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

SIM CARDIO TEST

Technical Report
D4.3 Database of virtual human cardiac models with drug interaction

Work Package 4 (WP 4)
Use Case 3 - Drug Efficacy & Cardiotoxicity

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DELIVERABLE INFORMATION

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EXECUTIVE SUMMARY

The goal of WP4 is to develop an in-silico method to test for the safety and efficacy of drugs for the heart. As a demonstrator of the progress made under this work package, a database of cardiac models with drug interactions is released to the public. Users will be able to investigate the effects of different drugs at different concentrations on the electrophysiology and mechanical properties of ventricular tissue. The deliverable consists of an online database of drug models (https://computationalphysiology.github.io/drug-database/README.html) which can then be used in conjuction with the simcardems software to perform electromechanical simulations (https://github.com/ComputationalPhysiology/simcardems/tree/master/demos).

The database of drug models and simcardems software are also accessible via the SimCardioTest website.

1- Introduction

The SimCardioTest project aims to advance the use of cloud-based platforms to perform in-silico clinical trials. Under this project, one of the applications that would be investigated is the use of this technology in the safety and efficacy testing of drugs in different cardiac populations. To achieve this goal, we have developed a workflow that uses software and code developed by Exactcure, UPV, SRL, and In-Silico Trials.

The workflow consists of 1) the user choosing a pre-defined population and known drug data, 2) this information will be used to simulate different free plasma concentrations (FPC) of the drug using the ExactCure software, 3) the FPC will be used to simulate drug effects on the electromechanical properties of the myocyte using algorithm developed by UPV, and 4) simulating electomechanical effects of the drug using the simcardems software developed by SRL. The workflow will be implemented in the In-Silico Trials web-based platform.

In this deliverable, an online database of drugs and cardiac models is presented. This database will be part of the release of the simcardems software and will be openly available to the public. This database will serve as a valuable resource to the in-silico trial community and also demonstrate the effectiveness of the platform that we have developed within SimCardioTest.

2- Database access and usage

Instructions for accessing the drug database care documented in https://computationalphysiology.github.io/drug-database/README.html. SRL developed this drug database software that can be used to generate the drug .json files that are used as input for the simcardems simulator.

```
$ drug-db list-drugs
    Drugs
```

Name
Sotalol
Azimilide
Ibutilide
Risperidone
Clarithromycin
Terfenadine
Bepridil
Pimozide
Dofetilide
Disopyramide
Cisapride
Tamoxifen
Vandetanib
Metropolol
Droperidol
Loratadine
Ranolazine
Quinidine
Diltiazem
Astemizole
Nitrendipine
Chlorpromazine
Clozapine
Control
Nifedipine
Verapamil
Domperidone
Ondansetron
Mexiletine

Figure **1***: List of Drugs in the Database*

Currently, the database consists of **28 different drugs** (Figure 1). These are the same drugs that have been used in the development and testing of the Comprehensive In Vitro Proarrhythmia Assay (CiPA) initiative by the FDA (Zhihua Li 2019). These drugs were chosen since their pro-arrhythmic effects on the heart are well known and can be used to validate the predictions obtained from the platform. For each drug, the FPC was calculated using the ExactCure software for an adult male with weight of 70kg. This was then used to determine the scaling of the different ion channels as has been done in the CiPA studies (Figure 2). In the platform, the FPC can be increased or reduced via specifying a variable multiplier with respect to the control value as done previously (Llopis-Lorente 2022) (Figure 2) and visualized (Figure 3).

```
$ drug-db show-drug Verapamil
   Scaling factors for drug
     Verapamil and FPC 1
```

Name	Value
scale_drug_INa	1.0
scale_drug_INaL	1.0
scale_drug_Ito	1.0
scale_drug_ICaL	0.7342
scale_drug_IKr	0.8815
scale_drug_IKs	1.0
scale_drug_IK1	1.0
scale_drug_IKb	1.0
scale_drug_INab	1.0
scale_drug_ICab	1.0
scale_drug_IpCa	1.0
scale_drug_Isacns	1.0
scale_drug_Isack	1.0

```
$ drug-db show-drug Verapamil --fpc 5
   Scaling factors for drug
     Verapamil and FPC 5
```

Name	Value
scale_drug_INa	1.0
scale_drug_INaL	0.9997
scale_drug_Ito	1.0
scale_drug_ICaL	0.3199
scale_drug_IKr	0.5588
scale_drug_IKs	1.0
scale_drug_IK1	1.0
scale_drug_IKb	1.0
scale_drug_INab	1.0
scale_drug_ICab	1.0
scale_drug_IpCa	1.0
scale_drug_Isacns	1.0
scale_drug_Isack	1.0

*Figure **2**: Scaling of the different ion channels with Verapamil at FPC=1 (control)and FPC=5 (5x control)*

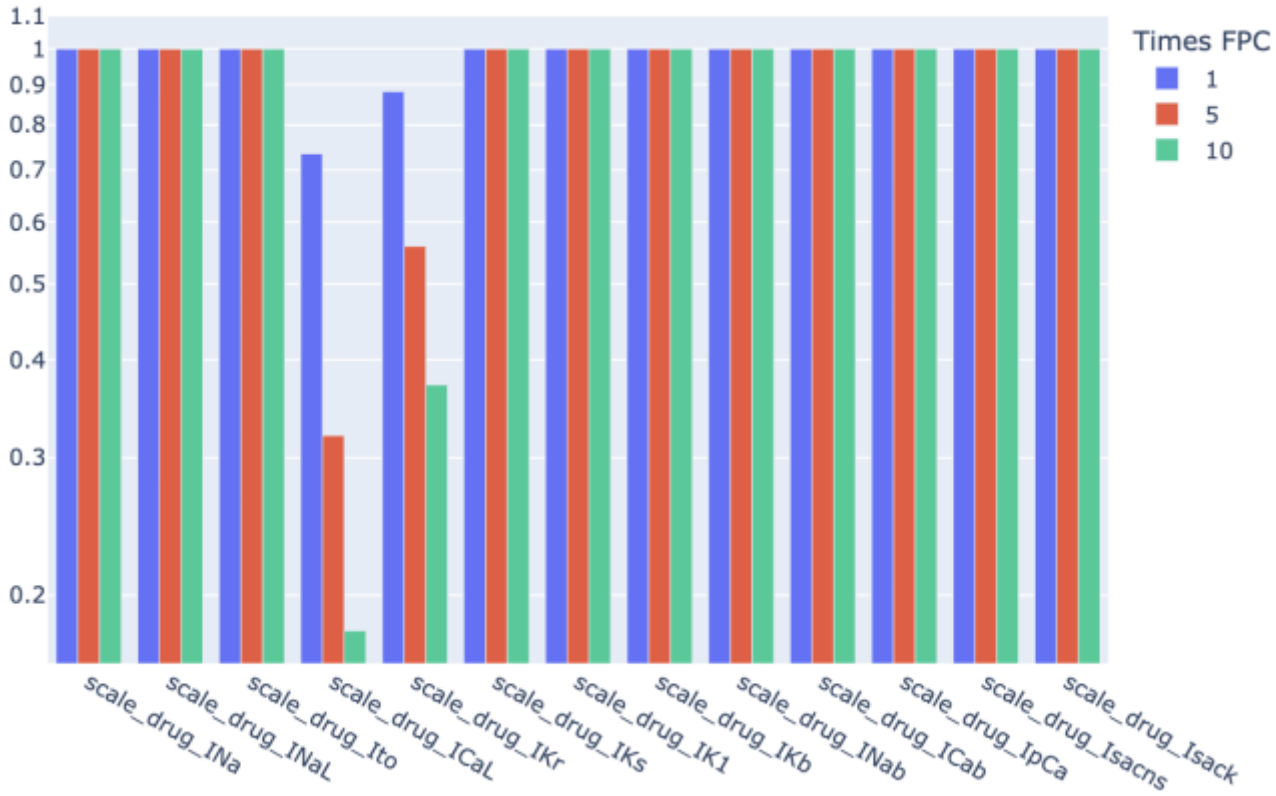

Figure **3***: Visualization of Verapamil effects on ion channels with different FPC multipliers*

The .json files for all 28 drugs at 3 different FPCs are included as demos in the simcardems repository (https://github.com/ComputationalPhysiology/simcardems/tree/master/demos). The python file "drug_effects_demo.py" shows an example of how to use the drug file to simulate the effects of the drug on a slab of human ventricle. The user can then visualize the results on the entire mesh or trace plots from different points to investigate the effects of the drug on the electromechanical properties of the slab (Figure 4).

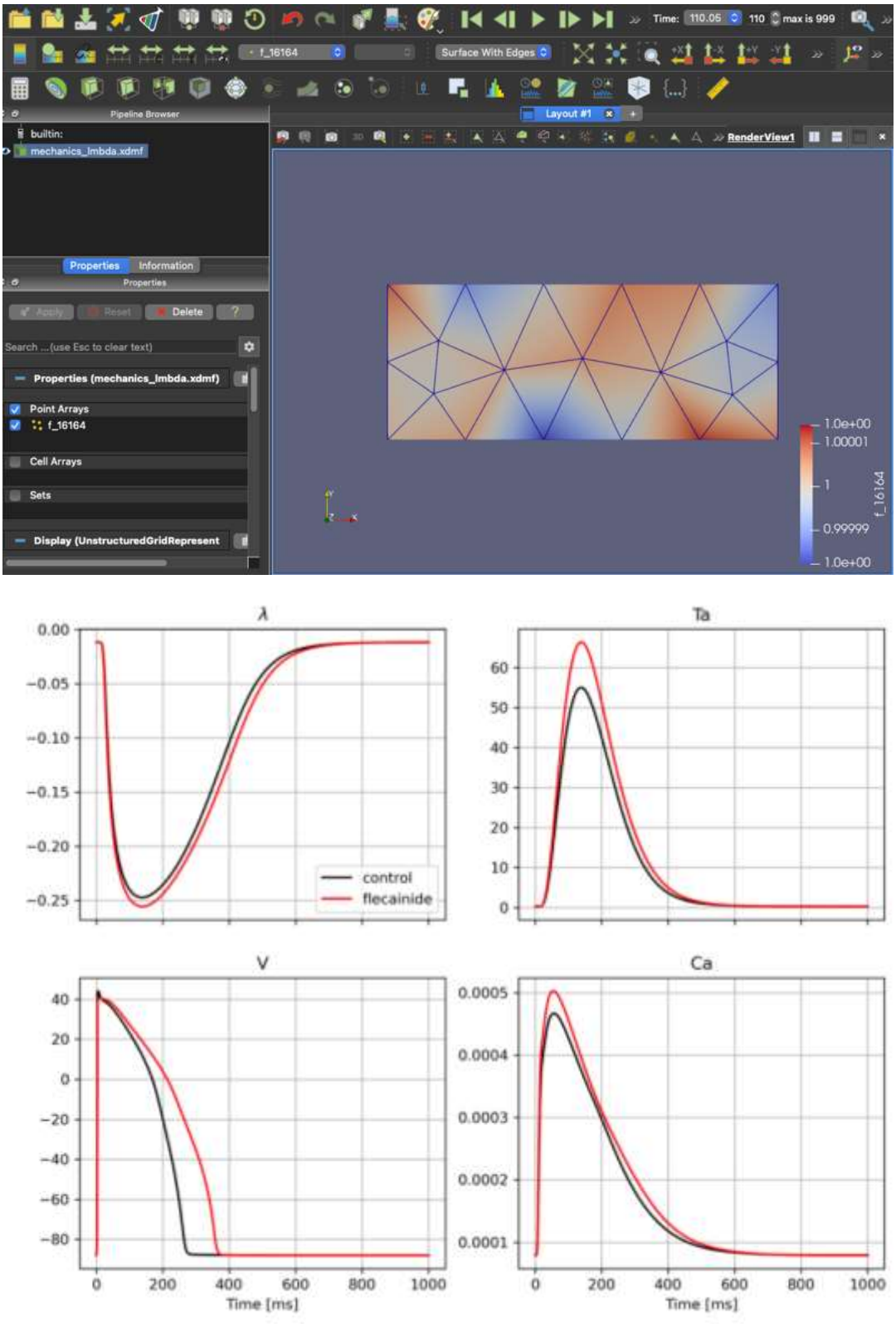

Figure **4***: Visualization of the contraction of the slab (top) with traces obtained at the center of the slab for the stress (*$\dot{\lambda}$*), tension (Ta), transmembrane potential (V), and intracellular calcium concentration (Ca).*

3- Conclusion

In this deliverable, we present a database of virtual electromechanical human cardiac models with drug effects. In this initial release, the drugs included in the database include the thoroughly tested CiPA drugs. These were chosen since they have been used to validate the results of the platform. As more drugs are tested using the platform, they will be added to the database to serve the research community. Currently, simcardems can perform simulations on only slabs of human ventricles. Further releases will include realistic geometries of healthy and diseased hearts (eg ischemia, cardiomyopathy, etc.) and options to utilize other ionic models representing the electromechanical properties of the myocyte. Finally, since the simcardems software and the drug database are released on open-source licenses (GNU Lesser General Public License v2.1 and MIT License, respectively), users have the freedom to adapt this code freely in pursuit of their own objectives. Thus, we expect that this deliverable will serve as a valuable resource to the *in silico* clinical trial community.

The database of drug models and simcardems software are also accessible via the SimCardioTest website.

4- Bibliography

Llopis-Lorente, Jordi and Trenor, Beatriz and Saiz, Javier. 2022. "Considering population variability of electrophysiological models improves the in silico assessment of drug-induced torsadogenic risk." *Computer Methods and Programs in Biomedicine.*

Zhihua Li, Bradley J. Ridder, Xiaomei Han, Wendy W. Wu, Jiansong Sheng, Phu N. Tran, Min Wu, Aaron Randolph, Ross H. Johnstone, Gary R. Mirams, Yuri Kuryshev, James Kramer, Caiyun Wu, William J. Crumb Jr., David G. Strauss. 2019. "Assessment of an In Silico Mechanistic Model for Proarrhythmia Risk Prediction Under the CiPA Initiative." *Clin. Pharmacol. Ther.*

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