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Simulation of angiogenesis and cell differentiation in a CaP scaffold subjected to compressive strains using a lattice modeling approach

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ABSTRACT

Mechanical stimuli are one of the factors that influence tissue differentiation. In the development of biomaterials for bone tissue engineering, mechanical stimuli and formation of a vascular network that transport oxygen to cells within the pores of the scaffolds are essential. Angiogenesis and cell differentiation have been simulated in scaffolds of regular porosity; however, the dynamics of differentiation can be different when the porosity is not uniform. The objective of this study was to investigate the effect of the mechanical stimuli and the capillary network formation on cell differentiation within a scaffold of irregular morphology. A porous scaffold of calcium phosphate based glass was used. The pores and the solid phase were discretized using micro computed tomography images. Cell activity was simulated within the interconnected pore domain of the scaffold using a lattice modeling approach. Compressive strains of 0.5 and 1% of total deformation were applied and two cases of mesenchymal stem cells initialization (*in vitro* seeding and *in vivo*) were simulated. Similar capillary networks were formed independently of the cell initialization mode and the magnitude of the mechanical strain applied. Most of vessels grew in the pores at the periphery of the scaffolds and were blocked by the walls of the scaffold. When 0.5% of strain was applied, 70% of the pore volume was affected by mechano-regulatory stimuli corresponding to bone formation; however, because of the lack of oxygen, only 40% of the volume was filled with osteoblasts. 40% of volume was filled with chondrocytes and 3% with fibroblasts. When the mechanical strain was increased to 1%, 11% of the pore volume was filled with osteoblasts, 59% with chondrocytes, and 8% with fibroblasts. This study has shown the dynamics of the correlation between mechanical load, angiogenesis and tissue differentiation within a scaffold with irregular morphology.

1. Introduction

Bone is a living tissue that under normal conditions regenerates by itself. Nevertheless, when a defect exceeds a critical size, bone regeneration can be induced through the implantation of a biomaterial in the diseased or damaged tissue region. This biomaterial serves as a scaffold for cells to migrate, proliferate, differentiate and synthesize new extracellular matrix. Within the characteristics of engineered scaffolds, the architecture has an important role. An appropriate porosity and interconnectivity are necessary to allow cells to enter into the scaffold and to promote the formation of a vascular network (angiogenesis); which supply cells with oxygen and nutrients essential for their survival. In addition, the mechanical environment plays a critical role in the biological process. The scaffold mechanical properties need to be adequate to withstand the mechanical loads at the implantation site and to transmit the appropriate mechanical stimuli to the cells so that they follow the desired differentiation pathway.

Several mechanoregulation theories relate the magnitude of stress and strain present at the extracellular matrix and the interstitial fluid velocity with the formation of bone, cartilage and/or fibrous tissue [1–3]. Computational models based on Prendergast et al. [3] theory have successfully simulated the time course of tissue regeneration during fracture healing [4–7]. Additionally, this theory has been used to predict tissue growth at bone/implant interfaces [8], in bone chambers [9,10] and in scaffolds for osteochondral defect healing [11]. All these models used a diffusion equation to describe the migration and proliferation of cells within the regenerating tissues, assuming that cells attempt to reach a uniform distribution. A random walk model was introduced by Perez and Prendergast [12] to model specific cell proliferation using a lattice modeling approach. This concept was used by Byrne et al. [13] to simulate tissue growth within a regular scaffold, in order to

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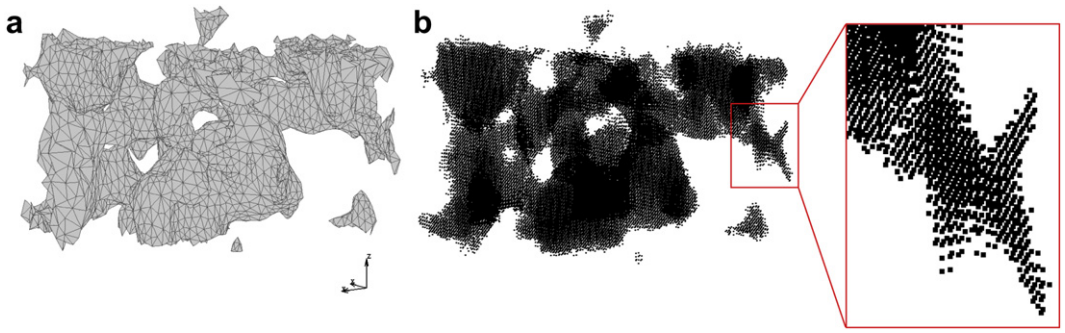

Fig. 1. Section of the scaffold used for the simulations. (a) Mesh of the interconnected pores used for FE models. (b) Lattice of the interconnected pores used for the cell activity simulation.

investigate the effect of scaffold design variables like porosity, Young's modulus and dissolution rate, and by Khayyeri et al. [14] to study tissue differentiation in an *in vivo* bone chamber.

In order to account for the role of angiogenesis during tissue differentiation, Geris et al. [15] developed a mathematical model to simulate tissue differentiation where cell density is regulated by the concentration of angiogenic factors. Checa and Prendergast [16] proposed a mechanobiological model to simulate capillary network formation and its effect on tissue growth in a bone/implant interface using the lattice modeling approach. This model

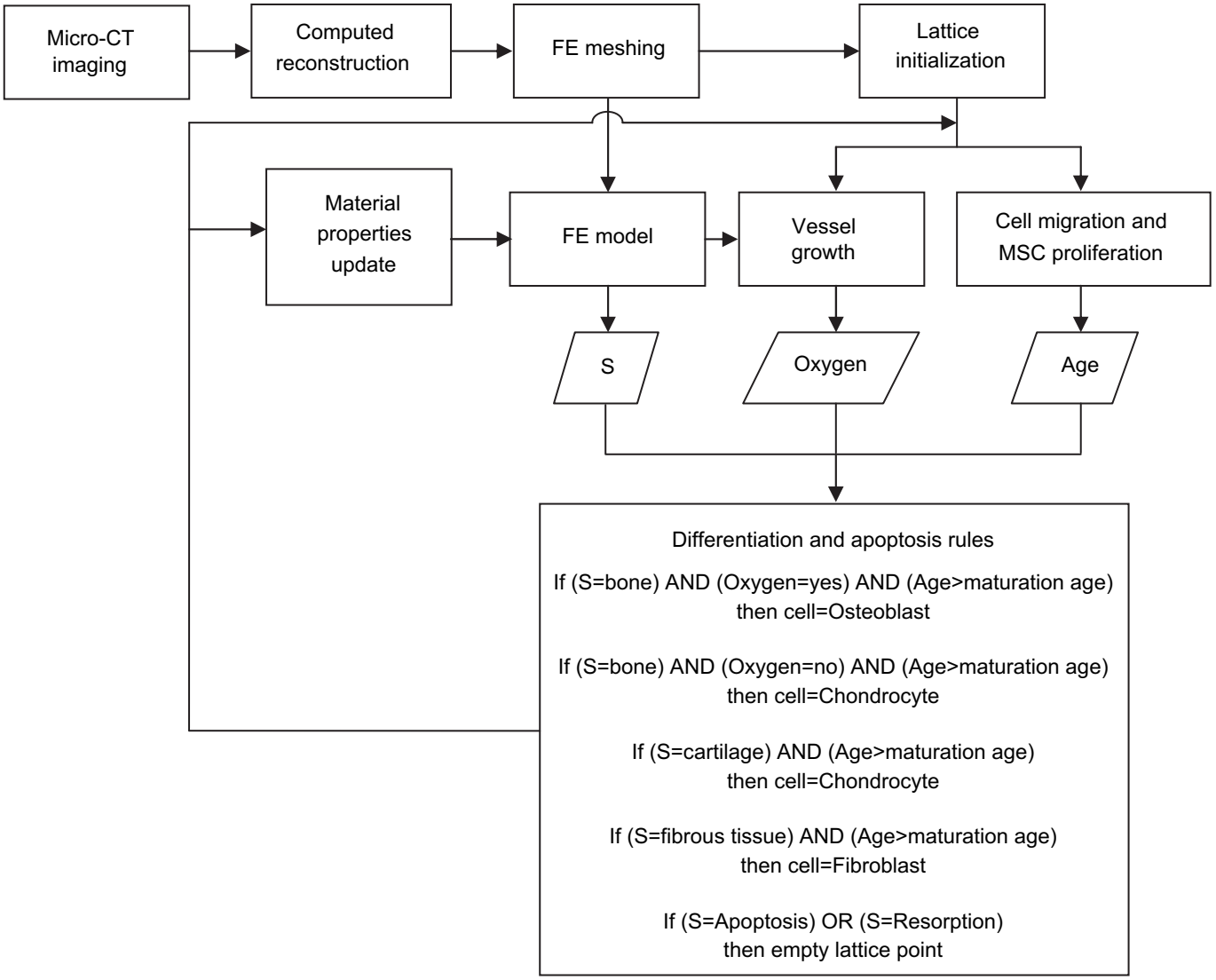

Fig. 2. Computational algorithm used to model cell differentiation and angiogenesis. The simulation of vessel growth, cell migration, MSC proliferation, MSC differentiation and cell apoptosis was performed in the lattice points within the interconnected pores of the scaffold. The mechano-regulatory stimuli *S* affecting cells were computed using a finite element model. Mature MSCs differentiated according to *S* and oxygen supply. Material properties for the FE model were updated according to cell differentiation. The simulations finished when homeostasis was achieved.