Computational Analysis Of The Dependence Of Ward’s Area Position With Physical Activity

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I dedicate this Dissertation to Eduarda Maia

Sincerely,
Miguel Machado
Abstract

Evidences between the interaction of Physical Activity (PA) and skeletal modeling and remodeling has been accumulated from hundreds of clinical studies.

One of this studies provided strong evidences that Moderate to Vigorous Physical Activity (MVPA) is positively associated with a central Ward’s area and consequently with a more balanced Femoral Neck (FN) bone mass distribution.

In the present work will be checked if there are reasons to support the result previously obtained through the use of the 3-D finite element method coupled with a pre-validated bone remodeling model whose the law is derived assuming that bone self-adapts in order to achieve the stiffest structure for the applied loads. A multiload environment was considered based on physiologic load cases gathered from the literature. In the bone adaptation model, there are some adjustable parameters, whose values were determined by a quantitative comparison to a biological reality: the weight factors associated with the multiload formulation were related with times measured with an accelerometer from an available database, while the parameters that control the biological expense associated with bone material were adjusted through a quantitative comparison with Dual Energy Radiograph Absorptiometry (DEXA) data from the same database.

The obtained results clearly predicted that as MVPA time increase, Ward’s area decrease in size, acquiring a more central position in the FN at expense of a guided and concerted trabecular rearrangement. Additionally, the results showed that different bone mass distributions are produced using load cases that intend to mimetic the same physical exercise, putting in evidence the subject-specific loading. The results also suggested that benefits obtained from PA occurs most efficiently in cases where there is less Bone Mineral Content (BMC) in the departure femur.

Keywords: Ward’s area; PA; Biomechanics; Bone Remodeling; 3-D Finite Element Method (FEM).
Resumo

Evidências da interacção da actividade física com modelação e remodelação óssea do esqueleto têm-se acumulado em centenas de estudos clínicos.

Um destes estudos forneceu fortes evidências que actividade física moderada a vigorosa está positivamente associada com uma área de Ward central e, consequentemente com uma distribuição de massa óssea no colo do fémur mais equilibrada.

No presente trabalho pretende-se verificar se há razões que sustentem os resultados anteriormente obtidos através do uso do método dos elementos finitos 3-D acopolado com um modelo de remodelação óssea previamente validado, cuja lei é derivada assumindo que o osso se adapta com o objectivo de obter a estrutura mais rígida para as cargas aplicadas. Foi considerado um ambiente multicarga baseado em casos de carga fisiológicos recolhidos da literatura. No modelo de adaptação óssea há alguns parâmetros ajustáveis, cujos valores foram determinados através de uma comparação quantitativa com a realidade biológica: os factores de ponderação associados à formulação de múltiplas cargas foram relacionados com os tempos medidos com um acelerómetro provenientes de uma base de dados disponibilizada, enquanto que os parâmetros que controlam o custo metabólico associado ao material ósseo foram ajustados através de uma comparação quantitativa com dados DEXA provenientes da mesma base de dados.

Os resultados claramente predisseram que à medida que o tempo dispendido em actividade física moderada a vigorosa aumenta, a dimensão da área de Ward diminui, adquirindo uma posição mais central no colo do fémur, à custa de um rearranjo trabecular guiado e concertado. Adicionalmente, os resultados mostraram que diferentes distribuições de massa óssea são produzidas usando casos de carga que pretendem mimetizar o mesmo exercício físico, pondo em evidência a especificidade do ambiente de carga inerente a cada indivíduo. Os resultados obtidos também sugeriram que benefícios obtidos através da actividade física ocorrem mais eficazmente em casos onde existe menos conteúdo mineral ósseo no fémur de partida.

Palavras-Chave: Área de Ward; Actividade Física; Biomecânica; Remodelação óssea; Método dos Elementos Finitos 3-D.
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Abbreviations

PA  Physical Activity
MVPA  Moderate to Vigorous Physical Activity
BMC  Bone Mineral Content
BMD  Bone Mineral Density
BMAD  Bone Mineral Apparent Density
aBMD  Areal Bone Mineral Density
DEXA  Dual Energy Radiograph Absorptiometry
HAL  Hip Axis Length
FN  Femoral Neck
FNW  Femoral Neck Width
FE  Finite Element
FEM  Finite Element Method
ROI  Region Of Interest
THR  Total Hip Replacement
DOF  Degrees of Freedom
BW  Body Weight
SD  Standard Deviation
PO  Postoperative
N  Unit of Newton
BMU  Basic Multicellular Units
SED  Strain Energy Density
CCN  Connected Cellular Network
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1.1 Motivation and Research Goals

Currently it is widely accepted that bone mass is an established determinant of bone strength and that bone mass of an individual in later life depends upon the peak attained during skeletal growth and the subsequent rate of bone loss. Skeletal disorder, as osteoporosis, characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture, represents a relevant social health problem (Canhão et al., 2005). Indeed, recent statistics studies suggested that 1 in 3 women and 1 in 5 men will experience an osteoporotic fracture at some point in their lifetime (Kanis and Johnell, 2005). These figures are set to rise exponentially over the next 40 years as the population ages, and by 2050 the total direct costs of hip fracture in Europe are projected to be € 76.7 billion (Kanis and Johnell, 2005). The incidence of osteoporotic fractures is increasing more than expected from the ageing of populations and this may reflect changing patterns of diet and/or Physical Activity (PA) in recent decades.

Regarding this last factor (PA), it is well known that one method to increase peak bone mass is precisely the PA, namely weight-bearing exercise that generate impact to the skeleton. There are studies suggesting that the years of childhood and adolescence represent an opportune period during which bone adapts particularly efficiently to such loading. Evidences supporting the role of weight-bearing exercise in bone accrual, as the femur bone, and consequently improvement of Femoral Neck (FN) bone strength, has accumulated from cross-sectional, longitudinal and intervention studies, e.g., Dowthwaite et al. (2006), Hind and Burrows (2007), Janz et al. (2007), Burrows (2007), Sardinha et al. (2008), Rizzoli et al. (2010), Meyer et al. (2011), Gracia-Marco et al. (2011), just to cite some.

Much less research however has been done in the way that this bone mass is distributed (namely in the proximal femur) as a function of PA. This is so because most of the clinical research employed photon absorptiometry, which, unfortunately, in many cases, are not very useful for understanding precisely where additional bone has been added or subtracted in response to exercise (Proff and Romer, 2009). Some exceptions include the reports of Kaptoge et al. (2007) and Cardadeiro et al. (2010). The former have shown that the asymmetric distributions of bone tissue in the FN and trochanter have complex relationships to physical activity variables, as well as being affected adversely by ageing. More recent is the latter study, where it was analyzed the FN bone mass distribution by Ward’s area location and its relationship with PA and body composition in 8– and 9– year-old boys and girls. A balanced FN mass distribution, expressed by a central location of Ward’s area suggest a more stable FN and they have found that Moderate to Vigorous Physical Activity (MVPA) was an important predictor variable of this scenario. Thus, the authors of this study brought this problem to our research group (Institute of Mechanical Engineering IDMEC / IST) that through the use of bone remodeling simulations using a pre-validated computational model (Fernandes et al., 2002, Folgado et al. 2004, Coelho et al. 2009, Santos et al. 2010) will try to check if there are reasons to support the results previously obtained. In this model, the bone remodeling law is derived assuming that bone self-adapts in order to achieve the stiffest structure for the applied loads (Fernandes et al., 1999).

If one exclude the work of Hazelwood and Castillo (2007), where a two-dimensional Finite Element
model of the femur was taken and only 3 load cases were considered to simulate the effects of marathon training on bone density, to the author knowledge this will be the first time that a wide range of loads environments will be tested in computational simulations in order to investigate the effect of PA in bone density, since the majority of bone remodeling applications that can be found in the literature have not already explored this aspect.

In this way, one propose to investigate through the use of a bone remodeling model the different bone mass distribution patterns produced in the proximal femur (and consequently the different positions of Ward’s area) under different load environments, namely the ones find in the literature, which intend to mimetic the real mechanical loads that the femur is subjected under different physical exercises. We want to go a little further and verify if the bone remodeling model is useful in designing training programs that could enhance FN mass distribution and thus reduce the fracture risk.

1.2 Thesis Structure

Disregarding the Introduction Chapter, the present thesis is divided into five main chapters: 2 Background; 3 Model of Bone Remodeling; 4 Methodology; 5 Results and Discussion; 6 Conclusions.

In Chapter 2 a mandatory exposition of some fundamental concepts and theory involved in the context of this dissertation is done. It starts with a simple introduction of the anatomy of the Hip Joint structure and its function. Then is described with a little more detail the bone tissue and the femoral inner trabecular architecture, giving a particular emphasis to the Ward’s area and its clinical importance.

Once absorbed these basic concepts, bone remodeling concepts will be introduced and a review of the literature will be presented regarding the dependence of these concepts with PA. The ‘state of the art’ of the assessment and measurement of the latter will also be addressed, wherein the basic principles of accelerometer and instrumented prostheses will be exposed and its advantages highlighted.

In the third chapter (Model of Bone Remodeling) the internal bone adaptation of the proximal femur is considered through the use of computational and mathematical models. An overview of some models that have been proposed is presented and a particular focus on the computational bone remodeling model developed by Fernandes et al. (1999) (from now on The Lisbon Model) is done.

In chapter 4 a very detailed description of the adopted methodology is presented and it will be done in such a way that will allow the reproduction of the results that we will get.

As the name suggest, in the chapter 5 the results to be obtain will be displayed and simultaneously discussed based on the applied methodology, which will be itself discussed too. Based on the results, conclusions will be drawn and some hypotheses will be raised.

Finally, in the last chapter 6 a resume and the main conclusions of this work will be exposed, more research will be advised in certain aspects and future developments will be suggested.
Background

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2.1 Hip Joint Structure and Function ........................................... 6
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2.1 Hip Joint Structure and Function

The general framework of the body is built up mainly of a series of bones - the skeleton. In the skeleton of an adult there are 206 distinct bones that are divisible into four classes, according to their shape: Long, Short, Flat, and Irregular. The bones of the skeleton are joined to one another at different parts of their surfaces, and such connections are termed Joints or Articulations (Gray, 2000).

The hip joint articulation is an enarthrodial or ball-and-socket joint, made up of four bones. That is not obvious when looking at the adult structure which only has two parts: the ball from the femur (long bone) and the socket (acetabulum) from the pelvis. However, a careful look at the pelvis allows to see that it is a composite bone, wherein three bones, Ilium or iliac bone, ishium and pubis, called innominate bones, joint together to create a single functional structure, the acetabulum (Gray, 2000), as can be visualized in Fig. 2.1. Both the femur and acetabulum are covered with a layer of cartilage to provide smooth articulation and to absorb load. The entire hip joint is surrounded by a fibrous, flexible capsule to permit large ranges of motion but to prohibit the proximal femur from dislocation. Several ligaments connect the pelvis to femur to further stabilize the joint and capsule. Muscles and tendons provide actuation forces for extension/flexion, adduction/abduction and internal/external rotation (Anderson, 2007).

Figure 2.1: Left human femur (anterior view) inserted in the hip joint, adapted from Visuals Unlimited (2010).
2.2 Bone Tissue and Femoral Trabecular Architecture: Ward’s Area

Bone or osseous tissue, is a connective tissue, especially designed for support, as this is the main function of the skeleton. It has a complex hierarchical structure which can be analysed at different scales. In a continuous upsizing analysis there are the molecular level (molecular structure of the constituents), the nanometer scale (fibril arrays of collagen and mineral phases), the submicrostructure scale (the intrinsic lamellae structure), the microstructural point of view (Harversian systems, osteons and trabeculae) and the macrostructural (cortical and trabecular bone) (Vaz et al., 2011).

At a nanometer-scale, bone can be compared to a composite material, composed by an organic phase, which is essentially collagen (type I collagen fibers) and also non-collagen proteins and lipids, and an inorganic phase, composed by inorganic material such as carbonated apatite ($Ca_5(PO_4, CO_3)_3(OH)_4$), which presents as small crystals. In dry bone, this inorganic material accounts for almost two-thirds of bone weight, while the remaining weight corresponds to organic material. In fresh bone, water constitutes around 25% of the bone weight, essentially localized inside blood vessels in Harversian canals (Vaz et al., 2011).

The mechanical properties of bone are related with its organic and inorganic material composition: collagen is related to the capacity of bone to absorb energy, i.e. to the toughness, while the mineral phase plays an important role in tissue stiffness. Both bone mineral crystals and collagen undergo biochemical changes with age that diminish their capacity to provide the strength and toughness that bones need (Pearson and Lieberman, 2004).

Taking a femur as an example of a long bone, at a macroscopic structural level, one can observe distinct parts with different characteristics, with trabecular (or cancellous or spongy) zones surrounded or protected by a cortical (or compact) shield (see Figure 2.2).

Moreover, this compact shield has itself an outer membrane, the periosteum, which consist of an outer and inner fibrous layer. The latter has osteogenic potential and allows the bone to enlarge. In
turn, the trabecular bone accounts for the main part (about 70%) of bone metabolism \cite{Proff and Romer 2009}. Since compact and trabecular bone have almost the same elemental composition, the main difference between them lies in their porosity: trabecular bone has a porosity around 80% while cortical bone is denser and has a porosity of less than 6% \cite{Vaz et al. 2011}.

Regarding these two macroscopic parts of bones, both are closely adapted to the mechanical conditions existing at every point in the bone instead of assuming random configurations. It was Koch in 1917 that for the first time did the first apparent correct mathematical analysis of the inner architecture of the upper femur in support of the theory of the functional form of bone proposed by Wolff and also Roux \cite{Gray 2000}. According to Koch, “in every part of the femur there is a remarkable adaptation of the inner structure of the bone to the mechanical requirements due to the load on the femur-head. The various parts of the femur taken together form a single mechanical structure wonderfully well-adapted for the efficient, economical transmission of the loads from the acetabulum to the tibia; a structure in which every element contributes its modicum of strength in the manner required by theoretical mechanics for maximum efficiency” \cite{Gray 2000}.

What many people are unaware is that was Frederick Oldfield Ward (1818 - 1877) himself who first investigated, by 1838, the mechanical properties of the bone and turned his attention to the proximal femur (see Figure 2.2, right). He noted that “It resembles in its mechanical principles a bracket..., in which a is the principal support, and b a cross piece tying a to the wall or column which sustains the whole. It is evident that the piece a contributes by its rigidity, and the piece b by its tenacity, to the support of the weight; in other words, that the weight tends to bend the former, and to stretch the latter” \cite{Lee and Taylor 1999}. Moving from the bracket to the femur, F. O. Ward demonstrated a similar arrangement of trabeculae in compression (rigidity) and tension (tenacity), between which was the triangular space filled with “loose reticular tissue”, the trigonum internum femoris, which was named after him \cite{Lee and Taylor 1999}.

Further progress was then made. The subject of bone adaptation or bone remodeling or even “Wolff’s Law” will be conveniently discussed in the next subsection \cite{2.3.1}. However, should be pointed out that nowadays is generally accepted that the spongy bone of the upper femur is composed of two distinct systems of trabeculae arranged in curved paths: the compressive system and the tensile system. A total of five different groups can be distinguished: the principal compressive, the secondary compressive, the principal tensile, the secondary tensile and the greater trochanter group, as represented in the Figure 2.3.
In general, the trabeculae of the tensile system are lighter in structure than those of the compressive system. Some argue that this difference in thickness is due to different stresses intensities (Gray, 2000).

In turn, and with the trabecular nomenclature introduced, Ward’s triangle, or Ward’s area, can now be defined as space formed near the center of FN by the intersection of three of those trabecular bundles, namely, the principal compressive, the secondary compressive, and the tensile trabecular. This central region, which most physicians and technologists are not familiar (Bonnick, 2009), contain some thin and loosely arranged trabeculae and defines a neutral axis where tensile and compressive forces balances each other. This region seems to be the first location where bone loss starts, usually due to aging and mainly in women in the beginning of menopause. While in healthy people this area tend to be well defined and centrally located, when bone loss becomes significant, it has a tendency to become biased. These facts are interpreted at the expense of standard radiographs, namely the gold standard technique for Bone Mineral Density (BMD) measurement and osteoporosis diagnosis, Dual Energy Radiograph Absorptiometry (DEXA). Regardless the position that Ward’s area can assume, it should lead to an increased susceptibility to fractures when not centered (Cardadeiro et al., 2010). Despite knowing that DEXA data (namely Areal Bone Mineral Density (aBMD)) does not explain per se the femur fracture risk of patients (there are others clinical risk factors, as previous fracture, parent fractured hip, current smoking, glucocorticoids, rheumatoid arthritis, etc - FRAX® tool), it may be particularly important to evaluate the risk of bone fragility.

When assessed using densitometry, Ward’s area is the FN region with the lowest BMD rather than a specific anatomic region and is identified as a square (see Figure 2.4). Its identification with Hologic equipment is made automatically by searching a specific portion of the femoral neck and intertrochanter (2.7 × 3.0 cm) for the minimum point of bone density, and then a fixed area box (10.5× 10.5 mm) is centered around this point. In case of system difficulty in locating an area of minimum density, Ward’s area is centered automatically at the intersection of the femoral midline and the initial position of the bottom edge of the femoral neck box. Since its location is not standardized between subjects, that is, is not always in the same position, usually Ward’s area is not considered useful for skeletal health evaluation by DEXA or for bone research because BMD of this region cannot be compared with a
Nevertheless, determination of the location of Ward’s area contributes to an understanding of bone mass distribution, given that its position, when it is not central, suggests a bone mass distribution imbalance, which can increase the fragility of the bone and thus the risk of fracture.

2.3 Bone Remodeling and its relationship with Physical Activity

2.3.1 Bone Remodeling and Physical Activity

Contrary to common sense, bone is a dynamic tissue that constantly undergoes turnover in order to maintain stability and integrity. This process of bone adaptation under altered load, or bone remodeling/turnover, is generally (inappropriately and unfairly) termed ‘Wolff’s Law’. This “law” is based on Wolff’s observations suggesting relationships (causal in some cases) between static mechanical forces and cortical/cancellous bone “transformations”. In his book (“Das Gesetz der Transformation der Knochen”, The Law of bone remodeling (translation)), published in 1892, Wolff promulgated the Law of Bone Remodelling which now bears his name: “…the law of bone remodelling is the law according to which alterations of the internal architecture clearly observed and following mathematical rules, as well as secondary alterations of the external form of the bones following the same mathematical rules, occur as a consequence of primary changes in the shape and stressing ... of the bones”. However, his analysis was based on a misinterpretation of mechanical data, a rejection of bone resorption and a lack of connection between his observations and the concept of “functional adaptation” (Lee and Taylor (1999) is pointed out that Wolff’s use the term “function” post-dates Roux’s work). According to many authors, was Wilhelm Roux the first who accurately described the adaptation of bone to altered load, so Roux’s ‘Law’ would be a more accurate eponym (Lee and Taylor (1999) Frost (2004) Skedros and Baucom (2007) Pearson and Lieberman (2004)). Thus, and according to historic literature, in 1885, Roux put the trabecular architecture of the proximal femur, as observed by Ward, Meyer, Culmann and Wolff, into a scientific perspective. He advocated that this “transformations” were functional adaptations, governed by “a quantitative self-regulating mechanism” controlled by a “functional stimulus” - in an “adaptation to a function by making use of it”. Details apart, Roux’s explanation of dynamic adaptation of bone architecture in response to altered load is more in keeping with our modern perception of bone remodelling.
Regarding the cellular and molecular mechanism behind the complex process of bone remodeling, two main classes of cells can be distinguished: osteoclasts and osteoblasts. The former is responsible by bone resorption, whereas bone formation is carried out by the latter. Both cells closely collaborate in what is called Basic Multicellular Units (BMU), allowing approximately 10% of bone material to be renewed every year (Proff and Romer, 2009). In addition to these cells, a third kind of cell, osteocytes (specialized osteoblast cells) are considered to influence bone remodeling. Osteocytes, the most abundant cellular component of the bone, have been proposed to be the ‘sensors’ of the bone, triggering subsequent osteoclast differentiation and bone resorption. They exert a negative regulation of osteoblast number and formation of bone by secreting sclerostin.

The achievement of this bone renewal is involved with a variety of molecular and biochemical information (signal pathways, osteoblast-osteoclast communication, osteoclast activation, etc.) that has arisen in the past decade and whose inherent mechanisms details fall outside the scope of this thesis.

Nevertheless, must be said that each remodelling cycle involves four different sequential steps: activation, resorption, reversal and formation (Proff and Romer, 2009) (there are authors that usually divide the cycle in five steps, with the addition of a termination phase, as in Raggatt and Partridge (2010)). Before starting the activation phase, the bone is in a resting phase, wherein bone surface is coated by resting flattened lining cells. Thus, the activation phase consist in the activation of cells that are at quiescent stage. This is done with the recruitment and dissemination of osteoclast progenitors (pre-osteoclasts) to the surface to be resorbed. There, a ligand (RANKL) is expressed by the lining cells, which in turn binds to the RANK that exists as a surface receptor on the membrane of pre-osteoclasts. This binding promotes an intricate and distinct signalling cascade for osteoclast activation. The expression of RANKL is up-regulated in the presence of interleukin-1 (IL-1), tumour necrosis factor α (TNF-α) or vitamin D, whereas transforming growth factor β (TGF - β) or estrogens have an opposite effect (Proff and Romer, 2009).

Then, these differentiated osteoclasts will degrade old bone matrix (resorption phase). Once these cells become adherent to the bone, they form a resorptive front side, attaching the bone matrix. Active osteoclasts are now capable of dissolving bone material, such as mineral hydroxyapatite, by secretion of hydrochloric acid. A V-type ATPase, which is present in the ruffled membrane of osteoclasts, translocates protons into the resorption lacuna and, thus, acidifies the environment (pH ≈ 4.5). In addition, a carbonic anhydrase II is present in osteoclasts to supply the need of protons. Because of demineralisation of bone material, the organic phase of bone becomes more accessible. It is assumed that lysosomal cathepsin K and, to a lesser extent, matrix metalloproteinases, are responsible for the degradation of organic bone matrix (Proff and Romer, 2009).

During bone resorption, a high concentration of calcium is observed in the microenvironment of the resorption site that subsequently inhibits osteoclast activity: the rise of calcium results in a re-organisation and disassembly process that leads to osteoclast apoptosis. Other substances have been reported to promote osteoclast apoptosis as well, such as TGF-β (Transforming Growth Factor-β), estrogens, some kinds of bisphophonats and taxomifen. The (described above) phase that comprise
the discontinuation of bone resorption with osteoclast apoptosis and that in addition includes the differentiation of osteoblast precursors is named reversal phase (Proff and Romer, 2009).

Once a small area of bone has been resorbed, osteoblasts move in to rebuild the bone in that area (formation phase). Osteoblasts become probably activated by secretion products from osteoclasts (like sphingosine 1-phosphate (S1P), myb-induced myeloid protein-1 (mim-1), a B polypeptide chain platelet-derived growth factor homodimer (PDGF-BB) and a hepatocyte growth factor (HGF)). After activation, osteoblasts lay down new bone material (i.e. collagen type I, osteocalcin, osteopontin, etc.) until the resorbed bone is entirely replaced by a new one. Osteoblasts that become encased in the new bone matrix during bone formation are transformed to osteocytes, while the osteoblasts that become quiescent at the end of bone remodelling form flattened lining cell on the bone surface until a new remodelling cycle is triggered (Proff and Romer 2009).

Other important subject is the way that bones sense mechanical loading and respond to it. The bone, as a complex tissue that it is, has the primordial function of be stiff in response to loads. These loads generates stresses of varying intensity, which produce strains of varying magnitude and mode. The process by which cells sense mechanical stimuli in their external environment and then translate the information into a signal that can potentially elicit some response is called mechanotransduction, which is the least understood stage of bone adaptation. As mentioned above, the hypothesis that has received most attention and support is the one that advocate that osteocytes act as strain receptors and transducers, and probably through several mechanisms. One of the proposed mechanisms is that osteocyte sense shear stress. Osteocytes are filled with fluid that is displaced every time a bone deforms, and the cells appear to be quite sensitive to pressure changes from these flows, inducing prostaglandin and nitric oxide production (which are inhibitory signal of bone resorption) and triggering communication at gap junctions (Proff and Romer 2009). Also related to prostaglandin and nitric oxide, some researchers thinks that they can be produced by osteocytes in response to mechanical stimulation (Proff and Romer 2009). So, it is argued that either diminished loading or microcracks can diminish the inhibitory affect, allowing the lining cells to activate osteoclasts and thus leading to bone resorption. Yet other mechanism suggest that the interstitial fluid flow generated by loading is crucial for generating rapid diffusion of oxygen and nutrients to osteocytes. Thus, a lack of loading may cause an withdrawal of that substances and consequently to osteocyte apoptosis that may lead to bone resorption (Proff and Romer 2009). Some innovative hypotheses as also been proposed, like the one done by Pavalko et al. (2003), wherein is presented a specific biomechanical model, in which strains ultimately lead to changes in gene expression in bone cells. It is the model in which “bending bones ultimately bend genes”.

Now we focus our attention to the osteogenic potential that [PA] have in humans, namely the capability that it seems to have in influencing the Bone Mineral Content (BMC) of bones. Evidences between the interaction of exercise and skeletal modeling and remodeling has been accumulated from hundreds of clinical studies. Indeed, clinical literature in this field reveals a variety of interesting things, whose the most important in the scope of this thesis will be mentioned bellow, based in two very complete and recent reviews carried out by Pearson and Lieberman (2004) and Rizzoli et al.
First, besides the variance of peak bone mass is likely influenced by factors amenable to positive intervention, such as adequate dietary intake of dairy products as a natural source of calcium and proteins, vitamin D, and regular weight-bearing PA is important to bear in mind that the majority of this variance of peak bone mass is due to genetic factors (between 60% and 80%) (Rizzoli et al., 2010), so one can not expect to find generally very big differences in, let’s say, BMC in the FN between two samples with very different exercise regimes, for example (Figure 2.5).

Figure 2.5: Determinants of peak bone mass. Genetics account for 60% to 80% of the peak bone mass variance (reproduced from Rizzoli et al. (2010)).

Other fact that has been observed is that the type, intensity, frequency and duration of exercise may influence the outcome. As an example, dynamic loading may be more effective for increasing aBMD than static loading and strain may be more important than the number of loadings. In Rizzoli et al. (2010) is concluded that on the whole, most studies reported that increasing weight-bearing PA have the potential to improve and sustain bone health and protect against fractures during childhood, adolescence and later in life. In Pearson and Lieberman (2004), although some studies produced exceptions, the majority showed that high-impact sports produce the highest BMD, particularly sports that involve sprinting or other short-duration and high-intensity forms of exercise, like jumping, soccer and gymnastics. On the other hand, lower impact endurance sports produce lower BMD. Swimming, for example, which involves strenuous but prolonged exertion in a very low-impact environment (water), did not produce markedly elevated BMD.

Evidences for interactions between age and loading on bone adaptation have also been documented. Since the mid-1990s, it has become increasingly apparent that there are substantial age-related differences in the body’s ability to increase BMD in response to exercise. In girls and boys, the adolescent growth spurt, especially its early stages, appears to be a major window of opportunity to build bone, while exercise in adulthood after the skeleton has matured appears to make less impact on skeletal. An interesting find is that it seems that much of the bone mass that adults add as the result of beginning an exercise regimen is rapidly lost after the exercise program ends. It has also been documented that there are low but significant correlations between historical activity and BMD and that the effects of exercise in older adults can act to slow the rate of bone loss, primarily by downregulating osteoclastic activity, but it is much less effective than exercise earlier in life in triggering osteoblastic activity.

It can be crudely summarized that the main finding from studies of BMD is that bone respond to mechanical loads from exercise in all the stages of life span, but they undergo a profound decline.
with age in their responsiveness to PA. Thus, the time around the growth spurt constitutes the most sensitive period for building bone mass in both boys and girls. In this way, peak bone mass acquired through bone mineral accrual during childhood and adolescence may be a key determinant of bone health and future fracture risk during adulthood. This idea is complemented with the graphic below (Figure 2.6), wherein can be seen that small differences in the BMD peak (± 10% of the mean), achieved during childhood and adolescence, have marked differences in the age at which it will appear osteoporosis (more than 10 years apart).

![Figure 2.6: Simulation of the influence of peak BMD on the age at which BMD may reach the diagnostic threshold for osteoporosis (reproduced from Hernandez et al. (2003)).](image)

### 2.3.2 Physical Activity Assessment: Accelerometer and Instrumented Prostheses

After exposing the positive effects that exercise has on BMC accrual, it’s time to turn attention to how different intensities of PA and the time spent on them can be measured. Over the last times, a lot of important advances have occurred in the field of PA assessment. Perhaps the most notable of these developments has been the proliferation of accelerometer-based activity monitors that provide real-time estimates of the frequency, intensity, and duration of free-living PA (Stewart G. Trost 2005).

Accelerometers are devices that measure body movements in terms of acceleration, which can then be used to estimate the intensity of PA over time. Most accelerometers in current use are piezoelectric sensors that detect accelerations (usually measured in gravitational acceleration units g, 1 g = 9.8 ms\(^{-2}\)) in one (unidirectional) to three orthogonal planes (omnidirectional). The conformational changes of these sensors, due to acceleration, generate a variable output voltage signal that is proportional to the applied acceleration. The rate of data acquisition is determined by the sampling frequency of the monitor computer. This sampling frequency must be at least twice the frequency of the highest frequency of movement to ensure that the full range of human motions are captured independently (Nyquist criterion). The sampling frequency for commercially available PA monitors generally range from 1 to 64 Hz. After data sampling, the signal is filtered using a band pass filter with cut frequencies somewhere between 0.25 and 7 Hz. This type of filtering increases the linearity of the output (measured acceleration) with respect to the true signal (body acceleration). After being filtered, the
signal is usually amplified. After that, this voltage signal is sampled at a prefixed frequency by the device to convert the analog voltage signal to a digital series of numbers (A/D conversion), which are called ‘raw counts’. The amplitude of this digital signal (‘raw counts’) is determined by the system hardware including the analog voltage, the amplification factor, and the A/D conversion factor. This ‘raw counts’ is bidirectional, i.e., include positive and negative numbers. These data are thus converted only in positive values by full-wave rectification (which convert the negative counts into positive ones) or by taking only the positive side (half-wave rectification). After these digital data strings reach the processor (microcomputer chips), different analytical approaches can be applied. The most commonly applied method is the digital integration or average algorithm, in which the ‘raw counts’ is summed for each given time window (an epoch, normally 1 min). The end result is often called the PA counts \( K_{\text{ong Y. Chen}, 2005} \).

It should be pointed out that the choice of this time window is particularly important, since the time period over which accelerometer counts are averaged can affect the interpretation of data. If a short epoch is used, it yields to a higher resolution of bout durations, which may be important if PA is accumulated in multiple short bouts, probably the most likely scenario observed in MVPA. On the other hand, a disadvantage of short epochs is that the energy expenditure associated with 10- to 30-s epochs has little physiological value. Choosing a longer epoch has the normal data-smoothing advantage of time averaging. The main drawback is that if a long epoch contains a mixture of two activities of different intensity, then the data will be averaged to reflect an intermediate intensity. If the bout of a higher intensity PA within a particular epoch is shorter than the width of the epoch, the averaged PA count for the epoch will be lower than the actual PA intensity. This can lead to misclassifying higher intensity PA that are more intermittent into moderate or light categories. These hypothetical cases are well represented in the Figure 2.7, where can be seen that besides the very different intensities of PA within the time window, the final output (counts) will be the same.

![Figure 2.7](image-url) Three sets of arbitrary data vectors (20 points each) with the same digital integrated output, but very different SD (reproduced from Kong Y. Chen (2005)).

Thus, there is a trade-off between choosing shorter versus longer epochs. For most applications, 1-min epochs appear to be a reasonable compromise Kong Y. Chen (2005), but some authors warn
that the use of count cut points based on 1-min time intervals may be inappropriate in children and may result in underestimation of PA (Stewart G. Trost, 2005).

Once one have these counts per epoch time, the total amount of PA can now be expressed as total counts divided by registered time (counts/min), which is an indicator of the total volume of PA. Moreover, if one use certain cut points to identify sedentary, light, moderate, and vigorous physical activity (these cut points are previously validated through different methods/criterions), one can calculate the numbers of minutes that a person spent in activity of different intensities per day.

Currently used accelerometry PA monitors can be separated into two generations: the first generation (current technology) and the second generation (emerging technology) (Kong Y. Chen, 2005).

The first generation consist of a single accelerometer placed on the waist (the most common position because it is closest to the center of body mass) or on an ankle or wrist. The advantages of this first class of accelerometry devices include their small size and the fact that they are wireless, noninvasive, and minimally intrusive to normal subject movements during daily activities. On the other hand, they also have some limitations, like the lack of potential to detect postural changes and slow motions. These limitations are overcome with the next generation of monitors, which have implemented two separate strategies: they use multisensor arrays applied at different body segments and they combine accelerometry with physiological sensor(s) in a single site device. However, these multiple-site monitors contain several wires, are not available outside the developing labs, and are expensive, all of which make them difficult for investigators to validate or apply in their field research (Kong Y. Chen, 2005).

Despite accelerometer allows the continuous assessment of PA intensities and time spent on it, they can not measure muscle and joint forces, the two types of loads that can be encountered when a musculoskeletal joint system is engaged during exercise. Actually, the quantification of these two loads are a fundamental pre-requisite when the goal is to study bone adaptation, namely through the method of FE.

Over the past decades, several analytical and experimental techniques have been developed and tested for determining and measuring these forces. Most of the studies of the muscle and joint forces are computational, and besides the improvements of computer technology it is still difficult to calculate the loads acting in human body (Need H. C. Hwang, 2003). As mentioned by Taylor and Walker (2003), while calculated results have the advantage that they can be applied to any number of subjects, the assumptions concerning relative muscle action and direction, joint contact points, and other factors, lead to uncertainty in the data. Precise in vivo data constitute not only a more accurate measure of these forces than do mathematical musculoskeletal models, as well it may help to make such computer simulations more realistic (Orthoload-Team, 2012). With in vivo data we mean data from telemetric devices in orthopedic implants (instrumented prostheses), which produce direct and valid measurements of loads applied in implants (Taylor and Walker, 2001).
Several studies have reported the application of telemetric devices in orthopedic implants. In 1966, Rydell introduced a strain-gauge hip prosthesis cable-connected to the external measuring equipment. Other groups subsequently used instrumented implants for in vivo measurements of loads acting in the hip, knee and shoulder such as, Davy et al., 1998; Bergman et al., 1993, 1995, 1998, 2001 and Taylor et al., 1998 (Graichen et al., 2007).

In this area, an important work has been carried out by Georg Bergmann, Josef Siraky and Friedmar Graichen from the Biomechanics Laboratory of the Free University of Berlin. They started in the early 1980th a research project with the goal of directly measuring the contact forces acting in implants, namely hip implants (see Figure 2.8). These measuring techniques have been permanently improved and today a relatively large number of forces of different daily activities are available free and online (Orthoload-Team 2012). The micro-electronics developed for this purpose allows to measure the contact forces acting in the joint for an unlimited time. The loads are transmitted by a telemetry at radio frequency from inside the body and received by an antenna. They are processed in a computer and directly displayed on a monitor. A full documentation of the measurements is thus provided, which includes the three components of the contact force (and in some cases the moments) for all the frames of the cycle activity, as well videos, images, animations and some informations about the patients (Orthoload-Team 2012). In addition, this same group provide the muscle forces acting in the intact femur for a ‘typical’ patient. However, this data is only available for two types of exercises: stair climbing and walking at 4 km/h. Thus, if one intend to simulate other types of exercises, some assumptions have to be made. Notice that the use of these in vivo data in intact bones assumes that an healthy person and one with an implant have the same motor behaviour (which may not be true), as well disregard the subject-specific loading that can be attributed to the differences in gait kinematics and gait kinetics by the use of a standard set of load conditions (Jonkers et al., 2008).
3

Model of Bone Remodeling

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3.1 Overview

As seen in the previous section, the process of adaptive bone remodeling is a complex mechanobiological phenomenon, a concept dating back to Roux. Several general descriptive models as well as a number of predictive equilibrium and optimization models were proposed in order to explain bone adaptation in response to mechanical loading (Pearson and Lieberman (2004), van der Meulen and Huiskes (2002)).

Each model makes its own mathematical formulations and assumptions, which are simulated in computers, usually integrated with the Finite Element Method (FEM). In fact, computer simulations have been cited not so long ago as the ‘third method of science’, after logic and experimentation (van der Meulen and Huiskes, 2002).

Most existing models, for simplicity, assume that the bone is isotropic, and are used to predict only the density distribution in bone. This assumption is inaccurate, since it is accepted that trabecular bone is effectively orthotropic (Baca et al. (2008), Miller et al. (2002), Antonio et al. (2011)). Most of these models are based on the hypothesis that bone adapts its structure such that a local stimulus will always tend towards a ‘target’ stimulus. The stimulus is a certain measure of the local stresses or strains (usually used is the strain energy density) due to mechanical load, and accordingly, only a single scalar is used to describe the stimulus that is received in each sensor. To overcome this, there are models that did not assume isotropy, and are based on a global optimization criteria, as the one that will be presented here. These models assume that the bone is an optimal structure and an optimization problem (minimal compliance subject to a constraint of given mass, for instance) is solved to predict bone density distribution and (oriented)-orthotropy. They have thus the advantage that is a clear statement of what bone is optimal for, contrary to the local models (Miller et al., 2002). However, it can be shown that some global models, like the one that will be explored in this thesis, when converted to the local level, relates to other known local criteria (Fernandes et al., 1999).

A relatively detailed description of the global optimization model used in this work is given below.

3.2 The Lisbon Model

The Lisbon Model is a bone remodeling model based on structural topology optimization, developed by Fernandes et al. (1999), in which bone tissue is formulated as a porous continuous and elastic material, with variable relative density \( \mu \) and periodic microstructure. Such a material is obtained by the repetition of cubic cells with prismatic holes with dimension \( a = (a_1, a_2, a_3) \).

The relative density \( \mu \) at each point depends on local hole dimensions and is given by \( \mu = 1 - a_1a_2a_3 \). This porous material is strictly orthotropic.

Regarding the orientation of these closed units cells, it is given by the Euler angles \( \theta = (\theta_1, \theta_2, \theta_3)^T \) (see Figure 3.1).
One have, thus, two different parameters sets for each cell unit, $\mathbf{a}$ and $\theta$. These project variables, when coupled, actually implies solving two different optimization problems, which allows the consideration of an optimal orientation of unit cells and consequently, the simulation of a bone as an oriented material. However, since in this work one are interested only in study bone density distribution, the orientation will be disregarded.

The topology optimization problem is in its traditional conception a discrete problem, where the objective is to identify regions filled with material and empty. Moreover, in this type of problems, the total available amount of material is known \textit{a priori} and is distributed in order to yield the stiffer structure. This fact constitute a drawback when one intend to simulate bone adaptation, since bone is an open system with respect to mass, as we saw in the previous chapter. Thus, some alterations were done by Fernandes et al. (1999) regarding the traditional formulation of structural optimization problems. First, the introduction of a material with variable relative density permits formulation as a continuous material optimization problem. Consequently, $a_i$ ($i = 1, 2, 3$) is a continuous function defined in the interval $[0, 1]$ and so, $\mu$ also $\in [0, 1]$. The limiting cases $\mu = 1$ and $\mu = 0$, corresponds respectively to full material and void. Second, to overcome the volume constraint (or mass constraint), it was replaced with an additional term in the objective function. This term can interpreted as the metabolic cost to the organism of maintaining bone tissue. The value that this term can assume is highly dependent on one parameter to be specified \textit{a priori} by the user (parameter $k$, which would include biological factors such age, hormonal status, disease, and so on). The elastic mechanical properties are computed by the homogenisation method (Fernandes et al., 1999). This model assumes that trabecular bone tissue has the same material properties as cortical bone (the true mineral density tissue is approximately constant). So, cortical bone can be seen as the material base. Thus high relative densities $\mu$ will correspond to cortical bone and vice-versa. The density boundary between these two macroscopic classes of bone is not clear and changes from bone to bone. This aspect will be
discussed later.

With respect to the mathematical formulation, let us consider bone to be a linear elastic solid occupying a volume $\Omega$, with boundary $\Gamma$, subject to a set of load cases defined by volume and surface loads $\mathbf{b}^r$ and $\mathbf{t}^r$, and the corresponding displacement fields $\mathbf{u}^r$ (see Figure 3.1). Using a multiple load optimisation criterion, the problem can be stated as:

$$
\min_{\mathbf{a}} \left\{ \sum_{r=1}^{P} \alpha^r \left( \int_{\Omega} b_i^r \mathbf{u}_i^r \, d\Omega + \int_{\Gamma_i} t_i^r \mathbf{u}_i^r \, d\Gamma + k \int_{\Omega} \mu^m(a) \, d\Omega \right) \right\} 
$$

(3.1)

subjected to:

$$
0 \leq a_i \leq 1, \, i = 1, 2, 3,
$$

(3.2)

$$
\int_{\Omega} E_{ijkl}^H(a) e_{ij}(\mathbf{u}^r) e_{kl}(\mathbf{v}^r) \, d\Omega - \int_{\Omega} b_i^r \mathbf{v}_i^r \, d\Omega - \int_{\Gamma_i} t_i^r \mathbf{v}_i^r \, d\Gamma = 0, \quad \forall \mathbf{v}^r = 0 \text{ and } \mathbf{u}^r = 0 \text{ on } \Gamma_u,
$$

(3.3)

where $P$ is the total number of applied load cases and $\alpha^r$ are the load weight factor with respect to the load case $r$. The multiple load formulation allows considering different load cases corresponding to various types of daily life activities that body structures are often exposed to. Thus, each load case should represent an instant of a certain load environment that the femur is exposed to when performing a certain physical exercise. It is obvious that the greater the time a person spends in one particular exercise, the greater should be its respective weight factor. If it is known the times that a person spends in a given activity throughout the day, then it can be established a correspondence between weight factor and time (in minutes), taking into account that $0 \leq \alpha^r \leq 1$. Usually the weights factors are normalized such that they sum up to 1 ($\sum_{r=1}^{P} \alpha^r = 1$). It is not however necessary the fulfilled of this condition.

The Equation 3.1 is the objective function to be minimized, while Equation 3.3 corresponds to the set of equilibrium equations, in the form of virtual displacement principle. In this equation, $E_{ijkl}^H(a)$ is the homogenised material properties (the superscript $H$ denotes homogenised) of the porous material, $e_{ij}$ is the strain field and $v_i^r$ the set of virtual displacements. As mentioned before, the parameter $k$ in the objective function is the metabolic cost associated with a unit of bone volume. Since it is known that even in the presence of identical loading environment the remodeling response may differ from individual to individual, this parameter should be seen as the one that lets contemplate the inter-individual biological variability. Some attempts have been done to calculate the parameter range that produces physiological results, as will be seen in the next section. The parameter $k$ is constant in all the areas of the bone, i.e., it is not assumed that different areas in the bone can have different metabolic costs associated with a unit of bone mass, although there are some evidences that bone, at different locations, maintains dissimilar strain thresholds for initiating modeling (Proff and Romer, 2009).

Regarding the parameter $m$, it do not belong to the first model formulation (was introduced subsequently) and its handling allows one to offset the metabolic cost as a function of density. The study of this parameter (as well others parameters of the model) will be cover subsequently.
For the resolution of the optimization problem formulated by Equations 3.1-3.3 is used a lagrangian method. The law of bone remodeling results from the stationarity condition of the Lagrangian method with respect to the design variable $a$, and is stated, in a local form, by the optimal condition:

$$
\sum_{r=1}^{P} \alpha^r \frac{\partial E_{ijkl}^{H}}{\partial a} e_{ij}(u^r) e_{kl}(u^r) + k \frac{\partial \mu^m}{\partial a} = 0,
$$

(3.4)

where $u^r$ is the displacement field at equilibrium.

As briefly mentioned above, the elastic properties of this material are calculated using asymptotic homogenization methods, from the theory of homogenization, that has the advantage of being a rigorous mathematical theory. In this particular case, the big purpose of this method is to find some kind of material model that should characterize the average mechanical behaviour of the macroscopic bone, as well as represent the effect of the composite material heterogeneities. It is assumed that the cell units when compared with the overall bone are very small (microscopic). In other words, it is assumed that the material properties are periodic functions of the microscopic variable, where the period is very small compared with the macroscopic variable. This assumption enables the computation of equivalent material properties by a limiting process when the microscopic cell size is reduced to zero. A fairly detailed description of the method fall outside the scope of this thesis, but, nevertheless, it can be found in [Guedes and Kikuchi 1990], as well in [Fernandes et al. 1999] (but less detailed).

It is assumed that the design variables $a_i$ are constant within each FE, which allows to write the optimality condition independently for each element. The solution can then be obtained with an iterative procedure based on a first order Lagrangian method. The formulae to update the cell design variable at the $k^{th}$ iteration are:

$$
(a_i^e)_{k+1} = \begin{cases} 
max[(1 - \zeta)(a_i^e)_k, 0] & \text{if } (a_i^e)_k + s(D_i^e)_k \leq max[(1 - \zeta)(a_i^e)_k, 0], \\
(a_i^e)_k + s(D_i^e)_k & \text{if } max[(1 - \zeta)(a_i^e)_k, 0] \leq (a_i^e)_k + s(D_i^e)_k \leq min[(1 + \zeta)(a_i^e)_k, 1], \\
min[(1 + \zeta)(a_i^e)_k, 1] & \text{if } min[(1 + \zeta)(a_i^e)_k, 1] \leq (a_i^e)_k + s(D_i^e)_k.
\end{cases}
$$

(3.5)

where $e$ ranges over all the finite elements and $i = 1, 2, 3$.

In the previous update scheme, the scalar $D_i^e$ is the negative of the Lagrangian gradient with respect to design variable $a_i$ at the $k^{th}$ iteration and is given by:

$$
D_i^e = \sum_{r=1}^{P} \alpha^r \frac{\partial E_{ijkl}^{H}}{\partial a_i} e_{ij}(u^r) e_{kl}(u^r) - k \frac{\partial \mu^m}{\partial a_i}
$$

(3.6)

The parameter $\zeta$ defines the active upper and lower bound constraints. This is so because the bone structure cannot change without limit in a time step. Thus a maximum change in bone mass has to be specified (limited bone turnover rate). A fixed value of 0.75 was chosen. The real number $s$ is the step length, chosen to be constant and selected by the user at the beginning of the process.

Computationally, the model is described by the following steps: initially, the homogenized elastic properties are computed for a prescribed initial solution $\mu_0$. Then, the set of displacement field, $u^r$, is calculated by FEM using software ABAQUS® (solution of equilibrium equation 3.3). Based on the displacement field FEM approximation, the stationary condition presented in Equation 3.4 is checked.
If satisfied (equal to zero) the process stops, which means that no remodeling will occur (remodeling equilibrium). This corresponds to the solution of the problem, which is the optimal distribution of bone density (the one where the bone is stiffer to the applied loads). If not satisfied, improved values of the design variables are computed using formulae 3.5 and the process restarts. The flowchart of the process is shown in the next Figure:

![Figure 3.2: Computational Model flowchart.](image)

### 3.2.1 Model Validation

The Lisbon Model, since it was developed in 1998, has continuously been used to try to capture some aspects of bone adaption to specific scenarios such as the use of prosthesis and osteoporosis. For example, in [Fernandes et al. (2002)](#), the model was capable to predict bone ingrowth in an implanted femur. The prediction of the model was consistent with clinical observations. In [Folgado et al. (2004)](#), a study was presented to evaluate the capacity of the model (with some extensions, as the inclusion of open cells units and not only closed cells units, as the ones presented here) to assess bone quality in presence of bone mass loss. It was shown, for a simplified model of a human vertebra, that the orthotropy of trabecular bone change in order to maintain bone integrity, a plausible scenario to happen with the trabeculae in vivo. In [Coelho et al. (2009)](#), an extension regarding the model presented above was made, where it was presented a hierarchical approach of bone apparent density and trabecular structure. The model was able to provide an apparent density distribution that fairly approximates the real femur at macroscale. The numerical results of compact bone also agreed with experimental measures. Finally, In [Santos et al. (2010)](#), a quantitative comparison of the remodeling model with DEXA data was made. A range of k values was found that leads to biological relevant results.
4
Methodology

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4.1 Finite Element Modelling

The bone remodeling model presented in the previous chapter was applied to a three-dimensional FE model of the proximal femur, the “Standardized Femur” model (large left femur, mod. 3310, Pacific Research Labs, Vashon Island, WA, USA), proposed by Viceconti et al. (1996) in order to allow the inter-laboratories replication of numerical studies, making evidences from numerical studies more ‘reliable’. For the purposes of this study, only the upper extremity is considered; the lower extremity will thus be disregarded henceforth.

The FE mesh (see Figure 4.1), corresponding to the discretization of the proximal femur geometry, is constituted by 12408 linear hexahedral elements of type C3D8 (three dimensional 8-node solid elements, also known in the FE literature as bricks), which makes a total of 13775 nodes and therefore 41325 Degrees of Freedom (DOF) (3 DOF per node).

![Figure 4.1: Three-dimensional FE model of the proximal femur and surfaces (in red) were loads will be applied. The axis +z points upwards, the axis +x points laterally and the axis +y is directed posteriorly. a) The chosen femoral head area (red surface); b) The chosen trochanteric area (red surface).](image)

It is known that FE models should be sufficiently refined to accurately represent the geometry and mechanical behaviour of the bone structure they simulate. Results are mesh sensitive and ideally convergence tests (comparing nodal displacements and/or total strain energy, or stresses and strains) should be performed to evaluate the model accuracy [Marks and Gardner, 1993]. However, because a pre-generated mesh that do not allow modifications was used, convergence testes were not performed. Nevertheless, Ramos and Simoes (2006) have done a study to assess the influence of mesh density and element type in exactly the same proximal femur model used in this work. They verified that no significant differences exist using refined meshes with more than 20000 DOF for hexahedral elements, which following Stolk et al. (1998) is the minimum necessary to obtain the convergence of the mesh for the proximal femur structure. The results obtained by Ramos and Simoes (2006) did not evidence significant differences too between 1st and 2nd order hexahedral elements, fact referred by Cifuentes and Kalbag (1992) for various other structural problems. Therefore, one can conclude that the mesh density and element type used here will not constitute a drawback in the results to be obtained.

It is important to point out that in our FE model, each hexaedron has a mean volume of $0.175 \pm$
This non-uniformity of the mesh, which is evident by noticing that the SD is far from zero, will be important and will be discussed in the next section.

The absolute densities were computed from Bone Mineral Apparent Density (BMAD), defined in $[0,1]$, multiplying it by a factor of 2, in accordance to a recent review carried out by Helgason et al. (2008). In this sense, the absolute densities range from 0 to 2 ($g/cm^3$). In this same review, is seen that among studies, the thresholds that separate soft tissues, trabecular bone and cortical bone are substantially different one from the other and depend on the site of the skeleton which they relate. Nevertheless, one have assumed that $0.075 \leq \text{relative trabecular volumetric BMD} \leq 0.225$, or equivalently, by using the factor of 2, $0.15 g/cm^3 \leq \text{absolute trabecular volumetric BMD} \leq 0.45 g/cm^3$, in accordance to Manske et al. (2009).

It was assumed too that the Young’s modulus $E$ and the Poisson’s ratio $\nu$ for the base material (the true density mineralized tissue) is 20 GPa and 0.3 and that it is equal in trabecular and cortical bone (it is indeed approximately constant) (Santos et al. (2010), Coelho et al. (2009)).

4.1.1 Boundary Conditions: Constraints and Loads

Simulation of bone physiological boundary conditions is of considerable importance and has important consequences for simulations that study bone remodelling. There has been considerable debate in the literature as to how the femur should be loaded. The majority of experimental and analytical studies assume the femur to be simplistically loaded, with the application of just a joint reaction force or the joint reaction force plus the abductors (Simoes et al., 2000).

For the first time Speirs et al. (2007) have proposed a method for constraining the femur in a FE model that produces physiological deflection of the femoral head under a physiologically based constraint configuration, the “Physiological Case”. This configuration consist in a “complex” set of all muscle and joint forces from a pre-validated musculoskeletal model (Heller et al., 2001), resulting in a balanced force and moment system, and an approximate physiological constraints at the knee and hip, referred to as “joint” constraints (see Speirs et al. (2007) for further details). In addition, they have studied the influence of various commonly used boundary conditions for comparison with the previous one, namely a “Simplified Case”. The latter include a hip contact force, an abductor force and a fully constrained three nodes at the mid-diaphysis. They have shown that the strains profiles on the femur cortex varied considerately under these boundary conditions, mainly in the diaphyseal part of femur. However, the main principal strains obtained in the proximal part of the femur (which is precisely the part of the femur that we intend to study) under the physical activities considered (walking and stair climbing) were quite similar for all the boundary conditions configurations. A similar study was done by Stolk et al. (2001) but in a cemented total hip reconstructions with a bonded and debonded femoral stem. The stress/strain distributions within the reconstruction, produced by the hip-joint contact force, were compared to ones produced after sequentially including the abductors, the iliotibial tract and the adductors and vastii. The results showed that the inclusion of the abductors had the most pronounced effect and the additional inclusion of the iliotibial tract, the adductors and the vastii produced relatively small effects during all gait phases, thus suggesting that a loading configuration
including the hip-joint contact force and the abductor forces can adequately reproduce in vivo loading of cemented total hip reconstructions in preclinical tests.

The small differences obtained in the proximally cortex under the different boundary conditions configurations, combined with the fact that, to the author knowledge, a validated and balanced set of loading conditions is available only in [Heller et al. (2001)] and just for walking and stair climbing (we are interested in considering other physical activities) have contributed to the choice of the boundary conditions that will be considered in this work: a boundary condition case similar to the “Simplified Case” presented above, with each load case comprising a hip contact force, abductors muscles forces (which include the gluteus maximus, medius and minimus, and the tensor fascia lata) and constraints in the mid-diaphysis.

Thus and firstly, in order to prevent the rigid body motion, it was adopted the strategy that is represented in Figure 4.2.

**Figure 4.2:** Location of the constrained nodes (in red) at the mid-diaphysis: a) 145 nodes with the constraint $U_z = 0$; b) 2 nodes with the constraint $U_y = 0$; c) 2 nodes with the constraint $U_x = 0$; $U_x$, $U_y$, and $U_z$ means the displacement in the x, y and z direction, respectively.

Therefore, we have 141 nodes, each one constrained in 1 DOF and 4 nodes, each one constrained in 2 DOF, giving a total of 149 constraints. Note that the total number of DOF of the system has now decreased from 41325 to 41176.

With respect to the loading conditions, 2 different general surfaces were considered, one in the femur head (Figure 4.1 a) and the other in the trochanteric area (Figure 4.1 b), with surfaces areas of 10.75 cm² and 16.33 cm², respectively. Loads were applied as distributed over a surface, giving a better physiological representation of the reality (since it is known that neither the muscle forces nor the hip contact forces acts in single points) and avoid creating unphysical/stress-concentration effects ([Wagner et al. (2010)]).

Regarding the trochanteric area, it correspond to the surface where a vector-sum of all the abductor muscles forces will be applied. Once known the values of the 3 components of this force, it is just needed to divide this values by the area of the trochanteric surface and insert the values into Abaqus® as surface traction.

Another 2 methodologies were however used to simulate the hip contact forces, since can be of interest to apply forces not uniformly distributed over the head of the femur. The first one take advantage of an option (Distributing Coupling Constraints, namely The Surface-based Coupling Constraint, introduced with ABAQUS®/Standard Version 5.8) that offer general capabilities in controlling loads.
transmission. The *Distributing Coupling Constraints* in Abaqus® provides coupling between a reference node and a group of nodes referred to as the “coupling nodes” that lies in a given surface (see Figure 4.3).

![Figure 4.3: Surface-based Coupling Constraint in the femur head: Reference node (yellow star) and the surface where lies the “coupling nodes” (in violet).](image)

Distributing coupling constraints the motion of the “coupling nodes” to the translation of the reference node and enables control the transmission of loads through weight factors at the coupling nodes. The default distributing weight factors, used to define the force distribution, are calculated automatically, based on the tributary area at each coupling node (or tributary edge length along a shell edge). Note that because of this, the results of the distributed forces will be dependent on the uniformity of the mesh. As already mentioned in the section 4.1 the used mesh is non-uniform, namely in the area of the femur head where the loads will be applied. Consequently, it is not possible to obtain for instance an uniform distributed load. To verify this fact, a single load case (walking activity) based on the data reported in [Heller et al. 2005] was used. One can see that the result Contact Surfaces Stresses $S_{Pressure}$ (an Abaqus® output variable), given by Eq.4.1 ([Russell et al. 2006](#)) is the expected one and thus not desired (see Figure 4.4 b).

$$S_{Pressure} = \frac{1}{3} \sum_{i=1}^{3} \sigma_{ii}, \quad (4.1)$$

where $\sigma_{ii}$ is each of the 3 principal stresses.

It is also possible modify the default weight distribution defined above. Various weighting methods are provided that monotonically decrease with radial distance from the reference node. For each case the default weight distribution that is based on the tributary surface area is scaled by the weight factor.

A linearly decreasing weighting scheme is given by Eq.4.2 while a quadratic polynomial weight distribution is defined by Eq.4.3, where $w_i$ is the weight factor at coupling node $i$, $r_i$ is the coupling node radial distance from the reference node, and $r_0$ is the distance to the furthest coupling node (see [Abaqus Manual](#) for further details).

$$w_i = 1 - \frac{r_i}{r_0}, \quad (4.2)$$

$$w_i = 1 - \left(\frac{r_i}{r_0}\right)^2, \quad (4.3)$$

If the weighting method is not specified, a uniform weighting method is used in which all weight factors are equal to 1.
The non-uniformity is evident if one observe that the surfaces areas of the elements near the reference node are smaller comparing with those that are farther from the center. Thus, this fact counterbalances the linear and quadratic weighting method and the final result is still not the desired (see Figure 4.4 c and d).

Figure 4.4: Different patterns of distributed loads over the femur head using a pontual load (a) and the Surface-based Coupling Constraint with uniform (b), linear (c) and quadratic (d) weighting methods.

In order to overcome this inconvenience, a new methodology was developed, taking advantage the fact that the mesh of the femur head be constituted by concentric ring-shaped geometric surfaces, approximately circulars (annulus). Thus, a total of 10 surfaces were considered, as depicted in Figure 4.5 a. Their areas and radius were measured and the latter was used in order to find the unknown parameters ($w_{\text{max}}$ and $a$) of the derived discrete functions 4.4 and 4.5 that give the weights to be attached to each surface with respect to their distances $r_i$ to the center. The function 4.4 consider a monotonically linear decrease with $r_i$, while the function 4.5 consider a quadratic decrease of the weights with $r_i$.

\[
W_{\text{linear}}(r_i) = w_{\text{max}} - a r_i
\]  

(4.4)

\[
W_{\text{quadratic}}(r_i) = w_{\text{max}} - a r_i^2
\]  

(4.5)

A system of equations (as the one given by 4.6 for the case of a linear decrease) is formulated taking into account the boundary conditions of this particularly problem and its resolution allows to calculate the unknown parameters. Once we have calculated this parameters, it is possible to associate each surface (or, similarly, each $r_i$) with their respective weight, as is displayed in the graphic of Figure 4.5 b.

\[
\begin{align*}
W_{\text{linear}}(r_{\text{max}} = 1.839) &= 0 \\
\sum_{i=1}^{10} W_{\text{linear}}(r_i) &= 1
\end{align*}
\]  

(4.6)
Finally and once the weights are known, one use the system of equations (4.7) (11 equations and 11 unknowns) to calculate the forces to apply in the surfaces. This is so because the surfaces $S_i$ have different areas and consequently we can not simply multiply the components of the hip contact forces by the weight factors calculated above to obtain a linear or quadratic distributed pressure. Thus, taking into account the surfaces areas, one obtain the system equation:

$$\begin{align*}
F_i A_i &= w_i \times P, \\
\sum_{i=1}^{10} F_i &= F
\end{align*}$$

(4.7)

where $F_i$ is the forces to apply in the respective surface $S_i$, $A_i$ is the area of the surface $S_i$ and $F$ is one the 3 components (it can be $F_x$, $F_y$ or $F_z$) of the hip contact forces. After solving the system of equations we can insert each pressure surface into Abaqus® as surface traction. One simulation was conducted to test the performance of this methodology. The obtained results are represented in Figure 4.6. It can be seen that the results are satisfactory and one conclude that the weighting method that
better match typical pressure patterns such as the ones represented in Figure 4.6. c and d is the linear decrease scheme (a) and therefore it will be used from now on.

Figure 4.6: Different patterns of distributed loads over the femur head using Surface Traction linear (a) and quadratic (b) decreasing schemes and observations from the literature to comparison purposes: (c) Contact pressure distribution on articular cartilage during walking (adapted from Cilingira et al. (2007)); (d) Contact pressure distribution at stance phase of walking (adapted from Fialho et al. (2007)).

Note that while the pressure distribution cases (c) and (d) are the result of having two bodies in contact (femur head and acetabulum), the cases (a) and (b) are simply a simulation of this scenario. In other words, these pressures distributions are imposed and are not the result of having two bodies in contact.

4.1.2 Parametric Studies

Before starting with the main study itself, a battery of tests was done to assess the sensitivity of the model to certain aspects, namely: the impact that changing certain parameters (such as \(k\), \(m\) and \(s\)) can have on the results; the dependence of the results regarding the initial density distribution and the number of iterations; evaluate the behaviour of the femur under very different loads configurations.

In this way, for the first two points, two load cases (that produces a pattern of densities distribution similar to typical healthy femur bones) were used and seven values of \(k\) in the range \([0, 0.2]\) were computed. For each chosen value of \(k\), four values of \(m\) in the range \([1, 1.5]\) were used. This means that 28 combinations of the type \([k, m]\) were computed and for each of them, the BMD of the FN was calculated.

To test the dependence of the results regarding the initial density distribution, 9 different initial configurations (5 uniform density distribution and 4 “special cases”) were evaluated for a given value of \(k\), \(m\) and \(s\).

A parametric study of the parameter \(s\) was also made.
Finally, and before starting applying the complete set of "physiologic forces" that appear in the literature, a parametric load study was carried out, with the main purpose of assess the behaviour of the femur under very different loads configurations and thus observe the different density distribution patterns produced. Different loads configurations in this context means the combination of different directions of the vector hip contact force with different directions of the vector muscles forces. Initially the magnitude of both forces constant was kept constant and then it was repeated the same procedure but with a different magnitude of the muscle forces. This study has, consequently, the advantage of allowing the evaluation of the importance of muscle forces in the pattern density distribution. This is particularly important, since some assumptions regarding muscle forces will have to be made.

Because a large number of combinations can be done (one can compute a large number of vectors with different directions in a 3-dimensional space by linear superposition) and the computational resources and time are finite, the extreme cases have to be chosen. Thus, it was considered an hip contact force of 900 Newton (which is equivalent of a force of 300% Body Weight (BW) with a body mass of 30 Kg) and eight different directions of this force. Each of these forces were combined with different eight muscles forces (with a magnitude of 450 Newton, half of the hip contact forces), which makes a total of 64 different configurations (see Figure 4.7).

![Figure 4.7: Adopted notation and an illustrative case as an example.](image-url)

Note that some assumptions were made. For example, and in accordance with the adopted global referential, the load configurations \( A = (0, 0, -1) \) means an hip contact force in which the force is mainly directed downwards (i.e. in the \(-z\) direction) but with residual components (\( \frac{1}{10} \) of the main component force) in the \( x \) and \( y \) direction (to a better approximation of the reality). Thus the notation \((0, 0, -1)\)
represents in Newtons \((89.1135, 89.1135, -891.35)\). Notice too that one have assumed that no other components of the vector hip contact force can be greater than the \(z\) component and that it is always pointed downwards \((-z)\), while the \(x\) component is always pointed laterally \((+x)\).

With respect to the muscles forces, it was assumed that the \(x\) and \(z\) components of the force are always positive and that no other components of the vector muscle force can be greater than the \(z\) component. In addition to these 64 simulations, another 128 were carried out, but instead of assuming a magnitude of the muscle force half of the hip contact forces, one have assumed another two extreme cases: a magnitude equal to the hip contact force (900 N) and \(\frac{1}{10}\) of the hip contact force (90 N). All these assumptions are based in the data collection presented in the CD-ROM HIP98 [Bergmann (2001)](available online). This database provides, among other things, forces acting in the hip joint and corresponding muscle forces during the entire cycle of normal walking (at 4 km/h) and stair climbing. From these data, it can be observed that the ratio between the magnitudes of hip contact forces and abductor muscles (gluteus and tensor fascia lata) in each frame of both cycles varied between almost one (which correspond to frames where magnitudes of hip contact forces and abductor muscle forces are equal) and infinity (which correspond to frames where magnitudes of muscles forces are much smaller than hip contact forces). It can be observed too that in the instants of maximal hip contact forces in both cycles, this ratio is very close to 2, as well are the means of these ratios over a wide range of frames near these maximum instants. For example, in the gait cycle, 20 equally spaced frames covering the entire cycle were chosen and the mean of the ratio hip contact force and abductor muscles for the first 12 frames (which correspond to the stance phase, first 60% of the total cycle) was calculated, giving approximately 2.49. A similar procedure was done for the stair climbing cycle and an identical result was found. Regarding the directions of muscles forces, it was not observed too in the database different scenarios from those that will be covered in the parametric load study.

### 4.2 Results Analysis Methods

In order to allow the interpretation of results from bone remodeling simulations to draw conclusions, it will be used the fact that computational bone remodeling simulation can provide \(2-D\) femoral global ROI images and thus, whenever one want to show and/or compare graphic results, these images will be presented. As these analysis are performed by slices not contemplating the bone in its entirety, it can sometimes lead to a hasty and inappropriate conclusion. Therefore, in addition, some strategies and metrics were developed that allows a more consistent and valid analysis of results, not restricted by only qualitative analysis.

[DEXA] exam outputs include, among other things, the values of \(\text{aBMD}\) and \(\text{BMC}\) for FN. In one first approach, a comparative analyse based on the former its not possible, since [DEXA] measure it in g/cm\(^2\) and not in g/cm\(^3\) as does the computational model. Indeed, [DEXA] only calculates BMD using area, \(\text{aBMD}\), which is not an accurate measurement of true bone mineral density, defined as mass divided by a volume. However exist a method to overcome this shortcoming, which include the calculation of a FN BMD using a cylindrical volume estimation. [DEXA] results adjusted in this manner are referred to as the \(\text{BMAD}\) and its formula is given by [Ward et al. (2007)]:
\[ FNBMAD(\text{gcm}^{-3}) = \frac{BMC}{\pi \left(\frac{w}{2}\right)^2 h} \] (4.8)

where \( BMC \) is the bone mineral content of the FN, \( w \) is the Femoral Neck Width (FNW), and \( h \) is the height of the scanned region of the FN (see Figure 4.8 a). The value of \( h \) depends on the scanner used. For the Hologic QDR 1500, \( h = 1.5 \text{ cm} \) (Cardadeiro et al., 2010).

Notice that this metric has the advantage of reducing the size dependence of DEXA aBMD since it is a metric independent of the volume of the bone (namely its size) and allow in the present work the use of a BMD criterion for results validation, as this measure is related to the real 3-dimensional bone, like the computational model. This is very useful, once in this work its used an adult femur and experimental data (namely DEXA results) are from 8- and 9-Year-Old Boys and Girls. It can therefore constitute an alternative way to the one adopted for instance by Santos et al. (2010), who use a BMC criterion, which is also itself very dependent on the size of the bone, since typically larger bones give rise to higher values for BMC and vice versa. It should be highlighted however that FN BMAD results do not accurately represent true BMD since it use an approximation of the bone volume. Actually, BMADFN is used primarily for research purposes and is not yet used in clinical settings (Ward et al., 2007).

**Figure 4.8:** Proximal femur DEXA image representing the volumetric approach (a) and the chosen ROI used for results analysis: b) Neck ROI c) CNM ROI

The next step was the selective choice of elements to mimic the femoral neck ROI from DEXA exam. This selection was processed according to Hologic (software 5.73) ROI demarcation algorithms (Figure 4.8 b). The computational model provides BMD and volumes as output for the wholes set of elements. BMC values were then computed for the whole set of elements, and sequentially for the elements composing the femoral neck ROI (1224 in total), using the relation:

\[ BMC_e = BMD_e \times V_e, \] (4.9)
with $V_e$ and $BMD_e$ representing the FE volume and its BMD, respectively.

The BMD calculation of the CN ROI is then the total BMC of the CN ROI divided by the total volume of this ROI.

As one of the goals of the work is trying to see if there is a shift in Ward’s area position, a metric (from now on, ‘CNM’, which stands for ‘Center of No Mass’) was developed:

$$CNM(x, y, z) = \frac{1}{\sum_{i=1}^{2659} (1 - V_e^i \times BMD_e^i)} \times \sum_{i=1}^{2659} (1 - V_e^i \times BMD_e^i) \times r_e^i(x, y, z), \quad (4.10)$$

where $r_e^i$ is the centroid positions of element $i$ and, as mentioned above, $V_e^i$ and $BMD_e^i$ are the FE volume and the BMD of element $i$, respectively.

There are a total of 2659 elements that constitute the chosen ROI choice based on real DEXA images of our samples (see Figure 4.8 c). One therefore have assumed that the center of the position $(x,y,z)$ of Ward’s area, given by Eq.4.10, can lie somewhere in the chosen ROI.

Finally, in order to compare results simulations and therefore evaluate in a quantitative way how far away are 2 different density distribution patterns, one have introduced the metric $\varepsilon(\%)$:

$$\varepsilon(\%) = \sum_{i=1}^{N} \left( \frac{V_e^i}{V_t} \right) \times \left| BMD1_e^i - BMD2_e^i \right| \times 100 \quad (4.11)$$

where $V_t = \sum_{i=1}^{N} V_e^i$ is the total volume of the bone.

### 4.3 Study with Experimental Data

All experimental data presented here comes from a study carried out by Cardadeiro et al. (2010) and were provided by that research group. The subjects for that study were drawn from 18 schools and 20 sports clubs (Portugal). The sample consisted of 88 children (48 boys and 40 girls) with ages between 8 and 9 years.

Proximal femur analysis BMC and aBMD of left leg proximal femur were measured with DEXA (QDR 1500, pencil beam mode, Version 12.4, Hologic, Inc., Waltham, MA, USA).

PA was assessed with the Actigraph accelerometer PA with epochs of 1 minute. Participants wore the monitor over 7 days, and the activity data were summed on a minute-by-minute basis. Subjects were excluded if they failed to provide a minimum of 3 days of at least 600 minutes per day of accelerometer data. The accelerometer was secured on the right hip, and the subjects were asked to wear the accelerometer during the daytime, except during water activities. Cut points of 100, 1952, and 5724 counts/min were used to identify sedentary, light, moderate, and vigorous physical activity. These cut points have been validated previously.

All the main characteristics of the sample are indicated in Table 4.1. The reader is encouraged to read the main article for details (available at: http://dx.doi.org/10.1002/jbmr.229 (DOI)).

The total (i.e., for both genders together) mean ± SD of light, moderate and vigorous PA time is 482 ± 73, 67 ± 24 and 9 ± 7 (in minutes), respectively, while the total CN BMD mean ± SD is (0.2820 ± 0.0313) g/cm$^3$. For this metric, the minimum-maximum found values for our male and
Table 4.1: Subjects characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Boys (n=48), mean (\pm SD)</th>
<th>Girls (n=40), mean (\pm SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone age, years</td>
<td>9.0 ± 1.1</td>
<td>8.6 ± 1.2</td>
</tr>
<tr>
<td>Age, years</td>
<td>8.6 ± 0.4</td>
<td>8.5 ± 0.4</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>33.0 ± 8.0</td>
<td>29.8 ± 6.1</td>
</tr>
<tr>
<td>Height, cm</td>
<td>134.0 ± 7.0</td>
<td>131.9 ± 5.3</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>18.1 ± 3.1</td>
<td>17.0 ± 2.6</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>24.5 ± 9.3</td>
<td>26.4 ± 7.5</td>
</tr>
<tr>
<td>Body fat, kg</td>
<td>8.7 ± 5.2</td>
<td>8.2 ± 4.3</td>
</tr>
<tr>
<td>Body lean mass, kg</td>
<td>23.2 ± 3.1</td>
<td>20.6 ± 2.5</td>
</tr>
<tr>
<td>Calcium intake, mg/d</td>
<td>1196 ± 532.8</td>
<td>1100 ± 448.1</td>
</tr>
<tr>
<td>Sedentary, min/d</td>
<td>878 ± 95</td>
<td>886.1 ± 62.1</td>
</tr>
<tr>
<td>Light [PA] min/d</td>
<td>474 ± 87</td>
<td>492 ± 50</td>
</tr>
<tr>
<td>Moderate [PA] min/d</td>
<td>78 ± 3</td>
<td>55 ± 3</td>
</tr>
<tr>
<td>Vigorous [PA] min/d</td>
<td>10 ± 1</td>
<td>7 ± 1</td>
</tr>
<tr>
<td>Moderate + vigorous [PA] min/d</td>
<td>88 ± 26</td>
<td>62 ± 24</td>
</tr>
<tr>
<td>Total [PA] counts/min</td>
<td>702 ± 135</td>
<td>587 ± 152</td>
</tr>
<tr>
<td>Fat left leg, kg</td>
<td>2.10 ± 1.11</td>
<td>1.98 ± 0.83</td>
</tr>
<tr>
<td>Lean left leg, kg</td>
<td>3.66 ± 0.63</td>
<td>3.27 ± 0.53</td>
</tr>
<tr>
<td>(\text{BMC}) left leg, g</td>
<td>185.00 ± 55.68</td>
<td>157.37 ± 43.80</td>
</tr>
<tr>
<td>(\text{BMD}) left leg, g/cm(^2)</td>
<td>0.894 ± 0.085</td>
<td>0.846 ± 0.071</td>
</tr>
<tr>
<td>Neck (\text{BMC}), g</td>
<td>3.43 ± 0.46</td>
<td>2.93 ± 0.37</td>
</tr>
<tr>
<td>Neck (\text{BMD}), g/cm(^2)</td>
<td>0.720 ± 0.073</td>
<td>0.642 ± 0.050</td>
</tr>
<tr>
<td>Ward’s area (\text{BMD}), g/cm(^2)</td>
<td>0.673 ± 0.121</td>
<td>0.565 ± 0.090</td>
</tr>
<tr>
<td>FN BMAD (g/cm^3)</td>
<td>0.2919 ± 0.0345</td>
<td>0.2701 ± 0.0223</td>
</tr>
</tbody>
</table>

Female samples was 0.2227-0.3932 and 0.2702-0.3260, respectively. All the calculated BMAD values are inside the range of calculated values of the UK reference data [Ward et al., 2007].

With respect to the mean [PA] intensity, the measured one was slightly lower than that of the 9-year old children in the European Youth Heart Study [Riddoch et al., 2004] (boys: 702 vs 784 counts/min; girls: 587 vs 649 counts/min) and higher than that of US 6- to 11-year-old children [Ricahrd P. Troiano, 2008] (boys 647 counts/min; girls 568 counts/min). Both studies have used the same time to average the movement counts. Regarding the duration of the [PA], a greatest discrepancy is found if one compares the duration of moderate + vigorous [PA] measured in “our” study with, for instance, the one measured in the European Youth Heart Study (boys: 88 min/d vs 192 min/d; girls: 62 min/d vs 160 min/d), which highlight the importance of the chosen cut-points (1952 counts/min vs 1000 counts/min for the moderate cut-point).

The duration spent in each level of [PA] is of particular importance in this work, since it is its handling that will allow the assessment that different amounts of time spent in different levels of [PA] have in the bone adaptation. The connection between the time spent in a certain exercise/load case...
with the model is achieved through the parameter $\alpha_t$ in the remodeling law, given, as mentioned above, by Equation Eq.5.1, where now it was putted in evidence the dependence of the weight factor $\alpha^r$ with the time engaged in a load case $r$:

$$\sum_{r=1}^{P} \left[ \alpha^r \frac{\partial E^H_{ijkl}}{\partial \mu} e_{ij}(u^r)e_{kl}(u^r) \right] - k \frac{\partial \mu^m}{\partial \mu} = 0, \quad (4.12)$$

To better understand how the handling of this parameter is done, watch out in the following case, as an example:

The total (for all the sample) mean of light, moderate and vigorous PA is, as mentioned above, 482, 67 and 9, which makes a total of 558 min (9.2 hours) engaged in PA per day. Once we intend to study the affect of MVPA in bone adaptation, we can say that almost 15% ($\frac{67+9}{558} \times 100$) of the daily activity is spent on it. Thus, the remainder is spent on light PA. If, for instance, one represent both the MVPA and light PA with 3 load cases each, and if we consider that in each PA intensity level all the 3 load cases are performed in the same proportion, we have that each load case in the light PA will have a weight of 0.05 and that each load case in MVPA will have a weight of 0.283(3). The values of $\alpha^r$ can then be varied and the results of the simulations be recorded.

The considered load cases were taken from the literature. Some of the considered load cases are represented in Figure 4.9 while all of them are summarized in Table 4.2.
The chosen frames in the Figure 4.9 (red line) corresponds to maximum instants of the hip contact force. The directions of the hip contact forces seems to be almost invariant over the entire cycles, and thus it can be expected that the chosen instants are fairly representative of the activities they seek to represent.

The hip contact forces \( F_h \) of load cases [1-3] and [8-10] are available in Orthoload-Team (2012). These loads were measured in a very active and healthy individual (“patient EB”, 83 years old male, BW of 650 Unit of Newton (N)) and according to Bergmann et al. (1993) are probably typical for healthy patients. All these data were measured and recorded 24 months or more Postoperative (PO) from his left implant.

In turn, load cases [4-5] are available either online in Orthoload-Team (2012) or in Bergmann (2001) and were measured by the same research group in another patient (“patient PF”). Load cases
Table 4.2: Load cases considered.

| Intensity of PA | Type of PA | Load Case | Type of Force ($F_x, F_y, F_z$) | % BW | $|F|$ % BW |
|----------------|------------|-----------|-------------------------------|------|------------|
| Light          | Walking at 3 km/h 1 | $F_h$ | (147, 26, −284) | 314  |            |
|                |            | $F_t$    | (−97.3, −23.6, 129.9) | 157  |            |
|                | Walking at 4 km/h 2 | $F_h$ | (142, 43, −305) | 337  |            |
|                |            | $F_t$    | (−104.5, −25.3, 129.7) | 168.5|            |
|                | Stair Climbing (normal velocity) 3 | $F_h$ | (150, 59, −298) | 328  |            |
|                |            | $F_t$    | (−105.0, −47.6, 116.4) | 164  |            |
|                | Walking at 4 km/h 4 | $F_h$ | (31, 58, −225) | 234  |            |
|                |            | $F_t$    | (−72.5, −17.6, 90.1) | 117  |            |
|                | Stair Climbing (normal velocity) 5 | $F_h$ | (39, 65, −224) | 227  |            |
|                |            | $F_t$    | (−72.6, −32.9, 80.6) | 113.5|            |
|                | Normal Walking 6 | $F_h$ | (42, 104, −209) | 237  |            |
|                |            | $F_t$    | (−73.5, −17.8, 91.2) | 118.5|            |
|                | Normal Walking 7 | $F_h$ | (30, 130, −301) | 329  |            |
|                |            | $F_t$    | (−103, −97, 162) | 215  |            |
| Moderate + Vigorous | Running at 8 km/h 8 | $F_h$ | (209, 73, −446) | 498  |            |
|                |            | $F_t$    | (−154.4, −37.4, 191.7) | 249  |            |
|                | Jumping on one leg (trampoline) 9 | $F_h$ | (191, 78, −414) | 460  |            |
|                |            | $F_t$    | (−142.6, −34.5, 177.1) | 230  |            |
|                | Stumbling 10 | $F_h$ | (259, 92, −678) | 720  |            |
|                |            | $F_t$    | (−223.2, −54.0, 277.2) | 360  |            |

for MVPA for him were not measured. This patient has been chosen only for illustrative purpose, since he presents a quiet different hip contact forces directions compared with, for instance, the patient EB. It is possible to verify that his contact force in the $y$ direction is higher than in the $x$ direction for both load cases. This same scenario can be found in the literature, as in Jonkers et al. (2008) (load case 6) and in Kuiper (1993) (load case 7). However, none of these two last hip contact forces were measured using telemetering total hip prostheses. Magnitudes of both hip contact force and muscle force in load case 7 were in units of $N$. Consequently, it was assumed the same BW of the “patient EB” to compute the values in % BW.

If on one hand the hip contact forces were applied without making any assumption about their magnitudes and directions, regarding the muscles forces it was not the case: a ratio of 2 between the magnitudes of hip contact forces and abductor muscles forces was chosen for all load cases (extrapolation based on the observations of gait and stair climbing cycles, discussed in subsection 4.1.2), except for load case 7, where muscle forces are known. This assumption allowed the calculation of the magnitudes of muscle forces, since the magnitudes of hip contact forces were known. Regarding the directions of these muscle forces, they were gathered from the two instants of maximum hip contact force for walking and stair climbing, and are (0.62, 0.15, 0.77) and (0.64, 0.29, 0.71), respectively. For all load cases, with the exception of load cases 3 and 5, was used the first muscle directions vector. As
mentioned previously, these muscle loads can be found in the CD Bergmann (2001) or in Heller et al. (2005).

In short, is being assumed that for all the different types of PA the ratio hip contact force magnitude and muscle force magnitude is constant and equal to two and that the directions of muscle forces are equal in almost load cases.
Results and Discussion
In this chapter we first start with the exposition of the results of the parametric studies carried out. Only then will be presented and discussed the final results, which resulted from the application of physiological load cases.

Regarding the effects that the computational model parameters have in the results, two generic load cases have been chosen. Then, it was fixed the values of $k$ and $m$ while the parameter $s$ (step length) was changed. It was considered the same initial density values (uniform density distribution with $\mu=0.6$). Only three results are presented (for $s = 0.03, 0.5$ and 10). A convergence test is displayed in the graphic 5.1 representing the value of the objective function for different numbers of iterations, while in figure 5.2 is presented the final coronal middle sectional views.

![Convergence tests for three different $s$ values.](image1)

**Figure 5.1:** Convergence tests for three different $s$ values.

![Coronal middle sectional views obtained for three different $s$ values.](image2)

**Figure 5.2:** Coronal middle sectional views obtained for three different $s$ values.

According to these results, it can be seen that different step lengths produced different final results and the smaller the step length is, slower is the convergence and therefore more iterations (and consequently time) is required to obtain a convergent result. However, it seems that small values of $s$ produce smoother results, allowing a thorough update of the project variables. These results can be interpreted taking into account the way the project variables are updated (see Formulae 3.5). There-
fore, there must be a compromise between the time needed to achieve the convergent solution and the step length, remembering that smaller step lengths produce better solutions.

With respect to the influence that initial density values have in the final solution, nine different initial configurations have been tested (Figure 5.3).

This evaluation was done for two different values of step length (s=0.03 and s=0.5). The density distribution solution in different times of the iterative process (for each initial configuration) was successively compared to the final one produced with initial uniform density distribution with $\mu=0.6$. These comparisons were done using Equation 4.11 which, as mentioned above, evaluate in a quantitative way how different are two density distributions patterns. The results for s=0.03 and s=0.5 are represented in Figure 5.4 and 5.5 respectively.

**Figure 5.3:** Initial density distributions: A,B,C,D and E - Uniform density distribution with relative BMD $\mu=0.05, 0.2, 0.4, 0.6$ and $0.99$, respectively; F- Proximal femur part with $\mu=0.05$, distal part with $\mu=0.3$ and a superficial cortical layer with $\mu=0.99$; G- Similar to F, but with a superficial cortical layer with $\mu=0.6$; H- Random distribution with values of $\mu$ between 0.05 and 0.99; I- Random distribution with values of $\mu$ between 0.2 and 0.6.
The results clearly show that some initial states indeed influence the final solution, and that this influence is more pronounced for smaller step lengths.

While for all initial uniform density distribution, with exception of the one with $\mu=0.99$ (configuration E) the final solution is the same, initial states with very high values of $\mu$ (as configurations E, F and H) tend to converge to different solutions. For $s=0.5$ the final solutions for configuration E, F and H are only slightly different from the one produced with configuration D, but with $s=0.03$ the
differences are much bigger. For example, it can be noted that with the configuration E the density of the elements remains almost unchanged along the iterative process. Once again, these results can be interpreted taking into account the way the project variables are updated.

As briefly mentioned in the description of the optimization model, k is one of the most important parameter in the model, being the amount of bone mass available highly dependent on it. The parameter m is also of some importance, and the amount of bone mass available is also controlled by it, but in a lesser extent. Usually this parameter takes the value 1. In such case it does not influence the results, as can be be deduced by the Equation 5.1.

\[ \sum_{r=1}^{P} \left( \alpha^r \partial E^H_{ijkl} e_{ij} u^r e_{kl} u^r \right) - km \mu^{m-1} = 0, \]  

(5.1)

Notice that this equation is similar to Equation 3.4. The difference is that here, the remodeling law is written with with respect to \( \mu \) (not explicitly in function of \( a \)).

In the Figure 5.6, the second term of the first member of the Equation 5.1 is plotted as a function of \( m \), for a fixed value of k (0.01) and different values of \( \mu \).

![Figure 5.6: Plot of the second member of Equation 5.1 as a function of \( m \), for a fixed value of k (0.01) and different values of \( \mu \).](image)

It can be seen that when the parameter \( m \) do not take the valor 1, the metabolic cost for a FE with a particularly relative density \( \mu \) change. For values of \( m \) higher than 1, it is more difficult to be added mass in areas where the density is already high, and vice-versa. The reverse process occurs when the parameter \( m \) is less than 1.

Consequently, the total amount of mass will also change, as shown in the next Figure.
The values of the FN BMD are in agreement with the expected. The higher the value of $k$, the higher the cost metabolic is and therefore less bone mass is deposited.

Contrary, the higher the value of $m$, the higher the amount of mass. This is so because for that values of $k$, the majority of the elements have a relative density (in general less than 0.5) whose metabolic costs are decreased with the increment of $m$.

Notice however that the parameter $k$ has a much larger effect related with the osteogenic index than the one that has the parameter $m$.

Comparing these predicted values with experimental data, like the one present in Figure 5.8, one can roughly conclude that the range of the empirical constant $k$ that leads to a biological reality is $k \in [0.02, 0.2]$ and thus may be considered clinical relevant for similar samples.

This range is different from the one calculated in Santos et al. (2010) ($k \in [0.053, 0.36]$). This is so
mainly because in the latter the study was done with a very different sample: adults (age ≈ 60 years old) with weight ≈ 65 kg and thus with more than twice the weight assumed here (30 Kg). The used criterion used for comparison was also different, as well the load cases applied.

Now, in the Figure 5.9 is presented the results of the parametric load study carried out.

![Figure 5.9: Results of the parametric load study carried out. Each coronal middle sectional view correspond to a certain load case, which the notation was given in table 4.7, section 4.1, subsection 4.1.2](image)

First, these results show that under very different loads environments, the bone adapts itself differently in order to optimize its stiffness. The model was able to capture these differences. The load cases A and H cause essentially bending of the femur, which is normal, since the hip contact force is pointed downward. More bone mass is deposited in its lateral side. Accordingly, Ward’s area would be shifted to the medial side.
Load cases $B$ and $G$ are unlikely to happen, given the pattern that has little to do with what is found experimentally (the femoral shaft is full of bone mass while the proximal part is almost empty).

All the others load cases leads to a mixture of compression, torsion and bending, especially load cases $D$ and $E$, where the vector hip contact force points laterally and downward. If these load cases were probable to happen, than the femur would have more bone mass on its medial side than on its lateral side. Consequently, Ward’s area would be shifted to the lateral side.

In Skedros and Baucom (2007) and Kalmey and Lovejoy (2002) is cited that trabecular bone experience more compression and torsion than bending, contrary to monkeys, who are more subject to bending. Interestingly, hip contact forces similar to $A/H$ and to $D/E$ can be found in the literature (load cases 2 and 6, for example), and for the same physical exercise, which puts in evidence the subject-specific loading due to differences in gait kinematics and gait kinetics. These aspects will be cover next.

In the report above, it is implied that much bigger differences are detected if one fix the muscles forces (numbers) varying the hip contact forces (letters). Indeed, if one compute the mean difference in the mass distribution due to hip contact forces, using once again Equation 4.11 one obtain $(15.7117 \pm 0.6129)\%$. This value was calculated firstly by computing the $\varepsilon(\%)$ for each line (comparing the mass distribution patterns with each other) and then computing the mean of the calculated values. The same procedure was done for the muscles forces, were it was found a mean difference of $(7.3601 \pm 2.8025)\%$. Thus, it can be concluded that for the load cases considered, the hip contact forces produces more than twice the difference that are produced by muscles forces and therefore play a much more important role in the mass distribution than do muscles forces.

As mentioned earlier, all the 64 load cases were again tested, but instead of assuming the ratio of $\frac{1}{2}$ between magnitude of muscles forces and magnitude of hip contact force, it was assumed a ratio of $\frac{1}{10}$ and 1, which intend to mimetic the scenario of almost absence of muscles forces and a very active muscular activity, with magnitude equal to the hip contact forces. To evaluate this aspect, each load case of the set with ratio $\frac{1}{2}$ was compared with its corresponded load case of the set with ratio $\frac{1}{10}$ and 1. It was calculated a mean difference of $(4.7255 \pm 2.4795)\%$ with respect to the set with the ratio $\frac{1}{10}$ and $(5.2115 \pm 2.4870)\%$ for the set with ratio 1.

Some of these results are presented in the figure bellow:
The effects of increasing the magnitude of muscles forces are an increasing of bone mass in the lateral part of the proximal femur, mainly the principal tensile group, and in the distal part, namely the secondary tensile and compressive group, which appear more pronounced. The medial part of the proximal femur remains unchanged. Consequently, Ward’s area change its position. Applying Equation 4.10, it was verified for all the cases above a very small dislocation of Ward’s area (always less than 0.5 mm) directed from the inferior-lateral to the superior-medial part of the proximal femur.

Concluded all the parametric tests (parameters study and load study), it was time to feed the model with loads taken from the literature. First, it should be said that characterize all PA with the considered load cases is a simplification. However, this is the only possible choice, whereas they are the only available in the literature.

Since there are ‘physiological’ load cases that pretend to simulate the same PA and which the predicted density distribution are very different, two different scenarios were considered (Table 5.1). Within each PA intensity level was used equal weight factors for the load cases that constitute them. This is so because the actual activity of the volunteers within each PA intensity level was not regulated.
Table 5.1: The two different scenarios considered.

<table>
<thead>
<tr>
<th>Scenario 1</th>
<th>Scenario 2</th>
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</thead>
<tbody>
<tr>
<td>Load Case 6</td>
<td>Load Case 1</td>
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<tr>
<td>Load Case 8</td>
<td>Load Case 8</td>
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<tr>
<td>Load Case 9</td>
<td>Load Case 9</td>
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<tr>
<td>Load Case 10</td>
<td>Load Case 10</td>
</tr>
</tbody>
</table>

Based in the study of the model parameters, discussed above, a value of $s = 0.06$, $k = 0.03$, $m = 1.3$ and an initial uniform density distribution were taken. It was observed that 200 iterations were sufficient to achieve convergence.

The choice of the parameters $k$ and $m$ was done by a trial-error method: these values have been successively changed until the predicted/computational $\text{FN BMD}$ for the total mean of light and MVPA (85% and 15%, respectively) for scenario 2 matched the total mean value of $\text{FN BMAD}$ of the sample, with a relative error of 0.14%.

The values of $\alpha^*$ were then varied. The results of the simulations for both scenarios are given bellow. In both scenarios, the first simulation represents only 50% of time spent in PA. It intend to simulate the effects in bone adaptation to situations such as cast immobilization, weightlessness, not weight-bearing exercise (swimming for example), bed rest and so on. In all the others simulations, the time engaged in light PA is gradually decreased at the expense of an increased time spent in MVPA which means that the total time spent in PA does not change (only the PA intensity level change).
Figure 5.11: Bone adaptation to increased time spent in MVPA (for scenario 1).
Figure 5.12: Bone adaptation to increased time spent in MVPA (for scenario 2).
Comparing the coronal middle sectional views for both scenarios in the case where all the time is spent in light PA, it is verified that there are marked differences in the density distribution. In scenario 1, light PA is represented only by one load case (walking at normal velocity), while in scenario 2 it is represented by three load cases (two load cases for walking and one load case for stair climbing). Additionally, the results of bone adaptation for each of these three loads simulated individually were quiet similar between them (results not shown), and thus similar to the multiload environment. The difference observed between both scenarios is mainly due to substantial differences found in the anteroposterior and mediolateral components of the contact force. In scenario 1, the calculation of hip contact force for load case 6 was made by Jonkers et al. (2008) using gait analyse and musculoskeletal modelling, while in scenario 2 the contact forces were measured by Bergman et al. using instrumented prostheses. Jonkers et al. (2008), when comparing their results with the ones measured by Bergman et.al, report that the non-similarity of forces may be attributed to the differences in gait kinematics and gait kinetics present in the subjects. They further add that future research must concentrate on the specific interaction between individual gait characteristics. Thus, these findings question the use of a standard set of load conditions to study hip loading. The result due to this disparity of contact forces is that in scenario 1 there is a lack of bone mass in the lateral side of the proximal femur, while in scenario 2 there is a lack of material in the medial part of the proximal femur. Thus, Ward’s area tends to position itself in different locals (it was found differences less than 0.2 mm between these two different configurations). Because the magnitude and directions of the hip contact forces are as well quiet different, distinct amounts of bone mass were deposited. An interesting fact is that the magnitude of the hip contact forces in scenario 1, despite of being larger than the ones in scenario 2, produces a lower FN BMD (0.2525 g/cm³ vs 0.3048 g/cm³). This finding highlight the importance of the hip contact forces directions in the produced density pattern.

In both scenarios, as MVPA time increased, the trabecular systems were formed gradually, in a guided and concerted mode. The cortical bone, present from the beginning, was slowly increased in thickness. It was never formed bone within the medullary canal of the femur. When all the trabecular systems were already evident, its thickness increased. The consequence of this guided arrangement was that Ward’s area decreased in size and simultaneously acquired a more central position in the FN. These two facts are linked. It can therefore be stated that one person who spends little time doing MVPA is more likely to have an expanded Ward’s area. A big Ward’s area will always imply a small value of the FN BMD. In vivo data (DEXA data) also point in this direction (see Figure 5.13).
Figure 5.13: Quantitative and Qualitative comparison between DEXA images from the sample (top) and predicted density distribution from computational model (bottom). In both cases left and right images represent a children with high and low FN BMD respectively. In the computational simulations, these differences in FN BMD are only due to PA.

The FN BMD can be mathematically related with the compressive, bending and impact strength, where it appears in the numerator of the mathematical formulas (see Sardinha et al. (2008)). Thus, an increase in MVPA time involves a gain in bone mass with the consequent increase in FN strength and therefore a less risk of a hypothetical FN fracture.

In both scenarios, as the time spent in MVPA was increased, it was calculated very small dislocations of the ‘Center of no Mass’ (Equation 4.10), always less than 0.1 mm for each increment of the intensity of PA and pointed mainly upwards. This is so because more BMC is deposited in the inferior part of the FN than in the superior part. However, should be pointed out two important things regarding the used metric: Firstly, its being assumed that Ward’s area is the ‘Center of no Mass’ of the chosen ROI. Actually, this is not the definition of Ward’s area and the dislocations to be measure change when the ROI change. Secondly, the measured small dislocations are probably due to the fact that the main changes in the density distributions occurs at the trabecular level, while the cortical layer is already formed since the first simulation (when time and intensity of PA is lower). Because this metric depends essentially in the BMC in a given volume and that the BMC of a small volume of cortical bone is usually higher than the BMC of a bigger volume of trabecular bone, small dislocations are measured. This fact is schematically illustrated in the Figure 5.14.
It was found a positive $\Delta \text{FN BMD}$ variation of 24% when comparing the situation where all the time is spent in MVPA and when all the time is spent in light PA (for scenario 1). For scenario 2 this variation was almost 37%. If one roughly assume linearity between bone mass gain and time spent in PA it is possible to say that a person would need to spent only 76% and 63% of its time in MVPA to have the same bone mass amount regarding a person who spent all its time in light PA (for scenario 1 and 2, respectively).

Of course that the case where a person spends all the time in MVPA is purely hypothetical and could not happen in reality. Besides the range of calculated $\Delta \text{FN BMD}$ is within the range of measured $\Delta \text{FN BMAD}$ in Ward et al. (2007) and in our sample, even when all the time is spent in MVPA one can not say that in a real situation would not occur bone resorption due to overload. Indeed, the used mathematical model for bone remodeling do not consider bone resorption due to overload, as do, for instance, Li et al. (2007).

The next Figure (Fig. 5.15) shows a ‘real situation’, in the sense that the used temporal variations were taken from the database of the available sample. There, it can be found that one of the most active children spends more than 20% (4.8 hours) and 7% (1.7 hours) of its day doing light PA and MVPA with respect to one of the most sedentary children. Thus, for each scenario (1 and 2) it was simulated this temporal variation (positive and negative variation) with respect to the children whose the computed $\Delta \text{FN BMD}$ is equal to the $\Delta \text{FN BMAD}$ mean of the sample (reference children).
Figure 5.15: Quantitative and Qualitative comparison in a ‘real’ situation: Top: Scenario 1; Bottom: Scenario 2. Left: Computer simulation of one children who makes less 20% and 7% of Light and moderate + vigorous [PA] (respectively), with respect to the reference children. Center: Reference children. Right: Computer simulation of one children who makes more 20% and 7% of Light and moderate + vigorous [PA] (respectively), with respect to the reference children. The values near the arrows are the absolute differences (in %) of the [FN BMC].

Through the observation of the Figure 5.15, it is possible verify that the real variations in time spent in [PA] have notorious effects in the density pattern produced, whose characteristics have already been mentioned above. It should be said that these variations were done comparing with a reference children. Obviously, if the density distribution of the reference change, then the results will also change. In fact, a careful look allows us to infer that the variations in the density distribution are more pronounced when the amount of bone mass is smaller in its entirety, since the differences registered between the reference children and the one who spent less time in [PA] are more significant, which is confirmed quantitatively through the calculus of the absolute differences of the [FN BMC] (see Figure 5.15). These findings suggest that benefits obtained from [PA] occurs most efficiently in the cases where there is less bone mineral content in the departure femur.

An interesting result, and finally, was found when crossing the results here obtained with the different grades of osteoporosis suggested by Manmohan Singh (1970), who observed that definite progressive changes occur in the trabeculae of the upper end of the femur as normal bone deteriorates to severe osteoporosis. According to the original article, with increasing degrees of bone loss, six different trabeculae patterns can be recognized in the upper femur, with grade 1 representing severe osteoporosis and grade 6 representing normal (healthy) bone. Very similar changes in the appearance of
these groups of trabeculae can be recognized when varying the time and intensity of PA, as illustrated in Figure 5.16.

Figure 5.16: Comparison between level of osteoporosis (through Singh Index - a)) and PA in the trabecular pattern of the upper end of the femur (for scenario 1 - b) and 2 - c)).

These similarities reinforces the well established benefits that PA has in the prevention of osteoporosis with ageing, suggesting us that the more we have a physically active life, specially when we are young, to a higher index of Singh we will eventually evolve when we get older.

Also through the observation of this figure, two different hypothesizes can be formulated. Firstly, it can be theorized that bone loss is not carried out in an arbitrary manner and occurs primarily and first in areas where it is less needed to keep maximal as possible the stiffness of the bone, since these areas are the ones where only is deposited mineral content when the intensity of PA is increased.

The another possibility is that this bone loss occurs uniformly in all the areas of the upper end of the femur. Actually, with the current state of knowledge one can not tell which one is right. This is so because the latter possibility will also lead to a qualitative similar result: notice that the areas where mineral content is less needed are simultaneously the areas wherein the mineral content is in smaller quantity, and thus disappear first when comparing with denser areas, which also loses the same amount of bone mass. However, as the latter are thicker, they can still be visible, giving thus the impression that only the less dense areas have lost bone content.

Nevertheless, both hypotheses leads us to one of the facts learned by 1950 in the area of physiology, which states that organ-level functions make a healthy life possible (Frost, 2004). In this particular context, one can think the statement “make a healthy life possible” as “make the bone as stiff as possible” with the inevitable reduction of bone mass with ageing.
Conclusions and Future Developments
The main purpose of this work was to study the effects of PA, namely MVPA, in the physiologic adaptation of the femur bone. To achieve this, the 3-D FEM coupled with a bone remodelling model was used, which constitute, probably, the most reliable and accurate way to accomplish this goal non-invasively. However, whilst FEM is a powerful tool that is frequently used in biomechanical studies, it is “easy to do poorly and very hard to do well” (Viceconti et al., 2005). Its success depends mainly (and not considering the accuracy with which the geometric model represent the bone structure) in the applied boundary conditions, which include the applied loads. This posed a very challenging problem because on one hand the applied forces (hip contact forces and abductor muscle forces) are of utmost importance in this work and in the other there are a lack of studies reporting physiologic forces for a wide variety of physical exercises. This is so because, unfortunately, these forces can not be measured in living subjects without the use of an invasive surgical procedure, which, in general, is not ethically permissible (Taddei et al., 2006).

There are, however, alternatives to overcome these setbacks, as the use of data measured with instrumented implants that provides external forces (in our case, hip contact forces), and/or inverse dynamic analysis integrated with optimization methods, which estimates muscle forces as well hip contact forces. Actually, these methods constitute the current state of the art in clinical movement analysis and assessment of the forces that bones are subject to. Part of the applied methodology was thus to use the available load cases presented in the literature and insert them, somewhat empirically, in two main classes: light PA and MVPA. The daily times spent on these two PA intensity levels were monitored with an accelerometer.

Note that in the majority of the cases, the hip contact forces gathered from persons subjected to Total Hip Replacement (THR) were applied in an intact femur. Consequently, the final results have to be interpreted based on this extrapolation (Stansfield and Nicol, 2002).

The fact of using a standard set of load conditions has its disadvantages, such as not considering the subject specificity in performing physical exercises (Jonkers et al., 2008). Exactly because of this, one have decided to create two different scenarios (scenario 1 and 2), where it was verified that load cases which intend to simulate the same physical exercise produce different patterns of bone mass distribution. This bone mass distribution is the output of the used bone adaptation model, wherein the driving stimulus for remodeling is the bone global stiffness.

In this model, there are some adjustable parameters, whose values were determined by a quantitative comparison to a biological reality: the weight factors $\alpha$ associated with the multiload formulation were related with times gathered from an accelerometer, while the parameters $k$ and $m$, that control the biological expense associated with bone material, were adjusted through the comparison with DEXA data from the available sample. This adjustment was made using a volumetric BMD criterion, which has the advantage of being independent on the volume of the bone. This was particularly useful in this work, since it was used a geometric model of an adult femur while the DEXA data were from the femur of children.

While the hip contact forces were simply applied in the femur model without doing any kind of assumption regarding their directions and magnitudes, for the muscle forces this was not the case.
These muscle forces were applied assuming a ratio of $\frac{1}{2}$ between their magnitudes and the magnitudes of the correspondent hip contact forces, whilst their direction correspond to directions of walking and stair climbing, collected from Bergman data. These assumptions were done based on Bergman data and taking into account the results of the parametric load study carried out, they are considered to be reasonable and reliable and thus not compromising the validation of the final results.

When the time spent in PA was varied, notorious differences were observed in bone mass distribution. As MVPA time increased, Ward’s area decreased in size, acquiring a more central position in the FN thus establishing a relation between intensity of exercise and Ward’s area. These changes were made at the expense of a new trabecular rearrangement. The thickness of the trabecular systems increased and consequently a gradually increase in BMC in the FN was also measured. The clearly differences here obtained with respect to Ward’s area are in accordance with the suspicions raised by Cardadeiro et al. (2010).

The results also suggested that benefits obtained from PA occurs most efficiently in the cases where there is less BMC in the departure femur.

Because all the results here obtained seems to be consistent with the majority of reports that have studied, in many different ways and applying quiet different methodologies, the effects of PA in bone adaptation, one can conclude that the methodology adopted here is capable and sufficiently robust. However, it is too early to judge the validity of this methodology and the used remodelling law, since others methodologies and bone remodeling models can lead to similar or even better results.

The methodology presented in this thesis has limitations in accuracy due to the assumed loading conditions. Nevertheless, the results still provide strong evidences in favor Roux’ paradigm, who states that bone should be a mechanically optimal structure, since the remodeling law used here is based on structural topology optimization. Roux may have been right. And if so, clinical applications of this bone remodeling model should be encouraged.

Further improvements on the applied methodology must lie essentially in:

- include a larger number of different types of physical activities;
- the use of a larger number of load cases within each cycle of physical exercise (ideally would be all the frames within each cycle, which is almost impossible, due to computational and time costs);
- consider the variation of the local where the hip contact forces are applied;
- consider the variation of the local where muscles forces are attached, as well their areas;
- better division of the applied load cases in the levels light PA and MVPA (translate the load case walking at 4 km/h from the light level to the MVPA, for instance);
- compute more simulations with ‘real’ temporal variations, based on the available sample;
- to model the three dimensional geometric structure of a femur of a child.

Most of the topics mentioned above are only realizable through the work of the scientific community, namely the one whose the subjects of studies are related to musculoskeletal models and measurement of hip contact forces. It is of the most importance to have musculoskeletal models validated, not only for walking and stair-climbing, but also for others kinds of physical exercises. This is, actually, crucial in the type of study carried out in this thesis.
Bibliography


