Documentation
BMGF: TB drug-induced cardiac risk modelling

Introduction

This purpose of this project was to establish an open source framework for predicting cardiac risk of anti-tuberculosis (TB) drugs in order to derisk early development.

Targeted Cardiac Safety Evaluation

This project focused in vitro and in silico analyses to identify possible toxicity on cardiac electrophysiology (QT interval or action potential prolongation risk) early in anti-tuberculosis drug development, enabling early mitigation strategies or compound deselection before advancing to later stages.

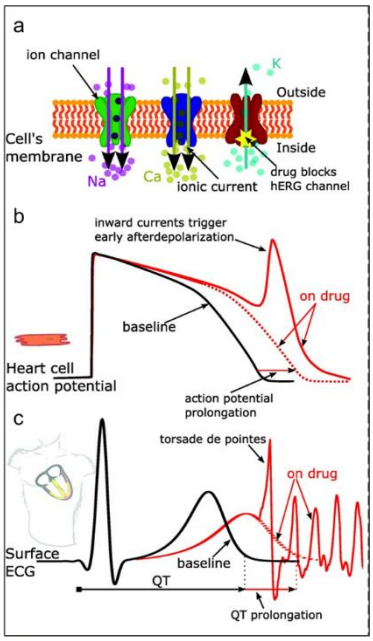
Content description

This repository contains code that was migrated and adapted from the proprietary software MATLAB to an open-source R framework. The MATLAB code was originally published by Llopis-Lorente J. et al. (2023).

It contains an ODE based model of the human cardiomyocyte electrophysiology (flux through ion channels and membrane electric potential) and predicts the action potential (AP) duration (Figure 1) as well as a series of typical biomarkers. It also contains a copy of the virtual population describing the variability of ion channel distribution and sensitivity in human males and females as built by Llopis-Lorente J. et al. (2023).

The new R implementation was validated through simulating the effect of benchmark CiPa drugs on the cardiomyocyte AP and comparing the output to the original published results.

The current implementation is designed in such a way that each patient within the population is simulated in parallel.



Vicente (2017)

The mathematical model describes ion current for the following channels and compute a resulting membrane action potential (in yellow are the ones that can be blocked with the input file):

Sodium (Na^+) Currents:

- Ina → Fast sodium current (NaV1.5, responsible for rapid depolarization)
- INaL → Late sodium current (persistent Na^+ influx)
- INaCa_i → Sodium-calcium exchanger (sub-membrane space)

- INaCa_ss → Sodium-calcium exchanger (subsarcolemmal space)
- Inab → Background sodium current (small leakage Na^+ current)

Calcium (Ca^{2+}) Currents:

- ICaL, ICanNa, ICaK → L-type calcium (long-lasting) current (Cav1.3 or 1.2) and associated sodium (ICanNa) and potassium (ICaK) components
- IpCa → Sodium-independent calcium pump (PMCA, Plasma Membrane Ca^{2+} ATPase)
- Icab → Background calcium current (small leakage Ca^{2+} current)

Potassium (K^+) Currents:

- Ito → Transient outward potassium current (responsible for phase 1 repolarization)
- Ikr → Rapid delayed rectifier potassium current (hERG, key for repolarization)
- Iks → Slow delayed rectifier potassium current (KCNQ1/KCNE1, contributes to repolarization)
- IK1 → Inward rectifier potassium current (Kir2.1, stabilizes resting membrane potential)

Sodium-Potassium ATPase (Na^+/K^+ Pump):

- **The sodium-potassium ATPase pump** is typically represented as **INaK** in models.
  - INaK maintains ionic homeostasis by actively transporting Na^+ out and K^+ in.

Input/Output description

Input

For simulating the effect of a new drugs (e.g. TB drugs) the current R workflow takes as input:

1. The virtual population (ion channel scaling factors). It is defined in *factors_population.csv* (patient 1:300 are males, 301 to 600 are females). Was built and described in (Llopis-Lorente J. et al. 2023).
2. The initial conditions for the state variables: defined in *X0.csv*
3. The free plasma concentration (Cmax) (e.g. typically predicted by the drug PBPK model)
4. The inhibition constant (IC_{50} and hill coefficient) for the following channels:
   - **IKr:** Rapid delayed rectifier potassium current (hERG, key for repolarization)
   - **INa:** Fast sodium current (NaV1.5, responsible for rapid depolarization)
   - **INaL**: Late sodium current (persistent NA+ influx)
   - **ICaL:** L-Type (long lasting) calcium current (CaV1.3)

The drug effect on each channel is then computed as:

$$Drug\ effect = \frac{1}{1 + \left(\frac{[drug]}{IC50}\right)^{hill\_coef}}$$

The final ion current is a product of the general conductance and the “drug effect”. This way, in absence of drug (concentration = 0nM), the ‘drug effect factor is set to 1’ and the resulting ion conductance is maximum.

The example input files for the benchmark CiPa drugs are located in: *Drug_Scenarios/* (see example below)

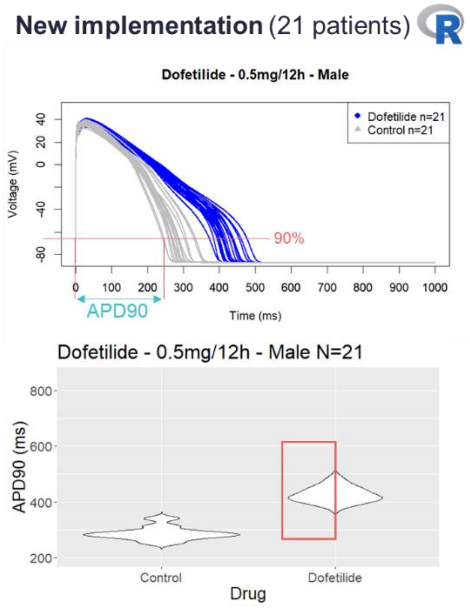
	Gender	FPC	IC50IKr (nM)	hIKr	IC50INa (nM)	hINa	IC50INaL (nM)	hINaL	IC50ICaL (nM	hICaL
Patient_M_70kg_200mg_24h	1	121.965015	828	0.75	363000	0.72	2940000	0.47	13200	0.71
Patient_F_70kg_200mg_24h	2	137.6713	828	0.75	363000	0.72	2940000	0.47	13200	0.71
Patient_M_70kg_150mg_24h	1	91.473333	828	0.75	363000	0.72	2940000	0.47	13200	0.71
Patient_F_70kg_150mg_24h	2	103.253091	828	0.75	363000	0.72	2940000	0.47	13200	0.71

Figure 1: Example input file for Azimilide. 4 scenarios are described. Gender is 1 for male or 2 for female. FPC: free plasma concentration (in nM), IC50s for each channel must be provided in nM.

Output

The model outputs an Action Potential (AP) with the membrane depolarization and repolarization phases and some computed biomarkers (e.g. APD90, repolarization abnormalities, etc.) for an individual cardiomyocyte.

Example output: Example simulation outputs are available in the folder 'Results' with a limited population size. They were generated with the input file ‘Dofetilide_maxC_IC50 – NRF.xlsx’ and ‘Control_maxC_IC50 – NRF.xlsx”



How to use

R workflow and scripts:

- Master file: *modelRunner_drugs.R* (the name of drugs to be simulated should be adapted within the script). It uses parallel computing (individual run in parallel).

- Results are saved in *'Results/'*

- A helper script is available (*SimResults_Analysis.R)* for postprocessing the results, calculating the biomarkers and getting figures. It needs to be adapted by user for each input result file.

References:

Llopis-Lorente J. et al. *Combining pharmacokinetic and electrophysiological models for early prediction of drug-induced arrhythmogenicity*. Comput Methods Programs Biomed. 2023 Dec;242:107860. doi: 10.1016/j.cmpb.2023.107860. Epub 2023 Oct 11. PMID: 37844488.

J. Vicente et al. *Mechanistic Model-Informed Proarrhythmic Risk Assessment of Drugs: Review of the "CiPA" Initiative and Design of a Prospective Clinical Validation Study.* Clinical Pharmacology and Therapeutics. 2017. https://doi.org/10.1002/cpt.896