A NUMERICAL MODEL OF MECHANICAL PROPERTIES OF CARDIAC TISSUE IN HEART-ON-A-CHIP DEVICES

Åshild Telle[1], Bérénice Charrez[2], Kevin E. Healy[2], Aslak Tveito[1], Samuel Wall[1]

[1]Simula Research Laboratory, Oslo, Norway [2]University of California Berkeley, Berkeley, CA, USA

OVERVIEW

- Organ-on-a-chip devices can be used to control and monitor the cellular microenvironment of human microtissues, providing a promising platform for disease and drug development studies.
- In this study we consider heart-on-a-chip devices, capturing the essential functions of cardiac tissue. Image techniques have proven useful for capturing essential mechanical properties, such as displacement, contraction velocity, beat rate and prevalence. However there are other important mechanical properties – such as internal forces and stress – which are not readily computable based on displacement data alone.
- We therefore propose to develop a numerical model for the system. The system can be used to simulate the mechanical behavior of the microtissue, to predict and help monitoring the effect of drugs and mutations on the contractility of the tissue. The model itself is a combination of two widely used models, capturing electrochemical and mechanical properties of cardiac tissue, and implemented over a mesh replicating the geometry of cardiac tissue in heart-on-a-chip devices.
- Combining our numerical model for mechanical simulation with experimental heart-on-a-chip data produced comparable dose response results. We observed similar trends for measurements of internal forces of the tissue under isometric conditions.

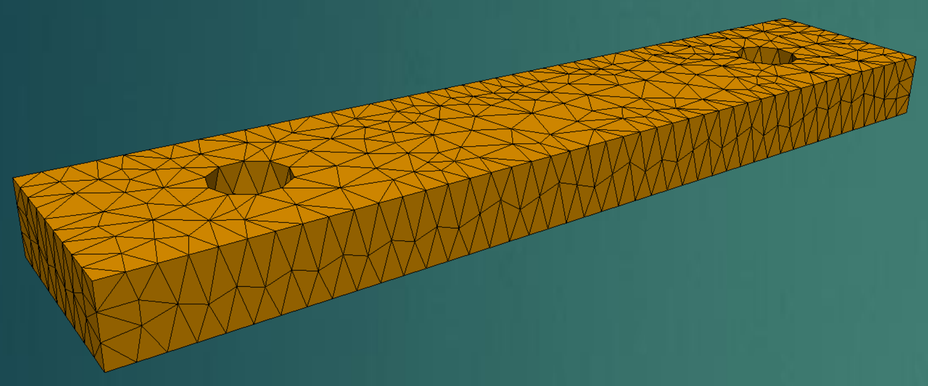

Figure 1: Mesh corresponding to the tissue chamber's geometry, having similar dimensions (800 x 170 x 60 µm) and internal structures. The large cylinders are fixed and necessary for robust tissue formation. The cylinders are fixed in the numerical model as well, while the rest of the mesh moves freely.

METHODS

- Combining a zero-dimensional point model of cardiac myofilaments developed by Rice et. al. (Biophysical Journal 2008) with a continuum three-dimensional model for the mechanics of ventricular myocardium given by Guccione et. al (ASME 1991), we get a system of partial differential equations describing the tissue's mechanical properties.
- The calcium-force relation is described by a system of equations,

$$\frac{\partial s}{\partial t} = f(\mathbf{s}, Ca, \mathbf{F}^T\mathbf{F}, t)$$

where ***s*** is a state vector, *Ca* the calcium transient and ***F*** the deformation gradient tensor and t time.

- The strain in the tissue can be expressed using the first Piola-Kirchhoff stress tensor, which can be decomposed into an active and passive part:

$$\mathbf{P} = \mathbf{P}^p + \mathbf{P}^a = \frac{W(F)}{\partial F} + |\mathbf{F}|\sigma^a(T_{ref}, \mathbf{s})\mathbf{F}^{-T}$$

where *W* is a strain energy function, σ the Cauchy stress – dependent on the state vector ***s*** – and T_{ref} a scaling parameter.

- For each time step we solve the two systems

$$\nabla \cdot \mathbf{P} = 0 \qquad \text{and} \qquad \frac{\partial s}{\partial t} - f = 0$$

numerically, using FEniCS an open-source software for solving differential equations. We evaluated the system's response to increasing extracellular calcium concentration using experimentally measured calcium transients to predict resulting Cauchy stresses.

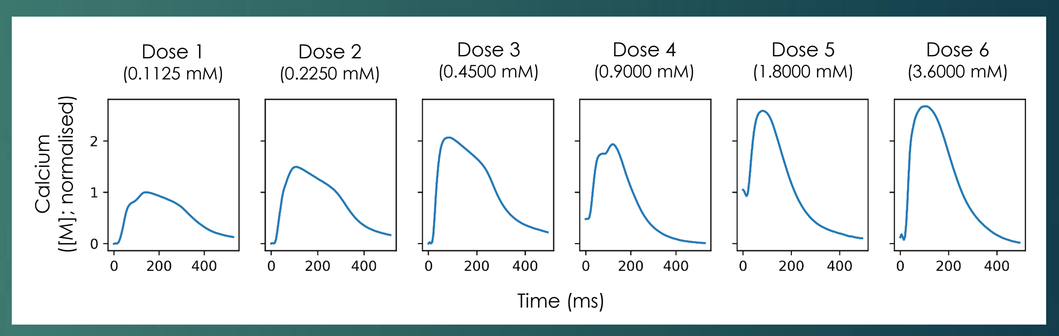

Figure 3: Calcium transient for one selected chip. The traces are proxies for intracellular calcium concentration during the cardiac cycle (first 500 ms), and corresponds to escalating calcium concentrations.

BACKGROUND

- An organ-on-a-chip is a microfluidic device which mimics the major features of an organ or a system of organs. The device has chambers where human microtissue is grown, and using microfluidic technology one can control and monitor the tissue.
- Organ-on-a-chip systems can be used for disease modelling and drug development studies. The vision is to develop a more accurate system for drug development, to complement and eventually replace current screening platforms that consist of animal and two-dimensional systems.
- Here we are working with a heart-on-a-chip system combining human induced pluripotent stem cell derived cardiomyocytes with microfluidic technology as a cardiotoxicity screening platform (Mathur et al. Sci. Rep. 2015).
- In the tissue chambers one can integrate mechanosensing pillars which the tissue will bend at each contraction. By optically tracking their displacement, one can deduce the contraction force of the tissue.

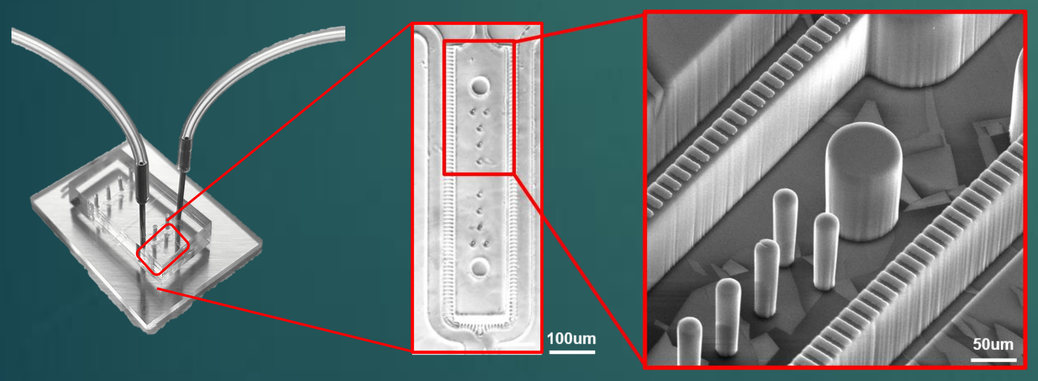

Figure 2: A heart-on-a-chip device consists of a cell chamber and media channels connected to fluidics for controlled nutrient and drug delivery to the tissue. The latter can be live monitored to obtain infomation about calcium, action potential and movement – which gives us force measurements – under different conditions.

RESULTS

- Combining our numerical model for mechanical simulation with experimental heart-on-a-chip data produced comparable dose response results. We observed similar trends for measurements of internal forces of the tissue under isometric conditions.
- This combined *in silico* / *in vitro* analysis system provides a possible computational framework for understanding the physiological complexity of the cardiac tissue's functionality, facilitating prediction of resulting Cauchy stresses as well as other mechanical properties. The framework might give valuable insight in microorgan functionality, focusing on drug screening and disease modelling in heart-on-a-chip systems.

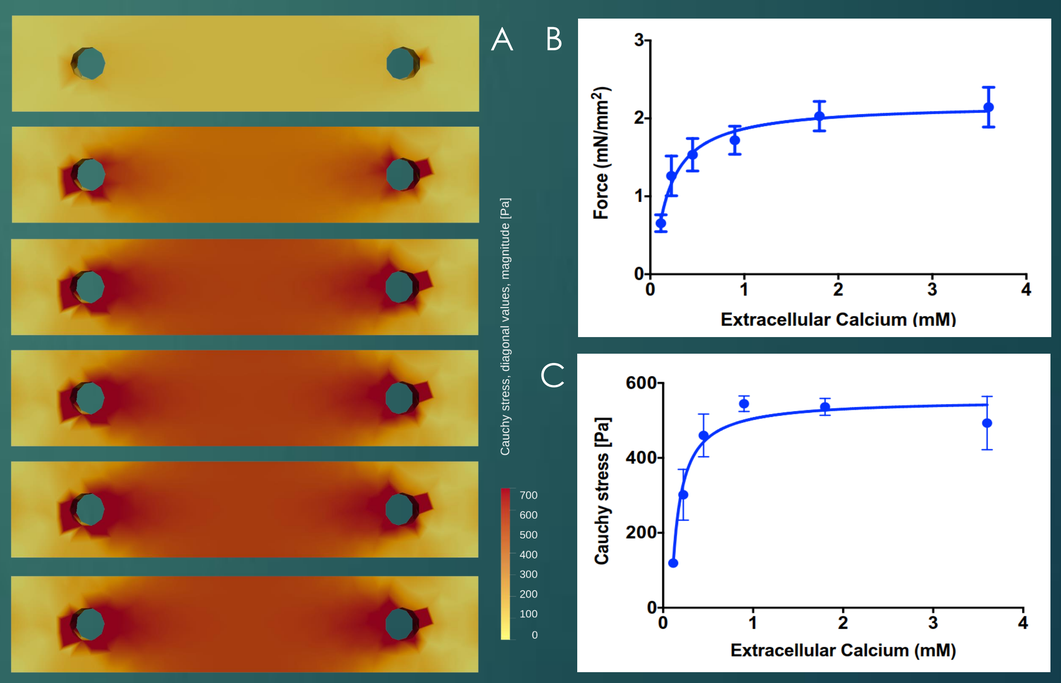

Figure 4: A – Cauchy stress distribution corresponding to the calcium transients given above, at their respective peak values. B – Force measurements at pillars based on displacement, for different calcium concentrations; C – corresponding Cauchy stress, based on calcium transients from the same experiments.

ACKNOWLEDGEMENTS

Thank you to Henrik Finsberg and David Cleres for support and assistance related to this project.

Funding sources: The Norwegian Ministry of Education and Research; The California institute for regenerative medicine (DISC2-10090); NIH (NIH-NHLBI HL 130417)