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A coupled diffusion-fluid pressure model to predict cell density distribution for cells encapsulated in a porous hydrogel scaffold under mechanical loading

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ABSTRACT

Tissue formation within tissue engineering (TE) scaffolds is preceded by growth of the cells throughout the scaffold volume and attachment of cells to the scaffold substrate. It is known that mechanical stimulation, in the form of fluid perfusion or mechanical strain, enhances cell differentiation and overall tissue formation. However, due to the complex multi-physics environment of cells within TE scaffolds, cell transport under mechanical stimulation is not fully understood. Therefore, in this study, we have developed a coupled multiphysics model to predict cell density distribution in a TE scaffold. In this model, cell transport is modelled as a thermal conduction process, which is driven by the pore fluid pressure under applied loading. As a case study, the model is investigated to predict the cell density patterns of pre-osteoblasts MC3T3-e1 cells under a range of different loading regimes, to obtain an understanding of desirable mechanical stimulation that will enhance cell density distribution within TE scaffolds. The results of this study have demonstrated that fluid perfusion can result in a higher cell density in the scaffold region closed to the outlet, while cell density distribution under mechanical compression was similar with static condition. More importantly, the study provides a novel computational approach to predict cell distribution in TE scaffolds under mechanical loading.

1. Introduction

Tissue engineering approaches strive to treat bone pathologies by exploiting the capacity for bone progenitor cells to grow and produce tissue constituents under specific biochemical and physical conditions. Bone tissue formation within porous biomaterial scaffolds requires a series of coordinated cellular fate processes, involving proliferation, migration and cell attachment to scaffold surfaces, which is followed by differentiation and extracellular matrix production [1–3]. Studies have shown that mechanical stimulation, in the form of fluid perfusion and mechanical strain, can significantly enhance tissue formation within biomaterial scaffold systems [1,4]. While this tissue formation is usually attributed to enhanced nutrient delivery and the promotion of osteogenic differentiation, it has also been suggested that mechanical stimulation also enhances cell distribution and promotes cell infiltration throughout the scaffold [5]. A recent study, in which chondrocytes were encapsulated within solid hydrogel has shown that the cell and extracellular matrix (ECM) transport can be significantly enhanced by the osmotic pressure [6]. However, the precise role of mechanical stimulation in directing cell transport within a porous 3D biomaterial scaffolds is not yet fully understood.

In a previous study, a combined numerical and experimental approach was employed to characterise the cell density distribution within a polylactide co-glycolide (PLGA) scaffold under static conditions, and the feasibility of using a mass diffusion model for predicting the MC3T3 cell transport at the whole scaffold level was demonstrated [7]. However, the influence of the mechanical environment on the cell transport has not been previously considered in a numerical model. To understand the role of mechanical stimulation on tissue formation within 3D scaffold systems, several computational models have been developed that incorporate mathematical representations of cellular activity [8–13]. For example, recent computational studies have assumed the neotissue as biphasic poroelastic, based on which computational fluid dynamic (CFD) approach was employed to compute the mechanical stimulation (i.e. shear stress and fluid velocity) within the Ti6Al4V scaffolds and inside the neotissue [12,13]. Another study, in which the Calcium Phosphate (CaP) scaffold pores (with infiltrated tissue) were homogenised and modelled as biphasic poroelastic, has computed the resultant mechanical

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stimulation (shear strain and fluid velocity) within the scaffold under fluid perfusion [14]. However, the cell density change due to the fluid transport has not been considered in these studies yet. Previous experimental studies have shown that cell density distribution can have important implication for nutrient delivery and mechanical environment [15–17]. To compute the cell density, mass-diffusion models and lattice-based models using random-walk theory have been proposed [8–10,18]. However, these approaches do not couple cell transport to mechanical stimulation, meaning that the effect of mechanical environment on the diffusion/transport process is not considered [8–10,18,19]. Given that mechanical stimulation has a distinct effect on cell/ECM transport in solid hydrogel [6], it is also likely that the mechanical environment influences cell transport within 3D porous scaffolds. Indeed a recent computational study, which investigated cell seeding under fluid perfusion conditions, has shown the distinct influence of fluid perfusion on the cell density within a poly (D,L-lactide) acid scaffold with gyroid pores [5]. However, in that study cells were modelled as discrete particles suspended in a fluid, as such cell migration was dictated entirely by the fluid drag force [5]. However, cell density distribution within scaffolds due to the cell transport after seeding was not investigated under either static or dynamic conditions. Therefore, to date no computational approach has incorporated the effects of mechanical stimulation on cell transport within scaffold.

Cell seeding is also one of the most significant strategies, which will affect the characteristics and functionality of engineered tissues [15]. For many bone tissue engineering studies, cells have been seeded on the periphery of tissue engineered scaffolds [7]. More recently cell-laden scaffold constructs have been explored as a bone tissue engineering strategy, in particular using 3D bioprinting, in which cells are initially encapsulated within the constructs (e.g. hydrogel) [20,21]. Therefore, two types of seeding approaches are commonly employed in tissue engineering experiments: (i) cells are seeded on periphery of the scaffolds; (ii) cells are encapsulated during scaffold formation [22]. However, the implication of these choices has not been fully understood yet.

In this study we develop a novel cell transport model using a coupled multiphysics approach, which is implemented in the Abaqus finite element solver. Cell transport through a porous cell (pre-osteoblasts MC3T3-e1) laden hydrogel scaffold is modelled by a mathematical analogy (thermal conduction), while the influence of pore fluid pressure under mechanical stimulation is included by a coupled cell transport-fluid pressure analysis. The model is applied to predict transport patterns of MC3T3-e1 cells under different seeding condition (i.e. initially encapsulation and peripheral seeding) and under a range of different loading regimes (i.e. mechanical compression and fluid perfusion). This study will not only provide a novel approach for predicting the cell density distribution within biomaterial scaffolds *in vitro*, but also can add new a value to the development of an adaptive algorithm to predict tissue differentiation and bone fracture healing.

2. Methods

2.1. Model formulation

Previous experimental and computational studies have suggested that tissue engineering (TE) scaffolds with a large pore size ($\geq$300 μm) are suitable for bone tissue engineering [23–25]. Therefore, we considered a single unit-cell of a spherical-pore architecture scaffold (0.5 × 0.5 × 0.5 mm) that had a pore size and porosity of 300 μm and 70%, respectively (see Fig. 1c). The scaffold was fabricated from a porous gelatin hydrogel crosslinked with microbial transglutaminase, which had a Young's modulus and Poisson's ratio of 3 kPa and 0.45, respectively [26]. In this study, the MC3T3-E1 were initially encapsulated within the hydrogel struts, but over time they migrated towards the porous area, due to the nutrient concentration gradient, and infiltrated the pores (see Fig. 2a). Cells could receive mechanical stimulation once they grew into the porous area. Therefore, the mechanical loading began once the cells/aggregates had already infiltrated the scaffold pores and a rudimentary extracellular matrix (ECM) had formed within the porous space (see Fig. 2a). Thus, in the computational model, the cell/ECM-infiltrated pores were homogenised and modelled using biphasic poroelasticity theory, whose constitutive behaviour was described in Eqn (1) [27],

$$-\frac{k_p}{\mu_f}\nabla^2 p + \alpha\cdot\frac{\partial}{\partial t}\left[\sum_{i=1}^{3}\frac{\partial u_i}{\partial x_i} + \frac{nK_s + (\alpha - n)K_f}{\alpha K_s K_f}\cdot p\right] = 0 \quad (1)$$

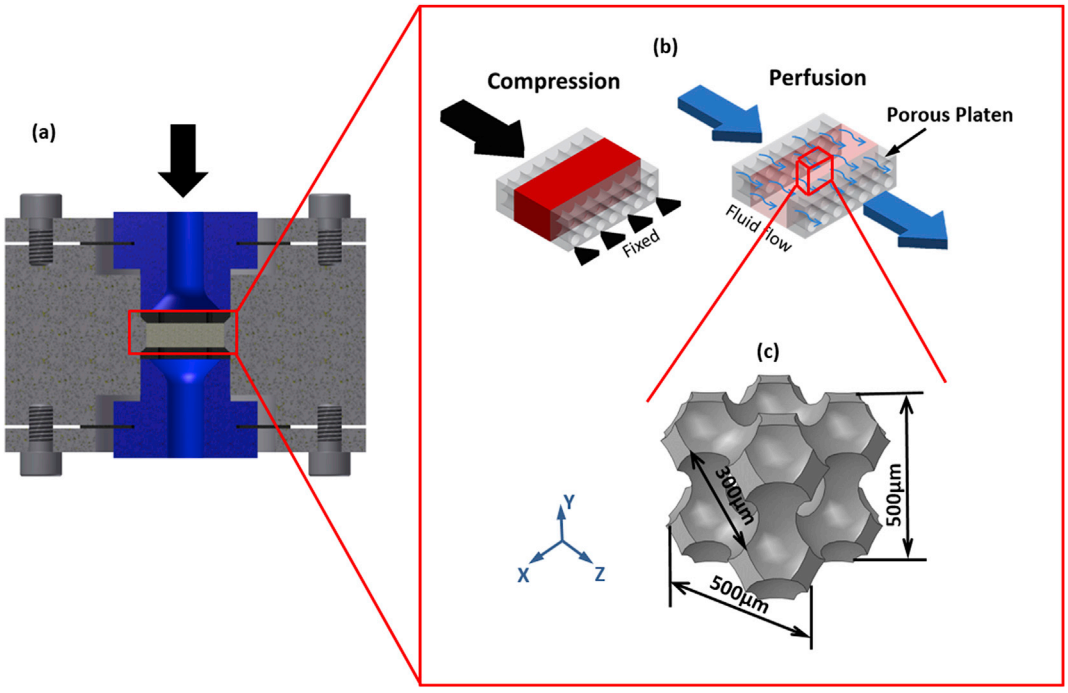

Fig. 1. Schematic image of **(a)** custom-made device and **(b)** fluid perfusion and confined compression of the scaffold **(c)** section of the regular scaffold used in computational model, which has a pore size and porosity of 300 μm and 70%, respectively.