–214. [One of the first work identifying the adaptive response of biological tissues as the result of searching for a state of minimal energy provision].

[24] Ogden RW. (1984) *Nonlinear elastic deformations*. Halsted Press, John Wiley&Sons, New York. [An essential reference to understand the physical behavior and mathematical bases of elastic bodies under finite deformations].

[25] Ottl HC, Matthiesen TS, Goh SK, Black LD, Kren SM, Netoff TI and Taylor DA. (2008) Perfusion-decellularized matrix: using nature's platform to engineer a bioartificial heart. *Nature Med* **14**:213-221. [Key paper trying to demonstrate the concept of tissue engineering using decellularized biological matrices as scaffolds. A decellularized heart of a rat is used to culture cells from another "patient" that after treatment in a bioreactor gave rise to initial signals associated to a functional heart that "ideally" could be transplanted in the second patient without rejection].

[26] Pena E., Pena JA, Doblare M. (2008) On modelling nonlinear viscoelastic effects in ligaments. *J Biomech* **41(12)**:2659-2666 [This paper describes different possibilities of modeling viscoelastic effects in soft issue, presenting several comparative results].

[27] Pena E, Perez-del Palomar AP, Calvo B, Martinez-Barca MA and Doblare M. (2007) Computational modelling of diarthrodial joints. Physiological, pathological and pos-surgery simulations. *Arch Comput Meth Eng* **14(1)**:47–91. [A review on the mathematical models and computational methods to predict the mechanical behavior of soft tissue such as ligaments, tendons or cartilage as well as the combined mechanical behavior of diarthrodial joints as the knee or the temporo-mandibular joint both physiological and after injury or surgery].

[28] Sanz-Herrera JA, Garcia-Aznar JM and Doblare M. (2008) A mathematical model for bone tissue regeneration inside a specific type of scaffold. *Biomech Model in Mechanobiol* **7**(5):355-366. [A multiscale approach for bone tissue regeneration within a porous scaffold. An FE2 approach is used with a voxel-FEM mesh at the micro level.

[29] Skalak R and Fox CF. (eds.) (1988) Preface in *Tissue Engineering* pp. 26–29. Ed. Alan R. Liss, New York. [One of the first books on tissue engineering including fundamentals, techniques, possibilities, difficulties and bottlenecks at the date of publication].

[30] Truesdell CA and Noll W. (1965) The nonlinear field theories of mechanics. In *Handbuch der Physik* (ed. S. Flugge). Springer Verlag, New York. [Fundamental book establishing the physico-mathematical models of non-linear continuum physics, including solid, fluid, multiphasic and mixture theory problems].

[31] Turing AM. (1952) The chemical basis of morphogenesis. *Proc R Soc Lond* B **237**:37–72. [This work is considered the basis of biological pattern formation and morphogenesis derived from competitive chemical reactions and tuned rates production (from cells) and diffusion of chemical bioproducts].

[32] van der Zwaag S. (2007) *Self Healing Materials: An Alternative Approach to 20 Centuries of Materials Science*. Springer Series in Materials Science, Berlin. [First compilation on the new concept of haling material, showing examples and concepts in polymers, concrete, metals and ceramics].

[33] Vincent J. (2006) Making biological materials. *J Bionic Eng* **3**:99-114. [One of the most cited works in biomimetics, describing the composition, properties and synthesis of many natural materials].

[34] Vunjak-Novakovic G. (2003) The fundamentals of tissue engineering: scaffolds and bioreactors. In Tissue engineering of cartilage and bone p. 34-51. Novartis Foundation Symposia. Novartis Foundation. New York: John Wiley, Sons. [A review of the fundamentals, techniques, methods, instruments and examples of application of tissue engineering in bone and cartilage].

[35] Warnke PH, Springer ING, Wiltfang J, Acil Y, Eufinger H, Wehmoller M, Russo PAJ, Bolte H, Sherry E, Behrens E and Terheyden H. (2004) Growth and transplantation of a custom vascularised bone graft in a man. *Lancet* **364**:766-770. [One of first successful clinical results of tissue engineering where an engineered jaw is treated in a biological bioreactor, as it the back of the patient, and then successfully transplanted].

[36] Wertheim MG. (1847) Memoire sur 1 eastocote et la cohesion des principaux tissues du corp humain. *Ann Chim Phys* **21**:385–414. [First work collecting the mechanical properties of living tissues from a scientific perspective].

[37] Wolff J. (1884) Das Gesetz der inneren Transformation der Knochen bei pathologischen VerŠnderungen der Šusseren Knochenform. Sitzungsber Preuss. *Akad.Wisse* **22**:475–496. [First time that an explicit relationship between bone microstructure and the acting stress state was explicitly stated in the famous “Wolff’s law” basis of the new field of mechanobiological tissue adaptation].

[38] Wolff J. (1870) Ueber die innere Architectur der Knochen und ihre Bedeutung für die Frage vom Knochenwachsthum. *Virchows Archiv Pathol Anat Physiol*. **50**:389–450. [A first indication on the existing relationship between bone microstructure and the acting stress state].

Biographical Sketches

M. Doblaré was born in Córdoba (Spain) in July, 1956. He got the degree of Mechanical and Electrical Engineering at the University of Seville (Spain) in 1978 and PhD degree at the Polytechnique University in Madrid (Spain) in 1981. From 1978 to 1982 he was research assistant, when he got the position of assistant professor of Structural Mechanics. In 1984, he was appointed as full professor at the Department of Mechanical Engineering of the University of Zaragoza (Spain) where he still teaches. He has occupied the positions of head of the Dept. of Mechanical Engineering (1985-87), dean of the Faculty of Engineering (1993-96), Director of the Aragón Institute for Engineering Research (2002-07) and Scientific Director of the Spanish Networking Center on Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN) (2007-11). Currently, he is head of the research group on Structural Mechanics and Materials Modeling (GEMM) and Scientific Director of the company Abengoa Research. Prof. Doblaré has been elected as ordinary member of the Spanish Royal Academy of Engineering, the Royal Academy of Mathematics, Physics, Chemistry and Natural Sciences of Zaragoza and the World Council of Biomechanics, and awarded with several distinctions including the Aragón Prize for excellence in research or the Doctorate “Honoris Causa” at the Technical University of Cluj-Napoca (Romania). He was visiting scholar at the Universities of Southampton (Dept. of Civil Engineering-1981) and New York (Courant Institute of Mathematical Sciences-1983) and visiting professor at Stanford University (Division of Applied Mechanics-1990). He is member of different national and international scientific associations and of the editorial boards of several high impact journals where he has published more than 200 papers. He has given plenary, semiplenary and invited lectures in many international congresses and research forums, being internationally recognized in the field of Biomechanics. Prof. Doblaré’s research interests are in computational solid mechanics with applications in structural integrity, biomechanics and mechanobiology, with special emphasis in hard and soft tissues modeling, interface behavior and interaction tissue-biomaterial, mechanobiological processes like bone remodeling, bone and wound healing, bone osteointegration or morphogenesis and, finally, tissue engineering.

J. Merodio gained his first degree in Mechanical Engineering at Universidad del País Vasco, Spain. He completed his PhD in Engineering Mechanics and a MS in Applied Mathematics at Michigan State University, USA. Currently, he is an Associate Professor in the Department of Continuum Mechanics and Structures at Universidad Politécnica de Madrid, Spain. His main research interests are in nonlinear elasticity theory, with particular application to the mechanics of soft biological tissues, instability phenomena as well as mathematical analysis of constitutive models. He has been co-editor of the Continuum Mechanics volume for the EOLSS-UNESCO encyclopedia. He has delivered a solid intellectual contribution to the field of continuum mechanics, evidenced by a steady stream of archival publications as well as by regular invitations to present his work at conferences and to contribute to different books. He has organized several international conferences and international courses for researchers in this area of work at several International Centers. He is in the editorial board of different journals in the broad area of Theoretical Mechanics and has served as guest editor for different international journals.