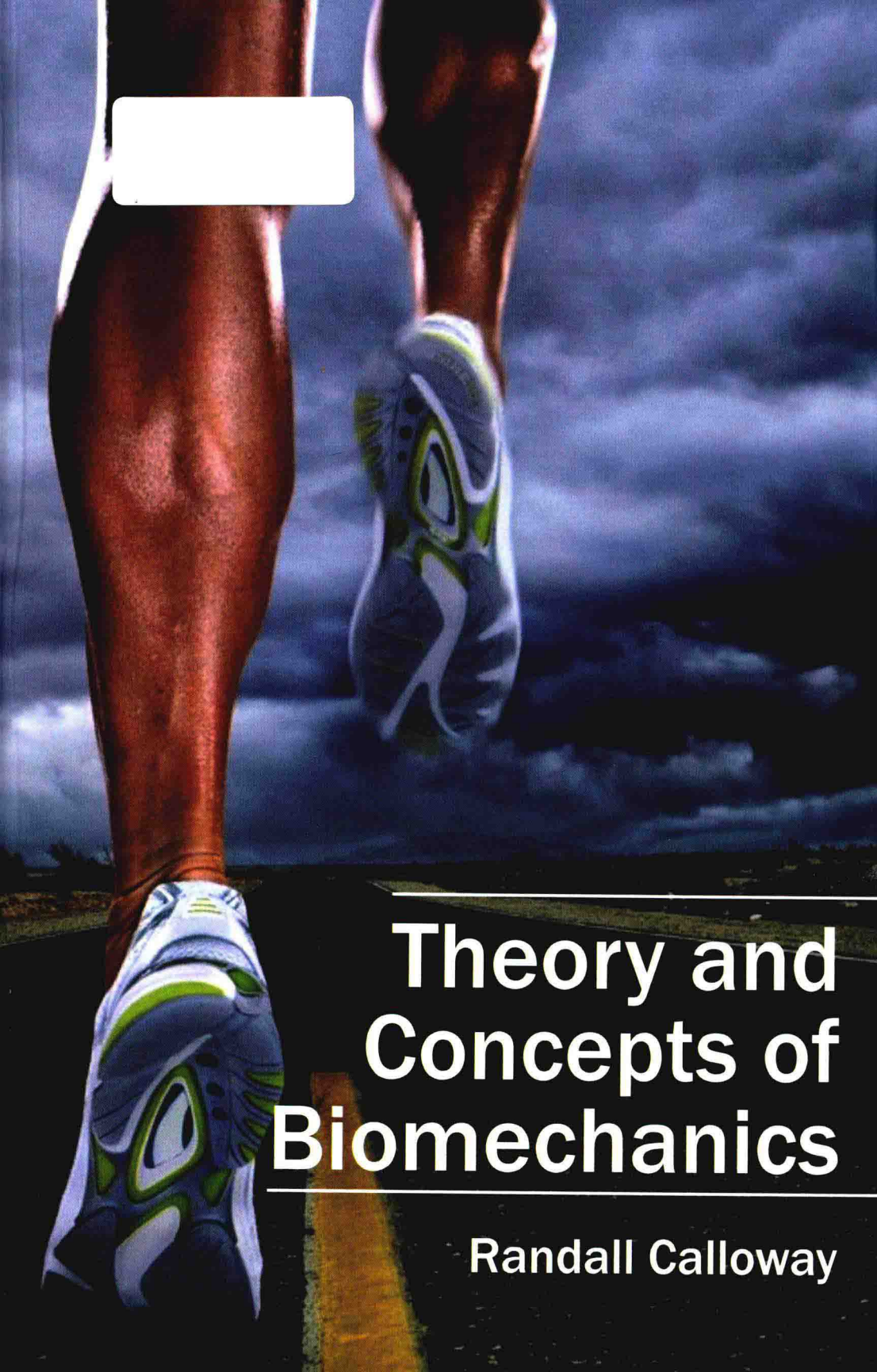

# Theory and Concepts of Biomechanics

Randall Calloway

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Edited by **Randall Calloway**



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# Preface

This book was inspired by the evolution of our times; to answer the curiosity of inquisitive minds. Many developments have occurred across the globe in the recent past which has transformed the progress in the field.

In the past few years, there has been an increasing awareness that issues emerging from biology or medicine require an interdisciplinary approach. Hence, certain forms of mathematics and applied physics have arisen; like biomechanics, mathematical biology and mechanobiology among others. This book discusses some general topics regarding biomechanics and mechanobiology, inclusive of theoretical contributions which provide explanations for certain aspects that experiments or clinical studies are unable to do. The book also discusses biomechanical modeling, a speedily growing field of biomechanical models and modeling methods utilized to increase the comprehension of various procedures occurring in the human body. Finally, this book also considers locomotion and joint biomechanics, which describe and analyze human movement, and the stability of the joints.

This book was developed from a mere concept to drafts to chapters and finally compiled together as a complete text to benefit the readers across all nations. To ensure the quality of the content we instilled two significant steps in our procedure. The first was to appoint an editorial team that would verify the data and statistics provided in the book and also select the most appropriate and valuable contributions from the plentiful contributions we received from authors worldwide. The next step was to appoint an expert of the topic as the Editor-in-Chief, who would head the project and finally make the necessary amendments and modifications to make the text reader-friendly. I was then commissioned to examine all the material to present the topics in the most comprehensible and productive format.

I would like to take this opportunity to thank all the contributing authors who were supportive enough to contribute their time and knowledge to this project. I also wish to convey my regards to my family who have been extremely supportive during the entire project.

**Editor**

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# Part 1

# General Notes on Biomechanics and Mechanobiology

1

# Mechanobiology of Fracture Healing: Basic Principles and Applications in Orthodontics and Orthopaedics

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## 1. Introduction

The Chapter describes how mechanobiological models can be utilized to predict the spatial and temporal patterns of the tissues differentiating within a fracture site during the healing process. It will be structured in four main Sections. Firstly, the basic principles of mechanobiology, the main theories and the principal models utilized to simulate the cellular processes involved in fracture healing will be illustrated. Second, two examples will be given showing how a mechano-regulation model, - where the bone callus is modeled as a biphasic poroelastic material and the stimulus regulating tissue differentiation is hypothesized to be a function of the strain and fluid flow-, can be utilized to assess bone regeneration in an ostetomized mandible submitted to distraction osteogenesis and in a fractured lumbar vertebra. Finally, the main limitations of the model utilized and, in general, of mechanobiological algorithms as well as the future perspectives will be outlined.
Fracture healing is a physiological process that initiates immediately after the fracture event and occurs by following two different modalities: by primary fracture healing or by secondary fracture healing. Primary healing involves a direct attempt by the cortex to re-establish itself once it has become interrupted. When stabilisation is not adequate to permit primary healing, the abundant capillaries required for bone repair are constantly ruptured and secondary healing takes place. Secondary healing involves responses within the periosteum and external soft tissues and subsequent formation of an external callus. Secondary fracture healing occurs in the following stages. Blood emanates from the ruptured vessels and a haemorrhage quickly fills the fracture gap space. Macrophages remove the dead tissue and generate initial granulation tissue for the migration of undifferentiated mesenchymal stem cells (MSCs), originating an initial stabilizing callus. These cells proliferate and migrate from the surrounding soft tissue (Einhorn, 1998, McKibbin, 1978) (Fig. 1a). Then, stem cells disperse into the fracture callus, divide (mitosis) and simultaneously migrate within the fracture site (Fig. 1b). In the next stage, mesenchymal cells may differentiate into chondrocytes, osteoblasts or fibroblasts, depending on the biological and mechanical conditions (Fig. 1c). These differentiated cells begin to synthesize the extracellular matrix of their corresponding tissue (Doblaré et al., 2004) (Fig. 1d). Intramembranous woven bone is produced by direct differentiation of the stem cells into osteoblasts. Endochondral ossification occurs when chondrocytes are replaced by osteoblasts.

## 2. Mechanobiology: Basic principles

Comparing patterns of differentiation during tissue repair to predictions of the mechanical environment within the mesenchymal tissue has led to the development of a number of hypothesis for mechano-regulated tissue differentiation. Theories on the relationship between mechanics and biology were originally proposed in relation to fracture healing. These theories later evolved into 'mechanobiological algorithms'; a finite set of rules that govern the effects of mechanical loading on stem cells and tissues. Mechanobiology merges the older science of mechanics with the newer and emerging disciplines of molecular biology and genetics.

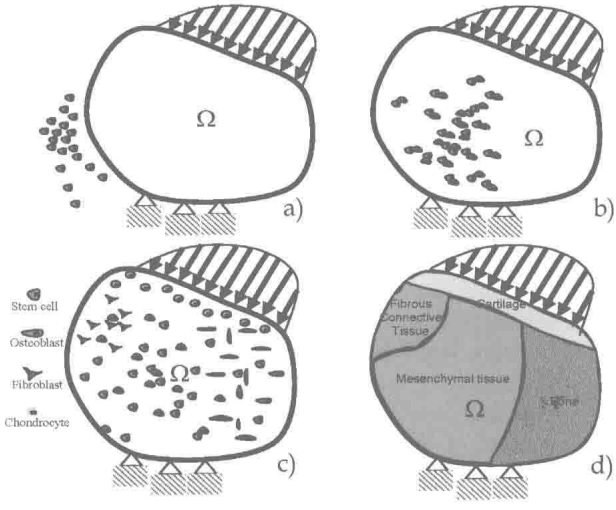


Fig. 1. Let Ω be an arbitrary fracture domain loaded and constrained over part of the surface. Immediately after the fracture event the mesenchymal stem cells (MSCs) reside outside the domain in the surrounding soft tissue (a). Then, stem cells disperse into the domain, divide (mitosis) and simultaneously migrate within the domain (b). Depending on the biological and mechanical conditions MSCs differentiate into fibroblasts, chondrocytes and osteoblasts (c). These differentiated cells begin to synthesize the extracellular matrix of their corresponding tissue (d).

At the centre of mechanobiology is the cellular process of mechano-transduction, or the way by which the cells sense and respond to mechanical forces or, in general to biophysical stimuli. Experimental and analytical models are often integrated in mechanobiology to gain a deeper understanding of the cells' response to mechanical factors. Experiments provide insights and measurements, which can then be interpreted within the context of analytical frameworks. Analytical simulations permit investigation of possible explanations that require in vivo validation and will suggest further experimental investigations (van der Meulen and Huiskes, 2002).

### 2.2 Mechanobiology of mesenchymal stem cells

Mesenchymal stem cells (MSCs) are nonhematopoietic progenitor cells found in adult tissues. They posses an extensive proliferative ability in an uncommitted state and hold the

potential to differentiate along various lineages of mesenchymal origin in response to appropriate stimuli (Chen et al., 2007). Bone marrow is the most important source for MSCs (Simmons, 1985, Brighton and Hunt, 1991, Glowacki, 1998). However, MSCs have been also identified in different other tissues such as adipose, periosteum, trabecular bone, synovium, skeletal muscle, dental pulp and periodontal ligament (Barry and Murphy, 2004, Ballini et al., 2007, Ballini et al., 2010). Quiescent MSCs become mobilised during repair and remodelling through regulation by external chemical and physical signals that control their activation, proliferation, migration, differentiation and survival i.e. their fate (Byrne, 2008). One key aspect in mechanobiology of MSCs is the modelling of the cellular processes such as the cellular dispersal, the proliferation, the apoptosis, etc.

Concerning the process of cellular dispersal, it has been suggested that the movement of stem cells can be thought of as an assemblage of particles, with each particle moving around in a random way (Murray, 1989). In a number of studies (Lacroix and Prendergast, 2002, Geris et al., 2004, Andreykiv et al., 2005), a diffusion equation has been used to simulate the movement of cells through regenerating tissues. If $c$ is the concentration of stem cells in a given volume and $D$ the diffusion coefficient, the derivative of $c$ with respect to the time is given by:

$$\frac{\mathbf{d}c}{\mathbf{d}t} = D\nabla^2 c \tag{1}$$

However such a modelling of cellular dispersal presents the limitation that the diffusion coefficient assumes a value that does not depend on the cell phenotype or the tissue through which the cell is moving. Furthermore, this approach implicitly assumes that cells attempt to achieve a homogenous population density within the area of analysis. Lacroix et al. (2002) developed further the diffusion equation (1) by including the processes of cellular mitosis and apoptosis (programmed cell death). Therefore, the rate of change in cell concentration assumes the form:

$$\frac{\mathbf{d}c}{\mathbf{d}t} = D\nabla^2 c + cs(c_c) - kc \tag{2}$$

The first term on the right-hand side of equation (2) describes cell migration by simple linear diffusion; the second term describes cell mitosis, where $c_c(x,t)$ is the chemical concentration of a mitosis-inducing factor; $s(c_c)$ is a function describing the mitosis rate per cell; and $k$ is a constant describing the cell death or removal rate (Sherratt et al., 1992). Since the mesenchymal stem cells can differentiate into cells of different phenotypes $i$ (i.e. fibroblasts, chondrocytes and osteoblasts) that produce different tissues $j$ (i.e. fibrous tissue, cartilage and bone), a logical progression of the idea proposed by Lacroix et al., (Lacroix et al., 2002), would be that the diffusion coefficient $D$ would depend on the cell phenotype $i$ and the tissue type $j$ through which the cell is moving. This modelling has been adopted in Kelly and Prendergast (Kelly and Prendergast, 2005, 2006). Boccaccio et al. (Boccaccio et al., 2007, 2008a), modelled the cellular dispersal by using the diffusion equation (1) however, they accounted for the fact that MSCs not only require time to differentiate, but that the differentiated cell types require time to synthesise and remodel new tissue. To this purpose, based on the results of Richardson et al. (Richardson et al., 1992) who observed an exponential increase in stiffness during tibial fracture healing, they assumed that the Young's modulus of all tissues within the fracture callus increases exponentially with time.

In reality, diffusion is not the mechanism of stem cell dispersal; cells disperse by crawling or proliferation or are transported in a moving fluid (Prendergast et al., 2009). In order to better simulate the cellular processes involved during the fracture healing process, Pérez and Prendergast (Pérez and Prendergast , 2007) developed a 'random-walk' model to describe cell proliferation and migration, with and without a preferred direction. In this approach, a regular lattice of points is superimposed on the fracture domain. Each lattice point is either empty, or occupied by a stem cell. Cell movement can be simulated by moving a cell from one lattice point to another; cell proliferation, by dividing a cell so that the daughter cell takes up a neighbouring lattice point; cell apoptosis, by removing a cell at a lattice point.

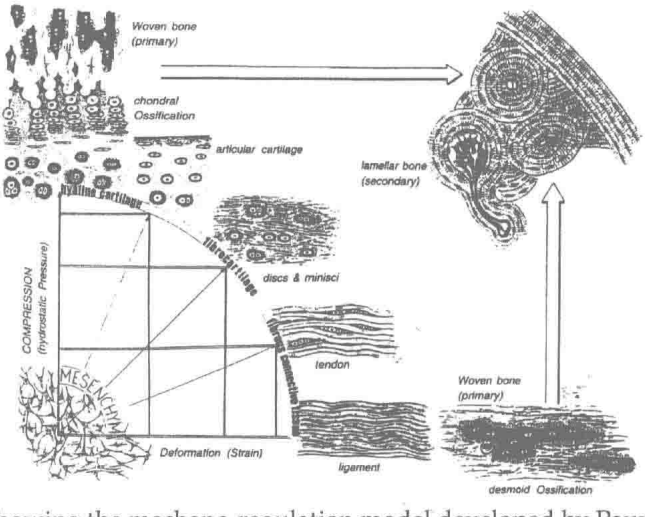


Fig. 2. Diagram showing the mechano-regulation model developed by Pauwels (Pauwels, 1960). The combination of two biophysical stimuli, shear strain and hydrostatic pressure, will act on the mesenchymal cell pool leading to either hyaline cartilage, fibrocartilage or fibrous tissue as represented on the perimeter of the quadrant. The larger arrows indicate that, as time passes, ossification of these soft tissues occurs, provided that the soft tissue has stabilized the environment. Reprinted from Bone, Vol. 19, Issue 2, Weinans H, Prendergast PJ, Tissue adaptation as a dynamical process far from equilibrium, Pages No. 143-149, Copyright (1996) with permission from Elsevier.

### 2.3 Principal mechano-regulation models

Pauwels, (Pauwels, 1960), who was the first to propose the hypothesis of a mechano-regulated tissue differentiation, suggested that the distortional shear stress is a specific stimulus for the development of collagenous fibres and that hydrostatic compressive stress is a specific stimulus for cartilage formation. When a soft tissue has stabilized the environment, differentiation of MSCs into osteoblasts is favoured leading to the formation of bone (Fig. 2).
Based on a qualitative analysis of clinical results of fracture healing, Perren (Perren, 1979) proposed that tissue differentiation is controlled by the tolerance of various tissues to strain. The basis of this theory, - normally known as 'the interfragmentary strain theory' - is that a tissue that ruptures or fails at a certain strain level cannot be formed in a region experiencing strains greater than this level. Based on the framework of Pauwels (Pauwels, 1960), Carter et al. (Carter et al., 1988, Carter and Wong, 1988) expanded the concepts

relating tissue differentiation to mechanical loading. They proposed that local stress or strain history influences tissue differentiation over time (Carter et al., 1988). These ideas were later developed further and a more general mechano-regulation theory was proposed (Carter et al., 1998) (Fig. 3). They postulated that: (i) compressive hydrostatic stress history guides the formation of cartilaginous matrix constituents; (ii) tensile strain history guides connective tissue cells in their production and turnover of fibrous matrix constituents; (iii) fibrocartilage is formed when a tissue loading history consists of a combination of high levels of hydrostatic compressive stress and high levels of tensile strain; (iv) direct bone formation is permitted, in regions exposed to neither significant compressive hydrostatic stress nor significant tensile strain, provided there is an adequate blood supply; (v) pre-osseous tissue can be diverted down a chondrogenic pathway in regions of low oxygen tension. The mechano-regulation theory of Claes and Heigele (Claes and Heigele, 1999) was initially presented in quantitative terms, and although the resulting concept is similar to that of Carter et al. (Carter et al., 1998), they based their mechano-regulation theory on the observation that bone formation occurs mainly near calcified surfaces and that both intramembranous and endochondral ossification exist in fracture healing. Depending on local strain and hydrostatic pressure different cellular reactions and tissue differentiation processes were predicted to occur (Claes et al., 1998; Claes and Heigele, 1999).

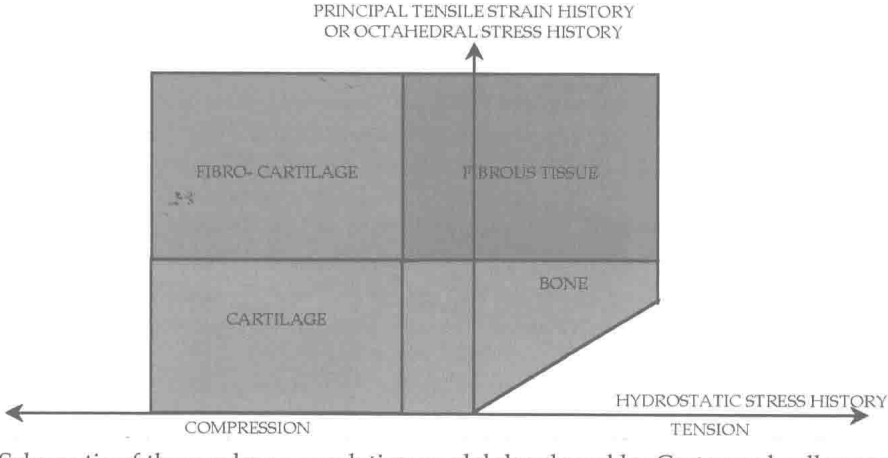


Fig. 3. Schematic of the mechano-regulation model developed by Carter and colleagues representing the role of the hydrostatic stress history and the maximum principle tensile strain history on the differentiation of mesenchymal stem cells in a well-vascularised environment (Carter et al., 1998)

Prendergast and Huiskes (Prendergast and Huiskes, 1995) and Prendergast et al. (Prendergast et al., 1997), created a poroelastic finite element model of a bone-implant interface to analyse the mechanical environment on differentiating cells. They found that the biophysical stimuli experienced by the regenerating tissue at the implant interface are not only generated by the tissue matrix, but also to a large extent by the drag forces from the interstitial flow. Based on this study, a new mechano-regulation theory was developed taking into consideration that connective tissues are poroelastic and comprise both fluid and solid. They proposed a mechano-regulatory pathway composed of two biophysical stimuli; octahedral strain of the solid phase and interstitial fluid velocity relative to the solid. Fluid

flow and substrate strain in the tissue, are used as a basis for the stimulus $S$ for cell differentiation as follows:

$$S = \frac{\gamma}{a} + \frac{v}{b} \tag{3}$$

where $\gamma$ is the octahedral shear strain, $v$ is the interstitial fluid flow velocity, $a$=3.75% and b=3μms$^{-1}$ are empirical constants. High stimulus levels ($S$>3) promote the differentiation of mesenchymal cells into fibroblasts, intermediate levels (1<$S$<3) stimulate the differentiation into chondrocytes, and low levels of these stimuli ($S$<1) promote the differentiation into osteoblasts. Simulation of the time-course of tissue differentiation was presented by Huiskes et al., (Huiskes et al., 1997) (Fig. 4). The solid line shows what would occur in an environment where a high shear persists (i.e. maintenance of fibrous tissue and inhibition of ossification) whereas the dashed line shows what would occur if the presence of the soft tissue could progressively reduce the micromotions (i.e ossification would occur). Recently, the mechano-regulation model of Prendergast et al., (Prendergast et al., 1997) has been further developed to include factors such as angiogenesis (Checa and Prendergast, 2009), and the role of the mechanical environment on the collagen architecture in regenerating soft tissues (Nagel and Kelly, 2010). Gómez-Benito et al. (Gómez-Benito et al., 2005), presented a mathematical model to simulate the effect of mechanical stimuli on most of the cellular processes that occur during fracture healing, namely proliferation, migration and differentiation. They simulated the process of bone healing as a process driven by a mechanical stimulus, $\Psi(x,t)$ assumed to be the second invariant of the deviatoric strain tensor.

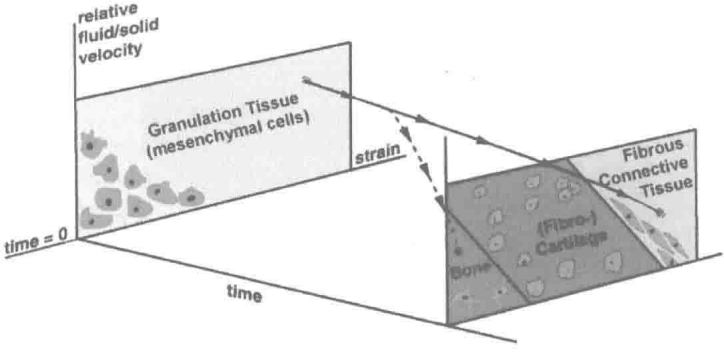


Fig. 4. Schematic of the mechano-regulation model proposed by Prendergast et al. (Prendergast et al., 1997). The solid line shows what would occur in an environment where a high shear persists (i.e. maintenance of fibrous tissue and inhibition of ossification) whereas the dashed line shows what would occur if the presence of the soft tissue could progressively reduce the micromotions (i.e ossification would occur).

The models above reviewed are based on theories of mechano-transduction, the way in which cells sense and respond to mechanical forces or displacements. Other bio-regulatory theories are reported in literature that put in relationship biochemical factors with the spatial and temporal patterns of tissue differentiation observed during the healing process of a fractured bone (Bailón-Plaza and van der Meulen, 2001, Geris et al., 2008).

### 2.4 Mechanobiology: Domains of applicability

Applications of mechanobiology can be found in three main areas:

i. In the development of new clinical therapies, for example in bone fracture healing, or osteoporosis. Different studies are reported in literature in which mechanobiological models are utilized to pursue this aim: Lacroix and Prendergast (Lacroix and Prendergast, 2002) predicted the patterns of tissue differentiation during fracture healing of long bones; Shefelbine et al. (Shefelbine et al., 2005) simulated the fracture healing process in cancellous bone.

ii. In the improvement of implant design. With implants such as prostheses, cells migrate up to the implant surface and begin to synthesis matrix, but if the micromotion is too high bone will not form to stabilise the implant – instead a soft tissue layer will form (Huiskes, 1993, Prendergast, 2006). A number of articles can be found in literature where mechanobiological models are utilized to predict the patterns of tissue differentiation at the tissue-implant interface: Andreykiv et al. (Andreykiv et al., 2005) simulated the bone ingrowth on the surface of a glenoid component; Moreo et al., (Moreo et al., 2009a,b) developed a mechano-regulation algorithm that models the main biological interactions occurring at the surface of endosseous implants and is able to reproduce most of the biological features of the osseointegration phenomenon.

iii. In bone tissue engineering and regenerative medicine. Appropriate biophysical stimuli are needed in bone scaffolds, in addition to nutrients and appropriate levels of oxygen supply, to favour an appropriate tissue differentiation process (Martin et al., 2004, Prendergast et al., 2009). A number of studies (Byrne et al., 2007, Milan et al., 2009; Olivares et al., 2009, Sanz-Herrera et al., 2009) are reported in literature that through a combined use of finite element method and mechano-regulation algorithms described the possible patterns of the tissues differentiating within biomimetic scaffolds for tissue engineering (Boccaccio et al., 2011a).

In this Chapter we will focus on the first domain of applicability (i) and, specifically, two examples will be illustrated that show how mechanobiology can be used to predict the patterns of tissue differentiation in a human mandible osteotomized and submitted to distraction osteogenesis as well the regrowth and the remodelling process of the cancellous bone in a vertebral fracture. Predictions were conducted by implementing the mechano-regulation model of Prendergast and colleagues (Prendergast et al., 1997).

## 3. Mechanobiology of mandibular symphyseal distraction osteogenesis

Mandibular Symphyseal Distraction Osteogenesis (MSDOG) is a common clinical procedure aimed to modify the geometrical shape of the mandible for correcting problems of dental overcrowding and arch shrinkage. Such problems are usually solved by tooth extraction or expansion protocols. However, these clinical procedures are unstable and tend to relapse towards the original dimension (McNamara and Brudon, 1993). Mandibular distraction osteogenesis may solve transverse mandibular deficiency problems. With this clinical procedure the mandibular geometry is definitively changed so that the risk of a relapsing towards the original dimension is avoided. In spite of consolidated clinical use, the process of tissue differentiation and bone regrowth in an osteotomized mandible remains poorly understood. Clinically, MSDOG can be divided into four stages: firstly the mandible is osteotomized and then instrumented with a distraction appliance; secondly a seven to ten day latency period is waited after the surgical operation in order to allow the formation of a

good quality bone callus; thirdly the distraction device is progressively expanded with a well defined rate for seven-ten day time period; the final stage is the maturation period during which the patient is maintained in rigid external fixation. At the end of this period, more space is available on the inferior arch so that the teeth which are initially in intimate contact, can be repositioned (through orthodontic treatments) in the correct locations.
The second stage is crucial for successful MSDOG. If the latency period is too short, a weak and insufficient callus will form, and without a good callus not enough new bone may form and complications may arise such as fibrous union, non-union, tooth loss and periodontal defects (Conley and Legan, 2003). On the other hand, too long a latency period may substantially increase the risk of premature bone union, which can hinder the subsequent expansion process. Furthermore, the duration of latency period depends strictly on the aging of patient (Conley and Legan, 2003). In the case of young children, the accelerated healing process allows clinical protocols with shorter latency period to be adopted while, in the case of elder patients, as the healing process progresses slowly, longer latency periods are required. The distraction period (i.e., the third stage) is also critical. Too fast a rate of expansion of the appliance can lead to poor bone quality within the distraction gap, partial union, fibrous union or atrophic non-union. Conversely, too slow a rate can lead to premature consolidation hence hindering the distraction process (Conley and Legan, 2003).
Such issues have been investigated by developing a mechano-regulation model of a human mandible osteotomized and submitted to distraction osteogenesis.

### 3.1 Finite element model

The 3D model of a human mandible has been reconstructed from CT scan data and the processing of the CT files was made by means of the *Mimics® Version 7.2* software (Materialise Inc.) (Fig. 5(a-c)). The model also includes an orthodontic distractor tooth-borne

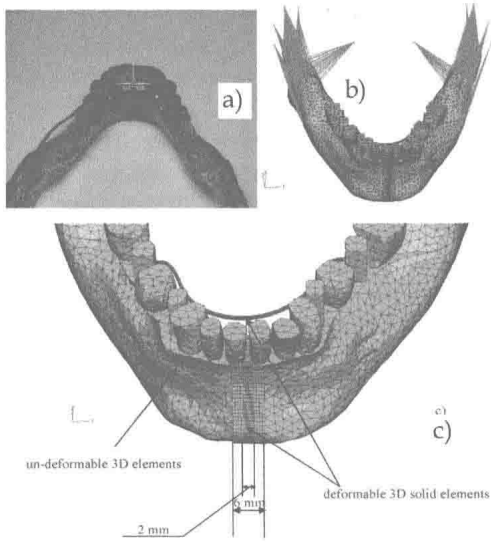


Fig. 5. (a) Epoxy resin model of the osteotomized mandible with a tooth-borne device; (b) mandible-distractor orthodontic device FEM model; (c) details of the osteotomized region and of the tooth-borne device