COMPUTATIONAL FLUID DYNAMIC MODELING OF 100ML AND SCALED-DOWN 10ML STIRRED SUSPENSION BIOREACTORS ENABLES PREDICTION OF EMBRYONIC STEM CELL CHARACTERISTICS

Breanna S. Borys, Biomedical Engineering Graduate Program, University of Calgary
bsborys@ucalgary.ca
An Le, Biomedical Engineering Graduate Program, University of Calgary
Charlie Yu-Ming Hsu, Department of Biochemistry and Molecular Biology, University of Calgary
Derrick E. Rancourt, Department of Biochemistry and Molecular Biology, University of Calgary
Ian D. Gates, Department of Chemical and Petroleum Engineering, University of Calgary
Michael S. Kallos, Biomedical Engineering Graduate Program, University of Calgary

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There is a growing necessity for cell cultivation using bioreactors to translate laboratory based culture protocols into reproducible, scalable, and robust bioprocesses. Stirred suspension bioreactors offer several advantages over planar static cultures, including: reduced labour and operating costs, reduced space requirements, greater cellular homogeneity, and increased cell density per volume [1]. An important consideration when using stirred suspension bioreactors is mechanical stimulation. Fluid shear at the fluid-cell interface triggers cellular responses through mechanotransduction and can modulate stem cell proliferation and differentiation. However, if the shear stress caused by the impeller exceeds the tolerance limit of the cells, it causes cell damage and death, resulting in a lower quality and yield of cells. The shear rate distribution depends on bioreactor geometry, impeller agitation rate, cell density, and cell media viscosity [2]. Current scale-up protocols to predict agitation rates rely on maximum values of hydrodynamic variables, which occur only at the impeller tip. The volume averaged shear stress and maximum shear stress differ greatly, and cells dispersed within the liquid experience different local and global forces. This makes it difficult to predict how cells will respond to changes in bioreactor geometries and sizes. Profiling distributed and average forces in the bioreactor is critical to ensure quality and yield in cell manufacturing. Hydrodynamics, specifically velocities, shear rates, and energy dissipation rates, can be studied using computational fluid dynamic (CFD) modeling.

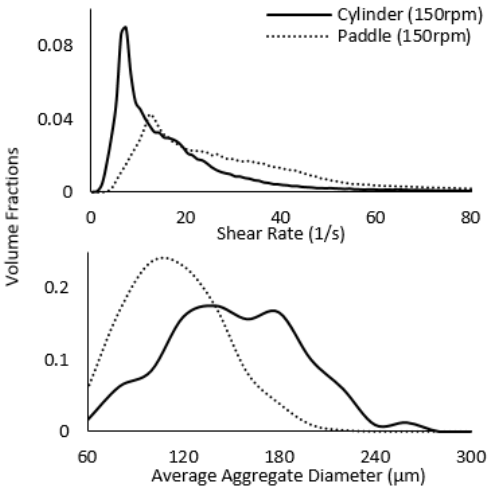

Figure 1 – Shear rate and mESC aggregate size distributions in 10mL stirred suspension bioreactors with different impeller geometries run at an agitation rate of 150rpm

In this study, CFD modeling was used to determine effects of shear rates and energy dissipation rates on formation and growth of murine embryonic stem cell aggregates. Contrary to commonly reported maximum shear stress values, these models enable calculation of local and volume-averaged shear stress values. Aggregate sizes, which correlate with cell health and pluripotency, are often described in relation to agitation rate. Agitation rate, however, is not a suitable representation of the hydrodynamic environment in bioreactors due to differences in vessel design and impeller geometries. The hydrodynamic properties of 100mL and 10mL stirred suspension bioreactors were simulated at various agitation rates and the results were compared with biological data for murine embryonic stem cell (mESC) aggregates cultured at the same conditions. It was found that both size and shape of the bioreactor vessel and impeller play a significant role in the shear stress distributions inside the fluid. Importantly, these parameters more accurately predict the aggregate size distribution and pluripotency profile for pluripotent stem cells. The change in the distribution of aggregate sizes within the bioreactor corresponds to changes of the shear rate distribution within the bioreactor. These models can be used as a tool to design new bioreactor vessels and predict agitation rates throughout scale-up.

References:

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