

From Time Delayed MRI to Patient-specific computational modeling of scar-related ventricular Tachycardia

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Abstract: Sudden cardiac death commonly occurs due to heart rhythm disorders called arrhythmia. Although recognized as the most efficient treatment options, Cardioverter Defibrillator implantation and tissue ablation are still not used to their full potential. Recently, advances in computational modeling and the increasing use of imaging tools have proven that patients' digital twins can play a role in addressing these limitations. This paper presents such an approach using the industrial software ADAS-3D and LS-DYNA. The workflow starts from Late Gadolinium Enhanced-Magnetic Resonance Imaging (LGE-MRI) data from a patient with structural heart disease. The left ventricle and fibrotic substrate were analyzed using ADAS-3D software, which enables to distinguish between tissue that is healthy, scarred, and intermediate, and to extract topological information. This segmentation and tissue classification are used to build, using LS-DYNA, a detailed electrophysiology model containing the relevant features for simulating arrhythmia. Using LS-DYNA, this model is then used to simulate a normal heartbeat and a clinical pacing protocol for inducing arrhythmia.

1 Introduction

Scar related Ventricular Tachycardia (VT) is the main cause of Sudden Cardiac Death (SCD), which continues to be a leading cause of death in Western countries [1]. This type of heart rhythm disorder occurs due to slow electrical pathways within scarred tissue of the heart, which generate extra electrical impulses. Ablation of the slow electrical pathways is the only curative option for such conditions: it consists in eliminating these slow pathways by burning them through energy delivery (most usually through radiofrequency delivery by means of a catheter) or chemical burning. However, the success rate is still low; up to 50% of patients experience recurrent VT after the procedure [2]. Implantable Cardioverter Defibrillators are another common option for stopping arrhythmia episodes. However, ICDs are expensive devices, and more importantly, current metrics used for patient stratification for this type of treatment is still suboptimal. With the recent advances in computational modeling of cardiac electrophysiology and Magnetic Resonance Imaging, in-silico studies offer an unprecedented tool to analyze physio-pathologies of the heart rhythm before the intervention. N. Trayanova and her colleagues are the group that has the most extensively contributed to this field [3-4], but other studies consolidate the feasibility of such an approach [5].

In this paper, we present a workflow designed for the diagnosis and therapy planning of scar-related VT using LS-DYNA for computational modeling and simulation and ADAS-3D software for image segmentation and tissue characterization. The workflow starts with Late Gadolinium Enhanced MRI data of the patient with scar-related VT that is used to build an image-based 3D computational mesh. The left ventricle and fibrotic substrate were analyzed using ADAS-3D software, which enables to distinguish between tissue that is healthy, scarred, and intermediate (associated with slow conduction pathways) and to extract topological information like candidate channels in MRI. A detailed computational left ventricular model that includes fiber orientation, action potential heterogeneity, Purkinje network and fibrotic information was built using LS-DYNA. Electrical propagation was represented by the monodomain formalism coupled with ToR-Ord model [6] for describing ionic exchanges between intra- and extra-cellular spaces, and simulations were run using LS-DYNA. We were able to produce electrical activation patterns that qualitatively match the electro anatomical Map obtained during the procedure, demonstrating the potential for designing digital twins of patients' electrophysiology. The paper also presents an attempt of inducing VT by simulating the clinical pacing protocols during ablation procedures.

The remainder of this document is organized as follows. Section 2 describes the different steps of the workflow from the segmentation to the creation of the ls-dyna keyword files. Section 3 presents the model components and equations governing cardiac electrophysiology. Section 4 describes the numerical experiments and the obtained results in terms of activation patterns and transmembrane potential screenshots. Finally, section 5 contains a general conclusion and the perspectives of this work.

2 Personalized computational model generation

The workflow for building a personalized computational model of a patient with structural heart disease consists in two main steps: i) the segmentation of a LGE-MRI data to obtain the left ventricle and its tissue information, and ii) the automatic generation of a computational mesh and LS-DYNA input files.

2.1 MRI-LGE segmentation using ADAS-3D

The myocardium of the left ventricle in the image is segmented semi-automatically in the ADAS 3D software, combining computational tools with supervision by an expert user. The fibrotic substrate within the myocardium is identified by thresholding the image intensities with cut-off values obtained by a variation of the Full Width at Half Maximum method. This enables us to distinguish between healthy tissue, dense scar, and inhomogeneous tissue (associated with slow conduction pathways) and to extract topological information like potential corridors responsible for VT. The resulting left ventricle geometry and fibrosis distribution are the basis for the 3D computational mesh.

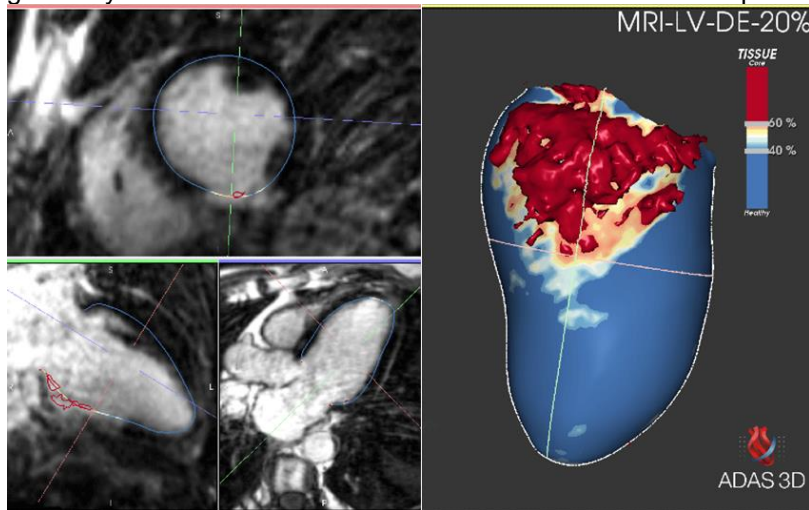


Figure 1: ADAS-3D segmentation process. Left: LGE-MRI image with delineated borders with colors corresponding to fibrosis. Right: surface geometry (at 20% of wall-thickness) obtained from the segmentation, and color display of fibrosis distribution.

2.2 Automatic generation of the computational model

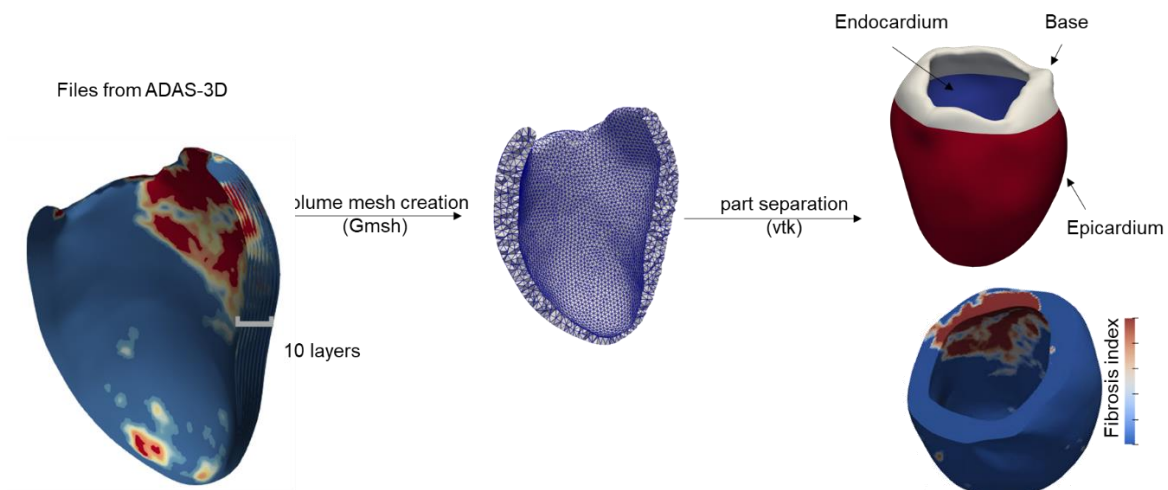


Figure 2: Workflow from ADAS-3D data to computational mesh.

The objective of this automated workflow is to create the keyword files needed to run simulations using LS-DYNA. This workflow is based on VTK (Visualization ToolKit) and Gmsh (3D finite element mesh generator) and used the Python programming language. Three different files from the ADAS-3D software are used as input: the LV surface mesh, the layers part that contain the fibrosis information. This

workflow is divided into 4 main steps. First, from the LV surface mesh, a volume mesh is created with Gmsh using the default “Frontal-Delaunay” 2D meshing algorithm. Then, the surface elements of the volume mesh are separated into 3 parts: the base, the endocardium and epicardium (see figure below). This partition is necessary to define some LS-DYNA simulation parameters such as the Purkinje network or potential stimulation zones. In this step, we define the Mitral Valve (MV) center as the center of the top edge of the LV, and the apical point as the furthest point of the volume mesh, from the MV center. The line passing through these two points represents the LV axis. A plane with the LV axis as a normal vector is created to separate the base from the rest. Endocardium surface elements in the rest of the LV are then separated from those representing the epicardium. In the third step, we set the fibrosis information using a Voronoi Kernel interpolator of the layers on the volume mesh.

3 Model description

This section first presents the monodomain equations and how it is coupled to cellular kinetics to model cardiac electrophysiology. Then, it describes the obtained computational mesh and enumerates the model components that have been considered for this study.

3.1 Model equations

The bidomain and the monodomain models are widely used to simulate cardiac electrical propagation in current research and are largely accepted for their physiological relevance. Briefly, the bidomain model assumes that cardiac tissue can be partitioned into two separate conducting media: the intracellular space, located inside the cardiac cells, and the extracellular space that connects cells between them. The monodomain model is a simplification of the bidomain model obtained by assuming an equal anisotropy ratio between the intracellular conductivity tensor and the extracellular conductivity tensor. This assumption considerably reduces the size of the system to be solved while keeping a comparable accuracy for the targeted application (see [7] for further details). The model used in this study implements the monodomain equation (selected by setting `emsol=11` in `*EM_CONTROL`), which is solved at each node of the mesh, and reads:

$$\beta C_m \frac{\partial V_m}{\partial t} + \beta I_{ion}(V_m, \mathbf{u}) - \nabla \cdot (\sigma \nabla V_m) = \beta I_{stim} \quad (1)$$

where V_m is the so-called transmembrane potential that measures the potential difference between the intracellular and extra-cellular space at time t , β is the cell surface to volume ratio, C_m is the cell membrane capacitance, $I_{ion}(V_m, \mathbf{u})$ is the resulting ionic currents flowing from the extracellular to the intracellular space through cell membranes, σ is an electrical conductivity tensor that expresses the anisotropic inhomogeneous character of heart tissue, and I_{stim} is the stimulation current applied on a small region of heart tissue in order to initiate the electrical wave. Finally, \mathbf{u} is a set of variables that satisfy a set of ordinary differential equations that describe how ionic currents evolve with time through a cardiac cell membrane. Such a system can be expressed by the following equation:

$$\frac{\partial \mathbf{u}}{\partial t} = f(\mathbf{u}, V_m) \quad (2)$$

The choice of the expression of f determines which type of cell model is used to describe ionic kinetics. These equations are completed by natural Neumann boundary conditions at the domain surface.

The system of equations was solved using a semi-implicit operator splitting scheme (`solvetype=4` in `*EM_CONTROL_EP`), see the appendix in [8] for more details. The equation 2 was integrated using the explicit Euler method, except for the gating variables of the cell model, for which the Rush-Larsen method was preferred.

3.2 General structure

Here we present the obtained computational mesh and how it is exploited to introduce fibrosis information and different tissue properties based on the imaging data. It also describes how the Purkinje network and fiber orientation are constructed

3.2.1 Heart tissue parts

The obtained computational mesh of the left ventricle consists of 7322196 tetrahedral elements and 1294181 nodes, with an average edge length of 0.5mm. A threshold was applied based on fibrosis data in order to separate the volumetric mesh into three parts: healthy tissue, scarred tissue, and intermediate tissue (Figure 4). In these three regions, the function f in equation (2) was defined by the recently developed ToR-Ord model [6], as it is recognized as the most comprehensive model for describing cardiac cell kinetics in healthy and diseased conditions.

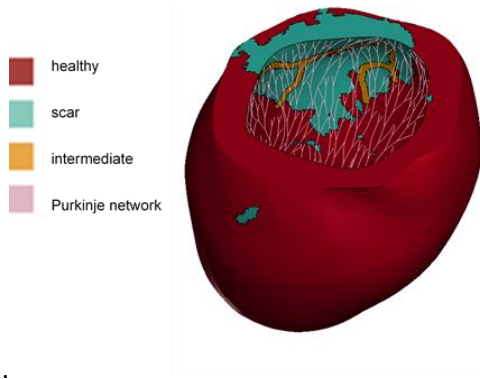


Figure 3: General structure of the computational model with its different components.

3.2.2 Fiber orientation

Cardiac cells are organized in a complex laminar sheet architecture termed fiber orientation. It is well known that the electrical signal travels much faster along the fibers than across them, which makes this fiber orientation a key element in the electrical propagation pattern and thus heart muscle contraction. Diffusion Tensor Imaging is a promising approach to capture patients fiber orientation, but this technique is not at a stage of being routinely used in the clinic. Alternatively, rule-based methods provide a convenient tool to assign fiber orientation to a given geometry based on anatomical knowledge.

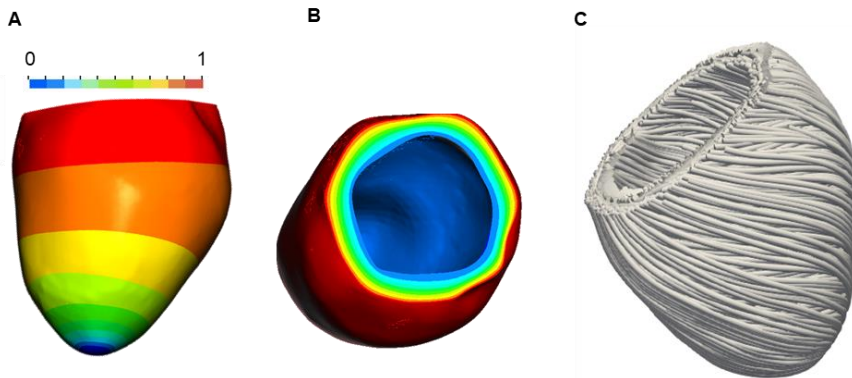


Figure 4: Intermediate variable value distribution, and fiber orientation display. A) Space distribution of long axis variable. B) Space distribution of the wall thickness variable. C) Streamlines obtained from the fiber direction vector field (displayed with Paraview [9])

In LS-DYNA, an automatic generation of fiber orientations, which can be used in EP with orthotropic conductivity tensors, as well as in the mechanical model *MAT_295 can be done using the card *EM_EP_CREATEFIBERORIENTATION. The method is based on [10] and consists in solving a Laplace-Dirichlet system, where Dirichlet boundary conditions and rotation angles are provided by the user. The Laplace-Dirichlet system generates two scalar variables varying between 0 and 1, one of them along the long axis direction, and the other one along the myocardial wall thickness variable (Figure 5 A and B). These two variables gradients serve to determine the wall outward direction apex-base direction. These two vector fields are then used together with the provided angles in order to define a local coordinate system at each element of the mesh, whose components are: the fiber direction, the sheet normal, and the transverse direction.

3.2.3 Tissue classification

Tissue electrophysiological properties differ in two elements, the electrical conductivity and ionic channel properties in the cell model. On the one hand, because fibrosis is considered to have a direct link with electrical conductivity, the electrical conductivity tensor shall be assigned depending on the fibrosis index. On the other hand, ionic properties are used to take into account tissue heterogeneity properties along the transmural direction (from endocardium to epicardium) that is inherent to cardiac electrophysiology. These ionic properties also serve to distinguish between healthy and remodeled tissue, also referred to as intermediate regions previously in this article.

Regarding conductivity, it is assumed that the higher the fibrosis index, the lower the conductivity. The electrical conductivity tensor σ was thus defined as a function of a nominal conductivity tensor σ_n and the fibrosis index f_i , such that:

$$\sigma = (1 - f_i)\sigma_n \quad (3)$$

The longitudinal, normal and transverse components of the nominal conductivity tensor σ_n were assigned to 0.189S/m, 0.036S/m and 0.036S/m respectively. These values were based on test simulations performed on a slab of tissue with dimensions (20x20x6mm) in order to reach physiologically acceptable conduction velocity in the heart tissue with respect to the modeling choices of the study. With equation (3), regions with a fibrosis index $f_i = 1$ are considered as scar and are electrically non-conductive, and healthy regions ($f_i = 0$) are assigned with a nominal conductivity value. Equation (3) can be achieved in LS-DYNA by using negative values for assigning conductivity values (sigmaXX, sigmaYY and sigmaZZ) in the *EM_MAT_003 card, which point to defined functions *DEFINE_FUNCTION, that in turn call a tabulated function *DEFINE_FUNCTION_TABULATED. The table in DEFINE_FUNCTION_TABULATED defines the values f_i for each element id of the mesh.

Regarding ionic properties, we used the three different parameter initialization suggested in [4] to distinguish between tissue in the endocardium, epicardium and myocardium. We defined three different layers based on the transmural scalar variable obtained by solving the Laplace dirichlet system in order to define the endocardial, myocardial and epicardial portions of the ventricle. Each layer has been assigned with the corresponding cell model definition.

Tissue remodeling in the intermediate tissue is characterized by altered cell function and is key in the arrhythmia mechanism. This was achieved as suggested in [4] by reducing some known ion currents through a scaling factor that varies between 0 and 1. It is worth mentioning that ionic properties of this model were assigned by modifying the corresponding Fortran subroutines in usermat versions of LS-DYNA. This is activated by using the *EM_EP_CELLMODEL_USERMAT card.

3.2.4 Purkinje network

The Purkinje network is a specialized conduction system within the heart that ensures the proper activation of the ventricles to produce effective contraction. It is located in the inner ventricular wall and is characterized by its rapid conduction compared to cardiac cells that ensures synchronized ventricular contractions. LS-DYNA offers an automatic 3D fractal network generation on a non-smooth surface (here, the endocardial surface of the ventricle), which is coupled to the 3D volume mesh, in a similar way as described in [11]. Several parameters can be used to define the Purkinje network (see *EM_EP_PURKINJE_NETWORK). The Purkinje network is composed of conducting beams, and the leaves of the network are connected to the nodes of the volume mesh of the ventricle, thus allowing a coupling of Purkinje network and the ventricle (Figure 5). In this example, a Purkinje network of 3696 beams and 3695 nodes was generated. In the network, function f in equation (2) is defined by the TenTusscher model [12].

4 Numerical experiments

The model was used to simulate a “normal” heartbeat scenario, referred to as sinus rhythm, and an arrhythmogenic scenario through the so-called S1-S2 pacing protocol. This section describes each scenario and the obtained results in terms of basic electrophysiology metrics. Before running these simulations we have performed small tests displaying that the cell behaviour described earlier could be seen on a small slab of tissue that was decomposed into healthy tissue and intermediate tissue, as depicted in figure 6.

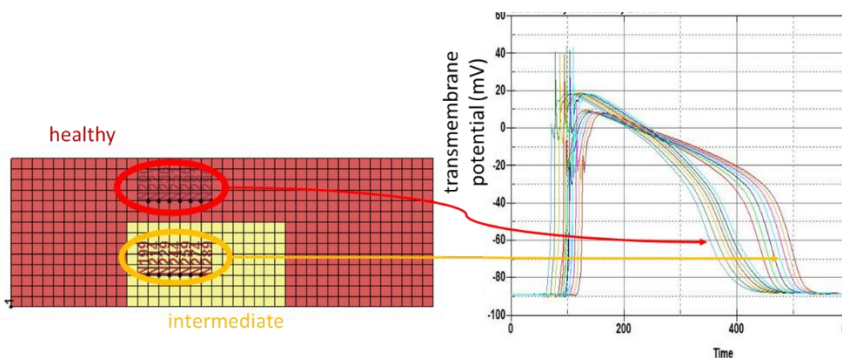


Figure 5: Transmembrane potentials of selected points in a slab of tissue constituted with a healthy and diseased tissue.

The displayed potentials from selected points in the healthy and the intermediate region show that although the activation time is roughly the same, the repolarization phase of the action potential is notably different.

4.1 Sinus rhythm

In a normal heartbeat the electrical wave originates from the Sino-atrial node, propagates through the atria, the His bundle and the bundle branches before reaching the apical region of the ventricles. Since we are only considering the left ventricle in this study, the electrical wave is initiated by a stimulus at the origin of the Purkinje network, in the apical region (*EM_EP_TENTUSSCHER_STIMULUS2). Figure 7 displays simulation results in terms of activation time and the evolution with time of transmembrane potential distribution. These results were exported using *DATABASE_BINARY_D3PLOT.

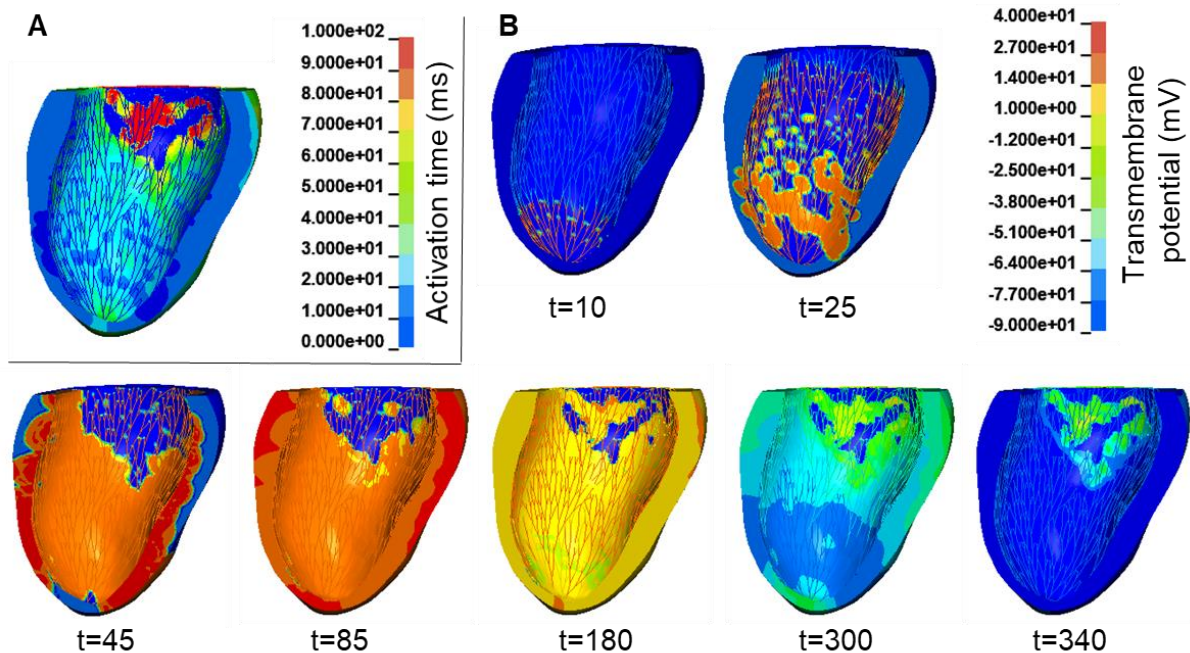


Figure 6: Sinus rhythm simulation results seen at a trans Sagittal cross section. A) Activation time. B) Screenshots of transmembrane potential distribution at different time steps (in ms).

The activation times in Figure 6 suggest that the overall activation pattern matches physiological knowledge. A rapid activation occurs in the Purkinje network (fully activated after 20ms), then, the electrical wave propagates from the epicardium in the inner layer towards the epicardium in the outer layer. One can also notice that the intermediate region has a slow depolarization and that the scar tissue is not conductive. When compared to the clinical data obtained during electroanatomical mapping (Figure 7), the activation times seem to match quite closely.

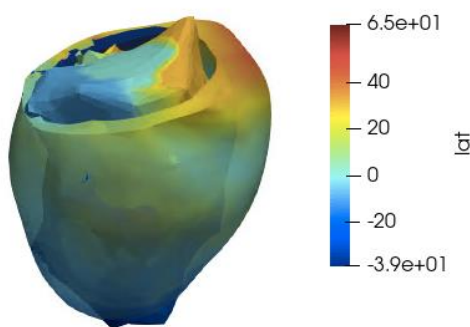


Figure 7: Superposed activation times in the ventricular mesh and in the clinical mesh obtained during electroanatomical recording (displayed in Paraview).

4.2 Ventricular Tachycardia

To virtually induce VT, we reproduce the so-called clinical S1-S2 pacing protocol used in electrophysiology rooms. This protocol is a programmed electrical stimulation used to investigate the heart's response to potential abnormal rhythms. It consists in pacing with several beats (S1) with a defined cycle, and then a premature stimulus (S2) is given to determine the response of the heart. When the protocol is successful, small electrical pathways are created due to the long refractory period of intermediate cells, and when the electrical wave exits these pathways, it re-excites the heart, which enters in a self-sustainable re-entry. The model used in this study has all the features necessary to simulate this type of behaviour. The S1-S2 protocol was achieved by using *EM_EP_TENTUSSCHER_STIMULUS2 such that a first beat is used to stabilize the model (800ms duration), then the S1 period consists in 6 beats of 600ms each, finally the S2 period consists in one beat 400ms after the last S1 beat. Overall, this scenario simulates 8s of electrophysiology. Since d3plots cannot contain electrophysiology only and because of the high number of screenshots desired, results have been exported on the endocardial surface only to ensure a reasonable size of the results file (*EM_DATABASE_NODOUT). Results have then been converted to vtk format and visualized in Paraview (see figure 8). We could not induce arrhythmia with the presented setup. In Figure 8, the first screenshot shows early activation of the first S1 beat, thus also displaying the chosen pacing site. The following screenshots show that the electrical wave enters the intermediate tissue while avoiding the non-conductive scar tissue. The screenshot at $t=4275$ ms shows the early activation of the S2 beat and a good synchronization between the ending of the previous wave and the beginning of the last induced one. Although these conditions were good signs, VT couldn't be induced for this setup. Overall, the simulation of the VT scenario took approximately 2 days to complete to simulate 8s of left ventricular electrophysiology.

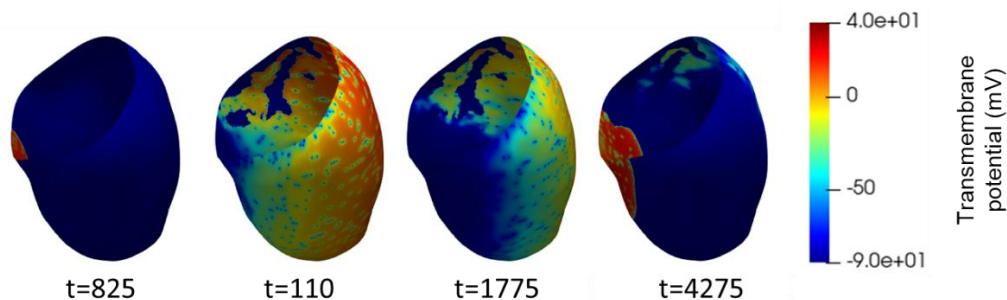


Figure 8: Screenshots of transmembrane potential distribution during the VT scenario (displayed using paraview)

5 Discussion & perspectives

This paper presents a workflow that relies on industrial software ADAS-3D for image segmentation and LS-DYNA for modelling and simulation in the context of patient specific ventricular arrhythmia simulation. The modelling choices presented here are in-line with what has already been demonstrated in the literature. Fiber orientation, the Purkinje network, cell heterogeneity along the transmural direction are all constitutive elements of the proposed model. To our knowledge, this article is the first one that implements the ToR-Ord for inducing VT. Regarding pathology modeling, electrical conductivity was altered using fibrosis information obtained from the image, and remodeled tissue was assigned with reduced ionic currents. We have shown that sinus rhythm simulations are in good concordance with basic cardiac electrophysiology. However, although the model seems equipped with all the necessary features, the S1-S2 scenario failed in inducing VT. Various tracks can be investigated to change this outcome, among which: changing the pacing site, tuning electrical conductivity as well as the S1-S2 protocol parameters.

The perspectives of this work from the user experience are various. The major one concerns the simulation time. Current investigations consists in coupling ls-dyna with cell models implemented and exported as Twins from ANSYS TwinBuilder. The main advantage would be the analysis of cell models on a dedicated environment, but also and more importantly taking benefit from the ODE integrators already developed in TwinBuilder for solving equation 2. Current work also involves the creation of new keyword cards that enable the user to implement ionic parameters instead of using usermat versions of LS-DYNA. Finally, it will be possible to export results of such long simulations in an Enight format, which is well-adapted for transient simulations on a static mesh.

Regarding the clinical application, it is intended to reproduce the presentend workflow on several patients. Ideally, we would reproduce pacing scenarii that have already been tested clinically and have been found successful on the studied patient.

To conclude, this work is a promising first step towards a clinical application of heart simulation in the context of VT.

6 Bibliography

- [1] Markwerth, P., Bajanowski, T., Tzimas, I., & Dettmeyer, R. (2021). Sudden cardiac death—update. *International Journal of Legal Medicine*, 135(2), 483-495.
- [2] Tzou, W. S., Tung, R., Frankel, D. S., Di Biase, L., Santangeli, P., Vaseghi, M., ... & Sauer, W. H. (2017). Outcomes after repeat ablation of ventricular tachycardia in structural heart disease: an analysis from the International VT Ablation Center Collaborative Group. *Heart Rhythm*, 14(7), 991-997.
- [3] Trayanova, N. A., Boyle, P. M., & Nikolov, P. P. (2018). Personalized imaging and modeling strategies for arrhythmia prevention and therapy. *Current opinion in biomedical engineering*, 5, 21-28.
- [4] Prakosa, A., Arevalo, H. J., Deng, D., Boyle, P. M., Nikolov, P. P., Ashikaga, H., ... & Trayanova, N. A. (2018). Personalized virtual-heart technology for guiding the ablation of infarct-related ventricular tachycardia. *Nature biomedical engineering*, 2(10), 732-740.
- [5] Lopez-Perez, A., Sebastian, R., Izquierdo, M., Ruiz, R., Bishop, M., & Ferrero, J. M. (2019). Personalized cardiac computational models: from clinical data to simulation of infarct-related ventricular tachycardia. *Frontiers in physiology*, 10, 580.
- [6] Tomek, J., Bueno-Orovio, A., Passini, E., Zhou, X., Mincholé, A., Britton, O., ... & Rodriguez, B. (2019). Development, calibration, and validation of a novel human ventricular myocyte model in health, disease, and drug block. *Elife*, 8, e48890.
- [7] Potse, M., Dubé, B., Richer, J., Vinet, A., & Gulrajani, R. M. (2006). A comparison of monodomain and bidomain reaction-diffusion models for action potential propagation in the human heart. *IEEE Transactions on Biomedical Engineering*, 53(12), 2425-2435.
- [8] L'Eplattenier, P., Bateau-Meyer, S., Benson, D., Kaul, V., Schu, C., Palmer, M., ... & Blauer, J. Cardiac Electrophysiology Using LS-DYNA®.
- [9] Ahrens, J., Geveci, B., & Law, C. (2005). Paraview: An end-user tool for large data visualization. *The visualization handbook*, 717(8).
- [10] Bayer, J. D., Blake, R. C., Plank, G., & Trayanova, N. A. (2012). A novel rule-based algorithm for assigning myocardial fiber orientation to computational heart models. *Annals of biomedical engineering*, 40(10), 2243-2254.
- [11] F.S. Costabal & Al, J Biomech, "Generating Purkinje Networks in the Human Heart" 2016 August 16; 49(12): 2455–2465.
- [12] Ten Tusscher, K. H., & Panfilov, A. V. (2006). Cell model for efficient simulation of wave propagation in human ventricular tissue under normal and pathological conditions. *Physics in Medicine & Biology*, 51(23), 6141.