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Mechanobiological stimuli for bone remodeling: mechanical energy, cell nutriments and mobility

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1. Introduction

Bone is a living material in continual renewal (Frost 1987). Each year, 5% of trabecular bone and 20% of cortical bone is renewed. It undergoes continual adaptation under applied external mechanical constraints as initially phenomenologically modeled by (Wolff 1892). Many multi-scale and/or multi-physic theoretical, numerical models have followed since (see for example George 2017; Giorgio 2016; Madeo 2012; Scala 2016; Spingarn 2017) trying to predict the kinetics of bone remodeling. But, many difficulties remain in the precise understanding of the mechanotransduction processes (Lemaire 2015) driving this remodeling. For example, in orthodontic treatment, bone remodeling occurs due to the applied orthodontic forces ranging between 0.5 and 2.5 N (Wagner 2017). The periodontal bone will resorb in the compressed area while being reconstructed in the tensile area enabling teeth displacements (Cattaneo 2009). Under these low amplitude forces, the vascularization of the periodontal ligament is partially occluded in the compression zone while being dilated in the tension zone. Cell differentiation and activation is altered, due to nutriments variation, resulting in the bone remodeling. When compression is too important, the ligament is no longer vascularized and hyalinization occurs, resulting in a decrease in the amount of cells and death of the surrounding tissue (Liao 2016). While a weak force allows steady and continual tooth displacement, an important force induces abrupt movement and necrosis of the bone. In the current work, we study the variations in vascularization blood flow in the periodontal ligament and thus in the supply chain of nutrients and oxygen to predict cell recruitment, proliferation and migration assuming that bone resorption occurs by the osteoclasts proliferating in hypoxia (Arnett 2003) and bone reconstruction occurs by the osteoblasts proliferating with oxygen increase (Tuncay 1994).

2. Method

Bone remodeling being the result of numerous mechanobiological mechanisms, we propose to describe its evolution through the use of a biomechanical stimulus ΔS, describing a variation from the state of mechanobiological equilibrium, defined in the Lagrangian configuration (Madeo, 2012; Scala, 2016), and newly expressed as:

$$\Delta\, \mathrm{S} = \int_{\Omega} \prod_{\mathrm{i}=1}^{\mathrm{n}} \alpha_{\mathrm{i}} \mathrm{S}_{\mathrm{i}} \exp\left(-\mathrm{D}_{\mathrm{i}} \chi(\mathrm{X}) - \chi\left(\mathrm{X}_0\right)\right) \mathrm{dX}_0 \qquad (1)$$

where n is the total number of external sources (mechanical, biological, electrical, neurological…) involved in the process and α_i are their weighting coefficients ($\sum_{i=1}^{n} \alpha_i = 1$), triggered by genetic and/or epigenetic factors, allowing to simultaneously control their impact on the overall response of the system as well as their interactions. $\chi(\boldsymbol{X})$ and $\chi\left(\boldsymbol{X}_0\right)$ are the kinematical fields that associate to any material point its current ($\boldsymbol{X}$) and reference ($\boldsymbol{X}_0$) position respectively, and D_i is a characteristic distance accounting for each independent effect. Among the potential external sources, we consider in this work: (i) the mechanical energy accounting for the compressive and tensile loads sustained by the bone cells and triggering bone growth and resorption respectively, (ii) the concentration of oxygen, glucose and other cell nutriments expressed as function of the hydrostatic pressure and of the vascular density in specifics regions of the system, and (iii) the osteoblasts and/or osteoclasts activity triggered by specific levels of oxygen and glucose concentration together with the intensity of the mechanical force applied. More specifically, the osteoblasts and osteoclasts recruiting and migration are described via two diffusion equations (Allena 2014; Schmitt, 2016) as follows

$$\frac{\partial c_j}{\partial t} = div\, \boldsymbol{D}\, \nabla c_j + \alpha_j \left(1 - c_j\right) c_j - \beta_j c_j \qquad (2)$$

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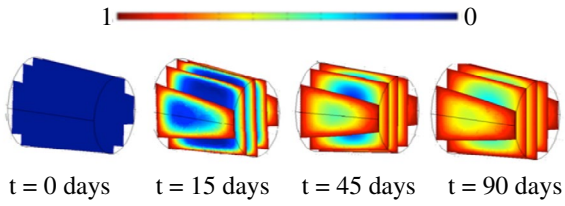

Figure 1. 3D FE simulation of osteoblasts density migration in a porous titanium scaffold submitted to cyclic bending (red: $c_i = 1$, blue: $c_i = 0$)

where c_j is the cell density (with j being the osteoblasts or osteoclasts), t is the time, α_j and β_j are two coefficients of proliferation and differentiation respectively. The diffusion tensor $\boldsymbol{D}$ depends on the principal strains (ϵ_i) and directions (θ_i) and reads

$$\mathrm{D} = \lambda_\mathrm{j}\mathrm{I} + \phi_\mathrm{j}.\sum_{\mathrm{i}=1}^{3} \epsilon_\mathrm{i}\ \theta_\mathrm{i} \otimes \theta_\mathrm{i} \tag{3}$$

with λ_j and ϕ_j two coefficients and $\boldsymbol{I}$ the identity matrix. The bone density variation in time ρ_b is given by

$$\frac{\partial \rho_\mathrm{b}}{\partial \mathrm{t}} = \mathcal{A}_\mathrm{b}\mathrm{s}_\mathrm{b}\mathrm{S}_+ + \mathcal{A}_\mathrm{b}\mathrm{r}_\mathrm{b}\mathrm{S}_- \tag{4}$$

where r_b and s_b are the rates for bone resorption and synthesis respectively, depending on the positiveness of the defined mechanobiological stimulus, and $\mathcal{A}_b$ is a fonction of the porosity φ^* which reads

$$\mathcal{A}_b = A_b k\varphi^*(1 - b\varphi^*) \tag{5}$$

with k and b indicating the intensity and the maximum threshold of the bone remodeling process depending on the porosity. The parameters of equations (1), (4) and (5) were identified using inverse methods from animal experimentations and modeling (Scala, 2016). For equations (2) and (3), the coefficients were quantified through histological analyses on sheep mandibles (Schmitt 2016).

A Finite Element (FE) method is used to predict bone kinetic remodelling when applied to different mechanobiological stimuli such as for example orthodontic forces. The major challenge lays in the identification and importance of each external source, their mutual interactions as well as the kinetics of each process.

3. Results

Some preliminary results have been obtained both in 2D (Schmitt, 2016) and 3D (Fig. 1) on the modeling of cell colonization of a porous titanium scaffold under simple cyclic bending. The cells migrate from the exterior to the interior of the implant following the principal directions and after 90 days most of the space is fulfilled with mature osteoblasts cells (Fig. 1).

4. Conclusion

A number of individual mechanical and biological phenomena are integrated within a single mechanobiological stimulus for bone remodeling. Each effect influences the bone density evolution and the remodeling process. The implications of these different effects could help the surgeons in the understanding and optimization of bone surgery parameters.

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