### 1

## Introduction

## 1.1 Introduction to Biomechanics

One of the astonishing secrets of life is probably the fact that any living organism is composed of non-living objects: atoms and molecules. Nevertheless, they form biomolecules and eventually constitute the living tissues and organs.

Biology is a comprehensive set of science that is related to living bodies, organs, tissues, cells, molecules and even smaller constituents, and their potential interactions. While biochemistry is part of the biology that is dedicated to what is going on within a biomolecule and their interactions, biomechanics is primarily used to study the wide range of mechanical responses of biosystems; from the biomolecule level up to the organ and body levels.

In this chapter, an introduction is provided to present an insight into the general concept of biomechanics and the wide variety of biological problems that can be solved by conventional or multiscale numerical methods. The numerical approach is widely used in research and development activities for medical-related industries and can be assumed as a reliable tool to assist the medical staff in assessing the existing damages or failures of living tissues or to resemble a specific procedure/operation based on the realistic conditions of a patient and to predict the level of success or potential consequences, before actually performing it.

## 1.2 Biology and Biomechanics

The word 'biology' gradually replaced the phrase of 'natural history' well over the centuries to denote the branches of science which deal with living animals or plants (Fung 1993). In fact, it was originally applied to all world-related scientific contributions and not to any individual living object. Nowadays, biology is adopted to designate any science related to the living bodies, organs, tissues, cells, molecules and even smaller constituents, and their potential interactions. It has also spanned to synthetic tissues and includes the technologies of making tailored and engineered materials to replace the existing malfunctioning tissues/organs. The important issue of the drug delivery mechanisms can also be considered within the general concept of biology.

Biomechanics represents an engineering approach to biology, where the general concepts of mechanics are adopted to formulate the biological phenomena and to study them

through the wealth of well-developed mathematical and numerical methods of solving general mechanical problems. While some basic mechanical concepts, such as stress or strain, constitutive equations, strength, fatigue and fracture, fluid flow, diffusion, composite action, etc., may not be well defined or used in biology, they are efficiently adopted in biomechanics to define and study the behaviour of living tissues and the existing interactions of different living objects in an organ or in a more complex set of tissues.

Biomechanics spans virtually all aspects of biology, ranging from molecular scales to surgery procedures and from micromodelling of aneurysm disease to the design of large orthopaedic items and haemodialysis machines.

While molecular and cell biology may seem to be only involved with biological and/or chemical phenomena in very small scales, nevertheless, the biomechanics has been adopted to simulate complex organs down to their cell microstructure, such as the brain and its nerve cells, as presented in Figure 1.1, and the heart and its leaflets, the corresponding microscale layers and even an interstitial cell, as depicted in Figure 1.2.



Figure 1.1 The brain organ and its nerve cell.



Figure 1.2 Sample biomechanical simulation of an organ, its tissue layers and the structural molecular/cell level.

It is not always necessary to examine a biomechanical problem down to the cell scale. For instance, in the study of the behaviour of a bone, it is sufficient to take into account its heterogeneous or porous microstructure, as typically presented in Figure 1.3.

In surgery-related topics, the whole process of healing of scars or damages of a soft tissue, as typically illustrated in Figure 1.4, can now be fully investigated by biomechanics. These predictions can also be quite useful in clinical orthopaedic or cosmetic surgeries. Similarly, modelling the way a tumour is evolved by the analysis of growth and mass transfer across a membrane/interface to predict how the tumour is contained or expanded by time may help the specialist to obtain a better diagnosis and more effective medical treatment.

Biomechanics has been involved in the study of various aspects of the cardiovascular system. For instance, it includes modelling of heart valves, blood flow, hemodynamic disorders and aneurysms, etc. More recently, modelling of the complete procedure of stenting



Figure 1.3 A typical bone with a porous microstructure.



Figure 1.4 An illustration of the process of healing in soft tissues.

by balloon or through the shape memory effects by detailed macro/microstructural simulation of the blood vessel helps the cardiovascular specialist to decide on a better way for stenting to proceed for any specific patient.

On the other hand, a large number of annual car and industrial accidents and military and terrorist activities have created a growing mass of traumatized and injured people who need orthopaedic replacements in order to get back to a normal life. The corresponding economic impact has justified governments and industries to provide sufficient funding to support the research and development of related biomechanical studies on synthetic biosystems and artificial tissues.

In general, the following steps are involved in any biomechanical computations:

- 1) Geometrical macro- and microstructures of the organ/tissue should be determined.
- The living organ/tissue performs in a specific environment that should be resembled by biomechanical computations.
- 3) The mechanical properties of the constituents must be known. This is probably one of the most challenging parts of a biomechanical analysis due to the size and conditions of a living tissue, which does not readily allow for accurate mechanical tests.
- The multiphase and complicated composite nature of the tissue requires a sufficiently accurate model with known constitutive equations.
- 5) The results should be verified and calibrated by experiments on the real tissue/organ.

## 1.3 Types of Biological Systems

Looking at the governing equations and the way the biomechanical systems can be simulated, the following types can be distinguished:

#### 1.3.1 Biosolids

The word biosolid is used to denote solid biological systems. It is noted that biosolid terminology is also used in some public health-related industries to discuss the solid wastes and even toxic chemicals, which are not related to this work.

The biosolid organs and tissues are usually of a composite nature, both in macro- and microscales. While they are solid in nature and are governed by the conventional rules of solid mechanics, they are usually in direct interaction with other types of biomaterials, even with different scales of their biological constituents.

For instance, a soft skin tissue is composed of several distinguishing layers. Some of them have a complex microstructure of collagen fibres within the grounds of a gel-like matrix. The collagen fibre itself is composed of a composite microstructure of fibrils and matrix. The fibres may form a straight or helical shape in different tissues, which constitute the major functionality of the tissue.

As another example, a fracture is a relatively common mode of failure for a bone (Figure 1.5). The bone, as a biosolid, is composed of several layers and a heterogeneous microstructure with different constituents and holes (representing the blood vessels, etc.). Both two- and three-dimensional simulations have been performed to study the fracture resistance of the bone as a single-scale porous solid medium or by advanced



Figure 1.5 Simulations of bones on different scales.

multiscale methodology. Such analyses are in practice based on the conventional continuum or fracture mechanics of solids or employ the multiscale analysis of solid materials. Recently, the study of healing of fractured bone has gained a lot of attention and in addition to conventional solid equilibrium equations, requires several coupled equations of the mass transfer and diffusion nature, to be solved simultaneously.

#### 1.3.2 Biofluids

While the earliest written document on blood circulation may be dated back to centuries ago, the breaking work can be attributed to one in the 17th century, where the motion of the heart and blood in animals was discussed for the first time (Harvey 1628), developing the so-called Poiseuille flow and pressure gradient theory in long tubes. It was followed by another major work based on the theory of circulation. Nowadays, massive research studies are being performed on various biofluid applications.

Biofluids (biological flows) cover a wide range of biological applications from organs to cells. Cardiovascular systems, lung and breathing mechanisms, urinary and reproductive systems and even some neurological systems may partially be studied using the biofluid mechanics/dynamics method (Figure 1.6).

While the fundamentals of fluid dynamics govern the mechanical responses of biofluids, the well-developed computational fluid dynamics (CFD) can practically and efficiently be used to analyse such systems and to study their interactions with other biological mechanisms. The complexity of the biofluid simulations arise from the fact that in addition to their basic physiological characteristics, their motion and subsequent interactions should also be considered. This is the case when drug delivery conditions are investigated or DNA/RNA and some proteins are sustained in the biofluid.



Figure 1.6 Typical bronchiole and biofluid (blood flow) simulations.

Moreover, CFD can be combined with conventional solid mechanics and advanced multiscale solutions to study the biomechanical response of different types of diseases such as aneurysms, coronary heart failure and pulmonary problems, leading to better understanding of the corresponding implications, diagnostic and even treatment procedures.

The cardiovascular system is composed of the heart and a blood-carrying network of arteries and veins. The blood flow through the pulmonary and systematic circulation system into the lung arterioles and capillaries allow for the exchange of oxygen and carbon dioxide. The oxygenated blood is then transferred to various organs and cells through systematic circulation. Biofluid mechanics is expected to contribute in the handling of all such complicated mechanisms.

The blood itself is a complex viscous biological fluid, composed of different cells suspended in a plasma, which exchanges oxygen and carbon dioxide within the lungs and other substances within other organs such as kidneys, etc. The plasma contains proteins and other constituents. In addition to the main role of flow mechanics of blood, it performs other roles, such as transfer and diffusion mechanisms of various components that affect the healing process of soft and hard tissues. These effects can be seen in the form of propagation and diffusion processes (Waite and Fine 2007), as will be described in dedicated sections.

#### 1.3.3 Biomolecules

Biomolecules are organic combinations of molecular structures that exist in bio-organisms and contribute to various processes of the bio-object (Figure 1.7). These processes are vital to the existence and performance of living organisms, such as growth factors, differentiation factors, etc.

The following biomolecular topics are among the important subjects of research in recent decades:

- Proteins are among the primary and essential bases of any biosystem, which affect the life-related functioning of the system.
- Lipids, which are mainly fatty acids, are the basic constituent of biological membranes.
- Vitamins are composed of a biomolecule or set of chemically related biomolecules and are essential for an organism to continue its specific functioning. Many types of vitamins may not be synthesized sufficiently within a bio-organism and therefore should be obtained by drug or diet prescriptions.



Figure 1.7 An illustration of a biomolecular structure.

- Carbohydrates generally consist of carbon, hydrogen and oxygen atoms. They may perform as a structural constituent, even for RNA, and a biostorage of energy. Carbohydrates are an essential part of the food and agriculture industries, and are important ingredients in pharmacological technologies and various clinical procedures.
- Nucleosides are molecules of more complex formations. For instance, DNA is dominated by a double helix structure, which constitutes a highly stable and reliable basis for genetic information storage.
- Amino acids are observed in proteins and influence their structure and interactions between proteins. They are also used in different industrial activities, such as cosmetics and drugs in the pharmaceutical industry, agriculture fertilizers and animal feeds, and the food industry.

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In biomechanics, the formation, design and function of the biomolecules can be studied. Simulation of biomolecules may require fundamentals of cell mechanics and molecular simulations, which should sufficiently employ the effects of both biochemistry and biomechanics.

#### 1.3.4 Synthesized Biosystems

Tissue engineering is an important interdisciplinary engineering and biological subject, with a variety of goals from function improvement of existing biosystems to repair and even replacement of existing biosystems with engineered artificial tissues/organs (Langer and Vacanti 1993; Galletti and Mora 1995). Human or animal tissues and organs and processed or synthesized materials can be used to design various biochemical processes and artificial biosystems. Extensive research and development reports on tailored engineering and artificial forms of skin, bone and blood vessels, etc. illustrate the extensive needs of the public health and the attention of corresponding industries towards this important issue. Such tailored or functional tissue engineering may allow the development of more realistic



**Figure 1.8** Synthesized systems: a shape memory alloy (SMA) implant and a nano shape memory polymer (SMP) drug delivery capsule.

biological substitutes that match the important properties of biological systems better, such as anisotropy, constitutive properties, inhomogeneity and microstructure, permeability, hardness and wear, multiphase nature, rate and viscous characteristics and physicochemo-mechanical effects.

Nevertheless, there are many important issues that should be taken into consideration. For instance, while many engineered tissues should perform according to specific mechanical functioning, their micromechanical properties may not be explicitly similar to the corresponding biological tissue and the way they control the overall biological response. There is also a lack of sufficient and integrated collection of data for some tissues, especially when they are related to complex microstructural characteristics, inhomogeneity, and ratedependent properties. Moreover, the issue is further complicated by the fact that the synthesized tissues may be developed and implanted in environments far different from the actual biological system.

Another important concern is the lack of unified standards in many synthesized applications, as they may be adopted for a very wide and different range of applications. On the other hand, the long-term effects, such as mechanical fatigue (for example in implants) and biological reactions against the constituents (for instance in a drug-delivery system), should also be considered (Figure 1.8). They may also have biomechanical side-effects, which should be considered in modelling and design of the synthesized systems.

# 1.4 Biomechanical Hierarchy

### 1.4.1 Organ Level

Biomechanical analysis of organs usually involves the study of several types of tissues and may require analysis of different phases (such as solids, fluids, etc.) in order to provide a realistically verifiable prediction of the way an organ model performs.



Figure 1.9 Simulation of an aortic heart valve leaflet.

As an example, the aortic heart valve is a one-way valve located between the left ventricle and the aorta, preventing the blood from flowing backwards into the heart. Its tissue is a composite one similar to other soft tissues, and the available hyperelastic formulations may well define the mechanical behaviour of the tissue and its constituents. The heart valve is mainly subjected to a pre-set blood flow pressure in most conventional and advanced multiscale simulations. Nevertheless, there may be cases that require a full fluid–solid interaction (FSI) analysis for the heart/valve/blood simulation (Shahi 2013). The model may need to be further refined to finer scales, even to the cell level, to provide a physiologically related outcome that can be used clinically (Figure 1.9).

### 1.4.2 Tissue Level

Accurate simulation of soft biological tissues, which may involve complex nonlinear analyses, has been active in recent decades. From a microscopic point of view, there exists a non-uniform distribution of collagen fibres embedded in a ground of gel like matrix. The collagen fibres are made from the fibrils, and the fibrils are composed of layers of collagen monomers, defining the whole microstructure in multiple scales (Figure 1.10).



Figure 1.10 Multiple scale structure of soft tissues.



Figure 1.11 Sample modelling of the dissection problem.

Such a complex multiscale characteristic makes the analysis and capture of the highly nonlinear mechanical response of soft tissue problems very complex (Figure 1.11), which requires a set of advanced coupled numerical formulations to obtain feasible results (Fathi et al. 2017).

#### 1.4.3 Cellular and Lower Levels

Complex individual and interactive responses of molecular and cellular structures of a tissue determine its physiological characteristics. Therefore, it is important to study the behaviour of biosystems at a cellular or molecular level (Figure 1.12).

For instance, assemblies of biomolecules or clusters of subcellular structures and any change in their functioning may indicate potential disordered phenomena that may eventually lead to a pathological disease. Such biological disorders, for instance in the extracellular matrix (ECM), may somehow be related to the biomechanical characteristics, such as porosity, viscosity, stiffness, etc., and then linked to higher scale properties by some sort of



Figure 1.12 A variety of cells, from a complex nerve cell to a simplified model.



Figure 1.13 Modelling of the shape memory stenting procedure.

multiscale approach. The same concept can be extended to examine any potential contamination with hostile particles and the corresponding biological effects.

## 1.4.4 Complex Medical Procedures

Advanced technologies have revolutionized the way medical treatments are performed nowadays. They have simplified the procedures, provided more accurate solutions and reduced the risk of conventional operations. Biomechanics has been involved in the study of various aspects of such high-tech procedures and their ultimate effects on the human body. For instance, modelling of heart valves, blood flow, hemodynamic disorders and aneurysms in the cardiovascular system are frequently performed nowadays. More recently, modelling of the complete procedure of stenting by balloon or through shape memory effects by detailed macro/microstructural simulation of a blood vessel, helps the cardiovascular specialist to make a better decision on the way stenting should proceed for any specific patient (see Figure 1.13).

# 1.5 Multiscale/Multiphysics Analysis

Multiscale and multiphysics methods involve the set of advanced computational techniques that allow for accurate, yet computationally affordable, analysis of highly complicated engineering problems and physical phenomena, which cover a vast wide range of problems from cosmology to subatomic physics and from conventional civil engineering projects to complex biological applications.

Due to the large range of applications, several categories of multiscale solutions have been developed over the years. Some of them provide tailored solutions for specific problems, whereas many others provide general procedures for a larger set of applications.

Conceptually, atomistic and molecular analysis should provide an accurate solution for any physical or engineering problem. However, it is limited to very small-scale models due to the extremely large cost of computations, required to handle billions of atoms necessary for a very tiny solid, even on advanced cloud-based cluster supercomputers. A logical remedy with affordable computational costs is to use the multiscale concept, where the micromodelling is performed only where needed and the rest of the problem is modelled by one of the conventional single-scale solutions. A proper link between the scales should also be designed and implemented to ensure the consistency of formulations and responses of different scales.

Among the multiscale methods, the sequential approaches are more straightforward and may span across a wider length scale. They avoid fully coupled solutions between the scales and perform in a one-way scheme, either from the large scales to the small ones or vice versa. For instance, in simulating a reinforced concrete with additive carbon nanotube (CNT) fibres, one may adopt a sequential multiscale solution by atomistic modelling of the CNT to determine its nanoscale properties. Then, the obtained nano properties can be used in a silicate–cement–hydrate (CSH) paste model to determine interactions of CNT and cement with hydrate reactions to assess a CSH equivalent response, which may include microscale damages and defects. The next stage is to use the microscale homogenized characteristics in a mesoscale model that includes aggregates and the cement (CNT-reinforced cement). This mesoscale solution leads to characteristics that can be used in the actual reinforced concrete specimen to evaluate some engineering goals, such as resiliency, durability, toughness, seismic response or impact resistance (Figure 1.14).



Figure 1.14 A sequential micro- to macroscale modelling.

Another important multiscale solution can be designed quite in an opposite direction: from macro- to microscale. For instance, to study heart valve functioning, one may begin with a fluid–structure interaction to evaluate the effect of blood flow pressure on the valve leaflet tissue. Then, for the most critical point, a lower scale model may be constructed to determine the induced stress, strain and other state variables within the microstructures of the tissue, which includes the collagen fibres, etc. Another step can be followed to analyse a further lower scale cell model of the biological constituent to determine if a biological criterion for cell activity is met (Figure 1.9). The same principles can be followed to study the excessive vitreous pressure on the optical nerve head (an indication of potential glaucoma), where the simulation begins from the full eye model and reaches to the cells, as typically presented in Figure 1.15.

A major category of multiscale solutions is the homogenization technique. While a simple one-way homogenization is usually used in micro to macro sequential techniques, the main concept of homogenization is defined in a coupled fashion to relate the macroscale response with the microstructure characteristics (Figure 1.16). Mathematical and computational homogenizations have been well developed over the years and applied to many engineering and physical problems. They have also been adopted in specific biomechanical applications.

Some biomechanical problems may require a further insight well into the cell and molecular levels. Such simulations may be performed by one of the concurrent multiscale models, which consider two or more scales at the same time. In fact, they use different scales to formulate different parts of the domain or to describe different responses of a domain at the same time.

Turning back to biomechanics, there has been a large amount of literature on the multiscale solutions in recent decades. They include almost every organ or tissue or even every physiological phenomena. To gain some idea of the extent of multiscale simulations of the main human organs, Figure 1.17 shows a typical illustration of the potential multiscale



Figure 1.15 From macro- to microscale modelling of an eye.

microscale model

Figure 1.16 Fully coupled macro-micro multiscale homogenization.



**Figure 1.17** Computational multiscale biomechanics; combining biology and mechanics in a numerical fashion. *Source:* Reproduced by permission of Stratasys, Inc.

biomechanics models, as originally presented by the HPC-Lab, University of Tehran (2020) (the central part design is by GrabCAD).

Several types of multiscale solutions may be performed on the biomechanical issues related to human organs or diseases. Some of the important topics of biomechanical applications can be presented as:

- Lamina cribrosa in the human eye
- NiTi SMA implants
- Micromechanics of bones
- Modelling of aneurysm disease
- Cardiovascular SMA stenting
- · Modelling of aortic dissection
- · Healing process of damaged soft tissues
- Healing in hard tissues
- Aortic heart valve simulation
- Traumatic brain injury
- Growth of cancerous tumours
- Drug delivery
- ...

Some of the mentioned topics will be dealt with and discussed in detail in Part III (based on the theoretical formulations and numerical methods presented in Part II).

## 1.6 Scope of the Book

The book is composed of three parts. This preliminary part is meant to provide an introduction and insight on the general concept of the biomechanics and the wide variety of biological problems that can be solved numerically, to assist the clinical staff and medical-related industries in assessing the existing procedures and products or to propose new engineered designs and concepts for future research and development.

Part II is dedicated to analytical and numerical bases in a systematic way, beginning with the very basics and approaching advanced computational techniques.

This part first covers the general concepts of continuum mechanics. For solid mechanics problems, a review is provided for elasticity, followed by principles of plasticity and damage mechanics. Then, fundamentals of fracture mechanics are presented. Viscoelasticity and rate-dependent behaviours are discussed. Poroelasticity is briefly reviewed and the concepts of large deformation are discussed in more detail, as it is the basis for many subsequent theories.

For fluid flow and field problems, the governing equations of fluid flow, convection and diffusion problems are explained and the fluid–structure interaction (FSI) is examined by discussing the coupled Lagrangian–Eulerian (CLE) formulation and the Arbitrary Lagrangian–Eulerian (ALE) technique.

The next chapters cover the conventional and advanced numerical methods, which are essential for explaining the multiscale concepts and techniques. It begins by briefly reviewing the finite difference method (FDM), followed by an introduction to the finite volume

method (FVM) and the finite element method (FEM). Then, the extended finite element method (XFEM) is described as an extension to the classical FEM for accurate and efficient analysis of a wide variety of discontinuity and singularity problems. Then, an introduction is provided for the extended isogeometeric analysis (IGA and XIGA). The principles of the powerful meshless methods are described and some of its main approaches, the element free Galerkin (EFG), the meshless local Petrov-Galerkin (MLPG) and the smoothed particle hydrodynamics (SPH), are further discussed. That chapter concludes by examining the variable node element method, which is a combination of finite element and meshless principles to provide a very flexible new element for multiscale purposes.

The final chapter of Part II is dedicated to the comprehensive discussion on the multiscale methods. It begins by an introduction to provide an overview of the subject. The next section discusses the concepts of the homogenization technique and covers both mathematical and computational homogenization techniques and presents the state-of-the-art concepts of the enriched multiscale homogenization, with sample results on microscale cracking problems.

Then, the atomistic and molecular modellings are discussed in detail. This covers the concepts of statistical mechanics and the governing equations of motion along with a review on major available potential functions. The section concludes by a sample modelling of a set of polymeric chains.

Then, the important subject of the sequential multiscale method is thoroughly discussed by providing details of a practical simulation, which spans the extremely wide range of molecular dynamics (MD) simulations, nanoscale analysis, microscale computations, mesoscale investigation and macroscale study of concrete specimen with additive CNT fibres.

The multiscale chapter is concluded by a comprehensive review of the concurrent schemes. It begins by briefly examining the main concepts of the concurrent techniques. Then the quasi-continuum (QC) approach is discussed and its main assumptions are presented, followed by the fundamentals of the bridging domain (BDM) and the bridging scale (BSM) methods. The so-called disordered multiscale method is presented for amorphous and polymeric material structures, which is expected to perform well for polymer and biomolecule applications. Finally, the variable node multiscale method (VNMM) and its extension to the enriched multiscale method (EMM) are presented.

Part III is dedicated to single and multiscale biomechanical simulations. It adopts the previously discussed theoretical concepts and numerical methods to discuss the way various biomechanical problems can be analysed. The chapter begins by reviewing the physiology of the problem and moves towards the governing equations and the way they can be numerically simulated and solved. They include several numerical examples to explain the adopted procedure for efficient simulation of the complex phenomena involved in various biomechanics problems.

The first chapter of Part III is dedicated to the modelling of soft tissues. Again, it begins with explaining the composition and physiology of soft tissues, with special attention given to its fibrous microstructure by collagen fibres, fibrils, etc. Then, the macro- and micro-structure mechanical properties are discussed in detail and the corresponding material models and constitutive laws in the form of hyperelastic models are presented. This chapter includes several single- and multiscale simulations of a number of soft tissue applications, including tendon and ligament, aortic heart valve, skin damage, arterial wall degradation, wound healing and the viscoelastic response of the brain.

The next chapter of this part is dedicated to hard tissues. It begins by explaining the composition and architecture of hard tissues and looks at their macro- and microstructures. Then, the necessary mechanical models are discussed. A number of single- and multiscale simulations are presented to provide more insight into the way hard tissue biomechanical studies are performed. Moreover, a discussion is provided on the healing processes of hard tissues by examining the governing equations and the numerical simulations.

Part III is concluded by a complementary chapter on brief reviews of supplementary topics, covering principles of artery stenting simulations, an initial assessment of the multiscale modelling of the eye, a look at the pulsatile blood flow in the aorta, analysis of the concept of a shape memory polymer drug delivery system and an introduction to the emerging computational technology of artificial intelligence and deep learning in biomechanical applications.

The contents of the book are completed by the list of references.