Torsades Metric Candidate, Uncertainty Quantification, and Validation Strategy

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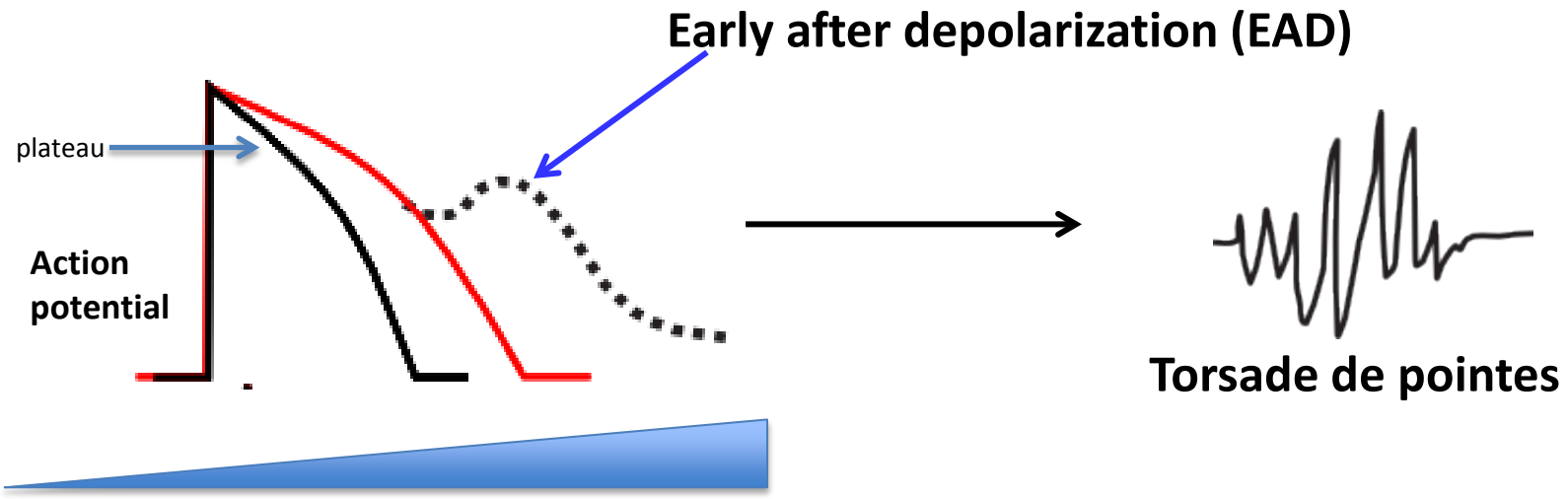
CiPA Drugs Selected for Model Development

High TdP Risk	Intermediate TdP Risk	Low TdP Risk
Training:	**Training:**	**Training:**
Bepridil	Chlorpromazine	Diltiazem
Dofetilide	Cisapride	Mexiletine
Quinidine	Terfenadine	Ranolazine
D,l Sotalol	Ondansetron	Verapamil
Validation:	**Validation:**	**Validation:**
Azimilide	Astemizole	Loratadine
Ibutilide	Clarithromycin	Metoprolol
Vandetanib	Clozapine	Nifedipine
Disopyramide	Domperidone	Nitrendipine
	Droperidol	Tamoxifen
	Pimozide	
	Risperidone	

Clinical Translational Working Group

Key Mechanism of TdP: imbalance of Inward and Outward Currents



Major currents modulating repolarization

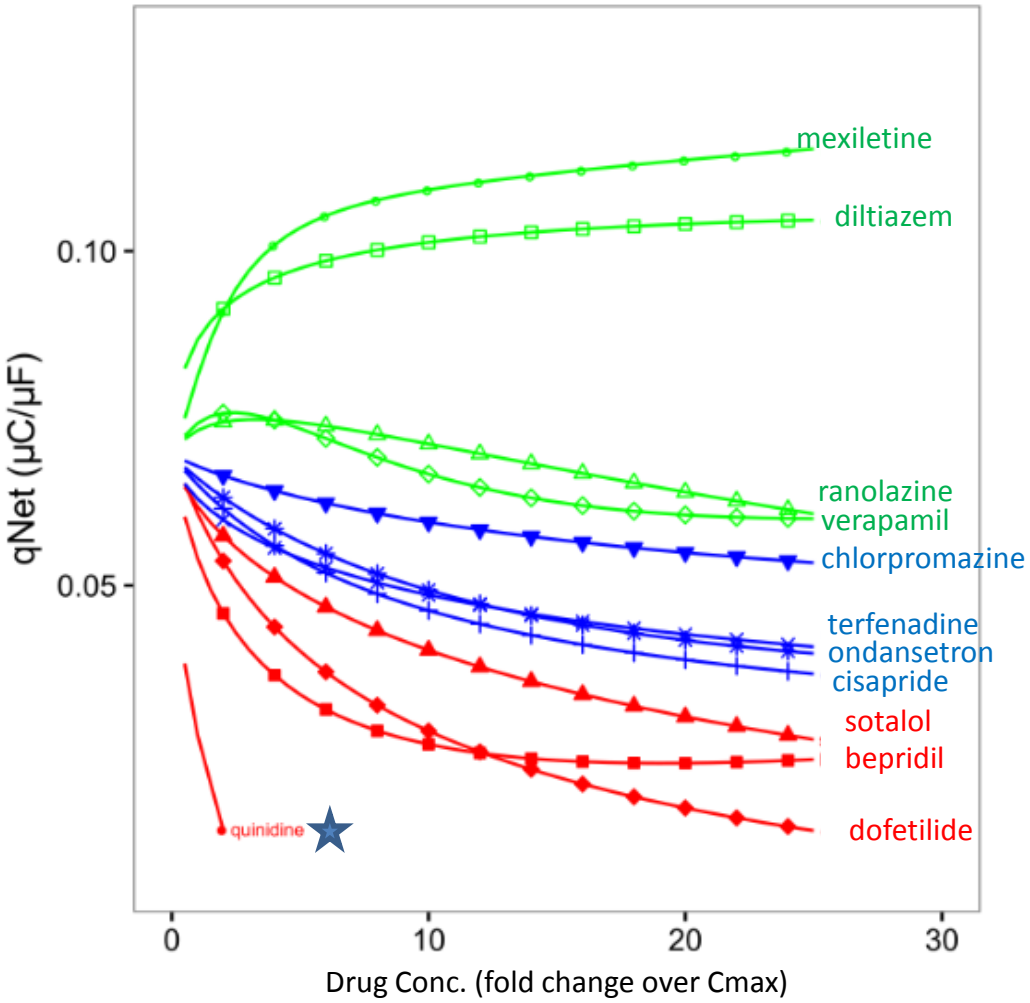
Inward	Outward
ICaL (L type calcium)	IKr (potassium)
INaL (late sodium)	IKs (potassium)
	IK1 (potassium)
	Ito (potassium)

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

Inet = ICaL+INaL+IKr+IKs+IK1+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

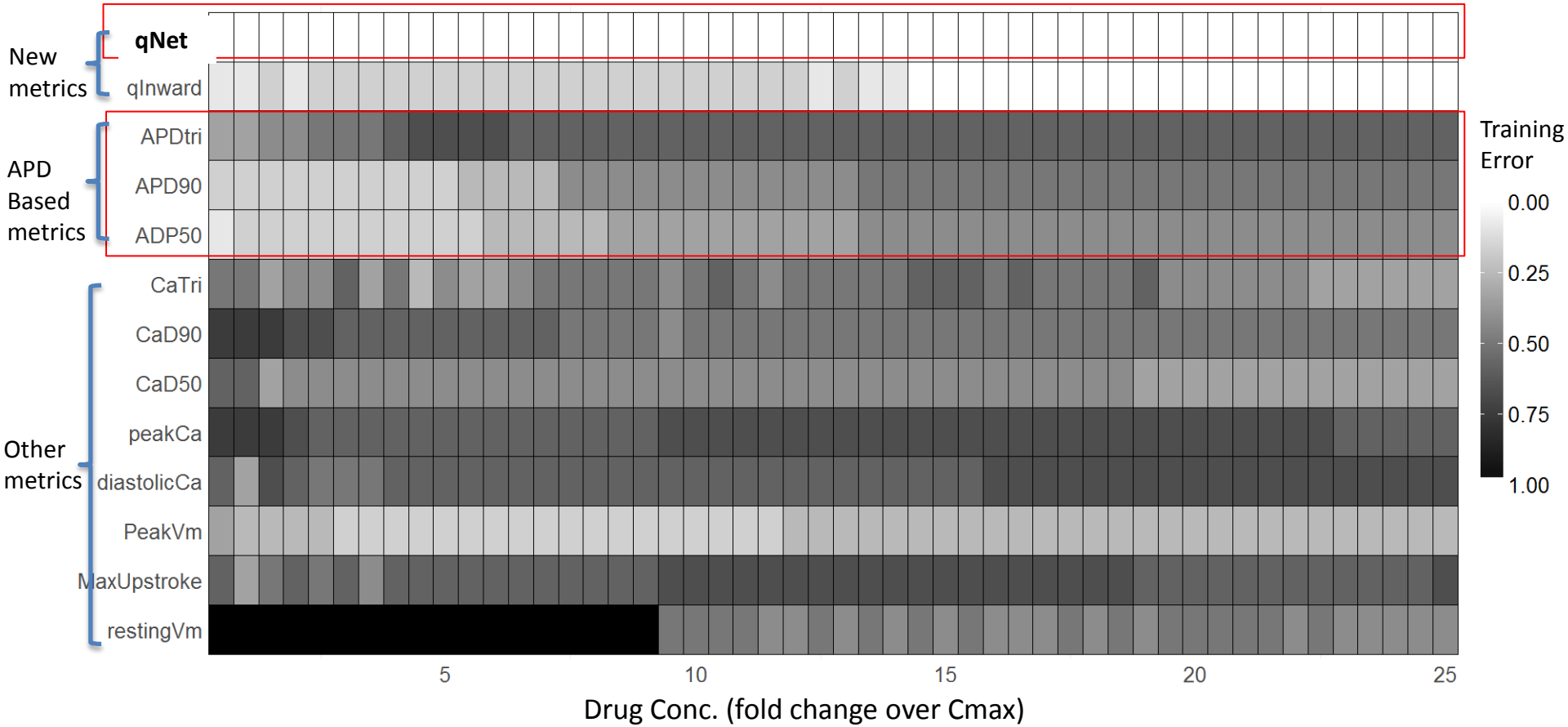
★: EAD induced

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

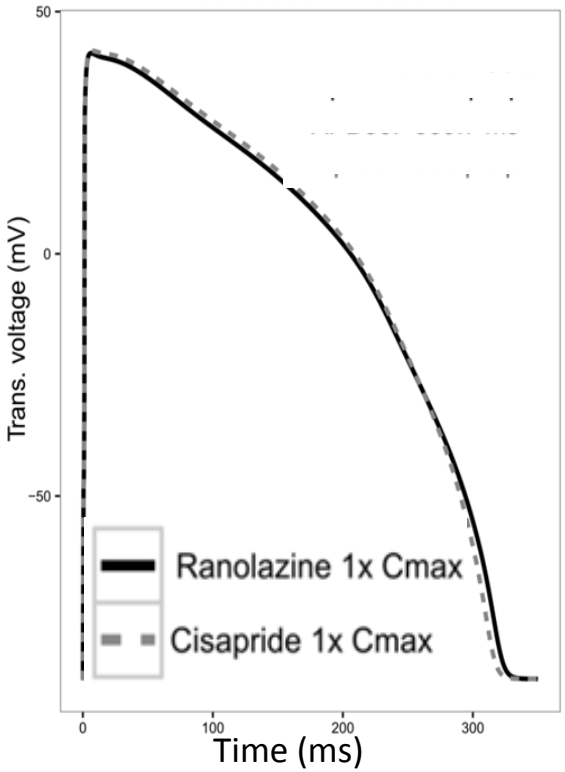


- qNet is the only metric with 0 training error across all concentrations
- Metrics based on action potential duration (APD), the cellular basis for QT interval, failed to classify all training drugs

qNet vs APD : A Case Study

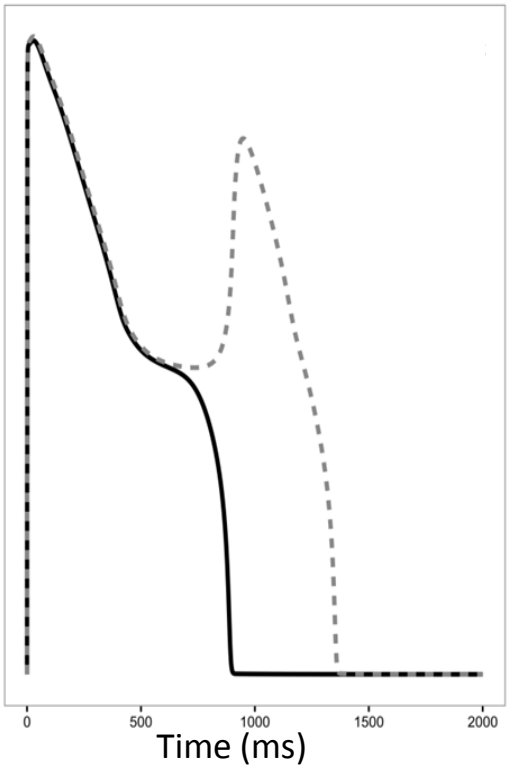
Q: **Which cell is in a more dangerous status (closer to EAD generation)?**

- **APD: The cell with ranolazine (black)**
- **qNet: The cell with cisapride (grey)**



Applying the same pro-EAD "push"

Added 91.6% IKr conductance reduction (perburbation)



- 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

frontiers in Physiology

ORIGINAL RESEARCH
published: 23 August 2017
doi: 10.3389/fphys.2017.00616

Optimization of an *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† and Zhihua Li**

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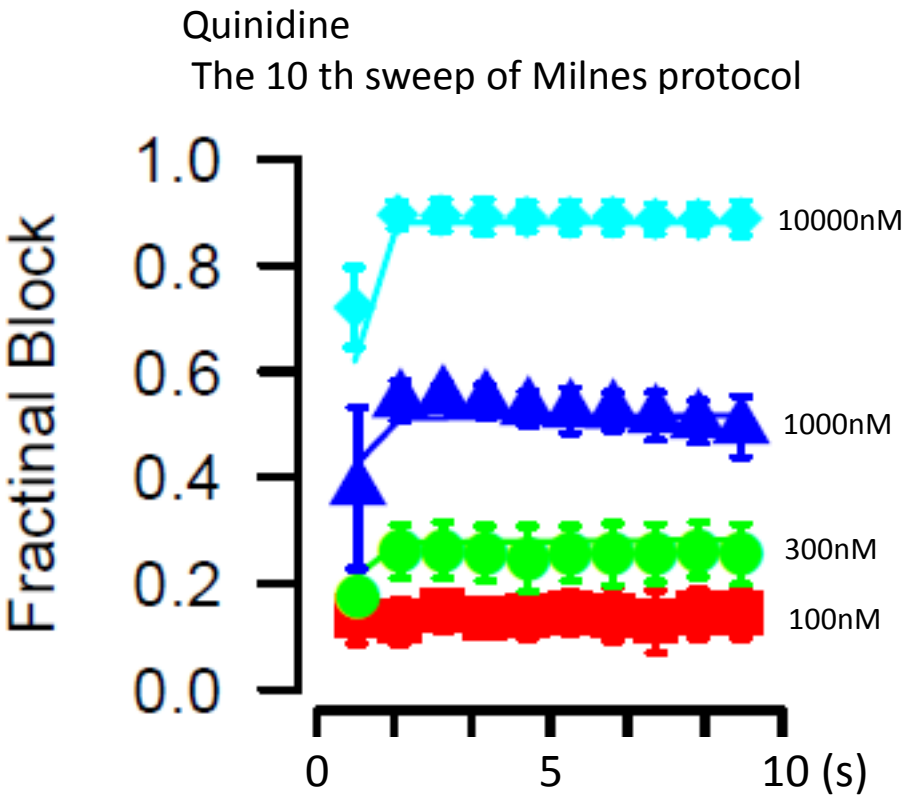
Incorporating Experimental Uncertainty

- 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

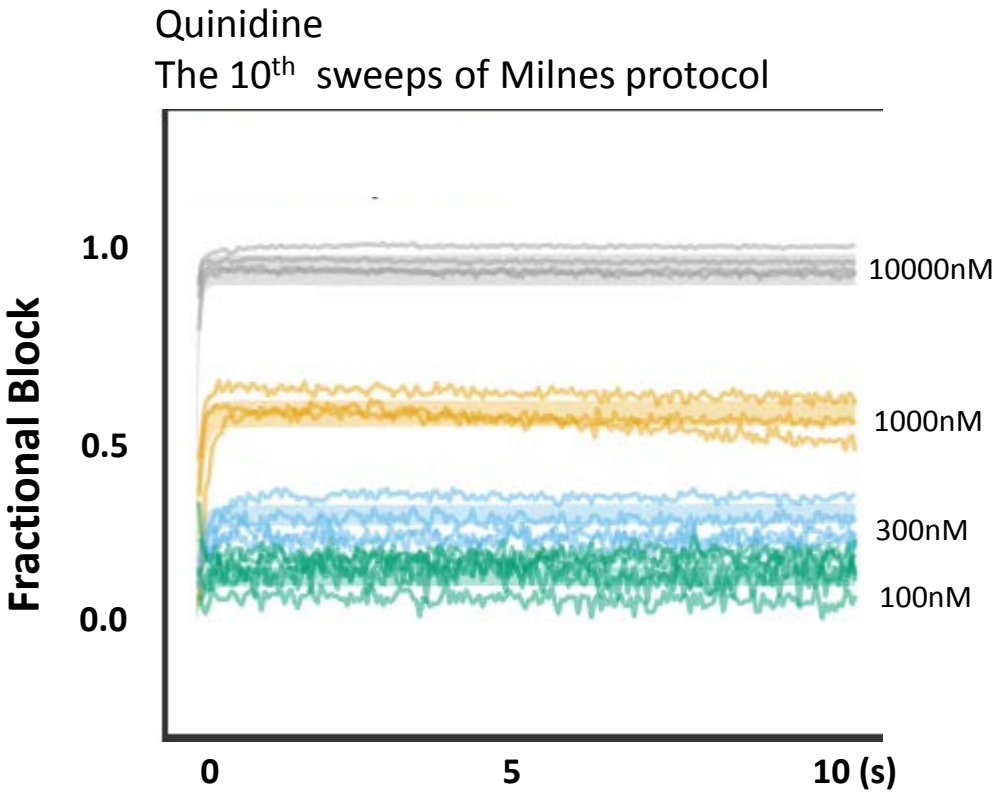
hERG Dynamic Model Fitting to Data Ignoring Variability



- 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

Li et al. Circulation: Arrhtymia & Electrophysiology. 2017. 10(2): e004628

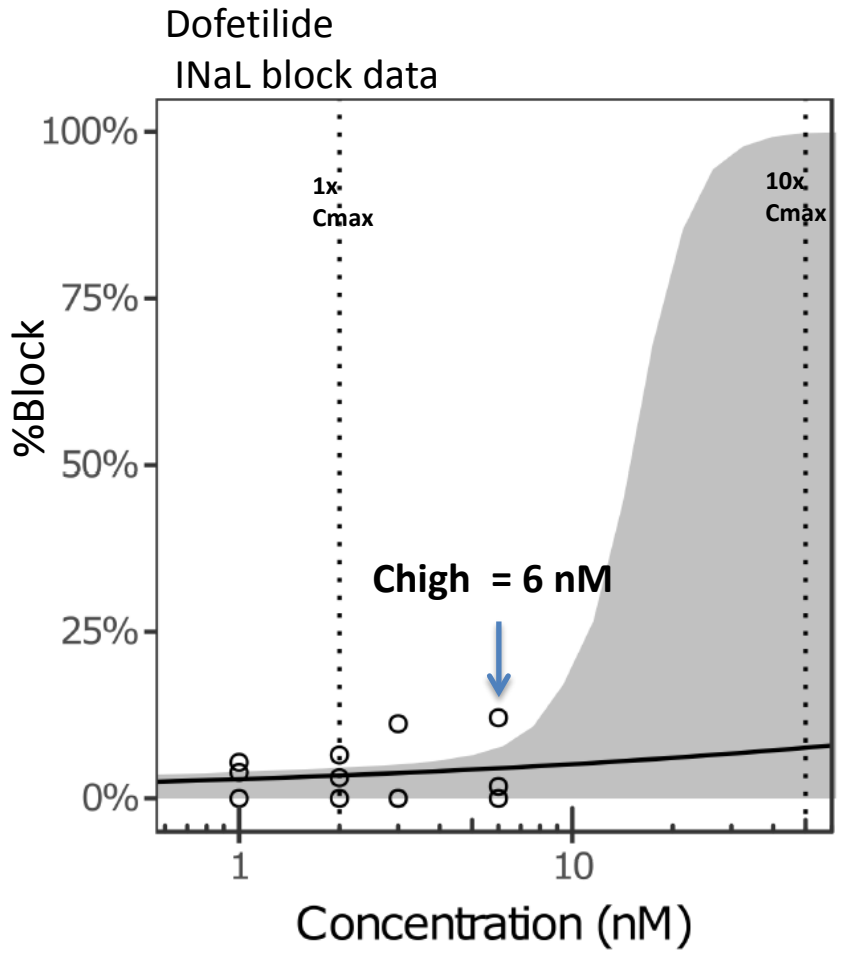
hERG Dynamic Model Fitting to Data with Uncertainty Quantification



- 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

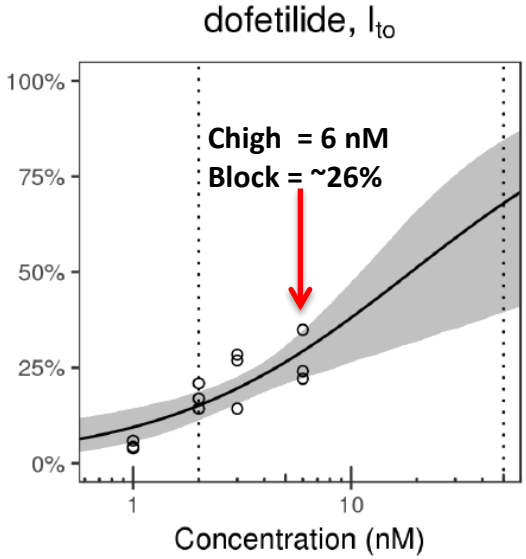
IC50 Fitting With and Without Uncertainty Quantification



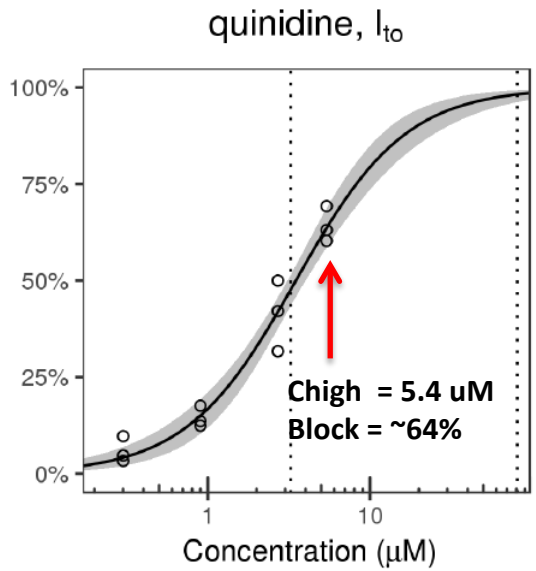
Uncertainty quantification was done through Markov Chain Monte Carlo (MCMC), details in:
Johnstone et al. Wellcome Open Res. 2016.
Chang et al. Frontiers in Physiology. 2017. In revision

- 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)

Relationship Between Highest Tested Concentration and Uncertainty

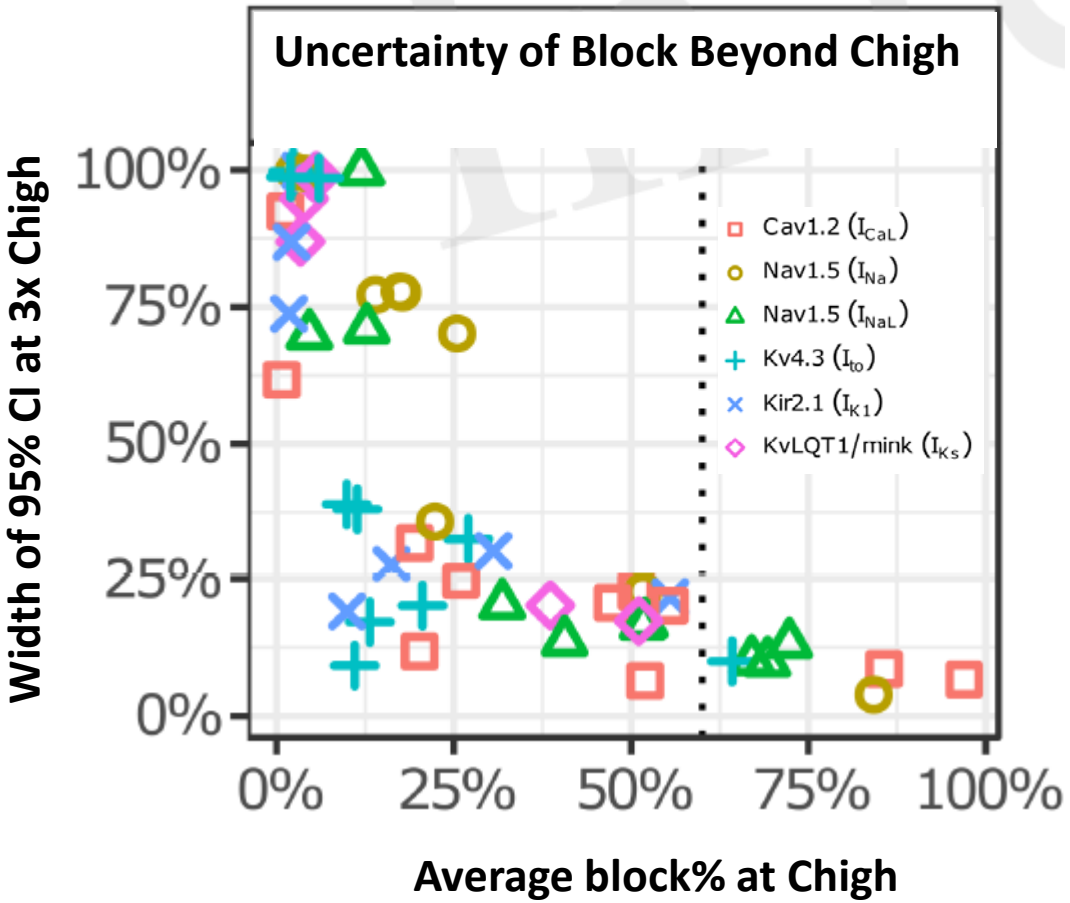


- Chigh : (Highest Tested Concentration)
- Average block at Chigh is ~26%
- At concentrations beyond Chigh, the 95% of confidence interval (CI) of predicted block (width of band) increases dramatically (high uncertainty)



- Chigh : (Highest Tested Concentration)
- 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)

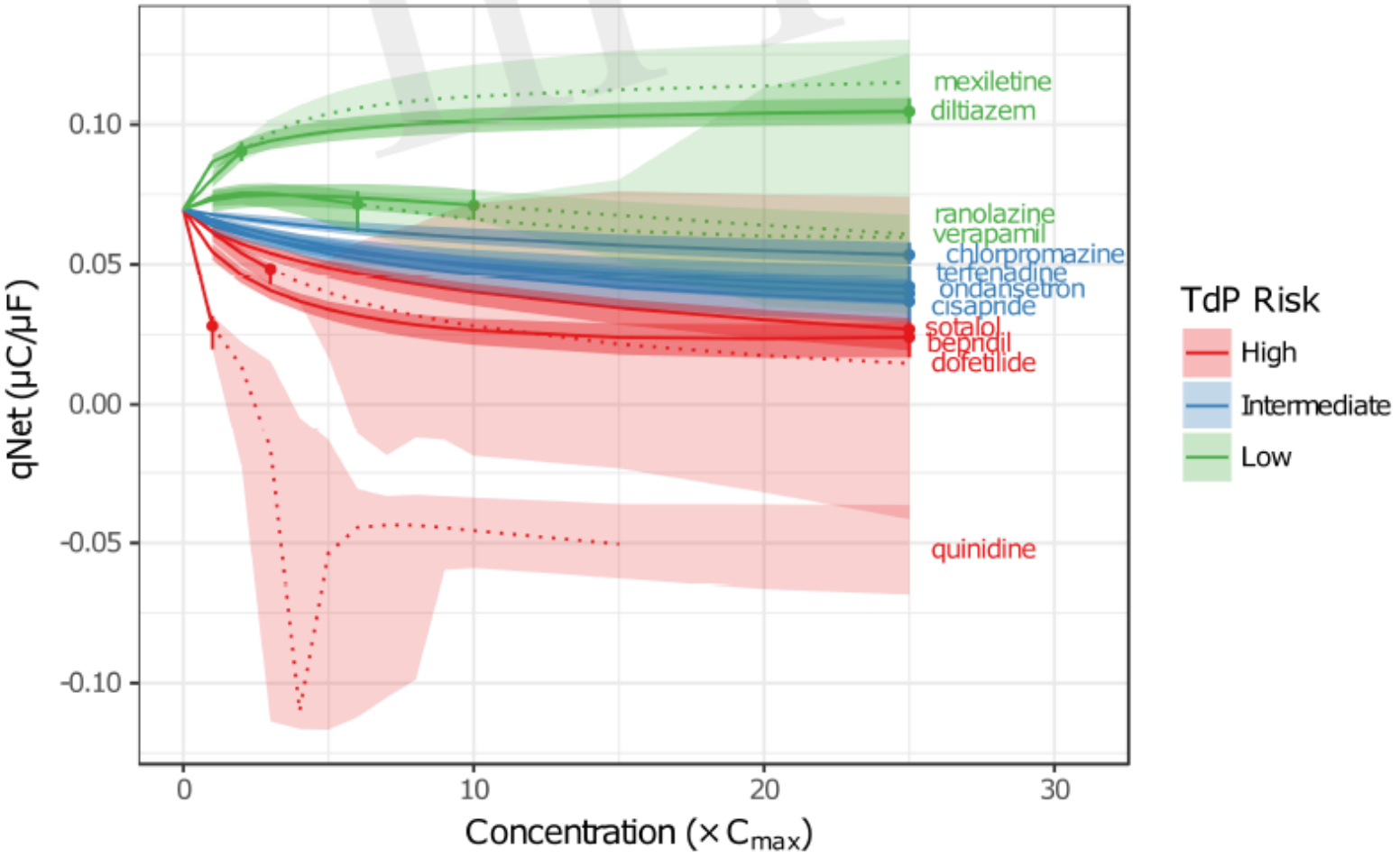
Relationship Between Highest Tested Concentration and Uncertainty



- 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

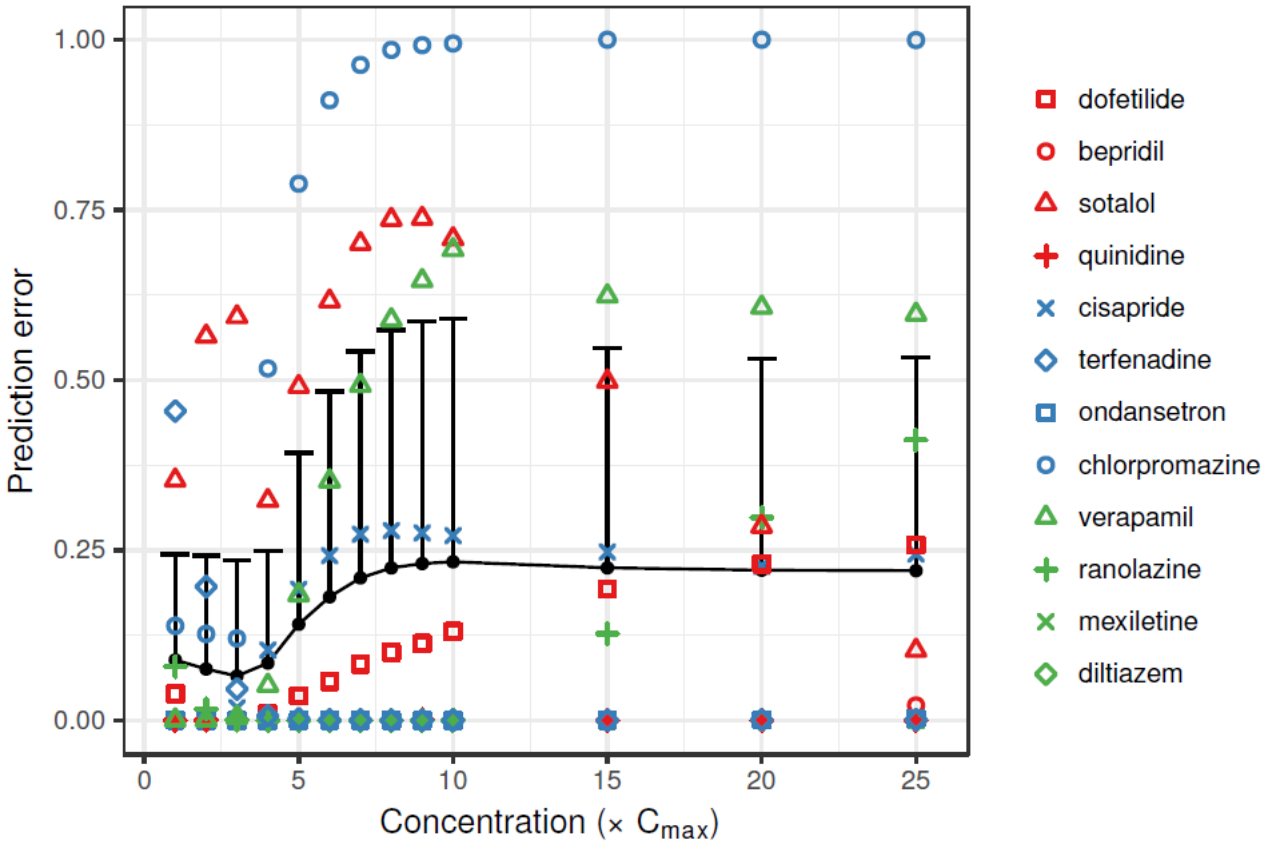
Important Implication: CiPA *In Vitro* assay needs to test as high concentrations as possible!

qNet Metric with Uncertainty



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

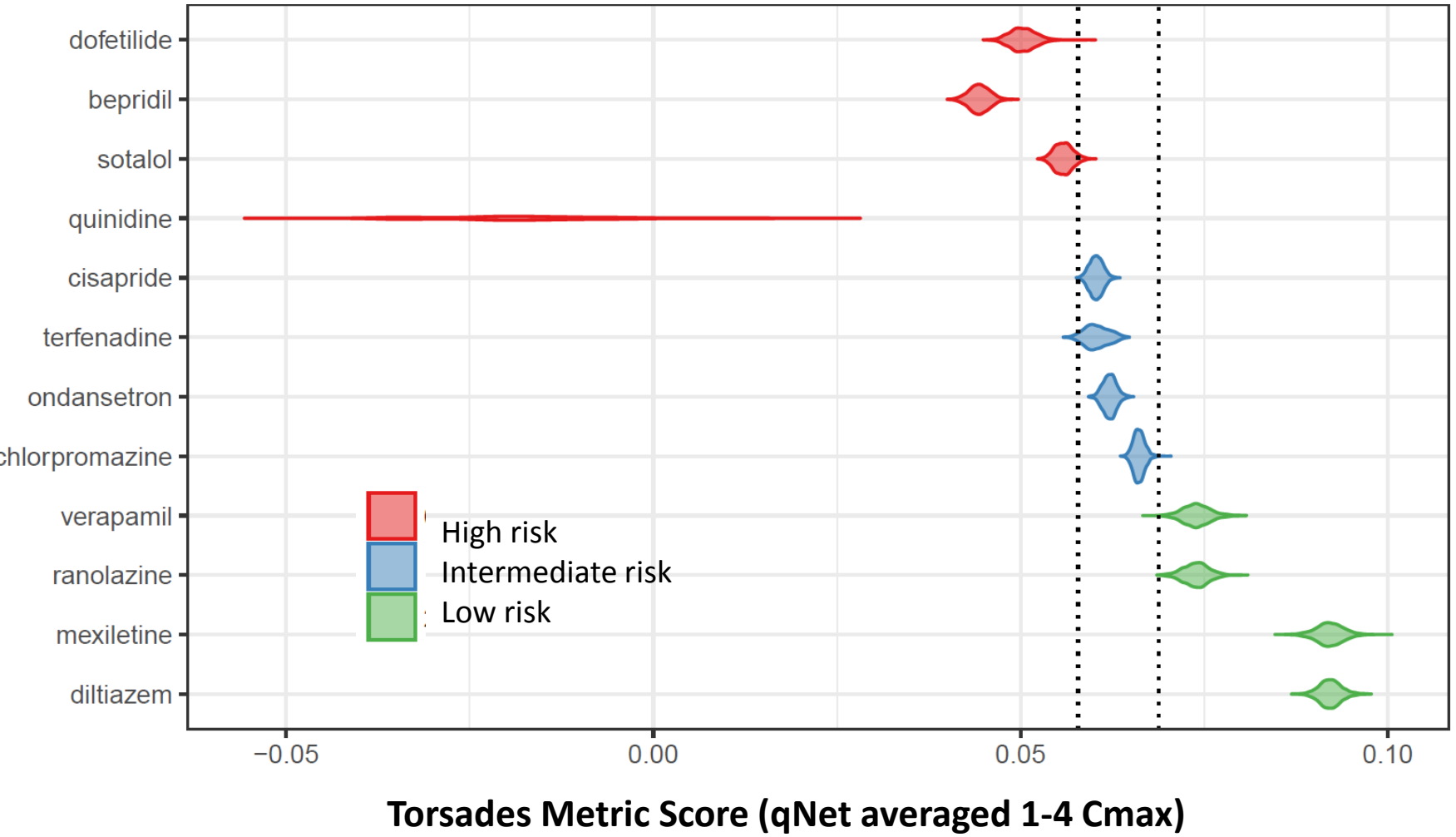
Concentration and Prediction Error



- 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

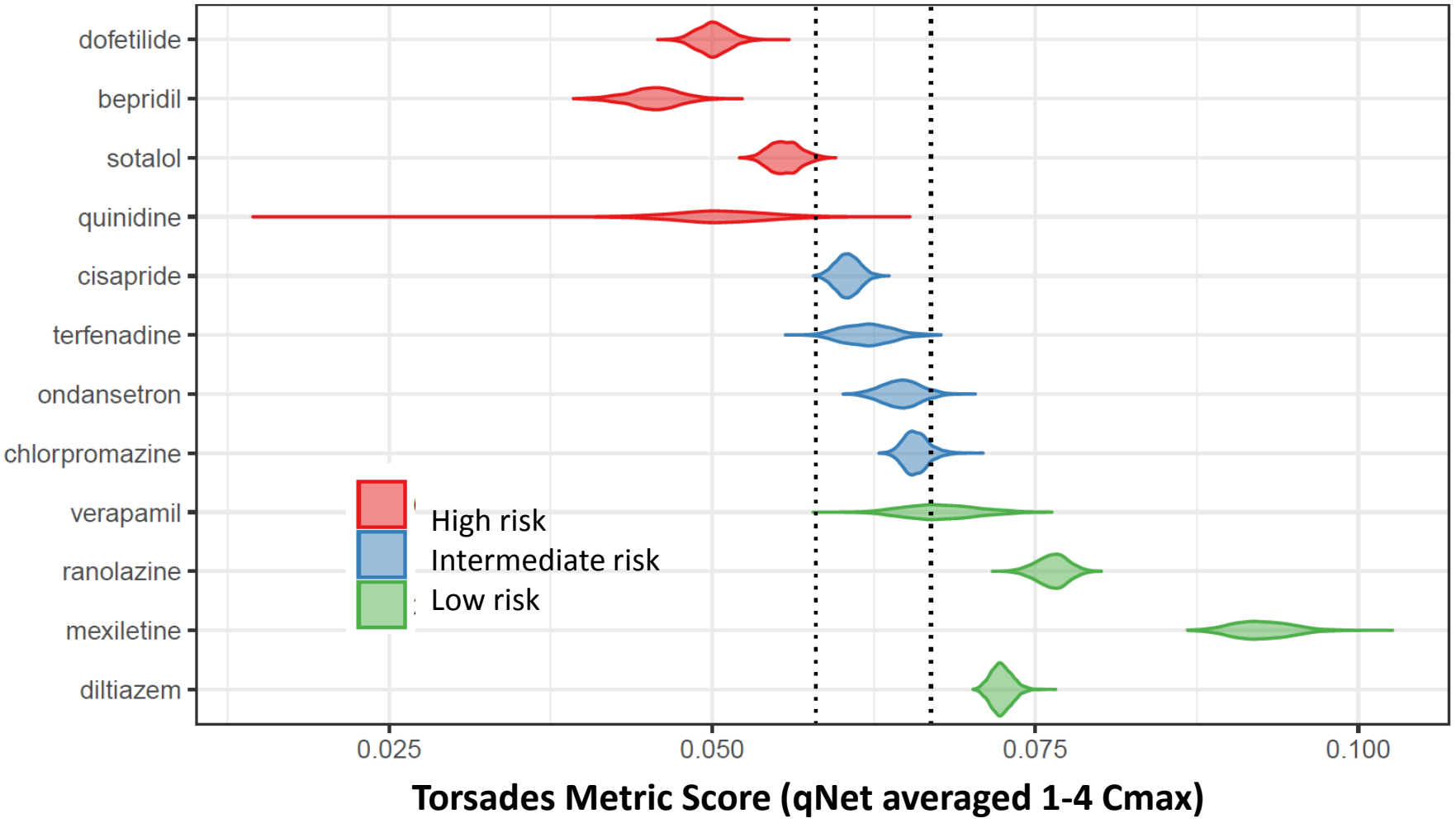
Conclusion: For CiPA manual training dataset, concentrations 1-4x Cmax should be used for qNet calculation and TdP risk prediction.

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



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

Performance Measure	*Interpretation*
AUC (Area Under the Curve) of ROC (Receiver Operating Characteristic)	When two drugs are coming from two risk categories, probability of ranking the higher-risk drug above the lower-risk drug
Pairwise comparison	Probability of correctly ranking a drug relative to CiPA reference drugs through a series of pairwise comparison
Likelihood Ratio (LR)	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
Mean Classification Error	Average error of classifying a drug into High, Intermediate, or Low risk category

Acknowledgements

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All CiPA Working groups

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

ALL contributors to CiPA (there are a lot!)

- Public-private partnerships: HESI, SPS, CSRC
- Regulatory Agencies: FDA, EMA, PMDA/NIHS, Health Canada
- Many pharmaceutical, CRO, and laboratory device companies
- Academic collaborators

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