Artificial Neural Networks in Cardiac Safety Assessment: Classification of Chemotherapeutic Compound Effects on hiPSC-derived Cardiomyocyte Contractility

J. L. Hunker 1, 2, M. Goßmann 1, A. H. Raman 1, P. Linder 1

1 innovitro GmbH, Artilleriestraße 2, 52428 Jülich, Germany
2 Institute of Bioengineering, FH Aachen University of Applied Sciences, Heinrich-Mußmann-Str. 1, 52428 Jülich, Germany

Abstract
In the last decades, technological progress in computing capacity, data acquisition and its storage has enabled new possibilities to analyze big data using machine learning, which is incomprehensible for manual analysis. Therefore, big data analysis and machine learning are well suited in the realms of drug development, to analyze the complexity of cellular processes. The objective of the present study is to develop and train an artificial neural network (NN) based on contractility parameters that differentiates compounds according to their influence on cellular pathways in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs).

Data Acquisition
The FLEXcyte technology enables high resolution contractility measurement of hiPSC-derived cardiomyocytes cultured on hyper-elastic silicone membranes, mimicking the physiological mechanics of cardiac tissue [1, 2]. Analysis of the biohybrid’s deflection provides the following features:
1. Contraction amplitude
2. Beating rate
3. Upstroke duration
4. Downstroke duration
5. Upstroke velocity
6. Downstroke velocity
7. Upstroke integral
8. Downstroke integral
9. Day of measurement

These features are used by a NN to classify 5 tyrosine kinases inhibitors (TKIs) into 11 signaling pathways (SPs) that are influenced by their effects.

Neural Network Design (Hyperparameters)
NNs consist of several application-dependent hyperparameters, e.g. hidden layer architecture (HLA), activation functions of neurons, learning rate (LR), and regularization. The aim is to optimize the weights of each neuron in the NN for a specific task. An analogy for this would be like skiing through the mountains (residual) in one-dimensional space (single weight) trying to reach the lowest valley.

The LR plays a critical role in reaching the optimal weights [3]. During training, dropout regularization prevents the NN from overfitting via random deactivation of neurons with a defined dropout rate (DR) [4].

Optimization (Training) of NN
Optimization starts with random initial weights [5] at each neuron to calculate the overall residual (Feedforward [3]). These random weights are optimized to attain the minimum residual (Backpropagation [3]). Adam algorithm [6] is employed in our case to optimize the weights. These new weights are then used for the next Feedforward step. This process is repeated until the stopping condition is met, e.g. the improvement of the residual drops below a certain tolerance level [7]. Afterwards the NN can be evaluated.

Performance Evaluation of the NN
Metrics for Evaluation are based on the measures TP, FP, FN, and TN [8].

Accuracy = \frac{TP}{TP + FP + FN + TN} \times 100\%

Exact Match Ratio = \frac{TP}{TP + FP + FN + TN}

Precision = \frac{TP}{TP + FP}

Recall = \frac{TP}{TP + FN}

Optimization of Hyperparameters
Optimization of hyperparameters was performed in 2 consecutive steps:
1. Optimization of HLA
2. Optimization of LR and DR using HLA from step 1

The best performance was achieved with the following hyperparameters:
HLA: [2 hidden layers with 99 ReLU-activated neurons each]
LR: 0.025
DR: 0.2

The best performance was achieved in run 72 of the 100-times repeated random sub-sampling validation.

Results
The best performing model on the best model development set.

Conclusion
On average our developed NN was able to correctly classify >90% of the corresponding target pathways using 65% of the development data for training. The remaining cross-validation (15%) and test (20%) sets ensured the functionality of the algorithm with predictive powers of 91% and 87% respectively. In summary, the NN has shown to be a reliable analysis tool for in vitro drug screening and cardiotoxicity assays using beat shape data of hiPSC-CMs obtained with the FLEXcyte technology, and thus offers insight into the effects of compounds on the target signaling pathways. Further experiments are planned with compounds not part of the development set to show the predicting power of this NN.

References:

Data for NN with 5 TKIs and their effect on 11 SPs

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