Modelling bone tissue fracture and healing: a review

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Abstract

This paper reviews the available literature on computational modelling in two areas of bone biomechanics: fracture and healing. Bone is a complex material, with a multiphasic, heterogeneous and anisotropic microstructure. The processes of fracture and healing can only be understood in terms of the underlying bone structure and its mechanical role.

Bone fracture analysis attempts to predict the failure of musculoskeletal structures by several possible mechanisms under different loading conditions. However, as opposed to structurally inert materials, bone is a living tissue that can repair itself. An exciting new field of research is being developed to better comprehend these mechanisms and the mechanical behaviour of bone tissue.

One of the main goals of this work is to demonstrate, after a review of computational models, the main similarities and differences between normal engineering materials and bone tissue from a structural point of view. We also underline the importance of computational simulations in biomechanics due to the difficulty of obtaining experimental or clinical results.

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1. Introduction

The main role of the musculoskeletal system is to transmit forces from one part of the body to another under controlled strain and to protect vital organs (e.g., lungs, brain). It also performs other important functions such as serving as a mineral reservoir.

Several skeletal tissues participate in this mechanical objective of transmission and protection: bone, cartilage, tendons, ligaments, and muscles. Bone mainly determines global structural stiffness and strength, whereas other tissues transmit loads between bones. The mechanical properties of bone are a result of a compromise between the need for a certain stiffness (to reduce strain and achieve a more efficient kinematics), and the need for enough ductility to absorb impacts (to reduce the risk of fracture and minimize skeletal weight).

As a result of this compromise, thousands of years of evolution have produced a complex, multiphasic, heterogeneous, anisotropic microstructure. In the first section of this paper we present the main aspects of bone biology in terms of its mechanical properties and constitutive behaviour. Another important aspect of bone behaviour is its self-adaptive capacity, modifying its microstructure and properties according to the specific mechanical environment. Bone is not like inert engineering materials. It undergoes substantial changes in structure, shape, and composition according to the mechanical and physiological environment, an adaptive process known as bone remodelling. A brief explanation of the basic aspects of bone remodelling is included in Section 2.

Bone adaptability allows for efficient repair, which in turn helps to prevent fractures. However, fractures are still quite common, usually caused by the sudden appearance of a load that exceeds bone strength, or the cyclic activity of loads (well below bone strength) that gradually accumulate damage at a rate that cannot be repaired. The stiffness and strength of the bone are reduced until a failure of the first type occurs under a much lower load. Predicting and preventing bone fractures is an important topic in orthopaedics due to their high frequency, surgical complications and socio-economic impact. For example, the number of hip fractures worldwide was estimated to be 1.66 million in 1990 and expected to increase to 6.26 million by 2050 [1]. In the third section of this paper we review the main studies and models developed to predict bone fractures.

Once a fracture occurs, the basic healing process is auto-activated naturally to repair the site. Healing involves the differentiation of several tissues (cartilage, bone, granulation, etc.), with different patterns that are directly influenced by the mechanical environment, which is in turn governed by the load applied and the stability of the fracture site. In fact, not all fractures are completely repaired. Sometimes there are non-unions or delayed fractures depending on specific geometric, mechanical and biological factors, justifying the many different kinds of fixations used to improve fracture stabilisation. In Section 4 we review the fracture healing process and the different computer simulation models.
Finally, the last section includes important conclusions on modelling bone fracture and fracture healing, indicating the main new trends.

2. Basic concepts of bone biology

Bone tissue has very interesting structural properties. This is essentially due to the composite structure of bone, composed by hydroxyapatite, collagen, small amounts of proteoglycans, noncollagenous proteins and water [2–5]. Inorganic components are mainly responsible for the compression strength and stiffness, while organic components provide the corresponding tension properties. This composition varies with species, age, sex, the specific bone and whether or not the bone is affected by a disease [6]. Another important aspect that also characterizes this peculiar mechanical behaviour of bone is its hierarchical organization. Weiner and Wagner [2] described this, starting from the nanometric level and ending at the macroscopic levels, relating the latter to the mechanical properties.

From a macroscopic point of view, bone tissue is non-homogeneous, porous and anisotropic. Although porosity can vary continuously from 5 to 95%, most bone tissues have either very low or very high porosity. Accordingly, we usually distinguish between two types of bone tissue (see Fig. 1). The first type is trabecular or cancellous bone with 50–95% porosity, usually found in cuboidal bones, flat bones and at the ends of long bones. The pores are interconnected and filled with marrow (a tissue composed of blood vessels, nerves and various types of cells, whose main function is to produce the basic blood cells), while the bone matrix has the form of plates and struts called trabeculae, with a thickness of about 200 μm and a variable arrangement [7].

The second type is cortical or compact bone with 5–10% porosity and different types of pores [9]. Vascular porosity is the largest (50 μm diameter), formed by the Haversian canals (aligned with the long axis of the bone) and Volkmann's canals (transverse canals connecting Haversian canals) with capillaries and nerves. Other porosities are associated with lacunae (cavities connected through small canals known as canaliculi) and with the space between collagen and hydroxyapatite (very small, around 10 nm). Cortical bone consists of cylindrical structures known as osteons or Haversian systems (see Fig. 2), with a diameter of about 200 μm formed by cylindrical lamellae surrounding the Haversian canal. The boundary between the osteon and the surrounding bone is know as the cement line.

Fig. 1. Bone section showing cortical and trabecular bone (From [8] with permission).
Cortical bone is usually found in the shafts of long bones and surrounding the trabecular bone forming the external shell of flat bones. This combination of trabecular and cortical bone forms a “sandwich-type” structure, well known in engineering for its optimal structural properties [10].

Throughout their useful life, both types of bone are formed by two different tissues: woven and lamellar bone. The skeletal embryo consists of woven bone, which is later replaced by lamellar bone. Normally there is no woven bone in the skeleton after four or five years but it reappears during the healing process after fracture. The two types of bone have many differences in composition, organization, growth and mechanical properties. Woven bone is quickly formed and poorly organized with a more or less random arrangement of collagen fibers and mineral crystals. Lamellar bone is slowly formed, highly organized and has parallel layers or lamellae that make it stronger than woven bone.

Bones can grow, modify their shape (external remodelling or modelling), self-repair when fractured (fracture healing) and continuously renew themselves by internal remodelling. All these processes are governed by mechanical, hormonal and physiological patterns. Growth and modelling mostly occur during childhood, fracture healing only occurs during fracture repair and internal remodelling occurs throughout our lifetime, playing a fundamental role in the evolution of the bone microstructure and, consequently, in the adaptation of structural properties and microdamage repair.

Bone remodelling only occurs on the internal surfaces of the bone matrix (trabecular surfaces of cancellous bone and Haversian systems of cortical bone). Bone can only be added or removed by bone cells on these surfaces. There are four types of bone cells, which can be classified according to their functions.

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Fig. 2. Microscopical structure of cortical bone. (a) 3D sketch of cortical bone, (b) cut of a Haversian system, (c) photomicrograph of a Haversian system (From [11] with permission).
Osteoblasts are the differentiated mesenchymal cells that produce bone. They are created at the periosteum layer or stromal tissue of bone marrow.

Osteoclasts remove bone, demineralizing it with acid and dissolving collagen with enzymes. These cells originate from the bone marrow.

Bone lining cells are inactive osteoblasts that are not buried in new bone. They remain on the surface when bone formation stops and can be reactivated in response to chemical and/or mechanical stimuli [12].

Like bone lining cells, osteocytes are former osteoblasts that are buried in the bone matrix. They are located in lacunae [9] and communicate with the rest of cells via canaliculi. Many authors [13–16] suggest that osteocytes are the mechanosensor cells that control bone remodelling, but this has not been proven yet. Furthermore, it is quite reasonable to assume that osteocytes, the only cells embedded in the bone matrix, are affected by processes that damage the bone matrix. Matrix disruption may be expected to directly injure osteocytes, disrupting their attachments to bone matrix, interrupting their communication through canalicular or altering their metabolic exchange. Fatigue microdamage may therefore create a situation resembling disuse at the level of the osteocyte cell body and lead to bone remodelling starting with osteoclast recruitment.

The remodelling process is not performed individually by each cell, but by groups of cells functioning as organized units, which Frost named “basic multicellular units” (BMUs) [17]. They operate on bone periosteum, endosteum, trabecular surfaces and cortical bone, replacing old bone by new bone in discrete
packets. The BMUs always follow a well-defined sequence of processes, normally known as the A–R–F sequence: activation–resorption–formation (Fig. 3).

Bone is also anisotropic. Cortical bone has a very low porosity and its anisotropy is mainly controlled by lamellar and osteonal orientation. On the contrary, trabecular bone has a higher porosity and its anisotropy is determined by trabecular orientation. It is difficult to quantify anisotropy experimentally. In fact, only recently have several measures of bone mass directional distribution been proposed for trabecular bone. Cowin [18] defines bone anisotropy by means of the so-called fabric tensor: a second order tensor that defines the principal values and directions of the bone mass distribution (for different ways of measuring the fabric tensor see also [19–22]).

In fact, structural anisotropy has a direct influence on stiffness properties as well as strength. For example, the average strength of a compact human bone in Reilly and Burstein [23] was 105 MPa in a longitudinal compression test, and 131 MPa in a transversal compression test. The average longitudinal strength in tension in the same experiment was 53 MPa.

3. Bone mechanical properties

As shown in Section 2, the mechanical properties of bone depend on composition and structure. However, composition is not constant in living tissues. It changes permanently in terms of the mechanical environment, ageing, disease, nutrition and other factors. Many reports try to correlate mechanical properties with composition [24–29]. Vose and Kubala [30] were possibly the first to quantify how much mechanical properties depend on composition, obtaining a correlation between ultimate bending strength and mineral content. One of the most cited works is Carter and Hayes [24], who found that elastic modulus and the strength of trabecular and cortical bone are closely related to the cube and square of the apparent wet bone density, respectively.

Although these preliminary models only took into account the apparent density, several authors [10,31–34] have shown that the mechanical properties of cortical and cancellous bone depend on apparent density and mineral content. The most representative compositional variable is the ash density with the following correlation:

\[
E (\text{MPa}) = 10500 \cdot \rho_s^{2.57 \pm 0.04} \quad \sigma_c (\text{MPa}) = 117 \cdot \rho_s^{1.93 \pm 0.04}
\]

where \(\rho_s\) is ash density. This expression explains over 96% of the statistical variation in the mechanical behaviour of combined vertebral and femoral data over the range of ash density (0.03–1.22 g cm\(^{-3}\)).

Keyak et al. [35] also studied the relationship between mechanical properties and ash density for trabecular bone, obtaining the following expressions with 92% correlation:

\[
\begin{cases}
E (\text{MPa}) = 33900 \cdot \rho_s^{2.2} & \text{if } \rho_s \leq 0.27 \text{ g cm}^{-3} \\
\sigma_c (\text{MPa}) = 137 \cdot \rho_s^{1.88} & \text{if } \rho_s \leq 0.317 \text{ g cm}^{-3}
\end{cases}
\]

One limitation of these models is that they do not separate the influence of bone volume fraction from the ash fraction. So, Hernández et al. [36] express the apparent density as a function of the bone volume fraction (bone volume/total volume) and the ash fraction (\(z\)):

\[
\rho = \frac{BV}{TV} \rho_t = \frac{BV}{TV} \left(1.41 + 1.29z\right)
\]

where \(\rho_t\) is the true tissue density of the bone, that is linearly related to the ash fraction \(z\). They determined the elastic modulus and compressive strength, independently of bone volume fraction and ash fraction, with a 97% correlation:
\[
\begin{align*}
E (\text{MPa}) &= 84370 (\frac{\text{BV}}{\text{TV}})^{2.58 \pm 0.02} \times 2.74 \pm 0.13 \\
\sigma_c (\text{MPa}) &= 749.33 (\frac{\text{BV}}{\text{TV}})^{1.92 \pm 0.02} \times 2.79 \pm 0.09
\end{align*}
\]

In these expressions, the exponent related to ash fraction is larger than that associated with bone volume fraction, suggesting that a change in mineral content will produce a larger change in mechanical properties.

We have focused on compression strength because the ultimate tension strength of bone tissue is usually established as a percentage of the compression strength. Different values have been used for this ratio, from 0.33 to 0.7 in bovine trabecular bone [37,38], to 0.5 to 0.7 for human cortical bone, depending on the test direction [23]. Keyak and Rossi [39] performed a FE analysis on the influence of this parameter and found that the best agreement was between 0.7 and 1. However, they considered that the parameter was constant, even though it should also depend on structural variables, as suggested by Keaveny et al. [37,40].

Although all these correlations can predict the main mechanical properties, they do not consider the influence of structural and microstructural features or the different behaviours in each direction. This aspect was first considered by Lotz et al. [41]. They determined the Young’s modulus and the compressive strength of cortical and trabecular femoral bone in the axial and transversal directions using the apparent density as a control variable. The elastic modulus and the compressive strength for cortical femoral bone in the axial direction was approximated by

\[
E (\text{MPa}) = 2065 \cdot \rho^{3.09} \quad \sigma_c (\text{MPa}) = 72.4 \cdot \rho^{1.88}
\]

and in the transversal direction by the correlation

\[
E (\text{MPa}) = 2314 \cdot \rho^{1.57} \quad \sigma_c (\text{MPa}) = 37 \cdot \rho^{1.51}
\]

Similarly, the compressive strength for trabecular bone was defined as,

\[
E (\text{MPa}) = \begin{cases} 
1904 \cdot \rho^{1.64} & \text{(axial direction)} \\
1157 \cdot \rho^{1.78} & \text{(transversal direction)}
\end{cases}
\]

\[
\sigma_c (\text{MPa}) = \begin{cases} 
40.8 \cdot \rho^{1.89} & \text{(axial direction)} \\
21.4 \cdot \rho^{1.37} & \text{(transversal direction)}
\end{cases}
\]

A different idea was suggested by Pietruszczak et al. [42], who included the directional dependence of strength using the expression:

\[
\sigma_c(I) = \sigma_{c0} \left( \frac{1 - \bar{n}(I)}{1 - n_0} \right)^\gamma
\]

where \(n_0, \sigma_{c0}\) are reference properties (the first is the average porosity, and the second the corresponding strength for this level of porosity), \(\gamma\) a constant in the interval \((1, 2)\), and \(\bar{n}(I)\) is the directional porosity that can be approximated as

\[
\bar{n}(I) \approx n(1 + \Omega_{ij} l_i l_j)
\]

being \(n\) the average porosity, \(l_i\) the orientation relative to a fixed Cartesian coordinate system and \(\Omega_{ij}\) a symmetric traceless tensor, which describes the distribution of voids.

These mathematical relationships have been used to predict proximal femoral fractures with finite elements. The 3D finite element model is generated from a geometrical model usually recovered from a CT scan of the specific organ. It is also calibrated in terms of K$_2$HPO$_4$ equivalent density. Then apparent density, porosity or apparent ash density are estimated using different correlations to model the heterogeneous distribution of mechanical properties. Most models consider isotropic behaviour, since it is not possible to quantify the whole anisotropic structure of a bone organ with current techniques. Only [42] includes this effect in femoral fracture simulations, but with a spatially constant anisotropy ratio, even
though it changes widely in the femur at different locations [21,43]. One way to overcome this limitation is to employ anisotropic internal bone remodelling models [44–48] that can predict density and anisotropy distribution, and some of them with sufficient accuracy.

Another assumption of most FE analyses in the literature is the linearity of the constitutive behaviour of bone tissue. This is usually accurate enough, but some authors obtain more accurate results by considering nonlinear material properties for cortical and trabecular bone [49,50].

An additional limitation is the lack of analyses on fracture initiation and growth until complete failure. Most studies obtain a stress distribution and a possible fracture load. The extension of the principles of Fracture Mechanics to bone fracture analysis is clearly underdeveloped, although it will probably be an important research field in the near future.

4. Mechanisms of bone fracture

The first mechanism of bone fracture appears when an accidental load exceeds the physiological range, inducing stresses over the strength that bone tissue has achieved after adaptation during growth and development (traumatic fracture). Following the clinical literature [51–53], there are two main causes for this type of fracture: an external impact produced, for example, by a fall, or fractures that occur “spontaneously” by a muscular contraction without trauma (see Fig. 4). The latter are quite common in elderly people with osteoporosis. Several authors suggest that the main cause of hip fracture is contraction of the iliopsoas muscle and gluteus medius [53,54].

This kind of fracture is often produced by normal loads acting on a bone that has been weakened by disease or age [55]. This type of fracture is normally called pathologic. Most are provoked by osteoporosis in the elderly and are more frequent in women than men. Another important cause of pathologic fractures are bone tumours, which modify bone mechanical properties and produce stress concentrators. Removing the tumour usually increases the risk of fracture. In fact, the higher risk of bone fracture in the elderly is not only due to the progressive reduction of bone consistency (osteoporosis), and therefore strength, but also to additional factors such as the inability of soft tissues to absorb the energy generated in a fall and the change

![Fig. 4. Scheme of two usual mechanisms of bone fracture.](image-url)
of the kinematic variables of the gait. Lotz and Hayes [56] report that only a small amount of energy is needed to break a bone (i.e. 5% of the energy available in a fall), what is due to the energy absorbing action of soft tissues that are deformed in the impact.

The second type of fracture is produced by creep or fatigue. Bones often support more or less constant loads for prolonged periods of time and cyclic loads that may produce microdamage. If the accumulation of microdamage is faster than repair by remodelling, microcracks (or other kinds of microdamage) can multiply to produce macrocracks and complete fracture. Clinically, this is called a stress fracture. It normally occurs in individuals who have increased repetitive-type physical activities such as soldiers, ballet dancers, joggers, athletes and racehorses [7,57–59]. It also occurs at lower activity levels in bones weakened by osteoporosis, especially at advanced ages when bone remodelling is almost inactive.

Many experimental [60–64] and theoretical [58,59,65–71] works have suggested that bone tissue can repair microdamage by remodelling. Indeed, some authors consider that the accumulation of microdamage is the mechanical stimulus for remodelling [66,69,70,120,121].

However, the prevention of stress fractures does not only depend on repair by remodelling. It is also controlled by the specific process of crack initiation and propagation. The microstructure of cortical bone is similar to fiber-reinforced composite materials. Osteons are analogous to fibers, interstitial bone tissue is analogous to the composite matrix and the cement line acts as a weak interface where cracks may initiate [72]. Many authors have tried to explain the mechanical behaviour of cortical bone tissue through composite models. Katz [73] considers the anisotropy of cortical moduli using a hierarchical composite model of osteons made of hollow, right circular cylinders of concentric lamellae. Crolet et al. [74] applied homogenization techniques to develop a hierarchical osteonal cortical bone model with several levels of microstructure: osteons, interstitial bone, and layers of lamellae with collagen fibers and hydroxyapatite. The results obtained agree well with the experimental data. Other authors suggest that osteons increase the toughness and fatigue resistance of cortical bone [71,75–79]. For example, Corondan and Haworth [79] found that crack propagation in bone is inhibited by more or larger osteons. Prendergast and Huiskes [80] also employed microstructural finite element analysis (FEA) to explore the relationship between damage formation and local strain of osteocyte containing lacunae for various types of damage. The high local strain around lacuna formed stress bands between lacunae, providing sites for crack nucleation and paths for crack growth, effectively unloading the lacunae adjacent to the damaged region.

Linear elastic fracture mechanics (LFM) have also been used widely to characterize bone resistance to fracture [76,81–87] by measuring the fracture toughness of cortical bone under various loading modes (see Table 1). However, changes in fracture toughness with age, microstructure and composition are not always the same in different species or bone locations in the same species, as shown by Yeni and Norman [88]. Only a few studies have addressed the fracture mechanics of microcracks in osteonal cortical bone [77,89,90] by analysing the interaction between microcracks and the distribution and type of osteon.

In general, fractures are caused by two main mechanisms: when the damage rate exceeds the remodelling/repair rate (excess damage) or when a normal damage rate is not repaired properly due to a defective remodelling/repair mechanism (deficient repair).

Damage accumulation in bone is similar to artificial structural materials. Schaffler et al. [93,94] showed that fatigue damage is similar in vitro and in vivo. The microdamage (related to the load and number of cycles), may appear in different ways at the microstructural level: debonding of the collagen–hydroxiapatite composite [95], slipping of lamellae along cement lines [96], cracking along cement lines or lacunae [97,98], shear cracking in cross-hatched patterns [99] and progressive failure of the weakest trabeculae [100]. At the macroscopic level damage is hardly visible before there is a large crack and global failure, even though the mechanical functionality may have altered substantially in earlier stages. In general, the evolution of microdamage during cyclic loading can be quantified in four ways [101] by measuring: (1) defects at microscale (number/density of cracks), (2) changes in different properties (material density, acoustic emission recordings, electrical resistivity, ultrasonic waves, microhardness measurements, etc.), (3) the remaining life to
failure, and (4) variations of macromechanical behaviour (changes in elastic, plastic or viscoplastic properties). The last measurement is often used to quantify fatigue cycling by a macroscopic analysis of stiffness, strength and creep relaxation [93,94,102–110], in addition to other methods [103,109–114].

Taylor and Prendergast [115] express the crack growth rate in terms of the cyclic stress intensity and crack length, concluding that the crack growth rate decreases rapidly with increasing length. This behaviour is typical of short-crack fatigue in many materials and can be interpreted in terms of microstructural barriers to growth. They propose the following equation for compact bone:

\[
\frac{da}{dN} = \{C(\Delta K - \Delta K_{th})^n\} + \left\{C'\Delta K'^{n'} \left[\frac{d-a}{d}\right]^{m'}\right\}
\]

(11)

where symbols \{\} means

\[
\{A\} = \begin{cases} 
A & \text{for } A \geq 0 \\
0 & \text{for } A < 0 
\end{cases}
\]

(12)

and \(a\) is the crack length, \(d\) the average spacing of cement lines, \(\Delta K\) is the range of cyclic stress density and the rest of parameters are constants determined by Prendergast and Taylor [115]. The first term describes the behaviour of cracks when they are long, and the second one is used for short cracks.

Carter and Caler [109,110,116] propose a damage variable, \(D\), between 0 and 1, that increases at a rate inversely proportional to the number of cycles to failure \(N_f\):

\[
\frac{dD}{dN} = \frac{1}{N_f}
\]

(13)

that is, a remaining lifetime criterion that identifies the damage level with proximity to failure. One of the main disadvantages is that it does not account for the current damage state or stress history.

Several years later, Zioupos et al. [117] and Pattin et al. [118] defined damage as the ratio between the elastic modulus in the current and the initial state:

\[
D = 1 - \frac{E}{E_0}
\]

(14)

depending on the stress history and the mechanical properties of the material. In fact, the accumulated damage at each stress level is a non-linear function of the number of cycles [117,118].

Table 1

<table>
<thead>
<tr>
<th>Bone type</th>
<th>Mode I: Transverse fracture</th>
<th>Mode I: Longitudinal fracture</th>
<th>Mode II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(K_c) (MPa m(^{1/2}))</td>
<td>(G_c) (J m(^{-2}))</td>
<td></td>
</tr>
<tr>
<td>Bovine femur [81]</td>
<td>5.49</td>
<td>3100–5500</td>
<td></td>
</tr>
<tr>
<td>Bovine tibia [82]</td>
<td>2.2–4.6</td>
<td>780–1120</td>
<td></td>
</tr>
<tr>
<td>Equine metacarpus [83]</td>
<td>7.5</td>
<td>2340–2680</td>
<td></td>
</tr>
<tr>
<td>Human tibia [84]</td>
<td>2.2–5.7</td>
<td>350–900</td>
<td></td>
</tr>
<tr>
<td>Bovine femur [81]</td>
<td>3.21</td>
<td>1388–2557</td>
<td></td>
</tr>
<tr>
<td>Bovine femur [91]</td>
<td>2.4–5.2</td>
<td>920–2780</td>
<td></td>
</tr>
<tr>
<td>Bovine tibia [85]</td>
<td>2.8–6.3</td>
<td>630–2238</td>
<td></td>
</tr>
<tr>
<td>Human femur [84]</td>
<td>2.2–5.7</td>
<td>350–900</td>
<td></td>
</tr>
<tr>
<td>Human tibia [76]</td>
<td>4.32–4.05</td>
<td>897–595</td>
<td></td>
</tr>
<tr>
<td>Human tibia [92]</td>
<td>3.7</td>
<td>360</td>
<td></td>
</tr>
<tr>
<td>Human tibia [84]</td>
<td>2.2–2.7</td>
<td>365</td>
<td></td>
</tr>
</tbody>
</table>
Many theoretical models have been developed in order to predict the accumulation of microdamage in bone. Recently Davy and Jepsen [119] have performed a detailed revision of the most important contribution in this field.

It is important to understand that fatigue failure is not only prevented by lamellar structure but also by remodelling. Several theories have been developed to explain how bone remodelling is activated by damage and mechanical load. The models hypothesize that bone tries to optimize strength and stiffness by regulating porosity and local damage generated by fatigue or creep.

Martin and co-workers have proposed several models where bone remodelling is activated by damage produced by fatigue or creep [66,70,120]. In their last work [66], a more realistic theory is proposed that includes the most important mechanical and biological processes. It assumes that bone remodelling is controlled by packets of cells, so-called BMUs. The BMUs act in a sequence of events that require three to four months based on measurements from biopsies. The events control the remodelling response and depend on the mechanical environment, microdamage accumulation and the surface available for remodelling.

Prendergast and Taylor [69] proposed a full bone internal remodelling model where damage occurs as a microcrack distribution even in the equilibrium situation. The stimulus that controls repair is the difference between the actual damage and the damage in the equilibrium situation. Ramtani and Zidi [121] also propose a model to explain the physiological process of couple damaged-bone remodelling, following the general framework of continuum thermodynamics.

Skeletal biomechanics is more and more focused on how skeletal tissues are produced, maintained and adapted as an active response to biophysical stimuli in their environment, currently known as mechanobiology [122]. Now that the human genome has been sequenced, it is apparent that the genetic code is only the beginning. It provides few answers about how skeletal tissues are generated and maintained. This emphasizes the importance of understanding the role of environmental influence, especially mechanical factors. The development of mechanobiology will bring great benefits to tissue engineering and to the treatment and prevention of different skeletal problems, such as congenital deformities, osteoporosis, osteoarthritis and bone fractures.

5. Bone fracture criteria

Different fracture criteria have been proposed for bone tissue and many experiments have been performed to validate them [37,40,123–127]. Many reports use FE models to evaluate fracture patterns and loads in terms of fracture criteria, especially in the proximal femur [39,125,128–131]. Here we review the most important criteria and their limitations.

The Von Mises–Hencky formula is an isotropic criterion traditionally used to predict yielding of ductile materials like metals. It assumes equal strength (ultimate stress) in tension and compression, which is not very realistic in bone tissue. Failure results when the equivalent Von Mises–Hencky stress equals the ultimate strength of the material

\[
\sqrt{(\sigma_2 - \sigma_3)^2 + (\sigma_3 - \sigma_1)^2 + (\sigma_1 - \sigma_2)^2} = \sigma_c
\]

with \(\sigma_i\) principal stresses and \(\sigma_c\) the ultimate strength in compression (or tension).

Although this criterion is not very realistic, it has been widely used for estimating proximal femoral fracture load and assessing hip fracture risk [39,126,128,129,132]. In fact, Keyak et al. [39] analysed that, when isotropic material properties are used, the Von Mises–Hencky criterion may be the most accurate for predicting fracture location, even after accounting for differences in the tensile and compressive strength of bone.
However, the experimental results obtained by Fenech and Keaveny [123] for bovine trabecular bone indicated that the Von Mises–Hencky criterion was not a good predictor of fracture load in trabecular bone, particularly when the stress state was dominated by shear.

Hoffman (1967) [164] proposed a fracture criterion for brittle materials that also takes into account the different strength in tension and compression. Nevertheless, it assumes the same behaviour in all directions:

$$C_1 (\sigma_2 - \sigma_3)^2 + C_2 (\sigma_3 - \sigma_1)^2 + C_3 (\sigma_1 - \sigma_2)^2 + C_4 \sigma_1 + C_5 \sigma_2 + C_6 \sigma_3 = 1$$

(16)

where $\sigma_i$ are the principal stresses, $C_i$ material parameters defined as $C_1 = C_2 = C_3 = \frac{1}{2} \frac{\sigma_t}{\sigma_c}$; $C_4 = C_5 = C_6 = \frac{1}{\sigma_c} - \frac{1}{\sigma_t}$, and $\sigma_c, \sigma_t$ are the ultimate strengths in compression and in tension, respectively. In expression (16), the linear terms represent the difference between tension and compression. The Hoffman criterion is equivalent to the Von Mises–Hencky criterion when $\sigma_c = \sigma_t$.

This criterion has been also used to predict load and pattern of proximal femoral fractures [39,132] obtaining results slightly worse than the Von Mises–Hencky criterion.

The maximum stress criterion (Rankine criterion) was initially introduced to predict failure of brittle materials. It assumes that failure takes places when the highest principal stress exceeds the ultimate strength in tension or compression. Keyak and Rossi [39] used it to predict the ultimate fracture load of bone tissue with less than 30% error in all cases. The parallel criterion in strains (Saint–Venant criterion) is even more correlated with the experimental data (less than 20% error), which is also a well-known situation in brittle materials. Fenech and Keaveny [123] were able to predict the failure of trabecular bone reasonably well using the principal strain criterion.

Keyak and Rossi [39] also obtained reasonably accurate results with the maximum shear stress (also known as the Tresca theory) and the maximum shear strain criteria.

The Mohr–Coulomb criterion is commonly used for materials with different behaviour in tension and compression, such as soils [133]. It is an isotropic criterion that is expressed as follows for non-cohesive materials, in the space of principal stresses:

$$\frac{\sigma_1 - \sigma_3}{\sigma_c} = 1$$

(17)

where $\sigma_1 \geq \sigma_2 \geq \sigma_3$ are the principal stresses and $\sigma_c$, $\sigma_t$ the ultimate strengths in compression and tension ($\sigma_c = \alpha \sigma_t$), respectively. Keyak and Rossi [39] used this criterion to predict the ultimate fracture load of bone tissue. It agreed well with the experimental data when coefficient $\alpha$ tended to one. For smaller values, the results are on the safety side, that is, the predicted fracture load is always lower than the experimental one [128].

The modified Mohr–Coulomb criterion solves some of the original problems [133]. It is expressed as

$$\frac{\sigma_1 - \sigma_3}{\sigma_c} = 1 \quad \text{when} \quad \frac{\sigma_1}{\sigma_c} \leq -1$$

$$\frac{\sigma_1 - \sigma_3}{\sigma_c} = 1 \quad \text{otherwise}$$

(18)

This criterion was used to predict fracture load due to a fall [39]. The results were better than the standard Mohr–Coulomb when coefficient $\alpha$ was low, but worse when $\alpha$ was above 0.5.

Other authors have tried to validate experimental tests using cellular solid multiaxial criteria [123,127]. These models are better than their predecessors but very difficult to implement in a general way for FE analyses of whole bones. They could be very useful to validate other more phenomenological criteria.

The Tsai–Wu quadratic criterion [134] is an obvious candidate for a multiaxial anisotropic failure criterion since it accounts for strength asymmetry (different tensile and compressive strengths) and anisotropy, as well as interactions between strengths under different loading conditions. Tsai and Wu [134] expressed this criterion in terms of the stress tensor and two material dependent tensors. The basic hypothesis is the existence of a failure surface in the stress space of the following form:
\( f(\sigma_k) = F_i \sigma_i + F_{ij} \sigma_i \sigma_j = 1 \) for \( i, j, k = 1, 2, \ldots, 6 \) (19)

being \( F_i \) and \( F_{ij} \) tensors of material dependent constants of second and fourth rank respectively and \( \sigma_i \) the principal stresses. The interaction terms must verify:

\[ F_{ii} F_{jj} - F_{ij}^2 \geq 0 \] (20)

which implies that all the diagonal terms of \( F_{ij} \) must be positive. The inequality guarantees that each principal stress axis intersects with the fracture surface. The linear terms in (19) take into account the difference between positive and negative ultimate stresses. Finally, it is interesting to remark that the Von Mises–Hencky and Hoffman criteria are particular cases of the Tsai–Wu criterion. The main disadvantage of the latter is the high number of constants that have to be determined by multiple experimental tests and the subsequent correlation procedure. For instance, for orthotropic material this number goes up to 12 and for a heterogeneous anisotropic material the correlation is almost impossible. However, the Tsai–Wu criterion has been used as the point of departure for simplified criteria [18,123], which strongly reduces the number of constants. Fenech and Keaveny [123] used a simplified Tsai–Wu criterion to predict the fracture load on trabecular bovine femurs with less than 20% error. Keaveny et al. [127] estimated the Tsai–Wu coefficients as a functions of apparent density, using uniaxial strength-density data from 139 bovine tibial specimens and multiaxial data from 9 similar specimens. So they predicted the failure criterion at different apparent densities indicating that the orientation of this surface depended on apparent density and was relatively well aligned with the principal material directions (see Fig. 5). This Tsai–Wu criterion has been also applied with varying degrees of success to cortical bone [135–137], and has been formulated in terms of the fabric tensor [18], as will be shown below.

Cowin [18] proposed a fracture criterion useful for porous materials and/or composites, based on the properties of the homogenized microstructure. The fracture criterion is a function \( f \) of the stress state, the porosity \( n \) and the fabric tensor \( \mathbf{A} \) as follows:

\[ f(A, \sigma, n) = f(QAQ^T, Q\sigma Q^T, n) = 1, \quad \forall Q \text{ orthogonal tensor} \] (21)

Cowin [18] considers that a quadratic function obtains a good compromise between reliability and computational cost, with the criterion expressed as

\[ G_{ij} \sigma_{ij} + F_{ijkm} \sigma_{ij} \sigma_{km} = 1 \] (22)

where \( \sigma_{ij} \) are the stress components and \( G_{ij}, F_{ijkm} \) functions of \( A, n \).

Eq. (22) may be simplified by working in the space of principal stresses and considering a symmetrical criterion with respect to the principal axes. It then depends on only three constants \( G_{ii} \) and six \( F_{iikk} \) of the material as follows:

Fig. 5. Tsai–Wu failure criterion for general triaxial normal loading for an apparent density of 0.6 g/cc. (From [127] with permission).
\[
G_{11}\sigma_{11} + G_{22}\sigma_{22} + G_{33}\sigma_{33} + F_{1111}\sigma_{11}^3 + F_{2222}\sigma_{22}^3 + F_{3333}\sigma_{33}^3 + 2F_{1122}\sigma_{11}\sigma_{22} + 2F_{1133}\sigma_{11}\sigma_{33} + 2F_{2233}\sigma_{22}\sigma_{33} = 1
\]  

Cowin [18] gives some indications to determine the constants from the ultimate strengths of the material in the different directions and orientations. Thus

\[
G_{ii} = \frac{1}{\sigma_i^+} - \frac{1}{\sigma_i^-}, \quad F_{iiji} = \frac{1}{\sigma_i^+} - \frac{1}{\sigma_i^-}
\]  

\[
F_{iiji} = \frac{1}{2} \left( \frac{1}{\sigma_i^+} - \frac{1}{\sigma_i^-} \right) - g(A)
\]

where \( \sigma_i^+, \sigma_i^-, \sigma_{ij} \) are the ultimate strengths in tension, compression, and in shear, respectively, along each direction and plane and \( g(A) \) is a function of the fabric tensor. The main innovation with respect to Tsai–Wu is the assumption that the tensors \( F_{ijkm}, G_{ij} \) are functions of the porosity and the fabric tensor, that is, of the properties of the homogenized microstructure of the material.

Although this criterion has been cited by several authors [42,138], it has not been used in computational simulations due to the difficulty of determining all the parameters involved. Only Gomez et al. [131] correlated the different directional parameters of the Cowin criterion with the apparent density and the fabric tensor, that were obtained after simulating the anisotropic bone remodelling and computing the density and fabric tensor distribution on femoral bone. The approach was used to predict hip fractures and the results were in accordance with the experimental work of Yang et al. [53].

Pietruszczak formulated a theory to explain fractures in concrete [139]. It has also been applied to frictional materials [140] and bone tissue [42], with behave differently in terms of tension and compression. This criterion takes into account the stress state \( \sigma_{ij} \), the fabric tensor \( A_{ij} \) and the porosity \( n \) that defines the failure criterion:

\[
F = b_1 \left( \frac{\bar{\sigma}}{g(\theta) \cdot \sigma_c} \right) + b_2 \left( \frac{\bar{\sigma}}{g(\theta) \cdot \sigma_c} \right)^2 - \left( b_3 + \frac{I}{\sigma_c} \right) = 0
\]

where \( I = -\sigma_{ii} \) is the (negative) trace of the stress tensor (negative first stress invariant); \( \bar{\sigma} = (s_{ij} s_{jk} s_{kl}/2\sigma_i^+)^{1/2} \) (related to the second stress invariant) being \( s_{ij} \) the stress deviatoric tensor, \( \theta = \sin^{-1}(\sqrt{3}s_{ij} s_{jk} s_{kl}/2\sigma_i^+)/3 \) (related to the third stress invariant), \( b_1, b_2, b_3 \) are adimensional material constants and \( \sigma_c \) the ultimate uniaxial compression strength. The \( g \) function of the third invariant is expressed as

\[
g(\theta) = \frac{(\sqrt{1 + b} - \sqrt{1 - b})K}{K\sqrt{1 + b} - \sqrt{1 - b} + (1 - K)\sqrt{1 + b} \cdot \sin 3\theta}
\]

with \( b \) a constant close to 1, \( K \) a material dependent constant that represents the ratio between the ultimate value of \( \sigma \) in compression and in tension. This criterion was used by Pietruszczak et al. [42] to determine the risk of fracture in human femurs, simulating the fracture produced by a fall. Gómez et al. [131] obtained similar results when they compared this criterion with Cowin’s criterion.

Finally, we can observe that there is a lack of agreement between different studies. Several authors [37,125] suggest that strain-based failure theories are better than stress-based ones, but others indicate the opposite [39]. For example, Keyak and several collaborators [39,49,129] mostly use distortion energy theories (Von Mises–Hencky or Tresca criterion) to represent femoral bone fracture. But Fenech and Keaveny [123], prefer maximum normal strain criterion in their study of trabecular bovine bone for uni-axial tensile or compressive loading along the principal trabecular direction combined with torsional loading about the same direction.
There may be several causes for this discrepancy. Most computational simulations do not differentiate between cortical and trabecular bone (only in porosity), but their structure is completely different, which could affect their failure mechanisms. Also, most of the criteria assume isotropic behaviour, which is unrealistic. All this controversy suggests that we are still far from getting a mechanobiologically based failure criterion for bone and that more experimental, analytical and simulation works should be performed in order to determine the appropriate bone failure theory. Some of the available results on the simulation of bone fractures according to the previously explained criteria are shown in Section 6.

6. Modelling traumatic and pathologic fractures

The importance and high cost of treating bone fractures has promoted the development of non-invasive methods of assessing fracture risk and prevention. The methods usually involve radiographic techniques to measure bone mineral density, such as dual-energy X-ray absorptiometry (DXA) or quantitative computed tomography (QCT) [56,141–147]. The methodology has been somewhat successful but it is still limited by a more precise estimation of fracture load and the identification of subjects with a high risk of fracture. It does not take into account different loading conditions, the distribution of bone material within the entire structure and the properties of the distributed bone material [148]. In order to solve some of these limitations, FEA have been widely used to predict and prevent the occurrence of hip fractures [39,42,49,50,126,128,129,132,138,149–151]. FEA helps to identify the most probable fracture mechanisms, the regions where the fracture initially appears and the forces and orientations needed to produce them.

All these models have similarities and differences that must be analysed in order to perform a comparative analysis that highlights their main limitations and the ideal properties that should be verified in future developments.

Lotz et al. [132] studied the stress distributions in the proximal femur during a one-legged stance and for a fall to the lateral greater trochanter. In the first case, the peak stresses were in the subcapital region. For the simulated fall, the peak stresses appeared in the intertrochanteric region. Cheal et al. [138] studied the fracture strength of the proximal femur with a lesion in the femoral neck due to a tumor. They considered four loading conditions corresponding to level gait and stair climbing. Lotz et al. [151] also examined the evolution of stress distribution in the proximal femur during the three phases of the gait cycle, but they did not compute fracture loads. Ford et al. [126] analyzed the effect of internal/external rotations on femoral strength for loading that represented impact from a fall onto the hip. Sabick and Goel [150] compared the failure loads for a posterolateral impact on the greater trochanter with a fall onto the buttocks, but they did not study other load directions. Keyak et al. [129] analysed the ability of finite element models to predict the fracture location and/or type for two different loading conditions: one similar to joint loading during single-limb stance and one simulating impact from a fall (the same fall that was simulated by Lotz et al. [132]). In the first condition, the FE models predicted that only cervical fractures occurred (72% agreement with experimental results). In the second case they predicted trochanteric and cervical fractures, obtaining a 79% agreement with laboratory tests. Keyak et al. [152] also determined the force directions associated with the lowest fracture loads for two types of loading: one simulating the impact from a fall and the other corresponding to joint loading during daily activities (atraumatic condition). For the fall, the force direction with lowest fracture load was an impact onto the greater trochanter at an angle of 60° or 70° respect to the shaft. For atraumatic loading, the lowest fracture load was determined in conditions very similar to standing on one leg or climbing stairs.

Gomez et al. [131] reproduced the experimental work performed by Yang et al. [53] using FEA. A computational simulation was developed to characterize the heterogenous structural distribution in the
femur and determine porosity and anisotropic properties. They were able to use the Cowin criterion as a function of the porosity and fabric tensor [18], obtaining promising results that will be below reviewed.

They examined hip fracture patterns due to two possible contractions: iliopsoas and gluteus medius muscle, in order to obtain a risk factor that is defined by the ratio between the Cowin equivalent stress and the considered ultimate stress.

In the case of psoas-iliac contraction, a high risk factor is obtained in the neck area (Figs. 6 and 7). The results obtained indicate that a neck fracture probably occurs since the risk factor is over the limit value 1 in this area, in a similar way that happened in Yang’s experiments for which all the seven femurs supporting this type of load broke along the neck zone.

They [131] also studied hip fracture patterns due to contractions of the gluteus medius muscle and were able to predict different subtrochanteric or intertrochanteric fractures (Figs. 8 and 9). It appears that subtrochanteric fracture (or fracture in region D) is the most probable, although neck and trochanteric fracture can also occur. Similar results were obtained in the Yang’s tests [53], where three femurs suffered intertrochanteric fracture and four of them were subtrochanteric.

7. Bone fracture healing

Bone is a living material that is routinely exposed to mechanical environments that challenge its structural integrity. As explained above, there are several causes of bone fractures. However, in contrast with inert materials, bone can regenerate to form new osseous tissue where it is damaged or missing. In fact, the healing of a fracture is one of the most remarkable of all the biological processes in the body.

Understanding tissue regeneration is also essential to explain similar biological processes such as skeletal embriogenesis and growth.

Bone ossification in the embryo and the growing child can occur in different forms: endochondral, intramembranous or appositional ossification. In the first, cartilage is formed, calcified and replaced by bone.
Fig. 7. (a) Regions of proximal femur; (b) volume percentage of factor of risk for different femoral regions in the case of iliopsoas contraction.

Fig. 8. (a) Factor of risk to fracture due to contractions of the gluteus medius muscle; (b) X-ray of intertrochanteric fracture (From [53] with permission).
In the second, bone is formed directly by osteoblasts (flat bones like skull or pelvis). In the third, ossification is adjacent to membrane layers of mesenchymal cells that differentiate into osteoblasts. When osteoblasts are not part of a membrane (i.e., endosteal, trabecular or Haversian canal surface) ossification is called appositional. The last type of ossification is normally the only one found in healthy adults but the two types can be activated during the fracture healing process. Therefore, this process is important to understand tissue repair as well as tissue generation.

Fracture healing is a natural process that can reconstitute injured tissue and recover its original function and form. It is a very complex process that involves the coordinated participation of immigration, differentiation and proliferation of inflammatory cells, angioblasts, fibroblasts, chondroblasts and osteoblasts which synthesize and release bioactive substances of extracellular matrix components (e.g., different types of collagen and growth factors).

We can differentiate between primary or secondary fracture healing. Primary healing occurs in cases of extreme stability and negligible gap size, involving a direct attempt by the bone to form itself directly [153]. Secondary healing occurs when there is not enough stabilisation and gap size is moderate. In this case, healing activates responses within the periosteum and external soft tissues that form an external callus, which reduces the initial movement by increasing stiffness. Most fractures are repaired by secondary healing, which does a more thorough job of replacing old and damaged bone.

Secondary fracture healing has a series of sequential stages than can overlap to a certain extent, including inflammation, callus differentiation, ossification and remodelling.

The first stage begins after bone fracture. Blood emanates from the ruptured vessels and a hemorrhage quickly fills the fracture gap space. Macrophages remove the dead tissue and generate initial granulation tissue for the migration of undifferentiated mesenchymal cells, originating an initial stabilizing callus. These cells proliferate and migrate from the surrounding soft tissue [153–156].

In the next stage, mesenchymal cells may differentiate into chondrocytes, osteoblasts or fibroblasts (Fig. 10), depending on the biological and mechanical conditions. These differentiated cells begin to synthesize the extracellular matrix of their corresponding tissue. Intramembranous woven bone is produced by direct differentiation of the stem cells into osteoblasts and appears adjacent to each side of the gap site, advancing to the center of the callus. At the same time, at the center of the callus, cartilage is formed by chondrogenesis, except right beside the gap where the stability is still very small and high relative displacement prevents the differentiation of mesenchymal cells (Fig. 11).

Once the callus is filled (mainly by cartilage), endochondral ossification begins following a complex sequence of cellular events including cartilage maturation and degradation, vascularity and osteogenesis.
The ossification continues until all the cartilage has been replaced by bone and a bony bridge surrounds the fracture gap, achieving a good stabilization and sufficient stiffness. When the fracture is completely stabilized, mesenchymal cells begin to invade the gap (Fig. 11). Once the gap has ossified, remodelling of the fracture site begins gradually in order to restore the original internal structure and shape (internal and
external bone remodelling). The last stage is much longer than the previous one (1 year compared to several weeks, depending on the animal species).

This summarizes the most important stages of bone fracture healing, although the evolution depends on many factors such as mechanical, type of fracture, gap size, blood supply, hormones, growth factors, etc. Fracture healing is an important topic of research in biomechanics. During the last years, many theories and simulation models have been proposed to develop a comprehensive view of the mechanisms that control bone morphogenesis. Pauwels [158] was one of the first authors to propose a theory of tissue differentiation in response to local mechanical stress and strain (Fig. 12). He assumed that deviatoric stresses are the specific stimulus for the formation of fibrous connective tissue or bone, whereas hydrostatic stresses control the formation of cartilaginous tissue.

Perren and Cordey [159,160] proposed that tissue differentiation is controlled by the resistance of various tissues to strain. Their main idea 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. This theory is normally known as “the interfragmentary strain theory” [161].

Carter et al. [162,163] developed a new tissue differentiation theory, which correlates new tissue formation with the local stress/strain history. They described qualitatively the relationship between the ossification pattern and the loading history, using finite elements to quantify the local stress/strain level, assuming that the tissue in the callus is formed by a single solid phase. They proposed several interesting differentiation rules that are graphically summarized in Fig. 13. In this figure there are two lines that separate the different tissue regions. On the contrary, to the left of the pressure line, the tissue is supporting a high hydrostatic pressure, which serves as stimulus for the production of cartilaginous matrix, to the right...
of this line the hydrostatic pressure is very low, causing the production of bone matrix. There is a limit from which this tissue is not differentiated, this one is limited by the boundary line of the right. When the tissue is subjected to high tensile strains (above the tension line) fibrous matrix is produced with cartilage or bone depending on the hydrostatic pressure level.

Many authors have also used computational models (mainly based on finite elements), to estimate local strains and stresses during the different stages of fracture healing [161–163,165–168], since there is experimental evidence [156,169] that tissue differentiation is mechanically dependent.

Kuiper et al. [170–172] developed a differentiation tissue theory using the tissue shear strain and fluid shear stress as the mechanical stimuli regulating tissue differentiation and the strain energy as the mechanical stimulus regulating bone resorption. They used an axisymmetric biphasic model of finite elements of a fracture and applied movements on the cortical bone in an attempt to predict typical healing patterns including callus growth. The results were that larger movements increased callus size and delayed bone healing.

Lacroix et al. [161,173,174] used the differentiation rules proposed by Prendergast et al. [175] (see Fig. 14) in combination with FEA to predict different fracture healing patterns depending on the origin of the stem cells. The model can predict the callus resorption produced in the last stage of the fracture healing process, but cannot predict callus growth during the initial reparative phase (assuming a determined callus size).

Ament and Hofer [176] proposed a tissue regulation model based on a set of fuzzy logic rules derived from medical experiments, using the strain energy density as the mechanical stimulus that controls the process of cell differentiation.

Fig. 13. Relationship between mechanical stimuli and tissue differentiation (From [162] with permission).

Fig. 14. Tissue differentiation law based on mechanical strain and fluid flow (From [174] with permission).
Bailon-Plaza and Van der Meulen [177] studied the fracture healing process produced by growth factors. They used the finite differences method to simulate the sequential tissue regulation and the different cellular events, studying the evolution of the several cells that exists in the callus.

More recently, García et al. [178] developed a continuum mathematical model that simulates the process of tissue regulation and callus growth, taking into account different cellular events (i.e., mesenchymal cell migration, mesenchymal cell, chondrocyte, fibroblast and osteoblast proliferation, differentiation and dead), and matrix synthesis, degradation, damage, calcification and remodelling over time. They also analysed the evolution of the main components that form the matrix of the different tissues (i.e., different collagen types, proteoglycans, mineral and water) to determine mechanical properties and permeability according to this composition.

In order to define all these processes, the fundamental variables were the number of cells \( N \) and the concentration \( c \) of each cell type (independent variables), with subscripts \( s \), \( b \), \( f \) and \( c \) indicating stem cells, osteoblasts, fibroblasts and chondrocytes respectively. They used the second invariant of the deviatoric strain tensor \( \psi \) as the mechanical stimulus that controls the differentiation process, which also depends on location and time. The rate of change of the number of cells in a control volume \( V \) of tissue at a point is defined via the continuity equation to take into account changes in concentration and boundary growth \( v \) along the surface normal:

\[
\dot{N}_i = \left[ \frac{\partial c_i(x,t)}{\partial t} + \text{grad} (c_i) v + c_i(x,t) \text{div}(v) \right] V
\]

where they assume that each term evolves differently for each cell type, influenced by mechanical conditions. When no growth occurs, cell concentration only changes by proliferation, migration, differentiation or cell death. However, stem cells proliferate so much that a saturation concentration \( c_{\text{sat}} \) can be reached. In that case, the boundary has to move to give space for the extra cells, which is described as

\[
\text{div}(v) = \begin{cases} 
0 & \text{if } c_s < c_{\text{sat}} \\
\frac{f_{\text{proliferation}}(x,\psi)}{c_{\text{sat}}} & \text{if } c_s = c_{\text{sat}}
\end{cases}
\]

\[
\frac{\partial c_s(x,t)}{\partial t} = f_{\text{proliferation}}(c_s, x, \psi) + f_{\text{migration}}(c_s, x) - f_{\text{differentiation}}(x, \psi, t_m)
\]

being \( t_m \) the maturation time. Growth also occurs when cartilage cells (chondrocytes) swell. In that case, the number of cells in the volume does not change, but their concentration decreases:

\[
\text{div}(v) = -\frac{1}{c_c(x,t)} \frac{\partial c_c(x,t)}{\partial t}
\]

\[
\frac{1}{c_c(x,t)} = g_{\text{growth}}(x,\psi, t_m)
\]

During osteoblast and fibroblast differentiation we assume a constant volume. The evolution of number of osteoblasts depends on whether intramembranous or endochondral ossification \(^1\) is produced:

\[
\dot{N}_b = \begin{cases} 

h_{\text{differentiation}}(\psi, t_m) & \text{intramembranous ossification} \\
h_{\text{remodelling}}(\psi) & \text{endochondral ossification}
\end{cases}
\]

\(^1\) In intramembranous ossification osteoblasts appear directly by differentiation from stem cells, while in endochondral ossification osteoblasts appear as consequence of calcification of cartilage and replacement by bone.
The different functions $f_{\text{proliferation}}$, $f_{\text{migration}}$, $f_{\text{differentiation}}$, $g_{\text{growth}}$, $h_{\text{differentiation}}$, and $h_{\text{remodeling}}$ have to be defined according to specific physiological features [178]. The underlying assumption in this work is that the level of mechanical deviatoric strains in different regions of the callus is the main factor determining differentiation of mesenchymal cells and consequently the process of tissue regeneration. It is very interesting that the hypothesis used by García et al. [178] agrees with the experimental work by Bishop et al. [179], who concluded that deviatoric strains may stimulate ossification more than volumetric strains.

García et al. [178] also characterized the composition and density of the extracellular matrix, assuming that composition is independent of density and the main components are water, minerals, ground substances and different types of collagen. With these hypotheses and assuming all tissues are isotropic and linear elastic, they evaluated the mechanical properties of the tissues using the next mixture rule depending on the proportion of each component $p_i$:

$$
\begin{align*}
E (\text{MPa}) &= 20000p_{\text{mi}} + 430p_{\text{cl}} + 200p_{\text{cII}} + 100p_{\text{cIII}} + 0.7p_{\text{gs}} \\
v &= 0.33p_{\text{mi}} + 0.48p_{\text{coll}} + 0.49p_{\text{gs}}
\end{align*}
$$

(34)

However, the mechanical properties in the lamellar bone are computed using the following structural rule where each subscript means mi: mineral, cl: collagen type I, cII: collagen type II, cIII: collagen type III, gs: ground substance:

$$
\begin{align*}
E &= 2014\rho^{2.5}, \quad v = 0.2 \quad \text{if} \quad \rho \leq 1.2 \text{ g cm}^{-3} \\
E &= 1763\rho^{3.2}, \quad v = 0.32 \quad \text{if} \quad \rho \geq 1.2 \text{ g cm}^{-3}
\end{align*}
$$

(35)

The rate of matrix production and degradation depends directly on the cell population, except for the lamellar bone that is controlled by bone remodelling.

This model has been implemented in a finite element code Marc. It correctly predicts tissue differentiation and callus shape during fracture healing and quantifies the regulatory role of mechanical influences. For example, Fig. 15 summarizes the evolution of the bone cells predicted by the model (human tibia with a 2 mm fracture), after applying a typical pattern of fracture movement. The model also predicts the damage that is generated in soft tissues during fracture healing, which allows the study of pathological conditions such as non-unions.

Although the model is a good predictor of qualitative tissue differentiation and callus growth, it still involves many simplifications that must be improved in the future. One example is the combination of mechanical and growth factors and the role of vascularisation [170–172,180] and macrophages [181].

Most of the models analyze the course of differentiation tissue from a known interfragmentary movement, which seems to be the main stimuli under sufficient vascularity [167,170–172,182–184]. However, this movement depends on the applied load and the stability of the fixation used in the treatment. The load sharing mechanism between the fractured bone and stiffness of the fixation should also be considered. Most fracture healing models only analyze fractures under compression, while there are some important situations (distraction osteogenesis) where tension is the main acting load.

Anisotropy should also be included in computational models, distinguishing between woven (more isotropic) and lamellar bone (more anisotropic).

From a purely numerical point of view, mesh evolution should also be treated correctly, including remeshing, rezoning and smoothing approaches. More recently, meshless methods that are less sensitive, such as natural elements, have been used on similar problems [185].

Several authors [122,186] have also remarked that computer models evaluate mechanical stimuli from a macroscopic (homogenized) continuum level. However, physiological cellular mechanisms are not yet well understood and it is not clear whether the continuum approach is completely valid.
8. Conclusions

More and more departments of Continuum Mechanics are becoming involved in orthopaedic research, especially in the analysis of mechanical behaviour of living tissues (bone, ligaments and tendons) and the design of implants. Both areas require in depth understanding of the behaviour of bone as a structural material, especially the mechanisms of bone failure under different loading conditions and how the mechanical factors affect bone fracture treatment.

It is very important to develop clinical and research tools to assess bone failure and healing in order to improve the treatment and diagnoses of skeletal diseases. At the same time this helps to unravel the interaction between mechanical and biochemical regulatory pathways.

Many experiments on skeletal failure and repair have been performed in the last century that include a range of factors (biological, mechanical, hormonal, sex, age, etc.). Despite this effort, there are still many unanswered questions. Some of the challenges arise from the difficulty of performing in vivo experiments and interpreting their results, which are very difficult to compare across species, ages, patients, geometries, bones, loading conditions and so on. All these facts indicate the complexity of the biological problems and have stimulated the development of computational models that can analyze the influence of all factors and make predictions under different conditions. These models must also be validated with experimental work.

However, in many cases the computational models cannot be validated directly because some measurements cannot be performed in vivo. Despite this, indirect validations can be performed if the conclusions of the computer simulations are similar to the experimental or clinical results. Indeed, simulations
of fracture healing are one of the clearest examples of this situation since it is impossible to measure the stress or strain level in each tissue during differentiation. But most computational works reviewed here has been helpful to study the influence of mechanical factors in this complex process.

Despite the limitations of computer models (e.g., lack of validation and biological information) much progress has been made on a clinical level, for example:

- Many designs of joint replacement prostheses have been studied using finite element models, either by the manufacturer or by university institutes [187].
- Automated patient-specific finite element models have been useful in the assessment of femur and spine fracture risk [188].
- Well-constructed computer models of bones have been used to investigate the effects of regional differences in age-related bone loss under different loading conditions [188].

Nevertheless, it is very difficult to obtain quantitative conclusions from computer simulations because of anthropometric and metabolic differences between patients and animal species. Thus, research groups should make an effort to quantify the range of variability of physiological parameters between individuals and animals species.

Moreover, most computational models make important simplifications, especially in terms of the characterization of material and boundary/loading conditions. Many computer analyses proceed without a precise determination of material behaviour. So, we believe that the critical task for biomechanics is to determine constitutive laws for living tissues. In particular, biomechanical models can be most improved by including time-dependent mechanical properties, damage and repair of living tissues. In this paper, we have focused on comparing the current theories of bone fracture and healing, indicating the fundamental considerations to take into account for future improvements.

In the near future, it will be important to focus research on the integration of simulations, experiments and theoretical aspects [122].

Use of computational simulations for the parametric examination of factors that are difficult or impossible to examine experimentally will contribute to the advance of biomechanics, as other authors have also indicated [187,189].

All these facts suggest that future research programs in bone biomechanics will probably use more complex and realistic computer simulations to reduce animal experimentation and clinical trials, with important economic benefits. Perhaps it will be possible to develop computer analysis as a methodology to perform realistic preoperative mechanical analysis of musculoskeletal disruptions, their prevention and clinical treatment.

References


