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

Technical Report

Report on the standardised models for use case 3

Work Package 4 (WP 4)

Use case 3: Drug efficacy & cardiotoxicity

Task Lead: UPV, Spain

WP Lead: UPV, Spain

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EXECUTIVE SUMMARY

This report defines the general use case 3 (UC3) workflow to be implemented in the cloud-based platform, where the in-silico trials for drug efficacy and safety will be run.

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

1. Introduction

The cloud-based platform to perform in-silico clinical trials on drug safety and efficacy is based on complex workflows that require the integration of different software and simulation environments. Throughout the different stages of the workflow, input and output data need to be provided in a standardised format.

These needs of standardisation have been initially introduced in Deliverable 1.1 (M 6), summarizing the answers to the survey performed to the partners on Use Case 3 pipeline and the technical requirements for the different software used in the present use case.

Furthermore, a specific workshop on standardisation was organised in October 2021 (INRIA, Sophia Antipolis) for the members of the consortium, where general discussions and work sessions in small work groups for each use case took place. Mainly during this workshop, but also in previous and posterior meetings, the members of the consortium agreed on how standardisation had to be tackled in SimCardioTest project and these ideas are described in detail in the present deliverable and specified for Use Case 3: drug efficacy and cardiotoxicity.

For Use Case 3 in SimCardioTest, a standardised approach for in-silico clinical trials on drug safety and efficacy is given by creating an integrated and secure cloud-based platform standardising & bridging model simulations, in-silico trials, and certification support.

Indeed, there is a crucial need to standardise and homogenise the existing cardiac modeling and simulation tools before entering the regulatory pathway. The standardisation 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.

Standarisation in the present document implies the use of common processes, standards, and language for data input/output and model formats for a better integration in the platform. This document also includes the definition and standardisation 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 standardised description of the models is provided to facilitate the interoperability of the different modelling software that will allow for more complex in-silico trials. On the other hand, standardisation of all different model inputs & outputs (including units, formats, model descriptions, etc.) will allow the creation of a user-friendly interface and assure compatibility throughout the different stages of the pipeline.

With regard to pharmacokinetic modelling in the industry scenario, fully accepted standards do not really exist, even though some well accepted commercial modeling softwares have their own standards (i.e. SimulX/Monolix, NONMEM, Phoenix softwares). In academia, some tentative standards exist, such as PharmaML, but to the best of our knowledge none of them is widely used.

With regard to electrophysiological models, in the last 20 years the scientific community has done big efforts to build centralized databases to store mathematical models of biological systems in standard formats to make 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 modelling, allows modular construction of models, and is considered as a community standard. Whole-cell 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 SimCardioTest we use the modular structure of cellular models, in MATLAB, based on CellML structure. In 3D simulations, the cell model is modular, but requires conversion from CellML structure to a suitable format for the solver in FEniCS. The in-house developed tool Gotran (General ODE Translator; Hake et al., 2021) generates ODE system definitions in various software languages and structures, including MATLAB, C, C++ and Python. This converter tool enables automatic conversion of cell models from repositories such as CellML, sustaining already implemented model structure and standardisation.

Since CiPA initiative included in-silico drug test as a crucial pillar in drug safety assessment, there have been inter-sectorial collaborations to define standards required for the qualification of electrophysiological models and simulations (Viceconti et al., 2021). Some examples of developed platforms at the cellular level are Virtual Assay (Passini et al. 2017) and APpredict (Williams & Mirams 2015).
In industry and academia, the most widely used modeling and simulation softwares for pharmacokinetic simulations are SimulX/Monolix, NONMEM, Phoenix softwares. They are mainly used by pharmacometrician involved in model development.

The standardised cloud-based platform described in the present document will help tackle the question of whether marketed drugs are safe and effective in the same way for adult men or women who are healthy or have a cardiac disease, considering different populations (gender/pathology).
The in-silico trial platform will be designed for pharmaceutical companies as well as regulatory bodies to assess cardiac safety and efficacy of already marketed drugs.
The platform will enable the user to select a specific drug with its dose, administered to a certain population that includes biological variation and can vary in gender and disease state. The first outcome obtained from PK simulations will be the time course of free plasma concentration. Then the user will be able to assess the effects of this concentration of the drug on a population of cells (healthy or diseased, women or men, young or old). Cellular simulations will provide specific biomarkers, which will assess the safety of this drug or its efficacy under a specific diseased situation. This assessment can be further explored in 3D atrial or ventricular electromechanical simulations through additional biomarkers.

2. Description of UC 3's pipeline objective and constraints

The general pipeline to build UC3 is depicted in Figure 1. The main objective is to design a workflow to be implemented in a cloud-based platform to perform in-silico clinical trials on drug safety and efficacy.
Initially, population and drug data (input dataset 1) will be provided to EXC models to simulate the time-course of the effective plasmatic concentration of the drug. The derived output, i.e. a specific plasmatic concentration will be the input to the cellular electrophysiological (EP) and electromechanical (EM) models built by UPV. These models will be selected according to specific population and drug data (input dataset 2). On the other hand, 3D simulations can be performed using 3D ventricular or atrial EP and EM models, selected according to population and drug data

inputs (input dataset 2). Populations for 3D simulations are determined by populations and drug data inputs (input dataset 2) as well as output from the 0D model. The output of these simulations will allow to compute selective biomarkers which will be crucial to assess the efficacy and/or safety of the drug.

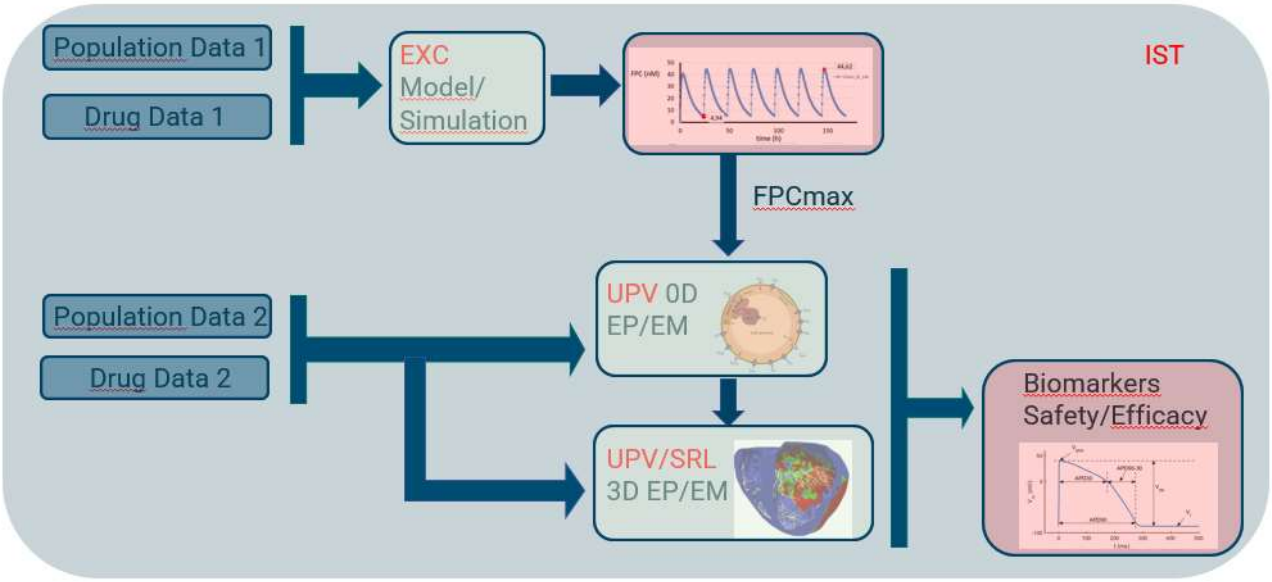

Figure 1: General workflow to perform in-silico clinical trials on drug efficacy and safety on the cloud-based platform. Exactcure (EXC) will be responsible for building pharmacokinetic drug models, Universitat Politècnica de València (UPV) for cellular and 3D electrophysiological (EP) models and electromechanical (EM) models in collaboration with Simula (SRL). In Silico Trials (IST) will be responsible for the cloud-based platform.

The workflow to perform in-silico clinical trials for drug safety and efficacy consists of 3 parts. The first part will simulate drug pharmacokinetics, the second part will consider populations of cellular models (0D), whereas the third part will consider populations of 3D models.

In the following sections, the detailed methodology for the three parts of the workflow will be described, as well as the standardised formats for inputs, outputs and the different models used. The technical requirements will also be defined to set the basis of the cloud-based platform.

3. Methodology

The cloud-based platform integrates 3 interacting parts where standardised inputs and outputs need to be defined. This section briefly describes the methodology used to obtain and define the inputs and outputs, as well as the methodology followed to run the simulations.

The simulation models considered in the web-based platform have been built according to experimental and clinical data.
Firstly, PK models need to be fitted to the PK parameters extracted from blood samples and clinical studies driven on different populations with specific features (weight, age, gender, comorbidities, etc.) and drugs.

Secondly, to build electrophysiological cellular models, data on experiments of ion channel function need to be available, and are extracted from the literature, as well as the effect of drugs on the different ion channels. For instance, IC50 values will be extracted from databases, such as DrugBank, DailyMed, or PubChem, or the scientific literature, whereas the concentration of the drug will be taken from the output of PK simulations.

Finally, the meshes used in 3D models need to be fitted to anatomical data extracted from MRI or TAC images, whereas the electrophysiological activity is based on the previous defined cellular models, and the mechanical activity needs to be fitted to echocardiographic measurements.
Once the models are formulated, they need to be validated and calibrated against other experimental and clinical data, mainly the output biomarkers of each model must be within experimental and clinical ranges found in the literature describing clinical and experimental studies.

Because several models will be considered in the cloud-based platform to run simulations, the specific data on population and drug need to be indicated to select the corresponding model. These input data need to be standardised as detailed in the following section.

Then the simulation will be run using the software indicated in each of the three parts of the workflow. The platform will redirect the simulation order the server where the software is allocated (PK simulations) or the software can be executed within the platform (cellular and 3D simulations).
Once the simulation ends, the output is processed and computed as specific biomarkers which will be available to the user to assess the efficacy or safety of the selected drug under specific conditions (normal conditions or disease) and population (age/gender).

4. Use Case's Refined Pipeline for compatibility

4.1 Part 1 in the pipeline

Figure 2 describes part I in the pipeline, which represents the workflow followed to perform pharmacokinetic simulations.

Figure 2: Description of the first part of the general workflow: pharmacokinetic simulations to assess the time course of plasmatic drug concentration.

Two important preliminary remarks must be formulated:

- When dealing with different marketed specialties of the same molecule, the end-user can be interested in either simulating the molecule effect or the specialty effect rather than the

underlying molecule one. Depending on what is preferred, input data preprocessing may be considered accordingly. For the sake of simplicity in the document we assume that marketed specialty is preferred.

- The global ambition is to address the simulation of a large set of drugs of interest. Each drug has its own PK model and each model must be calibrated with its own set of covariates that can differ from model to model. Prior to PK model calibration and simulation, the relevant covariates set must be retrieved together with its standard units.

Input data:

All input data are encoded in json formats and must be requested from ExactCure Partner API (aka PAPI).

- Drug data 1: route (i.e. oral, intravenous, etc.), formulation (ie. pill, perfusion), dose features (unit quantity for a pill, unit quantity intake time for a perfusion, etc.), frequency (in case of recurrent intake), and time horizon for prescription (start/end dates).
- Population data 1: PK model covariates together with their relevant units.

Model/simulation:

Model management, calibration and simulation is performed under ExactCure platform directly. Requested inputs and outputs are managed by PAPI.

Output data:

The output data correspond to the simulated blood concentration curve (time points and concentration values together with their respective units). All data are encoded in json formats and are provided by PAPI.

4.2 Part 2 in the pipeline

The objective of 0D electrophysiological (EP) and electromechanical (EM) simulations is to assess drug effects on population of cells. Parameters in the cellular model are varied to represent population variation per gender, age, and pathology. 0D EP and EM simulations enable the assessment of drug safety and efficacy on cardiac electrophysiology, as well as contraction.

Both the electrophysiological and mechanical models are programmed in MATLAB and the ode15s solver is used for the numerical computation. Simulations of a single cellular model only can run on one processor but computation time is acceptable. However, the simulation of a population of models, which is more time consuming, can be parallelised on multiple processors to reduce runtime.

Inputs and outputs have been adapted to improve interaction within the platform, and although there are multiple settings that the user can select and modify, default values facilitate the use for specific predefined purposes.

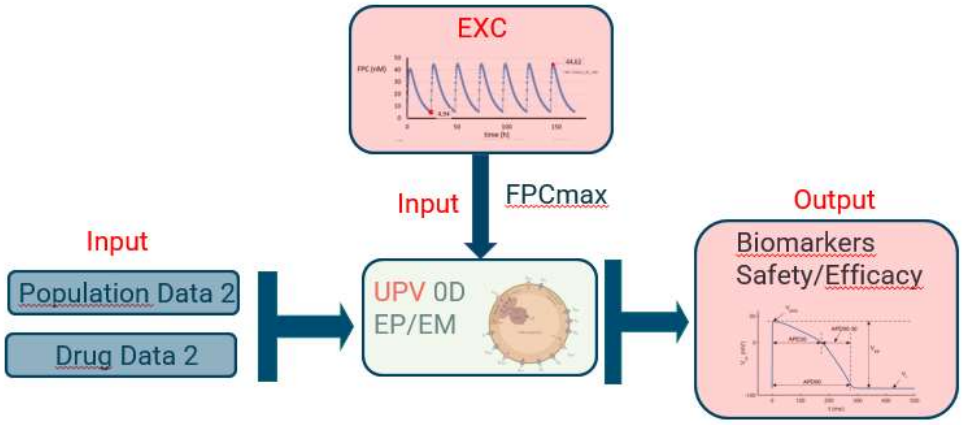

Figure 3: Description of the second part of the general workflow: cellular electrophysiological and electromechanical simulations to assess drug safety and efficacy.

Input data:

Population data 2:
The population of cellular models has to be selected and the following data are required:
Age: Adult/child
Gender: Women/men
Conditions: healthy/heart failure/atrial fibrillation/infarction/ischemia/mutation
Analysis: EP/EM
Sample: baseline model/Population of models
Drug data 2:
Name of the drug
IC50 for the different channels (tables)
H (table)
Drug concentration:
As indicated in the workflow, the free plasmatic concentration used in the simulations will be the output from EXC PK simulation.

Standardised Input data:
- Sex [integer, (0,1)]
- Disease [integer, (0,1)]
- Population_models [integer, (0,1)]
- Mature [integer]
- Drug_list [file, format=csv]
    - header (text, text): 'drug_id', 'drug_concentration_nM'
    - lines (integer,float)
- Drug_ic50 [file, format=csv], filename is passed as text
    - header (text, text, text, text, text, text): 'drug_id', 'drug_name', 'IC50_IKr', 'IC50_IKs', 'IC50_Ito', 'IC50_IK1', 'IC50_ICaL', 'IC50_INaL'
    - Lines (integer, text, float, float, float, float, float, float)

Model/Simulation:
Simulation protocol: number of pulses, Basic cycle length.
Software: MATLAB
Platform: cloud-based IST platform

Output data:
For EP simulations: Time course of membrane potential (Vm), Ion currents and Calcium transient.
For EM simulations: Time course of membrane potential (Vm), Ion currents, Calcium transient and active force (Ta).
Calculation of biomarkers:
Files.m will be available to compute biomarkers using the simulation outputs:
APD, triangulation, Qnet, Ca2+ features, Ta, etc.

Standardised Output data:
EP simulations:

- Simulation files [file, format=csv] named 'Sim_1.csv' to 'Sim_823.csv' (if Population_models = 1) or only one file named 'Sim_1.csv' (if Population_models = 0)
    - Header (text, text, text, text, text, text, text, text, text): 'Time', 'Vm', 'Cai', 'IKr', 'IKs', 'Ito', 'IK1, 'ICaL', 'INaL'
    - Lines (float, float, float, float, float, float, float, float, float)
- Biomarker files

EM simulations (differences with prior output list are marked in **bold**):

- Simulation files [file, format=csv] named 'Sim_1.csv' to 'Sim_823.csv' (if Population_models = 1) or only one file named 'Sim_1.csv' (if Population_models = 0)
    - Header (text, text, text, text, text, text, text, text, text, text): 'Time', 'Vm', 'Cai', 'IKr', 'IKs', 'Ito', 'IK1, 'ICaL', 'INaL', **'Ta'**
    - Lines (float, float, float, float, float, float, float, float, float, **float**)
- Biomarker files

4.3 Part 3 in the pipeline

The objective of 3D electrophysiological and electromechanics simulations is to assess drug effects on a tissue slab. Parameters in the tissue are tailored at the cell and tissue level to represent population variation per gender and disease state. 3D EP tissue simulations enable assessment of drug safety on cardiac electrophysiology, whereas 3D EM simulations assess effects on contraction as well.

The electromechanics solver SimCardEMS is developed to simulate EP, mechanics and their bidirectional feedback. The solver is scalable and can run in parallel on multiple processors to reduce runtime. Simulations are adjustable by a large number of settings regarding the EM cell model, tissue parameters and analysis, but easy in use for pre-defined purposes due to default values.

The simulations run on an academic platform as a Python package, with in-/output consistent with communication within the in-silico trials cloud platform. This enables easy implementation in the

cloud service, with options to control software and dependency versions in a virtual machine or image.

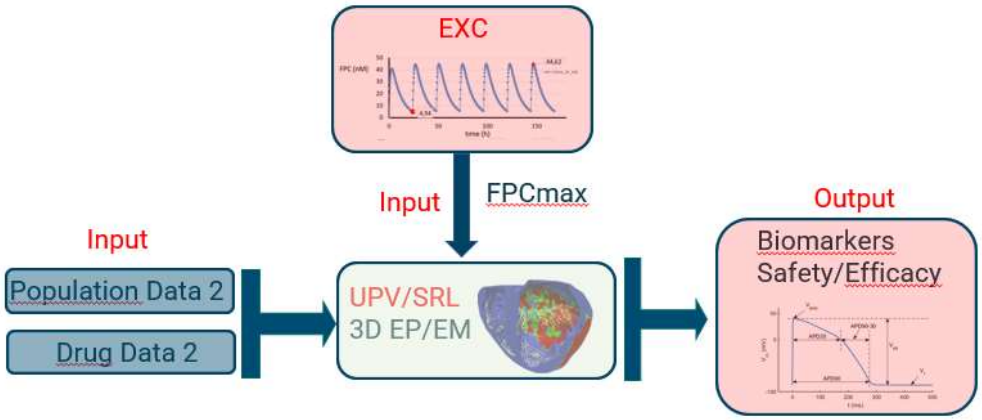

Figure 4: Description of the third part of the general workflow: 3D electrophysiological and electromechanical simulations to assess drug safety and efficacy.

Input data:

Population data 2:
Gender: Women/men
Conditions: healthy
Model type: EP/EM
Sample: Single/Population
Parameter settings for population of cell models
Spatial features: Mesh size and refinement
Boundary conditions
Drug data 2:
Parameter settings for drug effects on tissue parameters
Parameter settings for drug effects on ion channels

Standardised input data:

- Gender [string ('f','m')]
- Disease condition [string]
- Model type [string ('EP','EM')]
- Sample [string ('single','population')]
- Parameters population models [file, format=json created from csv file output from part 2]
  - key (string): target parameter
  - value (float): scaling factor for population model
- Mesh parameters [file, format=json]
  - Tissue size
  - Spatial resolution
- Boundary conditions [string]

- Drug factors [file, format=json]
  - key (string): target parameter
  - value (float): scaling factor for drug effect

Model/simulation:
Software: Open source python packages SimCardEMS, FEniCS, CBCbeat, Pulse
Platform: the Norwegian academic high-performance computing and storage services
Protocol: Simulation duration, basic cycle length

Output data:
Qualitative explanation of the kind of data:
Tracked variables for cells in tissue: Vm, Ca and Ta (only for EM simulations)
Tracked variables for tissue: distribution across tissue, displacement (only for EM simulations)
Biomarkers to be extracted from single cell in tissue (same biomarkers as in 0D simulations)
Biomarkers to be extracted from tissue (displacement, strain, conduction velocity)

Standardised output data:
Simulation results [file for each simulation, format=hdf5]
- Group (parameter)
- Group (location in mesh)
  Data (over time)

Biomarkers [file for each simulation, format=json]
- key (string): APD, Ca features, Ta features, strain, etc
- value (float)

Video on contraction results [file, format=avi]

5. Discussion and Conclusion

The cloud-based platform built for Use Case 3 in SimCardioTest project will be designed to perform in-silico trials assessing drug safety and efficacy. To this aim the general workflow and methodology described in the present document will be followed. The assessment of drug safety and efficacy from the electrophysiological and electromechanical perspective involves a complex computational pipeline that requires the integration of heterogeneous data and tools to carry out computationally demanding simulations. Starting with the dose of the drug the user wants to test, and with the selection of the features of the individual or population, the platform will carry out pharmacokinetic and multiscale electrophysiological/electromechanical simulations, requiring the integration of different software and solvers, justifying the need of a multidisciplinary team. To allow a seamless data exchange and simulations execution, standardisation is required for input/output formats as well as for model's structure.

The platform developed in SimCardioTest will go beyond the state of the art, implementing for the first time a modular cloud-based tool which integrates pharmacokinetic, electrophysiological, and electromechanical multiscale simulations, from cell to organ, to assess cardiac safety and efficacy. SimCardioTest is aligned with the important efforts made in the in-silico community to develop tools to assess drug effects, such as Virtual Assay described in Passini et al. 2017 and APpredict

described in Williams & Mirams 2015, which focused on electrophysiological effects at the cellular level.
The definition of clear standards for input/output formats in SimCardioTest platform, will help in the initial validation of the models, to assess credibility and enable the formulation of predictions on drug effects based on the platform outcome. Furthermore, other researchers will benefit of this standardisation, by for instance defining benchmarks where different solvers could be tested on the same data, and definitely make progress on the field.

As a first step, selected marketed drugs, such as CiPA drugs and specific antiarrhythmic drugs to assess cardiac safety and efficacy, respectively, will be tested in the in silico SimCardioTest platform. The platform will enable to leverage our capacity to test other drugs, following the defined input standards. An additional context of use can even consider drug screening, testing new non-marketed molecules in their initial state of development, which would be of great interest for pharmacological and biotech companies, saving time and resources in the pipeline of drug development.

6. References

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