Global optimization of ventricular myocyte model to multi-variable objective improves predictions of drug-induced Torsades de Pointes

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a model’s performance often diminishes as it’s pushed beyond the regime for which it was designed

all 3 models have comparable baseline APD (~270-300ms), but differing morphology, and very different responses to simulated LQTs

difficulty that each model has representing at least some LQTs raises concerns about abilities to predict drug-induced LQT and TdP

Mann, et al., JMCC 100:25–34 (2016)
same parameters may produce same single AP, but different output for other variable(s)

key: information-rich data

one approach: population of models

another approach: global parameter optimization methods
one **information-rich data + global optimization** approach

cell-specific model generation

Groenendaal, et al., *PLoS Comp Bio* 11:e1004242 (2015)
“In-silico models of cardiac electrophysiology have the potential to be tremendously useful in complementing traditional preclinical drug testing studies. However, our results demonstrate they should be carefully validated and optimized to clinical data before they can be used for this purpose.”

Mann, et al., JMCC 100:25–34 (2016)
it works!

except, in the process, $[\text{Ca}^{2+}]_i$ and $[\text{Na}^+]_i$ becomes unphysiological, which is problematic given that both can affect arrhythmogenesis.

Mann, et al., JMCC 100:25–34 (2016)
$[\text{Na}^+]_i$ influencing EAD formation

Krogh-Madsen and Christini, Chaos (2017)
add optimization constraints on $[\text{Na}]_i$ and $[\text{Ca}^{2+}]_i$

- **Baseline**: published ORd
- **APD$_{\text{LQT}}$**: optimized to APD errors for LQTs
- **multi-var**: optimized to APD errors, plus penalized solutions with $[\text{Na}^+]_i$ and $[\text{Ca}^{2+}]_i$ outside published physiological values

Krogh-Madsen, et al., (2017)
constraint solution: discard models with unphysiological $[\text{Na}^+]_i$ and $[\text{Ca}^{2+}]_i$ during global optimization

Krogh-Madsen, et al., (2017)
model with more physiological constraints is better at separating TdP risk drugs

tested 86 $I_{Kr}$, $I_{CaL}$, $I_{Na}$ blockers as in Lancaster & Sobie (Clin. Pharm. Therap. 2016)

more flexibility in boundary line location

three low-risk drugs show APD prolongation in all models except the new multi-var optimized model

Krogh-Madsen, et al., (2017)
conclusion and next steps

• rich data are needed in cardiac myocyte model optimization

• optimization to such data can generate models with higher accuracy - including for predictions of drug-induced cardiotoxicity

• extend +TdP / -TdP drug segmentation using population-of-models approach built on top of multi-var tuned model

• $I_{Ks}$ levels?
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