Deep Neural Networks based Drug safety assessment using qNet variability and qInward variability

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Abstract

As a part of the CiPA project, Li et al. proposed a logistic regression model to classify the proarrhythmic risk of drugs using qNet as a TdP risk assessment biomarker. However, the single qNet value or the single qInward value, which are the amount of charge moving through Inet and inward currents, respectively, could well miss important characteristics of drug-induced TdP. Therefore, with the hypothesis that the variability of qNet or qinward in the whole pacing includes the important features and can classify the TdP risk accurately compared to the single TdP value, this study proposes a deep Convolutional Neural Network model using qNet variability and qInward variability to classify proarrhythmic risk levels: high, intermediate, and low. The lab-specific 28 drugs data by Chantest et al. were used and discriminated as1 2 drugs for training data and 16 drugs for test data. qNet variability and qInward variability were obtained from in silico simulation using Tomek Ohara Rudy (ToRd) model. The accuracies of the proposed model for qNet variability were 0.58, 0.63, and 0.49 for high, intermediate, and low-risk levels, respectively, and for qInward variability are 0.94, 0.74, and 0.93 for high, intermediate, and low-risk levels, respectively. As a result, we finally propose the deep CNN model using qInward variability as the best model to assess the TdP risk.

1. Introduction

Torsade de Pointes (TdP) is one of the disorders of the heart that can be caused by a drug reaction. This condition causes disturbances in the ventricular heart rhythm polymorphic tachycardia. Because of that, from 1,990 to 1,999, several drugs were withdrawn from the market because they posed the TdP risk [1]. The assessment of drugs using conventional methods has high sensitivity and low specificity. However, some drugs that can cause QT interval prolongation but do not induce by TdP were removed from the list of drug development even though they might have therapeutic potential. To improve it, a new non-clinical guideline by the Comprehensive in vitro Proarrhythmia Assay (CiPA) project, was recently suggested by thirteen advanced medical institutions in seven countries. Li et al. based on the CiPA guidelines have succeeded in classifying the proarrhythmic risk of drugs using qNet [2]. However, the single qNet value or the single qInward value, which are the amount of charge moving through Inet and inward currents, respectively, could well miss important characteristics of drug-induced TdP. Therefore, with the hypothesis that the variability of qNet or qinward in the whole pacing includes the important features and can classify the TdP risk accurately compared to the single TdP value, we proposed the deep Convolutional Neural Network (CNN) to classify the toxicity of the drug's risk levels (high, intermediate, and low).

2. Method

2.1 In silico simulation

The following are several steps to determine the effect of the drug on the six ion channels. The patch-clamp data obtained from the CiPA group will go through the same steps as Li et al [2]. In silico model for action potential (AP) simulation was implemented using C++ based on Tomek Ohara Rudy's in silico model (ToRd). Then, we extracted 2,000 hill coefficients and IC50 values for the six ion channels by bootstrapping 95% using the Markov-chain Monte Carlo (MCMC) method by including drug concentration, percentage of ions block, and velocity as inputs [3]. In-silico simulation was performed using the bootstrapped IC50 and hill coefficients under drug concentration conditions of 1, 2, 3, and 4 times the Cmax value, running for 1,000 beats to reach steady states with stimulation of 0.1 ms and a 2,000 cycle length. Then, we obtained two in silico biomarkers from 28 types of drugs (12 training drugs and 16 test drugs) with drug risk levels: high-risk, intermediate-risk, and low-risk, which are qInward variability and qNet variability. qNet is the total number of charged ions that pass through the six ion channels (INaL, ICaL, IKr, IKs, IK1, and Ito) from the depolarization state to the repolarization state in the action potential (AP) generation. qInward is the amount of charge through the ICL and INaL ion channels during drug-induced action potential during AP generation [4].

2.2 Deep Convolutional Neural Network

The qInward variability and qNet variability obtained The qInward variability and qNet variability obtained from the simulation of the ToRd in silico model will be used as input data into the proposed deep CNN model, respectively. Previously, Chang et al [3] used the single qNet value obtained from the last 250th pacing as input data. Meanwhile, the signal was still repolarization. Here, we propose variability of in silico biomarkers during the last 500 pacings as input data into the proposed deep CNN model simulation. The proposed CNN model consists of 29 layers with a filter size of 5, max-pooling

2, and stride 2 for each layer. To prevent overfitting and speed up the learning process, we implemented a dropout of 0.2. In the first hidden layer, we use the Rectified Linear Unit (ReLu) activation function, then for the output layer, we use the softmax activation function. Furthermore, the best model from the deep CNN simulation results obtained from 300 training epochs will be tested using 16 test data sets (32,000 samples) and 28 test data sets (56,000 samples). Each test simulation uses 16 test data sets and 28 test data sets will be randomly selected 10,000 times where one sample is selected from 2,000 samples and the group will be tested using 16 test data sets and 28 test data sets.

3. Result

After the data was tested 10,000 times, then we evaluated the performance using AUC and logistic regression based on the study conducted by Li et al [2], the results of which are shown in Table 1 for drugs tested using 16 test data and Table 2 for drugs tested using 28 test data.

Table 1. Performance comparison of the proposed CNN model according to input features using 16 test drugs of the Chantest dataset.

Model		Proposed Deep Convolutional Neural Networks (Tested using 16 drugs)	
		qNet	qInward
AUC	High	0.58 (0.4 – 0.75)	0.94 (0.65 – 1)
	Inter	0.63 (0.48 – 0.83)	0.74 (0.5 – 0.94)
	Low	0.49 (0.18 – 0.78)	0.93 (0.82 – 1)
LR+	High	1.28 (0 – 6.99)	5,713 (1.67 – 9999)
	Inter	1.25 (0.67 – 3.21)	6.5 (0.96 – 7.7)
	Low	1.08 (0.42 – 1.39)	6.5 (2.89 – 6.5)
LR -	High	0.36 (0 – 1.57)	0.43 (0 – 0.83)
	Inter	0.83 (0.37 – 1.33)	0.48 (0.22 – 1.33)
	Low	0.96 (0.43 – 1.39)	0 (0 – 0.49)
F1 score		0.38 (0.24 – 0.63)	0.69 (0.42 – 0.88)
Accuracy		0.38 (0.25 – 0.62)	0.69 (0.44 – 0.88)

Table 2. Performance comparison of the proposed CNN model according to input features using 28 test drugs of the Chantest dataset.

Model		Proposed Deep Convolutional Neural Networks (Tested using 28 drugs)	
		qNet	qInward
AUC	High	0.71 (0.47 - 0.82)	0.81 (0.57 – 0.92)
	Inter	0.71 (0.56 - 0.83)	0.7 (0.54 – 0.84)
	Low	0.6 (0.37 -0.78)	0.87 (0.73 – 0.94)
LR+	High	3 (0 - 10.8)	5.39 (1.8 – 14.75)
	Inter	2.31 (1.11 - 4.5)	0.45 (0.16 – 0.77)
	Low	1.83 (0.6 - 4.22)	2.16 (1.03 – 7.49)
LR -	High	0.53 (0 - 1.47)	0.55 (0.21 – 0.98)
	Inter	0.61 (0.28 - 0.93)	5 (2 – 8.74)
	Low	0.69 (0.35 - 1.23)	0.29 (0.14 – 0.67)
F1 score		0.38 (0.24 – 0.63)	0.54 (0.37 - 0.65)
Accuracy		0.38 (0.25 – 0.62)	0.54 (0.36 - 0.64)

The best results are found in qInward variability as input data which is tested using 16 test data with the best results at a high-risk level with an accuracy of 0.94 (>0.9) which includes the very good performance category, then good category 5.713 (> ~5) and the minimal category 0.43 (<~0.4) [2] for positive logistic regression (LR+) and negative logistic regression (LR-), respectively. Meanwhile, by using 32 data tests, the accuracy of the qInward variability obtained results that were less than optimal, while compared with the qNet results as input data, the qInward variability was still superior to the qNet variability tested by 16 drugs and 28 drugs. Here, our hypothesis is able to classify high, intermediate, and low-risk levels and shows that using the deep CNN model using qInward variability is the best model to assess the TdP risk. However, the limitations of available drugs make this study less than optimal. In the future, this performance can be improved by adding several types of drugs.

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