

Cardiac computational models. Research Spanish Network (V-Heart SN)

Modelización Computacional Cardíaca. Red Española de Investigación (V-Heart SN)

Jean R. BRAGARD^a, Oscar CAMARA^b, Blas ECHEBARRIA^c, Luca GERARDO GIORDA^d, Esther PUEYO^e, Javier SAIZ^{f,*}, Rafael SEBASTIÁN^g, Eduardo SOUDAH^h y Mariano VAZQUEZ^{i,◊}

^a *BIOFIS, Universidad de Navarra*

^b *PhySense, BCN-MedTech, Universitat Pompeu Fabra*

^c *BIOCOM-SC, Universitat Politècnica de Catalunya*

^d *Mathematical Modeling in Bioscience (MMB), Basque Center for Applied Mathematics, 48009 Bilbao, Spain*

^e *BSICoS, I3A, Universidad de Zaragoza & CIBER-BBN*

^f *Ci2B, Universitat Politècnica de València*

^g *CoMMLaB, Universitat de València*

^h *CIMNE, International Centre for Numerical Methods in Engineering*

ⁱ *Barcelona Supercomputing Center & ELEM Biotech*

◊ Todos los autores, listados en orden alfabético, han tenido igual participación en el artículo.

* Autor para correspondencia:

Correo electrónico: jsaiz@ci2b.upv.es (J. Saiz).

ABSTRACT

Cardiovascular diseases currently have a great social and economic impact, constituting one of the leading causes of mortality and morbidity. Personalized computational models of the heart are demonstrating their usefulness both to help understand the mechanisms underlying cardiac pathologies, and to optimize their treatment and predict the patient's response. Although a simulation encompassing the intertwined physical processes of the heart (electrophysiology, mechanics, hemodynamics) in all its substructures (atria, ventricles, valves, vascular system) is an extremely complex task. Within this framework, the Spanish Research Network for Cardiac Computational Modelling (V-Heart SN) has been launched. The general objective of the V-Heart SN network is the development of an integrated, modular and multi-scale multi-physical computational model of the heart. This general objective is addressed through the following specific objectives: *a)* integrate the different numerical methods and models taking into account the specificity of patients; *b)* assist in advancing the knowledge of the mechanisms associated with the different cardiac and vascular pathologies; *c)* support the application of different personalized therapies; and *d)* contribute to greater use of cardiac and vascular models in a clinical setting. This article presents the current state of cardiac computational modelling and different scientific works conducted by the members of the network to gain greater understanding of the characteristics and usefulness of these models.

Keywords: Cardiac models, cardiovascular models, virtual heart, multi-scale modelling, patient-specific models, electromechanical modelling, hemodynamics models.

RESUMEN

Las enfermedades cardiovasculares tienen en la actualidad un gran impacto social y económico y constituyen una de las principales causas de mortalidad y morbilidad. Los modelos computacionales personalizados del corazón están demostrando ser útiles tanto para ayudar a comprender los mecanismos subyacentes a las patologías cardíacas como para optimizar su tratamiento prediciendo la respuesta del paciente, si bien una simulación que abarque los diferentes fenómenos físicos que se producen en el corazón (electrofisiología, mecánica, hemodinámica) en todas sus subestructuras (aurículas, ventrículos, válvulas, sistema vascular) es una tarea extremadamente compleja. En este contexto, se ha puesto en marcha la Red Española de Investigación en Modelización Computacional Cardíaca (V-Heart SN). El objetivo general de la red V-Heart SN es el desarrollo de un modelo computacional multifísico y multiescala integrado del corazón. Este objetivo general se aborda a través de los siguientes objetivos específicos: *a)* integrar los diferentes modelos numéricos teniendo en cuenta la especificidad de los pacientes; *b)* ayudar a avanzar en el conocimiento de los mecanismos asociados a las diferentes patologías cardíacas y vasculares; *c)* apoyar la aplicación de terapias personalizadas; y *d)* contribuir a un mayor uso de los modelos cardíacos y vasculares en el entorno clínico. Este artículo presenta el estado actual de la modelización computacional cardíaca y los diferentes trabajos científicos desarrollados por los miembros de la red para favorecer una mayor comprensión de las características y utilidad de los modelos.

Palabras clave: Modelos cardíacos, modelos cardiovasculares, corazón virtual, modelos multiescala, modelos específicos de paciente, modelos electromecánicos, modelos hemodinámicos

INTRODUCTION

Cardiovascular pathologies have a major social and economic impact in Spain, and in the rest of the world, in terms of morbidity, mortality and cost for the healthcare system. The diagnostic and therapeutic assessment of patients still depends on empirical studies in which the results are compared statistically between large groups of patients with similar pathology. The choice of the optimum treatment is difficult and their efficacy is limited because each patient has a unique disease profile. Computational models of the heart (also called virtual heart, in silico heart or digital twin) are emerging as a helpful tool by providing a framework to integrate various data from individual patients that can be used for improvement of diagnosis and for optimization and planning of personalized treatments.¹

Biophysically based multiscale mathematical models of the heart provide a bridge between cell models at smaller scales, and organ function at larger scales. For instance, in cardiac electrophysiology experimental and clinical data are integrated by improved computational models of human action potential² and its propagation in bidimensional (2D) and three-dimensional (3D) cardiac structures. These models are being used to test and generate hypotheses that are difficult to address experimentally. Non-diseased cardiac models of human atria^{3,4} and ventricles⁵ have been built with a high degree of electro-anatomical detail. Models of the human torso are also currently available⁶ allowing the reconstruction of the electrical field changes that generate the surface electrocardiogram.

To realistically simulate the complex multi-physics behaviour of the heart, comprehensive computational models need to simulate electrophysiology, muscular contraction and blood flow mechanics.⁷ In the last decade, advancements on mathematical modelling and computational resources allow now to solve highly complex, tightly coupled, multi-physics models that can take into account feedback mechanisms at the biophysical level to perform reliable in silico studies, useful for patient risk stratification, therapy planning, or in silico clinical trials, among others.^{8,9}

The increasing availability of in vivo cardiac images together with the rising trend towards personalized medicine made patient-specific models possible. The cardiac anatomy of a certain human subject can be extracted from in vivo medical images (e.g. computed tomography or magnetic resonance [MR]). Parameters estimated from population-based statistics or ex vivo experiments (fiber orientation, anisotropy, electrophysiological heterogeneity, among others) can also be incorporated into the models when patient-specific data are not available, ensuring that these parameters stay within the physiological range. The patient-specific model is then obtained by adjusting relevant parameters so that model simulation results are in agreement with clinical recordings.

However, the way from the development of a patient-specific cardiac model to its clinical application is complex and requires a multidisciplinary team. Clinicians provide the anatomical and physiological data and prior knowledge to build the models, personalize and validate them. Professionals with different mathematical, engineering and physics backgrounds will formulate the equations and develop the software needed to solve them and run simulations that mimic heart multi-physics phenomena in healthy and pathological conditions. Recently, the Spanish Research Network for Cardiac Computational Modelling (VHeart SN) was founded, including 9 well-known Spanish universities and research centers with ample experience in different aspects of the cardiac computer models. The main goal of the network is to develop an integrated, modular and multi-scale multi-physics computational model of the heart and to increase collaborations with clinicians and medical companies, ultimately contributing to the translation of virtual heart models into clinical applications. In this work, the current state of cardiac computational modelling and different scientific works developed by the partners of the network is summarized.

METHODS

Anatomical modelling

There is a large number of available techniques to obtain a patient specific 3D heart model from in vivo images acquired by MR or computed tomography¹⁰ (figure 1, geometry). Among them, it is worth mentioning those based on a-priori knowledge of the heart anatomy such as those based on statistical atlases,¹¹ or more recent ones based on deep learning techniques.

In addition to the 3D geometry, every cardiac computational model has to include other properties: cardiac fiber orientation, or pathologies affecting the myocardial structure (figure 1, cardiac conduction system [CCS] and structure). Thereby, one has to use mathematical models to define the preferential direction in which the electrical excitation^{6,12} or mechanical deformation will propagate to its neighbors. The last critical anatomical component required in cardiac models is the CCS. Some existing cardiac models have included the CCS at functional level (fast endocardial propagation), or have been based on ex vivo data.¹³ More recent advanced methods include the Purkinje network of a given patient by inverse estimation based on electro-anatomical map data.¹⁴

In addition to those anatomical components, it is possible to define regions where structural and functional remodelling is observed, such as scar or fibrotic tissue. These fibrotic lesions can be segmented from in vivo delayed enhancement-MR,⁵ that provides accurate information about the location of ischemic injuries (infarct scar and the border zone).

Electrophysiological and mechanical models

The application of different experimental methodologies, such as patch-clamp, has allowed to quantify the biophysical properties of cardiac myocytes both at the cellular and tissue levels. This knowledge enabled the development of computational models of individual myocytes (figure 1, EP models). In general, they are based on the mathematical formalism of Hodgkin-Huxley,¹⁵ where the cellular action potential is described by a system of equations that models the kinetics of individual ion channels, pumps and exchangers, as well as their electrical interactions. Several computational models of cellular cardiac electrical activity have been

developed, including ventricular² and atrial¹⁶ myocytes, and Purkinje fibers.¹⁷ Commonly used tissue propagation models are the bidomain model and the monodomain model,¹⁸ which are coupled to cellular models to form a multi-scale model. These tissue models (one-dimensional [1D], 2D or 3D) can include the heterogeneous structure of cardiac tissue and heterogeneous expression at the cellular level (apico-basal, endocardial-epicardial and left-right ventricles), giving them a high level of realism.¹⁹

3D cardiac models aimed at electromechanical computational simulations must include the electromechanical coupling, also known as excitation-contraction coupling. In this, electrical activation induces contraction of the cardiac tissue, which in turn influences the action potential through the stretch activated currents.²⁰ Contraction is initiated by an increase in intracellular calcium, whose dynamics has to be also considered, to account for the appearance of several arrhythmias.²¹

Hemodynamics models

Thanks to the computational fluid dynamics (CFD) we are able to obtain mathematically the behaviour of the blood inside the heart. Heart models take into account large-scale motion and deformation, fluid-structure interaction of the valves, complex-flow induced dynamics inside the chambers and the transmission of the electrical impulse through the tissue, among others. We can solve computationally all these coupled phenomena using multiscale and multiphysics computational codes.^{8,22} With regard to the model personalization, advanced diagnostic techniques, e.g., 4-dimensional (4D) phase-contrast MR or 3D/4D ultrafast echocardiography have allowed to obtain the complex blood flow inside the vessels and heart of the patient. Hence, combining these image technologies with CFD, allows us to personalize the numerical simulation getting patient-specific computational models.²³

Simpler computational models, so-called 0D/lumped models, are also interesting computational tools to study hemodynamics in the whole cardiovascular system, which is not possible with

higher-dimensional models such as CFD and FSI. For example, a foetal circulation model, personalized with available Doppler ultrasound data was developed to quantify blood redistribution in intrauterine growth restriction cases.²⁴ Lumped models were also recently employed to study heart-brain interactions in a holistic way, personalizing cardiovascular models with data from thousands of cases from the UK Biobank dataset, finding new relations between neurological factors such as white-matter hyperintensity lesions and cardiac abnormalities such as atrial fibrillation (AF).²⁵ In that line, it is also possible to create a reduced order model based on coupling 1D or 0D models with 3D models to study efficiently hemodynamics problems.²⁶ 1D models allow us to investigate physical mechanisms underlying changes in pressure and flow pulse waveforms that are produced by a cardiovascular disease²⁷.

CLINICAL APPLICATIONS

Atrial arrhythmias

It is well known that atrial arrhythmias can be caused by different mechanisms, including single-circuit re-entry, multiple-circuit re-entry, rapid local ectopic activity and rotors. Unravelling the mechanisms underlying AF can have an important impact in tailoring treatment to individual patients or populations. One of the applications of computational models is in helping to understand the relationship between atrial activation patterns and characteristics of electrograms recorded by catheters^{8,28,29} and in proposing improved electrogram biomarkers that can provide information about AF dynamics and the site of the AF drivers. Figure 2 shows the relationship between two atrial activations, in sinus rhythm (left) and AF (right), electrograms recorded through an intracavitary catheter, body surface maps and P-wave at the precordial lead V3.

Computer models are also a good platform to study inter-patient electrophysiological differences as well as the contribution of patient-specific remodelling (i.e., electric remodelling, fibrosis distribution) to AF initiation and maintenance and this can serve to guide treatment.

Using 2D tissue models and 3D patient-specific models of left and right atria it has been shown that fibrosis and atrial wall thickness gradient can affect the stabilization of AF drivers.³⁰

Additionally, to gain knowledge on AF initiation and perpetuation mechanisms, computer simulations could play a role in planning and predicting the effect of a therapy in the near future. AF ablation is nowadays the first-line treatment for the control of the rhythm of AF in selected patients, mostly patients with paroxysmal AF who prefer an interventional treatment. However, it is well known that the results of AF ablation depend on many important factors, such as the type of AF (paroxysmal, persistent or permanent), age, comorbidities, atrium size, the use of antiarrhythmic drugs, and the number and time of repeated ablation procedures. The great challenge in AF ablation procedures is a correct selection of patients and the identification of the adequate size of the generated lesions to avoid unnecessary damage to the atrium. The efficacy of AF ablation may be improved with an optimized patient-specific ablation strategy predicted by a computer model prior to an ablation procedure. For instance, recently an *in silico* study demonstrated the thermal impact of balloon occlusion of the coronary sinus during mitral isthmus radiofrequency ablation.³¹

As proof of concept that computational models can guide ablation procedures, Boyle et al.¹ carried out a prospective study using 10 patients with persistent AF and atrial fibrosis for targeted optimum ablation. The authors used personalized computational models of the atria reconstructed from each individual late gadolinium enhancement MR imaging scans to know the sites that are maintaining the AF or that are potential sources of AF in the future. They claim that the use of this methodology increases the efficacy of the procedure.

The location of ectopic foci during focal atrial tachycardia is complex to determine by non invasive techniques. Methods based on either standard 12-lead electrocardiograms or body surface potential maps have not shed sufficient light on how to accurately correlate ectopic focus locations with the distribution of potential and P-wave characteristics on the torso surface.

This limitation results in longer intra-operative invasive mapping procedures, which could lead to suboptimal ablation of focal triggers. Recently, a highly detailed multi-scale atrial-torso model has been used to develop a machine learning methodology to classify BSP into groups associated with ectopic atrial foci sites.^{6,32}

Computational modelling and simulation have also made additional contributions to the characterization of autonomic effects on atrial electrical activity and the establishment of actions leading to atrial arrhythmia termination or perpetuation, with recent interest in modelling the intrinsic cardiac autonomic nervous system to assess ganglionated plexi ablation in combination with pulmonary vein isolation.³³

Ventricular tachycardias and cardiac resynchronisation therapy intervention planning

Electrophysiological ventricular models have helped to shed light on the mechanisms underlying ventricular repolarization phenomena^{34,35} and to improve the definition of arrhythmic risk markers quantified from electrogram and electrocardiogram signals. As an example, low-frequency oscillations of ventricular repolarization, recently proposed to guide prophylactic implantable cardioverted-defibrillator implantation,³⁶ has been investigated through computational modelling and simulation to uncover its cellular bases, establish a relation to arrhythmic risk and link it to other arrhythmogenic phenomena.^{37,38} Another recent patient-specific electrophysiological model, so called *in silico* pace-mapping, predicted the right outflow tract origin in idiopathic ventricular arrhythmias in 10/11 cases.³⁹ A patient-specific model has also been used to investigate the mechanism of micro-reentry that leads to the generation of ectopic beats near infarct areas.^{40,41} The simulation results explain how ectopic beats emerge from micro-reentries that are sustained by the heterogeneous structure of the infarct regions.

Cardiac resynchronisation therapies, also called biventricular pacing, is the most widespread treatment for this kind of cardiac malfunction. A comprehensive fluid-electro-mechanical model of the heart, involving blood dynamics inside the cardiac cavities, becomes an invaluable

predictive simulation tool to analyse cardiac resynchronisation therapy at different stages and by different stake-holders, such as medical technology companies to improve design and deployment or practitioners to improve treatment by adapting it to a given patient.

The cardiac computational model implemented within the code Alya⁷⁻⁹ comprises the main mechanisms for the function of the cardiac muscle including the electrophysiology, the cardiac muscle and blood flow mechanics, the excitation-contraction-coupling and the mechano-electric feedback to study the cardiac muscle in a holistic manner. Thanks to this model it is possible to simulate cardiac resynchronisation therapy performed using a traditional pacemaker (figure 3, above) and transcatheter intraventricular one (figure 3, below). In particular, in the second case, fluid mechanics inside the ventricles and the vortices the presence of the pacemaker generates are analysed.

Defibrillation

Another application where numerical models have been very helpful in the improvement of the technology is the design of pacemakers and defibrillators.⁴² State of the art numerical studies have shown that the fiber orientation and membrane kinetics (electroporation) are crucial in determining the outcome of defibrillation.⁴³ The ultimate goal of an optimized personal electrical device to support our failing heart is yet to be reached. Though we have assisted to improvements in this direction we still need to push further the computational models to accomplish this objective. The major insights that the computer models have uncovered are that realistic heart geometry and disease remodelling are important.⁴²

Realistic 3D numerical simulations of the defibrillation problem were conducted and analyzed in a ventricular geometry. Upon increase of the shock strength the defibrillation success rate increases and follows the classical logistic curve (dose-response curve) as shown in figure 4. The simulation data were in good agreement with the clinical data. In subsequent studies we have used numerical simulations to help in the design of the ideal waveform⁴⁴ and the electrode

placement.⁴⁵ Much more research is still needed in order to find the optimum strategy for defibrillation.

Cardiovascular hemodynamics

Heart hemodynamics can also contribute to a better understanding of blood flow patterns in complex cardiac chambers such as the left atria and optimize medical devices such as the left atrial appendage occluders (LAAO). In patients with contra-indications to oral anticoagulants, LAAO devices are implanted to prevent blood flow entering the left atrial appendage, where 99% of the thrombi related to AF are formed. A sub-optimal LAAO implantation can generate thrombi outside the device. A web-based 3D interactive virtual implantation platform,⁴⁶ so-called VIDAA, was created to select the most appropriate LAAO configurations for a given patient-specific left atrial appendage morphology, predicting the region of peri-device thrombus formation in some cases.⁴⁷ Related to cardiovascular hemodynamics, the US Food and Drug Administration approved the clinical tool HeartFlow FFR_{CT} Analysis to assess the fractional flow reserve. HeartFlow's FFR_{CT} software was one of the first CFD codes to use in clinical routine, opening the way to advanced computational codes such as CAAS 3D-QCA vFFR developed by Pie Medical Imaging. The 3D-QCA vFFR workflow builds a 3D reconstruction of coronary artery by combining orthogonal angiographic projections and assesses pressure drop, resulting in vFFR value using a CFD code.²⁷

DISCUSSION

The technological progress during the last few years, including advanced high-computing infrastructures, open-source softwares and open-access medical databases, have brought biophysical models closer to clinical translation. They are currently being used in academia and industry for a better understanding of the physiology and for the optimization of medical devices and therapies. On the other hand, modelling-based tools are rarely employed in other clinical decisions such as diagnosis and treatment recommendations.

There are several reasons for not having a more established use of biophysical models in clinical routine. The necessary large process of clinical validation imposes robustness and time requirements that are not simple to achieve. Despite several clinical research studies based on biophysical models have shown their potential, they still need to demonstrate their added value in randomized clinical trials. Even if difficult, setting up multi-disciplinary teams, jointly defining from the very beginning projects is necessary to bring biophysical models closer to clinical routine. Biophysical models require prior knowledge by clinicians to obtain realistic simulations mimicking the complex behaviour of the heart. Moreover, computational tools are usually data-hungry but not any type of clinical data is useful: data needs to be appropriate to the question that the model is designed to answer, ideally acquired prospectively. Furthermore, data needs to be fully curated and annotated, which is often a tedious and time-consuming process. Biomedical engineers need to be embedded in clinical units with modern information technology infrastructure to provide the required technological skills and tools to perform data-related tasks such as harmonization, anonymization and standardization. Moreover, large databases, with an appropriate balance of controls and pathological cases with events, require multi-site studies, with clinical centers adopting data sharing philosophies, always fulfilling data protection laws. Finally, implementation efforts are required to go from the development of tools in an academic environment to a regular use in clinical workflows, creating clinician-friendly and application-specific visualization interfaces to search, integrate and explore patient-specific multi-modal data, population-based statistics, simulation results and clinical knowledge. Software environments such as the Rocket ecosystem (<https://www.upf.edu/web/bia/rocket>) are currently being developed to tackle these challenges.

The future of computational tools in cardiology is bright; we are at the beginning of a paradigm change in medicine where advanced biophysical models will play a significant role in cardiology pathways. During the next years biophysical models will significantly improve thanks to the

strong involvement of clinicians in their design and development, defining the most relevant questions to be answered, and incorporating high-quality patient-specific data to validate the added value of the simulations. Therefore, clinicians must not fear computational tools but they need to fully embrace them; biophysical models and artificial intelligence algorithms are not going to replace clinicians but are going to support them, allowing a focus on more interesting human-related tasks such as reasoning and patient-doctor communication.

In Spain there are excellent research teams with worldwide experts in their respective medical and engineering fields. The VHeart-SN initiative helped to integrate the national research groups working on cardiac modelling, with the spirit of sharing knowledge and resources. The next step should be to fully integrate medical teams in the initiative and form multi-disciplinary units to ease the clinical translation of computational tools to improve clinical decisions for our patients and foster innovation through the connection with large healthcare companies and the creation of start-ups.

FUNDING

This work was partially supported by: Acciones de Dinamización Redes de Excelencia 2016, Plan Estatal de Investigación Científica y Técnica y de Innovación, Ministerio de Economía y Competitividad (DPI2016-81873-REDT) and CompBioMed2, Grant agreement ID: 823712. The authors also thank the support of the European Research Council (ERC-StG 638284) and the Spanish Government through the following programmes: Retos I+D (TIN2014-59932-JIN, RTI2018-093416-B-I00, SAF2017-88019-C3-3R, RTI2018-101193-B-I00, DPI2016-75799-R and PID2019-105674RB-I00); María de Maeztu (MDM-2015-0502); and Severo Ochoa (SEV-2017-0718 and CEX2018-000797-S).

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. Boyle PM, Zghaib T, Zahid S, et al. Computationally guided personalised targeted ablation of persistent atrial fibrillation. *Nature biomedical engineering*. 2018. <https://doi.org/10.1038/s41551-019-0437-9>.
2. O'Hara T, Virág L, Varró A, Rudy Y. Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation. *PLoS Comput Biol*. 2011;7:e1002061.
3. Tobón C, Ruiz-Villa CA, Heidenreich E, et al. A three-dimensional human atrial model with fiber orientation. Electrograms and arrhythmic activation patterns relationship. *PLoS ONE*. 2013;8:e50883.
4. Ferrer A, Sebastian R, Sánchez-Quintana D, et al. Detailed anatomical and electrophysiological models of human atria and torso for the simulation of atrial activation. *PLoS ONE*. 2015;10:e0141573.
5. Lopez-Perez A, Sebastian R, Ferrero JM. Three-dimensional cardiac computational modelling: methods, features and applications. *Biomed Eng Online*. 2015;14:35.
6. Ferrer-Albero A, Godoy EJ, Lozano M, et al. Non-invasive localization of atrial ectopic beats by using simulated body surface P-wave integral maps. *PLoS ONE*. 2017;12:e0181263.
7. Santiago A, Aguado-Sierra J, Zavala-Aké M, et al. Fully coupled fluid-electro-mechanical model of the human heart for supercomputers. *Int. J. Numer. Meth. Biomed. Engng*. 2018;34:1-30.
8. Vázquez M, Houzeaux G, Koric S, et al. Alya: Multiphysics engineering simulation towards exascale. *J Comput Sci*. 2016;14:15-27.
9. Garcia-Canadilla P, Dejea H, Bonnin A, et al. Complex Congenital Heart Disease Associated With Disordered Myocardial Architecture in a Midtrimester Human Fetus. *Circ Cardiovasc Imaging*. 2018;11:e007753.

10. Niederer SA, Lumens J, Trayanova NA. Computational models in cardiology. *Nat Rev Cardiol*. 2019;16:100-111.
11. Hoogendoorn C, Duchateau N, Sanchez-Quintana D, et al. A high-resolution atlas and statistical model of the human heart from multislice CT. *IEEE Trans Med Imaging*. 2013;32:28-44.
12. Doste R, Soto-Iglesias D, Bernardino G, et al. A rule-based method to model myocardial fiber orientation in cardiac biventricular geometries with outflow tracts. *Int J Numer Method Biomed Eng*. 2019;35:1-17.
13. Sebastian R, Zimmerman V, Romero D, et al. Characterization and Modeling of the Peripheral Cardiac Conduction System. *IEEE Trans Med Imaging*. 2013;32:45-55.
14. Barber F, Lozano M, Garcia-Fernandez I, Sebastian R. Automatic Estimation of Purkinje-Myocardial Junction hot-spots from Noisy Endocardial Samples: A simulation study. *Int J Numer Method Biomed Eng*. 2018;34:e2988.
15. Hodgkin AL and Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol*. 1952;117:500-544.
16. Courtemanche M, Ramirez RJ, and Nattel S. Ionic mechanisms underlying human atrial action potential properties: insights from a mathematical model. *Am J Physiol Circ Physiol*. 1998;275:H301-H321.
17. Stewart P, Aslanidi OV, Noble D, et al. Mathematical models of the electrical action potential of Purkinje fibre cells. *Philos Trans R Soc A Math Phys Eng Sci*. 2009;367:2225-2255.
18. Potse M, Dube B, Richer J, et al. A Comparison of Monodomain and Bidomain Reaction-Diffusion Models for Action Potential Propagation in the Human Heart. *IEEE Trans Biomed Eng*. 2006;53:2425–2435.

19. Liu DW, Gintant GA, and Antzelevitch C. Ionic bases for electrophysiological distinctions among epicardial, midmyocardial, and endocardial myocytes from the free wall of the canine left ventricle. *Circ Res.* 1993;72:671-687.
20. Hunter PJ, McCulloch AD, Ter Keurs DJ. Modelling the mechanical properties of cardiac muscle. *Prog Biophys Mol Biol.* 1998;69:289-331.
21. Lugo CA, Cantalapiedra IR, Peñaranda A, et al. Are SR Ca content fluctuations or SR refractoriness the key to atrial cardiac alternans?: insights from a human atrial model. *Am J Physiol Heart Circ Physiol.* 2014;306:H1540-H1552.
22. Dadvand P, Rossi R, Oñate E. An object-oriented environment for developing finite element codes for multi-disciplinary applications. *Arch Comput Methods Eng.* 2010;17:253–297.
23. Soudah E, Casacuberta J, Gamez-Montoro PJ, et al. Estimation of wall shear stress using 4D flow cardiovascular MRI and computational fluid dynamics. *J Mech Med Biol.* 2017;17:175.
24. Garcia-Canadilla P, Rudenick PA, Crispi F, et al. A computational model of the fetal circulation to quantify blood redistribution in intrauterine growth restriction. *PLoS Comput Biol.* 2014;10:e1003667.
25. Banus J, Lorenzi M, Camara O, Sermesant M. Large scale cardiovascular model personalisation for mechanistic analysis of heart and brain interactions. In: Functional Imaging and Modeling of the Heart. Coudière Y, Ozenne V, Vigmond E, Zemzemi N, editors. Heidelberg: Springer-Verlag; 2020. p. 285-293.
26. Soudah E, Rossi R, Idelsohn S, Oñate E. A reduced-order model based on the coupled 1D-3D finite element simulations for an efficient analysis of hemodynamics problems. *Comput Mech.* 2014;54:1013-1022.
27. Soudah E, Oñate E, Cervera M. Computational fluid dynamics indicators to improve cardiovascular pathologies. *CIMNE M167*; 2016. p. 115-140.

28. Martinez-Mateu L, Ferrer-Albero A, Sebastian R, et al. Factors affecting basket catheter detection of real and phantom rotors in the atria: A computational study. *PLoS Comput Biol*. 2018;14:e1006017.
29. Sánchez C, Bueno-Orovio A, Pueyo E, Rodríguez B. Atrial fibrillation dynamics and ionic block effects in six heterogeneous virtual atria with distinct repolarization dynamics. *Front Bioeng Biotechnol*. 2017;5:29.
30. Roy A, Varela M, Aslanidi O. Image-based computational evaluation of the effects of atrial wall thickness and fibrosis on re-entrant drivers for atrial fibrillation. *Front Physiol*. 2018;9:1352.
31. González-Suárez A, d'Avila A, Pérez JJ, et al. Thermal impact of balloon occlusion of the coronary sinus during mitral isthmus radiofrequency ablation: an in-silico study. *Int J Hyperthermia*. 2019;36:1167-1176.
32. Godoy E, Lozano M, García-Fernández I, et al. Atrial fibrosis hampers non-invasive localization of atrial ectopic foci from multi-electrode signals: A 3D simulation study. *Front Physiol*. 2018;9:1-18.
33. Hwang M, Lim B, Song JS, et al. Ganglionated plexi stimulation induces pulmonary vein triggers and promotes atrial arrhythmogenicity: In silico modeling study. *PLoS ONE*. 2017;12:e0172931.
34. Cantalapiedra IR, Peñaranda A, Mont L, et al. Reexcitation mechanisms in epicardial tissue: Role of Ito density heterogeneities and INa inactivation kinetics. *J Theor Biol*. 2009;259:850-859.
35. Pueyo E, Dangerfield CE, Britton OJ, et al. Experimentally-based computational investigation into beat-to-beat variability in ventricular repolarization and its response to ionic current inhibition. *PLoS ONE*. 2016;11:e0151461.

36. Bauer A, Klemm M, Rizas KD, et al. EU-CERT-ICD investigators. Prediction of mortality benefit based on periodic repolarisation dynamics in patients undergoing prophylactic implantation of a defibrillator: a prospective, controlled, multicentre cohort study. *Lancet*. 2019;394:1344-1351.
37. Sampedro-Puente DA, Fernandez-Bes J, Porter B, et al. Mechanisms underlying interactions between low-frequency oscillations and beat-to-beat variability of cellular ventricular repolarization in response to sympathetic stimulation: implications for arrhythmogenesis. *Front Physiol*. 2019;10:916.
38. Sampedro-Puente DA, Fernandez-Bes J, Szentandrassy N, et al. Time course of low-frequency oscillatory behavior in human ventricular repolarization following enhanced sympathetic activity and relation to arrhythmogenesis. *Front Physiol*. 2020;10:1547.
39. Doste R, Lozano M., Gomez JF, et al. Predicting the Origin of Outflow Tract Ventricular Arrhythmias Using Machine Learning Techniques Trained with Patient-Specific Electrophysiological Simulations. *Computing in Cardiology Conference* 2019;34.
40. Sachetto R, Alonso S, Dos Santos RW. Killing many birds with two stones: hypoxia and fibrosis can generate ectopic beats in a human ventricular model. *Front Physiol*. 2018;9:764.
41. Oliveira RS, Alonso S, Campos FO, et al. Ectopic beats arise from micro-reentries near infarct regions in simulations of a patient-specific heart model. *Scientific reports*, 2018;8(1):1-14.
42. Trayanova NA, Rantner LJ. New insights into defibrillation of the heart from realistic simulation studies. *Europace*. 2014;16:705-713.
43. Trayanova N, Constantino J, Ashihara T, Plank G. Modeling defibrillation of the heart: approaches and insights. *IEEE Rev Biomed Eng*. 2011;4:89-102.
44. Bragard J, Simic A, Elorza J. Shock-induced termination of reentrant cardiac arrhythmias: Comparing monophasic and biphasic shock protocols. *Chaos*. 2013;23:3119.

45. Bragard J, Simic A, Laroze D. Advantage of four-electrode over two-electrode defibrillators. *Phys Rev*. 2015;92:2919.

46. Aguado AM, Olivares AL, Yagüe C, et al. In silico optimization of left atrial appendage occluder implantation using interactive and modeling tools. *Front Physiol*. 2019;10:237.

47. Mill J, Olivares AL, Arzamendi D, et al. The impact of flow-dynamics on device related thrombosis after left atrial appendage occlusion. *Can J Cardiol*. In press.

FIGURE LEGENDS

Figure 1. Schematic representation of the pipeline to build a three-dimensional (3D) cardiac computational. This flowchart shows the main stages in the construction process of a 3D cardiac model aimed at biophysical simulation: 3D cardiac geometry generation and meshing, CCS generation, myocardial structure generation, biophysical modelling (cardiac EP, and electromechanics), and finally multi-scale multiphysics simulation. Arrows show the flow from the clinical/biological data (ex vivo and in vivo) to the final Computational Model and electromechanical simulation. Blue boxes correspond to methods that allow to obtain a patient-specific personalization of specific model properties, while gray boxes represent population-based or generic descriptions of other properties.

Figure 2. On the top, atrial propagation produced by a sinus rhythm (left) and by an ectopic pacing from the coronary sinus (right) and their electrogram signals registered at one intracavitary electrode. On the bottom, body surface potential maps at one instant of the above simulations and P-wave registered at the precordial lead V3.

Figure 3. Transcatheter intraventricular pacemaker. Above, cardiac wall stresses evolution during pacing. The tissue is colored by the VonMises stress. Below, blood mechanics evolution inside the ventricles. The tissue is colored by the electrical activity propagation. Fluid mechanics is analysed through the vortices produced.

Figure 4. Above, 4 consecutive snapshots taken during a successful defibrillation shock of 12 ms duration. A, electrical activity before the shock. B, strong polarized activity during the shock. C, activity 50 ms after the end of the shock. D, no activity 100 ms after the end of the shock. Below,

setup and plot showing the defibrillation success rate as a function of electrical shock strength as obtained through 50 numerical simulations. The logistic curve (dose-response curve) represents the best fit of the data. EB: extra beat. DR: dose-response.

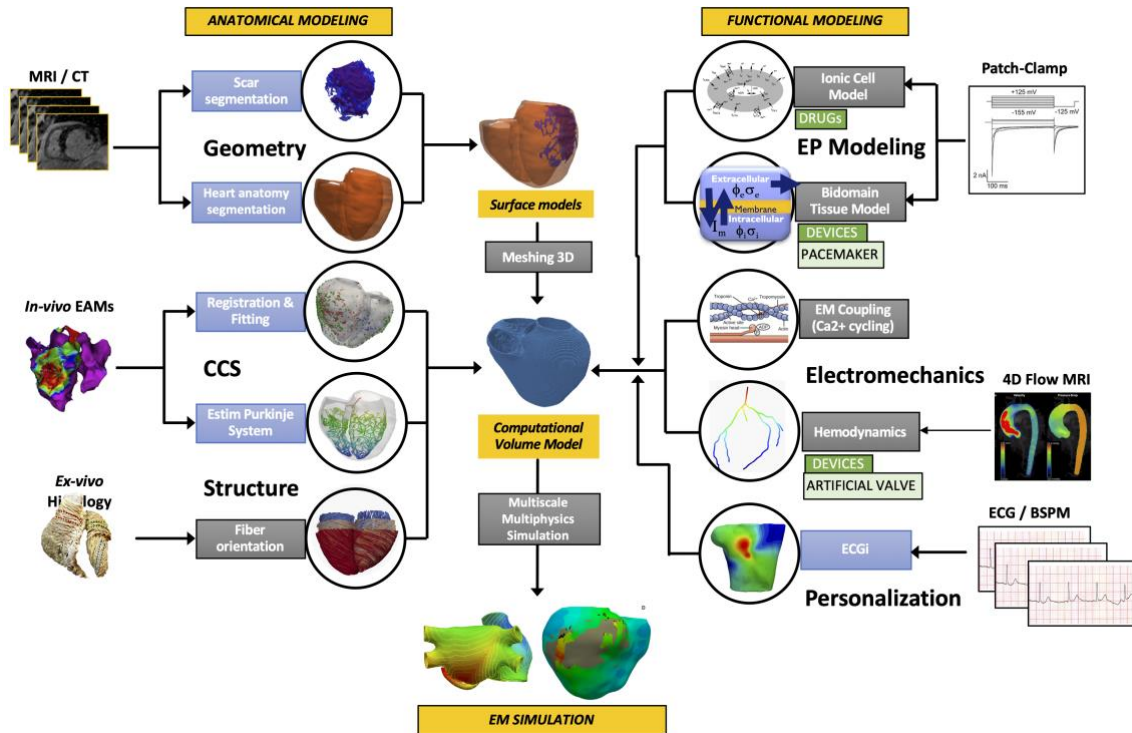


Figure 1

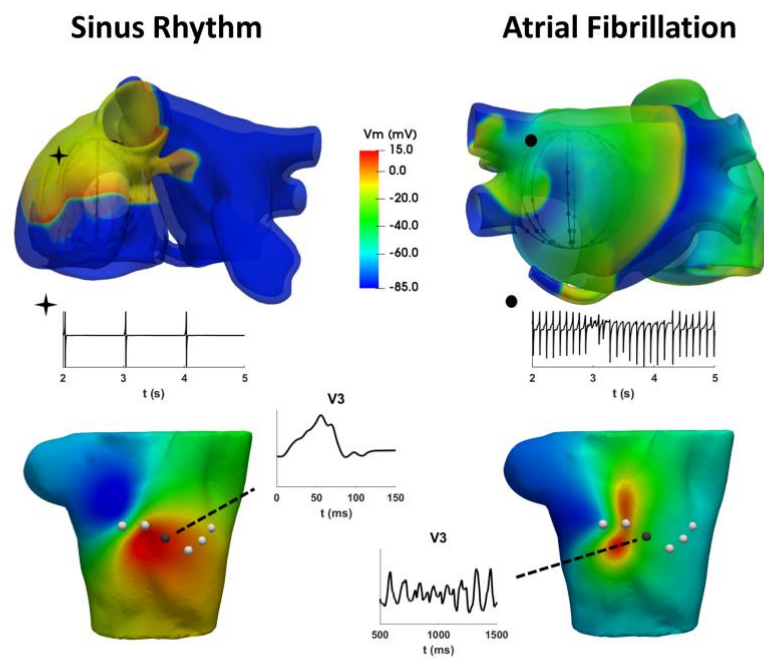


Figure 2



Figure 3

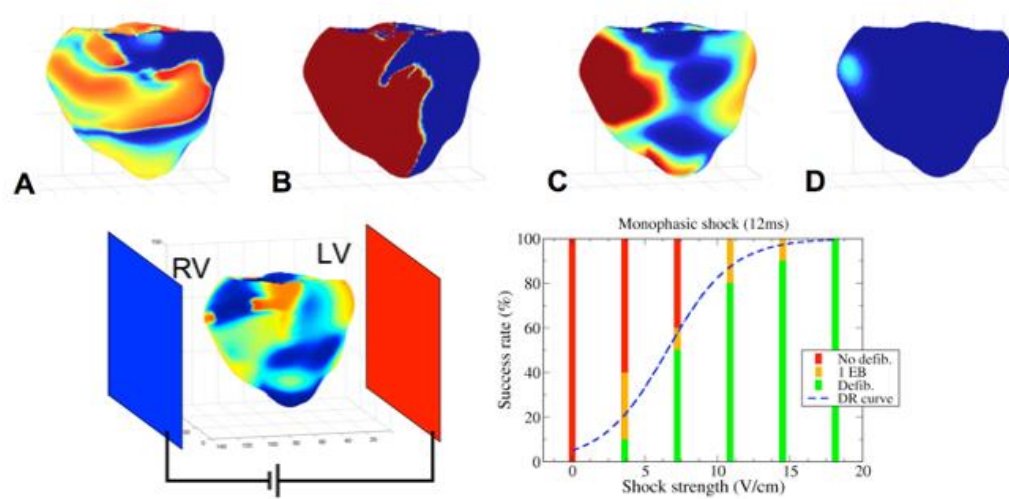


Figure 4