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Partnership for Advanced Computing in Europe

Multidisciplinary Coupling in Cardiac Computational Mechanics

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Abstract

This paper describes the work done in Alya multiphysics code, which is an open source software developed at Barcelona Supercomputing Center BSC-CNS. The main activities of this socio-economic application project concern the development of a coupled fluid-electro-mechanical model to simulate the cardiac computational mechanical problem of the heart. Several aspects involved in the simulation process, methodology and performance of the code are carefully shown.

1. Introduction

Computational mechanics plays an important role in many engineering fields, and cardiac mechanics is no exception. Nowadays, some models allow realistic simulations of the heart beat, and could be used to study different pathologies or to understand better the physiological mechanisms regulating the contraction of the heart [1, 2]. Cardiac mechanics simulations represent a challenge in terms of numerical algorithms, programming techniques and computational resources. If today's models can take several weeks on single core computers with coarse meshes, the use of parallel resources will be essential for tomorrow's models.

This project aims at enhancing a high performance computational biomechanics simulation tool, to simulate cardiac mechanics. Although large scale supercomputers are worldwide available to researchers, almost no high performance computational biomechanics simulations tool can profit from these resources, not even at a modest performance level. Alya Red is the application of Alya system to biomechanical problems and, in particular, to cardiac mechanics. Alya is a high performance computational mechanics code developed at BSC-CNS . It is a flexible platform designed for running with the highest efficiency standards in large-scale supercomputing facilities, and it is capable of solving different physics in a coupled way: fluids, solids, electrical activity, species concentration, etc. Both main features are intimately related, meaning that all complex coupled problems solved by Alya must retain the parallel efficiency. In particular, by introducing a highly parallel model capable of running in thousands of processors, cardiac simulations can be performed on realistic conditions, using meshes of million elements with turnaround times of hours.

The Finite Element space discretization and the parallelization based on automatic domain decomposition for distributed memory facilities are the main features of this strategy. The automatic domain partition is done using the widely known open source software Metis [3]. Based on a master-slave strategy, one core is used to partition the problem and send each subdomain mesh to each of the other cores taking part in the run. Metis partitions the original mesh by minimizing the surface between subdomains and maximizing load balance. Communication is done using MPI and hybrid parallelization with OpenMP and MPI in part of the code, which has been implemented in WP9 of PRACE-2IP [4]. Parallelization is done transparently, so if properly coded, each of the coupled problems retains the scalability properties: the fact that all the coupled problems are solved on the same mesh avoids interpolation, mesh imbalance, etc. For a thourough descritpion, refer to [5]. Fully implicit and explicit schemes are implemented. The resulting code is able to run using elements of different space order (P1, P2,..., Q1, Q2,...) and higher order time schemes, in 2D and 3D domains of a non-homogeneous anisotropic excitable media.

The socio-economic challenge of the Alya Red Project is to perform simulations of biological systems at organ level, creating a computational infrastructure to achieve the following objectives: first to help medical researchers to better understand cardiovascular mechanisms and improve their physiological models, second to reduce the time from the lab to the patient in pharmacological and clinical research in both the private sector and academia (hence, reducing production costs and animal essays), and third, to help medical doctors to better understand what causes illness, improve diagnose and design treatments and new healing strategies. To

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attain these objectives, it is proposed to develop the fluid-electro-mechanical coupling in Alya Red. The process is simulated from the beginning: from the generation of the mesh to the validation of simulations through comparison with experimental results of cardiac motion. The full process is summarized with the following subgoals:

1. Improve the in-house mesh generator (Iris) to produce a fluid-solid mesh of the heart and large blood vessels.
2. Develop an efficient parallel strategy for coupling different physical problems, in particular the fluid-electro-mechanical problem.
3. Implement in Alya a cardiac fiber field generator with a rule-based strategy for the ventricles.
4. Test the scalability of the coupled code, running the model in parallel up to thousands cores on the Marenostrum machine, using resources provided by PRACE.
5. Run the simulation on large scale geometries of a full heart.
6. Validate simulations through comparison with experimental results of cardiac motion: axis rotation, ejection rate, specific material points tracking, etc.

This paper is divided into three main sections. First, the electophysiological model and the mechanical model used is described in detail in section 2. Section 3 describes the computational strategy and the methodoly developed, addressing the mesh generation, the coupling model and parallel strategy and the fiber field generation algorithm. Finally, in section 4 some results of the contraction of a simple geometry and a complete heart are presented. Mathematical models and simulations developed in the paper are qualitatively compared with clinical data, taken from real measurements.

2. Physiological model

At the organ level, figure 1 describes the heart as a coupled system: the electrical action potential propagation activates the mechanical deformation which, in turn, produces the pumping function against the blood. Coupling is in both ways because blood exerts a pressure on the endocardium and tissue deformation acts upon electrical propagations.

Fig. 1. The heart as a physical system.

2.1. Electro-mechanical model

In this case, Alya is used to simulate the cardiac ventricular contraction, showing the potential for simulating coupled problems. For a complete discussion of the methodology see [6] . The heart is made of elongated cells called myocites arranged as a compact fibered helicoidal structure. As an electrical impulse propagates, the fibers contract longitudinally making the heart pump the blood out of its cavities thanks to the fiber arrangement. At organ level, tissue is considered as a continuum composite material with anisotropic behaviour.

The cardiac computational model can be decomposed into three parts:

- **Electrophysiology:** Action potential propagation $\phi(x_i, t)$ is modelled through a transient anisotropic diffusion equation with a non-linear reaction term:

$$\frac{\partial \phi}{\partial t} = \frac{\partial}{\partial x_i}\left(D_{ij}\frac{\partial \phi}{\partial x_j}\right) + L(\phi) \tag{1}$$

  Diffusion is governed by the tensor D_{ij}, which represents the fiber orientation at each physical point. Its diagonal components are the axial and crosswise fibre diffusion. The crosswise diffusion is around one third of the axial diffusion. Finally, $L(\phi_\alpha)$ is the non-linear reaction term corresponding to the cell model. Depending on the model used, this term ranges from a simple cubic equation to an ordinary differential equation system of one hundred equations coupled and solved simultaneously. This term models the ionic currents interaction behind the muscular cellular mechanisms.

- **Mechanical deformation:** From a mechanical point of view, cardiac tissue is a thick layered structure: endo-, epi- and myocardium. The material is compressible hyperelastic, with anisotropic behaviour ruled by the fibre structure. The composite character of the material is determined by the internal stress, which is developed in two parts, active and passive:

$$\boldsymbol{\sigma} = \boldsymbol{\sigma}_{pas} + \sigma_{act}(\lambda, [Ca^{2+}])\boldsymbol{f} \otimes \boldsymbol{f} \tag{2}$$

where λ and Ca^{2+} are specific parameters relative to the model, see [7]. The passive part is governed by a transverse isotropic exponential strain energy function $W(b)$ that relates the Cauchy stress σ to the right Cauchy-Green deformation tensor $\boldsymbol{b}$ [6]:

$$J\boldsymbol{\sigma}_{pas} = (a\ e^{b(I_1-3)} - a)\boldsymbol{b} + 2a_f(I_4-1)e^{b_f(I_4-1)^2}\boldsymbol{f} \otimes \boldsymbol{f} + K(J-1)\boldsymbol{I} \tag{3}$$

The strain invariant I_1 represents the non-collagenous material while strain invariant I_4 represents the stiffness of the muscle fibers, and a, b, a_f, b_f are parameters to be determined experimentally. K is the bulk modulus and $\boldsymbol{f}$ defines the fibre direction. The active part comes through the electro-mechanical coupling and is described as follows.

- **Electro-mechanical Coupling:** The contracting electrical component of the electro-mechanical coupling is initiated almost simultaneously in several zones of the ventricular epicardium. Cardiac mechanical deformation is the result of the active tension generated by the myocytes. The model assumes that the active stress is produced only in the direction of the fibre and depends on the calcium concentration of the cardiac cell:

$$\sigma_{act} = \gamma\ \frac{[Ca^{2+}]^n}{[Ca^{2+}]^n + C_{50}^n}\sigma_{max}(1 + \beta(\lambda_f - 1)). \tag{4}$$

In this equation, C_{50}^n, σ_{max}, λ_f and $0 < \gamma < 1$ are model parameters.

3. Methodolgy

3.1. Mesh generation: Iris

To be able to simulate a full human heart it is necessary to be able to couple fluid and solid interactions (FSI). The generation of advanced multi-region meshes is therefore a crucial step for running FSI simulations. This involves identifying closed regions of an object, in the case the human heart, by utilizing region-growing algorithms. The boundaries of the different regions must then be set as constraints while meshing, hence giving rise to an accurate interface between mesh elements belonging to neighboring regions. In this project the in-house mesh generator named Iris, which has been developed at BSC, has been used. The region growing algorithms have been implemented as a new feature. It is necessary to constrain the final mesh so that the elements respect the various interfaces between two or more regions. Figure 2 shows the process of the mesh generation of a heart geometry with Iris.

3.2. Coupling parallel strategy

A general coupling strategy for multi-physics problems is developed in Alya. The basic idea is to have independent codes, one for each physical problem, and communicate the coupling variables using MPI. Usually, the multi-physics problems involve different space and time scales that can lead to situations in which optimised algorithms for the individual problems are useless in the coupled one. Thus, different coupling algorithms and relaxation schemes are considered and tested. In order to have a general scheme, the main concern of the approach is to exchange the information in the proper section of the code at the right time. Different kind of couplings lead to different information exchange. In some cases the information needs to be exchanged only in a contact surface, while in others it is necessary to exchange information in the whole domain. Moreover, the numerical use of the exchanged information has to be taken into account, such that, if the exchanged information is a source term, a boundary condition or a part of the matrix in the target code. In each of those cases, the treatment should be different.

A possible coupling scheme for a FSI problem is shown in Figure 3, where NSI refers to the Incompressible Navier-Stokes module and SLD refers to the solid mechanic problem. In this case a strongly coupled model is shown, solved with a block Gauss Seidel algorithm. However, in Alya code, loosely coupled algorithms have been also implemented.

3.3. Cardiac fiber-field generation

The cardiac tissue fiber orientation has a complex distribution that varies in the transmural direction and from base to apex. Fiber orientation is one of the most determining factors of cardiac functions. Determining this orientation is fundamental to simulate a coupled electromechanical model of the heart properly. For this purpose, an algorithm based on a mathematical model for the generation of the muscular fiber field of the heart has been implemented in Alya. This algorithm generates the fiber field in a ventricular 3D mesh using the description in [8]. The formulae used to generate the fibre orientations are in [9]. The algorithm implemented

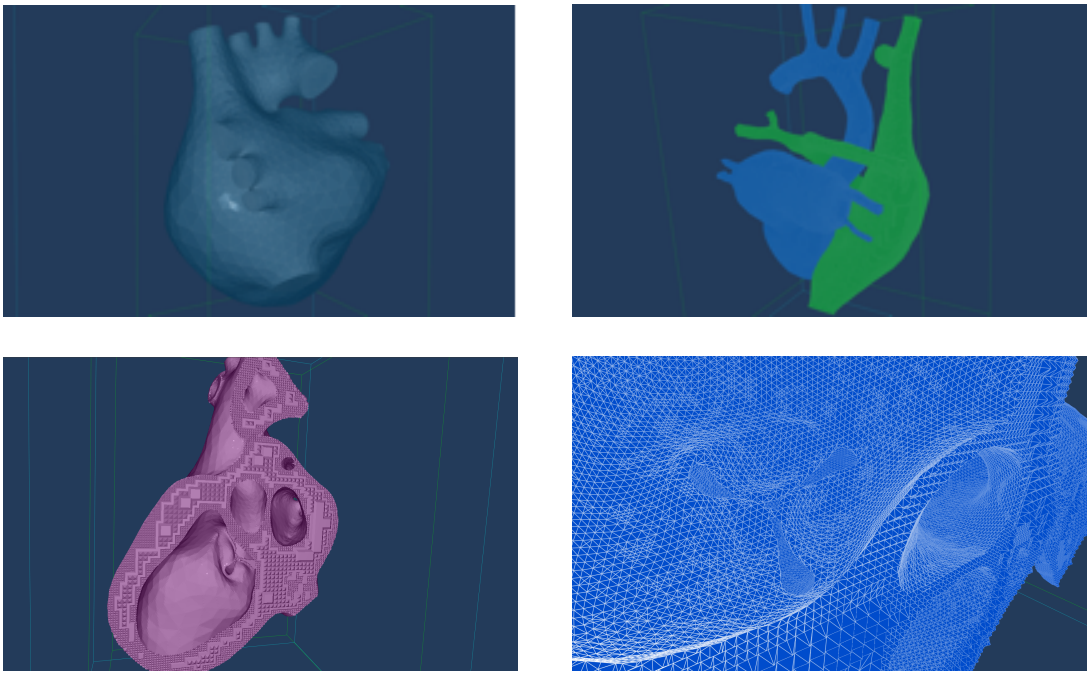

Fig. 2. Snapshots of the process to generate the multi-region mesh for a heart geometry.

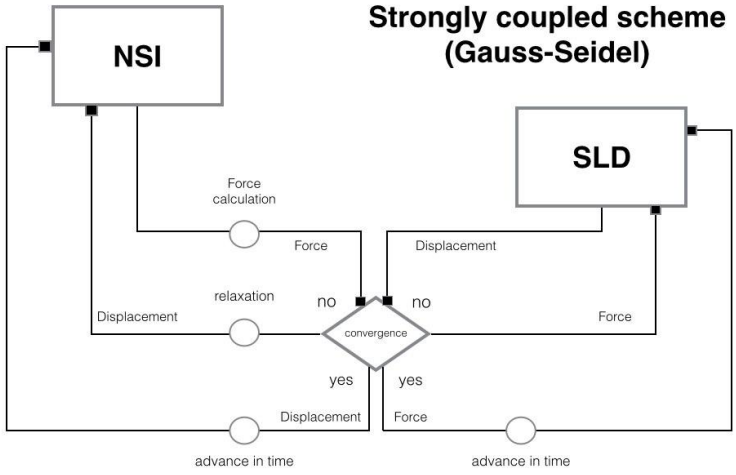

Fig. 3. Scheme for coupling FSI problems.

in Alya has four basic steps. Firstly, Alya calculates the relative thickness parameter for each node of the mesh, taking it equal to 0 for the nodes located in the endocardium and 1 for those which are in the epicardium. Secondly, Alya calculates the average of the relative thickness parameter for each node, considering its closest neighbors. Thirdly, Alya computes the gradient of the average in each node and finally, it computes the fiber orientation angle, which depends only on the relative thickness parameter. The local fiber direction in each node is orthogonal to the gradient of the average calculated in the previous step. Figure 4 depicts the fiber-field in a full human heart.

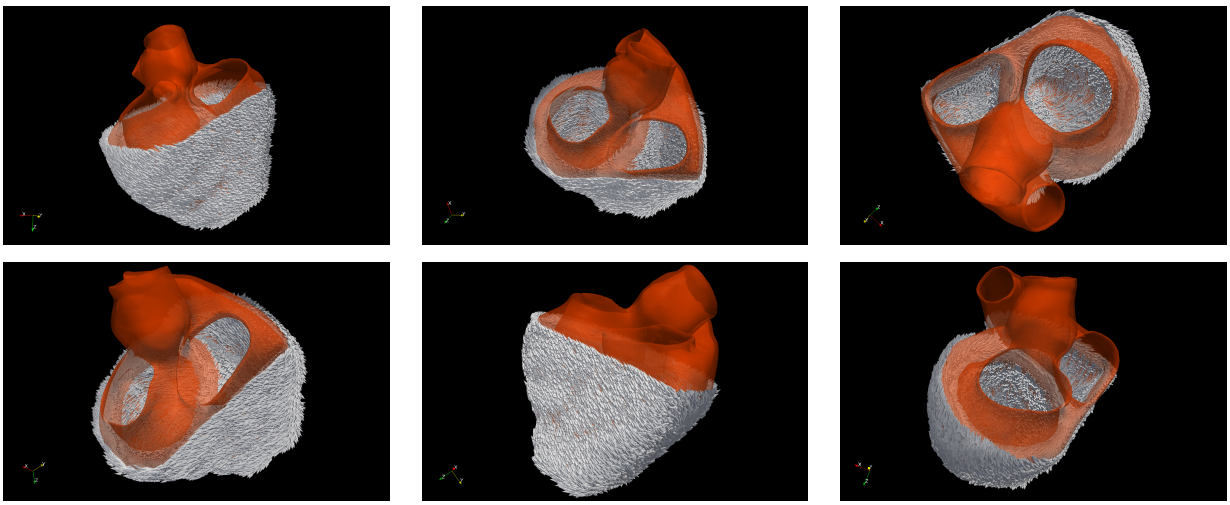

Fig. 4. Fiber orientation in the heart model.

4. Results

4.1. Example 1: electro-mechanical test

Both electrophysiology and mechanical action is simulated in Alya on the same mesh, as fine as the case demands. The time integration scheme is a staggered scheme [13], with both problems solved explicitly. The fibre fields can come either from measurements (using a so-called Diffusion Tensor MRI technique) or from semi-empirical rule-based models [6].

Figure 5 shows several snapshots of a bi-ventricular geometry of the full heart during systole. Figure 6 shows the evolution of the ejection rate, which represents the heart pumping action, measuring the change in the ventricular cavities volume.

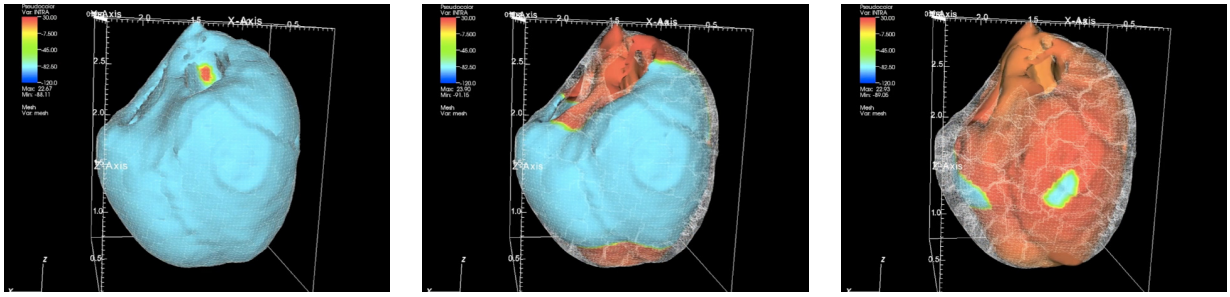

Fig. 5. Bi-ventricular electrical activation propagation of a dog heart during systole.

4.1.1. Parallel efficiency

A key feature of the computational model is its parallel efficiency. This allows either to solve very large problems in a reasonably turnaround time or medium size problems very quickly. In this example, the turnaround wall clock time for running one heart cycle using 200 processors was of around 10 hours. Parallel efficiency is measured by analyzing scalability. Strong scalability means how much faster a problem of fixed size is solved when the number of processors increase progressively. This scalability measure is linear when the speedup increases linearly with the number of processors involved. To measure it, we have used this problem as a benchmark, with runs of 128, 256, 512, 1 024, 2 048, 4 096 and 8 192 processors, taking the smallest one as the reference value. Then, perfect linear scalability means that the 8 192 run goes 64 times faster than the reference.

The computation has been performed on Marenostrum III (BSC), which is a supercomputer based on Intel SandyBridge processors that uses a Linux OS. The machine consists of 3028 nodes, two 8-core processors (Intel Xeon E5-2670 cores at 2.6 GHz) per node and 32 GBytes of memory per node. The total PeakPerformance is 0.7 Petaflops. Given the architecture of Marenosmtrum III, the number of threads per MPI task is 16, since each node consist of two 8-core processors, and the number of MPI tasks will be the number cores divided by 4. Scalability results are presented in Figure 7. In this case the scalability for 8 192 cores is 80% of the ideal due to the low amount of elements (3 400) per core and the proportionally large amont of communication per iteration. It has been checked with several tests that the minimum amount of elements per core needed for an optimal scalability is at least 4 000.

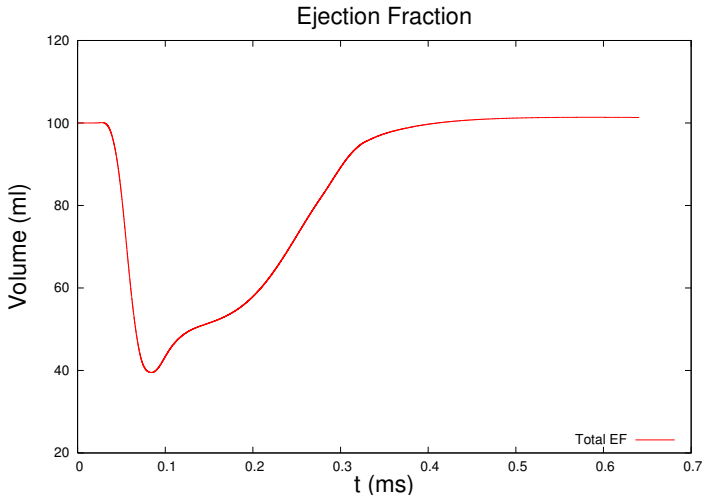

Fig. 6. Heart ejection rate.

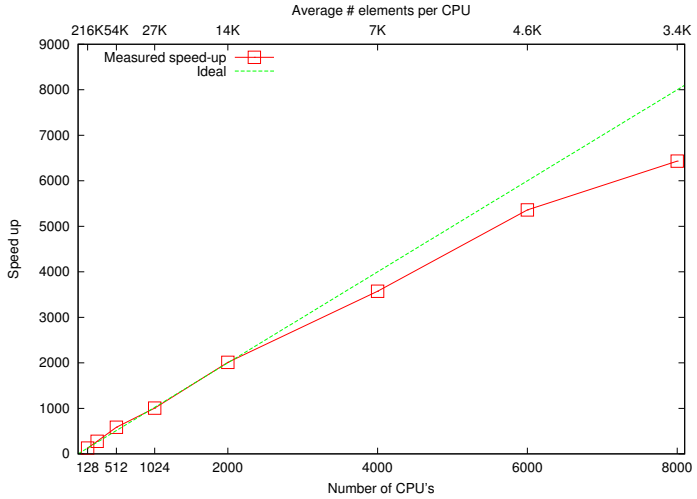

Fig. 7. Scalability test of the coupled electro-mechanical problem at Marenostrum III.

4.2. Example 2: fluid-electro-mechanical test

The following test consists on a piece of cardiac tissue, modeled with an Ogden-Holzapfell constitutive model [12]. The piece consists on a small block of cardiac tissue, made of 2 250 tetrahedral elements and 576 nodes. An electrical impulse is applied and electrophysisolgy is coupled to mechanical deformation throug a Hunter-Niederer model [11]. The electrical propagation is solved using a monodomain model with fibers in the z-direction. Then, an FSI model is considered for coupling the fluid and the structure, hence obtaining the full fluid-electro-mechanical coupling model. Due to the inherent difficulty of the coupled problem, first and for testing purposes, a simple geometry is considered: it consists on a prism, which is meshed with tetrahedral elements. Figure 8 depicts the velocity field for the fluid at four different instants of the simulation. The direction of the flow is correctly captured. Further research is addressed to run the model with a more realistic geometry of the heart, taken from a 3D image.

Figure 9 shows a snapshot of the activation potential wave contracting the tissue. Deformation of the piece is also captured.

4.3. Validation: comparison with experimental results

Mathematical models of the human cell are generally developed from measurements in single myocytes extracted from various human patients or donor hearts. Drug testing on human cells constitutes a huge challenge logistically and ethically. The use of mathematical models for the drugs testing requires validation by simulating the experiments perfomed in the wet lab, following established protocols. One of those protocols is the animal (generally the dog) isolated, arterially perfused ventricular wedge preparation. The mathematical models used here have been compared to measurements made to the ventricular wedge under a compound named NS5806, that generates the phenotype of the Brugada Syndrome, see [10]. The Brugada Syndrome is a genetic disease

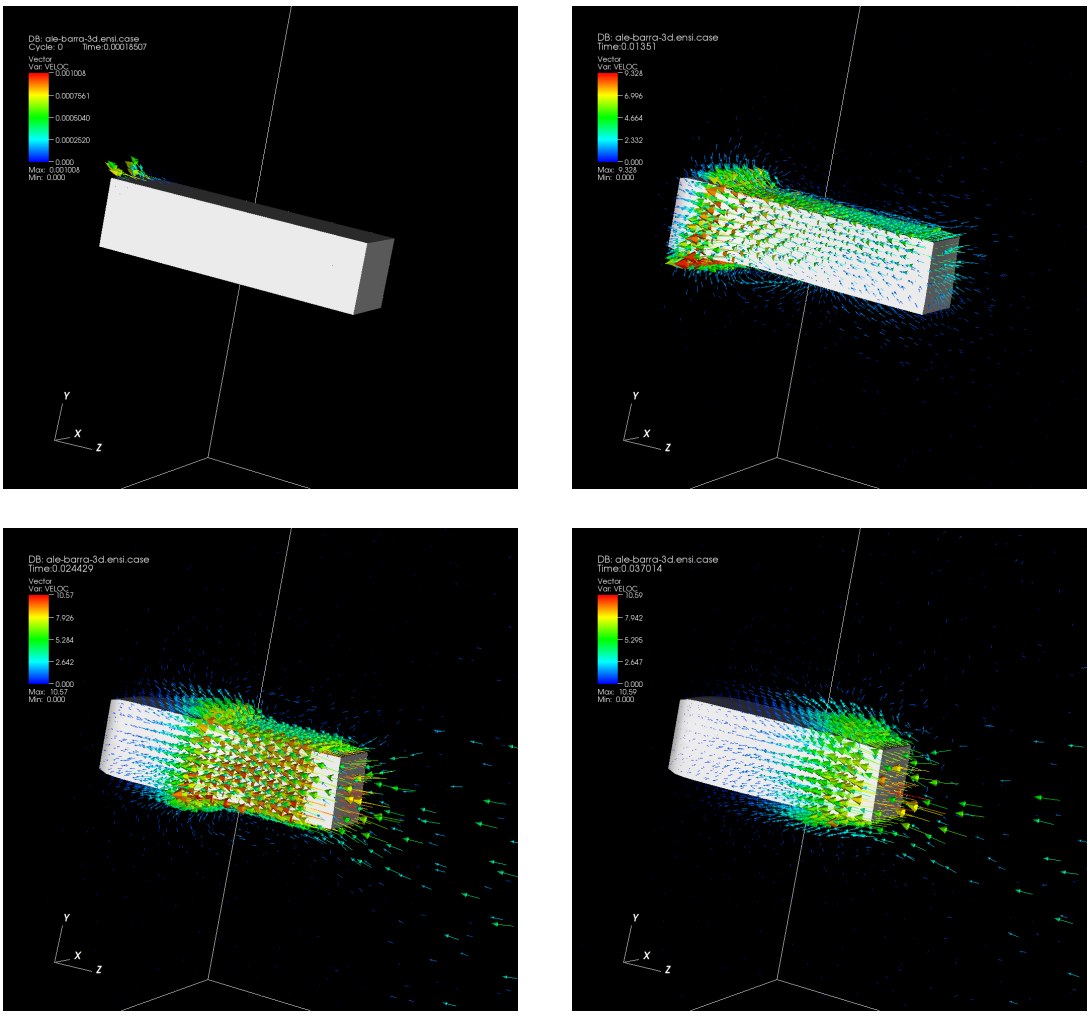

Fig. 8. Snapshots of the process to generate the multi-region mesh for a heart geometry.

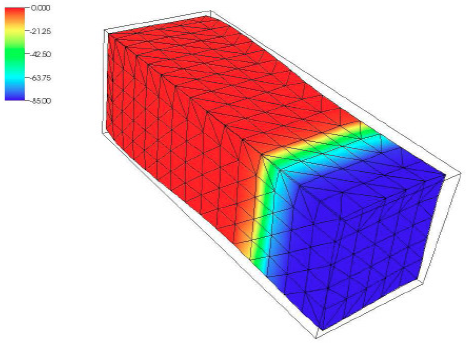

Fig. 9. Small piece of contracting cardiac tissue: activation potential propagation. Longitudinal direction is aligned with the z-axis.

that is characterised by abnormal electrocardiogram (ECG) findings and an increased risk of sudden cardiac death. It is the major cause of sudden unexplained death syndrome (SUDS), also known as sudden adult death syndrome (SADS), and is the most common cause of sudden death in young men without known underlying cardiac disease in Thailand and Laos.

For validating the results, the code has been run for three subjects with different cardiac systems: a normal system, a system affected by the Brugada syndrome and a system affected by the Brugada syndrome with the prescribed drug Quindine (5μM). Metrics like Action Potential Duration (APD) are some of the results used. In table 1 the comparison of a normal system, a system affected with the Brugada syndrome and a system afected with the Brugada syndrome with the prescripted drug Quindine (5M) , for 90 beats per minute (BPM)

are shown.

90 BMP	ADP (50ms)	ADP (90ms)
Normal	298.8±14.1	325.6 ± 9.3
Brugada (NS5806)	290.12.9±12.9	318.9 ± 9.7
Brugada (NS5806) + Quindine	311.0±18.2	350.1 ± 12.3

Table 1. Action potential duration in the virtual human wedge.

In figure 10 the data measured from the wedge is shown. The action potential fo the endocardial surface is plotted for a Brugada affected system, against a normal one. Results can be qualitatively compared with the experimental ones shown in figure 11. The model is able to reproduce qualitatively the experimental results. Further validation of the full heart simulation is ongoing work.

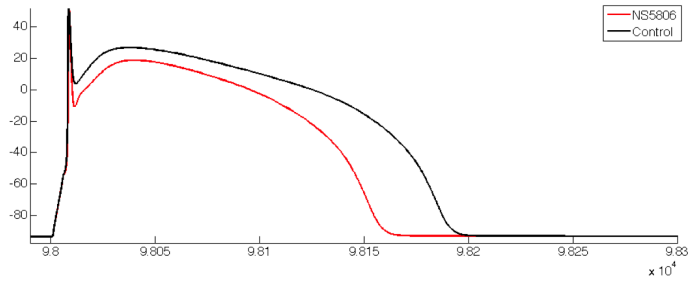

Fig. 10. Control curve and NS2806 curve computed with Alya for the action potential variable.

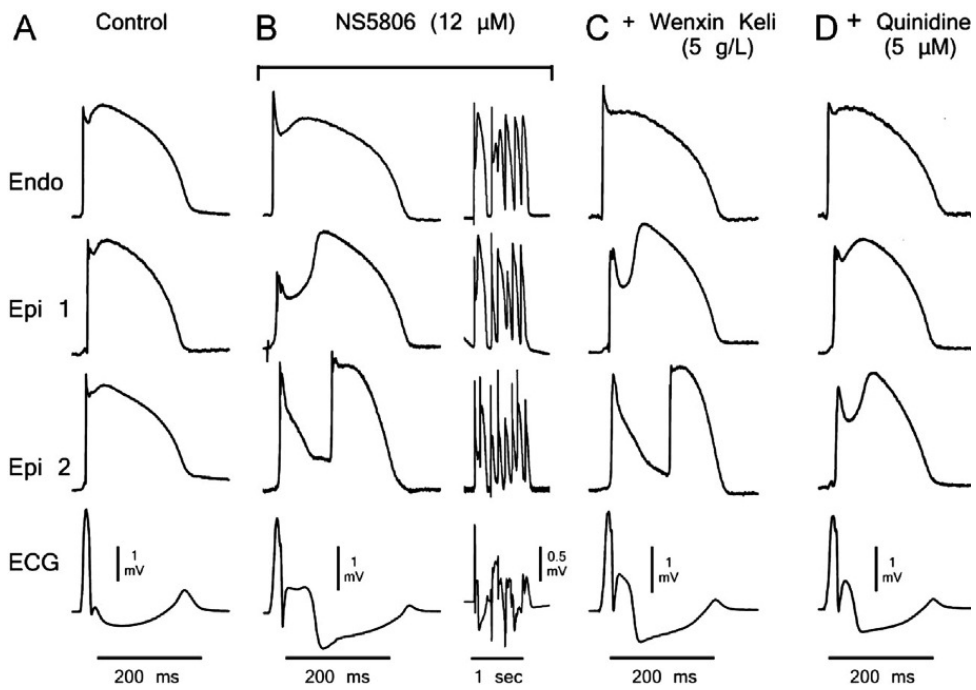

Fig. 11. Arrythmogenesis in an experimental model of Brugada syndrome. Wenxin keli (5g/L) and quindine (5μM supression of NS5806-induced Brugada syndrome phenotype. Shown are transmembrane action potenials (APs) recorded simultaneously from 2 sites of the epicardial (Epi) surface and 1 site on the endocardial (Endo) surface of a coronary-perfused right ventricular wedge preparation. **A:** Control. **B:** The transient outward potassium channer current agonist NS5806 (12μM) accentuates the Epi AP notch electrocardiographic J wave, leading to the loss of the AP dome at Epi1 but not Epi2. Heterogeneous loss of the dome leads to the development of a closely coupled phase 2 reentrant extrasystole, which precipitates a polymorphic ventricular tachycardia. **C:** Wenxin Keli (5g/L) suppressed ventricular fibrillation but did not prevent phase 2 reentry. **D:** The combination of Wenxin keli (5g/L) and qinidine restored homogeneity and aborted all arrhythmic activity. Basic cycle lenght = 2000ms.

5. Summary

A parallel cardiac computational model is developed in this work. The model is implemented in the Alya code, which is a Computational Mechanics code developed at the Barcelona Supercomputing Center (BSC-CNS), named Alya Red. The model is implemented from the beginning to the end of the process: the heart geometry is generated with an in-house mesh generator using the region-growing algorithms, a parallel strategy for coupling different modules of the code (electrical activation, mechanical deformation and incompressible flow) is proposed and implemented in the code, a cardiac-fiber field generator is also implemented and, finally, experimental data is provided in order to validate the simulation. The underlying challenge is to simulate the human heart at organ level with the highest possible detail. Alya Red Cardiac Computational Model (CCM) is a coupled fluid-electro-mechanical model scalable on thousands of CPUs. The simulation size could reach meshes of 200-300 million elements and a few hundred thousand time steps, producing up to terabytes of data to analyse. In the next future, real and complex geometries of the heart will be considered for the fluid-electro-mechanical problem. The simulation on large scale geometries of a full heart will be run and compared to experimental data. As a start, we target to simulate systole, so valves will be simply modelled as open/close boundary conditions, depending on the pressure on both sides.

Acknowledgements

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