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Mathematical modelling of cell layer growth in a hollow fibre bioreactor

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Abstract

Generating autologous tissue grafts of a clinically useful volume requires efficient and controlled expansion of cell populations harvested from patients. Hollow fibre bioreactors show promise as cell expansion devices, owing to their potential for scale-up. However, further research is required to establish how to specify appropriate hollow fibre bioreactor operating conditions for expanding different cell types. In this study we develop a simple model for the growth of a cell layer seeded on the outer surface of a single fibre in a perfused hollow fibre bioreactor. Nutrient-rich culture medium is pumped through the fibre lumen and leaves the bioreactor via the lumen outlet or passes through the porous fibre walls and cell layer, and out via ports on the outer wall of the extra-capillary space. Stokes and Darcy equations for fluid flow in the fibre lumen, fibre wall, cell layer and extra-capillary space are coupled to reaction-advection-diffusion equations for oxygen and lactate transport through the bioreactor, and to a simple growth law for the evolution of the free boundary of the cell layer. Cells at the free boundary are assumed to proliferate at a rate that increases with the local oxygen concentration, and to die and detach from the layer if the local fluid shear stress or lactate concentration exceed critical thresholds. We use the model to predict operating conditions that maximise the cell layer growth for different cell types. In particular, we predict the optimal flow rate of culture medium into the fibre lumen and fluid pressure imposed at the lumen outlet for cell types with different oxygen demands and fluid shear stress tolerances, and compare the growth of the cell layer when the exit ports on the outside of the bioreactor are open with that when they are closed. Model simulations reveal that increasing the inlet flow rate and outlet fluid pressure increases oxygen delivery to the cell layer and, therefore, the growth rate of cells that are tolerant to high shear stresses, but may be detrimental for shear-sensitive cells. The cell layer growth rate is predicted to increase, and be less sensitive to the lactate tolerance of the cells, when the exit ports are opened, as the radial flow through the bioreactor is enhanced and the lactate produced by the cells cleared more rapidly from the cell layer.

Keywords: tissue engineering, bioreactor, cell population growth, oxygen and lactate transport, fluid shear stress

1. Introduction

The aim of *in vitro* tissue engineering is to produce cells and tissues in the laboratory that can be used to replace or repair damaged or lost tissues in a patient's body. Generating these cells and tissues from the patient's own cells (autologous cells) has several advantages, including that decreased likelihood of immune rejection, but requires expansion of the original cell population taken from the patient. This can be achieved by seeding the cells onto a biomaterial scaffold and incubating the cell-scaffold construct in a bioreactor.

Hollow fibre bioreactors (HFBs) show great promise as cell expansion devices. They consist of a cylindrical glass module housing a single or multiple porous, hollow, biodegradable polymer fibres. Nutrient-rich culture medium is pumped through the fibre lumen(s) and forced through the fibre wall(s) (membranes) to cells seeded in the surrounding space (the extra-capillary space or ECS). There are ports at either end of the ECS, which may be opened to promote radial flow through the bioreactor, or left closed (see Figure 1). With the ECS ports open, and hence at atmospheric pressure, the flow through the membrane is controlled by fixing the

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