THERMODYNAMIC MODEL OF BONE REMODELING: NUMERICAL IMPLEMENTATION

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ABSTRACT

The paper presents an algorithm that simulates the internal remodeling of bone. This model is based on the thermodynamic theory of open systems applied to biology. It takes into account the coupled influence of the mechanical state and chemical properties and was set-up as a 5x5 differential system. An algorithm based on this system has been implemented into a Finite Element software (Altair Hypermesh©). Tests on femur have been conducted. The results show a good correlation with experimental data.

Key words: bone remodeling, biothermodynamics, finite element model

INTRODUCTION

The bone remodeling behaviour has been studied for the last thirty years and many interesting works have been performed. A full bone remodeling model would enable us to fight osteoporosis by preventive advices and treatments. It could also improve fracture healing through a better understanding of loading influence. Better orthopaedic prosthesis design would diminish the risk of failure; increase the life span of implants while reducing of the design-costs.

The two main classes of functional adaptation models are the phenomenological and the optimization ones. The second often gives good results for the density distribution.[1] However, they do not simulate the real biological phenomenon with a representation of the density evolution through time. They give the final state, but the time evolution of the process is required to understand the influence of the mechanical and chemical stimuli on the prosthetic integration.

In the mean time, the majority of old phenomenological bone remodeling models are too restrictive on their hypotheses, often considering either only mechanical or biological stimulus.[2] Current improved models now simulate the coupled influence of chemical and mechanical stimuli.[3]

The latest improvement in the understanding of the biological pathway of bone remodeling lies in the so-called RANK-RANKL-OPG theory.[4] It describes the interactions between biological components (mainly cells and proteins) that generate the known remodeling behaviour. Moroz [5] performs a wide and complete mathematical study of the biological parameters influence on remodeling. However, this model shows some missing points. The influence of osteoclasts and osteoblasts on the bone density is considered linear. Moreover, the kinetics of chemical reactions is independent of the mechanical state. In addition, as this model has been implemented into a mathematical solver, it only simulates the evolution of a single volume of bone, without taking into account the influence of the surrounding bone.

NEW MODEL THEORY

The chemical reaction leading to bone adaptation were deduced from the RANKL-RANK-OPG theory. The chemical process was simplified to the five main steps of bone remodeling: initialization, bone resorption by osteoclasts (OC), osteoblast (OB) activation, creation of osteoid (apposition) and mineralization of osteoid.[6] The theoretical model is described in [7].

The cells involved are mononuclear cells, multinucleated osteoclasts and osteoblast activators. The bone is represented by the osteoid and the old bone. The biological steps are translated into kinetic equilibrium reactions and then into a set of five coupled ordinary autonomous differential equations. These equations (Equation 1) are composed of the normalized concentration of biological components (N_i) as variables, J_i the biological components fluxes, δ the reaction speed, β the effect of initial concentration and D_i the influence of mechanical state through the strain applied on the cells. As shown, the mechanical state affects every chemical reaction thanks to a linear function between the D_i parameter and the product between the strain and the frequency. This product represents the strain rate, which is one of the most representative mechanical stimuli.[8] For multi load-cases, the stimulus is the larger strain created by all

$$\begin{cases} \dot{N}_2 = -\delta_1(\beta_1 + N_2)N_2 + \mathcal{J}_3 + \mathcal{J}_{14} - \mathcal{D}_1 \\ \dot{N}_5 = -(\beta_3 - N_2 + N_5 + N_8 + N_{11} + N_{14})N_5 - \delta_3(\beta_7 - N_5 - 2(N_8 + N_{11} + N_{14}))N_5 + 2\mathcal{J}_{14} - \mathcal{D}_2 - \mathcal{D}_3 \\ \dot{N}_8 = \delta_3(\beta_7 - N_5 - 2(N_8 + N_{11} + N_{14}))N_5 - \delta_4(\beta_{10} - N_{11} - N_{14})N_8 + \mathcal{D}_3 - \mathcal{D}_4 \\ \dot{N}_{11} = \delta_4(\beta_{10} - N_{11} - N_{14})N_8 - \delta_5(\beta_{13} - N_{14})N_{11} + \mathcal{D}_4 - \mathcal{D}_5 \\ \dot{N}_{14} = \delta_5(\beta_{13} - N_{14})N_{11} - \mathcal{J}_{14} + \mathcal{D}_5 \end{cases}$$

Equation 1: Mathematical system

the loadings.[9] The overall density is calculated as the addition of newly-formed and old bones.

As the differential system used does not have an analytical solution, an iterative scheme is necessary to solve it. After some tests, the best results were found with a Runge-Kutta-Fehlberg method.[10]

With this theory, in the case of unloaded bones, the density reached is almost 30%. This is more physiologic than many models in which the density drops to 0%.

IMPLEMENTED ALGORITHM

Based on this theory, an algorithm that simulates the evolution of density in time was designed and set as a macro into Altair Hypermesh© v8.0sr1.[11] Its different steps are described in the **Error! Reference source not found.**.

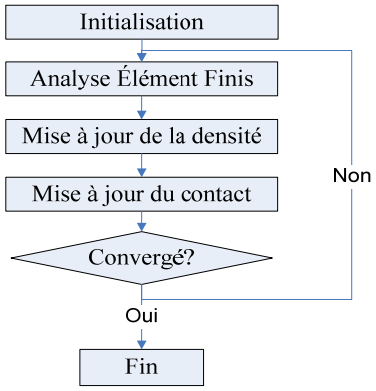

Figure 1: Algorithm

The Finite Element solver determines the strain on every bone element throughout the whole model. Considering a loading frequency, the algorithm can then deduce the strain rate of those elements, which is our mechanical stimulus. According to this stimulus, it calculates the mechanical influence parameter of the differential system (D_i). This value changes for each element and at each iteration. As a mathematical process, it can yield negative concentrations. To avoid this, some data are corrected.

Once this parameter is known, the algorithm solves the differential system. Its resolution is done using the Runge-Kutta-Fehlberg scheme. The time increment is deduced also for each element with this method. It calculates from an estimation of the error the time step required to reach a precision set by the user. A global time step is imposed to obtain synchronism between elements as they all simulate the same period of time. Considering those two times parameters, we can deduce then the number of loops that each element has to perform.

Once this step is performed for each element, the larger time step is chosen as the next iteration global time step. This parameter is checked to be lower than an extreme value set by the user and it directly influences the quality of the results.

For each element, the resolution of the differential system gives the updated value for the five concentrations. All of them are corrected to have physic values (between 0 and 1). Then, the algorithm adds the old and new bone concentrations to obtain the update value of the density of the given element.

Each element is composed of old and newly mineralized bones. As the two components do not have the same Young modulus, each element is biphasic. Using the “mixture law”, the equivalent density is calculated. Then, due to modeling limits, the elements density can only have discrete values, so they are corrected. The three densities used (calculated, equivalent and discrete) are adjusted to stay positive and inferior to one. The real density must remains inside limits set by the user.

The mean density of the model is calculated from each element real density and is called here the Bone Mineral Density (BMD). It is divided into two parts, the cortical BMD (for more than 70% density elements) and the trabecular BMD. The evolutions of the three BMD between two successive iterations indicate the convergence state. Then the process loops and starts a new finite element analysis.

As a convergence criterion, the algorithm uses the mean value of the density variation between the iterations (n) and (n-1) and between the iterations (n-1) and (n-2). Considering three successive iterations avoids declaring convergence when elements are oscillating. There are two convergence criteria. The first is local and represents the maximum variation of density of each element. The second criterion is global and uses the variation of the BMD.

The relation between the Young modulus and the density depends on the orientation of the element and the type of bone (cortical or trabecular). Meanwhile, it

always has the following form $E = E_0.d^r$ where E_0 stands for the full-dense Young modulus and *d* the density. Some authors consider as value for the r parameter 2 or 3.[1, 3] but accurate values depending on the type of bone and its orientation can be used.[6] For the trabecular bone, the values are 1.64 in the axial direction and 1.78 in the transverse one. For the cortical bone, those values are 3.09 and 1.57.

Please notice that in this article, “density” is used for volume fraction. Consequently, it stands for the ratio between the used space and the available space, so it is are non-dimensional and range from 0 to 1.

RESULTS

The algorithm was applied on several mechanical parts with good results. The algorithm always converges except for overload when too many elements are destroyed. It is the only case where a steady value of density is not reached. Finally, the process has then been used to simulate the density evolution of a femur. The numeric model used for the femur is the "Standardized Femur" solid model designed by M. Viceconti and available on the BEL Repository (Istituti Ortopedici Rizzoli, Bologna, Italy). For this study, only the upper part of the femur has been used. It has been imported into Altair Hypermesh© v8.0sr1. The meshing consists of 16250 tetrahedral elements and 3825 nodes. Refined models will be used to obtain more accurate results. With this model, the running time is approximately 8 hours.

The load is constant throughout the process. The load case from Heller [12] is composed of walking and stair climbing for a 90kg person.

The loading frequency is the one felt by cells, not the actual frequency applied on the bone.

The starting point of the simulation is a coarse repartition of the elements between two limits of density (5% and 95%). The chosen material for bone is orthotropic with its main direction on the x-axis. The compliance matrix based on the literature [13] is shown in the Table 1.

Table 1: Old bone material properties

$$C_{ijkl} = \begin{bmatrix} 20 & 10,9 & 11,5 & 0 & 0 & 0 \\ 10,9 & 21,7 & 11,5 & 0 & 0 & 0 \\ 11,5 & 11,5 & 30 & 0 & 0 & 0 \\ 0 & 0 & 0 & 6,56 & 0 & 0 \\ 0 & 0 & 0 & 0 & 5,85 & 0 \\ 0 & 0 & 0 & 0 & 0 & 4,74 \end{bmatrix}$$

The new bone properties are 11 GPa for the main direction and 16.5 for the others. The Poisson ratio is 0.4 in all directions for both bones. The volume fraction is between 5 and 95% with a full density of 1.6 g/cm^3. The reference strain is 0.0075. The biologic parameters are the speed ratio of OC maturation (20.29), OC activation (10.03), deposit of osteoid (5.75) and mineralization of bone (3.08). The sums of initial component concentration are for initial mixture (5.23), for multinucleated OC (15.10), for OB activator mixture (3.22), for OB (2.28) and for mineralization mixture (3.98), in the end, the OC (2.38) and the mineralized bone fluxes (5.07).

The **Error! Reference source not found.** plots represent the density evolution vs. time on the overall model. Different cases have been represented. For the four first ones, the standard forces were applied with several different frequencies.[12] For the last one, the loads have been reduced by half.

The curves of the variation of density in time fit the density evolution found with Basic Multicellular Units BMU) theory. We can notice three different phases: a quick bone resorption followed by bone apposition and completed by bone mineralization. The time length of each phase depends on the applied load. The overall behaviour is very similar to the local behaviour of each element.

For the two last cases, the first one is obtained with a 60% reduced frequency and the second with a 50%

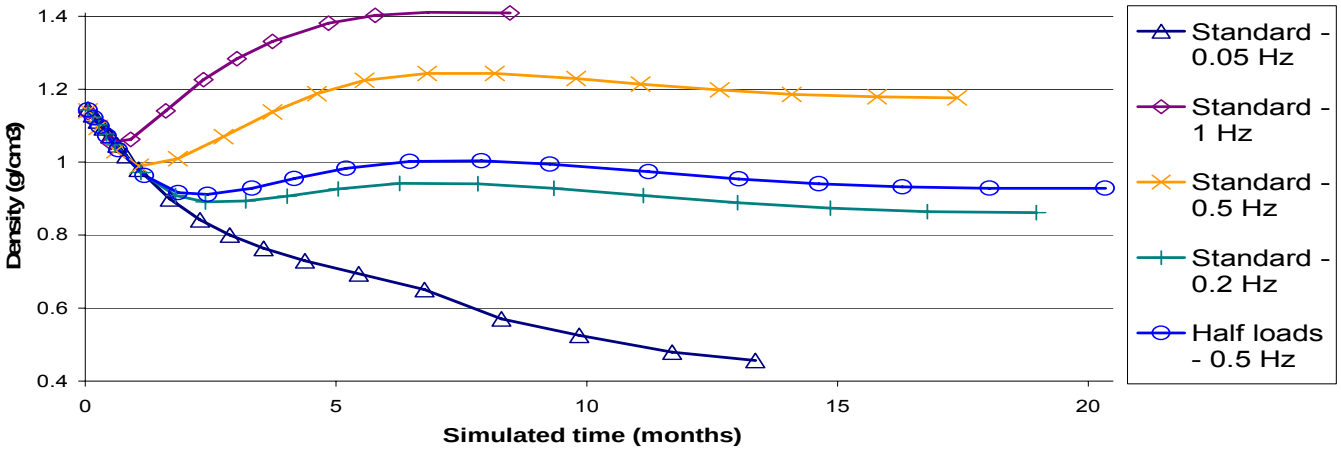

Figure 2 : Density vs. time evolution

lower loading. As the two responses are very similar, it enables us to conclude that loading force and frequency act the same way on the remodeling process. This validates our hypothesis about the strain-rate stimulus.

We can notice as well that the algorithm converges more quickly for high and low loadings. In the case of standard loadings, the time distribution of the three stages is 1.1 month for the bone resorption, 5.7 months for the apposition and 9.2 months for the mineralization. Those values are in accordance with Tovar [3].

Error! Reference source not found. shows on the left, the meshed geometry of the bone used to perform the simulations. On the right, there is the result of volume fraction repartition after convergence (in 17.4 months) of bone remodeling with a standard loading and a 0.5 Hz frequency. The mid-section shown enables to visualize the internal distribution of bone density. We can notice that this distribution is similar with the one of real bones with a hollow center and a part of the medullary cavity.

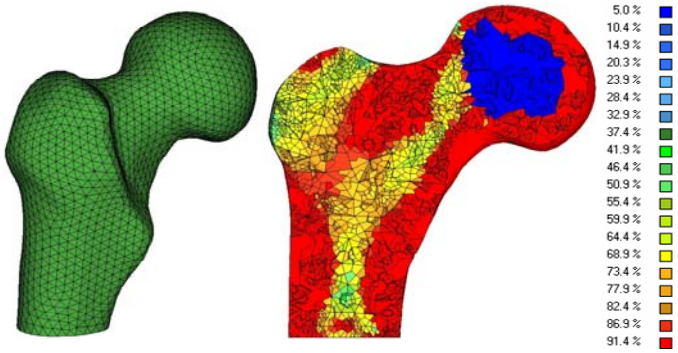

Figure 3: Geometry of the initial and final states

However, the density range is too high to fit with the physiological data. Likewise, the medullary cavity has not a binary density like real bones (high density and no bone). Furthermore, the result for the spherical head is not physiologic. Up to our comprehension of the phenomenon, the shape of the femur head as well as its density come from a cinematic functional purpose (to enable the movement of the limb). Its presence could not be justified as a process of the bone remodeling alone, then it is not simulated here.

DISCUSSION

Because of the lack of experimental data, we only used five chemical reactions of remodeling. Based on specific experiments, it would be useful to have more accurate parameters and use more than five equations. This would provide a more detailed and accurate model.

Because of simulation limit, every element is defined in the global orientation. It would be interesting to manage elements orientation and anisotropy (increase of rigidity in the more stressed direction).

To conclude, our model is able to globally reproduce the adaptation of bone to loadings and its evolution through time. The thermodynamic theory enables to avoid the hypothesis made in many models, particularly for the unloaded cases and for the description of the “Wolf’s law”.[3, 14] This method seems to be closer to the physiological process. However, its increased complexity implies more parameters that induce a much more sensitive model. For example, the starting point (density distribution for the first iteration) needs to be more precise to obtain accurate results.

As a perspective, further investigations will be performed in order to acquire a complete validation as well as to precisely determine the values of the different parameters and their influence on the bone remodeling.

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