Computing Microscopic Structure-Function Relationships in Contraction of the Heart

A. Project Scope

Contraction of cardiac muscle cells (cardiomyocytes), and thus the whole heart, are critically dependent on dyads. These functional junctions between T-tubules ("TT" in Figure 1A), which are invaginations of the surface membrane, and the sarcoplasmic reticulum (SR) allow efficient control of calcium release into the cytosol (Figure 1B). It is this release of calcium that is responsible for initiating contraction of the heart and regulating contractile force. Dyads are formed gradually during development, and this structural organization is believed to support the similarly gradual strengthening of the heartbeat. Dyads also break down during diseases such as heart failure, and this structural derangement is believed to contribute to disease by weakening contraction. However, the precise nature of dyadic structure-function relationships is very poorly understood. To gain insight into this critical topic, our group has employed state-of-the-art imaging techniques to examine 3D dyadic structure in developing, adult, and failing hearts. During the period of this fellowship, the group of Dr. William Louch at the University of Oslo will provide new experimental data describing very detailed aspects of dyadic structure. These data will be collected via state-of-the-art Correlative Light Electron Microscopy (CLEM). This technique combines the benefits of super-resolution imaging (dSTORM) and electron microscopy to create 3D "dyadic maps" (Fig. 1A), capable of indicating not only the membrane structures involved in the structure, but the precise location of proteins responsible for controlling dyadic calcium release. Our data show that dyadic disruption during heart failure includes changes in the shape of both t-tubules and sarcoplasmic reticulum, and displacement of dyadic proteins such as the Ryanodine Receptor (Figure 2). We believe that these changes are a reversion to an immature, developing phenotype. Dyadic function, however, remains very difficult to assess experimentally, as existing technologies for measuring Ca\textsuperscript{2+} homeostasis are limited to 2D and modest spatial resolution.

In this project we will extend the detailed geometric computational models built by members of Dr. McCulloch’s lab at UCSD by including new details gleaned from the experimental data collected in the Louch lab, as described above. Together these two very advanced approaches will allow us to interrogate structure-function relationships of the cardiac dyad in a much more detailed and realistic manner than has previously been possible. The chief goals of the project will be to answer 2 questions regarding the structure-function relationships in the dyad, which remain unknown and cannot be experimentally disentangled: (1) how does variation in dyadic structure within a healthy cardiomyocyte, or resulting from disease, alter the calcium release properties independent of changes in protein localisation? (2) How does altered expression (content) of major proteins involved in dyadic calcium regulation (e.g. RyR) impact dyadic calcium handling independent of changes in dyadic structure. To address these questions the successful candidate will be tasked with creating a
new pipeline (possibly automated) for reconstructing dyadic geometries from the CLEM data collected in cardiomyocytes taken from healthy and failing hearts—similar approaches have previously been used on a single dyadic geometry from EM tomography, see Figure 1. With these meshes the candidate will need to develop new simulation tools and numerical approaches for locally defining and modulating the fluxes associated with key calcium handling proteins that will be discretely located within the mesh geometries. Together these two pipelines will be used to assess the questions described above in the greatest detail possible, and with reference to most realistic experimental data available.

B. Inter-Institutional Collaboration
(1) This project will be based primarily at Simula
(2) List the contributing faculty at Simula and/or UiO, and their roles (e.g. Primary advisor, etc.)
   - Primary Advisors: Andy Edwards, Senior Research Scientist, Simula
   - Secondary Advisors: William Louch, Assistant Professor, UiO/OUS

B. Inter-Institutional Collaboration
(3) List the contributing faculty at UCSD, and their roles (e.g. Primary advisor, etc.)
   - Primary Advisors: Andrew D. McCulloch, Professor, UCSD

(4) The goals and approach of this project are necessarily collaborative in that they rely upon data sources and computational approaches that are both highly technically challenging, and in the case of the experiments, also necessitate very specific and costly equipment for microscopy. As such, this project requires a degree of specialization that cannot easily be achieved by single investigative groups, and will involve intense interaction between the computational groups (Simula/ UCSD) and Dr. Louch’s group at UiO/OUS. Dr. Edwards’ prior training with Dr. McCulloch specifically involves this type of modeling work, and his further training with Dr. Louch and current work with Dr. Tveito and Simula will serve as an ideal platform for coordinating this project. Together the work described here will provide an excellent opportunity to extend the collaboration between Simula and UCSD to involve Dr. Louch’s experimental group at UiO.

C. International and Local Training
(1) Courses to be taken at UiO: MNSES9100 (Science, Ethics, and Society – 5 credits), Communicating Scientific Research (Simula – 5 credits), INF9560 (Computational Physiology, 10 credits)
(2) Additional professional/research training activities at UiO/Simula: The annual Simula-UCSD Summer School in Computational Physiology held in Oslo and San Diego. In Oslo, the student will be expected to attend and contribute to regular (fortnightly) project meetings held by the Cardiac Modeling group at Simula, and also to less regularly present progress on the project to Dr. Louch’s group at UiO and Oslo University Hospital Ullevål, where project meetings are held weekly.
(3) Describe additional professional/research training activities at UCSD: Dr. McCulloch’s group has weekly meetings, which require student presentations including from the successful candidate. In addition, Dr. McCulloch’s connections with other experimentalists at UCSD conducting similar CLEM-based analyses (particularly the laboratory of Masahiko Hoshijima) will provide excellent additional technical advice for these aspects while at UCSD.
(4) Describe how advisors at both institutions will monitor the student’s progress and development: In Oslo the successful student will meet at least weekly with Drs. Edwards and Louch to discuss progress on the project, in addition to presenting that progress less often at the Simula and UiO/OUS meetings. In San Diego, the student will meet with Dr. McCulloch and collaborators similarly often to deal with technical details of implementing the type of simulation frameworks and numerics required for this project, and in which this group is expert.
Curriculum vitae – Andrew Edwards

PERSONAL INFORMATION
Family name, First name: Edwards, Andrew
Date of birth: 23.06.1980
Sex: Male
Nationality: Canadian, Australian (dual citizen)

EDUCATION
2010 PhD (Integrative Physiology): May 7th 2010
Department of Integrative Physiology, University of Colorado at Boulder, USA
2005 Master of Science (Integrative Physiology): August 6th 2005
Department of Integrative Physiology, University of Colorado at Boulder, USA
2002 Bachelor of Science (Exercise Science): November 2002
Department of Biomedical Sciences, University of Wollongong, Australia

EMPLOYMENT
Current Senior Research Scientist
Simula Research Laboratory, Lysaker, Norway, and
Institute for Experimental Medical Research, Oslo University Hospital, Norway
2013-2014 Postdoctoral Fellow
Institute for Experimental Medical Research, Oslo University Hospital, Norway
2010-2013 Postdoctoral Fellow
Department of Bioengineering, University of California San Diego, USA
2006-2010 Graduate Research Assistant
Cellular Cardiac Physiology Laboratory, Department of Integrative Physiology,
University of Colorado at Boulder, USA
2005-2006 Professional Research Assistant
Applied Exercise Science Laboratory, Department of Integrative Physiology,
University of Colorado at Boulder, USA
2005-2006 Consultant Physiologist
Berkeley Heart Lab, Los Angeles, CA, USA
2003-2005 Graduate Research Assistant
Applied Exercise Science Laboratory, Department of Integrative Physiology,
University of Colorado at Boulder, USA
2002-2003 Consultant Physiologist
Cycling Australia, Australian Sports Commission, Homebush, NSW, Australia

GRANT FUNDING
2014-2016 University of Oslo, Forskerlinje scholarship (Olav Eken), supervisor: Andrew Edwards
2012-2014 American Heart Association, Western States Affiliate, Postdoctoral Fellowship
Primary Investigator: Department of Bioengineering, UCSD/USA.
2011-2012 Heart Rhythm Society, Michel Mirowski International Fellowship in Cardiac Pacing and Electrophysiology. Primary Investigator: Department of Bioengineering, UCSD/USA.
2011 American Heart Association, Western States Affiliate, Postdoctoral Fellowship
(Gratefully declined). Primary Investigator: Department of Bioengineering, UCSD/USA.
2009-2010 American Heart Association, Mountain States Affiliate, Predoctoral Fellowship
Primary Investigator: Department of Integrative Physiology, CU Boulder/USA.
2007-2009 American Heart Association, Mountain States Affiliate, Predoctoral Fellowship
Primary Investigator: Department of Integrative Physiology, CU Boulder/USA.
LIST OF PEER REVIEWED PUBLICATIONS

* Co-first authors


SELECTED ACTIVITIES

**Invited talks, conference responsibilities, and commissions of trust**

2014 Invited talk: “Non-equilibrium reactivation of myocardial Na⁺ channels”. University Medical Center Hamburg-Eppendorf. September 15th.


2014 Panelist: Na⁺-Ca²⁺ Exchange in Cardiomyocytes. UC Davis Na⁺ Symposium


2013 Invited talk: “Mechanisms of arrhythmia accompanying genetic CaMKII hyperactivity” Institute for Experimental Medical Research. Oslo University Hospital. Ullevål, Norway. 23rd April.

2012 Invited talk: “Calcium-driven early afterdepolarizations prior to heart failure in the CaMKIIδ_C transgenic mouse”. NSR Physiome International Meeting. San Diego. 1st November.


2010 Invited talk: “Cellular mechanisms of sustainable cardioprotection” Department of Integrative Physiology, University of Colorado at Boulder, 29th April.

2010 Committee member: Responsible Conduct of Research Steering Committee, CU Boulder

2009 Co-founder: Forum on Science Ethics and Policy, Colorado Chapter, 2009-2010

2008 Invited talk: “Mechanisms of sustainable cardioprotection: what can we glean from models involving physiologic stimuli?” Biomedical Sciences Dept., Colorado State University, September.

**Editorships:** *Frontiers in Pharmacology* (Guest Editor)


**Supervision of graduate students and research fellows (2008-Current):**

Number of Postdocs: 0  
PhD Students: 2  
Masters/Forskerlinje Students: 3

**PROFESSIONAL MEMBERSHIPS**

American Physiological Society (2008-present)  
Physiome Society (2012-present)  
Biophysical Society (2010-present)  
American Heart Association (2010-present)

**TEACHING EXPERIENCE**

Unique courses as instructor of record: 1  
(Chlorine CV Physiology, CU Boulder)

Unique courses as co-instructor: 3  
(CU Boulder, UCSD, University of Oslo)

Unique courses as teaching assistant: 11  
(CU Boulder)
Curriculum Vitae - William E. Louch, Ph.D.

Citizenship: Canadian
Date of birth: 14/09/1976, at St. John's, Canada
Present position: Research Associate Professor
Address: Institute for Experimental Medical Research
University of Oslo & Oslo University Hospital Ullevål
4. etg. Bygg 7, Kirkeveien 166
0407 Oslo, Norway
Contact: E-mail: w.e.louch@medisin.uio.no

LANGUAGES:
Spoken: English (mother tongue), Norwegian
Understood: Swedish, Danish, French

ACADEMIC DEGREES:
2001: PhD Pharmacology, Dalhousie University, Halifax, Canada
1997: BSc Chemistry/Neuroscience, Dalhousie University, Halifax, Canada

EMPLOYMENT HISTORY:
Jan 2013-present: Head, Confocal Imaging Core Facility, Oslo University Hospital Ullevål
May 2012-present: Research Associate Professor / Research Scientist with Professor Competence, Institute for Experimental Medical Research, University of Oslo, Oslo, Norway
2008-2012: Research Scientist, Institute for Experimental Medical Research, University of Oslo, Oslo, Norway
2004-2008: Post-doctoral fellow, Institute for Experimental Medical Research, University of Oslo, Oslo, Norway
2002-2003: Post-doctoral fellow, University of Leuven, Belgium

THESSES:
PhD: Louch WE (2001) Cardiac Ischemia and Reperfusion: Cellular Physiology and Pharmacological Intervention.

PUBLICATIONS:
Articles published to date: 63, last 5 years: 38
Citations: 938, h-index: 16

ORAL PRESENTATIONS:
Invited: 36
Conference abstracts: 15

ADMINISTRATIVE EXPERIENCE:
Research networks and symposia:
- Organizing committee member – Scandinavian Physiological Society Annual Meeting, Oslo, Aug 2016.
- Symposium panelist – “Disrupted Na” Homeostassis”, UC Davis Cardiovascular Symposium, Feb 20 2014.

Organizing committee - the 4th Biennial MyoNaK meeting, Beitostølen, Norway, Sept 22-26 2012.


Referee for Grant Evaluations – New Zealand Heart Foundation, 2012-present.

Board member of the Scandinavian Physiological Society, Representative for Norway, 2012-present.

Board member - KG Jebsen Cardiac Research Center, 2011-present.


Member – Centre for Heart Failure Research, 2005-present

PhD defense committees:

- PhD candidate Lei Yuan, Mar 3 2015, Copenhagen, Denmark
- PhD candidate Einar Eftestøl, Feb 4 2015, Oslo, Norway
- PhD candidate Søren Grubb, Apr 10 2014, Copenhagen, Denmark
- PhD candidate Rønnaug Strandabø, Nov 27 2013, Oslo, Norway
- PhD candidate Thomas Stølen, May 28 2010, Trondheim, Norway

Grants/Fellowships:

Present Funding:

- PhD Stipend for David Lipsett, Centre for Heart Failure Research, “Molecular mechanisms controlling T-tubule structure in healthy and failing cardiomyocytes”, 2015.
- PhD Stipend for Michael Frisk, Raagholtstiftelsen, “Spreading of dysfunction during heart failure”, 2014.
- Research stipends for PhD students Terje Kolstad and Marianne Ruud, Norwegian Research School in Medical Imaging (MedIM), 50 000 NOK each, 2014.
- Core Facility for Confocal Microscopy grant, South-Eastern Norway Regional Health Authority, 2014.
- Postdoctoral fellowship for Andrew Edwards, South-Eastern Norway Regional Health Authority, “Relaxing a Rigid Heart”, 2013-2015.
- Infrastructure grant for Incubator-Based Live Cell Imaging, University of Oslo, 123 000 NOK, 2013.
- Infrastructure grant for Confocal Core Facility Renovation, Oslo University Hospital Ullevål, 500 000 NOK, 2013.
- Research stipends for PhD students Michael Frisk and David Lipsett, Norwegian Research School in Medical Imaging (MedIM), 50 000 NOK each, 2013.
- Equipment grant for CellTester system, University of Oslo, 1 000 000 NOK, 2013.
- Operating grant, partner, KG Jebsen Center for Exercise in Medicine, 2011-present.
- Operating grant, partner, KG Jebsen Cardiac Research Center, 2011-present.
- Operating grant, partner, Centre for Cardiological Innovation, Research Council of Norway, 2011-present.
- PhD student fellowship for Michael Frisk, European Union Collaborative Project, “MEDIA (The Metabolic Road to Diastolic Heart Failure)”, 2011-2014.

Past Funding:
- Travel grant for Michael Frisk, exchange with laboratory of J.A. Wasserstrom (Chicago, USA), Centre for Heart Failure Research, Oslo, 2012
- Medical student research fellowship for Kristian Loose, University of Oslo, “Heartbreakers: Can changes in cell structure cause heart failure?”, 2010-2012.
- Summer student fellowship for medical student Kristian Loose, University of Oslo, 2010
- Equipment grant, “Na”-Dependent Control of the Heartbeat”, University of Oslo, 2009
- Fellowship for scientific assistant Guro Five Jølle, Centre for Heart Failure Research, Oslo, 2009
- Equipment grant, VIRUUS – Oslo University Hospital Ullevål, 2006
- VIRUUS Post-doctoral fellowship, Ullevål Hospital, Oslo, Norway, 2005
- Canadian Institute of Health Research Doctoral Fellowship, 1997-2001

Scientific journal duties:
- Acta Physiologica
  - Associate Editor, 2014-present
- Referee duties:

AWARDS:
- Award for Research Excellence, Oslo University Hospital, for publication of Swift et al., PNAS, 2012.
- Best Presentation, Centre for Heart Failure Research Annual Meeting, Oslo, Norway, 2011
- Poster Prize, Annual meeting of the European Working Group for Cardiac & Cellular Electrophysiology, Cologne, Germany, 2009
- Best Presentation, Centre for Heart Failure Research Annual Meeting, Oslo, Norway, 2008
- Best Presentation, Centre for Heart Failure Research Annual Meeting, Oslo, Norway, 2007
- Direktørens Belønning for Fremragende Forskning (Director’s Award for Excellent Research), Ullevaal Hospital, 2006
- Best Presentation, Centre for Heart Failure Research Annual Meeting, Oslo, Norway, 2006
- Servier Best Communication Award, Annual meeting of the European Working Group for Cardiac & Cellular Electrophysiology, Antwerp, Belgium, 2005
- Young Investigator Award, Annual meeting of the European Society of Cardiology, Munich, Germany, 2005
TEACHING/SUPERVISORY EXPERIENCE:
- supervisor for PhD student Marianne Ruud, Jan 2014-present
- supervisor for postdoc Andrew Edwards, Dec 2013-present
- co-supervisor for PhD student Terje Kolstad, Aug 2013-present
- supervisor for PhD student David Lipsett, Nov 2012-present
- supervisor for medical research student, Åsmund Røe, May 2012-present
- co-supervisor for PhD student Kiarash Tazmini, January 2012-present
- supervisor for PhD Michael Frisk, May 2011-present
- supervisor for medical research student, Kristian Loose, July 2010-present
- supervisor for PhD student Guro Five Jølle, 2009-2012
- supervisor for PhD student Halvor Mørk, 2005-2009
- lecturer in masters-level course “Cellular Signaling”, University of Oslo, 2011-present
- lecturer in course “Methods in Molecular Biology”, Ullevål Hospital, Sept 2009
- lecturer in masters-level course “Quantitative Biology”, University of Oslo, 2009-present
- lecturer in masters-level course “Advanced Physiology and Cell Biology”, University of Oslo, 2008-present
- lecturer in graduate student course “Methods in Cardiac Research”, 2004-present
- lecturer in 1st year pharmacy, “Cardiovascular Drugs”, 2001
- lab demonstrator, “Introduction to Pharmacology” course, 1999-2001

TECHNICAL EXPERTISE:
- conventional electrophysiology
- voltage-clamp techniques using high-resistance and patch electrodes
- confocal microscopy and image analysis
- whole-cell photometry for examination of cytosolic Ca^{2+}, Na^{+}, and pH
- high-pressure liquid chromatography
- electron microscopy
- flash photolysis of caged compounds
- cardiac myocyte isolation from human, pig, guinea pig, and murine myocardium

PROFESSIONAL AFFILIATIONS:
- International Union of Physiological Sciences, 2009-present
- American Heart Association, 2007-present
- International Society for Heart Research, 2005-present
- Scandinavian Physiological Society, 2004-present
- European Society of Cardiology, 2002-present
- American Biophysical Society, 1998-present

PERSONAL REFERENCES:
Professor Susan E. Howlett
Relation: Ph.D. supervisor
Department of Pharmacology
Dalhousie University
Halifax, NS
Canada B3H 4H7
Phone: +1-902-494-3552
E-mail: susan.howlett@dal.ca

Professor Ole M. Sejersted
Relation: Institute Head
Inst. for Experimental Medical Research
Ullevål University Hospital
4. etg. Kirurgisk bygning
0407 Oslo, Norway
Phone: +47 23 01 68 31
E-mail: o.m.sejersted@medisin.uio.no
Curriculum Vitae

Name: Aslak Tveito
Born: 17.02.1961
Nationality: Norwegian
Present position: Managing Director (CEO), Professor of Scientific Computing

Academic degrees
1988 Dr. Scient (PhD) in Numerical Analysis, Department of Informatics, University of Oslo
1985 Cand. Scient (MSc) in Numerical Analysis, Department of Informatics, University of Oslo

Work experience
2002–present Managing Director/CEO, Simula Research Laboratory
Summer 2014 Visiting professor, University of California, San Diego
Summer 2013 Visiting professor, University of California, San Diego
2011–2012 Visiting professor, University of California, San Diego
2001–2002 Research Director, Simula Research Laboratory
1994–present Professor of Scientific Computing, University of Oslo
1993–1994 Chief Scientist at SINTEF Applied Mathematics
1991–1992 Senior Scientist at SINTEF Applied Mathematics
1991–1993 Professor II, University of Oslo
1989–1990 Postdoctoral Researcher, University of Oslo
1986–1988 Research Assistant, University of Oslo

Professional Activities
• High-Performance Computing Board, Research Council of Norway, 1999
• Board of the Department of Informatics, University of Oslo, 1997–2000
• Board of SINTEF Applied Mathematics, 1994–1996
• Evaluation Committee for Mathematics in Swedish Universities, 2001
• ICT Forum, Research Council of Norway, 2001
• Chairman of the Committee for Planning, ICT Research, Norway, 2003–2004
• Evaluation panel, for the Swedish Research Council, 2005
• Evaluation panel, for research at Uppsala University, 2007
• Chairman of the board of Simula Innovation a.s., 2006–2008
• Chairman of the board of Kalkulo a.s., 2006–2008
• Chairman of the board of Simula School of Research and Innovation a.s., 2007–2010
• Advisor for Insilicom Inc., 2008–present
• Committee on Memberships, Society for Industrial and Applied Mathematics (SIAM), 2008–2011
• Resource Advisory Committee of the National Biomedical Computation Resource, University of California San Diego, 2009–present
• Member of the Norwegian Academy of Technological Sciences, the Biophysical Society, and a lifetime member of SIAM
• Editor in chief of the Simula Springer Briefs on computing starting in 2014.

Leadership and management My research career over the past 10 years has been based on a strong commitment to combine my personal research with leading a growing research lab. Ever since I became the managing director (CEO) of Simula Research Laboratory, it has been my ambition to continue working on the technical aspects of research and be the lead author of scientific papers and books. In particular I have very actively tried to avoid

1 ICT: Information and Communication Technology
As a pure leader of researchers; rather I have insisted on doing technical aspects of projects. I estimate that I have spent about half my time in research during this period and this estimate is quite stable. However, to manage a lab of more than 140 employees and still remain active in research, I have had to respectfully decline most offers to act on committees and editorial boards or give talks and other obligations that naturally follow from being active in a research field. This has also been necessary due to plentiful family obligations.

In 1997, I formed a new research group in scientific computing at the University of Oslo, and in 1999 Professor Hans Petter Langtangen joined the group. In 2001 the scientific computing group was evaluated as excellent (the highest degree) in a national evaluation of informatics and mathematics conducted by a group of leading international scientists on behalf of the Research Council of Norway.

In 2000 the Research Council of Norway held a competition among information and communications technology research groups in Norway to participate in a new research laboratory to be established as part of a knowledge park at Fornebu, outside Oslo. The scientific computing group was one of three winners, and became the Scientific Computing department, where I was the department head, when Simula Research Laboratory was established in 2001. Simula Research Laboratory performs long-term research aiming at possible applications and focuses on communication technology, scientific computing, and software engineering. Simula had NOK 20 million (about 2.5 million euros) in total income the first year. I took over as managing director (CEO) of the lab in 2002 and have been its leader since. In 2014, Simula will have total income of about 153 million NOK (19 million Euros). At present the Simula lab consists of the main company (Simula Research Laboratory a.s.), three subsidiaries (Simula School of Research and Innovation, Simula Innovation and Kalkulo), and Simula is co-owner of 11 start-up companies with about 45 employees. In the period from 2001 to present, 284 MSc students and 82 PhD students completed their degrees supervised by Simula employees. There are currently 57 MSc, 36 PhD students and 27 Post Docs at Simula.

Although the lab has grown considerably over the last decade, I have kept focus on my own research. I believe this to be important in order to signify that research is our core activity and that leaders at every level should be as involved in actual research as possible. In my view, it is not sufficient to be involved as a leader but also as a researcher. In order to this, it has been absolutely essential to build up a well functioning lab. It is of course also necessary to be involved in all major strategies initiatives. I have therefore been deeply involved in the work on garnering industry funding, in major grant initiatives (Center of excellence, Center for research driven innovations, basic funding of Simula and Simula’s educational efforts) and most recently I have initiated a shift in attention from national funding bodies to EU and US funding schemes. The EU funding has very recently paid off very well. Furthermore, we also quite recently obtained substantial funding for research driven educational collaboration with the University of California, San Diego.

In 2014, Simula and Springer entered an agreement to publish a series of books entitled Simula Springer Briefs of Computing with me as the editor in chief.

The construction and development of Simula have received considerable political attention in Norway. The way the lab is organized is referred to as the Simula model and is described in the book Simula Research Laboratory: By Thinking Constantly about It (edited by Tveito, Bruaset, and Lysne, Springer, Heidelberg, 2009, 666 pages).

Teaching/Supervision Since Simula’s start-up, I have remained in a professorship at the University of Oslo, with 80% leave. I have been an active supervisor and participated in educational efforts to strengthen the university’s education program in computational partial differential equations. Of the four textbooks I have co-authored, I am the first author of three. The books are published by Springer-Verlag and used internationally, with one book having been translated into German.

I have supervised 16 PhD students (completed) and 15 postdoctoral candidates, and I teach an introductory course in Scientific computing at the University of Oslo.

Innovation As a long-time member of the board of directors for a commercial start-up company and having supervised the establishment of 12 commercial companies from Simula Research Laboratory, I have considerable experience with industrial innovation. In particular, I initiated and led the work on establishing Simula Innovation, Kalkulo, and the Simula School of Research and Innovation (non-commercial but co-owned by commercial companies). Over a period of six years, Simula has contracted projects totaling NOK 140 million (17.5 million euros) funded by Statoil, the largest company in Norway. The innovation part of Simula is by now starting to create good result for the lab. In 2013 I initiated the Gründergarage in Simula - a free office space for IT-related entrepreneurs. The garage now counts close to 100 start-up projects.
Research
My research interests have covered a) the numerical solution of linear systems arising from the discretisation of partial differential equations, b) the numerical and mathematical analysis of hyperbolic conservation laws, c) mathematical models of two-phase flow, d) computing box-splines, e) upscaling, f) nonlinear water–waves, g) the numerical solution of the Black–Scholes equations, h) parallel computing for partial differential equations, and i) numerical software tools. Over the last 10 years, I have been working almost exclusively on mathematical and computational issues related to understanding the electrophysiology of the heart.

During 2005–2013 I co-authored 33 scientific papers published in reviewed international journals, three textbooks, and edited three books; all books published by Springer-Verlag. A list of the 10 most important publications in which I have been the lead author during this period is provided below.

From June 2011 to August 2012, I was a visiting professor at the Cardiac Mechanics research group at the Department of Bioengineering at the University of California, San Diego. During this period, I was still the leader of Simula Research Laboratory but stayed in San Diego to have stronger focus on my own research. I have also spent the summer of 2013 and 2014 at UCSD in order to be able to focus as much as possible on my research.

In the ten-year period I have co-authored two research monographs [1], [2] and a text book in scientific computing [3].

My research over the last 10 years has focussed on the following topics:

A. A theory for the origin of cardiac arrhythmia. Normal contraction of the heart is governed by an electrical wave traversing the entire cardiac muscle. If the wave is corrupted, contraction deteriorates and the heart is unable to provide sufficient blood to the body. This is lethal if not corrected within minutes. It is well established that fibrillation can be initiated by extra waves (ectopic beats) interacting with the heart’s regular electrical signal in an ill-fated manner. Therefore, it is of great importance to completely understand how these extra waves can appear. Through a series of papers, we developed a mathematical understanding of the origin of a certain type of cardiac arrhythmia based on existing mathematical models of electrophysiology. The analysis provided shows that pathological regions in cardiac tissue reduce the stability of the heart’s resting state, and can therefore act as drivers of cardiac arrhythmia [4, 5].

B. Anti-arrhythmic drugs. A major problem in devising drugs against cardiac arrhythmia is that the drug must improve the properties of injurious cells while not harming the healthy cells. An approach to this problem was provided in [6], where we show how to compute optimal properties for an anti-arrhythmic drug in the presence of ischemia. Furthermore, we compute optimal properties of drugs for patients affected by the long-QT syndrome, and in [7] we show that a drug currently under development may have severe pro-arrhythmic properties.

C. Numerical methods for solving differential equations modeling the electrophysiology of the heart. Numerical simulations are indispensible for understanding the electrochemical waves underpinning each heartbeat. From a computational point of view, the very steep upstroke of the cardiac action potential is the key issue because it severely restricts the computational mesh in time and space. A credible simulation of one cycle for the human ventricles requires about 30 million computational nodes and about 1000 time steps. This calls for great care in choosing and implementing numerical methods. We derived order optimal solvers for the linear systems arising from discretizations of the bidomain model [8]. This result is important because of the very large number of computational nodes needed to resolve the problem. New numerical methods for solving the bidomain model are introduced [1], and an improved version of the classical Rush–Larsen scheme used in electrophysiology is derived.

D. Calcium-driven instabilities. We develop methods and software for understanding the stability of the resting state of cardiac tissue. This amounts to analyzing the stability of an equilibrium point of a system of reaction diffusion equations and understanding how the stability depends on parameters in the model that will change under pathological conditions. A similar approach can be applied to analyzing the behavior of models of a single cell. In [9] we derive analytical expressions revealing when the resting state of a cell becomes unstable as the extracellular calcium level is increased, or as the strength of the sarco/endoplasmic reticulum calcium ATPase (SERCA) pump is changed.
E. Calcium-Depolarization-Calcium (CDC) waves  
Delayed afterdepolarizations (DADs) can arise in the resting phase of ventricular cells and is believed to be able to set off ectopic waves in cardiac tissue. The underlying mechanism on the cellular level is known, but it is not known how an extra depolarization in a single cell can overcome the strong damping by neighboring cells and set off a wave in tissue. In the paper [10] we propose a mechanistic explanation of this in terms of a new type of wave represented as a concatenation of successive calcium waves and depolarization waves. The paper disrupts a fifty years old modeling regime for cardiac electrophysiology.

F. Computing characterizations of drugs for ion channels and receptors using Markov models  
During my research visit to UCSD the summer of 2013, I started to work on a theory for computing optimal drugs based on probability density functions of the states of various Markov models used in models of ion channels and of the Ryanodine receptor governing intracellular calcium dynamics. The work was completed recently and formulated in terms of the lecture notes [2] accepted for publication by Springer-Verlag. The book presents detailed models and methods for computing optimal properties of drugs that can be used to repair the effect of serious mutations known to induce serious difficulties for ion channels and Ryanodine receptors. Accurate theoretical predictions on what sort of drugs should be used for specific types of mutations are provided.

Top 10 publications

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.)*

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>MM/YY</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Auckland, New Zealand</td>
<td>B.E.</td>
<td>05/81</td>
<td>Engineering Science</td>
</tr>
<tr>
<td>University of Auckland, New Zealand</td>
<td>COP</td>
<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>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>Year</th>
<th>Position and Department</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-</td>
<td>Distinguished Professor of Bioengineering and Medicine</td>
</tr>
<tr>
<td>2010-</td>
<td>Adjunct Professor of Medicine (Cardiology), UCSD</td>
</tr>
<tr>
<td>2009-</td>
<td>Co-Director, UCSD Cardiovascular Biomedical Science and Engineering Center</td>
</tr>
<tr>
<td>2009-</td>
<td>Director, Interdisciplinary PhD Specialization in Multi-Scale Biology</td>
</tr>
<tr>
<td>2006-present</td>
<td>Director, UCSD Interfaces Graduate Training Program</td>
</tr>
<tr>
<td>2005-2008</td>
<td>Professor and Chair, Department of Bioengineering, UCSD</td>
</tr>
<tr>
<td>2002-2005</td>
<td>Professor and Vice Chair, Department of Bioengineering, UCSD</td>
</tr>
<tr>
<td>2000-present</td>
<td>Affiliate Professor of Bioengineering, University of Washington, Seattle, WA</td>
</tr>
<tr>
<td>2004-present</td>
<td>Member, California Institute for Telecommunications and Information Technology</td>
</tr>
<tr>
<td>1997-present</td>
<td>Professor, Department of Bioengineering, UCSD</td>
</tr>
<tr>
<td>1997-</td>
<td>Fellow, AIMBE, American Institute for Medical and Biological Engineering</td>
</tr>
<tr>
<td>1997-present</td>
<td>Senior Fellow, San Diego Supercomputer Center</td>
</tr>
<tr>
<td>1996-present</td>
<td>Member, UCSD Center for Research in Biological Structure</td>
</tr>
<tr>
<td>1994-2005</td>
<td>Chair, Bioengineering Graduate Studies Committee</td>
</tr>
<tr>
<td>1994-1997</td>
<td>Associate Professor, Department of Bioengineering, UCSD</td>
</tr>
<tr>
<td>1993-1994</td>
<td>Associate Professor of Bioengineering, Department of AMES, UCSD</td>
</tr>
<tr>
<td>1991-present</td>
<td>Member, UCSD Institute for Engineering in Medicine (formerly Whitaker Institute)</td>
</tr>
<tr>
<td>1987-1993</td>
<td>Assistant Professor of Bioengineering, Department of AMES, UCSD</td>
</tr>
<tr>
<td>1985-87</td>
<td>Junior Lecturer in Engineering Science, University of Auckland, New Zealand</td>
</tr>
</tbody>
</table>

**Awards**

<table>
<thead>
<tr>
<th>Year</th>
<th>Award Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-</td>
<td>Fellow, Cardiovascular Section, American Physiological Society</td>
</tr>
<tr>
<td>2009-2014</td>
<td>Jacobs Distinguished Scholar</td>
</tr>
<tr>
<td>2006</td>
<td>Konrad Witzig Lecturer</td>
</tr>
<tr>
<td>2005</td>
<td>Donald Wasserman Memorial Lecturer</td>
</tr>
<tr>
<td>2002</td>
<td>Outstanding Teacher Award, UCSD</td>
</tr>
</tbody>
</table>
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
1993-2001  Editorial Board, American Journal of Physiology: Heart and Circulatory Physiology
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) 03/01/14-02/28/19
- 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.