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Challenges in ion channel model calibration, selection and discrepancy

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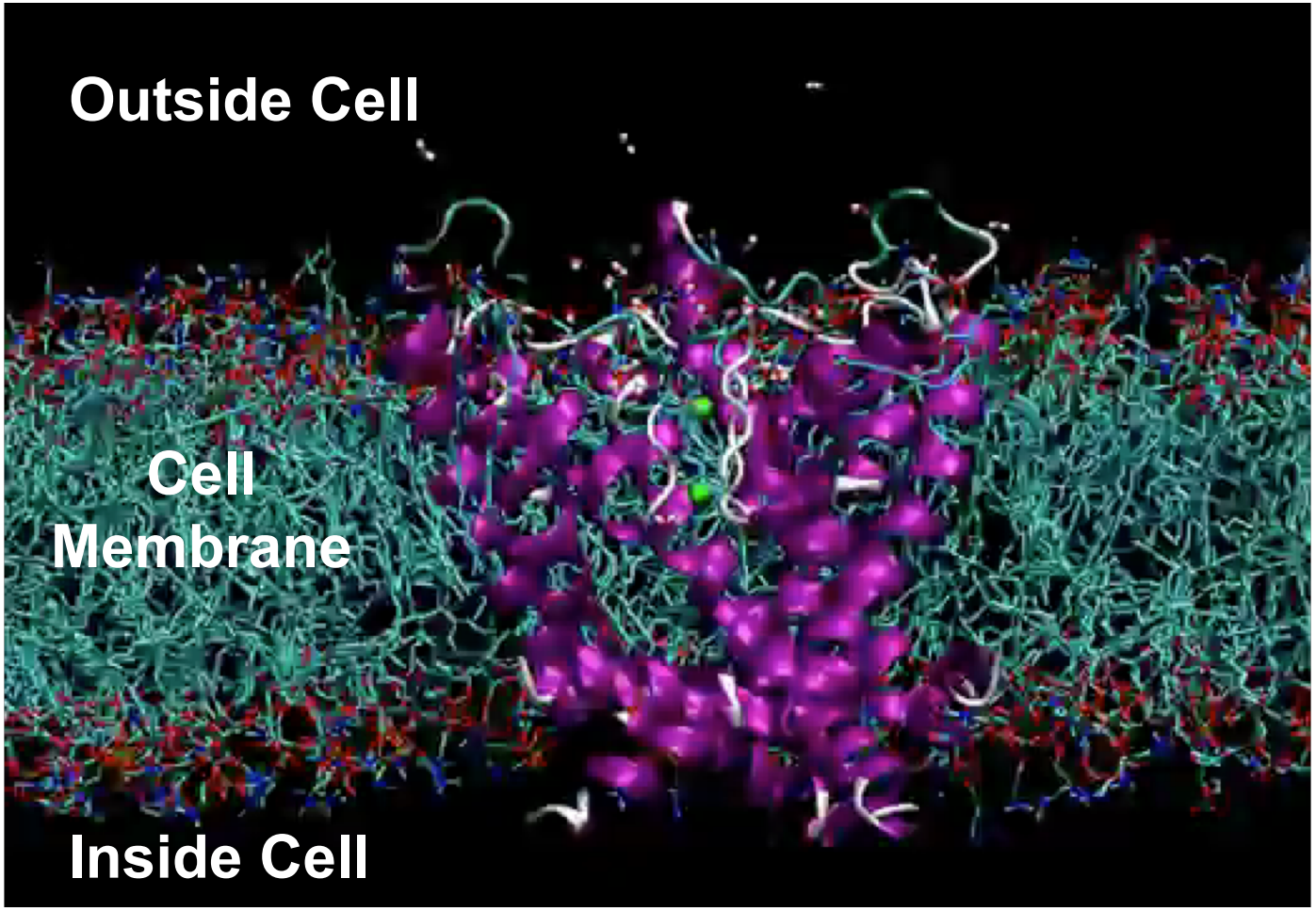
Modelling ion channels

Biology Background – ion channels

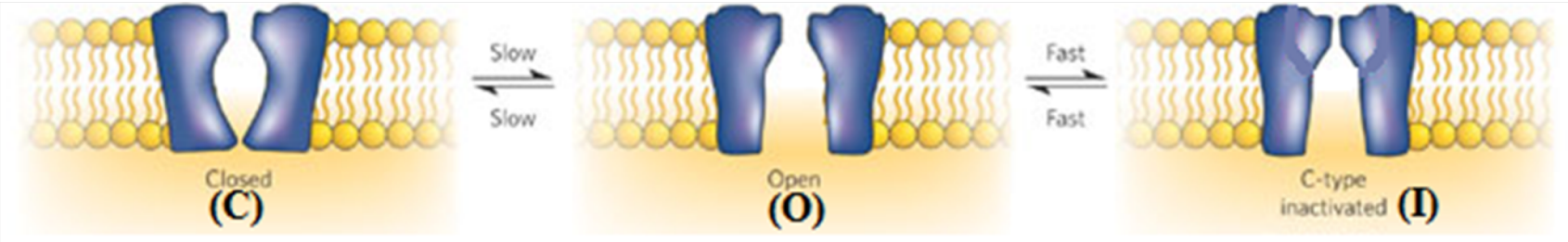


Movie by Alessandro Grottesi
https://www.youtube.com/watch?v=gNSeN7NMJRA

Biology Background – ion channels

- Ion channels are fundamental for your cells maintaining ion gradients, but also for muscle contraction, and via nerve activity pain, taste, etc. etc.
- Ionic currents flow through proteins ('ion channels') in the cell membrane.

- Many ion channels are 'voltage gated':



Low voltage Intermediate voltage High voltage

Figure adapted from: Sanguinetti &Tristani-Firouzi.

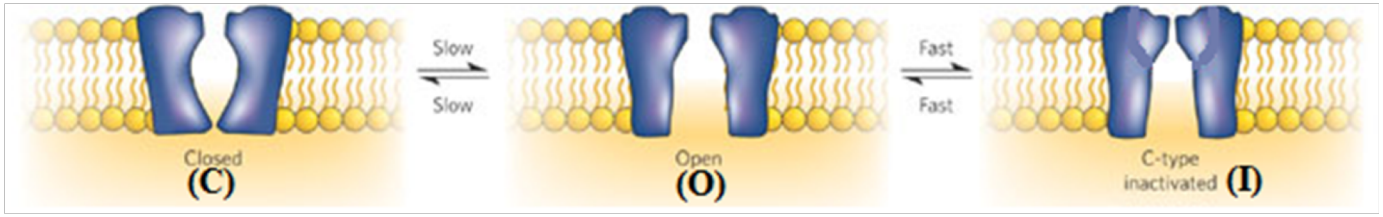
"hERG potassium channels and cardiac arrhythmia." *Nature* 440 (2006): 463-469

Ionic Current Models

- *"Current is proportional to:*
  - *i) maximum current that can flow through a single channel;*
  - *ii) number of channels;*
  - *iii) probability a channel is open;*
  - *iv) driving voltage"*

g

- In equation form: $I = g * P(Open) * (V - E_{Na})$
- Complicated bit is the open probability. The proportion of channels in open state:



Simplest model of a voltage-dependent ion channel

- Work with probability of being in Closed (C) or Open (O) states.
- Each transition rate/arrow has two parameters to be fitted.
- We can then write down differential equations for the state occupancies over time…

General form of transition rates (how fast the arrows go!)

:

$$\alpha = \theta_1 \exp\left(\theta_2 V(t)\right)$$

(from Eyring rate theory)

$$C \underset{\beta}{\overset{\alpha}{\rightleftarrows}} O$$

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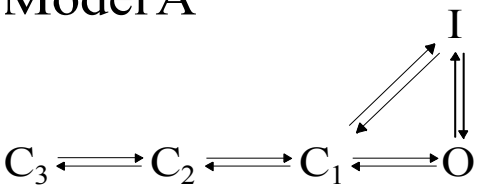
What's uncertain?

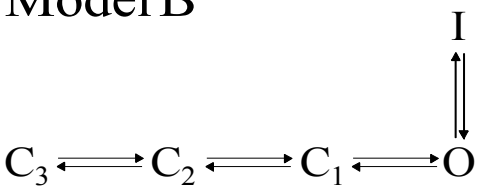
Different models of a particular potassium channel (hERG, I_{Kr}) that have been published.

Model structure is a big bone of contention!

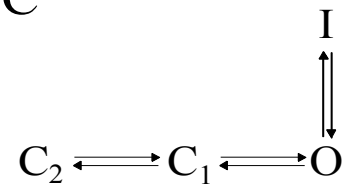
Model A



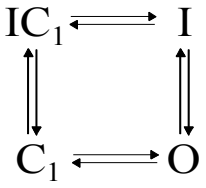
Model B



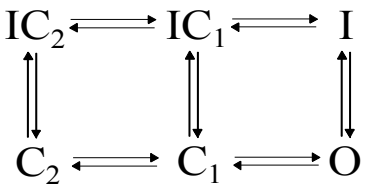
Model C



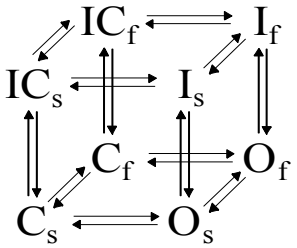
Model D



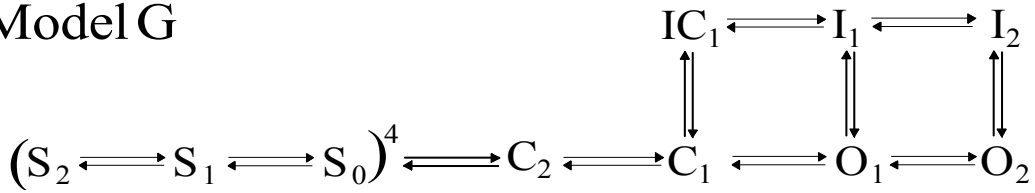
Model E



Model F



Model G



C = closed

O = open

I = inactivated

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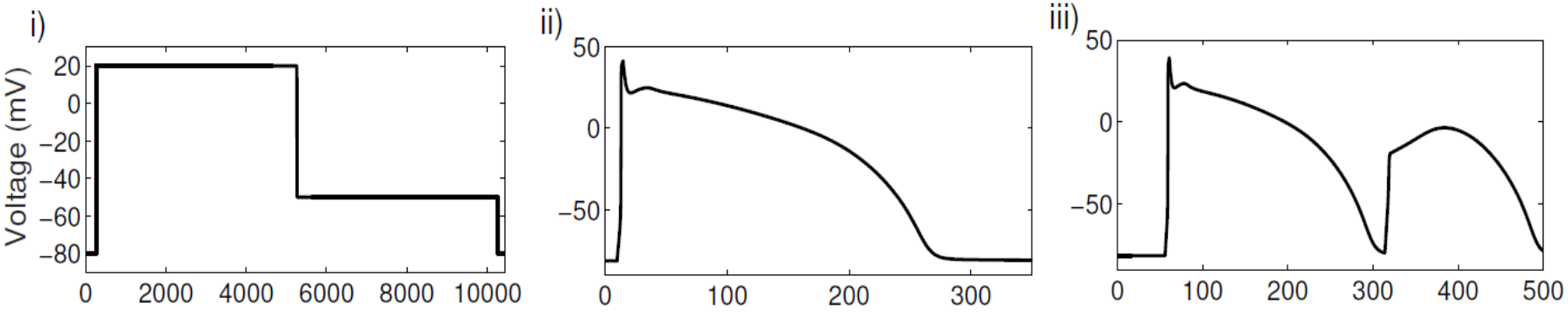
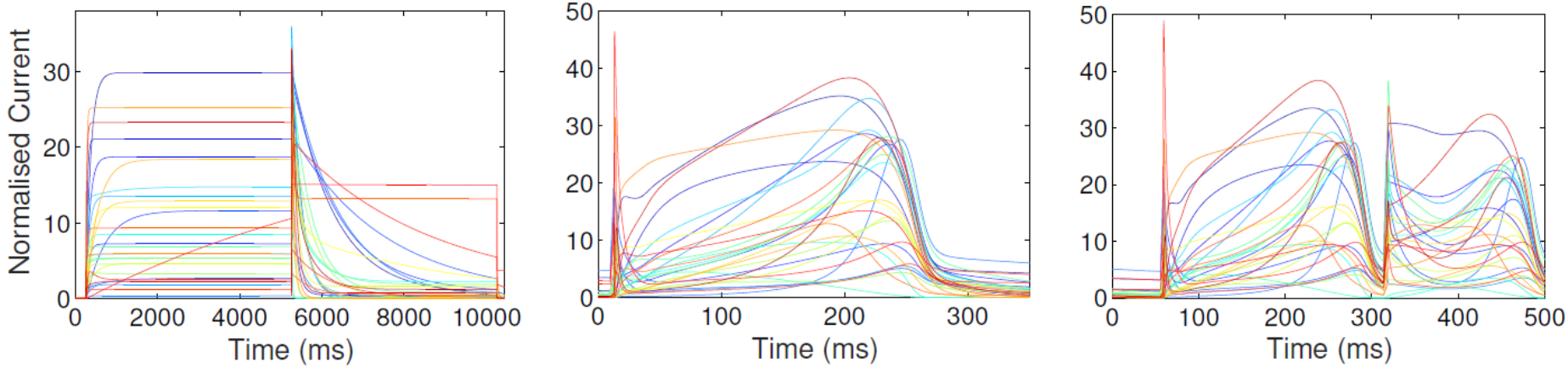
Different models, very different predictions

Model inputs (voltage)



Outputs (current)



- Some of this is to be expected (different temperatures, cell types, species)
- But many of the wildly different predictions are for the same setting

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Model Fitting with Funky Protocols

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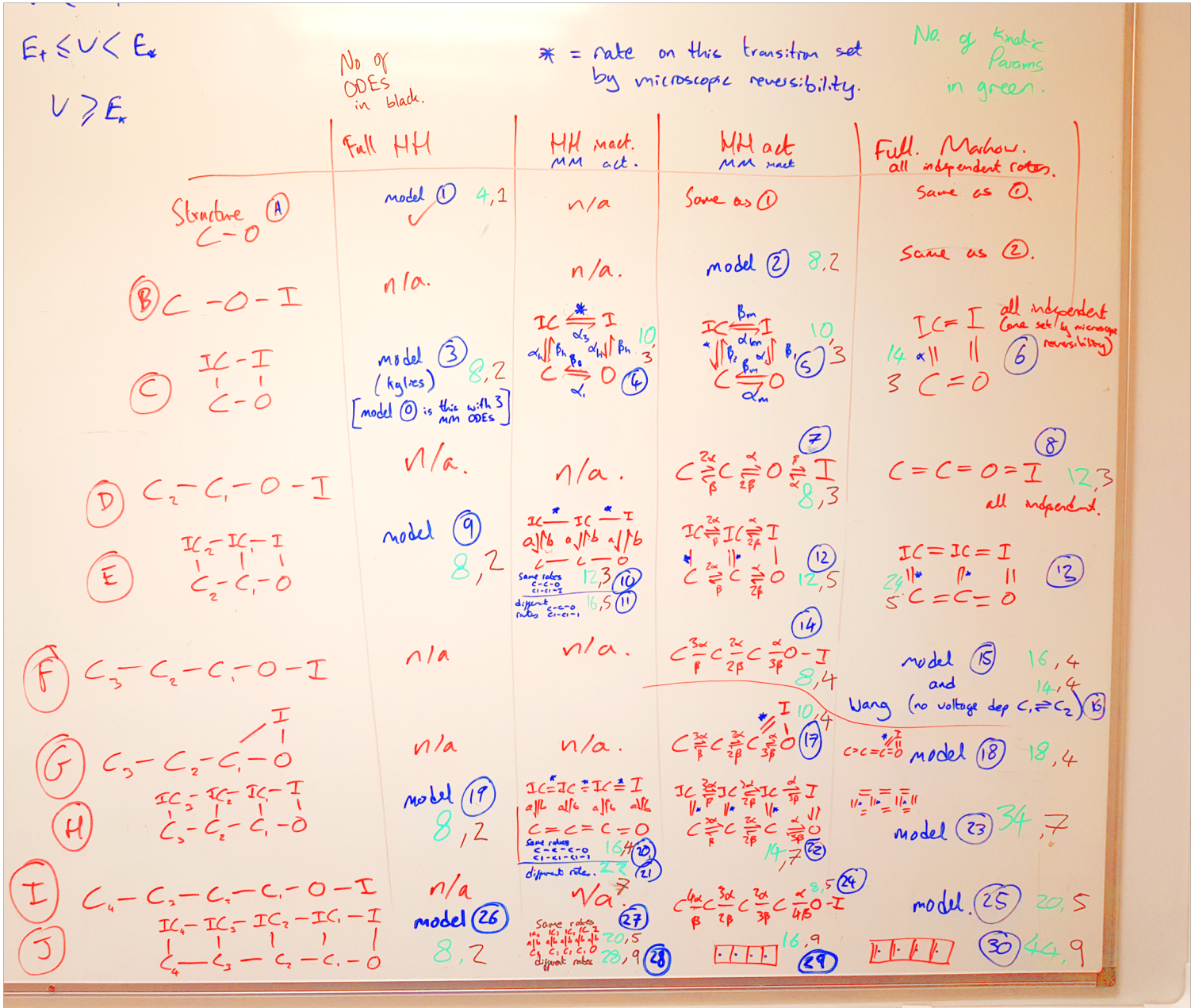
Possible Model Structures and Parameterisations

- My office whiteboard at the moment
- At least 30 possible models
- Equally plausible(?)



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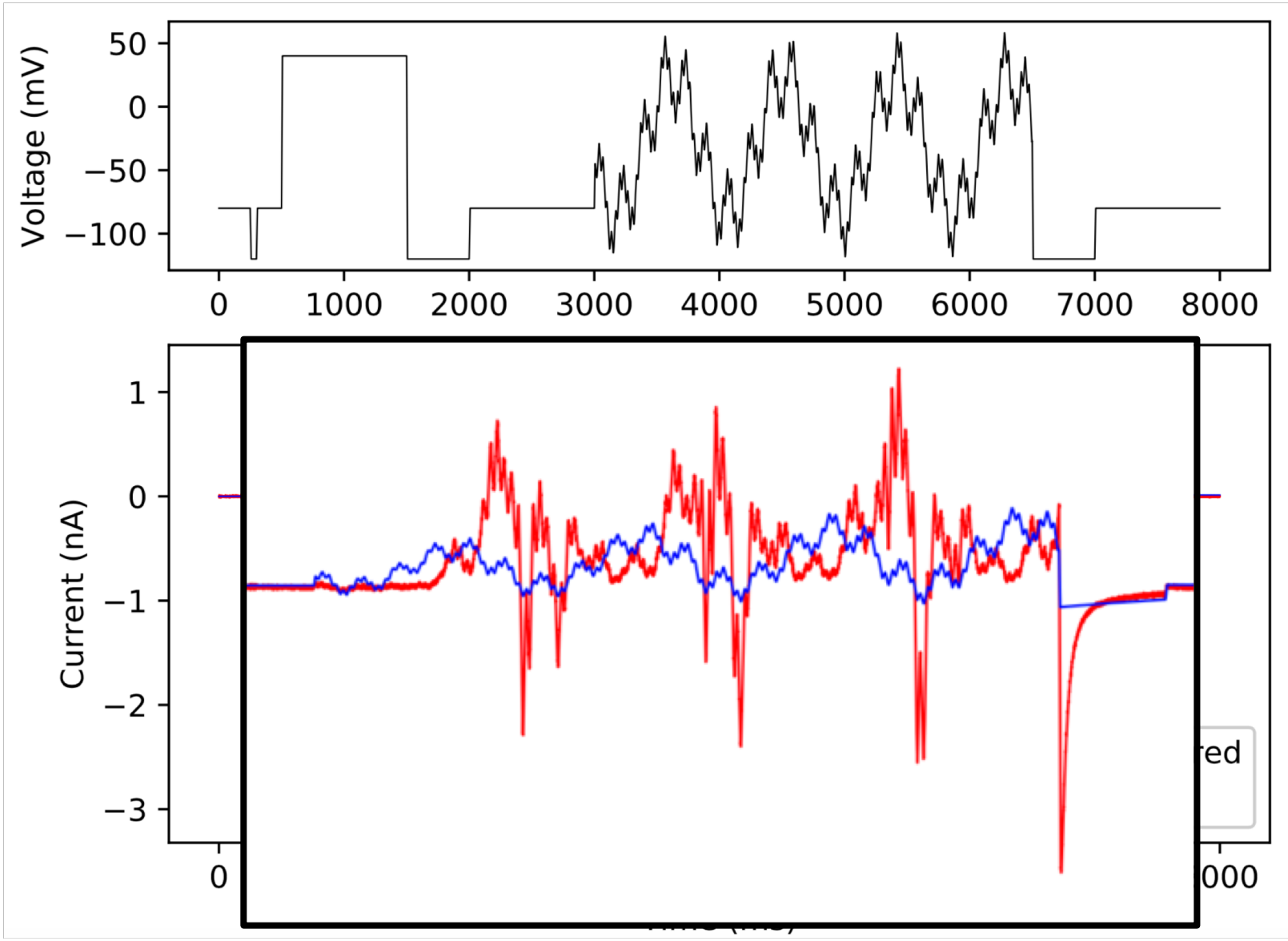
Too simple…

C-O



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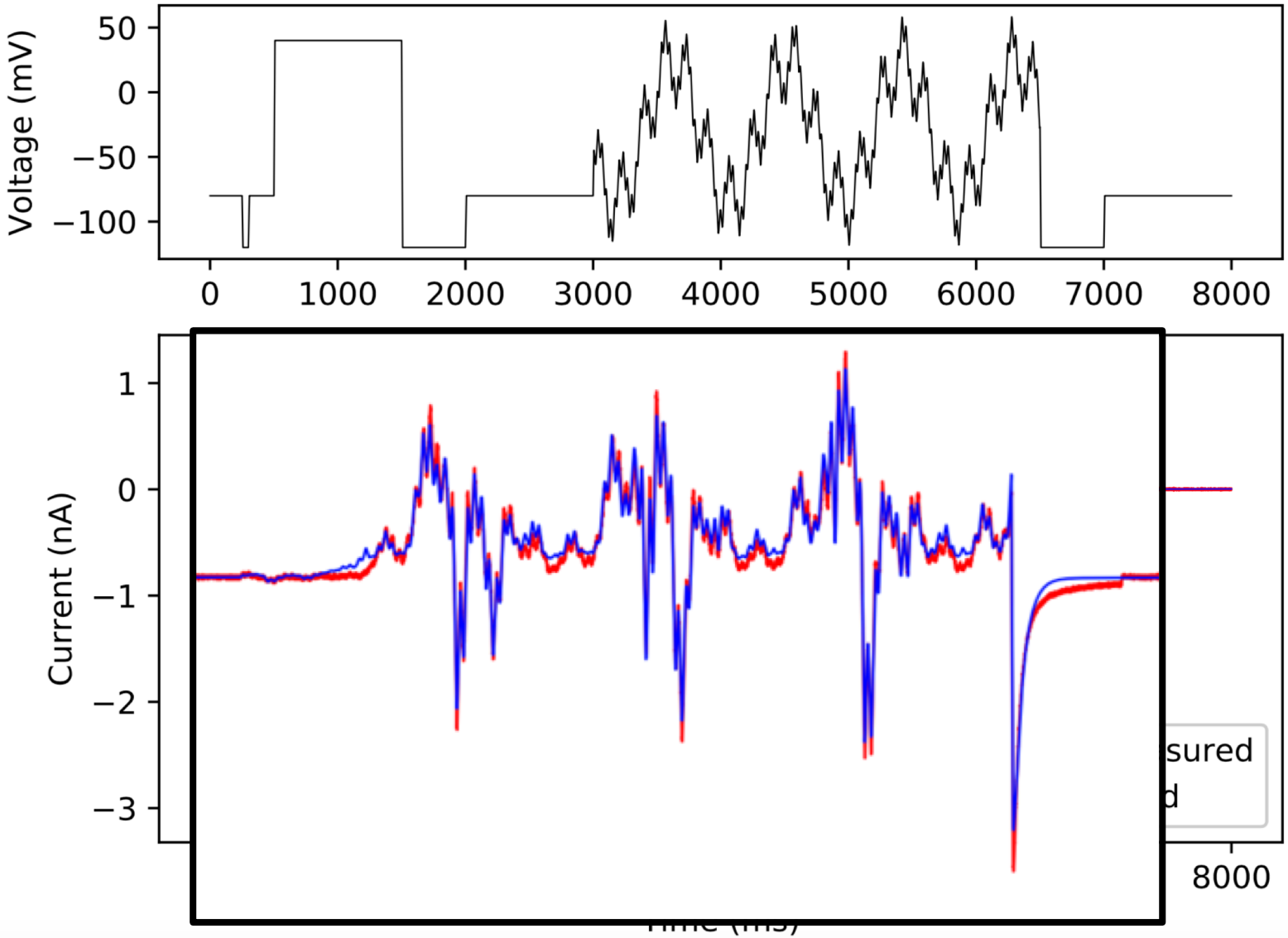
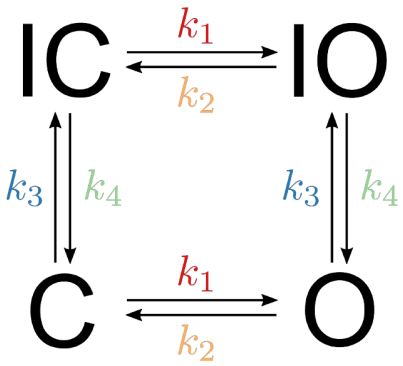
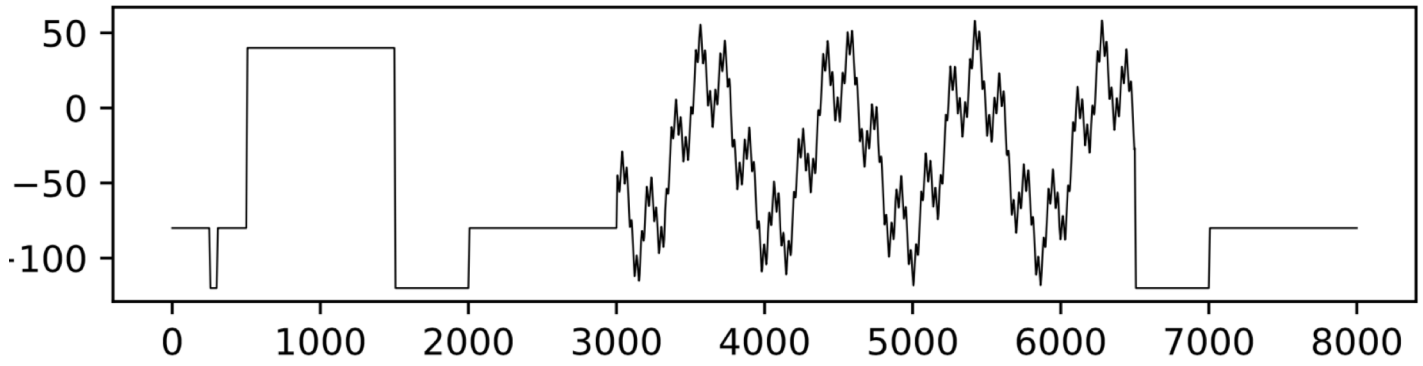
Getting Somewhere…

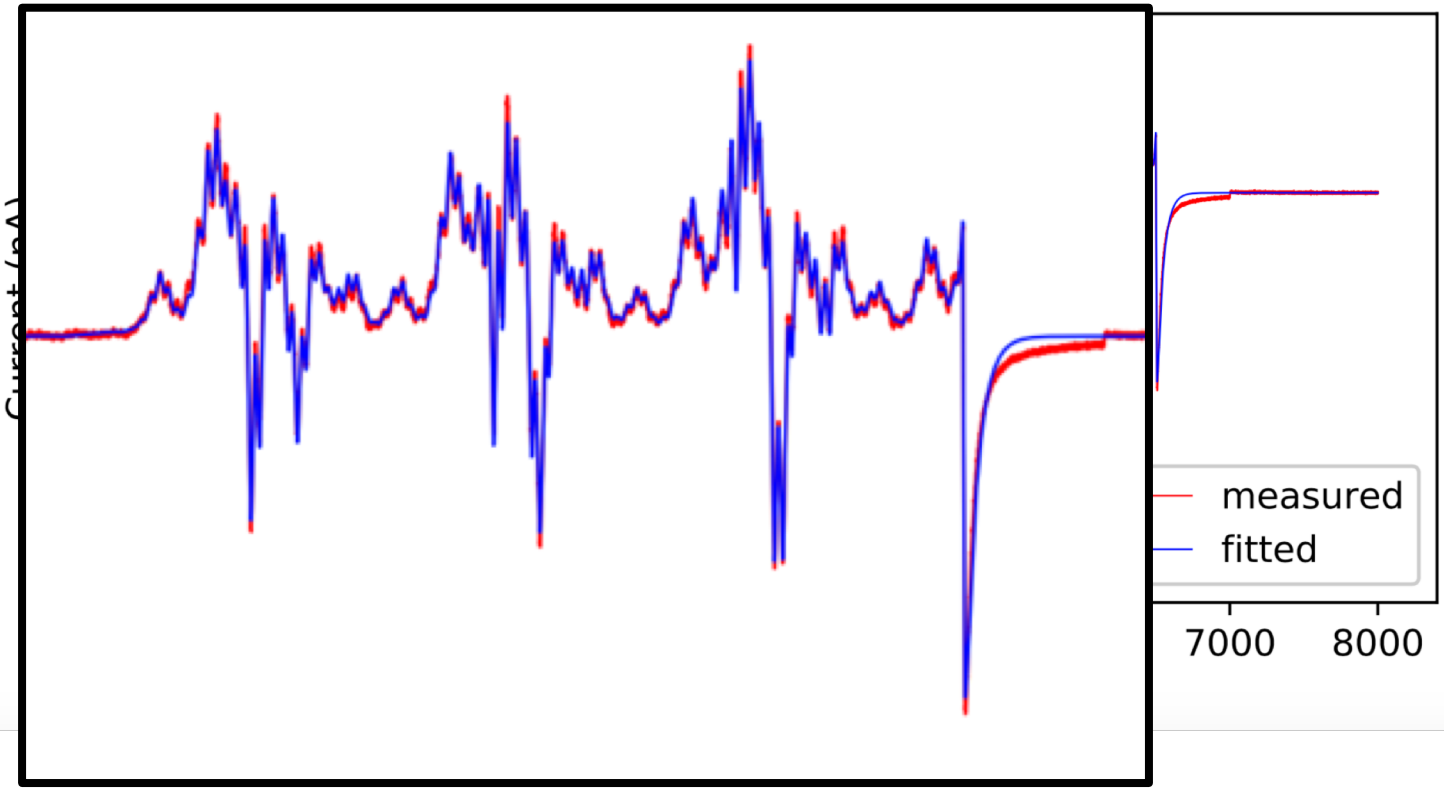
C-O-I

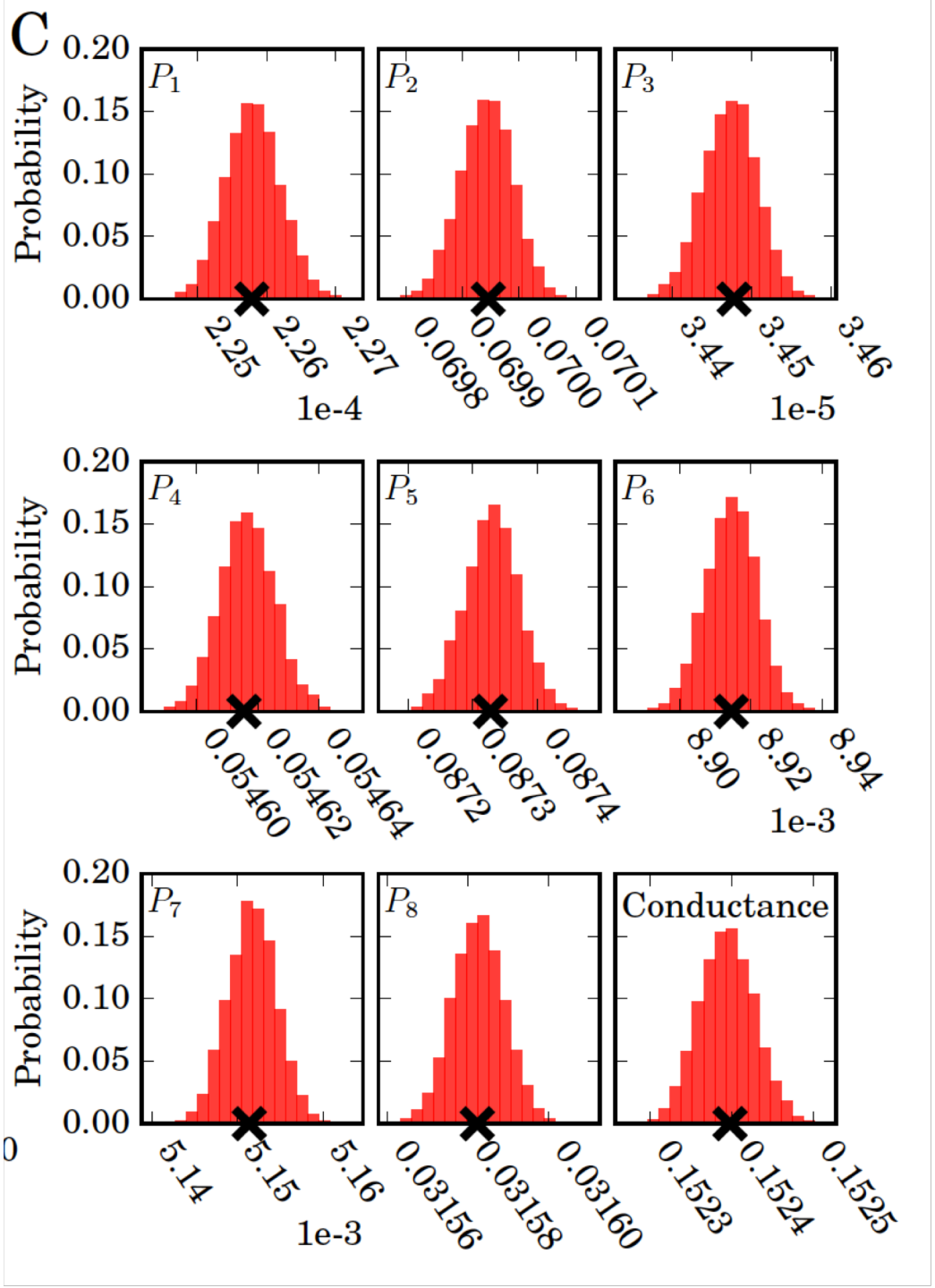


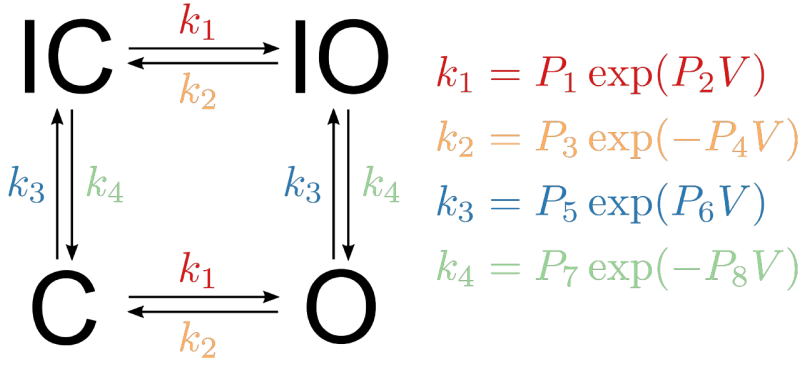
Better


IC
IO
C
O
k_1
k_2
k_3
k_4


50
0
−50
-100
0
1000
2000
3000
4000
5000
6000
7000
8000


Current (pA)
measured
fitted
7000
8000





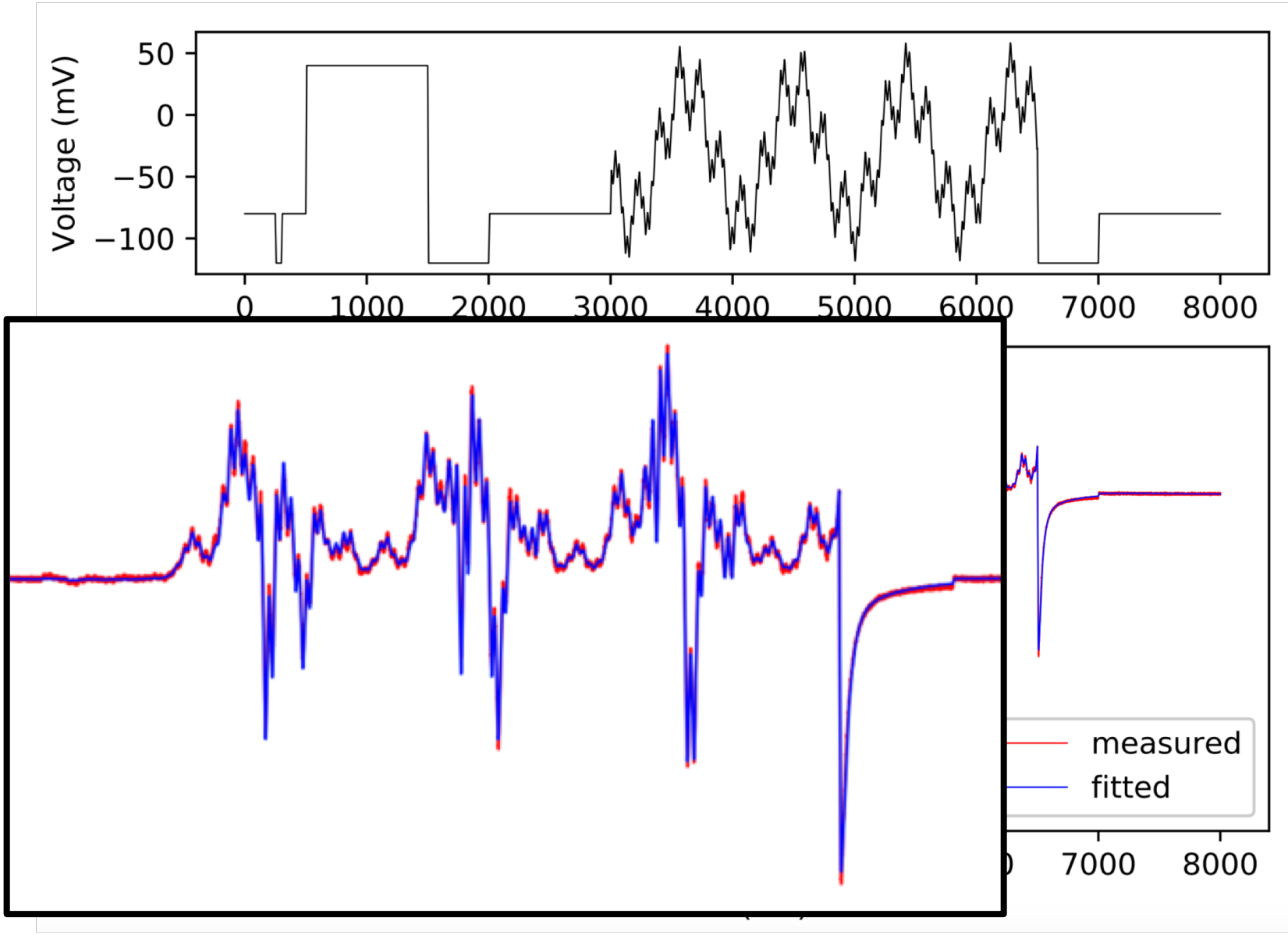
i.i.d. Gaussian noise model.

There are a lot of traps to fall into, but done correctly MCMC provides a nice ‘Brute force’ practical identifiability assessment.

Time trace is so rich (almost appears continuous, >10,000 data points). Hence very very narrow posteriors…

Brilliant – or Overfitting?

IC–IC –I
| | |
C–C –O



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Validation & Model Selection

Model Selection Criteria

Training

- Fit to data
- AIC
- BIC
- WAIC
- Bayes' Factors
- ...

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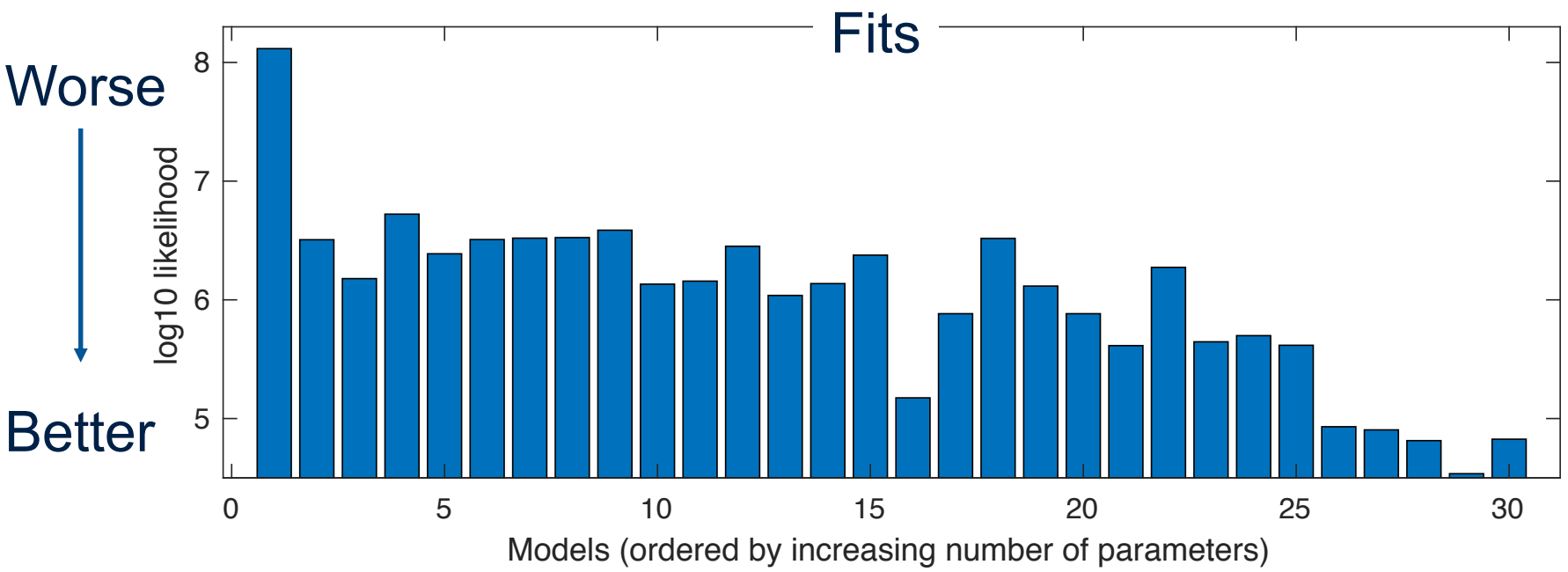
Fitting loads of models



Because likelihood values are very negative and large (due to i.i.d. noise assumption across 80k points) information criteria look completely identical to this.

Not quite sure what will happen with Bayes Factors…?

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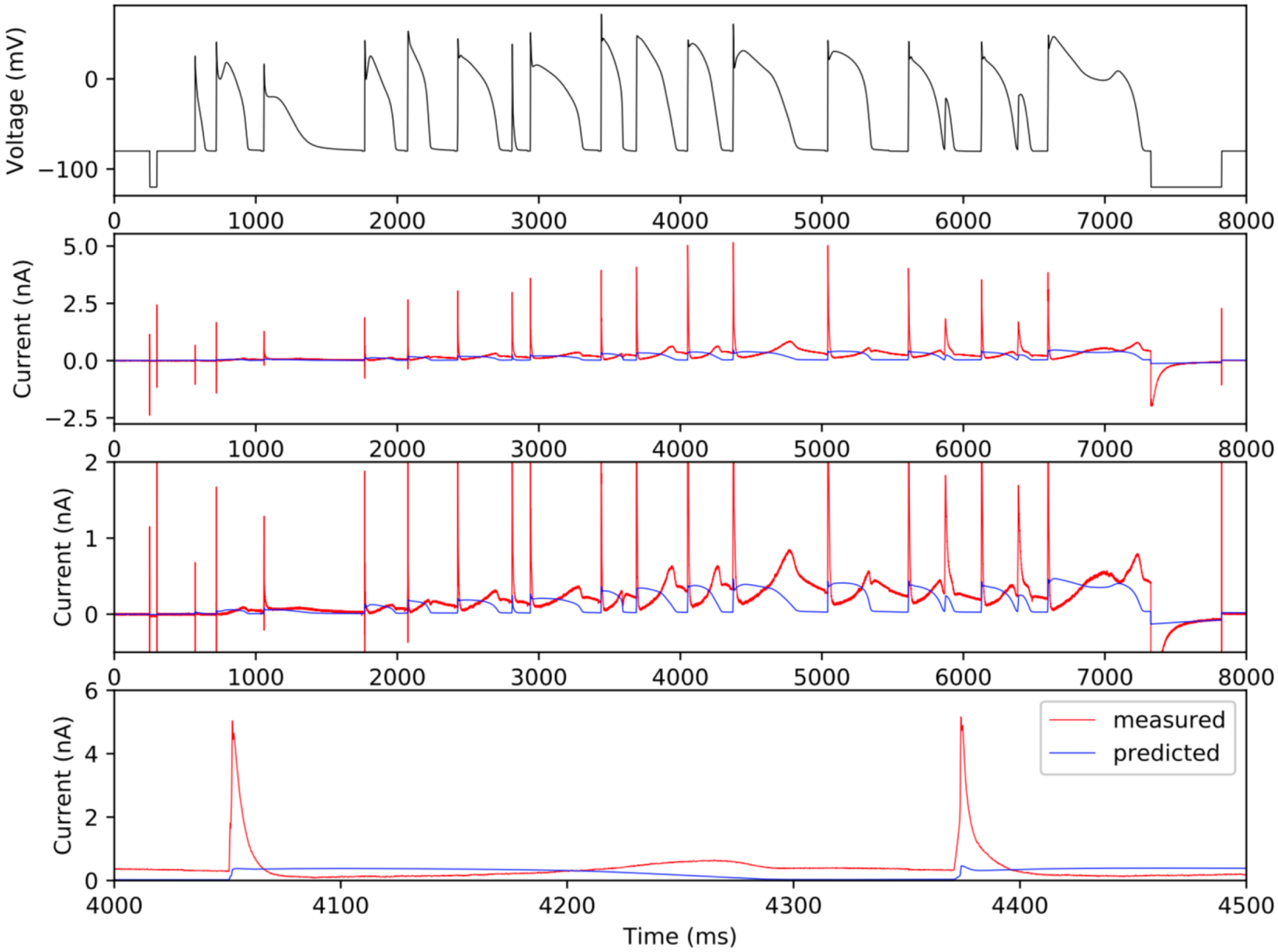
Some predictions (data from same cell)

C-O



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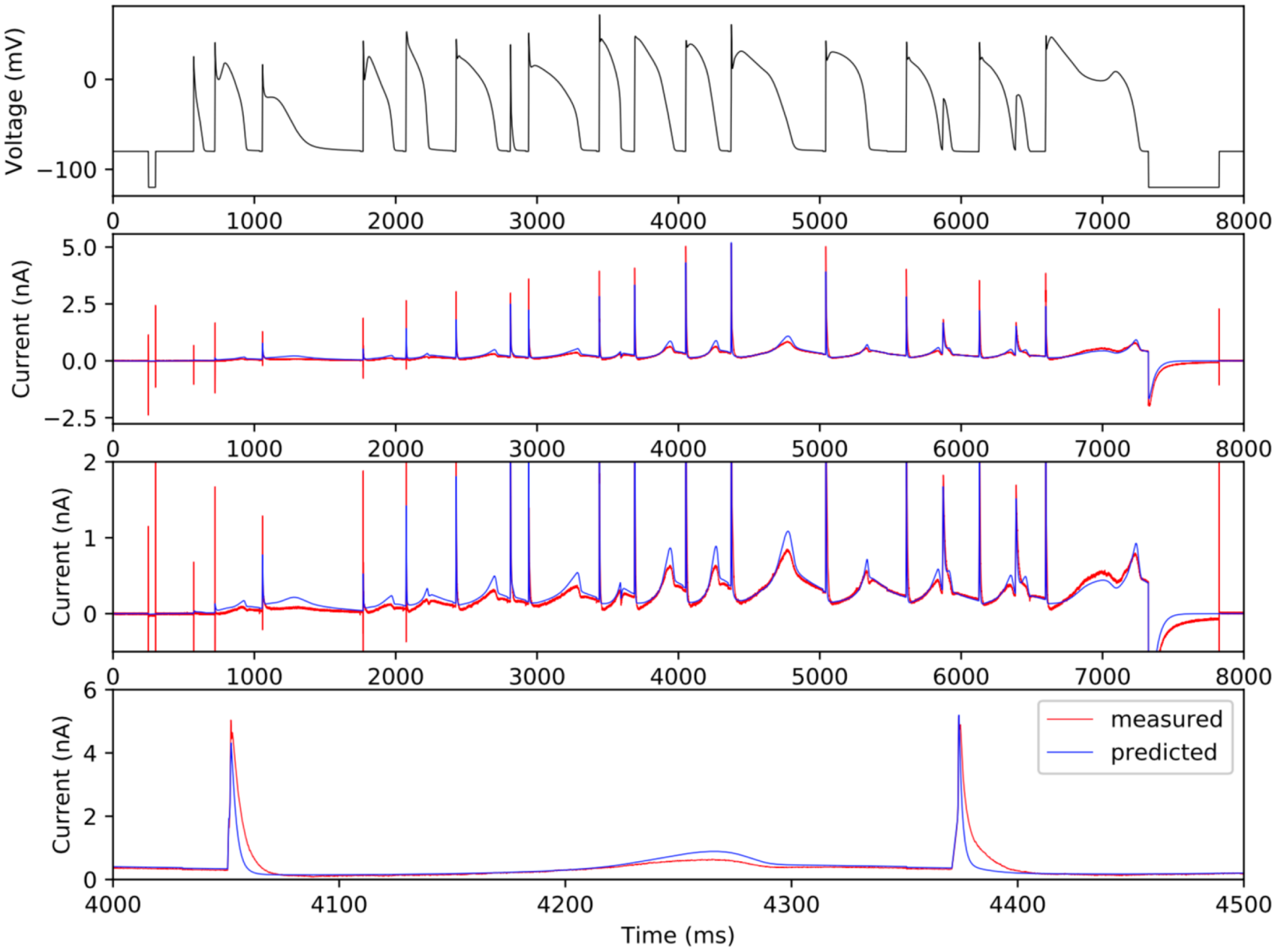
Getting Somewhere…

C-O-I



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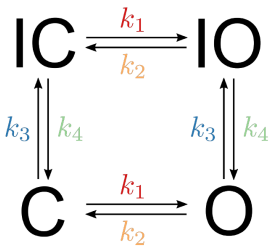
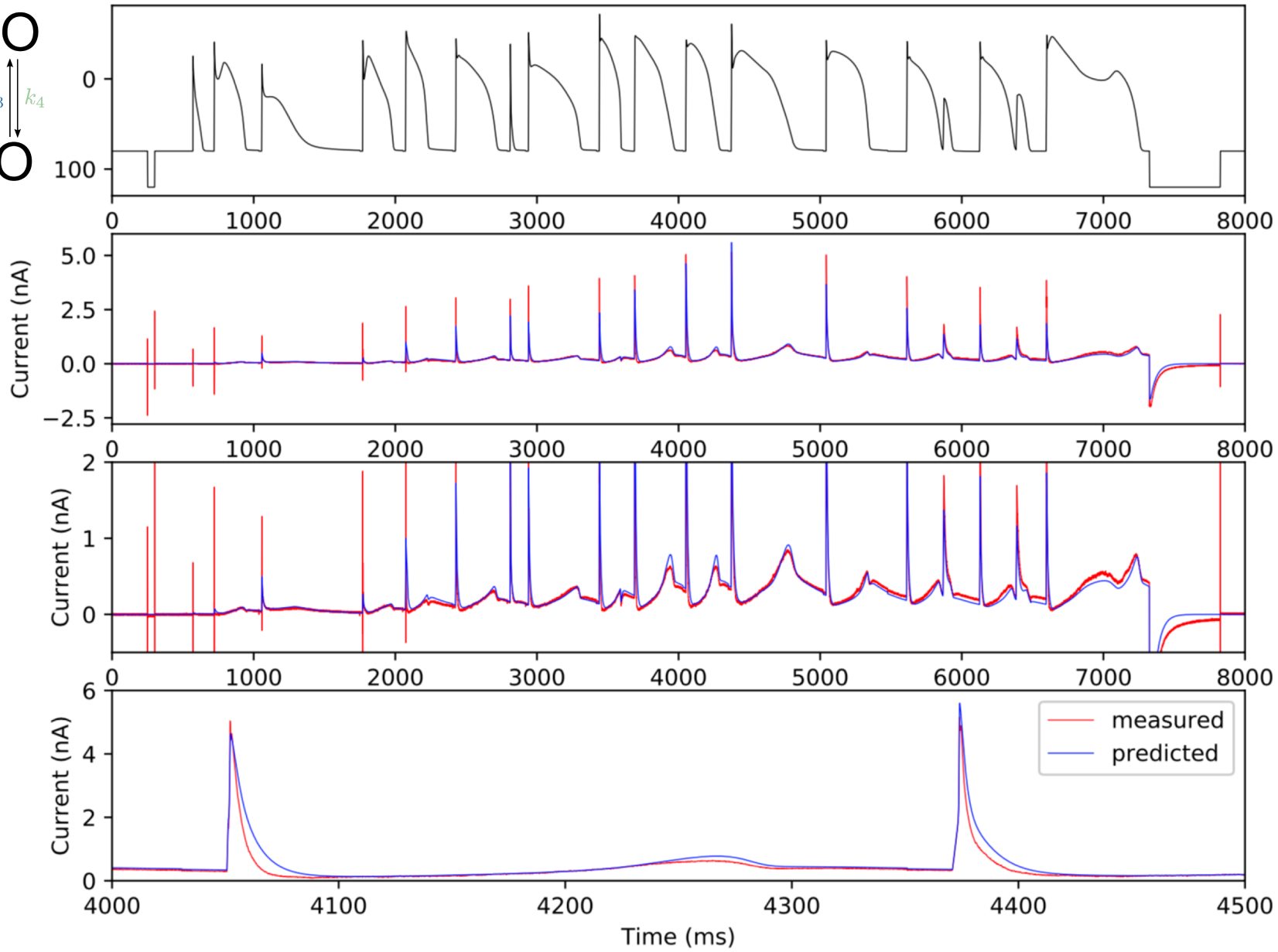
Not bad for a 1952 model structure!





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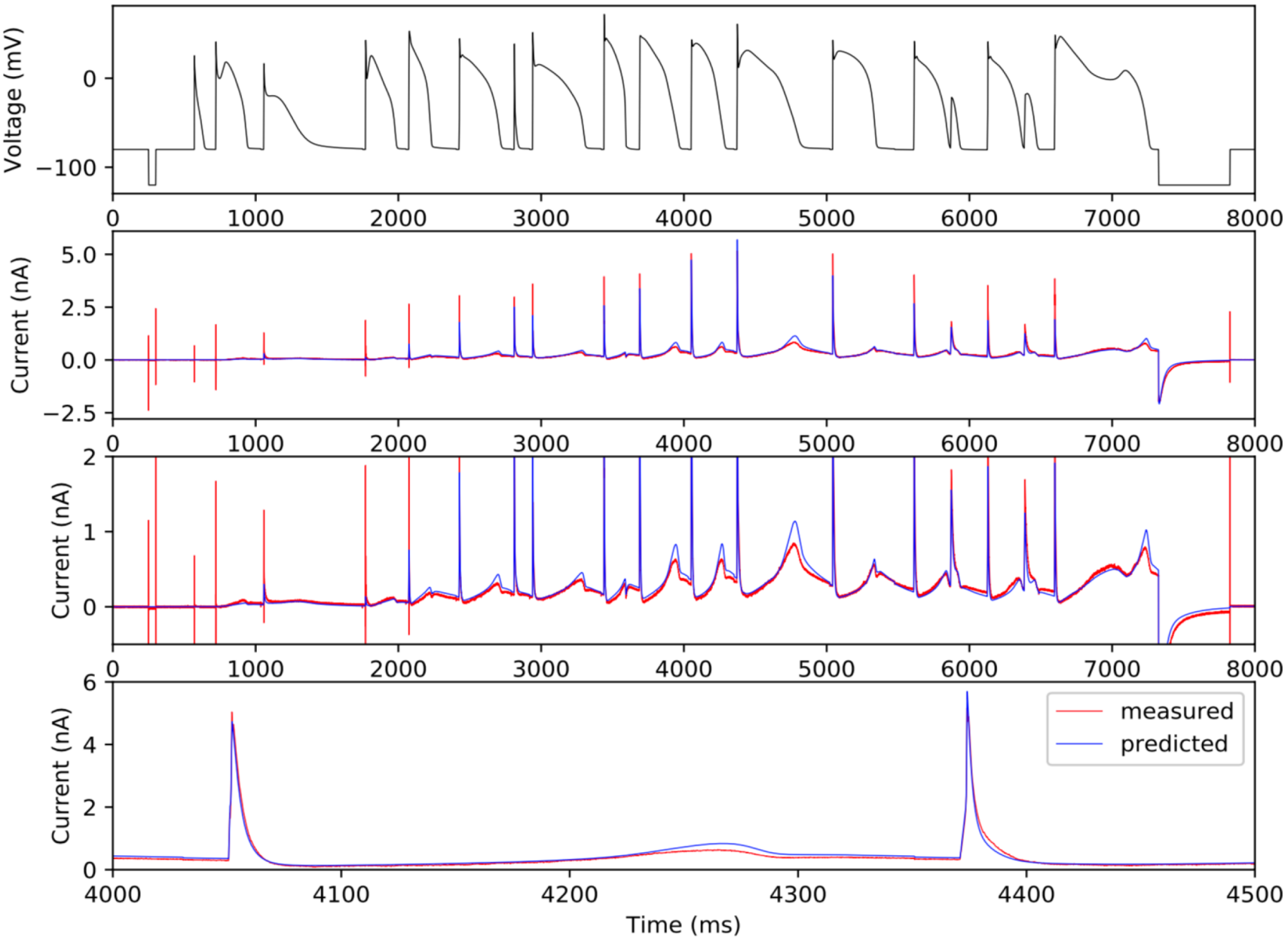
One of the best: C-C-C-O-I



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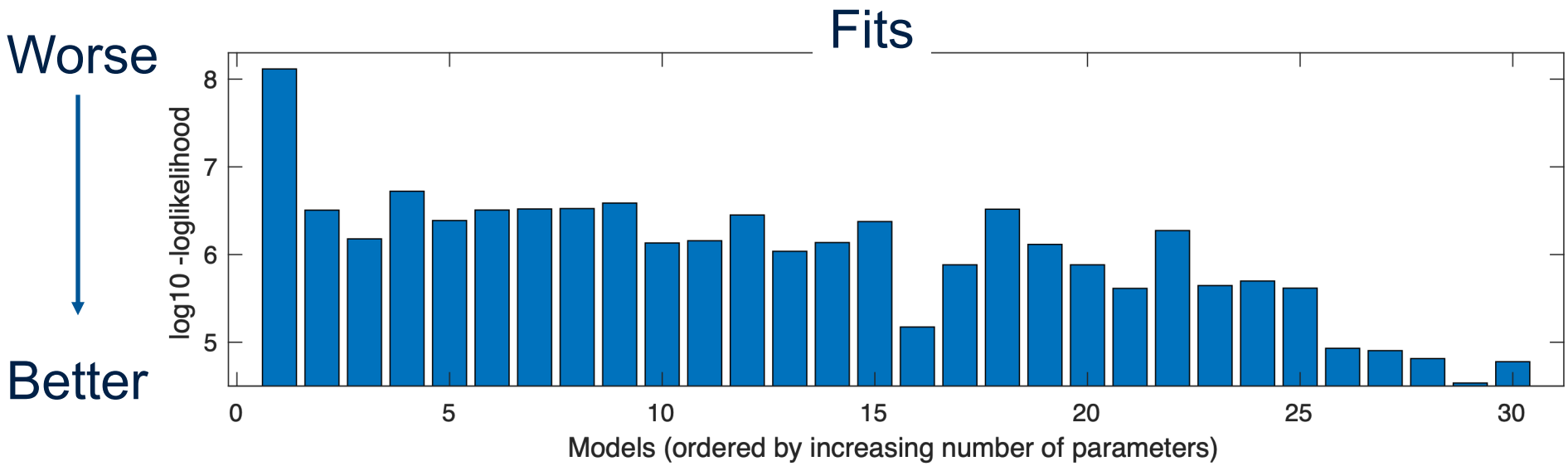
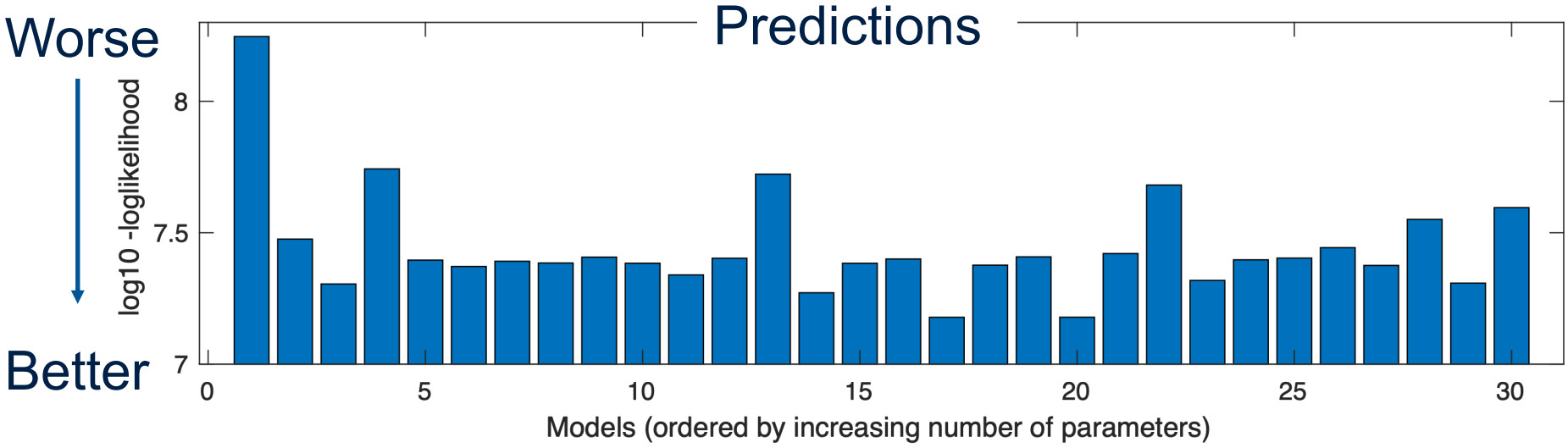
Fitting loads of models





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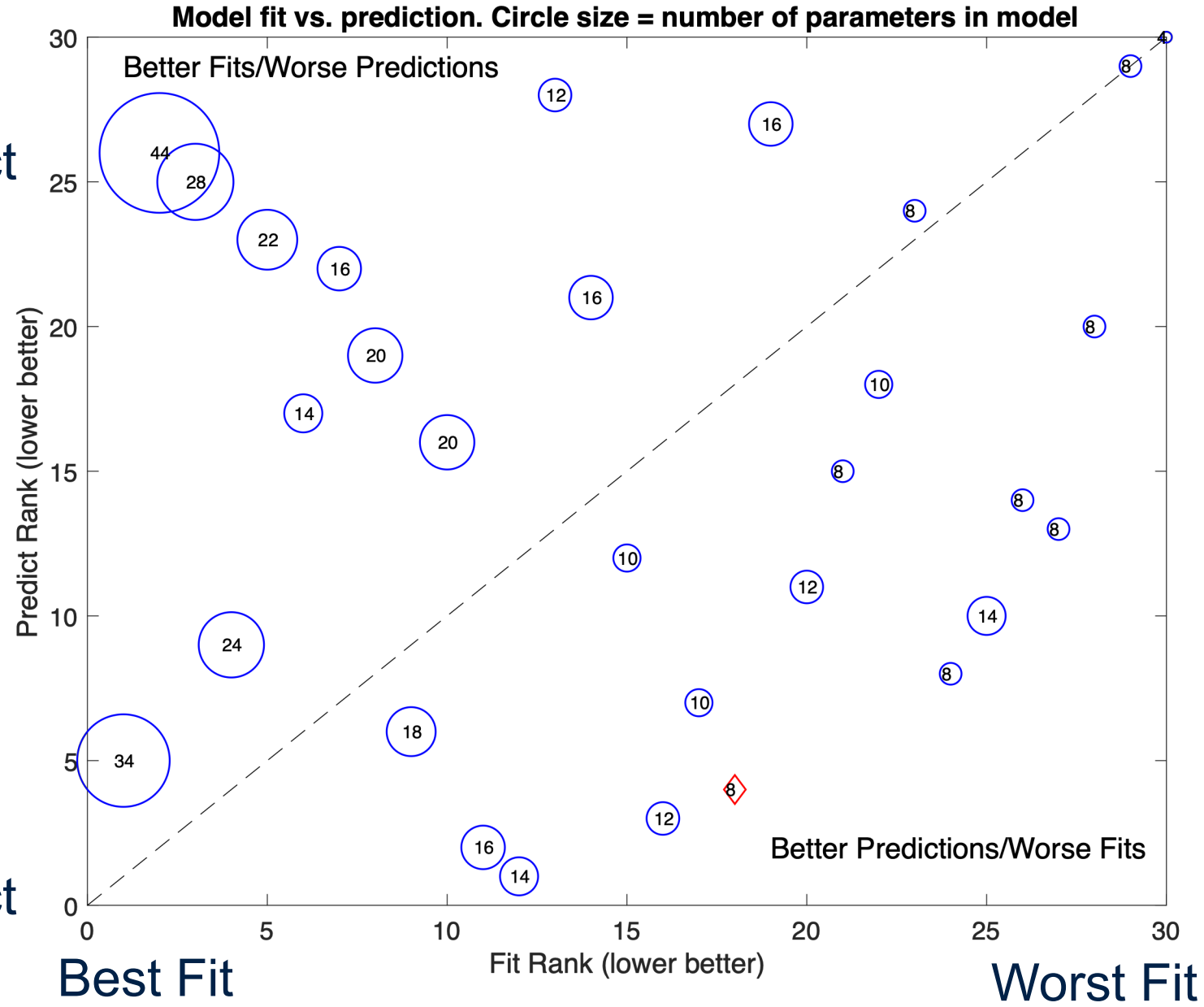
Fit Quality versus Prediction Quality

Worst Predict

Best Predict



Best Fit

Worst Fit

Model Selection Criteria

Training

- Fit to data
- AIC
- BIC
- WAIC
- Bayes' Factors
- ...

??

All rubbish with model discrepancy?
Or just because model discrepancy is unaccounted for in my noise model?

Validation

- Predictive Power

Seems a lot safer!

How to design best validation experiments?

~~Optimal~~ Better experimental design

- We designed more sine-wave based voltage protocols to provide information about all the transitions within hERG channel models.
    1. **For identifiability / parameterisation**: so the channel spends an equal proportion of time in each state (in one leading model) over the duration of the protocol.

    2. **For model selection**: maximise the difference between predictions from two of the 'best' models.

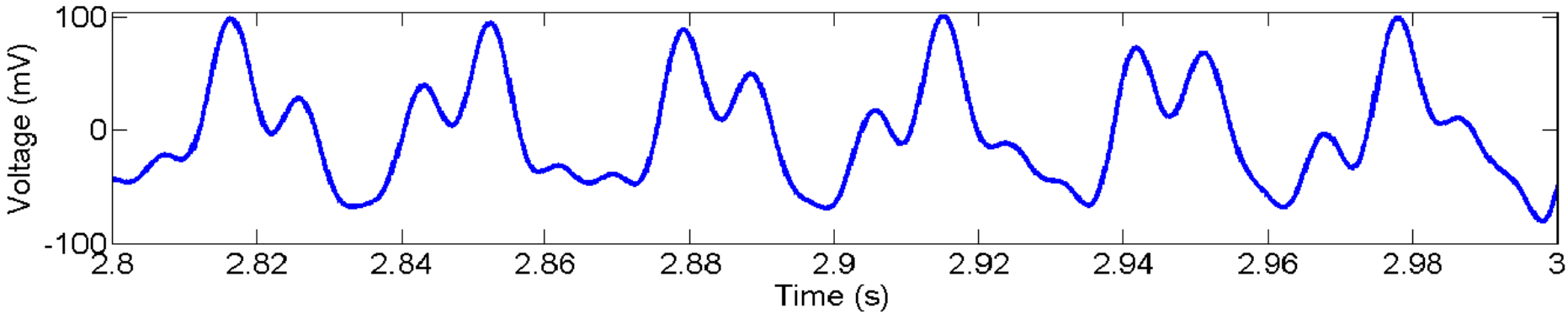
    3. **For both**, with an ad-hoc design…

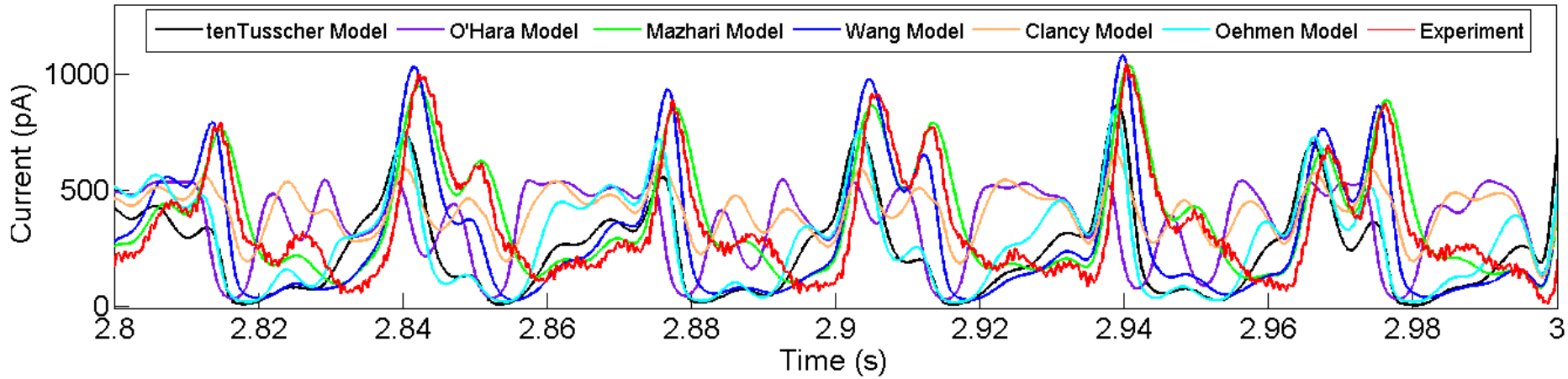
Designing sine wave protocols

$$V(t) = A \sin(2\pi f_1 t) + B \sin(2\pi f_2 t) + C \sin(2\pi f_3 t)$$

Protocol parameters optimised to maximise difference in predicted current output from Mazhari and Wang models

0.2 seconds of protocol:





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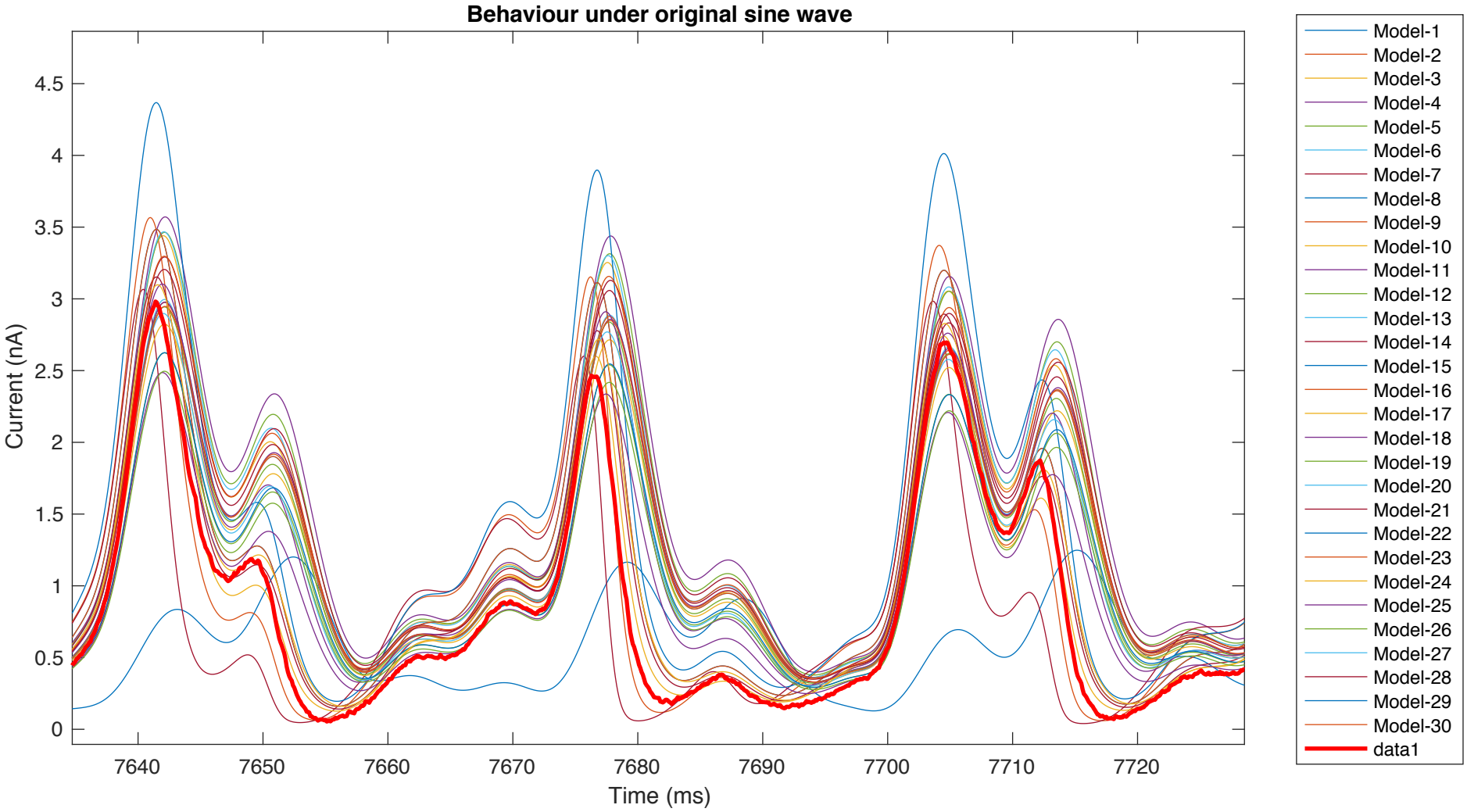
Behaviour in our 30 re-trained models



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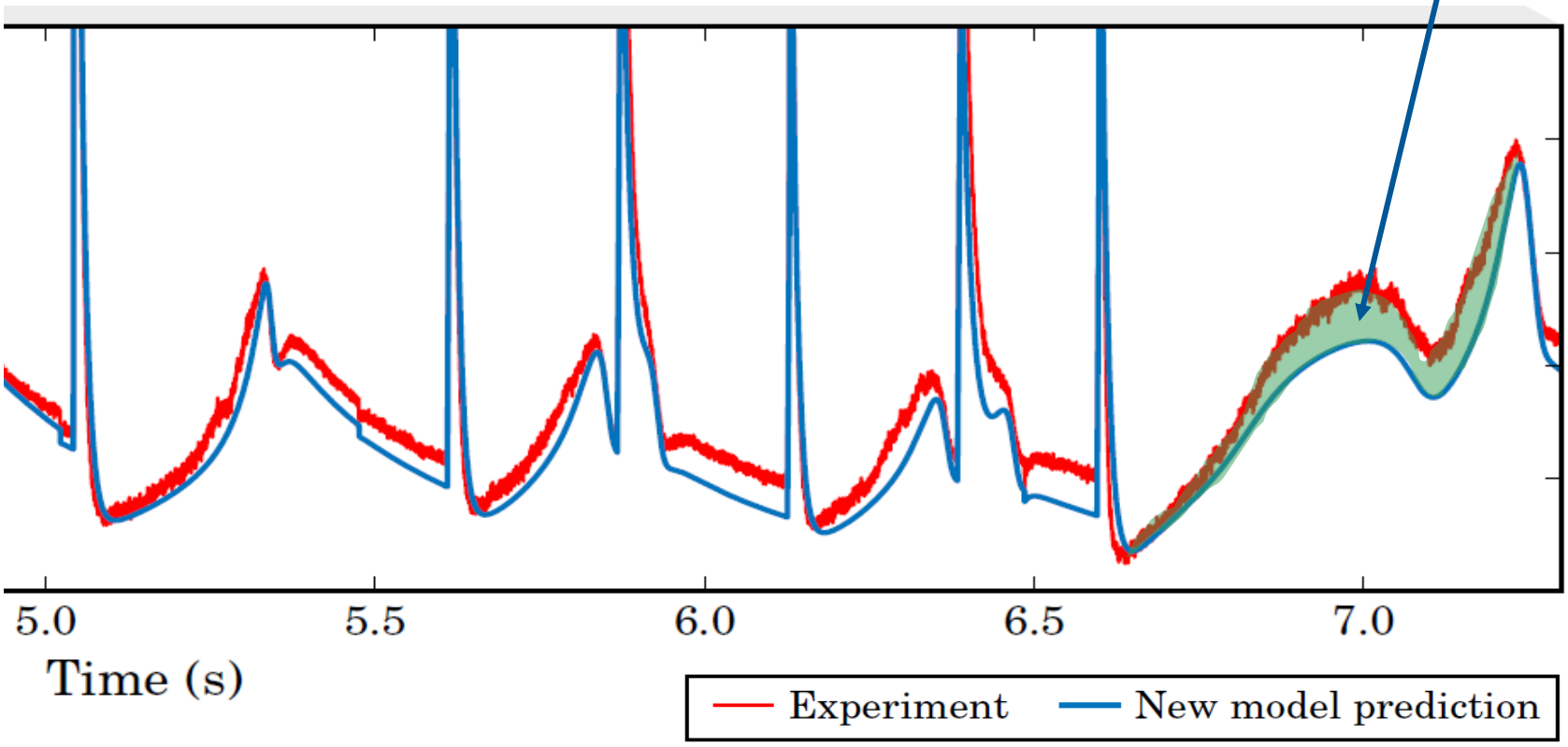
Model Discrepancy: the related next big challenge

More thoughts from the Model Selection exercise

- If I can prove bigger discrepancy then I presumably have a better criterion for model selection?
- Perfect model would get same parameters back from any experiment (that had sufficient information in it)
- We get back different parameter sets from different experiments - because of model discrepancy I think.
- What can this tell us about model discrepancy?

My burning question for all of you…

- How do I predict ***model discrepancy*** in new situations?
- Could I train something to learn it from validation experiments?
- How should I optimally design these validation experiments?



Do we know anything else?

Model discrepancy with added biophysics?

$$I = g * P(Open) * (V - E_{Na})$$

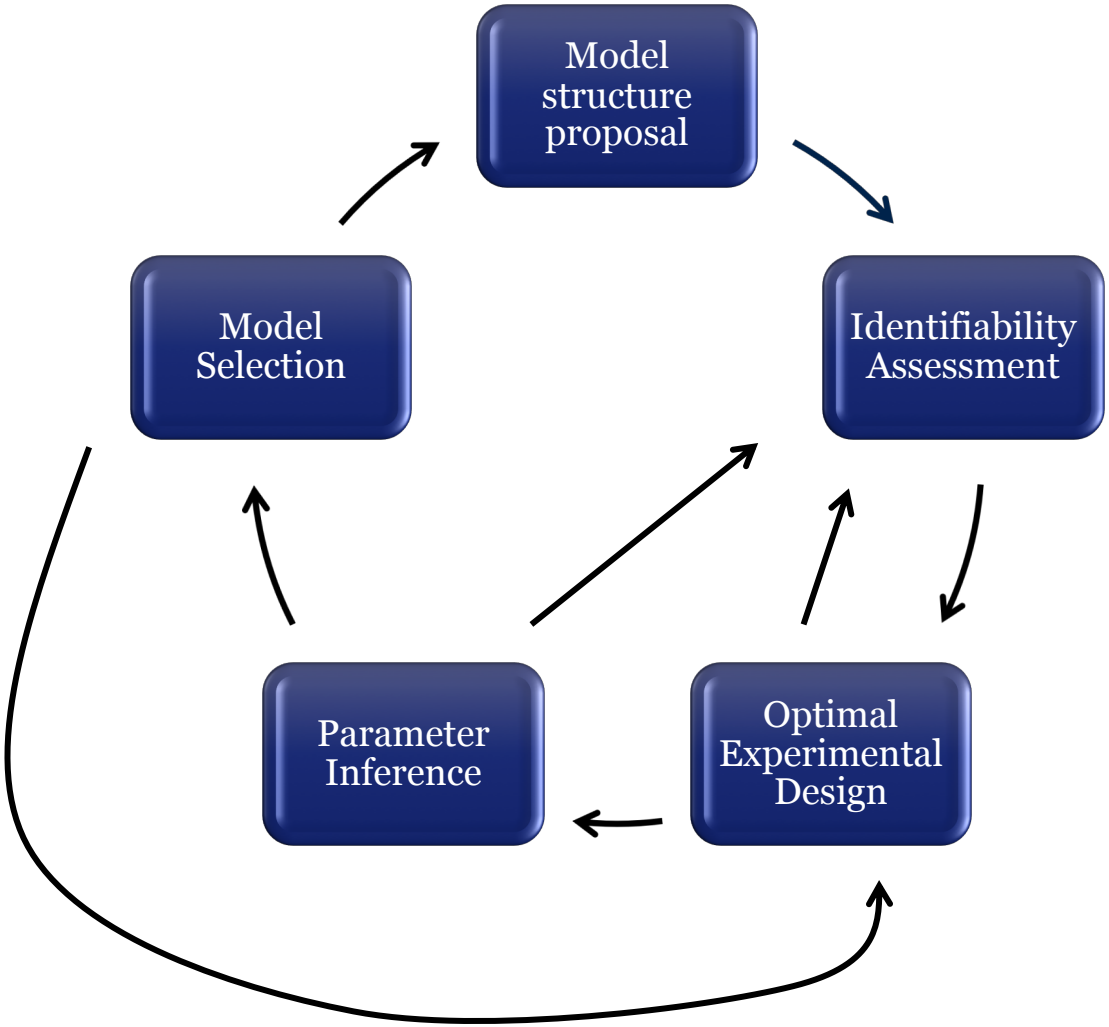
Happy with these bits of the model – low discrepancy

Not so happy about this bit – higher discrepancy

But will the bit we aren't happy with have knock-on effects?

Bringing it all together?

- Something like this.
- With more arrows…



What next?

- If the experiment protocol is 'good enough' to produce a defined parameter spread, we can stop optimising and just use it.
- But we need to investigate more formal ways to link Optimal Experimental Design to sensitivity / identifiability (A-optimal, D-optimal etc.), but also model selection and model discrepancy assessment?
- **A plea: please share all the data, fitting algorithms, training and validation protocols, not just model equations and parameters!**
- Time for databases of simulate-able experiment descriptions stored together with the data that were generated in the lab: https://chaste.cs.ox.ac.uk/WebLab **need to make model development a science and not an art!**
- See www.github.com/pints-team/pints for our software

Acknowledgements

- **Kylie Beattie**
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- Denis Noble

The original idea

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- Remi Bardenet – Lille
- Yi Cui, Jim Louttit – GlaxoSmithKline
- Teun de Boer – UMC Utrecht
- Adam Hill & Jamie Vandenberg – Victor Chang Cardiac Research Institute, Sydney

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