Modelling Living Tissues: Mechanical and Mechanobiological Aspects

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Summary. Mechanical modeling of living tissues is currently one of the most crucial challenges in research for mechanical engineers and mathematicians. Mechanics is a key factor to understanding the mechanisms that regulate many biological processes, such as mitosis, migration, and differentiation. This work aims to present the most crucial aspects, in the authors' opinion, to approach this challenge.

1 Introduction

"Classical science is a conversation between theory and experiment" [1]. However, nowadays, computer simulation has been recognized as a key tool for scientific research. Some of the most useful applications of computational modelling belong to Biology [2], and specifically to modelling living tissues with a structural function, supporting and transferring loads and moving other organs [3].

In fact, Mechanics has a strong influence on many biological processes characteristics of living tissues, such as, regulation of different biological processes (homeostasis), morphological and structural adaptation or tissue damage and repair, and it is responsible directly or indirectly of many diseases such as scoliosis, osteoporosis, malaria, etc. This fact has motivated that a wide number of research works have been recently developed with the purpose of modelling the active and passive behaviour of living tissues. Modelling the functional mechanical behaviour of living tissues has historically followed two approaches: (1) considering living tissues as inert structural materials, only dealing with Mechanics and (2) considering the biological reaction of living tissues to mechanical strains/stresses and the associated changes in microstructure and therefore in the mechanical behaviour itself.

The first field corresponds to classical *Biomechanics* and applies the principles of Mechanics to predict the mechanical behaviour (movement, strains and stresses) of a tissue or an organ, taking into account the acting loads, its microstructure and the external boundary conditions. The second one,

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known as *Mechanobiology*, tries to predict the evolution of the microstructure and biological constitution of a tissue or an organ as consequence of the mechanical environment.

In both cases, however, computational modelling presents strong difficulties that are necessary to keep in mind:

- We have to deal with very complex geometries that are sometimes evolutive. Therefore, computational geometry, medical imaging and data visualization are complementary tools.
- Most tissues involve large displacements and strains and internal material constraints which require sophisticated computational and mechanical models.
- Loads, boundary conditions and interactions are usually not known and very complex, which imply the need of accurate and complex experimental protocols to estimate them.
- Living tissues are regulated by multiple biophysical stimuli, thus, coupled fields (Multiphasic Mechanics, Biology, Chemistry) with very different time scales have to be modeled.
- Living tissues are hierarchically structurally composed materials, with their macroscopic properties depending on the different spatial scales involved. Therefore, a multiscale analysis is usually required.
- In contrast to usual engineering materials, living tissues have been optimally designed by the blind force of natural selection and show the remarkable ability to adapt not only their material properties and geometry, but also their functionality to environmental changes. Consequently, living tissues are evolving materials.
- Available experimental data present a strong variability that complicates the estimation of the parameters of the model, sometimes requiring stochastic approaches.

2 Biomechanical Tissue Modelling

Traditionally, Biomechanics in tissue modelling has been divided into two main fields of application due to the main characteristics of each tissue: hard and soft tissues.

On one hand, hard tissues typically undergo small deformations and behave nearly elastically in the range of interest. The first rigorous mathematical models for biological tissues that were introduced in the mid-1970s mainly addressed hard tissues such as bone [4].

The first modelling works of bone were elastic. For example, several authors try to model its mechanical behaviour through a mixture rule: Voigt's model [5] or Reuss's model [6]. Wagner and Weiner [7] modelled bone considering a composed material defined by its microstructure. Several authors [8, 9]

proposed experimental correlations that define the mechanical properties assuming isotropic behaviour as a function of the apparent density. However, bone is a porous and anisotropic material. Therefore, additional, correlations have been proposed including the directional influence of the microstructure through the so-called "fabric tensor" [10–14]. More recently, poroelastic models have been proposed to model the complex behaviour of bone and the interaction with the fluid that flows within its pores, lacunae and canaliculi [15–19].

On the other hand, biomechanics models for soft tissues needs a more sophisticated theory involving geometrically non-linear approaches [20, 21]. Soft tissues have a non-linear stress-strain behaviour, and many of them are viscoelastic and highly incompressible. Most models consider hyperelastic anisotropic theories with different types of strain energy density functions (polynomial, exponential, stochastically-based). Polyconvexity considerations; internal constraints (incompressibility); linear and strain-dependent viscoelasticity; residual stresses; damage; and in some case (muscular tissue) coupled electro-mechanical active behaviour are only a few of the topics addressed when dealing with the structural constitutive behaviour of soft tissues [20–25].

3 Mechanobiological Tissue Modelling

The main aim of mechanobiological models is to evaluate how a mechanical stimulus can regulate biological mechanisms, such as, remodelling, healing, etc. Therefore, these models allow improving our understanding of how tissues react to changes in the mechanical environment. In this sense, there are two main approaches: phenomenological and mechanistic.

Phenomenological models are able to predict the long-term behaviour of a biological tissue under physiological and pathological loads by establishing direct relations between external causes (mechanical stimuli) and external effects (internal microstructure or morphology) without considering the intermediate actors as they are the cells.

Mechanistic models, on the other hand, try to unravel the mechanotransduction mechanisms that regulate tissue reactions, such as: how tissues interact with cells; how cells sense strain (mechanosensing); how cells express biochemical substances after sensing strain (mechanotransduction); and how individual cells communicate with each other (signalling).

3.1 Phenomenological-Based Approaches

Phenomenological models are particularly useful to predict the adaptive tissue changes regulated by mechanical factors without information of how cells actually do it. In this sense, these models have been used to solve some important engineering problems like improving implant design [26,27], clinical therapies evaluation [28] or tissue engineering applications [29].

3.2 Mechanistic-Based Approaches

Mechanistic models try to incorporate the effect that cells exert on the evolution of the microstructure, accounting for processes like cell proliferation, differentiation, extracellular matrix production, etc. Although very difficult to validate, they are much more bio-physical and allow checking different hypotheses and design new experiments useful for a better understanding of the specific problem analyzed. Multiphasic formulations are usually used, including complex interactions between Mechanics, cells and volume growth in the framework of open systems [30, 31].

As for as the authors know, the most general mechanistic model that considers coupled equations between multiphasic and multicellular tissue mixtures in a continuum setting has been proposed by Doblare and García-Aznar [32]. This model incorporates different and crucial factors to achieve this goal: multiple species and different types of cells; sources, sinks and diffusion of both mass and cells; possible energy transfer between the different species and cells; tissue growth, differentiation, remodeling and damage; cell proliferation, migration, differentiation and necrosis.

This formulation has been particularized to different biological processes, such as, bone tissue adaptation [33] (see Fig. 1), bone healing [34, 35] (see Fig. 2) or cell migration [36].

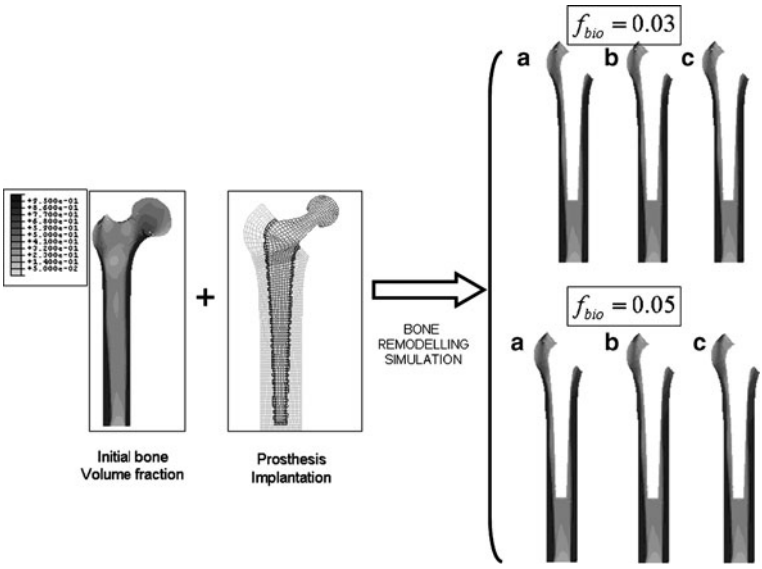

Fig. 1. Numerical simulation of the long-term adaptation process of a 2D model of a femur after implantation. Evolution of the bone volume fraction distribution for different biological factors and for different periods of time: (**a**) 330, (**b**) 660 and (**c**) 990 days [32]

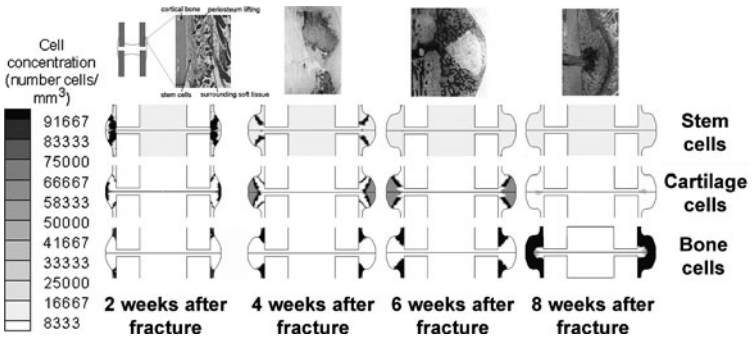

Fig. 2. Cellular distributions at different times of the healing process [32]: numerical results and histological sections (histologies taken from van der Meulen, Cornell University, NY; Sarmiento and Russell `http://www.hwbf.org/ota/bfc/index.htm`, 2002)

4 Conclusions and Further Work

Computational models including multi-scale and multi-physics approaches are a promising tool to better understand complex biophysical processes and are also essential in the growing field of quantitative and "evidence-based" Medicine. In fact, this kind of models allows exploring mechanotransduction at the cellular level and carry the information all the way up to the organ scale [4]. While the cellular scale can provide new insight into the fundamental mechanisms and help to explain signalling pathways (closer to biologists), large scale are essential to successfully address clinical and engineering problems.

Although these numerical techniques do already exists, their computational cost is still very high and the underlying biophysics is still not fully understood, so we are not able yet to fully analyze with sufficient confidence and accuracy a tissue at all the different scales incorporating all the relevant biophysical stimuli.

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