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Chemical Engineering Science 62 (2007) 5821–5839

Chemical Engineering Science

www.elsevier.com/locate/ces

Modelling nutrient transport in hollow fibre membrane bioreactor for growing bone tissue with consideration of multi-component interactions

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Received 22 December 2006; received in revised form 1 June 2007; accepted 11 June 2007
Available online 20 June 2007

Abstract

Current work in bone tissue engineering (BTE) suggests that hollow fibre membrane bioreactors (HFMBs) can be used to grow artificial bone tissue which may then be implanted in humans to treat various bone defects. The HFMBs mimic the blood capillary networks in human bones and are able to maintain high concentrations of nutrients by minimising mass transfer distance. To further establish this method and to develop effective BTE protocols, nutrient transport behaviour in the HFMB must be characterised. By doing so, the quantitative relationships between the cell environments and, bioreactor operating conditions and designs can be elucidated. This also paves the way for possible improvement and optimisation of the HFMB performance. However, characterising the nutrients transport properties in HFMB are not straightforward as online measurements of key parameters are almost impossible at the moment. This is due to the very small size and the stringent operating conditions of the bioreactors. Hence, much work is needed on mathematical modelling of mass transport in these bioreactors. In this paper, we present a rigorous framework for modelling mass transport in HFMB for growing bone tissue. In particular, we consider the effects of hydrodynamics and multi-component interactions on nutrient transport profiles. The developed framework is then used to study the behaviour of nutrient transport in HFMB for bone tissue growth for various operating conditions with a view to generalise their effects as far as possible. Maxwell–Stefan, Navier–Stokes and reaction kinetic equations are combined to quantify the multi-component nutrient transport behaviour in the bioreactor. The framework also relies on the use of a single hollow fibre (Krogh cylinder assumption), which is representative of the whole fibre bundle. The numerical solutions of the governing model equations are obtained using finite element method. The effects of different bioreactor designs (e.g., fibre length, lumen thickness, etc.) and process parameters (e.g., nutrient inlet concentration, fluid velocity, etc.) on multi-component nutrient concentration profiles (e.g., glucose and oxygen) are simulated. The results show that the HFMB designs and process parameters may be optimised to further enhance mass transport for growing bone tissues.

Keywords: Nutrient transport; Hollow fibre membrane bioreactor; Krogh cylinder approximation; Multi-component interactions; Navier–Stokes equations; Maxwell–Stefan equations; Finite element modelling

1. Introduction

The number of medical cases related to human bone defects is alarming at the moment. Many of these cases require continued medical attention and need suitable materials as bone substitutes. To address these needs, current clinical therapies generally rely on autografting, allografting and inserting man-made materials to replace diseased or dysfunctional bone. However, these substitute materials are far from being ideal and have many associated problems. For example, autografts are expensive and can have significant donor site morbidity. Allografts meanwhile show less favourable biomechanical properties (e.g., strength) after remodelling, compared to autografts. As for the synthetic materials used as bone substitutes, they wear more rapidly and do not behave like true bone. Bone tissue engineering (BTE) promises to provide an alternative solution by creating engineered bone tissue (soft tissue) of desired size and shape in specially designed bioreactors. These may then be implanted in humans to treat bone defects. There is significant amount of work on BTE at the moment, and excellent reviews on the topic can be found in the literature (e.g., Abdullah et al., 2006; Ye et al., 2006; Meyer et al., 2004a,b; Schmelzeisen et al., 2003; Wiesmann et al., 2004; Lanza et al., 1997;

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doi:10.1016/j.ces.2007.06.024

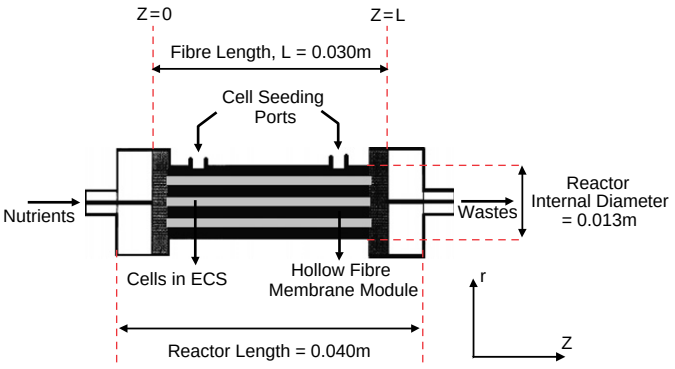

Fig. 1. A schematic diagram of a hollow fibre membrane bioreactor for bone tissue growth. Symbols r and Z refer to radial and axial directions, respectively.

Yaszemski et al., 1996). It is clear from these literatures that design of appropriate bioreactor, in which the mass transport behaviour are well understood, is crucial to growing artificial bone tissues. It is also imperative that the tissue culture conditions in the bioreactor have sufficient nutrients to support cell growth in a scaffold, which then form functional bone tissues. In principle, many types of bioreactors may be used to perform these tasks. However, the bioreactors need certain features for engineering bone tissues, as discussed in the next section.

Natural bones are highly vascularised and they rely on blood vessels to deliver nutrients to cells situated deep in the mineralised bone matrix. In an artificial environment such as the scaffold in a bioreactor, it is difficult to supply nutrients to the cells adequately without a capillary network (Abdullah et al., 2006; Ye et al., 2006; Freed and Vunjak-Novakovic, 1998). Relying on nutrient diffusion alone from the boundary of the scaffold without capillaries would limit the size of engineered bone tissue to less than 0.5 mm thick, which is not of much value for clinical practice (Ye et al., 2006; Freed and Vunjak-Novakovic, 1998). The hollow fibre membrane bioreactor (HFMB) currently shows a lot of promise in growing bone tissue due to its unique design (Fig. 1). The HFMB consists of a hollow fibre (HF) bundle contained in an external housing. The cells can be cultured in a spongy matrix around the HFs but are more commonly maintained in the extracapillary space (ECS). The annulus of the HFMBs contains a scaffolding material where cells proliferate and attach to. Nutrients are fed through the lumen of the HFs, which diffuse to the ECS across the fibre membranes. The HFMB design offers better mass transfer behaviour as the HFs enable nutrients to be supplied to the centre of the bone tissues, mimicking the in vivo blood vessels in human bones, as discussed above (Abdullah et al., 2006; Ye et al., 2004, 2006; Martin and Vermette, 2005). Thus, sufficiently high nutrient concentration can be maintained in HFMB. This minimises mass transfer limitations and enhances the possibility of growing thick bone tissue.

The operation of HFMBs is similar to those described in literature and is not discussed here in length (Abdullah et al., 2006; Ye et al., 2006; Brotherton and Chau, 1996; Labecki et al., 1995). However, it must be pointed out that because of the way the HFMBs are operated in bone tissue engineering (i.e., very small in size (Fig. 1), need to keep them sterile; operating under very specific cell culture conditions), in situ (direct) monitoring of nutrient concentrations in the bioreactor is almost impossible at the moment. Therefore, computational modelling is increasingly being used to understand the mass transport behaviour in HFMBs and to characterise their functions at different operating conditions (Abdullah et al., 2006; Ye et al., 2006). As expected, it has been shown that for specific cells (e.g., bone cells as in this case) and materials (e.g., scaffold, membrane, etc.), the nutrient transport behaviour is influenced by an interplay of reactor design parameters (e.g., geometry, fibre spacing, fibre length, etc.) and operating conditions (hydrodynamic behaviour, inlet nutrient concentrations, cell density, etc.). However, Abdullah et al. (2006) have also argued that while operating HFMB for BTE, the inlet nutrient concentrations should be chosen considering two important effects. The authors demonstrate that by increasing the concentrations of nutrients at lumen inlet for a given fluid velocity, the mass transport limitations can be minimised in the ECS which encourages cell growth and hence promotes tissue formation. But, as the inlet concentration reaches certain levels, further increment does not change the concentration profiles of the nutrients in the HFMB significantly. Therefore, there is a maximum inlet concentration one should choose in order to obtain the maximum solute concentration in the HFMB for given operating conditions (e.g., cell density). Secondly, a very high nutrient concentration may poison the cells affecting them physiologically and, perhaps causing death (Nielsen, 1993). Therefore, the HFMB must be operated in such a way that the range of nutrient concentrations are safe to the cells and do not affect them adversely in the bioreactor at any location.

In general, the modelling approaches for solute transport in bioreactor for growing bone tissue assume that the effects of multi-component interactions on transport behaviour can be disregarded (Abdullah et al., 2006; Ye et al., 2006; Labecki et al., 1996). However, the above scenario raises a fundamental question that should be addressed. With increasing concentrations of various solutes in HFMB, some of which may be large molecules, the multi-component interactions increase. However, it is not certain if these interactions are significant enough to affect the mass transport behaviours and if so, in what scenarios. To this end, one may continue to presuppose that the frictional parameters that govern the multi-component transport are insignificant. Therefore, transport of each solute introduced in the HFMB can be modelled separately. Hence, an approach that relies on solving Fick's diffusion law with appropriate source and/or sink term to account for the cellular reactions is sufficient (e.g., Abdullah et al., 2006). On other hand, one does not necessarily need to take the above assumptions if a more rigorous approach is available where the multi-component interactions are inherently accounted for. To address these issues, we have developed a generic modelling framework for simulating nutrient transport behaviour in HFMB for growing bone tissue. The framework relies on the steady-state solution of coupled Maxwell–Stefan (MS), Navier–Stokes (NS) and reaction kinetics equations for cellular reactions on a Krogh