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Nutrient transport through deformable cylindrical scaffold inside a bioreactor: An application to tissue engineering

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ABSTRACT

Tissue engineering deals with the development and growth of cells to obtain tissue structure or organs. In this process, a porous material known as a scaffold is designed to support the cells to grow in the desired form. This designed structure is incubated inside a bioreactor which provides adequate nutrient supply for the cells to grow. The major challenge in tissue engineering is to model a bioreactor and the scaffold which supports high-density cells so that adequate nutrient can be delivered in inner regions to get the significant cell growth. Mathematical modeling of such processes is essential to understand the entire mechanism. Correspondingly, a mathematical model for fluid flow and nutrient transport is developed inside a cylindrical bioreactor containing tubular scaffold which is degradable as well as deformable due to its elastic property. Living biological cells are assumed to adhere to the solid matrix of scaffold firmly. The volume fraction of the solid phase which includes cells and scaffold matrix is assumed to be constant despite the fact that proliferation of cells and degradation of scaffold matrix are undergoing simultaneously. Fluid flow and deformation of the tissue (scaffold) are modeled based on biphasic mixture theory. Navier–Stokes equation accounts for the free fluid in the annular region of the bioreactor. Advection–diffusion-reaction equation governs the concentration of a nutrient in the scaffold region whereas advection–diffusion equation governs the nutrients in the free lumen. Semi-analytical treatment on the mathematical model includes Laplace transformation to deal with the time dependency of the governing fluid flow equation and consequently, Durbin's algorithm is used to retrieve the time-dependent variables. The model allows the uniform nutrient transport inside the scaffold region so that cells get sufficient amount of nutrient to grow and reduce the cell death. Moreover, Sherwood number has been calculated to analyse the mass transport of solute concentration from scaffold region to the free fluid region and vice-versa through the interface.

1. Introduction

Tissue engineering approaches have gained focus and attention of researchers to regenerate human tissue in the laboratory for the repair and replacement of damaged or lost tissue. Also, this technique is used to regenerate skin, muscle

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or bone tissue or may involve reconstruction of entire organs such as heart, kidney or liver, etc (Shakeel, 2011). In order to generate a tissue, one of the primary requirements is to have a biodegradable extracellular matrix (ECM), also termed as scaffold, where cells are implanted so that a three-dimensional growth of the tissue can occur. Due to the elastic nature of the scaffold and growth of cells, the whole ECM along with the cells is considered as a deformable porous material (Sacco et al., 2017). In the case of deformable porous media, the solid matrix gets deformed due to any applied force. When an external force is applied to a deformable porous medium, the volume fraction of the pores is affected. The change in pressure causes fluid-filled pores to undergo deformation, and the corresponding pressure is called the pore pressure. In order to deal with these two moving phases, i.e., fluid and solid phases, one can adopt biphasic mixture theory equations which are derived from the theory of mixtures. Rajagopal (2007) can be suggested for the detailed description of the theory of mixtures. Most of the theoretical studies dealing with the biological tissues, like, blood flow through capillaries and the influence of glycocalyx on flow within blood vessels have assumed glycocalyx medium as deformable porous medium. In the case of tissue engineering, recent work on the fluid flow, nutrient delivery and consumption, along with deformation of the scaffold has been studied by Sacco et al. (2017). Cell type, suitable scaffold, cells growth factor, bioreactors, are fundamental components in order to develop a tissue from the cells. The scaffold should be modeled as a highly porous bio-compatible and bio-degradable component so that the cells can be seeded to inner regions of the scaffold and can get proper space to grow. The main challenge is to supply adequate nutrients transport to the inner regions of the scaffold so that homogeneous cell growth takes place. Scaffolds are engineered to be biodegradable and the growth of cells allow us to take the scaffold as a deformable porous medium. Manufacturing of scaffolds include variety of artificially synthetic polymers and natural materials which support the cells to grow without any side effects and infection. Some of the natural materials are collagen, glycosaminoglycan, and chitosan; and some of the artificially synthetic polymers are polyglycolic acid (PGA), polylactic acid (PLA), and polycaprolactone (PCL) (Lanza et al., 2011). To obtain the optimum growth of a tissue, cells are picked up on their potential to develop faster and their ability to conduct biological activities. In the case of *in vitro* experiments, once cells are seeded in the scaffold, the scaffold is cultured into a closed system which provides the biological and biochemical environment to cells so that they develop as in *in vivo*. This closed system which provides the controlled environment is known popularly as a bioreactor.

Coletti et al. (2006) developed a mathematical model to study the mechanism of convection and diffusion inside a perfusion bioreactor. Chung et al. (2006) modified the perfusion bioreactor to a three layer model which consists porous scaffold between two fluid layers or culture medium. Chung et al. (2007) proposed a compact single layer in the subsequent model which includes the scaffold construct. They studied the cell growth due to nutrient distribution within the scaffold and compared the results with their earlier three layer model. According to them, the accuracy of cell growth was found to be same for single layer and three layer model. Lemon et al. (2006) developed a general multiphase model of tissue growth consisting an arbitrary number of phases, using multiphase porous flow mixture theory. The model includes mass and momentum balance equations for each tissue component, together with the material deformation in response to the stresses. In a subsequent paper, Lemon and King (2007) presented a multiphase model of nutrient limited engineered tissue growth and examined the multiphase nature of tissue mechanics and nutrient transport. They presented a three-phase case of motile cells, water and scaffold. Lemon et al. (2007) presented a mathematical model for the cell growth with different oxygen concentrations inside the porous scaffold. Waters et al. (2006) have developed a mathematical model of rotating bioreactor to investigate the tissue construct formed from single-cell suspension in culture media. In their model, a viscous fluid layer is surrounded by an extensible membrane in a viscous fluid where viscosity differs in the scaffold (due to the presence of cells). Whittaker et al. (2009) developed a mathematical model for nutrient transport through culture medium where a porous walled hollow fibres were penetrated inside the scaffold which helps as additional source of nutrients to the cells. Shakeel (2011) developed a mathematical model of fluid flow, nutrient concentration and cell growth in a perfusion bioreactor. One can refer O'Dea, Byrne, and Waters (2012) to understand the fundamental processes that regulate the biological tissue growth and the optimal design of *in vitro* methods, where they have demonstrated the combination of mathematical modeling, analysis and in silico computations. In order to obtain better insights of cell population growth, they described the advantages and limitations of different mathematical modeling approaches. Pearson et al. (2013) considered a hollow fibre membrane bioreactor (HFMB) and studied the fluid flow and nutrient transport based on the multiphase model developed by Lemon and King (2007). However, the multiphase models that they have used were imposed on the cells and the culture medium within the scaffold assuming non-degradable scaffold with constant volume fraction. They also studied the evolution of mass by considering cell production rate in the conservation of mass term. One can treat a tubular scaffold as a deformable hydrogel-like material; for example, endothelial glycocalyx layer inside the blood vessel. The hydrodynamics of interstitial flow field inside endothelial glycocalyx can be treated as Newtonian (Barry et al., 1991; Damiano et al., 1996; Dey & Raja Sekhar, 2016; Wang & Parker, 1995; Wei et al., 2003). Similarly, in this study, the fluid phase inside the scaffold is Newtonian in nature. There are numerous studies on the cell growth inside different bioreactors with different models where some of these have been discussed above, example, perfusion bioreactor, rotating wall vessel bioreactor, spinner flask bioreactor, hollow fibre membrane bioreactor (HFMB), etc. However, all the bioreactors mentioned above are not yet at their optimal levels regarding the production of healthy tissue with the optimum growth of cells. Therefore, in this field, there is a scope to design new techniques where the optimal growth of cells with formation of healthy tissues or organs can be achieved. As discussed above, a supply of adequate nutrient inside the bioreactor is another challenge to reach every part of the scaffold homogeneously so that homogeneous growth can take place. Mass balance equation for nutrient transport inside the scaffold region is usually modeled using advection–diffusion-reaction equation where the rate of nutrient uptake