EU Horizon 2020 Research & Innovation Program
Digital transformation in Health and Care
SC1-DTH-06-2020
Grant Agreement No. 101016496

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

Technical Report

Report on global standardisation

Work Package 1 (WP 1)
Model Standardisation & Interoperability

Task Lead: Simula, Norway
WP Lead: Simula, Norway

PUBLIC

DELIVERABLE INFORMATION

Deliverable number	D1.2
Deliverable title	Report on global standardisation
Description	Specification document on the chosen formalism for standardized modelling and personalization.
Lead authors	Hermenegild Arevalo, Simula
Contributors	Michele Barbier, Inria, Alessia Baretta, IST
Due date	M18
Submission date	1 July 2022
Comments	

Document history			
Date	**Version**	**Author(s)**	**Comments**
29/06/2022	V1	H. Arevalo	Feedback Alessia Baretta
30/06/2022	V2	H. Arevalo	Final
15/11/2022	V3	M. Barbier	Format editing

Table of Contents

EXECUTIVE SUMMARY

This report defines the global standardisation that will be implemented in the SimCardioTest cloud-based platform. This report details the common input and output formats between the different Use Cases that will be standardised to facilitate interaction between the different workflows.

1. Introduction

The main goal of WP 1 is to develop a standardised description of in-silico models that will be implemented in the SimCardioTest platform. This effort is necessary as the platform has the ambitious goal of being used to address several questions of interests with respect to the performance of different cardiac devices as well as pharmacological safety and efficacy. Since a computationally efficient multiscale and multiphysics cardiac simulator does not yet exist, the platform will instead implement different workflows that utilise mature software that simulates different aspects of cardiac function and which can be used to address the three different Use Cases that we aim to investigate.

The software that will be implemented in the SimCardioTest platform is being independently developed by different members of the consortium. Thus, the first step in creating a smooth workflow is to standardise the inputs and outputs such that the different modules can interact with each other. This need has been initially introduced in Deliverable 1.1 (M6) in which the consortium members filled out surveys with information on the technical requirements of the software that will be implemented in the platform. This initial survey was followed by regular virtual meetings throughout the year among the developers of the different Use Cases to define the specific question of interest, design the workflow and homogenise the inputs/outputs of the different software components within the workflow. Additionally, a workshop with handson on standardisation was held in person on October 2021 at INRIA Sophia Antipolis, to facilitate the standardisation process.

During the workshop, the consortium agreed that within the context of this project, standardisation implies the use of common processes, standards, and language for data input/output and model formats for a better integration in the platform. The standardisation efforts will ensure the creation of a user-friendly interface and assure compatibility throughout the different states of the pipeline. Additionally, a standardised description of the models will facilitate the interoperability of the different software and allow for more complex in-silico trials that go beyond the Use Cases described in the original proposal.

The efforts resulted in Deliverable 2.1, 3.1, and 4.1 (M12) which reported the standardised models and workflows that will be implemented within the three Use Cases. In the current report, we will summarise the findings in these reports and identify different aspects of the workflow that can be globally standardised throughout the entire platform. This report will also identify different connection nodes that can be used to link the different workflows. These links expand on the utility of the platform by potentially creating new workflows that can address different questions of interest.

2. Summary of Use Case Workflows

The following section provide summaries for the different use case workflows that will be implemented in the SimCardioTest platform. More detailed descriptions of the workflow are provided in Deliverables 2.1, 3.1, and 4.1.

1. Use Case 1 – Pacing Leads and Catheters

The aim of UC1 is to provide a standardized approach for in-silico evaluation of the electrical and mechanical performance of pacing leads. To achieve this, two different workflows are under development. The first workflow (Fig 1) will be used to investigate the electrophysiological response of cardiac tissue to different lead geometries and placements. The workflow starts with a parameter file that contains user specified (lead geometry, placement, tissue geometry, tissue fibrosis composition, etc.) as well as built in variables (tissue electrical properties such as conductivities, different populations of built-in geometries, etc.) that will be implemented in the simulations. The specified parameters will then be used to generate finite element models of the lead and tissue as well as parametrise the action potential model that will be implemented in the in-silico trial. This set of input will then be fed to the CEPS software (Cardiac electrophysiology solver) which is a bidomain solver which will then output variables of interest such energy thresholds, lead sensing, statistics over population capture vs non-capture, etc.

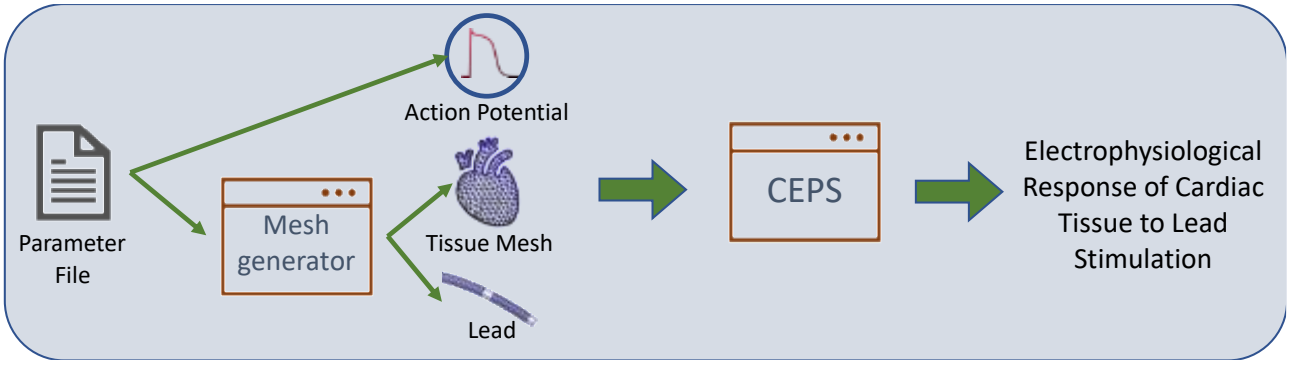

Figure 1: Workflow for UC1, electrophysiology simulation scenario

The second workflow (Fig 2) will investigate the mechanical response to lead placement. Similar to the first UC1 workflow, a parameter file will be used to collect user-defined and built variables that will define different mechanical properties associated with the heart and the lead. The user will then be able to upload cardiac mesh as well as the device model. In this workflow, the simulator SOFA (Simulation Open Framework Architecture) will be used to simulate mechanical interactions between the cardiac mesh and the device model. Realistic lead navigation through the cardiac geometry will be simulated as well fatigue response of the lead after implantation.

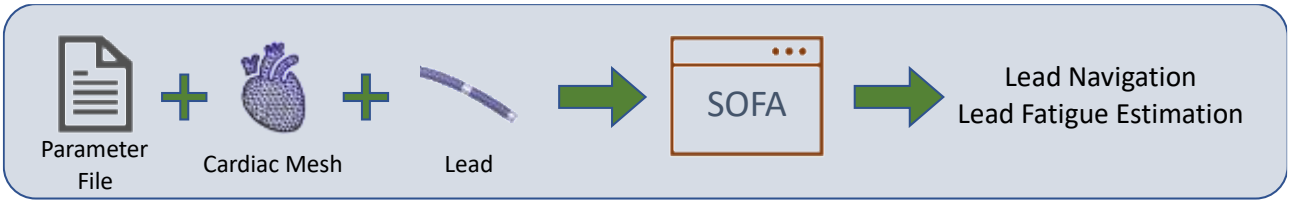

Figure 2: Workflow for UC1, mechanical simulation scenario

2. UC2 – Left Atrial Appendage Occluders (LAAO)

The main goal of UC2 is to generate in-silico personalised haemodynamic indices of left atrial geometries, complementing their morphological analysis, to identify the risk of thrombus formation in atrial fibrillation patients, improve patient selection for the implantation of left atrial appendage occluders (LAAO) and optimise their settings (e.g., size, positioning). In deliverable 3.1, we present 2 different scenarios that will be investigated to achieve this goal. The first one relies on a library of fluid simulations on a large population of left atria (LA) which will be used to find the closest case to a new patient LA geometry. This is computationally efficient as it does not require costly CFD simulations.

In this report we will focus on the more computationally demanding scenario which will require de novo CFD simulations. Figure 3 illustrates the workflow for this scenario. Users will be able to choose from a library of already generated LA geometries to investigate new LAAO device geometries/properties that can be uploaded by the user. Fluid flow through the combined device geometry/parameters and LA appendage geometry will then be simulated by using either the commercially-developed CFD solver ANSYS or the open source software OASIS The simulation results will then be analysed to determine the likelihood of thrombus formation around the device.

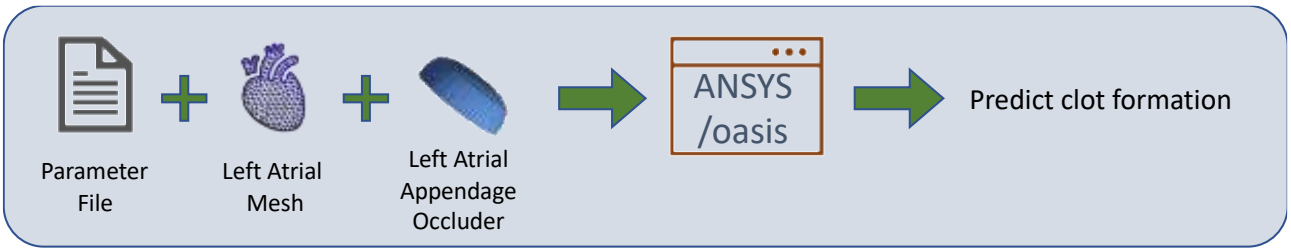

Figure 3: Workflow for UC2, fluid simulations

3. UC3 – Drug Safety and Efficacy

The goal of UC3 is to investigate the safety and efficacy of drugs in different populations. Figure 4 demonstrates the general workflow of UC3. Initially, the user can choose from pre-defined sets of populations and known drug data which will be encoded in a parameter file. This will then be passed on to the ExactCure web-based platform which will be used to simulate different blood concentration curves. This information will then be used to parametrise the population of action potential models to simulate drug effect at the cellular level. Finally, these action potential models will then be implemented on 3D models of the heart that will then be implemented in the open source electromechanical simulator simcardems to calculate different biomarkers for drug safety and efficacy.

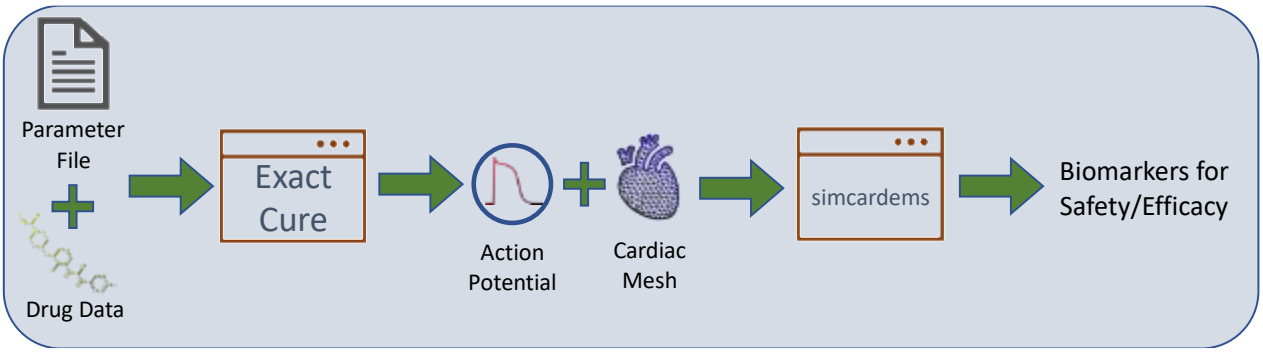

Figure 4: Workflow for UC3, drug dosing, cellular electrophysiological response, and 3D electromechanical response

3. Standardised Descriptions of Global Inputs

In the workflows defined above, several components appear in multiple workflows. In this section we describe the standard format for these components.

Parameter files – These are text files that include all the parameters that can be chosen or modified by the user as well as some pre-defined parameters. These can range from solution type, input mesh, variables defining action potential or tissue properties, etc. Variable names will be standardised within each workflow.

Mesh file – All Use Cases utilise some form of cardiac mesh in their implementation. The resolution and geometry as well as type of finite element varies among the Use Cases. They can range from simple tissue blocks such as those used in EP workflow of UC1 or larger anatomically accurate meshes suitable for mechanical simulations used in the mechanical workflow of UC1. The resolution of the meshes also will differ depending on the requirements of each simulator for computational tractability and numerical accuracy. These can range from fine meshes in the order of microns needed for electrophysiological models in UC3 to coarser meshes in the order of mm for the mechanical simulations performed in simcardems.

To facilitate compatibility of the meshes used among the different workflows, we will utilise standard formats of mesh definition such as .vtk or .vtu or .msh. These formats are well used in the modelling community and the software that will be implemented in each workflow can already support several of these file formats. Additionally, tools such gmsh can be used to convert any mesh into another format that will be required for the workflow. Gmsh can also be used to remesh any mesh so that it satisfies the resolution and element type requirements needed by each software.

Action potential model – Use Cases 1 and 3 both utilise action potential models to represent the cellular electrophysiology of the myocyte. In both cases, we take advantage in current standardisation efforts in defining electrophysiological models spearheaded by the CellML Project. The base action potential models will be downloaded from the CellML repository to assure the compatibility between the models. In both UCs 1 and 3, the conductances and other variables defined within the action potential model can be modified via the parameter file in order to represent different tissue types as well as to simulate drug effects.

4. Potential Future Workflows

The overview presented in the previous sections highlight the potential nodes that can be used to connect the different workflows. With the standardised description of cardiac mesh files, we can easily utilise meshes generated for one workflow in another workflow. For example, the population of left atrial meshes generated in UC2 can be converted into finer electrophysiological meshes in UC3 and allow for the investigation of drug effects in the atria.

Figure 5 presents another potential in-silico trial that can be performed by exploiting commonalities among the workflows. In this scenario, pharmacokinetic information on certain drugs calculated from UC3 can be combined with novel pacing lead designs in UC1 to investigate the role of drug effects on tissue capture. This workflow could help identify the combination of drug, lead design, and tissue substrate that could lead to potential failure of pacing leads to stimulate the tissue.

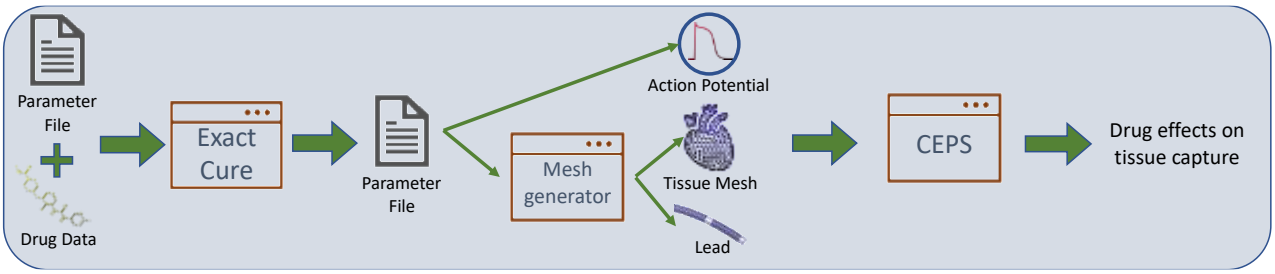

Figure 5: Potential workflow investigating drug-device interaction

5. Discussion and Conclusion

The ambition of the SimCardioTest project is to develop a web-based platform that can be used to perform in-silico clinical trials of cardiac devices and drugs. Since no single software currently exist that can achieve the multiscale and multiphysics requirements of the platform, we have embarked on a strategy of using a modular approach in the creation of the platform. Each of the modules comprise of different simulators developed in different institutions and range from open-source software to proprietary commercial software.

The heterogeneous composition of the different workflows necessitated a coordinated effort among the consortium partners to standardise data formats to facilitate data exchange between the different workflow components. This report summarises the results of the collective efforts of the consortium in achieving a global standardisation process towards creating the platform. We have started by defining the workflow within each Use Case and settling on a standardised format of exchanging data between different software components. With this in place, a global overview of the different Use Case workflows helped identify nodes of interoperability that can be used to combine different workflows which can then be used to perform more complex in-silico trials. The standardisation and interoperability efforts that have been incorporated into this process will ensure that the utility of the platform can grow beyond the initial objectives presented in the project.

This project SimCardioTest received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101016496