Torsades Metric Candidate, Uncertainty Quantification, and Validation Strategy

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Disclaimer

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<table>
<thead>
<tr>
<th>High TdP Risk</th>
<th>Intermediate TdP Risk</th>
<th>Low TdP Risk</th>
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<tbody>
<tr>
<td><strong>Training:</strong></td>
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<tr>
<td>Bepridil</td>
<td>Chlorpromazine</td>
<td>Diltiazem</td>
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<tr>
<td>Dofetilide</td>
<td>Cisapride</td>
<td>Mexiletine</td>
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<tr>
<td>Quinidine</td>
<td>Terfenadine</td>
<td>Ranolazine</td>
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<td>D,l Sotalol</td>
<td>Ondansetron</td>
<td>Verapamil</td>
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<td><strong>Validation:</strong></td>
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<tr>
<td>Azimilide</td>
<td>Astemizole</td>
<td>Loratadine</td>
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<tr>
<td>Ibutilide</td>
<td>Clarithromycin</td>
<td>Metoprolol</td>
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<tr>
<td>Vandetanib</td>
<td>Clozapine</td>
<td>Nifedipine</td>
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<tr>
<td>Disopyramide</td>
<td>Domperidone</td>
<td>Nitrendipine</td>
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<td></td>
<td>Droperidol</td>
<td>Tamoxifen</td>
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<td></td>
<td>Pimozide</td>
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<td>Risperidone</td>
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Clinical Translational Working Group
Key Mechanism of TdP: imbalance of Inward and Outward Currents

Inward and Outward Currents:
- ICaL (L type calcium)
- INaL (late sodium)
- IKr (potassium)
- IKs (potassium)
- IK1 (potassium)
- Ito (potassium)

The net current between inward and outward currents reflect their balance.

\[ \text{Inet} = \text{ICaL} + \text{INaL} + \text{IKr} + \text{IKs} + \text{IK1} + \text{Ito} \]

qNet: AUC of Inet (amount of electronic charge carried by Inet)
Performance of qNet on 12 CiPA Training Compounds

- **Red**: CiPA TdP High Risk
- **Blue**: CiPA TdP Intermediate Risk
- **Green**: CiPA TdP Low/No Risk

🌟: EAD induced

**qNet**: Net amount of electronic charges passing through the membrane carried by selected currents

Simulation with 2000 ms cycle length

- Drug separation is good along all concentrations from 1x to 25x Cmax
Comparison of the New Metric(s) with All Other Tested Markers

- qNet is the only metric with 0 training error across all concentrations
- Metrics based on action potential duration (APD), the cellular basis for QT interval, failed to classify all training drugs
**qNet vs APD : A Case Study**

**Q:** Which cell is in a more dangerous status (closer to EAD generation)?
- APD: The cell with ranolazine (black)
- qNet: The cell with cisapride (grey)

- qNet, but not APD, correctly predicts the distance from EAD
- qNet, but not APD, independently supports the rank order of the two drugs in CiPA categories
Recent Publication about the qNet Metric and Its Physiological Significance

Optimization of an \textit{In silico} Cardiac Cell Model for Proarrhythmia Risk Assessment

Sara Dutta, Kelly C. Chang, Kylie A. Beattie, Jiansong Sheng, Phu N. Tran, Wendy W. Wu, Min Wu, David G. Strauss, Thomas Colatsky$^{7}$ and Zhihua Li$^{*}$

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Incorporating Experimental Uncertainty

• Experimental data have intrinsic (i.e. inherent randomness) and extrinsic (i.e. cell-to-cell variability) uncertainty

• This will lead to uncertainty in model parameterization, metric calculation and TdP risk assessment
hERG Dynamic Model Fitting to Data Ignoring Variability

- Each concentration was tested with 4-7 cells
- Cells from the same concentration were averaged to produce mean time-dependent fractional block (symbols)
- Model was fitted to mean values to estimate single-point fractional block at each time point
- Best fit (solid lines) is close to the mean data but ignores variability

hERG Dynamic Model Fitting to Data with Uncertainty Quantification

- **Traces**: data from individual cells
- Uncertainty/variability among individual traces are quantified and translated to uncertainty in model parameters and predictions
- **Bands**: 95% confidence interval (CI) of model-simulated fractional block

Uncertainty quantification was done through bootstrapping, details in Kelly Chang et al. Frontiers in Physiology. 2017. In revision
IC50 Fitting With and Without Uncertainty Quantification

- Circles: Experimental data
- Solid line: best fit to the data showing fixed-point %block at each concentration
- Uncertainty/variability among individual cells are quantified and translated to uncertainty in model parameters and prediction
- Shaded area: 95% confidence interval of predicted %block at each concentration
- Note that the width the uncertainty band increases dramatically after the highest experimentally tested concentration (Chigh)

Uncertainty quantification was done through Markov Chain Monte Carlo (MCMC), details in:
Relationship Between Highest Tested Concentration and Uncertainty

- **Chigh**: (Highest Tested Concentration)
- Average block at Chigh is ~26%
- At concentrations beyond Chigh, the 95% of confidence interval (CI) of predicted block (width of band) increases dramatically (high uncertainty)

**Chigh = 6 nM**
- **Block = ~26%**

**Chigh = 5.4 uM**
- **Block = ~64%**
- Average block at Chigh is ~64%
- At concentrations beyond Chigh, the 95% of confidence interval (CI) of predicted block (width of band) is still narrow (low uncertainty)
Relationship Between Highest Tested Concentration and Uncertainty

Average block% at Chigh

Width of 95% CI at 3x Chigh

Uncertainty of Block Beyond Chigh

- When block percentage < 60% at Chigh (dotted line), extrapolated block% (at 3x Chigh) has high uncertainty
- When block percentage > 60% at Chigh (dotted line), block% can be extrapolated to 3x Chigh with low uncertainty

Important Implication: CiPA In Vitro assay needs to test as high concentrations as possible!
qNet Metric with Uncertainty

- At low concentrations, good separation due to low uncertainty
- Beyond certain concentration, high uncertainty leads to bad separation
Concentration and Prediction Error

- Prediction error based on leave-one-out cross validation
- At each concentration, there are 12 errors, corresponding to 12 training drugs
- Black line: mean error across 12 training drugs
- Lowest prediction error achieved for 1-4x Cmax

Conclusion: For CiPA manual training dataset, concentrations 1-4x Cmax should be used for qNet calculation and TdP risk prediction.
Torsades Metric Score of Manual Data

hERG data: manual CiPA dynamic protocol (modified Milnes protocol)
Non-hERG data: Manual AP wave form protocol
Torsades Metric Score of Hybrid Data

- High risk
- Intermediate risk
- Low risk

- hERG data: manual CiPA dynamic protocol (modified Milnes protocol)
- Non-hERG data: High Throughput CiPA step/ramp protocols
Summary and Validation Strategy

- CiPA Model and Metric had been developed using manual patch clamp data for 12 CiPA training compounds.
- CiPA Model and Metric had been tested using hybrid training dataset (manual dynamic data for hERG and HTS data for non-hERG).
- The model (CiPAORdv1.0) and metric (qNet, with qNet averaged 1-4x Cmax being Torsades Metric Score) had been frozen for independent validation.
- The 16 validation drugs are being assessed by both manual and HTS systems, generating a manual validation dataset and a hybrid dataset.
- The model and metric will be evaluated based on their performance on two tasks:
  - Rank order the TdP risk levels of the validation compounds.
  - Assign each of the validation compounds into one of the three risk categories.
- Performance measures are pre-defined for objective assessment of model prediction power.
## Pre-defined Performance Measures

<table>
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<tr>
<th>Performance Measure</th>
<th>Interpretation</th>
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<tr>
<td>AUC (Area Under the Curve) of ROC</td>
<td>When two drugs are coming from two risk categories, probability of ranking the higher-risk drug above the lower-risk drug</td>
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<tr>
<td>ROC (Receiver Operating Characteristic)</td>
<td>Probability of correctly ranking a drug relative to CiPA reference drugs through a series of pairwise comparison</td>
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<td>Pairwise comparison</td>
<td>Likelihood ratio of a certain prediction (i.e. high risk) occurring in a drug coming from the correct category vs a drug coming from another category</td>
</tr>
<tr>
<td>Mean Classification Error</td>
<td>Average error of classifying a drug into High, Intermediate, or Low risk category</td>
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Acknowledgements

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• Ion Channel working group
• In silico working group
• Cardiomyocyte working group
• Phase 1 ECG working group

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