Predicting drug-induced arrhythmia using afterdepolarisations.

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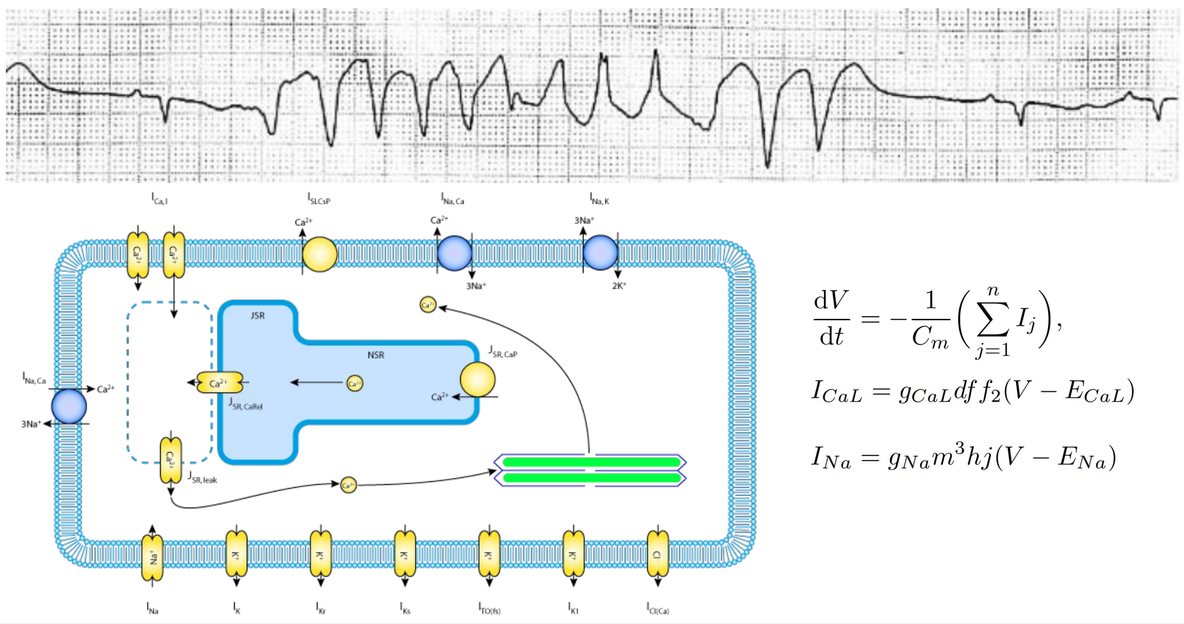
Introduction.

Torsades-de-Pointes is a type of arrhythmia that can be caused by drug effects. Existing methods for predicting Torsades include measuring block of the hERG channel, which may be too restrictive, or animal studies, which are expensive. We have investigated a novel method for predicting arrhythmic risk, combining simulated ion channel block with provoked afterdepolarisations.



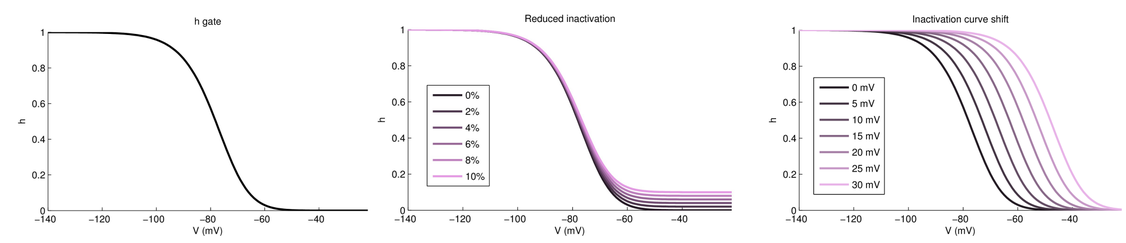
$$\frac{\mathrm{d}V}{\mathrm{d}t} = -\frac{1}{C_m}\left(\sum_{j=1}^{n} I_j\right),$$

$$I_{CaL} = g_{CaL} df f_2 (V - E_{CaL})$$

$$I_{Na} = g_{Na} m^3 h j (V - E_{Na})$$

Methods.

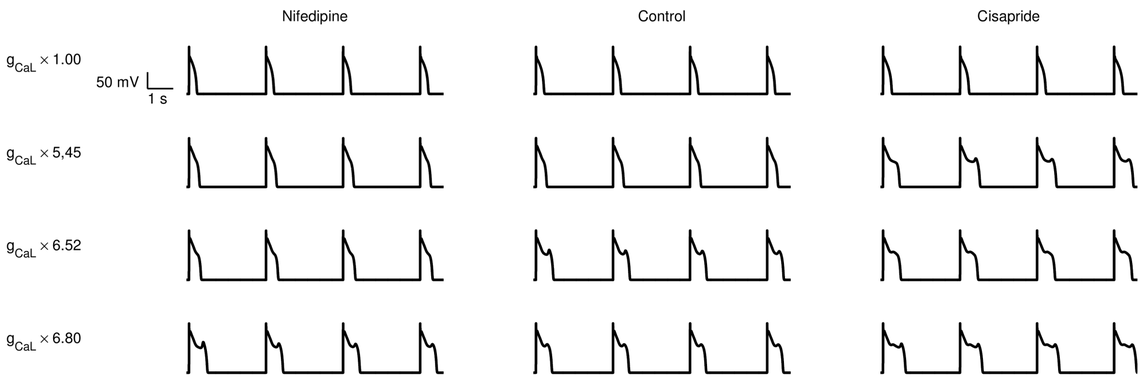
Drug block was applied to CellML models of myocytes by decreasing the conduction of the relevant ionic currents. Afterdepolarisations were provoked using several interventions: increasing the L-type calcium current conductance (g_{CaL}), reducing the hERG current conductance (g_{Kr}), shifting the inactivation curve of the fast sodium current, and increasing the persistent sodium current by reducing the inactivation of the fast sodium current. The two sodium protocols work by modifying the 'h' gate, as shown in these graphs:



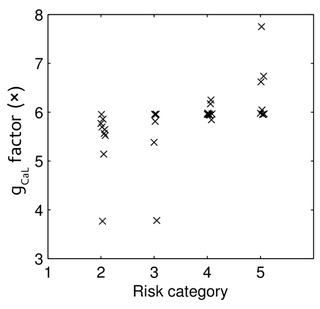
Our approach differs from that of Christophe (2013) in that we consider the effects of outside factors, rather than the consequences of overdose. The threshold values of intervention at which afterdepolarisations occurred were then used to sort drugs into risk categories using linear discriminant analysis. This information was then compared to clinical incidence, using the five torsadogenic risk categories from Redfern et al. (2003).

Results.

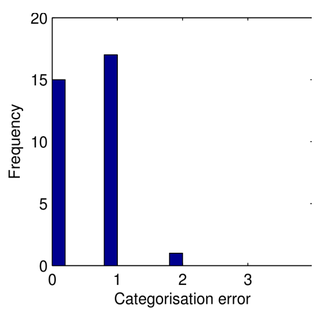
The effects of simulated drug block altered the threshold values of intervention required to provoke an afterdepolarisation. In general, safe drugs raised the threshold, and drugs with high Torsades risk lowered the threshold.



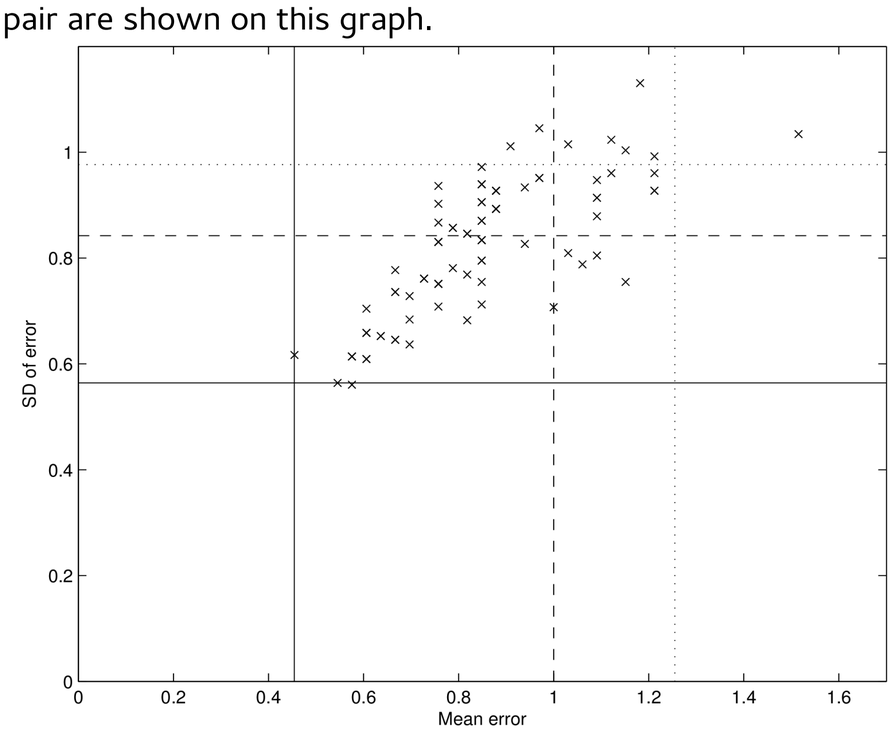
The differences in threshold for different categories of drug are shown in this graph. Drugs in risk category 5 are the safest, and tend to raise the afterdepolarisation threshold, while the dangerous drugs in category 2 tend to lower the threshold.



Afterdepolarisation threshold values were then used to assign drugs to risk categories using Linear Discriminant Analysis and a leave-one-out method. The assigned category was then compared to the drug's real category to find the error in classification. The errors for the previous method are shown in this histogram.



The mean and standard deviation of the errors in classification were used as a metric for the accuracy of the technique. The errors for each protocol-model pair are shown on this graph.



The solid line shows the mean and standard deviation of errors from the APD90 metric from Mirams et al. (2011), the dotted line shows an entirely random allocation, and the dashed line

shows the $\log_{10}\left(\frac{\text{hERG IC}_{50}}{\text{EFTPC}_{\max}}\right)$ measure from Redfern et al. (2003).

Our novel afterdepolarisation-based methods for predicting arrhythmic risk are generally more accurate than considering hERG block alone, and in some cases are as accurate as using simulated APD90. In addition, many of the protocols had maximum errors of less than 2, meaning that the most dangerous drugs were never mistaken for the least dangerous, and vice versa.

Discussion.

The threshold values for provoking after-depolarisations in models of cardiac cells were altered by simulated drug block, indicating that afterdepolarisation tendency is altered by drug actions, with combinations of drug block making cells more or less prone to showing afterdepolarisations in combination with other factors such as genetic susceptibility. Nearly all of the protocols under investigation showed some level of predictive power, which points to a connection between afterdepolarisation susceptibility and Torsades-de-Pointes.

References.

Redfern et al. Cardiovascular Research, **2003**, *58(1)*, 32–45.
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Christophe, Pharmacological Reports, **2013**, *65*, 1281-93.

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