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Prediction of permeability of regular scaffolds for skeletal tissue engineering: A combined computational and experimental study

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ABSTRACT

Scaffold permeability is a key parameter combining geometrical features such as pore shape, size and interconnectivity, porosity and specific surface area. It can influence the success of bone tissue engineering scaffolds, by affecting oxygen and nutrient transport, cell seeding efficiency, in vitro three-dimensional (3D) cell culture and, ultimately, the amount of bone formation. An accurate and efficient prediction of scaffold permeability would be highly useful as part of a scaffold design process. The aim of this study was (i) to determine the accuracy of computational fluid dynamics (CFD) models for prediction of the permeability coefficient of three different regular Ti6Al4V scaffolds (each having a different porosity) by comparison with experimentally measured values and (ii) to verify the validity of the semi-empirical Kozeny equation to calculate the permeability analytically. To do so, five CFD geometrical models per scaffold porosity were built, based on different geometrical inputs: either based on the scaffold's computer-aided design (CAD) or derived from 3D microfocus X-ray computed tomography (micro-CT) data of the additive manufactured (AM) scaffolds. For the latter the influence of the spatial image resolution and the image analysis algorithm used to determine the scaffold's architectural features on the predicted permeability was analysed. CFD models based on high-resolution micro-CT images could predict the permeability coefficients of the studied scaffolds: depending on scaffold porosity and image analysis algorithm, relative differences between measured and predicted permeability values were between 2% and 27%. Finally, the analytical Kozeny equation was found to be valid. A linear correlation between the ratio Φ^3/S_s^2 and the permeability coefficient k was found for the predicted (by means of CFD) as well as measured values (relative difference of 16.4% between respective Kozeny coefficients), thus resulting in accurate and efficient calculation of the permeability of regular AM scaffolds.

1. Introduction

Bone tissue engineering scaffolds are porous materials which assist the healing of large or non-healing bone defects when combined with osteoprogenitor cells and appropriate growth factors [1,2]. A porous scaffold must behave as a carrier for cells and molecules during in vitro culture, and it also has to support the external loads after in vivo implantation [3]. Thus, the scaffold architecture is a crucial factor in fulfilling this combination of mechanical and biological requirements. The mechanical properties (i.e. scaffold stiffness) and the geometrical parameters such as pore shape and size, pore interconnectivity and specific surface area have been shown to influence the success of bone scaffolds [4–6]. The scaffold permeability is a key parameter that best represents all the aforementioned geometrical features [7]. It affects the way in which nutrients (such as glucose) and oxygen disperse through the porous scaffold [8], it influences cell seeding efficiency [9], scaffold degradation [10], three-dimensional (3D) in vitro cell culture [10] and ultimately in vivo bone formation [11]. On the one hand, attaining an optimal value for the permeability is not straightforward, as it depends on the desired biological outcome (e.g. a high-permeability value was found to improve in vivo bone formation [3], whereas a lower value was found to enhance cell seeding efficiency [9]). On the other hand, quantifying and controlling the permeability is crucial to understanding its effect on tissue regeneration.

The intrinsic permeability coefficient k of an open porous structure is a measure of the ability of a fluid medium to flow through it and, in the simplest formulation, it can be determined

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by measuring the amount of fluid (or gas) flowing through the porous material in a given time under an applied external pressure, as captured by Darcy's law [13].

$$k = (Q\mu L)/(A\Delta P) \tag{1}$$

where Q is the volumetric flow rate, ΔP is the pressure drop, A and L are the cross-sectional area and the length of the porous material, respectively, and μ is the dynamic viscosity of the fluid. It is assumed that Darcy's Law is valid if the Reynolds number (using the mean pores diameter) is below a limit somewhere between 1 and 10 [14]. Several studies measured the permeability coefficient of porous scaffolds or tissues using perfusion systems, either by applying a constant flow rate with a pump and measuring the pressure drop [15] or by applying a hydrostatic pressure head over the sample and measuring the mass or volumetric flow rate with a weighing scale [16,17]. When studies are limited to those modelling fluid flow and permeability in regular scaffolds, either analytical formulae [18] or homogenization techniques [19–21] are used to determine the permeability tensor. In the first case, the semi-empirical Kozeny equation concisely expresses the relation between the (isotropic) permeability k, the porosity Φ and the specific surface area S_s as follows:

$$k = \frac{1}{c_K}\left(\frac{\phi^3}{S_s^2}\right) \tag{2}$$

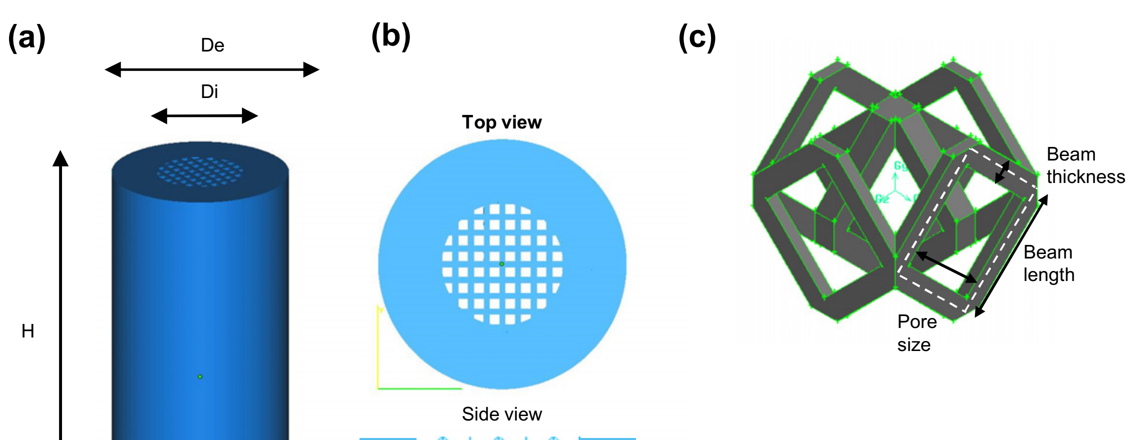
with C_K the empirical Kozeny constant. This relation has been frequently extended to estimate the permeability coefficient for different porous media (Carman–Kozeny equation [22] and adapted versions [23]) given its wide range of applicability to all types of soil [24]. The main limitation of this equation is the fact that the determination of the C_K coefficient strongly depends on the pore geometry and therefore cannot be estimated a priori. Another limitation of the Kozeny equation is that it is intended for isotropic porous media. Indeed, C_K is a scalar value rather than a tensor quantity. Applying the Kozeny equation to capture the flow through an anisotropic medium in a given direction will only yield information on a single component (on the diagonal) of the permeability tensor. As an alternative to these analytical approaches, fluid flow modelling on a simplified geometry of the scaffold (i.e. periodic unit cell) was used to compute the permeability coefficients based on the average Stokes flow velocity (neglecting any inertial effects, i.e. for low Reynolds numbers) and calculated in response to an applied pressure gradient. The geometrical features of the unit cell used for building up the model (pores and strut size) can be obtained either from computer-aided design (CAD) of the scaffold [25] or from microfocus X-ray computed tomography (micro-CT) image analysis [12,26]. In the first case, care is required, since the designed scaffold architecture can differ from the manufactured one, depending on the manufacturing technique. This, in turn, can strongly influence the flow field [27]. In the second case, although micro-CT can be considered the gold standard for non-destructive assessment of the scaffold architecture [28–30], dimensional values are dependent on the spatial image resolution and the image analysis algorithms used to extract them. Again, this can bias the modeling results.

The objectives of this study are twofold. First, the accuracy of computational fluid dynamics (CFD) models for the prediction of the scaffold permeability is determined. This will be done for three different designed, additive manufactured (AM) open porous Ti6Al4V scaffolds, with the same architecture but with different pore sizes and beam thicknesses. CFD models will be created based on two different geometrical inputs for the internal architecture: either based on the scaffold's CAD design (further referred to as CAD-based modelling) or derived from micro-CT data of the AM scaffolds (further referred to as micro-CT-based modelling). For the latter, the influence of the spatial image resolution and the image analysis algorithms used to extract the pore and strut dimensions of the scaffold architecture on the predicted permeability will be analysed. The predicted permeability values will be compared with experimental measurements of permeability. Secondly, the validity of the semi-empirical Kozeny equation for analytically calculating the permeability will be verified, and its application within the context of a scaffold design process will be discussed.

2. Materials and methods

2.1. Scaffold design, production and surface treatment

The scaffolds used in this study were open porous titanium alloy (Ti6Al4V) structures produced by a non-commercial selective



Overall dimensions	
Height H [mm]	30
Internal diameter Di [mm]	6
External diameter De [mm]	12

Fig. 1. (a) CAD of the Ti6Al4V scaffold. (b) Top view and side view of a cross section of the scaffold. (c) Repetitive unit cell.