CHAPTER 4

A coupled mechanical-biological computational approach to simulate antiresorbitive-drugs effects on osteoporosis

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Abstract

Most of mathematical models that describe bone adaptation deeply focus on the mechanical laws involved and less attention is paid to the biological processes. Moreover factors like drugs, hormones, genetics or nutrition also play an important role and must be considered as well. In order to have a more realistic description of the biological processes, models must be developed to incorporate biological parameters, like e.g. cellular turnover and mineralization processes. In order to achieve this we provide more insight on the coupling of biological variables to a mechanical model that handles the structural aspect. The biological model we propose is based on two elements that are changing as a consequence of an altered activation frequency of the BMUs. These affected variables are mineralization and the surface of remodeling. The model is implemented through an existent robust bone remodeling model based on damage mechanics. It considers porosity as the damage variable and the consequences of the biological changes are implemented in such a way that they affect the temporary evolution law of the damage as well as the mechanical properties of bone. The coupling of the models is applied to the study of the effects of biphosphonates in the treatment of osteoporosis. Our simulations are based on histological data reported from patients treated with alendronate, a drug used in the treatment of osteoporosis. Preliminary results show a good qualitative correlation compared to clinical data.
1 Introduction

Bone as a living tissue has the capacity to adapt to mechanical loads by modifying its external and internal structure. This process is known as adaptative bone remodeling and can occur in any bone of the skeleton during our life. Bone adaptation is associated with the evolution of apparent density and many theoretical models have been presented to study this phenomenon [1–4]. Most of these models were designed specifically to simulate changes in the bone architecture due to mechanical influences. However this is only one of the stimuli to which the bone responds during its adaptation process. Metabolic factors, such as an illness, nutrition and medication treatments also influence the bone’s response to mechanical loads. In the same way, the mechanical properties of the bone are not only sensitive to the porosity and density as considered in some of these models, but to the bone’s degree of mineralization [5]. This variable is included into the approach proposed in this chapter.

In order to predict the effects of these metabolic or medication induced changes, a more detailed description of the biological processes related to the remodeling is required. A model that represents the changes in the bone biology by means of histomorphometric parameters of the bone tissue is proposed in this chapter. Several authors have worked on this biological aspect, covering from cellular models in which the main variable is the probability that a new remodeling cycle would begin [6], to computer models that simulate individual time dependent remodeling zones (entities) on a bone sample [7–10]. However, these proposals do not cover rigorously the mechanical aspect and some are not implemented through numerical techniques to study the mechanical effects.

Regardless of the type of bone – cancellous or cortical – the remodeling process is a continuous sequence of bone removal by osteoclasts cells, followed by new bone formation by osteoblasts cells. Osteoclasts and osteoblasts act together and coordinated in so-called Bone Multicellular Units (BMUs), which are considered to be the main biological entity in remodeling. The mentioned sequence of events can further be divided into six phases [11]: activation: when a group of osteoclasts are recruited on the bone surface, indicating that a new BMU cycle has started; resorption: when the osteoclasts begin to resorb bone, thereby creating a cutting cone that will give rise to a new osteon (in case of cortical bone); reversal: the transition from the osteoclastic to the osteoblastic activity, which results in a spatial and temporal interval between the resorptive region and the refilling region; formation: the osteoblasts start filling the cavity with new non-mineralized bone named osteoid; mineralization: after a few days mineral starts to be deposited that will mineralize the osteoid to form mature bone and finally quiescence: is reached after osteoblasts have refilled the resorption cavity and become either osteocytes or lining cells. Two different types of mineralization are defined. On the one hand we have the primary mineralization period, which starts briefly after the apposition of new osteoid and which take place over a few days. This mineralization occurs very fast (5 days in this model) and it considers the period of time that the recently formed bone needs to reach up to 65%–75% of the maximum value of the mineralization [12]. Then a secondary mineralization starts that can take several months from the end of the
primary, during this period the bone tissue continues accumulating mineral material at a decreasing exponential rate until the bone gets mature and reaches 95% of its theoretical maximum (in this model 0.7 is considered according to table 2).

The number of remodeling cycles starting in a given volume of bone in a given time can be estimated from a histological cross-section of a bone sample, and is defined as the “activation frequency” of the BMUs [13]. The intensity of the remodeling process can then be derived from the activation frequency of the BMUs. Activation frequency is the major indicator of biochemical indices of whole body resorption and formation of bone, which is very useful to analyze drug effects and pathological behavior, among others.

The “remodeling space” is another measurable variable in bone histology defined to further quantify bone remodeling. During the reversal phase there is a finite time when the resorption cavity created by the osteoclasts remains empty, while it is prepared for bone formation [14]. The number of cavities waiting to be refilled is termed the “remodeling space” and its size (and therefore the deficit of bone) depends largely on the rate of bone remodeling.

The model’s applicability in this chapter focuses on the alterations and effects that the biphosphonate based medications have on the bone remodeling and specifically on the bone’s mechanical properties. The alendronate_sodium or alendronate is a biphosphonate which is broadly used nowadays to increase the amount of bone mineral in patients that suffer osteoporosis. One of the consequences of osteoporosis is the negative balance that occurs during the coupling of the bone re-absorption and bone formation, which results in a loss of bone tissue, see fig. 1. This loss is accelerated due to the increase in the new BMU’s activation frequency; this process is induced during menopause and persists throughout life.

The study and simulation of the alendronate is relevant, since when studying the remodeling alterations due to joint replacements, we must consider that a great part of the population that have implants are seniors with an osteopenic state or with osteoporosis.

The model we present here considers aspects of the BMU (bone multicellular units) activities and defines, in a particular way, the changes in the bone tissue’s degree of mineralization and the BMU’s activation frequency. The model uses measurements taken from histomorphometric studies of the human bone to represent

Figure 1: Details of the quality of the trabeculae in a healthy vertebra (left) and a vertebra with osteoporosis (right).
the BMU’s rate of appearance, progress and life period, as well as the time periods in which the bone is reabsorbed and deposited in each individual remodeling entity. Once developed, the model is implemented and coupled to the García and Doblaré model [4], which is based on damage mechanics and will be briefly described.

2 Bone histomorphometrical values

The bone dynamic histomorphometry is a quantitative analysis of a bone sample which has been tracked with chemical markers in order to quantify the formation of bone tissue and the cellular activity.

A histomorphometric study uses a histological slice as a photograph of the cellular activity occurring immediately before the extraction of an individual’s bone sample. By illustrating the activity of certain groups of cells, this photograph provides direct information about the cellular activity and its repercussion on the form and density of bone. The bone histomorphometry is especially important in bone remodeling computer models since it describes the bone’s cellular activity in a quantitative way. Towards the end of the 1950’s, doses of tetracycline were used as an innocuous and effective marker to label and identify recently formed bone (osteoid). This allowed the first studies on bone formation in humans. A series of techniques for the histomorphometric measurements were rapidly developed, many of which were created by Frost and his colleagues during the 1960’s [15], likewise the inclusion of new chemical markers have evolved with these techniques. Since then, the bone histology has contributed to the understanding of the bone adaptation and the metabolic processes affected by diseases altering the bone functions.

The most common techniques that are used to measure parameters in a histological section are the perimeter and area measurements. The perimeter based measurements are achieved by superimposing a grid over the surface of the slice and counting the number of contacts or intersections between the grid and the surface being studied. The area measurements are achieved by superimposing a point grid and counting those that fall in the area being studied [16], as shown in fig. 2. The area measurements tend to be associated to volumes in the bone sample.

Figure 2: Some techniques to make histological measurements (a) Spongy bone slice; osteoid is shown in black and mineralized tissue in shadowed areas. (b) Perimeter measurements with Merz type grid. (c) Area measurements with point’s grid.
Table 1: Some histomorphometric parameters relevant in this model.

<table>
<thead>
<tr>
<th>Calculated parameter</th>
<th>Description</th>
<th>Symbol or equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formation period</td>
<td>Time over which bone formation occurs at a remodeling site (days)</td>
<td>FP</td>
</tr>
<tr>
<td>Eroded period</td>
<td>Time during which bone surface is eroded during remodeling (days)</td>
<td>EP</td>
</tr>
<tr>
<td>Quiescent period</td>
<td>Average time during which there is no active remodeling at a site (days)</td>
<td>QP</td>
</tr>
<tr>
<td>Total period</td>
<td>Time between two remodeling cycles at a site on the bone surface (days)</td>
<td>( T_t.P = FP + EP + QP )</td>
</tr>
<tr>
<td>Activation frequency</td>
<td>The rate of appearance of a BMU on the bone surface (1/days)</td>
<td>( Ac.f = 1/T_t.P )</td>
</tr>
</tbody>
</table>

From a histological slice, parameters can be either measured or calculated. Histomorphometric parameters that are directly measured are: the eroded surface, the bone surface not undergoing remodeling, the surface covered by osteoid, the total bone surface, the erosion depth and the osteon wall thickness. Some parameters that are normally calculated from the chemical marker measurements and from the value’s parameter mentioned above are presented in table 1. These calculations are done by assuming that all of the bone sample’s cellular activity is that of a BMU and that the activity of remodeling observed in the slice is representative of the system in equilibrium.

3 Biphosphonates: Alendronate

The biphosphonates have been known for more than 100 years, but they have only been used in the treatment of osteoporosis for 30 years. They have a characteristic structure that allows it to adhere to the hydroxiapatita crystals in the bone. They act over the precursor cells of the osteoclasts by inhibiting the resorption and modulating the bone formation. The first biphosphonates used in the treatment of osteoporosis (specifically the etidronate) had negative consequences in the mineralization process [17]. Although this problem is associated with the appropriate dosage of new biphosphonates, it is still under discussion by pharmacology field researchers. Amongst the new biphosphonates, the alendronate has received lots of attention due to its capacity to increase the bone mass with little collateral effects. Despite the therapeutic benefits of the alendronate, there still exist many effects on the bone metabolism that are not fully understood.
Nowadays alendronate is indicated in doses of 10 mg/day or 70 mg once a week. It is prescribed as an oral drug both for prevention and treatment of the post-menopausal osteoporosis, for cortico-steroids induced osteoporosis and for the treatment of the Paget’s disease. To mention an example, women with post-menopausal osteoporosis under the treatment of alendronate have shown an increase in the bone mineral density (BMD) and a reduction in the tendency to fractures, including hip fractures [18, 19]. The BMD can be related directly to the mechanical properties of the bone, since the same quantity of bone showing a high or low degree of mineralization will correspond to a high or low BMD. This permits to make a follow up of the treatments with this drug through bone densimetry or Dual energy X-ray Absorbtionmetry (DXA).

Studies show that after giving the doses of alendronate, the action mechanism of this medication is located in areas of the bone where there is great physiological activity [20]. This medication, as mentioned before, acts on the bone remodeling and among the results associated to the treatment is the reduction on the bone remodeling surface and the increase in the mineralization of the bone.

3.1 Characteristics of the medication to be simulated: pharmaco-kinetics and pharmaco-dynamics

To simulate the doses of the medication, the distribution of it in the body (pharmacokinetics), as well as the relation between the concentration of the medication and its effects (pharmacodynamics) should be properly understood. The pharmacokinetics of the alendronate is relatively simple, because the tissue response to the alendronate is related directly to the concentration of the alendronate that is present in the bone [20]. Due to this, the more relevant aspect in administrating the alendronate is the pharmacokinetics that describes the amount of medication that is absorbed by the bone and the rate at which it is removed or eliminated from the bone.

The rate of absorption of the alendronate by the bone is fast (less than an hour) and the fraction of the doses that is actually absorbed by the body is not influenced by the amount of the doses, this means that large doses are absorbed by the bone as well as small doses [20]. These properties of the alendronate suggest that if the medication were not eliminated by the body, no cellular response of the bone would be observed if it were to be a large dose or a number of small doses that add up to be equivalent to the large doses.

The alendronate is eliminated by the body in a natural way. Studies of the elimination of the alendronate have shown that it is captured by the bone and removed in a decreasing exponential rate in which 66% remains even after six months of taking the last doses [21]. In relation to the concentration of the alendronate that remains in the bone once the treatment has finished, it can be predicted by a logarithmic function expressed in eqn (1) [22], that represents \( R_f \) the physiological response to the concentration of the doses or the fraction of the medication that continues during \( \tau \) days after the take has stopped, where \( m \) represents a constant obtained from information on the elimination, this is, the 66% of the response that remains in the body during the next 6 months.
\[ R_f = 1 - m \times \ln(t + 1). \] (1)

In Hernandez et al. [7] proposal the response of the BMUs is supposed to adopt its original level as in the pre-treatment condition in the same proportion in which the alendronate is eliminated from the mineralized tissue.

### 3.2 Effects of the drug on the biological parameters of the bone

Based on histomorphometric studies [18], it has been observed that the frequency of activation of the BMUs is reduced in an average of 87% per alendronate doses of 10 mg/day.

A fundamental relation of our statement is the one expressed by the Parfitt group who explained that the activation frequency, seen as a measurement of the birth rate of cross-sectional new remodeling cycles is also a valuable measure of the magnitude of the remodeling space [13]. This variable is represented in our model by the remodeling surface and the effect of the alendronate is simulated by a factor that reduces this variable in the same proportion as the one observed in the activation frequency of clinical data.

Another aspect to be considered to simulate the alendronate’s effect is the degree of mineralization of the bone. In adults this variable depends on the rate of remodeling, in other words, the biological determinant of mineralization is the rate of turnover or related activation frequency of the new BMUs.

As explained in the Introduction section, there are two different types of mineralization processes happening after the deposition of osteoid, as it is represented in fig. 3.

This represents an important input in our model since the increased activation frequency that osteoporosis generates leads to a shorter lifespan of the BMUs. Consequently, the new formed bone will not have enough time to reach its total mineralization before it is prematurely reabsorbed by osteoclast of the new BMU starting a new remodeling sequence. Data obtained from patients with osteoporosis before the treatment, indicate that the average value for ash fraction (ash mass/bone mass) was random; however, high values of this variable observed after the treatment with alendronate have been attributed to long periods in the secondary mineralization [5]. This data reinforce the hypothesis used in this chapter in which the reduction in the activation frequency, caused by the antireabsorptive effect of the alendronate, is followed by a long process of secondary mineralization that increases the lifetime of the BMUs and this allows the bone to mature reaching at least normal levels of mineralization [19]. This result associated to treatments with alendronate is simulated in our model, calculating the variations of the degree of mineralization and increasing this parameter based on daily calculations. According to the proposal of these authors, the bone mass and the bone mineral density represent different entities, and it is important to observe the therapeutic implications in this difference, especially when analyzing the effects of the medication that acts on bone resorption.
4 Proposed model

4.1 The mechanical model: overview

To establish the biological model and combine it with a mechanical approach, a model based on damage mechanics was used. This model developed by Doblaré & García [4] considers the porosity of a bone sample as the damage variable which is defined through a tensor for the two possible cases in bone adaptation:

\[
\text{Damage} \leftrightarrow \text{Bone resorption,} \\
\text{Repair} \leftrightarrow \text{Bone formation.}
\]

Since there is a relation between porosity and apparent density (eqn (2)),

\[
p = 1 - \left(\frac{\rho_a}{\bar{\rho}}\right). \tag{2}
\]

They proposed a damage tensor directly related to this concept of porosity with two possible values:

\[D = 0\text{ corresponding to a intact state or no damage (no local porosity)}

\[0 < D \leq 1\text{ corresponding to local damage.}

The changes within this range of damage are reflected as well in the mechanical properties of the bone through the eqn (3) which is an experimental relation proposed by Beaupré et al. [23] and Jacobs et al. [24] where the differences between
the mechanical properties of cortical and trabecular bone can be expressed as (Young modulus is expressed in MPa):

\[
E = \begin{cases} 
2014\rho^{2.5}, & \text{if } \rho \leq 1.2 \text{ g/cc} \\
1763\rho^{3.2}, & \text{if } \rho \geq 1.2 \text{ g/cc}, 
\end{cases}
\]

\[
\nu = \begin{cases} 
0.2, & \text{if } \rho \leq 1.2 \text{ g/cc} \\
0.32, & \text{if } \rho \geq 1.2 \text{ g/cc}. 
\end{cases}
\]  

The model of Doblaré and García defines the damage \( D \) variable through an intermediary tensor \( H \) directly related to the damage in resorption and in formation.

Since the model studies the evolution in time of the damage, a stimulus variable is defined to generate a change in the damage value. For this statement the formulation from the Stanford model \([1, 23]\) defining a mechanical stimulus that involves the effective stress is used with some considerations to make it coherent regarding the differences between formation and resorption.

As a function of this stimulus they proposed the two conditions under which either formation or resorption mechanism are activated. This can be interpreted as the limits established in an elastoplastic law, depicted in fig. 4.

Then, following the formulation of a damage theory, a flow law is defined to establish the evolution in time of the damage variable, as it was done in the Stanford model for the density through eqn (4)

\[
\dot{\rho} = k\dot{\tau}\nabla\rho,
\]  

where \( \dot{\tau} \) is the surface remodeling rate that quantifies the volume of bone generated or eliminated by site per unit of time, \( \nabla\rho \) is the bone available surface to be under remodeling per volume unit of bone and \( k \) is the percentage of active surface that is available for remodeling.
Then, a formulation is developed for the continuous variations of the formation and resorption tensors in the damage model. The $\beta$, $J$, $\hat{\omega}$ are variables related to anisotropy calculations.

Resorption

$$\dot{H} = \frac{3\beta k \dot{S}_v}{4\text{tr}(H_n^{-1}J_n^{-3} \hat{\omega}_n)} \rho_n J_n^{-3} \hat{\omega}_n.$$ (5)

Formation

$$\dot{H} = \frac{3\beta k \dot{S}_v}{4\text{tr}(H_n^{-1}J_n \hat{\omega}_n)} \rho_n J_n \hat{\omega}_n.$$ (6)

4.2 The biological model

As an initial condition in the model, there is a known apparent density ($\rho$) in each integration point. This apparent density is related to the mechanical properties of the bone through the expressions in eqn (3).

Using the definition of the ash fraction that indicates the quantity of mineral that contains a bone sample, experimental measurements relating this variable to the density [25] were used to establish a relationship as:

$$\text{ash}_0 = 0.2264 \times \ln(\rho) + 0.1772.$$ (7)

With this relation, after the apparent density is taken from i.e. CTs, the initial ash fraction is calculated.

It is known for humans that the values of the degree of mineralization range from osteoid ($\text{ash} = 0$) to completely mineralized bone ($\text{ash} = 0.70$). The dry density values for this range correspond to $1.41 \text{g/cc}$ and $2.31 \text{g/cc}$, respectively [26, 27], see table 2. From these data Martin [27] suggests that it is possible to use these points in order to define a linear relation between density of the total mineralized sample ($\hat{\rho}$) and its degree of mineralization

$$\hat{\rho}(\text{g/cc}) \approx 1.41 + 1.29 \times \text{ash}.$$ (8)

The mineralization periods, as already defined, are implemented in the model through a linear curve representing the primary mineralization period and a logarithmic curve to represent the secondary mineralization period. This is shown in fig. 3 and values used are in table 3. From the graph the temporary variations of the degree of mineralization are easily defined.

<table>
<thead>
<tr>
<th>Table 2: Range of values for the total mineralized bone and the ash values used in our statement.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\hat{\rho}$ (g/cc)</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Osteoid</td>
</tr>
<tr>
<td>Cortical bone</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
It is possible to calculate the variations in the degree of mineralization per increment of time. The slope is then calculated for each of the two different zones ($m_p$ for the linear zone and $m_s$ for the logarithmic zone):

$$m(\text{ash}/t) = \frac{\Delta \alpha}{\Delta t}$$  \hspace{1cm} (9)

and for each zone the variation of the mineralization per time interval:

$$\Delta \alpha_p = m_p \cdot \alpha_{max} \cdot \Delta t.$$  \hspace{1cm} (10)

$$\Delta \alpha_s = |\alpha - \alpha_{max}| \cdot \frac{\log(0.05/0.3)}{P_{MinSec}} \cdot \Delta t.$$  \hspace{1cm} (11)

Once the daily variation of the degree of mineralization is known, the variable “ash” is updated:

$$\alpha_n = \alpha_{n-1} + \Delta \alpha_n$$  \hspace{1cm} (12)

and the total mineralized density ($\hat{\rho}$) is then recalculated (in eqn (8)) for the next increment and its implications in the mechanical properties of the bone are reflected in the mechanical model. All these parameters are loaded in arrays by integration point and then recalculated for each new increment.

In histology the remodeling space represents the volume that is occupied by a porous (hole) and only appears temporarily during the resorption and reversal periods before deposition of osteoid by the osteoclasts preceding mineralization [14].

Table 3: Some parameters used to describe bone remodeling process and the values used in our simulation.

<table>
<thead>
<tr>
<th>Remodeling parameter</th>
<th>Description</th>
<th>Nominal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resorption period</td>
<td>Time during which resorption occurs at a remodeling site</td>
<td>60 days$^a$</td>
</tr>
<tr>
<td>Reversal period</td>
<td>Time between osteoclast and osteoblast activity</td>
<td>57 days$^a$</td>
</tr>
<tr>
<td>Mineralization lag time</td>
<td>Time between osteoid formation and the start of mineralization</td>
<td>22 days$^a$</td>
</tr>
<tr>
<td>Primary mineralization period</td>
<td>Time required for bone to mineralize up to 70% of its theoretical maximum</td>
<td>5 days$^a$</td>
</tr>
<tr>
<td>Secondary mineralization period</td>
<td>Time required for bone to mineralize from 70% to 95% of its theoretical maximum</td>
<td>6 years$^b$</td>
</tr>
</tbody>
</table>

$^a$ Value based on healthy postmenopausal women’s histology [32].

$^b$ Estimated value can take from 6 month [6] to many years [22].
When the activation frequency decreases, only few of these temporary spaces are present. This implies a reduction in the remodeling space. As well, an increase in the bone mass and volume is observed. As we have seen before, the treatment with alendronate generates a significant decrease in the activation frequency of the BMUs [18]. A decrease in this parameter causes a reduction in the remodeling space [27, 28].

To reflect these changes in the remodeling surface we use in this model the eqn (1) to represent the pharmaco-kinetics and pharmaco-dynamics and their influence on these temporary spaces or surfaces. To fit the clinical data to the behavior expressed by this equation a factor "a" is added modulating the decreased percentage in the activation frequency induced by alendronate (see eqn (8)).

$$S_{rv} = a \times (1 - m \times \ln(t + 1)).$$

Being $S_{rv}$ the value that will multiply the existent value of the remodeling surface under healthy conditions; “a” is the value representing a decrease of 87% of the remodeling surface; “m” is a constant to fit the clinical data depending on the concentration of the doses (70 mg/week, m = 0.06); “t” represents dimensionless values for daily, weekly or monthly takes of the drug. The simulations performed in this chapter only consider weekly doses that are the ones currently prescribed to patients. A graphical detail of eqn (13) is depicted in fig. 5.

The resultant changes of the biological simulation were implemented using two dynamic feedback loops. One of the loops is established between the surface of remodeling and the flow law indicating the temporary evolution of the damage (porosity) in the mechanical model.

The second loop is implemented between the total mineralized density in the mechanical model, and the variations of the degree of mineralization calculated in the biological model. All the calculated parameters for the biological model are loaded in arrays by keeping the sampling points and updated for every new increment. A diagram of the coupling between the two models is depicted in fig. 6.
5 Results

5.1 Simple model of a cantilever beam

To obtain preliminary results a cyclic load of 40 N was applied to a beam in which control nodes were defined as shown in fig. 7. Hexahedral elements were used to build the mesh and 18 month simulations were performed.

In the control nodes an average increment of 5.6% in the density was obtained for the first 12 simulated months and an increase of 6.6% at the end of the 18th simulated month. These tendencies are depicted in fig. 8.

Regarding the degree of mineralization, simulations in which the secondary mineralization period were longer, showed a pronounced increment in the apparent density [7, 29, 30]. The simulation considering a secondary mineralization period of 6 years lead to more accurate predictions compared to clinical data.

Results from the simulations on the pharmaco-kinetics and pharmaco-dynamics of alendronate showed a periodic decrease of the activation frequency, interpreted in our model as the changes in the surface of remodeling depicted in fig. 9. Although the high non-linearity characteristics of the mechanical model, the results offer a good evaluation of the coupling between the two models, this can be observed when induced changes by the biological model bring coherent results overall.
Figure 7: Schematic of the beam’s example.

Figure 8: Results of the density variations in time. The upper line shows the predictions for the alendronate in reference with the lower line stands for the control simulation done with the mechanic model.

Figure 9: Detail of the variations of the surface of remodeling after introducing the weekly doses of alendronate.
We consider relevant the comprehension of which parameter is more influential with respect to others in the resultant density predictions. This point is analyzed as well when important changes in the histomorphometric indicate some metabolic disorder [31]. Due to this, a sensibility analysis was performed for the model to evaluate which of the feedback loop is more influential in the density results. The analysis showed that variations in the parameters involved in the mineralization equations induce relevant changes in the resultant density. Less correlation was found regarding changes in the remodeling surface and the density.

5.2 Female patient with osteoporosis

Once the algorithm and the coupling with the main program were tested, a simulation of data from a female osteoporotic femur was performed. Figure 10 is showing a detail of the quality of the head of the femur observed in a CT prior to surgery for a total hip replacement.

A technique developed in the Bioengineering Centre of the Central University of Venezuela [33] allows the capture of the bone quality of the patient and to have it as the initial condition of the simulation. The methodology reads the Hounsfield

![Figure 10: Detail of the tomography showing the damage in the head of the femur caused by osteoporosis.](image)

![Figure 11: Initial density (g/cc) distribution in the outer surface of the model.](image)
Figure 12: Left: Anterior-posterior cut showing the density distribution of the patient with osteoporosis. Right detailed cuts related to the axial lines marked in the head of the femur.

units from the CTs and then creates a voxel matrix. Once these values are converted into mechanical properties, the program enables the coupling of the data to each sampling Gauss point of the finite element model directly from the voxel model; this allows a personalized model with high heterogeneous data.

The proximal part of the femur was meshed with 50,717 linear tetrahedral finite elements and 9541 nodes. Loads and boundary conditions were applied regarding the body weight of the patient ($\approx$600 N). Since we focus on the simulation of the head of the femur only the proximal part is considered thus avoiding really huge and unwieldy models.

Different cuts of the head of the femur are showing the internal density distribution. A representation of the initial density distribution in the outer surface is depicted in fig. 11 while fig. 12 presents a longitudinal cut and different axial cuts in the zone of interest: femoral head.
The apparent density increments for the 12th month of weekly doses simulated treatment are depicted in fig. 13. The results are coherent with the preliminary ones giving increments between 5 to 6%.

Although the model generates less accurate results at the beginning of the simulation (very high density increase), the response of the coupling tends to be stable and logical for the rest of the period simulated. Further work should be done in order to correct this misfit during the first increments; meanwhile results should be read only from the first year simulated and on. Under this convention we consider that the model offers a good correlation with the expected results. Simulations considering long term treatments (10 years) should be studied as well in order to test accuracy and stability of the model.

Due to differences between the surface-volume relationships in different types of bones, the rate of cellular activity is slower in cortical bone than in cancellous bone. As a future step this behavior will be included in the model in order to improve the accuracy of the results. This represents a difficulty when modeling drugs effect; in the model a filter is preventing the alendronate effect to act on low densities representing bone marrow. This can cause that points with a low density value affected by osteoporosis are only analyzed under the mechanical model laws for adaptation but they are not considered in the biological actions we attempt to model.

6 Conclusion

A biomechanics simulation platform that couples mechanical and biological behavior of the bone under the administration of a drug used to treat osteoporosis was developed and discussed. The biological model is based on histological data that allows the evaluation of the metabolic activity of the bone tissue.
Simplified models of the femur were analyzed considering its geometry, boundary conditions and bone quality from the CTs. The analyses are done under static assumptions but they consider cyclic loads. The simplifications done to the boundary conditions of the femur i.e. the muscular forces, are not the best approach to these type of problems, more relevant muscle forces should be involved in order to have more accurate results. The same considerations should be done regarding ligaments and soft tissues involved in the articulation, but this implies a large deformation approach of the mechanical problem.

Regarding the changes done to the mechanical model in order to integrate it to the biological one, we should mention that it was necessary to redefine some variables that where originally either constant values ($\dot{\rho}$) or dependent only on one variable ($S_v$). These changes imply some instability and were done taking care of the coherence of the results as well as the high non linearity of the mechanical model based on damage mechanics. The coupling of the two models affects the numerical convergence of the analysis since introducing more variables brought more iterations for every increment. Nevertheless this increased calculation time is not dramatic and the convergence of the problem remains stable.

It should be remarked herein that this type of simulation represents a powerful predicting tool for medical doctors but the manipulation of all the parameters involved to create and analyze the model is no longer straightforward. A future goal after quantitative validations of the model should be to develop a friendly interface to make this model more useful for the health sector.

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References


