Simulation of microcrack growth and repair in living bone

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Abstract

The mechanics of how the bone can sustain, accumulate and ultimately repair damage are an important part of biomechanical studies. This work wants to take an analytical approach to the problem, trying to model a system that simulates and predicts the behaviour of microcracks under various conditions of load and other parameters. Materials and methods: this system is built with the Simulink™ suite of the program Matlab™. It is composed of 3 sub models: the first simulates microcrack growth under stress, the second simulates how the damage done by the microcrack is translated into a biological signal and the third mimics the cellular reactions that come into act to repair the damage. Results: the system has been used to mimic what happens during experiments and the results from experiments have been confronted to the outputs from the system. We have compared the number of remaining cellular processes obtained in the simulation with the number observed by using a SEM microscope on the tested specimen to check how the damage signalling subsystem worked. The system has finally been used to predict the cycle of damage accumulation and repair in military trainee during the first weeks of training. Discussion: the results show that the system predicts with good approximation the behaviour seen in the experiments and statistics taken as a reference. The simulated microcracks grow until given sizes and stop like in real bone, where they stop because of the osteons, and only a number of them grow further, usually bringing the bone to failure. The number of cracks that grow beyond this critical size is dependent by factors as stress intensity and the distance between osteons, all modelled in the system. The system is able to simulate the specific effects of diseases and aging on bone fatigue behaviour.
Keywords: bone, simulation, microcracks, repair.

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1 Introduction

When subject to cyclic stress, the bones accumulate damage in the form of microscopic cracks (Frost [1]). These cracks increase in number and size according to the amount of stress and the number of cycles applied to the bone (Taylor and Lee [2]). The effects of fatigue are well known in engineering practice, where it is the main cause of mechanical failure. In bone biomechanics, the fatigue failure is less common, usually showing in specific categories like racing horses (Bathem [3]), athletes (Orava *et al.* [4]) and soldiers (Meurman and Elfving [5]) in what have been usually labelled as "stress fractures". Stress fractures can be extremely dangerous, because the consequences of a fractured bone are crippling, sometimes permanent and in the wild can even prove fatal. The problem of how bones manage to avoid fatigue fractures with the long lifespan they need has intrigued scientists since the times of Galileo and Leonardo (Martin [6]), but it was only in the last century that the reality of bone microcracks has finally been discovered (Frost [1]). Bone is a material that has specific mechanisms to control the growth of microcracks and their accumulation; it has been proved that bone cells are able to repair microcracks and that this repair is not a stochastic phenomenon, but a targeted action triggered by the presence of damage (Martin [7]). Together with this active response to the presence of microcracks, a passive mechanism to prevent their growth has been found in the microstructure of bones, with the osteons acting as barriers to the propagation of microcracks (O'Brien *et al.* [8], Presbitero *et al.* [9]). The goal of this work is to create a system able to replicate how these mechanics work and how they affect the growth of microcracks in living bone.

2 Materials and methods

To replicate the mechanics of microcrack growth and repair in living bone we have created a Simulink™ model composed of 3 subsystems. Each subsystem models a part of the cycle of damage accumulation and repair, forming a closed loop. The main input of the system is a numerical array composed of the initial length of the microcracks in the section of bone we are simulating. The system gives a matrix as output which provides the values of the crack length calculated at every cycle of stress during the time of simulation. Analyzing this output we can predict the behaviour of microcracks in different situations and observe how repair and crack growth are affected.

2.1 Crack growth mechanics

The first subsystem replicates the growth of cracks with every cycle applying eqn (1), which was first developed as an application of the Paris formula by Taylor and Predergast in 1995 [10].

$$da/dN = C(\Delta K-\Delta K_{th})^{n} + C'(\Delta K)^{n'}((d-a)/d)^{m} \quad (1)$$

Here da/dN is the rate of crack growth per cycle and ΔK is the stress intensity range which is related to the cyclic stress range, $\Delta\sigma$ and the crack length, 2a, through the standard fracture mechanics equation eqn (2).

$$\Delta K = F\,\Delta\sigma\,(\pi a)^{1/2} \tag{2}$$

C, C', m, n and n' are constants, d is the distance between osteons, F is a constant which depends on the geometry of the crack and ΔK_{th} is the stress intensity range threshold required for the crack to grow following the standard fracture behaviour. Units for C and C' are such that da/dN is given in mm/cycle with ΔK in $MPa(m)^{1/2}$.

Eqn (1) is integrated at every cycle and provides the increase of crack length caused by the application of stress. It is composed of two parts. The left part represents the behaviour of a crack whose energy is enough to follow the standard crack mechanics formula shown in eqn (2). This behaviour is characterized by a rising rate of crack growth with crack size, which implies a fast and potentially unstable growth of cracks with every application of stress. The right part of the equation represents the crack growth rate when the presence of osteons can affect it (O'Brien *et al*. [8]). It is characterized by a falling rate of crack growth with size, which can reach the value of zero when the size of the crack is equal to the distance between the osteons enclosing it. The constants for this equation are shown in table 1 (Taylor [11]).

Table 1: Parameters for equation (1).

Parameter	Value
C	3.46×10^{-7}
C'	1.51×10^{-4}
n	4.5
n'	5
m	3
F	1.22

2.1.1 Stress layout

The system can simulate the effects of a cyclic application of stress with a fixed stress range, which is the standard approach used to model fatigue damage, but it is also able to change the value of stress for every cycle of fatigue, to replicate more realistic situations, like alternating rest periods and periods of high stress.

To simulate the load conditions of a trainee during the first week of army training the stress has been patterned on the schedule written in table 2.

From this schedule we can model a stress layout for the whole day, making a distinction between 3 regimes: training, non-training and rest.

The training regime is when the soldier is engaged in training, as the name suggests. It is the more stress intensive regime and we have given to it a stress of 50 MPa. To set a value to the training stress we can compare it to running a long

march with a full set of equipment on (a typical exercise of the army training regime); supposing that the average recruit weights 70 kg and wears an equipment load of around 35 kg, comparable to 50% of his weight and observing the variation of stress on lower limbs during a fast marching pace (Genk *et al.* [13]) we can suppose that during the training period the stress on the bones is increased by a factor of 2.5, changing so a physiological stress of around 20 MPa into a stress of 50 MPa.

Table 2: Daily schedule for army trainees [12].

5 am.	Wake up
5:30 am.	Physical Training
6:30 am.	Breakfast
8:30 am.	Training
Noon	Lunch
1 pm.	Training
5 pm.	Dinner
6 pm.	Drill Sergeant Time
8:30 pm.	Personal Time
9:30 pm.	Lights Out

The non-training regime is the regime of near physiological stress that we have during the other activities of the day, like lunch or personal time. We have modelled 20 MPa of stress for this regime.

The rest regime is the state of almost complete inactivity that the soldiers have between the "lights out" command and the "wake up" time. We have modelled a stress of 10 MPa for this period, leaving a light stress to simulate small movements and the effect of gravity even during sleep.

2.2 Crack detection

To simulate how cracks are detected by the cells surrounding them we have made use of the "scissors model" presented by Hazenberg *et al.* [14] and Taylor and Hazenberg [15]. Following this theory, the displacement of crack faces because of applied stress is able to rupture the dendritic processes which connect osteocytes together. To measure the number of broken processes the system applies eqn (3) to calculate the distribution of shear displacement along each crack.

$$\delta s(x) = \left(3.25\left(\frac{b}{a}\right)^{0.1}\frac{\sigma}{E}(1-\upsilon^2)\sqrt{(a^2-x^2)}\right) \tag{3}$$

where b and a are respectively the greater and minor axes of the crack, σ is the stress, E and υ are respectively the module of Young and the module of Poisson and x is the coordinate along the axis of the crack. Assuming that the processes are broken when the displacement caused by shear is greater than the average diameter of a process (0.2μm) we can use the distribution of stress to measure how many processes are ruptured (Dooley *et al.* [16]).

2.3 Repair

Bone is repaired by a BMU (Basic Multicellular Unit), a cluster of two types of cells: osteoclasts (removing bone) and osteoblasts (depositing new bone) (Frost [1]). These cells are usually dormant and are activated by the signal released by osteocytes (Stejskal *et al.* [17]. The substances that are thought to promote activation of the cells composing a BMU are, among others, members of the tumour necrosis factor family especially the receptor activator of NFκ B Ligand (RANKL) and its receptors, receptor activator of NFκ B (RANK) and osteoprotegrin (OPG), along with other factors, such as ephrins and interleukins [18]. It has been established that the RANKL-RANK-OPG signalling pathway is a main actor in the activation of bone remodelling by BMUs. RANKL causes the activation and differentiation of osteoclasts from their inactive precursors, and so it stimulates bone remodelling. Osteoclast activation occurs as RANKL binds to the RANK receptor on the cell surface of both precursors and mature osteoclasts. OPG, a member of the TNF superfamily, functions by binding to and sequestering RANKL, impeding the resorption. It binds to it on the surface of osteoblasts, impeding further activation of osteoclasts (Wright *et al.* [19]).

The presence of broken processes has been shown as being accompanied by an increase in the concentration of RANKL (Mulcahy *et al.* [20]). In our system we have modelled the varying concentrations of the actors in the pathway activating a BMU using the Hill equation (eqn (4)) and obtaining a way to quantitatively predict the number of active osteoclasts and osteoblasts forming BMUs in response to the detected cracks during the simulation period.

$$f(X) = \beta * \frac{X^n}{X^n + K_A^n}. \tag{4}$$

The equation regulates the concentration of the activated actor as function of X, the concentration of the unbound activating actor. The constants β, K_A and n are respectively the growth coefficient regulating the maximum level of the activated actor, the half concentration coefficient representing the concentration of X necessary to have an activated actor of β/2 and the Hill coefficient, a shape factor for the equation. Once the BMU is formed, the effects of its action on the crack sizes are modelled to act with a delay simulating the time required for the BMU to reach the crack (Martin *et al.* [21]).

3 Results

3.1 Simulation of military training

The results of a simulation of crack behaviour during eight weeks of simulated stress compatible with military training regime is shown in figure 1. The figure shows the growth of cracks and how the effects of repair act first on the larger and more dangerous cracks, instead that on the older. This effect is compatible with the literature which has found a linear correlation between the number of repairs and the average crack length in living bone (Martin [7]), as can be seen in figure 2, which shows a linear correlation between the average crack length and

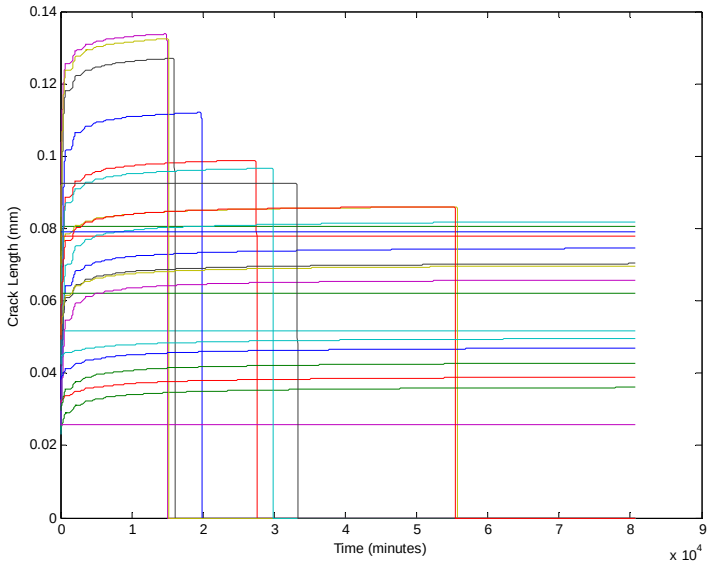

Figure 1: Simulation of military training. The lines represent the sizes of individual cracks during the simulation. The graph shows how cracks are repaired in order of dimension and some cracks are not repaired at all.

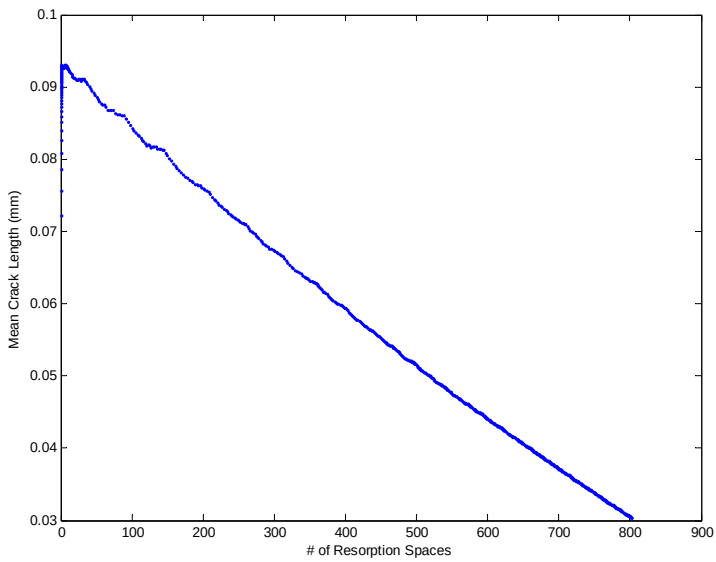

Figure 2: Correlation between resorption spaces and mean crack length.

the number of BMUs generated by the system.We have also recorded the time of failure from a series of simulator runs that have returned a bone failure. Figure 3 shows how the failures are mainly concentrated in the first weeks of simulated time, especially between the third and the sixth week.

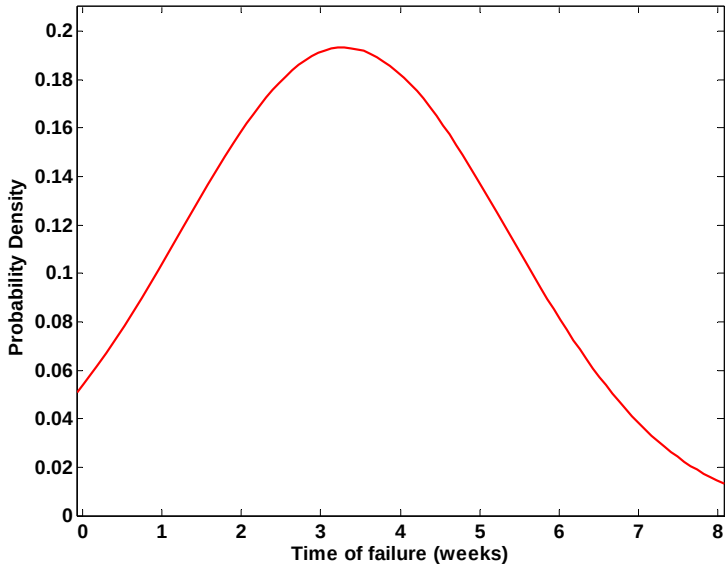

Figure 3: Distribution of time of failure for the simulator.

3.2 Effects of aging

The effects of aging are simulated by modifying the values of crack growth toughness and of the presence of osteons in the simulated bone (Ager *et al.* [22]) and are shown in figure 4. It can be observed how the effects of aging cause the crack growth to be different compared to the younger subject simulated in figure 1. The reason for this shape is that the cracks in this simulation alternate between a prevalent long crack behaviour in the training period and a short crack behaviour in the rest and non training periods. An increased risk of fracture is present as it is possible that some cracks cannot be repaired completely because of their fast growth.

3.3 Effects of osteoporosis

The effect of osteoporosis can be simulated by modelling a decrease in bone strength with every repair, caused by an unbalance of bone removed by osteoclasts and restored by osteoblasts. This unbalance causes a reduction of bone mass which can be simulated with an increase of stress. We have deliberately increased the unbalance to emphasize the effects for an increased visibility. The results in figure 5 show how every time a crack is repaired the other cracks are subject to an increasing stress, which causes some of them to grow and increases the risk for one or more of them to bring the bone to failure.

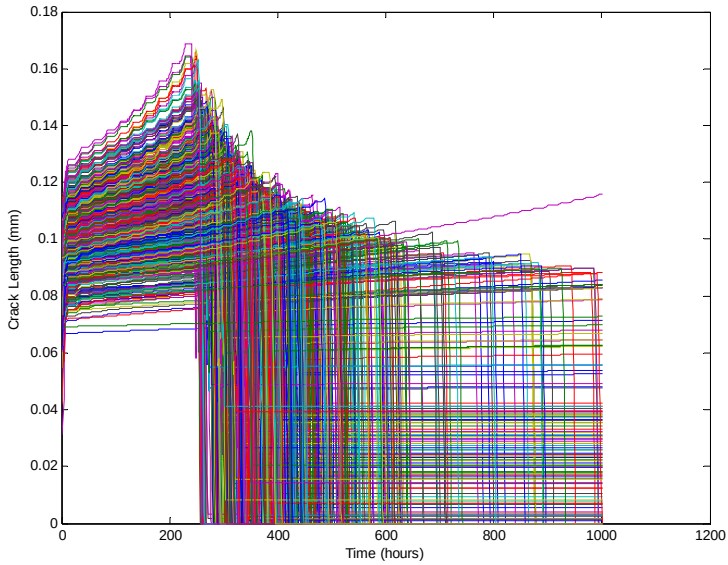

Figure 4: Simulation of military training with aged bone.

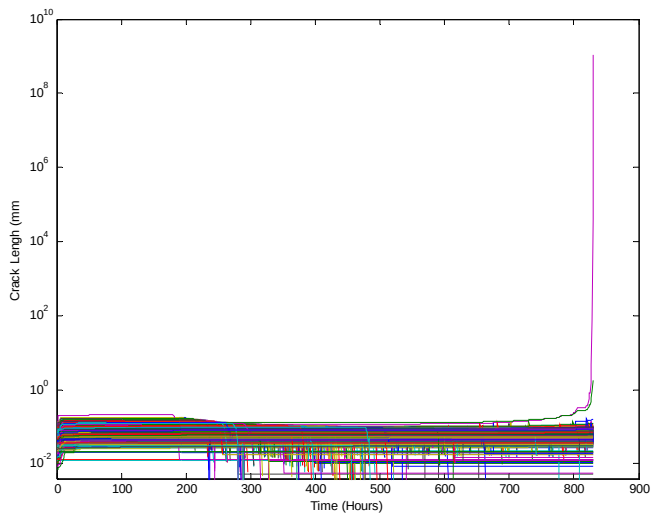

Figure 5: Simulation of the effects of osteoporosis.

3.4 Effects of drugs in the treatment of osteoporosis

The effectiveness of drugs like bisphosphonates in the treatment of osteoporosis is validated by a large number of clinical tests (Peter *et al.* [23], Chavassieux

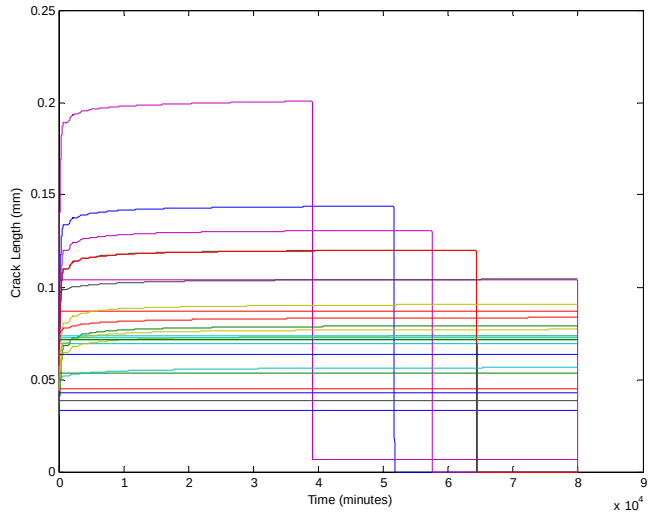

Figure 6: Simulation of the effects of bisphosphonates for osteoporotic patients.

et al. [24]) and their mechanism of action can be modelled in our system by modifying the balance in the simulation of repair accordingly to the known properties of these drugs (Allen *et al.* [25]). The results, shown in figure 6, can be compared to the results for untreated osteoporosis. The effects of bisphosphonates reduce the negative effect of osteoporosis avoiding the loss of bone mass and the increased risk of failure, but the variations in the pathway forming a BMU delay the repair and reduce its effectiveness.

4 Discussion

The mechanics of bone fracture mechanics applied to fatigue and of the cycle of repair are not completely clear, but this study has proposed a method to simulate them analytically using quantitative equations. The results show how a simulation of bone microcrack growth and repair can be obtained using this model. Knowing the initial size of microcracks and the stress applied to them this model allows a quantitative prediction of the times required to repair them and the variations of microcrack size because of growth and repair. This allows the simulation of situations which are extremely difficult to reproduce in experiments, like the use of drugs and the effect of osteoporosis, by replicating the effects of these situations in the constituting equations of the system. Also factors like a variable stress layout or the effects of age, which are difficult to model using empirical equation, can be factored in the mechanics of the system, providing extreme versatility.

References

[1] Frost, HM 1960, *Presence of microscopic cracks in vivo in bone.* Henry Ford Hospital Medical Bulletin.

[2] Taylor, D and Lee, TC 2003, *A crack growth model for the simulation of fatigue in bone.* International Journal of Fatigue, pp. 387-395.

[3] Bathem, AP 1994, *245 fractures in Thoroughbred racehorses: results of a 2-year prospective study in Newmarket.* Proceeding of the American Association of Equine Practitioners, pp. 175-6.

[4] Orava, S, Jormakka, E, Hulkko, A 1981, *Stress fractures in young athletes.* Archives of Orthopaedinc Trauma Surgery, pp. 271-274.

[5] Meurman, KAO, Elfving, S 1980, *Stress fracture in soldiers: a multifocal bone disorder.* Radiology, pp. 483-487.

[6] Martin, RB 2007, *The importance of mechanical loading in bone biology and medicine.* Journal of Musculoskeletetal Neuronal Interactions, pp. 48-53.

[7] Martin, RB 2007, *Targeted bone remodeling involves BMU steering as well as activation.* Bone, pp. 1574-1580.

[8] O'Brien, FJ, Taylor, D. and Lee, TC 2007, *Bone as a composite material: The role of osteons as barriers to crack growth in compact bone.* International Journal of Fatigue, pp. 1051-1056.

[9] Presbitero, G, *et al.* 2012, *Distribution of microcrack lengths in bone in vivo and in vitro.* Journal of Theoretical Biology, pp. 164-171.

[10] Taylor, D and Prendergast, PJ 1995, *Damage accumulation in compact bone: a fracture mechanics approach to estimate damage andrepair rates.* Advances in Bioengineering, pp. 337-338.

[11] Taylor, D 1998, *Microcrack growth parameters for compact bone deduced from stiffness variations.* Journal of Biomechanics, pp. 587-592.

[12] Base Ops. (Online) www.baseops.net.

[13] Genc, KO, Humphreys, BT and Cavanagh, PR 2009, *Enhanced daily load stimulus to bone in spacefl ight and on Earth.* Aviat Space Environ Med, pp. 919-926.

[14] Hazenberg, JG, *et al.* 2006, *Microdamage: A cell transducing mechanism based on ruptured osteocyte processes.* Journal of Biomechanics, pp. 2096-2103.

[15] Taylor, D and Hazenberg, J and Lee, TC 2006, *The cellular transducer in bone: What is it?* Technology and Health Care, pp. 367-377.

[16] Dooley, C, *et al.* 2012, *Rupture of osteocyte processes across microcracks: the effect of crack length and stress.* Biomechanics and Modeling in Mechanobiology, pp. 759–766.

[17] Stejskal, D, Bartek, J, Pastorkova, R, Ruzicka, V, Oral, I, Horalik, D 2001, *Osteoprotegerin, RANK, RANKL.* Biomedical Papers, pp. 61-64.

[18] Lacey, DL, Timms, E, Tan, HL, Kelley, MJ, Dunstan, CR, Burgess, T, Elliott, R, Colombero, A, Elliott, G, Scully, S, Hsu, H, Sullivan, J, Hawkins, N, Davy, E, Capparelli, C, Eli, A, Qian, YX, Kaufman, S, Sarosi, I, Shalhoub, V, Senaldi, G, Guo, J, Delaney, J, Boyle, WJ. 1998,

Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell, pp. 165-176.
[19] Wright, HL, *et al.* 2009, *RANK, RANKL and osteoprotegerin in bone biology and disease.* Current Reviews in Musculoskeletal Medicine, pp. 56-64.
[20] Mulcahy, LE, *et al.* 2011, *RANKL and OPG activity is regulated by injury size in networks of osteocyte-like cells.* Bone, pp. 182-188.
[21] Martin, RB, Burr, DB and Sharkey, NA 1998, *Skeletal tissue mechanics.* New York, USA : Springer-Verlag.
[22] Ager III, JW, Balooch, G and Ritchie, RO 2006, *Fracture, aging, and disease in bone.* Journal of Material Research, pp. 1878-1892.
[23] Peter, CP, Cook, WO, Nunamaker, DM, Provost, MT, Seedor, JG, Rodan, GA 1996, *Effect of alendronate on fracture healing and bone remodeling in dogs.* Journal of Orthopaedic Research, pp. 2692–2696.
[24] Chavassieux, PM, Arlot, ME, Reda, C, Wei, L, Yates, AJ, Meunier, PJ 1997, *Histomorphometric assessment of the long term effects of alendronate on bone quality and remodeling in patients with osteoporosis.* Journal of Clinical Investigation, pp. 1475–1480.
[25] Allen, MR, *et al.* 2010, *Morphological Assessment of Basic Multicellular Unit Resorption Parameters in Dogs Shows Additional Mechanisms of Bisphosphonate Effects on Bone.* Calcified Tissue International, pp. 67-71.
[26] Taylor, D 1997, *Bone Maintenance and Remodeling:A Control System Based on Fatigue Damage.* Journal of Orthopaedic Research, pp. 601-606.