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TISSUE ENGINEERING THROUGH SIMULATION AND EXPERIMENTS

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ABSTRACT

Introduction. Bioreactor experiments on native tissue and on cell-seeded constructs, to study the interaction of mechanical stimulation and cell response, are expensive and time consuming. Additionally, local stresses and strains in the cells and their surrounding environment are not directly experimentally determinable. Therefore, numerical methods, such as the finite element method, are becoming a powerful tool to simulate the mechanical environment to which cells are subject during bioreactor culture and to provide useful suggestions for a more effective tissue engineering process [1].

Computational fluid dynamics (CFD). In the design and subsequent culture of porous biomaterials to serve as implants in tissue engineering and drug-delivery applications, a central concern is control of mass transport. For tissue grown ex vivo on porous scaffolds in bioreactors, a quantitative understanding of the interplay among porosity, medium flow and cellular behaviour would accelerate the scaffold design process and limit the amount of trial-and-error steps required for the development of any functional implant. While control over the scaffold material properties, surface chemistry and morphology and degradation behaviour are believed to be important, transport of nutrients to cells and of catabolites away from cells has been established as the crucial factor affecting cell survival. Biology responds to mass transport limitations using flow, vasculature and interstitial flow being primary examples. Tissue engineering may use flow as well: the cell-seeded scaffold is immersed in a medium which can be induced to flow through or around the scaffold surface with a perfusion flow apparatus. A simple means of increasing mass transport to cells would be to increase the medium flow rate., High flow rates, however, induce high shear stresses on cells, which may be harmful instead of beneficial, at least at the early stages of tissue growth. This complexity presents serious hurdles in determining what flow rates and medium solute concentrations are adequate. Homogeneous models of diffusion-limited nutrient transport in tissue and tissue-engineered constructs have proven useful in achieving a rough understanding of transport limitations in porous constructs, in the absence of flow. Flow around the scaffolds in a concentric cylinder bioreactor may be simulated by

the use of a CFD model, allowing to calculate flow fields, shear stresses and oxygen profiles around constructs. Including flow through the scaffold in an interstitial-perfusion configuration complicates the situation by establishing a velocity scale which is related to the actual fluid velocities in the scaffold, which are impossible to measure. This problem is currently being dealt with by the use of detailed pore-scale CFD simulations of fluid and chemical transport in tissue-engineering scaffolds populated with living cells [2-3]. CFD numerical techniques are able to capture flow, pressure and concentration fields resolved at the scaffold's pore level. The simulations show how the scaffold micro architecture influences the hydrodynamic shear imposed on cells within constructs. Calculations of culture medium flow indicate that inappropriately designed dynamic culture environments can lead to regions of low nutrient concentration, insufficient for cell viability maintenance. These studies provide a foundation for exploring the effects of dynamic flow on cell function and provide important insights into the design and optimization of suitable 3D scaffolds and bioreactors for in vitro tissue engineering.

Multicellular simulations. In CFD models, cells can be incorporated as sources or sinks of chemical species, for example of oxygen. What CFD models in general cannot provide, however, are rules governing the behaviour of these sources and sinks. For this reason, such models may be integrated with other computational tools known as multicellular simulations. In multicellular simulations, simple rules governing cell behaviour are imposed and emergent behaviour from cell populations is observed and analysed. The technique used is known as biased random walk (BRW) and has found widespread use in the simulation of angiogenesis. Recently, it has been applied to simulate cell populations that migrate, collide, and proliferate to build a tissue inside a 3D scaffold subject to interstitial perfusion [4]. Simulation results show that the speed of cell locomotion modulates the rates of tissue regeneration by controlling the effect of contact inhibition and that the magnitude of this modulation strongly depends on the spatial distribution of the seeded cells.

In conclusion, the field of computational models in tissue engineering is progressing rapidly. Several computational tools are available to model cellular events. Possible directions to improve these tools require to properly address the fundamental processes that induce growth of engineered tissue on scaffolds, i.e. cell adhesion, migration, proliferation and death. This would open new prospectives for engineering design using validated predictive tools in the field of tissue engineering.

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