173a Modeling of Cell Culture Processes in a Micro Channel Reactor

Khamir Mehta, Geeta Mehta, Shuichi Takayama, and Jennifer J. Linderman

Recently developed perfusion microbioreactors offer the promise of more physiologic in vitro systems for tissue engineering (Gu et al., PNAS 101: 15861, 2004; Andersen & van den Berg, Lab on a Chip 4: 98, 2004). In this work, we present a mathematical model to describe nutrient/growth factor delivery and cell growth along the length of a microfluidic cell culture channel in order to design and optimize the bioreactor.

We use an unsteady state species transport model for the soluble nutrients and growth factors in the culture. The dynamics of cellular processes, e.g. proliferation, differentiation and nutrient/growth factor uptake, can be influenced by the concentrations of the nutrient/growth factors inside the reactor. The transport model in form of partial differential equations is thus intrinsically coupled with the equations describing the dynamics of cellular processes. Most of the model parameters can be obtained from static culture experiments. Model equations are solved using the numerical solvers FEMLAB and MATLAB.

It has been observed that continuous flow systems can exhibit significant spatial gradients in soluble nutrient (e.g. oxygen) concentrations (Allen & Bhatia, Biotechnol. Bioeng. 82: 253, 2003). First, using our coupled cell growth/nutrient transport model, we show that the nature and existence of gradients can be controlled by both design and operating conditions and are a strong function of cell uptake rates. Model results are compared with our data on oxygen concentration gradients within a microreactor during the culture of osteoblasts. We also explore the model results for a representative cell culture of rat hepatocytes. We further find that spatial gradients in nutrient concentrations can bring about spatial heterogeneity in the cell density distribution inside the bioreactor. Important consequences of heterogeneous cell density in the reactor include the difficulty in control and also lowered actual working volume of the bioreactor.

Second, we use the model to understand the effect of nutrient and spatial limitations on the composition of proliferating heterogeneous cell populations. Many applications require the use of heterogeneous cell populations; the presence of cell types with different properties (e.g. cell doubling times) is common. For example, the expansion of stem cells in a heterogeneous cell population is of critical importance in tissue engineering. We find that spatial limitations can affect the composition of cell populations and can selectively favor the proliferation of a particular cell type. Further, spatial limitations are important even in absence of nutrient gradients and the survival of a given cell type can also be dependent on the initial cell density. These results can be of crucial significance to develop and design micro-channel systems to co-culture different cell types.

Cellular processes such as proliferation and differentiation are often controlled by signaling molecules, which are secreted from cell populations in an autocrine or paracrine manner. We extend our model to investigate the spatial distributions of soluble autocrine and paracrine growth factors in the bioreactor and their effects on the cell growth and differentiation. Convective transport can significantly alter the concentration distributions of soluble signaling molecules as compared to the static culture case and thus must be considered in reactor design. Lastly, we explore the possibility of using the experimental results from such a system to infer quantitative relationships between cell behavior and the environment. As an illustration, we present results for inference on dose-dependent behavior of cell growth on oxygen concentration using test data.