SCHEDA RELAZIONE DOTTORANDI

Al collegio docenti del Dottorato in Medicina Molecolare

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Ciclo XXXIV° - Tutor Prof. Corrado Poggesi, Prof. Elisabetta Cerbai

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Introduction

In my PhD project I want to increase our understanding in the relationship between heart structural organization and electrophysiological dysfunctions. We are using a multi-side approach to investigate morphology and electrical propagation in several hearts. During last year, I worked to create a computational framework able to perform electrophysiological investigations based on mice whole heart reconstructions.

Methods

We used high-performance imaging and analysis techniques to correlate the whole heart cytoarchitectonic organization with action potential kinetics recorded at mesoscale resolution. We used a wide-field mesoscope in combination with voltage sensitive dye to map the action potential propagation in Langendorff perfused hearts. During last year, we are optimizing a new tissue clearing technique and a new high-throughput light-sheet microscope to perform high resolution mesoscale reconstructions of whole mouse hearts at sub-cellular resolution. During my first year of PhD, I developed a cytoarchitectonic analysis software to map myofilaments alignment in 3D using the Structure Tensor Analysis, defining the conduction pathways of action potential propagation at intercellular level. During this second year, I spent 6 months at the Biomedical Department of the King's College London, in the Dr. Martin Bishop's laboratory. There, I learned how use computational tools to perform accurate action potential (AP) propagation simulations based on our integrated structural information. In particular, heart contractile tissue is segmented in three dimension and its anatomical model is created by means of high-resolution 3D finite-element meshes. Real fibers organization previously extracted is combined to the mesh and, moreover, theoretical fibers organization was defined over our anatomical reconstructions and used as control (Fig. 1A). Finally, AP propagation model is coupled with the virtualized heart and activation protocols are applied to simulate its electrical behaviour.

Results

The new multi-step simulation platform developed allows us to investigate on the electrical activity of the heart accordingly with the real fibers organization of the tissue. We are able to quantify the local fibers disarray across the entire heart, to investigate its correlation with the electrical activity. AP propagation across the whole heart will be simulated to allowing a directly comparison with functional data previously acquired on the same heart by means of optical mapping. Preliminary results show differences between theoretical fibers and real fibers (Fig. 1B). It suggests that this approach takes account of the property of the real tissue organization. In the future, we would like to

stain and add more biological structures to the model. We would like to use this computational platform to investigate about the electrical properties of different structures in different pathologies, driving our model parameters by experimental data.

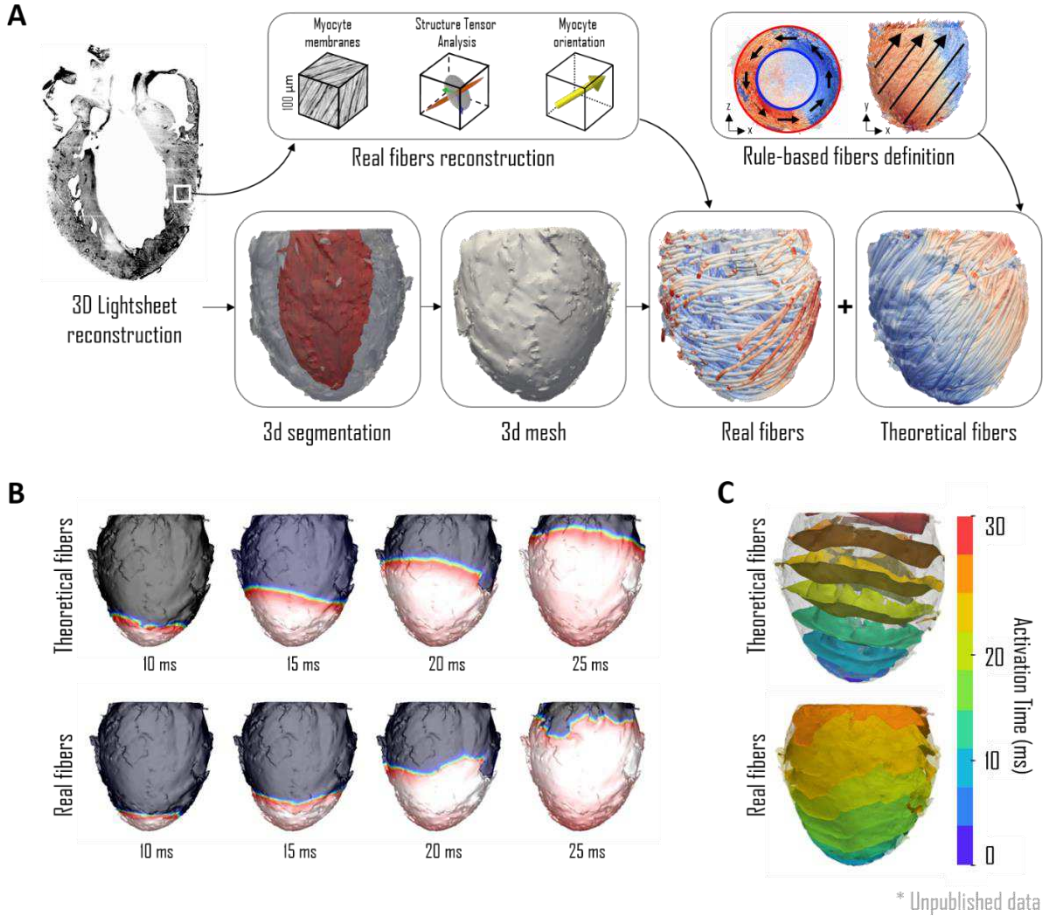

Figure 1 –Electrophysiology computational modeling based on integrated cytoarchitectonic reconstruction. (A) *Cytoarchitectonic reconstruction pipeline of the ventricular myocardium. On the left, a representative frame of an entire mouse heart obtained with light-sheet microscopy. On top, the pipeline of fibers orientation analysis based on the Structure Tensor Analysis. Segmentation is used to generate a 3D finite elements mesh, allowing to map the fibers architecture on the 3D high-resolved anatomy of the heart. Rule-based theoretical fibers orientations are created as control.* ***(B)*** *An apex pacing protocol is simulated applying an accurate model of Action Potential Propagation (APP) on both fiber architectures. Differences between real and theoretical fibers are clear. This result confirms the sensitivity of the proposed method for next investigations on control and pathological hearts. (C) The 3D maps of APP wave fronts of (B) are shown. These accurate representations will allow us to understand the actual correlation of the myocardial 3D fibers architecture and the APP wave fronts inside the myocardium walls.*

Publications - academic year 2019/2020

2020 - Olianti C, Costantini I, Giardini F et al. *3D imaging and morphometry of the heart capillary system in spontaneously hypertensive rats and normotensive controls*. Sci Rep 10, 14276 (2020). https://doi.org/10.1038/s41598-020-71174-9

Conference abstracts - academic year 2019/2020

2020 - *Structural mapping of action potential propagation pathways through healthy and diseased heart*, Biophysical Society, San Diego, Platform Talk performed by Dott. Sacconi.
2020 - *Whole heart cytoarchitecture at sub-cellular resolution*, Frontiers in CardioVascular Biomedicine, Budapest (conference postponed).
2020 - *Action potential propagation modeling based on high resolution structural data in healthy and diseased mouse heart* – Working Group, Amsterdam (conference postponed).
2020 - *Modeling of action potential propagation based on high-resolution optical imaging of cardiac* tissue - NOtiCE, Glasgow (conference postponed).

Fellowships - academic year 2019/2020

2019 – Erasmus for traineeship – 6 months – King's College London, Biomedical Department.
2019 – EMBO short term fellowship – 3 months – King's College London, Biomedical Department.