Mathematical Biosciences 242 (2013) 86–94

Contents lists available at SciVerse ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

2-D coupled computational model of biological cell proliferation and nutrient delivery in a perfusion bioreactor

Muhammad Shakeel

Air University, PAF Complex, E-9 Islamabad, Pakistan

ARTICLE INFO

Article history:
Received 24 June 2012
Received in revised form 9 December 2012
Accepted 18 December 2012
Available online 3 January 2013

Keywords:
In vitro tissue engineering
Nutrient concentration
Cell proliferation
Flow filed
Perfusion bioreactor

ABSTRACT

Tissue engineering aims to regenerate, repair or replace organs or tissues which have become defective due to trauma, disease or age related degeneration. This engineering may take place within the patient's body or tissue can be regenerated in a bioreactor for later implantation into the patient. Regeneration of soft tissue is one of the most demanding applications of tissue engineering. Producing proper nutrient supply, uniform cell distribution and high cell density are the important challenges. Many experimental models exist for tissue growth in a bioreactor. It is important to put experiments into a theoretical framework. Mathematical modelling in terms of physical and biochemical mechanisms is the best tool to understand experimental results.

In this work a mathematical model of convective and diffusive transport of nutrients and cell evolution in a perfusion bioreactor is developed. A cell-seeded porous scaffold is placed in a perfusion bioreactor and fluid delivers the nutrients to the cells for their growth. The model describes the key features of the tissue engineering processes which includes the interaction between the cell growth, variation of material permeability due to cell proliferation, flow of fluid through the material and delivery of nutrients to the cells. The fluid flow through the porous scaffold is modelled by Darcy's law, and the delivery of nutrients to the cells is modelled by the advection–diffusion equation. A non-linear reaction diffusion system is used to model the cell growth. The growth of cells is modelled by logistic growth. COMSOL (a commercial finite element solver) is used to numerically solve the model. The results show that the distribution of cells and total cell number in the scaffold does not depend on the initial cell density but depend on the material permeability.

1. Introduction

Tissue engineering, the regeneration of organs or tissues in the laboratory for the replacement of damaged or lost tissue, is a multidisciplinary science since it aims to apply the principles of engineering and life sciences to reinstate the functions of devastated organs or tissues. Tissue engineering faces several challenges of which achieving significant cell growth in the supporting scaffold is one. To achieve the optimal cell density tissue engineers must ensure adequate delivery of nutrients to the inner region of the scaffold and uniform cell distribution in the final construct. During cell growth biochemical and physical mechanisms interact in a very complex manner.

To understand the complex interacting phenomena of these mechanisms in the scaffold–bioreactor system number of mathematical models have been developed. Translating complex biological systems into mathematical equations with well defined parameters, we aim to provide a better understanding of these systems. The crucial benefit of mathematical modelling is that a simple mathematical model can help to predict and analyse the complex mechanisms involved in the system. Due to these reasons mathematical models of pathological and physiological processes have already been developed in various areas *e.g.* solid tumour growth [3].

Lewis et al. [14] developed a model for the spatial and temporal distribution of oxygen within a scaffold and accounted for cell proliferation. They compared the results with the experimental data of Malda et al. [17]. The authors showed that cell -scaffold constructs that rely on diffusion for nutrient transport produce proliferation dominated regions near the outer edge of scaffold when cell density and oxygen consumption rate exceed critical levels. Croll et al. [8] developed a model of oxygen diffusion and cell proliferation during the early stages of implantation in a dome-shaped PLGA scaffold. The cell's oxygen consumption was again described by Monod's kinetics. Simple models were incorporated for vascular proliferation, cell migration and the effect of cell density on the effective oxygen diffusivity. They found that a homogeneous cell seeding strategy, even with a moving oxygen source provided via vascularization gives rise to hypoxic conditions in some regions

* Tel.: +92 3325474901.
E-mail address: apshakeel2004@yahoo.com

0025-5564/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.mbs.2012.12.004

of the scaffold for an unacceptable period of time. They proposed that heterogeneous seeding strategy may be more appropriate for large scale tissue engineering. Landman and Cai [13] extended the work of Croll et al. [8] and Lewis et al. [14]. They developed and investigated a 1-D model of oxygen concentration, cell proliferation and cell migration inside a scaffold. An arteriovenous loop is placed inside the scaffold, in order to form a vascularizing network within a scaffold. The cells proliferation rate is described by a Heaviside step function $H(C - C_h)$, where C is the nutrient concentration and C_h is the minimum nutrient concentration required for the cells to survive. They considered the additional effects of vascular proliferation, homogeneous and heterogenous seeding, diffusion of cells and critical hypoxic oxygen concentration.

In all the above models the transport of nutrients is by diffusion alone. This transport mechanism is useful when the thickness of tissue is less than the few millimetres. However, when the size of the tissue construct is large then the supply of nutrients is limited to the exterior of the scaffold and cells in the internal regions of the scaffold become hypoxic very quickly. One way to overcome the diffusion limitations is to consider advective transport. Several authors developed mathematical models of advective and diffusive transport of nutrients in perfusion bioreactors. Coletti et al. [7] developed a comprehensive mathematical model of convection and diffusion in a perfusion bioreactor. The fluid dynamics of the culture medium flow inside the bioreactor but external to the scaffold is described using Navier–Stokes equations for an incompressible fluid while flow through the scaffold is modelled by Brinkmans extension to Darcy's Law for porous materials. The nutrient uptake rate is described by Michaelis–Menton kinetics and cell proliferation is modelled as a function of nutrient concentration through the Contois equation, accounting for contact inhibition. Chung et al. [6] developed a mathematical model to investigate the cell proliferation, nutrient uptake and culture medium circulation within a porous scaffold under direct perfusion. They proposed a three layer model consisting of a porous scaffold sandwiched between two fluid layers. The nutrient uptake rate is described by Michaelis–Menton kinetics and cell proliferation is described by the modified Contois function. The fluid flow outside the cell scaffold construct was modelled by the Navier–Stokes equation while the fluid dynamics within the cell scaffold construct is modelled by the Brinkmann equation for porous media. The effect of time-dependent porosity and permeability changes of the scaffold due to the cell proliferation were also included. They concluded that cell proliferation can be enhanced by media perfusion and it is possible to obtain more spatially uniform distribution of cells compared to static culture. In a subsequent paper, Chung et al. [5] proposed a compact single layer model consisting of a scaffold construct only. They studied the cell proliferation and nutrient distribution and compared the results with the three layer model. They found that the single layer model predicts the cell proliferation and nutrient distribution as accurately as the three layer model [6] developed earlier.

We focus here on developing mathematical models for tissue growth in bioreactors which will not only enhance the understanding of the mass transfer and cell growth processes but will also demonstrate the utility and potential of computational models in choosing the various parameters for optimal cell growth.

In this work we describe a simple coupled mathematical model of nutrient transport and cell growth in a perfusion bioreactor. The model includes the important features of the tissue engineering process including the fluid flow, nutrient transport, cell growth and permeability variation of the material due to cell growth. We solve the model numerically by using the finite element solver COMSOL.

The paper is organised as follows. In Section 2 we have discussed the main interacting phenomena taking place in the scaffold bioreactor system. In Section 3 we present the dimensional model equations and in Section 4 we present the dimensionless model. The parameter values and solution method are described in Section 5. We present the results for various initial seeding strategies, permeability distributions and different imposed flow rates in Section 6.

2. Conceptual model

Cell growth and nutrient transport are the two major phenomena taking place in the perfusion bioreactor. Apart from these two phenomena, during the cell growth different biochemical and mechanical forces are also in operation in a perfusion bioreactor and they influence the bioreactor performance. Fig. 1 shows the main interacting phenomena taking place in a perfusion bioreactor when convective and diffusive transport of nutrient and cell growth take place within a scaffold. Nutrient transport is due to convection and diffusion and it affects the nutrient uptake rate *i.e.* if the nutrient transport is high then the nutrient uptake rate is also high and as a result cell growth will also be high. As cells grow and occupy the scaffold voids, the porosity and permeability of scaffold decreases from its initial value and the space left for the new cells is smaller. Due to the decrease in porosity the rate of diffusion of nutrients also decreases; on the other hand the decrease in permeability will have a direct effect on the convective velocity. Consequently the decrease in convective velocity and diffusion will influence the mass transfer and hence cell growth.

3. Geometry and model equations

Let us assume that a cell-seeded porous scaffold consisting of interconnected porous network is placed in the bioreactor. Let the length and width of scaffold be $2L^*$ (stars are used to denote dimensional quantities throughout). We consider a Cartesian coordinate system (x^*, y^*) aligned with the porous scaffold. The scaffold is characterised by the usual properties of porous material (porosity, void fraction and permeability). In this model we assume that the fluid is viscous, incompressible and Newtonian with viscosity μ^*(kg/m s). Fluid is pumped in at the boundary $y^* = L^*$ and drawn out at the boundary $y^* = -L^*$ as shown in Fig. 2.

The model consist of three differential equations, the first representing the flow of fluid through the porous material, with the velocity denoted by $\mathbf{u}^*$ (m/s) and pressure denoted by p^* (kg/m s^2), the second representing convection and diffusion of nutrients, with the concentration of nutrient denoted by S^* (mol/m^3), and the third representing the cell proliferation, in terms of cell density $N^*(x^*, y^*)$ (cells/m^3). Nutrients are assumed to move due to convection and diffusion, with a constant diffusion rate D_s^* (m^2/s) and to be consumed by the cells at the rate G_s^* (mol/m^3 s). Cells are assumed to diffuse with a constant diffusion rate D_n^* and they grow in number at a rate Q_n^* (cells/m^3 s). We assume that the initial cell density in the scaffold is $N_{init}^*(x^*, y^*)$, where the form of $N_{init}^*(x^*, y^*)$ is determined by cell

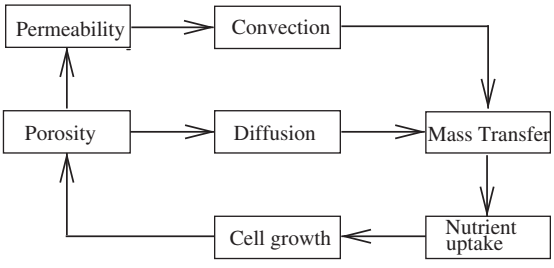

Fig. 1. Interacting phenomena in perfusion bioreactor.