Computational modeling of fluid structure interaction in the heart

A. Project Scope
(1) Clinical motivation

Left Ventricle (LV) Ejection Fraction (EF) is widely used clinically as a surrogate for LV contractility. However, this index fails to accurately describe function and hemodynamic performance of the LV precisely. In particular in structural abnormalities, dilated ventricles, and valvular regurgitations, the assumption used to calculate EF clinically do not hold. Quantification of flow volumes during LV filling and ejections is important to understand both insufficiencies of the valves and heart failure (HF). Accurate quantification of flow and back flow through the mitral and aortic valve are therefore important factors in risk stratification and determination of time to surgery. Other hemodynamic effects such as vortex flow in the LV can also prove important in quantifying acute response to cardiac resynchronization therapy (CRT) in HF. It has been shown that the peak flow velocity component of vortex at the level of the tip of mitral valve during end diastole is highly correlated to peak positive dP/dt. dP/dT max is currently the gold standard (measured invasively) for LV contractility and acute CRT response.

(2) Flow simulations

We plan to develop fluid structure interaction (FSI) models for the LV that can be assimilated with measurements using novel blood speckle tracking with ultra-high frame-rate echocardiography. This combination of measurements and an accurate flow model for the LV will be highly novel and with high potential for clinical impact. The peak Reynolds number in the left ventricle during peak systole is around 5000, which combined with pulsatile effects and complex geometry is a breeding ground for flow instabilities, maybe even turbulence. Hence, the smallest length- and especially time-scales present in the blood flow are orders of magnitudes below those which are normally of interest in cardiac electrophysiology, or a moving heart. Naturally, this will also affect the computational needs, and also the choice of numerical solver for the FSI problem. Specifically, monolithic implicit iterative schemes become too expensive when the small temporal scales require tens of thousands of time steps per cardiac cycle.

We have developed flow solvers with similar performance and accuracy to the flagship solver from Stanford Center for Turbulence Research. This solver has been shown to handle turbulent flows well and we obtain results comparable to those from spectral element solvers. Key elements in this success lies in linearizing nonlinear terms using semi-implicit discretization schemes, and solving each velocity component in a segregated manner (as opposed to coupled) in order to save memory. The intention is to use the same ideology in redesigning existing tissue mechanics and electrophysiology solvers, strong coupling between the fluid and the structural domains, and frequent interface updates.

The candidate should build on, merge, and expand existing code implemented in the FEniCS framework. The implementation must then be extensively verified against existing benchmark problems. Patient-specific medical images are available from clinical collaborators and the Vascular Modelling Toolkit can be used to segment medical images. The FSI framework should further be validated against high frame-rate in vivo measurements. The majority of the work involved in this PhD project will be of a computational nature, devoted to developing a robust and usable solver framework for cardiac FSI problems. However, close contact with clinical and industrial collaborators will be emphasized from the start, to guide design choices and direction of research. The aim for the final part of the PhD project is to address the above-mentioned clinical hypotheses.

B. Inter-Institutional Collaboration
(1) This project will be based primarily at Simula.
(2) Key faculty at Simula/UiO will be Joakim Sundnes (Primary advisor, UiO/Simula), Kristian Valen-Sendstad (advisor, Simula), Eigil Samset (advisor, UiO/GE Vingmed). In addition, the project will include collaboration with the Norwegian University of Science and Technology (NTNU), with Lasse Lovstakken in an advisory role.
(3) Key faculty at UCSD will be Professor Andrew McCulloch
(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 fluid flow and fluid structure interaction is a natural step with interesting clinical potential, and is of interest to both parties.

The project will be centered and organized at 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, MEK9250 - Finite Element Methods in Computational Mechanics, and MEK9470 - Computational Fluid 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.
Curriculum Vitae

Joakim Sundnes

Norwegian, born Jul 4, 1974, homepage: http://simula.no/people/sundnes

Employment history

2015-: Senior Lecturer and Associate Professor, Dept. of Informatics, Univ. of Oslo
2009-: Senior Research Scientist, Simula Research Laboratory (partial leave from April 2015)
2007-2009: Assistant Director of Basic Research, Simula Research Laboratory
2007-: Deputy Director of Center for Biomedical Computing
2004-2006: Research Director, Scientific Computing, Simula Research Laboratory
2002-2015: Adjunct Associate Professor, Dept. of Informatics, Univ. of Oslo (20%)
2002-2004: Postdoctoral Fellow, Simula Research Laboratory
2002-2002: Visiting Postdoctoral Fellow, University of California, San Diego
2000-2002: PhD student, Simula Research Laboratory and Dept. of Informatics, Univ. of Oslo

Main research interests

Computational mechanics, numerical solution of partial and ordinary differential equations, modeling heart mechanics and electrophysiology, scientific software

Research management/Project funding

2011-2014: Research project In Silico Heart Failure - tools for accelerating biomedical research, project grant from the eVITA program of the Research Council of Norway (total budget 7.7 MNOK over 4 years)
2007-2017: Centre of excellence (SFF) grant Center for Biomedical Computing (CBC). Grant proposal was written jointly by Professor Hans Petter Langtangen (CBC director) and myself (deputy director) (total budget 75 MNOK over 10 years).
2004-2009: Outstanding Young Investigator (YFF) grant Computing the mechanics of the heart, from the Research Council of Norway (total budget 7 MNOK over five years).

Selected scientific activities

• Several visits to the Cardiac Mechanics Research Lab, UC San Diego (Prof. Andrew McCulloch), as a visiting scholar. (Total duration appr. 10 months)
• Editorial board; Simulation Modeling Practice and theory, 2009-2013
• Review editor for Frontiers in Computational Physiology and Medicine, 2012- and Frontiers in Computational Physics, 2012-
• Program committees; 11th European conference on computational biology (2012), IEEE international conference on bioinformatics and biomedicine (2012)
• Organized more than 10 workshops and minisymposia at international conferences
• Member of the expert panel for the EU funded project Strategy for the EuroPhysiome, 2006.

Teaching

2015-: Numerical Calculations (INF-MAT2351), Department of Informatics, University of Oslo.
2002-2014: Mathematical models in medicine (INF 5610), joint with Glenn Lines, Department of Informatics, University of Oslo.
2010-: Problem solving with high level languages (INF 3331), Department of Informatics, University of Oslo.
2003-2004: Mathematical modeling of flow, heat transfer and deformation (MEK-INF 4210), joint with Hans Petter Langtangen, Department of Informatics and Department of Mathematics, University of Oslo.
An introduction to continuum mechanics, short course at the eVITA Winter School in Computational Mathematics, Geilo, January 2012.

Student supervision

- PhD students: Siri Kallhovd (current), Bernardo Lino de Oliveira (current), Gabriel Balaban (current), Martin Sandve Alnaes (2009), Johan Hake (2009), Mary MacLachlan (2006), Tom Thorvaldsen (2006), Monica Hanslien (2006)

Publications

Books


PhD thesis


Articles in international journals


**Chapters in books**


**Articles in refereed proceedings**


Invited talks


Contributed talks


BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

**NAME**
Andrew D. McCulloch

**POSITION TITLE**
Distinguished Professor of Bioengineering and Medicine

**eRA COMMONS USER NAME (credential, e.g., agency login)**
AMCCULLOCH

**EDUCATION/TRAINING** *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

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<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>MM/YY</th>
<th>FIELD OF STUDY</th>
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<tr>
<td>University of Auckland, New Zealand</td>
<td>B.E.</td>
<td>05/81</td>
<td>Engineering Science</td>
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<td>05/83</td>
<td>Physiology</td>
</tr>
<tr>
<td>University of Auckland, New Zealand</td>
<td>Ph.D.</td>
<td>09/86</td>
<td>Bioengineering</td>
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**A. Personal Statement**

Professor McCulloch has expertise in experimental and computational models of heart disease especially arrhythmia and heart failure, which he studies from molecular to organ system scales. He has published over 200 peer-reviewed articles, is Associate Editor of three major journals and Editor-in-Chief of *Drug Discovery Today: Disease Models*. Dr. McCulloch is an investigator of the *National Biomedical Computation Resource*, an NIGMS P41 Biotechnology Research Center, of the *Virtual Physiological Center for the Study of Complex Disease* an NIGMS P50 Systems Biology Center, and an NHLBI PPG on *Hypoxia Tolerance and Susceptibility.*

**B. Positions and Honors**

**Positions and Employment**

2013- Present  **Distinguished Professor of Bioengineering and Medicine**
2010- Adjunct Professor of Medicine (Cardiology), UCSD
2009- Director, Interdisciplinary PhD Specialization in Multi-Scale Biology
2006-2005 Director, UCSD Interfaces Graduate Training Program
2005-2008 Professor and Chair, Department of Bioengineering, UCSD
2002-2005 Professor and Vice Chair, Department of Bioengineering, UCSD
2000-present Affiliate Professor of Bioengineering, University of Washington, Seattle, WA
2004-present Member, California Institute for Telecommunications and Information Technology
1997-present Professor, Department of Bioengineering, UCSD
1997- Fellow, AIMBE, American Institute for Medical and Biological Engineering
1997-present Senior Fellow, San Diego Supercomputer Center
1996-present Member, UCSD Center for Research in Biological Structure
1994-2005 Chair, Bioengineering Graduate Studies Committee
1994-1997 Associate Professor, Department of Bioengineering, UCSD
1993-1994 Associate Professor of Bioengineering, Department of AMES, UCSD
1991-present Member, UCSD Institute for Engineering in Medicine (formerly Whitaker Institute)
1987-1993 Assistant Professor of Bioengineering, Department of AMES, UCSD
1985-7 Junior Lecturer in Engineering Science, University of Auckland, New Zealand

**Awards**

2010- Fellow, Cardiovascular Section, American Physiological Society
2009-2014 Jacobs Distinguished Scholar
2006 Konrad Witzig Lecturer
2005 Donald Wasserman Memorial Lecturer
2002 Outstanding Teacher Award, UCSD
1998 1997 Best Paper Award, ASME International, Bioengineering Division
1991-1996 NSF Presidential Young Investigator
1989-1992 Whitaker Foundation Biomedical Research Award
1988-1993 NIH FIRST Award
1984 Medical Research Council of New Zealand Postgraduate Scholarship
1983 Physiology Annual Prize, University of Auckland

Responsibilities
2014- Member, World Council of Biomechanics
2011-13 Member, International Scientific Program Committee, IUPS
2010-2012 Chair, IUPS Physiome and Systems Biology Committee
2010- Associate Editor, *Biophysical Journal*
2010- Associate Editor, *Journal of Physiology (Lond)*
2009- Associate Editor, *PLoS Computational Biology*
2008-2010 Associate Editor, *Medical and Biological Engineering and Computing*
2007- Editorial Board, *Cellular and Molecular Biomechanics*
2006- Editorial Board, *Synthetic and Systems Biology*
2006- Co-Editor-in-Chief, *Drug Discovery Today: Disease Models*
2002-2008 Associate Editor, *Journal of Biomechanical Engineering*
2002- Editorial Board, *Computer Methods in Biomechanics and Biomedical Engineering*
2002-2005 Board of Directors, Biomedical Engineering Society
2000-2002 US National Committee on Biomechanics (APS Representative)
1994-2005 Chair, Bioengineering Graduate Studies Program
2004-2007 Member, Bioengineering and Physiome Committee of the IUPS
2004- Member, International Academy of Astronautics
1992- Member, Basic Science Councils of the American Heart Association
1995- Member, Biophysical Society
1990- Member, American Physiological Society
1990- Member, Bio-Medical Engineering Society
1989- Member, American Society of Mechanical Engineers

C. Selected Peer-Reviewed Publications (from a total of >200)

Most relevant to the current application


Additional recent publications of importance to the field (in chronological order)


D. Research Support

Ongoing/ Active

NIH NIBIB 1 T32 EB009380 (McCulloch PI) 03/01/14-06/30/15

Training In Multi-Scale Analysis of Biological Structure and Function

This training grant supports PhD students participating in interdisciplinary training program.

NIH/NIGMS 8 P41 GM103426-19 (Amaro) 5/1/2014 – 4/30/2019

National Biomedical Computational Resource: Project 4A.2B (McCulloch PI) Multiscale Modeling Environment for Tissue and Organ Biophysics

Development of high performance computational software for modeling three-dimensional cardiac mechanics, electrophysiology and transport processes for use by biomedical researchers.

NIH NHLBI 1R01HL96544-1 (McCulloch PI) 07/01/09-06/30/15 (NCE)

Multi-Scale Modeling of the Failing Heart for Cardiac Resynchronization Therapy

The goal of the proposed research is to develop patient-specific models of ventricular electromechanics for predicting outcomes of cardiac resynchronization therapy.
Molecular Mechanisms of Hypoxia Tolerance and Susceptibility Core B (McCulloch): Systems Biology
The overall goal of Core B is to provide training, tools, technologies and model analyses for phenotyping and systems analysis of hypoxia responses in Drosophila, mouse and human studies.

The Virtual Physiological Center for the Study of Complex Disease. Project 3 (McCulloch)
Dr. McCulloch’s contribution to this proposed center includes developing multi-scale models of cardiac function in consomic and congenic rat strains and using microscopy and MRI to create anatomic models and validate functional predictions.

Multi-Scale Systems Models of Murine Heart Failure
The overall goal of this project is to develop and experimentally validate systems and multi-scale models of cardiac signaling, electrophysiology, excitation-contraction coupling in the normal and diseased mouse heart using murine models that have over- or null-expression of CaMKII.

The Cardiac Atlas Project
The overall goal of this project will be to build on existing technology for developing and deploying a web accessible biomechanical atlas of the heart with congenital disease for clinical and research purposes. This resource will help accelerate the translation of clinical and basic research into improved strategies for patient-specific and disease-specific care.

Completed in the last three years
Molecular Pathways for Cardiac Hypertrophy and Cardiomyopathy: Core A (McCulloch PI): Bioengineering Core for Cardiac Cell and Tissue Models
Core A provides training, tools, technologies and model systems that enable the projects of the PPG to analyze the structure and function of key adhesive junctions of the cardiac myocyte and to investigate how defects in cardiac cell-cell and cell-extracellular matrix molecular complexes disrupt structural integrity, electrical, mechanical and signaling functions in isolated cardiac cells, tissues and whole hearts.

Multi-scale model of the human heart for imaging research
The goal of this multi-institutional, collaborative proposal is to develop and validate a 4D finite element (FE) multi-scale computational model of the human heart, spanning biophysical scales from cell to population, based on state-of-the-art human imaging data.

Interfaces Training Grant: Multi-Scale Analysis of Biological Structure and Function
The purpose of this project is to develop an interdisciplinary training program at the interfaces of biological, medical and physical sciences.