Global optimization of cardiac myocyte models

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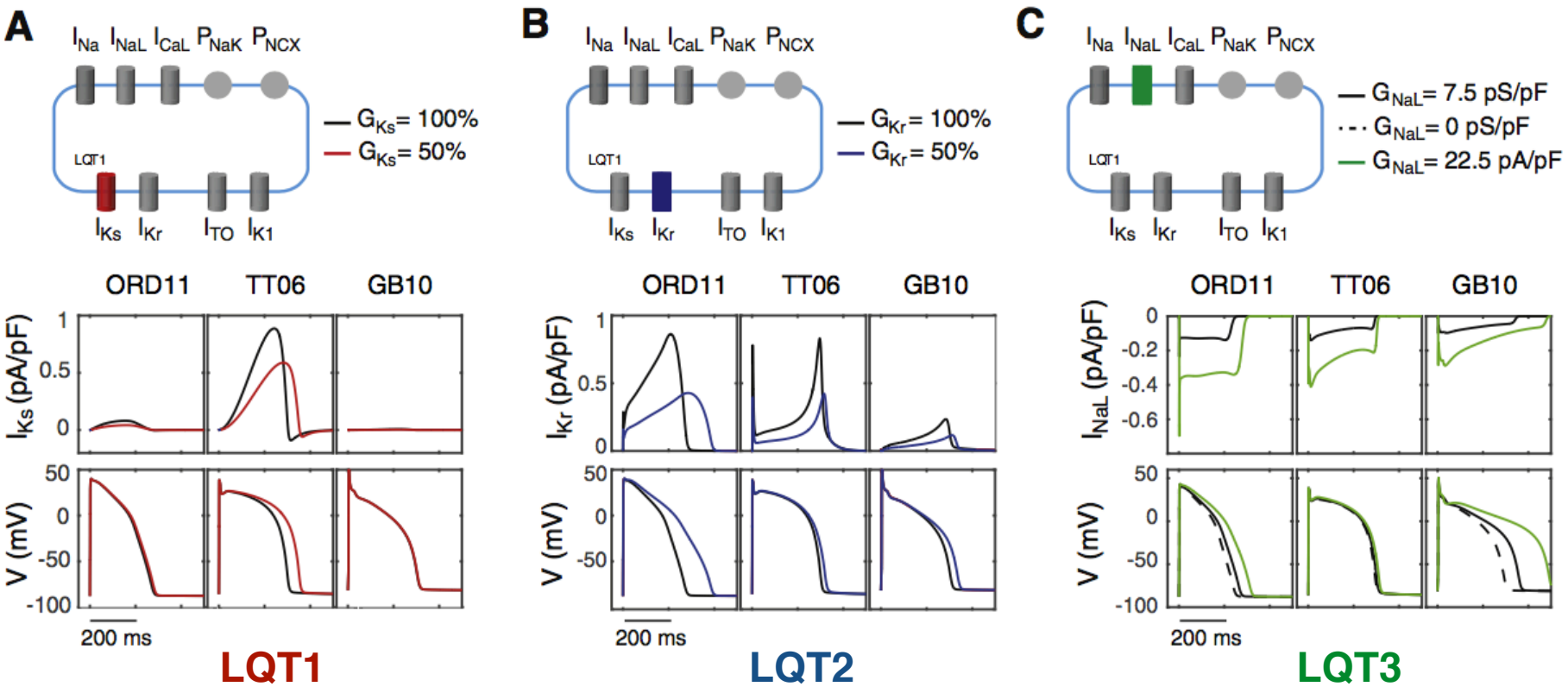
Main question

Ionic models sometimes fail in their predictions - can we improve models by redesigning the model development process?

Congenital LQT simulations

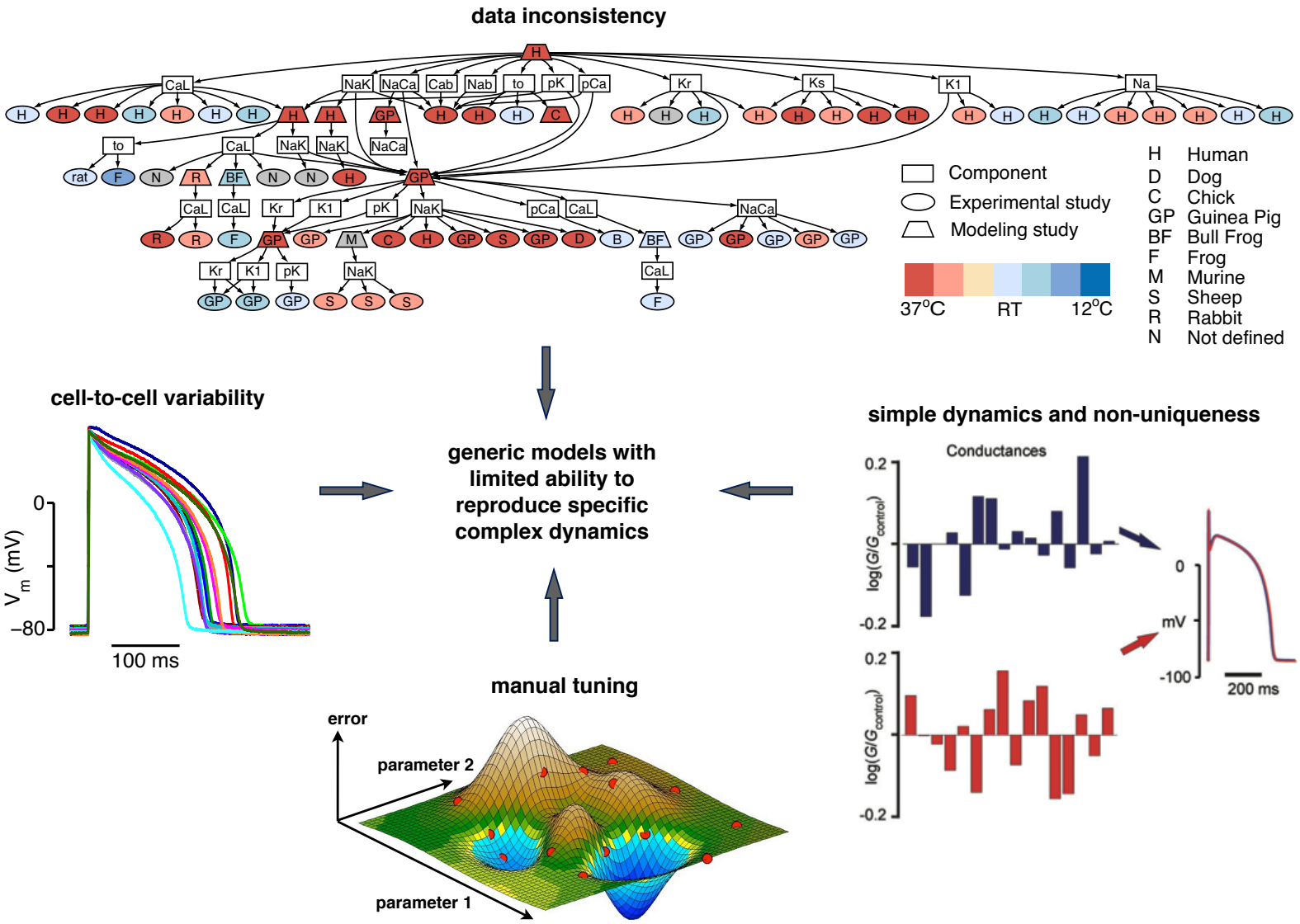


all 3 models have comparable baseline APD (~270-300ms), but differing morphology, and very different responses to simulated LQTs

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)

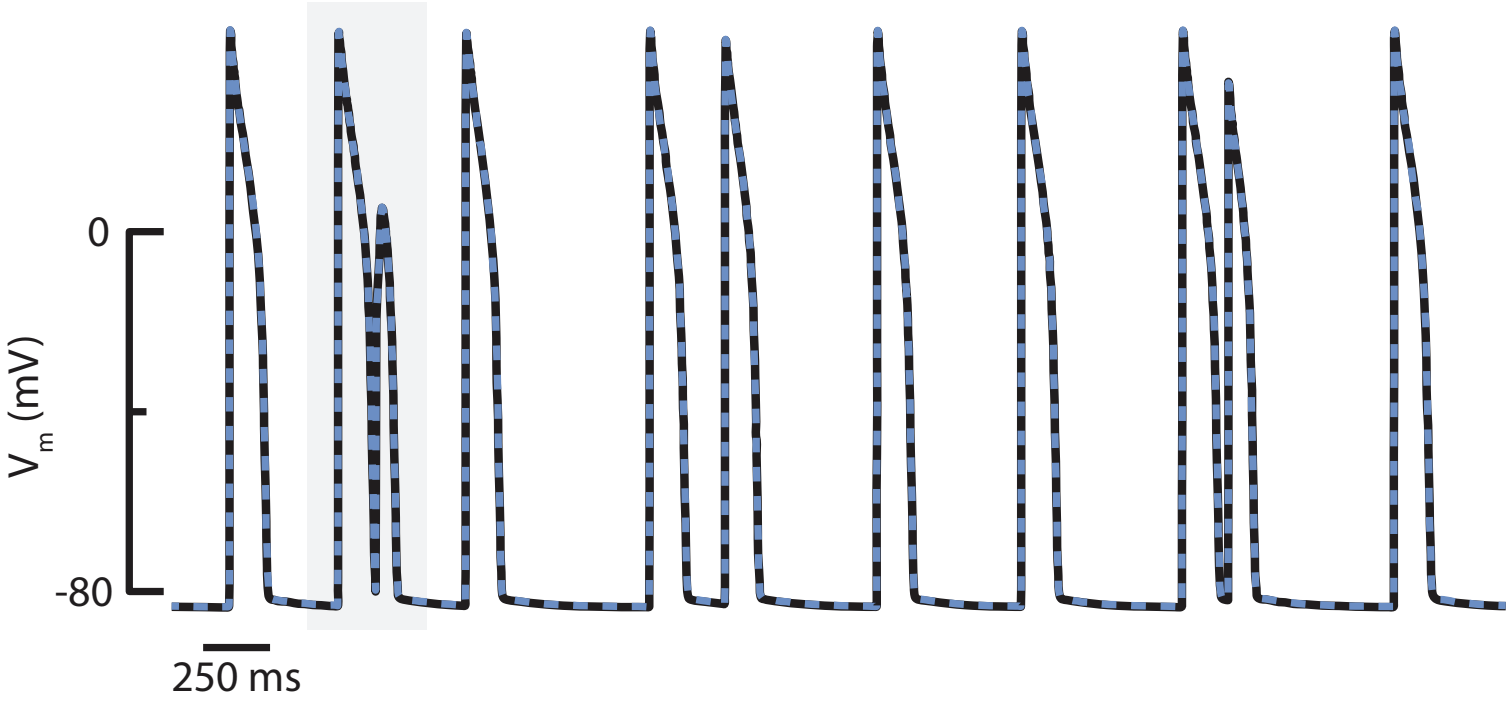
Model development limitations



Krogh-Madsen *et al.*, *J Physiol* (2016)

one *information-rich data + global optimization* approach

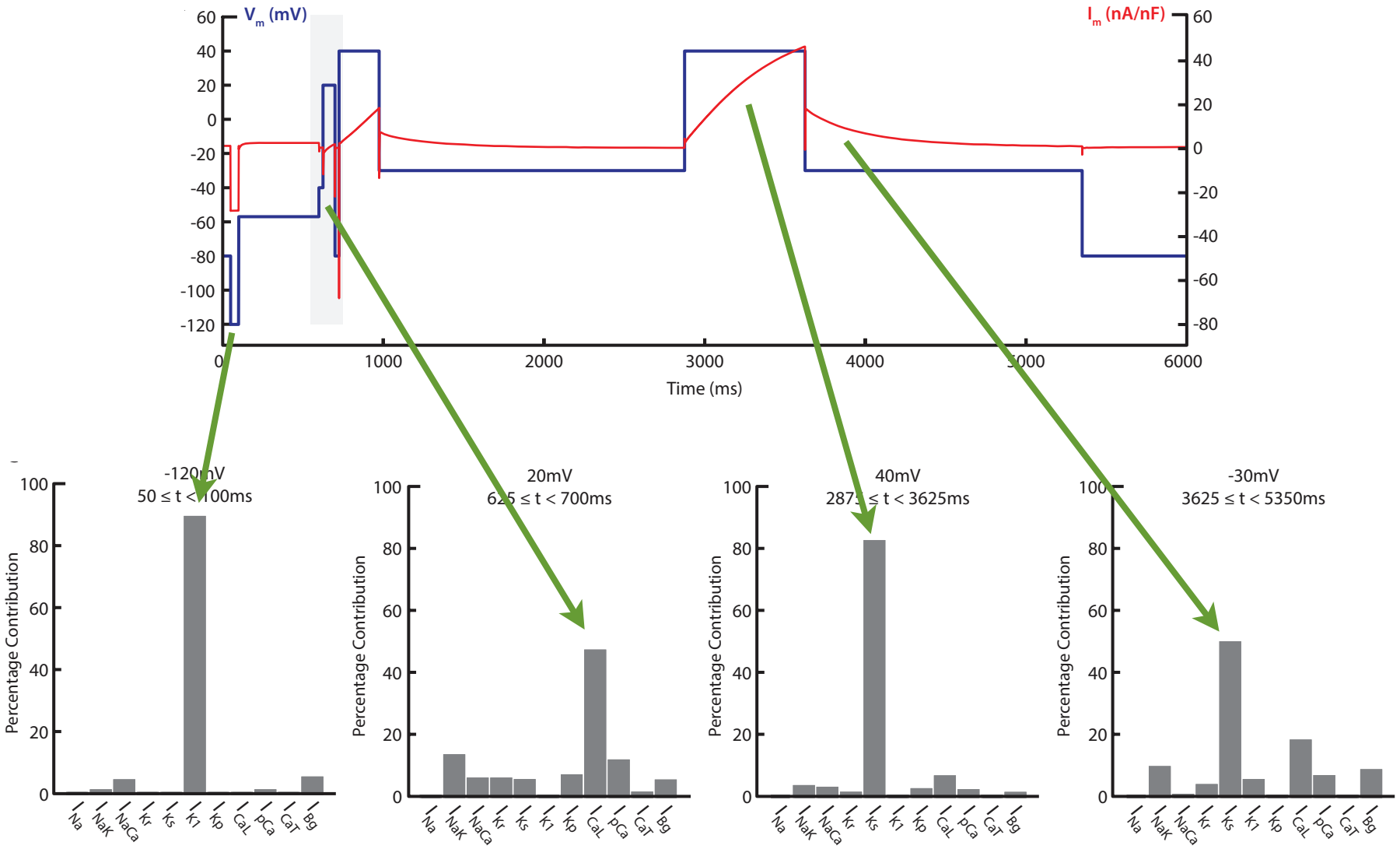
1. Use APs obtained during irregular pacing



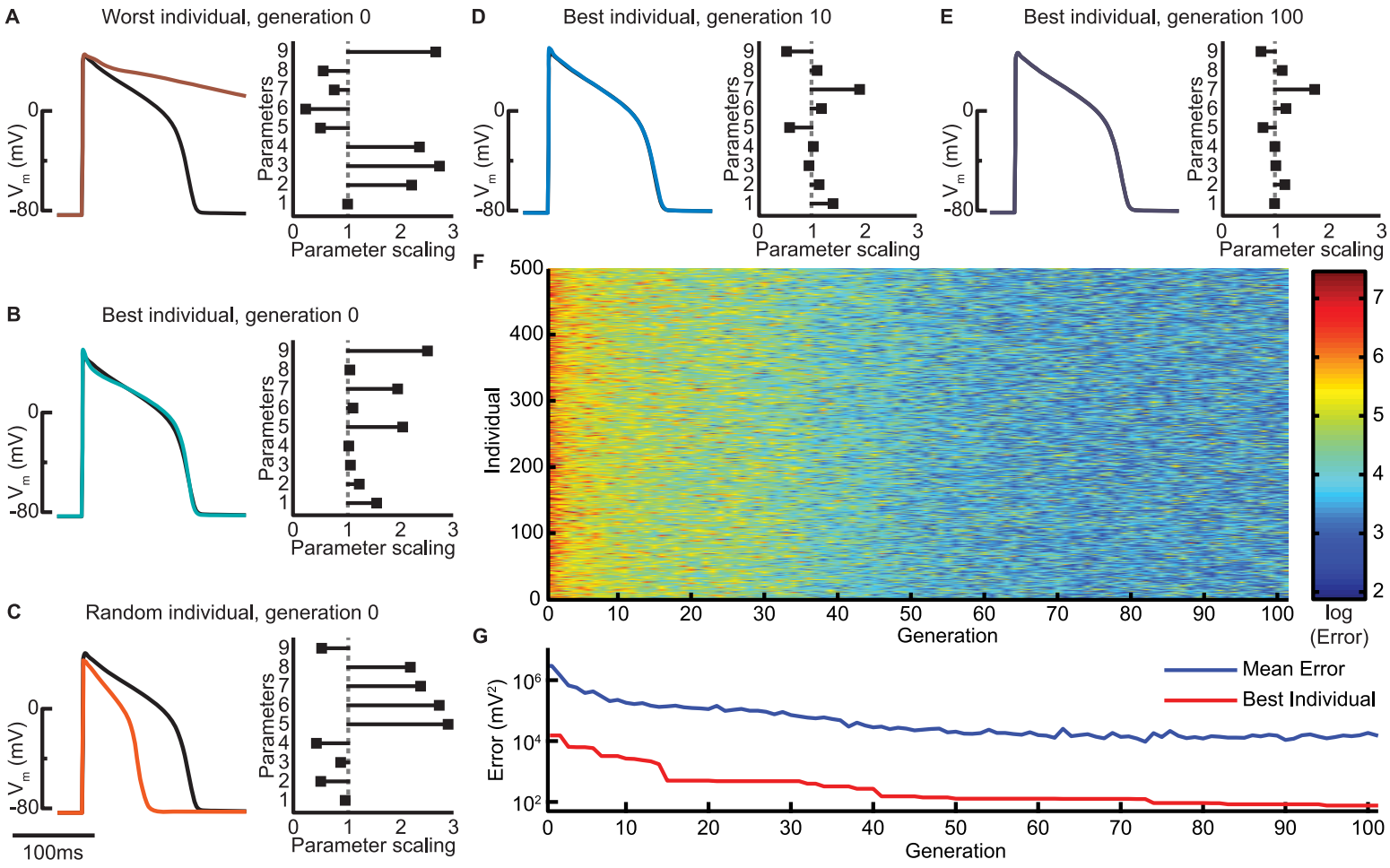
Groenendaal, *et al.*, *PLoS Comp Bio* **11:**e1004242 (2015)

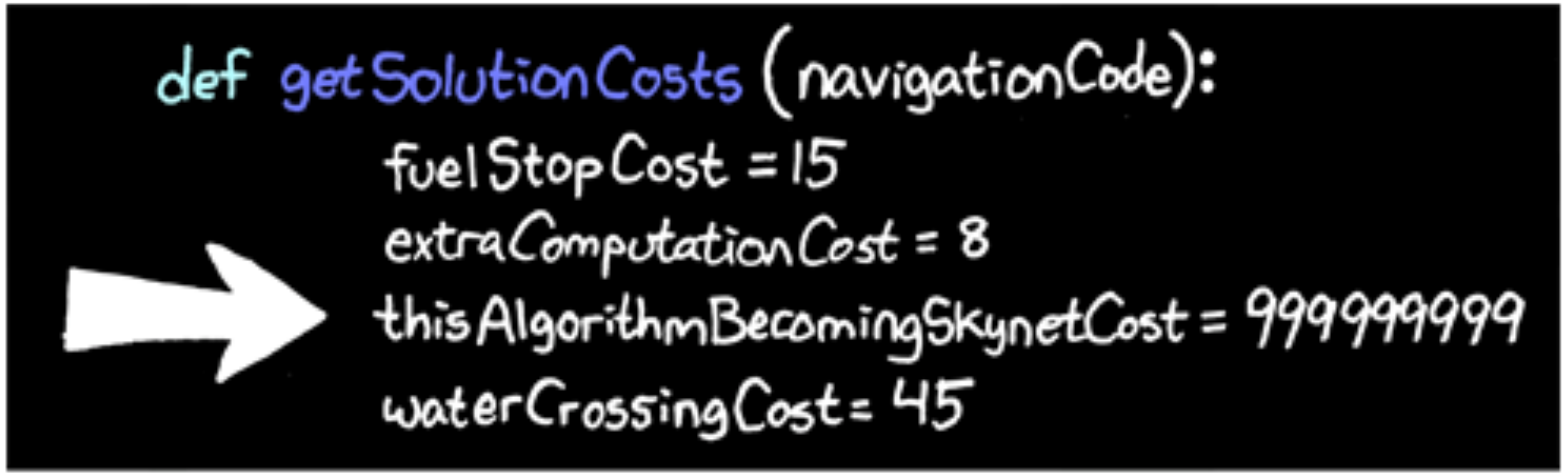
2. How about incorporating voltage-clamp data?

Can carefully designed voltage-clamp protocols inform model building?

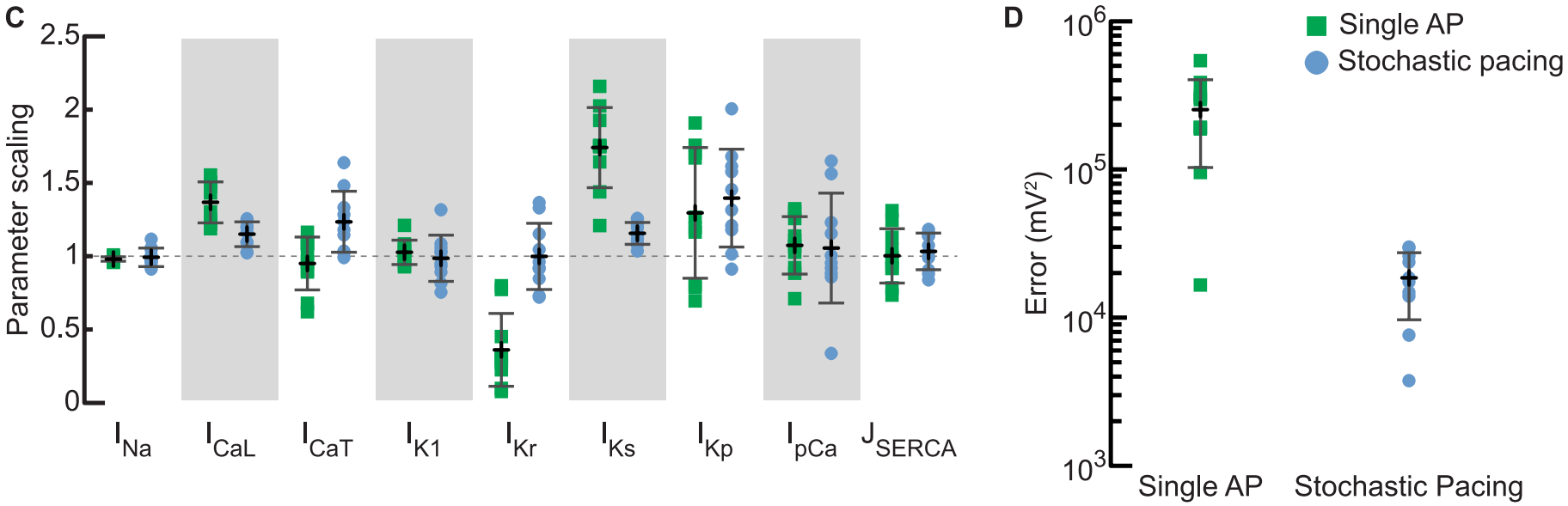


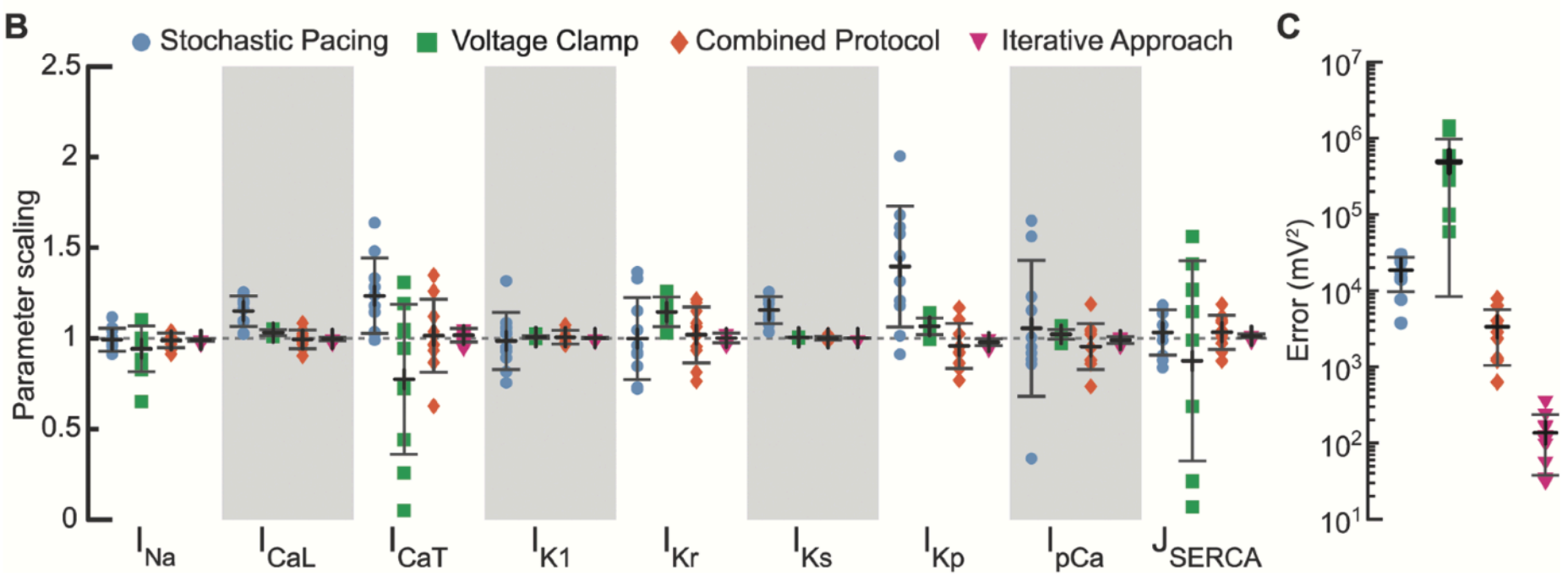
3. Use genetic algorithm



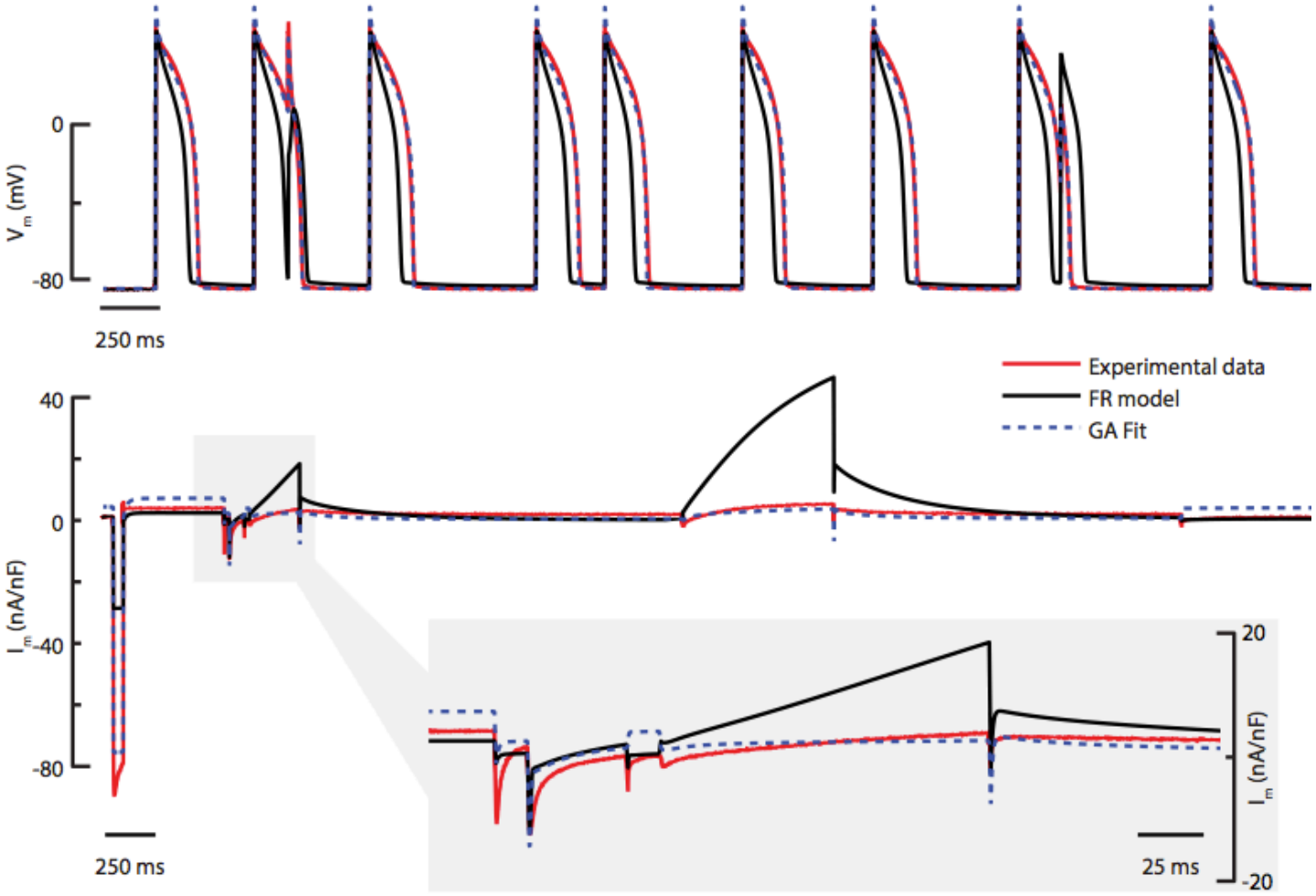


GENETIC ALGORITHMS TIP:
ALWAYS INCLUDE THIS IN YOUR FITNESS FUNCTION


C
Parameter scaling
2.5
2
1.5
1
0.5
0
I_Na
I_CaL
I_CaT
I_K1
I_Kr
I_Ks
I_Kp
I_pCa
J_SERCA
D
Error (mV²)
10^6
10^5
10^4
10^3
Single AP
Stochastic pacing
Single AP
Stochastic Pacing


B
Stochastic Pacing
Voltage Clamp
Combined Protocol
Iterative Approach
Parameter scaling
2.5
2
1.5
1
0.5
0
I_Na
I_CaL
I_CaT
I_K1
I_Kr
I_Ks
I_Kp
I_pCa
J_SERCA
C
Error (mV²)
10^7
10^6
10^5
10^4
10^3
10^2
10^1

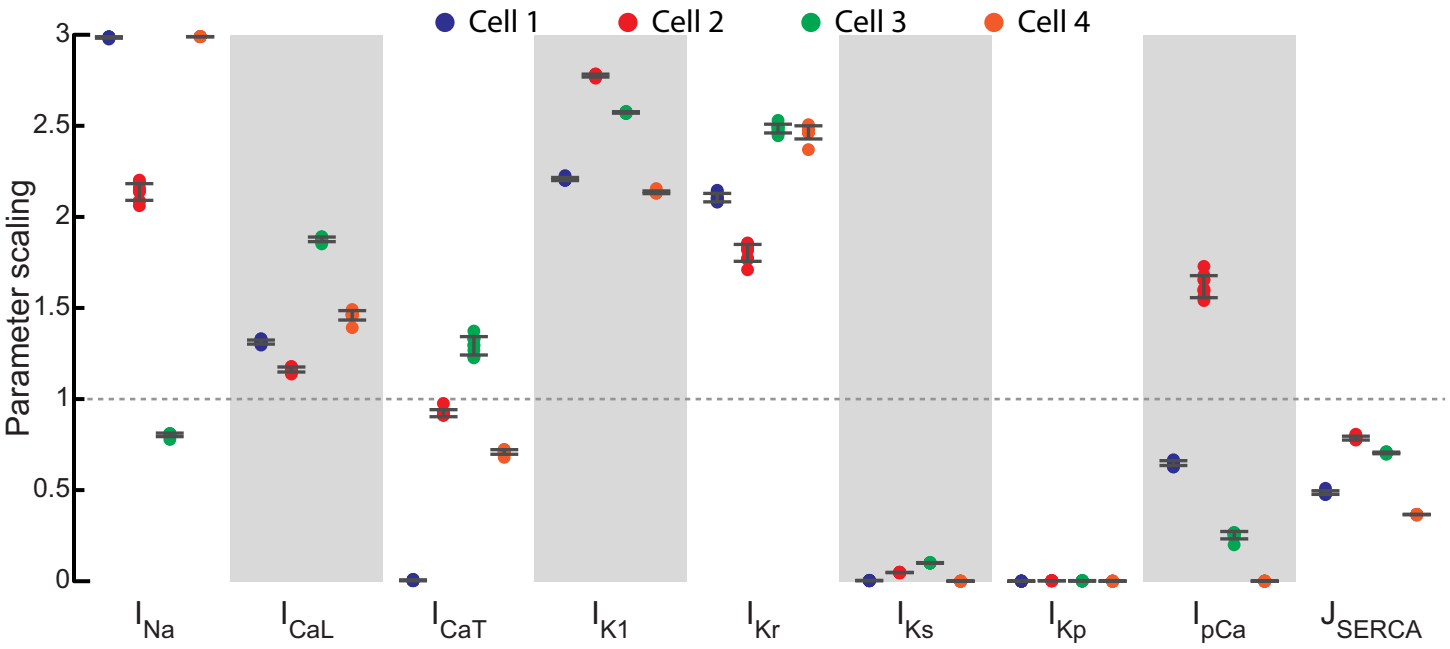
Fitting current and voltage clamp *in vitro* data



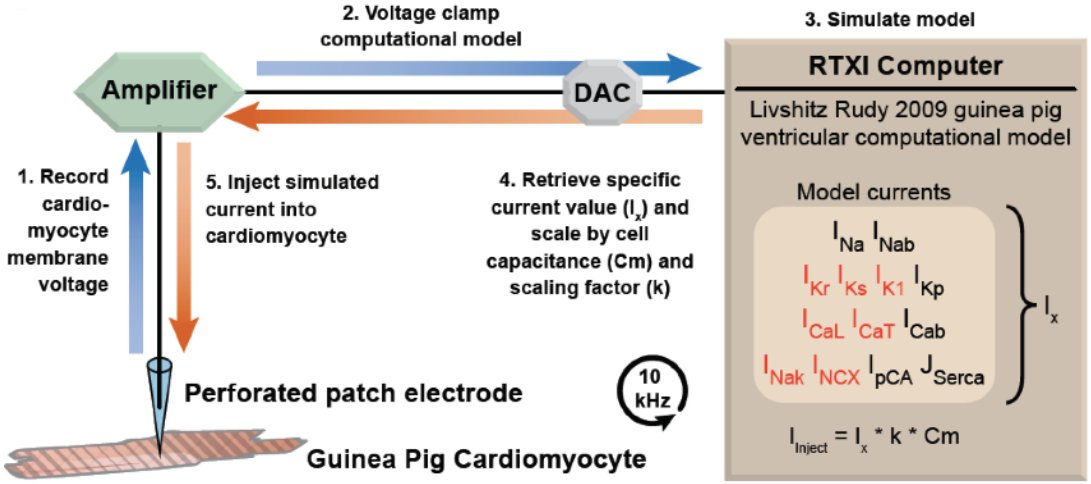
Stochastic pacing

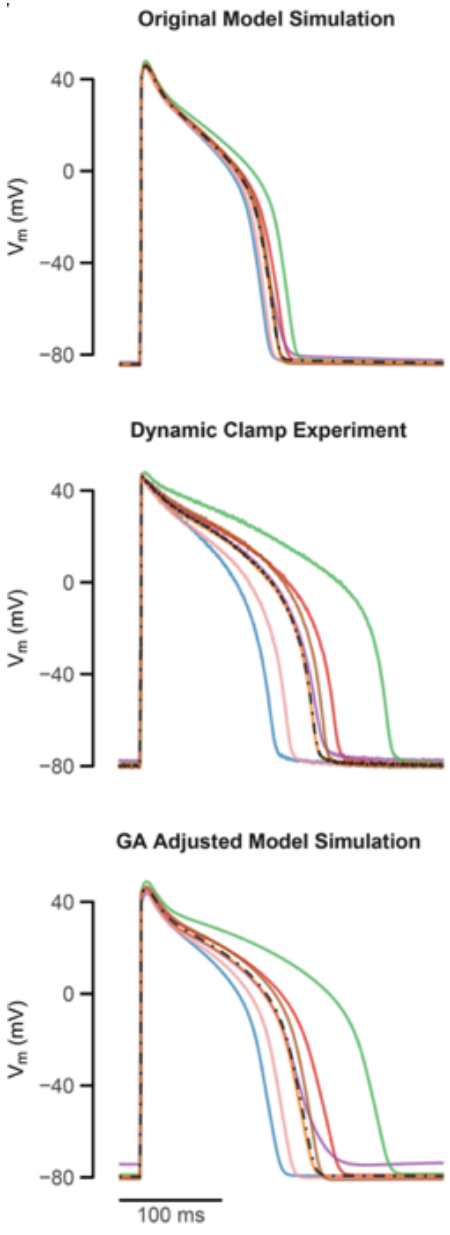
Voltage clamp

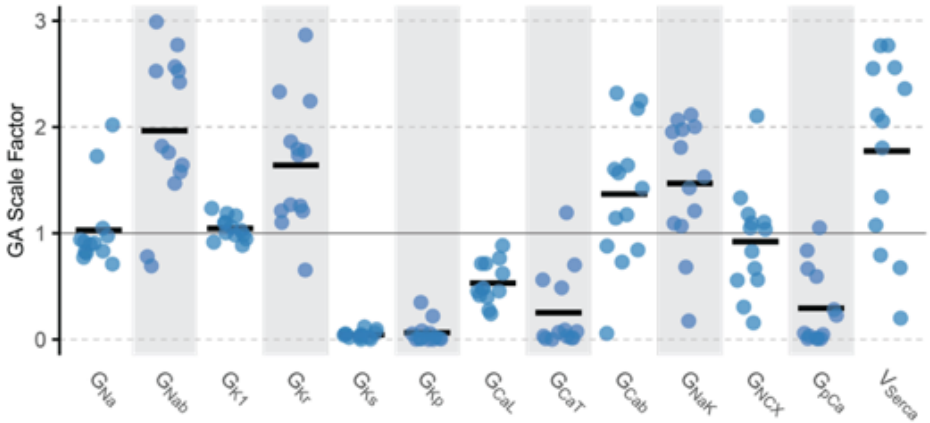
Parameter estimation for individual myocytes



another *information-rich data + global optimization* approach - *dynamic clamp*



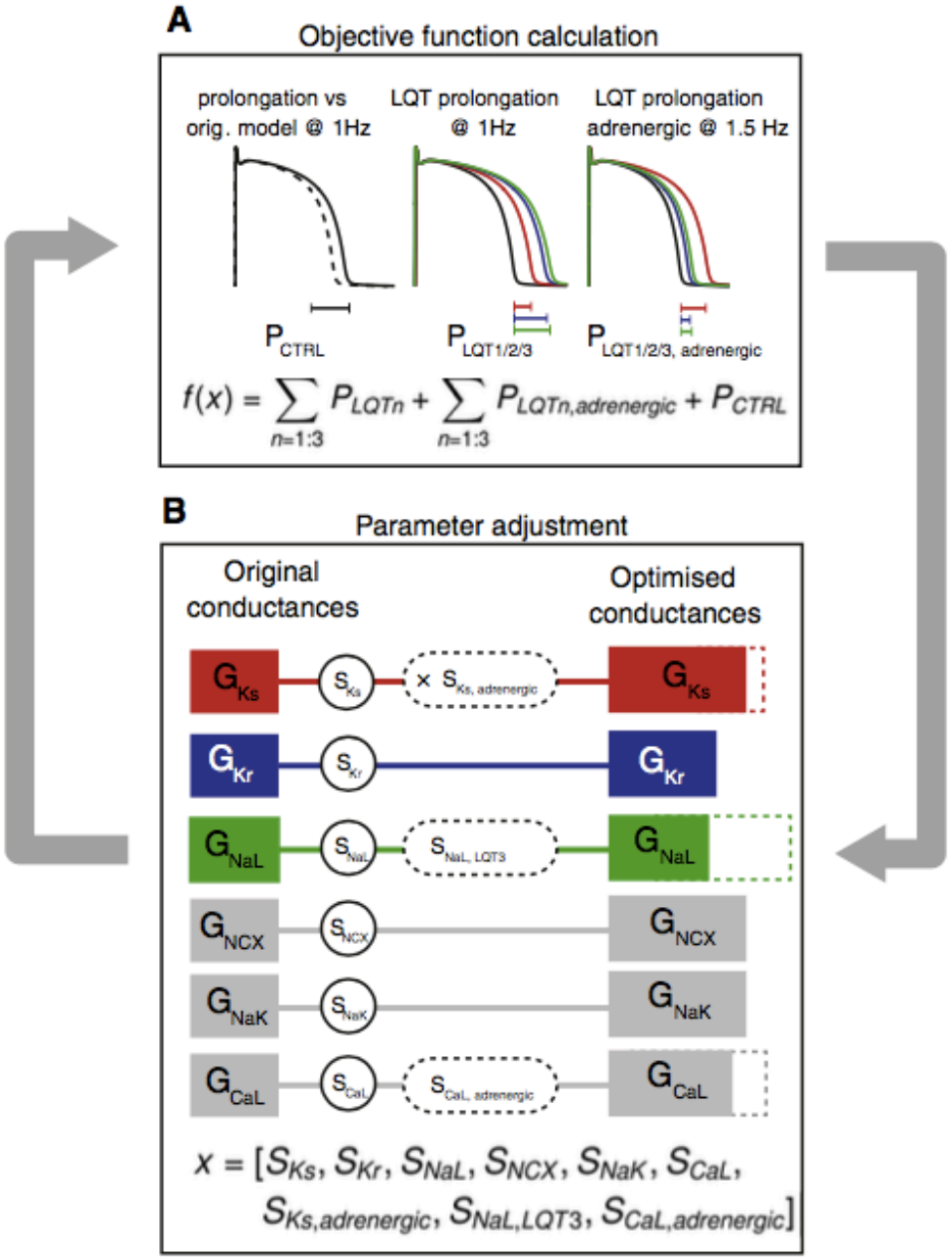




+/- 40% →

Devenyi, Ortega, *et al.*, *J Physiol* (2016)

and another *information-rich data + global optimization* approach

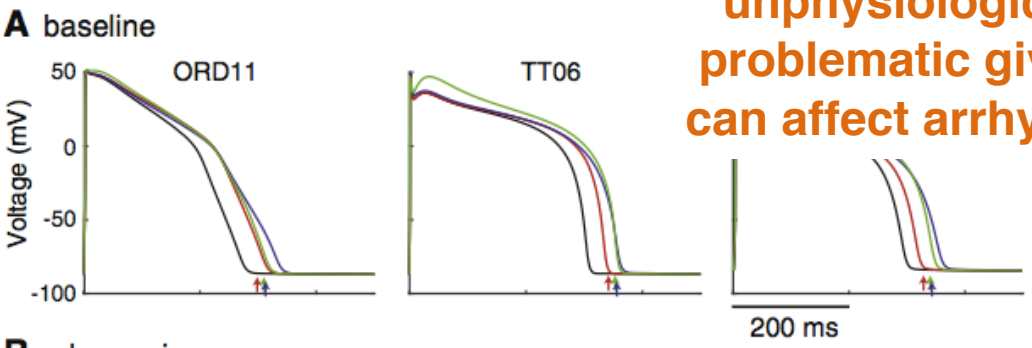


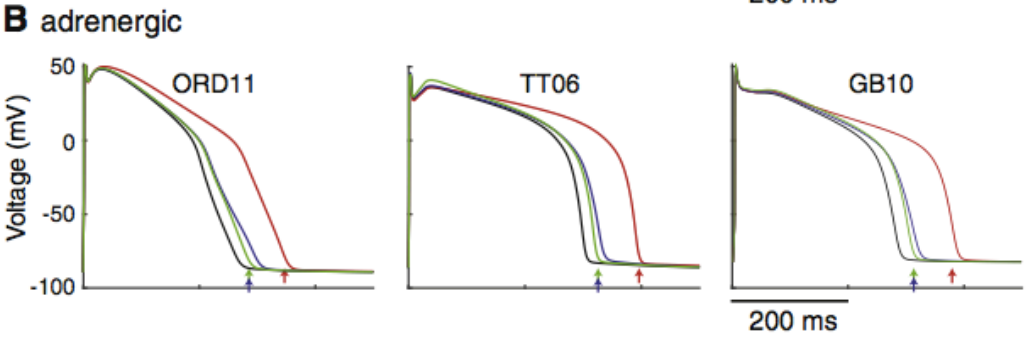
"In-silico models of cardiac electrophysiology have the potential to be tremendously useful in complementing traditional preclinical drug testing studies. However, our results demonstrate they should be carefully validated and optimized to clinical data before they can be used for this purpose."

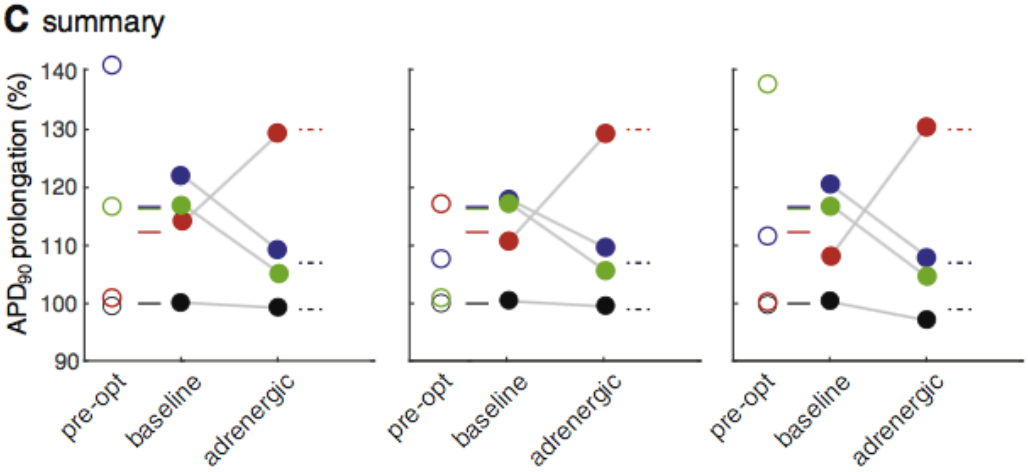
Mann, *et al.*, *JMCC* **100**:25–34 (2016)

it works!

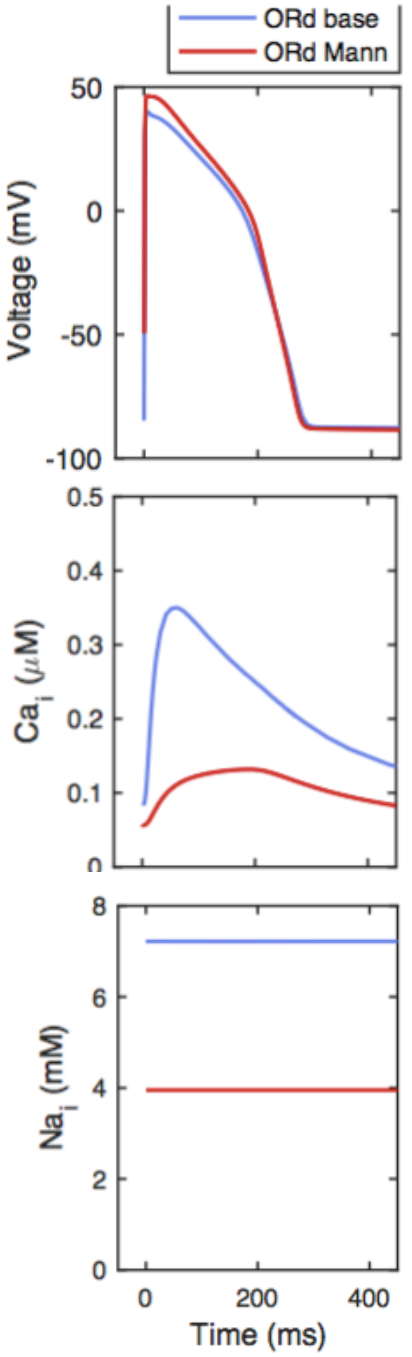
except, in the process, $[Ca^{2+}]_i$ and $[Na^+]_i$ becomes unphysiological, which is problematic given that both can affect arrhythmogenesis





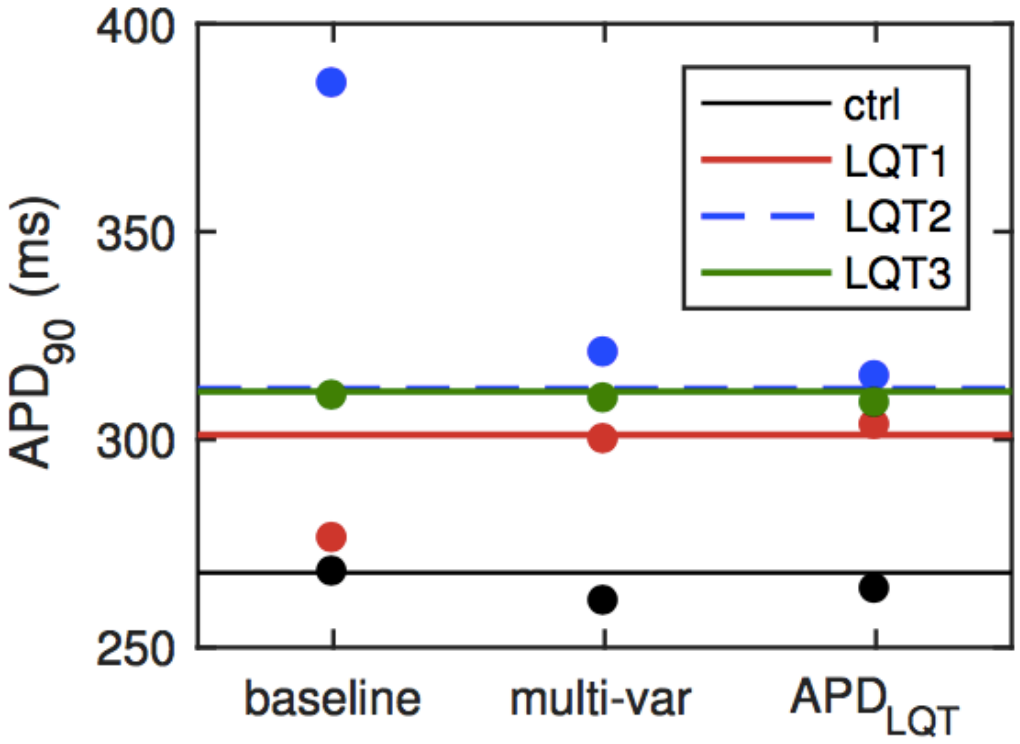


LQT1
LQT2
LQT3



Mann, *et al.*, *JMCC* **100**:25–34 (2016)

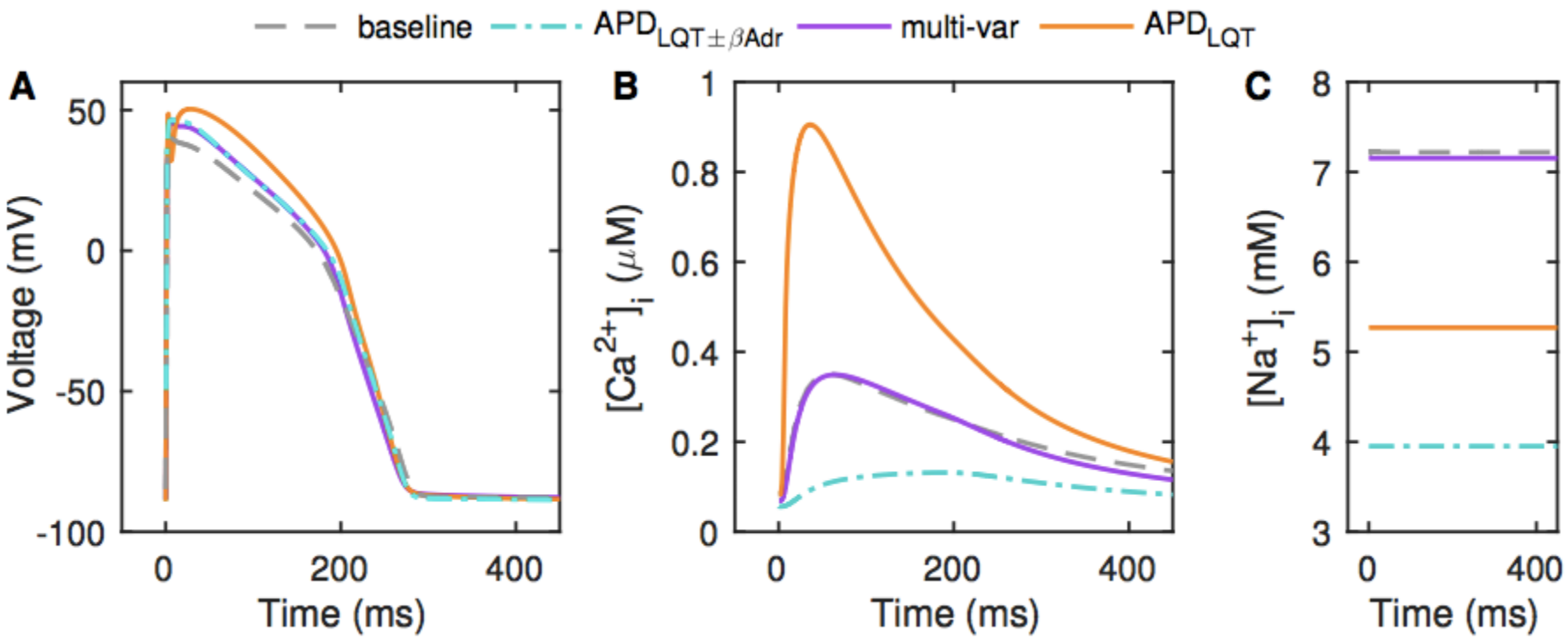
add optimization constraints on $[Na]_i$ and $[Ca^{2+}]_i$



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

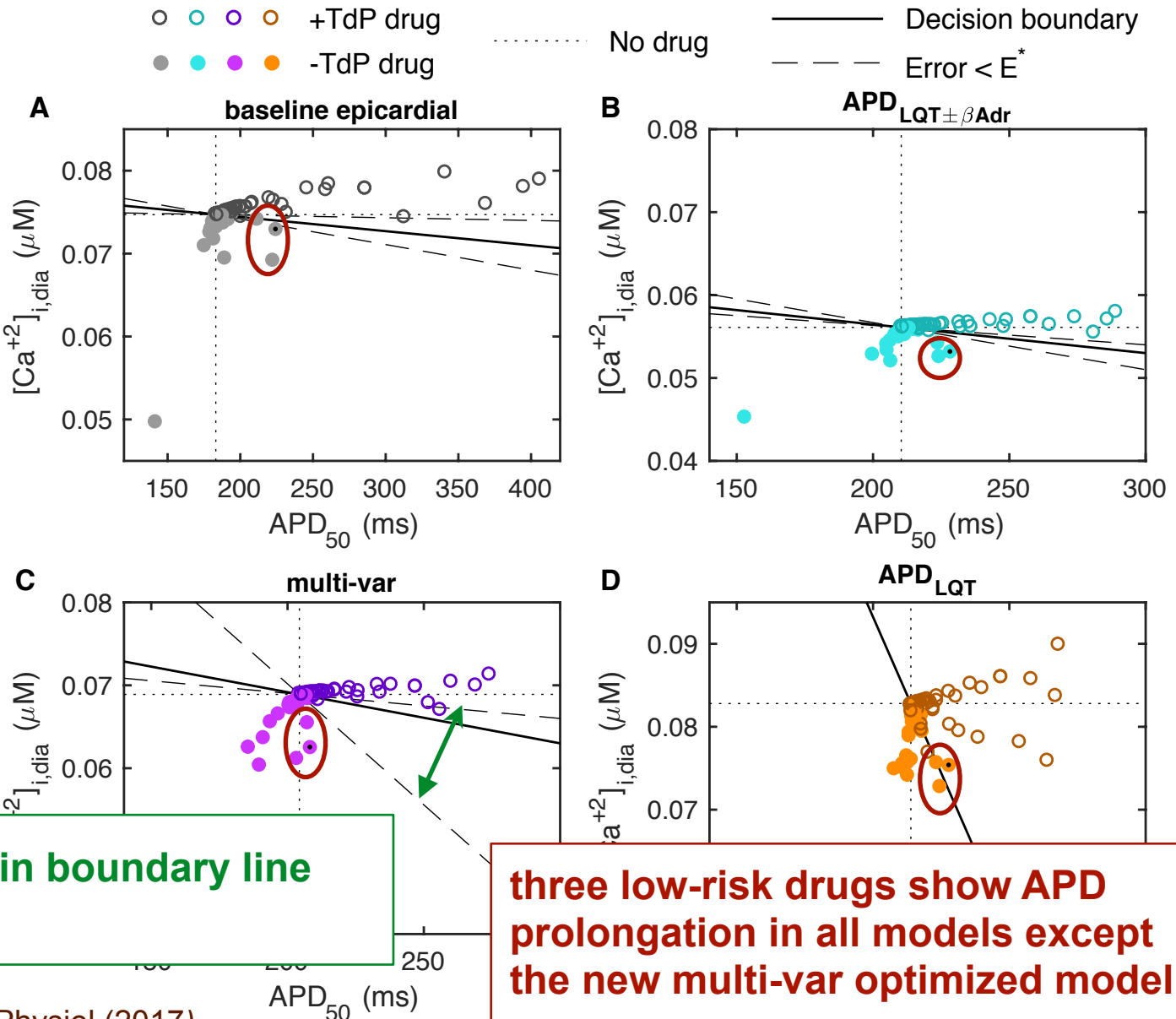
Krogh-Madsen *et al.*, Front Physiol (2017)

constraint solution: discard models with unphysiological $[Na^+]_i$ and $[Ca^{2+}]_i$ during global optimization



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)

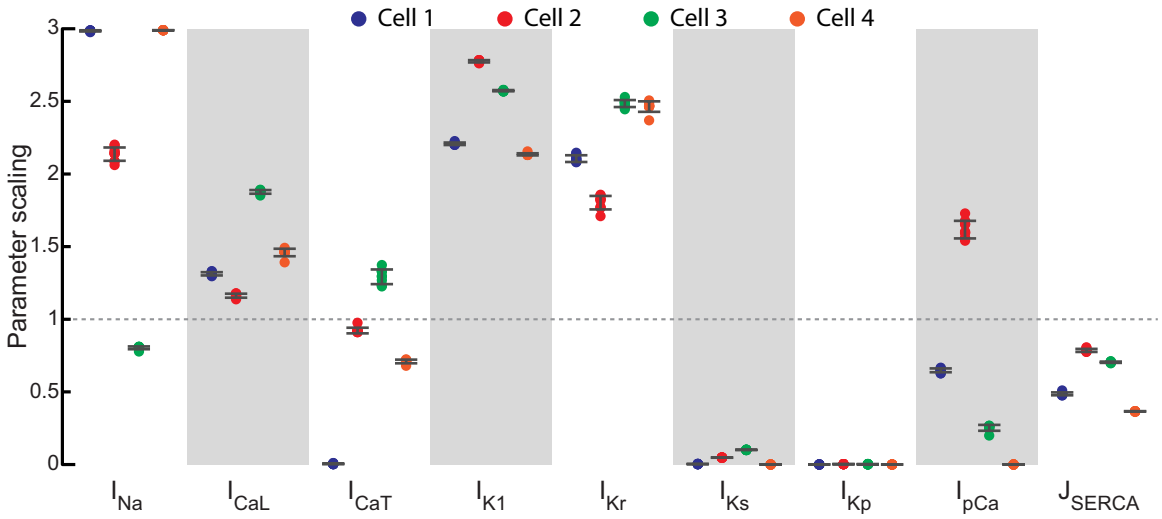


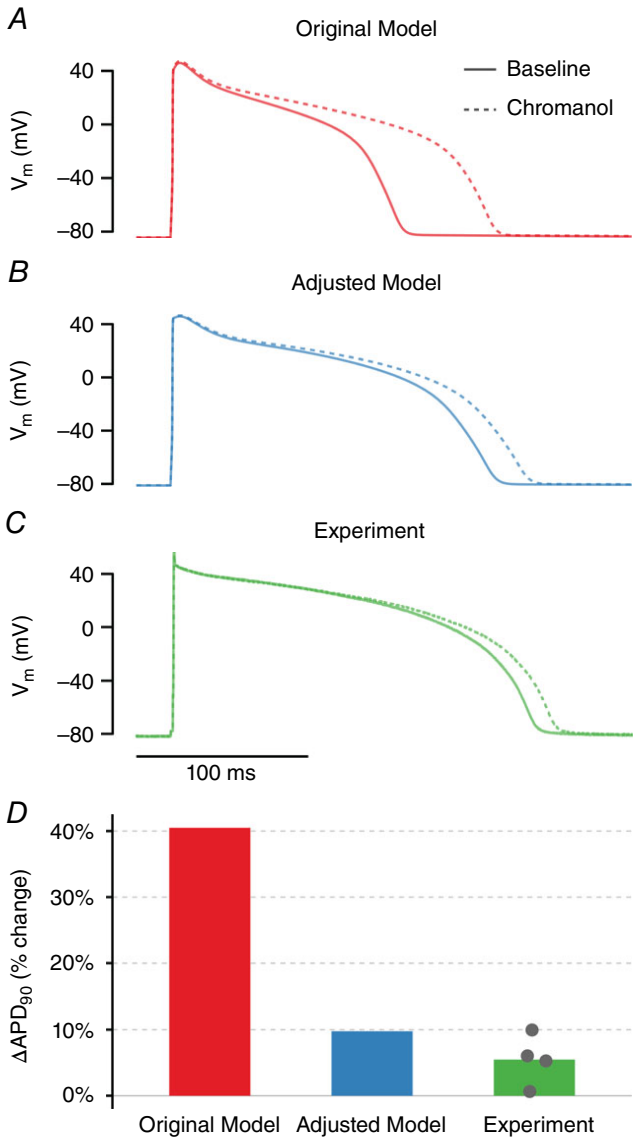
more flexibility in boundary line location

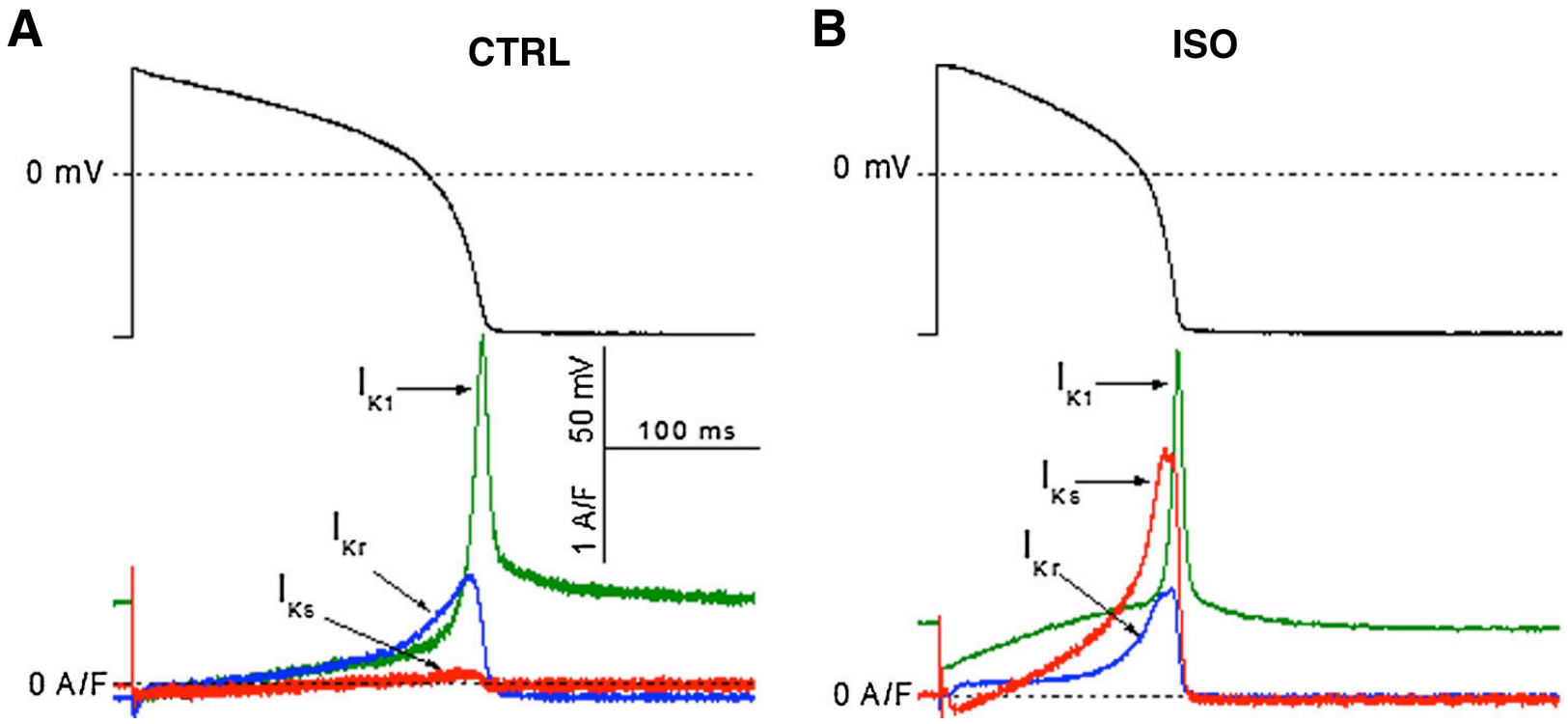
three low-risk drugs show APD prolongation in all models except the new multi-var optimized model

Krogh-Madsen *et al.*, Front Physiol (2017)

I_{Ks} in GP ventricular myocytes







Banyasz et al. *Pflugers* Arch 2014.

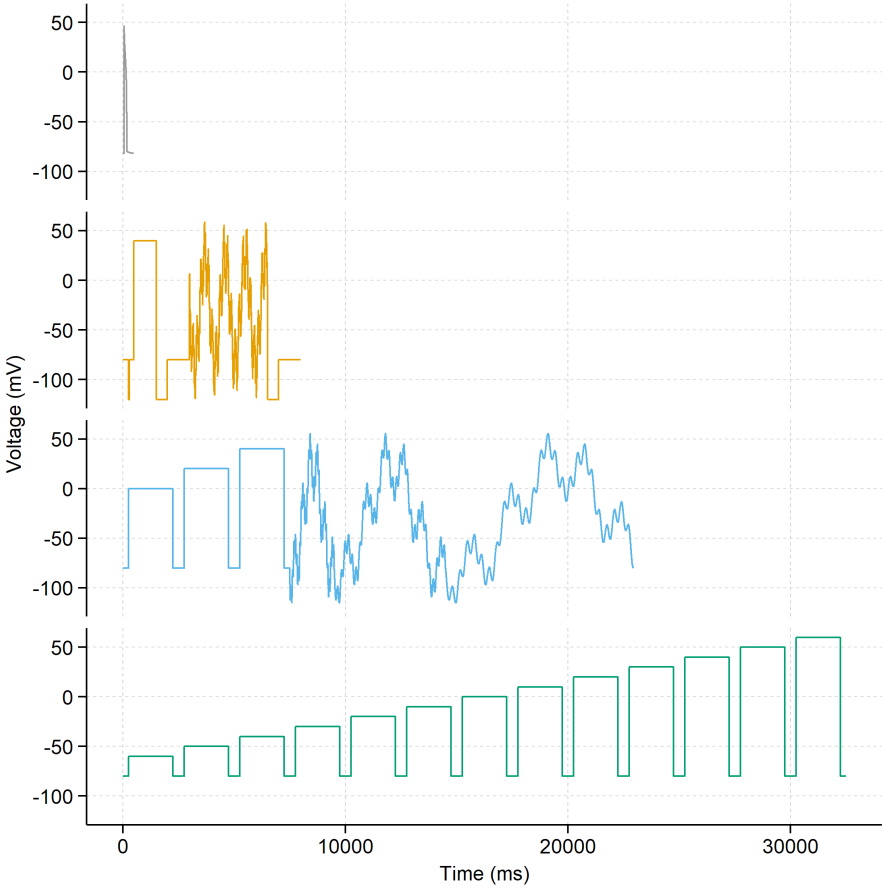
Questions

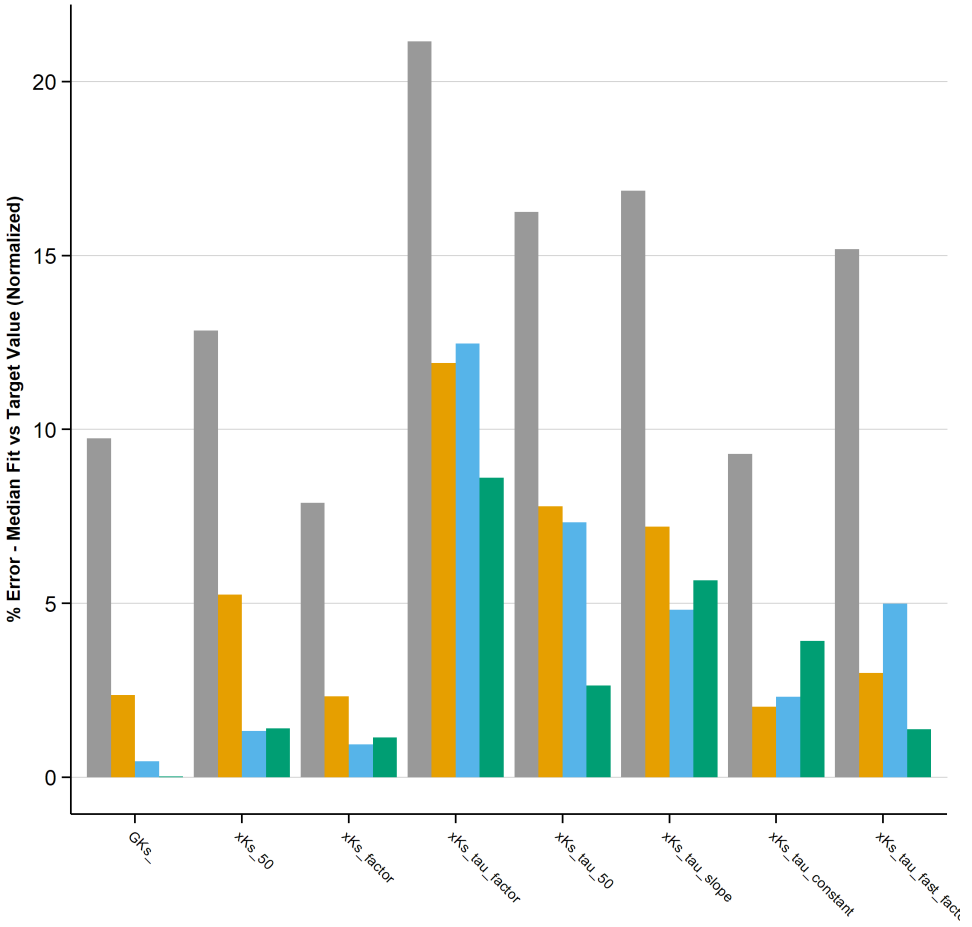
- What is the ratio of the delayed rectifier currents in the guinea pig?
- How does this ratio vary with ß-adrenergic stimulation?

Approach

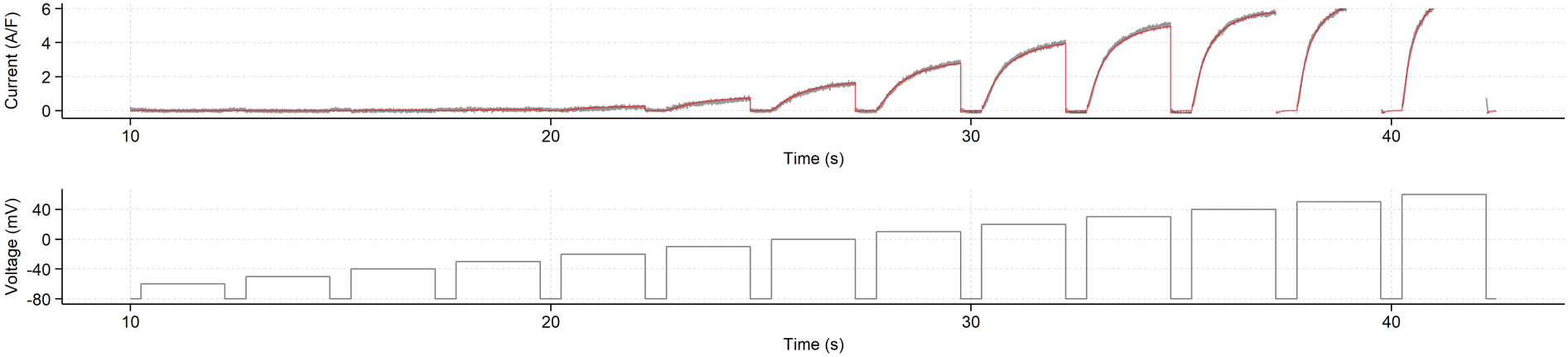
- Use computational modeling to identify a voltage clamp protocol that allows for accurate parameterization of the formulations of I_{Ks} and I_{Kr}
- Develop and perform *in vitro* experiment to gather current-specific information

I_{Ks} protocol testing

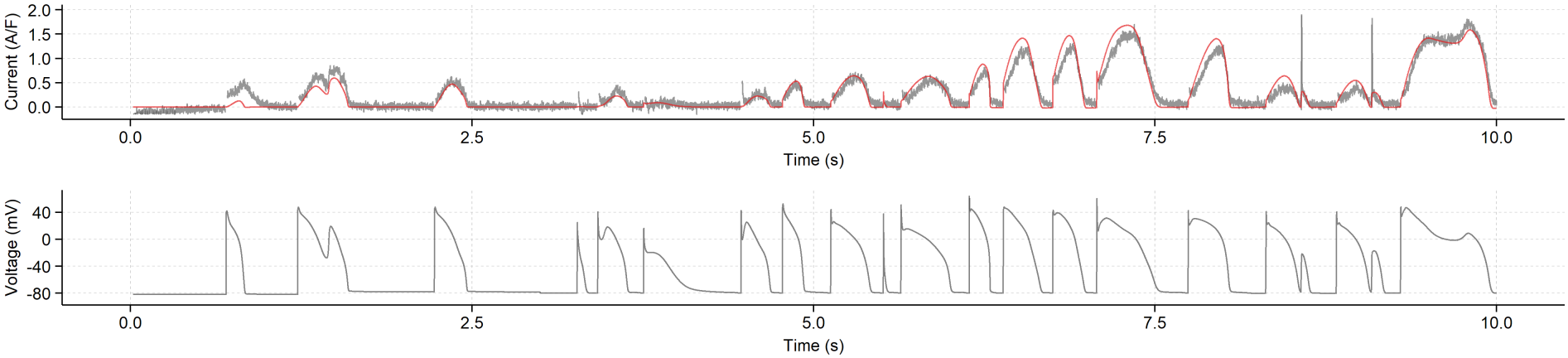




GA fit



Validation



conclusions 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
  - tissue simulations
- I_{Ks}/I_{Kr} protocols and levels
- Add Ca transient measurements to optimization objective
- Use cell-specific models to study cellular heterogeneity

Acknowledgements

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