576c Dynamics of Heterogeneous Cell Populations Growing under Transport Limitations: a Hybrid, Multi-Scale Model

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A better understanding of the fundamental mechanisms that modulate the heterogeneity and the complex dynamics of cell populations will allow us to overcome the barriers that have slowed down the development of bioartificial tissues. Because of transport limitations, nutrient and growth factor concentrations vary significantly inside scaffolds and nonideal bioreactors, leading to large differences in the state and behavior of cells. However, population heterogeneity also results from the complex regulatory mechanisms that occur at the single-cell level. In addition, the single-cell and scaffold/bioreactor scales are tightly coupled through complex cell-cell and cell-environment interactions, as well as interactions occurring among the numerous cellular components. Clearly, comprehensive mathematical models are necessary for integrating the biological processes occurring at the bioreactor, tissue, cell and sub-cellular scales.

This study will describe the development of a hybrid, multi-scale computational model that describes the growth dynamics of heterogeneous cell populations under conditions leading to significant transport limitations. This comprehensive model consists of: (a) partial differential equations quantifying the simultaneous diffusion, convection and consumption of nutrients and growth factors in the interior of the scaffolds; and (b) a discrete model that tracks the migration and proliferation of heterogeneous cell populations on a 3D cubic lattice. An implicit-explicit finite difference method is employed to discretize the transient PDE's and the resulting sparse linear system is solved with a preconditioned GMRES method. The computed local concentrations of nutrients or growth factors are used to modulate the cell locomotory properties and their division times. To account for different cell phenotypes, the model considers cell populations that exhibit bimodal distributions of migration speeds, persistence and division times. The model also allows for cell death when the nutrient or growth factor concentrations drop below a certain level that can be different for each phenotype.

Two special cases will be discussed here. The first case (NT) assumes that tissue growth is limited by the availability of a key nutrient. Experimentally determined algebraic relations (Monod) are used in this case to modulate the cell proliferation rates and migration speeds according to the local concentrations of the critical nutrient. The second case (GF) assumes that tissue growth is limited by the availability of a mitogenic growth factor. In this case, cell proliferation rates are modulated by solving a detailed binding/trafficking model for the growth factor. Five ODE's are integrated for each cell to determine the strength of mitogenic signal generated by the local concentration of the soluble growth factor.

Simulation of 3D tissue growth is a computationally challenging problem requiring large grids to capture the growth of tissues of practically significant size. Also, the various processes occur at multiple time scales, dictating the use of small time steps for the integration of the differential equations. To meet these computational challenges, our algorithms have been parallelized to run on computer clusters. Our computational domain is partitioned into subdomains along one dimension (slab decomposition) and each subdomain is assigned to a different processor.

While a static load balancing approach works well in the NT case, a dynamic load-balancing scheme is necessary in the GF case. GF runs require the solution of five ODE's for each cell, increasing significantly the work needed to update the state of each computational site occupied by a cell. As a result, large load imbalances among processors may appear during the simulation when subdomains contain different numbers of cells. By appropriately rebalancing the workload during execution, the dynamic load-balancing scheme we have developed for the GF case provides significantly better performance than a static scheme.

We will finally discuss how cell locomotory properties, the initial seeding pattern and mass transfer rates affect the growth rates and the structure of developing tissues. An interesting observation here is that large differences in the locomotory properties or metabolic requirements between cell subpopulations lead to the formation of stratified tissues, where cells are segregated according to their phenotype.