Complex versus simple models: ion-channel cardiac toxicity prediction

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There is growing interest in applying detailed mathematical models of the heart for ion-channel related cardiac toxicity prediction. However, a debate as to whether such complex models are required exists. Here an assessment in the predictive performance between two established large-scale biophysical cardiac models and a simple linear model B_{net} was conducted. Three ion-channel data-sets were extracted from literature. Each compound was designated a cardiac risk category using two different classification schemes based on information within CredibleMeds. The predictive performance of each model within each data-set for each classification scheme was assessed via a leave-one-out cross validation. Overall the B_{net} model performed equally as well as the leading cardiac models in two of the data-sets and outperformed both cardiac models on the latest. These results highlight the importance of benchmarking complex versus simple models but also encourage the development of simple models.

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6 **Abstract**

7 There is growing interest in applying detailed mathematical models of the heart for ion-channel
8 related cardiac toxicity prediction. However, a debate as to whether such complex models are
9 required exists. Here an assessment in the predictive performance between two established large-
10 scale biophysical cardiac models and a simple linear model B_{net} was conducted. Three ion-
11 channel data-sets were extracted from literature. Each compound was designated a cardiac risk
12 category using two different classification schemes based on information within CredibleMeds.
13 The predictive performance of each model within each data-set for each classification scheme
14 was assessed via a leave-one-out cross validation. Overall the B_{net} model performed equally as
15 well as the leading cardiac models in two of the data-sets and outperformed both cardiac models
16 on the latest. These results highlight the importance of benchmarking complex versus simple
17 models but also encourage the development of simple models.

Introduction

19   There is a growing belief within the pharmaceutical industry that in order to improve predictions
20   of future experiments more detailed mathematical models of biology are required (Peterson &
21   Riggs, 2015; Knight-Schrijver et al., 2016). However by including more detail not only does the
22   number of parameters that need to be estimated increase but so does the degree of structural
23   uncertainty if the biology is not well understood i.e. the degree of confidence in the actual
24   structure of the equations (Beven, 2005). The objective of this study is to look at this issue within
25   the field of drug induced ion-channel cardiac toxicity. This area has a well-defined question
26   relating to prediction where a debate about the complexity of the model needed is ongoing.

27   Numerous drugs were withdrawn from the market during the 1990s and early 2000s for causing a
28   fatal arrhythmia, termed Torsades de Pointes (TdeP) (Yap & Camm, 2003).   Current
29   pharmaceutical industry screening strategies on identifying these compounds at an early stage in
30   drug development are based on the following biological insights (Antzelevitch & Sicouri, 1994;
31   Witchel, 2011). Prior to observing drug induced TdeP, prolongation of the QT interval is
32   commonly seen within a patient. This prolongation is due to delayed repolarisation of cardiac
33   cells within the ventricular wall, which is due to the drugs effect on the hERG ion-channel. Thus,
34   the current approach in drug development involves screening a compounds effect against hERG
35   in a high-throughput manner. However, there are other ion-channels involved in this process
36   which the safety pharmacology community are now also screening compounds against (Colatsky
37   et al., 2016). The question of interest then to the safety pharmacology community is: does
38   measuring more than hERG improve prediction for TdeP, in humans?

39   In order to answer this question a clear definition of whether a compound has TdeP liabilities or
40   not is required (Wiśniowska & Polak, 2017). The first study to examine the association between
41   multiple ion-channel inhibition and TdeP risk (Mirams et al., 2011) used a database created by
42   AstraZeneca (Redfern et al., 2003). This database was built using literature data only and has
43   never been updated since its initial publication. More recent studies (Kramer et al., 2013;
44   Lancaster & Sobie, 2016) have used the CredibleMeds database (Woosley, RL & Romero, KA;
45   Woosley et al., 2017) which was formerly known as AzCERT. Their classification is based on an
46   extensive search of both the literature and public databases and is continuously updated in-light
47   of new evidence. Furthermore it is recognised by the clinical community unlike the AstraZeneca
48   database.

49   In terms of the modelling approach used the literature is divided in terms of the complexity
50   required (Mistry, 2017). The complex models used are based on biophysical models which
51   describe the changes in ionic currents over time within a single cardiac cell (Trayanova, 2011).
52   They contain 100s of parameters and 10s of differential equations. The drug input into these
53   models involves scaling ion-channel conductance's by the amount of block at a given drug
54   concentration (Brennan, Fink & Rodriguez, 2009). Two biophysical models that have gained
55   favour in the literature are the *gold-standard*, as described by Zhou *et al. (Zhou et al., 2015)*,
56   model by O'Hara *et al.* (O'Hara et al., 2011), herein referred to as ORD, which is being put
57   forward for use by regulatory agencies (Colatsky et al., 2016) and another, by TenTusscher *et al.*

58 *(ten Tusscher & Panfilov, 2006)*, forms a part of the *cardiac safety simulator (Glinka & Polak,*
59 *2015)*, herein referred to as TT. An alternative simpler mechanistic model being put forward
60 analyses the net difference, *via* a linear combination, in drug block of the ion-channels of interest,
61 termed B_{net} *(Mistry, 2017)*. In that study B_{net} gave similar performance to a joint three biophysical
62 model/machine learning approach which used more than 300 metrics derived from the
63 biophysical models (Lancaster & Sobie, 2016).

64 In this study the predictive performance of ORD, TT and B_{net} models using a consistent and
65 reliable definition of TdeP risk from CredibleMeds across three literature data-sets (Mirams et al.,
66 2011; Kramer et al., 2013; Crumb Jr. et al., 2016) was analysed. Two of these data-sets, Mirams
67 *et al. (Mirams et al., 2011)* and Kramer *et al. (Kramer et al., 2013)*, measured drug effect against
68 3 ion-channels, hERG, Cav 1.2 and Nav 1.5 peak. The third and latest data-set, from Crumb *et*
69 *al.* (Crumb Jr. et al., 2016), considers drug effect on 7 ion-channels, hERG (IKr), KCNQ1 +
70 KCNE1 (IKs), Kv4.3 (Ito), Kir2.1 (IK1), Cav 1.2 (ICaL), Nav1.5 peak (INa) and Nav1.5 late
71 (INaL), the largest number studied so far.

72 By using a consistent definition of TdeP risk across different data-sets that have different
73 dimensionality in terms of ion-channels studied the analysis conducted will provide a detailed
74 view on the performance of each model. Thus enabling scientists to make a more informed
75 decision about which modelling approach is likely to be the most useful for the prediction
76 problem considered.

Methods

77

Data

78

79 Ion-channel IC50 values, defined as concentration of drug that reduces the flow of current by
80 50%, were collected from three publications (Mirams et al., 2011; Kramer et al., 2013; Crumb Jr.
81 et al., 2016). Compounds within those data-sets were placed into two classification schemes
82 based on the information in Credible Meds (Woosley, RL & Romero, KA; Woosley et al., 2017),
83 see Table 1. The first classification scheme termed QT/TdeP focusses on both QT prolongation
84 and TdeP risk, which was used in two previous studies (Kramer et al., 2013; Lancaster & Sobie,
85 2016). The second classification scheme focusses on known TdeP risk only. All data is provided
86 in supplemental material.

Model input data

87

88 The percentage block against a given ion-channel inputted into all models was calculated using
89 the mean maximal concentration observed corrected for plasma protein binding and is referred to
90 as the effective therapeutic concentration (EFTPC), which was provided in the original articles,
91 using a pore block model,

$$Block = \frac{1}{1 + \dfrac{IC50}{EFTPC}} \quad (1)$$

92   **Models**

93   **Single cell cardiac model simulations**

94   The AP predict platform (Williams & Mirams, 2015) which is a web-based cardiac modelling
95   simulation platform (https://appredict.cs.ox.ac.uk) was used to simulate the ORD and TT models
96   in all cases except for one simulation study. A MATLAB version of the ORD model available on
97   the Rudylab website (http://rudylab.wustl.edu) was used when simulating the block of 7 ion-
98   channels since that model on AP predict does not allow blocking of INaL – a current measured in
99   the Crumb *et al.* data-set. The default settings within the AP predict platform were used i.e. 1Hz
100   pacing for 5 minutes with the APD90, time taken for the action potential to repolarise by 90%,
101   recorded using the last cycle. The same protocol was applied in MATLAB when exploring the 7
102   ion-channels within the ORD model i.e. 1Hz pacing for 5 minutes with APD90 recorded using
103   the last cycle. In all simulations drug block was initiated at the beginning of simulations.

104   B_{net}

105   B_{net} was defined as the net difference in block between repolarisation and depolarisation ion-
106   channels as,

$$B_{net} = \sum_{i=1}^{n} \lparen R_i - \sum_{j=1}^{m} D_j \rparen$$

107   where R_i and D_j represent the percentage block against repolarisation and depolarisation ion-
108   channels respectively for a specific drug. Ionic currents responsible for repolarisation are IKr IKs
109   and Ito, and that for depolarisation are ICaL, INa (peak), INa (late) and IK1.

110   **Classification evaluation**

111   For each compound the percentage change in APD90 compared to control (no block) from the
112   biophysical model simulations was recorded as was the B_{net} value. These values were then placed
113   within a logistic regression analysis to assess their correlative value to either QT/TdeP or TdeP
114   risk. This was done via a leave one out cross validation (LOOCV). This involves training a
115   classifier to *n-1* compounds and testing on the nth. Thus all compounds perform part of the test-
116   set. The predicted probability of risk for each test compound is then used to generate a ROC
117   AUC (area under the receiver operating characteristic curve) which is reported. Note that
118   LOOCV has been the method of choice within this field when assessing the correlation between
119   metrics and drug risk (Mirams et al., 2011; Kramer et al., 2013; Lancaster & Sobie, 2016).

120   **Results**

Data

The total number of compounds and their classification according to CredibleMeds across the 3 data-sets of interest can be seen in Figure 1. Although the total number of compounds differs from one data-set to another the proportions that are KR, PR and CR/NR does not appear to.

The distribution of block against each ionic current, at the EFTPC, across all data-sets can be seen in Figure 2. The plots show that the activity of the compounds is greatest against IKr across all data-sets. After IKr, ICaL appears to be the next channel for which a substantial amount of activity is seen. A somewhat surprising result is the degree of activity against INaL but not INa in the Crumb *et al.* data-set. The amount of activity against INaL in that data-set mirrors that of ICaL activity.

Classification Evaluation

The results of the leave-one-out cross validation for each data-set using various models for the two classification schemes can be seen in Tables 2 and 3. For the Mirams *et al.* data-set it's noticeable that ORD performs no better than using just block against hERG for either classification scheme. Furthermore for the QT/TdeP classification ORD is no better than random chance. Both TT and B_{net} show a similar improvement over using just hERG block for both classification schemes.

Moving onto the Kramer *et al.* data-set the performance of all models improves dramatically over the Mirams *et al.* data-set. Here all 3 models show superior performance over just hERG block regardless of the classification scheme used. Note that again the performance of ORD is not as high as B_{net} or TT. In addition the difference between B_{net} and TT is negligible.

Within the latest data-set by Crumb *et al.* the performance of all models, when using only 3 ion-channels, drops to a level similar to that seen within the Mirams *et al.* data-set. The key difference between the results between those two data-sets is that ORD now shows similar performance to TT regardless of the classification scheme used. Furthermore neither biophysical model performs overly better than using hERG block. B_{net} however appears to give reasonable performance again and appears to show an improvement over using hERG block for both classification schemes. Finally when moving onto using all the ion-channel data from the Crumb *et al.* data-set the difference in performance between the models is quite striking. B_{net}'s performance improves with the addition of more information whereas there is little improvement in either biophysical model.

In summary the results show that the performance of the models is data-set dependent. However, within each data-set the B_{net} model performs just as well if not better than leading biophysical models.

Discussion

There appears to be a strong belief within the field of ion-channel cardiac drug toxicity that large scale single cell (Mirams et al., 2011) and even whole heart models (Okada et al., 2015) are

158   required to answer a well-defined question: does measuring more than hERG improve prediction
159   for TdeP, in humans? The evidence base, that suggests that large-scale biophysical models
160   perform better than simpler models for this question, simply does not exist. Previous studies have
161   shown that the performance of the large-scale cardiac models can be mirrored by simpler models
162   (Mistry, Davies & Di Veroli, 2015; Mistry, 2017).

163   This study builds on those previous studies (Mistry, Davies & Di Veroli, 2015; Mistry, 2017) of
164   comparing the performance of complex biophysical models versus simpler models in the
165   following way. First a consistent definition of TdeP risk based on the CredibleMeds database was
166   used across all data-sets (Woosley, RL & Romero, KA; Woosley et al., 2017). Second in addition
167   to data-sets that considered drug activity against only 3 ion-channels (Mirams et al., 2011;
168   Kramer et al., 2013) a third data-set (Crumb Jr. et al., 2016) which measured drug affinity against
169   7 ion-channels was also assessed.

170   The three models evaluated in this study were: 1) the *gold-standard (Zhou et al., 2015)* single
171   cell model by O'Hara *et al.* (O'Hara et al., 2011); 2) the single cell model by TenTusscher *et al.*
172   *(ten Tusscher & Panfilov, 2006)* which is used within the *cardiac safety simulator (Glinka &*
173   *Polak, 2015)*; 3) a linear mechanistic model evaluating the net difference in block between ion-
174   channels involved in repolarising and depolarising the action potential, B_{net} (Mistry, 2017). Each
175   model was assessed via a leave-one-out cross validation using two different classification
176   schemes based on the CredibleMeds database. The first scheme focussed on the joint QT
177   prolongation and TdeP risk whereas the second scheme focussed on TdeP risk only. In addition to
178   using outputs from the aforementioned models within the classification exercise the amount of
179   block against hERG channel was used as a naïve benchmark.

180   Overall the analysis conducted showed that the performance of B_{net} was superior to the more
181   complex cardiac models regardless of the classification scheme used. B_{net} was also the only model
182   that consistently showed the benefit of measuring more than hERG. Finally B_{net} was the only
183   model whose performance improved when moving from using information against 3 ion-channels
184   to 7. These results may appear surprising but are not uncommon in prediction problems in other
185   fields (Makridakis & Hibon, 2000; Green & Armstrong, 2015). The key reason why complex
186   models are not necessarily more predictive than simpler models is due to model error i.e. error in
187   the structure of the model itself (Beven, 2005). The concept of model error has only recently been
188   assessed (Beattie et al., 2017) within the cardiac modelling field and so more needs to be done.
189   Thus the effect of model error on predictivity is largely unknown, although in other fields it tends
190   to dominate prediction uncertainty (Orrell et al., 2001; Refsgaard et al., 2006).

191   This study is not without its caveats. The first is that the data-sets used may be too small to
192   understand how large a discrepancy there truly is between the different models. However it is
193   hoped that by continuing to assess new data-sets as they become available that the community
194   will eventually have a comprehensive compound list. Second, the latest data-set by Crumb *et al.*
195   *(Crumb Jr. et al., 2016)* although measured the affinity of drugs against 7 ion-channels the
196   compounds only really showed activity against 3. Thus, whether the results seen here will hold
197   for a set of compounds with activity against a large number of ion-channels still remains

198 unknown. Similar to the previous caveat this can only be assessed as more data is generated. The
199 final caveat relates to the B_{net} model itself. The model currently doesn't consider the kinetics of
200 blocking which has been highlighted as an important factor (Di Veroli et al., 2014). However
201 these studies have been on a small numbers of compounds and so a true assessment of the
202 importance of kinetics cannot be determined from those studies alone. If sufficient evidence
203 regarding the importance of drug kinetics does eventually become available adjustments to the
204 B_{net} model could be made.

205 Conclusion

206 In summary the study conducted here highlights the importance of benchmarking complex
207 models against simpler ones. Furthermore it highlights that simple mechanistic models can not
208 only give similar performance to large-scale mechanistic models but can out-perform them.
209 Finally it is hoped this study highlights that there is more than one solution to a problem and that
210 although the question and quality of data dictates the modelling approach it should not dictate the
211 size of the model.

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294 **Figure Legends**

295 **Figure 1:** Stacked bar-chart shows the proportion of compounds in each data-set that are KR, PR
296 or CR/NR based on information within the CredibleMeds database.

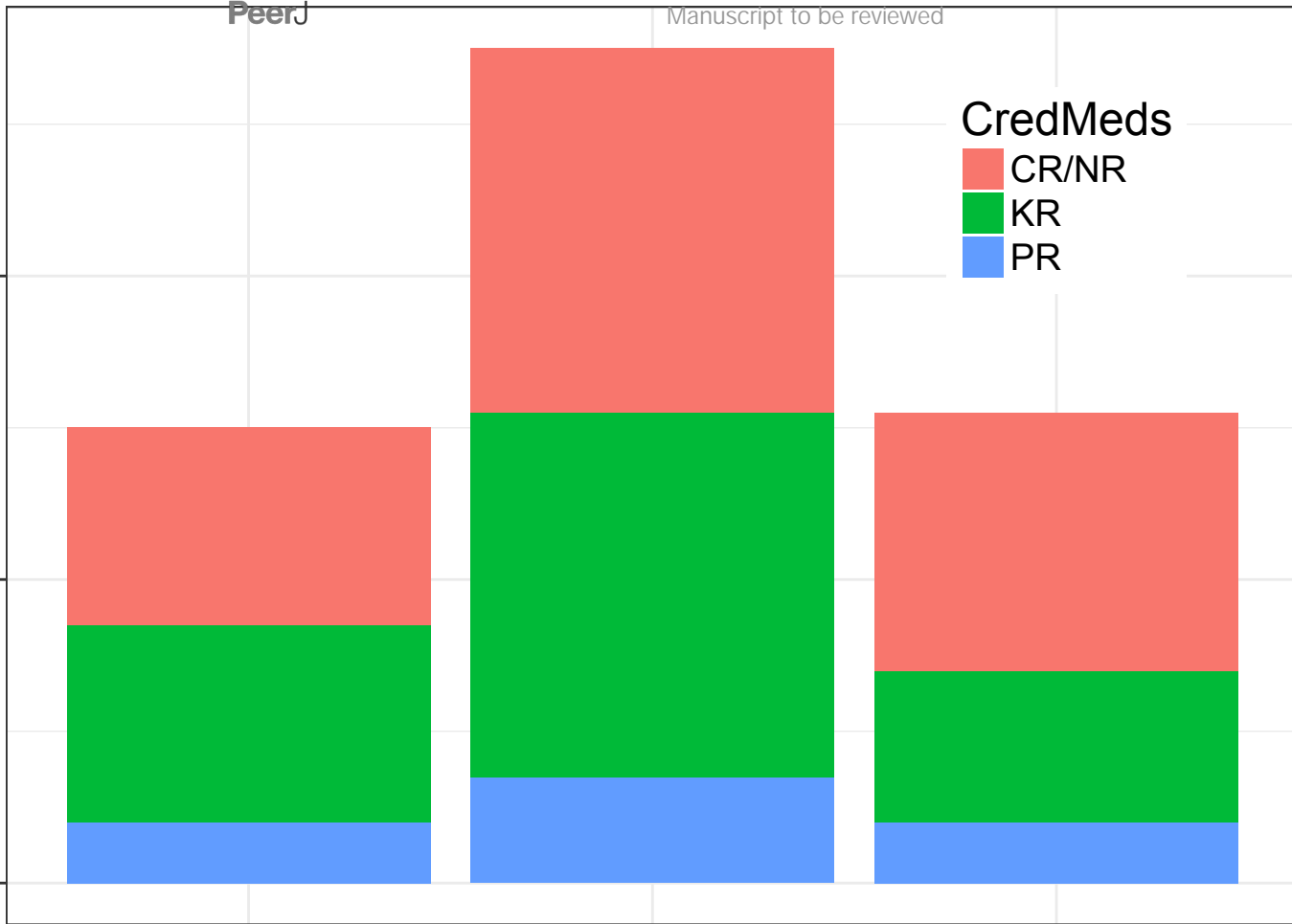
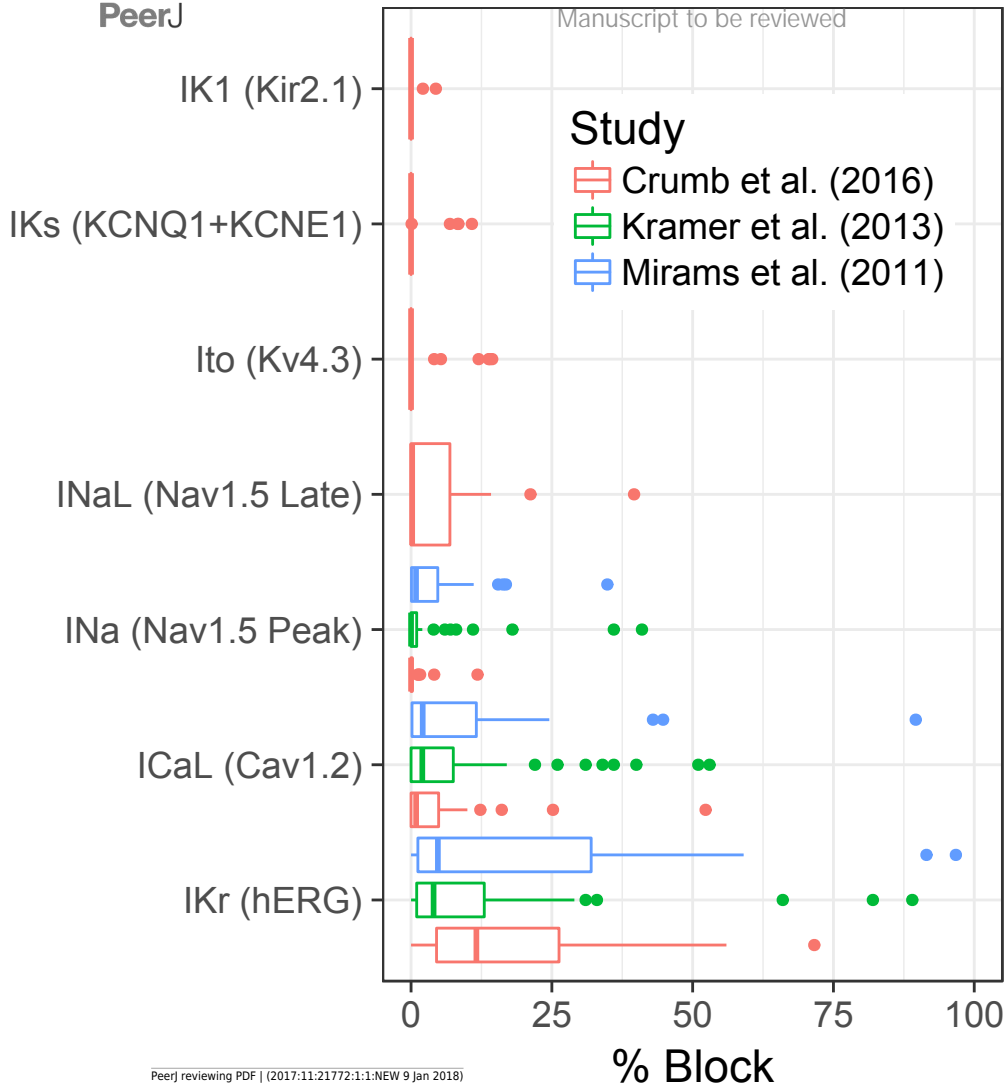
297 **Figure 2:** Boxplots show the distribution of block for each ionic current across all 3 data-sets.

298 **Table Titles**

299 **Table 1:** Description of the two classification schemes constructed from the CredibleMeds
300 database.

301 **Table 2:** ROC AUC values from the leave one out cross validation for assessing the joint
302 QT/TdeP risk across all data-sets for all models considered.

303 **Table 3:** ROC AUC values from the leave one out cross validation ROC AUC for assessing TdeP
304 risk only across all data-sets for all models considered.

Stacked bar-chart shows the proportion of compounds in each data-set that are KR, PR or CR/NR based on information within the CredibleMeds database.

Boxplots show the distribution of block for each ionic current across all 3 data-sets.

Description of the two classification schemes constructed from the CredibleMeds database.

CredibleMeds	Description	QT/TdeP	TdeP
Known Risk (KR)	Known TdeP Risk	+ive	+ive
Possible Risk (PR)	Known QT Risk	+ive	-ive
Conditional Risk (CR)	Conditional TdeP Risk (e.g. drug-drug interaction)	-ive	-ive
No Risk (NR)	Not listed on CredibleMeds	-ive	-ive

ROC AUC values from the leave one out cross validation for assessing the joint QT/TdeP risk across all data-sets for all models considered.

Leave One Out Cross Validation ROC AUC				
Data-Set	3 ion-channels			hERG
	B_{net}	ORD: ΔAPD90	TT: ΔAPD90	% Block IKr
Mirams (2011)	0.71	0.53	0.68	0.51
Kramer (2013)	0.96	0.86	0.94	0.67
Crumb (2016)	0.71	0.65	0.65	0.61
	7 ion-channels			
Crumb (2016)	0.82	0.67	0.60*	

1 *based on 6 ion-channels – INaL not modelled by TenTusscher et al. (TT); ΔAPD90: percentage change in
2 APD90

ROC AUC values from the leave one out cross validation ROC AUC for assessing TdeP risk only across all data-sets for all models considered.

	Leave One Out Cross Validation ROC AUC			
Data-Set	3 ion-channels			hERG
	B_{net}	ORD: ΔAPD90	TT: ΔAPD90	% Block IKr
Mirams (2011)	0.78	0.66	0.75	0.62
Kramer (2013)	0.86	0.80	0.84	0.68
Crumb (2016)	0.68	0.61	0.62	0.57
	7 ion-channels			
Crumb (2016)	0.77	0.63	0.59*	

1 *based on 6 ion-channels – INaL not modelled by TenTusscher et al. (TT); ΔAPD90: percentage change in

2 APD90