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SimCardioTest - Simulation of Cardiac Devices & Drugs for in-silico Testing and Certification

Technical Report

D2.1- Report on the standardised models for use case 1

Work Package 2 (WP 2)

UC1 - Pacing leads and catheters

Task Lead: University of Bordeaux, France

WP Lead: University of Bordeaux, France

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Lead authors	Yves Coudière, UBx
Contributors	Michael Leguèbe (UBx), Matteo Selmi (Microport), Camille Krewcun (Inria), Clément Vidal (Microport)
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EXECUTIVE SUMMARY

This report defines the general use case 1 (UC1) workflow. This use case considers computational models of the mechanical, pacing and sensing properties of cardiac stimulators and their associated insertion accessories. The report describes several computation pipelines that aims to be implemented in the cloud-based platform, where the in-silico trials for the mechanical and electrophysiological efficacy and safety of the devices will be run.

The details on standardized inputs and outputs throughout the pipelines are described, as well as the methodological requirements.

1. Introduction

The main objectives of WP2 are to quantify mechanical and electrical properties of cardiac stimulation devices. In general, such devices are composed of electrical leads connected to a canister, that contains a control system. The leads are introduced in the body by using an insertion device, then navigated towards their chosen location in the heart of the patient, where they are securely anchored, in most of the cases. Over time, they regularly pace and sense the heart's electrical activity, undergoing a repeated stress by the heart's movements, leading to mechanical fatigue. Numerical models could aid to evaluate the efficacy and safety of such devices with respect to navigation, pacing, sensing, and fatigue. Within WP2, workflows have been designed to answer questions related to a typical, standard, implantation scenario, while they aim at being a generic process that is extensible to other scenarios. The workflows make heavy use of computational pipelines to address these questions.

Theses computational pipelines are complex, requiring the integration of several types of data provided by different consortium members, such as imaging data, device modeling, simulation processing and so forth. Therefore, it is crucial to consistently delineate a standardization pipeline to guarantee seamless user-experience and common language. Technical requirements for standardization were initially introduced in Deliverable 1.1 (month 6), summarizing the answers to the survey performed by the partners on Use Case 1 pipelines and the technical requirements for the different software tools used in the present use case. All these aspects prompt for having a standardization approach for UC1.

Standardization in the present document implies the use of common processes and standards for input/output data and model formats for a better integration in the platform. This document also includes the definition and standardization of technical requirements to assure that, once developed, models will be properly integrated in the platform and will be made available to end-users. On the one hand, a standardized description of the models is provided to facilitate the interoperability of the different modeling software tools that will allow for more complex in-silico trials. On the other hand, standardization of all different model inputs & outputs (including units, formats, model descriptions...) will allow the creation of a user-friendly interface and assure compatibility throughout the different stages of the pipeline.

In UC1, we aim at providing a standardized approach for in-silico evaluation of the lead navigation, its mechanical interaction and possible fatigue estimation, together with pacing and sensing properties of the device, by creating an integrated and secure cloud-based platform standardizing & bridging model simulations, in-silico trials, and certification support.

The specific objectives of the target scenario, the standardization of the inputs and outputs of the computational pipelines, and additional data were discussed during plenary meetings with all participants of WP2. In particular, the members split into two separate technical subgroups to address questions and objectives specific to each biophysical domain, mechanical and electrophysiological respectively. A third group discussed the overall computational processes, and focused on data needed to prepare and run the computations. All these meetings were organized online. Finally, a specific workshop on standardization was held on October 27th - 29th, 2021 in Nice for the members of the consortium, where the members of WP2 agreed on the main objectives of the numerical pipelines, and therefore the elements to be standardized.

By mutual agreement, UC1 primarily involves the evaluation of bradycardia leads that are inserted into the body with a stylet. This is a well-established and common practice that can be considered as a representative standard procedure. It consists in: i) lead insertion into the venous system at a subclavian entry point, ii) lead navigation towards the right atrium or ventricle by using a stylet within it, aiding in positioning the lead into the desired location, and iii) fixation to the heart tissue. The leads are expected to safely pace the heart and sense electrical signals to assess its own function.

From the computational standpoint, the UC1 is based on two types of biophysical models: i) mechanical models including large deformation and the management of contact between objects, and ii) models of cardiac electrical activation and propagation of action potentials. Both types of models rely upon the current state-of-the-art knowledge. They concern three-dimensional complex geometries, and consider a high number of parameters of the biophysical model at hand, such as mechanical properties of the devices, working boundary conditions of the vessels and myocardium, and electrophysiological function of the myocardium coupled to its environment (blood, other tissues and organs).

There is obviously a crucial need to standardize and homogenize the existing cardiac modeling and simulation tools before entering the regulatory pathway. The standardization of all aspects of the in-silico trial platform (input/output and models) will facilitate the evaluation of the accuracy and predictive value of the simulation results, thus easing external assessment of the platform by authorities and regulatory bodies. In the last 20 years the scientific community has undertaken coordinated efforts to build centralized databases to store mathematical models of biological systems in standard formats, making them easily accessible and reusable, such as CellML Model Repository (http://www.cellml.org/models) (Lloyd et al., 2008). CellML is used in cellular and physiological modeling and allows modular construction of models, being considered as a community standard. These models need to be integrated in multi-scale frameworks to encompass tissue, organ, or organism levels, and to this aim principles for complex model construction with the Physiome standard modeling protocol have been designed (Cooling et al., 2016).

In UC1, concerning electrophysiological modeling, we make use of cell models from the CellML model database to describe the ionic activity of cardiomyocytes (cell electrophysiology). Anyway, they require a suitable preprocessing to be inserted in our solver. Besides this standard, we need to incorporate a description of the pacing and sensing device, and of its interaction with tissue or blood. In order to avoid sharing proprietary data, a fixed electrical circuit is adopted to model the pacing and sensing device. Concerning the interface polarization phenomenon, which is not classically considered in cardiac action potential simulations, the literature (Grimnes et al., 2015) lists a small number of equivalent circuits modeling this effect. They will be described in a standard manner. In addition, the evolution of the fibrosis around the lead insertion will be considered. The fibrosis is linked to cardiac electrical conductivity coefficients, and ionic model. This document will provide information concerning the models and standard ways chosen to provide information to the models regarding the cell electrophysiology, the pacing and sensing protocols, the electrode polarization, and the fibrosis of the myocardium. Standardized list of outputs of the computations will be specified as well.

As far as mechanical biophysical modeling is concerned, UC1 computational approach relies on structural Finite Element Analysis (FEA) simulations, which solve Partial Differential Equations (PDEs) problems to compute and predict stress-strain behavior under a given load. Input of this

workflow are usually geometries either extracted from routine imaging data or built by means of Computer-Aided Design (CAD) tools, then discretized in a numerical finite element mesh and coupled with a set of boundary conditions and mechanical properties. The output of UC1 models are 3D maps of field variables, such as stress, strain and contact pressure, as well as deformed geometrical configurations. Output visualization is typically obtained either within the computational software itself or by elaborating the results using other tools, such as Open-Source Paraview (https://www.paraview.org).

FEA techniques are widely exploited in multiple industrial (e.g., automotive, aerospace, construction industries, and biomedical devices design, etc.) and academic applications, with publication numbers increasing from few hundreds to more than two thousands in the last 20 years (https://pubmed.ncbi.nlm.nih.gov/?term=finite+element+analysis), with several commercial software solutions (e.g., Ansys, COMSOL, Abaqus) and Open-Source initiatives (e.g., SOFA, OpenFOAM, FEniCS). As far as research activity and cardiovascular environment are concerned, it is worth mentioning the Living Heart Project (Dassault Systèmes, SIMULIA), a translational research initiative aiming at developing and validating highly accurate personalized digital human heart models, sponsored by the FDA (https://www.3ds.com/products-services/simulia/solutions/life-sciences-healthcare/the-living-heart-project/). Even though a consensus on standards is still missing, there is the possibility to define input/output formats that can be compatible and exchanged among several software. Thus, we have been following this rationale to build the UC1 standardized workflow, establishing modular computational pipelines that include several components, fully integrated and seamlessly communicating between themselves. Modularity will allow a given module to be updated in the future, without disrupting the whole workflow.

For a user, the standardized cloud-based platform described in the present document will help to inform about:

• the force exerted by the lead on the anatomical district while navigating to the implantation site and the mechanical stress the lead undergoes while heart cyclic movement is simulated (fatigue estimation) ;

• the capture (triggering and propagation of an action potential) capability, its variation with respect to cardiac fibrosis, and its sensing properties.

2. Description of UC 1's workflow objective and constraints

Since the mechanical aspects regarding the insertion, navigation and fatigue of the leads, and the electrical ones regarding pacing and sensing may be disconnected from each other, UC1 gathers several pipelines in accordance with the main objectives of the computations.

2.1 Electrophysiology Pipelines

The pipelines on electrophysiology aim at computing some key numbers related to the electrical functions of cardiac leads. It is described in Figure 1. The workflow answers three practical questions, so that it implements three computational pipelines that share the same software and types of inputs. One input for these pipelines consists in a mesh file that describes the spatial discretization of the computational domain. This file optionally contains information on the biological properties of the tissue (e.g. fibrosis density). The second main input is a text file which contains parameters that control the way the CEPS software runs. The entries in this file will vary

from a pipeline to another. The outputs also differ between pipelines, as well as the total computational cost required to produce results. As follows, we detail each of the three electrophysiological pipelines.

- **Pipeline 1.1 (P1.1)** *Energy requirements for capture, from a preselected lead and adjusted geometrical and electrical contact parameters*. The goal of this pipeline is to generate a so-called Lapicque curve that indicates the limit of capture and non-capture domains in a diagram of intensity versus duration of the stimulation. This pipeline will involve computations on a virtual slab of healthy tissue, with a volume of blood above, around the lead. The geometry, in particular the implantation of the device in the tissue, will be fixed. Geometrical parameters of the lead such as the diameter or the inter-electrode distance will be decided by the user. Electric parameters that describe the component of the circuit that delivers current can be adjusted by the user as well.

- **Pipeline 1.2 (P1.2)** This pipeline is designed to account for the variability of the tissues where the lead is implanted. With several population parameters that the user will provide, a collection of pieces of tissue will be generated, with various levels of fibrosis. The output of this pipeline will be *statistics over the population of capture/non-capture and delivered energie*s. For this pipeline, the design of the lead and the electrical parameters will be the same for all simulations, but still selected by the user, like in pipeline 1.1.

- **Pipeline 1.3 (P1.3)** *Sensing*. This pipeline will be dedicated to computations of the signal that is sensed by the lead, either from regular spontaneous events, or from the response of the tissue after a pacing. The inputs of this pipeline will be the same as for pipeline P1.1. In this case, a larger portion of tissue is required, as the propagation of an action potential in the whole ventricle can be seen on the sensed signal. We will then use a schematic representation of the ventricles, as done by (Nielsen et al., 1991). In addition, several filtering parameters may be added in order to model the device.

In each of these pipelines, the parameters are numbers, or binary choices (i.e. boolean), that can be all gathered into text files. These inputs can then be passed to meshing software that generates the computational mesh, and to the electrophysiology solver CEPS.

The ionic models which are a key-component of the AP-propagation models were hard coded in CEPS with numerical data imported from the CellML repository. This implementation was done manually in order to fit into our software in a readable manner. It is therefore different from the exported CellML syntax, but it was done in such a way that it remains possible to adjust every single ionic parameter through the input text file of CEPS simulations.

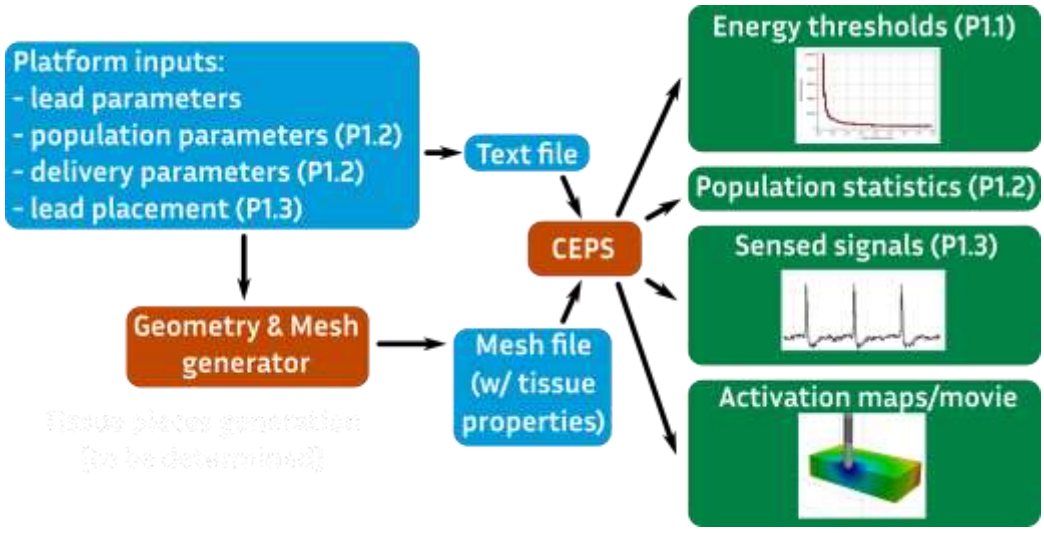

Figure 1: schematics of the input (blue), output (green) and numerical software (orange) in the electrophysiological pipelines P1.1 to P1.3.Input and output are specific to a pipeline when specified. Additional parameter for pipelines 1.2 and 1.3 are stated in brackets .

2.2 Mechanical Pipelines

The simulation of navigation and fatigue both rely on SOFA (Simulation Open Framework Architecture). However, each aspect involves different inputs and outputs, mainly because the implanted lead configuration obtained after the navigation simulation is used as a starting point for fatigue estimation. The corresponding global workflow is illustrated on Figure 2, and associated computational pipelines are described below.

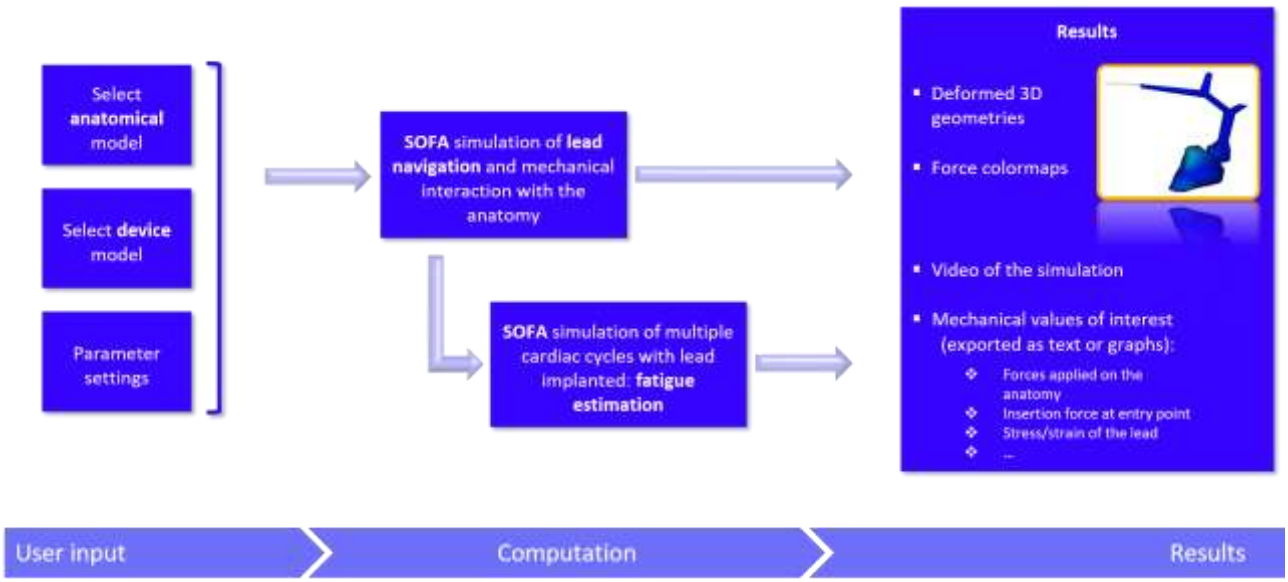

Figure 2: illustration of the numerical workflow for the mechanical simulation (navigation and fatigue estimation), in terms of user input, output, and software used for the computations.

- **Pipeline 2.1 (P2.1: simulation of navigation)** The simulation of navigation aims at modeling the insertion of a lead inside an anatomical structure consisting of the left subclavian vein, the left brachiocephalic vein, the superior vena cava, and the right atrium and ventricle. An important feature is that the anatomy follows a realistic beating motion during the insertion. The input data for the navigation simulation can be split into four categories, respectively relative to: the anatomical data, the device (lead and stylet), the navigation controls, and the simulation general settings.

  The anatomical data is passed directly to the simulation as a set of finite element meshed files (typical formats are OBJ or VTK, but Gmsh, Off, STL, XPS, STEP, BVH formats are also handled by SOFA). No mechanical parameter will be required to describe the behavior of the anatomy, for which only an approximated compliance model will be used, allowing to measure the forces applied by the lead during navigation.

  Regarding the device, the wire-like structure of the lead and the stylet will be approximated by 1D connected beam elements. Thanks to the reduced dimension of the corresponding model, a finite element mesh will be generated automatically in SOFA for both the lead and the stylet. Input parameters expected from the user will consist only of geometry features (length, cross-section shape and dimensions) and mechanical parameters describing the behavior of each object. All parameters will be provided in the form of a standardized text file, which will be processed internally in SOFA to build the corresponding simulation.

  Regarding the simulation setup, a standardized sequence of user actions needs to be provided as further input, either by direct user interactive control (e.g, keyboard/mouse) or by exploiting an automated approach (e.g., macro file).

  The last type of user input is related to the simulation general settings, regarding the existing tools implemented in SOFA.

  Two types of output will be provided by the simulation. The first category will be visual outputs, including 3D renderings of the simulated objects at the final step of the simulation and 3D colormaps of field variables of interest, such as force intensities at lead-anatomy interface or stresses and strains inside the lead. The second category will consist in mechanical data of interest, which will be exported either in the form of text files, or graphs.

- **Pipeline 2.2 (P2.2: estimation of fatigue)** The simulation of fatigue essentially consists in determining the stress level inside the pacemaker lead during one or a given number of heart cycles. From this information and additional experimental data (typically in the form of a Whöler curve), it is possible to estimate which parts of the lead are more prone to failure over a given amount of time/heart cycles.

  The two main inputs of the simulation of fatigue are a beating heart anatomical mesh, similar to the one used for the navigation simulation, and an implanted lead mesh. The fixation point of the lead on the anatomical mesh has also to be specified. In addition to these two meshes, the same set of geometry and mechanical parameters for the lead, as well as the simulation general settings, have to be provided.

  The simulation of fatigue is primarily intended to be run following the navigation simulation, as the estimation of fatigue is highly dependent on the final position of the lead in the

anatomy, as well as on the history of deformation the lead underwent while being navigated inside. In this context, most of the fatigue simulation inputs mentioned above would not have to be explicitly given by the user, but would simply be deduced from the navigation simulation. The dependency between both aspects of the mechanical simulation is discussed further in section V.

Outputs of the fatigue simulation will also be similar to the outputs of the navigation simulation. As before, visualization outputs will be provided with a 3D view of the deformed lead inside the anatomy, and 3D colormaps showing the stress levels inside the lead and the parts most prone to failure. Mechanical quantities of interest will also be exported in the form of text files or graphs.

3. Methodology

3.1 Electrophysiology Pipelines

Pacing and sensing simulations will be performed with the CEPS software, an open-source C++ parallel code (https://carmen.gitlabpages.inria.fr/ceps/), which solves the classical bidomain or monodomain equations, and incorporates ionic models obtained from the CellML repository. These equations describe the propagation of an action potential from a given stimulation (Potse et al., 2006). The parameters of these models are well known, and should not be directly tuned by the user of the cloud-based platform. Within CEPS, the transmembrane voltage and other state variables (of the ionic models) are computed using the Lagrange P1 finite element method on a simplicial mesh, coupled with time-stepping numerical schemes that were designed specifically for the cardiac evolution problems (Coudière et al., 2020). In addition to this model, specific equations account for the the pacing and sensing devices.

Firstly, the electronic circuit inside the canister linked to the electrodes has been fixed, based on designs from Microport CRM, that are considered standard among manufacturers for bradycardia leads. It will include parameters such as resistances, capacitances and durations, that allow for different shapes of the delivered pulses.

Secondly, we will propose a model of electrical contact between the electrodes and the tissue or blood, that accounts for significant physical phenomena, like electrode polarization, occurring in the vicinity of these regions. Several electrical properties of this model will be defined as standard inputs for the pipelines. The user will consequently be able to modify the electrode coating properties by changing these contact parameters.

The geometries of the lead will be generated from a base geometrical design with some elements to be tuned by the end user, like electrode width or inter-electrode distance. Then, meshing software tools will be required to generate the input meshes for CEPS.

In pipeline 1.2, the user will be able to provide a range of fibrosis level, as a finite set of minimum and maximum values, as an input for the statistical study provided by the pipeline.

In pipeline 1.3, time signals of the extracellular potential at the surface of the electrodes will be computed. The output time signals will be filtered to match the usual specifications of such leads. The user will be able to adjust some specifications of the filters.

3.2 Mechanical Pipelines

The mechanical aspects of the simulation (modeling navigation and fatigue of the pacemaker lead) rely on the open-source simulation software SOFA (www.sofa-framework.org). SOFA is a C++ library, mainly targeting the interactive physical simulation of interacting objects. Although it provides additional types of simulation, the framework is used primarily, in the context of the present pipeline, to solve a Lagrangian formulation of mechanical equations of motion, deformation, and interaction, describing the evolution of deformable solid continuums along time. Approximated solutions of the equations are computed using the finite element method (for spatial discretization) and numerical schemes (for time integration). As the software is conceived as much as possible in a modular way, it allows users to easily test several combinations of model discretization, mechanical behavior, collision handling, or time integration schemes, in order to get the best trade-off between precision and computational efficiency (depending on the considered application). A general description of the framework's possibilities can be found in (Faure et al., 2012).

In the context of UC1, the inputs for the simulation in SOFA consist in the description of the geometry and mechanical properties of the simulated objects: on the one hand the lead and stylet, and on the other hand the anatomical structure the lead is inserted in. The mesh files describing the geometries, as well as the text files containing the mechanical parameters (with additional simulation settings) are passed directly to SOFA to be parsed by internal tools. From this inputs, a simulation is built and run. The outputs, generally consisting of visualization data (videos, 3D meshes, colormaps), or mechanical quantities of interest (local forces, stress, strain, displacement) will be generated directly by SOFA during the simulation, and made available to export.

As the entirety of the lead has to be considered for navigation and fatigue, both the lead and the stylet are approximated in the simulation by connected beam elements, using a discrete Cosserat beam model (Renda et al., 2016). This approach allows to generate automatically a finite element mesh for both objects from basic properties of the lead and stylet. The inputs that are required from the user are therefore the length and section dimensions of the stylet and lead (considered as homogeneous), as well as mechanical properties obtained through standard mechanical testing (such as uniaxial tension or bending tests). All these properties are described locally and can vary lengthwise. We stress out that it is up to the user (typically a lead manufacturer) to provide the relevant data, corresponding to the simulated lead model.

Regarding the anatomical structure in which the insertion will be simulated, a choice will be given to the user among a few predefined models, considered as representative of what can be encountered in clinical practice. For the anatomy, it means different combinations of patient characteristics such as gender, age or pathology. Predefined meshes will be obtained by the segmentation of CT data available at CHU Bordeaux.

4. Use Case's Refined Pipelines for compatibility

4.1 Electrophysiology pipelines

4.1.1 Pipeline 1-1 (Energy requirements for capture)

In this pipeline, the cardiac geometry is a fixed simple rectangular wedge of tissue with blood. The mesh is generated with the open-source software Gmsh 4.0.4 (http://gmsh.info) and even regularized by the open-source software MMG (https://www.mmgtools.org). All other inputs are numbers.

Input

- *Choice among family of leads (i.e. base design, integer)*
- *Adjustable properties of the lead*
  - *Geometrical properties [floats]*
  - *Coating properties [floats]*

Output

- *Lapicque and charge thresholds curve for both leads [picture and csv file]*
- *Capture movie [mp4 file]*
- *3D map of activation times [vtk file]*

The Lapicque curve splits the duration-voltage plane into a region with capture and a region without capture. Capture is determined by the relative volume of cardiac tissue that has depolarized after a fixed period of 100 ms. A capture movie is an example propagation of action potential in a case of capture. The activation time map is the spatial map of the time of arrival of the action potential in case of capture.

4.1.2 Pipeline 1-2 (variability of the tissue characteristics)

This pipeline shares its first two inputs with P1.2. The pacing duration and voltage are fixed input parameters, while a population of tissues is generated according to the corresponding input parameters.

Input

- *Choice among family of leads (i.e. base design, integer)*
- *Adjustable properties of the lead*
  - *Geometrical properties [floats]*
  - *Coating properties [floats]*
- *Pacing characteristics: voltage, duration [floats]*
- *Fibrosis parameters: fixed specification of geometrical regions [3 floats], and ranges of intensity level of fibrosis [6 float]*

The geometry will be split into an epicardial layer which width is specified by the end user (1 float), an ellipsoid around the electrode insertion point which lengths are given by the end user (2 floats: depth and endocardial radius), and the remaining computational domain. The overall fibrosis in the complete domain and the additional fibrosis in each subdomain (epicardial and electrode) are

modeled by scaling down the conductivity coefficients by a fixed number (the level of fibrosis) within a given range.

Output

- *Percentage of capture among population [float]*
- *3D maps of activation time [vtk file] (few, optional)*
- *Capture movie [mp4 file] (few, optional)*

The first output is computed as the number of cases with capture over the whole population of possible tissues. The other two outputs are like in pipeline 1.1.

4.1.3 Pipeline 1.3 (sensing)

This pipeline still shares its first two inputs with pipelines 1.1 and 1.2, but contains additional specification that describes the location and orientation of the leads. A complete cardiac ventricular anatomical mesh is used in this pipeline, in order for the model to represent both far field and local signals.

Input:

- *Choice among family of leads (i.e. base design, integer)*
- *Adjustable properties of the lead*
  - *Geometrical properties [floats]*
  - *Coating properties [floats]*
  - *Orientation of the lead w/ respect to the tissue [2 floats]*
  - *Choose the location of the lead (among several predefined ones) [integer]*
  - *Filtering parameters [floats]*

The filtering parameters are frequencies of low and high pass filters commonly used.

Output:

- *Time signals for both leads [plots, csv file], extracted amplitudes [floats], for spontaneous events*
- *Time signals for both leads [plots, csv file], extracted amplitudes [floats], post pacing*

4.2 Mechanical pipelines

4.2.1 Pipeline 2-1 (simulation of the lead navigation)

Input

- *Set of anatomical mesh files (representing the evolution of a single anatomy during a heart cycle) [format=.obj, .vtk, .gmsh (not exhaustive)]*
- *Type of lead (e.g.: bradycardia, ...) [choice among a library]*
- *Geometry properties of the lead [format= standardized .txt]*
  - *Length [float]*
  - *Number of segments [integer]*
  - *Length of each segment [float]*
  - *Cross-section shape (among a list of options : circle, hollow circle, rectangle)*
  - *Cross-section dimensions of each segment [float]*
- *Mechanical properties of the lead [format= standardized .txt]*

  - *Young modulus (for each segment) [float]*
  - *Poisson ratio (for each segment) [float]*
  - *Yield stress (for each segment) [float]*
  - *Plastic modulus (for each segment) [float]*
  - *Coefficient for mixed linear hardening (in [0, 1]) [float]*
  - *Material density (entire lead) [float]*

- *Geometry properties of the stylet [format= standardized .txt]*
  - *Length [float]*
  - *Number of segments [integer]*
  - *Length of each segment [float]*
  - *Cross-section shape*
  - *Cross-section dimensions (for each segment) [float]*

- *Mechanical properties of the stylet (as an homogeneous object) [format= standardized .txt]*
  - *Young modulus [float]*
  - *Poisson ratio [float]*
  - *Yield stress [float]*
  - *Plastic modulus [float]*
  - *Coefficient for mixed linear hardening (in [0, 1]) [float]*
  - *Material density (entire stylet) [float]*

- *Simulation general settings*
  - *Time step [format=float]*
  - *Time integration scheme [format=choice among a drop-down list]*
  - *Linear solver [format=choice among a drop-down list]*

Output

- *Visualization of simulated objects [format = .obj file]*
- *3D colormaps [format = .vtk, .obj, .png/.jpg]*
  - *Force intensities on the anatomy*
  - *Stress/strain inside the lead and stylet*
- *Video of the simulation [format = .mp4]*
- *Generic mechanical quantities of interest [standardized .txt or .xls files], e.g.:*
  - *Matrix of force intensity on each node of the anatomical mesh [float]*
  - *Matrix of stress/strain on specified points inside the lead [float]*
  - *...*
- *Graphs representing the evolution of quantities along time [format = .png, .xls]*
  - *Force intensity on a specified node of the anatomy [float]*
  - *Stress/strain at given places inside the lead [float]*
  - *Force intensity at the entry point [float]*
- *Index of the fixation point on the anatomy [format = .txt]*

4.2.2 Pipeline 2-2 (fatigue estimation)

Input

- *Same input as Pipeline 2-1 for the lead and anatomy, no stylet (cf: section II)*
  - *Can be deduced directly from Pipeline 2-1 outputs (no need for user action)*
- *Fixation point index on the anatomy [format = .txt]*
  - *Can be deduced directly from Pipeline 2-1 outputs (no need for user action)*
- *Experimental data (Whöler curve) [format = .txt]*

Output

- *Visualization of simulated objects [format = .obj file]*
- *3D colormaps [format = .vtk, .obj, .png/.jpg]*
  - *Stress/strain inside the lead*
  - *Positions identified with higher risk of failure*
- *Video of the simulation [format = .mp4]*
- *Generic mechanical quantities of interest [standardized .txt or .xls files], e.g.:*
  - *Matrix of stress/strain on specified points inside the lead*
- *Graphs representing the evolution of quantities along time [format = .png, .xls]*
- *Stress/strain on specific positions inside the lead*
  - *Force intensity at fixation points*

5. Discussion and conclusion

UC1 cloud-based platform will be designed to perform in-silico trials to quantify and evaluate pacemaker device efficacy and safety. from both the mechanical and electrophysiological points of view. To this aim, this document reports in particular the methodology used to build computational pipelines of interest, and proposes standard inputs and outputs for these pipelines.

Even though the two biophysical domains are considered separated, UC1 involves complex computational pipelines that require integration of multi-modal data from heterogeneous sources, such as 3D computational meshes of convoluted geometries or fibrosis parameters. It also involves sophisticated multi-physics simulations as well as the use of advanced tools (e.g., interactivity). In the last decades, cardiac computational modeling has become pivotal to evaluate the majority of devices, especially aiding their design or assessing their performance in patient-specific cases. However, as long as pacemakers are concerned, we could mention very few examples for mechanics or pacing investigation (Zhao et al., 2011(1), Zhao et al., 2011(2)) and one for defibrillation (Connolly et al., 2019), respectively, but no standardization effort has been made, at least to our knowledge. The platform developed in SimCardioTest will go beyond the state-of-the-art, trying to fill the gap where consensus on standards is still missing, implementing for the first time a modular cloud-based tool with standardized input/output formats and model structures, guaranteeing seamless data exchange.

Concerning the electrophysiological computational workflow, meshes will be generated depending on the geometrical input parameters provided by the user. This may lead to poor quality meshes or situation in which no mesh can be built. A technical solution will be investigated to deal with these cases on the cloud-based platform.

During the elaboration of the electrophysiology pipelines, we considered the possibility for the user to upload directly CAD-files describing the lead geometry, and the description of the pacing and sensing electronic circuits in a standardized file format. This possibility was discarded because it would have greatly complicated the models, and created too many sources of failure of the pipelines. For instance, a custom lead geometry would have implied a specific format of file, in which the user would have identified the surfaces of the anode and cathode, and from which both meshing software and CEPS would have been able to read.

We also choose to run computations on simplified cardiac geometries, which may appear as a limitation of our approach. Anyway, we believe that the triggering of capture is a local phenomenon, so that we have to focus only on a small tissue sample that surrounds the electrodes. Hence, the simplified geometries are relevant. Our rationale is that the electrode surface, the inter-electrode distance, the coating properties are more important factors of failure to capture, together with the local fibrosis of the tissue in the vicinity of the electrodes. Hence our simplified cardiac geometries will not account for heterogeneity, except for fibrosis, that will be distributed in a fixed manner (though adjustable).

Regarding the mechanical computational workflow, the main advantages consist in the numerical tool and its high modularity. Indeed, even though it is still an open question within the UC1 pipeline technical development on the platform, SOFA could allow for a fully online interactive user interface, thus closer to reality. Of course, we strongly believe that validation perspective will play a key role in defining what the navigation control final solution will be. Moreover, the modular design could allow future extensions to be implemented as seamlessly as possible. A good example is the fact that the simulation of navigation and the simulation of fatigue can be considered independently from one another, potentially allowing to only run lead navigation simulation whether fatigue estimation is out of interest. Other long-term examples are discussed in the last paragraph below.

Regarding pipeline inputs, whether the user is given the possibility to import a new anatomy for the navigation simulation, he would possibly face an orientation problem for the anatomy position with respect to the lead. A solution would be provided to accordingly position the numerical domains at the input in the simulation, co-registering the corresponding coordinate reference systems.

Overall, the modularity of the pipelines and the standardization effort made to describe the communication between, and within pipelines will make easier perspectives like chaining the two workflows, or other long-term perspectives. Chaining the workflows is relevant since the electrical computational model would benefit from an accurate description of the lead implantation obtained through a standardized process. However, it would require different types of mechanical modeling with a much more precise simulation of the tip of the lead. It was estimated not to be currently feasible. Other long-term perspectives may include other clinical scenarios, such as different lead implantation sites or types of lead.

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