Quantiying Discrepancy Between Electrophysiology Models and Data

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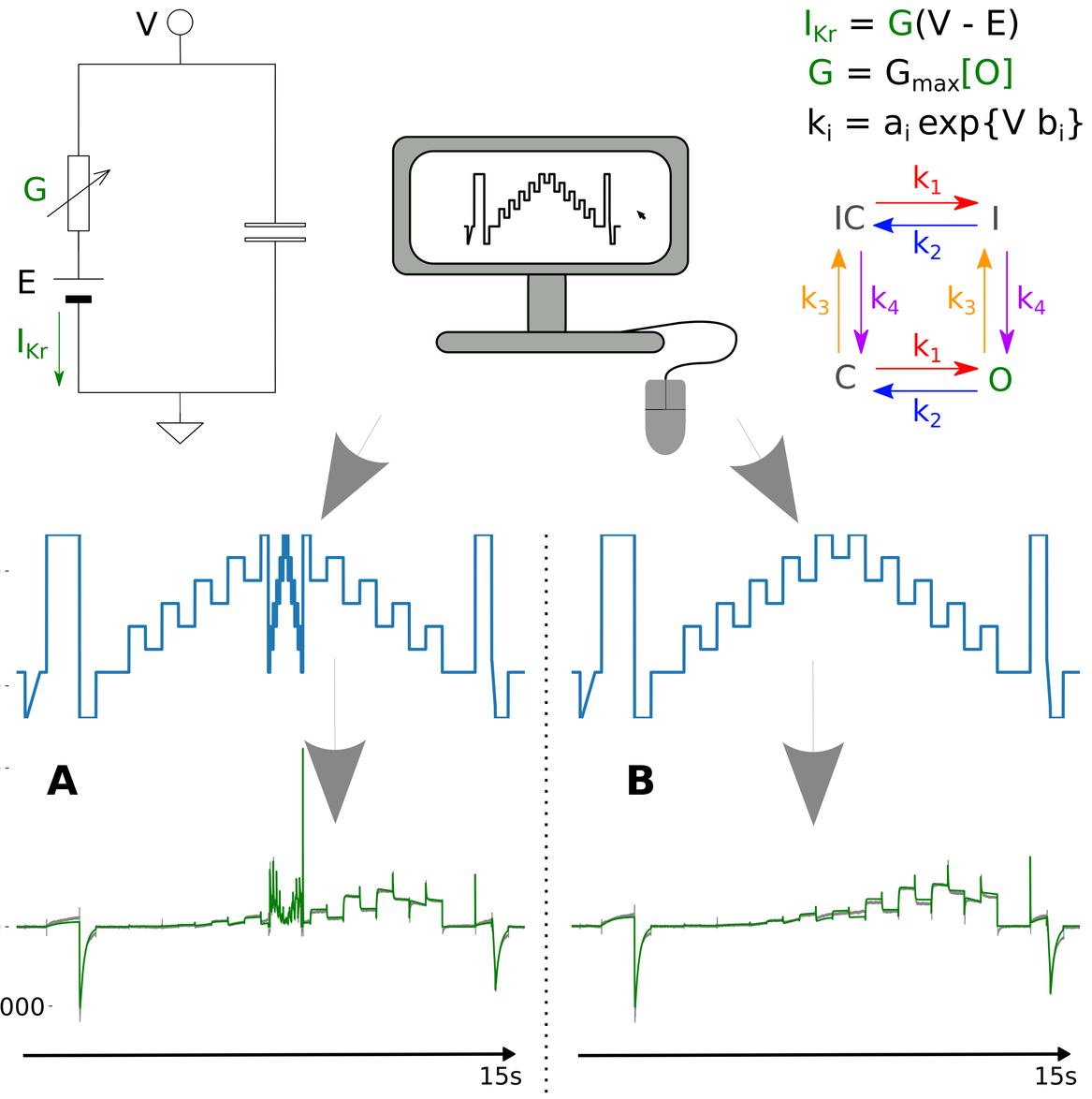
INTRODUCTION

• The *hERG* channel is one type of ion channel found in the membrane of many cells in the human body (including heart tissue)

• Quantifying the pro-arrythmic risk of drugs requires accurate *hERG* models

• Model discrepenancy is the mismatch between our models and the real-world process we are modelling

• Too much model discrepancy may lead to inaccurate predictions



BEATTIE MODEL [1]

• Most models of the *hERG* current can be represented as a simple electrical circuit

• The Beattie odel is a four state Markov model with 9 parameters

• The conductance of the variable resistor, G, is commonly modelled with ODEs (Markov models) [2]

• There are many competing models in the literature with different differing numbers of states and parameters

FITTING

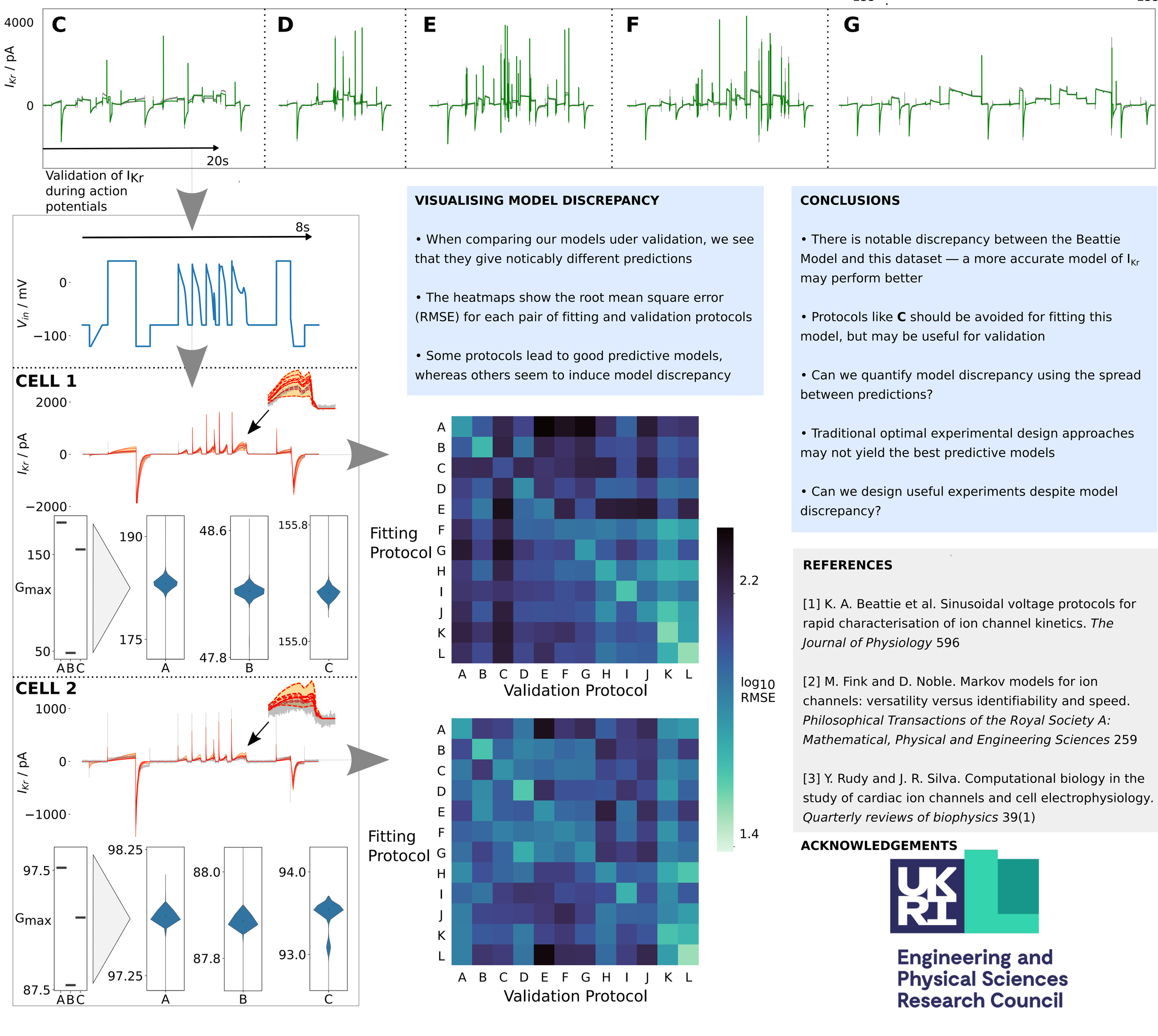
• We stimulate each cell with voltage traces (**A**-**M**)

• We assume known i.i.d additive Gaussian noise, and find the MLE

• Optimisation is performed using CMA-ES

• We also use MCMC to check for identifiability

• We fit the Beattie Model to the each of the resulting current traces individually resulting in 12 seperate models for each cell



VISUALISING MODEL DISCREPANCY

• When comparing our models uder validation, we see that they give noticably different predictions

• The heatmaps show the root mean square error (RMSE) for each pair of fitting and validation protocols

• Some protocols lead to good predictive models, whereas others seem to induce model discrepancy

CONCLUSIONS

• There is notable discrepancy between the Beattie Model and this dataset — a more accurate model of I_{Kr} may perform better

• Protocols like **C** should be avoided for fitting this model, but may be useful for validation

• Can we quantify model discrepancy using the spread between predictions?

• Traditional optimal experimental design approaches may not yield the best predictive models

• Can we design useful experiments despite model discrepancy?

REFERENCES

[1] K. A. Beattie et al. Sinusoidal voltage protocols for rapid characterisation of ion channel kinetics. *The Journal of Physiology* 596

[2] M. Fink and D. Noble. Markov models for ion channels: versatility versus identifiability and speed. *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences* 259

[3] Y. Rudy and J. R. Silva. Computational biology in the study of cardiac ion channels and cell electrophysiology. *Quarterly reviews of biophysics* 39(1)

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