Computing of Transport Processes in Biological Systems (Biological Computing)

Abstract

Flow and thermal transport processes have a vital function in the functioning and operation of many biological and bio-medical systems. In such systems, diagnostic procedures or experiments are often difficult to perform, and reliable numerical simulations can provide great value in our understanding of the functioning of the biological system and in designing suitable diagnostic and treatment procedures. However such simulations are complicated by the need to resolve small scales, complex geometries with compliant moving walls, and sometimes non-Newtonian flow rheology. Thus accurate, properly resolved simulations are extremely challenging, and are only now becoming possible with the availability of powerful parallel computing facilities.

The proposed program is a multi-disciplinary effort involving the colleges of engineering and basic sciences and aims to develop computational and visualization tools that will unravel the flow and transport processes in complex biological systems. The program aims to use massively parallel computing coupled with sophisticated visualization tools to resolve and render the flow processes spanning the spectrum of scales in a biological system.

Introduction

Flow and thermal transport processes play an intrinsic role in biological and bio-medical systems. Examples include the flow of red and white blood cells through different organs (e.g., the heart), air flow through tracheal and lung passages, fluid movement in the eye, the response of tissues and organs to extremes of heat and cold, and the ingestion and transport of food and liquid through the mouth, the intestinal and the urinary tract systems. Further, diagnostic and treatment procedures inherently require the use of bio-fluidic devices such as syringes, pumps, centrifuges, etc., and efforts are underway using microsystem technologies to make these devices smaller and less invasive.

An underlying feature of biological and bio-medical systems are the geometrical complexity of such systems and the small scales that are necessary to resolve to accurately represent such systems. These complexities have posed severe restrictions on analytical and/or numerical solution of the relevant transport processes and required significant computing power that were not available in the last two decades. However, with recent advances in computing, and the availability of low-cost parallel computing , it is now becoming possible to properly address the numerical challenges posed by biological and medical problems.

A wide range of flow regimes are encountered in biological flows where characteristic length scales (d) can range from less than 1 micron to several millimeters. For Knudsen number, Kn ($=\lambda/d$, where λ is the mean free path of the fluid molecules), smaller than 0.001, the fluid can be considered to be a continuum where the Navier-Stokes equations are applicable, while for Kn greater than 10 the flow is considered to be in free molecular flow governed by the Boltzmann equation. In between these regimes, the flow is in either the slip regime or the transitional regime, where the flowfield can still be determined from the continuum equations with velocity-slip and temperature jump conditions specified at the walls to account for incomplete momentum and energy exchange of the molecules with the surfaces. These equations governing the motion of the fluid particles have to be numerically solved in order to understand the transport of

biological fluids. The understanding gained from computational solution of the flowfield can be extremely beneficial in developing diagnostic and treatment procedures.

Below we describe four specific projects that are currently in progress, and represent the range of interests in biological computing in mechanical engineering, and the potential for interaction with biological sciences, computer sciences, and the medical school. Further fostering this effort and providing suitable resources will clearly provide additional impetus to this group and the potential collaborators setting the stage for large-scale inter-disciplinary efforts.

Specific Projects of Current Interest

1. Modeling the fluid movement in the eye

In order to understand the transport mechanisms inside the eye, and how they are affected by eye disorders such as glaucoma, flow calculations will be performed to predict the movement of aqueous humor which enters the posterior chamber of the eye from the ciliary epithelium and passes on to the anterior chamber through the pupil. The aqueous humor leaves the anterior chamber through two primary routes: (1) the trabecular meshwork connecting to the Schlemm's canal and (2) the uvescleral outflow that enters the ciliary muscle and drains through the sclera. The resistance encountered by the aqueous humor in the outflow path leads to high intra-ocular pressure (IOP) in the anterior chamber and keeps the eyeball distended. Morphological changes in the eye, e.g., narrowing of the anterior chamber angle, lead to changes in the resistance to the outflow of aqueous humor, and reflect in a changed IOP level. For example, in glaucoma, IOP levels are elevated, and this can lead to a variety of optic disk abnormalities including disk hemorrhage, changes in cupping, localized thinning of the cup edge, and spatial shifting of the eye vessels. Flow simulations can be used to enhance our understanding of how morphological changes influence the pressure distribution in the eye, and with suitable inverse mapping procedures, this knowledge may permit the measured pressure distributions to be used in evaluating the nature of morphological changes.

The treatment of glaucoma rests on the reduction of aqueous production (medically) or increased aqueous flow (surgically). Treatment through drug delivery requires an understanding of the drug-flow pathway, and if the drug can be transported to the desired regions. This information can be determined through the proposed flow simulations, where the drug flow injection can be simulated, and the trajectory of the drug represented as pathlines. The effectiveness of the various surgical procedures can be evaluated *a priori* through flow simulations where the effect of the surgical procedure is simulated by incorporating the morphological or geometrical changes produced by surgery into the computational domain.

2. Modeling the transport of fluid through the gill structure of a suspension feeding bi-valve

The first focus of the proposed CFD effort is to understand the movement of water and to identify the mechanisms of particle capture and transport through the gills of typical suspension feeding aquatic invertebrates (e.g., mytilus edulis). A typical gill structure consists of frontal (F), latero-frontal (LF), and lateral (L) ciliary tracts. Fluid mechanics plays a critical role in both the delivery of the particle to the gill structures, and the transport through the gill cirri and cilia. Several groups, including Silverman and coworkers at LSU, have been exploring the flow and particle pathways through the gill-filament structures, and various mechanisms have been proposed in the literature ranging purely from "fluid mechanical and hydro-mechanical particle

trapping mechanisms" to "biological mechanisms". The various proposed mechanisms have been based on either *in vivo* endoscopic studies or *in vitro* studies of surgically isolated gill-filaments and associated cilia tracts. Both approaches are invasive but intrinsically assume that the feeding process is unaffected by the invasive procedure. More importantly, the controversies associated with the different mechanisms proposed underscore the lack of understanding of the basic feeding mechanisms. In this context, computational solution of the flow and particle transport can be invaluable in delineating the fundamental mechanisms. This represents a major goal of the proposed effort.

In performing the proposed research we will work collaboratively with Silverman and his group at LSU who have been engaged in performing pioneering *in vitro* experimental studies in understanding particle retention mechanisms in the gills of several aquatic species. We will also work closely with the parallel computing and vizualization group in Physics and Computer Science (Kalia, Vasistha, Nakano and Iyengar), and will benefit from their long-standing expertise in parallel computing and high-speed vizualization.

3. Heat and mass transfer during freezing of biological systems

The process of freezing biological tissue continues to be actively studied because of its central role in two important biomedical applications, cryosurgery and cryopreservation. Numerical modeling has proven to be extremely useful in studying tissue freezing problems. Most models of tissue thermal response assume the tissue to be a single-compartment, homogeneous medium, e.g. pure water or isotonic saline. In this case, phase change is described by the phase diagram of the chosen medium. Mathematically, latent heat content is assumed to be a function of temperature $\Lambda(T)$, and the energy equation is solved in the enthalpy form or with a modified specific heat which incorporates this function. In native biological tissues, a significant portion of the water in tissue is intracellular, separated from the surrounding tissue by a cell membrane. Phase change in tissue is therefore governed not only by the phase diagram for tissue fluids but also by the dynamics of the biophysical processes of cellular dehydration and intracellular ice formation (IIF).

Recently Devireddy presented a coupled tissue freezing model in which the coupling of the biophysical phenomena into the calculation of phase change is accomplished by creating a latent heat function similar to those used in enthalpy or modified specific heat formulations, i.e. the latent heat is a function of both temperature and time, $\Lambda(T,t)$. However, the coupled model neglected the effect of metabolic heat generation and the effect of blood flow on the freezing process, which makes it clearly less valid for simulating an *in-vivo* (inside the body) cryosurgical scenario than an *in-vitro* (outside the body) cryopreservation case. In addition, the coupled model assumed that the latent heat released by the extracellular solution during the freezing process follows the phase diagram. Recent studies suggest that the latent heat released by the extracellular solution also has a cooling rate dependence (i.e. it is both temperature and time dependent). Future improvements to the models should include these effects appropriately. And finally, the coupled thermal/biophysical model can be improved upon or extended to predict: 1) the thermal and biophysical response during freezing of tissues in the presence of cryoprotective agents or CPAs (CPAs are used to limit the freezing damage experienced by tissues); 2) vascular distension throughout the tissue during a freezing process, which can be used to develop vascular injury theories; and 3) partial or complete vitrification in cells and extracellular/vascular space. This project will require extensive computational time and will

result in a more complete understanding of the effect of various chemical and cooling conditions on a tissue system during freezing.

4. Bio-fluidics for diagnosis and drug delivery

Bio-fluidic computation is an essential tool for the design of microfabricated devices for biomedical applications. Manufacturing process complexity and costs require that extensive modeling be used to establish system performance and identify critical parameters early in the design sequence. LSU researchers are currently working on the development of stackable, microfluidic systems for genetic analysis. These advanced 'lab-on-a-chip' instruments will incorporate several separate device modules, for example a PCR chip for DNA amplification and a capillary electrophoresis chip for separation of samples. Two significant problems are being addressed by a combination of bio-fluidic simulation of the heat and mass transfer through the devices and microscale particle image velocimetry (μPIV), a computationally-intensive imaging process for making direct measurements of flow velocities in small channels. Interconnects between the different modules must have 'near-zero' dead volume to prevent cross-contamination of small sample volumes. Any residual genetic material from early samples could invalidate the analyses for later samples, especially if they are from different subjects. Modeling is also being used to balance the need for packing the devices in as small a footprint as possible and the requirement that sample volume dispersion is minimized. Low dispersion means sample plugs can be sequenced closer together in the system, decreasing analysis time, while a small footprint implies more turns in the microfluidic channels leading to greater dispersion. The packing problem is exacerbated in the next generation of instruments, which will contain the same analytical capabilities on endoscopes (2-10 mm diameter) for direct use by surgeons. Designing 'lab-on-a-scope' instruments will require modeling and measurement of flows in nano-dimensional channels. In addition to the analytical instrumentation, development of an intravenous oxygenator based on micro-bubble formation with physicians at LSUMC-Shreveport is underway. This project will require simulation of devices to produce large volumes of oxygen micro-bubbles over extended periods.

Resources Requested

As noted above, there is significant ongoing activities in mechanical engineering in the area of biological computing. There is also potential for significant collaboration with the biological sciences group at LSU, the medical group at LSU Medical Center, and the computational sciences group in Physics and Computer Sciences at LSU. We are therefore requesting that our activities in this area be strengthened and enhanced by providing additional resources in the following areas:

1. Additional faculty lines in mechanical engineering in biological computing and computational fluids
2. Additional space, and resources to establish a state of the art high performance computing facility in engineering (space plus state of the art workstations for visualization)
3. Additional post-doc and graduate assistant positions in the area of biological computing.