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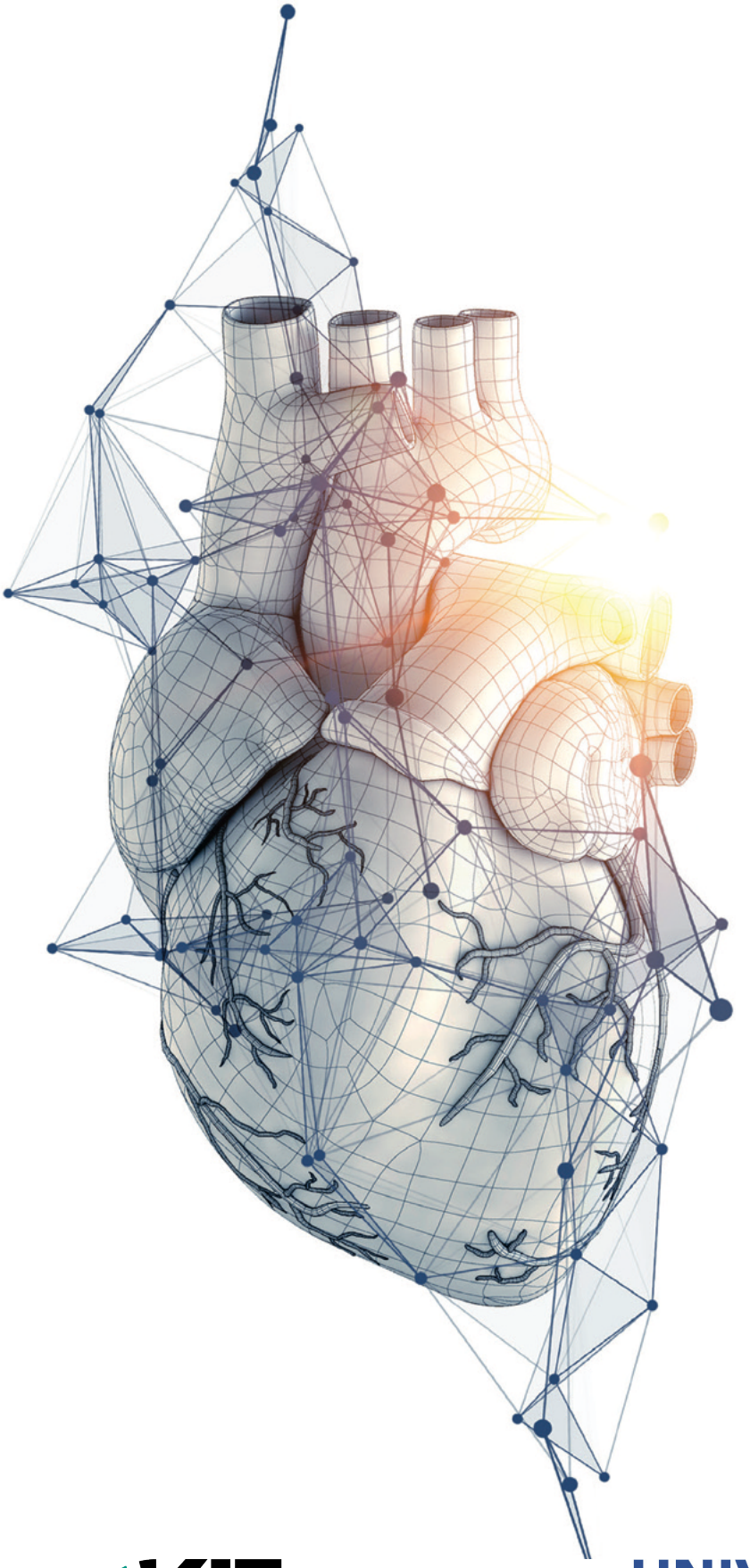


CARDIAC PHYSIOME 2024

Karlsruhe Institute of Technology

UNIVERSITÄTS KLINIKUM FREIBURG

Proceedings

Freiburg, Germany
12 - 14 September 2024

Cardiac Physiome Workshop 2024

Conference Chairs
Peter Kohl
Axel Loewe
Viviane Timmermann

Julia Verheyen (Administration)

Welcome Note

Freiburg, Germany
12 - 14 September 2024

It is with great pleasure that we welcome you to the **Cardiac Physiome Workshop 2024**, organised by the University of Freiburg, the University Hospital Freiburg and the Karlsruhe Institute of Technology.

This year's event will once again be held in Freiburg and we are honoured to be able to hold the sessions in the prestigious **'Aula'** - the university's ceremonial hall. The meeting will feature a rich program of scientific presentations, including **invited talks**, **selected short talks**, **two poster sessions**, and a **final wrap-up discussion**. After the sessions, we will gather for a closing dinner at the Peterhof Keller, just a short walk from the main venue.

We hope you enjoy your stay in the beautiful Black Forest region of Germany. If you need any assistance during the meeting, please feel free to stop by the registration desk.

Please note some important guidelines:

- Participants are requested to wear their name badges throughout the event, including social events attended by accompanying persons.
- Accompanying persons are not permitted to attend the scientific sessions.
- Please switch off mobile phones during presentations and refrain from taking photographs of slides or posters unless permission has been granted by the presenter.
- Each delegate will be provided with a unique internet access code; please keep this access to yourself.

We are confident that the **Cardiac Physiome Workshop 2024** will be as engaging, informative and stimulating as previous meetings. We hope that you will find both the scientific sessions and the social activities rewarding and enjoyable.

The Organising Committee

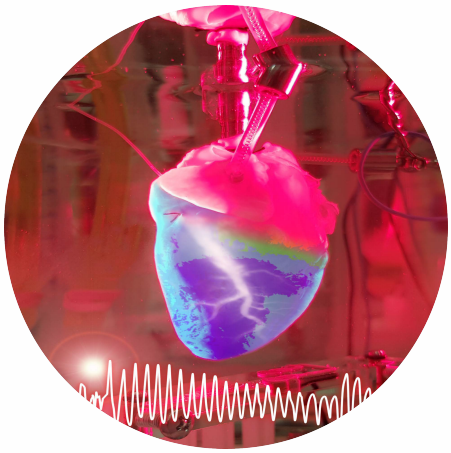
The Journal of Physiology

The Physiological Society

SPECIAL ISSUE

CALL FOR PAPERS

Integrating experimental and mathematical approaches
to advance cardiac physiology research



TOPICS INCLUDE

- Multi-scale modelling of cardiac structure and function across scales
- Innovative experimental techniques to investigate cardiac structure and function, including the use of artificial intelligence/machine learning
- Mathematical modelling and simulations for molecular mechanisms underlying cardiac diseases
- Translational perspectives on the development of novel therapeutic concepts

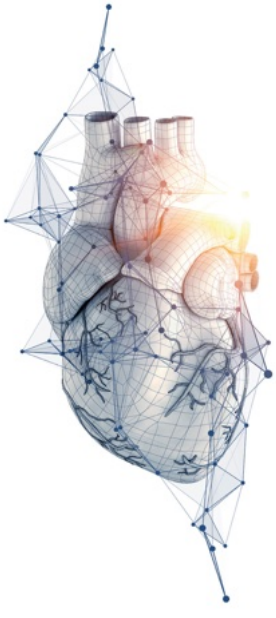
Guest edited by Dr Axel Loewe
and Dr Viviane Timmermann

SUBMISSION DEADLINE
31 January 2025

CARDIAC PHYSIOME
2024

Programme

Integrating experimental and mathematical approaches to advance cardiac physiology research



Freiburg, Germany
12 - 14 September 2024

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Poster Abstracts I

Poster Abstracts II

Thursday, 12 September 2024

08:30 - 09:15	**Registration**	

Session 1: From Structure to Function: Nano

Chair: Andrew McCulloch

09:15 - 09:30	Peter Kohl, Axel Loewe Viviane Timmermann	Cardiac Physiome Workshop 2024: Welcome
09:30 - 10:00	Eva Rog-Zielinska	3D time-resolved electron microscopy: a contradiction in terms?
10:00 - 10:15	Ayako Takeuchi (abstract-selected talk)	Theoretical analyses of the roles of mitochondrial Ca^{2+} dynamics during exercise using an integrated model of human ventricular myocyte
10:15 - 10:30	Dennis Ogiermann (abstract-selected talk)	A pressure- and voltage-dependent Piezo ion channel model for cardiomyocytes
10:30 - 10:45	Susan Chang (abstract-selected talk)	Optogenetic depolarisation of fibroblasts prolongs action potentials of cardiomyocytes in murine cryo-ablated heart
10:45 - 11:15	**Coffee Break** (posters on display)	

Session 2: From Structure to Function: Micro

Chair: M Molly Maleckar

11:15 - 11:45	Jan Lebert	Mapping cardiac electrics and mechanics at high spatio-temporal resolution: AI to the rescue?
11:45 - 12:00	David Nordsletten (abstract-selected talk)	Computational modelling of desmoplakin cardiomyopathy
12:00 - 12:15	Seshan Sridhar (abstract-selected talk)	Fibroblast mediated dynamics in diffusively uncoupled myocytes
12:15 - 12:30	Paula Dominguez-Gomez (abstract-selected talk)	Validated sex-specific in-silico clinical trials for cardiac safety: assessing drug pro-arrhythmic risk in real-time
12:30 - 14:00	**Lunch** (posters on display)	

Session 3: From Structure to Function: Macro

Chair: Martyn Nash

14:00 - 14:30	Sandy Engelhardt	Cardiac macroscopy: how to see the wood for all the trees
14:30 - 14:45	Salla Kim (abstract-selected talk)	Cardiac impact of preterm birth: insights from modelling
14:45 - 15:00	Simone Pezzuto (abstract-selected talk)	Reconstruction of the local contractility of the cardiac muscle from deficient apparent kinematics
15:00 - 15:15	Vladimir Sobota (abstract-selected talk)	Age-associated changes in the apicobasal repolarisation gradient affect arrhythmia vulnerability in the human ventricles
15:15 - 15:30	Hans Dierckx (abstract-selected talk)	Beyond the phase singularity concept: a quasi-particle viewpoint on transient and complex arrhythmia patterns
15:30 - 16:00	**Coffee Break** (posters on display)	
16:00 - 16:30	Michael Gotthardt	From alternative splicing to Frank-Starling: can cardiac mechanics be quantitatively conceptualised bottom-up
16:30 - 17:00	**Meeting Photo**	
17:00 - 19:00	**Poster Session I** with refreshments, and nibbles, and more...	

Friday, 13 September 2024

Session 4: Linking Analogue and Digital Worlds - I

Chair: Viviane Timmermann

09:30 - 10:00	Daniel Hook	Research data management at the interface between the analogue world and its digital representation: what next?
10:00 - 10:15	Peter Hunter (abstract-selected talk)	Bond graph protein models for cardiac physiology
10:15 - 10:30	Janice Reid (abstract-selected talk)	Building a ligand transcriptome encyclopedia for the heart
10:30 - 10:45	Gregory Sands (abstract-selected talk)	Extended-volume 3D imaging and functional recordings of the human intrinsic cardiac nervous system
10:45 - 11:15	**Coffee Break** (posters on display)	

Session 4: Linking Analogue and Digital Worlds

Chair: Ayako Takeuchi

11:15 - 11:45	Andrew Taberner	Optimised wet-lab instrumentation for dry-lab research into cardiac structure and function: how to engineer the bi-directional cross-talk between the analogue world and its digital representation
11:45 - 12:00	Sofia Botti (abstract-selected talk)	In-silico modelling of multi- cardiac drug testing on heteroge- neous hiPSC-CM tissues electrode arrays to enhance
12:00 - 12:15	Nicole Collins (abstract-selected talk)	Myocardial metabolic response to acute ischaemia causes mechanical dysfunction following reperfusion
12:15 - 12:30	Leonardo Sacconi (abstract-selected talk)	Cardiac fibrosis affects electrical conduction and arrhythmogenesis in a pacing-rate-dependent manner
12:30 - 14:30	**Poster Session II** with Lunch	

Session 5: Linking Analogue and Digital Worlds - II

Chair: Axel Loewe

14:30 - 15:00	Igor Efimov	Heart-AI interface: flexible and transient bioelectronics
15:00 - 15:15	Jairo Rodríguez Padilla (abstract-selected talk)	Model personalisation in the infarcted porcine heart: insights from ARI-based action potential calibration
15:15 - 15:30	Mathias Peirlinck (abstract-selected talk)	Automated cardiovascular material model discovery
15:30 - 15:45	Mark Potse (abstract-selected talk)	Modelling the heart cell by cell: the MICROCARD project
15:45 - 16:15	**Coffee Break** (posters on display)	

Chair: Peter Kohl

16:15 - 16:45	Blanca Rodriguez	Modelling drug effects on cardiac function for personalised medicine: hope or hype?
16:45 - 17:30	Dennis Noble	Cardiac computational modelling of electrophysiology: from relaxation oscillators, to Hodgkin-Huxley, Markov, big data and AI: are we nearly there yet?
18:00 - 00:00	**Meeting Dinner at Peterhofkeller**	
18:00 - 18:30	Reception	Poster Awards Ceremony
18:45 - 21:00	Meeting Dinner	
21:00 - 00:00	Entertainment	

Saturday, 14 September 2024

Session 6: Structure & Function, Analogue & Digital: Going Full Circle

Chair: Hermenegild Arevalo

09:30 - 10:00	Natalia Trayanova	Clinical translation of cardiac modelling and image analysis: digital twins to the rescue!
10:00 - 10:15	Laura Bevis (abstract-selected talk)	Production of atrial models at scale: investigating fibres, fibrosis, and the importance of the end-user
10:15 - 10:30	Mary M Maleckar (abstract-selected talk)	New in-silico models and data-driven methods for valvular heart disease: the first automatic detection pipeline for the mitral valve in cardiac magnetic resonance imaging
10:30 - 11:00	**Coffee Break** (posters on display)	

Session 6: Structure & Function, Analogue & Digital: Going Full Circle

Chair: Edward Vigmond

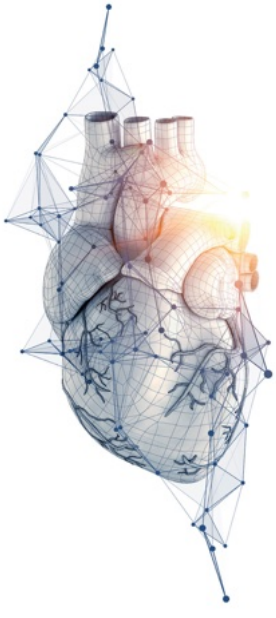
11:00 - 11:15	Stephanie Appel (abstract-selected talk)	Roles of stretch-activated channels in atrial fibrillation: from cellular dynamics to whole-heart simulations
11:15 - 11:30	Tim van Loon (abstract-selected talk)	Accelerated atrial pacing reduces left-heart filling pressure: a combined computational-clinical study
11:30 - 12:00	Discussion, Participant Feedback; Presentation for Feb/Mar 2026 Meeting (at Auckland); Election of Chair for 2027/28	
12:00 - 12:15	Wrap-up	

CARDIAC PHYSIOME

2024

Lecture Abstracts

Integrating experimental and mathematical approaches to advance cardiac physiology research



Freiburg, Germany
12 - 14 September 2024

3D time-resolved electron microscopy: a contradiction in terms?

Rog-Zielinska EA[1], Greiner J[1], Kohl P[1]
[1]*Institute for Experimental Cardiovascular Medicine, University Heart Centre and Faculty of Medicine, University of Freiburg, Freiburg, Germany*

Electron microscopy allows investigators to bypass the diffraction limit of visible light and thereby visualise nanoscopic cellular structures. Electron microscopy of subcellular structures has been instrumental to improving our understanding of cardiac cell function. However, after steady growth in the 1960s and early 1970s, electron microscopy came to be regarded as somewhat unfashionable, at the limit of its performance and 'not worth the effort'. One of the main limitations of electron microscopy is the fact that it is not compatible with living specimens. Recently, electron microscopy has undergone a renaissance, largely because it now allows 3D imaging. New approaches are also starting to convey an element of temporal resolution to electron microscopy, using an approach akin to stop–motion pictures.[1]
The mechanical environment of cardiomyocytes in a beating heart is highly dynamic, and all cardiac cellular and extracellular components are subject to continual cyclic deformation. This deformation is expected to affect the function of individual organelles, cells and, ultimately, the entire heart. However, the assessment of nanostructural dynamics is challenging.
Here we describe an experimental approach that allows for assessment of beat-by-beat changes in cardiomyocyte nanostructure, conferring pseudotemporal resolution to electron microscopy studies of beat-by-beat mechanical organelle deformations. This advance is possible by electrically stimulating live biological samples within the freezing chamber of a high-pressure freezer, with rapid freezing programmed to occur at specific time points after stimulation (for example, to capture cardiomyocyte contraction) with millisecond precision.
Action potential-synchronized high-pressure freezing allowed us to explore the deformation of cardiac organelles. We have demonstrated that cardiac transverse tubules undergo directional deformation (squeezing) with every contraction, which leads to faster luminal content exchange with the bulk extracellular space.[2] We have also demonstrated the deformation of mitochondria, which could serve as a mechanisms linking cardiac contraction with energy production. In addition to biological insight, we present custom machine learning-based approaches towards segmentation of large amounts of data volumes, and the utility of generative adversarial networks in synthesising time-resolved data into a 'live-EM' movie of a contracting cardiomyocyte.

References:
[1] Kohl P, Greiner J, Rog-Zielinska EA. Electron microscopy of cardiac 3D nanodynamics: form, function, future. Nat Rev Cardiol 2022/19:607-619
[2] Rog-Zielinska EA, Scardigli M, Peyronnet R et al. Beat-by-beat cardiomyocyte T-tubule deformation drives tubular content exchange. Circ Res 2021/128:203-215

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Theoretical analyses of the roles of mitochondrial Ca^{2+} dynamics during exercise using an integrated model of human ventricular myocyte

Takeuchi A[1], Matsuoka S[1]
[1]*Department of Integrative and Systems Physiology, Faculty of Medical Sciences, and Life Science Innovation Center, University of Fukui, Fukui, Japan*

We previously reported that mitochondrial Ca^{2+} efflux transporter NCLX was closely localized with sarcoplasmic reticulum (SR) Ca^{2+} pump SERCA in mouse ventricular myocytes, and that this spatial coupling, together with the spatial coupling between mitochondrial Ca^{2+} uniporter MCU and SR Ca^{2+} release channel RyR[1], was required to reproduce the SR Ca^{2+} dynamics and the generation of automaticity obtained in experiments using HL-1 cell line[2]. However, the roles in the ventricular myocyte functions remained to be clarified. Since Ca^{2+} is involved in both excitation-contraction and mitochondrial energetics, it is strongly suggested to work especially during exercise where both energy demand/supply dynamically change. In the present study, we newly developed an integrated model of human ventricular myocyte considering the spatial couplings and analysed excitation-contraction-mitochondrial energetics coupling during exercise.

We chose a human ventricular myocyte model by Grandi et al.[3] as a base model, and incorporated our models of mitochondria-SR interaction[2] and detailed mitochondrial energetics[4], and a contraction model[5] into it. "Exercise" was expressed as applications of stimulus frequency increase, half sarcomere length increase, and b-adrenergic stimulation to the model.

The model well reproduced the exercise-induced increases of cytosolic Ca^{2+} transient, force generation, and half sarcomere length shortenings as well as of myocardial oxygen consumption rate. The ATP level was maintained at the expense of phosphocreatine. The NADH, a reducing equivalent connecting metabolism and oxidative phosphorylation, showed biphasic dynamics; an initial drop followed by an increase, the latter was owing to the efficient increase of mitochondrial Ca^{2+} formed by the spatial couplings. Taken together, it was suggested that the mitochondrial Ca^{2+} dynamics contributed to NADH constancy.

References:
[1] De La Fuente S, Lambert JP, Nichtova Z et al. Spatial separation of mitochondrial calcium uptake and extrusion for energy-efficient mitochondrial calcium signaling in the heart. Cell Rep 2018, 24:3099-3107
[2] Takeuchi A, Matsuoka S. Spatial and functional crosstalk between the mitochondrial Na^{+}-Ca^{2+} exchanger NCLX and the sarcoplasmic reticulum Ca^{2+} pump SERCA in cardiomyocytes. Int J Mol Sci 2022, 23:7948
[3] Grandi E, Pasqualini FS, Bers DM. A novel computational model of the human ventricular action potential and Ca transient. J Mol Cell Cardiol 2010, 48:112-121
[4] Saito R, Takeuchi A, Himeno Y et al. A simulation study on the constancy of cardiac energy metabolites during workload transition. J Physiol 2016, 594:6929-6945
[5] Shim EB, Amano A, Takahata T et al. The cross-bridge dynamics during ventricular contraction predicted by coupling the cardiac cell model with a circulation model. J Physiol Sci 2007, 57:275-285

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A Pressure- and Voltage-dependent Piezo Ion Channel Model for Cardiomyocytes

Ogiermann D[1], Mohamed A[1], Perotti LE[2], Balzani D[1]
[1]*Chair of Continuum Mechanics, Ruhr University Bochum, Bochum, Germany*
[2]*Department of Mechanical and Aerospace Engineering, University of Central Florida, Orlando, USA*

The Piezo ion channel family is a group of mechanosensitive ion channels, which gained considerable attention in the last decades. These ion channels play a significant role in physiological processes involving oscillating mechanical stimuli across a wide range of tissues. While the Piezo ion channels' function is quite well understood in neural tissues, this is not the case in cardiac tissue. In this context, knockout studies suggest that the Piezo ion channels play a key role in homeostasis of myocardial tissue and their distinguishing feature is a complex interaction between pressure and voltage gating, as demonstrated by Moroni et al.[1].
As our contribution towards understanding the role of the Piezo1 ion channel in cardiac function, we present a novel pressure- and voltage-dependent Markov chain model. Parameters were determined by fitting voltage trajectories of our proposed model against published experimental data[1]. Additionally, we present a preliminary integration of our novel ion channel model into the Mahajan-Shiferaw ventricular cardiomyocyte model[2] to investigate it's role during electromechanical pacing. It has been experimentally observed in in vitro electromechanical pacing experiments of rabbit hearts that: 1) Mechanical stimuli can trigger electrical activation of the heart; 2) Pure mechanical pacing of hearts lead to a stimuli-frequency-dependent loss of capture; and 3) Alternating electrical and mechanical pacing leads to even faster loss of capture. Our preliminary studies suggest that our Piezo1 ion channel model can explain (1) and (2). However, the current form of our model could not replicate observation (3), suggesting that further refinement of the model is still required.

References:
[1] Moroni M, Servin-Vences M, Fleischer R et al. Voltage gating of mechanosensitive PIEZO channels. Nat Commun 2018/9:1096.
[2] Mahajan A, Shiferaw Y, Daisuke S et al. A Rabbit Ventricular Action Potential Model Replicating Cardiac Dynamics at Rapid Heart Rates. Biophys J 2008/94:392-410.
[3] Quinn T, Kohl P. Comparing maximum rate and sustainability of pacing by mechanical vs. electrical stimulation in the Langendorff-perfused rabbit heart. Europace 2016/18:85-93.

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Optogenetic depolarization of fibroblasts prolongs action potentials of cardiomyocytes in murine cryo-ablated heart

Chang S[1], Calderón-Fernández M[1], Simon Chica A[2], Kohl P [1], Zgierski-Johnston CM[1], Schneider-Warme F[1]

[1]*Institute for Experimental Cardiovascular Medicine, University Heart Center Freiburg ▪ Bad Krozingen, and Faculty of Medicine, University of Freiburg, Freiburg, Germany*

[2]*Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain*

In the heart, fibroblasts (FB) can be electrically coupled to cardiomyocytes (CM) via gap junctions.[1] In order to study FB-CM interactions and how they alter electrical activity during remodeling responses to ventricular injury, we established an optogenetic mouse model targeting the light-gated cation channel Channelrhodopsin-2 specifically to FB (Tcf21-MerCreMer-ChR2 mice). This allowed us to activate ChR2 in FB upon blue-light stimulation, to directly assess effects on CM of light-induced changes in FB conductance and membrane potential. We performed electrical pacing and optical stimulation of isolated Langendorff-perfused hearts at 28 days after ventricular cryo-ablation, while simultaneously recording the surface electrocardiogram and membrane voltage changes via dye-based optical mapping. We further established a computational model allowing us to assess how FB modulate action potentials (AP) in coupled CM at different basic cycle lengths (BCL), both in the absence and presence of optogenetic stimulation. The Wang-Sobie neonatal mouse ventricular CM model[3] was selected for coupling to the MacCannell et al. FB model,[4] which was equipped with an additional light-gated current using the Williams et al. ChR2 model.[5] Our experimental results show that ChR2 activation in FB significantly prolongs the AP duration in CM in all tested areas of cryo-ablated ventricles, but not in hearts from sham-operated mice. We do not observe a difference in mean conduction velocity upon ChR2 activation across experimental conditions tested. Our preliminary computational results indicate prolongation of the CM AP with ChR2 activation in electrically coupled FB (Fig. 2). Together, our data from optogenetic experiments and computational modelling highlight the electrophysiological relevance of cardiac FB in scarred ventricular tissue.

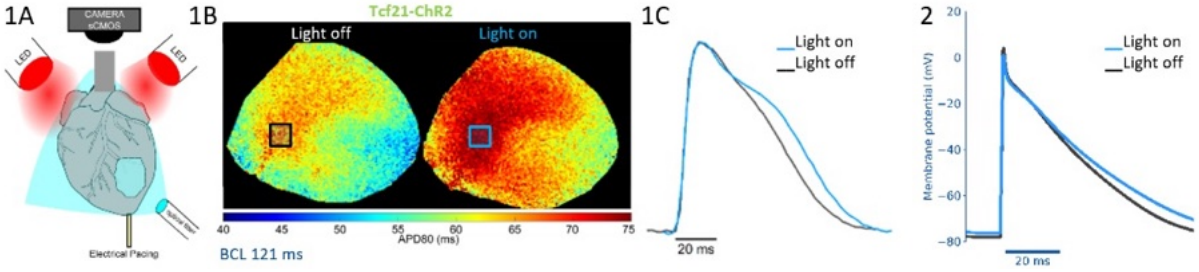

Figure 1: *in situ* optical mapping in isolated mouse heart (A) with representative AP duration at 80% repolarization (APD80) heatmap (B) and AP traces (C), both at BCL 121 ms.

Figure 2: Membrane potential with and without ChR2 activation at BCL 121 ms, as predicted by computational model.

References:

[1] Quinn AT et al. Electrotonic coupling of excitable and nonexcitable cells in the heart revealed by optogenetics. Proc Natl Acad Sci USA 2016/113(51):14852-14857 [PMID: 27930302]

[2] Fernandez MC et al. Channelrhodopsins for Cell-Type Specific Illumination of Cardiac Electrophysiology. Methods Mol Biol 2021/2191:287-307 [PMID:32865751]

[3] Wang LJ, Sobie EA. Mathematical model of the neonatal mouse ventricular action potential. Am. J. Physiol Heart Circ Physiol 2008/294:H2565-2575. [PMID: 18408122]
[4] MacCannell KA et al. A mathematical model of electrotonic interactions between ventricular myocytes and fibroblasts. Biophys J 2007/92:4121-4132 [PMID: 17307821]
[5] Williams JC et al. Computational optogenetics: empirically-derived voltage- and light-sensitive channelrhodopsin-2 model. PLoS Comput Biol 2013/9: e1003220 [PMID: 24068903]

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Mapping cardiac electrics and mechanics at high spatio-temporal resolution: AI to the rescue?

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[3]*Division of Cardiology, University of California, San Francisco, USA*

The intricate coupling of electrical and mechanical activity in the heart is fundamental to cardiac function, yet the intertwined nature of these processes has made simultaneous electro-mechanical mapping and the ability to isolate their individual contributions very challenging. We hypothesize that by exploiting this inherent relationship and leveraging deep learning, it is possible to solve the inverse mechano-electric problem: predicting underlying electrical activity from observed mechanical motion. This could enable the non-invasive identification of electrical triggers or drivers responsible for arrhythmias solely by analyzing structural imaging.
To address this challenge, we have developed a novel electro-mechanical imaging system that integrates 360° panoramic optical mapping[1] with high-speed volumetric ultrasound imaging. This system captures synchronized surface electrical and volumetric mechanical dynamics of beating rabbit hearts in unprecedented detail. Our 12-camera optical system reconstructs the complete electro-mechanical activity on the ventricular surface using a 3D mesh reconstruction and tracking approach. Our current focus is on demonstrating the feasibility of solving the inverse mechano-electric problem in isolated hearts ex-vivo, expanding on our previous in-silico work[2].
In this talk, I will present preliminary results and our latest advancements in high-resolution electro-mechanical imaging. This will include demonstrating the localization of electrical triggers from ventricular motion using a neural network trained on ex-vivo and in-silico datasets, and discussing our ongoing work to utilize 4D ultrasound imaging as input data. Additionally, I will discuss how deep learning and generative AI[3], combined with electro-mechanical mapping, could be used for a data-driven approach to cardiac modelling. By providing detailed, high-resolution data of both electrical and mechanical activity, our system could help to refine existing models and develop new, more accurate models of cardiac function.

References:
[1] Chowdhary S, Lebert J, Dickman S, Christoph J. Panoramic Voltage-Sensitive Optical Mapping of Contracting Hearts using Cooperative Multi-View Motion Tracking with 12 to 24 Cameras. arXiv [preprint] 2023/2305.07822
[2] Lebert J, Deng D, Fan F, et al. Deep Learning-based Prediction of Electrical Arrhythmia Circuits from Cardiac Motion: An In-Silico Study. arXiv [preprint] 2023/2307.07943
[3] Baranwal T, Lebert J, Christoph J. Dreaming of Electrical Waves: Generative Modeling of Cardiac Excitation Waves using Diffusion Models. arXiv [preprint] 2023/2312.14830

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Computational Modeling of Desmoplakin Cardiomyopathy

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[3]*Department of Cardiac Surgery, University of Michigan, Ann Arbor, USA*

Introduction: Desmoplakin Cardiomyopathy (DSP-CM) is a genetic condition resulting from abnormal variants of the desmoplakin protein [1]. Serving as one of the primary proteins in the complex linking sarcomeres across cell-cell junctions, DSP-CM presents with subepicardial fibrosis that spreads around the heart. While the genetics of DSP-CM are known, the cause of this phenotype, disease progression, and how progression can be mitigated are not well known. We hypothesize that this is driven by adverse myocardial mechanics, leading to elevated stresses that manifest into progressive cell damage and fibrotic remodeling.
Methods: To examine this hypothesis, we approached the problem from two scales. At the microscale, we used engineered heart tissues (EHTs)

References:
[1] Smith, Eric D., et al. Desmoplakin cardiomyopathy, a fibrotic and inflammatory form of cardiomyopathy distinct from typical dilated or arrhythmogenic right ventricular cardiomyopathy. Circulation 202/141.23: 1872-1884.
[2] DePalma, Samuel J., et al. Matrix architecture and mechanics regulate myofibril organization, costamere assembly, and contractility of engineered myocardial microtissues. BioRxiv (2023): 2023-10.
[3] Jilberto, Javiera, et al. "A data-driven computational model for engineered cardiac microtissues." Acta Biomaterialia 2023/172: 123-134.

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Fibroblast Mediated Dynamics In Diffusively Uncoupled Myocytes

Sridhar S[1], Clayton RH[1]
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While myocytes (M) are typically coupled to nearest neighbours through gap junctions in healthy hearts, under pathological conditions such as fibrosis or across ablation lines, myocytes can uncouple from their neighbours. However even in such situations electrical conduction may still occur via fibroblasts (F) that not only couple proximal myocytes but can also couple otherwise unconnected regions (non-local coupling). In vivo fibroblasts are known to have long cytoplasmic processes and are believed to electrically influence a large region around themselves [1].

In our studies we have modelled heterocellular electrical coupling between diffusively uncoupled mycoytes via fibroblasts. We adopted a bottom-up Occam's razor approach to develop the simple structural motifs that can in principle be scaled to build scar boundary zones. These motifs provide a possible structural mechanism to couple disconnected regions in tissue, such across ablation lines. We created a minimal set of parameters that determine the behaviour of myocytes coupled with fibroblasts and thereby identified the key building blocks underlying tissue behaviour especially in scenarios where myocytes are isolated in an environment of fibroblasts. We then extended the idea of structural motifs to investigate conduction in 2D tissue for the scenario of a non-conducting scar surrounded by a border zone that is diffusively identical to rest of the medium. The border zone itself is electrically coupled via M-F links to the myocytes in the scar. We characterized the uncertainty in the strength and location of M-F coupling in 2D tissue by considering distributions in number of non-local M-F links and variation in their spatial location.

We observed that non-local coupling could result in the initiation of action potentials in the quiescent myocytes and identified parameters that described several dynamical regimes possible for different connection topology[2]. We observed that such fibroblast-mediated coupling can modify tissue electrophysiology and dynamics via conduction delays and by exciting resting and partially recovered regions. Furthermore we identified and characterized the uncertainty in the conditions under which long-range M-F coupling can initiate reentry in the border zone.

References:
[1] Simon-Chica A, Wülfers EM, Kohl P. Nonmyocytes as electrophysiological contributors to cardiac excitation and conduction. Am.J.Phys.H.C.P, 2023/325(3) pp.H475-H491
[2] Sridhar, S. and Clayton, R.H., 2024. Fibroblast mediated dynamics in diffusively uncoupled myocytes: a simulation study using 2-cell motifs. Sci. Rep, 2024/14(1), p.4493

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Validated sex-specific in-silico clinical trials for cardiac safety: assessing drug pro-arrhythmic risk in real-time

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Drug-induced arrhythmias are a major health issue worldwide, significantly highlighted during the COVID-19 pandemic with the use of potentially pro-arrhythmic drugs as initial treatments. Traditional clinical trials involve extensive human and animal testing, whereas in-silico trials offer a promising alternative. Computational trials can be conducted using 3D electrophysiological (EP) simulations. The reliability of these trials significantly depends on the accurate calculation of drug-induced QT interval prolongation (ΔQT) validated against in vivo data.
In this study, we developed biventricular electrophysiological models to simulate a human cardiac population of 32 subjects, incorporating intersubject variability in a sex-specific manner[1]. To quantify pro-arrhythmic risk, pseudo-ECGs were computed to estimate ΔQT. The ΔQT of four benchmark drugs (moxifloxacin, dofetilide, ondansetron, and verapamil) was validated against clinical trial data[2]. Computationally derived concentration-response relationships of ΔQT showed slopes within the confidence intervals of clinical trial regressions, confirming the model's accuracy.
While 3D EP models provide detailed organ-level dynamics essential for cardiotoxicity assessment, they are computationally expensive. Simplified single-cell (0D) models, though cost-effective, miss critical organ-level interactions by predicting action potential duration prolongation (ΔAPD). To address this, we developed a sex-based Gaussian process emulator (GPE)[3], trained with 1000 simulations (approximately 3M CPU hours), which computes ΔQT and ΔAPD in real time based on specific drug characteristics. Our results demonstrated average relative errors of approximately 5% compared to the full-order model, underscoring the surrogate model's efficiency. Our GPE enabled us to conduct systematic studies with extensive variations in ion channel blockade. Ultimately, this allowed us to thoroughly explore results from both 3D and 0D models, thereby highlighting when organ-level dynamics are crucial in cardiac pro-arrhythmic risk modeling.

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Cardiac macroscopy: how to see the wood for all the trees

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Introduction: In the traditional strain measure each frame of a cardiac magnetic resonance scan is compared to the end-diastolic (ED) key frame. Due to varying number of frames and variable lengths of cardiac cycles and sub-phases, strain curves are not temporally aligned between patients. For an inter-patient comparison either the peak strain, the peak systolic strain or the end-systolic strain are considered, with the goal of comparing maximal deformation of the myocardium during the systolic phase, however, this assumption may not hold in certain patient cohorts.
Methods: The proposed deep learning based aligned strain measure [1] automatically identifies five cardiac key frames throughout the cardiac cycle. This enables to derive composed strain (ED2K) between the end-diastolic and the other key frames or sequential strain (K2K).
Results and Discussion: This approach allows for a higher sampling rate of strain values along the temporal axes at pre-defined points. In consequence, more significant different changes in myocardial strain may be detected. In a reproducibility scenario (57+82 patients), our results reveal five times more significant differences (22 vs. 4) between patients with myocardial scar and without, enhancing scar detection by +30%, improving detection of patients with preserved ejection fraction by +61%, with an overall sensitivity/specificity of 82/81%.

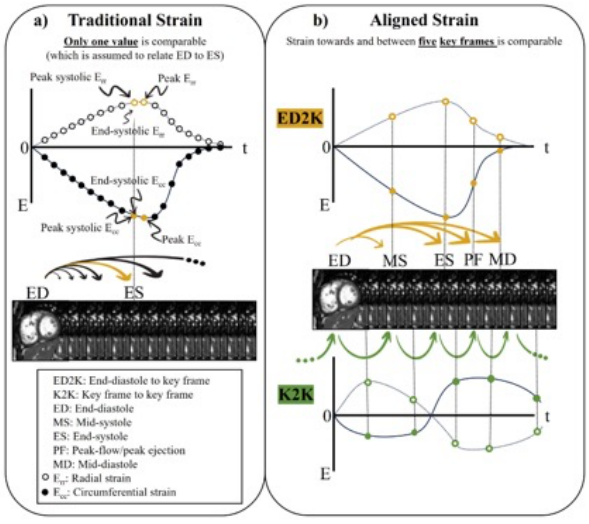

Figure 1: Cardiac Strain computation for inter-patient comparison benefits from using information from clearly pre-defined frames as shown in (b). Image from Koehler et al., 2024 [1].

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Cardiac impact of preterm birth: Insights from modeling

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Preterm birth (<32 wks gestation) is associated with an up to 17-fold increased risk for heart failure through early adulthood. It is commonly thought that increased right ventricular (RV) afterload from the damaged pulmonary vasculature drives RV dysfunction in preterm birth, but clinical and preclinical studies suggest direct injuries to the RV itself contribute to early and long-term dysfunction. When combined with robust experimental data, in silico modelling can test proposed mechanisms and glean physiological insights. We use the TriSeg heart model[1] with myofiber mechanics[2] within a lumped circulation model calibrated to biventricular pressure-volume data from a rat model of preterm birth (PRE) and control animals (CTL) to investigate the impact of preterm birth on cardiac biomechanics.

The TrigSeg model simulates interventricular dynamics[1,3] using three semi-spherical thick-walled segments for the left ventricular (LV), RV, and septal free walls. Ventricular contraction and relaxation are driven by a 5-state crossbridge (XB) dynamics model with dynamic calcium (Ca) activation. Heart and circulation model parameters are estimated, as in[3], from rat body-weight and ventricular wall weight ratios, heart rate, stroke volume, and time-series ventricular pressure and volume from CTL and PRE animals as described previously[4]. Experimentally, PRE animals demonstrated increased RV pressures, RV hypertrophy, depressed XB mechanics and corresponding altered contractile properties.

A local sensitivity analysis identified the cardiac timings for peak systole and relaxation, the cardiac reference areas, the systemic arterial resistance, and the rate constant of Ca unbinding from troponin C (a XB dynamics parameter) as the most influential on RV and LV pressure and volume simulations. These parameters were then calibrated to fit biventricular pressure-volume data from three CTL and three PRE animals. Model parameters reflect an increase (up to 2x) in pulmonary arterial resistance in PRE compared to CTL. Next steps include investigating differences and trends in XB parameters between the CTL and PRE groups to gain physiological insights and propose further studies to investigate the multiscale cardiac impact of preterm birth.

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Reconstruction of the local contractility of the cardiac muscle from deficient apparent kinematics

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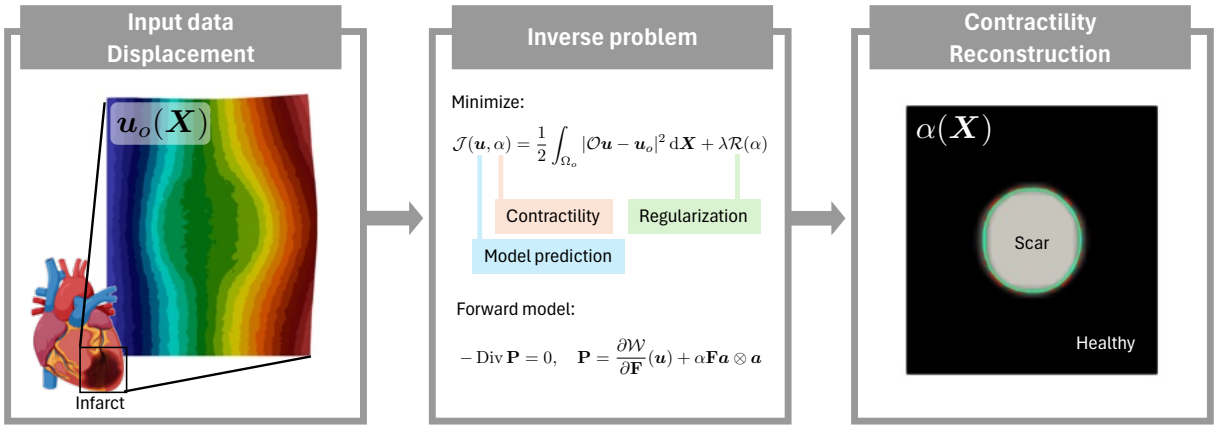
Active solids are a large class of materials, including both living soft tissues and artificial matter, that share the ability to undergo strain even in absence of external loads. While in engineered materials the actuation is typically designed a priori, in natural materials it is an unknown of the problem. In such a framework, the identification of inactive regions in active materials is of particular interest. An example of paramount relevance is cardiac mechanics and the assessment of regions of the cardiac muscle with impaired contractility. The impossibility to measure the local active forces directly suggests us to develop a novel methodology exploiting kinematic data from clinical images by a variational approach to reconstruct the local contractility of the cardiac muscle.



By finding the stationary points of a suitable cost functional we recover the contractility map of the muscle. Numerical experiments, including severe conditions with added noise to model uncertainties, and data knowledge limited to the boundary, demonstrate the effectiveness of our approach. Unlike other methods, we provide a spatially continuous recovery of the contractility map at a low computational cost.

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Age-associated changes in the apicobasal repolarization gradient affect arrhythmia vulnerability in the human ventricles

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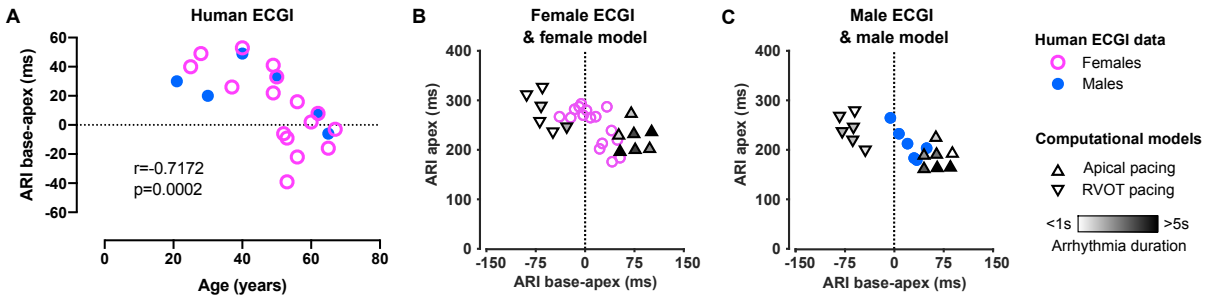
The apicobasal repolarization gradient (ABRG) plays an important role in human ventricular electrophysiology. The effect of sex and age on ABRG is currently unknown. This study investigates the sex- and age-related differences in ABRG and evaluates their possible role in arrhythmia vulnerability. Electrocardiographic imaging (ECGI) was performed in 22 healthy volunteers (16 females, 6 males) during sinus rhythm, and ABRG was determined from average activation-recovery intervals (ARI) at the ventricular apex and base. Different ABRGs were simulated in a male and a female model of human ventricular epicardium with sex-specific electrophysiology[1,2] by simultaneously adjusting the apicobasal gradient of I_{Kr} and I_{Ks}. The models were burst paced from the ventricular apex and right ventricular outflow tract (RVOT) to assess the effect of ABRGs on arrhythmia vulnerability. In patients, longer ARIs at the ventricular base than the apex were observed in 10/16 females and 5/6 males. ABRG tend to diminish and eventually invert (longer ARIs at the apex than at the base) with increasing age (Fig. A). In the simulations, ventricular re-entry was inducible in the presence of |ABRG|>50 ms in both the male and the female models, irrespective of the ABRG orientation (Fig. B, C). We conclude that ABRG diminishes with age in both the male and female human ventricles, and steep ABRG increases ventricular arrhythmia vulnerability, regardless of its orientation. Additional studies should investigate the underlying mechanism of the age-related ABRG changes and their clinical relevance.



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Beyond the phase singularity concept: a quasi-particle viewpoint on transient and complex arrhythmia patterns

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During cardiac arrhythmias, complex spatiotemporal patterns emerge that are still incompletely understood. To analyse these patterns, isochrone maps can be used, which display local activation time (LAT). For repeated activity, it is convenient to also compute the activation phase. During ventricular fibrillation, Gray et al. [1] identified isolated singularities of phase. Recently, it was noted that at the center of linear core rotors, an extended phase discontinuity occurs [2,3], also called phase defect. These phase defects appear either where an incoming wave hits unrecovered tissue, or at the interface of a local inhomogeneity. While conduction block sites are clearly visible in LAT maps, phase singularity detection algorithms identify false pairs of phase singularities instead.

To analyse short-lived critical processes during arrhythmogenesis, we determined the following special points [4]: (1) The intersection of a wave front with a phase defect is called a head; (2) we call the intersection of a wave back with a phase defect a tail; (3) the end points of a conduction block line have been described before as pivots. We show that these three points are robust against small deformations of the medium and are therefore topologically conserved quasi-particles in the bulk of the medium, just like classical phase singularities. We propose to name the quasi-particles 'cardions'. In three dimensions, cardions form string-like objects that generalize classical filaments.

As a first result we so far identified four bound states of cardions. We reveal that conduction block growth involves typically three cardions moving together, while their shrinking involves only two quasi-particles. Secondly, we present a fast numerical tracking method for heads and tails on optical mapping datasets. Thirdly, the 'twiston' identified by Fenton and Karma [5] appears naturally in our framework as a quasi-particle of co-dimension 3. Lastly, we predict new complex states of branching phase defect surfaces that can explain different activation patterns on epi- vs. endocardial surfaces.

In conclusion, we present a unified theory that integrates phases, fronts, backs, conduction blocks and filaments in two or three spatial dimensions. First applications to simulated and experimental data suggest that the framework can help reveal arrhythmia mechanisms and facilitate analysis.

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From alternative splicing to Frank-Starling: can cardiac mechanics be quantitatively conceptualised bottom-up

Gotthardt M[1,2], Radke MH[1], Deminanenko L[1,2], Badillo-Lisakowski V[1]
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Cardiac function is tightly regulated at different timescales – in response to exercise, healthy aging, and disease. Alternative splicing, a pivotal mechanism in the diversification of gene expression, plays a crucial role in the long-term adaptation of cardiac muscle dynamics. Short-term adaptation in response to mechanical input has been studied down to the context of beat-to-beat variations and includes the Frank-Starling law of the heart, which describes the relationship between stroke volume and end-diastolic volume. Still, the integration of molecular mechanisms into this macroscopic phenomenon remains inadequately understood. In a bottom-up approach, we work from identifying the proteins that make up and associate with the sarcomere, their differential isoform expression, and their interaction within and between two large molecular machines in the cell: the spliceosome and the sarcomere. Utilizing a combination of multi-omics approaches, high-resolution imaging, and computational modelling, we investigated the impact of alternative splicing on sarcomere function and overall cardiac mechanics. RNA sequencing (RNA-seq) and mass spectrometry were employed to profile splice variants and their corresponding protein isoforms in both healthy and diseased myocardium[1]. We take our findings to the single-cell level, iPSC-derived engineered heart tissue, and the isolated heart to reveal how mechanical input is converted to short-term functional adaptations and long-term trophic adaptations. Further analysis showed that deleting full-length titin versus the titin M-band region led to differential mechanosignaling and cardiac phenotypes, emphasizing the importance of specific regions of titin in mechanotransduction and cardiac response[2]. Additionally, studies using titin-BioID knock-in mice have provided insights into the sarcomeric structure-function relationship, further validating the crucial role of titin in cardiac mechanics[3].
These findings underscore the critical role of alternative splicing in regulating cardiac mechanics and illustrate a direct molecular mechanism influencing the Frank-Starling law through the modulation of sarcomere properties, such as those in the TTN gene. This study highlights the potential of alternative splicing as a critical regulator of cardiac mechanics and offers a quantitative framework for future research in cardiac pathophysiology.

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Research data management at the interface between the analogue world and its digital representation: What next?

Hook D

The rate of production of research data is outpacing the speed of evolution of the established mechanisms of the scholarly record. This single fact means that research is less impactful as it is more difficult to understand what is known, it is less efficient as experiment are reproduced unwittingly rather than intentionally, and it opens the door to fraud at multiple levels. This talk will examine some of the key issues of the use of data in research today and suggest some technologies that are beginning to address these challenges.

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Bond graph protein models for cardiac physiology

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Bond graphs provide a useful level of abstraction for modelling protein function for a wide range of protein functions ... metabolic reactions, membrane transporters and ATPase pumps, ion channels, myofilament mechanics, receptors and signalling, etc,[1]. They can also be used for modelling at the level of systems physiology (e.g. for understanding homeostasis of blood electrolytes, blood pressure and fluid volume, etc). This talk will show how bond graph approaches ensure that the equations of physics (conservation of mass, charge and energy, respectively) are automatically satisfied, and how they can generate CellML-encoded models both at the level of proteins and intracellular mechanisms and at the whole-body systems level. In particular we show how bond graph templates are developed for cardiac myocyte proteins, including enzyme-catalysed metabolic reactions, the sodium-potassium and calcium ATPase pumps, myofilament ATPase and control proteins, and members of the SLC transporter superfamily (including glucose transport, bicarbonate transport and sodium-calcium exchange, and sodium-hydrogen exchange). These can be parameterised for a specific cell and tissue type for which the experimental kinetic data is available. We also show how analytic expressions can be derived for a representative four- or six-state models, given reasonable assumptions associated with steady state flux conditions, while always preserving thermodynamic consistency. Finally, we present details on fitting parameters to experimental data for the glucose and other transporters/exchangers and show how well the steady state flux expressions match the full kinetic analysis.

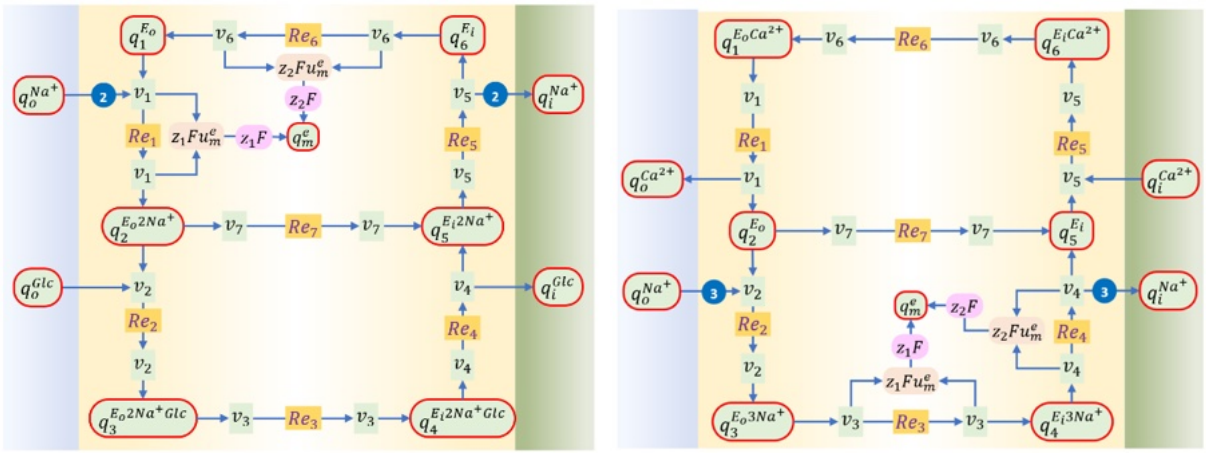

Figure 1: Examples of bond graph models: (left) the electrogenic sodium-glucose cotransporter (SLC5A1/SGLT1), and (right) the sodium-calcium exchanger (SLC8A1/NCE).

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Building a ligand transcriptome encyclopedia for the heart

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Cardiac ligands mediate cell-cell communication and control cardiac biology and function. Adrenergic drivers of disease have been extensively studied and targeting these pathways remains the front line of cardiac th¬erapeutics. However, the full repertoire of ligands that control heart function and their mechanisms remain unknown and can be difficult to dissect in vivo when many ligands may impact other cardiovascular parameters such as vessel dilation or fluid retention. To address this, we have characterised contractile function and transcriptional signatures for cardiac ligands across 500 human cardiac organoids (hCO) to create an encyclopedia of these responses.

A library of 80 endogenous ligands and 10 small molecule agonists was curated to target >100 plasma membrane receptors expressed in both the human heart and hCO. The library included catecholamines, peptide hormones, cytokines, lipid mediators, and growth factors. hCO contractility parameters were assessed 4 and 24 hours after ligand stimulation (n=5 hCO per ligand). A semi-automated single hCO RNA-seq pipeline was developed to assess the transcriptional responses to each ligand which we could directly correlate with hCO contractile parameters (i.e. rate, force).

Dimensionality reduction of the transcriptomic data revealed distinct clusters, including inotropes, endothelins, fibrotic factors, and multiple inflammatory clusters separating interleukins and interferons (Fig 1A). By overlaying contractile data, we identified cluster-specific functional differences, for example opposite activation and relaxation parameters for inotropes vs endothelins despite both increasing force and rate (Fig 1B). Using differential expression analysis, unique ligand-induced transcriptional signatures have been identified which we have started exploring in human heart failure transcriptomes to predict aberrant cellular signalling. Together, this study provides a novel resource for a systems-level approach to understanding ligand control of cardiac function with the goal of understanding disease drivers and improving patient stratification.

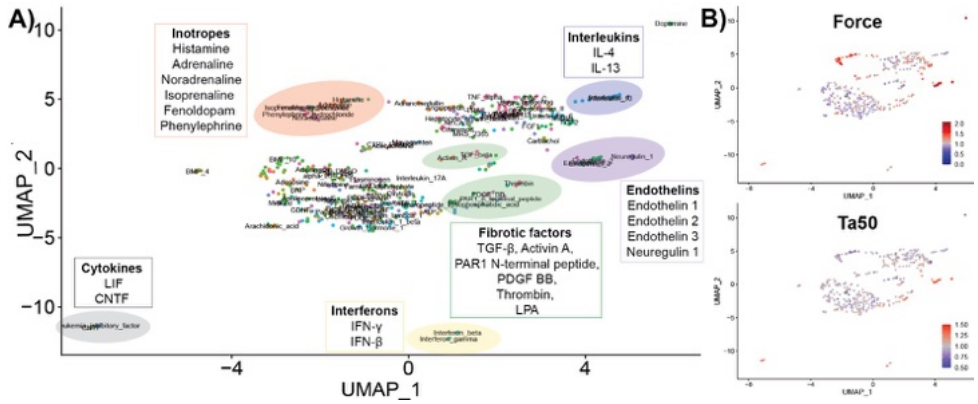

Figure 1: Dimensionality reduction of hCO ligand transcriptional profiles provides broad overview of shared and divergent pathway regulation for ligand signalling in the heart. A) UMAP plot of single hCO bulk RNA-seq conducted 24 hours after ligand stimulation. B) UMAP labelled by contractile function: force and Ta50 (time to 50% activation).

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Extended-volume 3D Imaging and Functional Recordings of the Human Intrinsic Cardiac Nervous System

Sands GB[1], Prince B[2], Ashton J[1,2], Ahmad A[2], Anderson M[3], Lever N[1,4], Ramanathan T[3], Baddeley D[1], Smaill BH[1], Montgomery JM[2]

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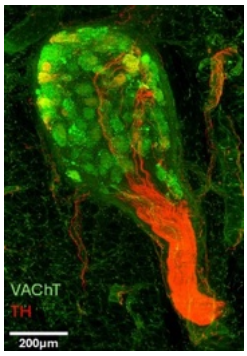

The intrinsic cardiac nervous system (ICNS) is a specialised part of the autonomic nervous system that innervates the heart at clusters of neurons named ganglionated plexi (GPs) that regulate cardiac function. Remodelling of innervation and altered GP activity have been shown in rats to correlate with atrial fibrillation (AF),[1] indicating neural plasticity of the arrhythmic substrate; however, not previously in humans.

Adipose tissue was resected from the region of the right atrial GP in both non-AF and AF patients undergoing open-heart surgery. Samples were cut into mm-thick slices, and electrophysiological properties of the GP neurons were acquired using whole-cell patch clamp techniques.[2] Slices were labelled for structural features and imaged at the single-cell level using confocal microscopy and across the entire GP using custom extended-volume imaging.[3] Human GP neurons showed a widely varying morphology and exhibited greater dendrite complexity compared to the rat, with frequent observation of a dendritic "halo" surrounding the soma and individual neurites extending hundreds of micrometres from the cell body. Whole-GP imaging showed most neurons are cholinergic, though GPs from AF patients showed decreased cholinergic and dual phenotype neurons and an increase in noradrenergic neurons. Single action potentials showed no difference in passive membrane properties or kinetics. However, GP neurons from AF patients displayed increased excitability and decreased accommodation, correlated with an increase in synapsin1 density.

The combination of cellular electrophysiological recordings with confocal imaging of ganglia reveals structural and functional differences in ICNS neurons from patients with and without AF. This neural plasticity contributes to the AF substrate through altered autonomic influence on atrial function and provides a potential AF therapeutic target to decrease GP excitability.

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Optimised wet-lab instrumentation for dry-lab research into cardiac structure and function: how to engineer the bi-directional cross-talk between the analogue world and its digital representation

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Every valid and useful model of reality is based on high-quality observations: 'to measure is to know'. Yet, often, new knowledge can only be teased out of measurements with the use of analytical and statistical methods, implemented in computational models. In the process, model predictions can suggest new hypotheses, which may in turn require the development of new measurement tools. How can one better engineer the 'bidirectional cross-talk' between model and reality? What are the conditions and practices that optimise this process? Our own pursuit of optimality has resulted in a suite of custom 'wet-lab' instruments with which we gather functional data from the heart and its tissues [1,2]. This requires a multidisciplinary approach, drawing upon knowledge and skills in physics, biology, chemistry, mathematics and computing. During experiments we tightly control the physical and biochemical inputs to cardiac samples (stimulation rate, temperature, chemicals, oxygen), observe the variables that define and affect their function (geometry, sarcomere length, $[Ca^{2+}]^i$, load), and measure the resulting performance-related outputs (force, heat, work). Tissues are often retained for post-experiment structure and biochemical analysis. Experimental data are analysed via mathematical modelling and interpreted using physiologically justified parameters, allowing an integrative 'whole-picture' understanding [3]. This approach often works well. The close link we maintain between instrumentation development, physiological experimentation and mathematical modelling [4] has produced insights that have implications for human heart health. But our tools and techniques are by no means optimal. There are several bottlenecks and barriers that impede progress. Here, we present an overview of what we think we are doing well, together with what we know we ought to be doing better.

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In-silico Modeling of Multi-Electrode Arrays to Enhance Cardiac Drug Testing on Heterogeneous hiPSC-CM Tissues

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Introduction: Cardiomyocytes derived from human induced pluripotent stem cells (hiPSC-CMs) [1] offer a new means to test in-silico patient-specific drugs and to study chamber-specific cardiac diseases [2]. At a tissue level, multi-electrode arrays (MEAs) [3] measurements of extracellular field potentials (FPs) from a network of hiPSC-CM have recently garnered significant attention for their applications in disease modeling [4]. The existing cardiac in-silico model accurately represents heart tissue using multiscale and multiphysics parabolic systems of nonlinear partial differential equations (PDE) and integrates the space-time evolution of intracellular, extracellular and transmembrane potentials but lack representation of the MEA's electrodes.
Methods: By calibrating conductivities for intra and extracellular spaces and considering membrane and electrode parameters such as membrane surface per volume (), membrane-specific capacitance (Cm), electrode capacitance (Cel), electrode ground and internal resistance (Rel and Ri), electrode thickness (zthick), and location of the initial activation, we construct a novel MEA-hiPSC-CM in-silico model. This model accurately replicates MEA recordings and enables us to investigate various factors influencing action potential biomarkers, thereby elucidating the conduction properties and field potentials in both healthy and senescent cardiomyocytes.
Results and Discussion: Our MEA-hiPSC-CM mathematical model allows us to identify phenotype-specific electrical biomarkers which are critical for understanding chamber-specific senescence-associated cardiac diseases and facilitating drug screening for age-related cardiac disorders. These advances will improve our insight into cardiac arrhythmias, guiding the development of targeted therapies for aging organs and potentially improving patient outcomes.

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Myocardial Metabolic Response to Acute Ischemia Causes Mechanical Dysfunction Following Reperfusion

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The balance between ATP supply and demand in the myocardium is impeded in ischemia, resulting in a series of metabolic changes that are hypothesized to lead to cell death and mechanical dysfunction after reperfusion. During ischemia, an accumulation of NADH and succinate occurs, creating an excessively reduced system affecting both mitochondrial matrix and cytosolic metabolic reactions[1]. In addition, ischemia leads to an elevation of AMP, and increased downstream adenine nucleotide degradation and depletion[2]. Upon reperfusion, respiration on accumulated succinate results in both the production of pathological levels of reactive oxygen species (ROS)[1] and high concentrations of oxaloacetate (OAA), a potent inhibitor of succinate dehydrogenase.

Pathological ROS production and adenine nucleotide depletion are hypothesized to contribute cardiac mechanical dysfunction after an ischemia. We hypothesize a route of OAA clearance is needed to restore physiological respiration. These hypotheses were tested using two methods: (1) experiments with purified mitochondria paired with predictions from our computational model of mitochondrial metabolism to determine metabolic profile during anoxia and reoxygenation and

(2) a conditional knockout of myocardial AMP deaminase, to assess if and how blocking purine degradation affects metabolic state and mechanical function in ischemia and after reperfusion.

Respiration and metabolic data from cardiac mitochondria revealed succinate accumulation occurs through succinate dehydrogenase reversal during anoxia and OAA clearance occurs rapidly through glutamate-oxaloacetate transaminase compared to malic enzyme and oxaloacetate decarboxylase. Additionally, diminished cardiac mechanical function following ischemia and reperfusion is associated with degradation of adenine nucleotide pools. Moreover, perturbation of the nucleotide degradation pathway alters myocardial mechanical function. These data indicate a link between adenine nucleotide degradation during ischemia and mechanical dysfunction after reperfusion.

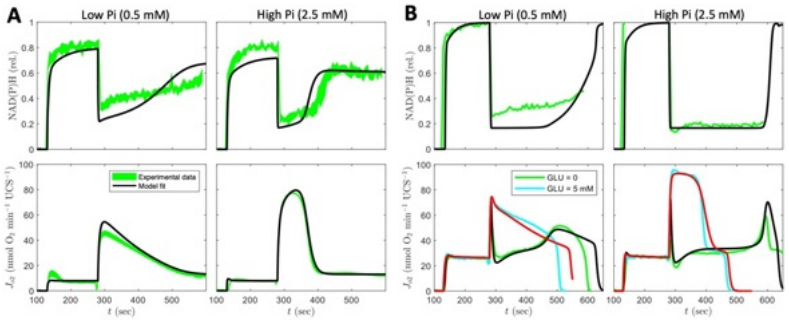

Figure 1. Experimental data and model fits of mitochondrial relative NAD(P)H and oxygen consumption during respiration on (A) pyruvate + malate and (B) succinate +/- glutamate.

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Cardiac fibrosis affects electrical conduction and arrhythmogenesis in a pacing-rate-dependent manner

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Cardiac fibrosis is recognised as one of the key factors contributing to electrical conduction disturbances. However, how various forms of fibrosis affect conduction is uncertain, hindering predictive concepts regarding cardiac electrophysiology and arrhythmogenesis. Here, we implemented a combination of advanced imaging techniques and image analysis software tools to quantify and correlate macro-scale cardiac electrophysiology with 3D micro-scale structural reconstructions of whole ventricles in an arrhythmogenic cardiomyopathy (ACM) mouse model. We characterised the dynamics of conduction wavefronts travelling through fibrotic regions, confirming that ACM involves a replacement of cardiomyocytes with fibrotic tissue, contributing to ventricular electrical dysfunction. Moreover, we observed that conduction through fibrotic areas shows a pacing-rate-dependent behaviour, where conduction failed at high stimulation frequencies, promoting reentrant arrhythmias. We generated a computational model of the electrical activity of representative hearts combining myocardial anatomy, a fine quantification of 3D myocyte alignment, and detailed 3D fibrosis maps based on structural reconstructions. We found that the dependency on the pacing rate of conduction through fibrotic areas cannot be explained solely by structural remodelling of the tissue (neither including fibrosis nor altered cardiomyocyte organisation). This suggests that an accurate prediction requires consideration of electrophysiological remodelling of the myocardium and/or heterocellular interactions. Taken together, this study describes a new pro-arrhythmogenic aspect of cardiac electrophysiology in fibrotic tissue, namely the frequency-dependence of conduction, highlighting the dynamic functional nature of conduction block in the presence of myocardial fibrosis, the need for dynamic protocols to characterise conduction, and the desirability of further exploration of underlying (hetero-)cellular electrophysiological mechanisms.

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Heart-AI interface: flexible and transient bioelectronics

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Introduction: Cardiovascular disease (CVD) remains the leading cause of death in Europe and the USA. Pharmacological therapy for heart failure and arrhythmias is disappointing despite decades of research into the biological mechanisms of CVD. In contrast, device therapies have been highly successful, including implantable pacemakers and defibrillators, ventricular assist devices, balloon angioplasty, stents, transvenous aortic valve replacement, ablation catheters, etc.

Methods: We aimed to develop novel bioelectronic approaches to cardiovascular diagnostics and therapy based on recent progress in materials science and organ conformal bioelectronics, including transient bioelectronics. We also aimed to empower the new generation of implantable and wearable devices through embedded machine-learning signal processing.

Results: Organ conformal bioelectronics platform allows the development of implantable and wearable devices for CVD, which are stretchable and flexible and conform to the shape and mechanics of a beating heart without obstructing its function while providing high-resolution multiparametric monitoring of physiological parameters, including metabolism, electrophysiology, mechanics, pH, temperature, molecular markers.[1] Combining implantable and wearable devices into a wireless network provides solutions for heart rhythm and heart failure management.[2] The development of novel bioresorbable materials and fabrication approaches resulted in the development of transient implantable devices for temporary pacing, defibrillation, and monitoring of cardiac patients.[3]

Discussion: Cardiovascular engineering has been highly successful in diagnosing and treating CVD, such as heart failure, coronary disease, and heart rhythm disorders. The development of a novel organ conformal bioelectronics platform resulted in novel approaches for multiparametric CVD monitoring, real-time machine learning-enabled data processing, and therapy delivery. The transient bioelectronics platform provided the foundation for mm-scale transient devices to monitor and stimulate the heart and nervous system. Empowered by machine learning, organ conformal and transient bioelectronics will revolutionize biomedical CVD research and clinical care.

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Model Personalization In The Infarcted Porcine Heart: Insights From ARI-based Action Potential Calibration

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Recent studies showed that in silico modelling can be used to predict scar-related arrhythmia risk and ablation targets (i.e., substrate of arrhythmia). However, model personalization is still relying on 'average' electro-physiological (EP) parameters taken from literature, largely due to a paucity of their identification from EP clinical data. In addition, the post-infarction time when such data is acquired is important and could be critical for reproducible simulations of action potential waves.

We hypothesized that activation-recovery interval (ARI), a surrogate for action potential duration (APD), can be extracted from catheter-based intracardiac electrograms (iEGMs) and further used to parametrize models for more accurate AP wave simulations per individual case. In this work we calibrated APDs using ARI values extracted from endocardial electro-anatomical maps recorded in sinus rhythm in post-infarcted swine (n=9), 5 weeks after the infarct induction. Specifically, we sought to investigate the differences in model parameters needed to calibrate simulated APDs in healthy tissue and border zone, BZ (i.e., arrhythmia substrate) when using an 'average' ARI computed from all cases versus those calibrated from ARIs extracted per each case.

We used a modified Mitchell-Schaeffer model with a FEniCSx implementation and simulated AP waves on a 2 cm virtual strand (400 elements, 100 m resolution) of healthy and BZ tissues activated by a stimulus applied 10 times, and then computed an average APD on strand from the last beat.

Results showed that average ARIs in healthy tissue and BZ for all cases were 206 $\pm$ 50.18ms (range [163, 278]) and 213 $\pm$ 52.1ms (range [170, 277]), respectively. These noticeable ARIs variations among our cases along with their corresponding simulated APDs, are supported by a complex electrical remodelling process during the post-infarction healing period. Figure 1 shows exemplary results from APD personalization using 'average' ARIs vs. per case ARIs, demonstrating significant absolute differences (i.e., up to 72 ms) which could potentially have an arrhythmogenic effect.

This work underlines the importance of EP model personalisation by individual case, indicating that it is fundamentally needed to accurately reproduce in silico the experimental observations.

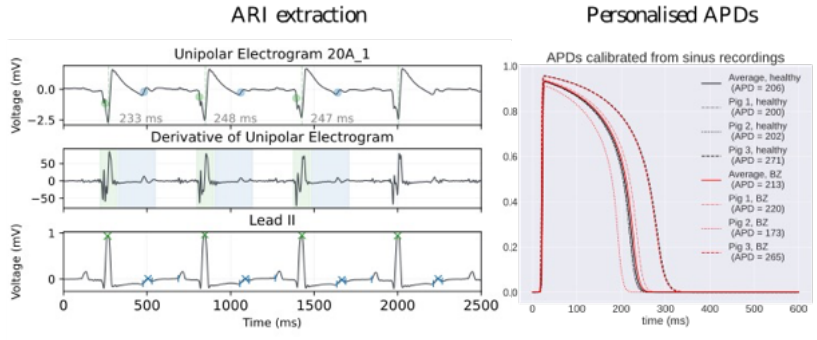

Figure 1: Left panel: Example of ARI extraction from an iEGM signal. Right panel: Calibrated APDs. Parameters τin, τclose and $u$gate were fixed in all simulations (0.3, 120 ms and 0.13, respectively). Varied parameters: τout, τopen; λ=0.2 for the BZ. Note that the tissue excitability was reduced in the BZ strand via the λ parameter.

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Automated cardiovascular material model discovery

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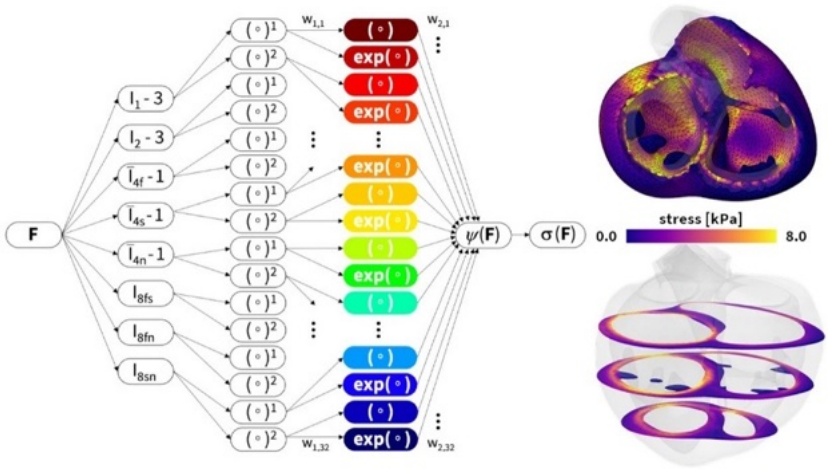
Quantifying the biomechanical behaviour of cardiovascular tissues holds immense potential to enhance our understanding of (i) smooth and cardiac muscle cell responses to mechanical cues and (ii) how structural and compositional alterations within these tissues impact their overall functional behaviour. Such insights are crucial to unravel disease mechanisms (e.g. atherosclerosis, aneurysm, myocardial infarction), to optimize and personalize current treatment strategies (e.g. annuloplasty ring or stent sizing), and to develop novel medical devices (e.g. artificial heart valves or vascular grafts). Such studies depend critically on the accuracy of the underlying constitutive models, which govern the thermodynamically consistent relationship between the tissue's deformation and internal stress state. Given cardiovascular tissue's highly non-linear, transverse isotropic or even orthotropic mechanical behaviour and a vast ever-increasing library of potential constitutive models, identifying the most accurate material model can be a challenging procedure prone to significant user bias. To resolve this subjectivity and democratize computational engineering analysis for all, we leverage constitutive artificial neural networks and machine learning to automate and democratize constitutive model discovery for these intricate materials. Based on arterial and myocardial biaxial tensile and triaxial shear testing data, our framework autonomously identifies the optimal material models and parameters from a library of over 4,294,967,296 possible material models[1]. By seamlessly integrating the discovered material models into a universal material subroutine for (in)compressible (an)isotropic tissues[2], our work advances the implementation of these models into cardiovascular finite element simulations. This not only enhances user-friendliness and robustness but also mitigates the vulnerability to human error. The automated approach signifies a significant stride towards a more inclusive, user-friendly, and accurate framework for cardiovascular biomechanics simulations, ultimately contributing to improved medical treatments for cardiovascular diseases.



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Modeling the heart cell by cell: the MICROCARD project

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Almost all cardiac arrhythmia are linked to fine-grained structural abnormalities in the cardiac tissue, but the numerical heart models that are used today cannot represent such abnormalities well because they work with elements that are far larger than a cell. The choice for such large elements has been well founded: computations with smaller elements or even individual cells were simply not feasible one or two decades ago. But the machines keep growing and with the arrival of exascale supercomputers (in the US in 2021 and in Europe in 2024) it becomes thinkable to simulate the electrophysiology of a whole heart, or a sizeable part of it, cell by cell. The MICROCARD project was funded by the European Union (EU) to develop a cell-by-cell cardiac simulation code, as one of the flagship applications of the EU's new exascale supercomputers. This application comes with many mathematical and numerical challenges which we are tackling with a collaboration between computer scientists, biomedical engineers, mathematicians, and numerical scientists, working on the simulation software itself and on the construction of geometrical models ("meshes") of the myocardium with sub-cellular resolution. Although neither the exascale machines nor our simulation software are ready to run at this time, the project has made much progress towards its goals, and many of its developments have also been made available in the widely-used OpenCARP simulation software. The recent decision to fund a second iteration of the MICROCARD project, which will run until 2027, gives us hope that we will see actual three-dimensional cell-by-cell simulations by next year.

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Modelling drug effects on cardiac function for personalised medicine: hope or hype?

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Human-based methodologies are at the central stage, as shown by the FDA Modernization Act 2.0, and 'Advancing alternative methods' (https://www.fda.gov/science-research/advancing-alternative-methods-fda/about-alternative-methods). This includes in silico techniques, such as machine learning and modelling and simulation, which are needed for the acceleration of drug safety and efficacy assessment by integrating, bridging and augmenting preclinical and clinical data. In this presentation, I will describe how two key and complementary visions have gained traction in this space, through intersectoral collaborations including regulators, industry, clinicians and academics: In Silico Trials for therapy evaluation using virtual patient populations (Viceconti et al, 2020), and Digital Twins (Corral-Acero et al, 2020).

In silico trials computationally mimic clinical trials, by evaluating therapies on populations of virtual patients using modelling and simulation powered by machine learning, large clinical datasets and high performance computing. Widely used in other industries such as automobile and aeronautics, in silico trials are crucial to follow the principle of 'doing no harm' in the evaluation of medical products, including drugs, biologicals and devices. I will describe methods and results on in silico trials for drug-induced effects on electrophysiology and contractility assessment (Dasi et al., 2024).

In silico trials rely on the construction of reliable computer models of human patho-physiology, linking to the vision of the Digital Twin, which in healthcare denotes a comprehensive, virtual tool that integrates coherently and dynamically the clinical data acquired over time for an individual using mechanistic and statistical models (Corral-Acero et al., 2020). I will describe progress in the development of virtual patient heart models personalised using clinical data including imaging and electrocardiogram recordings, and capable of explaining clinical disease phenotypes (Wang et al. 2024).

During the presentation, I will describe cardiac modelling and simulation methodologies, their application to drug development, current state-of-the-art as well as my vision for future advancements and challenges.

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Cardiac computational modelling of electrophysiology: from relaxation oscillators, to Hodgkin-Huxley, Markov, big data and AI: are we nearly there yet?

Noble D[1]

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The first mathematical model in 1928 represented the heart as a relaxation oscillator.[1] In 1960 I used Hodgkin-Huxley equations modified to fit potassium current channels to create the first experimentally-based model.[2] With just 4 ionic channels that model was very fragile. Block of a single component would abolish rhythm. Many more ionic channels were subsequently discovered. Later models became robust, thus showing that evolutionary complexity makes the heart functionally buffered against genetic or other abnormalities.[3] In most organisms, around 90% of gene functions are buffered in this way, so explaining the low association scores in GWA Studies,[4] and why polygenic scores do not successfully predict diseases states.[5] These are major challenges for Big Data Analysis and AI, since it is hard to see how these disappointing outcomes of genomics can be overcome simply through the analysis of more data. The way forward will require focus more on functional levels of organisation in living systems.[6] Physiology, and the Physiome Project, will now need to rescue gene-centred biology from the impasse it has led us into.[7-8] I speculate that AI may need to be based on water-based computation rather than silicon-based computation.[9] It took evolution 3-4 billion years to achieve that.

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Clinical translation of cardiac modeling and image analysis: digital twins to the rescue!

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Precision medicine is the vision of health care where therapy is tailored to each patient. As part of this vision, digital twinning technology promises to deliver a digital representation of organs or even patients by using tools capable of simulating personal health conditions and predicting patient or disease trajectories on the basis of relationships learned both from data and from biophysics knowledge. Such virtual replicas would update themselves with data from monitoring devices and medical tests and assessments, reflecting dynamically the changes in our health conditions and the responses to treatment. In precision cardiology, the concepts and initial applications of heart digital twins have slowly been gaining popularity and the trust of the clinical community. In this article, we review the advancement in heart digital twinning and its initial translation to the management of heart rhythm disorders.

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Production of Atrial Models at Scale: Investigating Fibres, Fibrosis, and the Importance of the End-User

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To ensure accuracy for large-scale in silico clinical trials and for realistic uptake in clinical practice, it is critical to consider reproducibility and user-friendliness during model development. We present a pipeline for constructing atrial models at scale, developed with the end-user in mind.

The atrial modelling toolkit (atrialmtk: https://github.com/pcmlab/atrialmtk) allows the user to produce patient-specific atrial meshes for electrophysiological simulation. Atrial regions and transmural variations across the atrial wall are incorporated into the meshes, and the user can select from bilayer or volumetric meshes and different fibre distributions. Fibrosis distributions can also be mapped from late-gadolinium enhancement MRI (LGE-MRI) imaging data and added to the models. To maximise usability, the pipeline includes workflows for several input types, including CT and MRI imaging data, electroanatomical mapping data, and artificial geometries such as those produced by statistical shape models. Clear instructions, details of computational requirements and the required expertise of the user are detailed at each stage of the pipeline, and relevant training materials identified, to the ensure correct use and implementation of the models.

In summary, we have developed a pipeline to reproducibly construct atrial models for electrophysiological simulation. Its success at scale has been demonstrated in a previous study of 1000 atrial geometries[1], and its usability improved through testing across multiple computer operating systems, completed by users of differing levels of expertise and familiarity with electrophysiology. By extending this testing to a wider audience and taking a similar approach in other areas of our research, we hope to further increase the engagement of clinicians with in silico modelling and digital twin initiatives and increase the likelihood of their uptake in clinical practice.

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New in-silico models and data-driven methods for valvular heart disease: the first automatic detection pipeline for the mitral valve in cardiac magnetic resonance imaging

Maleckar MM

Valvular heart disease (VHD) is increasingly a major contributor to cardiovascular morbidity and mortality worldwide, with mitral valve (MV) disease standing out due to its severe impact on cardiovascular health. Assessing the MV leaflets via medical imaging is a crucial initial step in evaluating valvular pathology. Automated identification of MV leaflets in cardiac magnetic resonance (CMR) imaging could significantly enhance clinical workflows, providing rapid diagnostic guidance and prognostic insights for patients with VHD. However, the application of advanced deep learning (DL) techniques for detecting the MV in CMR is not yet well-established. To address this gap, we introduce DeepValve (Figure 1), the first automated DL pipeline for MV detection using CMR. We evaluate the performance of various DL models for predicting MV leaflets, both as regression and segmentation tasks, and establish a baseline performance for future research. Our models were developed and tested on a clinical dataset comprising 120 CMR scans from patients with mitral valve prolapse and mitral annular disjunction. We propose novel metrics tailored for evaluating the quality of MV detection, including Procrustes metrics (PRA, PD) for the regression task and include customized Dice-based metrics (Dilated Dice, Centerline Dice) for the segmentation models. DeepValve successfully predicts the MV leaflets automatically. Our proposed hybrid model achieved the best performance with RMSE, PRA, and PD values of 6.39, 3.17, and 0.18, respectively. Additionally, the segmentation model achieved Dice, Dilated Dice, and Centerline Dice scores of 0.70, 0.77, and 0.81, respectively. This work represents a critical first step towards automated mitral valve assessment using deep learning in cardiac magnetic resonance, paving the way for improved diagnostic and prognostic capabilities in clinical settings. In a corollary in-silico patient model, we demonstrate that abnormal stretch in the left ventricle may initiate reentry in patients with mitral valve disease. The electrophysiological mechanism linking mitral valve prolapse (MVP), premature ventricular complexes, ventricular arrythmia and sudden cardiac death is unknown. Frequently hypothesized is the involvement of stretch activated channels (SACs), which can trigger depolarizations or cause early repolarization due to myocardial stretch. Through these mechanisms, pathological traction of the papillary muscle (PM), as has been observed in patients with MVP, may lead to abnormal electrical activity and subsequent arrhythmia. Based on a patient with MVP and mitral annulus disjunction, we modeled the effect of abnormal PM traction in a detailed medical image-derived ventricular model by activating SACs in the PM insertion region (Figure 2). Vulnerability windows for reentrant arrhythmia were identified by varying the timing of SAC activation; from 1 to 350 ms after simulated QRS onset. We investigated conditions for reentry by varying the size of the activated SAC region (radius = 7-10 mm), the SAC reversal potential (E_{SAC} = -10 to -70 mV) and tissue conductivity (0-60% reduction in conduction velocity). Reentry required a region of SAC activation of at least 8 mm radius. For E_{SAC} -10 to -30, SAC activation during the T wave could trigger local depolarizations which resulted in reentry. For E_{SAC} -40 to -70, SAC activation during the QRS complex could cause local early repolarization which lead to reentry. Reduction of tissue conductivity influenced the reentry vulnerability window and sustainability but did not cause a consistent increase in inducibility. Stretch of the PM insertion region following sinus activation may initiate ventricular reentry in patients with MVP. Depending on the SAC reversal potential and timing of stretch, the

reentrant mechanism may be either local depolarizations or local, early repolarization.

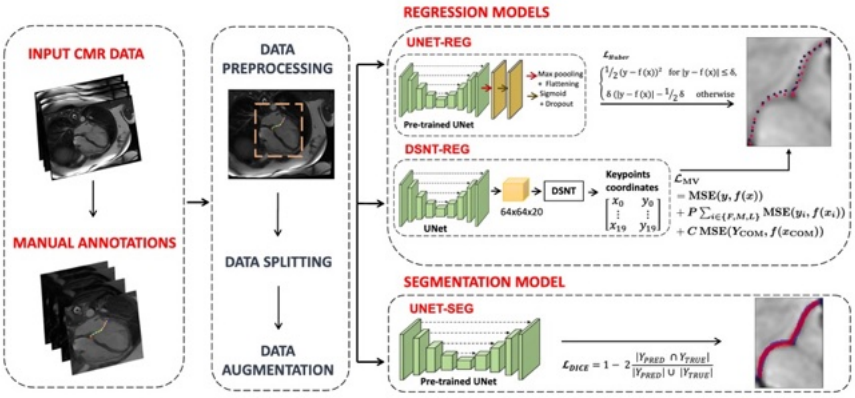

Figure 1. Overview of the DeepValve pipeline for automatic MV detection. From left, input CMR sequences undergo manual annotation. Subsequent steps include data preprocessing, splitting, and augmentation prior to model training. At right, the three models developed and tested in the DeepValve pipeline: a regression model utilizing a pre-trained U-Net architecture for point coordinate prediction (UNET-REG), a hybrid model leveraging U-Net combined with DSNT for keypoint coordinate extraction (DSNT-REG), and a segmentation model based on a pre-trained U-Net (UNET-SEG) finetuned for out task. Loss functions LHuber, LMV and LDice are employed to evaluate the regression and segmentation models, respectively, against ground truth annotations.

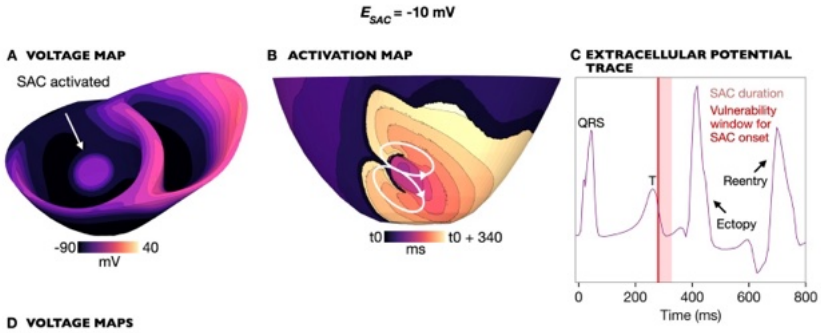

Figure 2. Example reentry for in a model with ESAC = -10mV, APD206290, healthy conductivities and a SAC region of 10 mm radius. SAC onset is at 278 ms after start of sinus activation. (A) Voltage map at 10 ms after SAC onset, showing a depolarized SAC region. (B) Activation map showing the reentrant circuit which forms when the SAC-induced activation escapes the SAC region, with t0 indicating the time of SAC onset. (C) Extracellular potential recorded from a point on the left shoulder during the same simulation withthe period of SAC activation (light red panel). The vulnerability window for which simulations resulted in reentry (SAC onset 278-284 ms) is overlaid (thin, dark red panel). The T-wave is followed by two spikes in extracellular potential: the first is an ectopic beat triggered by SAC-induced depolarization and the second is caused by the reentrant wave (see arrows). Time is measured from start of sinus activation.

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Roles of Stretch-Activated Channels in Atrial Fibrillation: From Cellular Dynamics to Whole-Heart Simulations

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Stretch-activated channels (SACs) in atrial myocytes may be involved in the pathogenesis of atrial fibrillation (AF), but their exact role remains unclear due to limited experimental data and the frequent omission of mechano-electric feedback in whole-heart simulations. This study investigates the impact of SACs on atrial electrophysiology at the cellular level and in whole-heart simulations. A non-selective SAC was modeled according to Gerach and Loewe[1], and included in the total ionic current of the atrial cell model following Courtemanche et al.[2]. Parameter uncertainty regarding the channel density was addressed by varying ± 50 % of the baseline value. A fully electro-mechanically coupled whole-heart framework[3] was used for tissue simulations. Besides healthy tissue parameters, AF-prone tissue characteristics were considered by reducing atrial myocardial conductivity by 60 %.

Figure 1 shows that SACs led to afterdepolarizations when stretch was applied to a previously electrically stimulated cell. Action potentials were induced for high cellular stretch and high SAC density. Whole-heart simulations identified regions of high cellular stretch, particularly in the upper regions of the atria and near the atrioventricular valves, as vulnerable to afterdepolarizations. These contributed to atrial refractoriness and conduction blocks. No ectopic beat was triggered for healthy tissue simulations, while SACs triggered one at reduced tissue conductivity. These findings suggest that SACs in vulnerable areas can cause ectopic beats and conduction blocks, leading to reentrant activation and contributing to AF pathogenesis.

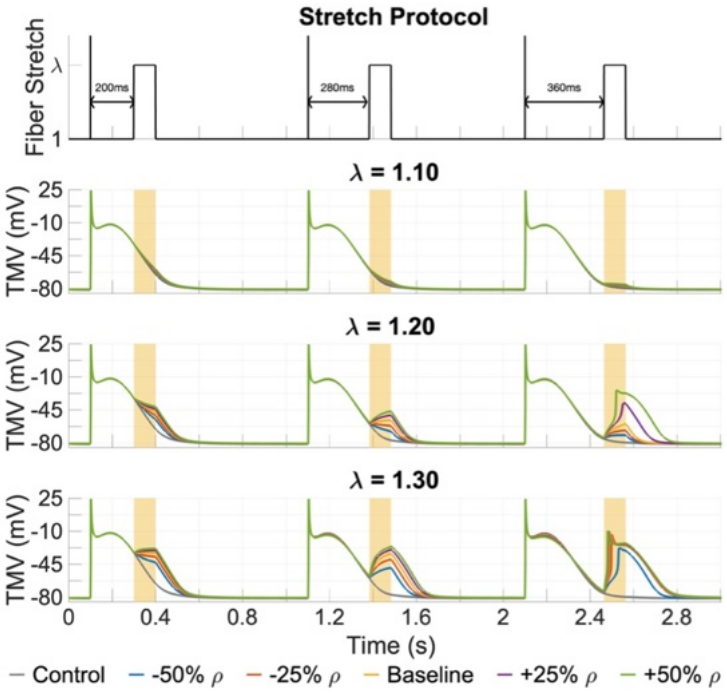

Figure 1: Transmembrane voltage of a repeatedly electrically stimulated cell in response to cellular stretches applied according to the shown stretch protocol.

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[2] Courtemanche M, Ramirez RJ, and Nattel S. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. Am. J. Physiol. Heart. Circ. Physiol. 1998:H301-H321.
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Accelerated atrial pacing reduces left-heart filling pressure: a combined computational-clinical study

Van Loon T[1], Rijks J[2], van Koll J[2], Cornelussen R[2,3], van Osta N[1], Luermans J[2], Prinzen F[3], Linz D[2], van Empel V[2], Delhaas T[1], Vernooy K[2], Lumens J[1]

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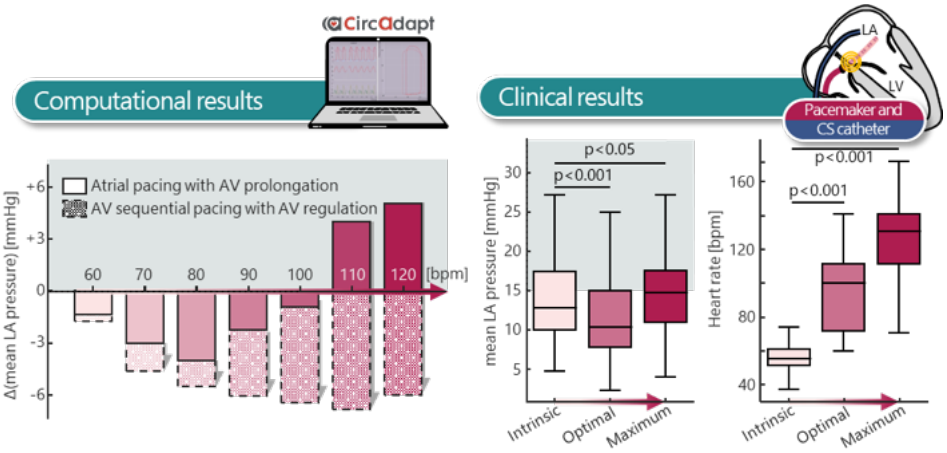
Introduction: Accelerated atrial pacing offers potential benefits for patients with heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF). In this study, we test the hypothesize that these benefits are caused by a pacing-induced reduction of left-heart filling pressure.

Methods: Firstly, the CircAdapt model was used for an in silico pilot study. A virtual accelerated atrial pacing protocol was simulated in a representative virtual HFpEF patient to investigate the relationships between mean left atrial pressure (mLAP), pacing rate and atrioventricular (AV) conduction delay under well-controlled circumstances. Secondly, 75 consecutive AF patients undergoing catheter ablation underwent invasive mLAP assessment and AV delay (PR interval) during intrinsic sinus rhythm and atrial pacing with 10bpm increments up to Wenckebach.

Results: Both computer simulations and clinical data demonstrate that moderately accelerated pacing (80-110bpm) significantly decreases mLAP, as compared to intrinsic heart rate. Furthermore, higher pacing rates (>110bpm) were associated with significant increases in mLAP, exceeding the value at intrinsic heart rate. In the clinical data, PR interval prolonged incrementally with increasing pacing rates. The computer simulations demonstrate that appropriately timed AV delay (i.e, reducing AV delay with increasing pacing rate) would result in more left-heart filling pressure reduction due to more optimal ventricular filling, even at higher pacing rates, thereby hypothesizing on a potential therapeutic improvement via AV sequential pacing.

Conclusion: Atrial pacing at moderately increased rate acutely reduces mLAP, suggesting its potential as a therapeutic intervention to alleviate left-heart filling pressures in patients with AF and/or HFpEF. Furthermore, the virtual patient simulations suggest that the beneficial effects of this therapy can be further optimized through AV sequential pacing.



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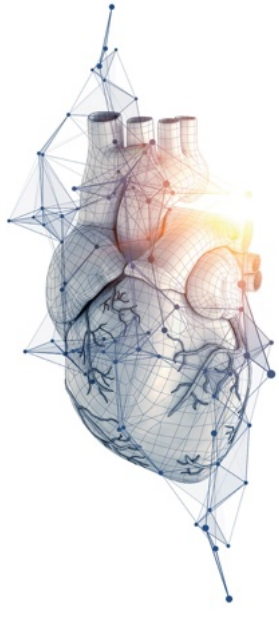
CARDIAC PHYSIOME
2024

Integrating experimental and mathematical approaches to advance cardiac physiology research



Freiburg, Germany
12 - 14 September 2024

Poster Abstracts I

P01: Multiscale and multiphysics computational modeling of cardiac electromechanics

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We present a comprehensive mathematical and computational framework for the numerical simulation of cardiac electrophysiology and electromechanics. The frameworks supports the modular and flexible combination of models of different fidelity and complexity for cardiac electrophysiology, muscular contraction, tissue mechanics, hemodynamics and the circulatory system[1, 2]. We discuss numerical methodologies that support the efficient solution of the proposed model, balancing accuracy and computational efficiency, and tackling the inherent complexity arising from the multiscale and multiphysics nature of the cardiac system. Moreover, we address effective methods to couple models of the cardiac conduction system to myocardial electrophysiology. Results of numerical simulations showcase the capabilities of the proposed framework in terms of realistically reproducing the behavior of the human heart, under both healthy and diseased conditions, and highlight the impact of the different modeling and numerical choices on the numerical outputs.

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P02: A strongly coupled electromechanical model of Heart Failure with myocardial infarction for in silico trials

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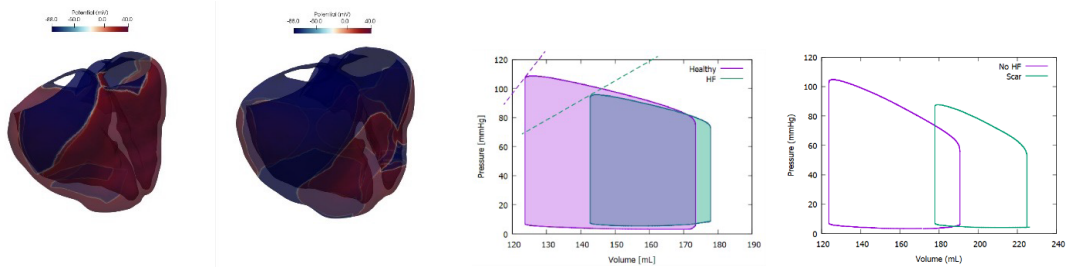
Introduction: Heart Failure (HF) is a common cardiovascular disease in which the failing heart undergoes electrical and structural changes that may lead to cardiac arrhythmias. In this study a multiscale model of the human ventricles from single cells to the 3D organ is presented.
Methods: In this study a clinical dataset from a patient with a history of infarct scar geometry is considered, also including the infarct scar geometry. The model considers the coupling between the electric[1] and mechanical[2] activities of the heart using an excitation-contraction model[3], which is the fundamental physiological process at the basis of the cardiac function. HF conditions are characterised by prolonged action potential and alterations in intracellular calcium handling, therefore the model includes the effects on the contractility and deformation to portray a complete picture of this cardiac pathophysiology. HF electrical remodel is considered following[4]. The infarct scar is considered as non-excitable tissue. Electrical remodelling in the border zone by reducing the maximum conductance in certain ionic channels has been considered, also reducing conductivity in the tissue. The electromechanical model is coupled with a 0D closed-loop circulatory model of the vascular network.
Results: The obtained pvloops showed a loss of inotropy for the HF condition and a decreased ejection fraction while left ventricles volumes increase. The presence of the infarcted scar accentuates the loss of contractility, as can be shown in Figure 1.
Discussion. This study presents a mathematical and computational framework for the simulation of cardiac electromechanics. The simulated results highlight the need to evaluate mechanical outcomes.



Comparison between a baseline state of the heart with respect to a HF condition. Pvloops for baseline, HF and infarcted heart.

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[3] Land S. et al. An analysis of deformation-dependent electromechanical coupling in the mouse heart. J Physiol, 2012
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P03: Multi-Modal Optical and Ultrasound Imaging of the Heart's Electromechanics: A High-Resolution Ex Vivo Platform

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The heart's contractions are triggered by action potential and calcium waves, which propagate through the cardiac muscle at high speeds. Imaging the contracting tissue as well as the electrophysiological wave phenomena simultaneously has remained a challenge, in parts because it lacked the numerical methods to process the corresponding imaging data. For instance, in the past, almost all optical mapping studies were performed with contraction-inhibited hearts uncoupled with pharmacological excitation-contraction uncoupling substances. As a consequence, there are very few studies in which optical imaging and structural imaging, such as ultrasound, are combined to measure the heart's electrophysiology and mechanics simultaneously[1]. Here, we introduce a high-resolution ex vivo imaging system, which comprises panoramic optical mapping and high-speed 4D ultrasound imaging. We use the system to study the electromechanics of isolated hearts at high spatial and temporal resolutions. The optical system comprises up to 24 high-speed cameras with which we image action potential and/or calcium waves on the entire contracting heart surface[2]. We use three-dimensional multi-view motion tracking and ratiometric imaging to compensate for motion artifacts and measure action potential waves as well as strain across the surface of isolated hearts placed inside a custom-designed soccer ball-shaped imaging chamber. The chamber facilitates even illumination with pulsed excitation light and imaging in a panoramic fashion. While generating three-dimensional reconstructions of the entire deforming ventricular surface with corresponding high-resolution voltage-sensitive optical measurements, we cross-register the superficial optical data with three-dimensional ultrasound data using opto-acoustic cross-registration calibration targets. With our setup, we can image action potential and calcium waves as well as ventricular deformation mechanics at unprecedented resolutions during sinus rhythm, paced rhythms as well as tachyarrhythmias. Our imaging setup defines a new state-of-the-art in the field and can be used to study the heart's electromechanical dynamics during health and disease.

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P04: The Effect of Left-Heart Myopathy on Diagnosing Mitral Valve Stenosis: An in-silico Investigation

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Introduction: The shift in mitral stenosis (MS) etiology from rheumatic to calcific valve disease, commonly seen in elderly patients with cardiomyopathy, challenges the non-invasive differentiation between valve- or tissue-related causes of hemodynamic abnormalities. This study examines the effect of left-heart myopathy on echocardiographic assessment of MS severity and potential therapy response.

Methods: The CircAdapt model of the human cardiovascular system was used to simulate the effect of MS on cardiac hemodynamics in virtual patients with varying types and degrees of diastolic dysfunction due to impaired left atrial (LA) contractile function and reduced left ventricular (LV) compliance.

Results: The obtained pvloops showed a loss of inotropy for the HF condition and a decreased ejection fraction while left ventricles volumes The mean gradient (MG) remained unaffected by LV and LA myocardial abnormalities (Fig. 1A), while the presence of reduced LV compliance resulted in disproportionately low pressure half-time (PHT) (Fig. 1B). Following mitral valve intervention, mean left atrial pressure (mLAP) decreased from 7 mmHg for healthy myocardium to 1 mmHg for combined LV and LA dysfunction (Fig. 1C).

Conclusions: The virtual cohorts indicate that MG is a specific metric for MS severity, whereas PHT may aid in revealing impaired LV compliance. However, neither MG nor PHT predicts intervention outcome in terms of mLAP. It is therefore important to recognize the significance of distinguishing between filling pressures driven by valvular or tissue factors in clinical decision-making.

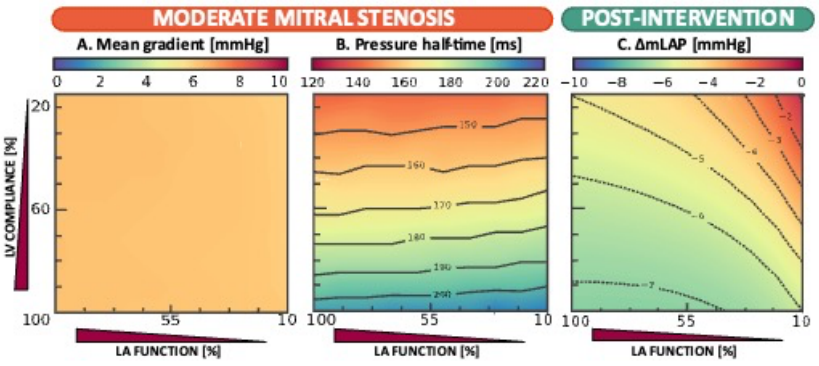

Fig. 1 Contour maps indicating the relation between changes in LA function (x-axis) and LV compliance (y-axis) for pre-intervention indices (MG and PHT) and post-intervention outcome in terms of change in mLAP.

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P05: Multiscale Integration of Active and Passive Cardiomyocyte Mechanics

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Recent studies reported that electrical stimulation of skeletal muscle resulted in an increase of muscle stiffness that was independent of active contraction[1]. The goals of the current study were: 1) to determine if activation of cardiac muscle by Ca2+ caused increased passive muscle stiffness, independent of active contraction, and 2) quantitatively assess the dynamic and calcium-dependent properties of titin mechanics in the intact cardiac sarcomere, and to describe the behavior of the system in a self-consistent mathematical model. The passive myocardial stiffness of mouse demembranated cardiac trabeculae was assessed by muscle stretches (20% initial length) using stretch velocities varying over three orders of magnitude [2.25 – 2.25 $\times$ 10^{-3} ML/s], at zero and high calcium levels by inhibiting active contraction using the myosin ATPase inhibitor para-nitroblebbistatin. To analyze the observed phenomena, we developed a mesoscopic-scale ensemble model of titin elastic domain mechanics that accounts for the dynamic unfolding of globular domains along the titin chain and for observed calcium sensitivity, employing PEVK domain binding to actin. Additionally, we have integrated the titin's model with strain-dependent active contraction model (i.e. the cross-bridge model), based on the approach outlined in [2] and compared the model behavior to a series of slack-restretch experiments. We observed the passive muscle force rise to a peak and then relax toward a lower steady-state level, consistent with the viscoelastic nature of cardiac muscle. Peak force was higher with faster stretch velocity (Figure 1A), but subsequent analysis revealed that stress relaxation follows a power law decay, with time constant independent of the stretch velocity. A major finding of this study was that with active contraction inhibited by PNB, Ca^{2+} increased the viscous force response to stretch 3-fold compared to the response measured under relaxed (low Ca2+) conditions. The developed model can reproduce both relaxed and high Ca^{2+} passive behavior, which, once integrated with the crossbridge model, can then contribute to several important features of slack-restretch experiments (see figure 1B). Future work focuses on using the combined model on investigating mechanisms driving the cardiomyocyte contraction at different ATP levels.

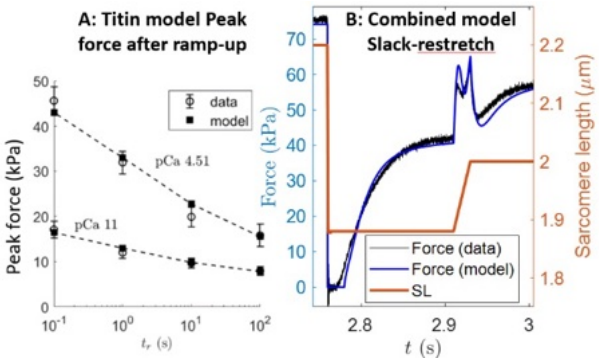

Figure 1: Model comparison to measured passive force at range of ramp durations tr and calcium concentration (A) and combined active and passive response to rapid slack and restretch protocol at saturated [Ca^{2+}].

References:
[1] Squarci C, Bianco P, Reconditi M et al. Titin activates myosin filaments in skeletal muscle by switching from an extensible spring to a mechanical rectifier. Proc Natl Acad Sci USA 2023. [2] Marzban, B., R. Lopez, and D.A. Beard, Computational Modeling of Coupled Energetics and Mechanics in the Rat. Physiome, 2020.

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P06: Challenges in meshing tissue at the micro-scale for cardiac modeling

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Numerical modeling has proven essential to understand the complex electrophysiology of cardiac cells and tissues. However, almost all modeling studies so far have used homogenised models, which cannot reproduce small-scale phenomena in structurally abnormal myocardium. Since structural abnormalities play a role in almost all cardiac arrhythmia it is important to develop models that represent the tissue cell by cell. For a faithful representation of the geometry and interconnections of the myocytes such models require micrometer resolution, meaning that millions of cells must be represented with thousands of elements each. The aim of this work was to develop efficient tools able to generate such huge and complex meshes.
Two approaches were developed: mesh generation from (i) segmented or (ii) synthetic data. (i) The first method used confocal microscopy stacks, providing volumetric images where individual cells were identified. A mesh adaptation process using the open-source remeshing software mmg[1] was then performed to obtain a final computational mesh. (ii) The second method created a synthetic cell network based on a set of rules designed to mimic real tissue. mmg was used to generate the final mesh and to improve its quality.
Both methods require the manipulation of very large and complex tetrahedral meshes, associated with a level-set function[2] and numerous internal boundaries. Our workflow and our remesher mmg have been improved and robustified to handle such difficult inputs and to target the very large mesh sizes required. Our innovative methods are able to generate volumes of cardiac muscle at cellular scale. Sample sizes achieved using method (i) were about 1.5x10-3 mm3 (1100 myocytes), limited by the imagery data available. Our workflow is able to produce computational meshed respecting the topology and connections of the input myocyte network. With method (ii), we were able to generate up to 1 mm3 of cardiac tissue (7500 myocytes) so far. The memory available on a computer node is our main limitation. ParMmg[3], the parallel version of mmg, is under development as one of the main prospects to scale our processes and reach up the size of a whole heart.

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[2] Dapogny C, Dobrzynski C, Frey P. Three-dimensional adaptive domain remeshing, implicit domain meshing, and applications to free and moving boundary problems.J Comput Phys 2014/262:358-378.
[3] Cirrottola L, Froehly A. Parallel unstructured mesh adaptation using iterative remeshing and repartitioning. INRIA Bordeaux, équipe CARDAMOM 2019.

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P07: Spatially-Explicit Simulations Predict How Different Modes of MyBP-C Function Modulate Isometric Twitches

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Multiple groups are trying to develop sarcomere-based therapies for Heart Failure with reduced Ejection Fraction. Trials that attempted to activate myosin with omecamtiv mecarbil showed minimal benefit, in part because the increased contraction compromised diastole. Cardiac Myosin Binding Protein-C (cMyBP-C) regulates both contraction and relaxation under physiological conditions and could be a more effective therapeutic target. However, cMyBP-C's complex function makes it difficult to study in biological experiments. Here we used FiberSim, a spatially-explicit model of half-sarcomeres (https://campbell-muscle-lab.github.io/FiberSim/) to investigate how different potential modes of cMyBP-C function modulate contractile properties. In the model, cMyBP-C molecules are restricted to 9 stripes in the C-zone of the half-sarcomere where they have the appropriate stoichiometry (3 cMyBP-C molecules to 18 myosin molecular per 43 nm thick filament repeat). The cMyBP-C molecules can transition between a null state (no effect) and two states that respectively stabilize myosin in its suppressed super-relaxed / interacting heads motif / OFF configuration or bind to available sites on the thin filament. cMyBP-C molecules that are bound to actin increase thin filament activation via cooperative effects.

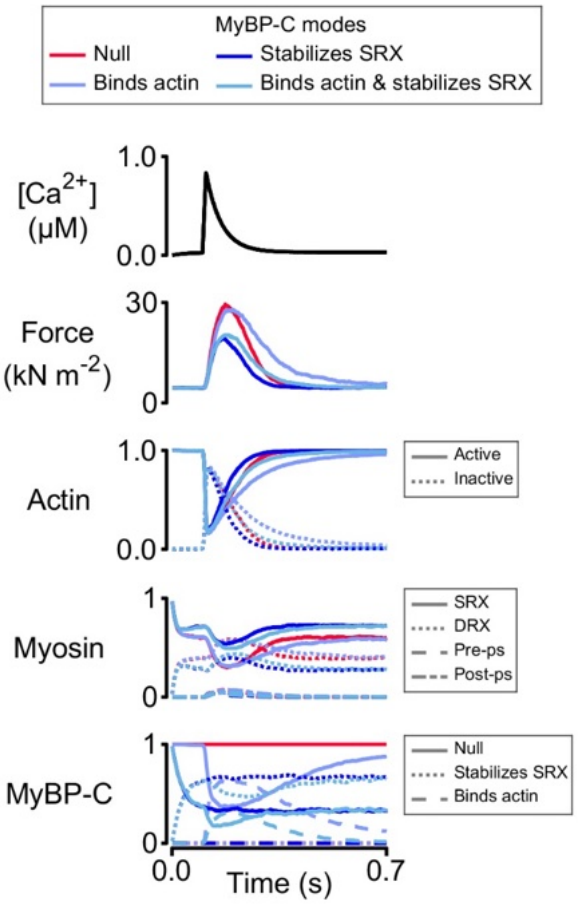

Figure 1: FiberSim-based simualtions of isometric twitches.

As shown in Fig 1, the time-course of isometric twitch contractions is prolonged when cMyBP-C molecules bind to the thin filament. Peak force is reduced when cMyBP-C stabilizes the SRX state. Simulations in which some cMyBP-C molecules bind actin and some stabilize myosin in the suppressed state have smaller slower twitches. Ongoing work is testing how cMyBP-C modulates afterloaded twitches that may be more representative of myocardial function in vivo.

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P08: N2BA Isoform Expression, Collagen Content, and Tubulin Abundance Increased in Ischemic Heart Failure in Humans

Wellette-Hunsucker AG[1,2], Gulbulak U[2], Milburn GN[1,2], Yackzan AT[2], Gupta VA[2], and Campbell KS[1,2]

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Myocardial stiffness, crucial for cardiac function, is regulated by factors that include the isoform and phosphorylation status of titin isoforms and the content of tubulin and collagen. Clinically, cardiac function is assessed via echocardiography. This study utilized wet lab biochemistry to investigate factors influencing myocardial stiffness in >175 organ donors and cardiac patients, encompassing various clinical sub-types of heart failure. The numbers of patients in each clinical sub-group were as follows: organ donors (21), dilated cardiomyopathy (29), ischemic heart failure (45), cardiac amyloidosis (5), titin truncation mutations (8), end-stage heart failure pre-Ventricular Assist Device (VAD) (35), and post-VAD (35). Additionally, this study assessed the correlation between wet lab biochemistry and dry lab echocardiography findings. Titin isoforms were separated using SDS-agarose gels, and phosphorylation levels were determined using agarose gel electrophoresis. Collagen content was assessed using a hydroxyproline assay, and tubulin abundance was measured through SDS-PAGE/Western blotting. Echocardiography data prior to transplantation was retrospectively analyzed for research-grade measurements. Data were analyzed using linear mixed models with clinical diagnosis as a main factor.

One of many statistically significant results was the finding that the relative content of the N2BA isoform of titin was increased relative to that measured in organ donors and in patients with dilated cardiomyopathy ($p<0.05$). Titin phosphorylation effects were complex and difficult to interpret in isolation. Collagen content was higher in samples from patients with ischemic heart failure than in organ donors ($p=0.0003$). Alpha-tubulin abundance was also elevated compared to ischemic heart failure. Ejection fraction measured from echocardiography displayed a correlation with N2BA isoform data ($p<0.05$).

These findings suggest that ischemic heart failure leads to increased collagen and tubulin abundance, potentially prompting a compensatory shift toward N2BA expression to maintain myocardial passive stiffness. This potentially could explain the resulting correlation to functional measures (i.e., ejection fraction).

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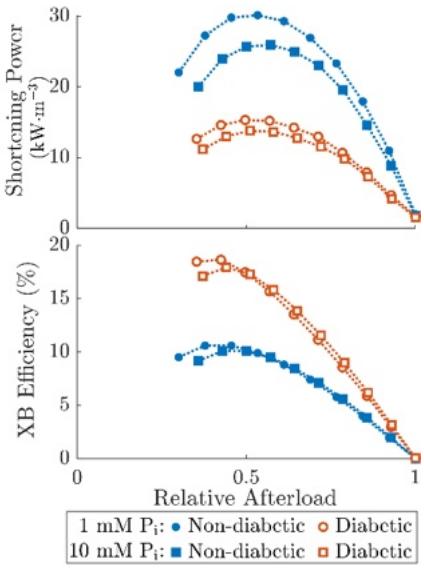
P09: Slower Cross-Bridge Cycling in Human Diabetic Cardiac Trabeculae Reduces Power but Increases Efficiency

Musgrave JH[1], Han J-C[1], Ward M-L[2], Taberner AJ[1,3], Tran K[1]
[1]*Auckland Bioengineering Institute*;[2]Department of Physiology;[3]*Department of Engineering Science and Biomedical Engineering; University of Auckland, Auckland, New Zealand*

Diabetic cardiomyopathy is a multifactorial disease that is associated with both mechanical and energetic dysfunction. At the cellular level, the interplay between myofilament force production and changes in metabolic state arising from diabetes is not well understood. In this study, we developed a cardiac cross-bridge model that is responsive to cellular metabolic state to understand the effect of diabetes on cross-bridge kinetics and metabolite sensitivity, and simulated the impact of these disease-induced effects on muscle power and efficiency.
Our experiment-modelling pipeline[1] was extended to explore the effect of type 2 diabetes on the mechano-energetic properties of human atrial trabeculae. We experimentally interrogated the cross-bridge kinetics of permeabilised diabetic and non-diabetic muscles (n=10/group) by using sinusoidal perturbation analysis to measure complex moduli under varied concentrations of ATP and Pi. Model linearisation was used for parameterisation to these data and to probe the mechanisms underlying functional differences arising from diabetes. The cross-bridge model was then incorporated into a muscle model and activated using Ca^{2+} transients measured from diabetic tissues[2] to predict the influence of diabetes on isometric twitch characteristics and force length work-loop mechano-energetics.

The experimental measurements revealed that diabetic trabeculae produced lower active stress and stiffness, with structural imaging linking this to lower myocyte density. The diabetic muscles also exhibited a leftward shift in the complex modulus, identified in model fitting to be driven by slower cross-bridge cycling rates, particularly the rate of detachment. Reflecting these parameter differences, muscle model simulations of isometric contractions revealed a prolonged relaxation phase in diabetes. Work-loop simulations showed that diabetes reduced shortening power and increased cross-bridge efficiency (Figure). A lower sensitivity to Pi in diabetic muscles diminished the extent to which muscle power was decreased under conditions of raised P_i. This reduced sensitivity and the increase in efficiency suggest the presence of compensatory mechanisms that mitigate the effects of metabolic dysfunction in the diabetic heart.



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P10: Branching Myofibrils Create Torsion During Contraction In Sheep Cardiomyocytes

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[3]*Cellular Physiology Lab, Monash Biomedicine Discovery Institute, Faculty of Medicine, Nursing and Health Sciences; European Molecular Biological Laboratory (EMBL) Australia; and Australian Research Council Centre of Excellence in Advanced Molecular Imaging, Monash University, Clayton/Melbourne, Victoria, Australia*
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Contraction of the heart, and the subsequent pumping of blood through the cardiovascular system, is driven by activation of muscle cell sarcomeres. Sarcomeres are contractile proteins which are organized within myofibrils that span the cell. Recent imaging has elucidated that myofibrils form a branching network throughout the cardiac muscle cell. This contrasts with the assumed strictly longitudinal and parallel organization that has been the basis of cardiac mechanobiology studies to date. A branching network organization could have biological implications on contraction dynamics in health, exercise, and pathology. We have developed a 3D anisotropic contraction model of a branched myofibril based on U-NET++ segmentation of electron microscopy images of sheep cardiomyocytes. We compare the stress distribution of a contracted myofibril in the idealised and branched cases. Our simulations indicate that branching myofibrils likely induce off-axial stress behaviour and transverse forces during contraction compared to the ideal structure. These findings may be critical for elucidating the structural differences observed in mammalian muscle fibres and changes with disease.

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P11: Modelling Mavacamten Action on Alpha and Beta Myosin Isoforms and Human Atrial and Ventricular Contractions

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Mavacamten (Mava) is an allosteric and reversible myosin inhibitor. Mava is an effective treatment for patients with obstructive hypertrophic cardiomyopathy (oHCM) that improves exercise capacity and left ventricular outflow tract obstruction[1]. Mava globally depresses cardiac contractility due to its generalized action on ventricular and atrial myosin heads (MHs). For oHCM, where atrial contraction plays a crucial role, its depression with Mava can lead to impairment of left ventricular function. In this work we have simulated the action of Mava at the sarcomere level for both human atrial (HA) and ventricular (HV) myosin isoforms. For modelling Mava action, we reduced the number of available MHs participating in a cross bridge (XB) formation and have analysed its impact on force development transition rates (Kact, Ktr) at sarcomere level. At sarcomere level, we have simulated the fast solution switching protocol[2], using a mean-field biophysically detailed contraction model[3] for a fixed Ca2+ step of pCa3.5 (Figure 1A). Using the same model, we extended the analysis to see impact of Mava on Ca^{2+}-activated twitch contractions for both myosin isoforms. For this, we created a pool of Ca2+-transient (CaT) profiles from the HA and HV computational models (Figure 1C and D) recorded at 1Hz and $[Ca^{2+}]_o$ 1.8mM and was fed to same contraction model as an input.
Under control condition, XB cycling in HA myosin isoform () was three times faster than the HV one (). In myofibrils, Mava reduced the maximal activated tension (Tamax) more in than (panel B) that shows increased Mava sensitivity to the isoform. This effect of Mava was consistent in contraction twitches, where all the computational models showed variation in Tamax consistently more in HV (panel D) in comparison to HA (panel C). In myofibrils, Mava slowed the force kinetics Kact more in (panel B) than that is in line with the experimental data (bars in filled pattern). Mava accelerated the twitch relaxation time about 10% in HA and much less in HV. Using Ca-simulated twitches, we have reproduced this behaviour and analysed the interplay between CaT profiles and Mava induced variation in twitches time course (panel C and D). In conclusion, Mava has a fast and fully reversible effect on Tamax with higher sensitivity for HV than HA. Myofibril kinetics were reduced more in HA than HV isoform and that can be related to the increased acceleration of twitch relaxation in HA than in HV cardiomyocytes.

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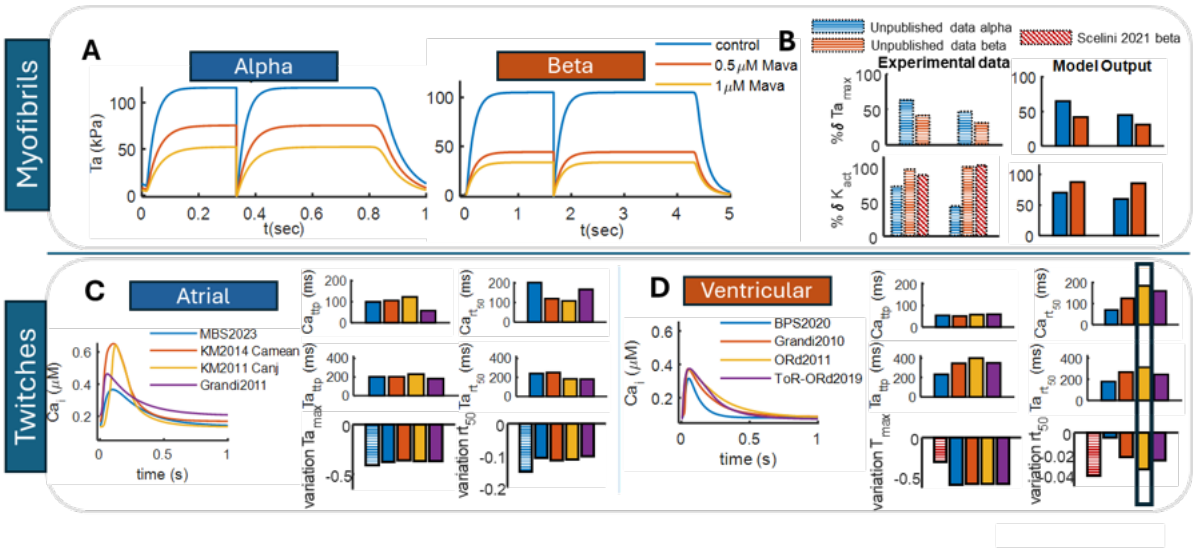

Figure 1: Mava action modelled for alpha and beta myofibrils and for human atrial and ventricular contraction twitches. A) Using fast solution switching protocol at pCa 3.5 for alpha (on left) and beta (on right) myosin isoforms for varying dose concentrations of Mava 0M (control in blue), 0.5 M (in red), and 1 M (in yellow). B) The percentage change in tension biomarkers, Tamax, Kact for varying Mava dose concentration for alpha (blue bars), beta (red bars) compared with experimental data (on left horizontal filled patterns (Scellini et al. 2023) and vertical filled pattern [4]). C D) Ca2+-transient (CaT) profiles extracted from human atrial and ventricular computational cardiomyocyte models. The right panels quantify the variation caused by Mava 5M in Tamax and Ta rt50 in comparison with experimental data (bottom panels) for a given CaT ttp and rt50 (top panels).

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P12: Methods comparison for ventricular end-systolic elastance and reference volume estimation

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Introduction: Ventricular time varying elastance, defined by $E(t) = P(t)/(V(t) - V_0)$ (with P(t) and V(t) being ventricular pressure and volume), is a useful concept which allows to provide, with minimal measurements, meaningful insights into cardiac mechanics, either for clinical or modeling purposes. For calibration purposes, the correction volume V_0 has to be estimated, ideally by 0-pressure extrapolation of the end-systolic pressure-volume points. However, the non-invasive methods currently used to estimate V_0 and the end-systolic elastance E_{es} are sensitive to measurements errors. In this study, we investigate a biomechanical approach to estimate E_{es} and V_0.

Methods: We employed a calibrated simplified biomechanical heart and circulation model[1,2] and created patient-specific models, using aortic flow and pressure data from 5 anesthetized patients, for whom norepinephrine has been administered. We estimated V_0 and E_{es} using 3 available methods[3,4,5] and in addition proposed 3 methods based on our biomechanical model – dynamic, static-isopressure and static iso-volume methods. We repeated the estimations for various in silico changes of hemodynamic or physiology conditions (preload, afterload, contractility) and assessed the independency of the estimated V_0 both to the varying loading and contractile conditions.

Results: We observed that V_0 estimated by the proposed static-isopressure method was consistently less sensitive to variations in loading and contractile conditions. Secondly, E_{es} estimated by the static-isopressure method was the best to track the changes in contractility ($r=0.9$; $p<0.001$).

Conclusion: By evaluating the physiological properties – load and contractility independency of V_0, and the ability of E_{es} to track the changes in contractility – we demonstrated that the proposed static-isopressure method is the most accurate to represent V_0 and E_{es}.

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P13: Impact of Scar Size and Location on Ejection Fraction

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Coronary artery disease (CAD) can lead to the formation of scar tissue and in turn to reduced ejection fraction (EF). EF is important for clinical decision-making, therefore we sought to understand how the size and location of scars affect EF. To investigate this effect, we performed electro-mechanical simulations for three different scars corresponding to obstructions in the left anterior descending artery (LAD), the right coronary artery (RCA) or the left circumflex artery (LCx). Scar sizes and locations were based on left ventricle LGE-CMR data of 34 patients with single-vessel CAD[1]. The grey zone separating scar and healthy myocardium had a width of up to 6 mm. We examined scar sizes of approximately 19.4 % (severe), 12.9 % (moderate) and 6.5 % (mild) of the left ventricle myocardial volume. Our study is based on the electro-mechanical and anatomical model of Gerach & Loewe[2]. The simulations were run for three heartbeats with full mechano-electric feedback. If not otherwise indicated, all model parameters were taken from the original paper. Scar tissue was modelled as electrically inactive. The cellular electrophysiology of healthy ventricular myocardium and the grey zone was described using the ten Tusscher et al. model and the modifications of Salvador et al.[3]. Mechanical stiffness for scar and grey zone was scaled in accordance with that study. Figure 1 shows a comparison of the resulting EFs. For all scar sizes, the largest reduction in EF was seen for scars resulting from an occlusion of the LCx, the smallest reduction for LAD occlusions while RCA EF results were in between both LCx and LAD values. In the severe cases, EF was reduced to 42.31 %, 40.35 % and 37.96 % for LAD, RCA and LCx, respectively (Control: 51.47 %).

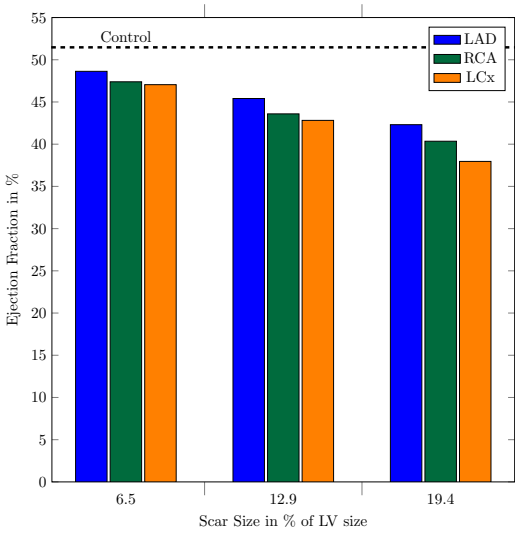

Figure 1: Ejection fraction for simulations of scars resulting from LAD (blue), RCA (green) or LCx (orange) occlusion. The dashed line represents control EF (no scar).

Our results indicate that not only the size, but also the location of the resulting scar tissue drives the reduction in EF for patients with CAD. To determine if the relationship between EF reduction and scar size varies by scar location, additional simulations using a finer grid of scar sizes are warranted.

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P14: 1D model of human atrial tissue to estimate elastic modulus based on histological images

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Fibrosis, characterized by excessive extracellular matrix (ECM) protein accumulation, is a common phenotype in cardiac diseases and contributes to arrhythmias like atrial fibrillation (AF). Collagen, one of the proteins deposited during fibrogenesis, is known for providing tensile strength to many tissues. This study aims to (i) compare atrial tissue elastic modulus (E) and viscosity () in patients with sinus rhythm (SR) vs permanent AF; (ii) investigate correlations between tissue structure and E; and (iii) use the acquired data to calibrate an in silico model based on histological images. This calibrated model will allow for deriving the relationship between tissue structure and passive mechanical properties based on images.
Atrial slices (400 m thick, 3–5 mm long and wide) from patients (SR and AF) were subjected to uni-axial tensile testing along the predominant cardiomyocyte (CM) orientation. Systolic and diastolic forces were continuously monitored. Computational simulations of slice E were based on segmented images (ECM vs CM components) of the same slices. Segmented images were projected onto the axis of experimentally applied stretch to obtain 1D representations. The 1D representations contained vertices with projected values representing the CM/ECM ratio of a corresponding image column. Each vertex was assigned a standard linear solid model (LSM, Kelvin-Maxwell representation) and connected to its neighbours. The LSM were parameterized according to the CM/ECM ratio between 2.5 kPa for pure CM and 8.4 kPa for pure ECM network (determined, respectively, by nanoindentation of single CM and tensile testing of decellularized slices, both not from slices otherwise included in this study); was determined based on the relaxation curve observed during in vitro stretching. One side of the simulated 1D tissue was fixed, while the opposite side was stretched to replicate the in vitro experiments (final deformation of 2% elongation).
In slices derived from patients in SR, average E and were 45.6±26.8 kPa and 21.07±7.9 kPas (respectively; Mean±SD N=5 patients, n=23 slices) vs 37.69±24.2 kPa and 15.36±5.6 kPas in AF samples (N=3, n=10). In the image-derived 1D models, E was 41.12±26.8 and 34.49±6.2 kPa for SR and AF, respectively. The average E showed no statistically significant difference between the 1D model predictions and the experimental results from corresponding slices (paired t-test, $p>0.05$). However, the median relative difference between model predictions and experimental measurements in corresponding slice was 27.8% (SR and AF simulation pooled).
The 1D model, derived from projected histological images, offers a fast method of slice stiffness estimation, with no statistical difference to experiments of the same group. However, differences in paired comparisons of 1D model predictions and experimental measurements indicates the need to improve the model and/or its parametrisation. Specifically, the 1D projection method and better consideration of structural orientation may lead to a better agreement between the individual model predictions and experiments.

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P15: A Novel Computational Model of the Zebrafish Atrial Action Potential and Intracellular Calcium Transient

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The zebrafish is an increasingly popular experimental model for the study of cardiac electrophysiology, due to its electrophysiological similarity to human[1]. Yet, while computational modelling of the cardiac action potential (AP) and intracellular calcium (Ca_{2+}) transient is highly advanced for many model species and has contributed to important pathophysiological insight, there currently exists no zebrafish-specific computational AP models. To address this, we have recently developed a novel model of the zebrafish ventricular AP and Ca_{2+} transient

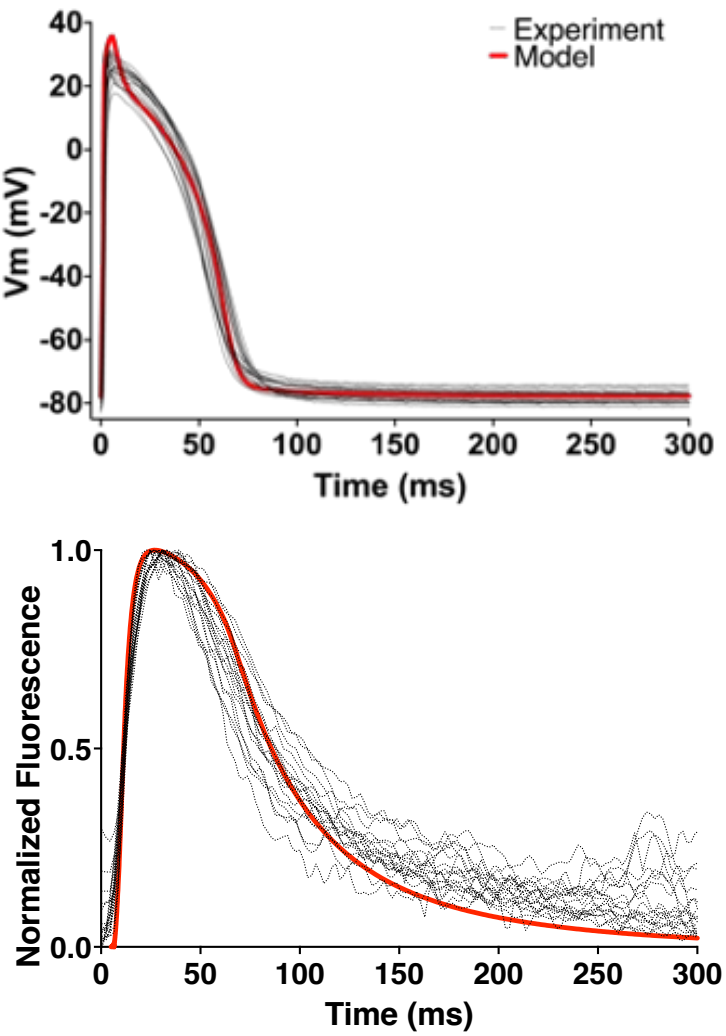

Fig 1. Model and experimental recordings of zebrafish atrial AP (top) and Ca_{2+} transient (bottom).

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P16: Uncertainty Quantification in a Cardiac Arrhythmia Model: Application to Intra-Atrial Reentrant Tachycardia

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In this study, we consider Intra-Atrial Reentrant Tachycardia (IART), an arrhythmia in which a non-linear excitation wave is attaching to an anatomical surgical scar in the atrium. The inter-individual variability in the pathophysiology of arrhythmia requires patient-specific treatment. To guide this precision medicine, patient-specific computational models of cardiac electrophysiology, also called cardiac digital twins, could be created. However, integrating patient data into such computational models remains challenging. State-of-the-art clinical imaging and electrophysiological mapping techniques come with measurement sparsity and uncertainty that limit the precision with which we can model cardiac tissue properties. Therefore, we need to capture such uncertainties into our models for trustworthy clinical decision-making[1,2].
The goal of this study is to develop a method to quantify the uncertainties due to measurement noise and sparsity when characterizing scarred tissue based on local catheter data. By introducing the Bayesian inference framework, we can estimate a full posterior parameter distribution instead of a single, optimal fit. This allows to study how the amount of available data and the measurement noise influence this posterior uncertainty. The sample mean of this distribution then acts as a best estimate for the parameters, while the variance and the shape of the estimated posterior describe the uncertainty on this estimate.
First, we define a computational atrial model over a 2D tissue slab. We model a scar as a region of non-conducting tissue and define a parameter vector that describes its location, orientation, and shape. Second, we formulate the problem of tuning this parameter vector to catheter data as a Bayesian inference problem by defining an appropriate likelihood function for the data. Finally, we estimate the posterior distribution of these parameters based on the local catheter data by using a Markov chain Monte Carlo (MCMC) algorithm. We will demonstrate the crucial importance of the chosen discretization methods for the atrial model to avoid discretization-induced artificial discontinuities in the Bayesian likelihood, which severely deteriorate the accuracy of the posterior.

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P17: Hemodynamics in atrial fibrillation: An in-silico study

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Hemodynamic changes in response to atrial fibrillation (AF) remain poorly understood. To study this, we combined a simplified rapid mechanical model of the heart and circulation[1] with a rapid network AV node model[2].

We calibrated the combined model by fitting it to clinical hemodynamic measures obtained during regular and irregular paced rhythm at 90 bpm with non-fibrillating atria[3]. AF was modelled using 50 independently and randomly activated spherical segments for each atrium. The ventricular activation times characteristic for AF were produced by the AV node model to initiate ventricular contraction in the mechanical model. For each realization, the combined model simulated 200 heart beats in 2 seconds.

We successfully calibrated our models to match human data (cf. Fig. 1 A-D). In the simulated hemodynamics of normal sinus rhythm (NSR) and AF at 90 bpm, we observed a decrease of 8% in SBP, 22% in LVEDP, 7% in SV and an increase of 30% in LAP (cf. Fig. 1 A+E).

Because of the lack of available human data, we compared hemodynamic changes between NSR and AF to porcine data[4] and observed a matching direction of change. Whereas the amplitude of change of SBP, LVEDP and LAP was comparable to [4], the SV was changing less than in [4], indicating that changes in electrical activation time of the spherical wall segments alone may not fully explain the decrease in SV. The unique combination of cardiovascular physiology and AV node models facilitate studying the relation between heart rate variability characteristics and hemodynamics.

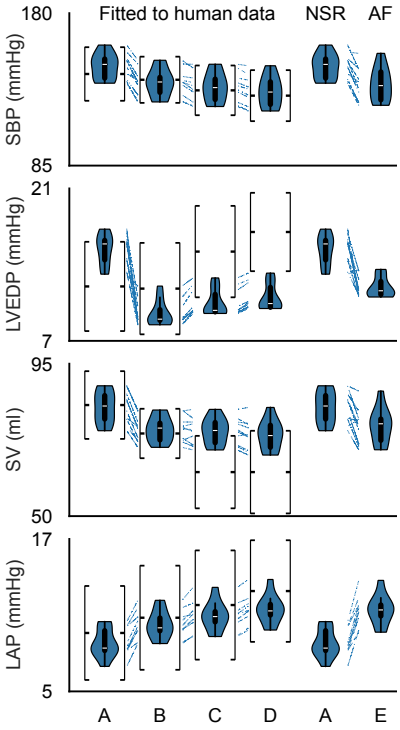

Figure 1: Hemodynamics at 90bpm (RR=666ms) for (A) regular heart rhythm with RR std=0ms and AV delay=120ms, (B) RR std=0ms and AV=0ms, (C) irregular rhythm with RR std=0.2*RR and AV=0ms, (D) RR std=0.3*RR and AV=0ms, (E) RR std=0.3*RR and fibrillating atria. Violin plots show simulated hemodynamics. Black lines show mean±1std reported in [3]. Blue dotted lines show relation between cases A-E for same model parameters. LAP, mean left atrial pressure; LVEDP, left-ventricular end-diastolic pressure; SBP, systolic blood pressure; SV, stroke volume.

References:
[1] Oomen PJA, Phung TKN, Weinberg SH et al. A rapid electromechanical model to predict reverse remodeling following cardiac resynchronization therapy. Biomech Model Mechanobiol 2022/21:231-247.
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P18: Simulation-free prediction of atrial fibrillation inducibility with the fibrotic kernel signature

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Computational models of atrial fibrillation (AF) can help improve success rates of interventions, such as ablation. However, evaluating the efficacy of different treatments requires performing multiple costly simulations by pacing at different points and checking whether AF has been induced or not, hindering the clinical application of these models. In this work, we propose a classification method that can predict AF inducibility in patient-specific cardiac models without running additional simulations. Our methodology does not require re-training when changing atrial anatomy or fibrotic patterns. To achieve this, we develop a set of features given by a variant of the heat kernel signature that incorporates fibrotic pattern information and fiber orientations: the fibrotic kernel signature (FKS). The FKS is faster to compute than a single AF simulation, and when paired with machine learning classifiers, it can predict AF inducibility in the entire domain. To learn the relationship between the FKS and AF inducibility, we performed 2371 AF simulations comprising 6 different anatomies and various fibrotic patterns, which we split into training and a testing set. We obtain a median F1 score of 85.2% in test set and we can predict the overall inducibility with a mean absolute error of 2.76 percent points, which is lower than alternative methods. We think our method can significantly speed-up the calculations of AF inducibility, which is crucial to optimize therapies for AF within clinical timelines.

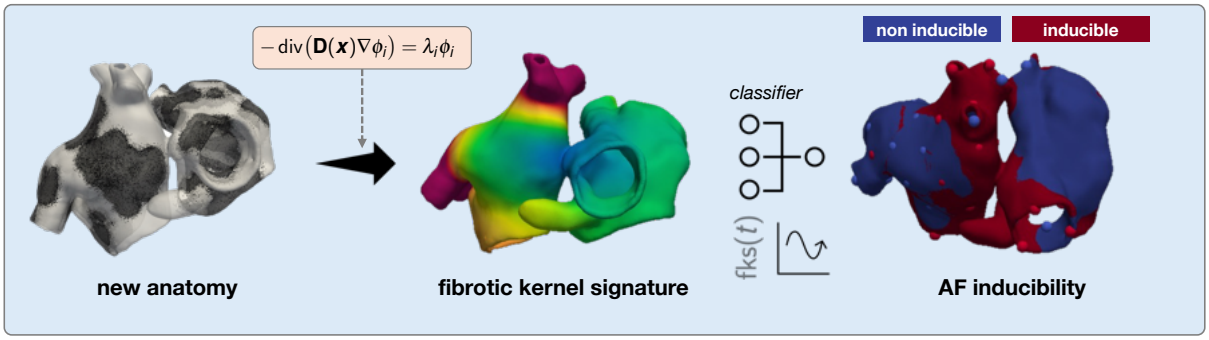

Figure 1 – overview of prediction of AF inducibility using the fibrotic kernel signature.

References:
[1] Oomen PJA, Phung TKN, Weinberg SH et al. A rapid electromechanical model to predict reverse remodeling following cardiac resynchronization therapy. Biomech Model Mechanobiol 2022/21:231-247.
[2] Plappert F, Engström G, Platonov PG et al. ECG-based estimation of respiration-induced autonomic modulation of AV nodal conduction during atrial fibrillation. Front. Physiol. 2024/15:1281343.
[3] Stojadinović P, Deshraju A, Wichterle D et al. The hemodynamic effect of simulated atrial fibrillation on left ventricular function. J Cardiovasc Electrophysiol. 2022/33:2569-2577.
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P19: Critical Insights Learned from Computer Modelling Analysis of Human Atria In-Vivo and Ex-Vivo

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Percutaneous catheter ablation therapy improves the quality of life for AF patients much more effectively than anti-arrhythmic drugs. Pulmonary vein isolation (PVI) is the cornerstone of current ablation techniques. However, ablation significantly reduces efficacy in patients with persistent or long-standing persistent AF. The success rate of a single ablation procedure in achieving long-term results is less than 29%. Thus, relying solely on PVI proves inadequate for patients with the sustained subtypes of AF. To address this challenge, we need to improve our understanding of atrial structural substrates responsible for maintaining AF and identify effective ablation targets outside PV regions by utilizing computer modeling of human atria ex vivo and in vivo, respectively.

A heart-specific computer modeling approach was developed to model five human atria ex vivo (170 μm^3) with a history of AF and/or comorbidities, which were functionally mapped and structurally imaged using optical mapping and 9.4T contrast-enhanced (CE-) MRI. This study utilized reconstructed 3D human atrial models of both realistic and control models, including uniform atrial wall thickness (AWT) and the absence of myofibers or fibrosis. The key modelling results of the human atria ex-vivo are threefold. Firstly, induced reentries drifted toward regions with AWT variations, localizing in regions with thin AWT while drifting along AWT variability. This pattern was more pronounced in the right atria (RA) than the left atria (LA). Reentries established in the thinner walls adjacent to a thickness variation had a higher tendency of wave breaking. Secondly, the introduction of myofibers led to a more complex, spatially and temporally heterogeneous activation pattern. Interestingly, stabilized reentries tended to coincide with well-aligned myofiber regions adjacent to highly disorganized myofiber regions. Further, it was discovered that AWT distribution in the localized reentries remained consistent regardless of myofibers. Finally, the presence of fibrosis modestly changed reentry anchoring locations in the LA while mostly remaining the same for the RA. In the LA, reentries were localized in boundary zones with low transmural fibrotic density of dense fibrotic patches. For regions with low transmural fibrotic density and in the absence of dense fibrotic patches, the synergy of AWT and myofibers dictated reentry locations, particularly in the RA.

To identify the arrhythmogenic fibrosis outside the PV region, we studied and modeled the fibrosis distribution and impact in both atrial chambers from patients with AF with (n=25) and without (n=35) AF recurrence post-PVI. The fibrosis percentage/burden in the atrial chambers (both LA and RA) for the two groups was similar. The RA of the AF recurrence group had slightly more fibrosis than that of the patients without AF recurrence, though it was not statistically significant (19.0 ± 7.2 % versus 18.0 ± 6.3 %, $p = 0.06$). Structural analysis of atrial fibrosis indicated that the AF recurrence group had lower fibrosis entropy. The computer simulations of the human atria in-vivo (n=4 in each group) showed that the lower entropy atria were able to anchor reentries more effectively with the denser patch fibrosis. For the very first time, our computer simulations of human atria ex vivo and in vivo distinguish the roles of atrial structure in AF and potentially improve targeted ablation.

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P20: Do we need to model drug-trapping in the ORd-CiPAv1 model for action potential predictions?

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The human Ether-à-go-go-Related Gene (hERG) channel is susceptible to drugs that inhibit its current and are thus associated with an increased risk of arrhythmia. Drugs can bind and stay trapped within the hERG channel, which is believed to play a role in the arrhythmic risk posed by a drug. We have previously shown that the drug-trapping component defined in the ORd-CiPAv1 model[1] has limited effect on action potential (AP) prediction[2].

To assess the role of the drug-trapping component in AP prediction, we fitted the drug-trapping parameter to synthetic data generated by the ORd-CiPAv1 model and showed that the drug-trapping parameter is not identifiable. The hERG current from the modified Milnes protocol[1] does not provide sufficient information to identify the drug-trapping component of the model. This could be due to the transition rates into the drug-trapping component being significantly smaller than the drug-binding rates, hence drugs bind to but are not trapped within the hERG channel.

We then simplified the drug-trapping component of the ORd-CiPAv1 drug-binding model. The ORd-CiPAv1 drug-binding model is reduced from three drug-bound states to one, and the number of parameters is reduced from five to three. Fitting of the parameters of the reduced model to the experimental data used in developing the original model, as well as to synthetic data generated by the original model, showed that the reduced model can replicate the original model's behaviour, including the drug-trapping behaviour, despite not having an explicit drug-trapping component.

Our results suggest that further study is required to identify the drug-trapping parameter and thus allow an investigation into the role of drug-trapping in the drug-binding process.

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P21: Optimising experimental designs for model selection of ion channel drug binding mechanisms

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The rapid delayed rectifier current carried by the human Ether-à-go-go-Related Gene (hERG) channel is susceptible to drug-induced reduction which can lead to an increased risk of cardiac arrhythmia[1]. Establishing the mechanism by which a specific drug compound binds to hERG can help to reduce uncertainty when quantifying pro-arrhythmic risk.
In this study, we introduce a methodology for optimising experimental voltage protocols to assist in model selection between several proposed models of drug-binding mechanism. We demonstrate the performance of this methodology via a synthetic data study. When the underlying model of hERG current is known, the optimised protocols generated show noticeable improvements in our ability to select the true model when compared to a simple protocol used in previous studies. However, when we introduce discrepancy between the data-generating hERG model and the hERG model used for fitting models, the optimised protocols become less effective in determining the 'true' binding dynamics.
While the introduced methodology shows promise, we must be careful to ensure that, if applied to a real-data study, we have a well-calibrated model of hERG current.

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P22: A model of calcium channel expression for dynamic action potential changes during drug exposure

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Using a cardiac microtissue test system built from human induced pluripotent stem cell-derived cardiomyocytes, we measured the temporal changes to the cardiac action potential (AP) for 16 hours after the application of calcium channel blockers. We investigated whether the measured changes could be associated with adaptations in the expression of calcium ion channels through the use of a recently developed mathematical model that describes the regulation of calcium ion channel expression as a means of maintaining intracellular calcium homeostasis.[1,2] According to the model, a decline in intracellular calcium levels below a target level triggers an upregulation of calcium ion channels. Such an upregulation would then counteract the drug's inhibitory effect on calcium currents. Experimental microtissue data showed a strong initial decrease to the action potential duration, which was then largely attenuated over the subsequent 16 hours. Models could be well fit to this data, and suggest that dynamic changes in cardiac cells in the presence of calcium blockers may be at least partially explainable by induced changes in channel expression. Such a regulations system may lead to challenges in understanding drug effects on the heart that affect calcium dynamics, unless the timings of applications are carefully considered, and could have important implications for therapies generally targeting channel block mechanisms.

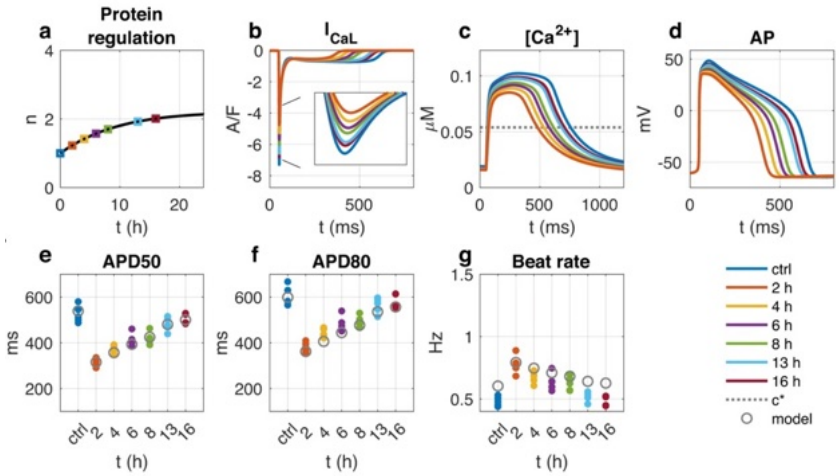

Fig. 1: Simulated and measured effect of nifedipine on cardiac microtissues. Top: Results the model when fit to application of 0.1 M of Nifedipine over 16hrs, with time evolution of the number of calcium channels, n (a), simulated inward L-type calcium current (b), cytosolic calcium (c) and action potential (d). Bottom: experimental biomarker results compared to model for action potential duration (APD50, e and APD80, f) and beat rate (g) sampled in the control case and for 16 hours after 0.1 M Nifedipine. The open grey circles are computed from the model solution and the filled circles are microtissue measurements.

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P23: PD modeling in transthyretin amyloidosis pharmacotherapy

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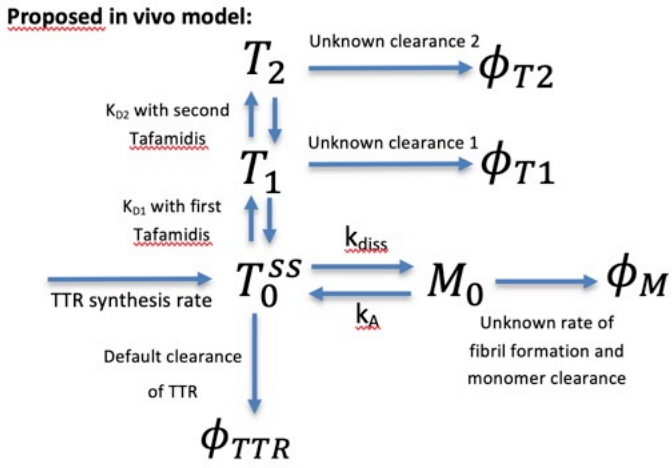
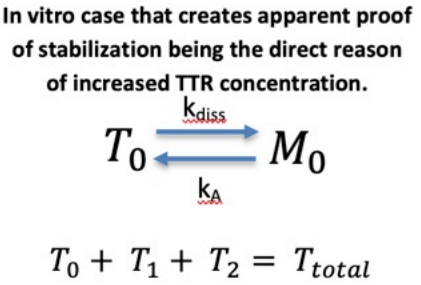
Transthyretin (TTR) amyloidosis (ATTR) is a disease caused by buildup of amyloid-like deposits made of misfolded transthyretin monomeric subunits. ATTR can affect many organs and tissues including heart where it is a cause of deadly Transthyretin Amyloid Cardiomyopathy (ATTR-CM). These deposits build up undetected for years until they are large enough to cause mechanical injuries, those being a direct cause of fatal outcome. One of the aims of pharmacotherapy is stabilization of transthyretin tetramers so that they do not dissociate to monomers that can further misfold and agglomerate. An example of such stabilizer is tafamidis. In the current work – with the help of mathematical modelling - we explain kinetics of TTR together with pharmacodynamic effect of tafamidis introduced to the system and try to explain the mechanism of increased TTR concentration after administration to the patient.





The main proof of tafamidis efficacy is a decreased all-cause mortality in ATTR patients. Other than that, it is assumed that increased TTR concentration after administration of tafamidis is a direct cause of stabilisation of TTR tetramer, thus decrease in its dissociation constant. However, we prove that it is not the case and the potential reason behind increased TTR concentration is change of the ratios affecting the steady state of total TTR concentration. Proof itself does not falsify or confirm the efficiency of the therapy yet gives better understanding of the process and show further possibilities for research in this area.

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P24: How to pick a drug-binding model of ion channel block

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Given the implication of dysfunctional ion channels in a wide variety of diseases, they are prime targets for drug-based intervention. A significant proportion of cardiac drugs in particular act to block ion channels. To better predict the full effects of drug binding on these channels, including potentially deadly side-effects, we require the assistance of computational models to complement experimental approaches. While there are a plethora of drug-binding models to choose from, based off both drug-induced channel behaviour and our knowledge of drug-protein interactions, it is not entirely clear which models will suffice for any given drug and ion channel combination.

Comparing different structures of drug-binding Markov models and their approximations, I'll propose some distinguishing considerations in model selection and talk through the differences in behaviour of various models of drug binding, when certain models might appear functionally identical will otherwise diverge, and what to keep in mind when choosing a drug binding model.

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P25: Inferring ion channel block from rabbit Purkinje fiber action potential recordings

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Mathematical action potential (AP) models describe the changes in the membrane voltage due to a complex interplay between ionic currents, and their interactions with drug compounds. These models can guide preclinical risk assessments for drug-induced cardiac arrhythmia and extract more information from animal-based experiments. The rabbit Purkinje fiber has been used in preclinical studies, as it includes the major currents present in human ventricular myocytes. A recently proposed mathematical AP model of the rabbit Purkinje fiber, combined with ion channel screening data, predicted drug effects on AP changes, with an agreement of up to 80%[1]. To explain the 20% mismatch, we first improve the original AP model by re-calibrating its parameters to fit control AP traces. Subsequently we test our inference method in terms of uncertainty quantification of the control parameters. Finally, we compare the calibrated model and the original model in terms of prediction of AP changes induced by reference drug compounds with well-studied channel block properties. We are currently working on fitting action potential model predictions to experimental AP changes in the presence of a new set of compounds, to infer the block of various ion channels, in terms of 50% inhibitory concentration (IC50). The aim is to perform an experimental test for any computationally inferred IC50s which have not been measured, particularly for those drug compounds whose action potential changes are not explained by the existing ion channel screening data

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P26: A Sympathetic Neuron Model to Calculate Neuro-Muscular Norepenephrine Release for in-silico Trials

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In-silico trials to test arrhythmia risk have the potential to be used to significantly decrease time and cost of drug discovery, and improve safety of developed drugs. However, current simulations for predicting electrophysiological treatment response do not account for treatment effects on sympathetic control of the heart, or the increased sympathetic activity due to exercise. Diseases such as LQTS and catecholaminergic polymorphic ventricular tachycardia (CPVT) have treatments that impact sympathetic control of the heart[1]; thus, the sympathetic neurons that innervate the heart must be modelled to predict treatment response accurately[2].

We developed a sympathetic neuron model that can predict norepenephrine changes in the neuromuscular junction due to neuron excitation. Circulatory$_{A}utogen$[3] was used to generate the model from new CellML modules and to do the semi-automatic model calibration. To test the generality of the models calibration, I have calibrated to both rat and Human induced Pluripotent Stem Cell (HiPSC)-derived postganglionic SNs in healthy (rat and HiPSC), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) (HiPSC), and sympathetic hyperactivity (SHR rat) disease conditions. Additionally we tested the models ability to predict the response to retigabine administration to show accurate prediction response to drug effects. The SN model had a calibration MSE of $<$10% for calibrating action potential features (frequency, min/max voltage, min/max period, AP width) to the Wistar rat, SHR rat, healthy HiPSC, and CPVT HiPSC. After calibration the model realistically predicted the change from tonic to phasic firing after administration of Retigabine, qualitatively matching our experimental data. The model realistically (to literature values) predicts K^+, Na^+, and Ca_{2+} transients in the soma and Ca_{2+} transients in the varicosity. Additionally, it predicts norepenephrine release in the neruomuscular junction.

We have developed a sympathetic neuron model that can accurately predict response to ion channel modulatory drug treatments. This model can now be coupled with cardiomyocytes and then with electrophysiology models to predict drug effects, via both direct cardiomyocyte modulation and modulation of the sympathetic innervation, on arrythmia risk. The model is suitable for calibration to rat data for experimental validation with electrical mapping and HiPSC data for calibration of human heart models to be used in in-silico human trials.

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P27: Deciphering Regulatory Biomarkers Associated with Cardiogenic Shock

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Endothelium, a pivotal component of vascular biology, crucially contributes to the orchestration of inflammation within blood vessels. Endothelial cells (ECs) play an active role by expressing chemotactic molecules that attract immune cells. EC also produces adhesion molecules that facilitate the attachment and infiltration of immune cells into cardiac tissues[1]. Cardiogenic shock (CS), a severe condition marked by hypoxia, entails significant disturbances in metabolic and cytokine environments. Utilizing a comprehensive biomarker panel, including cystatin C, lactate, interleukin-6, and N-terminal pro-B-type natriuretic peptide (CLIP score), several studies reveal remarkable sensitivity in predicting 30-day mortality in individuals with cardiovascular stroke[2]. This multidimensional biomarker approach provides comprehensive insight into the complex pathophysiological terrain of CS.
In pursuit of a deeper understanding, our investigation is focused on characterizing the inflammatory response of ECs to molecular patterns associated with cardiogenic shock. Employing in-vitro settings, we aim to elucidate the molecular mechanisms governing the endothelial response to CS-associated signaling. During myocardial infarction, various inflammatory cells, including neutrophils, monocytes, and IL-6, are activated. A literature review indicates that patients with CS exhibit elevated levels of IL-6, correlating positively with cardiac dysfunction [3]. However, the precise impact of IL-6 levels on the severity of CS remains unclear. First, we conducted a comparative analysis of cytokine effects on human and bovine ECs to identify a suitable cell model and found that both cell types showed comparable responses to a challenge with IL6.
Preliminary results from our research reveal an intriguing inversely proportional relationship between interleukin-6 and the proliferation rate of endothelial cells. Additionally, we are conducting a comparative analysis of cytokine effects on different cell types (human and bovine). This research seeks to provide meticulous insights into the fundamental mechanisms of cardiogenic shock and holds potential implications for the development of targeted treatments.

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P28: Reproducing hiPSC-CM in vitro 2D culture in silico

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Cardiomyocytes (CM) work in tandem to achieve synchronous well-paced behaviour with constant need of energy, process that conditions such as ischemia disrupts. Human induced pluripotent stem cell derived CM (hiPSC-CM) 2D multi-electrode array (MEA) studies have shown that ischemia can reduce conduction velocity to 52 %[1], or even to $<$ 20 %[2]. In silico models of single hiPSC-CM have been frequently studied e.g., Paci et al.[3]. We developed an in silico hiPSC-CM 2D tissue conduction propagation model and validated it against these in vitro models. To model hiPSC-CM 2D tissue in silico, Paci2013[3] model was imported from CellML into OpenCARP[4] EasyML. Cells were positioned in a 2-dimensional grid. Cell concentration is set to 93 000 cells/cm2 (similar to [1]), i.e. shortest distance between two cells is 32.79 µm. Ischemia is introduced to model by adjusting parameters[5]. With two severities of ischemia (Table 1), conduction velocity reductions to 57% and 40% were observed (see Figure 1).

	K^+	I_{Na}/ I_{CaL}	I_{NaK} / I_{pCa}	Velocity
Control	5.40 mM	1.000	1.000	100 %
Severity 1	6.25 mM	0.875	0.800	56.98 %
Severity 2	9.00 mM	0.750	0.690	40.22 %

Table 1: Simulation of ischemia adjusting K^+ I_{Na}/ I_{CaL}, I_{NaK} / I_{pCa}, and resulting velocities, for control, and two severities of ischemia

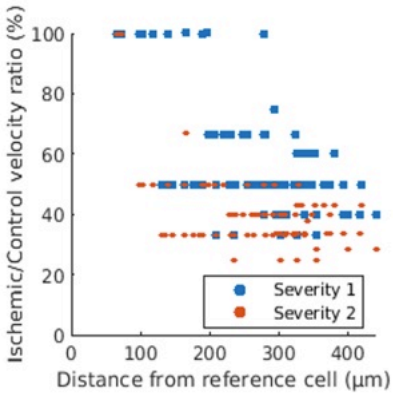

Figure 1: Distribution of conduction velocity reduction due to two severities of ischemia

Our results correspond to results from Häkli et al.[1], but reduction from Oleaga et al.[2] might not be completely explained by electrophysiological changes. Our model can reproduce results from MEA studies but does not cover more extreme behaviour. Our developed model augments MEA studies by enabling fast iteration of experiments and can be used to predict efficiency of drugs.

References:
[1] Häkli M, Kreutzer J, Mäki AJ, et al. Human induced pluripotent stem cell-based platform for modeling cardiac ischemia. Sci. rep., 2021/11(1):4153.
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P29: Impact of sex specific parameters on 0D cardiovascular models

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Personalisation of cardiovascular models is critical to accurately achieve patient-specific outputs. However, despite this, current "patient-specific" models often utilise a population-informed model as a baseline, limiting themselves to assumptions about the average person which may not remain true for specific individuals. The frequent use of these assumptions may therefore give rise to potentially misleading results and incorrect conclusions.
In this work, the blood flow distribution to each organ system in the body is modified by a set of allometric scaling laws altering the model parameters based on patient-specific height, weight, age, and sex. The model terminal resistance and unstressed volume parameters are then fit to the aortic pressure waveform of the patient and the blood flow distribution. To demonstrate this, parameters from 50 patients indicated for left heart catheterisation were put into a 0D cardiovascular model, and compared to a population-informed model.
Comparing the allometrically scaled model to the population-informed model, a larger parameter space was captured allowing for patient-specific personalisation. It was also seen that as the parameters moved further away from the population average, the changes in blood flow distributions led to significant differences in pressures and flows both globally and regionally. It has been seen that personalisation of the model by forming allometric scaling laws dependent on height, weight, age, and sex is beneficial to draw accurate conclusions from model outputs, and to enable cardiovascular models to make use of routine clinical variables. This work also lays the foundation for modelling parts of the system that cannot often be accurately represented, through accounting for multiple sources of uncertainty.

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P30: Unveiling Sex Dimorphism in Healthy Cardiac Anatomy

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Despite increasing awareness of sex differences in cardiovascular disease, many unanswered questions about sex dimorphism in cardiovascular pathology and the effect of risk factors such as obesity, ageing, and hypertension remain. Recent research revealed sex-specific differences in cardiac morphology, both general and age-associated, which are only partially accounted for by simplistic scaling models[1]. These results highlight the urgent need for a more thorough sex-stratified morphological analysis of cardiac anatomy. In this regard, statistical shape analysis forms a promising technique for capturing complex global and local shape variation in large cohorts of anatomical shapes. In this study, we conducted statistical shape analysis on 282 (159 F/123 M) biventricular anatomies, derived from a healthy subset of the UK Biobank CMR imaging population. More specifically, we segmented the left and right ventricular volumes from the imaging dataset, created an anatomical atlas from the resulting meshes, and leveraged dimensionality reduction and regression analysis techniques to explore the influence of sex, age, blood pressure and anthropometry on cardiac anatomy. Extracting the principal modes of anatomical variation of the biventricular cardiac anatomy, we assessed the effect of sex, age, body surface area (BSA) and mean arterial pressure (MAP) on anatomical shape variations. Multivariate analysis of variance (MANOVA) on the first 20 modes of variation showed a significant effect of sex, age and BSA on cardiac anatomy (p-value < 0.01), while MAP did not show to have a significant effect. Additionally, logistic regression analysis on the same modes, showed that mode 1, mode 4 and mode 6, visually associated with the chambers size, elongation and left ventricular bulging respectively, were the most discriminating predictors between the male and female subgroups ($p < 0.01$), after correction for age and BSA (Figure 1). These results suggest that, independently from age and BSA, female hearts tend to be smaller and more elongated, and display more pronounced LV bulging. Our work provides an in-depth quantification of sex dimorphism in the healthy population and forms a crucial stepping stone towards robust, and reliable early diagnosis of cardiovascular disease, both in men and women.

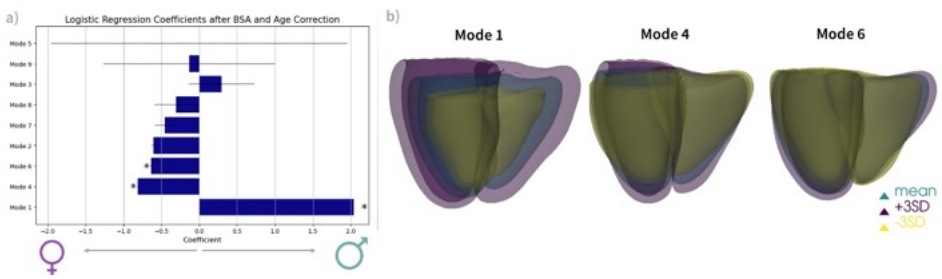

Figure 1: a) Logistic regression coefficients of male vs. female subgroup. (*) indicates statistical significance ($p<0.01$).b) Synthetic visualization of the most discriminating modes between the subgroups.

References:
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P31: Sex-specific and Genetic Influences on Cardiac Morphology and Structural Remodelling

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Cardiac structure and function are very specific, and are strongly linked to the presence and risk of cardiovascular disease. Cardiac morphology can predispose risk of disease or be remodeled during disease, worsening cardiac function and increasing likelihood of future cardiac events. Studies have found genetic associations with traditional measures of cardiac structure and function, such as LV mass, ejection fraction, etc[1]. We propose to find genetic associations of shape modes, derived from principal component analysis on a shape atlas. Heart shape and function generally differs between men and women[2]. Men and women also have different prevalence for disease, and varying disease outcomes. This study uses statistical methodology to investigate sex-stratified sex differences in cardiac shape, and genetic differences that are associated with shape changes. Changes in left and right ventricle morphology significantly increase risk for certain cardiovascular diseases[3]. We investigated the genetic architecture that contributes to cardiac shape. Using 35,000 patients from UKBiobank with available CMR imaging and whole genome sequencing data, we first dimensionally reduced 3D cardiac shape models into 11 principal component (PCs) measures that explained a cumulative 83.4% variance of shape. Subsequent genome-wide association analyses (GWAS) on these 11 PCs identified 43 significant genome-wide signals, with 14 never previously identified in GWAS for cardiovascular traits[4]. Upon stratifying by sex and adjusting for height, significant differences were observed in 9 out of the first 10 shape modes, each with a p-value < 0.001. We also observe how polygenic risk scores (PRS) from the PC GWASs can identify risk for cardiovascular diseases and how sex is related. These findings underscore the critical role of sex in shaping cardiac morphology and highlight novel insights derived from integrating genetic and shape analyses.

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P32: A Computational Analysis of the Impact of Sex Hormones on Cardiomyocyte Hypertrophy

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It has been become abundantly clear over the past two decades that sex differences play a significant role in cardiac health and disease. However, knowledge of the underlying mechanisms remains incomplete. The goal of this study was to assess the impact of estrogen and testosterone on cardiac hypertrophy through a data-informed biophysics model. We created an intracellular signaling model of cardiomyocyte hypertrophy based on 38 in vitro and in vivo literature studies. The model had 4 input nodes: estrogen (estradiol, E2), testosterone (T), angiotensin II (AngII), and mechanical stretch; and the output was captured as a change in cardiomyocyte cell area (CellArea) (Fig. 1a). Signaling pathway reactions were modeled using normalized Hill-type ordinary differential equations[1] using Netflux[2]. Sex-hormone sensitive pathways included calcineurin, CamKII, eNOS, IP3, AMPK and NF-B.
The model was successfully validated by upregulation individual and combinations of input nodes and comparing qualitative changes in species activity to the literature data (Fig. 1b). We performed up-regulations and knockdowns across the entire model to assess the influence of each node, defined as the sum of absolute change in activity of all others nodes upon up-regulation knockdown of the node. Interestingly, testosterone was more influential than estrogen in both knockdown and upregulation analyses, despite the sex hormone nodes being connected to a similar number of downstream nodes. These results suggest that it is the lower amount of testosterone, and not higher amount of estrogen, that makes women less susceptible to hypertrophic cardiomyopathy then men.

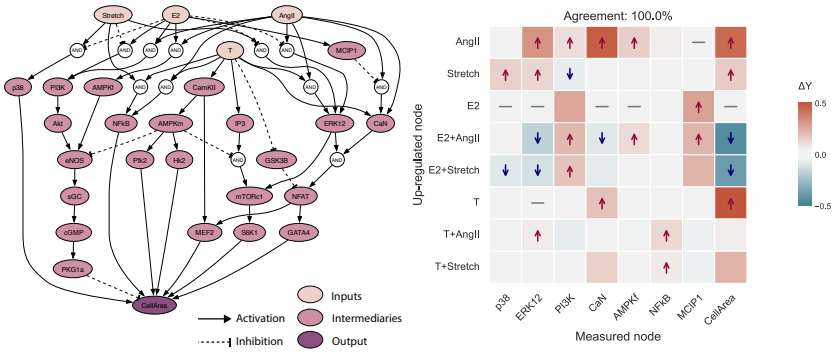

Figure 1: (a) Schematic representation of the sex hormone-specific cardiomyocyte hypertrophy model and (b) qualitative validation of the model, the shades indicate predicted fractional changes in species activity while the arrows indicate up- or down-regulation reported in the literature.

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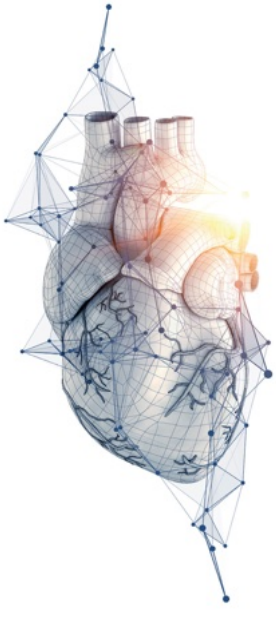
CARDIAC PHYSIOME
2024

Poster Abstracts II

Integrating experimental and mathematical approaches to advance cardiac physiology research



Freiburg, Germany
12 - 14 September 2024

P33: Deep Learning-Based 3D Segmentation of Cardiomyocytes

Greiner J[1], Frangiamore F[2], Sonak F[1], Kohl P[1], Rog-Zielinska E[1]
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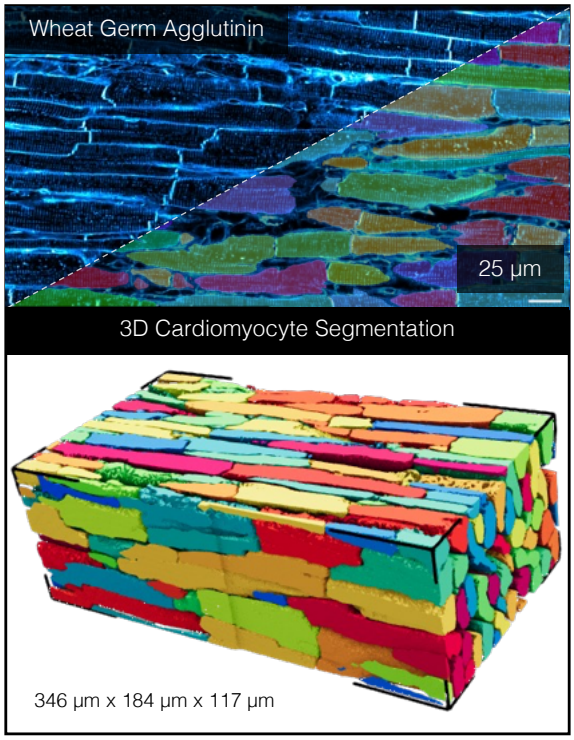
3D segmentation of cardiomyocytes at the microscale is an important but challenging research task. This challenge is further amplified when using deep tissue stacks, where scattering and reduced signal-to-noise ratios hinder fully automated segmentation. Consequently, researchers often resort to using 2D segmentations to infer 3D information. Deep learning-based methods have shown promise in robustly segmenting objects in images and volumes acquired using various modalities, yet they have not been applied to cardiomyocyte segmentation at the microscale.

Here, we develop methods for automatic processing and segmentation of cardiomyocytes in 3D confocal microscopy volumes. First, we present a deep learning-based workflow to reduce the detrimental effect of scattering in thick non-cleared tissue slices. Second, we present two methods to automatically generate 3D segmentations of cardiomyocytes. These segmentation methods are complemented by a semi-automatic segmentation method, termed 'SegmentPuzzler', which generates segmentations from scratch and refines existing ones. To benchmark our segmentation methods, we curated an extensive dataset of 3D confocal microscopy volumes with annotated cardiomyocytes. Importantly, these datasets were acquired in various laboratories worldwide, representing a wide range of characteristics. In total, the dataset consists of over 200 GB of image volumes, focussing on rabbit ventricular myocardium in control and disease conditions, as well as after ex vivo culture. The rabbit dataset is further complemented with a multi-species dataset containing control tissue from rat, mouse, pig, horse, elephant, whale, and human.



Automated Deep Learning-based segmentation of cardiomyocytes. Top: Confocal microscopy image volume of cardiac tissue with overlaid cardiomyocyte segmentation. Bottom: 3D rendering of instance-aware cardiomyocyte segmentation.

In summary, we have developed comprehensive methods, datasets, and tools, providing researchers with a foundation for further exploration of cardiac microstructure — whether they apply our tools to new data or utilise our extensive dataset of reconstructed tissues. Our deep learning-based approach has proven sufficiently accurate (F1 score: 0.84), and, given the size and diversity of our dataset, we expect it to perform well across various conditions, protocols, and diseases, facilitating large-scale 3D reconstructions.

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P34: Reinforcement Learing for Optimal Experimental Design in hERG Current Identification

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The hERG channel is a vital ion channel, also used for cardiac toxicity evaluation. However, to computationally evaluate the effects of a drug on the hERG channel, mathematical models that describe the channel current are needed. Those models involve unknown parameters that need to be inferred from experimental data.[1] Hence, the question arises how to conduct the experiment in order to obtain most informative data for the parameter identification problem. In this study we analyse a recently published reinforcement learning approach that is supposed to be robust to parametric uncertainty[2] and obtain a short high-information protocol. Furthermore, we compare the reinforcement learning approach to a more classical optimal experimental design.[3]

References:
[1] Song J, Kim YJ, Leem CH. Improving the hERG model fitting using a deep learning-based method. Front Physiol. 2023 Feb 6;14:1111967. doi: 10.3389/fphys.2023.1111967. PMID: 36814480; PMCID: PMC9939657.
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[3] Lei, C. L., Clerx, M., Gavaghan, D. J., et al. (2023). Model-driven optimal experimental design for calibrating cardiac electrophysiology models. Computer Methods and Programs in Biomedicine, 240, 107690.

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P35: Physiology-Informed Machine Learning to Guide Heart Failure Diagnosis, Prognosis, and Treatment

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Heart failure with preserved ejection fraction (HFpEF) is a prevalent form of heart disease with a diverse clinical manifestations and etiologies. To characterize phenotypic subgroups in the heart failure population we have developed a framework to categorize and stratify patients using a combination of physiology-/physics-based simulation and machine-learning approaches. Based on a longitudinal data set that includes imaging (cardiac MRI and transthoracic echocardiography) and invasive hemodynamic measurements (right heart catheterization), we have identified patient-specific digital twins simulating cardiac mechanics and cardio-vascular systems function on 346 heart failure patients. Combining model-augmented data with additional clinical data (NT-ProBNP, CPET, ECG, cardiac events, clinical outcomes) we performed unsupervised machine learning to identify clusters of differential phenotypes. Performing longitudinal outcome analysis on identified cluster phenogroups, we have identified optimal predictors of outcomes including death, rehospitalization, heart transplant, and LVAD implantation. By comparing the performance of predictors based on raw data, and based on model-augmented data and parameters, we demonstrate how the model-based precision phenotyping affords additional insight not provided from raw clinical data alone. This physiology-informed machine learning classification approach has the potential to represent a novel and uniquely powerful tool to guide diagnosis, therapy, and clinical trial design in the cardiovascular disease space. Beyond utility in precision phenotyping and diagnostics, our approach yields a comprehensive simulation-based "digital twin" of each patient's dynamic cardiovascular state. Thus this simulation-based framework provides a unique tool for not only identifying differential prognosis and treatment outcomes, but also identifying the major mechanistic functional drivers of differential outcomes.

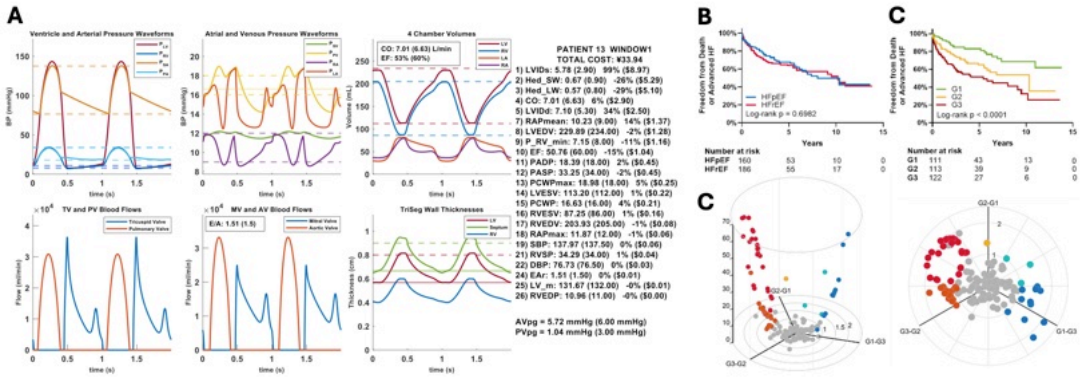

Figure: Model-based phenotyping of heart failure. A. Illustration of a model fit to a heart failure patient. B. Kaplan-Meier (KM) survival curves categorized by clinical diagnosis. C. KM survival curves for phenotype cluster identified by unsupervised clustering of patient-specific models. D. Volcano plot showing significances of relative differences in model-based and raw-data predictors for the three phe-notype clusters. Red dots: risk factors; blue dots: protective factors.

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P36: Synergistic Biophysics and Machine Learning Modeling to Rapidly Predict Cardiac Growth Probability

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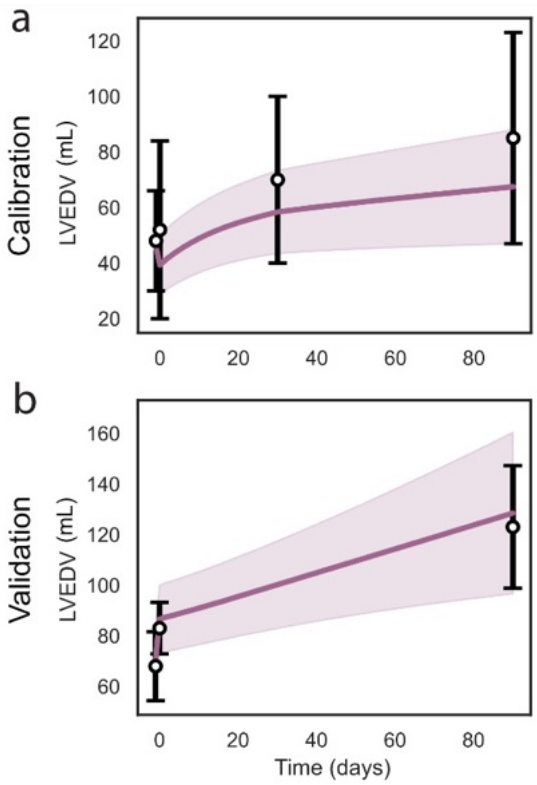
Biophysics models advance personalized medicine and facilitate a more comprehensive understanding of heart disease progression. However, long-term predictive capabilities can be limited without considering cardiac growth and remodeling, along with data uncertainty and variability, which are inevitable within clinical measurements. To address this need, we coupled a rapid biophysics model of cardiac mechanics and growth with Bayesian-based machine learning models to enable rapid calibration and predictions of long-term cardiac growth probability.
We utilized our recently published biophysics model[1] to simulate cardiac mechanics and strain-driven growth. We optimized the model's parameters using a two-step Bayesian history matching approach with Gaussian process emulators to accelerate biophysics model evaluation. First, adjusting cardiac and hemodynamic parameters for pre- and immediate post-MVR conditions, and second, calibrating growth parameters to match long-term changes. We randomly sampled the optimized baseline parameters before tuning growth parameters to guarantee that our calibrated model captures the progression of MVR from its onset to chronic stages across varying degrees of initial disease severity.

We successfully used the two-tiered calibration method to optimize our model to previously published canine MVR data[2] (Fig. 1a). Next, we used an independent MVR study[3] to validate the ability of our calibrated model to accurately predict cardiac growth outcomes (Fig. 1b). This study demonstrates that biophysics and machine learning modeling can predict cardiac growth probability with high accuracy and computational efficiency. While here we tested our model framework on animal data, we envision this method having great potential for personalized treatment strategies that account for data uncertainty with improved computational performance for quicker predictions.



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[3] Nakano K et al. Depressed contractile function due to canine mitral regurgitation improves after correction of the volume overload. J. Clin. Invest. 1991/87:2077-2086

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P37: Neural Network Based Surrogate Modeling of Cardiac Function Encoding Geometric Variability

Martinez E[1,3], Salvador M[1,3], Kong F[1,3], Moscoloni B[2], Peirlinck M[2] Marsden AL[1]
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[2]*Biomechanical Engineering, Delft, Netherlands*
[3]*Stanford University Cardiovascular Institute*

The combination of physics-based modeling with data-driven methods enables the clinical translation of computational cardiology. Today, the use of rigorous differential equations combined with machine learning tools allows patient-specific parameter personalization with uncertainty quantification in time frames compatible with clinical practice. However, accurate and efficient surrogate models of cardiac function are still mostly geometry-specific and require retraining for different patients and pathological conditions. We propose a novel computational framework to embed different cardiac anatomies into neural network based surrogate models. We generate a dataset of numerical simulations using mathematical models based on differential equations. We consider Branched Latent Neural Maps (BLNMs) as an accurate and efficient computational tool to encode complex space-time fields into a neural network.[1] We employ statistical shape modeling to represent different human hearts. This framework would allow for fast and robust parameter estimation on patient cohorts without the need to modify the surrogate model.

References:
[1] Salvador, Matteo, Marsden Alison. Branched Latent Neural Maps. Computer Methods in Applied Mechanics and Engineering 2024/418.

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P38: A multimodal machine learning model for predicting elevated left ventricular end-diastolic pressure

Verlyck MA[1], Zhao D[1], Ferdian E[1], Dillon JR[1], Creamer SA[1], Dunphy RA[1], Babarenda Gamage TP[1], Nash MP[1,2]

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Elevated left ventricular end-diastolic pressure (LVEDP) is an important marker of diastolic dysfunction. While the current ASE/EACVI decision-tree algorithm[1] is able to non-invasively classify LVEDP as normal or elevated (15mmHg) using echocardiography, this can produce indeterminate classifications. We investigated whether a combination of the guideline variables, additional existing clinical variables and computational model outputs could provide an alternative data-driven LVEDP classification method using invasive left heart catheterisation as the reference. A multimodal machine learning model was developed using three modalities: 2D echocardiographic clips, time-varying 3D geometric meshes of the left ventricle derived from 3D echocardiography, and binary or scalar routine clinical variables. The model used four encoders to extract modality-specific features, subsequently aligned through multilayer perceptron before concatenation. Finally, a classifier was trained to predict LVEDP status from the concatenated features (Figure 1).

The model was trained for 50 epochs on 102 cases and tested on 26 cases; 27% of the cases in each set had elevated LVEDP. The model achieved a classification accuracy of 0.73, sensitivity of 0.57, specificity of 0.79, positive predictive value of 0.5, and negative predictive value of 0.83. These initial results show the feasibility of combining routine and computational parameters for LVEDP classification. Although further fine-tuning is required to optimise parameter selection, model complexity and class balance, a multimodal approach may provide additional information for non-invasive LVEDP classification.

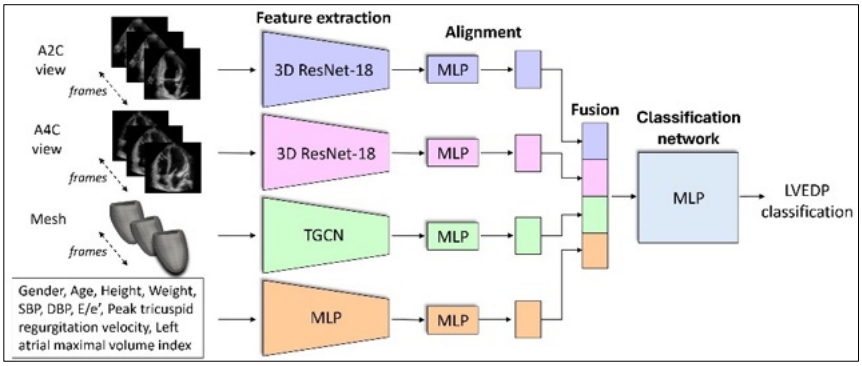

Figure 1. Multimodal model architecture including feature extraction, alignment and fusion steps and a classifier network to predict LVEDP (left ventricular end-diastolic pressure) status (elevated or not). MLP: Multilayer perceptron. TGCN: Temporal Graph Convolutional Network. A2C: Apical 2 Chamber. A4C: Apical 4 Chamber. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure.

References:

[1] Nagueh S. F., Smiseth, O. A., Appleton, C. P et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.Eur J Echocardiogr 2016/17:1321-1360.

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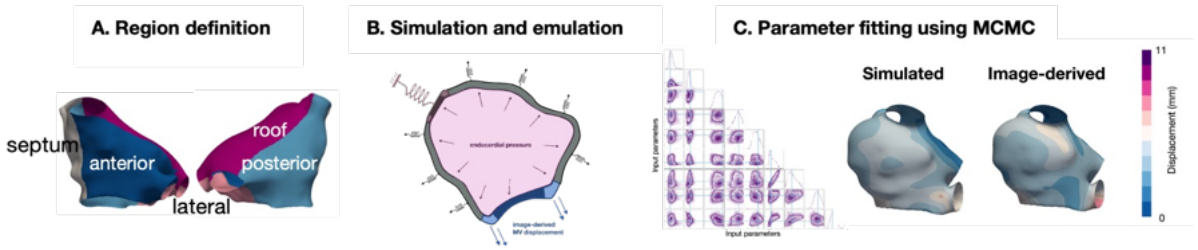
P39: A calibration study to uncover regional influences on passive left atrial biomechanics in a cohort of patient-specific models

Baptiste TMG[1], Rodero C, Sillett CP, Strocchi M, Lanyon CW, Augustin CM, Lee AWC, Solis-Lemus JA, Roney C, Ennis DB, Rajani R, Rinaldi CA, Plank G, Wilkinson RD, Williams SE, Niederer SA

[1]*School of Biomedical Engineering and Imaging Science, King's College London, London, United Kingdom*

The incidence of atrial fibrillation has been associated with anatomical and structural remodelling of the left atrium (LA). These remodelling changes combine to impact atrial biomechanics, leading to increased stiffness and reduced contraction. LA biomechanical changes in AF have received far less attention in previous research. Little is also known about how factors such as the heterogenous LA anatomy, myocardium stiffness and boundary conditions imposed by surrounding physiological structures combine to impact LA biomechanics. Physics-based models provide a systematic framework to integrate and account for anatomy, boundary conditions and material properties when analysing atrial biomechanics. Therefore, we aimed to develop a modelling framework for passive LA function and examined the impact of regional heterogeneity in LA anatomy and stiffness on the chamber biomechanics.

We constructed patient-specific LA models from the ventricular end-diastolic frame of a gated CT image set and used feature tracking to estimate global and regional LA deformation from the CT image set. In the simulator, CT-derived mitral valve displacement and an idealised pressure transient drove LA deformation. LA myocardium was modelled as a regionally varying and transversely isotropic material. We then trained fast evaluating emulators to replace the computationally expensive simulator. We used Gaussian process emulators to identify and exclude unimportant stiffness parameters and perform parameter calibration using history matching and Markov chain Monte Carlo (MCMC) methods. Through MCMC, we obtained an estimate of the input stiffness parameters most likely to recover the image-derived deformation. These estimates suggest that stiffness varies regionally over the LA and this heterogeneity plays a role in dictating physiological LA biomechanics.



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P40: Estimating left-heart filling pressures using Digital Twins

van Osta N[1,*], van Loon T[1,*], Martinez-Legazpi P[2], Knackstedt C[3], van Empel V[3], Bermejo J[2], Lumens J[1]

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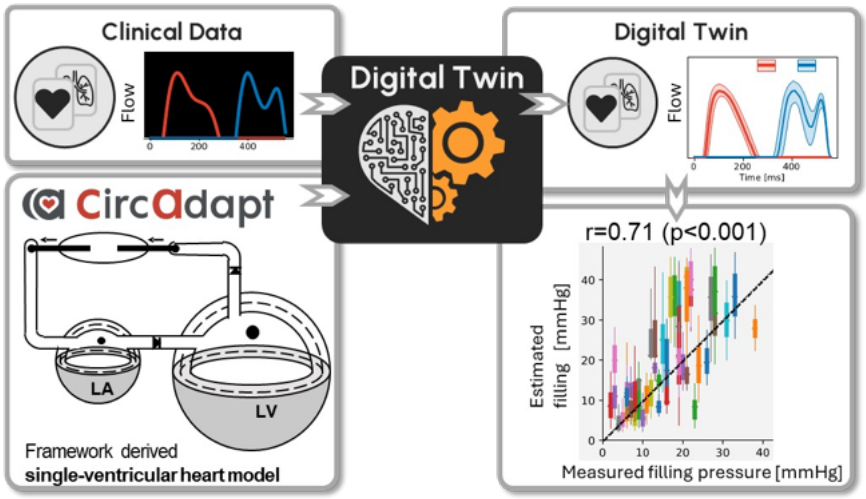
[3]*Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, the Netherlands*

Introduction: Accurate assessment of left-heart filling pressure is important for the diagnosis of heart failure (HF) and guiding effective treatment strategies. However, current diagnostic methods often involve invasive procedures or have limited diagnostic accuracy. In this study, we created Digital Twins of subjects with suspected congestive heart failure and investigated the accuracy of a non-invasive Digital Twin-based method to estimate left-heart filling pressure from conventional echocardiographic information.

Methods: We retrospectively analysed 42 patients from the University Hospital Gregorio Marano (Madrid, Spain) who were referred to right heart catheterization within 48 hours after routine echocardiographic assessment of left-heart function to assess mean pulmonary capillary wedge pressure (mPCWP). Due to limited right-heart information, a simplified single ventricular-atrial model was created using the CircAdapt framework (http://framework.circadapt.org/). Using a recently developed Digital Twin algorithm, the CircAdapt framework was personalized to the conventional echocardiographic information of the individual patient to estimate mean left atrial pressure (mLAP) and compared to the invasively measured mPCWP.

Results: Flow patterns and indices of DTs are in good agreement with the patients' measured signals. The DT-based filling pressures were significantly correlated with mPCWP ($r=0.71$, $p<0.001$). The DT approach demonstrated an accuracy of 84% in determining whether individuals have normal or increased filling pressure (mPCWP>15mmHg).



Conclusion: This study investigates the use of a biophysical Digital Twin approach for non-invasive filling pressure estimation, demonstrating a good correlation with invasively measured mPCWP. Future studies should investigate what data is needed to further increase accuracy in a larger prospective cohort. Additionally, the related DT-based tissue characterization may provide unique and clinically valuable insight in the patient-specific disease substrates underlying increased filling pressure.

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P41: Comparative study to evaluate measurement uncertainties and influencing factors in PPG and blood pressure measurement data

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Introduction: The use of photoplethysmography (PPG) sensors is crucial for health monitoring, such as measuring oxygen saturation, but also an increasing number of health conditions [1]. However, various pre-processing methods can impact the accuracy of these measurements, especially for blood pressure estimation [2,3]. This study evaluates measurement uncertainties in PPG and blood pressure data, assesses the signal quality of different PPG sensors, and examines the effects of pre-processing on data correlation and variability.
Methods: Continuous blood pressure, electrocardiography (ECG) and PPG data were recorded from 5 participants using a TMSi-Porti7 and Polybench software. PPG signals are measured at locations of various fingers and the wrist. Blood pressure fluctuations were induced by the Valsalva manoeuvre and recorded using Monitor CNAP-500 Device [4]. PPG signals were compared to a raw PPG reference signal, subsequently all signals underwent standard pre-processing using low-pass and high-pass filters. The variance between the signals was assessed qualitatively and quantitatively after phase and amplitude correction, normalization by using a difference norm between all signals.
Results and Discussion: Results indicate that raw PPG signals exhibited greater consistency in signal form compared to pre-processed signals, which showed significant form-specific differences. Furthermore, visual and qualitative assessments confirmed that the trend of the raw PPG signals correlated better to the blood pressure signals. Pre-processing degraded the signal quality and could potentially affect the accuracy of blood pressure estimations. These findings highlight the need for standardized PPG pre-processing and suggest that future studies should involve more participants and employ enhanced comparison methods. We note that device specific differences in the signals can have significant impacts, especially when large amounts of data are analysed using machine learning.

References:
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P42: Assessing the Effects of the Purkinje Network Density and Fast Endocardium Layer on the ECG

Arantes Berg L[1], Camps J[1], Dotse R[1], Sachetto Oliveira R[2], Weber dos Santos R[3], Rodriguez B[1]

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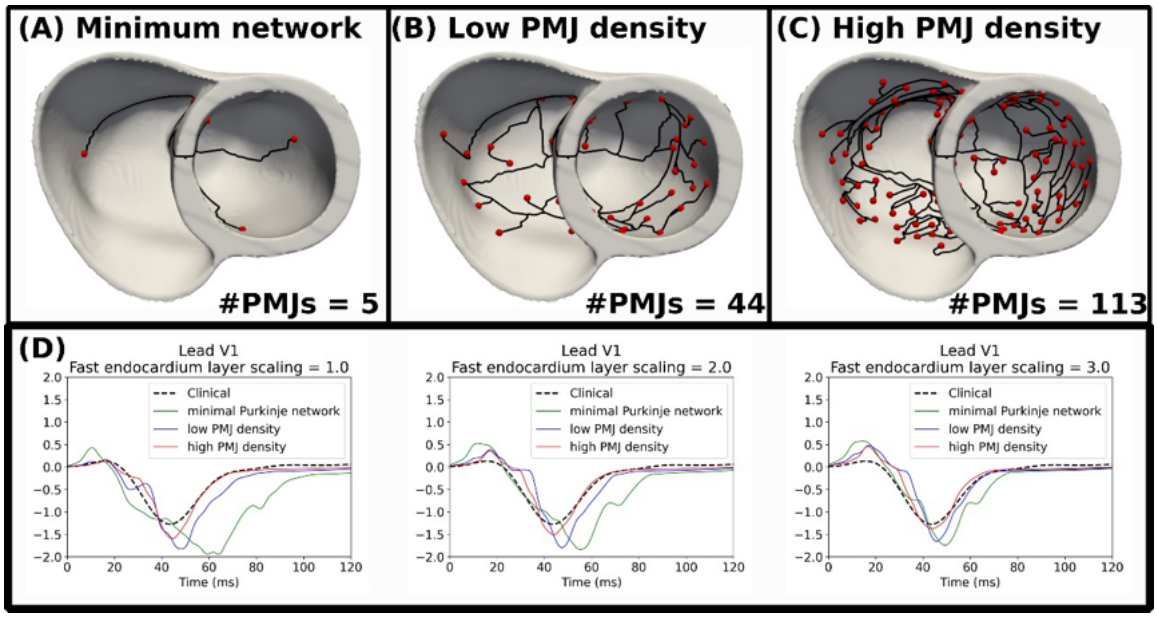
The development of cardiac digital twin models with a high level of detail is becoming a powerful tool to reproduce patient-specific physiological behaviours observed under healthy and diseased conditions. Within this context, the inclusion of the Purkinje network is consider an important step towards the development of more realistic models to study a variety of cardiac arrhythmias associated to this structure. However, patient-specific modelling of Purkinje networks remains a challenge due to their high morphological complexity. For that reason some models simplify the Purkinje network activation by employing a fast endocardium layer. The main objective of this work is to investigate the effects that the Purkinje network density has on the electrocardiogram (ECG) when compared to different scaling factors for the fast endocardium layer. A human-based biventricular mesh is used as the domain to generate three different Purkinje networks topologies with a varying number of Purkinje-muscle-junctions (PMJs) by using an optimized-based generation method. Alongside with that, the conduction velocity of the fast endocardium layer is also varied for each Purkinje network topology to verify its effects on the QRS complex duration. The numerical simulations are performed by solving the Purkinje-myocardium coupled monodomain simulations using a high-performance GPU cardiac solver and are executed to evaluate the electrical activation of the generated Purkinje networks in a realistic scenario using the most recent Purkinje/ventricular human cellular models and physiological values for the anterograde PMJ characteristic delay. The results demonstrate that Purkinje networks with an increased density can not only decrease the overall anterograde PMJ delay, but also reduce the duration of the QRS complex.



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P43: Utility of 3D echocardiography in the generation of cardiac digital twins for ventricular electrophysiology

Zhao D[1,*], Camps J[2,*], Dillon JR[1], Doste R[2], Creamer SA[1], Verlyck MA[1], Babarenda Gamage TP[1], Wang VY[1], Young AA[3], Rodriguez B[2], Nash MP[1]

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[2]*Department of Computer Science, University of Oxford, Oxford, United Kingdom*

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Cardiac digital twins can be used to virtually assess the safety and efficacy of new therapeutic interventions. While magnetic resonance imaging (MRI) can provide detailed characterisation of cardiac anatomy to be used as input to computational modelling frameworks, echocardiography (echo) is more prevalent and widely accessible. This study investigates the utility of 3D echo and 12 lead electrocardiogram (ECG) recordings in modelling cardiac electrophysiology.

Paired cardiac MRI, 3D echo, and 12-lead ECG data from 3 human subjects were used to generate QRS simulations using a novel pipeline.[1] Biventricular geometries were automatically extracted from each imaging modality using a deep learning approach,[2] followed by calibration of the Purkinje network and conduction speeds to produce QRS complexes with normal morphology.

Pearson Correlation Coefficients between 3D echo and MRI-based ECG simulations were 0.97, 0.94, 0.95, 0.96, 0.61, 0.94, 0.96, and 0.98, for leads I, II, V1, V2, V3, V4, V5, and V6, respectively (Figure 1). The largest ECG discrepancy was observed for precordial lead V3, likely affected by differences in the right ventricular and septal geometries between 3D echo and MRI.

These preliminary results suggest that 3D echocardiography paired with 12-lead ECG data may be used as an alternative modality to MRI for the generation of cardiac digital twins for ventricular electrophysiology. However, further work is needed to improve the characterisation of right ventricular and septal anatomy to ensure accurate and reliable simulations across all leads.

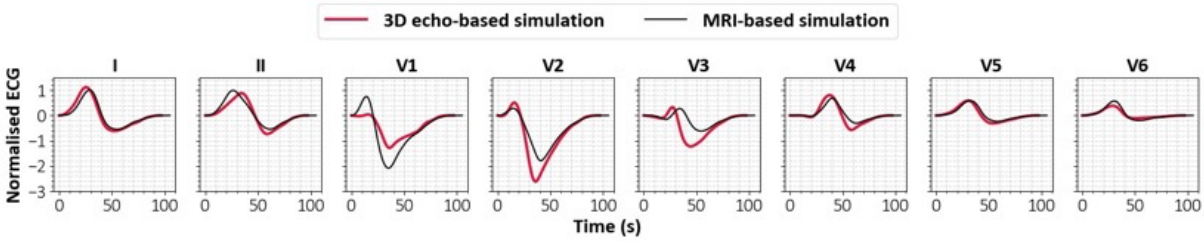

Figure 1. Comparison of simulated QRS complexes using geometries from 3D echocardiography and MRI for one subject.

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P44: Patient-Specific Phenogrouping of HFpEF within the Landscape of Heart Failure

Daily N[1], Elson J[1], Ježek F[2], Muyizere M[3], Wakatsuki T[1], Carlson BE[2]
[1]*InvivoSicences, Inc. Madison, Wisconsin, USA*
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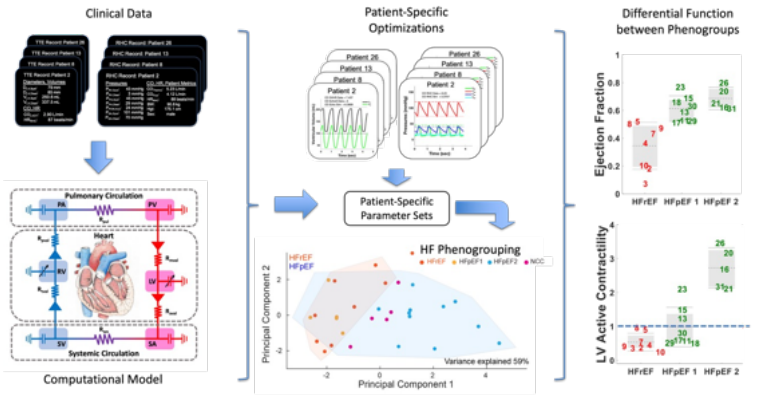
[3]*Northern Illinois University, DeKalb, Illinois, USA*

Introduction: It has become apparent that some broad classes of heart failure (HF) used as a clinical diagnosis are in fact a constellation of different types of heart failure under a single diagnosis. One such HF diagnosis is heart failure with preserved ejection fraction (HFpEF) and recent conversations call for better methods of understanding different subtypes that make up HFpEF[1].

Methods: We have obtained clinical narratives for over 500 patients heart failure patients from DataDirect, a University of Michigan searchable clinical database. From these narratives we have extracted measures from two procedures, right heart catheterizations (RHC) and transthoracic echocardiographs (TTE). Previously we have developed a proof-of-concept methodology that was able to find phenogroups within HFpEF on 21 patients which we have now used on this larger cohort of HF patients with and without the comorbidity of type II diabetes which includes a large fraction of HFpEF patients. This methodology is shown to the right where emergent phenogroups can be compared to each other to understand underlying mechanistic differences.

Results: Using this methodology we have found more than 15 phenogroups across all heart failure patients. One large phenogroup exhibits increased stiffness in the passive properties of left ventricle along with increased active contractility indicative of the classic definition of HFpEF. Within this group there exists subgroups with varying degrees of pulmonary hypertension.



Phenogrouping methodology. Clinical measures are used to identify patient-specific computational models and then parameter sets from each model are used to cluster patients into phenogroups and understand differential function

Discussion: Understanding different mechanistic phenogroups comprising HFpEF and how they position themselves in the HF landscape can be a better path to treatment than current diagnostic methods. Additionally, stratification is useful for enriching heart failure patient cohorts in clinical trials, enabling validation of therapeutic candidates' efficacies with fewer subjects.

References:
[1] Shah SJ, Borlaug BA, D. W. Kitzman DW et al. Research priorities for heart failure with preserved ejection fraction: National Heart, Lung, and Blood Institute Working Group summary. Circulation 2020/141:1001-1026.
[2] Jones E, Randall EB, Hummel SL et al. Phenotyping heart failure using model-based analysis and physiology-informed machine learning. J Physiol 2021/599:4991-5013.

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P45: Evaluating Novel Cardiac Resynchronization Therapy Techniques for Different Types of Left Bundle Branch Block: A Pilot In Silico Study

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Introduction: Recent guidelines from the European Society of Cardiology[1] and the American Heart Association[2] have highlighted the potential of cardiac conduction system pacing (CSP) as an alternative to biventricular pacing (BiV-CRT) for CRT. The key criterion for CRT application is the presence of LBBB, whose identification poses challenges due to the heterogeneity of conduction block levels.

Methods: We developed a patient-specific ventricular model using clinical data from a BiV-CRT implanted patient. This model incorporated detailed computational simulations of myocardial fiber architecture and electrophysiological characteristics to replicate various CRT strategies (His bundle pacing (HBP), left bundle branch pacing (LBBP), and HOT-CRT) and proximal or distal LBBB types (Fig. 1).

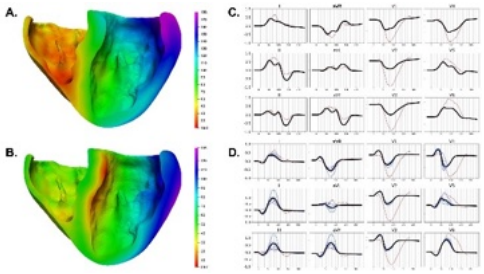

Figure 1. Activation maps and 12 lead ECG for proximal (A) and distal (B) LBBB models.

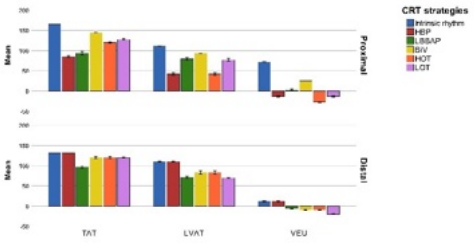

Figure 2. Ventricular activation characteristics for proximal and distal LBBB during different CRT strategies.

Results: Our computational experiments indicated that the effectiveness of CRT strategies varied with the conduction block location. HBP and HOT-CRT were particularly effective in cases of proximal LBBB, significantly improving electrical synchronization. Conversely, LBBP and LOT-CRT provided the most benefit in distal LBBB scenarios.

Discussion: This in silico method provides a promising avenue for refining therapeutic interventions in a patient-specific manner, potentially improving both diagnostic accuracy and outcomes in CRT and CSP.

References:
[1] Glikson M, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. European Heart Journal. 2021;42(35):3427–3520.
[2] Chung MK, et al. 2023 HRS/APHRS/LAHRS guideline on cardiac physiologic pacing for the avoidance and mitigation of heart failure. Heart Rhythm. 2023;20(9)–e91

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P46: A Resource-Efficient Open-Source Solver for Monodomain Equations in Cardiac Electrophysiology

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Background: The monodomain equation serves as a key mathematical model in cardiac electrophysiology, describing the electrical activity occurring within cardiac tissue. However, the numerical solution of this equation, especially on fine meshes, requires significant computational resources. Existing software tools such as openCARP and fenics-beat (based on the FEniCS project) offer platforms for conducting these simulations, but their operational speed can be a barrier to clinical use.
Aims: This research seeks to introduce an innovative open-source program that can quickly resolve monodomain equations. We aim to improve cardiac electrophysiology modeling by trying to surpass the speed and preserve the precision of established software tools such as fenics-beat and openCARP. The study analyses the efficiency of the new software compared to these current computational tools.
Methods: This newly developed program is written in C, specifically designed to optimize the numerical solution of monodomain equations. To assess its accuracy and performance, we replicate the Niederer benchmark simulations across the three software codes. The measured wall time of these simulations is broken into solver components and across different temporal and spatial resolutions. Each solver employs operator splitting methods to separate the ODE and PDE computation steps. Consistency is maintained by using equivalent numerical approaches for each software package.
Results: Preliminary performance evaluations indicate that openCARP exceeds fenics-beat by a factor of 8-9. Our solver shows competitive speed performance, exhibits robust computational stability, and produces outcomes that align with those derived from globally accepted cardiac electrophysiology models.
Conclusions: The findings indicate that the new open-source software holds promise as a tool for facilitating real-time clinical decision-making in cardiac electrophysiology. To further enhance performance, future improvements will focus on expanding the software's capabilities, including the integration of GPU support.

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P47: Multi-Precision computing for cardiac simulation

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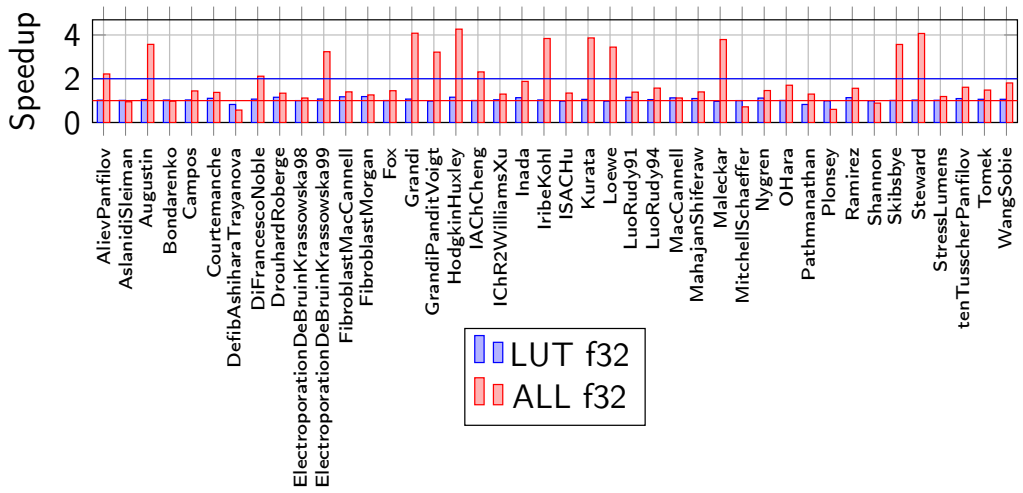
We investigate the benefits of using single precision numbers in the openCARP cardiac electrophysiology simulator. The openCARP code generator for ionic models based on MLIR[1] allows for fine control over which part of the code runs on double or single precision. This optimization comes at the cost of reduced precision.
The ionic models are written in a domain-specific language (DSL) named easyML. A python code generator called limpet creates an AST from which MLIR instructions are generated. These instructions are very precise and allows us to choose when we convert numbers to single precision and when to use single precision operations. Here we present two levels of single precision computing. One way is to have the whole computation run on single precision (ALL f32). This makes for maximum speedup but degrades numerical precision the most. The other way (LUT f32) is to have state variables (ion concentrations) and lookup tables stored in single precision and run computations on double precision. This method has better numerical precision but is slower than the full single precision computation.
These methods were evaluated on a 2x 18-core Cascade Lake Intel Xeon Gold 6240 @2.6GHz. The multi-precision version is implemented on top of openCARP and can be found on the lut-f32-inmemory git branch of the repository. The following figure shows the speedup (ratio of execution time) of the two methods compared to the MLIR generated double precision vectorized CPU code, on 1024 cells and 1,000,000 time steps (0.01 ms time steps).



Experiments show that using single precision numbers make the models slightly deviate after a certain number of time steps. However, after 1000 seconds of physical simulation time with stimulations every second, most models remain visually accurate. We are currently investigating finer tuning of multi-precision computing in openCARP, having for example only the most important operations run on double precision and the rest on single precision.

References:
[1] Thangamani A, Trevistan Jost T, Loechner V, Genaud S, Bramas B, Lifting Code Generation of Cardiac Physiology Simulation to Novel Compiler Technology. CGO '23, ACM Feb 2023, Montréal, Canada, 10.1145/3579990.358008.

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P48: Jupyter-based Notebooks for Cardiac Simulations

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Introduction: Simulations of cardiac electrophysiology rely on a suitable software. However, the installation and configuration of such software packages and its dependencies can be complicated, with a number of users reporting difficulties in installing the software on their machine or HPC systems, which are essential for large scale simulations. In this presentation, we introduce a web-based platform for simulations with openCARP that can be readily accessed using a standard web browser.

Methods and Results: The web-based cardiac simulation environment was prepared using several technologies. The core is JupyterLab interface for creation of Jupyter notebooks. The notebooks are short documents combining text, code and media such as graphs, tables and animations generated by that code. This facilitates composition and documentation of numerical experiments in a way that is easy to reproduce and learn from. A virtual computing container image in docker was built and uploaded to a public repository to allow a simple launching of all relevant parts. The image is built with an installation of the openCARP cardiac simulator together with its dependencies, carputils utilities for the experimental setup and the above mentioned JupyterLab. The docker container can be run on local computer or on an HPC server.

Alternatively, Binder allows a load-balanced launch of the reproducible interactive environments just by clicking a link.

Discussion: We investigate the benefits of using single precision numbers in the openCARP cardiac electrophysiology simulator. The openCARP The developed interface simplifies the on-boarding of new researchers to cardiac electrophysiology simulations. The easy setup and large toolbox of Python packages also caters to the needs of experienced users who can develop their own reproducible notebooks and share it with the cardiac modelling community.

The currently running survey for the ease of use of the web-based environment will provide data for analysis of user experience and provide a base for further improvements of the platform.

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P49: Global Uncertainty Analysis of Ion Channel Gating Parameters: Method and Application

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Experimental measurements of ion channel properties often exhibit significant variability, reflecting inherent uncertainties and the fragile nature of these channels even among genetically identical clones. A widely adopted modelling approach to elucidate ion channel gating mechanisms is the continuous-time aggregated Markov model, which represents observable open and closed states with multiple discrete states. Traditionally, parameter values for these models are determined through point estimation from experimental data. However, these estimates are uncertain due to the high variances in measurements. Given the variability among individual clones, a model parameter should be identified as a probability distribution rather than a single value. This study addresses these challenges by estimating the probability distributions of model parameters using advanced Bayesian inference techniques.

The posterior probability of a set of model parameters for the observed data is derived from the likelihood of the parameters through Bayesian inference. Parameter sets are sampled according to the posterior probability using a Markov chain Monte Carlo (MCMC) method. Global sampling in the parameter space is achieved with replica exchange MCMC sampling. We validated this approach using a three-state gating model for the calcium-dependent gating of the RyR2 channel, estimating parameter probability distributions from experimental data by Uehara et al.[1] on both the open probability dependence on cytosolic calcium levels and histograms of dwell time distributions at three cytosolic calcium levels.

Our results reveal that the parameter space is inherently non-smooth with multiple local minima, posing challenges for conventional optimization methods. The advanced MCMC method effectively identifies the global optimum parameters and provided a comprehensive probability distribution of the model parameters. This probabilistic approach enhances understanding of ion channel dynamics compared to traditional methods.

The Bayesian MCMC methods offer a powerful tool for estimating the parameters of ion channel models in cardiac physiome studies. By surpassing the limitations of point estimation, this approach improves the reliability and accuracy of model predictions, contributing to a deeper understanding of cardiac ion channel behaviour.

References:
[1] Uehara A, et al., Extensive Ca2+ leak through K4750Q cardiac ryanodine receptors caused by cytosolic and luminal Ca2+ hypersensitivity. J Gen Physiol, 2017/149:199-218.

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P50: Relative contributions of ionic currents in models of the human cardiac AP

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Since their introduction in the 1960s, computational models of the cardiac action potential (AP) have been highly successful tools for studying the biophysical processes that lead to the formation and propagation of the PA. While originally these models were used only in research settings, for example to test the feasibility of a hypothesis, recently they have moved out of the lab, and are now used or proposed to make predictions in clinical settings, in development, testing, and regulation of pharmaceuticals, and as a (partial) replacement for animal experiments. While hugely exciting, the safety critical nature of these applications requires that our models are subjected to a much higher level of scrutiny than before.

Plots of the relative contribution of ionic currents to the AP provide a graphical, effective, and provocative tool to scrutinise and compare published models. In this work, we create such plots for human ventricular, atrial, and Purkinje models, as well as models of stem-cell derived "cardiomyocytes".

We show that there is widespread disagreement within the models, but that "families" of models can be identified with much more similar predictions. In many cases, the plots reveal the strong influence of currents usually thought of as "minor players", for example the background chloride current. The diastolic phase in particular, is dominated by such currents, even though very little data exists for these currents, and they are usually simply postulated as a tool to reach dynamic equilibrium in internal concentrations from beat to beat.

Finally, we ask the reader to consider the impact of these model differences for future studies.

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P51: Myocardial Metabolic Response to Acute Ischemia Causes Mechanical Dysfunction Following Reperfusion

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The balance between ATP supply and demand in the myocardium is impeded in ischemia, resulting in a series of metabolic changes that are hypothesized to lead to cell death and mechanical dysfunction after reperfusion. During ischemia, an accumulation of NADH and succinate occurs, creating an excessively reduced system affecting both mitochondrial matrix and cytosolic metabolic reactions[1]. In addition, ischemia leads to an elevation of AMP, and increased downstream adenine nucleotide degradation and depletion[2]. Upon reperfusion, respiration on accumulated succinate results in both the production of pathological levels of reactive oxygen species (ROS)[1] and high concentrations of oxaloacetate (OAA), a potent inhibitor of succinate dehydrogenase.

Pathological ROS production and adenine nucleotide depletion are hypothesized to contribute cardiac mechanical dysfunction after an ischemia. We hypothesize a route of OAA clearance is needed to restore physiological respiration. These hypotheses were tested using two methods: (1) experiments with purified mitochondria paired with predictions from our computational model of mitochondrial metabolism to determine metabolic profile during anoxia and reoxygenation and

(2) a conditional knockout of myocardial AMP deaminase, to assess if and how blocking purine degradation affects metabolic state and mechanical function in ischemia and after reperfusion.

Respiration and metabolic data from cardiac mitochondria revealed succinate accumulation occurs through succinate dehydrogenase reversal during anoxia and OAA clearance occurs rapidly through glutamate-oxaloacetate transaminase compared to malic enzyme and oxaloacetate decarboxylase. Additionally, diminished cardiac mechanical function following ischemia and reperfusion is associated with degradation of adenine nucleotide pools. Moreover, perturbation of the nucleotide degradation pathway alters myocardial mechanical function. These data indicate a link between adenine nucleotide degradation during ischemia and mechanical dysfunction after reperfusion.

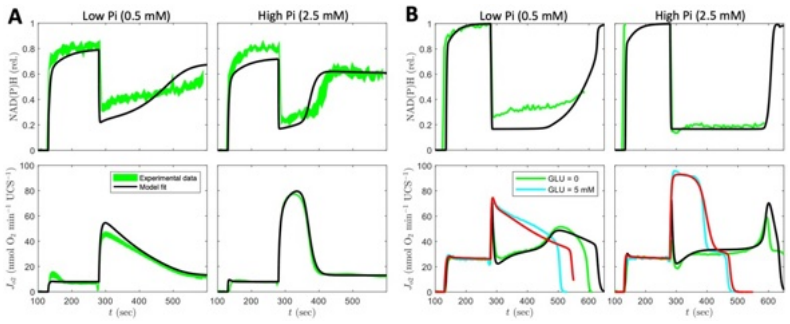

Figure 1. Experimental data and model fits of mitochondrial relative NAD(P)H and oxygen consumption during respiration on (A) pyruvate + malate and (B) succinate +/- glutamate.

References:
[1] Chouchani ET, Pell V, Gaude E, et al. Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS. Nature 2014/515(7527):431-435.
[2] Martin J, Costa A, Gruszczyk, et al. Succinate accumulation drives ischaemia-reperfusion injury during organ transplantation. Nat Metab 2019/1(10):966-974.

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P52: Global sensitivity analysis informs a deep learning design for mitochondria to study hypertrophic cardiomyopathy

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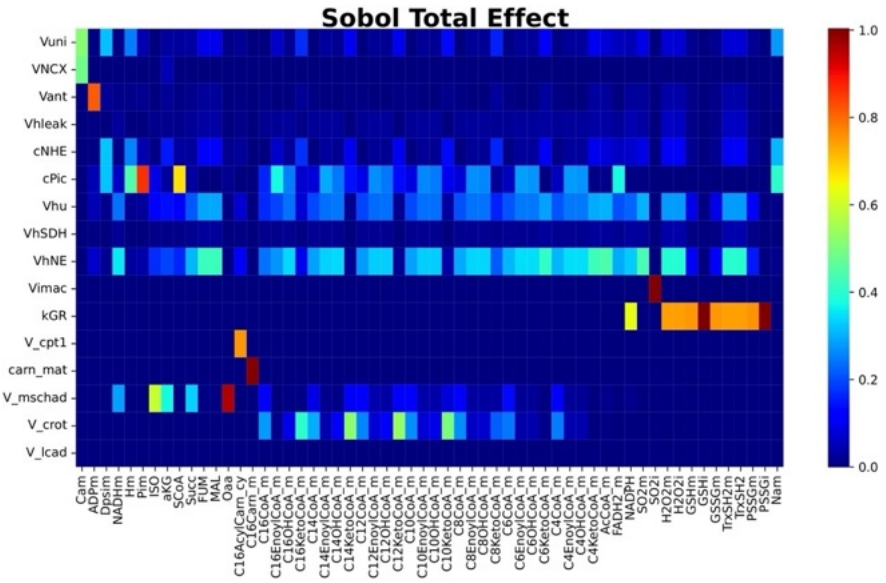
Computer models of mitochondria have reached a level of sophistication enabling numerous applications in pharmacology and disease risk assessment, including hypertrophic cardiomyopathy. However, interfacing these models with experimental data can impose a substantial computational load. To address this challenge, we introduce an artificial neural network (ANN) that emulates key readouts of a detailed in silico model of mitochondria[1], such as Ca_{2+} concentration (Cam), reactive oxygen species (SO2m & H2O2m), and reduced and oxidized glutathione (GSHm & GSSGm), based on maximum rates of enzymes and transporters. Using SALib library, we performed a Sobol' global sensitivity analysis (GSA) generating 34816 samples of 16 rate parameters listed on the Y-axis of the figure. The GSA parameter space was $\pm$30% of baseline values. Informed by in vitro data on HCM impaired energetics[2], we targeted calculation of Cam, SO2m, H2O2m, and GSHm & GSSGm. Based on Sobol total effect sensitivity results, we selected six parameters (Vuni, VNCX, cNHE, Vhu, VhNE, and kGR) for the five outputs (Cam, SO2m, H2O2m, GSHm, and GSSGm) to train an ANN with only one hidden layer (10 neurons) and a standard loss function on the generated data with a 5-fold cross-validation. The best ANN model simulated the outputs with a root mean squared error of 0.02. In summary, our results demonstrate the potential of ANN emulators as tools for enhancing efficiency in forthcoming quantitative systems pharmacology investigations.



References:
[1] Cortassa, S.; Sollott, S. J.; Aon, M. A. Mitochondrial Respiration and ROS Emission during -Oxidation in the Heart: An Experimental-Computational Study. PLoS Comput Biol 2017, 13 (6), e1005588e.
[2] Wijnker, P. J. M.; Sequeira, V.; Kuster, D. W. D.; van der Velden, J. Hypertrophic Cardiomyopathy: A Vicious Cycle Triggered by Sarcomere Mutations and Secondary Disease Hits. Antioxid Redox Signal 2019, 31 (4), 318–358.

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P53: Modeling Ion Channel Reorganisation Due to Ischemia in Cell-Based Models of the Myocyte

Jæger K[1], Trotter J[1], Cai, X[1], Arevalo H[1], Tveito A[1]
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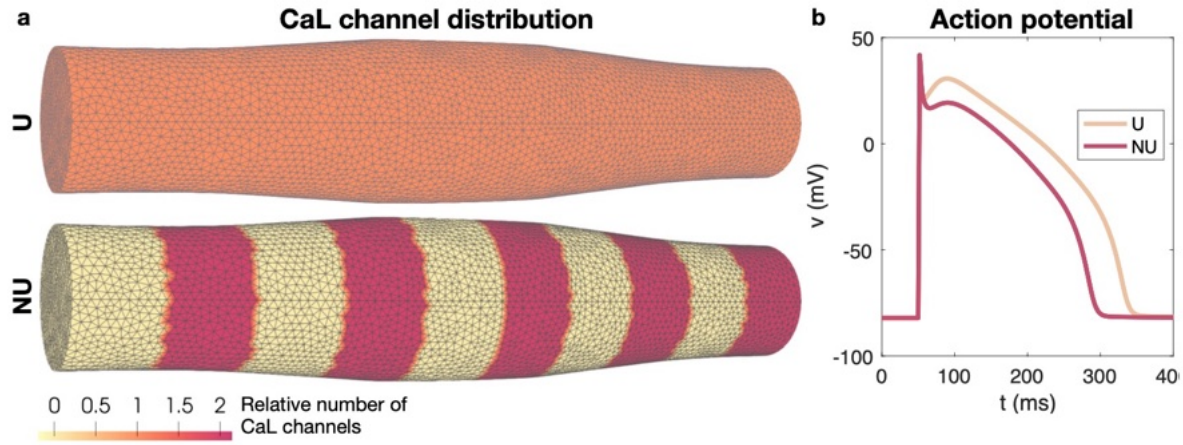
Computational techniques have significantly advanced our understanding of cardiac electrophysiology, yet they have predominantly concentrated on averaged models that do not represent the intricate dynamics near individual cardiomyocytes. Recently, accurate models representing individual cells have gained popularity, enabling analysis of the electrophysiology at the micrometer level. Here we investigated the effect of non-uniform distribution of ICaL channels, as occurs during ischemia, on the action potential morphology using a recently developed model that distinctively accounts for the extracellular (E), membrane (M), and intracellular (I) spaces[1]. We compared the case when all the L-type calcium channels are uniformly distributed throughout the membrane (U), to the non-uniform (NU) case where the channels were located in five bands along the length of the cell (Figure). Simulation results showed that the action potentials computed in single-cell EMI model simulations using these two channel distributions, and we observe that the duration of the action potential is considerably reduced in the NU case. Such simulation set-ups are currently not possible to investigate using non-EMI formulations due to the lack of representation of the subcellular ion channel organization. While computationally more expensive compared to monodomain or bidomain formulation, these results show that the EMI formulation can possibly yield novel insights into electrophysiological remodelling following injury.



References:
[1] Tveito A, Jæger K, Kuchta M et al. A cell-based framework for numerical modelling of electrical conduction in cardiac tissue. Front Phys 2017/Vol 5.

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P54: Effect of Optogenetic Defibrillation on Cardiomyocytes

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Introduction: Optogenetic defibrillation represents a new approach to terminate cardiac arrhyth-mias by activating light-gated channelrhodopsins (ChR). Previous studies have mainly focused on cation non-selective ChR (CCR), such as ChR-2 (ChR2), or anion non-selective ChR (ACR), such as Guillardia theta ACR-1 (GtACR1)[1]. However, in cardiomyocytes (CM), both cause membrane depolarisation, which might lead to intracellular Ca^{2+} and Na^{+} overload. In contrast, K^{+}-selective ChR (KCR), such as Wobblia inhibitory ChR (WiChR),[2] may be better alternatives for optogenetic defibrillation by keeping CM near their natural resting potential.
Methods: We incorporated models for ChR2[3], GtACR1[1], and a KCR (simple K^{+}-conductance during activation) into the O'Hara model[4] of human ventricular CM. To assess CM behaviour without optogenetic intervention, we paused electrical pacing during the illumination period as a control scenario. Moreover, we constructed the first computational model of WiChR based on the 4-state photocycle structure of ChR2,[5] and fitted the model parameters to published as well as unpublished experimental data. In ongoing work, we incorporated WiChR into the O'Hara model.
Results: Simulations showed an increase in intracellular Ca^{2+} and Na^{+} concentrations during activation of ChR2 and GtACR1, especially in the first seconds of illumination. In contrast, activation of KCR resulted in a similar behaviour as control (Fig.1).

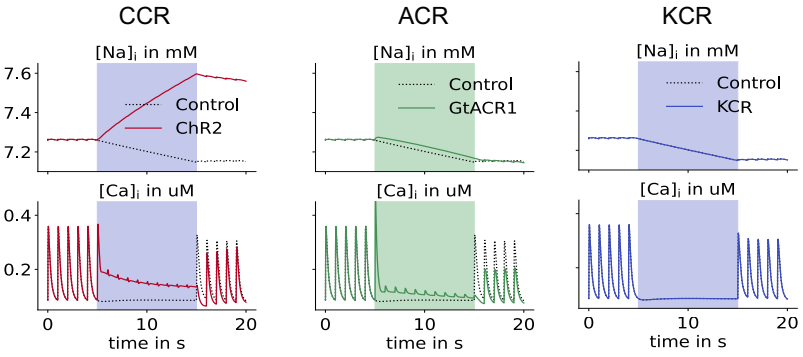

Fig. 1: ChR effects on intracellular ion levels.

Outlook: We will further use 2D simulations to investigate our hypothesis that the ChR ion selectivity influences the efficacy of optogenetic defibrillation. In addition, the WiChR model offers a new possibility to numerically predict and understand the behaviour of KCR in different cells of interest.

References:
[1] Ochs AR, Karathanos TV, Trayanova NA et al. Optogenetic Stimulation Using Anion Channelrhodopsin (GtACR1) Facilitates Termination of Reentrant Arrhythmias with Low Light Energy Requirements: A Computational Study. Front Physiol 2021/12:718622
[2] Vierock J, Schiewer E, Grimm C et al. WiChR, a hightly potassium-selective channelrhodopsin for low-light one- and two-photon inhibition of excitable cells. Sci Adv 2022/8:eadd7729
[3] Wülfers E, Kohl P, Seemann G. Mathematical Modeling of Non-Selective Channels: Estimating Ion Current Fractions and Their Impact on Pathological Simulations. 2018 CinC 2018/45:1-4
[4] O'Hara T, Virág L, Varró A et al. Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation PLoS Comput Biol 2011/7:e1002061
[5] Nikolic K, Grossman N, Grubb M et al. Photocycles of Channelrhodopsin-2. J Photochem Photobiol 2009/85:400-411

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P55: Sodium depletion in intercalated disc cleft nanodomains and intercellular exchange of sodium ions between cardiomyocytes during ephaptic coupling: a model study

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Cardiac action potential propagation depends essentially on sodium (Na^+) channels and on gap junctions. However, it has been proposed that ephaptic coupling can assist action potential propagation, especially under conditions of reduced gap-junctional coupling.[1,2] Ephaptic coupling relies on negative extracellular potentials within narrow intercellular clefts in intercalated discs, where Na^+ channels and gap junction plaques form clusters and complex nanodomains. Our aim was to evaluate how cleft potentials and ion concentrations evolve in such nanodomains during ephaptic coupling and modulate the Na^+ currents and action potential transmission.

We developed a new finite element model of the intercalated disc separating two cardiomyocytes, in which electric potentials, ion fluxes and ion concentration changes obey Nernst-Planck equation and the principles of mass balance and electroneutrality. Intercalated disc geometry and the distribution of gap junctions and Na^+ channel clusters can be parametrized arbitrarily. Realistic morphologies and distributions of channels and gap junctions can be generated using a rule-based model.[3]

Upon the excitation of the first cell, in the presence of Na^+ channel clusters, transient Na^+ depletion occurs in the cleft near these clusters and is associated with transient potassium accumulation and chloride depletion. During action potential transmission, the Na^+ current through the pre-junctional membrane switches from inward to outward due to the very negative extracellular potential in the cleft, and thus contributes Na^+ ions for the open Na^+ channels in the post-junctional membrane. Blocking this outward Na^+ current impedes ephaptic coupling and action potential transmission. In contrast, forcing ion concentrations to remain constant improves ephaptic coupling.

Hence, during ephaptic coupling, Na^+ ions can pass from one cell to the next through the intercalated disc cleft. Furthermore, ephaptic coupling is accompanied by marked ion concentration changes in cleft nanodomains. Our model contributes to understand how ephaptic coupling influences conduction at the nanoscale level.

References:
[1] Mori Y, Fishman GI, Peskin S. Ephaptic conduction in a cardiac strand model with 3D electrodiffusion. Proc Natl Acad Sci USA 2008/105:6463-6468.
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P56: The Impact of Explicitly Represented Electrodes on Electrograms in a Cell-by-Cell Electrophysiology Model

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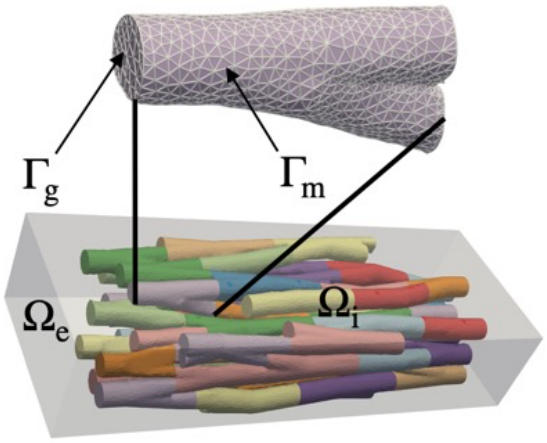
Homogenised cardiac electrophysiology models, such as the mono- and bidomain models, average over several hundreds of myocytes. While they provide insights on the macroscopic behaviour of cardiac excitation waves, information on a cell-by-cell scale, shown to play a role in arrhythmogenesis, is lost. In our study, we use the novel extracellular-membrane-intracellular (EMI) model[1] and synthetically generated cardiac tissue meshes[2] explicitly considering these domains, which allows for simulation and analysis of the excitation dynamics on a microscale.



Synthetically generated mesh, explicitly representing intra- and extracellular domains, Ω_i and Ω_e, as well as the membranes Γ_m and Γ_g (the latter being intercalated discs)

In homogenised models, a healthy (often plane) wave propagation yields almost completely symmetrical biphasic EGMs. In the EMI model, due to the multimodal excitation spread caused by the intertwined myocyte alignment and deceleration of the excitation wave at the intercalated disks, small fractionations are present in the, consequently asymmetrical, EGMs. Here, we work with spatially extended electrodes present in the extracellular domain, consequently imposing corresponding conductivities for its material, which makes the approach more realistic than considering only point electrodes[3]. Specifically, we want to study the impact of a) electrode size and b) electrode distance to the tissue on EGM morphology. Concerning the dynamics, we consider purely longitudinal and transversal propagation, as well as a mixture of both. We want to compare the results with the same setup in bidomain models and anticipate that EGM amplitudes are smaller the bigger or the further away the electrode is. This study provides a simplistic basis for a thorough understanding of EGM genesis, but several aspects, e.g. intracellular anisotropy or a larger tissue domain, need to be considered in future follow-up studies.

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P57: Optoacoustic Imaging of Transmembrane Voltage

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Tissue-non-destructive transmurally-resolved measurement of action potentials (AP) is not currently possible in whole hearts. Optoacoustic (OA) tomography holds promise to overcome this limitation.[1] The unique strength of OA imaging results from the combination of optical and acoustic modalities, harnessing the OA effect[2] to potentially enable 3D measurement of voltage signals in biological samples. OA images of voltage, however, have a low signal-to-noise-ratio (SNR) that restricts the detailed functional analysis of data. Therefore, state-of-the-art denoising architectures were utilized to improve the voltage signal.
OA images were obtained from genetically modified HEK cells with a multispectral OA tomography system (iThera Medical). The trans¬membrane voltage of these cells was controlled optogenetically to create AP-like swings. The developed denoising pipeline is based on the DeepCAD-RT algorithm[3], which, together with appropriate pre-processing, has allowed up to 4-fold improvement of the SNR of the voltage signal of 4D OA image stacks.

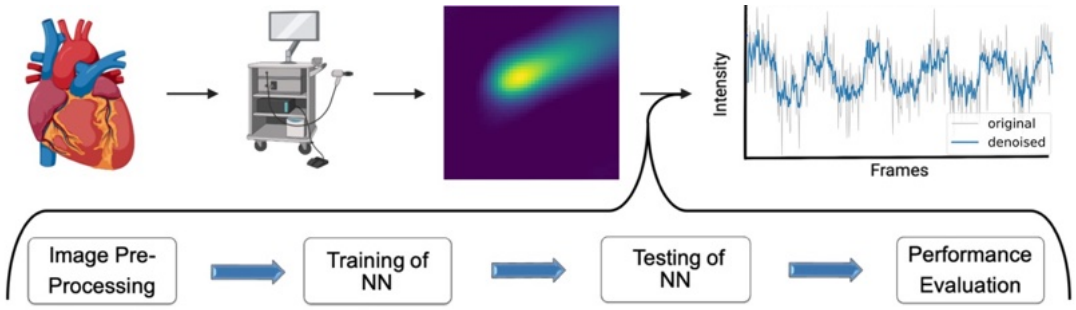

Figure 1: Visualization of the denoising workflow (DW) and representative denoising results from paced cell data. The DW involves acquiring OA image data followed by a computational denoising pipeline (DP) to enhance SNR. The DP is composed of four main elements: pre-processing, training, testing and performance evaluation. Ultimately, users can compare denoising performances.

This denoising approach will be extended to more complex voltage signals in cardiac tissue to assess whether it is possible to not only improve temporal, but also spatial resolution. Once validated, it will be applied to assessing transmural AP properties in whole hearts.

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P58: Panoramic Imaging and 3D Structure-Function Mapping in Whole Murine Hearts

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Cardiac structure and electrophysiology are intricately linked. Changes in cardiac microstructure can lead to changes in conduction at the macroscale, however methods to link these are challenging. We are developing a panoramic optical mapping system for whole mouse hearts that will allow us characterize the EP activity across the entire cardiac surface (Fig. 1A). The functional activity will then be mapped onto the underlying structures recorded at cellular resolution with a mesoSPIM light-sheet microscope (Fig. 1B).
The panoramic system has been designed with eight cameras for recording and four light crafters for illumination. Four cameras are positioned perpendicular to one another on the equatorial plane with the four others 45° out of phase and angled upwards at 45° to record the lower parts of the ventricles including the apex. The cameras are positioned to ensure multiple views of each part of the ventricles to ease motion tracking and 3D reconstruction. The four light crafters are used for illumination of the whole heart and enable patterned optogenetic stimulation of specific regions of the heart. Current work includes the ongoing development of motion correction and 3D reconstruction software, and the integration of the structural and functional images.
This structure-function pipeline will be used to investigate changes in trans-scar conduction and EP dynamics across multiple lesion models. These will be altered via increased electrotonic coupling between CM and NM[1] as well as supra- or sub-threshold optogenetic stimulation of CM.[2-3]

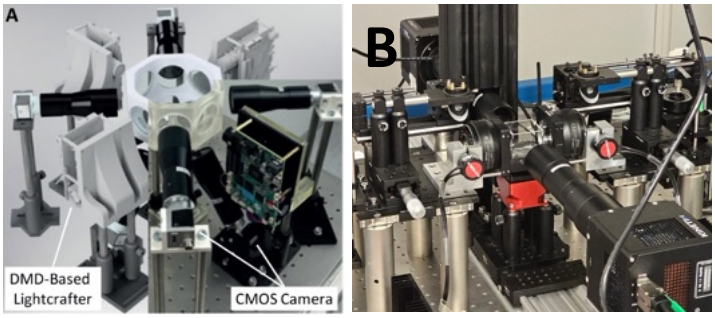

Fig. 1: Imaging systems. A: Panoramic OM setup.
B: Prototype mesoSPIM imaging system.

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P59: Modelling the interventricular dependency of left and right ventricular systolic function

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Heart function depends on the coordinated contraction of the right (RV) and left ventricles (LV). We sought to model the dependence of LV and RV systolic function on the motion of the other ventricle.

Point-correspondent biventricular (BiV) meshes were created from cardiac magnetic resonance (CMR) imaging for 70 subjects using a semi-automated pipeline.[1] The motion of each ventricle was characterised by the Cartesian displacements of a set of endocardial mesh points during systole. There were 1211 points for RV free wall (RVFW), 745 points for RV septum (RVS), and 1572 points for the LV. For each ventricle, a partial-least-squares-regression (PLSR) model was used to predict ejection fraction (EF) as a function of RVFW, RVS, and LV displacements together, using leave-one-out cross-validation. Variable-importance-in-projection scores were used to discard non-important displacements considering possible multi-collinearity across displacements. The relative contribution of each ventricle to each EF was calculated through the sum of the dot products of model coefficients with displacements for each region, with the RVS treated as part of the LV.

Variation in the systolic function of both ventricles was explained well by BiV motion (R2 of 0.83 for RVEF and R2 of 0.76 for LVEF, Figure 1). LV+RVS motion accounted for 59% of RVEF, while RVFW motion accounted for the remaining 41%. RVFW motion accounted for 26% of LVEF, while LV+RVS motion accounted for the remaining 76%.

These results are consistent with LV motion being the largest contributor to both LV and RV systolic function. RV motion accounted for a moderate amount of LV systolic function, indicating that interventricular interaction is important for both ventricles. Further analysis of the size and regional characteristics of this interaction could yield insights into the biventricular dynamics of different cardiac disease groups.

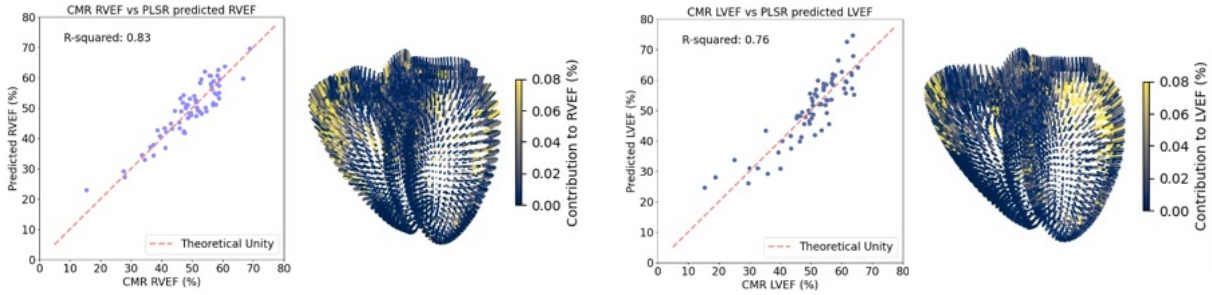

Figure 1 – Results of model predictions of RVEF (a) and LVEF (c) and contributions of each displacement overlayed on mean BiV shape at end-diastole (b, d)

References:
[1] Govil, S., Crabb, B.T., Deng, Y. et al. A deep learning approach for fully automated cardiac shape modeling in tetralogy of Fallot. J Cardiovasc Magn Reson 25, 15 (2023). https://doi.org/10.1186/s12968-023-00924-1

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P60: Hemodynamics-driven mathematical model of murmur generation

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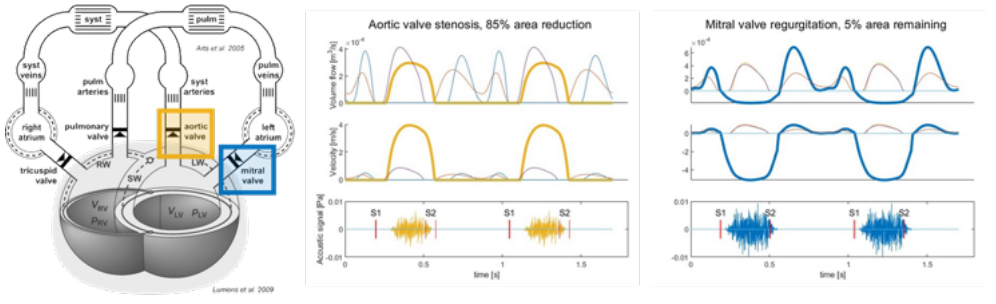
Cardiac bruits arise from disruptions in blood flow caused by anomalies such as valvular stenosis or regurgitation. Traditionally, these sounds have been attributed to turbulence, but we propose a new perspective. Pressure perturbations and flow separation phenomena, including vortex shedding and fluctuating drag forces, generate sound waves with distinct frequencies and amplitudes. We suggest that these intricate flow separation phenomena may be the primary contributors to the generation of cardiac bruits.
To test this hypothesis, we created a novel real-time acoustic module for CircAdapt, a model of the cardiovascular system, to simulate murmurs in various cardiac conditions. From the simulation we extract flow velocities across valve orifices and compute the characteristic Strouhal number (St=(fD)/v), where f is the frequency of vortex shedding, D is the valve diameter, and v is the flow velocity across the valve orifice. This number predicts the power spectral density (PSD) of the murmur, governing a frequency band with uniform power distribution, while the decay beyond this band is influenced by the mix of acoustic source mechanisms. Utilizing time-frequency domain information of the predicted PSD, we obtained time-domain signals via inverse short-time Fourier transform. Thereafter we calculated sound intensity over time using an established acoustic analogy[2] based on simulated velocity and diameter parameters.
Our model successfully simulated distinct murmurs linked to aortic valve stenosis and mitral valve insufficiency, based on hemodynamic scenarios simulated in CircAdapt. The generated sound signals closely resembled recorded murmurs. Results from the various simulations showed that orifice diameter and flow velocity play a key role in murmur generation. In all simulated conditions, murmur loudness and pitch were proportional to the severity level of leakages/stenoses and, hence, to cardiac output.
In conclusion, our hemodynamics-driven mathematical acoustic model offers a promising avenue for fast and realistic simulations of murmurs across diverse conditions. By emphasizing the significance of flow separation phenomena such as vortex shedding and fluctuating drag forces, this perspective provides a framework for understanding the diverse characteristics of murmurs observed clinically.



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P61: Computational Modeling of Myocardial Perfusion

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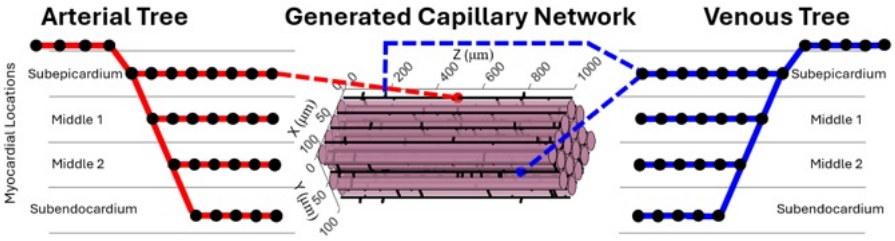
Myocardial perfusion is determined capillary network structure and the upstream (arterial) and downstream (venous) hemodynamics. Intramyocardial pressure, which is greatest during systole and in the subendocardium, causes diastolic-dominant flow in the coronary arteries and places the subendocardium at an elevated risk of ischemia/hypoxemia. Coronary blood flow can be measured in large arteries and veins on the epicardial surface of the heart, yet it is not well understood how intramyocardial pressure affects capillary blood flow and oxygen perfusion. This work presents a computational myocardial hemodynamic model with anatomically informed coronary arteries, veins, and capillary networks that accounts for mechanical interactions between transmural layers.



Arterial and venous networks traversing multiple myocardial depths (epicardium to endocardium) are constructed using a tree structure with a Strahler numbering system and average branching ratios between generations. Vessel segments of a given generation and myocardial depth are represented by a single 3-element Windkessel model with values for resistance (proximal and distal) and compliance estimated based on literature[1,2]. A periodic capillary network is constructed with capillaries traveling parallel to the muscle fibers and cross-connecting capillaries[3] and is validated using microvascular imaging data. Pressures and flows through the networks are calculated by simulating the dynamics of the associated LPM. Physiological pressure conditions are applied to the arterial inlet and venous outlet of the network and spatially- and time-varying intramyocardial pressures are prescribed. Using this computational model, we can predict hemodynamic patterns within coronary vasculature that includes arterial and venous trees and capillary networks. Within capillaries, preferential paths of fluid flow can occur depending on the location of cross connecting capillaries. Pulsatility of pressure and flow in response to inlet pressure and intramyocardial pressure is highly dependent on compliance values. Further model refinement is needed to introduce non-linear compliance, to account for changes to diameter over the cardiac cycle due to intramyocardial pressure.

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P62: Selective RyR2 Inhibition reduces Arrhythmia Susceptibility in Human Cardiac Slices

Madrid MK[1], George SA[1], Rytkin E[1], Trampel K[1], Salman B[1], Efimov IR[1]
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RyR2 hyperactivity has been shown to be prevalent in structural heart diseases, most commonly from ischemic heart disease.[1] This hyperactivity can result in abnormal calcium release, leading to irregular electrical activity and life-threatening arrhythmias.[2] This study evaluated the antiarrhythmic potential of a selective RyR2 antagonist, [ent-(+)-verticilide][3], in human ventricular slices. We obtained human hearts not designated for transplantation and prepared slices from the right (RV) and left ventricles (LV). We recorded pseudo-ECGs to assess premature ventricular contraction (PVC) incidence, and optical mapping was used to identify arrhythmogenic substrates. Baseline optical recordings were first obtained (1), followed by treatment with isoproterenol (250 nM) and caffeine (200 mM) (2). Subsequently, two concentrations of ent-verticilide (1μM and 3μM) were administered (3-4), with optical recordings taken after each treatment. Combining isoproterenol and caffeine increased PVC incidence, while ent-verticilide reduced the PVC burden. Additionally, isoproterenol and caffeine shortened the action potential duration (APD) in both RV and LV slices, but ent-verticilide did not alter APD in either slice type. In conclusion, ent-verticilide effectively suppresses arrhythmic triggers and reverses arrhythmogenic substrates in the human heart, presenting potential as a novel antiarrhythmic therapy for patients with structural heart disease.

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P63: Unlocking Therapeutic Pathways for Arrhythmogenic Cardiomyopathy with Human Cardiac Organoids

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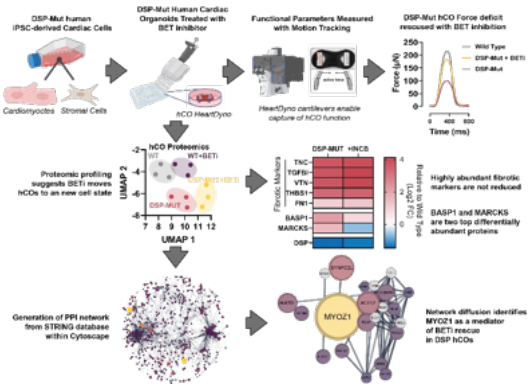
Complex cardiac diseases perturb multiple physiological processes and cell types in the heart. Simple in vitro cardiac models, which are often generated from purified cardiomyocyte populations, will not be able to completely capture the pathophysiology of many of these diseases. Our multicellular human cardiac organoid (hCO) model was designed to capture the interaction between cardiomyocytes and stromal cell types, providing a platform for modelling complex cardiac diseases and therapeutic target discovery[1]. We have previously used the hCO platform in the identification of bromodomain and extra-terminal domain (BET) inhibitors as novel therapeutic candidates for inflammatory cardiac disease[2]. In this study we wanted to extend this approach to genetically inherited arrhythmogenic cardiomyopathy (ACM), a disease driven by inflammation, fibrosis and electrophysiological changes in the heart. hCOs were generated from an human induced pluripotent stem line (hiPSC) derived from cells of a patient diagnosed with ACM who had a heterozygous missense mutation in desmoplakin (DSP-MUT). We analysed the contractile kinetics of the DSP-MUT and WT hCOs with our established analytical pipeline and saw a significant decrease in peak force production. This was rescued by treatment of the DSP-MUT hCOs with the BET inhibitor, INCB054329. Proteomics analysis of differentially abundant proteins did not provide an obvious explanation for the functional rescue by BET inhibition, as a significant fibrotic signature was still present and DSP abundance was unchanged. However, we did identify two proteins, MARCKS and BASP1, which were differentially abundant. These to our knowledge have not been previously implicated in cardiac disease. Suspecting that there were other mechanisms that explained the functional rescue by BET inhibition, and that these were being missed by just comparing the fold-change of single proteins, we constructed a 3,471 node protein-protein-interaction network by querying STRING from within the program Cytoscape. We then performed network diffusion to identify pathways and processes that were differentially 'heated' in the BETi-treated DSP-MUT hCOs. This method implicated MYOZ1, a Z-disc associated protein involved in transducing calcineurin signalling and myofibrillar development. We are now following up BASP1, MARCKS, and MYOZ1 as therapeutic leads for ACM and other cardiac diseases.



Graphical Abstract. Functional and proteomic profiling of hCOs carrying a DSP mutation

References:
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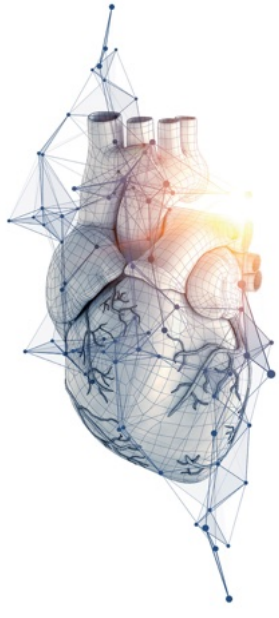

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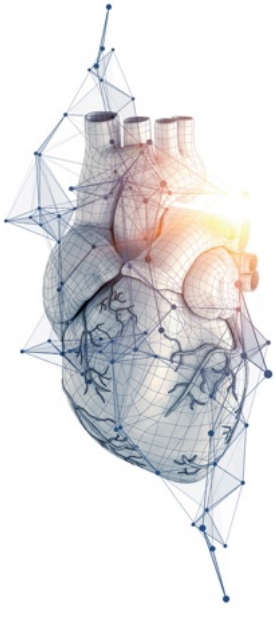
Taberner	Andrew	University of Auckland	Auckland
Takeuchi	Ayako	University of Fukui	Fukui
Tanger	NIklas	KU Leuven	Leuven
Timmermann	Viviane	University of Freiburg	Freiburg
Tran	Kenneth	University of Auckland	Auckland
Trayanova	Natalia	Johns Hopkins University	Baltimore
Trotter	James D.	Simula Research Laboratory	Oslo

Name	First Name	Organisation	City
Ulaszek	Seweryn	Jagiellonian University Medical College	Kraków
Van Den Acker	Gitte	Maastricht University	Maastricht
van Loon	Tim	Maastricht University	Maastricht
Verheyen	Julia	University of Freiburg	Freiburg
Verlyck	Mathilde	University of Auckland	Auckland
Vigmond	Edward	University of Bordeaux	Pessac
Volkaerts	Maarten	KU Leuven	Leuven
Vu	Michael	University of Hohenheim	Stuttgart
Wachsmann	Stefanie	University of Freiburg	Freiburg
Wall	Samuel	Simula Research Laboratories	Oslo
Wellette-Hunsucker	Austin	University of Kentucky	Lexington KY
Wülfers	Eike	University of Freiburg	Freiburg
Zgierski-Johnston	Callum	University of Freiburg	Freiburg
Zhao	Jichao	University of Auckland	Auckland
Zhao	Debbie	University of Auckland	Auckland

CARDIAC PHYSIOME
2024

Maps & Best of Freiburg

Integrating experimental and mathematical approaches to advance cardiac physiology research



Freiburg, Germany
12 - 14 September 2024

DIRECTIONS

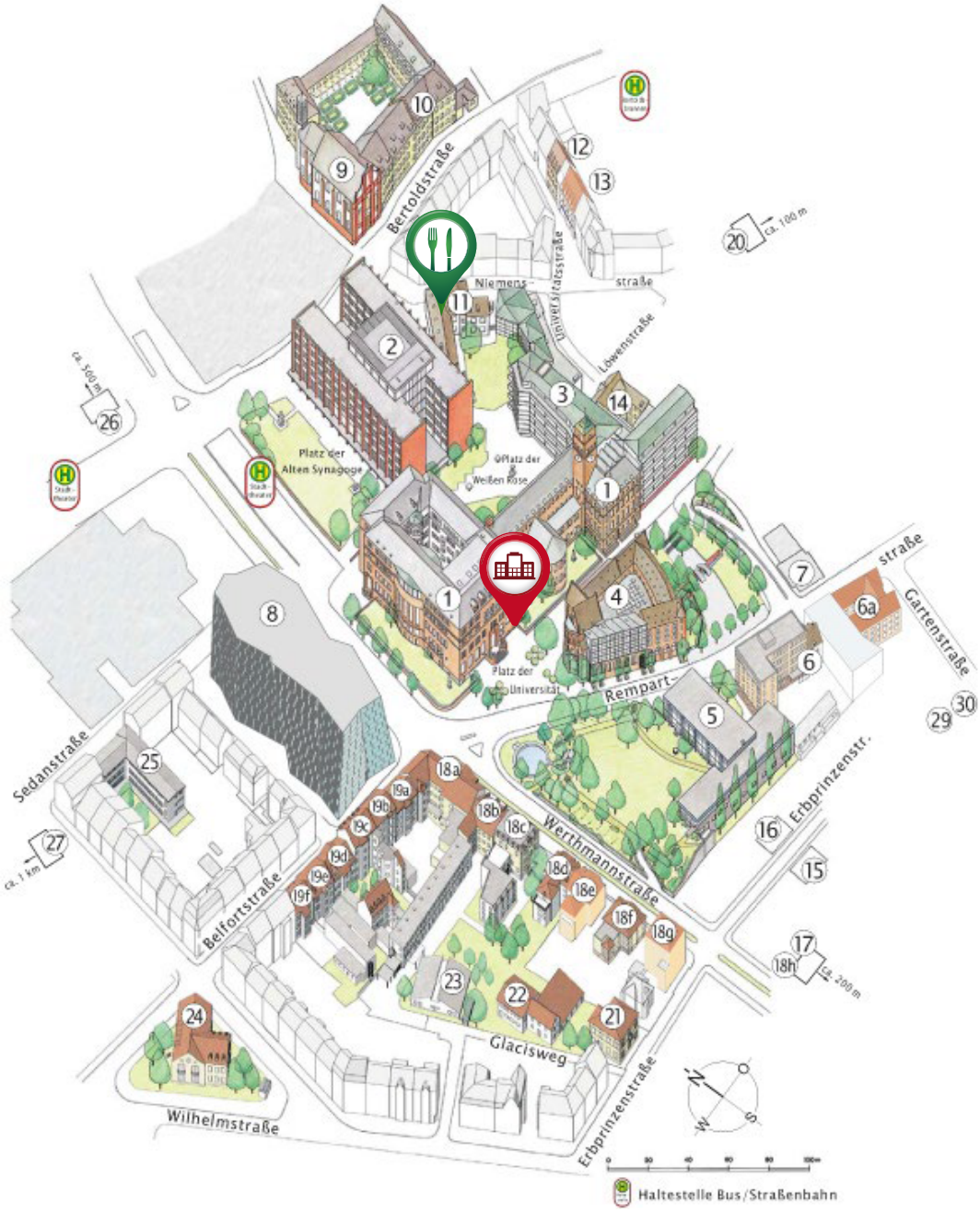
Main Conference Venue
Festive Lecture Theatre (Aula)
Platz der Universität 3
79098 Freiburg

Meeting Dinner Location
Peterhofkeller Freiburg
Niemensstraße 10
79098 Freiburg

Bus and Train Station
Freiburg Hauptbahnhof
79098 Freiburg

Online map:
https://www.uniklinik-freiburg.de/experimental-cardiovascu - lar-medicine/cardiac-physiome-2024/venue-and-travel.html

LOCATION MAP



Main Conference Venue
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MAIN CONFERENCE LOCATION & DINNER LOCATION

Main Conference Venue
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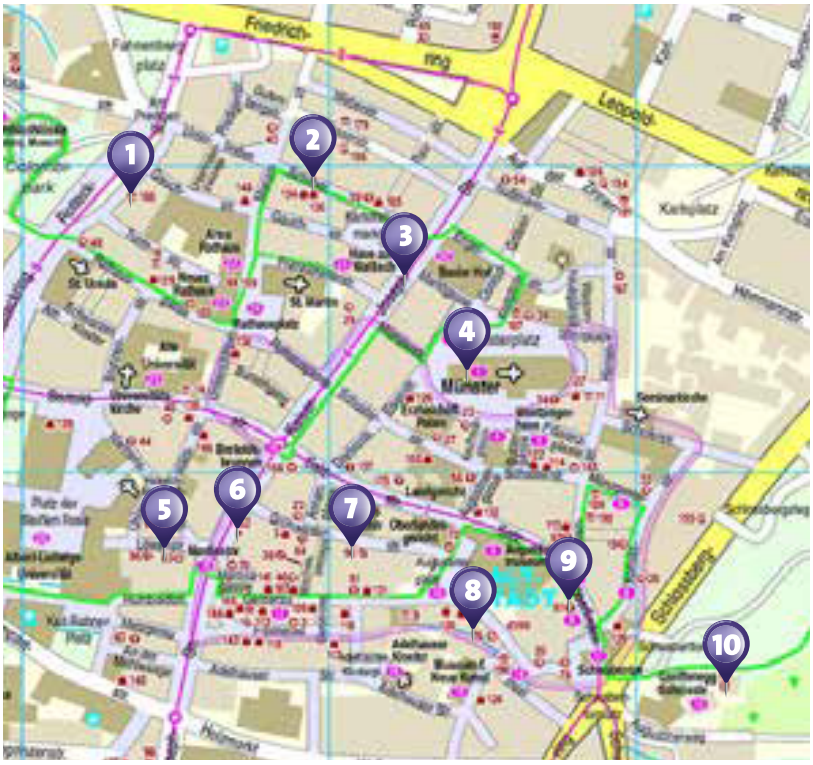
79098 Freiburg

BEST OF FREIBURG



1 BEST FINE DINING
Zirbelstube at Colombi
Rotteckring 16

2 BEST BURGERS
Der freiBurger
Schiffstr. 16

3 BEST ROOFTOP BAR
SKAJO
Kaiser-Joseph-Str. 192

4 BEST VIEWS
Münsterturm
Münsterplatz

5 BEST STUDENTS BAR
SCHLAPPEN
Löwenstr. 2

6 BEST FOODCOURT
Markthalle
Grünwälderstr. 4

7 BEST KARAOKE BAR
Tacheles
Grünwälderstr. 17

8 BEST BEER
Hausbrauerei Feierling
Gerberau 46

9 BEST COCKTAIL BAR
One Trick Pony
Oberlinden 8

10 BEST BEER GARDEN
Kastaniengarten
Schlossbergring 3

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CARDIAC PHYSIOME PROGRAMME 2024

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