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On scaffold designing for bone regeneration: A computational multiscale approach

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Abstract

Scaffold design for bone tissue engineering applications involves many parameters that directly influence the rate of bone tissue regeneration onto its microstructural surface. To improve scaffold functionality, increasing interest is being focused on in vitro and in vivo research in order to obtain the optimal scaffold design for a specific application. However, the evaluation of the effect of each specific scaffold parameter on tissue regeneration using these techniques requires costly protocols and long-term experiments. In this paper, we elucidate the effect of some scaffold parameters on bone tissue regeneration by means of a mathematically based approach. By virtue of in silico experiments, factors such as scaffold stiffness, porosity, resorption kinetics, pore size and pre-seeding are analyzed in a specific bone tissue application found in the literature. The model predicts the in vivo rate of bone formation within the scaffold, the scaffold degradation and the interaction between the implanted scaffold and the surrounding bone. Results show an increasing rate of bone regeneration with increasing scaffold stiffness, scaffold mean pore size and pre-seeding, whereas the collapse of the scaffold occurs for a faster biomaterial resorption kinetics. Requiring further experimental validation, the model can be useful for the assessment of scaffold design and for the analysis of scaffold parameters in tissue regeneration.

Keywords: Bone tissue engineering; Porous scaffold; Computational mechanobiology; Multiscale analysis

1. Introduction

Tissue engineering covers a broad field that applies the principles of engineering and life sciences to the development of biological substitutes with the aim of restoring, maintaining or improving tissue or organ functions [1]. This definition addresses itself to comprehensive multidisciplinary research. Therefore, integrating biology, biochemistry and clinical medicine with materials science, physics and engineering disciplines is imperative to achieve clinical applications [2].

Focusing on bone tissue engineering, a temporary structural support usually known as a scaffold or bioscaffold is needed to fill the bony defect and withstand early loads, as well as to serve as a guide for the formation of the new bone, i.e. osteoconduction. In addition, it is desirable that the scaffold degrades over time, so that the whole defect can finally be filled with new tissue [3–5]. The usual procedure follows these steps: first, mesenchymal stem cells (MSCs) and bone cells are aspired directly from the patient or a donor, the main sites of these cells being the bone marrow [6,7] and the periostium. However, the number of MSCs in fresh adult bone marrow is small, around 1 per 100,000 nucleated cells, and decreases with age [8]. To overcome this lack, the number of stem cells can be amplified about 10 times with only a single passage in culture [9]. Using in vitro expansion of MSCs a more rapidly and uniform bone formation is observed [10,11]. The culture-expansion and cell seeding tasks tend to take place in bioreactors in preference to under static conditions. The biore-

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actor eliminates mass transport limitations to the scaffold interior and provides mechanical stimulation to the seeded cells through fluid shear [12]. After in vivo implantation of the functionalized scaffold, bone remodelling occurs in the neighborhood of the defect filled with the scaffold. Here, the bone matrix microstructure is modified by the combined action of osteoblasts and osteoclasts in adaptative response to the mechanical perturbation (stiffness/compliance) introduced by the scaffold implantation. Moreover, the stiffness of the scaffold also varies as a consequence of scaffold degradation and new bone apposition.

In this scenario, the overall success is directly dependent on scaffold properties such as biocompatibility, pore size, overall porosity, resorption kinetics, mechanical and flow properties, hydrophilicity and pre-seeding. The works by Hutmacher [13] and Rezwan et al. [14] are useful qualitative guidelines in this sense.

However, following a complete procedure for scaffold design is rather expensive from a purely experimental perspective. Therefore, to advance the understanding of the scaffold behaviour under different environments, computer techniques and mathematically based models (see [2], for a review) are becoming very useful tools for material engineers and biologists.

Tissue regeneration using scaffolds in vivo inherently works on two well-differentiated spatio-temporal scales: the tissue level and the pore scaffold level. Mathematical modelling of tissue regeneration within scaffolds has been traditionally restricted to one of these scales. For example, at the tissue (macroscopic) scale, the numerical simulation of osteochondral defect repair using a mathematical theory of cell differentiation [15] has been proposed by Prendergast and Kelly [16]. Moreover, an approach for the simulation of bone tissue regeneration within scaffolds considering the effect of the scaffold microstructure is introduced in Ref. [17]. At the microscopic or pore scaffold scale, homogenization techniques together with computer-aided design (CAD) tools allow macroscopic mechanical properties to be designed by controlling porosity and pore size [18–20]. On this same scale, bone regeneration in a unit cell of a scaffold microstructure was simulated by Adachi et al. [21] using concepts and hypotheses of previous remodelling mathematical models [22,23]. Recently, Byrne et al. [24] presented a mechanobiological model applied to a unit-cell scaffold to study the influence of several factors on tissue regeneration under uniaxial loading.

In this paper, we propose a new micro–macro mathematical approach for bone tissue regeneration within scaffolds. The model has been described previously [25] and it accounts for both scales. At the tissue level, the macroscopic mechanical, diffusive and flow properties are derived by means of the asymptotic homogenization theory [25–27]. At the microscopic scale, bone tissue regeneration at the scaffold microsurface is simulated using a certain bone growth model based on a bone remodelling theory [28], whereas scaffold degradation is implemented following Ref. [21]. Scaffold degradation and bone growth are mathematically modelled by the voxel finite element method (voxel FEM) [21,29]. As an example of its application, the experimental case analyzed in vivo in Ref. [30] is reproduced numerically here. In the reference scaffold used in Ref. [25] we analyze the effect of changing the following variables: (i) Young's modulus (stiffness) of the bulk biomaterial; (ii) resorption kinetics of the bulk biomaterial; (iii) overall porosity; (iv) mean pore size; and (v) the effect of pre-seeding. The results are compared qualitatively, where possible, with experimental ones, and the effect of each parameter on the overall bone tissue regeneration is elucidated.

2. Materials and methods

In this section, the methodology and mathematical models used to predict bone growth in a specific application are briefly explained. A more detailed explanation and additional mathematical derivations may be found in Ref. [25]. Two scales of analysis are here considered, i.e. the tissue (macroscopic) and pore (microscopic) scales (see Fig. 1). First, the multiscale analysis and the interaction between the two scales are presented, followed by the introduction of the models of bone growth and scaffold resorption both at the microscopic scale.

2.1. Micro–macro coupling

Bone and scaffold are treated in different ways. For simplicity, the bone organ domain (Fig. 1b) is treated only macroscopically through a fully heterogeneous model, with the Young's modulus (E) and Poisson ratio (ν) defined by the following experimental correlations [31]:

$$E(\mathrm{MPa}) = \begin{cases} 2015\rho^{2.5} & \text{for } \rho \leqslant 1.2\ g/cc \\ 1763\rho^{3.2} & \text{for } \rho > 1.2\ g/cc \end{cases}$$
$$\nu = \begin{cases} 0.20 & \text{for } \rho \leqslant 1.2\ g/cc \\ 0.32 & \text{for } \rho > 1.2\ g/cc \end{cases} \tag{1}$$

where ρ is the macroscopic apparent bone density. This variable is not fixed but changes with the external mechanical stimulus, as is well-known from many experimental observations [32–35] and associated bone remodelling theories [28,31]. Therefore, the apparent bone density is treated as a state variable, the evolution of which is controlled by the strain energy at each location of the bone organ [31]. Moreover, the process of healing and vasculogenesis is modelled as the diffusion or invasion of cells (considered in the sense of cell populations) and formation of blood vessels within the scaffold core. This is simulated, as a first approach, through Fick's law in the macroscopic domain. This analysis provides the variable $\bar{c}$, used in the bone growth model explained below.

On the other hand, the scaffold macroscopic properties are directly and explicitly related to its underlying microstructure by using homogenization techniques [25–27,36]. This allows the macroscopic or apparent properties to be obtained through analysis and averaging at the micro-

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