Variability in the Activity of the Heart

Techniques for the calibration of populations of models

AUSTRALIAN RESEARCH COUNCIL CENTRE OF EXCELLENCE FOR
MATHEMATICAL AND STATISTICAL FRONTIERS

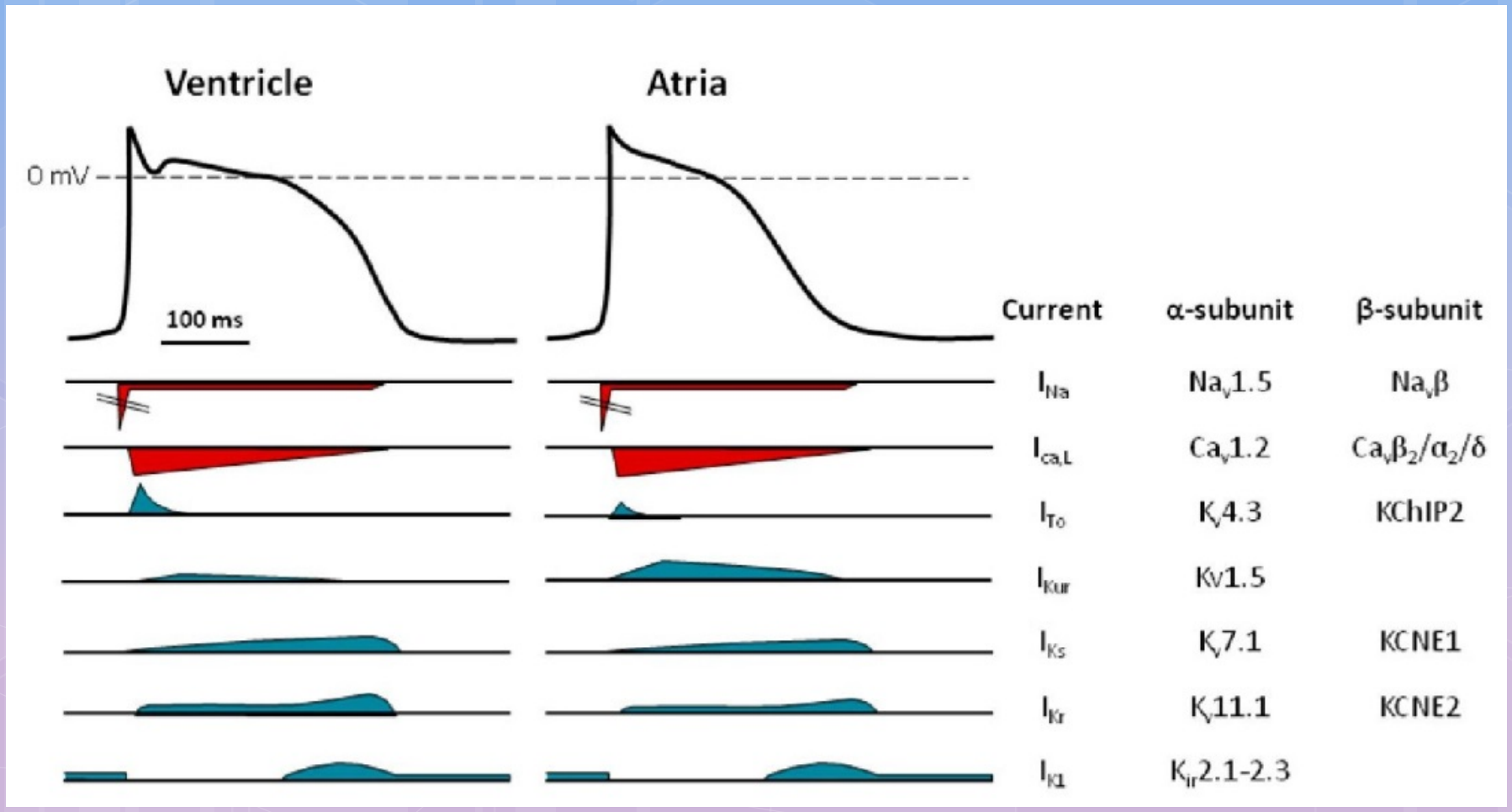
Variability in the Heart

- **Within-subject Variability:** Individual heart cells show considerable variance in electrophysiological properties, even cells of the same type

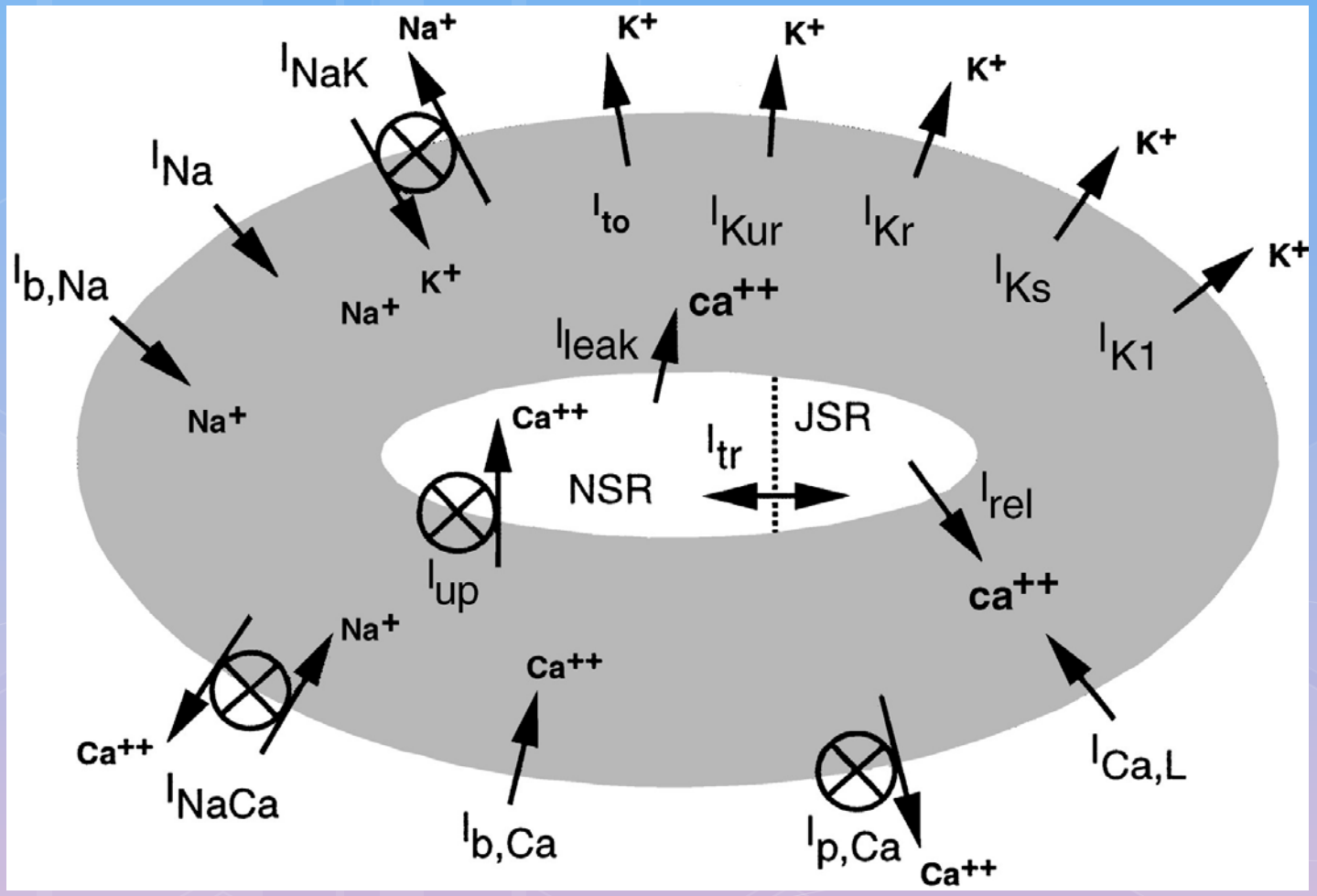
- **Between-subject Variability:** Further variance occurs between different members of the population. Factors include: genetics, gender, age, pathologies

The Action Potential

- I work with single cell data for the **action potential** (AP):



Ion Channels

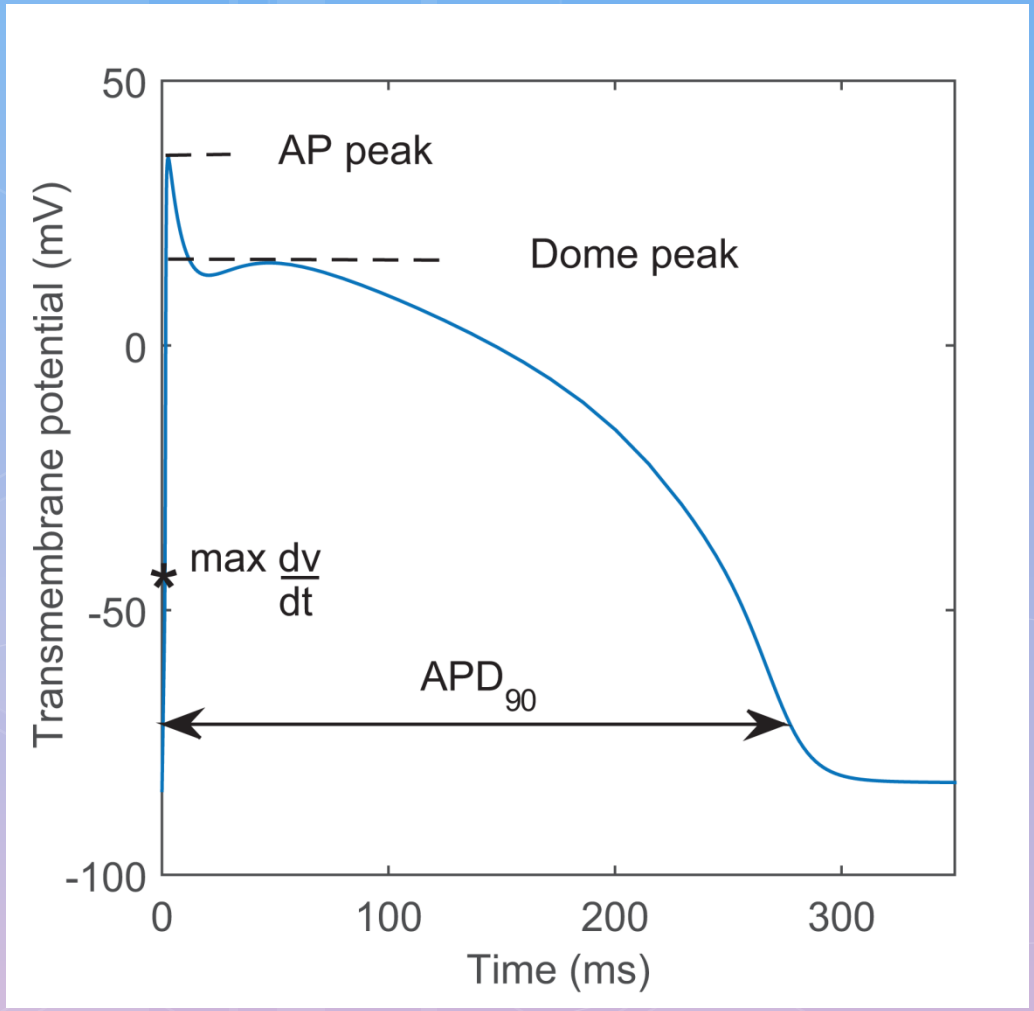


- Cell polarisation is achieved by flow of ions, predominantly Na^+, K^+ and Ca^{2+}.
- These currents activate and deactivate in a complex fashion that produces the action potential.

Cardiac Models

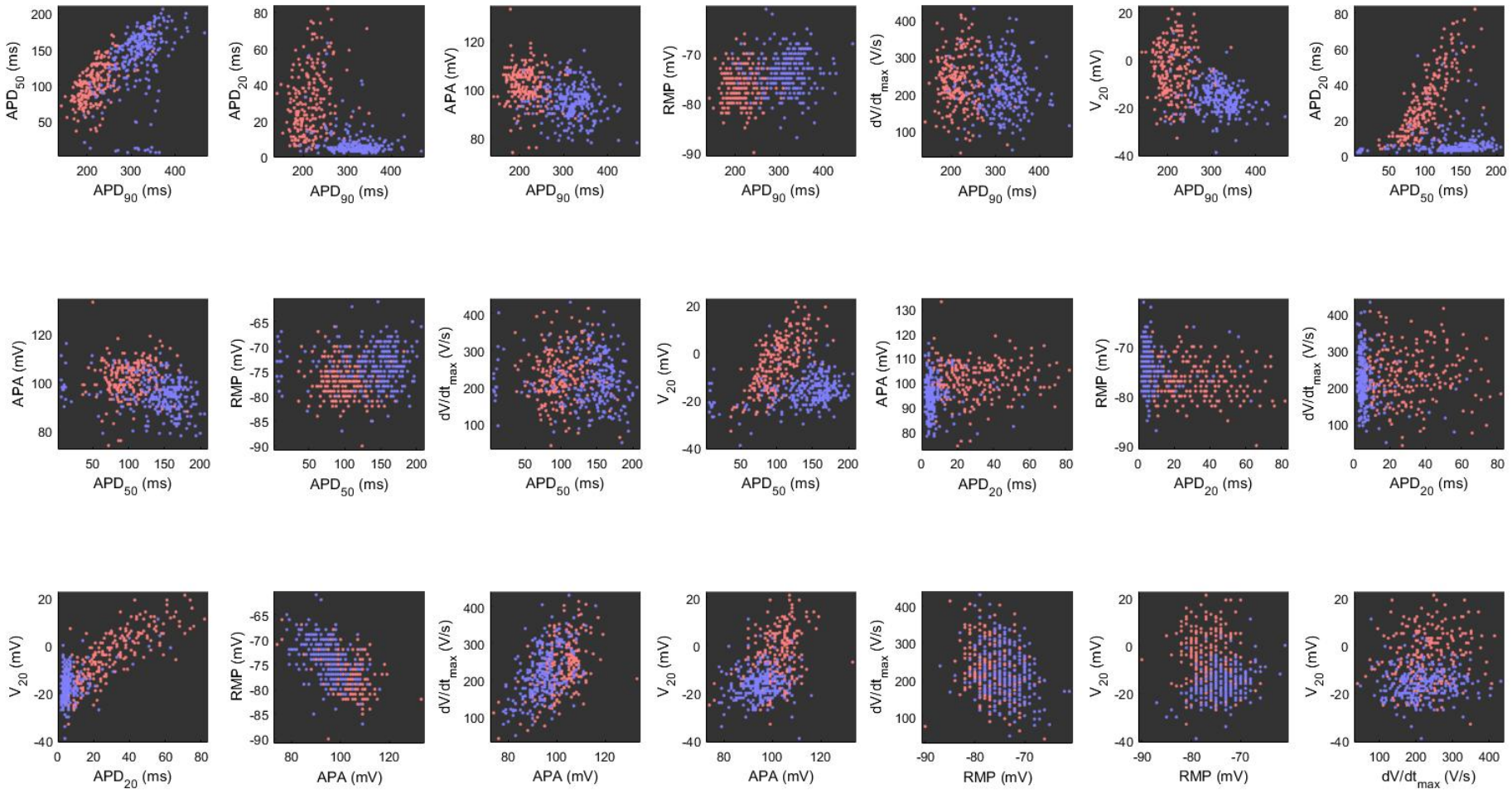
- In a single cell, represent the changing values in time of:
  - Voltage
  - Gating variables
  - Ion concentrations
- Systems of 40+ ODEs, highly nonlinear
- Jolt them with stimulus current repeatedly until steady state
- Can be solved by e.g. MATLAB's *ode15*

Measuring the Action Potential



- Data is provided in terms of **biomarkers**, measurements of the key properties of the curve

Cardiac Data



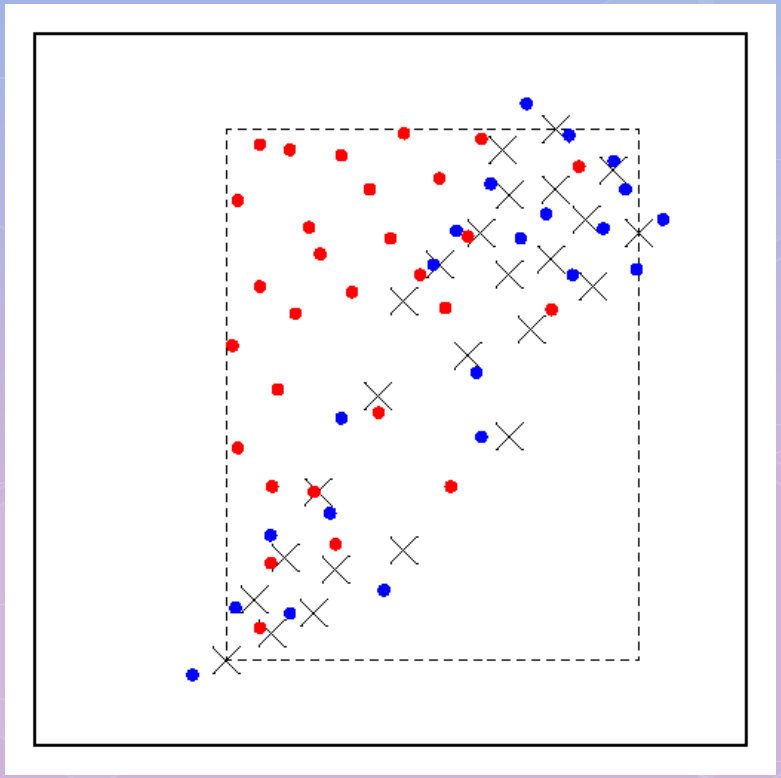
Blue – healthy sinus rhythm, Red – chronic atrial fibrillation

Populations of Models

- Highly variable data – how do we handle that with a single deterministic model?
- Perhaps **multiple** models, then?
- Representing a population of people with a *population of models* (POM) – the same model, but with different parameters to represent each individual's properties

Calibrated POMs

- We can select models from some parameter space, but how do we choose?
- Calibration is typically performed by ensuring all model outputs fall within the ranges of the data (and are hence physiologically realistic)



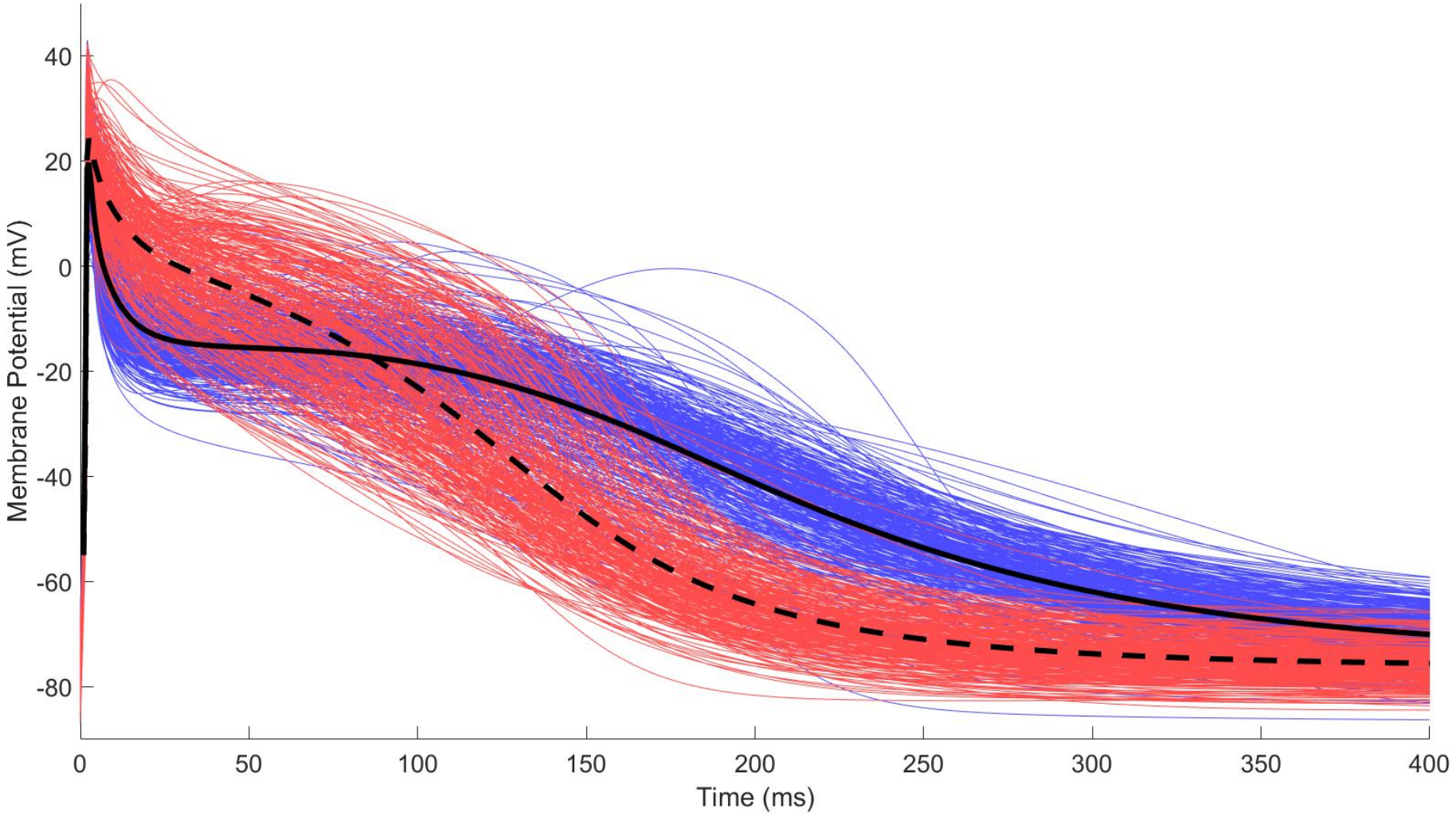
- Not good enough!

Calibrating to Density

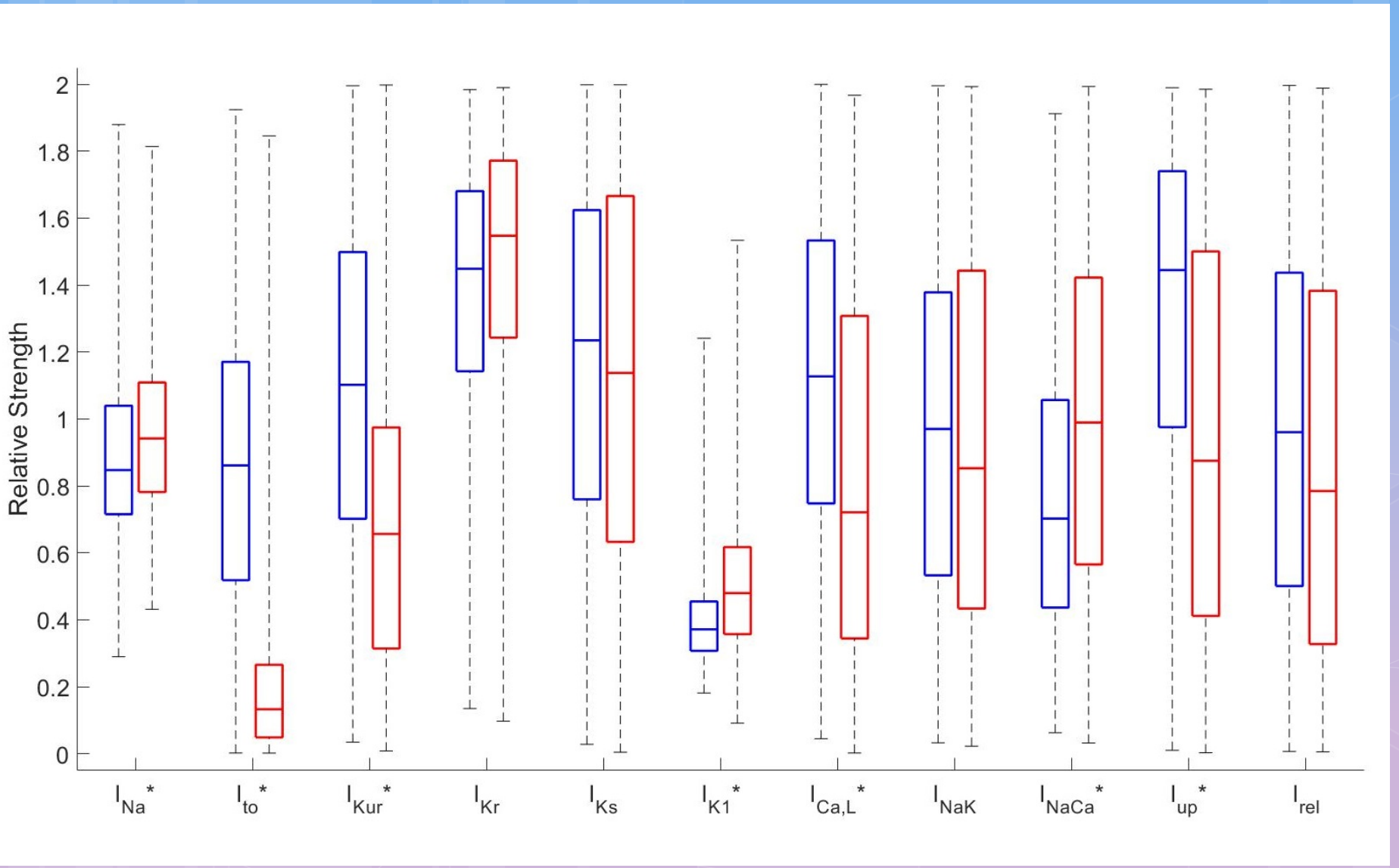
- We want to calibrate to the **distribution** of the data directly:

1. Estimate distribution (MVKDE)
2. Try to sample according to this distribution (SMC)
3. Clean the results using an optimally-selected subpopulation (simulated annealing)

Results 1


Membrane Potential (mV)
40
20
0
-20
-40
-60
-80
0
50
100
150
200
250
300
350
400
Time (ms)

Results 2


Relative Strength
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
I_Na*
I_to*
I_Kur*
I_Kr
I_Ks
I_K1*
I_Ca,L*
I_NaK
I_NaCa*
I_up*
I_rel

Burning Questions

- Can we use this technique on other stratified data? What about outside of cardiac electrophysiology?
- Could we solve this instead as a fully Bayesian inverse problem?

$$\boldsymbol{b} = \mathcal{M}(\boldsymbol{\theta}) + \boldsymbol{\varepsilon}$$

- What new research questions can we tackle once adding in the spatial dimension? (Travelling waves of excitation in multiple cells)