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# 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.

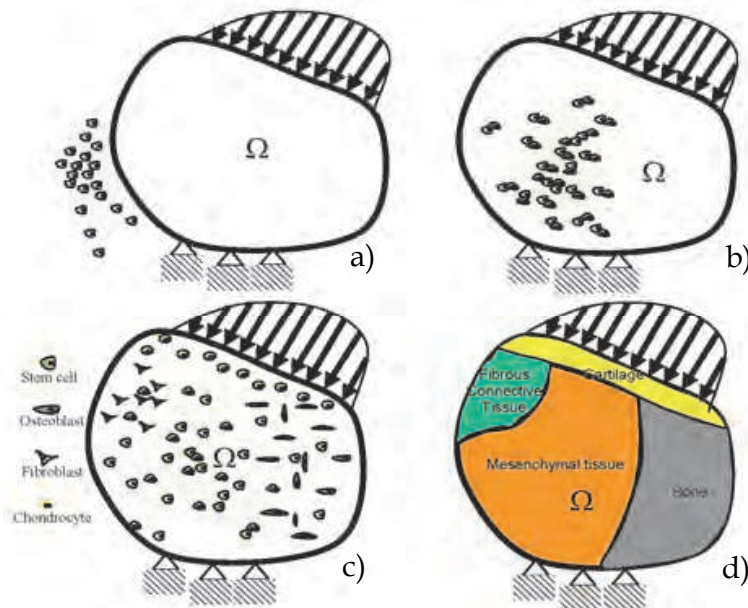


Fig. 1. Let  $\Omega$  be an arbitrary fracture domain loaded and constrained over part of the surface. Immediately after the fracture event the mesenchymal stem cells (MSCs) reside outside the domain in the surrounding soft tissue (a). Then, stem cells disperse into the domain, divide (mitosis) and 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 possess 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:

$$\frac{dc}{dt} = D\nabla^2 c \quad (1)$$

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:

$$\frac{dc}{dt} = D\nabla^2 c + cs(c_c) - kc \quad (2)$$

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.

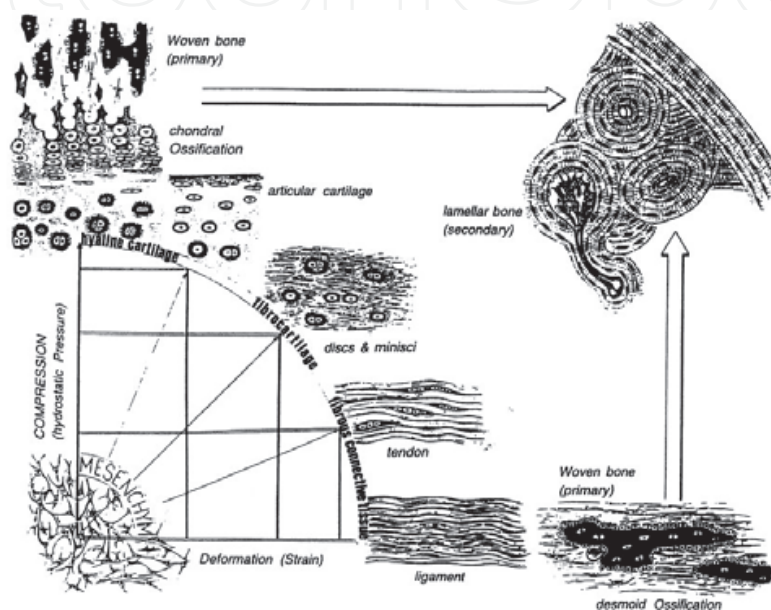


Fig. 2. Diagram showing the mechano-regulation model developed by Pauwels (Pauwels, 1960). The combination of two biophysical stimuli, shear strain and hydrostatic pressure, will act on the mesenchymal cell pool leading to either hyaline cartilage, fibrocartilage or fibrous tissue as represented on the 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-ossseous 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).

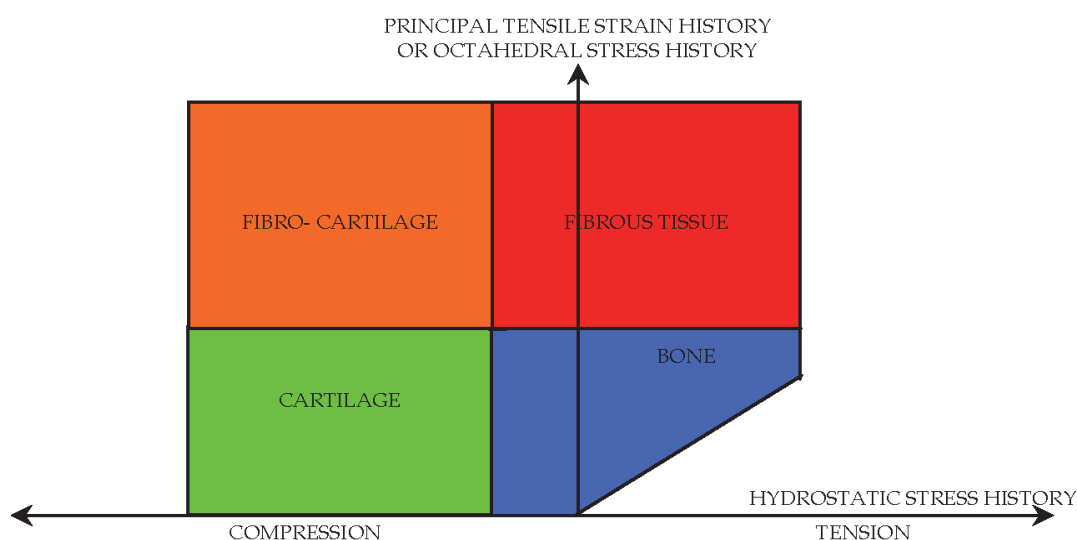


Fig. 3. Schematic of the mechano-regulation model developed by Carter and colleagues representing the role of the hydrostatic stress history and the maximum principle tensile strain history on the differentiation of mesenchymal stem cells in a well-vascularised environment (Carter et al., 1998)

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:

$$S = \frac{\gamma}{a} + \frac{v}{b} \quad (3)$$

where  $\gamma$  is the octahedral shear strain,  $v$  is the interstitial fluid flow velocity,  $a=3.75\%$  and  $b=3\mu\text{ms}^{-1}$  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 Huijskes et al., (Huijskes 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.

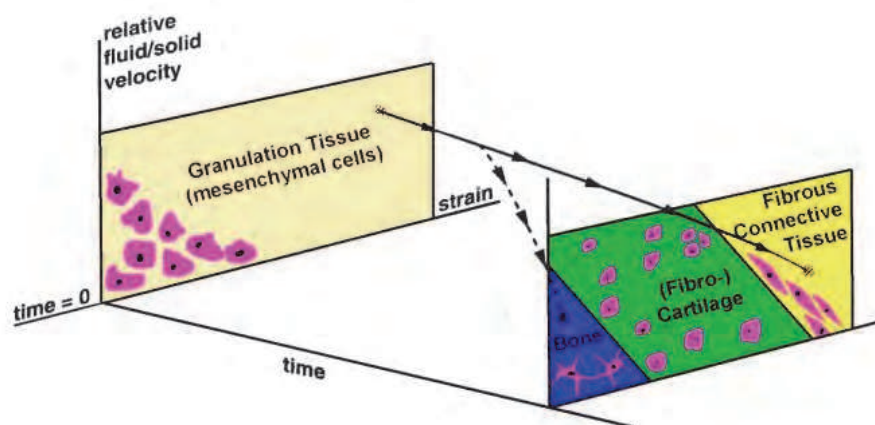


Fig. 4. Schematic of the mechano-regulation model proposed by Prendergast et al. (Prendergast et al., 1997). The solid line shows what would occur in an environment where a high shear persists (i.e. maintenance of fibrous tissue and inhibition of ossification) whereas the dashed line shows what would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

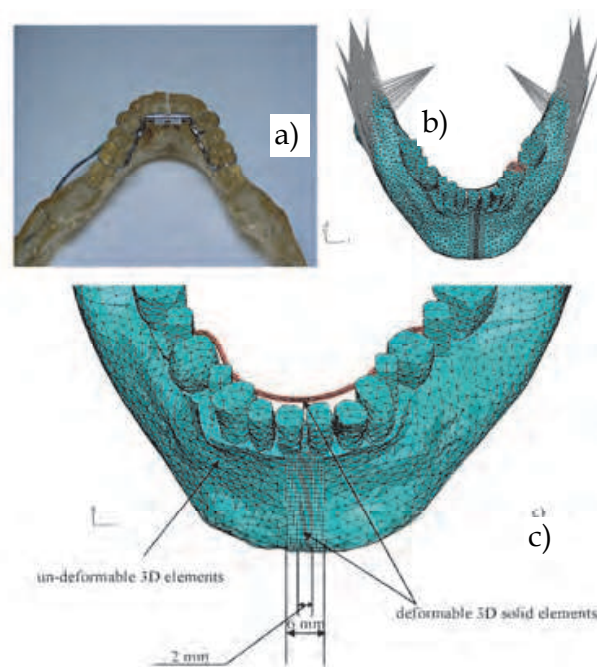


Fig. 5. (a) Epoxy resin model of the osteotomized mandible with a tooth-borne device; (b) mandible-distractor orthodontic device FEM model; (c) details of the osteotomized region and of the tooth-borne device

device. Since the stiffness of the mandibular bone is orders of magnitude greater than the callus, we modelled the portion of bone and of the device far from the osteotomized region as a rigid body. Conversely, the portion of the bone, of bone callus and of the device near to the middle sagittal plane was modelled with 3D deformable elements. With this strategy we reduced the computational cost of the analysis without introducing significant alterations with respect to the anatomic-physiological behaviour of the mandibular district. The finite element model consists of about 12000 3-node un-deformable triangular elements (see Fig. 5b) and about 5400 8-node hexahedral elements for meshing the osteotomized region and the deformable portion of the distractor device (Fig. 5c).

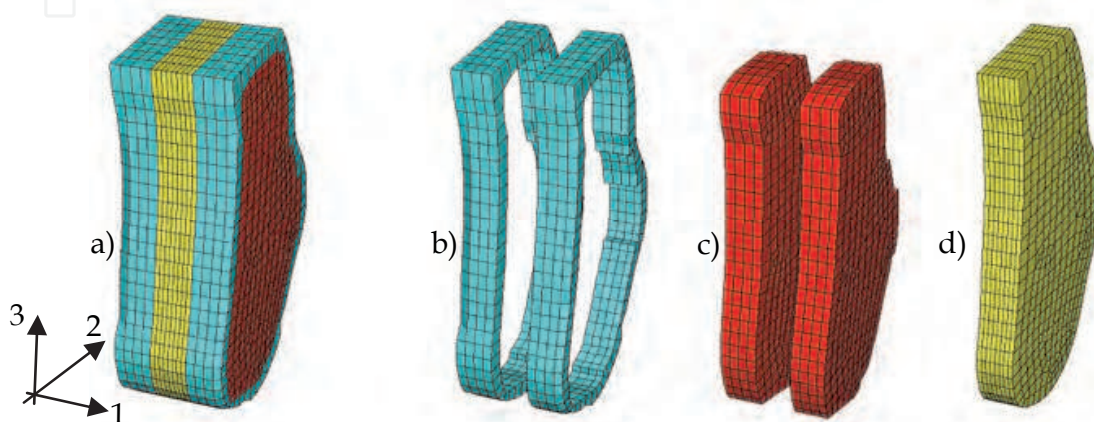


Fig. 6. (a) FEM model of the osteotomized region. Different regions and materials included in the model: (b) cortical bone (in light blue), (c) cancellous bone (in red), (d) fracture callus (in yellow).

Following Meyer et al., (Meyer et al., 2004), a 2 mm thick gap between the two mandibular *ramus* was created. The gap, surrounded by cortical and cancellous bone (Fig. 6) was hypothesized to be initially occupied by granulation tissue. The callus and bone tissue forming the portion of mandible near to the middle sagittal plane were modelled as biphasic poroelastic materials. Following Schwartz-Dabney and Dechow, (Schwartz-Dabney and Dechow, 2003) the cortical bone was modelled as an orthotropic material. The material properties used for all the other tissues are the same as used in previous models (Lacroix and Prendergast, 2002, Kelly and Prendergast, 2005).

### 3.2 Boundary and loading conditions

The FEM model is subjected to three boundary conditions applied simultaneously (Fig. 5b). Boundary condition (i) simulates the temporomandibular joint. The condyles are represented by two reference points at the locations of articulation. These reference points are connected to the mandible arms through coupling constraints. The behaviour of the temporomandibular joint disc is modelled by constraining these reference points to three fixed points by means of spring elements aligned to the coordinate system. The mandible hence can rotate about an axis defined by the line connecting the two condyles and translate along the coordinate directions. Boundary condition (ii) models the mastication. The action of the most important muscles involved in the mastication process, was simulated. Force intensity and direction are those used in a previous study (Boccaccio et al., 2006). Boundary condition (iii) simulates the unilateral occlusion on one tooth on the right mandibular arm.

The occlusion is modelled by constraining, with simple-supports preventing  $u_3$ -displacements (see direction 3 in Fig. 6), the second premolar.

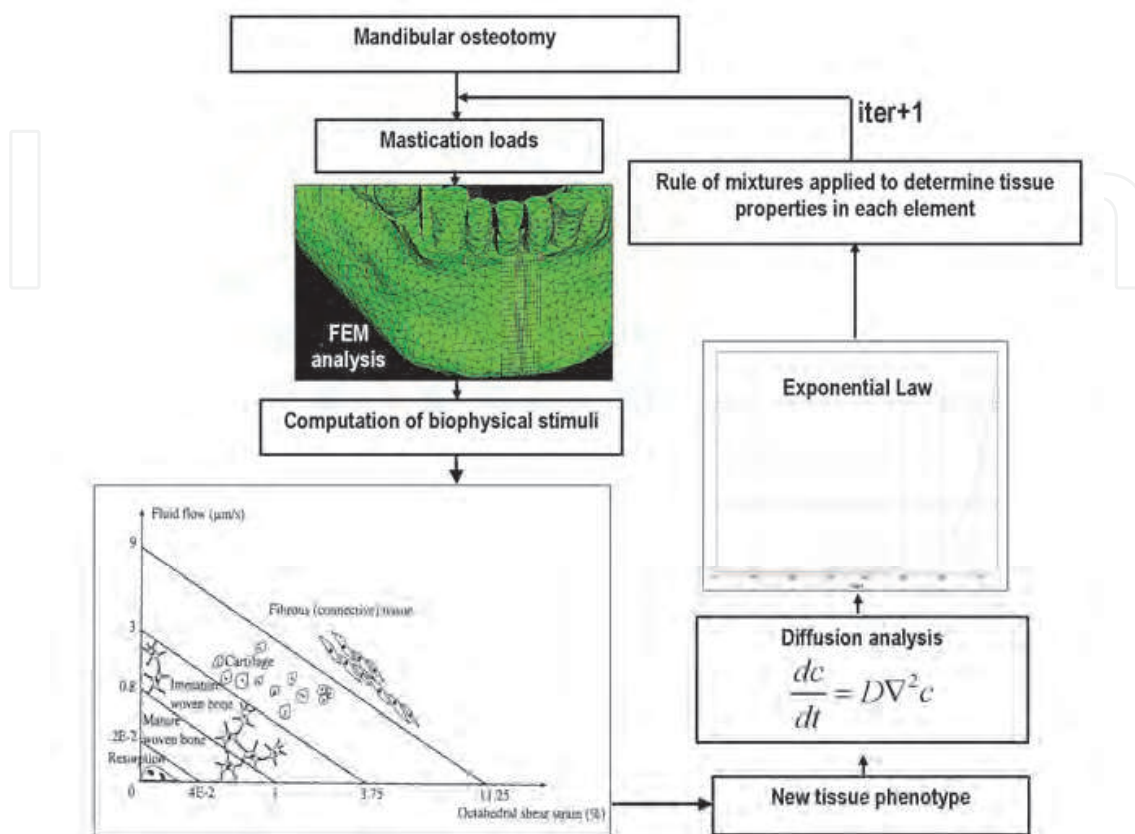


Fig. 7. Schematic of the implemented mechano-regulation algorithm

### 3.3 Determination of the optimal duration of the latency period

The mechano-regulation model of Prendergast and colleagues (Prendergast et al., 1997), combined with the above described finite element model was utilized to investigate the tissue differentiation process after osteotomy and to carry out an investigation on the optimal duration of the latency period and on its effects on the bone regeneration process. The spreading of mesenchymal stem cells throughout the bone callus was simulated with the diffusion equation (1) (Boccaccio et al., 2008a). The diffusion coefficient  $D$  was set so that the complete cell coverage in the callus is achieved two weeks after the osteotomy. As MSCs disperse from the bone marrow throughout the callus, they will differentiate into different cell phenotypes based on the value of a biophysical stimulus  $S$  computed with the equation (3). After the calculation of the new tissue phenotype and of the number of the MSCs invading the bone callus domain, the algorithm evaluates the mechanical properties for every element based on the exponential law described above (Section 2.2) and a simple rule of mixtures. The diffusion equation, the formulation for the calculation of the stimulus, the exponential law as well as the rule of mixtures were implemented into an algorithm a graphical summary of which is depicted in Fig. 7. If  $\bar{E}$  is the Young's modulus for a given element averaged over the previous 10 iterations and  $c$  is the concentration of cells invading the domain in the current iteration  $iter$ , then the Young's modulus for that element and for next iteration  $iter+1$  can be computed as follows:

$$E(iter + 1) = \frac{c}{c_{max}} \cdot \bar{E} + \frac{(c_{max} - c)}{c_{max}} \cdot E_{granulation} \quad (4)$$

where  $c_{max}$  is the highest concentration of cells which may occupy any one element domain,  $E_{granulation}$  is the Young's modulus of the granulation tissue. This rule of mixtures has been successfully adopted by Lacroix and Prendergast (Lacroix and Prendergast, 2002), to describe the delay between the time when stimulus first acts on the cells and the process of differentiation into a new phenotype. The algorithm was written in FORTRAN environment and each iteration corresponds to 4.8 hours, that is, the diffusion equation (1) computes the change of cells concentration occurring every 4.8 hours. Therefore, with 5 iterations a time period of 1 day is covered. This algorithm has been used to predict the patterns of the tissues differentiating within the bone callus of the osteotomized mandible during a ten day latency period.

The analyses carried out revealed that the Young's modulus of the bone, cartilage and fibrous tissue decreases towards the centre of the callus as we move away from the adjacent bone marrow (Fig. 8a). In order to investigate if premature bone bridging between the two sides of the fracture callus could hinder the subsequent distraction process, the amounts of new bone within the callus with a predicted Young's modulus greater than 0.7 MPa were isolated (see Fig. 8b which illustrates the process of bone formation in the frontal plane 1-3). After eight days, portions of bone tissue linking the left with the right side of the callus are predicted to form. The presence of bone bridges will hinder the distraction process. This suggests that is better to apply clinical protocols with a latency period not longer than seven-eight days so that the risk of a premature bone union is avoided. This is in agreement with Conley and Legan, (Conley and Legan, 2003) who suggest a latency period of seven days.

### 3.4 Determination of the optimal duration of the latency period for differently aged patients

The mechano-regulation model schematically illustrated in Figure 7 has been further developed to investigate how the optimal duration of the latency period changes for differently aged patients (Boccaccio et al., 2008b). Three different cases were considered: young (up to 20 years old), adult (about 55 years old) and elder (more than 70 years old) patients. Based on the histological analyses conducted by Chen et al., (Chen et al., 2005), Baxter et al., (Baxter et al., 2004), Mendes et al. (Mendes et al., 2002), and Park et al. (Park et al., 2005), the diffusion coefficient  $D$  was hypothesized to be a function of the patient's age. Let  $t_{elder}$ ,  $t_{adult}$  and  $t_{young}$  be the time periods required by MSCs for recovering completely the bone callus domain respectively for the elder, adult and young patients. Following Chen et al. (Chen et al., 2005) who measured the proliferation of MSCs in an *in vitro* culture at different time intervals (4, 8, 12 16 and 20 days) the diffusion coefficient  $D$  for the differently aged patients has been set:  $t_{elder}$  =3 weeks,  $t_{adult}$  =2 weeks and  $t_{young}$  =1 week. Patterns of tissue differentiation were predicted for each case (Fig. 9).

A bony bridge between the left and right sides of the fracture callus forms after 5, 8 and 9 days for the young, adult and elder patients, respectively (Fig. 9). Such results lead us to conclude that the optimal duration of the latency period is: 5-6 days for the young patient, 7-8 and 9-10 days for the adult and the elder patients, respectively. These evaluations are in agreement with literature. For instance, Conley & Legan (Conley and Legan, 2003) suggest a



latency period not longer than 7 days. Mattik et al. (Mattik et al., 2001), reported three clinical cases of young patients 18, 19 and 28 years old, for whom a latency period of 5 days was adopted. Lazar et al. (Lazar et al., 2003) submitted a 62-years old patient to mandibular distraction osteogenesis. The first distraction was given to the mandible following a delayed latency period of 10 days.

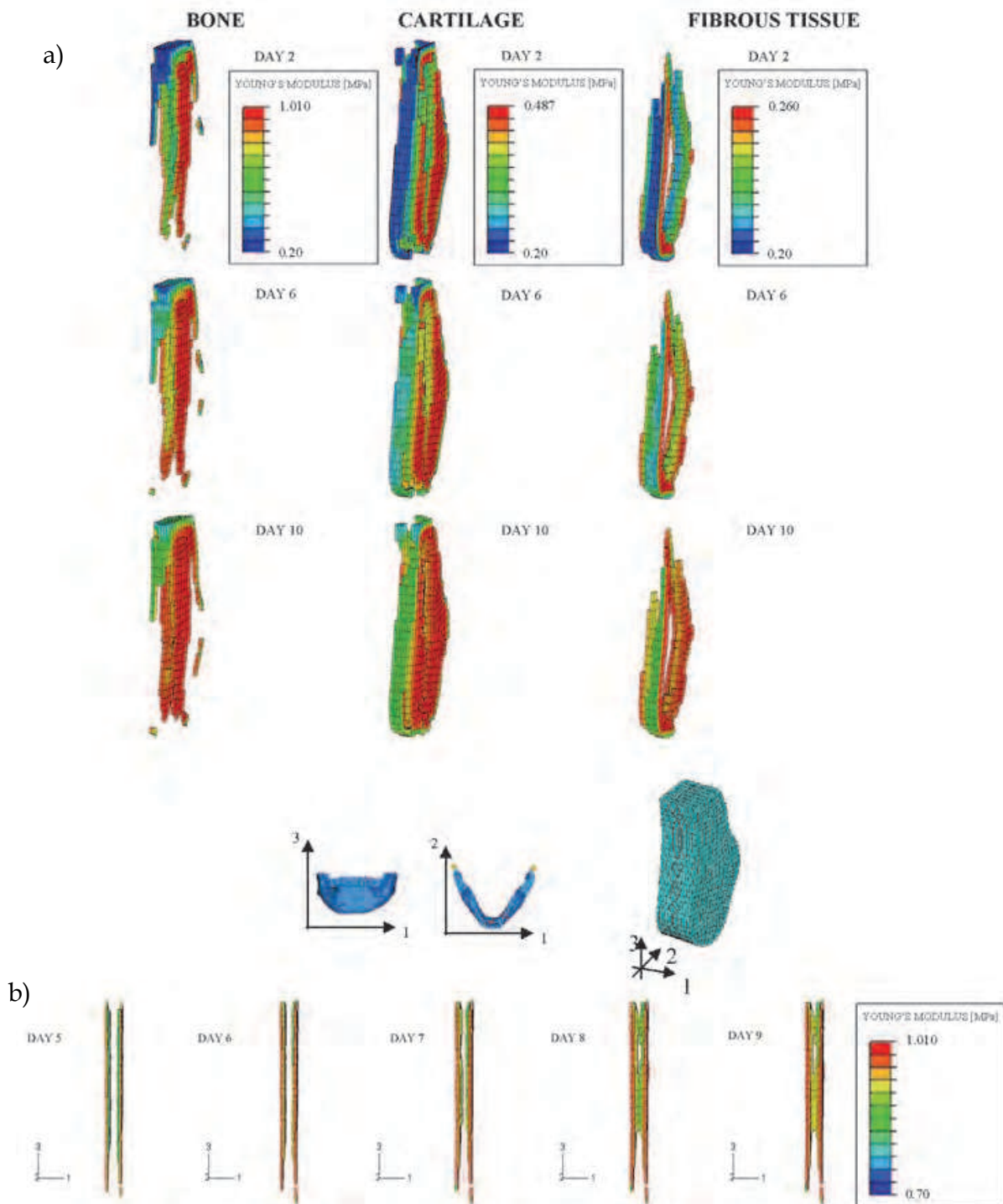


Fig. 8. (a) 3D visualization of tissue differentiation in the bone callus; (b) 3D visualization of the bone regeneration process in the frontal plane 1-3



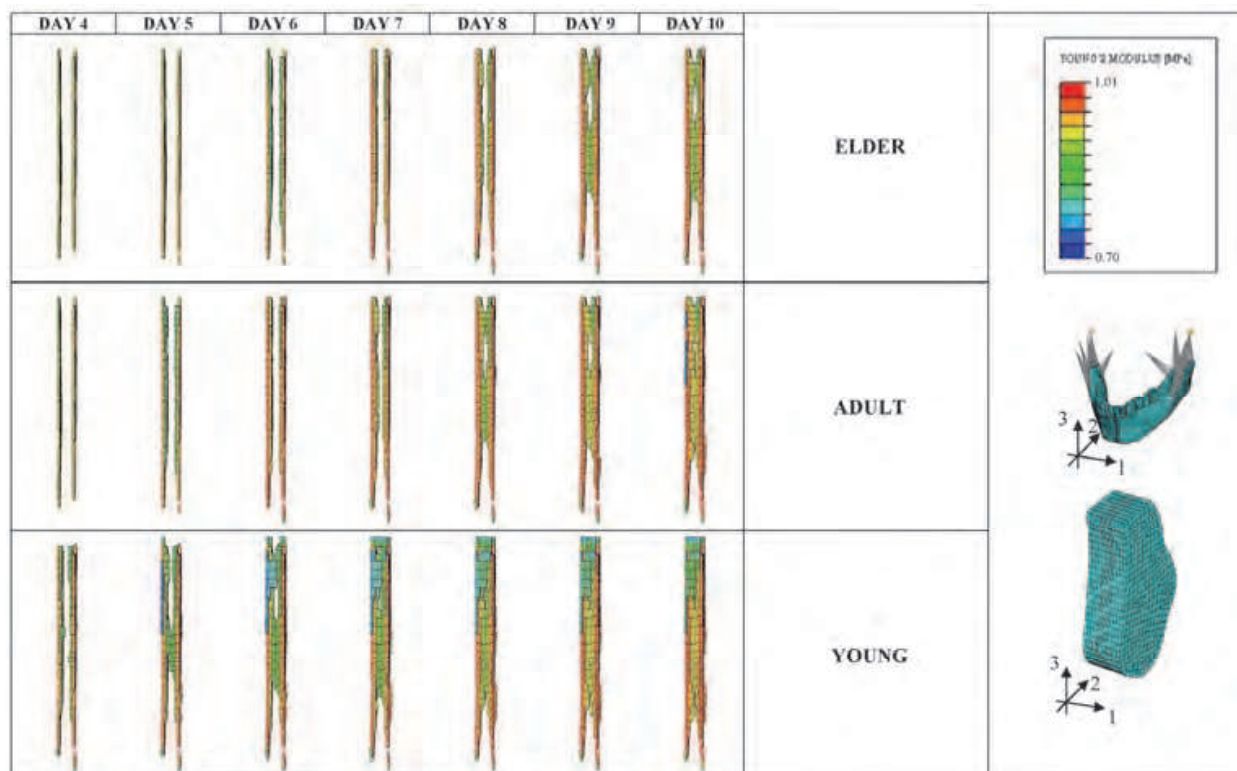


Fig. 9. Bone regeneration process for the young, adult and elder patients

### 3.5 Influence of expansion rates on mandibular distraction osteogenesis

Another important issue investigated with the mechano-regulation model of Prendergast and colleagues (Prendergast et al., 1997) and the above described finite element model, is the influence of expansion rates on the distraction process. The algorithm shown in Fig. 7 has been expanded to include the modelling of the distraction of the orthodontic appliance. Two different protocols of expansion were investigated: the first one where the device is distracted by 0.6mm/day for a period of ten days, the second where the device is distracted at 1.2 mm/day for five days. The final result with the aforementioned protocols is a widening of mandibular arch by about 6 mm corresponding to the space occupied by a lower incisor. The total number of iterations was set in order to cover a time period of 43 days, consisting of a one week latency period and a 37 day distraction and maturation period. In the case of the 0.6 mm/day distraction rate, this latter period included ten days of distraction and a 27 day maturation period, while the 1.2 mm/day distraction rate consisted of five days of distraction and a 32 day maturation period. In each iteration which simulates a distraction process, a structural FE analysis was run in order to model just the expansion of the appliance. In this analysis a given displacement was imposed to the arms of the distractor. Further details about the implemented algorithm are reported in Boccaccio et al. (Boccaccio et al., 2007). The spatial and temporal changes in tissue differentiation produced with these two different protocols were predicted and compared (Fig.10).

The computational analyses revealed that the lower expansion rate of 0.6 mm/day leads to greater amounts of bone tissue 'bridging' the left and right sides of the callus (Fig. 10). It is possible that excessive bone quantities in this area may hinder the process of distraction

because a premature bone union can occur. Therefore a faster distraction rate of 1.2 mm/day is preferable in cases where there is an increased risk of bone union.

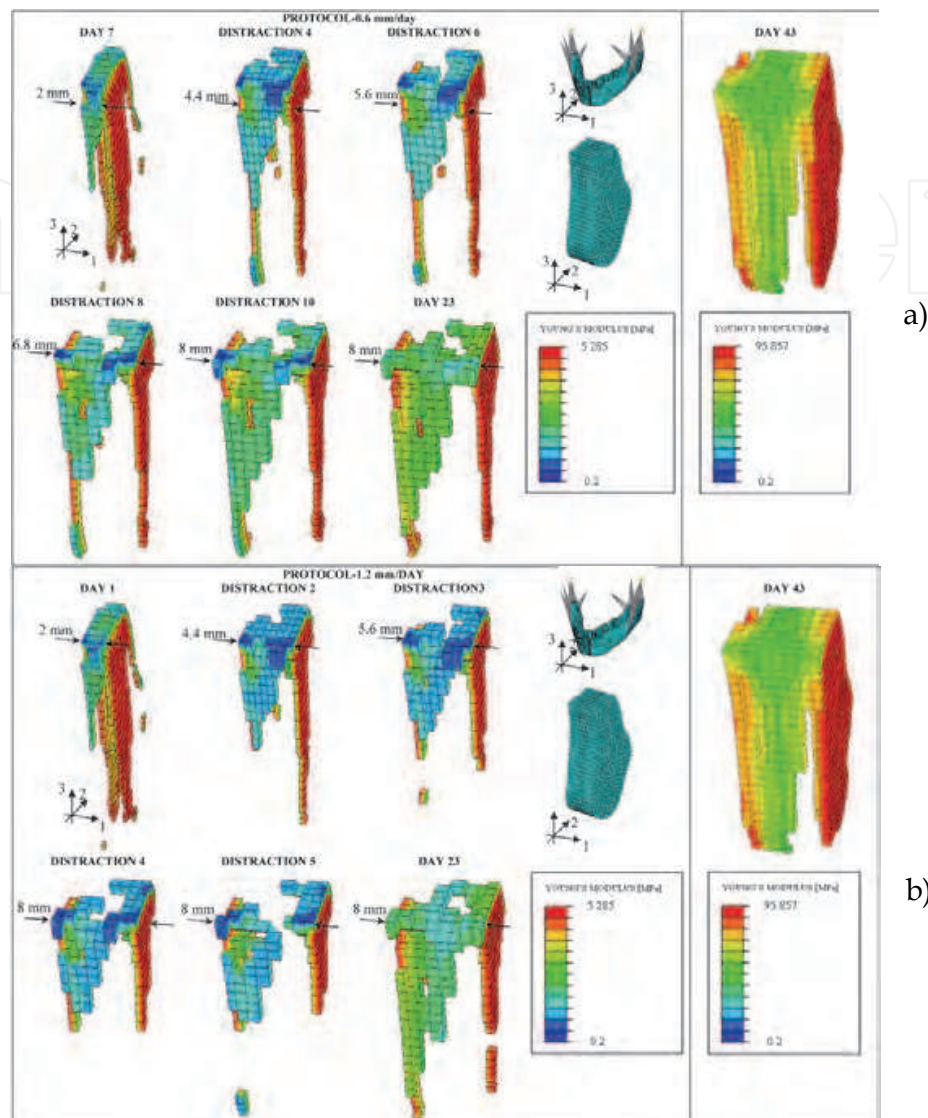


Fig. 10. Bone regeneration process for a distraction rate of (a) 0.6 mm/day and (b) 1.2 mm/day

#### 4. Mechanobiology of fracture repair in vertebral bodies

Vertebral fractures commonly occur in elderly people with osteoporosis. For example, in the United States vertebral fractures account for nearly half of all osteoporotic fractures (Cummings et al., 2002). With age the structure of cancellous bone within vertebral bodies transforms from that characterized by predominately plate-like trabeculae to rod-like trabeculae. This change leads to an age-related decrease in trabecular bone mass (Amling et al., 1996). The reduced bone mass observed in vertebral bodies, particularly with osteoporosis, is generally accompanied by greater amounts of microcallus formations around injured trabeculae (Hansson and Roos, 1981). This weakening of the tissue means that spine fractures may occur after minimal trauma (Einhorn, 2005).

The objective of this study was to investigate if biophysical stimuli play a role in regulating the process of tissue differentiation and bone remodeling in a fractured vertebral body. Our hypothesis is that the mechano-regulation model for tissue differentiation proposed by Prendergast et al. (Prendergast et al., 1997) and that has previously been used to predict the time-course of fracture repair in long and flat bones (Lacroix and Prendergast, 2002, Boccaccio et al., 2007) can be used to predict trabecular bone healing in fractured vertebrae at the level of individual trabeculae.

To determine the magnitude of such stimuli at the level of individual trabeculae, a multi-scale finite element approach has been adopted. A macro-scale finite element model (Fig. 11) of the spinal segment L3-L4-L5, including a mild wedge fracture in the body of the L4 vertebra, is used to determine the boundary conditions acting on a micro-scale finite element model of a portion of fractured trabecular bone. The micro-scale model, in turn, is utilized to predict the local patterns of tissue differentiation within the fracture site and then how the equivalent mechanical properties of the macro-scale model change with time.

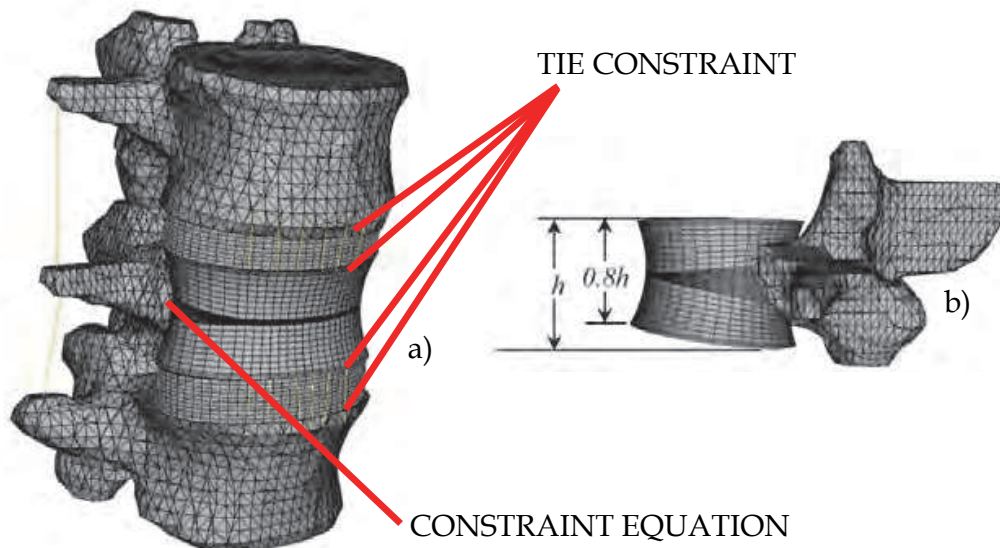


Fig. 11. (a) Finite element models of the spinal segment L3-L4-L5; (b) the body of fractured vertebra L4; its height decreases towards the anterior side.

The L3, L5 vertebrae and the posterior processes of the L4 were modelled as un-deformable rigid bodies. Deformable elements have been utilized to model the body of the L4 vertebra as well as the intervertebral discs. Between the intervertebral disc and the vertebral bodies a 'tie' constraint was applied (Fig. 11a). Constraint equations were used to attach the posterior processes to the body of the L4 vertebra (Fig. 11a). Each intervertebral disc includes the cartilaginous endplates, the nucleus pulposus, the annulus fibrosus with the collagen fibres. The effects of the flavum, intertransverse, interspinous and supraspinous ligaments have been included in the model. Further details about the geometry of the intervertebral discs and the modelling of the ligaments are reported in Boccaccio et al. (Boccaccio et al., 2008c). The height of the fractured vertebra decreases by the 20% from the posterior processes towards the anterior side (Fig. 11 (b)). In the Genant grading (Genant et al., 1993), such a fracture is classified as a mild wedge fracture. The body of L4 includes the cortical

shell of 0.5 mm thickness (Mizrahi et al., 1993), the cancellous bone and the fracture gap (Fig. 12(a-c)). The cancellous and the cortical bone have been modelled as biphasic poroelastic materials possessing transversely isotropic elastic properties. The distribution of the cancellous bone Young's modulus was assumed to be heterogeneous. An anisotropy ratio of 7/10, -i.e. the Young's modulus in the transversal plane is 7/10 the Young's modulus along the cranio-caudal direction-, was assumed (Eberlein et al., 2001). Further details about the spatial distribution of the Young's modulus of the cancellous bone are reported elsewhere (Boccaccio et al., 2008c).

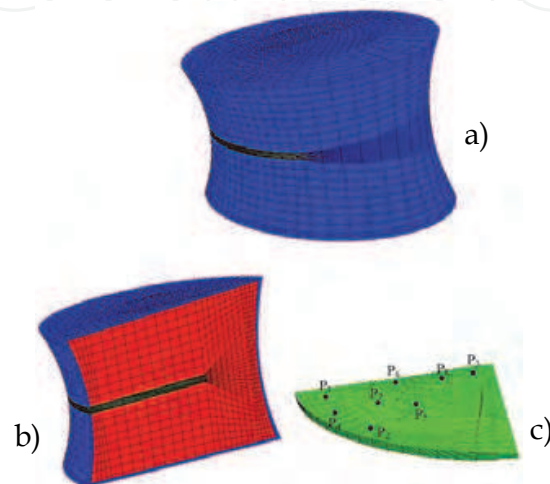


Fig. 12. The body of the fractured vertebra L4 includes the cortical shell (in blue, (a), (b)) the cancellous bone (in red, (b)) and the fracture gap (in green, (c)). The points  $P_1, P_2, \dots, P_8$  within the fracture gap in correspondence of which the analysis of the fracture repair process was carried out are indicated.

The micro-scale model of the trabecular bone was similar in geometry to that used by Shefelbine et al. (Shefelbine et al., 2005) (Fig. 13). A diastasis of 0.5 mm was simulated, with the trabeculae bordering the gap idealized as prismatic domains 0.1 mm thick. The space between fractured trabeculae was hypothesized to be occupied by granulation tissue. Both, the trabecular bone and the granulation tissue were modelled as biphasic poroelastic materials.

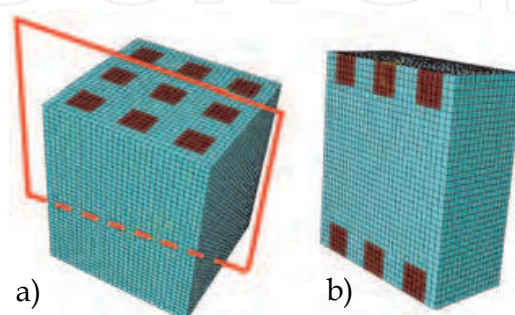


Fig. 13. Geometry (a) and section (b) of the micro-scale model. In red are represented the trabeculae spicules, in blue sky the granulation tissue.



Further details about the micro-scale finite element model of trabecular bone are reported in Boccaccio et al., (Boccaccio et al., 2011b).

A multi-scale approach was adopted. The equations describing tissue differentiation were implemented into an algorithm, a graphical summary of which is depicted in Fig. 14. The time period investigated corresponds to the first 100 days after the fracture event. The macro-scale model of the spinal segment was utilized to determine the elastic and poroelastic boundary conditions acting on eight different micro-scale models which were

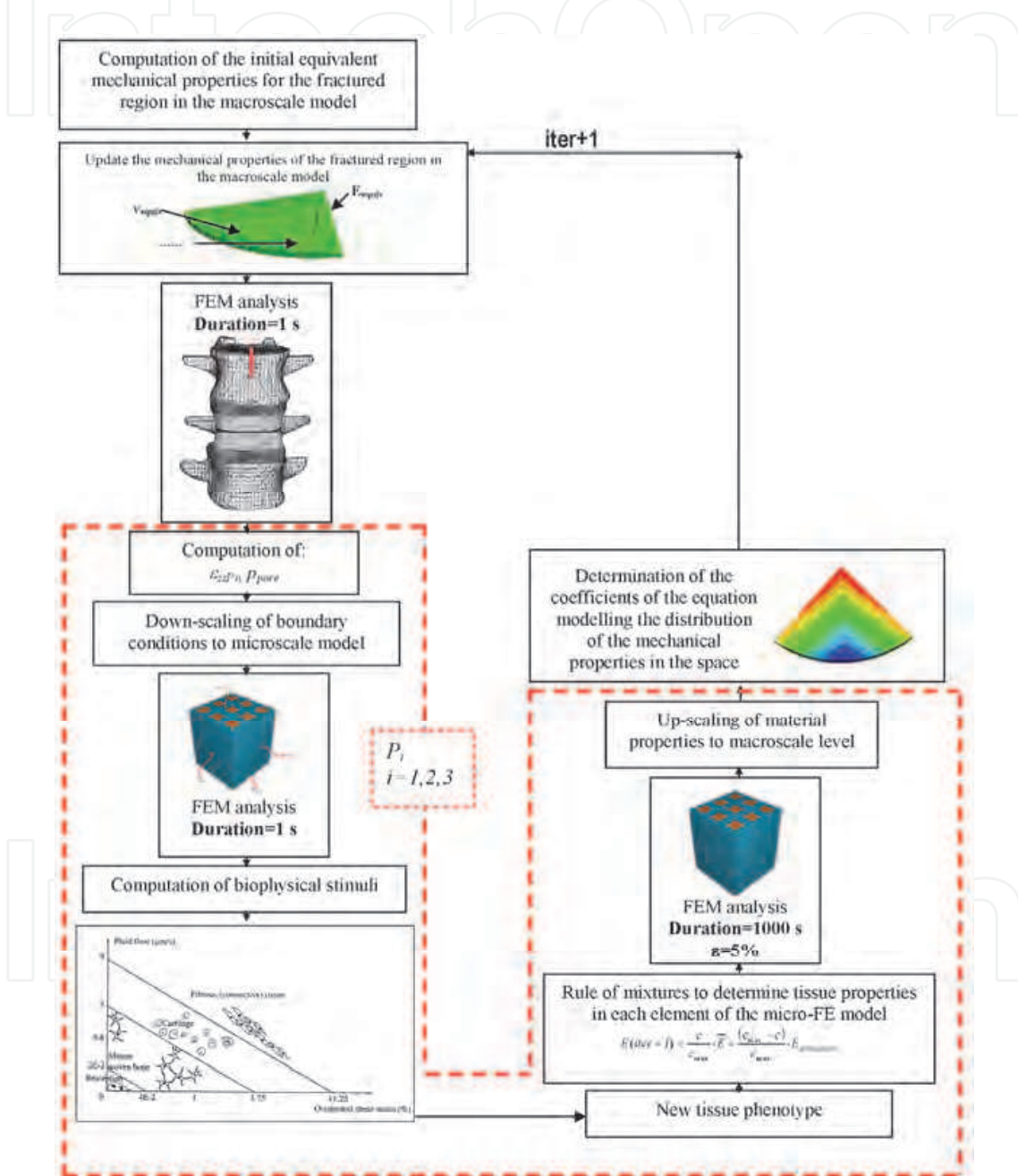


Fig. 14. Schematic of the algorithm utilized to model the fracture repair process in the L4 vertebra.

hypothesized to represent different regions in the fractured cancellous bone located in the neighbourhood of the points  $P_1, \dots, P_8$  (Fig. 12(c)). In order to evaluate the above mentioned



boundary conditions, an axial compression of 1000 N -which is the typical load acting on the lumbar vertebrae of a 70 Kg subject in the erect standing position- was applied in the centre of mass of the L3 vertebra and ramped over a time period of 1 s (which can be considered the time in which a subject assumes the erect position). The nodes located on the inferior surface of the L5 vertebra have been clamped. To switch from the macro to the micro-scale model, proper localization rules have been utilized. The micro-scale model, in turn, served to predict the local patterns of the tissues differentiating during the fracture repair process. A compression test was simulated on the micro-scale model reproducing the same elastic and poroelastic boundary conditions as those determined from the macro-scale model. The results obtained from this finite element analysis were used to determine the biophysical stimulus acting in each element of the micro-scale model and then to implement the mechano-regulation model of Prendergast et al. (Prendergast et al., 1997). The change of the tissue phenotype led to a change of the equivalent mechanical properties possessed by the fracture gap of the macro-scale model. By adopting homogenization techniques the information obtained from the micro-scale model regarding the material properties was up-scaled to the macro-scale level. The new material properties were implemented into the macro-scale model and a new iteration initiated. Further details regarding the algorithm are reported in a previous study (Boccaccio et al., 2011b).

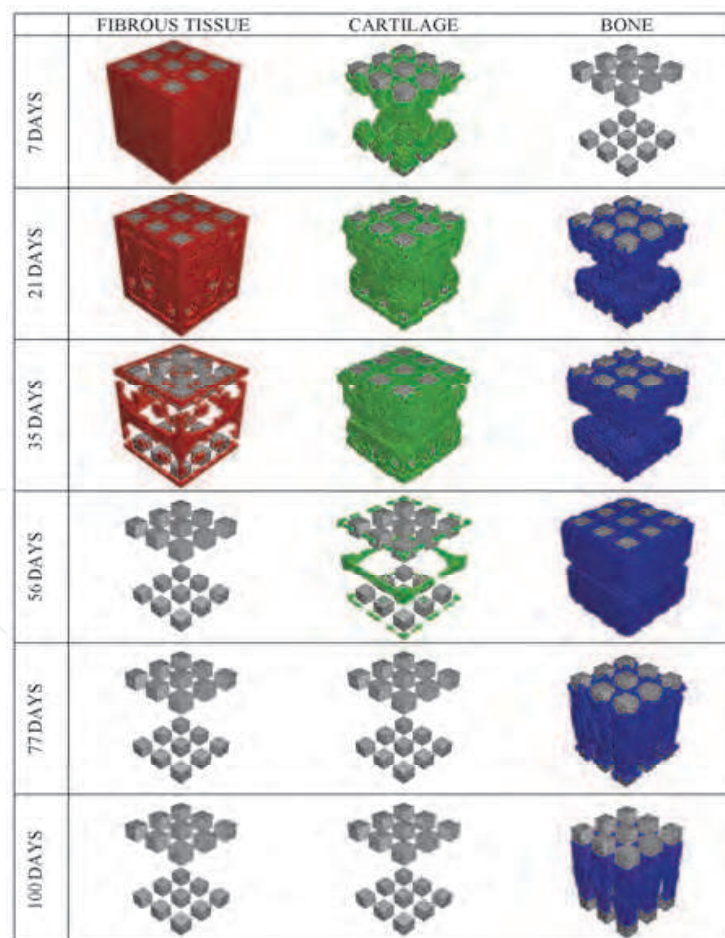


Fig. 15. Patterns of the tissues differentiating within the fractured vertebra during the fracture healing process.

The analyses carried out predicted that the space between the fractured trabeculae is mostly occupied by fibrous tissue in the first days after the fracture event (Fig. 15). During the first 30-35 days after the fracture event the amount of fibrous tissue decreases significantly and disappears completely after six weeks. Small amounts of cartilage appear during the first week, and approximately 40% of the space between the fractured trabeculae is occupied by cartilage after one month. This cartilaginous tissue is completely replaced by bone after two months (Fig. 15). Small amounts of bone are predicted after the first two weeks and after the second month the space is entirely occupied by bone. Bone deposition is predicted to initiate at the fractured trabecular ends. The bone remodeling process appears to start after the second month and reaches equilibrium at the end of the third month. The remodeled trabeculae are aligned with those bordering the fractured region (Fig. 15).

The spatial and temporal patterns of tissue differentiation predicted by this model are in general agreement with those observed experimentally. Diamond et al., (Diamond et al., 2007) describe 4 stages of fracture healing process in the vertebral body, with significant overlap between the various stages of healing. Chondrogenesis was evident in the second stage of the fracture healing process, which followed the initial granulation tissue stage. The appearance of cartilaginous tissue in the days following the fracture event is also predicted by the model (Fig. 15). This cartilaginous tissue is predicted to be gradually replaced by woven bone. The model then predicts a peak in bone formation (see 56<sup>th</sup> day, Fig. 15).

Hyperostoidosis/Osteosclerosis (excessive formation of osteoid) is also observed experimentally at comparable time-points (Diamond et al., 2007). Finally remodeling of the cancellous bone architecture is predicted. Complete new trabeculae are predicted to form due to bridging of the microcallus between the remnant trabeculae, leading to restructuring of the bone architecture (Amling et al., 1996).

## 5. Discussion

In this Chapter the basic principles of mechanobiology are described as well as the principal theories and the main models utilized to simulate the cellular processes involved in fracture healing. Two examples have been 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 fractured lumbar vertebra.

Different are the limitations of the above outlined mechano-regulation theories. The main criticism raised against the models of Pauwels (Pauwels, 1960), Carter and colleagues (Carter et al., 1988, Carter and Wong, 1988) and Claes and Heigele (Claes and Heigele, 1999) is that there are several reasons that interstitial fluid flow could be a more realistic mechanical variable for feedback information to the cells during tissue differentiation than hydrostatic pressure (Owan et al., 1997, Jacobs et al., 1998). The interfragmentary strain theory, although has the advantage of being simple to be used since interfragmentary movement can be easily monitored, presents the limitation that it models the fracture as a one dimensional entity thus ignoring the three dimensional complexity of the callus. The model of Prendergast et al. (Prendergast et al., 1997) although takes into account the interstitial fluid flow neglects osmotic effects and charged-density flows in the tissue (Mow et al., 1999). Several mechano-regulation algorithms proposed to control tissue differentiation during bone healing have been shown to accurately predict temporal and spatial tissue distributions during normal fracture healing. As these algorithms are different

in nature and biophysical parameters, it raises the question of which reflects the actual mechanobiological processes the best. Isaksson et al. (Isaksson et al., 2006), addressed this issue by corroborating the mechano-regulatory algorithms of Carter and colleagues (Carter et al., 1988, Carter and Wong, 1988), Claes and Heigele (Claes and Heigele, 1999, Claes et al., 1998) and Prendergast and coworkers (Prendergast et al., 1997), with more extensive in vivo bone healing data from animal experiments. They compared the patterns of tissue differentiation predicted by the different models and the patterns observed in vivo in an ovine tibia model. They concluded that none of the algorithms predicted patterns of healing entirely similar to those observed experimentally. However, patterns predicted by the algorithm based on deviatoric strain and fluid velocity (i.e. the model of Prendergast et al., (Prendergast et al., 1997)) was closest to experimental results.

Another important limitation for computational mechanobiology is represented by the fact that the mechano-regulatory algorithms include empirical constants, the values of which must be determined by comparison to a biological reality. For example, in the mechano-regulation rule developed by Prendergast et al. (Prendergast et al., 1997) the constants  $b$  and  $a$  (see equation (3)) do not have a specific physical meaning and can be determined by following the 'trial and error' method outlined in van der Melulen and Huiskes (van der Melulen and Huiskes, 2002): "Computational mechano-biologists hypothesize a potential rule and determine if the outcome of this hypothesis produces realistic tissue structures and morphologies, hence 'trial-and-error'. If the results correspond well, they might be an explanation for the mechanism being modelled. This method of research is common practice and productive in physics, less common in biology (Huiskes, 1995); although 'theoretical biology' is based on this type of approach". Certainly, physicists can use this approach (the computational gedanken experiment) because there are so few rules in physics and the predictions are amenable to exact quantitative testing. In biology the phenomena to be observed and analysed are much more complicated than in physics, so cut-and-try theoretical experimentation could not be really useful. Further research should be carried out on the efficiency and the correctness of this philosophy of biological research.

Concerning the mechano-regulation model of fracture repair in the body of the L4 vertebra, the most important limitation is that the implemented algorithm does not include a damaged tissue region that would allow tissue to fracture and new callus to form in regions experiencing high levels of biophysical stimulation (e.g. strain). Therefore this study has only considered the original injury event. In reality, histological analyses (Diamond et al., 2007) revealed that a typical feature of vertebral fractures is the overlap between the different tissues corresponding to the different temporal stages of the fracture healing process. This can be justified with the argument that in vertebral bodies the fracture stabilization that permits orderly repair in long bones is not possible due to repetitive injury. As far as concerns the model of the human mandible osteotomized and distracted, the most important limitation is that after the first simulation the numerical predictions state that the callus consists of a mixture of bone, cartilage and fibrous tissue (Figures 8-9), where it might be more accurate to state that in the first few days after the osteotomy the callus consists of progenitor cells subjected to a stimulus that if maintained will result in these cells differentiating into either fibroblasts, chondrocytes or osteoblasts, depending on the magnitude of the stimulus. This may explain why histological findings (Loboa et al., 2005) from animal model studies differ from the initial model predictions as progenitor cells take time to differentiate and produce a tissue phenotype that is recognised by appropriate histological staining. For example, significant bone and soft tissue formation is predicted

during the latency period which is not observed histologically. Explicitly including in the model the time taken for mineralization etc following differentiation of progenitor cells into osteoblasts may result in model predictions more comparable to *in vivo* findings. Another important limitation of the mechano-regulation model used to assess the bone regeneration process in a human mandible osteotomized and distracted as well as in a fractured vertebra is represented by the utilization of the exponential law. Such a law was introduced to account for the fact that mesenchymal cells not only require time to differentiate but, that differentiated cells require some time also for synthesising and remodelling new tissue. In reality, the exponential law should be utilized only to model the early stages of the fracture healing process; when this process is close to the end, saturation phenomena (e.g. the mineralization process) occur within the fracture callus and therefore, at this point, the exponential law should be replaced with another law that allows to better describe these conclusive processes. As a first approximation, we utilized the exponential law to model the early stages of the fracture healing (Boccaccio et al., 2011b) while, toward the end of the process, we replaced the exponential law with a linear constant law. Further research should be carried out on the mathematical function that better describes the entire process of fracture healing, both, in the early and in the final stages.

Many experiments on skeletal failure and repair have been performed in the last century aimed to determine the influence of biological, mechanical, hormonal factors on the healing process. Despite this effort, there are still many unanswered questions. This indicates the complexity of the biological problems and has stimulated the development of computational models that can analyze the influence of all factors and make predictions under different boundary and loading conditions. These models must also be validated with experimental analyses. However, in many cases the computational models cannot be validated directly because of the difficulties in performing some measurements *in vivo*. Despite this, indirect validations can be performed if the conclusions of the computer simulations are similar to the experimental or clinical results. Once the mechano-regulation model has been validated, it can be conveniently utilized to assess the regeneration process within the fracture site in the case in which different boundary and loading conditions act on it. For instance, the mechano-regulation model of fracture repair in vertebral bodies illustrated above can be used to predict the spatial and temporal patterns of repair during altered loading conditions, which may prove beneficial in developing rehabilitation regimes following vertebral fractures. Also, this same model can be utilized to evaluate how the patterns of tissue differentiation change if the fractured vertebra is supported with minimally invasive percutaneous fixation devices (Palmisani et al., 2009). Furthermore, the mechanobiological model of the human mandible osteotomized and distracted can be utilized to estimate how the bony tissue regeneration process within the fracture callus change for different mandibular distraction devices such as those analyzed in previous studies (Boccaccio et al., 2008d; Boccaccio et al., 2011c).

Future perspectives include the development of computer power. A more robust integration is required, in future, between biology, mechanics and materials science. This should lead to the development of mechano-regulation models that more accurately describe physiological processes such as fracture healing, tissue genesis etc. A very promising research area for mechanobiology is in the field of tissue engineering. Mechanobiology could be an efficient and cheap tool to determine optimal parameters governing scaffold performance. Future perspectives of numerical simulations of biomaterial scaffolds for tissue engineering rely also on the development of new methods to account for the multi-scale dimension of the problems. At the micro-scale level one can analyse cell/biomaterial interactions and how



these interactions influence the tissue differentiation process, at the macro-scale level one can evaluate the 'average' boundary and loading conditions acting on the scaffold implanted in the specific anatomical site.

## 6. Conclusions

This Chapter presented the principal mechano-regulation theories recently developed to simulate the tissue differentiation and the main cellular processes involved in fracture healing. Two examples have then been given illustrating how a mechano-regulation algorithm - 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 the bone regeneration process both, in a human mandible submitted to distraction osteogenesis and in a fractured lumbar vertebra. The principal limitations of mechanobiological algorithms as well as the future research lines in the field have been finally outlined.

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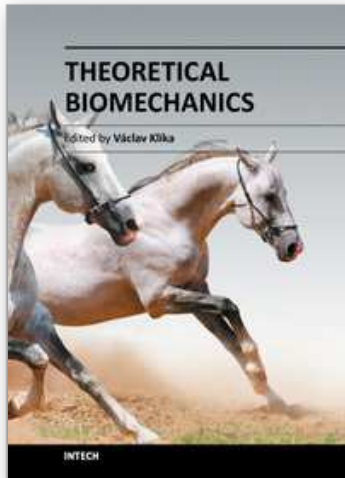


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