Computational models of growth and remodeling in heart failure

A. Project Scope

(1) Clinical motivation
Heart failure (HF) is a progressive condition where the heart loses its ability to pump sufficient blood, and leaves the tissues of the body starved for oxygen and nutrients. HF statistics all over the world are overwhelming. It is estimated that 26 million people have HF worldwide, and about one million new cases are diagnosed each year in the USA and European Union alone. The condition remains hard to treat in spite of considerable research efforts, with a five-year mortality of about 50%. While there are numerous root causes of HF, its progression is often tied to physiological regulative and adaptive processes becoming maladaptive. These mechanisms normally adapt cardiac function to the changing demands of the body over a person’s lifetime by a variety of control systems. Changes to organ physiology, cell biochemistry and biophysics, and changes in gene expression all work on different time-scales, enabling the heart to adapt to short- and long-term demand changes such as exercise and body growth. However, in HF, these control mechanisms respond to stimuli in a maladaptive manner. For example, after a myocardial infarct, cellular processes such as apoptosis, altered collagen production, and changes in protein production all can lead to significant changes in the organ. Such changes alter the mechanical function of the heart dramatically, which can then feedback into the same processes, producing a vicious cycle of cardiac hypertrophy, which progressively reduces the function of the heart. It is of vital importance to understand how these adaptive processes of cardiac regulation become maladaptive in different pathological conditions, and how this feedback may be prevented.

(2) Computational models and challenges
Over the last four decades we have witnessed remarkable developments in computational models of the cardiovascular system. Driven by improvements in computer hardware, numerical methods, experimental techniques, and medical imaging, these models simulate cardiac function and allow testing of hypotheses related to dysfunction as well as potential treatment. Still, the complex etiology of HF represents a formidable challenge for computational models, which in recent years has received significant attention from the modeling community. Common to all current computational heart models is that they describe acute phenomena, with predictive abilities in the range of milliseconds to a few seconds. The overall goal of this project is to develop and integrate a number of cardiovascular models to extend this predictive ability from the acute to the chronic, to help understand the adaptive processes that occur over hours, days and weeks.

Developed computational models will be used to test hypotheses on cardiac remodeling mechanisms, and to provide a quantitative understanding of remodeling in the context of pathological stimuli. Specifically, this will entail development of a suite of models informed from longitudinal animal data being collected at the Institute for Experimental Medicine (IEMR) at Ulleval. This hierarchy of multiscale models will couple cardiovascular adaptation over days and months to detailed models of heart function, and match models to trajectories in the data through the use of modern optimization methods. The main components of the required modeling framework already exist, including detailed models of a single to a few heart cycles, a widely adapted framework for describing the kinematics of soft tissue growth, detailed models of cell regulation and adaptive processes, and well tested models for the short and medium-term adaptive processes of the cardiovascular system. However, putting all these components together in a reliable and efficient computational framework that can feasibly assimilate experimental data will be highly challenging. The most important questions are related to the multiscale nature of the problem, which will easily give rise to non-feasible computational problems. Although the main components of the modeling framework already exist. Brute force integration techniques will obviously fail when trying to bridge spatial scales from sub-cell to organ level, and time scales from milliseconds to years. A combination of model analysis, to uncover the required level of coupling between individual scales, and state-of-the-art numerical techniques must be applied to arrive at a feasible computational problem.

B. Inter-Institutional Collaboration

(1) This project will be based primarily at UiO.
(2) Key faculty at UiO/Simula will be Joakim Sundnes (Primary advisor, UiO/Simula), Samuel Wall (co-advisor, Simula)
(3) Key faculty at UCSD will be Professor Andrew McCulloch (co-advisor)
(4) The project will strengthen and expand the existing Simula-UCSD collaboration on heart mechanics modeling. This collaboration dates back to 2002, includes numerous researchers at both institutions, and has resulted in joint publications on several aspects of multiscale heart electrophysiology and mechanics models. Expanding this joint modeling effort to consider growth and remodeling, is a natural step with interesting clinical potential, and is of interest to both parties.

The project will be centered and organized at UiO, in close interaction with Simula. The training part, including courses, will primarily be conducted at UiO, focusing on numerical analysis, computational fluid mechanics, and fundamental biomedical modeling. The project will involve (at least) one longer visit to UCSD, which will be planned for the second half of the PhD period. The goal for this visit will be to gain a deeper insight into the biomedical engineering and experimental side of modeling, in addition to added competence on fluid structure interaction.

C. International and Local Training

(1) The curriculum will be decided based on the background and interests of the candidate. Natural courses to include are INF9560 Computational physiology, INF9620 Numerical methods for PDEs, and MEK9250 - Finite Element Methods in Computational Mechanics.

(2) The candidate will be enrolled in the regular training activities for PhD students at Simula, including the course in scientific communication skills (presentation and writing).

(3) No formal training component is planned at UCSD. The nature of the research visit(s) will be decided based on the interest of the candidate and progress of the project.

(4) The course INF9560, which includes training sessions in Oslo and San Diego, will be scheduled as early as possible in the project, and used as an opportunity for all involved parties to meet and lay out detailed plans for the project and progress follow up. The tentative plan for progress monitoring is to keep a fairly strict schedule of weekly email updates, monthly Skype/phone conferences and at least one meeting per year, which involves the candidate and advisors from both UCSD and UiO/Simula.