Organizing Committee

Martin Falcke, Max Delbrück Center for Molecular Medicine, Germany

Gernot Plank, Medical University of Graz, Austria

Zhilin Qu, University of California, Los Angeles, USA

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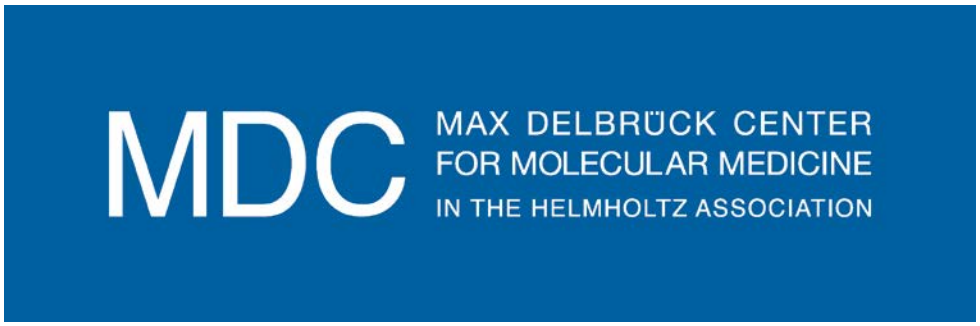

September 2018

Dear Colleagues,

We would like to welcome you to the Biophysical Society Thematic Meeting, *The Heart by Numbers: Integrating Theory, Computation and Experiment to Advance Cardiology,* co-sponsored by the Max Delbrück Center for Molecular Medicine, the German Centre for Cardiovascular Research, and the Berlin Institute of Health. We hope you enjoy the conference and the city of Berlin.

Cardiovascular medicine and neurobiology have been leading disciplines in quantifying research methods and results over the past decades. Cardiovascular modelling is becoming progressively translational, integrating new technologies to inform models at the structural and molecular level of detail of individual cells as well at the organ and systems levels incorporating both anatomy and dynamics. Mechanistic modelling is stronger than ever in our field and is at the forefront of integrating the novel data sources made available to us by advances in biomedical data science. This is what you will see illustrated in this meeting.

Thank you for attending this meeting. We hope you enjoy all Berlin has to offer!

The Organizing Committee
Martin Falcke, Max Delbrück Center for Molecular Medicine, Germany
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Biophysical Society Code of Conduct Anti-Harassment Policy

Adopted by BPS Council November 2015

The Biophysical Society (BPS) is committed to providing an environment that encourages the free expression and exchange of scientific ideas. As a global, professional Society, the BPS is committed to the philosophy of equal opportunity and respectful treatment for all regardless of national or ethnic origin, religion or religious belief, gender, gender identity or expression, race, color, age, marital status, sexual orientation, disabilities, veteran status, or any other reason not related to scientific merit. All BPS meetings and BPS-sponsored activities promote a working environment that is free of inappropriate behavior and harassment by or toward all attendees of Society meetings and Society-sponsored activities, including scientists, students, guests, exhibitors, staff, vendors, and other suppliers.

This global policy applies to all locations and situations where BPS business is conducted and to all BPS-sponsored activities and events. This policy does not replace the specific staff policies for situations in which only staff are involved.

Reported or suspected occurrences of harassment will be promptly and thoroughly investigated. Following an investigation, BPS will immediately take any necessary and appropriate action. BPS will not permit or condone any acts of retaliation against anyone who files harassment complaints or cooperates in the investigation of same.

Definition of Harassment
The term "harassment" includes but is not limited to epithets, unwelcome slurs, jokes, or verbal, graphic or physical conduct relating to an individual's race, color, religious creed, sex, national origin, ancestry, citizenship status, age, gender or sexual orientation that denigrate or show hostility or aversion toward an individual or group.

Sexual harassment refers to unwelcome sexual advances, requests for sexual favors, and other verbal or physical conduct of a sexual nature. Behavior and language that are welcome/ acceptable to one person may be unwelcome/offensive to another. Consequently, individuals must use discretion to ensure that their words and actions communicate respect for others. This is especially important for those in positions of authority since individuals with lower rank or status may be reluctant to express their objections or discomfort regarding unwelcome behavior. It does not refer to occasional compliments of a socially acceptable nature. It refers to behavior that is not welcome, is personally offensive, debilitates morale, and therefore, interferes with work effectiveness. The following are examples of behavior that, when unwelcome, may constitute sexual harassment: sexual flirtations, advances, or propositions; verbal comments or physical actions of a sexual nature; sexually degrading words used to describe an individual; a display of sexually suggestive objects or pictures; sexually explicit jokes; unnecessary touching.

Investigative Process
Anyone who feels harassed is encouraged to immediately inform the alleged harasser that the behavior is unwelcome. In many instances, the person is unaware that their conduct is offensive and when so advised can easily and willingly correct the conduct so that it does not reoccur. Anyone who feels harassed IS NOT required to address the person believed guilty of inappropriate treatment. If the informal discussion with the alleged harasser is unsuccessful in remedying the problem or if complainant does not feel comfortable with such an approach, he/she should contact BPS's Executive Director or the Society President, or any BPS Officer. All complaints will be promptly and thoroughly investigated.

All reports of harassment or sexual harassment will be treated seriously. However, absolute confidentiality cannot be promised nor can it be assured. BPS will conduct an investigation of any complaint of harassment or sexual harassment, which may require limited disclosure of pertinent information to certain parties, including the alleged harasser.
No retaliation will be taken against any employee, member, volunteer, exhibitor, or supplier because he or she reports a problem concerning possible acts of harassment. Employees, members, volunteers, exhibitors, or suppliers can raise concerns and make reports without fear of reprisal.

Investigative Procedure
Once a complaint of harassment or sexual harassment is received, BPS will begin a prompt and thorough investigation.

- An impartial investigative committee, consisting of the Past-President, current President, and President-Elect will be established.
- The committee will interview the complainant and review the written complaint. If no written complaint exists, one will be requested.
- The committee will speak to the alleged offender and present the complaint.
- The alleged offender will be given the opportunity to address the complaint, with sufficient time to respond to the evidence and bring his/her own evidence.
- If the facts are in dispute, the investigative team may need to interview anyone named as witnesses.
- The investigative committee may seek BPS Counsel's advice.
- Once the investigation is complete, the committee will report their findings and make recommendations to the Society Officers.

Disciplinary Actions
Individuals engaging in behavior prohibited by this policy as well as those making allegations of harassment in bad faith will be subject to disciplinary action. Such actions range from a verbal warning to ejection from the meeting or activity in question without refund of registration fees and the reporting of their behavior to their employer. Repeat offenders may be subject to further disciplinary action, such as being banned from participating in future Society meetings or Society-sponsored activities. In the event that the individual is dissatisfied with the results of the investigation, he or she may appeal to the President of the Society. Any questions regarding this policy should be directed to the BPS Executive Officer or other Society Officer.

BPS Management Responsibility
Every officer, director, supervisor, and manager is responsible for ensuring that BPS provides an environment free of harassment and inappropriate behavior and that complaints are handled promptly and effectively. The BPS Society Office and Officers must inform the Society membership and all vendors and suppliers about this policy, promptly investigate allegations of harassment, take appropriate disciplinary action, and take steps to assure retaliation is prohibited

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GENERAL INFORMATION

Registration Hours/Information Location and Hours

On Monday, registration will be held during the reception at NH Collection Friedrichstrasse located at Friedrichstraße 96, 10117 Berlin, Germany. On Tuesday, Wednesday, Thursday, and Friday registration will be located in the Grand Foyer at the Max Delbrück Center for Molecular Medicine (MDC). Registration hours are as follows:

Monday, September 3	17:30 – 20:00	NH Collection Friedrichstrasse
Tuesday, September 4	8:00 – 18:00	MDC
Wednesday, September 5	8:00 - 17:50	MDC
Thursday, September 6	8:00 - 14:50	MDC
Friday, September 7	8:00 – 15:30	MDC

Instructions for Presentations

(1) Presentation Facilities:

A data projector will be available in Auditorium Axon I. Speakers are required to bring their own laptops and adaptors. It is recommended to have a backup of the presentation on a USB drive in case of any unforeseen circumstances. Speakers are advised to preview their final presentations before the start of each session.

(2) Poster Session:

1) All poster sessions will be held in the Building 84 foyer of the Max Delbrück Center for Molecular Medicine.

2) A display board measuring 200 cm wide x 120 cm high (6.6 feet wide x 3.9 feet high) will be provided for each poster. Poster boards are numbered according to the same numbering scheme as listed in the e-book.

3) Posters should be set up in the morning of September 4 and removed by noon September 7. All Posters are available for viewing during all poster sessions; however, there will be formal poster presentations at the following times:

Tuesday, September 4	13:25 – 14:05	Odd-numbered poster boards
Tuesday, September 4	14:05 – 14:45	Even-numbered poster boards
Wednesday, September 5	13:10 – 13:50	Odd-numbered poster boards
Wednesday, September 5	13:50 – 14:30	Even-numbered poster boards
Thursday, September 6	13:30 – 14:10	Odd-numbered poster boards
Thursday, September 6	14:10 – 14:50	Even-numbered poster boards

4) During the assigned poster presentation sessions, presenters are requested to remain in front of their poster boards to meet with attendees.

5) All posters left uncollected at the end of the meeting will be disposed.

Meals and Coffee Breaks

There will be a two hour Welcome Reception on Monday Evening from 18:00 – 20:00. This reception will be held at the NH Collection Friedrichstrasse hotel

The address of the NH Collection Friedrichstrasse hotel is listed below:
Friedrichstraße 96
10117 Berlin, Germany

Coffee Breaks and Lunches (Tuesday, Wednesday, Thursday and Friday) will be served on the second level in the Grand Foyer.

On Thursday, there will be a Banquet on the Reederei Riedel Cruise from 18:00 – 21:00. Information regarding dinner cruise location will be provided at onsite registration.

Advanced sign-up was required for the Welcome Reception and the Dinner Cruise Banquet. Tickets are required for admittance to these two functions and will be provided at onsite registration.

Smoking

Please be advised that smoking is not permitted at the Max Delbrück Center for Molecular Medicine.

Name Badges

Name badges are required to enter all scientific sessions, poster sessions, and social functions. Please wear your badge throughout the conference.

Internet

Wifi will be provided at the venue. Attendees will receive account number and password at registration.

Contact

If you have any further requirements during the meeting, please contact the meeting staff at the registration desk from September 4–7 during registration hours.

In case of emergency, you may contact the following:

Martin Falcke
Cell: +49 151 5119 7786
Email: martin.falcke@mdc-berlin.de

Umi Zhou
Email: uzhou@biophysics.org

The Heart by Numbers:
Integrating Theory, Computation, and Experiment to Advance Cardiology

Berlin, Germany
September 4-7, 2018

PROGRAM

Monday, September 3, 2018

17:30 – 20:00	**Registration/Information**	**NH Collection Friedrichstrasse**
18:00 – 20:00	**Welcome Reception**	**NH Collection Friedrichstrasse**

Tuesday, September 4, 2018

8:00 – 18:00	**Registration/Information**	**Grand Foyer**
8:45 - 9:00	Martin Lohse, Max Delbrück Center for Molecular Medicine, Germany ***Opening Remarks***	
Session I	**Disease Modelling I** Martin Falcke, Max Delbrück Center for Molecular Medicine, Germany, Chair	
9:00 - 9:35	Stefan Luther, Max Planck Institute for Dynamics and Self-Organization, Germany ***Low-Energy Control of Cardiac Arrhythmias***	
9:35 - 10:10	Colleen Clancy, University of California, Davis, USA ***Sex, Drugs, and Funky Rhythms: Cardiology Insights from Modeling and Simulation***	
10:10 - 10:30	Hermenegild Arevalo, Simula Research Laboratory, Norway * ***Using Virtual Hearts Models to Investigate Arrhythmogenesis during Acute Myocardial Infarction***	
10:30 - 10:50	Marcus Kelm, German Heart Institute Berlin, Germany * ***EurValve***	
10:50 - 11:10	**Coffee Break**	**Grand Foyer**
Session II	**Disease Modelling II** Martin Falcke, Max Delbrück Center for Molecular Medicine, Germany, Chair	
11:10 - 11:45	Edward Vigmond, University of Bordeaux, France ***Biophysical Models of the Fibrillating Atria: Fibrosis and Electrophysiological Considerations***	
11:45 - 12:20	Yohannes Shiferaw, California State University, Northridge, USA ***Synchronization of Stochastic Calcium Waves in Atrial Tissue***	
12:20 - 13:25	**Lunch Break**	**Grand Foyer**
13:25 - 14:45	**Poster Session I**	**Building 84 Foyer**
Session III	**Disease Modelling III**	

	Karin Sipido, University of Leuven, Belgium, Chair	
14:45 - 15:20	Natalia Trayanova, Johns Hopkins University, USA ***Computational Cardiology: Blending Engineering and Medicine***	
15:20 - 15:55	Steven Niederer, King's College London, United Kingdom ***Clinical Translation of Cardiac Models***	
15:55 - 16:30	Emilia Entcheva, George Washington University, USA ***Massively-Parallel All-Optical Cardiac Electrophysiology***	
16:30 - 16:50	**Coffee Break**	**Grand Foyer**
Session IV	**Disease Modelling IV** Karin Sipido, University of Leuven, Belgium, Chair	
16:50 - 17:25	Martyn Nash, University of Auckland, New Zealand ***Structure-Function Mechanisms of Heart Failure***	
17:25 - 18:00	Andrew McCulloch, University of California, San Diego, USA ***Multi-Scale Biomechanics and Systems Mechanobiology of Heart Failure***	

Wednesday, September 5, 2018

8:30 - 17:50	**Registration/Information**	**Grand Foyer**
Session V	**Excitation Contraction Coupling I** James Weiss, University of California, Los Angeles, USA, Chair	
9:00 - 9:35	Julia Gorelik, Imperial College London, United Kingdom ***Microdomain Specific Regulation of L-type Ca Channels and Arrhythmias***	
9:35 - 10:10	Alexandra Zahradnikova, Slovak Academy of Sciences, Slovakia ***Allosteric Aspects of Ryanodine Receptor Gating***	
10:10 - 10:30	David J. Christini, Cornell University, USA * ***Designing Intact Cardiac Cell Electrophysiological Protocols to Improve Computational Model Fidelity***	
10:30 - 10:50	Jamie I. Vandenberg, Victor Chang Cardiac Research Institute, Australia * ***Impact of Correlated Gene Expression Patterns on Population Models of the Cardiac Action Potential***	
10:50 - 11:10	**Coffee Break**	**Grand Foyer**
Session VI	**Metabolism & Mitochondria** James Weiss, University of California, Los Angeles, USA, Chair	
11:10 - 11:45	Daniel Beard, University of Michigan, USA ***Elucidating Links Between Disruptions to Myocardial Energy Metabolism and Mechanical Dysfunction in Heart Failure***	

11:45 - 12:20	Brian O'Rourke, Johns Hopkins University, USA ***Cascading Mitochondrial Network Failure: Computational and Experimental Studies***	
12:20 - 12:40	Zhen Song, University of California, Los Angeles, USA * ***A Spatially Detailed in Silico Model of Excitation-Contraction-Metabolism Coupling of Cardiac Cells***	
12:40 - 13:10	**Lunch Break**	**Grand Foyer**
13:10 - 14:30	**Poster Session II**	**Building 84 Foyer**
Session VII	**Excitation Contraction Coupling II** Zhilin Qu, University of California, Los Angeles, USA, Chair	
14:30 - 15:05	Daniela Panáková, Max Delbrück Center for Molecular Medicine, Germany ***Wnt, L-type Calcium Channel, and the Developing Heart***	
15:05 - 15:40	Christian Soeller, University of Exeter, United Kingdom ***Characterisation of Ryanodine Receptor Clusters in Cardiac Myocytes Using Quantitative Imaging Methods***	
15:40 - 16:00	Richard Clayton, University of Sheffield, United Kingdom * ***Calibration of Human Atrial Cell Models Using Bayesian History Matching with Gaussian Process Emulators***	
Session VIII	**Data Driven Modelling** Zhilin Qu, University of California, Los Angeles, USA, Chair	
16:00 - 16:55	Elizabeth Cherry, Rochester Institute of Technology, USA **Reconstructing Cardiac Electrical Dynamics Using Data Assimilation**	
16:55 - 17:30	Leonid Goubergrits, Charité – Universitätsmedizin Berlin, Germany ***Modelling and Simulation for the Aortic Valve Treatment Planning Using Image-based CFD***	
17:30 - 17:50	Juan Carlos del Alamo, University of California, San Diego, USA * ***Patient-specific Mapping of Blood Stasis in the Left Atrium by Computational Fluid Dynamics***	

Thursday, September 6, 2018

8:30 - 14:50	**Registration/Information**	**Grand Foyer**
Session IX	**Arrythomgenesis and Its Control I** Gernot Plank, Medical University of Graz, Austria, Chair	
9:00 - 9:35	Martin Bishop, King's College London, United Kingdom ***Identifying the Arrhythmogenic Mechanisms Driven by Midwall Fibrosis in Non-Ischemic Dilated Cardiomyopathy***	
9:35 - 10:10	Jonathan Lederer, University of Maryland, USA ***Diastolic Calcium in Heart: CA^{2+} Quarjs, CA^{2+} Sparks, CA^{2+} Waves and Arrhythmias***	

10:10 - 10:30	Johann Schredelseker, Ludwig-Maximilians-University of Munich, Germany * ***_Activation of Mitochondrial Calcium Uptake Suppresses Arrhythmogenesis in Cardiomyocytes_**	
10:30 - 10:50	Michael B. Liu, University of California, Los Angeles, USA * ***_Arrhythmogenesis in Long QT Syndrome: Mechanism of Initiation and Therapeutic Insight from an in Silico Human Model_**	
10:50 - 11:10	**Coffee Break**	**Grand Foyer**
Session X	**Arrythomgenesis and Its Control II** Gernot Plank, Medical University of Graz, Austria, Chair	
11:10 - 11:45	Donald Bers, University of California, Davis, USA ***Cardiac Excitation-Contraction Coupling, Arrhythmias and Signaling: Experiments and Modelling***	
11:45 - 12:20	Alexander Panfilov, Gent University, Belgium ***In Silico–in vitro Approach to Study the Mechanisms of Cardiac Arrhythmias***	
12:20 - 12:40	Vivian Timmermann, Simula Research Laboratory, Norway * ***_A Computational Study of the Contribution of Mechano-Electric Feedback to Arrhythmogenic Current Generation_**	
12:40 – 13:00	Fernando O. Campos, King's College London, United Kingdom * ***_Optimization of an Activation-Repolarization Time Metric to Detect Localized Susceptibility to Reentry_**	
13:00 - 13:30	**Lunch Break**	**Grand Foyer**
13:30 - 14:50	**Poster Session III**	**Building 84 Foyer**
14:50 – 18:00	**Free Time**	
18:00 – 21:00	**Boat Trip/Banquet**	**Station: Märkisches Ufer**

Friday, September 7, 2018

8:30 – 15:30	**Registration/Information**	**Grand Foyer**
Session XI	**Excitation Contraction Coupling III** David J. Christini, Cornell University, USA, Chair	
9:00 - 9:35	Pieter de Tombe, Loyola University Chicago, USA ***Frank-Starling Law of the Heart: Molecular Mechanisms of Myofilament Length Dependent Activation***	
9:35 - 10:10	Michael Gotthardt, Max Delbrück Center for Molecular Medicine, Germany ***Theory and Practice of Titin Based Mechanotransduction***	
10:10 - 10:30	Kenneth Campbell, University of Kentucky, USA * ***_Force-Dependent Recruitment of Cross-bridges from the Myosin Off-state Can Contribute to Length-dependent Activation in Cardiac Muscle_**	

10:30 - 10:50	Lorenzo Marcucci, University of Padova, Italy * ***Proposed Mechanism of Length Dependent Maximum Force Developed in Striated Muscle at High Calcium***
10:50 - 11:10	**Coffee Break** **Grand Foyer**
Session XII	**Excitation Contraction Coupling IV** David J. Christini, Cornell University, USA, Chair
11:10 - 11:45	Mary Maleckar, Allen Institute for Cell Science, USA ***Modeling Experimental Insights from hIPSC and Derived Cells: Integrating the Cardiomyocyte***
11:45 - 12:20	Frank Heinzel, Charité – Universitätsmedizin Berlin, Gernmany ***Regulation of Subcellular Ca^{2+} as Source of Intracellular Dyssynchrony in Cardiomyocytes***
12:20 - 12:40	Samuel Wall, Simula Research Laboratory, Norway * ***In Silico Modeling of Cardiac Microphysiological Systems for Evaluating Drug Side Effects***
12:40 - 13:20	**Lunch Break** **Grand Foyer**
Session XIII	**Excitation Contraction Coupling V** Markus Bär, Physikalisch-Technische Bundesanstalt, Germany, Chair
13:20 - 13:55	Peter Kohl, Institute for Experimental Cardiovascular Medicine, Germany ***Sat-Nav for the Inner Cities of the Heart: Mapping 3D Cell-Nanostructure***
13:55 - 14:15	Enrique Alvarez-Lacalle, Polytechnic University of Catalonia, Spain * ***A General Equilibrium Model to Study Intracellular Calcium Homeostasis. New Insights on Ventricular Function***
14:15 - 14:35	**Coffee Break** **Grand Foyer**
Session XIV	**Re-Entry** Markus Bär, Physikalisch-Technische Bundesanstalt, Germany, Chair
14:35 - 14:55	Vladimir Zykov, Max Planck Institute for Dynamics and Self-Organization, Germany * ***Fast Propagation Regions of a Specific Geometry can Cause Reentry in Excitable Media***
14:55 - 15:15	Michael Colman, University of Leeds, United Kingdom * ***Dynamic Organ-scale Modelling of Sub-cellular Calcium Release Events in the Heart: After-Depolarisations, Premature Excitation and Re-Entry***
15:15 - 15:30	Martin Falcke, Max Delbrück Center for Molecular Medicine, Germany **Closing Remarks and *Biophysical Journal* Poster Awards**

**Short talks selected from among submitted abstracts*

SPEAKER ABSTRACTS

LOW-ENERGY CONTROL OF CARDIAC ARRHYTHMIAS

Stefan Luther[1,2,3], Jan Christoph[1,3], Ulrich Parlitz[1,3,4]
[1]Max Planck Institute for Dynamics and Self-Organization, Biomedical Physics, Goettingen, Niedersachsen, Germany [2]University Medical Center, Institute of Pharmacology and Toxicology, Goettingen, Niedersachsen, Germany [3]German Center for Cardiovascular Research (DZHK), Partnersite Goettingen, Goettingen, Niedersachsen, Germany [4]Georg-August- Universität Göttingen, Institute for Nonlinear Dynamics, Goettingen, Niedersachsen, Germany

The self-organized dynamics of vortex-like rotating waves, which are also known as scroll waves or rotors, is the basis of the formation of complex spatiotemporal patterns in many excitable chemical and biological systems. In the heart, filament-like phase singularities that are associated with three-dimensional scroll waves are considered to be the organizing centers of life-threatening cardiac arrhythmias. The mechanisms that underlie the onset, maintenance and control of electromechanical turbulence in the heart are inherently three-dimensional phenomena. However, it has not previously been possible to visualize the three-dimensional spatiotemporal dynamics of scroll waves inside cardiac tissues.
We show that three-dimensional mechanical scroll waves and filament-like phase singularities can be observed deep inside the contracting heart wall using high-resolution four-dimensional ultrasound-based strain imaging. We found that mechanical phase singularities co-exist with electrical phase singularities during cardiac fibrillation.
To further elucidate the nonlinear, transient vortex dynamics and intermittent fluctuations in spatial-temporal complexity during arrhythmias, we will discuss results obtained from numerical simulations and time series analysis and summarize recent advances in the development of numerical algorithms for data assimilation, parameter estimation and model validation.
Understanding the complex spatiotemporal dynamics of electromechanical rotors opens the path towards low-energy control of atrial and ventricular arrhythmias. We will review the current state of the art of low-energy defibrillation approaches and discuss the roadmap towards clinical application.

SEX, DRUGS, AND FUNKY RHYTHMS: CARDIOLOGY INSIGHTS FROM MODELING AND SIMULATION

Colleen E. Clancy
University of California Davis, Physiology, Davis, California, United States

Common paroxysmal electrical diseases that affect millions of people worldwide are notoriously difficult to manage with drug therapy, and some drugs intended for therapy can even exacerbate disease. A vital hindrance to safe and effective drug treatment of excitable disorders is that there is currently no way to predict how drugs with complex interactions and multiple subcellular targets will alter the emergent electrical activity of cells and tissues. Our work involves the development of a novel quantitative systems pharmacology approach derived from a combination of experiments, computational biology, high performance computing and clinical observation that allows for probing the mechanisms of action of drugs in the settings of one of the most common excitable diseases: cardiac arrhythmias. These new tools can be applied to preclinical screening of compounds for therapeutic benefit or harm. A computer-based approach can be used to determine mechanisms of drugs, with a specific focus to conduct failure analysis for once promising drugs that have failed clinically. Finally, models are applied to demonstrate utility in guiding therapy for specific clinical situations and to identify optimal “polypharmacy” to inform the common practice of clinical empirical mixing and matching of drugs to create multidrug therapeutic regimens. The computational processes that we have developed are paradigms for how the explosion in systems and computational biology can be utilized to assist drug-screening, determination of mechanisms and to guide therapy. The eventual goal is a scalable, automated platform that will interact with other cutting edge technologies to serve purposes in industry, academia and in clinical medicine that will be widely expanded to pharmacology of other common disorders of excitability such as epilepsy, ataxia and even pain.

USING VIRTUAL HEARTS MODELS TO INVESTIGATE ARRHYTHMOGENESIS DURING ACUTE MYOCARDIAL INFARCTION

Vilde Strøm[1], Maciej Marciniak[1], Charlotte Glinge[2], Reza Jabbari[2], Kiril Ahtarovski[2], Niels Vejlstrup[2], Thomas Enstrøm[2], Kristin Mcleod[1], Molly Maleckar[1], Thomas Jespersen[3], **Hermenegild Arevalo**[1].Jacob Tfelt-Hansen[2].
[1]Simula Research Laboratory, Lysaker, Oslo, Norway, [2]Rigshospitalet, Copenhagen, Hovedstaden, Denmark, [3]University of Copenhagen, Copenhagen, Hovedstaden, Denmark.

Background: Ventricular fibrillation (VF) occurs in ~10 % of myocardial infarction (MI) patients. These patients have higher in-hospital mortality and increased risk to lethal arrhythmias. The susceptibility for VF during acute MI and the underlying mechanisms remain incompletely understood. The goal of this study is to utilize patient specific computer heart models to gain insight into arrhythmogenesis during 1st acute MI before primary percutaneous coronary intervention.
Methods: 8 patients (3 VF & 5 non-VF) underwent MRI 5 days post MI. Models were constructed by segmenting MRI into healthy and infarcted tissue, modeled as gradient of ischemia 15 minutes post occlusion with decreased conduction and altered action potential morphology. Models were paced from 17 sites in the left ventricle to simulate ectopic activity and assess arrhythmia inducibility.
Results: Simulations accurately predicted arrhythmia inducibility in all VF models and 60 % of the non-VF patients. In the models inducible for arrhythmia, only pacing sites located near the ischemic border resulted in reentry. All reentrant circuits were initiated and persisted within the ischemic zone. Furthermore, the patients that were inducible had significantly larger infarcts (38 % vs 14 %, $p<.05$).
Conclusion: Patient specific models of post MI hearts can be used to accurately simulate VF in acute MI patients. Simulations also revealed that propensity of ectopic beats to initiate reentry in hearts with large infarcts could underlie arrhythmia vulnerability for this patient group.

EURVALVE

Marcus Kelm
German Heart Institute Berlin, Germany

No Abstract

BIOPHYSICAL MODELS OF THE FIBRILLATING ATRIA: FIBROSIS AND ELECTROPHYSIOLOGICAL CONSIDERATIONS

Edward Vigmond
University of Bordeaux, Talence, France

No Abstract

SYNCHRONIZATION OF STOCHASTIC CALCIUM WAVES IN ATRIAL TISSUE

Yohannes Shiferaw
California State University, Northridge, California, USA

No Abstract

COMPUTATIONAL CARDIOLOGY: BLENDING ENGINEERING AND MEDICINE

Natalia Trayanova
Johns Hopkins University, Baltimore, Maryland, USA

No Abstract

CLINICAL TRANSLATION OF CARDIAC MODELS

Steven A. Niederer
King's College London, Biomedical Engineering, London, United Kingdom

There has been significant scientific investment into the analysis of cardiac function using mathematical and computational models. To fully realise the potential of these studies requires the translation of these models into clinical applications to aid in diagnosis and clinical planning. To achieve this goal requires the integration of multiple disparate clinical data sets into a common modelling framework. To this end we have developed biophysical models of the human heart. These model combines simulate patient anatomy, mechanics, electrophysiology haemodynamics personalised using comprehensive imaging, diagnostic and catheter clinical measurements. These computational model allows us to link patient physiology, pathologies and outcomes. This provides a novel tool to determine the mechanisms that underpin successful treatments and offers the ability to determine hidden variables that provide indices of cardiac function

MASSIVELY-PARALLEL ALL-OPTICAL CARDIAC ELECTROPHYSIOLOGY

Emilia Entcheva
George Washington University, Biomedical Engineering, Washington, District of Columbia, United States

Optical targeting (stimulation or recording) allows distributed parallel access to thousands and even millions of cells and locations at the same time, and within the tissue setting; optical targeting is high-throughput by nature. **Objective:** This talk will discuss and demonstrate the combination of optogenetic stimulation with optical imaging of electrical activity in cardiomyocytes, i.e. the realization of â€œall-optical electrophysiologyâ€ in a high-throughput manner (HTS). **Results:** Application of this automated HTS framework will be demonstrated for drug screening using patient-derived cardiomyocytes (iPS-CMs) in multicellular arrangements. The impact of such approaches on removing bias, increasing reproducibility and strengthening predictive power will be illustrated by a blind drug testing study (12 compounds of different cardiotoxicity risk) under the Cardiac In Vitro Proarrhythmia Assay (CiPA) initiative. We find that pacing increases specificity of the pro-arrhythmia assay by reducing or eliminating false positives, intracellular calcium, especially under spontaneous activity, is not a good surrogate for voltage or QT prolongation; beat rate of the hiPS-CMs is not informative for drugsâ€™ pro-arrhythmic action. **Conclusions:** Our quantitative data supports the utility of a hiPSC-CM based model under paced conditions, where voltage recordings, rather than calcium transients, provide superior predictive information.

STRUCTURE-FUNCTION MECHANISMS OF HEART FAILURE

Martyn P Nash
University of Auckland, Auckland, New Zealand

Heart function is known to depend on tissue-specific biomechanical factors, such as myocardial stiffness and stress, which cannot be measured directly. Mathematical modelling provides a rational basis for identifying these biomarkers by integrating the rich variety of physiological data that are now available in the laboratory and clinical settings. The structural basis for the biomechanical differences between normal and failing hearts is an area of intense research. This presentation will discuss how image-based, individualised biomechanical models of the heart can be used to characterise the relative roles of anatomical, microstructural and functional remodelling in heart failure. Data from pre-clinical and clinical studies will be presented to demonstrate this approach. In the clinic, individualised mathematical modelling of myocardial mechanics has the potential to help more specifically stratify the different forms of heart failure, and thus to guide patient therapy and management of care.

MULTI-SCALE BIOMECHANICS AND SYSTEMS MECHANOBIOLOGY OF HEART FAILURE

Andrew D. McCulloch
University of California, San Diego, California, United States

Multi-scale computational modeling in conjunction with experimental studies using mouse models of heart disease has been an effective strategy for elucidating the molecular mechanisms underlying cardiac electromechanical dysfunction in the failing heart. The goal of this work is to develop and test new multi-scale computational models of cardiac biomechanics and mechanobiology that extend spatio-temporal scales in two ways: (1) downwards in spatial scale to that of atomic-resolution molecular models of key proteins involved in myofilament interactions; and (2) upwards in temporal scale to the timecourses of gene expression, protein translation and myocyte growth involved in the hypertrophic response of ventricular myocytes to mechanical load.
Molecular dynamics, molecular electrostatics and Brownian dynamics were used to compute parameters of Markov state models of myofilament activation and tension development. These model findings are elucidating how producing even low levels of 2-deoxy-ATP (dATP) using gene therapy to upregulate ribonuclease reductase in cardiac myocytes can activate cardiac myosin and enhance contractility in the failing heart.
At the organ scale, continuum growth and remodeling models suggest that myocyte fiber and cross-fiber strain may differentially regulate the series and parallel addition of sarcomeres during eccentric and concentric ventricular hypertrophy in response to diastolic *vs.* systolic hemodynamic overload. To elucidate the underlying mechanosignaling pathways, we developed a systems model of myocyte signal transduction and gene expression in response to stretch and compared model results with transcriptomic responses induced in stretched micropatterned mouse ventricular myocytes. While all nine mechanoreceptors in the model were required to explain transcriptional responses to fiber strain, only three were required to explain the major effects of cross-fiber strain.

Supported by NIH grants from the NHLBI and NIGMS.

MICRODOMAIN SPECIFIC REGULATION OF L-TYPE CA CHANNELS AND ARRHYTHMIAS

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Rationale: Although L-type calcium channels (LTCCs) have been the focus of many studies in the last decades, no emphasis has been put on the regional variation as it was largely assumed that all the channels were identical. However previously we found that LTCCs are distributed unevenly on the surface of healthy ventricular cardiac myocytes, being organised in microdomains in different regions of sarcolemma (T-tubules and intermediate crest of sarcolemma) and disruption of this arrangement occurs in myocytes from failing hearts in rats. **Objective**: To explore remodeling of LTCCs signaling microdomains in failing human ventricular myocytes. **Methods and Results**: With super-resolution patch-clamp method and confocal microscopy, we examined distribution of functional LTCCs of cardiomyocytes from patients suffering from ischemic and dilated cardiomyopathies, as well as from patients with implanted Left Ventricular Assistant Devices (LVAD). Functional LTCCs in failing myocytes were removed from T-tubules to crest of the sarcolemma, and their activity (open probability) was dramatically increased. In ischemic cardiomyopathy, the increase in LTCC opening occurs exclusively in the T-tubules and depends on the activity by protein kinase A, whereas in dilated cardiomyopathy, the increased LTCC opening is seen exclusively on the crest of sarcolemma and depends on the enhanced calcium-calmodulin kinase II modulation. A 3D anatomically realistic mathematical model of LTCC function human ventricles in HF was developed. Early afterdepolarizations were predicted to occur in the ischemic cardiomyopathy, whereas ventricular fibrillations were predicted in the dilated cardiomyopathy. LVAD implantation corrected the pathophysiological activity of the LTCCs, although it did not improve their distribution. **Conclusions**: These findings point out disturbances in LTCC compartmentation within sarcolemma of an individual cardiomyocyte may play a role in human disease. Targeting this LTCC rearrangement at an early stage of heart failure could help to avoid later maladaptive changes.

ALLOSTERIC ASPECTS OF RYANODINE RECEPTOR GATING

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Ryanodine receptors (RyRs) are large tetrameric ion channels in the membrane of sarcoplasmic reticulum (SR). RyRs form the pathway for release of calcium ions, necessary for contraction, from SR calcium stores into the cytoplasm of skeletal/cardiac muscle cells. Dysregulation of calcium release in cardiac myocytes is believed to contribute to pathophysiology of cardiac diseases such as hereditary arrhythmias or heart failure.
The primary activator of RyRs in cardiomyocytes is cytoplasmic calcium; however, RyR open probability is regulated by a plethora of modulators such as cytosolic Mg^{2+} and ATP, luminal calcium, calmodulin, as well as by RyR phosphorylation and/or redox status. Moreover, RyRs are clustered in submicrosopic structures - dyads - where they interact with each other directly or by way of released calcium ions. Several conformations of RyRs have been observed by cryoelectron microscopy (cryo-EM), implicating that RyR domains, by means of dynamic inter-domain interactions, communicate signals about their modulation status to the channel gate.
All the above processes require allosteric coupling between ligand/ion binding, protein-protein or domain-domain interaction on one hand, and channel opening on the other hand. Our single-channel and whole-cell data and computer simulations suggest that a Monod-Wyman-Changeux-type allosteric model of RyR gating [1] captures the effects of cytosolic Ca^{2+}, Mg^{2+}, ATP and luminal Ca^{2+} on RyR open probability as well as on Ca^{2+}-mediated interaction of RyRs within a single dyad. Recent high-resolution cryo-EM and X-ray structures together with protein modelling provide first glimpses on the structural basis of functional effects of ligands as well as of disease-causing mutations.
Support: Slovak Research and Development Agency APVV-15-032, Grant Agency of the Ministry of Education, Science, Research and Sport of the Slovak Republic VEGA 2/0143/17.

[1] Zahradníková et al., J Gen Physiol. 136:101-116, 2010

DESIGNING INTACT CARDIAC CELL ELECTROPHYSIOLOGICAL PROTOCOLS TO IMPROVE COMPUTATIONAL MODEL FIDELITY

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The traditional paradigm for developing cardiac computational cell models utilizes data from multiple cell types, species, laboratories, and experimental conditions to create a composite model. While such models can accurately represent data in limited biological scenarios, their ability to predict behavior outside of a narrow dynamic window is limited. This presentation will describe the rationale behind using novel electrophysiological protocols that aim to densely sample the dynamics of intact cardiac myocytes. The information-rich data from such protocols are then fit using global parameter optimization algorithms to tune multiple model parameters simultaneously. By so doing, this approach yields cell models that fit wide-ranging cellular behavior, making them better suited for physiological and pathophysiological predictions.

IMPACT OF CORRELATED GENE EXPRESSION PATTERNS ON POPULATION MODELS OF THE CARDIAC ACTION POTENTIAL

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Why are different people more susceptible to certain diseases and not others? why do some patients respond well to drugs and others do not? In the case of cardiac electrical diseases, there has been considerable interest in the development of computer models to test the hypothesis that there are multiple different combinations of gene expression patterns that can achieve a "good enough solution" in terms of baseline cardiac electrical activity but each of these different combinations respond differently to pathophysiological stimuli (Weiss et al., 2012). In previous in silico cardiac action potential studies, the density of all molecular components have been allowed to vary independently and then the combinations that satisfy pre-defined criteria for the normal action potential selected for future investigation (e.g. Britton et al., 2013). However, there is considerable evidence to suggest that the expression levels of many ion channels are co-regulated. The aim of this in silico study was to investigate how keeping patterns of ion channel expression correlated rather than allowed to vary completely randomly affected the population of models that could generate normal baseline action potentials. The correlated patterns of ion channel expression in a population of independent iPSC-derived cardiac myocyte were determined using mRNA nanostrings. The correlated patterns of variation were incorporated into the modified O-Hara Rudy model of the ventricular action potential based on the optimisations published by Krogh-Madsen et al. (2017). Simulations are in progress and an update will be presented.

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Krogh-Madsen T et al. Front. Physiol. 8:1059. doi: 10.3389/fphys.2017.01059,
Weiss JN et al. Circ Res. 2012;111:493-504

ELUCIDATING LINKS BETWEEN DISRUPTIONS TO MYOCARDIAL ENERGY METABOLISM AND MECHANICAL DYSFUNCTION IN HEART FAILURE

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The energetic status of the myocardium is compromised in decompensated hypertrophy in the failing heart, with the chemical energy (in the form of the ATP hydrolysis potential) available for the heart to do work diminished compared to normal. Using multi-scale computer models to interpret data from humans and animal models of cardiac decompensation and heart failure, we have developed two novel hypotheses to guide our investigations of how the biochemical/metabolic state of the heart in heart failure affects the mechanical pumping of the heart: (1.) Diminished cytosolic ATP and increased inorganic phosphate (associated with impaired energy metabolism and depletion of cytoplasmic adenine nucleotides) impairs the mechanical function of the heart; and (2.) By blocking purine degradation pathways that may be overactive in the chronically stressed and/or periodically ischemic myocardium, we can increase/restore the nucleotide pool and protect the heart against mechanical dysfunction and failure. Testing these hypotheses using a combination of genetic and surgical models, and computer models, our studies point to the potential promise of whole new classes of pharmacological targets associated with purine nucleotide dephosphorylation, deamination, degradation, and transport.

CASCADING MITOCHONDRIAL NETWORK FAILURE: COMPUTATIONAL AND EXPERIMENTAL STUDIES

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The mitochondrial network of cardiac cells is finely tuned for ATP delivery to sites of energy demand and to maintain redox balance. Nevertheless, emergent phenomena, such as widespread propagating or oscillatory depolarization of $\Delta\Psi$ or isolated cluster oscillations have been reported. Mechanisms for transmission include direct connections between mitochondria or regenerative signaling by diffusible messengers, such as reactive oxygen species (ROS). ROS-induced ROS release has been invoked to explain “mitochondrial criticality”, when the network becomes hypersensitive to failure under oxidative stress. The oscillation coherence depends on the topology of the network; adult cardiomyocytes, with an organized lattice-like array of mitochondria, show a high degree of synchrony, while neonatal cardiomyocytes, with a more variable arrangement of mitochondria, display unsynchronized intracellular oscillations. This suggests a local diffusible messenger, which we have proposed is superoxide. However, the short half-life and diffusion distance of superoxide begs the question of how cells reach the threshold for criticality during propagated $\Delta\Psi$ waves or oscillations. Here, we (Millare, O'Rourke and Trayanova) present a new computational model of RIRR transmission that takes into account both short- and long-range effects of ROS, with superoxide mediating neighbor-neighbor triggering of energy-dissipating ion channels and H_2O_2 distributing oxidative stress throughout the network to bring the mitochondria close to criticality. Simulations revealed that phenomena observed in experiments were reproduced by the model, including 1) a delay (1-2min) between a local oxidative stress and activation of a $\Delta\Psi$ wave, 2) spontaneous oscillation of $\Delta\Psi$, and 3) a first-in last-out order of depolarization-repolarization. These behaviors depended on the rate of H_2O_2 scavenging by the antioxidant system of the cell, the depletion of which was responsible for setting the envelope of wave propagation in the model. This study demonstrates the feasibility of ROS as a synchronizing factor across the dimensions of the adult heart cell and illustrates how a cascade of failures at the organellar level can scale to impact cell and organ level functions of the heart.

A SPATIALLY DETAILED IN SILICO MODEL OF EXCITATION-CONTRACTION-METABOLISM COUPLING OF CARDIAC CELLS

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The interactions between mitochondria and sarcoplasmic reticulum calcium (Ca) release play important roles in arrhythmogenesis and sudden cardiac death. At the cellular level, it has been shown that metabolic stress can generate abnormal voltage and Ca cycling dynamics. However, understanding the underlying mechanisms is a nontrivial task, even at the single cell level. Besides the complex molecular signaling interactions, a ventricular myocyte contains ~7,000-10,000 mitochondria and ~20,000 Ca release units which are intermingled in space, forming a complex coupling network with local interactions to cause spatiotemporal dynamics. In addition, the elementary Ca release events (e.g. Ca sparks) occur randomly due to random L-type Ca channel (LCC) and Ryanodine receptor (RyR) openings. Similarly, the mitochondrial membrane potential flickering and reactive oxygen species (ROS) flashes also occur randomly at the single mitochondrion level. Therefore, both spatial distribution and random behaviors need to be taken into account. Here, we develop an *in silico* model that incorporates spatiotemporal Ca dynamics of cardiac cells with CaMKII activation and autophosphorylation, and mitochondrial Ca, ATP, and ROS dynamics. LCC, RyR and mitochondrial permeability transition pore (mPTP) openings are modeled by Markov chain to reproduce quantitatively similar statistical behaviors as in experiment. Simulations with this model show that 1) mitochondrial depolarization increases spark frequency by two-fold and decreases spark amplitude by 10-20%; 2) mitochondrial Ca uniporter (MCU) localization affects local Ca activity, e.g., MCU facing the dyad reduces Ca spark frequency by 50% than facing the cytosol; 3) at the control condition, mitochondrial free Ca has a 10-20% diastolic-to-systolic variation, ~-182mV, and ATP level in the cytosol is ~ 4.9 mM. 4) Ca transient alternans is observed with enhanced mPTP opening. This detailed spatiotemporal cardiac cell model provides a powerful complimentary tool for mechanistic study of excitation-contraction-metabolism coupling dynamics at both sub-cellular and cellular levels.

WNT, L-TYPE CALCIUM CHANNEL, AND THE DEVELOPING HEART

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The L-type calcium channel (LTCC) is central to excitation-contraction coupling and Ca^{2+} handling in cardiac physiology. Membrane depolarization or ß-adrenergic pathway stimulate LTCC, and mediate Ca^{2+} influx. In parallel, we have identified Wnt11 signaling to attenuate LTCC conductance leading to establishment of a myocardial electrical coupling gradient, the lack of which results in cardiac dysfunction. Here, we found that in rat cardiomyoblasts, Wnt11/Fzd7 signaling modulates LTCC conductance by affecting the proteolytic processing of the LTCC C-terminus. Conversely to ß-adrenergic pathway, Wnt11 prevents C-terminal proteolysis through compartmentalization of PKAsignaling mediated byA-kinase anchoring proteins (AKAP). Bycombining biochemistrymethods, quantitative light microscopy, and calcium measurements,we found a novel AKAP2 binding to LTCC C-terminus, and regulating its activity. In zebrafish, loss of AKAP2 leads to cardiac defects. Markedly, Wnt11-dependent emergence of the electrical coupling gradient in developing myocardium requires AKAP2 modulation of LTCC conductance. Taken together, our data unravel Wnt11 signaling as a conserved alternative GPCR-like system regulating LTCC conductance, and Ca^{2+} homeostasis. Such regulation of LTCC by non-canonical Wnt signals may not be limited to cardiomyocytes, but might represent an integral part of Wnt/Ca^{2+} signaling in a plethora of cells, tissues, and organs.

CHARACTERISATION OF RYANODINE RECEPTOR CLUSTERS IN CARDIAC MYOCYTES USING QUANTITATIVE IMAGING METHODS

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Ryanodine receptors (RyRs) are calcium release channels in the sarcoplasmic reticulum of ventricular myocytes. They provide the molecular basis of the process of calcium-induced calcium release (CICR) that is critical for cardiac excitation-contraction coupling. It has been known for some time that RyRs form clusters within the sarcoplasmic reticulum membrane. Many of these clusters are located in junctions between the sarcolemmal membrane and the sarcoplasmic reticulum. The number and spatial arrangement of RyR clusters is a major determinant of the biophysical RyR cluster excitability. We have therefore developed and applied novel quantitative methods to measure RyR cluster properties in cardiac myocytes of several species. The use of recent optical super-resolution imaging approaches has been a critical enabling technology for this undertaking. We will present results from a number of approaches that we have applied, such as multicolour dSTORM imaging of RyRs and related proteins involved in excitation-contraction coupling and CICR, as well as more recent fully quantitative data using the DNA-PAINT technique. We will discuss the data in relation to models of RyR gating and mathematical models of cardiac diads.

CALIBRATION OF HUMAN ATRIAL CELL MODELS USING BAYESIAN HISTORY MATCHING WITH GAUSSIAN PROCESS EMULATORS

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Biophysically detailed cardiac cell models are complex systems of equations, and their behaviour is determined by a large number of model parameters or inputs. Calibrating cell models against experimental data is difficult because the parameter space is high-dimensional, so many model evaluations are required to explore it thoroughly. The objective of this study was to use a technique called history matching to calibrate two models of the human atrial action potential. In this approach, the cardiac cell model is replaced by a Gaussian process emulator, and the input space is iteratively refined in a series of waves. In each wave, 130 sets of model inputs were obtained by sampling the parameter space. The cell models were run using the design data, paced at a cycle length of 100 ms for 40 beats. For each run, a set of action potential biomarkers were obtained from the final beat, and these served as model outputs. The design data and outputs were then used to fit an emulator for each output. The parameter space was sampled again to obtain a new set of $3x10^6$ inputs. The fast-running emulator was run on these inputs, and corresponding outputs were compared with experimental observations using an implausibility measure that takes into account uncertainty in both emulator fit and experimental data. Regions of implausible parameter space were identified, and the remaining non-implausible space was used to generate new inputs for the next wave. This process continued for 11 waves, until the non-implausible parameter space was reduced to around 1% of the original. The three conclusions of this study are (i) history matching for cardiac cell models is a feasible approach, (ii) the set of action potential biomarkers used in this study was a limitation, and (iii) additional model parameters could also be examined.

RECONSTRUCTING CARDIAC ELECTRICAL DYNAMICS USING DATA ASSIMILATION

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Numerical techniques have predicted that reentrant electrical scroll waves underlie many cardiac arrhythmias, but experimental limitations have hampered a detailed understanding of the specific mechanisms responsible for reentrant wave formation and breakup. To further this effort, we recently have begun to apply the technique of data assimilation, widely used in weather forecasting, to reconstruct time series in cardiac tissue. Here we use model-generated surrogate observations from a numerical experiment to evaluate the performance of the ensemble Kalman filter in reconstructing such time series for a discordant alternans state in one spatial dimension and for scroll waves in three dimensions. We show that our approach is able to recover time series of both observed and unobserved variables that match the truth. Where nearby observations are available, the error is reduced below the synthetic observation error, with a smaller reduction with increased distance from observations. Using one-dimensional cases, we provide a deeper analysis showing that limitations in model formulation, including incorrect parameter values and undescribed spatial heterogeneity, can be managed appropriately and that some parameter values can be estimated directly as part of the data assimilation process. Our findings demonstrate that state reconstruction for spatiotemporally complex cardiac electrical dynamics is possible and has the potential for successful application to real experimental data.

MODELLING AND SIMULATION FOR THE AORTIC VALVE TREATMENT PLANNING USING IMAGE-BASED CFD

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In aging population, the prevalence of heart valve diseases and heart failure with >8% of the population in their 70s (valve disease) and 10% in their 80s (heart failure) is one of the most relevant diseases for the healthcare system in industrial countries. Both diseases are chronic and can amplify each other. Wrongly treated valve diseases can lead to severe heart failure and vice versa. The prognosis of heart failure is still very poor (6-year mortality rate >67%).
CFD approach promises precise diagnosis without invasive procedures. Furthermore, CFD allows predictiv modelling allowing to support clinicians with treatment decision as well as treatment planing and optimization. Finally CFD approach promises risk and cost minimization. Current CFD abilities, challenges and requirements for CFD translation into the clinical practice are presented and discussed.

PATIENT-SPECIFIC MAPPING OF BLOOD STASIS IN THE LEFT ATRIUM BY COMPUTATIONAL FLUID DYNAMICS

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During atrial fibrillation (AF), the irregular beating of the heart disturbs left atrial (LA) hemodynamics, which can lead to thrombus formation especially in the left atrial appendage (LAA). Consequently, patients with AF are at increased risk of systemic embolism and stroke. However, the current lack of personalized quantitative tools to predict the risk of LA thrombogenesis makes it difficult to decide whether to anticoagulate patients with AF. To evaluate blood stasis in patient-specific LA anatomies, we developed a computational fluid dynamics model of LA hemodynamics with moving boundaries, coupled to a 0D model of the pulmonary circulation. The time-dependent LA geometry was obtained from x-ray computed tomography scans. Blood stasis was evaluated from the computed velocity field by calculating blood residence time (RT). We present data from simulations performed on N = 4 patient-specific anatomies, including one patient with atrial fibrillation. For each patient, we performed simulations with moving LA walls, as well as simulations with fixed LA walls in order to investigate how LA contractility and anatomy influence blood stasis. In all subjects, blood residence time was highest inside the LAA, consistent with evidence that thrombus formation preferentially occurs in the appendage. The averaged residence times inside the LAA correlated inversely with LAA ejection fractions across different subjects ($R = -0.8$, $p = 0.2$). Furthermore, blood residence time in the LAA was markedly higher in the patient with atrial fibrillation (RT = 3.5 s vs RT = 2.3 +/- 0.5 s). However, the residence time for each patient showed a weak dependence on LA wall motion (Mann-Whitney $p = 0.9$), suggesting that additional factors such as atrial geometry may play a role in governing LA blood stasis and thrombus formation.

IDENTIFYING THE ARRHYTHMOGENIC MECHANISMS DRIVEN BY MIDWALL FIBROSIS IN NON-ISCHEMIC DILATED CARDIOMYOPATHY

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Background: Patients who present with non-ischemic dilated cardiomyopathy (NIDCM) and midwall fibrosis, visible in late gadolinium enhanced magnetic resonance imaging (LG-CMR), are at high risk of arrhythmic sudden cardiac death (SCD). However, elucidating a mechanistic understanding of exactly why arrhythmic risk is elevated in the context of fibrotic remodelling is vital for clinical translation. Our goal is to use detailed computational models of NIDCM to gain important insight into the possible mechanisms of reentry in this patient cohort and understand its dependence on fibrosis microstructure.
Methods and Results: Computational models were created from a single short axis LG-CMR image, with variations in type (replacement or interstitial) and density of fibrosis, as well as presence or absence of gap junction remodelling (GJR). Transmural activation times (TAT) at coupling intervals (CI) 500-210 ms were measured, as well as reentry inducibility. We found that TAT increased with both pacing rate and fibrosis density, that reentries were inducible above certain density thresholds, and that GJR reduced these thresholds. Reentries were classified as rotor, micro-reentry, macro-reentry, or figure-eight. Rotors were associated with low fibrosis density and interstitial fibrosis, and micro and macro-reentries with high fibrosis density and replacement fibrosis. A critical threshold of difference in TAT between slow and fast CIs was found to be predictive of reentry with high sensitivity and specificity.
Conclusions: Computational models of fibrosis micro-structure underlying areas of LGE in NIDCM can provide insight into the mechanisms of reentry, as well as reentry inducibility, and their dependence upon the texture and density of fibrosis. Transmural activation times can estimate reentry inducibility in the absence of knowledge of the fibrotic microstructure.

DIASTOLIC CALCIUM IN HEART: CA^{2+} QUARKS, CA^{2+} SPARKS, CA^{2+} WAVES AND ARRHYTHMIAS

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Calcium (Ca^{2+}) dynamics in the beating heart depend critically on diverse and important spatiotemporal factors. The spatial distribution and structural organization of the elements of the Ca^{2+} release units (CRU) are important to the initiation and termination of Ca^{2+} release from the sarcoplasmic reticulum (SR). Additionally, the SR organization, tortuosity, buffering components, cytoskeletal anchors, and signaling-organizational proteins (e.g. junctophilin) significantly influence how SR Ca^{2+} uptake is balanced by CRU activity to determine SR Ca^{2+} content. Transverse tubules (TT), axial tubules (AT), and the non-tubule (NT) sarcolemma contain diverse channels and transporters that control the action potential (AP) and these channels include L-type Ca^{2+} channels (LCC) responsible for triggering the intracellular Ca^{2+} release that drives contraction. Each of these elements and systems depend critically on local $[Ca^{2+}]_i$ dynamics, often, in complex ways. Here, we focus on how changes in diastolic $[Ca^{2+}]_i$ alter Ca^{2+} release in heart. The diastolic period is a critical interval in the excitation-contraction cycle where the stability of RyR2-dependent Ca^{2+} release can tip the balance between life and death. We use a series of quantitative experimental tests to guide and constrain an advanced 3D model of Ca^{2+} signaling in heart. This computational model allowed us to investigate and discuss the effects of diastolic $[Ca^{2+}]_i$ on dynamic Ca^{2+} movement, Ca^{2+} signaling and Ca^{2+} function with high temporal and spatial resolution. This work provides new insights into how diastolic $[Ca^{2+}]_i$ influences Ca^{2+} quarks, Ca^{2+} sub-sparks, and Ca^{2+} sparks to set the balance between stable $[Ca^{2+}]_i$ transients and pro-arrhythmic Ca^{2+} waves.

ACTIVATION OF MITOCHONDRIAL CALCIUM UPTAKE SUPPRESSES ARRHYTHMOGENESIS IN CARDIOMYOCYTES

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Cardiovascular disease-related deaths frequently arise from arrhythmias associated with perturbations in intracellular Ca^{2+} handling. With the aim to identify novel target structures for antiarrhythmic therapies we previously performed a small molecule screen on a zebrafish model for Ca^{2+} overload induced cardiac arrhythmia. From this screen we identified compound efsevin by its potent ability to restore rhythmic cardiac contractions in this fibrillation model. To evaluate its translational potential we tested efsevin in a mouse model for a human arrhythmia, namely catecholaminergic polymorphic ventricular tachycardia (CPVT). In CPVT mice efsevin significantly reduced episodes of ventricular tachycardia.
To identify the molecular mechanism underlying efsevin's antiarrhythmic effect we performed a pull-down assay and identified the voltage-dependent anion channel 2 (VDAC2) in the outer mitochondrial membrane as the protein target of efsevin. In cultured cardiomyocyt esefsevin significantly enhanced the transfer of Ca^{2+} from the sarcoplasmic reticulum into mitochondria. Through this mechanism it enhances removal of cytosolic Ca^{2+} and temporally and spatially restricts single Ca^{2+} sparks, unitary Ca2+ release events, in isolated ventricular cardiomyocytes from CPVT mice. By restricting Ca^{2+} sparks efsevin reduces propagating, diastolic Ca^{2+} waves and spontaneous action potentials. This antiarrhythmogenic effect of efsevin was abolished by Ru360, a blocker of the mitochondrial Ca^{2+} uniporter (MCU) and could be reproduced using the MCU activator kaempferol, demonstrating that the enhanced mitochondrial Ca^{2+} is responsible for the antiarrythmic effects. These data identify the mitochondrial Ca^{2+} uptake complex as an important regulator of excitation-contracion coupling and a new drug target for the treatment of cardiac arrhythmia.
Our results suggest a model in which enhanced mitochondrial Ca^{2+} uptake in the Ca^{2+} microdomain creates a barrier for cytosolic Ca^{2+} diffusion and thus suppresses propagation of Ca^{2+} sparks into potentially arrhythmogenic Ca^{2+} waves. To further evaluate this hypothesis cardiomyocyte models are required that incorporate mitochondrial Ca^{2+} uptake.

ARRHYTHMOGENESIS IN LONG QT SYNDROME: MECHANISM OF INITIATION AND THERAPEUTIC INSIGHT FROM AN IN SILICO HUMAN MODEL

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QT prolongation is a major risk factor of sudden cardiac death in both congenital and acquired long QT syndrome (LQTS). Although the genetic or ionic causes of LQTS can vary widely, a key question remains whether they share a common mechanism of arrhythmia initiation. In this study, 1D, 2D, and whole heart computational simulations were used to investigate the mechanisms of arrhythmogenesis in the different LQTS subtypes. Our results reveal a common underlying mode of arrhythmia initiation that is consistent with the specific clinical characteristics of different LQTS subtypes. Elevating $I_{Ca,L}$ in the setting of QT prolongation resulted in premature ventricular complexes (PVCs) emerging spontaneously from the repolarization gradient, manifesting with a “R-on-T” pattern on electrocardiogram (ECG). The R-on-T phenomenon is generally described as an ectopic PVC colliding with the repolarizing T-wave of a preceding beat, possibly resulting in conduction block and reentry. However, our results demonstrate that this ECG phenomenon does not necessarily involve an extra ectopic PVC, but can instead arise spontaneously from the area of repolarization itself. Since these PVCs arise and propagate unidirectionally, they can directly initiate reentry right when they emerge without the need for further conduction block. In this sense, we believe this phenomenon is more aptly named <u>“R-from-T” and represents an arrhythmogenesis paradigm where the PVC does not act as a traditional trigger, but instead can degenerate into sustained arrhythmias directly without need for further substrate. Indeed, in our whole heart simulations, we observed many examples of both pause or non-pause dependent “R-from-T” complexes initiating runs of ventricular tacycardia and fibrillation. The critical requirement of elevated I_{CaL} is consistent with the effectiveness of beta blockers as mainstay treatment for congenital LQTS. Finally, our results suggest that I_{CaL} window current modification would be an effective universal therapy regardless of the underlying molecular LQTS subtype.

CARDIAC EXCITATION-CONTRACTION COUPLING, ARRHYTHMIAS AND SIGNALING: EXPERIMENTS AND MODELING

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We perform quantitative mechanistic experimental work to understanding cardiac function in health and disease. We also incorporate detailed cardiac myocyte computational models (including ion channels, Ca & contraction and b-adrenergic (b-AR) and CaMKII signaling (for human, rabbit & mouse). These models provide quantitative tests of our mechanistic understanding of myocyte function and allow in silico tests that are impractical experimentally. We have elucidated a new positive feedback vicious cycle involving CaMKII-RyR-I -[Na] -[Ca] -CaMKII, which may perpetuate arrhythmogenesis in heart failure (HF; Morotti-PMID24421356). We also parsed the relative contributions of 8 different PKA targets in mediating electrophysiological and contractile effects of b-AR activation in cardiac myocytes (Negroni-PMID25724724). This clarified, for example, how changing Ca transients kinetics couple to decreased myofilament Ca sensitivity but increased crossbridge rate induced by b-AR stimulation. A third area combined modeling with novel nanodomain-targeted cAMP sensor experiments to understand differential kinetics and amplitude of cAMP-PKA signaling at the sarcolemma, sarcoplasmic reticulum and myofilaments nanodomains in health and HF (Surdo-PMID28425435). We showed how very local cAMP heterogeneity is necessary to optimize cardiac contractility upon b-AR activation. Fourth, emergent experiments showed that in HF, small clusters of weakly coupled myocytes in the ventricular wall with spontaneous Ca transients could drive ectopic foci for triggered arrhythmias (Lang-PMID28970285). Counterintuitive aspects of these observations were clarified by computational tissue models . This computational modelling systems biology complements experiments in providing novel fundamental mechanistic insights into subcellular signalling in normal and pathological cardiac function.

IN SILICO-IN VITRO APPROACH TO STUDY THE MECHANISMS OF CARDIAC ARRHYTHMIAS.

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[1]Ghent University, Physics and Astronomy, Ghent, Flandre Orientale, Belgium [2]LUMC, Cardiology, Leiden, Zuid-Holland, Netherlands [3]MIPT, Laboratory of Biophysics of Excitable Systems, Dolgoprudny, Moscow Oblast, Russian Federation

I will report on results of our two recent studies both of which combine in-silico and experimental approaches.
Study one is aimed at developing the first mathematical model to describe the formation of cardiac tissue, using a joint in silico-in vitro approach. We performed experiments under various conditions to carefully characterise the morphology of cardiac tissue in a culture of neonatal rat ventricular cells. We considered two cell types, namely, cardiomyocytes and fibroblasts. Next, we proposed a mathematical model, based on the Glazier-Graner-Hogeweg model, which is widely used in tissue growth studies. The resultant tissue morphology was coupled to the detailed electrophysiological Korhonen-Majumder model for neonatal rat ventricular cardiomyocytes, in order to study wave propagation. Using this model we studied the main factors underlying the formation of electrical anisotropy of cardiac tissue and also studied the conditions of block of wave propagation during fibrosis, which is one of the most important arrhythmogenic conditions.
In the second study we address the question of how geometry of the abnormal region affects the onset of ectopy using a combination of optogenetics, experimental electrophysiology, in-silico modelling and theoretical approaches. We paradoxically find that for any studied geometry of the depolarized region in optogenetically modified monolayers of cardiac cells, primary ectopic excitation originates from areas of maximal curvature of the boundary, where the stimulating electrotonic currents are minimal. It contradicts the standard critical nucleation theory applied to nonlinear waves in reaction-diffusion systems where a higher stimulus is expected to produce excitation more easily. I discuss the mechanism of this effect revealed via in-silico analytical study and its possible applications.

A COMPUTATIONAL STUDY OF THE CONTRIBUTION OF MECHANO-ELECTRIC FEEDBACK TO ARRHYTHMOGENIC CURRENT GENERATION

Viviane Timmermann[1,2,3], Kenneth S Campbell[5], Joakim Sundnes[1,2,4], Samuel T Wall[1,4], Andrew D McCulloch[3], Andrew G Edwards[1,2,4]
[1]Simula Research Laboratory, Fornebu, Oslo, Norway, [2]University of Oslo, Oslo, Norway, [3]University California San Diego, San Diego, California, USA, [4]Center for Cardiological Innovation, Oslo, Norway, [5]University of Kentucky, Lexington, Kentucky, USA.

Dysregulated cardiac mechanics have been implicated in many arrhythmogenic phenotypes. Strain-dependent perturbations to cardiomyocyte electrophysiology may contribute to this arrhythmogenesis through processes referred to as mechano-electric feedback (MEF). Two examples of MEF mechanisms are: opening of stretch activated ion channels, and mechanically-driven induction of Ca^{2+}-sensitive currents secondary to strain-rate dependent myofilament calcium release. While computational studies suggest that these mechanisms are not quantitatively sufficient to induce arrhythmia, it has been hypothesized that gradients in mechanical strain may promote arrhythmia by facilitating calcium wave propagation. To interrogate this possibility, and the contributions made by both MEF mechanisms, we have implemented a spatially discretized and electromechanical version of the Shannon et al. rabbit myocyte model in one-dimension.
We created this compartment-based model consisting of fifty strongly coupled electromechanical units connected in series. The model includes bi-directional coupling of the contractile mechanics and electrophysiology including both MEF mechanisms, and is fitted to reproduce experimentally recorded calcium transients and calcium waves during homogeneous mechanical perturbation. Additional end-to-end mechanical interactions of sarcomeres enables the model to capture 1) the effects of mechanical feedback at the sarcomeric level, and 2) the combined effects of mechanical and calcium heterogeneities at the cellular level. With this model we observe that calcium wave velocity, and key properties of the action potential, can be modulated by strain-rate dependent MEF mechanisms.
We have created a computational framework to investigate the potential for mechanical heterogeneity to influence MEF arrhythmogenesis. Strongly coupling between mechanics and electrophysiology can modulate calcium dynamics in time and space leading to calcium-dependent MEF acceleration of subcellular calcium waves. In larger scale tissue constructs this spatial coupling via mechanics may contribute to synchronizing arrhythmogenic calcium handling and afterdepolarizations. This model framework therefore provides a basis for understanding the contribution of heterogeneous mechanical perturbations to arrhythmogenic alterations in cardiac electrophysiology.

OPTIMIZATION OF AN ACTIVATION-REPOLARIZATION TIME METRIC TO DETECT LOCALIZED SUSCEPTIBILITY TO REENTRY

Fernando O Campos[1], Michele Orini[2], Ben Hanson[2], Pier Lambiase[2,3], Bradley Porter[1,4], Christopher Aldo Rinaldi[4], Jaswinder Gill[1,4], Peter Taggart[2], Martin J Bishop[1]
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Background: Identification of targets for catheter ablation of ventricular tachycardias remains a significant challenge. We have recently developed a novel substrate mapping procedure, termed the Reentry Vulnerability Index (RVI), which incorporates both activation (AT) and repolarisation (RT) times to identify regions of high susceptibility to reentry. Despite showing promise in a series of experiments, the algorithm requires further development to enable its incorporation into a clinical protocol.
Objective: To employ computer simulations to optimize the RVI procedure for its future usage within the clinic.
Methods: An idealized cardiac infarct model was employed to investigate the behaviour of the RVI algorithm under mapping catheters recordings resembling clinical conditions. Conduction block following premature stimulation was induced and mapped in the 2D computational tissue model including repolarization heterogeneity reported in infarcted hearts. RVI maps were computed based on the difference between RTs and ATs between successive pairs of electrodes within a given search radius. A colour map is then constructed to highlight small RVI values which identify vulnerable sites for reentry.
Results: Within a 2D sheet model with an idealized infarct scar we show that RVI maps computed on sparse recording sites randomly placed on the tissue surface were in good agreement with high resolution maps. Moreover, RVI maps computed on recording sites resembling a decapolar electrode placed linearly as well as on a fan-like arrangement also captured regions of small RVIs.
Conclusion: The RVI algorithm performed well under a wide range of clinically-relevant mapping conditions. The RVI metric could identify pro-arrhythmic regions which may be used to guide ablation.

FRANK-STARLING LAW OF THE HEART: MOLECULAR MECHANISMS OF MYOFILAMENT LENGTH DEPENDENT ACTIVATION.

Pieter P. de Tombe
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[2]Magdi Yacoub Institute, Cardiac Biophysics, Harefield, Hertfordshire, United Kingdom
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[4]Freiburg University, Hertzzentrum, Freiburg, Baden-Württemberg, Germany

The cellular basis of the Frank-Starling mechanism is sarcomere length modulation of myofilament Ca^{2+} sensitivity. The molecular mechanisms that underlie length sensitivity are unknown, but recent evidence has implicated the giant protein titin as possible sarcomeric strain sensor responsible for the phenomenon by an, as of yet unidentified, signal transduction pathway. Our studies over the past decades have employed various biophysical approaches to elucidate the underlying mechanisms of the problem at the level of: multicellular muscle bundles, single cardiac contractile cells, and sub-cellular single myofibrils. Our studies were performed both at steady state as well as during rapid activation/relaxation dynamics, while structure was assessed by utilizing fluorescent probe and x-ray diffraction analysis. Our results indicate that myofilament length dependent activation involves structural changes in both thick and thin filaments that are mediated by titin strain that may involve length dependent as well as phosphorylation dependent interaction of regulatory light chain, troponin-I, and myosin binding protein C interacting with actin and myosin to mediate the length sensing property of the cardiac sarcomere.

THEORY AND PRACTICE OF TITIN BASED MECHANOTRANSDUCTION

Michael Gotthardt
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Heart and skeletal muscle respond to mechanical strain with structural adaptations and hypertrophy. The giant sarcomeric protein titin has been proposed to contribute to these changes and convert force into cellular signals via its Z-disc based mechanosensor, the elastic I-band elements, and the mechanically activated titin kinase domain at the M-band. The combination of structural information and molecular dynamics simulations has provided a theoretical framework that we build on to address the function of titin-™s individual domains in adapting the mechanical properties of the sarcomere and regulating growth. Adjusting titin based stiffness through genetic engineering of the titin locus and modulation of titin isoform expression, we have tested the role of titin as a mechanosensor and find differential effects of the I-band sensor and the titin kinase domain. We show that titin intersects different signalling pathways and that the kinase domain acts as a hub to regulate muscle growth dependent on mechanical load. Together, our findings suggest a feedback loop that links titin isoform expression and growth signalling and a role of titin kinase in mechanotransduction that is independent of its proposed enzymatic activity.

FORCE-DEPENDENT RECRUITMENT OF CROSS-BRIDGES FROM THE MYOSIN OFF-STATE CAN CONTRIBUTE TO LENGTH-DEPENDENT ACTIVATION IN CARDIAC MUSCLE

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Cardiac muscle develops more force when it is activated at longer lengths. The concentration of Ca^{2+} required to develop half-maximum force also decreases. These effects are known as length-dependent activation and play critical roles in the Frank-Starling relationship and cardiovascular homeostasis. The molecular mechanisms underpinning length-dependent activation remain unclear but recent experiments suggest that they may include recruitment of myosin heads from the OFF (sometimes called super-relaxed) state. This manuscript presents a mathematical model of muscle contraction that was developed to test this hypothesis. Myosin heads in the model transitioned between an OFF state (that could not interact with actin), an ON state (that could bind to actin), and a single attached state. Simulations were fitted to experimental data using multidimensional parameter optimization. Statistical analysis showed that a model in which the rate of the OFF to ON transition increased linearly with force reproduced the length-dependent behavior of chemically permeabilized myocardium better than a model with a constant OFF to ON transition rate (F-test, $p<0.001$). This result suggests that the thick filament transitions are modulated by force. Additional calculations showed that the model incorporating a mechanosensitive thick filament could also reproduce twitch responses measured in a trabecula stretched to different lengths. A final set of simulations was then used to test the model. These calculations predicted how reducing passive stiffness would impact the length-dependence of the calcium-sensitivity of contractile force. The prediction (a 60% reduction in ΔpCa_{50}) mimicked the 58% reduction in ΔpCa_{50} measured by Patel et al. (PMID 2214043) in myocardium from rats that expressed a giant isoform of titin and had low resting tension. Together, these computational results suggest that force-dependent recruitment of myosin heads from the thick filament OFF state contributes to length-dependent activation and the Frank-Starling relationship.

PROPOSED MECHANISM OF LENGTH DEPENDENT MAXIMUM FORCE DEVELOPED IN STRIATED MUSCLE AT HIGH CALCIUM

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[1]University of Padova, Padova, Italy, [2]The University of Tokyo, Kashiwa-shi, Chiba, Japan, [3]RIKEN, Suita, Osaka, Japan.

A recent discovery in the regulation of muscle contraction, associates to the classical calcium-mediated thin filament activation, a tension-mediated thick filament activation. In this activation, myosin motors switch between an OFF, or super-relaxed state, where actomyosin interaction is prevented by their folded configuration along the thick filament, and an ON, or active, state, where a more perpendicular configuration is assumed, toward the thin filament, allowing contraction. This so-called mechanosensing mechanism (MSM), has been associated, through in-vitro, in-situ and in-silico methods, to the lenght-dependent activation in cardiac muscle, potentially representing the molecular basis of the Frank-Starling law. However, to match the high efficiency required in muscle contraction, the MSM is likely to be saturated, i.e. the myosin motors are fully activated, when the tension is locally high. This is particularly true at the tensions reached during the unphysiological high calcium conditions used to construct the force-pCa curve.
In this work we show, through an in-silico method, that the distribution of the active tension along the thick filament, due to the summation of the single forces generated by the myosin motors toward the M-line, generates a “reservoir” of always OFF heads which can be recruited only by the passive tension generated at higher sarcomere lengths, allowing for a quantitative explanation of the observed higher tension.
The fiber model is then included into a ventricle model to estimate the effect of the described mechanism on the beating heart. Our results further support the idea that MSM has a determinant role in the LDA of cardiac muscle.

MODELING EXPERIMENTAL INSIGHTS FROM HIPSC AND DERIVED CELLS: INTEGRATING THE CARDIOMYOCYTE

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Allen Institute for Cell Science, Models & Theory, Seattle, Washington, United States

An integrated representation of the cardiomyocyte (CM) and its subcellular structures would enhance understanding of cellular organization: howthis produces characteristic phenotypes and changes as CMdifferentiate and otherwise change state, offering keyinsight into CMfunction. Fluorescence microscopyallows the imaging of labeled cellular components; however, current methodologylimits the number of fluorescent tags that can be imaged simultaneouslywithout gross cellular perturbations from tagging and imaging. To address these limitations towards understanding cell and specificallyhiPSC-derived CM,we developed two deep learning tools: (a) a deterministic,"label-free" method to predict fluorescently-labeled structures patterns solelyfrom 3Dtransmitted light microscopyimages, and (b) a probabilistic, conditional 3D model of cell organization (the “Integrated Cell”) to predict the integrated location of cellular organelles from high replicate fluorescent microscopyimages of hiPSC-derived CM. In combination, the result is 3D, integrated representations ofCMorganization. In initial evaluation of model performance,we see excellent correspondence for several well-stereotyped intracellular structures.Ongoing work includes expanding predictions to several additional CM-specific structures, increasing image resolution, and enhancing model interpretability.

REGULATION OF SUBCELLULAR CA2+ AS SOURCE OF INTRACELLULAR DYSSYNCHRONY IN CARDIOMYOCYTES

Frank Heinzel
Charité – Universitätsmedizin Berlin, Berlin, Germany

No Abstract

IN SILICO MODELING OF CARDIAC MICROPHYSIOLOGICAL SYSTEMS FOR EVALUATING DRUG SIDE EFFECTS.

Samuel Wall[1], Kevin E Healy[2,3], Karoline Horgmo Jæger[1], Nathaniel Huebsch[2], Bernice Charraz[2], Aslak Tveito[1]
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Experimental systems utilizing human induced pluripotent stem cells (IPSCs) hold immense promise for evaluating drug compounds on human phenotypes. This holds in particular for screening of cardiotoxicity, where current reliance on animal models prior to clinical trials can lead to false positives and false negatives. However, even though these "heart-on-a-chip" technologies have started to fill this critical gap in early understand of human drug cardiotoxicity, their usefulness is limited by the relatively immature state of the derived cardiomyocytes (hIPSC-CMs) used in the systems, which can make interpreting screening results challenging. Here we present an integrated *in silico* computational framework that takes measurements of transmembrane potential and intracellular calcium from cardiac micro physiological systems (MPS) and inverts them into detailed mathematical models of hIPSC-CM activity. This inversion is performed through the minimization of a cost function which quantifies the key differences between the measurements and *in silico* predictions. This data inversion can give critical information about the MPS dynamic function and can quantitate the molecular effect of tested drugs on key ion channels. Through a second framework assuming functional invariance of proteins during maturation, we then use inversion results to map how drugs will alter action potential dynamics in adult human ventricular cells in order to predict potential cardiotoxicity. We demonstrate the techniques applicability and sensitivity first for synthetic data, and then on MPS challenged with the two drugs, cisapride and verapamil. Our results indicate that drug induced changes to calcium and potassium channel ion activity can be well captured, even in the high dimensional search space of multiple competing ion channel variations. These changes then map into expected dose effects on the action potential of adult tissue. We see that combination of organ-on-chip measurements, and advanced *in silico*tools offers tremendous potential for screening cardiotoxicity.

SAT-NAV FOR THE INNER CITIES OF THE HEART: MAPPING 3D CELL-NANOSTRUCTURE

Peter Kohl
Institute for Experimental Cardiovascular Medicine, Germany

Careful mapping of three-dimensional (3D) cardiac structure in the micro-to-macro domain has provided an atlas for exploration of structure-function cross-talk in the heart. This has laid basis for previously unthinkable progress in conceptual and computational models of the heart, inspired hypothesis formation for novel experiments, and it is starting to translate into guidance for patient diagnosis and treatment. In order to advance our understanding of integrated signalling inside cardiac cells, the same comprehensive spatio-temporal characterisation is needed in the nano-to-micro domain. The spatial resolution of a variety of available techniques, from super-resolution fluorescent imaging $(10^2\,\text{nm})^3$ to focussed ion-beam / scanning electron microscopy (EM) $(10^1\,\text{nm})^3$ and EM-tomography $(10^0\,\text{nm})^3$ provides 3D insights into membranous and filamentous structures of various cardiac cells over increasingly meaningful cellular volume fractions. This talk will focus on cardiac EM-tomography which, over the past decade, has started to move from a rather outlandish effort (*Circ Res* 2009 Mar/104:787-95; *J Cell Sci* 2009 Apr/122:1005-13) to becoming productive for (nearly) everyday research questions (e.g. *J Clin Invest* 2016/126:3999-4015; *PNAS* 2016/113:14852-14857; *Sci Rep* 2017/17:40620; *Biophys J* 2017/113:1047-1059; *Circ Res* 2018/122:58-73; *PNAS* 2018:201805979 [in press]). Experimental challenges include optimised sample preservation and addressing deformation-induced dynamics in what inherently is a single snapshot technique. Computational challenges involve generalisation of available information and inclusion into a structured understanding that links ‘pathways’ to structures – to allow better navigation of the challenges associated with exploring the dynamically deforming, densely populated, and highly structured reactor that is ‘the cell’.

A GENERAL EQUILIBRIUM MODEL TO STUDY INTRACELLULAR CALCIUM HOMEOSTASIS. NEW INSIGHTS ON VENTRICULAR FUNCTION

Enrique Alvarez-Lacalle[1], David Conesa[1], Blas Echebarria[1], Inmaculada R Cantalapiedra[1], Angelina Peñaranda[1], Yohannes Shiferaw[2]
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Calcium homeostasis is reached when calcium concentrations in a cell along consecutive beats return to the same values on average. The amount of calcium entering the cell via LCC channels, must be the same amount that leaves the cell, mainly due to Sodium-Calcium exchanger. Also, the amount of calcium leaving the SR via the RyR2 must be the same as the calcium entering the SR mainly via SERCA. Since large calcium loads lead to large contractions and vice versa cell functionality is thus directly related with the homeostatic balance.
We present a general framework to understand and analyze the homeostatic process in order to make predictions about calcium levels when key properties of the different proteins involved in calcium handling or external pacing are changed. We demonstrate how non-linear interactions render linear intuition worse than useless, misleading. More specifically, we show why some species may increase the level of calcium upon decreasing the pacing rate, or how increasing the conductivity of the LCC can lead directly to depletion of calcium in the cell. We find ourselves in a similar situation as macroeconomists. A system with highly complex interactions where we would like to know whether a global averaged parameter such as GDP in macroeconomics, calcium level in our case, would decrease or increase when facing a particular shock. We actually demonstrate that the proper way to think about the nonlinearities in ventricular cell is the same used in the IS-LM Keynesian macroeconomic model. In both, a minimum model of simultaneous double equilibration captures the essential nonlinearities and interactions providing impressive insights on cell function. We show that the independent variables of this model are pre-systolic SR calcium load and pre-systolic total calcium in the cell. Once this framework is understood, further predictions are possible without falling into false linear projections.

FAST PROPAGATION REGIONS OF A SPECIFIC GEOMETRY CAN CAUSE REENTRY IN EXCITABLE MEDIA

Vladimir Zykov, Alexei Krekhov, Eberhard Bodenschatz
Max Planck Institute for Dynamics and Self-Organization, Goettingen, Niedersachsen, Germany.

Many theoretical and experimental studies indicate that a propagation block represents an important factor in spiral wave initiation in excitable media. The analytical and numerical results we obtained for a generic two-component reaction-diffusion system demonstrate quantitative conditions for the propagation block in a one-dimensional and a two-dimensional medium due to a sharp spatial increase of the medium's excitability or the coupling strength above a certain critical value. Here we prove that this critical value strongly depends on the medium's parameters and the geometry of the inhomogeneity. For an examplary two-dimensional medium we show how the propagation block can be used to initiate spiral waves by a specific choice of the size and shape of the medium's inhomogeneity.

DYNAMIC ORGAN-SCALE MODELLING OF SUB-CELLULAR CALCIUM RELEASE EVENTS IN THE HEART: AFTER-DEPOLARISATIONS, PREMATURE EXCITATION AND RE-ENTRY

Michael A. Colman
University of Leeds, Leeds, North Yorkshire, United Kingdom.

Objective: Spontaneous sub-cellular calcium release events (SCRE), controlled by microscopic stochastic fluctuations of the ryanodine receptors, are conjectured to promote the initiation and perpetuation of arrhythmia in multiple cardiac conditions: SCRE may underlie the emergence of spontaneous excitation in single cells, resulting in arrhythmic triggers in tissue. Computational modelling provides a viable approach to mechanistically assess these multi-scale phenomena in the dynamics of arrhythmia. However, there remains a significant challenge in accurately and efficiently modelling this probabilistic behavior in large-scale tissue modes. The aim of this study was to develop an approach to overcome this challenge.
Methods: The dynamics of SCRE under multiple conditions (pacing rate, disease remodeling) observed in a computational model of stochastic, spatio-temporal calcium handling were analyzed in order to develop analytical waveforms which capture stochastic variability in the timing and amplitude of SCRE. These were integrated with tissue models including idealized 2D sheets and 3D reconstructions of ventricular and atrial anatomy.
Results: The analytical waveforms reproduced the dynamics of SCRE and its dependence on environment variables. In homogeneous tissue, the mechanism of emergence of a focal excitation from a single source was demonstrated. Sustained re-entrant excitation promoted calcium overload and led to focal excitation both after termination of re-entry and occasionally during excitation. A purely functional mechanism of localization of focal excitation with the re-entrant core was revealed, determined by the additional relaxation time in the inexcited scroll wave core.
Conclusion: A novel approach has been developed to dynamically and accurately model SCRE at the tissue scale, in-line with behavior observed in detailed single-cell models. Such an approach permits evaluation of the potential importance of SCRE in arrhythmia in both general-mechanistic and disease-specific investigation.

POSTER ABSTRACTS

TUESDAY, SEPTEMBER 4
POSTER SESSION I
13:25 – 14:45
Building 84 Foyer

All posters are available for viewing during all poster sessions; however, below are the formal presentations for Tuesday. Presenting authors with odd-numbered poster boards should present from 13:25 – 14: 05 and those with even-numbered poster boards should present from 14:05 – 14:45. The presenters listed below are required to remain in front of their poster boards to meet with attendees.

Bazil, Jason	**1-POS**	**Board 1**
Butkevich, Eugenia	**4-POS**	**Board 4**
Clerx, Michael	**7-POS**	**Board 7**
Diem, Alexandra	**10-POS**	**Board 10**
Garcia-Perez, Angelica	**13-POS**	**Board 13**
Guthof, Tim	**16-POS**	**Board 16**
Hohendanner, Felix	**19-POS**	**Board 19**
Iaparov, Bogdan	**22-POS**	**Board 22**
Kucera, Jan	**25-POS**	**Board 25**
Landaw, Julian	**28-POS**	**Board 28**
Lilienkamp, Thomas	**31-POS**	**Board 31**
Macianskiene, Regina	**34-POS**	**Board 34**
Miranda, Williams	**37-POS**	**Board 37**
Ni, Haibo	**40-POS**	**Board 40 -Cancelled**
Polonchuk, Liudmila	**43-POS**	**Board 43**
Rodero, Cristobal	**46-POS**	**Board 46**
Ryvkin, Alexander	**49-POS**	**Board 49**
Song, Zhen	**52-POS**	**Board 52**
Tajabadi, Ataollah	**55-POS**	**Board 55**
van Herck, Ilse	**58-POS**	**Board 58**
Vendelin, Marko	**61-POS**	**Board 61-Cancelled**
Wülfers, Eike	**64-POS**	**Board 64**

Posters should be set up the morning of September 4 and removed by noon September 7.

1-POS Board 1

MODELING CALCIUM-INDUCED INHIBITION OF MITOCHONDRIAL METABOLISM

Sathyavani Malyala, Yizhu Zhang, **Jason N Bazil**.
Michigan State University, East Lansing, Michigan, USA.

Ischemic myocardium is characterized by a chronic elevation in cellular calcium concentration. In this setting, mitochondria accumulate calcium to levels that compromise their ability to synthesize ATP. Although total mitochondrial calcium can reach up to 1 M, the vast majority is presumed to be present as insoluble calcium phosphate granules. Our group recently reported calcium levels below thresholds that trigger mitochondrial permeability transition significantly lowers the rate of ADP-stimulated respiration. To explain these data, we used both experimental and a computational modeling approaches to test the following hypotheses: i) calpain activation leading to inactive complex I and complex V, ii) depressed membrane potential caused by sodium/calcium cycling lowering the driving force for ATP production; iii) direct inhibition of calcium on mitochondrial processes critical for ATP production; and iv) depletion/reduction of available ADP for phosphorylation caused by calcium binding, incorporation into calcium phosphate granules, or net loss of adenine nucleotide. To computationally test these hypotheses, we developed a new model of the calcium sequestration system to explicitly include calcium phosphate formation. The model also includes mechanistic descriptions of mitochondrial metabolism and energetics in addition to calcium uptake, sequestration, and efflux pathways. Based on the model analysis, sodium/calcium cycling lowers mitochondrial membrane potential but does not lead to lower rates of oxidative phosphorylation. ADP complexation with calcium did not affect the rate of oxidative phosphorylation, but a net loss of nucleotides via incorporation into calcium phosphate granules or efflux out of mitochondria agrees with these data. Finally, direct inhibition of calcium on ATP production did agree with these data. Of the possible enzymes inhibited by calcium, complex I is the most likely candidate as succinate supported respiration is only minimally inhibited by calcium overload.

4-POS Board 4

DREBRIN IN HUMAN CARDIOMYOCYTES

Eugenia Butkevich[1], Daniel Härtter[1], Christina Jayachandran[1], Arindam Ghosh[1], Wolfram-Hubertus Zimmermann[2], Christoph F Schmidt[1,3]
[1]Georg-August-Universität Göttingen, Göttingen, Niedersachsen, Germany, [2]Universitätsmedizin Göttingen, Göttingen, Niedersachsen, Germany, [3]Duke University, Durham, North Carolina, USA.

Actin filament organization and stability in the sarcomeres of striated muscle cells are crucial for force generation. We have identified and functionally characterized an actin-binding protein, Drebrin, as a novel constituent of the muscle-contraction machinery. Using antibodies against human Drebrin, we analyzed its localization in sarcomeres relative to other actin-binding proteins. Native gel electrophoresis and single-molecule fluorescence correlation spectroscopy revealed that Drebrin in cells might exist as monomer as well as dimer and oligomer containing 3-5 molecules. In in-vitro experiments, excess of Drebrin added to solutions of actin filaments resulted in a network structure composed of long curved bundles. Overexpression of Drebrin in cardiomyocytes differentiated from induced pluripotent human stem cells led to the displacement of alpha-actinin-2 and tropomyosin and the disorganization of the sarcomere lattice. In contrast, down-regulation of Drebrin using shRNA did not cause significant changes in sarcomere architecture. We currently analyze the contraction dynamics of Drebrin-depleted cells at the single-sarcomere level. A regulatory role of Drebrin in the control of actin-myosin interaction will be discussed.

7-POS Board 7

COMPARING PARAMETER ESTIMATION TECHNIQUES FOR CARDIAC ION CURRENT MODELS

Michael Clerx[1], Kylie A Beattie[1], David J Gavaghan[1], Gary R Mirams[2]
[1]University of Oxford, Oxford, Oxfordshire, United Kingdom, [2]University of Nottingham, Nottingham, Nottinghamshire, United Kingdom.

For an organ roughly the size of a human fist, the heart can be remarkably sensitive to tiny changes such as the effects of drugs or mutations on its ion currents. Models of these currents, combined into models of the cellular action potential and its propagation, can help us predict how and when organ-level consequences arise from molecular-level origins. But to make confident predictions about such a sensitive a system, we need to equip ourselves not just with careful measurements and excellent models, but also with reliable methods of fitting one to the other.
We compare three methods of fitting ion current models to data. First, a traditional `disjoint' method, in which separate voltage-step protocols are used to bring out different aspects of ion channel behaviour. In this method, measured currents are not used directly, but transformed into `summary statistics' (e.g. plots of peak current against voltage) to which model equations are fit. The `whole-trace fitting' method uses the same step protocols, but instead of summary statistics an error-measure is defined over the full recording, and then minimised using mathematical optimisation. Finally, we discuss whole-trace fitting to data from novel sinusoidal protocols designed to provide greater information in a shorter time frame (Beattie et al. J Physiol, 2018). For each type of fitting, we investigate (1) how well the method constrains the parameters, (2) how the method performs in the presence of different types of noise, and (3) how the method fares in unexpected regions of the parameter space, e.g. when a current behaves differently than expected due to pharmacological intervention or mutations. Our results show how modern protocols and parameter estimation techniques can provide better fits and lead to models with greater predictive power, even when experiments yield unexpected (interesting) results.

10-POS Board 10

MODELLING DRUG DELIVERY VIA NANOPARTICLE DEPOSITION IN THE MYOCARDIUM OF THE LEFT VENTRICLE

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The use of nanoparticles (NP) target drug delivery directly to the heart for treatment of diseases via nanoparticles (NP) has been a major goal of cardiovascular research since the early 2000s. The benefits of such a NP drug delivery system would include the reduction of side effects by the administration of smaller dosages, cost reduction and reducing the need for invasive treatments. However, the development of a NP-based drug delivery system also poses a number of challenges, such as the optimisation of physico-chemical parameters of the NP, in order to achieve efficient distribution throughout the tissue. We address this challenge by presenting a finite-element model of NP delivery via perfusion through the myocardium in the left ventricle (LV). Perfusion is represented by the three compartment porous media equations based on Darcy's law. A 0D lumped parameter model is used to represent the inflow boundary condition to the perfusing blood vessels. NP transport is modelled via the scalar transport equations based on reaction-advection-diffusion kinetics, where deposition via endocytosis follows zero order reaction kinetics. The model is solved on a human LV geometry with randomly set arterial entry points throughout the outer surface of the myocardium. Efficiency of NP endocytosis is tested based on varied kinetic rates, initial NP concentration, NP inflow rate, chemical properties of NP, and perfusion pressure. These simulations provide a framework to virtually prototype physico-chemical properties of the NP and predict their distribution within the tissue.

13-POS Board 13

TOWARD BIOENGINEERING A TISSUE-BASED PACEMAKER USING NON-VIRAL DELIVERY OF HCN4 GENE BY SLEEPING BEAUTY IN HIPSC.

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Automaticity of the heart is generated from specialized cells in the sinoatrial (SA) node. These cells are small, branched, with large surface to volume ratios and oscillate from maximum diastolic potentials of -55mV while electrically connected to larger atrial cells resting at -90mV. The ability of SA nodal cells to resist the atrial hyperpolarizing force is conferred by *HCN4* gene expression generating a slowly activating inward current (I_f) at potentials negative to -70mV. This current **functionally insulates** the SA-nodal cells from the atrial electrical sink, yet allows transmission of electrical signal between the two. This is a novel concept for HCN4/I_f, as *this system* is thought to serve as the pacemaker mechanism. Recent advances in stem cell biology and cardiomyocyte differentiation have made it possible to consider creating tissue-based and patient-specific pacemaker cells. We undertook a combined cell and gene therapy strategy, using the non-viral integrating transposon system *Sleeping Beauty* (SB) to overexpress hHCN4 in human induced pluripotent stem cells (hiPSC). Upon differentiation, hHCN4 overexpression in cardiomyocytes (hHCN4-CM) would *functionally insulate* them from the large atrial electrical sink when transplanted in the heart. The hHCN4 overexpressing hiPSC showed stable, long-term expression of I_f while maintaining pluripotency. Differentiated hHCN4-CM showed 3-10-fold larger I_f and resemble SA nodal cells morphology. Electrophysiological comparison of the bioengineered and SA nodal cells showed equivalent and large expression of I_{Ca} and Ca^{2+} release, low expression of I_{K1} and similar pharmacology. Spontaneous activity in both cell types was independent of the level of expression of I_f, but depended on I_{Ca} and Ca^{2+} signaling. Co-cultures of these cells with freshly isolated rat cardiomyocytes showed that the hHCN4-CM do electrically connect with and pace adult rat cardiomyocytes, suggesting animal trials as the next step.

16-POS Board 16

ACUTE EFFECTS OF PALMITOLEIC ACID, AN OBESITY-RELATED FREE FATTY ACID, ON VENTRICULAR CARDIOMYOCYTE CALCIUM SIGNALING

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Previously, we have found palmitoleic acid (PE16:1) to be involved in adipositas-related heart failure with reduced ejection fraction (HFrEF) in mouse and human. We tested the acute effects of PE16:1 on intracellular Ca^{2+} homeostasis and t-tubule structures in cardiomyocytes.
Cytosolic Ca^{2+} transients (Ca^{2+} dye Fluo-4, confocal line scans) and t-tubule density (Di8ANEPPS) were recorded in adult rat ventricular cardiomyocytes incubated with 0.7mM PE16:1 or vehicle (BSA, control) for 30 minutes. Synchrony of Ca^{2+} release was assessed by calculating the percentage of early Ca^{2+} release (local time to half maximum, TF50 ,< 5ms) along the scan line. Ca^{2+} spark and wave frequency and propagation velocity were recorded and matched for sarcoplasmatic-reticulum (SR) Ca^{2+} load (caffeine).
Myocytes incubated with PE16:1 showed a normal CaT amplitude but slowed Ca^{2+} removal (TAU decay, 156ms vs. 97ms, $p<0.05$).SR Ca^{2+} content was increased (2.8 vs. 2.3 F/F0, $p<0.05$) and the decay of caffeine-induced CaTs slowed (1353ms vs. 606ms, $p<0.05$). With PE16:1 Ca^{2+} release (1Hz) was more dyssynchronous with less early-release sites (PE16:1: 25% vs. control: 50%, $p<0.05$) and slowed TF50 of late release sites (15ms vs. 9ms, $p<0.05$), resulting in an overall slowing of Ca^{2+} release (mean global TF50: 9.4ms vs. 5.4ms, $p<0.05$). T-tubule signal density (20.4% vs. 21.4%) and intracellular t-tubule variation were not significantly different.
The probability of Ca^{2+} release at early-release sites in consecutive beats was lower (0.61 vs. 0.71, $p<0.05$) and the propagation velocity of waves slower (120.4 microm/ms vs. 150.4 microm/ms, $p<0.05$). However, PE16:1 induced more sparks (2.1 vs. 0.7 sparks per nl*s, $p<0.05$) and increased diastolic Ca^{2+} at 5Hz (F/F0: 1.11 vs. 1.04, $p<0.05$).
Conclusion: In cardiomyocytes PE16:1 acutely reduces the synchrony and global kinetics of Ca^{2+} homeostasis and at the same time increases arrhythmogenic Ca^{2+} release, which may trigger dysfunction and remodeling in adipositas related HFrEF.

19-POS Board 19

LOW-VOLTAGE AREAS ASSESSED BY ULTRA-HIGH-DENSITY ELECTROANATOMICAL MAPPING CORRELATE WITH LEFT ATRIAL FUNCTION

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Introduction: The extent of left atrial (LA) adverse remodeling as a cardiac disease marker has become increasingly important. In patients with atrial fibrillation (AF), atrial remodeling (AR) is accompanied by increased mortality. The relation between LA function and the extent of low-voltage areas (LVAs) has not yet been systematically investigated.
Methods: In patients with AF undergoing catheter-ablation, LA was studied using echocardiography and ultra-high-density mapping (Rhythmia ®). Fibrosis (i.e. extent of LVAs) was estimated by quantifying areas with bipolar electrogram amplitudes of =0.5, =0.4, =0.3, =0.2 or =0.1 mV.
Results: A total of 22 patients with a mean LVEF of 53±2 % were studied. Mean LA volume index (LAVI) was significantly increased at 39±3ml/m^2 indicating AR. Size of LVAs was 57±7 cm^2 representing 47±5 % of the total LA area (low-voltage set to =0.5 mV). With low-voltage set to =0.4, =0.3, =0.2 and =0.1, total area decreased to 34±6, 28±6, 22±5 and 12±3 cm^2. LAVI positively correlated with the extent of LVAs at all cut-offs. Mean LA emptying fraction was 42±3 % and showed a negative correlation with LVAs with low-voltage set to =0.4 mV. Moreover, mean LA strain was 13±2 % and correlated with LVAs with low-voltage at all cut-offs further supporting the notion that the extent of LVAs impacts LA function. Notably, with low-voltage set to =0.2, =0.3 and =0.4 mV impaired LA strain was detected with an accuracy of >76 % ($p < 0.05$).
Conclusion: Structural (i.e. LAVI) and functional (i.e. LA emptying fraction and LA strain) parameters of the LA correlate with the extent of LVAs.

22-POS Board 22

EFFECT OF RYANODINE RECEPTOR ALLOSTERIC COUPLING ON CALCIUM SPARKS AT DIFFERENT DISTRIBUTIONS INSIDE DYAD

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Recent electron tomographic analysis of rat ventricular myocytes fixed *in situ* has shown RyR2s inside dyads distributed in clusters and as isolated RyR2s. The clusters showed a combination of checkerboard and side-by-side configurations. The distribution of RyR2s was neither uniform nor static [1] and depended on external conditions such as intracellular [Mg2+]. In most calcium spark models, RyR2s were arranged in a checkerboard lattice, hence simulation of calcium sparks at different RyR2 arrangements is an open problem.
Here we use Markov models of Ca2+ release sites to investigate relationships between coupling of RyRs via local [Ca2+] and via allosteric RyR2-RyR2 interactions [2] at different RyR2 distributions and the statistics of Ca2+ spark generation and termination. Allosteric interactions promoted synchronous channel gating by stabilizing neighboring closed-closed and/or open-open channel pairs [3]. The aHTG model [4] was used for description of RyR2 gating. Local Ca2+ in the presence of mobile buffers was calculated according to [5].
We studied the dependence of Ca2+ spark characteristics on RyR2 distribution and allosteric coupling using both Monte-Carlo and mean-field approaches. We found that at a physiologically reasonable range of model parameters, changes in RyR2 distribution within the dyad did not change Ca2+ spark generation and termination at any [Mg2+] if allosteric interaction was not included. At low [Mg2+], allosteric interaction was also required for Ca2+ spark termination. We show that the proposed effect of Mg2+ on RYR2 distribution in the dyad may affect spark statistics only if RyR2s are allosterically coupled. That is, RyR2 distribution will not affect spark statistics via calcium-mediated RyR2 gating.

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25-POS Board 25

EPHAPTIC EFFECTS IN THE HEART: EVIDENCE FROM PATCH CLAMP EXPERIMENTS AND HIGH-RESOLUTION COMPUTER MODELS OF THE INTERCALATED DISC

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Background: Cardiac action potential propagation relies on gap junctions. However, recent studies proposed that ephaptic coupling is involved in cardiac conduction and supports impulse propagation when gap junctional coupling is reduced. Ephaptic interactions are mediated by large changes of the extracellular potential in intercalated discs. Furthermore, Na^+ channels form clusters, suggesting that their distribution in intercalated discs may modulate ephaptic interactions.
Objective and methods: Our aim was to conduct patch clamp experiments demonstrating ephaptic effects on the Na^+ current (I_{Na}) and to investigate the effects of Na^+ channel clustering using high-resolution models of the intercalated disc based on the finite element method.
Results: In experiments with HEK293 cells stably expressing Na^+ channels, approaching the cell to a non-conducting obstacle systematically increased peak I_{Na} at voltage steps near the activation threshold of Na^+ channels and decreased peak I_{Na} at voltage steps far above the threshold. We observed the same modulation of I_{Na} in corresponding computer simulations taking ephaptic interactions into account. In the intercalated disc model, ephaptic interactions were greatly modulated by the distribution of Na^+ channels. Aggregating Na^+ channels into a cluster potentiated the modulation of I_{Na}. Moreover, redistributing Na^+ channels in clusters in the intercalated disc enhanced ephaptic coupling, especially when gap junctional coupling was reduced and when both cell membranes presented clusters facing each other across the intercellular cleft.
Conclusions: Our experiments demonstrate that cardiac I_{Na} is modulated by a restriction of extracellular space and support the existence of cardiac ephaptic coupling. Our simulations highlight the functional role of the clustering of Na^+ channels in the intercalated disc.

28-POS Board 28

MECHANISMS OF ARRHYTHMIAS CAUSED BY SMALL CONDUCTANCE CALCIUM-ACTIVATED POTASSIUM CURRENT (ISK) IN EARLY REPOLARIZATION SYNDROME

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Small-conductance Ca^{2+} -activated K^+ (SK) channels play important roles in cardiac repolarization and arrhythmogenesis under both physiological and pathophysiological conditions. Since the conductance of SK current (ISK) tracks the Ca^{2+} transient, it may behave functionally like a transient outward K+ current. In this study, we use computer simulation and mathematical methods to investigate the role of ISK in promoting arrhythmias in early repolarization syndrome. We show that a pronounced and early-onset Ca^{2+} transient can cause ISK to behave in a very similar manner to the transient outward K^+ current (Ito). Specifically, under the right conditions, increasing ISK causes so-called spike-and-dome action potential (AP) morphology. AP duration (APD) alternans and chaos were also promoted when the strength of ISK is in the range of an all-or-none behavior in which a spike-and-dome AP transitions to a spike AP with a shortened APD. These AP dynamics are similar to the complex APD dynamics caused by Ito. At the multicellular/tissue-scale level, the spike-and-dome AP morphology and APD alternans and chaos caused by ISK can promote dispersion of repolarization and phase-2 reentry. Our simulation results agree with our experimental observations that activation of ISK induces J-wave elevation and spontaneous ventricular fibrillation initiated by phase-2 reentry in the rabbit ventricles.

31-POS Board 31

THE ROLE OF CHAOTIC TRANSIENTS IN CARDIAC ARRHYTHMIAS

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Spiral and scroll waves determine the complex spatio-temporal dynamics during cardiac arrhythmias (e.g. ventricular fibrillation). Complementary to experimental observations, we observe in numerical simulations of cardiac tissue that the spiral/scroll wave dynamics often terminates by itself. Thus, the chaotic dynamics is transient. We investigate the underlying mechanisms which lead to self-termination of the dynamics and discuss interpretations and implications for the understanding of cardiac arrhythmias in real hearts [1].
Furthermore, although the transition from the chaotic dynamics to the non-chaotic attractor of the system is known to be abrupt, we found that the state space structure changes a significant amount of time before the actual self-termination. We denote this transition phase as the "Terminal Transient Phase", which we verified in the investigated cardiac models, but also in other spatially extended systems (e.g. Morris-Lecar neuron model) and low-dimensional maps [2, 3]. The existence of this transition of a finite length could provide the conceptual foundation for a reliable prediction of the self-termination of chaotic transients, and specifically may open up the path towards improved control schemes of cardiac arrhythmias.
Using the obtained knowledge about the state state space structure it can also be shown that an efficient control of the spatio-temporal chaotic dynamics is possible using spatially localized perturbations. Novel defibrillation strategies could benefit from these insights about the efficient control of high-dimensional chaotic dynamics.

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34-POS Board 34

VOLTAGE-SENSITIVITY OF INDOCYANINE GREEN IN THE HEART: DETAILED SPECTRAL EVALUATION

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Background: Indocyanine green (ICG) fluorescent dye has been approved by the FDA for use in medical diagnostics. Recently, we demonstrated that ICG dye has voltage-sensitive properties with a dual-component (fast and slow) response in the Langendorff-perfused rabbit heart (Biophys J, 2016;110:723-732). Here, we extended our studies by showing the different spectral properties of both components for analysis of the fractional change in ICG fluorescence in response to voltage changes.
Methods: We used light from four LEDs to obtain excitation; emission was measured using an EMCCD camera with band-pass filters and a spectrometer. We applied a graphical model with Gaussian functions to construct and evaluate the individual emission curves and calculated the voltage-sensitive portion of each component of the ICG fluorescence in the rabbit heart.
Results: The results revealed that each isolated component (fast and slow) emanates from a unique ICG pool in a different environment within the cell membrane and that each component is also composed of two constituents (ICG-monomeric and ICG-aggregated).
Conclusions: We propose the existence of different voltage-sensitive mechanisms for the components: (I) electrochromism and field-induced reorientation for the fast component; and (II) field-induced dye squeezing that amplifies intermolecular interactions, resulting in self-quenching of the dye fluorescence, for the slow component.

This research was funded by a grant (No.SEN-15/2015) from the Research Council of Lithuania.

37-POS Board 37

CARDIOTOXICITY OF ANTITUMORAL CERAMIDES RELATED TO HERG CHANNEL INHIBITION: MECHANISTIC INSIGHTS FROM MOLECULAR SIMULATIONS

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Human ether-à-go-go related gene (HERG) potassium-selective channels are membrane proteins that play a key role in cardiac action potential repolarization. The off-target inhibition of HERG by commonly prescribed medications is associated with long QT syndrome and the onset of cardiac arrhythmias. In this regard, promising antitumoral agents based on ceramide sphingolipids (*i.e.* Cer6) have shown to inhibit HERG channels in cell cultures, posing an elevated risk of cardiotoxicity. Nevertheless, the molecular mechanisms underpinning HERG inhibition by ceramides are still unknown. Encouraged by the recent determination of HERG structure at near atomic resolution (Cryo-EM), we used sequential-multiscale molecular dynamics simulations to investigate the association mechanisms of ceramides to HERG. We inserted the channel in a membrane patch of POPC:Cer6 (8:2) and used the coarse-grained approximation (4 atoms are represented as one bead) to equilibrate the lipids around the channel for ten microseconds. Then, we increased the resolution of our system to all-atoms (back-mapping) and performed simulations for 1 us. As a result, we observe accumulation of ceramides at the interface between the voltage sensors and the pore domains (VSD and PD, respectively) of the channel. This outcome agrees with electrophysiology studies performed by our group where the VSD mutants F557L, F65C, and M651T; and PD mutants A504S, L523M, and T526N showed decreased HERG inhibition by ceramides. Furthermore, these residues establish close contacts (< 8 Å) with ceramides during microsecond-lasting binding events. Overall, our combined modelling and experimental studies suggest that inhibition of HERG by ceramides involves binding at the VSD-PD interface and not direct blocking of K+ permeation pathway in the PD. This knowledge could be used to design ceramide-based antitumoral agents with reduced cardiotoxicity.

40-POS Board 40 - Cancelled

CROSSTALK BETWEEN BETA-ADRENERGIC STIMULATION AND CAMKII ACTIVITY IN A NOVEL COMPUTATIONAL MODEL OF HUMAN ATRIAL ELECTROPHYSIOLOGY

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43-POS Board 43

CARDIAC FUNCTIONAL INDICES IN IPSC-DERIVED CARDIOMYOCYTES

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The recent progress in biosensor technology combined with availability of human iPSC-derived cardiomyocytes (iPSC-CMs) provides an exciting possibility to assess novel biomarkers of cardiac function in vitro.
The goal of the present study was to perform multi-parameter profiling of endogenous responses in human iPSC-CMs on CardioExcyte 96 (Nanion Technologies GmbH, Germany). Combined impedance and extracellular field potential (EFP) signals were recorded to simultaneously assess electrical activity, beating and electromechanical coupling in a variety of multi-cellular cardiac preparations. Cell cultures were treated with reference drugs from various pharmacological classes affecting cardiac ion channels, pumps, adrenergic receptors and intercellular communication to evaluate their effect on various parameters of impedance and EFP signals. The cross-cell comparison displayed different pharmacological sensitivity and minimal effective concentrations for the functional parameters. In addition to the pharmacological effects, dynamics of the cell growth and development in culture were monitored to derive an analytical expression for the system. Detailed investigation of the cellular beat signal facilitated multi-parameter evaluation allowing integrative assessment of cardiomyocyte behavior. The resulting multiplex signatures can be used as a fingerprint tool to highlight changes in cardiac function and potentially to categorize drugs based on their mechanisms of action. This integrative approach for multi-parameter profiling would meliorate the early drug screening pipeline by bridging receptor-based assays and ECG measurements for translational application.

46-POS Board 46

IN-SILICO AND CLINICAL BASED PIPELINE FOR THE ELECTRODE LOCATION OPTIMISATION IN QUADRIPOLAR LEFT VENTRICULAR LEADS FOR CARDIAC RESYNCHRONIZATION THERAPY

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One of the main therapies for treating left ventricular dyssynchrony in the heart is cardiac resynchronization therapy (CRT), where the normal cardiac rhythm is recovered pacing both ventricles. Nevertheless, approximately 40% of the patients do not respond to CRT, showing no improvement to this therapy. One of the main causes of this poor response to CRT is a non-optimal positioning of the electrodes in the left ventricle (LV). A recent technique based on quadripolar leads have been used on the LV to improve the treatment, since several pacing sites are achieved at the same time with one lead, yet no optimal design has been developed.
In this work we provide a framework to include the heart anatomy in the quadripolar design and activation protocol. Using high resolution CT images of CRT and non-CRT patients we have developed patient-specific 3D computer models of the heart chambers and the coronary sinus. Using a range of different quadripolar lead designs, we have measured the total activation time of both ventricles, of the LV and the time taken between the 10 and 90% of the myocardium of the ventricles is activated, obtaining the best lead configurations for each patient. These *in-silico* clinical models provide a rapid and effective procedure to obtain the optimal design of this novel lead design based on patient-specific data.

49-POS Board 49

MODELING OF THE STOCHASTIC BEHAVIOR OF RYR-CHANNELS: CALCIUM SPARKS AND LEAKY CLUSTERS

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In cardiac cells the action potential generation and the contraction are a result of a complex process of triggered by calcium release from the sarcoplasmic reticulum (SR). Elementary events of Ca^{2+} release from the sarcoplasmic reticulum (SR) through ryanodine receptors (RyR-channels or RyRs) are called calcium sparks.
Previously developed original Electron-Conformational Model of the RyRs stochastic dynamics (Moskvin e.a., PBMB, 2006) is able to describe most of important effects of RyRs functioning in normal conditions and in the pathology (Ryvkin e.a., Bophysics, 2015).
Here we introduce a mathematical model of calcium sparks initiation-spread-termination. We describe Ca^{2+} ions dynamics in a single isolated calcium release unit (RU), taking into account Ca^{2+} diffusion in the subspace and consecutive RyRs' activation which is the base of Calcium Induced Calcium Release (CICR) process. We've solved 2D diffusion problem using a rapid finite differences method.
We take into consideration two cases of RyRs' spatial distribution: regular 9x9 square cluster and randomly distributed 81 RyRs. Each RyR is described in terms of ECM, which allows the description of the RyR behavior on the macromolecular level.
Sparks' initiation and termination rate dependence on the Ca^{2+} diffusion velocity is observed. We show that SR lumen local depletion and RyRs' stochastic attrition could be the reasons of Ca^{2+} spark termination.
Also we investigate conformational and allosteric coupling between RyRs. We show that calcium diffusion plays a cooperative role in RyRs' activation and can be a reason of the appearance of the leaky clusters of open RyRs during Ca^{2+} dynamics in the RU.

Supported by RFBR grant 16-34-60223.

52-POS Board 52

MECHANISMS OF SUBCELLULAR SPATIALLY DISCORDANT CALCIUM ALTERNANS IN CARDIAC MYOCYTES

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Subcellular spatially discordant calcium alternans (SDCA) is a behavior in which calcium transient alternates with opposite phase in different regions of a cell. Experimentally, SDCA has been observed in both atrial and ventricular myocytes in various experimental conditions. Previous studies suggested that SDCA could be resulted from a Turing instability under the condition of negative calcium-to-voltage coupling. However, this theory cannot explain the SDCA observed in voltage clamp experiments. Here, we carried out computer simulations using a physiologically detailed spatial cell model to investigate the mechanisms of SDCA. We showed that SDCA can be induced by 1) T-tubule disruption; 2) reducing ryanodine receptor open probability; and 3) using out-of-phase initial conditions, which agree well with previous experimental observations. We also showed that both weak and strong cytosolic calcium diffusion strength suppressed SDCA while the intermediate cytosolic calcium diffusion strength promoted SDCA. On the other hand, SDCA was suppressed monotonically by increasing sarcoplasmic reticulum calcium diffusion strength. The nodal lines of the SDCA tend to appear in a random manner and the sizes of the out-of-phase regions are irregular. Our results demonstrated that SDCA formation depends on the subcellular structures and/or initial conditions under proper calcium diffusion strengths to synchronize the calcium release units locally but not globally. Therefore, SDCA is not necessarily caused by dynamical instabilities but can be just an out-of-phase phenomenon mediated by heterogeneous subcellular structure and/or initial conditions with a proper calcium diffusion strength.

55-POS Board 55

COMPLEX ACTIVATION PATTERNS DURING ATRIAL FIBRILLATION CAN BE SUSTAINED BY TRANSMURAL ROTORS

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Introduction
Currently the understanding of atrial fibrillation (AF) mechanisms, as well as the success of its treatments, remain limited. Various phenomena, including rotors and breakthroughs, have been observed experimentally and proposed as the main drivers sustaining AF. This work aims to elucidate the mechanistic links between rotors and breakthroughs by considering 3D transmural rotors that propagate within the atria via pectinate muscles.

Methods
A computational model of atrial electrical activity was created using a canine 3D atrial geometry combined with Fenton-Karma and Varela et al. atrial cell models. The model included ionic and/or structural heterogeneities in the atria, and specifically between the right atrium (RA) and pectinate muscles (PMs). Sustained AF was generated by ectopic rapid pacing in the pulmonary veins (PVs). Results were visualized with 3D atrial membrane voltage maps, along with 2D isochronal maps (IM). The effects of Amiodarone were also studied by introducing its action on relevant ion channels after 5 seconds of AF.

Results
AF was initiated in the entire 3D atria and maintained by several epicardial rotors in the PVs and RA, as well as an additional transmural rotor propagating through the PMs and emerging at the RA epicardium. IM showed multiple breakthroughs in the RA, which were due to the re-entrant transmural activations emerging from various insertions of the underlying network of PMs. Amiodarone resulted in the termination of both the transmural rotor and epicardial rotors in the RA, leaving a single rotor in the PVs.

Conclusion
The 3D atrial simulations showed that complex AF patterns can be explained by interactions of epicardial rotors with transmural waves propagating through the depth of 3D atrial tissue, and appearing as rotors in the PMs or breakthroughs on the RA surface. These results can reconcile apparently controversial viewpoints on AF mechanisms and potentially improve mechanism-based AF treatments.

58-POS Board 58

IN SILICO MODEL OF SK CHANNEL GATING, TEMPERATURE DEPENDENCE AND CALCIUM SENSITIVITY

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The small conductance calcium activated potassium (SK) channel affects atrial repolarization and is implicated in the onset and progression of atrial fibrillation (AF). *In vitro, in vivo* and genetic studies have provided functional and molecular links between SK channels and AF. SK inhibition promotes AF termination and protects against AF re-induction in large animal models, but the effect of SK modulation in humans remains limited and controversial.
Objective: To provide a detailed computational SK model for interrogating the role of these channels in human atrial electrophysiology and arrhythmogenesis.
Methods and Results: We have constructed a detailed Markov SK model from single channel and excised inside-out macropatch recordings. Single channel data confirmed the previously reported gating structure of neuronal SK2 channels (4 closed and 2 open states), and were used to define the transition kinetics for calcium-dependent SK activation. Inside-out macropatch recordings uncovered a strong temperature-dependence of SK Ca^{2+}-sensitivity. At room temperature, the EC50 for hSK2 and hSK3 was 0.38 ± 0.02 µM and 0.53 ± 0.07 µM, respectively. Increasing the temperature to 37°C shifted SK Ca^{2+}-sensitivity towards the diastolic range for both hSK2 and hSK3 (EC50 = 0.22 ± 0.01 µM and 0.18 ± 0.02 µM, respectively). The associated Q_{10} values were 1.44 (hSK2) and 2.05 (hSK3). This temperature dependence will be incorporated into the Markovian formulation, which itself will be embedded in a human atrial myocyte model and tissue constructs, to assess the implications for SK channel function *in vivo*.
Conclusions: The novel temperature dependence of SK channel Ca^{2+}-sensitivity indicates partial channel activity during atrial diastole. This finding implies that SK channel localization may be less important than previously assumed, and that SK channels may be capable of modulating atrial resting potential and repolarization, particularly during calcium overload and AF.

61-POS Board 61- Cancelled

CARDIAC MUSCLE COOPERATIVITY STUDIED BY THERMODYNAMICALLY CONSISTENT CROSS-BRIDGE MODEL

Mari Kalda**, Marko Vendelin.**
Tallinn University of Technology, Tallinn, Harjumaa, Estonia

64-POS Board 64

DELAYED DEPOLARIZATION IN THE RIGHT VENTRICULAR OUTFLOW TRACT CAUSES COVED-TYPE BRUGADA ECG RESEMBLING PATIENT RECORDINGS IN A WHOLE HEART COMPUTATIONAL MODEL

Eike M Wülfers[1,3], Gunnar Seemann[1,3], Konstantin Krieger[4], Corinna Lenz[4], Boris Keweloh[4], Christoph Bode[2,3], Katja E Odening[1,2,3], Johannes Steinfurt[2,3]
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Brugada syndrome (BrS) is characterized by dynamic ST-elevations in right precordial leads and an increased risk of sudden cardiac death due to ventricular fibrillation (VF). VF triggers and abnormal electrograms in the right ventricular outflow tract (RVOT) can be silenced by epicardial catheter ablation, leading to ECG normalization. The pathophysiological mechanisms underlying BrS are not fully understood and discussed controversially in current research. Using computational modeling, we investigate the effects of delayed depolarization in the RVOT, the "depolarization disorder hypothesis."
Simulations were performed on a 3-dimensional computational model of the heart and torso created from MRI data of a healthy volunteer. The model was altered based on epicardial maps of a BrS patient undergoing epicardial electro-anatomical mapping of the RVOT and substrate ablation. To reproduce the observed activation delay in the RVOT of the BrS patient, we altered the substrate in the model. Conductivity was reduced 50- to 100-fold (approx. 7–10x reduction of conduction velocity) in an epicardial layer of 5 mm^2 area and 0.4–0.8 mm thickness. A post-ablation state was simulated by setting the same layer to be electrically inactive. Excitation conduction was simulated using the monodomain model and the ten Tusscher & Panfilov cardiomyocyte model. ECGs were derived from body surface potentials resulting from forward calculations.
Reduced epicardial RVOT conductivity resulted in ST-elevation of 2 mV and 0.9 mV in V_1 and V_2, respectively. T-waves were more negative and prolonged. Epicardial electrograms in the RVOT were delayed and prolonged. The post-ablation simulation showed a remaining ST-elevation of 0.2 mV in both, V_1 and V_2.
Our computational model reproduces coved-type BrS ECGs by only incorporating reduced (macroscopic) conductivity in the epicardial RVOT. These results therefore support the depolarization disorder hypothesis as the main electrophysiological mechanism underlying BrS.

WEDNESDAY, SEPTEMBER 5
POSTER SESSION II
13:10 – 14:30
Building 84 Foyer

All posters are available for viewing during all poster sessions; however, below are the formal presentations for Wednesday. Presenting authors with odd-numbered poster boards should present from 13:10 – 13:50 and those with even-numbered poster boards should present from 13:50 – 14:30. The presenters listed below are required to remain in front of their poster boards to meet with attendees.

Bode, David	**2-POS**	**Board 2**
Campos, Fernando	**5-POS**	**Board 5**
Cosi, Filippo	**8-POS**	**Board 8**
Edwards, Andrew	**11-POS**	**Board 11**
Gillette, Karli	**14-POS**	**Board 14**
Härtter, Daniel	**17-POS**	**Board 17**
Holmes, Maxx	**20-POS**	**Board 20**
Iskratsch, Thomas	**23-POS**	**Board 23**
Kudaibergenova, Meruyert	**26-POS**	**Board 26**
Lei, Chon Lok	**29-POS**	**Board 29**
Loewe, Axel	**32-POS**	**Board 32**
Martens, Johannes	**35-POS**	**Board 35**
Nagaiah, Chamakuri	**38-POS**	**Board 38**
Niedermayer, Thomas	**41-POS**	**Board 41**
Quinonez Uribe, Raul	**44-POS**	**Board 44**
Roy, Aditi	**47-POS**	**Board 47**
Sacco, Federica	**50-POS**	**Board 50**
Stevenson-Cocks, Harley	**53-POS**	**Board 53**
Tanner, Bertrand	**56-POS**	**Board 56**
Varela, Marta	**59-POS**	**Board 59**
Wall, Samuel	**62-POS**	**Board 62**
Zaniboni, Massimiliano	**65-POS**	**Board 65**

Posters should be set up the morning of September 4 and removed by noon September 7.

2-POS Board 2

FIBROBLAST-MEDIATED ATRIAL MECHANICAL DYSFUNCTION IN HFPEF AND HYPERTENSIVE HEART DISEASE.

David Bode[1,2], Diana Lindner[4,5], Dirk Westermann[4,5], Robert Klopfleisch[6], Sophie Van Linthout[1,3], Carsten Tschöpe[2], Burkert Pieske[1,2,3], Frank R Heinzel[1,2], Felix Hohendanner[1,2]
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Atrial contractile dysfunction is associated with increased mortalityin heart failure (HF). We have shown previouslythat atrial function is impaired in a metabolic syndrome (MetS)-based HFpEFrat model in-vivo. We hypothesize that atrial cardiomyocyte (ACM) function and its reaction to extracellular matrixcomponents is pivotal for the manifestation and progression of atrial remodeling (AR) and mechanical dysfunction in HF.
Fibrosis was evaluated in paraffin-embedded sections with PicroSirius Red staining. TGF-ß mRNAwas quantified as a surrogate of atrial paracrine activity(Realtime PCR).Contractile function of ACM(cell shortening, video edge detecting) and cytosolicCa transients (CaT, confocal Fluo-4) were evaluated in wild type (WT) and ZFS-1 rats without (Ln; hypertension) and with MetSand AR(Ob;HFpEF). CaTwere recorded also in the presence of conditioned medium of cultured unstressed or stressed (stretch-induced activation) fibroblasts isolated from Ln andOb respectively.
Histologyunveiled increased myocardial fibrosis in the upper atrium inOb vs. WTand Ln.Ob showed enhanced expression of TGF-ß mRNAvs. Ln and WT. ACM contractile function showed shortened time to peak (TTP) inOb and Ln vs. WT.Ob showed shortened relaxation vs. WTand Ln and increased cell shortening amplitude vs. WT, most likelyrelated to compensatoryenhanced Ca release. Treatmentwith conditioned, activated medium vs. medium from unstressed fibroblasts was associated with impaired Ca homeostasis (i.e. increased diastolicCa content, prolonged CaTTTPand Ca removal) inOb. In Ln, in-vivo atrial function was preserved.Here, conditioned medium from Ln fibroblasts accelerated Ca removal in ACM.
Our results indicate profound etiology-dependent changes in ACMfunction in AR,which depend on the fibroblast secretome induced bymechanical stress and potentiallycontribute to in-vivo atrial decompensation

5-POS Board 5

A MULTI-SCALE COMPUTATIONAL MODEL TO INVESTIGATE CALCIUM-MEDIATED ECTOPY IN THE HUMAN INFARCTED HEART

Fernando O Campos[1], Joao Cardoso Pires Timoteo Fernandes[1,2], Yohannes Shiferaw[4], Titus Kuehne[2,3], Martin J Bishop[1], Gernot Plank[6]
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Background: A variety of malignant ventricular tachycardias are implicated with premature ventricular complexes (PVCs) resulting from spontaneous calcium (Ca) release (SCR) events at the subcellular level. However, investigation of such arrhythmias is hindered by the lack of adequate techniques to assess abnormalities at the subcellular scale and organ-scale arrhythmogenic events.
Objective: The aim of this study was to construct a multi-scale computational model to investigate SCR-mediated PVCs within the human post-infarction heart.
Methods: An experimentally-based phenomenological model of SCR events was coupled into the equations for Ca cycling of a state-of-the-art model of the human ventricular action potential (AP). Key parameters of the cell model were modified to represent remodelling conditions known to occur in heart failure (HF). This augmented myocyte model was employed in in-silico experiments on a post-infarction biventricular (BiV) model. Magnetic resonance imaging data from a patient who suffered myocardial infarction was used to build the BiV model in this study. The infarct scar and border zone were segmented by thresholding the voxel intensity within the ventricular wall. These were then used to build a tetrahedral finite element mesh including realistic fibre architecture. Finally, repolarization heterogeneity known to exist across the ventricular wall as well as in the infarcted region were also included in the BiV model.
Results: In single-cell experiments, stochastic SCR events were shown to become more likely as the cell was overloaded with Ca. These SCRs caused triggered APs in HF experiments. In the human BiV model, cells exhibiting SCRs within the infarcted border zone could overcome local source-sink mismatches to trigger PVCs.
Conclusions: The results presented here are the first to show that PVCs resulting from abnormalities at the subcellular level can be studied using highly detailed human heart models.

8-POS Board 8

CALCIUM ALTERNANS AND WAVES ARISING FROM SUBCELLULAR DEFECTS IN CARDIOMYOCYTES

Filippo G Cosi[1,3], Wolfgang Giese[2], Wilhelm Neubert[2], Stefan Luther[1,4,5], Nagaiah Chamakuri[7], Ulrich Parlitz[1,3,5], Martin Falcke[2]
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Heart failure is often related to defects of molecular and subcellular components in single cardiomyocytes that result in delayed or early after depolarisations and calcium alternans. Understanding how these defects are affecting the calcium cycling in single cells can help pinning down the origin of cardiovascular disease and, therefore, allow for better treatments. A multi-scale model is used, which combines the stochastic nature of sub-cellular and molecular components (like Ryanodine Receptors, RyR or L-type Calcium Channels, LCC), their spatial arrangement as well as spatiotemporal calcium and buffer gradients at the whole cell level.
The model takes advantage of a modular formulation that allows to incorporate any organism specific ionic model, which is capable of describing the main ionic fluxes as well as the transmembrane action potential, AP.
The subcellular defects can manifest themselves through so called disrupted T-tubuli, also known as orphaned RyR or uncoupled Calcium Release Units (CRUs), or simply through an overall change in the calcium sensitivity of the RyR. We focus on the effects these modifications have on the calcium cycling. First results from the simulations have been achieved showing how the calcium handling is altered in the case of orphaned RyRs.
Further on, an analysis of the calcium spark behaviour with altered RyR or Sodium-Calcium Exchanger (NCX) properties are carried out to check whether it is possible to reproduce, and as a follow up then study in greater detail, experimentally observed calcium waves. Calcium waves represent a serious threat to the functioning of excitation-contraction coupling in human cardiomyocytes, since non-synchronised calcium sparks can prevent the cell from contracting properly.
The present study aims to lay a quantitative fundament for the analysis of defect cardiomyocytes to deepen the understanding of how diseased heart tissue might be treated.

11-POS Board 11

SUBCELLULAR SODIUM CHANNEL LOCALIZATION MODULATES MACROSCOPIC CARDIAC CONDUCTION

Andrew G Edwards[1,2], Karoline Horgmo Jæger[1], Andrew D McCulloch[3,1], Aslak Tveito[1]
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Computational simulation and analysis of cardiac electrical activation and propagation is commonly accomplished using the Bidomain model or related Monodomain model. These models are based on homogenization of cellular structure to provide continuous approximations of the macroscopic relationships between intracellular potential, extracellular potential and transmembrane current. These models have been successfully applied to interrogate the dynamics of activation and conduction at the tissue level. However, it is becoming increasingly clear that cellular and subcellular structure-function relationships, for example involving ion channel localization, are important for determining aspects of these macroscopic properties. Because these structural details are lost in the continuum models, it is not possible to interrogate their impact in a genuinely multiscale manner. Our objective in the current study was to extend on prior efforts to model these nano- and micro-scale electrophysiologic structure function relationships, with an approach that can be scaled to address questions of electroconduction in whole cells, and eventually in tissue.
Methods and Results: we report computational results obtained by a model where the extracellular space, membrane, and intracellular space are explicitly represented in space (the EMI model). Thus, the important spatial details determining how these components interact can be represented with minimal abstraction from the protein to the multicellular scales. Applying this framework we describe how regionalization of sodium channels at the intercalated disk impacts conduction velocity and the safety factor for impulse propagation in 1- and 2-D, compared with conventional uniform channel distributions.
Conclusions: we observe that conduction velocity increases when the sodium channels are located at the intercalated disk compared uniformly distributed. This was due to decreased time delay over gap junctions and simultaneous increase in the safety factor for conduction. Furthermore, we show that ephaptic coupling can permit to conduction across blocked gap-junctions under conditions of simulated ischemia.

14-POS Board 14

AUTOMATIC GENERATION OF BI-VENTRICULAR MODELS OF CARDIAC ELECTROPHYSIOLOGY FOR PATIENT-SPECIFIC PERSONALIZATION USING NON-INVASIVE RECORDINGS

Karli Gillette[1], Anton Prassl[1], Jason Bayer[2], Ed Vigmond[2], Aurel Neic[1], Gernot Plank[1]
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Background: Clinical utilization of *in-silico* models of cardiac electrophysiology (EP) necessitates efficient, automated workflows for model generation compatible within clinical time scales. Furthermore, generated models must be capable of automated, patient-specific personalization based on non-invasive, clinical measurements, such as the 12-lead electrocardiogram (ECG).
Objective: We therefore aimed to develop a fully-automatic workflow for image-based generation of bi-ventricular (BV) cardiac EP and torso models capable of rapidly simulating 12 lead ECGs using a boundary element method (BEM) formulation.
Methods: A conforming torso and four-chamber heart segmentation was generated from clinical MRI scans using semi-automated approaches and meshed into a tetrahedral finite-element mesh at 1 mm resolution. A BV mesh was automatically extracted, as well as coarsened epicardial and torso surface meshes for BEM. Universal ventricular coordinates (UVC) were computed to incorporate a rule-based fiber architecture, define a fast-conducting endocardial layer, and define stimulation sites of earliest activation on the endocardium. Stimulus profiles and conduction velocity of the endocardium were parameterized. Extracellular epicardial potential distribution was recovered from a reaction-eikonal model using a pseudo-bidomain approach and projected with BEM for reconstruction of a 12 lead ECG at MRI-derived electrode placements.
Results: Meshing of the conforming torso and heart along with subsequent construction of the model architecture for simulation required approximately 1.8 hours. On 10 cores, calculation of the BEM lead field matrix required 16.92 minutes and automated simulation of a single activation sequence required 6.08 minutes on average.
Conclusion: Efficient generation of adaptable and personalized cardiac EP models is key in any clinical model utilization. The proposed workflow integrated recently developed technologies to fully automate both the generation and parameter modification of a cardiac EP model capable of simulating 12 lead ECGs. Patient-specific parameterization can then be performed using stochastic sampling or machine learning techniques.

17-POS Board 17

MECHANICAL ENVIRONMENT AFFECTS SARCOMERE COHERENCE IN HUMAN EMBRYONIC STEM CELL-DERIVED CARDIOMYOCYTES

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Cells are affected by their mechanical micro-environment. For instance, rigid scar tissue formed in infarcted heart inhibits the global contraction of cardiomyocytes. Direct insight into how the mechanical environment determines dynamics on the sarcomere level has been lacking. We have tracked the contractile motion of individual sarcomeres using endogeneous z-line labeling in CRISPR/Cas9 modified hESC-derived cardiomyocytes on micro-patterned substrates with elastic properties mimicking physiological settings (7 kPa to 60 kPa Young's modulus). Sarcomere contraction was impeded at high substrate stiffness. On soft substrates, sarcomeres contracted coherently, whereas contractions became increasingly incoherent and heterogeneous with increasing substrate stiffness.
These findings suggest that rigid mechanical surroundings force sarcomeres into competition, impede long-range force transmission and thus perturb dynamic coherence. Using a simplified mechanistic model, we show that elastic coupling of z-lines to the substrate in conjunction with some heterogeneity in the force-generating elements can account for many observed features. Theories of collective molecular motor dynamics predict emergent phenomena such as dynamic instabilities. Our experiments provide quantitative data on the single-sarcomere level with high temporal and spatial resolution to validate such mesoscopic theories and, to ultimately better understand cardiac muscle dynamics on multiple length scales.

20-POS Board 20

A NOVEL MODEL OF RABBIT ATRIAL CARDIOMYOCYTES FOR THE STUDY OF SPONTANEOUS CA^{2+} RELEASE MEDIATED ARRHYTHMIC MECHANISMS

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Background: The morphology of T-systems in atrial myocytes is conjectured to be remodeled within two cardiac conditions of increasing incidence, atrial fibrillation (AF) and heart failure (HF). Dysfunction in calcium (Ca^{2+}) handling, considered to involve alterations in T-system structure and remodeled channel expression, is suggested to promote both disrupted excitation-contraction coupling and increasing frequency of arrhythmic events at the cellular scale; the importance of T-system remodeling in the development of pro-arrhythmic events such as spontaneous Ca^{2+} release and Ca^{2+} alternans remains unclear.
Methods: A previously published computational model describing rabbit atrial electrophysiology (*Aslanidi, et al., Biophys. J. 96(3):798-817, 2009*) was integrated with our recently published model describing stochastic spatio-temporal Ca^{2+} dynamics (*Colman et al. PLOS Comp. Biol. 13, e1005714, 2017*). Atrial T-system remodeling was implemented in isolation from other potential forms of HF-associated remodeling, through removal of sarcolemmal ion-channel currents from individual CRUs, assigned either randomly or in pre-defined areas of heterogeneous size. Rapid pacing protocols were applied to induce Ca^{2+} transient alternans, and load SR Ca^{2+} content.
Results: Rabbit atrial action potential and Ca^{2+} morphology in normal cardiac excitation is reproduced in the model. In isolation to other forms of HF-associated remodeling, variations in T-system density and organisation demonstrated a negative correlation between T-tubule density and susceptibility to Ca^{2+} alternans and spontaneous Ca^{2+} release events, the former determined by alternating successful and failed propagation of Ca^{2+} into regions devoid of T-tubules; the latter determined by an interaction of localized SR Ca^{2+} loading and reduced efflux, promoting successful Ca^{2+}wave propagation.
Conclusion: A novel model of rabbit atrial electrophysiology and Ca^{2+} handling was produced. Our model suggests that alterations in T-system morphology may comprise an important role in the predisposition of atrial cardiomyocytes to arrhythmogenic mechanisms associated with AF in the presence of HF.

23-POS Board 23

INVESTIGATING CARDIOMYOCYTE RIGIDITY SENSING WITH NANOPILLAR AND NANOPATTERN

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Mechanical properties are cues for many biological processes in health or disease In the heart, changes to the extracellular matrix composition and cross-linking results in stiffening of the cellular microenvironment during development. Moreover, remodelling after myocardial infarction, or in cardiomyopathies lead to fibrosis and a stiffer environment. Previous studies established a direct relationship between rigidity and the contractile forces of cardiomyocytes. However, it is still elusive how cardiomyocytes sense matrix stiffness. By combining nanopillar arrays, PDMS gels with defined stiffness and FRET molecular tension sensors, we identified a fundamental mechanism for cardiomyocyte rigidity sensing, whereby single cardiomyocyte adhesions sense simultaneous (fast oscillating) cardiac and (slow) non-muscle myosin contractions. Together this leads to oscillating tension on the mechanosensitive adaptor protein talin on substrates with a stiffness of healthy adult heart tissue, compared to no tension on embryonic heart stiffness and continuous stretching on fibrotic stiffness. We further employ various micro and nanopatterning strategies to investigate the specific integrin receptor mechanosignalling pathways in high throughput and/or single molecule resolution.

26-POS Board 26

STATE-DEPENDENT BLOCK OF THE HERG K+ CHANNEL BY IVABRADINE: ALLOSTERIC COUPLING TO DRUG LIPOPHILIC ACCESS

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Abnormal cardiac electrical activity is a common side effect caused by unintended block of the promiscuous drug target hERG, the pore-forming domain of the delayed rectifier K^+ channel in the heart. hERG1 block leads to prolongation of the phase of the cardiac cycle that corresponds to underlying cellular repolarization, otherwise known as long QT syndrome. Even newly released anti-arrhythmic drugs, like ivabradine, block the $I_{Kr,}$ prolonging action potential duration (APD) and inducing a potentially lethal arrhythmia known as Torsades de Pointes *(TdP*). To date, the dominant hypothesis in the field is that promiscuous drug binding is a result of amphipathic or weak-cationic drug interactions with water-filled intra-cellular cavity present in hERG1 channel. However, we describe a critical drug-binding pocket located on the lipid-facing surface of hERG1 channel that may play a mechanistic role in drug binding To show allosteric coupling between drug access via lipophilic route and channel conformational dynamics, we performed extensive mutagenesis and electrophysiological studies. Functional data in combination with docking and multi-microseconds Molecular Dynamics simulations mapped a binding site for small-molecule compounds at the interface between the lipid bilayer and the transmembrane segments S5 and S6 of the pore domain. Our data show unambiguously that high-affinity block exhibited by ivabradine is strongly associated with a conserved binding pocket on the lateral pore surface facing lipid membranes. The allosteric coupling between drug and channel conformational dynamics revealed by micro-seconds long MD simulations is achieved by state-dependent orientation of one of the key aromatic residues implicated in high-affinity block by various substances. We show that mutations impeding state-dependent dynamics of aromatic cassette at the protein-lipid interface has a potential to obliterate drug blockade to the channel. This fundamentally new mechanism of coupling between channel dynamics and small-molecule access to hERG1 intra-cavitary site provides simple rational for well-established state-dependence drug blockade and informs the design of new types of cardiosafe drugs against diseases caused by altered excitability.

29-POS Board 29

RAPID CHARACTERISATION OF HERG KINETICS USING OPTIMISED PROTOCOLS ON A HIGH-THROUGHPUT SYSTEM

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The *in vitro* hERG channel assay has been introduced into the drug development process to evaluate the proarrhythmic potential of small molecules. The gold standard for assessing ion channel functionality is the manual patch clamp technique, but automated platforms are now widely used in the pharmaceutical industry to allow high-throughput. These automated high-throughput systems, together with *in silico* modelling, form the backbone of a proposed future drug safety pipeline in the Comprehensive *in vitro* Proarrhythmia Assay (CiPA) initiative led by the US Food & Drug Administration.
Mathematical models of ion channels, which constitute the core of whole-cell electrophysiology models, are typically constructed through fitting to patch clamp data. The patch clamp data is typically generated using long, dedicated protocols for studying particular gating processes, which are usually unable to characterise the full kinetics of an ion channel model. A recent study (Beattie et al. 2018) has demonstrated that it is possible to characterise hERG kinetics rapidly via parameterisation of a model using much shorter protocols. However, this study applied the technique only on a manual patch clamp platform.
To advance this technique, and complement the CiPA initiative, we have developed a protocol that is applicable to any patch clamp setup, including high-throughput automated systems. We demonstrate its use in the Nanion SyncroPatch 384PE. We are able to construct 86 cell-specific variants/parameterisations of a hERG model using data from CHO cells stably transfected with hERG1a at physiological temperature, as well as 30 cells at room temperature. We also validate all our cell-specific models against 5 other voltage clamp protocols performed in the same cells. In future, we aim to design protocols to allow high-throughput systems to be used to investigate not only how much the hERG channel is blocked by a drug, but also how that drug influences channel kinetics.

32-POS Board 32

THE CHALLENGE OF TRANSFERRING IN VITRO EXTRACELLULAR CALCIUM CONCENTRATIONS TO MODELS REFLECTING IN VIVO CONDITIONS

Axel Loewe[1], Yannick Lutz[1], María Hernández Mesa[1], Nicolas Pilia[1], Olaf Dössel[1], Stefano Severi[2]
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Objective: The physiological extracellular calcium concentration ($[Ca^{2+}]_o$) range in humans is 1.1-1.3mM. However, most experimental data is obtained using Tyrode's solution with 1.8 or 2.0mM $CaCl_2$ content and most *in silico* models of cellular electrophysiology use $[Ca^{2+}]_o$=1.8mM as reference working point, which reflects severly hyerpcalcaemic conditions *in vivo*. We studied how recent models of human atrial (Koivumäki) and ventricular myocytes (O'Hara-Rudy, Himeno) as well as sinus node cells (Fabbri-Severi) respond when adjusting $[Ca^{2+}]_o$ to the physiological range.
Results: The Koivumäki and O'Hara-Rudy models responded with an action potential duration (APD) decrease of 6ms (Koivumäki) and 27ms (O'Hara-Rudy) when decreasing $[Ca^{2+}]_o$ from its default value of 1.8mM to a physiological *in vivo* value of 1.15mM. The Himeno model reproduced the experimentally reported APD increase for decreasing $[Ca^{2+}]_o$ (+20ms/+6.9%), which translated to a 7.7% QT prolongation during multiscale ECG simulations matching human *in vivo* ECG data quantitatively. The inverse relation between $[Ca^{2+}]_o$ and APD/QT was monotonous within the investigated range of 0.6-3.0mM. Moreover, ST elevation correlated with $[Ca^{2+}]_o$. An extended version of the Fabbri-Severi human sinus node cell model considering the dynamics of intracellular ion concentrations responded with a monotonous decrease of spontaneous beating rate when lowering $[Ca^{2+}]_o$ to the physiological range (51bpm at 1.15mM compared to 73bpm at 1.8mM).
Conclusions: As highlighted almost 10 years ago (Severi et al. 2009), most models of cellular cardiac electrophysiology operate at $[Ca^{2+}]_o$ far from physiological *in vivo* conditions and do not reproduce experimental results regarding the $[Ca^{2+}]_o$-dependence of APD and QT qualitatively. We showed that this is also the case for more recent models with the notable exception of the Himeno model of human ventricular myocytes, which responds realistically to $[Ca^{2+}]_o$ changes. We conclude that i) experimentalists and modelers should work towards a physiological $[Ca^{2+}]_o$ reference value moving away from hypercalcaemic conditions, ii) the $[Ca^{2+}]_o$-dependency of cardiac electrophysiology should attract our attention and might hold relevant mechanisms, such as hypocalcaemia-induced sinus bradycardia.

35-POS Board 35

COMPUTATIONAL FLUID DYNAMICS ANALYSIS OF CONTRAST AGENT BOLUS DISPERSION IN THE CORONARY VASCULATURE INCLUDING ARTERIOLES

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In dynamic contrast-enhanced magnetic resonance perfusion imaging the passage of an intravenously injected contrast agent (CA) bolus through tissue is monitored to assess myocardial blood flow (MBF). This requires knowledge of the shape of CA wash-in through upstream epicardial vessels. For technical reasons this cannot be quantified in the supplying vessels and is measured in the left ventricle, which introduces the risk of systematic errors in quantification of MBF due to bolus dispersion in coronary vessels. The influence of epicardial vessels on CA bolus dispersion and resulting systematic errors in MBF have been investigated in several studies using computational fluid dynamics (CFD) simulations. These analyses show systematic MBF underestimation due to various parameters (flow velocity, length, curvature). Furthermore, they suggest decreasing influence of smaller vessels on dispersion and prompt the existence of a limiting vessel generation, after which influence of smaller vessels vanishes. In this project, CFD simulations on 3D geometries including arterioles down to generations nine and ten (diameter~160µm) are performed to obtain more accurate estimations of errors in MBF-quantification. With dedicated software 3D coronary vascular networks are extracted from high-resolution cryomicrotome imaging data of an ex-vivo pig heart and subsequently meshed with computational grids of predominantly hexahedral type. CFD simulations are performed in a 2-step procedure. First we solve the Navier-Stokes equations for blood flow and store the resulting physical fields on disk. In the second step CA transport through the coronary tree is computed over several cardiac cycles by repeatedly reading-in these fields. Dispersion of the injected bolus is observed at all model outlets by means of vascular transit times and bolus widths. Resulting errors in MBF-quantification amount up to 50%. Depending on the exact anatomical region systematic errors in blood flow assessment are prone to spatial variance, which applies to all methods of bolus-enhanced MBF-quantification.

38-POS Board 38

PARALLEL AND SPACE-TIME ADAPTIVITY FOR SPATIOTEMPORAL CALCIUM CYCLING IN CARDIAC MYOCYTES

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The work is devoted to study the multiscale modeling and simulation of excitation-contraction coupling (ECC) in ventricular cardiac myocytes. A set of reaction diffusion equations describes the behavior of the intracellular Ca^{2+} concentration fields on length scales from tens of nanometers to cell size and milliseconds to tens of seconds. We present a concept for a multiscale mathematical model of Ca^{2+}-induced Ca^{2+} release (CICR) and whole cardiomyocyte electrophysiology which incorporates stochastic simulation of individual LC- and RyR-channels, spatially detailed concentration dynamics in dyadic clefts, rabbit membrane potential dynamics and a system of partial differential equations for myoplasmic and lumenal free Ca^{2+} and Ca^{2+}-binding molecules in the bulk of the cell. The main focus of the talk is to study the applicability of spatial adaptivity which is realized within multilevel finite element methods and the temporal adaptivity determined by a linearly implicit time integration techniques for the simulation of stochastic channel opening and closing in sub-compartments like the calcium release units (CRUs). Thereby, the parallelization of such space-time adaptivity based on non-overlapping domain decomposition techniques and dynamic load balancing is investigated. Convergence studies justify to choose the appropriate mesh resolution of large-scale simulations with many CRUs on multiple z-discs. The test case examples show that, as comparing with fixed uniform grids, the adaptivity gain is 1.8 for full action potential duration and approximately 7.2 for Ca^{2+} sparks which are the elementary events of calcium release from the sarcoplasmic reticulum. Finally, we present the parallel performance and scalability of the resulting method for the simulation of action potentials and Ca^{2+} sparks.

41-POS Board 41

UNDERSTANDING LOW-ENERGY ANTIFIBRILLATION PACING (LEAP)

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The application of an electrical shock (defibrillation) is an effective therapy to terminate ventricular fibrillation, but also causes severe side effects. Experimental studies have shown that a sequence of low-energy electrical far-field pulses is able to terminate fibrillation more gently than a single high-energy pulse [1]. During this so-called low-energy antifibrillation pacing (LEAP), only tissue at major conduction heterogeneities, such as large coronary arteries, may be activated by each of the very weak pulses. Therefore, global tissue activation and wave termination originates from few localized activation sites. In order to decipher the interplay of the individual pulses, we performed extensive simulations of cardiac tissue perforated by blood vessels and tested a variety of cellular models. It turns out that the pulses are highly cooperative if the period between these pulses matches the dominant period of electrical turbulence. These findings are elucidated by the analysis of predictive macro-variables, such as the fraction of excited tissue and the number of phase defects. We also developed a simple stochastic model which integrates our results in an intuitive way. Moreover, we found a simple explanation, why underdrive pacing is favorable in practice: The optimal pacing period is related to the mean cycle length of the transmembrane potential during electrical turbulence and this cycle length is increased by the applied electrical field. We expect that this understanding enables one to a priori determine the optimal pacing period in experiment.

[1] Luther et al., Nature 475 (2011)

44-POS Board 44

PANORAMIC OPTOGENETIC STIMULATION OF MURINE HEARTS

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Life-threatening ventricular arrhythmias are clinical symptoms of chaotic excitation patterns, whose wave dynamics are primarily based on interactions of tissue characteristics with electrical signal conduction. Up-to-date medical treatments include application of pharmaceuticals as well as high-energetic shocks, which are under consideration of having worsening side effects and tissue damage. In contrast, the emerging field of cardiac optogenetics and its light sensitive ion channels, like Channelrhodopsin-2 (ChR2), enable low energy optical control of cardiac tissue with high spatial and temporal control. Here, we present a custom-built panoramic stimulation setup based on three light emitting diodes surrounding the vertically positioned Langendorff-perfused transgenic murine hearts. Optical mapping with the voltage sensitive dye DI-4-ANBDQPQ was performed in order to visualize the effect of panoramic optogenetic stimulation under sinus rhythm and arrhythmic conditions. Experimental evidence shows that panoramic stimulation of the whole epicardial tissue enables arrhythmia termination with a 10 - 1000 ms single-pulse using light intensities comparable to the intensities used for local pacing (0.56 - 1.1 mW/mm^2). Furthermore, it was possible to visualize principle mechanisms like unpinning of spiral waves and complete annihilation induced by panoramic stimulation. In conclusion, due to its pulse-length and pattern versatility, optogenetic stimulation offers a promising tool for further investigation and therefore better understanding of complex spatiotemporal cardiac dynamics with much less interfering side-effects than electrical stimulation. The presented study represents the first successful proof-of-principle study to investigate panoramic optogenetic stimulation and its effects concerning control of arrhythmic cardiac dynamics.

47-POS Board 47

PREDICTING CATHETER ABLATION TARGETS FROM PATIENT-SPECIFIC FIBROSIS DISTRIBUTION IN THE LEFT ATRIUM

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Background: Catheter ablation (CA) is a first-line treatment for atrial fibrillation (AF), but its success rates are suboptimal due its empirical nature and poor knowledge of optimal ablation sites. Mounting clinical evidence suggest links between fibrosis in the left atrium (LA) and success of CA. However, mechanistic links between patient-specific fibrosis distributions and the presence of re-entrant drivers (RDs) sustaining AF – ultimate CA targets – remain elusive. We use patient-specific LA models to explore the mechanisms of RD stabilization in fibrotic regions and generate maps of RD locations that can be targeted by CA.
Methods: LA models with patient-specific geometry and fibrosis distribution were derived from late-gadolinium enhanced magnetic resonance imaging of 6 AF patients with varying degree of fibrosis in Utah 2-4 categories. In each LA model, RDs were initiated in multiple locations by pacing near the pulmonary veins (PVs) during plane wave propagation through the LA. For each LA model, the map of RD locations was constructed by calculating the number of times each voxel was visited by the RD tip.
Results: In patient-specific LA models, RDs always anchored to large fibrotic patches or their border zone (BZ). In Utah 4 patients, RDs anchored to specific locations within fibrotic patches. In Utah 3 patients, RDs typically anchored at the BZ between fibrotic patches and healthy tissue. In Utah 2 patients, RDs either moved near small fibrotic patches or anchored around PVs. The probability maps identified target areas of RD localization, which were much smaller than the entire fibrotic areas. These maps were then used to terminate AF by applying linear ablation lesions through the predicted target areas.
Conclusion: RDs typically anchor to large fibrotic patches in the LA, which enables the creation of patient-specific RD location maps – ablation targets.

50-POS Board 50

ELECTROPHYSIOLOGY SIMULATIONS OF FEMALE AND MALE HUMAN VENTRICLES: INFLUENCE OF GENDER PHENOTYPE AND ENDOCARDIAL ANATOMY ON SIGNAL PROPAGATION

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Human ventricles have a complex endocardium, characterised by trabeculations and false tendons. The latter are thin chord-like structures that interconnect different left ventricular endocardial areas forming conduction short-cuts. Their position and amount vary from heart to heart. Fundamental gender differences are found in cardiac electrophysiology, as female hearts present reduced repolarization resources. The diversity in heart anatomy and electrophysiological characteristics may lead to different conduction patterns within female and male hearts.
In this study we aimed at analysing both gender phenotype and anatomical influence on signal propagation and activation patterns in one female and one male human biventricular geometries.
Anatomically detailed geometries were reconstructed from ex-vivo human hearts high-resolution MRI. Human gender phenotypes were modelled incorporating into the O'Hara-Rudy model changes to ion channels conductances and conduction velocities listed in Yang et al. 2012. Myofibers were generated with a rule-based model.
Four electrophysiology simulations were run, applying the two phenotypes to both hearts, to assess separately the influence of both gender phenotype and male/female geometry.
Initial endocardial activation was simulated using Durrer isochrones and electrophysiology simulations were carried out with the *MareNostrum4* supercomputer, using the multi-physics, HPC solver *Alya*. To the best of our knowledge, it is the first time that anatomically detailed human heart geometries addressing gender-based characteristics are being used for electrophysiology simulations.
Results reflect the sex-based phenotype defined on the single cell model: action potential prolongation was observed in female heart in comparison to the male one.
The existence of the false tendons shortcutting the anatomy determines different patterns of activation of the myocardium, which also depend on the location of the initial activation points.
Anatomical and gender-based differences in human hearts anatomy and arrhythmogenesis can be further explored with the models described here.

53-POS Board 53

SPONTANEOUS CALCIUM RELEASE IS PROMOTED BY INWARD RECTIFIER CURRENT DOWNREGULATION IN A NOVEL MODEL OF RAT VENTRICULAR ELECTROPHYSIOLOGY

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Irregular intracellular calcium (Ca^{2+}) handling in diseases such as heart failure (HF) predisposes to lethal ventricular arrhythmias and sudden cardiac death. The underlying mechanisms for these processes are difficult to explore experimentally, yet recent data from our laboratory suggests that reduced inward rectifier current (I_{K1}) expression in failing rat myocytes is associated with increased pro-arrhythmic spontaneous Ca^{2+} release. However, we have been unable to use existing computational models of rat cardiac electrophysiology to explore the hypothesis that this spontaneous activity results from increased sarcoplasmic reticulum (SR) loading in the presence of a destabilised membrane.

A new computational model was therefore developed by the integration of a recent rat ventricular electrophysiology model with a novel model of stochastic spatio-temporal Ca^{2+} handling dynamics developed in our laboratory. Our newly-developed model was used to dissect and quantify the electrophysiological changes associated with I_{K1} current and subsequent Ca^{2+} homeostasis remodelling in HF. A similar reduction in I_{K1} to that observed experimentally resulted in a 57% increase in action potential duration (APD) in our simulations, from 58.1 to 91.4 ms. This prolonged APD allowed for greater SR loading, leading to increased $[Ca^{2+}]_{SR}$ and more frequent spontaneous release events. These, in turn, triggered forward-mode sodium-calcium exchange, resulting in triggered action potentials. Resting membrane potential was also depolarised by 3.3 mV in HF myocytes in our simulations.

The newly-developed model has reproduced experimental findings from the laboratory and provided insight into the mechanisms of spontaneous Ca^{2+} release in HF. Such a model provides a platform for future investigations into how sub-cellular remodelling in HF may promote arrhythmogenesis at the tissue and organ levels.

56-POS Board 56

A COMPUTATIONAL CROSS-BRIDGE MODEL TO HELP EXPLAIN THE FREQUENCY-DEPENDENT STIFFNESS RESPONSE OF CA^{2+}-ACTIVATED HUMAN MYOCARDIAL STRIPS

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Sinusoidal analysis has been used for almost 50 years to study the mechanical properties of striated muscle. In brief, small sinusoidal length perturbations are applied by a motor at one end of the muscle and the force response is measured at the other end. This stress-strain response is separated into components that are in phase (the elastic response) and 90° out of phase (the viscous response) with the length perturbation. The frequency-dependent stiffness response is created by repeating sinusoidal perturbations over a range of frequencies; plotting the viscous moduli against the elastic moduli creates a Nyquist plot. We used sinusoidal analysis to characterize chemically permeabilized human myocardium from organ donors (n=6 hearts and n=24 strips in total) under maximally activated conditions (pCa=4.8) at physiological temperature (37°C). Low frequency data points between ˜1-3 Hz showed negative viscous moduli, thereby representing active muscle power output. Frequencies greater than 3 Hz showed positive viscous moduli due to the muscle absorbing power. A number of research groups have contributed to the current understanding of Nyquist plots in muscle biophysics, and the cross-bridge theory underlying these work producing and work absorbing transitions. Here we performed new computational simulations using MyoSim software (http://www.myosim.org) to predict the mechanical properties of striated muscle and probe the transition rates and distributions of attached cross-bridges. Sinusoidal perturbations were simulated by changing muscle length in silico and the associated force responses were used to calculate the Nyquist plot. Rate constants defining the transitions between cross-bridge states and stiffness of the sarcomere were adjusted to optimize the fit between experimental and simulated Nyquist data. These simulations suggests that a three-state cross-bridge model with strain-dependent attachment and detachment kinetics can explain many features of the frequency-dependent mechanical response in human myocardium.

59-POS Board 59

INTERACTIVE ELECTROPHYSIOLOGY SIMULATOR TO STUDY OPTIMAL ABLATION PATTERNS IN ATRIAL FIBRILLATION

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Background: Atrial fibrillation (AF) is caused by ectopic firing and/or re-entrant drivers (RDs) in the atria. Catheter ablations aim to restore sinus rhythm by destroying these abnormal circuits, but have limited success rates. Recently, it has been proposed that ablating the sources of the RDs may improve the efficacy of ablation procedure. It is controversial, however, whether RDs can be identified using *in vivo* electrograms and, if so, what the optimal ablation strategy for destroying them would be.
In this study, we create an interactive electrophysiology simulator to determine the best strategies for ablating AF in different scenarios.
Methods: The simulator was created in Matlab, using the isotropic (diffusion coefficient D = 0.12 mm^2/ms) monodomain equation with an atrial Fenton-Karma model, in a 7x7 cm^2 tissue, with homogeneous properties and Neumann boundary conditions. Electrographic signals were also computed. We considered scenarios in: a) baseline; and for tissue with: b) fibrotic (low D) patches and c) circular openings mimicking the pulmonary veins (PVs). Ablation lesions (D=0, 5-mm diameter) were interactively created by the user in real-time.
Results: We found that RDs tended, in general, to anchor around fibrotic patches or the PV openings. It was not possible to identify RDs unequivocally from electrographic signals or properties thereof, due to signal blurring.
Point-wise ablation lesions led, in general, to pinning of the RDs around them. Linear ablations terminated RDs by: 1) joining the tips of RDs with opposite chiralities; 2) partitioning the tissue into regions smaller than the rotor wavelength; or 3) guiding the RDs to the boundary of the tissue.
Conclusions: The interactive simulator is a useful tool to study different ablation scenarios. Similarly to what is observed in clinical practice, point-wise ablations had limited success, but guiding RDs to unexcitable boundary layers was highly effective.

62-POS Board 62

ADJOINT BASED PERSONALIZATION OF MECHANICAL MODELS FOR QUANTIFICATION OF RIGHT VENTRICLE FAILURE IN PULMONARY HYPERTENSION.

Henrik FInsberg[1], Martin Genet[2], Ce Xi[3], Ju Le Tan[4], Liang Zhong[4,5], Lik Chuan Lee[3], **Samuel Wall**[1]
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Individualized analysis of cardiac mechanics offers promise for improved diagnosis and treatment of patients. However, while detailed models and constitutive laws accurately describing myocardial behavior exist, efficiently fitting these models to data is made difficult by the number of interacting parameters that are often needed. Although numerous techniques, from trial and error to advanced optimization, can be used to fit data, challenges still exist, often due to the computational requirements when many control parameters are needed.
Here we discuss the use of adjoint methods as an attractive, efficient means to rapidly assimilate large data sets into personalized models of cardiac mechanics. These adjoint-based optimization techniques allow us to fit models at a cost that does not significantly depend upon the numbers of parameters to be fit, and thereby provide an excellent means to assimilate high dimensional parameter spaces at a relatively low computational cost. These methods are enabled by the new generation of software tools that automatically create physical models and derive adjoint equations for problems of interest.
We test this method in the clinical case of pulmonary hypertension. For a cohort of healthy and hypertensive patients, we use an efficient pipeline to create biventricular models directly from medical imaging, and assimilate strain data and pressure measurements. The parameterized mechanical models exhibit clear differences in active and passive properties of the myocardium correlating to the progression of the disease, and may have diagnostic use in clinical applications.

65-POS Board 65

SHORT TERM CARDIAC MEMORY IS STORED IN ION CHANNELS KINETICS AND INTRACELLULAR CALCIUM CYCLING: A RESTITUTION STUDY ON A MODEL OF HUMAN VENTRICULAR AP

Massimiliano Zaniboni
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Electrical restitution (ER) describes the dependence of cardiac action potential duration (APD) from the previous beat, when this is at its steady state (classical ER) or not (dynamic ER). Restitution can be described for other beating features, like the amount of calcium entering the cell during a cycle (Cai).
The dependence, under dynamic conditions, of APD not only from the previous, but from a given number of preceding beats has been related to short term memory (STM). Despite its relevance for the onset of arrhythmias, an univocal definition of STM is lacking. By means of simulations on a human ventricular AP model, I define STM, based on the ER or CaR (restitution of Cai) properties measured under dynamic pacing. STM reflects the phase shift between the dynamics of APD (or Cai) and that of cycle length (CL) or diastolic interval (DI) and can be predicted from the hysteretic behavior of their restitution curves.
In the simplified case of a pacing CL changing sinusoidally within a range (clv) around a value (CLst) and with a given angular velocity (omega), dynamic restitution describes whether there is a phase shift (Ph) between beat-to-beat changes in CL (or DI) and APD (or Cai) and the extent of it. $Ph_{CL,APD}$ (and $Ph_{CL,Cai}$) are always greater than $Ph_{DI,APD}$ (or $Ph_{DI,Cai}$) and proportional to omega-increase and CL-decrease. Results with random pacing and with two additional AP models have been simulated.
In conclusion, STM compactly represents dynamic properties of cardiac excitability at high pacing rate, of interest for better understanding a variety of pathological states, like the latent instability of repolarization in LQT1 syndrome, which has also been simulated.

THURSDAY, SEPTEMBER 6
POSTER SESSION III
13:30 – 14:50
Building 84 Foyer

All posters are available for viewing during all poster sessions; however, below are the formal presentations for Thursday. Presenting authors with odd-numbered poster boards should present from 13:30 – 14: 10 and those with even-numbered poster boards should present from 14:10 – 14:50. The presenters listed below are required to remain in front of their poster boards to meet with attendees.

Buran, Pavel	**3-POS**	**Board 3**
Clancy, Colleen	**6-POS**	**Board 6**
del Álamo, Juan	**9-POS**	**Board 9**
Fabbri, Alan	**12-POS**	**Board 12**
Gmach, Philipp	**15-POS**	**Board 15**
Hatano, Asuka	**18-POS**	**Board 18**
Hussaini, Sayedeh	**21-POS**	**Board 21**
Jacqueline, Maxandre	**24-POS**	**Board 24**
Laasmaa, Martin	**27-POS**	**Board 27**
Lewalle, Alexandre	**30-POS**	**Board 30**
Longobardi, Stefano	**33-POS**	**Board 33**
Mendonca Costa, Caroline	**36-POS**	**Board 36**
Grandi, Eleonora	**39-POS**	**Board 39**
Pires, Ricardo	**42-POS**	**Board 42**
Radocaj, Ante	**45-POS**	**Board 45**
Ruben, Peter	**48-POS**	**Board 48**
Seemann, Gunnar	**51-POS**	**Board 51**
Strocchi, Marina	**54-POS**	**Board 54**
Vagos, Márcia	**57-POS**	**Board 57**
Varghese, Anthony	**60-POS**	**Board 60**
Whittaker, Dominic	**63-POS**	**Board 63**
Campbell, Stuart	**66-POS**	**Board 66**

Posters should be set up the morning of September 4 and removed by noon September 7.

3-POS Board 3

MECHANISM OF UNDERDRIVE PACING FOR LOW-ENERGY DEFIBRILLATION

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Rotating excitation waves and electrical turbulence in cardiac tissue are associated with arrhythmias such as life-threatening ventricular fibrillation. Experimental studies have shown that a sequence of low-energy electrical far-field pulses is able to terminate fibrillation more gently than a single high-energy pulse. During this low-energy antifibrillation pacing (LEAP), only tissue near sufficiently large conduction heterogeneities, such as large coronary arteries, is activated. Theoretical approaches to understand LEAP have often focussed on unpinning and removal of a small number of stable spirals and suggest LEAP protocols using overdrive or underdrive pacing or combinations of it. We demonstrate that for typical cellular models, which exhibit stable pinned spirals, the process of unpinning and drift of spirals does not appear during successful LEAP. We present an alternative mechanism of underdrive pacing, which explains both the termination of stable spirals and spatiotemporal chaos. This mechanism relies on the fact that the optimal pacing period is related to the mean cycle length of the transmembrane potential for spirals and electrical turbulence, respectively. It turns out that this cycle length is increased by the applied electrical field.

[1] Luther et al. Nature 2011.

6-POS Board 6

USING ATOMISTIC MODELING AND SIMULATION TO SEARCH FOR THE MOLECULAR MECHANISMS OF DRUG-INDUCED ARRHYTHMOGENESIS VIA HERG BLOCKADE

Kevin R DeMarco[1,3], Igor Vorobyov[1,2], Aiyana M Emigh[1,3], Slava Bekker[4,1], John Dawson[1,3], Vladimir Yarov-Yarovoy[1], **Colleen E Clancy[1,2]**
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The cardiac voltage gated potassium channel encoded by the human Ether-à-go-go-Related Gene (hERG), is responsible for a major repolarizing potassium current I_{Kr} in ventricular cardiomyocytes. The hERG channel transitions between distinct states and possesses unique gating properties, such as fast inactivation at depolarized potentials. It is also infamous for promiscuously interacting with a diverse set of drug molecules, which can attenuate I_{Kr}. Drug-induced hERG blockade can lead to an acquired long QT syndrome, often associated with potentially deadly arrhythmias. QT prolongation is a major reason that drugs are abandoned during development or withdrawn from the marketplace. However, not all hERG blockers are pro-arrhythmic, but the underlying mechanisms that relate hERG blockade to a prolonged QT interval remain unknown. Multi-scale modeling studies performed by our laboratory have indicated that the state-dependence of drug-induced hERG block may be a significant factor in cardiac safety. Here we used a combination of atomistic structural modeling and molecular dynamics (MD) simulations to investigate possible molecular mechanisms of such dependence. We used recently published cryo-EM hERG and closely related EAG1 channel structures to develop models of open and closed hERG states using Rosetta computational modeling software. We tested the stability of those models and investigated the structural determinants of the channel conduction and gating using multiple multi-microsecond MD simulations. Furthermore, we studied the interactions of the hERG channel in several conformational states with drugs of different pro-arrhythmia proclivities using molecular docking as well as MD simulations. We developed and validated accurate atomistic structural models of those drugs in different ionization states, which allowed us to identify hERG state-specific drug binding sites, entry and egress pathways and also estimate their binding affinities. These data will be used to fine-tune our functional models for predicting drug pro-arrhythmia risks and developing safer pharmaceuticals.

9-POS Board 9

HIGH-THROUGHPUT METHOD FOR QUANTIFICATION OF FORCE GENERATION AND STIFFNESS OF IPS DERIVED CARDIOMYOCYTES

Ricardo Serrano[1], Wesley L McKeithan[2], Mark Mercola[2], **Juan C del Álamo**[1]
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Cardiovascular disease is the leading cause of death in the U.S. and the rest of the World. Physiological assays with iPSC-cardiomyocytes have been quickly adopted for cardiac drug discovery, most commonly, focusing in the characterization of the action potential and calcium transient kinetics. However, high-throughput assays that measure cardiomyocyte contraction and relaxation kinetics are less prevalent. Furthermore, there are no high-throughput methods to quantify cardiomyocyte force generation and cell stiffness changes simultaneously during a cardiac cycle. We present a method to measure the mechanical tension exerted by cardiomyocyte monolayers as well as their elastic modulus. Our method is solely based on optical measurements, removing the necessity of using an external probe in contact with the cells. In our experimental setup, iPSC-cardiomyocytes were seeded on a deformable substrate embedded with fluorescent beads. In addition, the membrane of the cells were live stained with fluorescent-labeled wheat germ agglutinin (WGA). We acquired high framerate image sequences of the cell membrane dye and the fluorescent bead signals. From the cell membrane dye movies, we measured the strain field and its variations during the cell cycle using image correlation techniques. From the beads channel, we calculated the traction stresses at the cell-substrate interface using Traction Force Microscopy, and the intracellular monolayer stress using Monolayer Stress Microscopy. We developed a method to measure the elastic modulus of the cells by fitting the relationship between the measured intracellular stress and strain maps. As proof of concept, we tested our method with experimental recordings of monolayers of iPSC-cardiomyocytes treated with a series of benchmark compounds. To our knowledge, this work represents the first high-throughput assay for simultaneous force and stiffness characterization in iPSC-cardiomyocytes.

12-POS Board 12

EXPLORING THE EFFECT OF IK1 MODEL STRUCTURE ON ACTION POTENTIAL WAVEFORM OF SIMULATED HUMAN INDUCED PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES

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Human induced pluripotent stem cell-derived cardiomyocytes (hiPS-CM) are a promising tool for drug screening, however their immature electrophysiological phenotype negatively affects their predictive reliability. Injection of simulated I_{K1} current through the dynamic clamp technique brings the hiPS-CM action potential (AP) closer to the human adult ventricular AP. Several I_{K1} mathematical models have been published that differ in the equations adopted to describe the current's time-dependence and rectifying behavior. It is expected that the choice of I_{K1} model has an important effect on dynamic clamp experiments with hiPS-CM.
In this study we assess the effects of 6 different I_{K1} formulations (Bett2013, Ishihara2009, Dhamoon2004, Ma2011, O'Hara2011 and tenTusscher2004) on the AP waveform of the ventricular hiPSC-CM computational model (Paci2013), in order to optimize dynamic clamp experiments on hiPS-CM.
First, the minimum value of G_{K1} that leads to a stable, hyperpolarized Resting Membrane Potential (RMP), $G_{K1,Critical}$, was found for each I_{K1} formulation. Next, the behavior of the hiPSC AP model was assessed by upscaling G_{K1} up to 10 times $G_{K1,Critical}$ and pacing the cell at 1 Hz. The changes in AP waveform were quantified by evaluating the RMP and Action Potential Duration at 90% of repolarization (APD_{90}).
We evaluate the performance of all six models by comparing the simulated results to published experimental data by Britton 2017, before selecting the model with the closest match for use in future dynamic clamp wet lab experiments. Simulations show that the upscaling of G_{K1} leads to a shortened APD_{90} and a hyperpolarized RMP. Simulated RMP (RMP_{min}=-88.2 mV, RMP_{max}=-72.1 mV) were close to experimental data in all the models, whereas I_{K1} from O'Hara2011 shows the APD_{90} range (APD_{90sim}=[234-528] ms) closest to experimental data (APD_{90exp}=[200-500] ms).

15-POS Board 15

ADRENERGIC RECEPTOR LOCALIZATION AND DYNAMICS IN CARDIOMYOCYTE T-TUBULES

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The plasma membrane of the adult cardiomyocyte (CM) t-tubules (TT) has been characterised as a cellular compartment giving rise to a spatially heterogeneous adrenergic second messenger signal (cAMP). In particular, ß1 and ß2 adrenergic receptors display diffuse and spatially localized cAMP waves respectively. In heart failure, the ß2-AR cAMP compartmentalization has been observed to fade.
Since the signaling mediated by the two AR has been demonstrated to play opposite roles in heart failure (HF), the problem has a marked clinical relevance. It is still unclear what could be the mechanism restricting ß2-AR diffusion in the TT and what is the interplay with the evolving TT morphology in heart failure.
We plan to address these open questions by using advanced fluorescence spectroscopy approaches to characterize receptor diffusion along the TT network and put this information in relation to the local TT morphology.
Our results demonstrate our ability to selectively label endogenous ß1 and ß2-AR in adult CM and extract their diffusion coefficient and concentration using fluorescent ligands (in collaboration with S. J. Hill, from the University of Notthingham). When coupled with the possibility, offered by confocal microscopes, to selectively target a region of the plasma membrane and TT network, this makes it possible to quantitatively compare ß1 and ß2-AR dynamics at the individual TT level.

18-POS Board 18

A CARDIOMYOCYTE MODEL COUPLING ELECTROPHYSIOLOGY, METABOLISM, AND MECHANICS INTEGRATING STOCHASTIC MYOSIN HEAD ROTATION

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The mechanisms of force development by actin-myosin interaction activated by Ca^{2+} are complex and yet controversial. It is experimentally shown that Ca^{2+} has a large intracellular gradient, higher at the sub-membrane and Z-line surroundings. Most of the proposed actin-myosin models refer to the averaged Ca^{2+} concentration in reproducing force-Ca^{2+} relationships, but because of high sensitivity and large gradient of Ca^{2+}, in-situ actin-myosin states might be highly inhomogeneous. We hypothesized that this inhomogeneity of Ca^{2+} could partly explain controversies over the steepness of force-Ca^{2+} relation.
Because of sarcomere-length sensitivity, microscopic actin-myosin interactions become coupled problem with macroscopic myofibril contraction, together with Ca^{2+} control and metabolisms. We have previously developed a model of cardiomyocyte integrating electrophysiology, metabolisms, and mechanics with 3D subcellular structure, which could reproduce local Ca^{2+} concentrations and delayed Ca^{2+} propagation in myocyte with deleted t-tubule. We extended our cardiomyocyte model incorporating the stochastic behavior of the myosin heads in the cooperative cross-bridge formation and the strain-dependent head rotations. Three myofibrils of half sarcomere length were modeled. A half sarcomere of a myofibril was transversely divided into 64 segments. Each segment spans between Z-line and M-line, contains thin and thick filaments equivalent to its transverse cross section. Troponin and tropomyosin units (T/T unit) and myosin heads are arranged at regular intervals on thin and thick filament respectively, therefore about 100,000 T/T units and myosin heads were modeled in total. Three state T/T unit model and five state myosin head model were simulated by Monte-Carlo method.
The results showed that the segment at the outside of a myofibril generates about twice larger force than the segment at the core. The developed force varied, and the area of larger force development co-localized within several segments and shifted from a myofibril to others during a beat.

21-POS Board 21
COMPUTATIONAL STUDY OF OPTOGENETICS IN MOUSE HEART

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Applying conventional treatments for cardiac arrhythmias such as electrical shocks and implantable cardioverter defibrillator (ICDs), have some disadvantages including tissue damage, intolerable pain, and requiring high energy. That's why, scientists are trying to use a new technique called optogenetics as an alternative method which is free of these side effects. Optogenetics is a new technology that enables selective photo-optical stimulation of the heart, whereby via light-sensitive ion channels electrophysiological and functional control of spatiotemporal excitation dynamics is achieved. Therefore, computational modeling can be of specific interest to predict changes in cardiac action potentials due to photo-optical stimulation and to optimize the application of optogenetic tools in cardiac defibrillation research. In this study, we successfully implemented the light-activated ion channel, Channelrhodopsin-2 (ChR2), in an ionic model of murine ventricular cardiomyocytes (Bondarenko model). Then we evoked the cell via light with different frequencies and compared the behavior of action potential with electrical stimulation. We observed similar morphology of action potential with both photo and electrical stimulation which confirms the ability and accuracy of the light-sensitive model. After that, we investigated the behavior of ChR2 current behavior by applying different light intensities and pulse durations. By applying enough pulse duration we saw ChR2 current has a fast peak with relaxation to a steady-state component and finally decaying to basal phase. We also observed, as we expected, ChR2 current is increased by enhancing light intensities. Ongoing work includes extending this single cell model into two dimensions, applying ventricular tachycardia (VT- a type of cardiac arrhythmias) to the domain and then try to annihilate it with different light intensities. All results will be discussed in comparison to the conventional electrical stimulation.

24-POS Board 24

COMBINED SIMULATION AND EXPERIMENTATION TO PREDICT THE ELECTRICAL RESPONSE OF ENGINEERED HEART TISSUE TO THE ADDITION OF DRUGS

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To design heart tissue with the appropriate properties, a myriad of features must be specified, for example, the number, type and ratio of the constituent cells, and their biochemical, mechanical and electrical stimulation. Mathematical modelling and computational simulation of human induced pluripotent stem-cell (hiPSC)-derived engineered heart tissue can help identify optimal design specifications. Specifically, we will establish a model-guided approach for designing hiPSC-derived heart tissue that recapitulates the electrical and mechanical properties of a human heart. As part of this endeavour, we will validate the theoretical model of the tissue by verifying that simulations reproduce experimental behaviour under normal conditions as well as when drugs are administered. The validated model will then be used to determine the tissue design specifications that optimise for selected tissue biomarkers.
In this study, we focus on the electrophysiology of engineered heart tissue. We model the electrical propagation within a two-dimensional tissue made of both atrial-like (AL) and ventricular-like (VL) hiPSC cardiomyocytes by combining the bidomain model (Tung, 1978) with the Paci *et al.* (2013) model of the electrophysiology of both AL and VL cells. We investigate *in silico* the electrophysiological effects of the administration of 16 drugs on the tissue using a model framework developed by Bowler (2018). We simulate the effects of drug administration by scaling the ion channel conductance in the cell-level model according to the inhibitory profile reconstructed using IC50 values (Mirams *et al.*, 2011). We compare the predictions of the theoretical model to experimental observations for biomarkers such as the field potential duration change between control and drug-perturbed experiments.

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27-POS Board 27

THE ABSENCE OF ACTIVE CREATINE KINASE SYSTEM INFLUENCES CARDIAC CALCIUM HANDLING

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Creatine kinase (CK) system is known as a high-energy phosphoryl buffering and transfer system between mitochondria and ATPases. Functional coupling between CK and adenine nucleotide translocase, ATPases, and ATP-sensing potassium channel, has been demonstrated suggesting a major role of CK system in heart. To study CK system role, we used two lines of creatine-deficient mice, which lack either guanidinoacetate methyltransferase (GAMT) or arginine-glycine amidinotransferase (AGAT) on creatine synthesis pathway. Intriguingly, there have been no significant adaptations to the absence of active CK system in GAMT and AGAT mice cardiomyocytes from bioenergetics perspective: mitochondrial arrangement, respiration kinetics, activities of alternative pathway enzymes, intracellular compartmentation are the same in wild-type (WT) and knock-out (KO) littermates. Using whole-cell patch clamp, we studied how the absence of CK system influences calcium handling in cardiomyocytes of AGAT KO and WT littermates. Voltage dependence of L-type calcium channel (LTCC) current was significantly different in KO and WT animals with the significant differences between sexes within groups. LTCC amplitude was influenced by the absence of CK system only in female mice in control conditions but was found to be the same in KO and WT male mice and mice of both sexes after adrenergic stimulation. The absence of active CK system had a major impact on calcium uptake, with the KO mice requiring more time for reducing calcium concentration to the resting level at the lower uptake rates. The effects of the active CK system absence on LTCC and calcium uptake, presumingly mainly by SR calcium ATPase, were fully reversed by creatine feeding to the KO animals. Our results suggest that there is a major role of CK system in providing energy to excitation-contraction machinery in the heart to maintain normal calcium homeostasis.

30-POS Board 30

MULTI-SCALE MODELLING OF ANTHRACYCLINE CARDIOTOXICITY IN HEART CONTRACTION

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The anthracycline family of chemotherapeutic drugs have well-known cardiotoxic side effects. However, decades of research have yielded a piece-wise picture of cardiotoxicity that remains to be integrated. Data-driven computational modelling provides a framework for simulating and analysing the mechanisms that collectively govern cardiac function, and hence for investigating the impact of drug exposure on specific physiological parameters in drug-induced heart failure. We developed a multi-scale computational model of the heart to simulate features of the cardiac cycle that are measured in the routine clinical treatment of cancer patients. The model implements mechanisms ranging from the cellular to the whole heart level, reproducing cardiac behavior under physiological conditions. An externally imposed signal generates contraction forces throughout the tissue, eliciting a viscoelastic deformation of the anatomy and the ejection of blood into the circulation. The model parameters are amenable to fitting using direct measurements or data available in the literature.
We compared heart-failure patients receiving anthracycline treatment, with healthy controls. For both groups, cardiac anatomy (left-ventricular (LV) cavity dimensions, wall thickness) and LV ejection fraction were characterised using echocardiography measurements. Hemodynamic measurements yielded maximum ejection pressures and heart rates. Biopsies taken from the heart-failure patients provided measurements of collagen volume fraction and underwent a proteomic analysis by mass spectrometry. We used the mechanical simulations to identify emerging correlations between the micro- and tissue-scale phenotypes and global cardiac functionality between the cohorts.
Simulation results suggest that a tissue-stiffness increase by at least 150% reproduces the phenotype changes between average healthy and cardiotoxic patients. This relative increase is comparable to the observed increase in collagen fraction, consistent with a passive mechanical cause of heart failure. Using proteomics analyses of the patient biopsies, we then consider the variations in relevant protein abundances in the light of the collagen hypothesis.

33-POS Board 33

A VIRTUAL DRUG DEVELOPMENT FOR THE RECOVERY OF A HEART FAILING RAT WITH PRESERVED EJECTION FRACTION CONDITION INDUCED VIA TRANSVERSE AORTIC CONSTRICTION

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Heart failure (HF) is a cardiovascular disease responsible for one of the highest figures of hospitalisations and morbidities. HF can be accompanied by a diastolic disfunction, where the heart retains the ability to contract preserving the ejection fraction (HFpEF), but cannot relax properly. At present, there is no treatment for HFpEF. Transverse aortic constricted (TAC) rats are used as an experimental animal model for HFpEF. Here we develop a mathematical model of the TAC rat heart to predict drug targets that recover the ventricular function. We combined previously developed models of cellular electrophysiology and calcium dynamics, sarcomere contraction and whole-organ mechanics derived from control and TAC rat hearts. Cardiac function was characterised by 9 phenotypes: ejection fraction, contraction time, ejection time, relaxation time, diastolic time, peak pressure, time to peak pressure, maximum rates of pressure rise and decay. Performing a sensitivity analysis over 11 model parameters corresponding to the current densities across the main sarcolemmal and sarcoplasmic ion channels and pumps, allowed us to determine which proteins could be targeted by drugs to revert the organ-scale phenotypes back from the TAC rat heart model to the control one. The control and TAC models had an ejection fraction of 56.56 % and 56.54 % respectively, while the remaining 8 phenotypes had mean percentage variations of 13 % in absolute value between the two models. The sensitivity analysis identified five proteins as the most significant across the organ-scale phenotypes: L-type calcium channel, transient outward and inwardly rectifying potassium channels, sarcolemmal and sarcoplasmic calcium pumps. We have developed a framework for predicting drug targets and required effects for treating HFpEF in a pre-clinical animal model.

36-POS Board 36

INVESTIGATING THE ROLE OF LEFT VENTRICULAR LEAD LOCATION IN ARRHYTHMOGENIC RISK IN INFARCT PATIENTS UNDERGOING CARDIAC RESYNCHRONIZATION THERAPY

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Introduction
Cardiac Resynchronization Therapy (CRT) is an effective treatment for heart failure. However, it may be arrhythmogenic in infarct patients depending on pacing location, with pacing near a scar associated with higher arrhythmogenic risk. We used computational models of patient-specific anatomy to investigate the role of pacing location on repolarization characteristics, which may be associated with arrhythmias.

Methods
LGE-MRI were acquired from 11 infarct patients undergoing CRT. Left ventricular (LV) wall, infarct scar and border zone (BZ) were semi-automatically segmented. A finite element (FE) mesh of tetrahedral elements was generated representing healthy, scar and BZ tissue. Fiber orientations were assigned to the mesh using a rule-based method. Activation and repolarization sequences were computed using a Reaction-Eikonal model. The models were assigned experimentally measured values of conduction velocity (healthy and BZ), with the BZ modelled with slow and isotropic velocity and scar modelled as an insulator. Propagation was initiated at different distances from the scar.

Results
Simulations show the presence of large repolarization gradients (10 mm) around the scar, particularly at the BZ and around the pacing site. The volume of tissue around the scar with high gradients (larger than 3 ms/mm), relative to the total LV volume, is affected by pacing location. Pacing near (5 mm) the scar leads to a 1.7 times larger volume on average than pacing away (45 mm) from it. The repolarization gradients around scar also depend on fiber orientation relative to the orientation of the scar, conduction velocity and wavefront curvature. Pacing near the scar parallel to the fiber orientation and perpendicular to the scar orientation leads to the largest volume of high gradients.

Conclusions
Increased volume of high repolarization gradients around the scar when pacing near it may explain the increased arrhythmogenic risk associated with CRT in infarct patients.

39-POS Board 39

POPULATIONS OF IN SILICO MYOCYTE MODELS REVEAL SYNERGY OF MULTI-ATRIAL-SPECIFIC K^+ CURRENT BLOCK IN ATRIAL FIBRILLATION

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The development of effective and safe pharmacological antiarrhythmics against atrial fibrillation (AF) remains an important unmet clinical need. Recently, both atrial-predominant and multi-channel block emerged as promising strategies for AF therapy. Atrial-specific channel block may enable antiarrhythmic effects while avoiding unwanted cardiotoxic consequences, namely ventricular arrhythmia. Multi-channel block has been suggested to produce synergistic anti-AF effects. We tested the hypothesis that combined block of multiple atrial-selective K^+ currents (ultra-rapid delayed rectifier K^+ current, I_{Kur}, small conductance Ca^{2+}-activated K^+ current, I_{KCa}, and $K_{2P}3.1$ 2-pore-domain K^+ current, I_{K2P}) produces synergistic action potential duration (APD) prolongation in human atrial myocytes *in silico*. Two of our previously developed computational models of human atrial cell electrophysiology were extended to incorporate models of I_{KCa} and I_{K2P}. To account for inter-subject electrophysiological variability and minimize model and parameter dependence of simulation results, we used the population-based approach with experimental calibration proposed by the Sobie group. AF-induced remodeling was simulated by including reported changes in atrial electrophysiology. In particular, we considered various alterations of I_{Kur}, I_{KCa} and I_{K2P} in AF myocytes based on published experimental studies. Simulations of one-dimensional strands of atrial tissue were performed to quantify effects of blocking the three currents on atrial wavelength. We evaluated synergistic effects by combined block through linear statistical contrast analyses. Our results show that when paced at 1Hz, partial block (50%) of atrial-specific K^+ currents individually produced APD prolongations in AF-remodeled myocytes and wavelength prolongations in tissue. These effects were greater in the combined block condition. At 3Hz, simultaneously partially inhibiting these K^+ currents exerted significant synergistic APD and wavelength prolongations. Our study suggests that combined block of atrial-predominant K^+ currents may be a valuable strategy for pharmacological antiarrhythmic management of AF.

42-POS Board 42

THE ROLE OF EPHRIN-A1 IN THE MECHANOBIOLOGY AND DIFFERENTIATION OF HUMAN CARDIOMYOCYTES

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Motivation. Recent studies suggest that manipulation of Eph/ephrin cell signaling can favorably influence cardiomyocyte viability and ultimately preserve cardiac function after myocardial infarction. Currently, several clinical trials are making use of induced pluripotent stem cells (iPSC), and iPSC-derived cardiomyocytes as part of a therapeutic strategy to promote the treatment of patients with heart failure. It has been suggested that the Eph/ephrin system may play a role in the process of cell differentiation of cardiac stem cells. However, the exact role that Eph receptors and ephrins play in myocardium repair is still not understood.
Methods. Here we introduce real-time deformability cytometry (RT-DC) to study the process of cardiomyocyte differentiation in the presence of ephrin-A1. RT-DC analyses cell mechanical properties as a label-free functional cell assay at a throughput of 1,000 cells/second. Using phase contrast video microscopy coupled to a custom developed algorithm that extracts dynamic properties from the beating pattern of cardiomyocytes we demonstrate that our assay is capable to trace specific mechanical phenotypes of cardiac progenitor cells (CPC), immature cardiomyocytes (iCM) and mature cardiomyocytes (mCM). We link these phenotypes with immuno-fluorescence data and RNA expression analysis of different members of the Eph/ephrin system.
Results. Our data shows that mRNA levels for the A-type Eph receptors are typically higher in mCMs relatively to CPCs. Ephrin A1 induces up-regulation of cardiomyocyte-specific markers during differentiation of CPCs into iCMs. In iCMs such changes correlate with decrease in the cells elastic modulus. Similar effects on mechanical properties are also observed in mCMs with no apparent impact on mCM contractility. These effects are not present in proliferating CPCs.
Conclusions. We were able to assign ephrin-A1 a direct role in enhancing the expression of cardiomyocyte-specific genes and in lowering the elastic modulus of cardiomyocytes during and after their differentiation.

45-POS Board 45

STOCHASTIC BURST-LIKE TRANSCRIPTION OF MUTANT AND WILDTYPE MYH7-ALLELES AS POSSIBLE ORIGIN FOR OBSERVED CELL-TO-CELL CONTRACTILE AND TRANSCRIPTIONAL IMBALANCE IN HYPERTROPHIC CARDIOMYOPATHY

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Hypertrophic Cardiomyopathy (HCM) has been related to different mutations mostly located in sarcomeric proteins. Between cardiomyocytes isolated from tissue of heterozygous HCM patients with identified missense mutations we found substantial variability in mRNA count and ratio of mutant/wildtype mRNA and a significantly larger variance of functional parameters as compared to cardiomyocytes from healthy controls. We proposed that this observed characteristic could be due to the mechanism of burst-like transcription where mutant allele and wildtype allele are activated and inactivated independently and stochastically. This hypothesis was strengthen by our observation that 27% of nuclei of cardiomyocytes of an HCM patient with mutation R723G in ß-myosin heavy chain (ß-MyHC-*MYH7*) showed no active transcription sites.
To test our hypothesis we developed a numerical model taking into account the expected polyploidy of cardiomyocytes estimated from nucleus sizes. The model is based on the Euler method and simulates (i) stochastic activation/inactivation of the mutant and wildtype *MYH7*-alleles, (ii) synthesis of pre-mRNA, (iii) splicing of pre-mRNA to mRNA and mRNA decay, and (iv) synthesis and decay of ß-MyHC protein. All synthesis and decay rate constants were taken from the literature. The only adjustable parameters of the model were the rate constants of activation/inactivation of transcription of the *MYH7*-alleles, and the splicing rate constant for generation of mRNA from pre-mRNA. From this we were able to fit the model to the observed percentage of cells without active transcription sites (step ii), to the observed mutant/wildtype mRNA distribution (step iii), and to the distribution of the observed shift in force-calcium relationship (step iv).
We conclude that independent stochastic burst-like transcription of mutant and wildtype alleles could indeed be a mechanism producing functional variability causing HCM-phenotype.

48-POS Board 48

ARRHYTHMOGENIC TRIGGERS IN HERITBLE CARDIAC CHANNELOPATHIES

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Voltage-gated sodium channels (NaV1.5) underlie phase 0 of the cardiac action potential. Mutations in the SCN5A gene that encodes NaV1.5 underlie potentially fatal arrhythmias, including Long QT Syndrome type 3 (LQT3) and Brugada Syndrome type 1 (BrS1). Some SCN5A mutations cause a disease phenotype that includes properties of both LQT3 and BrS1. Known as overlap or mixed syndrome mutations because they have both gain-of-function and loss-of-function properties, the sodium current recorded from the mutant channels has lower peak current density and increased persistent (late) current. The altered sodium current leads to an elongated ventricular action potential with a slower rise time and loss of the peak of phase 1. We studied the most common mixed syndrome mutant, E1784K, and found that it is more sensitive than wildtype NaV1.5, or some other sodium channel mutants, to temperature, extracellular pH, and cytosolic calcium. Incorporating our results into the Ohara-Rudy cardiac action potential model, we found that epicardial action potentials are lost at high heart rates. Further, our results led to a new, simplified model of sodium channel gating, the Peters-Ruben model, which successfully recapitulates both ionic and gating currents of wildtype and mutant channels, and incorporates the biophysical properties of activation, fast inactivation, and slow inactivation. Finally, we found that ranolazine, which is intended to reduce persistent sodium current and LQT3, is ineffective under conditions of high heart rate that include elevated cytosolic calcium, exactly when it may be most needed. Taken together, our results argue strongly for a personalized approach to cardiac health care that includes genotyping to identify the specific mutations underlying heart disease.

51-POS Board 51

EFFECTS OF CARDIAC TASK-1 CHANNELS IN SINUS RHYTHM AND ATRIAL FIBRILLATION: A COMPUTATIONAL STUDY

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Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia. A multitude of contributors to AF pathogenesis are identified, including structural, mechanical, and electric remodeling. Investigations in patients with sinus rhythm (SR) and AF identified the two-pore domain potassium channel TASK-1 as an important new player in the modulation of the atrial action potential (AP). In cardiomyocytes from patients with chronic AF, TASK-1 was significantly upregulated. TASK-1 upregulation was correlated with shortening of the AP by approximately 30%. In this work, we integrated pig TASK-1 data into a human atrial model and investigated the effects of TASK-1 on single cell AP and tissue properties.
The Courtemanche et al. human atrial electrophysiological model was extended by a previously published ion channel model of TASK-1. The density of the TASK-1 channel was set according to IV-relations measured in pig atrial myocytes in the following 7 settings: SR; SR + TASK-1 Inhibitor (complete block of TASK-1, SR-); SR + TASK-1 overexpression (approximately double TASK-1 expression, SR+); AF; AF + TASK-1 Inhibitor (AF-); AF + TASK-1 overexpression (AF+); AF + heart failure (approximately 1/2 of TASK-1 expression, AF+HF). For AF cases, I_{K1}(+25%) and I_{Kur}(+20%) were increased to represent electrical remodeling.
The control AP duration (APD) in SR is 283ms. In the modelled settings, following APD were observed: SR+: 252ms; SR-: 313ms; AF: 182ms; AF+: 131ms; AF-: 286ms; AF+HF: 225ms. Additionally, the model predicts minor conduction velocity changes from SR: 638 mm/s to: SR+: 636mm/s; SR-: 641mm/s; AF: 626mm/s; AF+: 621mm/s; AF-: 633mm/s; AF+HF: 628mm/s). Computed APD changes agree with pig experimental data qualitatively: SR: 463ms; SR+: 258ms; SR-: 493ms; AF: 252ms; AF+: 206ms; AF-: 466ms; AF+HF: 412ms. Differences may be caused by the fact that the model used was representative of human, while data included was from pig and that pig APs were measured at room temperature.

54-POS Board 54

TOWARDS A HIGH-RESOLUTION FOUR-CHAMBER HEART MODEL FOR WHOLE HEART MOTION SIMULATION

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Computational models of cardiac electromechanics are increasingly used for clinical applications simulating normal physiology, pathologies and treatments. Previous models have focused on the ventricles, which limit the capacity to simulate the effects of the atria, aorta and pulmonary artery on cardiac physiology. Developing models that explicitly represent these surrounding structures will move models closer to representing the clinical setting. In this work we present our four-chamber cardiac modelling framework in a clinical case study.
The multi-label segmentation generated from CT images acquired from a 78-year-old female heart failure indicated for cardiac resynchronization therapy was meshed with an element target size of 0.8mm. Ventricular and atrial fibers were generated using two different rule-based mapping methods based on histological and DT-MRI measurements. A reaction-eikonal model was used to simulate electrical activation of cardiac tissue, modelled as a transversely isotropic conducting medium stimulated at one right atrial and three ventricular endocardial sites. Longitudinal and transverse conduction velocities were tuned to match patient's QRS duration of 172.82ms. Mechanical deformations of the heart were modelled with the finite elasticity equations. Ventricular myocardium was modelled as hyperelastic, incompressible, non-linear, transversely isotropic and actively contracting material. Atria were modelled as isotropic and passive. Homogeneous Dirichlet boundary conditions were applied at the cropped aorta, pulmonary arteries and veins, venae cavae and left atrial appendage. Two three-element Windkessel models were used to provide pressure-volume relationships for the ventricles. Simulated QRS duration was of 172.81ms, and apex-to-base shortening resulted in an ejection fraction of 27.4%, peak in systolic pressure of 140.0mmHg and dP/dtmax of 1325.1mmHg/s. We have demonstrated in a single case the capacity to simulate electromechanics on a four-chamber heart. This provides the foundation framework for developing patient-specific four-chamber heart models for studying the electrical and mechanical interaction between the atria and ventricles, in healthy and diseased states.

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PROARRHYTHMIC EFFECTS OF FLECAINIDE AND DOFETILIDE ON ELECTROPHYSIOLOGICAL PROPERTIES OF ATRIAL MYOCYTES: A COMPUTATIONAL APPROACH

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Flecainide and Dofetilide are commonly used drugs for cardioversion of atrial fibrillation and rhythm control, but pose proarrhythmic risks in patients with underlying structural heart disease. Therefore, quantification of their effects on electrophysiological properties of atrial myocytes can provide further insight into their potential arrhythmic risk.
In this study, we used *in silico* modeling to assess the effects of Flecainide and Dofetilide on action potential (AP) and calcium transient (CaT) morphologies, repolarisation instabilities, and rate adaptation of an atrial myocyte model. We built populations of models to take electrophysiological variability into account, and varied maximal ion channel conductances within a 30% range. The effect of dose-dependent drug block was modeled by tuning the maximal conductance of seven ionic currents: INa_{fast}, INa_{late}, ICaL, IKr, IKs, IK1, and Ito, according to published data. Steady state and rate adaptation simulations were performed by pacing the models at 1Hz and then dynamically pacing from 1 to 6.7 Hz. Biomarkers related to AP, CaT, and AP duration (APD) alternans were extracted from the simulated data.
Both Flecainide and Dofetilide resulted in prolonged APD, as expected. Results showed a dose-dependent occurrence of repolarization abnormalities (repolarization failure and afterdepolarizations) with both Flecainide (58%) and Dofetilide (22%). Repolarization abnormalities were concomitant with reduced CaT amplitude. Additionally, results showed a significant reduced incidence of APD alternans with 10x Cmax Flecainide by 16%, while Dofetilide caused only a slight increase in predisposition to alternans of 2%.
This study provides a framework for the systematic quantification of arrhythmic risk of rhythm control drugs. Furthermore, it indicates a proarrhythmic effect of Flecainide and Dofetilide on the electrophysiology of single atrial myocytes, and points to the need of further elucidation of their effect on atrial arrhythmias.

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A HERG GATING MODEL INCORPORATING MODE-SHIFT AND THE EFFECTS OF N-TERMINAL LQTS2 MUTATIONS

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The human ether-a-go-go related gene (hERG) encodes the Kv11.1 potassium channel, the pore forming subunit of the rapidly activating delayed rectifier current in the heart. Reduced Kv11.1 channel activity as a result of inherited mutations causes Long QT syndrome type 2 (LQTS2), characterised by prolongation of the QT interval on the surface ECG and a markedly increased risk of arrhythmias and sudden cardiac death. In particular, many disease-causing mutants are clustered in the N-terminal cytoplasmic domain of the channel that modulates the channel deactivation. Attempts to reproduce the accelerated deactivation phenotypes associated with these mutants *in silicohave* simply shifted the $V_{0.5}$of the activation/deactivation equilibrium to more positive potentials. While this does result in an acceleration of deactivation at a given membrane potential, it also reduced I_{Kr}current by reducing activation, an effect that is not seen in *in vitro*. This approach therefore potentially misrepresents the primary mechanism of pathogenesis. The aim of this study was to construct a mathematical model of hERG gating incorporating observations of hERG mode-shift where prolonged depolarisation caused slower deactivation, and furthermore to incorporate the effect of LQTS2 mutants that reduce or abolish mode shift, resulting in faster deactivation. Two Markov state models corresponding to wild-type and the R5A mutant hERG channel have been constructed. These models can be incorporated into cellular models of cardiac action potentials to assess the effects of N-terminal LQTS2 mutants on changes in action potential duration and susceptibility arrhythmias arising from premature stimuli.

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EXPLORING THE ROLE OF CARDIAC MICROSTRUCTURE AND ITS VARIABILITY IN VENTRICULAR ARRHYTHMOGENESIS

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Objective: Propagation of cardiac electrical excitations is influenced by tissue microstructure, although quantitative characterisation of this relationship under normal and arrhythmia conditions remains a significant research challenge. Computational modelling of cardiac electrophysiology which incorporates both dynamic electrical activity and myocardial structure offers a viable method of studying the influence of microstructure and its variability on complex excitation patterns.
Methods: The role of tissue microstructure (cardiomyocyte and sheetlet orientations) on normal and arrhythmic excitation patterns at the organ scale was investigated using five healthy rat ventricle reconstructions, obtained at 100 μm isotropic resolution from diffusion tensor MRI (DTI). The primary, secondary, and tertiary eigenvectors from DTI have been shown previously to align with the myocyte, sheetlet plane, and sheetlet normal directions, respectively. The Fenton-Karma 3 variable action potential (AP) model was modified to reproduce the rat AP duration (APD) and its restitution. Localised pacing and scroll wave re-entry were simulated in the five anatomical models at prescribed locations for three different microstructure scenarios: (i) isotropic (no microstructure); (ii) anisotropic (myocyte but no sheetlet microstructure); and (iii) orthotropic (myocyte and sheetlet microstructure).
Results: DTI-based microstructure was shown to modulate the ventricular activation pattern and increase dispersion of repolarisation following apical pacing. In addition, anisotropic and orthotropic microstructure increased the mean number of scroll wave filaments, and fast Fourier transform analysis of pseudo ECGs revealed that inclusion of microstructure favoured the transition from narrow, single-peaked spectra to a broader range of peaks, associated with more complex electrical activity. The extent to which microstructure modulated arrhythmia dynamics differed between the five reconstructions, highlighting the important and under-appreciated role of structural variability.
Conclusion: This study shows that microstructure variability influences arrhythmia dynamics including specific properties such as lifespan and mean filament number.

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MULTISCALE MODELING AND EXPERIMENTS REVEAL MOLECULAR MECHANISMS FOR HYPERCONTRACTILITY AND DIASTOLIC DYSFUNCTION IN AN HCM-ASSOCIATED TPM1 MISSENSE VARIANT

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We have used modeling and experiments at the molecular, molecular ensemble, and tissue levels to reconstruct the molecular pathophysiology of the TPM1 (alpha-tropomyosin) variant E192K, which was identified in a young hypertrophic cardiomyopathy (HCM) patient. Molecular dynamics (MD) simulations predicted a decrease in tropomyosin stiffness after introduction of E192K at various residues throughout the molecule. Using a spatially explicit coarse-grained model incorporating the residue-level stiffness measurements from MD, we computed a 30% decrease in the relative energetic requirement of tropomyosin azimuthal displacement for the E192K TPM1 molecule, suggesting that E192K leads to easier displacement of TPM1. Regulated in vitro motility assays showed increased motility of TPM1 E192K-decorated actin filaments at low calcium. Fitting these with a model of thin filament activation suggested that measured thin filament dysregulation was consistent with the predicted increase in tropomyosin flexibility and a simultaneous alteration in tropomyosin affinity for the inactive actin state. The model further predicted that these molecular changes would lead to increased systolic and diastolic twitch force production. To test these predictions in the context of intact human tissue, we generated induced pluripotent stem cell cardiomyocytes (iPSC-CMs) from the TPM1 E192K-positive HCM proband. Engineered heart tissues (EHTs) were created from patient IPSC-CMs and contractile characterization showed that the peak force generated by mutant EHTs was several times higher than in two independent sets of non-mutant control EHTs. Contraction kinetics were also changed, exhibiting significantly slower time to peak and relaxation time. Altogether, experimental observations and modeling indicate that E192K leads to altered TPM1 flexibility and altered TPM1-actin interactions. We posit that this multiscale, multi-modal approach may be generally useful for predicting and understanding pathogenicity of TPM1 variants in cardiomyopathy.