Towards the Development of Virtual Heart Technology for Creating Digital Twins of Cardiac Electrophysiology

Matthias AF Gsell[1,2], Luca Azzolin[2], Karli K Gillette[1,3],
Aurel Neic[2], Thomas Schrotter[1,2], Franz Thaler[1], Gernot Plank[1,2,3]

[1] Gottfried Schatz Research Center: Biophysics, Medical University of Graz, Graz, Austria
[2] NumeriCor GmbH, Graz, Austria
[3] BioTechMed-Graz, Graz, Austria

Abstract

Introduction: *Virtual heart technologies (VHTs) promise to offer an detailed view on cardiac electrophysiology (EP). However, only very few VHTs simulating EP of four-chamber hearts have been reported so far and widespread use is limited due to labor intense workflows and the difficulty of ascertaining a close match between simulations and observations. This motivates the development of efficient workflows for both critical stages of creating a digital twin of cardiac EP: i) the generation of patient-specific anatomical models, and ii) the calibration of EP models to match clinical observations.* ***Methods:*** *A workflow for the generation of anatomically accurate models of the heart, with emphasis on the atria, from imaging data was developed. This includes, automated creation of multi-label segmentations using a convolutional neural network (CNN), a meshing step, annotation of tissue regions, and assignment of fibers. To speed up functional twinning, a prototype to run close to real-time EP simulations that can be used to find a good initial guess for model calibration methods that fit physiologically more accurate mono- or bidomain EP models to clinical data has been designed.* ***Results:*** *A semi-automated workflow to create atrial models at scale was developed, implemented and applied to a first clinical data set. A GUI based tool to plan and run whole heart EP simulations was prototyped.*

1. Introduction

Computational models of human cardiac EP show high promise in a broad range of application areas, including basic EP studies, medical device simulation, clinical research up to clinical applications where cardiac EP models are used to aid in diagnosis, therapy stratification and planning. The utility of these type of models relies on the assumption of a close correspondence between simulated data and clinically observable data like electrocardiograms (ECGs). However, achieving such a close correspondence is a challenging endeavor and two major problems must be tackled to create a digital twin model of human cardiac EP. The first problem is the automated generation of anatomically accurate four-chamber models tailored to individual patients at scale. This comprises the creation of multi-label segmentations from clinically acquired scans such as magnetic resonance imaging (MRI) or computed tomography (CT), the generation of a computational grid in form of a 3D mesh suitable for finite element simulations, the assignment of fiber architectures to the ventricles and atria, the assignment of tissue properties, the registration of structures like the terminal crest or the pectinate muscles, and the integration of a cardiac conduction system comprising sinoatrial node, atrioventricular node and His-Purkinje network, [1].

The second challenge is functional twinning, where various parameters need to be tuned to match clinically observable data. This includes parameters in the ionic model, tissue parameters such as conductivity or conduction velocity (CV), and the position and size of the His-Purkinje fascicles that characterize ventricular activation. In previous work [2, 3] an optimization approach for functional model calibration has been reported.

Calibration of the model is based on a stochastic derivative-free sampling method of the parameter space. Simulations were performed using the monodomain equation with a reaction-eikonal propagation model, but is readily still a time-consuming and challenging endeavor and not suitable for future clinical applications. This motivated the development of a preview tool that allows lightweight EP simulations to be performed in near real-time based on a newly developed re-entrant eikonal solver. This tool can then be used in a pre-processing step of the actual model calibration to find a good initial guess as a starting point for the optimization and thus reduce the number of more expensive simulations.

2. Methods

2.1. Model Generation

Generation of anatomically accurate four-chamber models of the human heart is sub-divided into several steps. The first step is the segmentation of clinical scans from tomographic imaging data such as MRI or CT. Here, a CNN based on [4, 5] was used to label anatomical structures like the blood pool of the left (LV) and right (RV) ventricle, of the left (LA) and right (RA) atrium, of the aorta (AO) and the pulmonary artery (PA), as well as the LV myocardial wall was used, see Figure 1.

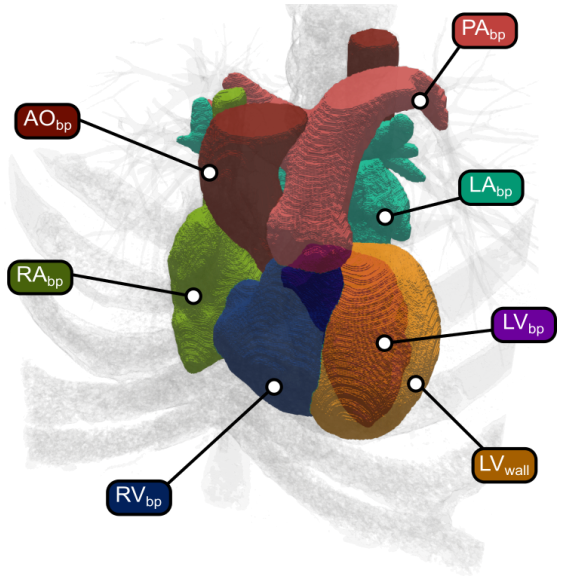

Figure 1: Multi-label segmentation from CT image with seven labels representing blood pools of LV, RV, LA, RA, AO, and PA as well as the LV myocardial wall.

After re-sampling the image stack to a uniform target resolution, missing myocaridal walls were inserted with a given constant thickness directly in the image stack by applying intrusion and extrusion steps of the corresponding blood pool. To obtain a model with all anatomical orifices, growth and shrinkage was restricted to a set predefined labels, respectively.

In the second step, a finite element mesh with a given target resolution was generated from the multi-label segmentation using the mesh manipulation software *Meshtool* [6]. Rule-based fibers and universal ventricular coordinates (UVCs) were assigned to the ventricles, see [2, 7, 8]. For the atria, a model building pipeline similar to [9] was applied to generate atrial mesh models including fibers, see Figure 2, and structures like terminal crest (TC), mitral value (MV), tricuspid valve (TV), or pectinate muscles

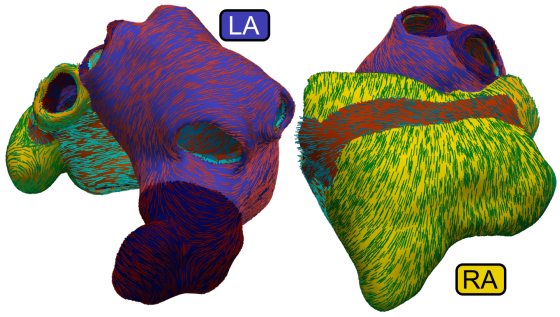

Figure 2: Fibers assigned to the LA and RA.

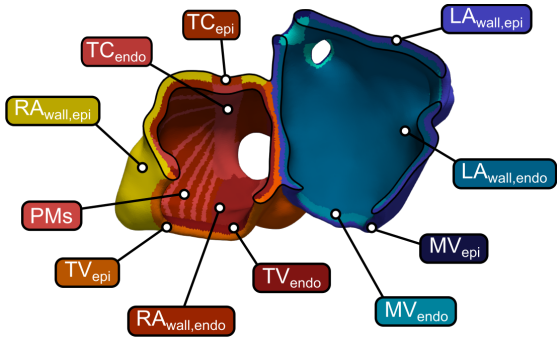

Figure 3: Structures registered in the atria (not all structures are given a label in this figure).

(PMs), see Figure 3. By extending the methods published in [10, 11] for atrial shell models, universal atrial coordinates (UACs) for volumetric meshes were generated, see Figure 4.

Using the UVCs and UACs, the position of the His-Purkinje fascicles and junction nodes of the His bundle can be described in a model-independent manner, allowing an abstract description of the His-Purkinje system, see [1] for further details.

2.2. Simulation Planning

The main building block for a fast and lightweight re-entrant eikonal based EP simulator is an efficient method to solve the underlying eikonal equation

$$\sqrt{\nabla t_{\mathrm{a}}^{\top}\, \mathbf{D}\, \nabla t_{\mathrm{a}}} = 1 \qquad \text{in} \quad \Omega$$

to get the activation times $t_{\mathrm{a}}(\mathbf{x})$ of a traveling wave at points $\mathbf{x} \in \Omega$ where $\Omega \subset \mathbb{R}^3$ is the mesh representing the model, and $\mathbf{D} \in \mathbb{R}^{3\times 3}$ is a symmetric tensor. In our newly developed method, a fast iterative method based eikonal solver was coupled to a finite state machine to keep track of the internal states and phases (depolarization, repolarization, resting) of then individual nodes in the mesh. A

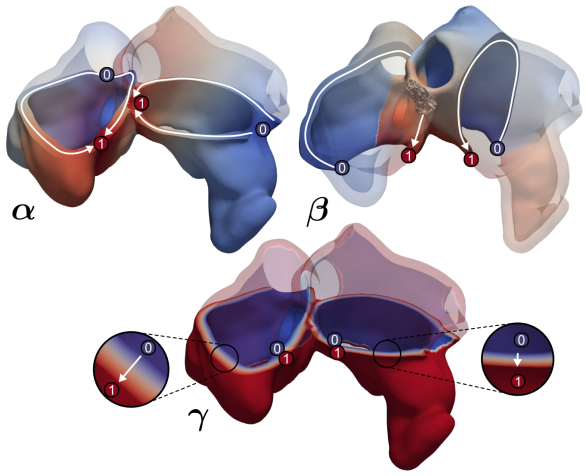

Figure 4: UACs for bi-atrial models. ***α–value*:** 0 at lateral side and 1 at septal side in LA; 0 at inferior vena cava and 1 at superior vena cava in RA. ***β–value*:** 0 at posterior side and 1 at anterior side in LA; 0 at lateral side and 1 at septal side in RA. ***γ–value*:** 0 at endocardium and 1 at epicardium in LA and RA.

first prototype to plan and run lightweight EP simulations was designed supporting: i) the definition of tissue regions and EP functions (this comprises conductivities and CVs) and their linkage, ii) the interactive selection of pacing sites and the definition of pacing protocols, iii) the interactive selection of activation blocks, and iv) the visualization of the transmembrane voltage V_m with a predefined action potential (AP) transient depending on the local activation times $t_{\mathrm{a}}(\mathbf{x})$, see Figure 5. Post-processing capabilities to compute and visualize ECGs were added based on the leadfield approach as proposed by [12].

3. Results

A semi-automated pipeline to create anatomically accurate four-chamber models of the human heart was developed and implemented in our in-house C++ framework based on *Meshtool*, minimizing the number of user interactions. This pipeline enables atrial models to be generated in a matter of minutes from clinical scans to complete models including fibers, anatomical structures, and reference system.

Combining the OpenGL-based graphical user interface *nuklear*[1] and the *Meshtool* software, a first prototype for the interactive planning and execution of lightweight EP simulations was developed, which will accelerate model calibration and thus facilitate the creation of digital twin models of cardiac EP. The solver runtime of a four-chamber EP simulation with a cycle length of 600 ms, a time step size of 2ms, and a model with an average edge length of $\sim$ 1.4mm with $\sim 1.5 \cdot 10^6$ elements and $\sim 3 \cdot 10^5$ points ranged from 10 to 15 seconds, depending on whether a His-Purkinje network was included or not.

4. Discussion

Individual manual interventions are currently still necessary in the model generation pipeline and involve only manual editing steps of the CNN-generated segmentation. Additional models must be created to ensure that the pipeline works reliably and robustly, as the individual models can vary greatly in their anatomical geometry. Scalability must be demonstrated by testing the pipeline on many data sets.

To create a high fidelity simulation tool for cardiac EP, additional physiological features such as AP-duration restitution, CV restitution, and cuvarture effects are currently being integrated into the eikonal solver, [13]. Validation to gold-standard bidomain simulations is not yet complete but preliminary analysis suggest that a close match between our eikonal solver and the bidomain equation can be achieved.

Acknowledgments

This research was funded by the InstaTwin[2] grant FO999891133 from the Austrian Research Promotion Agency (FFG).

References

[1] Gillette K, Gsell MA, Bouyssier J, Prassl AJ, Neic A, Vigmond EJ, Plank G. Automated Framework for the Inclusion of a His–Purkinje System in Cardiac Digital Twins of Ventricular Electrophysiology. Annals of Biomedical Engineering 2021;49(12):3143–3153. ISSN 15739686.

[2] Gillette K, Gsell MA, Prassl AJ, Karabelas E, Reiter U, Reiter G, Grandits T, Payer C, Štern D, Urschler M, Bayer JD, Augustin CM, Neic A, Pock T, Vigmond EJ, Plank G. A Framework for the generation of digital twins of cardiac electrophysiology from clinical 12-leads ECGs. Medical Image Analysis jul 2021;71:102080. ISSN 13618415.

[3] Gillette K, Gsell MAF, Strocchi M, Grandits T, Neic A, Manninger M, Scherr D, Roney CH, Prassl AJ, Augustin CM, Vigmond EJ, Plank G. A personalized real-time virtual model of whole heart electrophysiology. Frontiers in Physiology sep 2022;13. ISSN 1664-042X.

[4] Payer C, Štern D, Bischof H, Urschler M. Multi-label whole heart segmentation using cnns and anatomical label configurations. In International Workshop on Statistical Atlases and Computational Models of the Heart. Springer, 2017; 190–198.

[1] https://github.com/vurtun/nuklear

[2] https://projekte.ffg.at/projekt/4298912

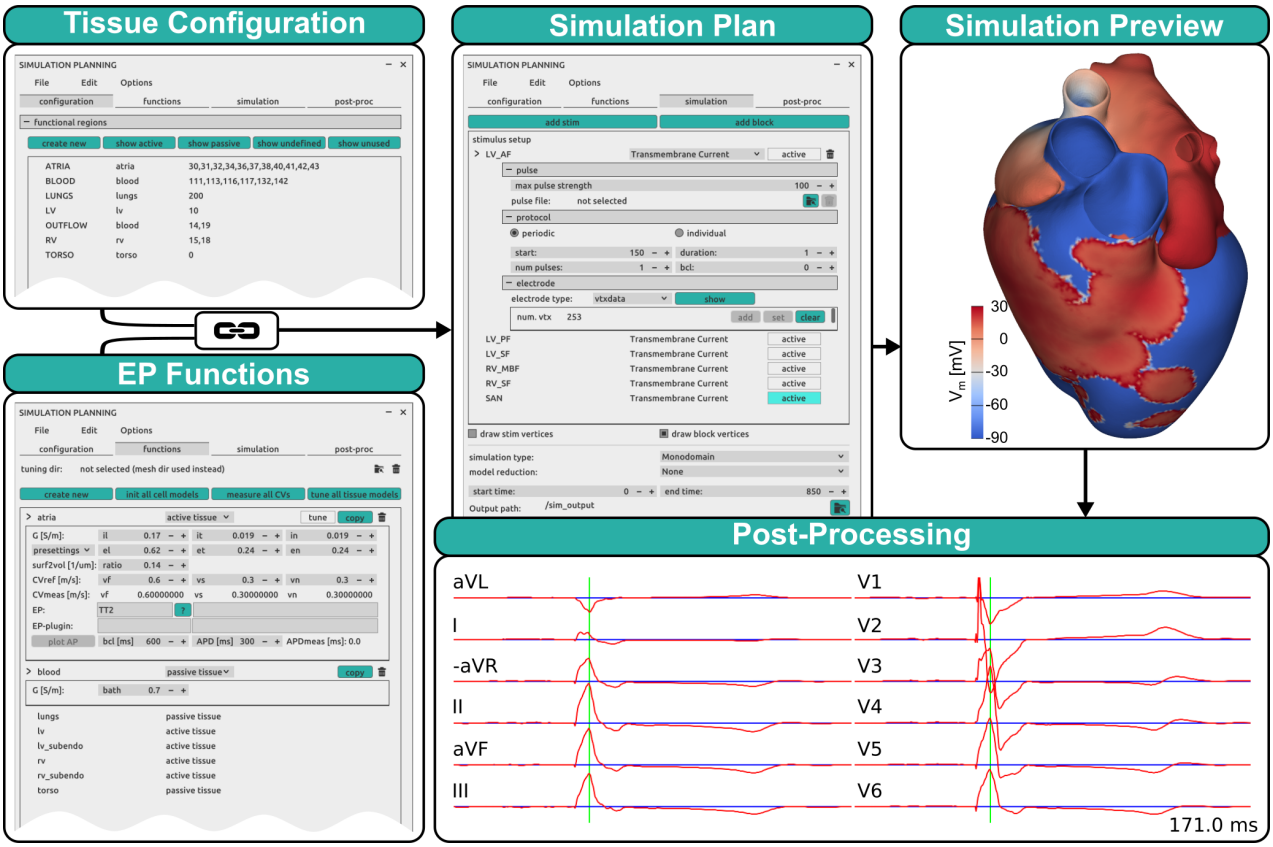

Figure 5: Simulation planning workflow. ***Left panel:*** Definition of tissue regions based on element tags and EP functions including for active and passive tissue. ***Middle panel:*** Plan of a simulation, this includes the definition of pacing sites and corresponding pacing protocols. ***Right panel:*** Simulation output, shown is the transmembrane voltage V_m. ***Bottom panel:*** ECGs computed in post-processing step.

[5] Payer C, Štern D, Bischof H, Urschler M. Integrating Spatial Configuration into Heatmap Regression based CNNs for Landmark Localization. Medical Image Analysis 2019; 54:207–219.

[6] Neic A, Gsell MAF, Karabelas E, Prassl AJ, Plank G. Automating image-based mesh generation and manipulation tasks in cardiac modeling workflows using Meshtool. SoftwareX 2020;11:100454. ISSN 2352-7110.

[7] Bayer JD, Blake RC, Plank G, Trayanova NA. A novel rule-based algorithm for assigning myocardial fiber orientation to computational heart models. Annals of Biomedical Engineering 2012;40(10):2243–2254. ISSN 00906964.

[8] Bayer J, Prassl AJ, Pashaei A, Gomez JF, Frontera A, Neic A, Plank G, Vigmond EJ. Universal ventricular coordinates: A generic framework for describing position within the heart and transferring data. Medical Image Analysis 2018;45:83–93. ISSN 13618423.

[9] Azzolin L, Eichenlaub M, Nagel C, Nairn D, Sánchez J, Unger L, Arentz T, Westermann D, Dössel O, Jadidi A, Loewe A. AugmentA: Patient-specific augmented atrial model generation tool. Computerized Medical Imaging and Graphics 2023;108:102265. ISSN 08956111.

[10] Roney CH, Pashaei A, Meo M, Dubois R, Boyle PM, Trayanova NA, Cochet H, Niederer SA, Vigmond EJ. Universal atrial coordinates applied to visualisation, registration and construction of patient specific meshes. Medical Image Analysis 2019;55:65–75. ISSN 13618423.

[11] Roney CH, Bendikas R, Pashakhanloo F, Corrado C, Vigmond EJ, McVeigh ER, Trayanova NA, Niederer SA. Constructing a Human Atrial Fibre Atlas. Annals of Biomedical Engineering 2021;49(1):233–250. ISSN 15739686.

[12] Potse M. Scalable and accurate ECG simulation for reaction-diffusion models of the human heart. Frontiers in Physiology apr 2018;9(APR). ISSN 1664042X.

[13] Schrotter T. A Real-Time Eikonal-Based Cardiac Electrophysiology Solver. In preparation.

Address for correspondence:

Dr. Matthias A.F. Gsell
Institute of Biophysics, Medical University of Graz
Neue Stiftingtalstraße 6 (MC2.H.)/III, A-8010 Graz, Austria
matthias.gsell@medunigraz.at