Multi-Scale Modeling of Lymphatic System Pumping and Signaling

James E. Moore, Jr., Ph.D.
Biomedical Engineering Department
Texas A&M University
jmoorejr@tamu.edu

The lymphatic system is an extensive vessel network featuring one-way valves and contractile walls that pump interstitial fluid, plasma proteins, lipids and immune cells through lymph nodes and then back to the blood circulation at the subclavian veins. This system is crucial in the function of the immune system, as well as being the pathway of distribution for metastatic cells arising from the most deadly forms of cancer. Failure to drain and pump this excess fluid results in an edema, characterized by fluid retention and swelling of limbs. This condition affects a large number of cancer survivors who have had lymph nodes removed as part of their treatment. It is, therefore, crucial to understand the mechanisms regulating lymph transport.

We are developing multi-scale computational models of lymphatic function from the sub-cellular to the whole organ level in conjunction with a series of experiments aimed at elucidating desirable model characteristics and providing model parameter estimations. Our modeling is based on lymphatic endothelial and smooth muscle cell mechanotransduction of flow-induced shear stress and vessel diameter. Models of individual lymphangions (the vessel segments between valves) provide estimates of the relevant parameters. Along with a quantitative description of valve behavior, we have constructed models of several lymphangions in series. With the description of more complex vessel groupings (parallel segments, vessel junctions, nodes, etc.), a more complete understanding of this system can be obtained. The process of integrating up to the whole organ level will likely involve surrogate modeling of these networks. With these goals in mind, the series vessel segments have been characterized through pump curves of steady pressure difference versus flow rate. These curves exhibit non-linear behaviors typical of mixed source pumps, with a sharp drop-off at the maximum flow rate in some cases. These models also provide the opportunity to quantify the importance of various modeling parameters through sensitivity analysis. For example, the phase angle between successive lymphangion contractions is an important determinant of pumping efficiency, with out-of-phase behavior being the most efficient.

Experimental support for the modeling efforts includes multiple approaches. We have measured nitric oxide (NO) production lymphatic endothelial cells exposed to flow-induced shear stresses in a parallel plate flow chamber. In contrast to arterial or venous endothelial cells, NO production was dependent on dynamic changes in shear stress and not sustained steady shear stress magnitude. Experiments with rat mesentery lymphatics revealed that these vessels quickly adapted to increased volume loads by increasing lymph flow rate and contraction frequencies. These experiments provide crucial information that, when combined with our previous in vivo observations of normal lymphangion behavior, guides the modeling efforts.

Unlike the arterial and venous systems, the lymphatic system has not been the subject of extensive modeling efforts. Our work is aimed at constructing models that strike a delicate balance between the need to represent complex physiological phenomena and the desire to keep the modeling feasible computationally. The multi-scale approach is ideally suited for this purpose.