Assessment of cardiotoxic effects from ion channel assay data

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BACKGROUND

Drug-induced cardiotoxicity or torsades de pointes (TdP), a potentially lethal cardiac ventricular arrhythmia, is an adverse effect that has long been a leading cause of attrition during drug development. Minimizing the risk of this cardiotoxic effect is thus an important task during the drug development process and regulatory guidelines require new drugs to be evaluated for pro-arrhytmic risk before entering clinical testing. At present, block of the cardiac potassium channel hERG and human QT intervals are assessed as part of the current safety guidelines. Although a block of the cardiac potassium channel hERG and subsequent prolongation of the cardiac QT interval are common features of cardiotoxic drugs, there is no simple one-to-one correlation. TdP involves changes in cardiac cell repolarisation, which is dependent on the concerted activity of several ion channels including hERG, Na-, and Ca-channels. Too much emphasis on hERG as a marker has most likely hampered the development of new drugs by premature discontinuation from development.

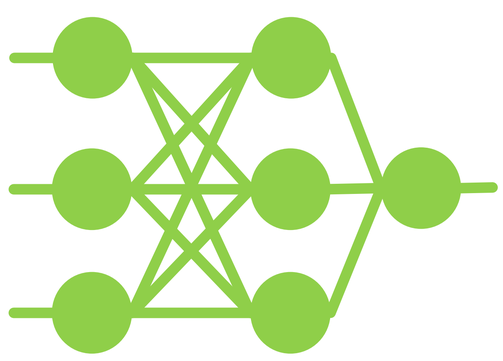
AIM

- We aim to directly assess the primary clinical endpoint, namely ventricular proarrhythmia (i.e., cardiotoxicity)
- To achieve this, we use a data driven approach based on published data to train a neural network architecture
- The technology is made easily accessible to potential users via a web based demonstrator

NEURAL NETWORK CLASSIFIER FOR TdP RISK AND QT PROLONGATION

INPUTS:

- Trained on IC_{50} values for hERG, hCav1.2 and hNav1.5
- Training set consisting of 72 compounds for which publicly available data exists [1]-[4] .
- One hidden layer, tanh() activations, trained with backpropagation

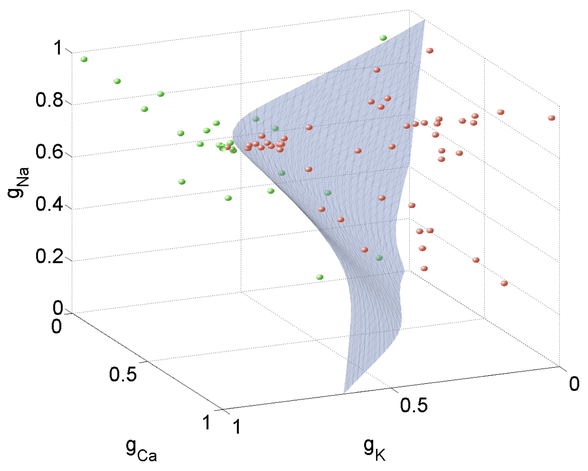


OUTPUTS:

- Binary predictions of TdP risk and QT prolongation
- Binary measure of certainty, based on density of training points in feature space

CLASSIFIER PERFORMANCE

- Table shows sensitivity and specificity for LOO-CV, but performance is similar with for example 5-fold CV
- Figure 1 shows training data and decision boundary



	TdP	QT
Sensitivity	98%	94%
Specificity	100%	90%

Figure 1: Data and decision boundary for the TdP classifier. TdP+ substances are shown in red and TdP- in green. Decision boundary is shown in blue. Values on axes are degree of channel block at 30 x C_{max}

COMPARISON TO hERG POTENCY

- hERG IC_{50} values are used to define safety margins: (hERG IC50/Predicted or measured mean unbound therapeutic plasma concentration (Cmax)),
- A margin of 30-45 fold is generally considered safe [1]
- To evaluate the difference in performance to the NN classifier, ROC curves were computed (see Figure 2)

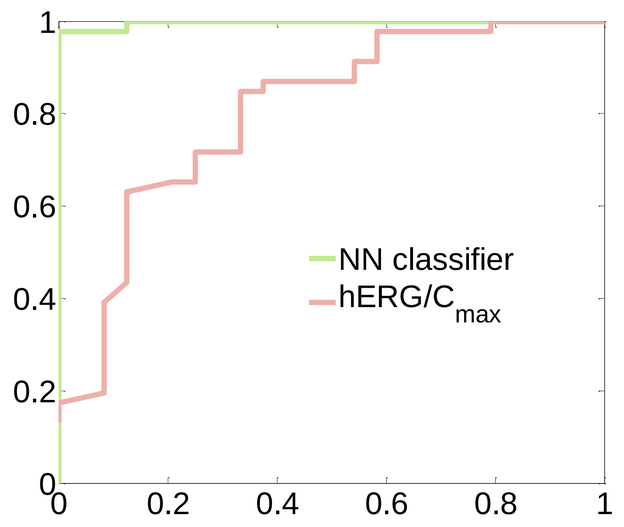
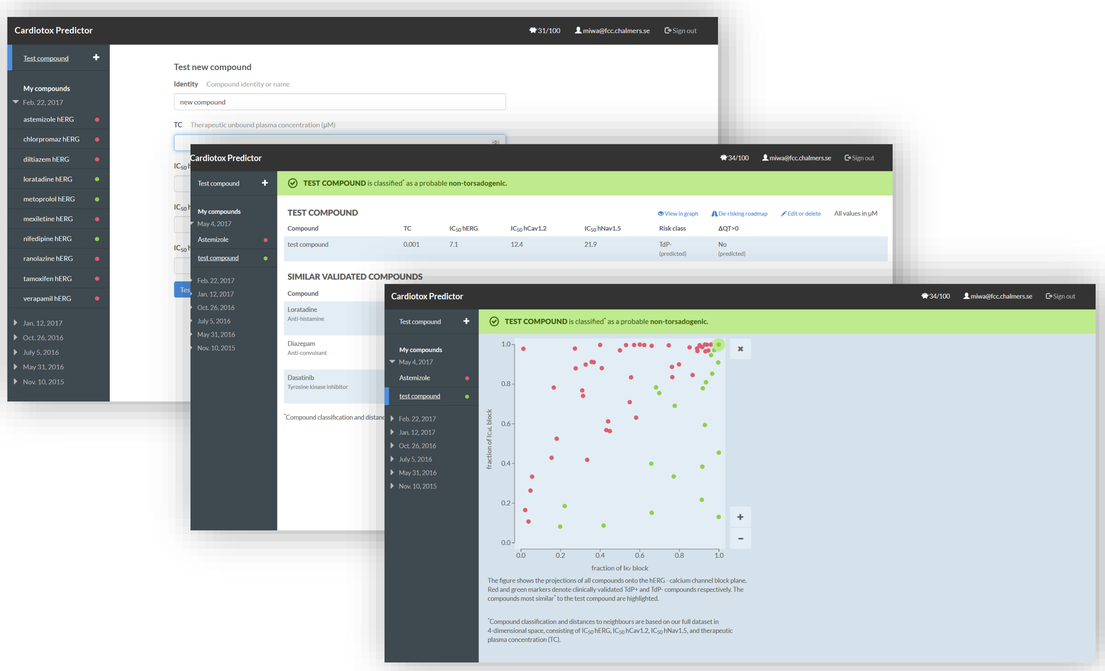


Figure 2: ROC curves for the NN classifier (green) and for the linear classifier based on the hERG IC_{50} / C_{max} quotient (red). The curve for the NN classifier was generated by varying the output threshold between -1 and 1. The curve for the linear classifier was generated by varying the output threshold between 0 and 30 000.

WEB INTERFACE



www.cardiotox-predictor.com

CONCLUSIONS AND REFERENCES

- A new tool for early cardiotox assessment is presented
- Incorporating data from hCav1.2 and hNav1.5 significantly increase prediction accuracy
- Web based interface makes it easy for others to use results

[1] Redfern et al. 2003, Cardiovasc Res 58: 32–45.
[2] Mirams et al. 2011, Cardiovasc. Res. 91, 53–61
[3] Kramer et al. 2013, Nat. Sci. Rep., 3:2100
[4] www.Crediblemeds.org

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