**CardioSim: GUI based simulator for drug-toxicity evaluation**

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**Abstract**

The field of cardiac safety pharmacology is focused on studying the potential for torsade de pointes (TdP) in new drugs. The Comprehensive In vitro Proarrhythmia Assay (CiPA) was developed to use computer simulations to predict the risk of drug-induced TdP. However, the current method of CiPA assessment often does not account for the natural variability in cardiac cells. This study aimed to investigate whether variability in metabolic status and cellular makeup could affect the accuracy of drug risk prediction. The researchers used a ventricular cell model to evaluate the proarrhythmic effects of 12 CiPA drugs on cells with varying levels of spermine concentration (as influenced by metabolic conditions) and L-type calcium permeability (due to genetic mutations).Our research aim to create this experiment into in-silico simulation for predicting the classification of those drugs using web-based Graphical User-Interface (GUI).

**1. Introduction**

Torsade de pointes (TdP) is a potentially fatal heart rhythm disorder. Researchers have proposed the Comprehensive In vitro Proarrhythmia Assay (CiPA) to address the limitations of current drug safety testing methods. CiPA incorporates in silico drug TdP risk assessment into drug evaluation, and previous studies have used it to predict and categorize the risk of TdP associated with various drugs. Early research by Mirams et al. [5] demonstrated that integrating the effects of drugs on multiple ion channels, including hERG, Na, and CaL channels, could improve in silico drug TdP risk assessment compared to evaluating drugs based on their impact on the hERG channel alone. Others have suggested considering additional ion channels, such as Ks, K1, to, NaL, and CaL channels, to better understand the pharmacological impact of drugs. Passini et al. used repolarization abnormality (RA) and electromechanical window (EMw) to assess the TdP risk associated with various medications. By considering multiple factors and channels, CiPA and related approaches have the potential to improve drug safety testing and minimize the risk of TdP and other serious cardiac complications.

This study aims to create a GUI-based simulation software for predicting drug classification using in-silico simulation of O’Hara-Rudy ventricular cardiac cell model to get the drug effect electrophysiology simulation and Artificial Intelligence to predict the severity of the drug.

**Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, highlighting the urgent need for efficient and reliable drug discovery pipelines. Current drug discovery pipelines face a significant challenge: the heavy reliance on animal testing. While this traditional approach has yielded important advancements, it raises significant ethical concerns regarding animal welfare. Additionally, animal models often exhibit limited ability to accurately mimic human physiology. This "species translation" issue can lead to misleading results, where drugs appear safe and effective in animals but fail to translate to human trials due to unforeseen safety risks or reduced efficacy.**

**In response to these limitations, in silico (computer-based) methods for drug cardiotoxicity prediction have emerged as promising alternatives. These methods offer a more ethical approach by eliminating the need for animal testing. Additionally, the potential for faster and more efficient drug development exists, as in silico models can potentially provide more accurate predictions of human drug safety and efficacy compared to animal models.**

**This research proposes a novel approach to address the computational bottleneck associated with complex in silico models by leveraging CUDA-based parallel processing on GPUs. This approach has the potential to significantly accelerate the execution of these models, making them more efficient and practical for real-world drug discovery applications.**

**By effectively addressing these challenges, your proposed approach has the potential to significantly contribute to the development of a more efficient, ethical, and reliable drug discovery process.**

**2. Method**

CardioSim is built using C++ programming language for both of the simulation code and its graphical user interface (GUI), and Python for the machine learning of toxicity classification. The simulation involves solving sets of ordinary differential equations (ODEs) with their respective initial values. CVode is used to solve such equations since the library is built using C programming language and supports initial value problems type of ODE, such as in this case the cardiac cell model [1]. Additionally, since there are various drug parameters for the simulation input, the software need to provide parallelization to run multiple simulations at the same time. Since we used C++ as the code base, Message Passing Interface, or commonly known as MPI, is choosen for the parallelization interface . As for the library, OpenMPI is used because it supports usage in different operating system [2]. Moreover, for the GUI, Qt is used as the GUI components because Qt provides plethora of GUI components to create impeccable user interface and Qt have been used in several famous companies and hospitals [3]. Furthermore, Qt also provides cross-platform deployment with universal user interface. It means that the user interface will have similar look and feel in multiple platofrms, even in the different operating systems. Lastly, for the classification prediction of the drug, Python programming language is used because there are several libraries that supports machine learning process, such as TensorFlow or Keras [4].

The flowchart of application process can be seen in the Firgure 2.1. User will input simulation parameters and drug data in the GUI desktop application, and generate the input parameter file for the in-silico simulator. Next, the simulator will run and generate time-series result and numerical results. Subsequently, the simulator will use Artificial Intelligence (AI) to classify the drugs with prior guess as the input, then provide the actual classification result. The AI use Artifical Neural Network and Logistic Regression as the algorithms for the predicition. Finally, all of the result will be shown in the desktop applications. Optionally, user can directly input the parameters directly through the console or command prompt, but they cannot get the visual result since the result will be comma-separated values (CSV) files.

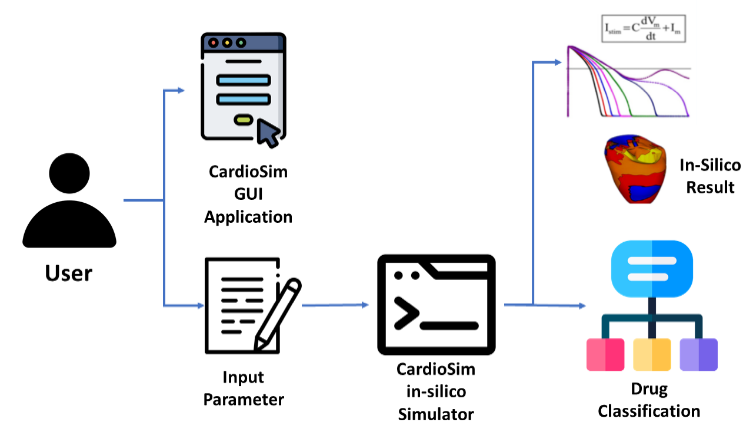


Figure 2. 1 CardioSim application workflow

**3. Results**

The user interface of CardioSim is show in Figure 3.1. The left part of the input lets the user choose which ion channel will be used for the simulation. The input deck will let user input the simulation parameters. IC50Files contains the information of the drug input. User can also choose the AI prediction algorithm for classification result. Some drugs will work only for certain AI prediction algorithm. The middle part is graphic for time-series result. It can also show output for numerical results (as shown in the Figure 3.2) and three-dimensional result (as shown in the Figure 3.3). The right part shows the system log of the simulations.

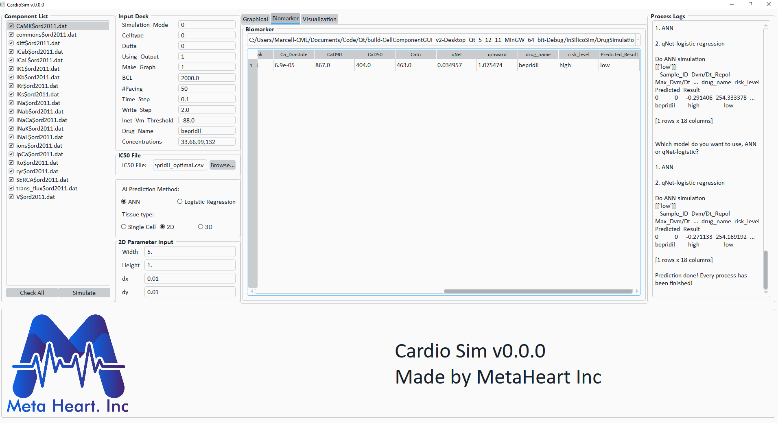


Figure 3. 2 Numerical data result

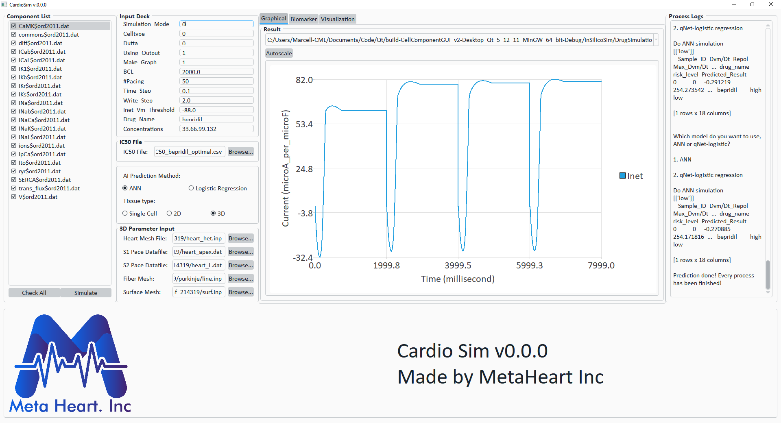


Figure 3. 1 User Interface of CardioSim

**4. Acknowledgements**

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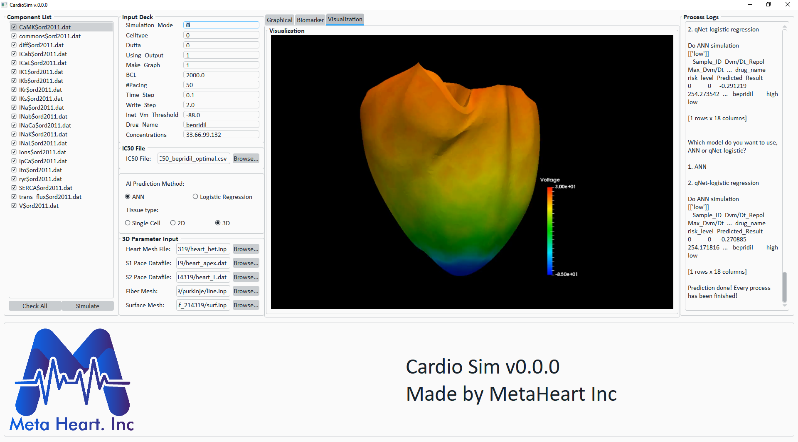


Figure 3. 3 Three-dimension result.