

Selecting and fitting a model for hERG channel kinetics



University of
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Sanmitra Ghosh¹, Kylie Beattie¹ & Gary Mirams²

1. Computational Biology, Department of Computer Science, University of Oxford, UK. 2. Centre for Mathematical Medicine & Biology, Mathematical Sciences, University of Nottingham, UK (gary.mirams@nottingham.ac.uk).

Abstract

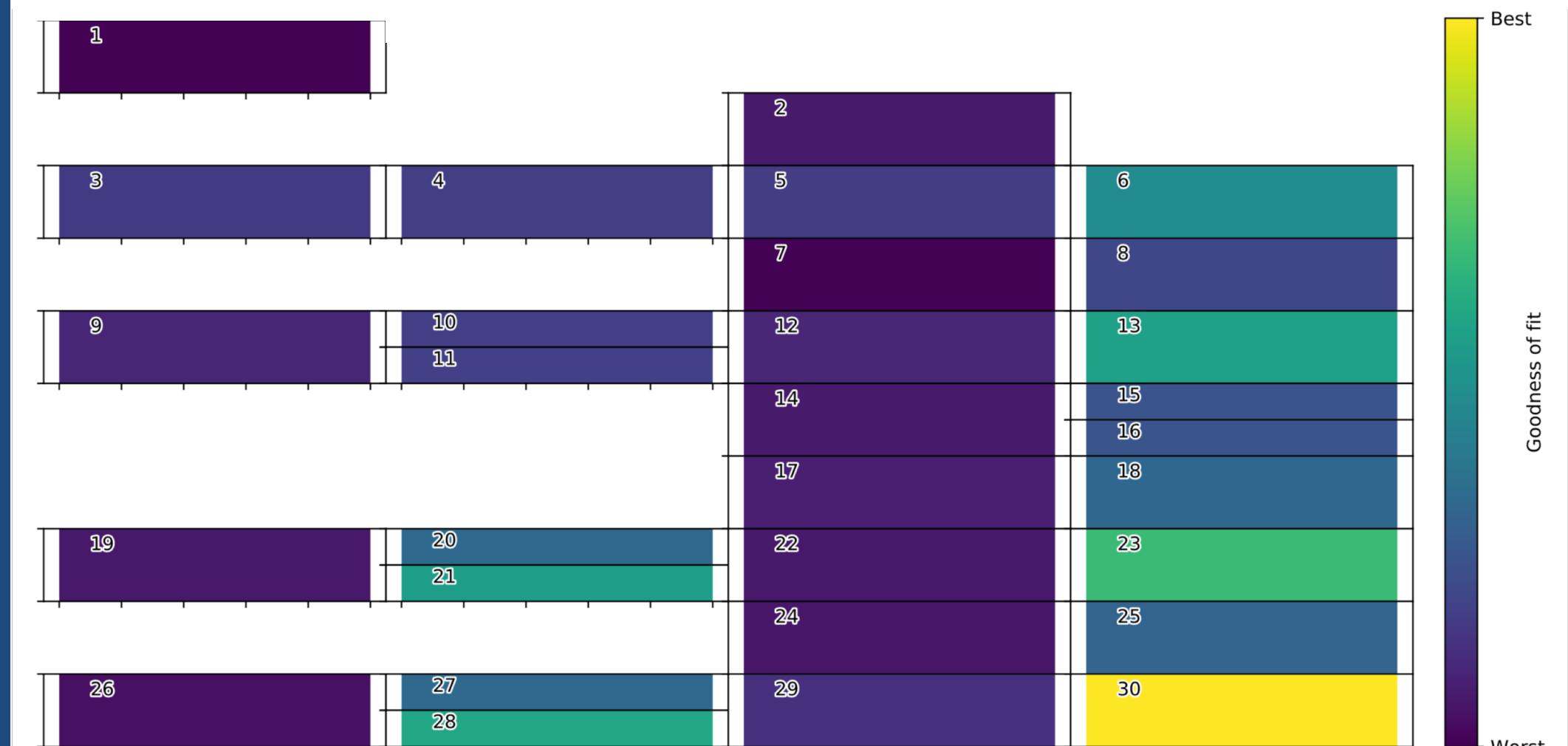
We present a comparison of 30 different possible mathematical models for the hERG potassium current. Each is fitted to a recent dataset published by Beattie et al. using sinusoidal, information-rich ion channel protocols, we compare how well different model structures (Hodgkin-Huxley and Markov models) fit the data and make new predictions.

Model Definitions

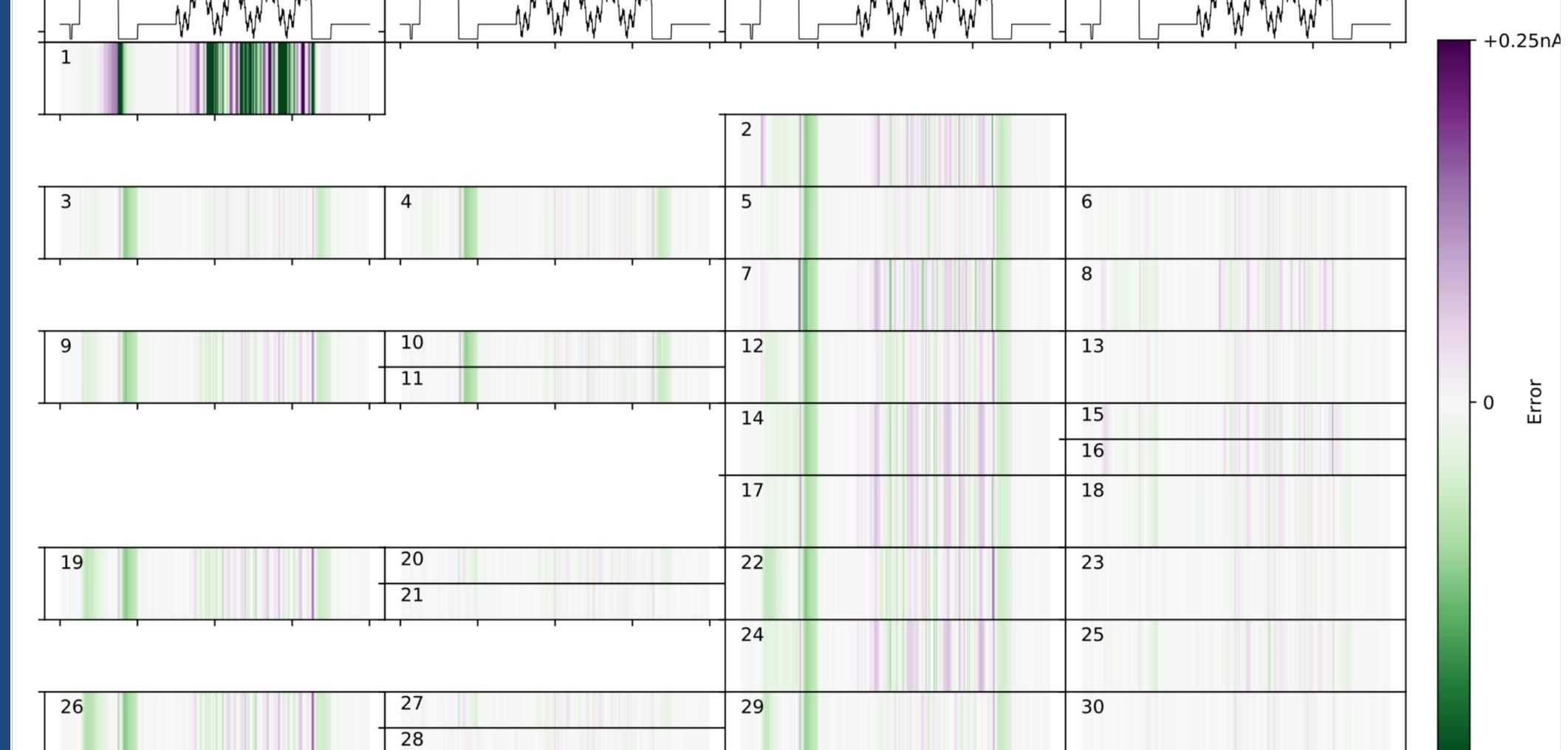
Structure	Full Hodgkin-Huxley (HH)	HH inactivation	HH act. MM inact.	Full Markov Model (MM)
A C - O	M1 (4,1)			
B C - O - I			M2 (8,2)	
C IC - I C - O	M3 (8,2)	M4 (10,3)	M5 (10,3)	M6 (14,3)
D C ₂ - C ₁ - O - I			M7 (8,3)	M8 (12,3)
E IC ₂ - IC ₁ - I C ₂ - C ₁ - O	M9 (8,2)	M10 (12,3) [same rates top and bottom]; or M11 (16,5)	M12 (12,5)	M13 (24,5)
F C ₃ - C ₂ - C ₁ - O - I			M14 (8,4)	M15 (16,4); or M16 (14,4) [no V-dep C ₁ , C ₂]
G C ₃ - C ₂ - C ₁ - O			M17 (10,4)	M18 (18,4)
H IC ₃ - IC ₂ - IC ₁ - I C ₃ - C ₂ - C ₁ - O	M19 (8,2)	M20 (16,4) M21 (22,7)	M22 (14,7)	M23 (34,7)
I C ₄ - C ₃ - C ₂ - C ₁ - O - I			M24 (8,5)	M25 (20,5)
J IC ₄ - IC ₃ - IC ₂ - IC ₁ - I C ₄ - C ₃ - C ₂ - C ₁ - O	M26 (8,2)	M27 (20,5) M28 (28,9)	M29 (16,9)	M30 (44,9)

Table 1: Markov model structures A-J and parameterisations. Brackets signify (# Parameters, # ODEs). This table structure used in later figs →

Training Results

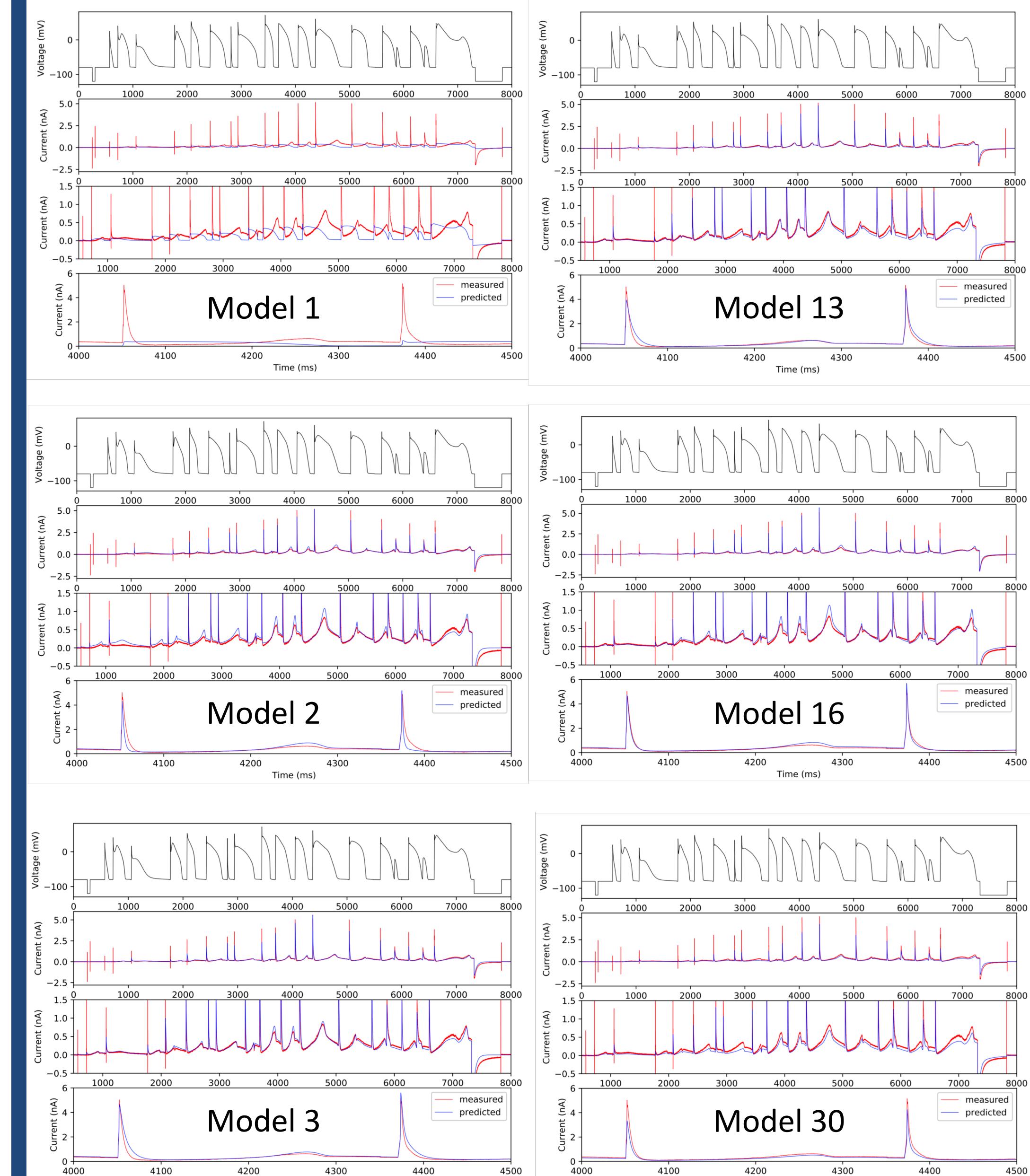


Above: overall goodness of fit to data. Below: errors in fit through time.

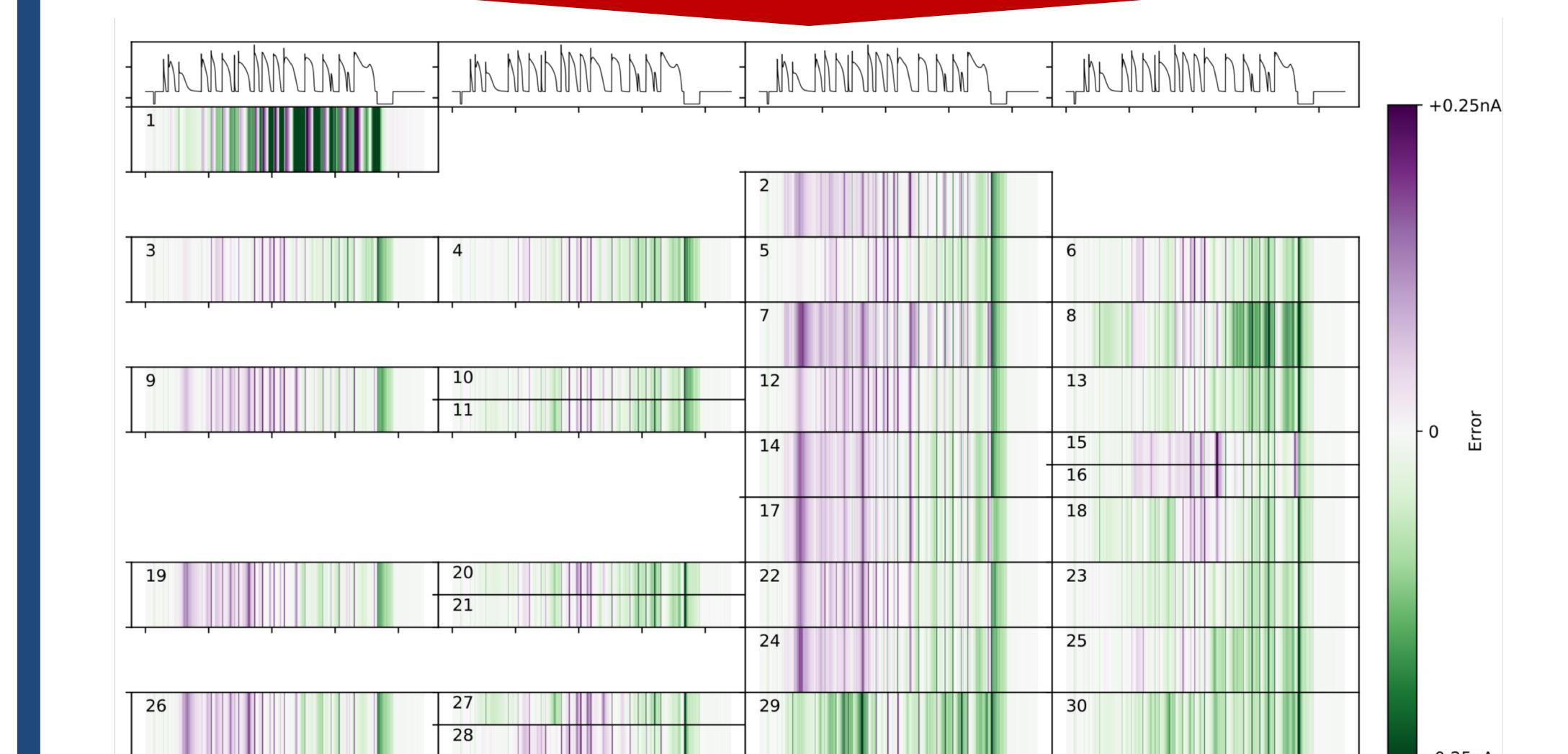


Model Validation

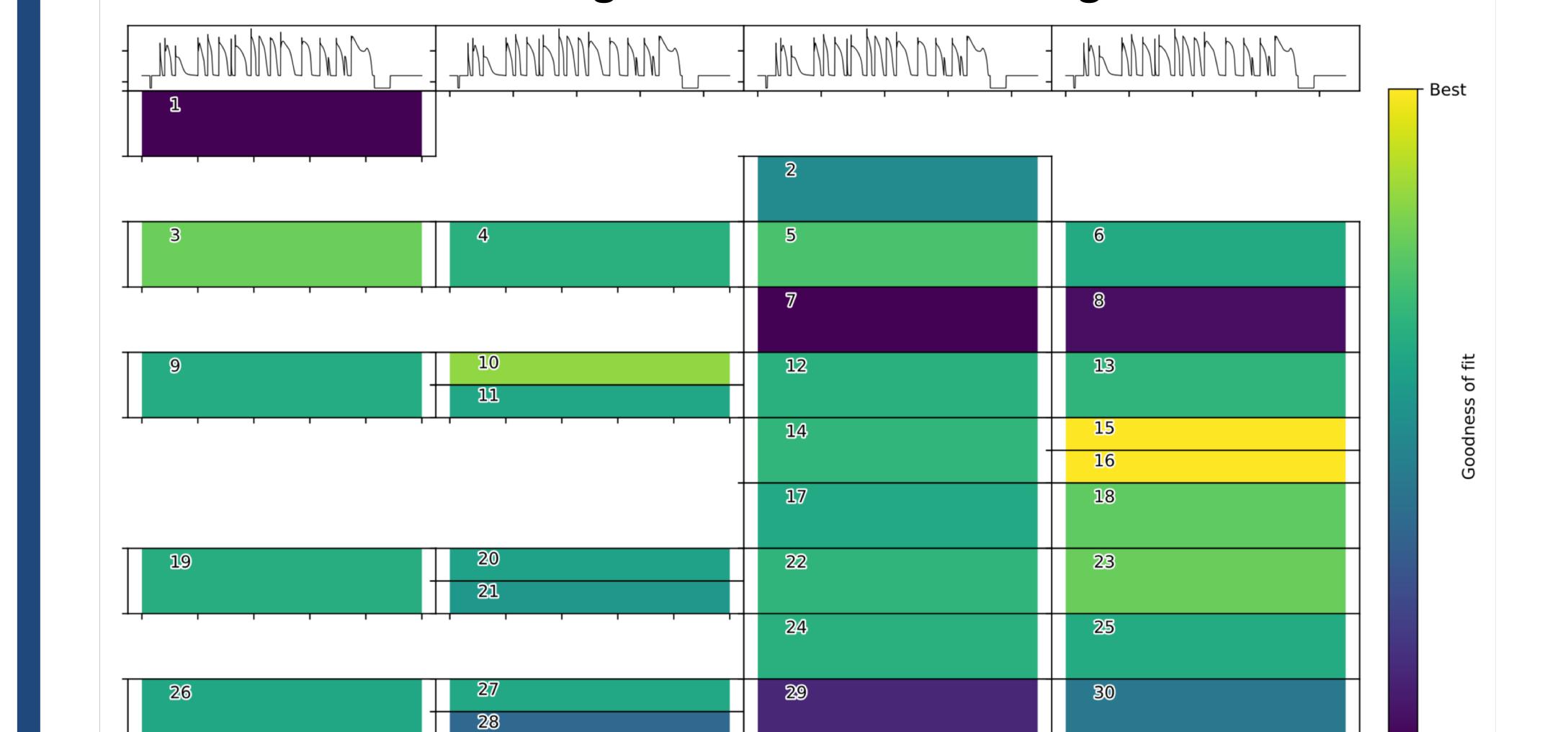
Using action potential clamps



For all models

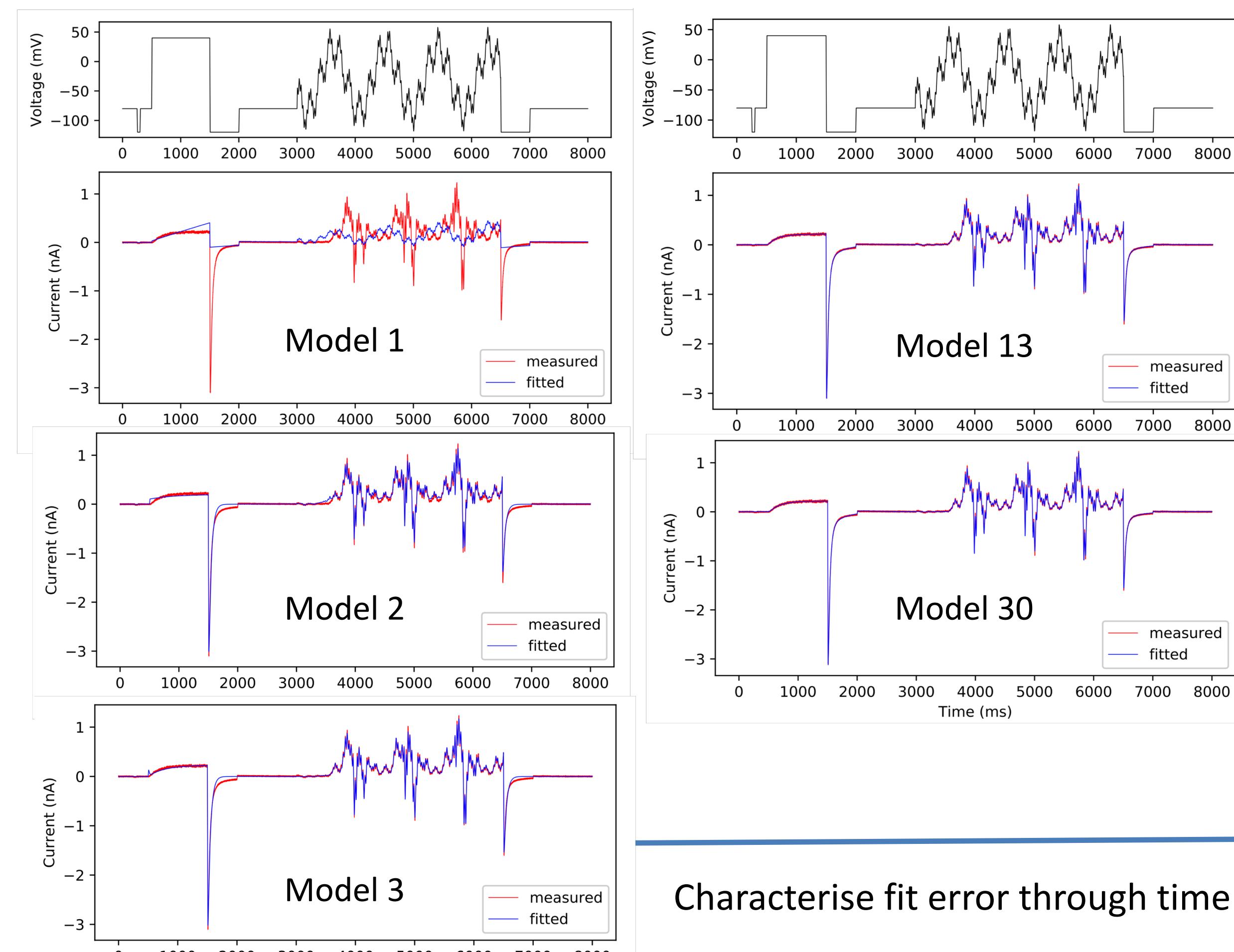


Above: errors in fit through time Below: overall goodness of fit to data.



Training / Calibration

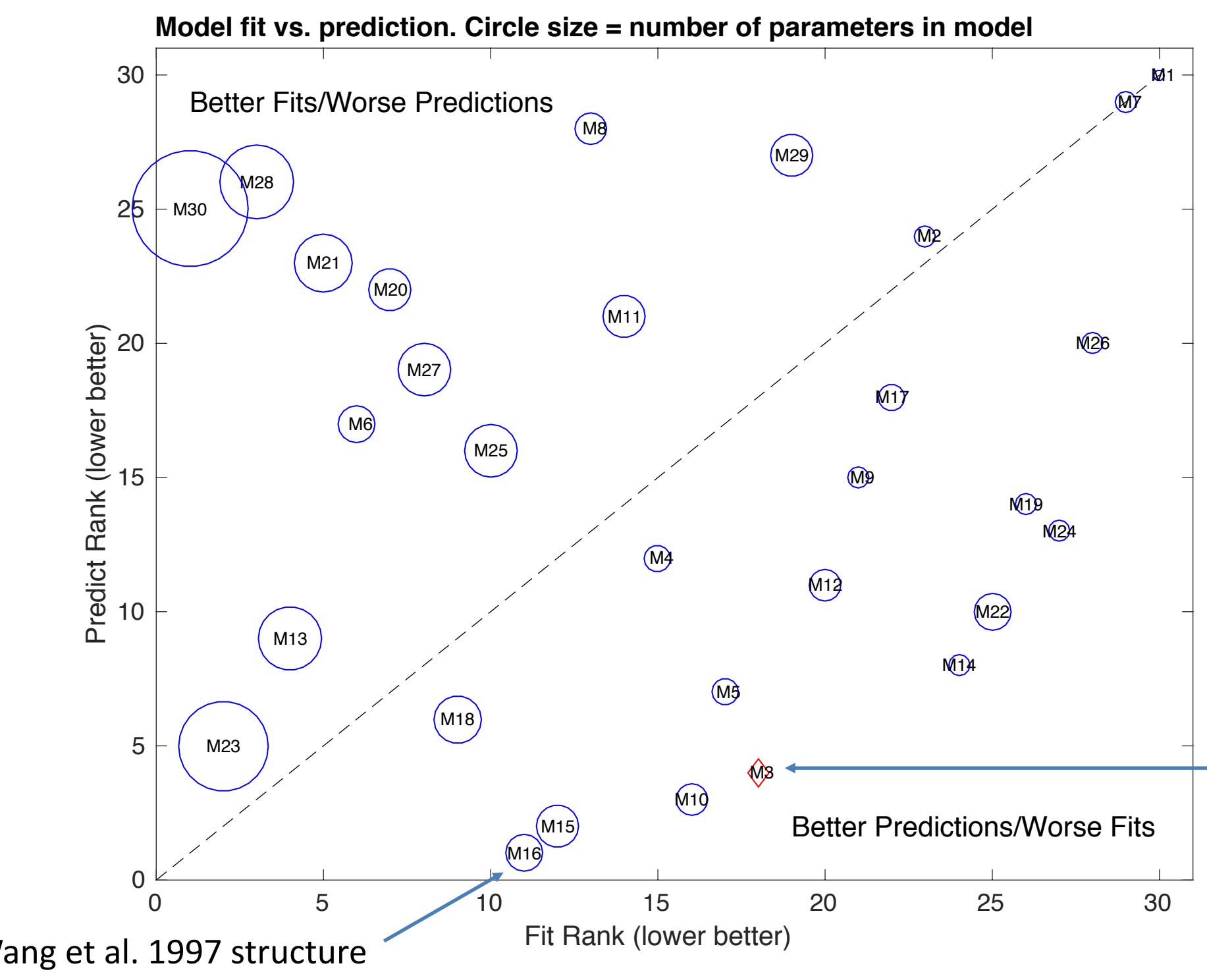
Parameters were fitted to data recorded from CHO cells overexpressing hERG1a at room temperature, as recorded by Beattie et al. (2018) under a new sinusoidal voltage clamp. We used a global optimiser (CMA-ES)



Characterise fit error through time

Model Complexity

The most predictive models are not the largest, best fitting ones:



Conclusions

It is important to separate parameter fitting and validation when building ion channel models. More complicated models with more parameters are likely to fit the data better, but may not provide better predictions in new unseen situations.

Future work will design extra experiments to highlight differences between models to aid in model selection and extend this work to choose between different modes of drug binding to hERG.

When making predictions for safety-critical use (in drug development or the clinic) we need to quantify uncertainty due to model structure choice.

References

[Model 3] Beattie, K. A., Hill, A. P., Bardenet, R., Cui, Y., Vandenberg, J. I., Gavaghan, D. J., de Boer, T. P. & Mirams, G. R. Sinusoidal voltage protocols for rapid characterisation of ion channel kinetics. *J. Physiol.* **596**, 1813–1828 (2018).

[Model 16] Wang, S., Liu, S., Morales, M. J., Strauss, H. C. & Rasmussen, R. L. A quantitative analysis of the activation and inactivation kinetics of HERG expressed in Xenopus oocytes. *J. Physiol.* **502**, 45–60 (1997).

Acknowledgements

This work was supported by a Wellcome Trust & Royal Society Sir Henry Dale Fellowship to GM, also employing SG.

