

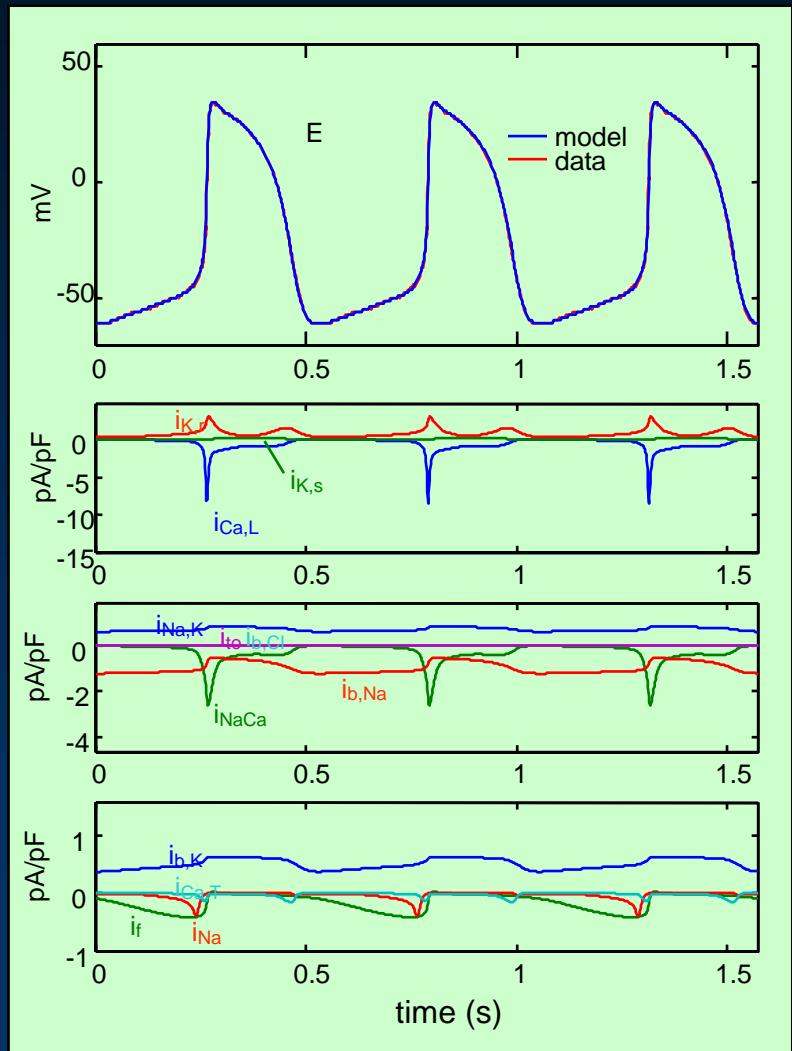
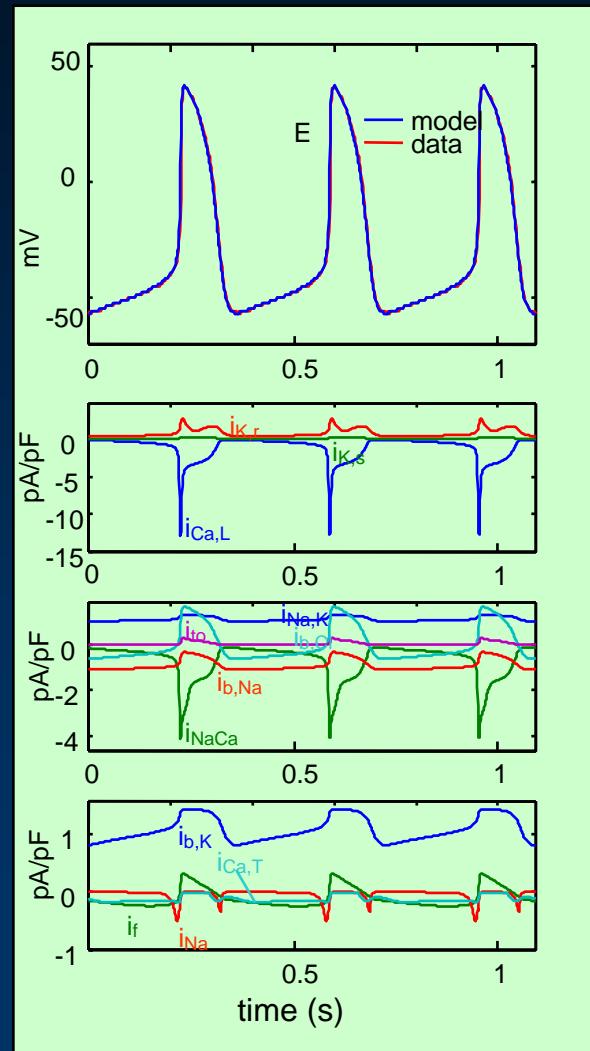
# Excitable Cell and Tissue Modelling using CellML/FML

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# Parameter Optimisation of Excitable Cell Models

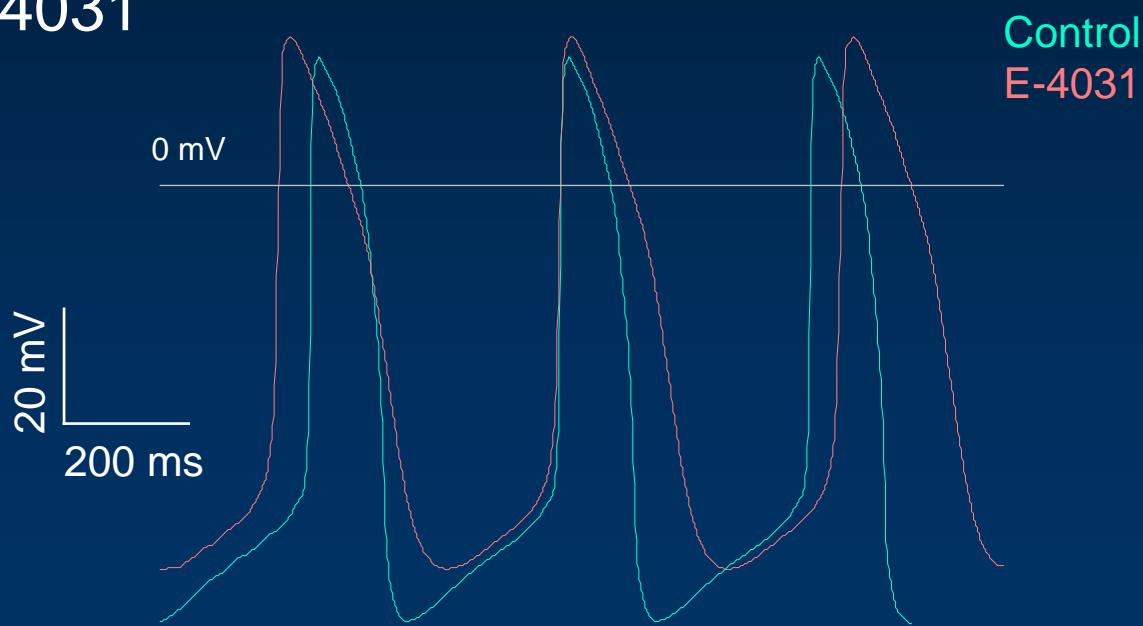
Large-scale non-linear least-squares fitting:



# Parameter optimisation using multiple data sets

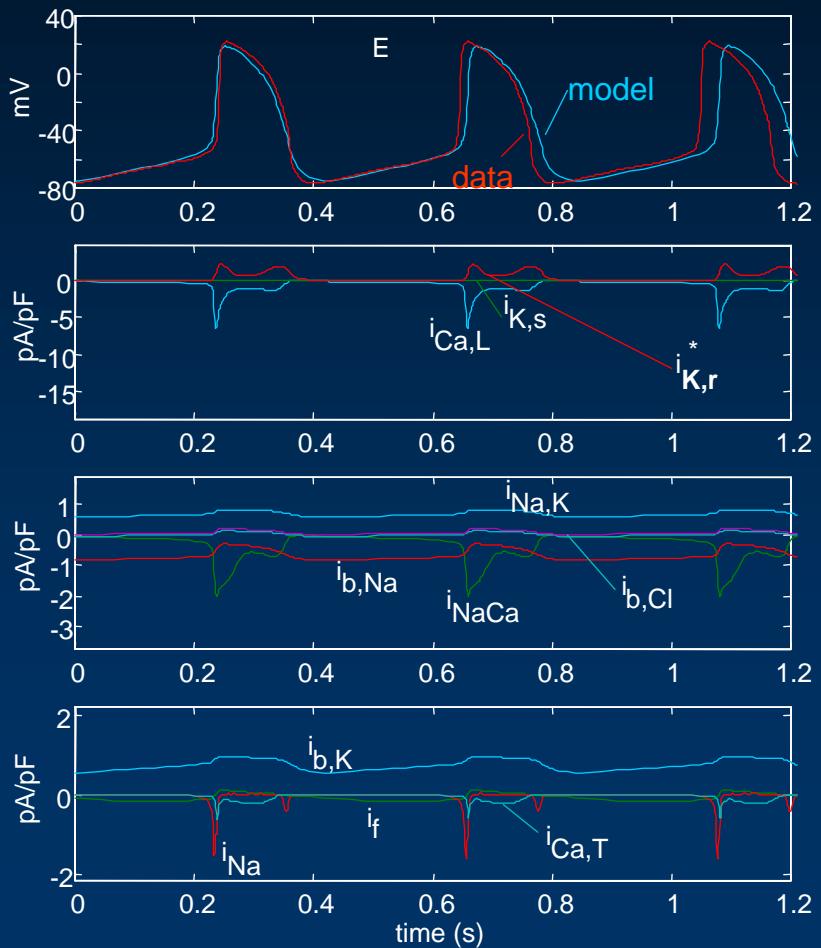
Effect of E-4031 on Peripheral SAN Myocytes

0.1  $\mu$ M E-4031

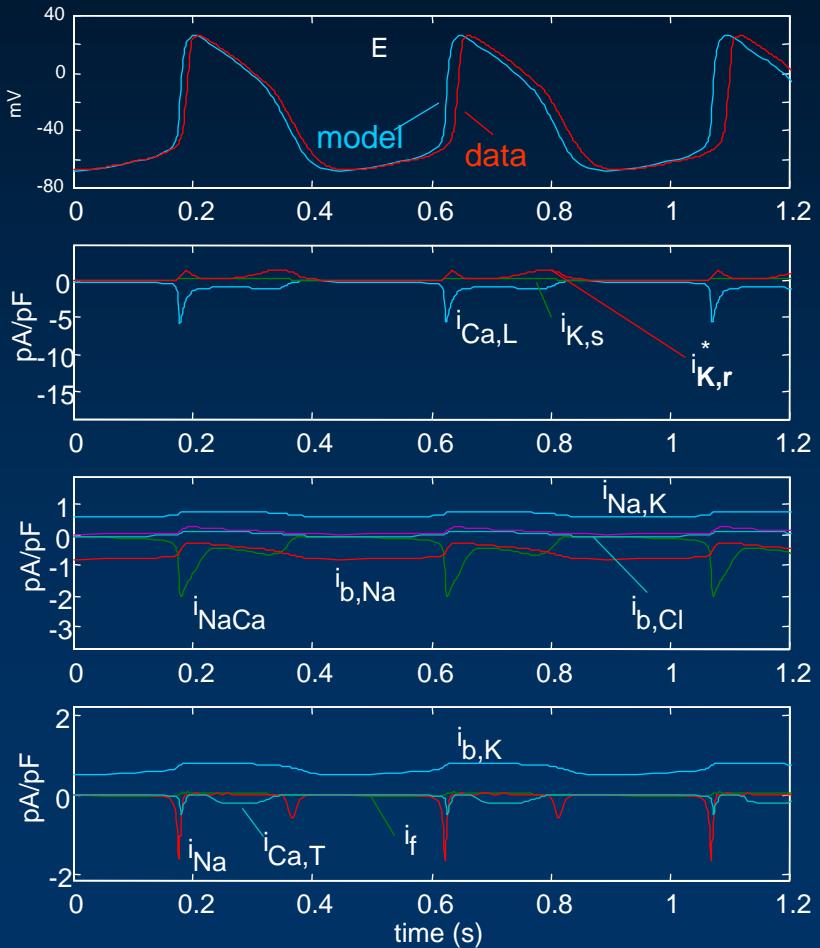


# E-4031 Fit

**Control**



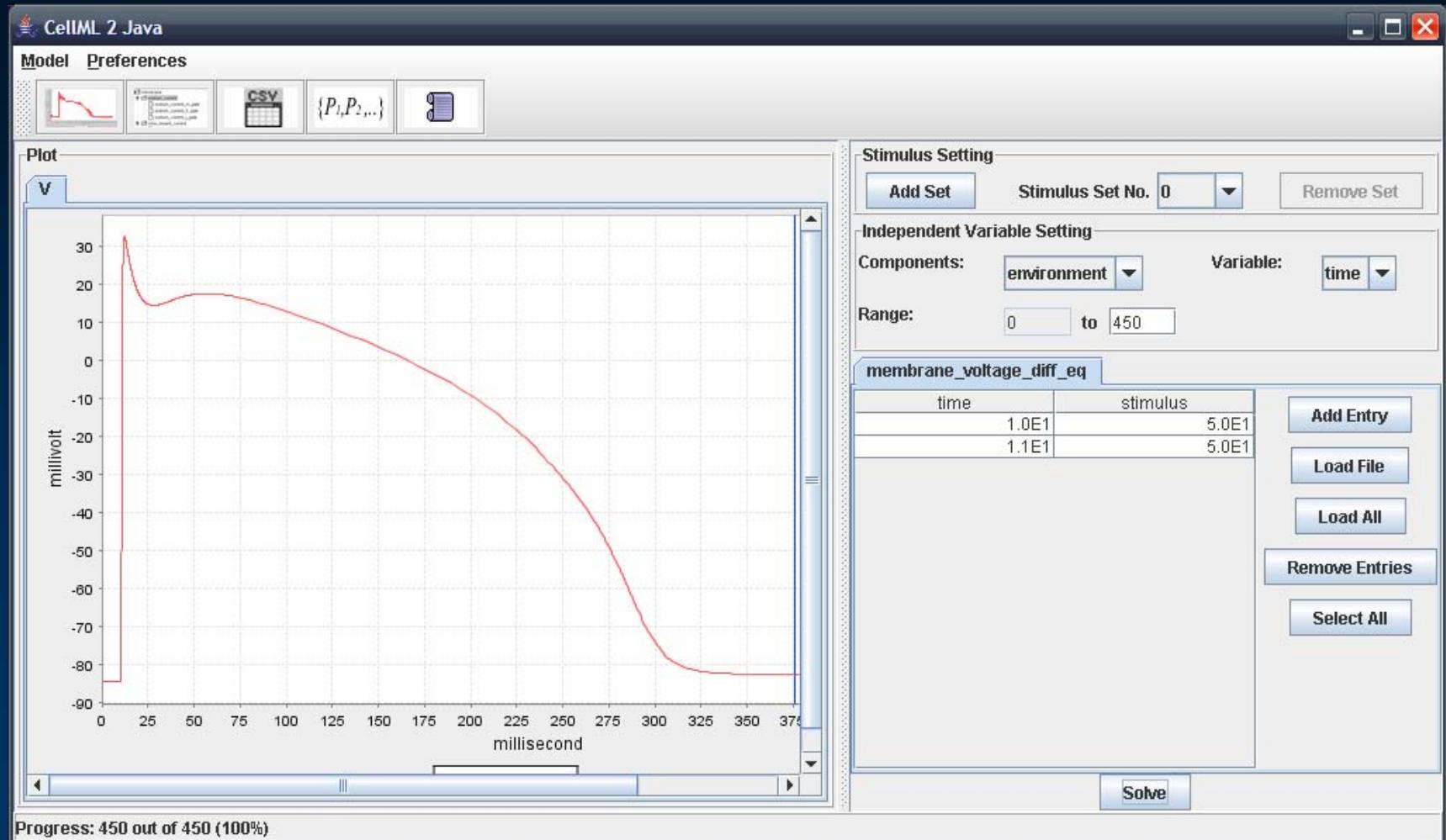
**E4031 Block**



# CellML for Parameter Optimisation

- Large repository of excitable cell models
  - Valid, bug free
- Models easily accessible
- CellML parser can be incorporated into parameter fitting software
  - current and future models can be optimised without model-specific re-coding of routines

# CellML Parameter Optimiser



# Component Viewer

CellML 2 Java

Model Preferences

V Variables     $\Sigma$  Equations

**membrane**

C

Current Value: Val: 1E0 Lower Limit: - $\infty$  Upper Limit:  $\infty$  Set Limit

Not Fitted  
 Shared Value  
 Data Spec.

Model Default: 1.0 microF\_per\_cm2

Source Component: Local

Source Variable: Local

Used In: membrane\_voltage\_diff\_eq at membrane

V

Current Value: Val: -8.4624E1 Lower Limit: - $\infty$  Upper Limit:  $\infty$  Set Limit

Not Fitted  
 Shared Value  
 Data Spec.

Model Default: -84.624 millivolt

Source Component: Local

Source Variable: Local

Containment Encapsulation

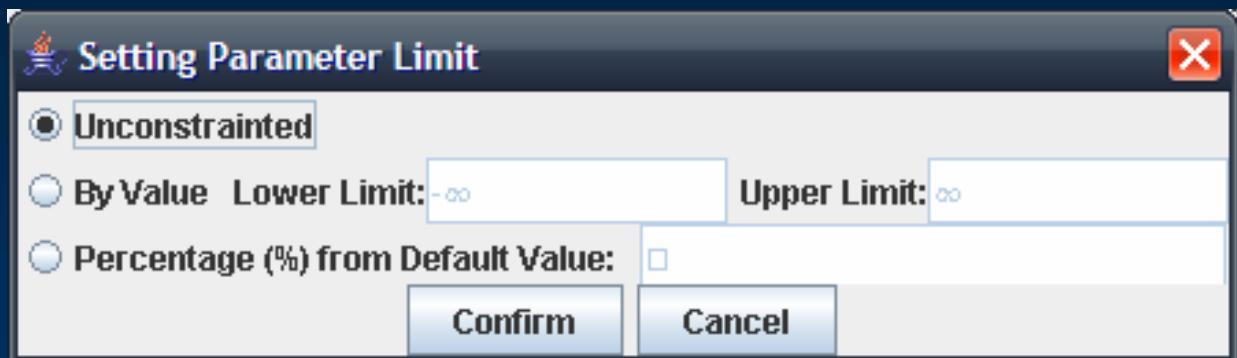
- membrane
  - sodium\_current
    - sodium\_current\_m\_gate
    - sodium\_current\_h\_gate
    - sodium\_current\_j\_gate
  - slow\_inward\_current
  - time\_dependent\_outward\_current
  - time\_independent\_outward\_current
- environment
- membrane
- slow\_inward\_current
- slow\_inward\_current\_d\_gate
- slow\_inward\_current\_f\_gate
- sodium\_current
- sodium\_current\_h\_gate
- sodium\_current\_j\_gate
- sodium\_current\_m\_gate
- time\_dependent\_outward\_current
- time\_dependent\_outward\_current\_x1\_gate
- time\_independent\_outward\_current

Progress: 450 out of 450 (100%)

# Parameter Selection

Current Value: Val:  Lower Limit:  Upper Limit:  Set Limit

Not Fitted  
 Shared Value  
 Data Spec.



# Optimisation Progress

Optimisation Result

- Shared Parameters
  - time\_independent\_outward\_current\_i\_K1\_calculation\_P0
- g\_s\_07.csv
  - slow\_inward\_current\_g\_s
- g\_s\_10.csv
  - slow\_inward\_current\_g\_s
- Cost
  - Raw cost
  - Weighted cost

Optimiser Choice	
slow_inward_current_g_s	
	0.085
	0.0891868471331142
	0.0891868471331142
	0.0891868471331142
	0.09454300220413643
	0.09685370066682325
	0.09685370066682325
	0.10388755367727205
	0.10388755367727205

Stop Set Parameters Create Report

CellML 2 Java

Model Preferences

Optimisation Result

Optimiser Choice Direct  Switching?

time_independent_outward_current_i_K1_calculation_P0	0.448713
0.3372465405106417	
0.3372465405106417	
0.3372465405106417	
0.3372503031730062	
3.43920579E-1	

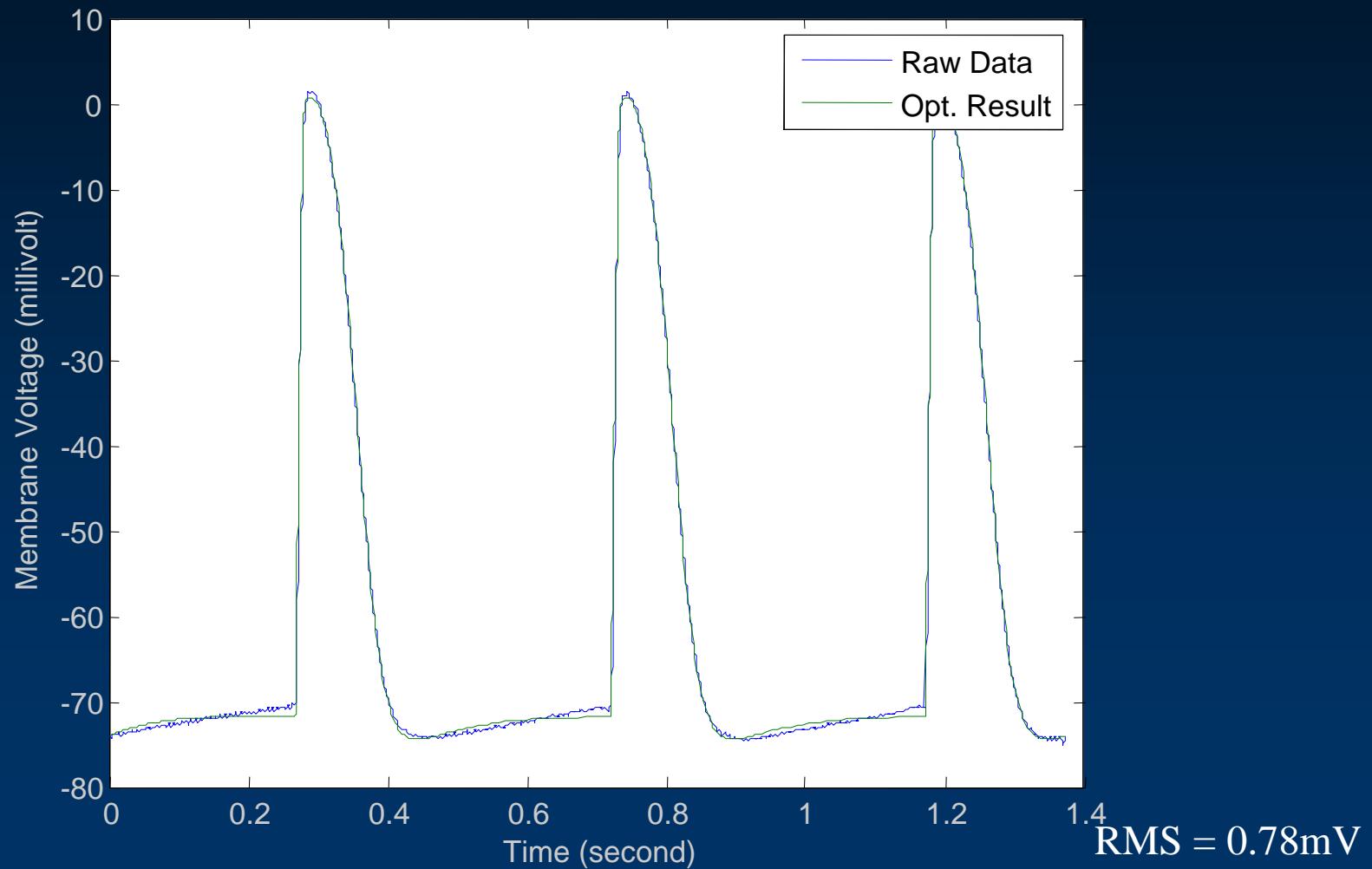
Optimisation Result

- Shared Parameters
  - time\_independent\_outward\_current\_i\_K1\_calculation\_P0
- g\_s\_07.csv
  - slow\_inward\_current\_g\_s
- g\_s\_10.csv
  - slow\_inward\_current\_g\_s
- Cost
  - Raw cost
  - Weighted cost

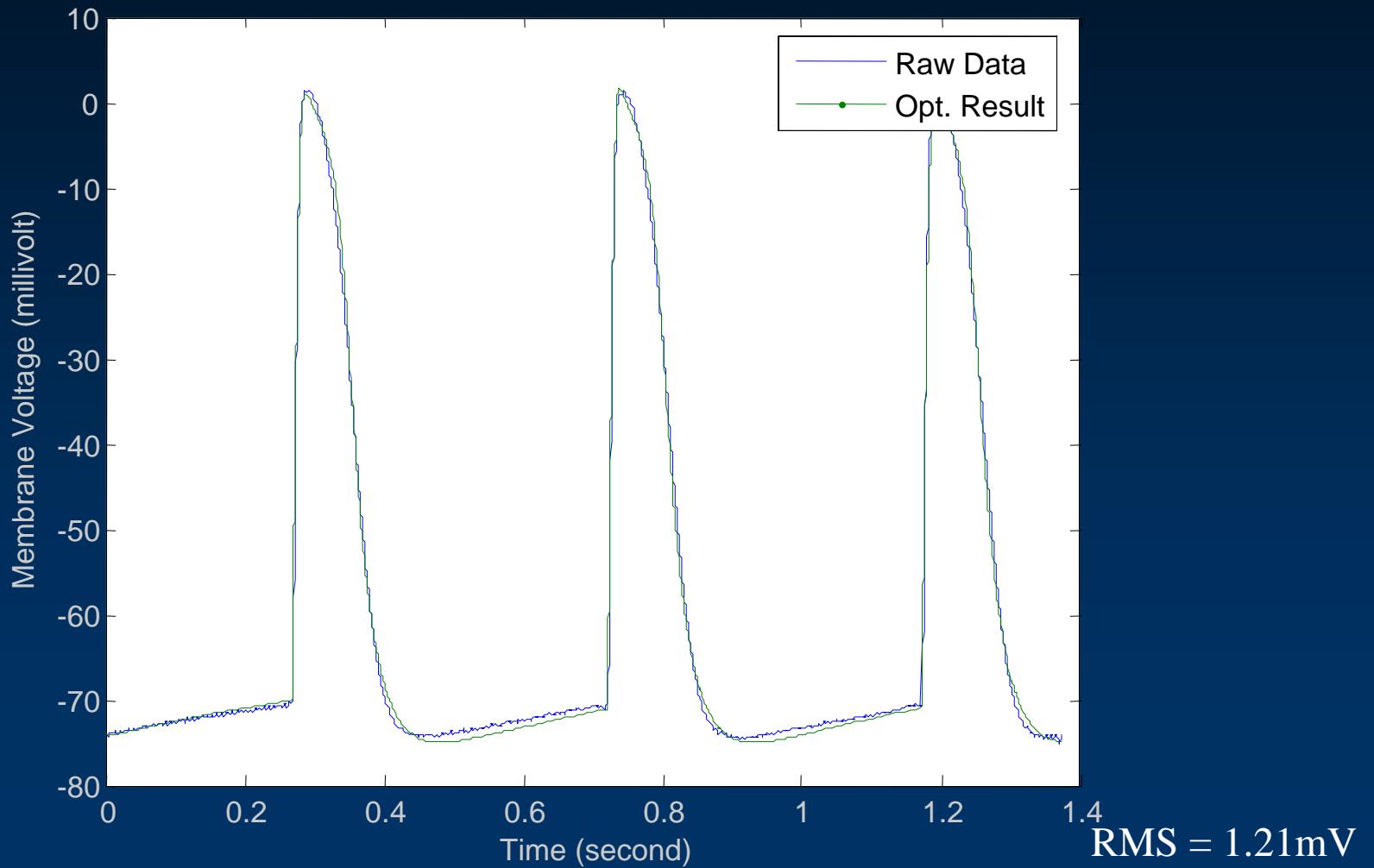
Confirm Set Parameters Create Report

Optimisation paused. Press "Confirm" when modification is done

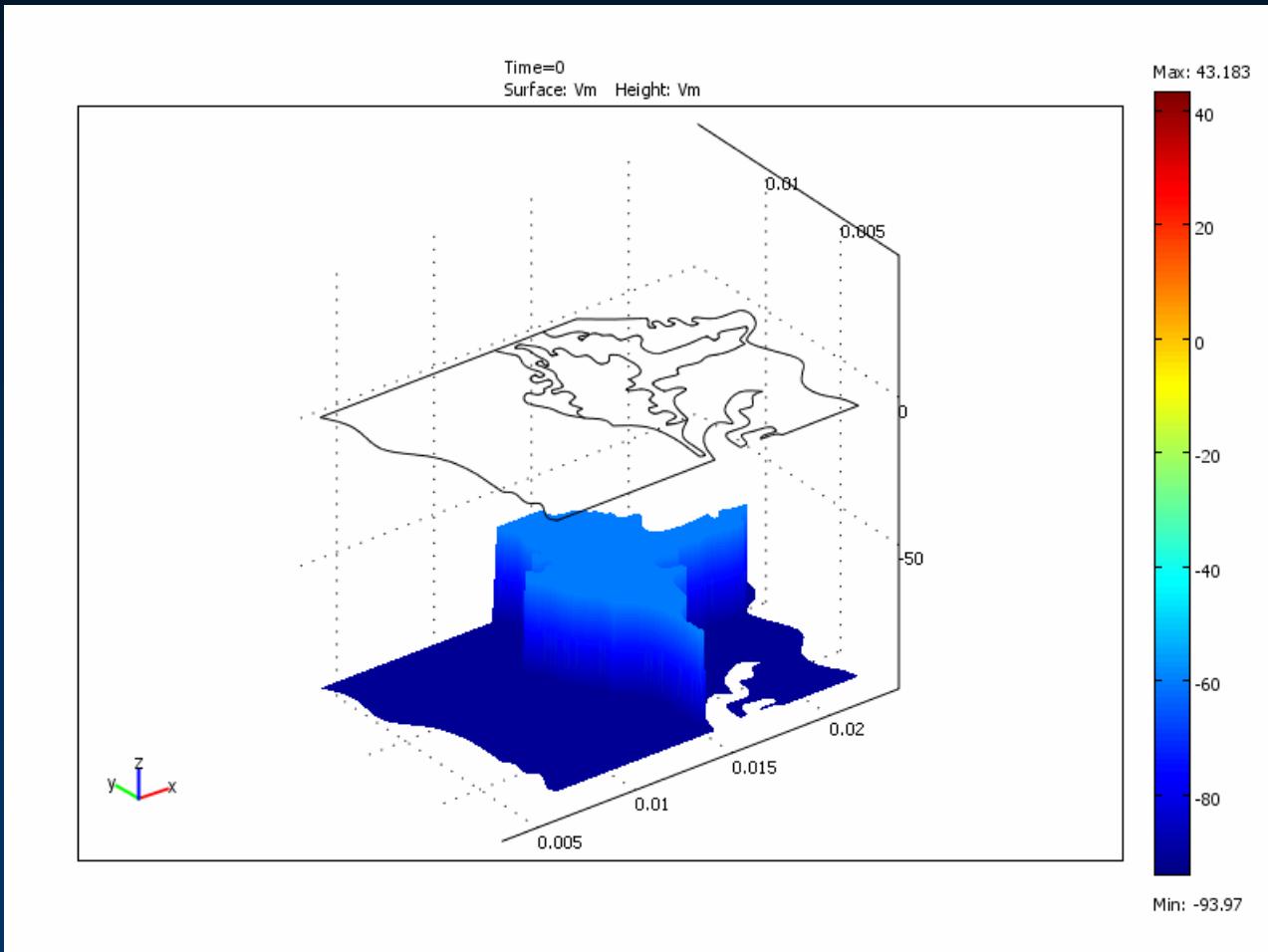
# Optimisation of peripheral SAN AP using Noble (1962) Model



# Optimisation of peripheral SAN AP using Lovell *et al* (2004) Model



# Excitable Tissue Modelling Using FML/ModelML



# MML Framework

- **FML and ModelML**
  - FML describes Geometry/Field information
  - ModelML describes the relational aspects of a multi-scale biological model
- **Share common syntax**
  - <Import> branch
  - <declaration> branch
    - Expressions, variables, functions, data set declarations.

# FML <frame>

```
<frame>
  <cell_list>
    <dim0>
    <dim1>
    <dim2>
    <dim3>
  <b_rep>
  <mesh>
  <fields>
  <dimension>
```

- **Cell Objects – Lines, PolyLine, Curves, Bezier Curves**
  - Can Attach Attributes such as Scalar, Vector etc to create data set

# FML (geometric models)

- **B-Rep (adjacency information)**
  - Vertex-Edge, Edge-Face
  - Parametric
  - Domain Information
- **Mesh**
  - 1 Dim, 2 Dim, 3 Dim, cell objects reference
  - Neighbouring information
  - Domain Information
- **Fields**
  - Field Function, basis function mapping
  - Data organisation

# FML <mapping>

- Combine/reuse FML models by using <mapping>.
- Operations including <scale>, <shift>, <rotate> etc
  - Restrictions apply

# ModelML (Overview)

- Relational Grouping  
(Subdomain/Boundary/Point etc)  
between CellML and FML
- Describes General Mathematical  
Model under <system>
- Responsible for naming and  
accessing objects between imported  
models

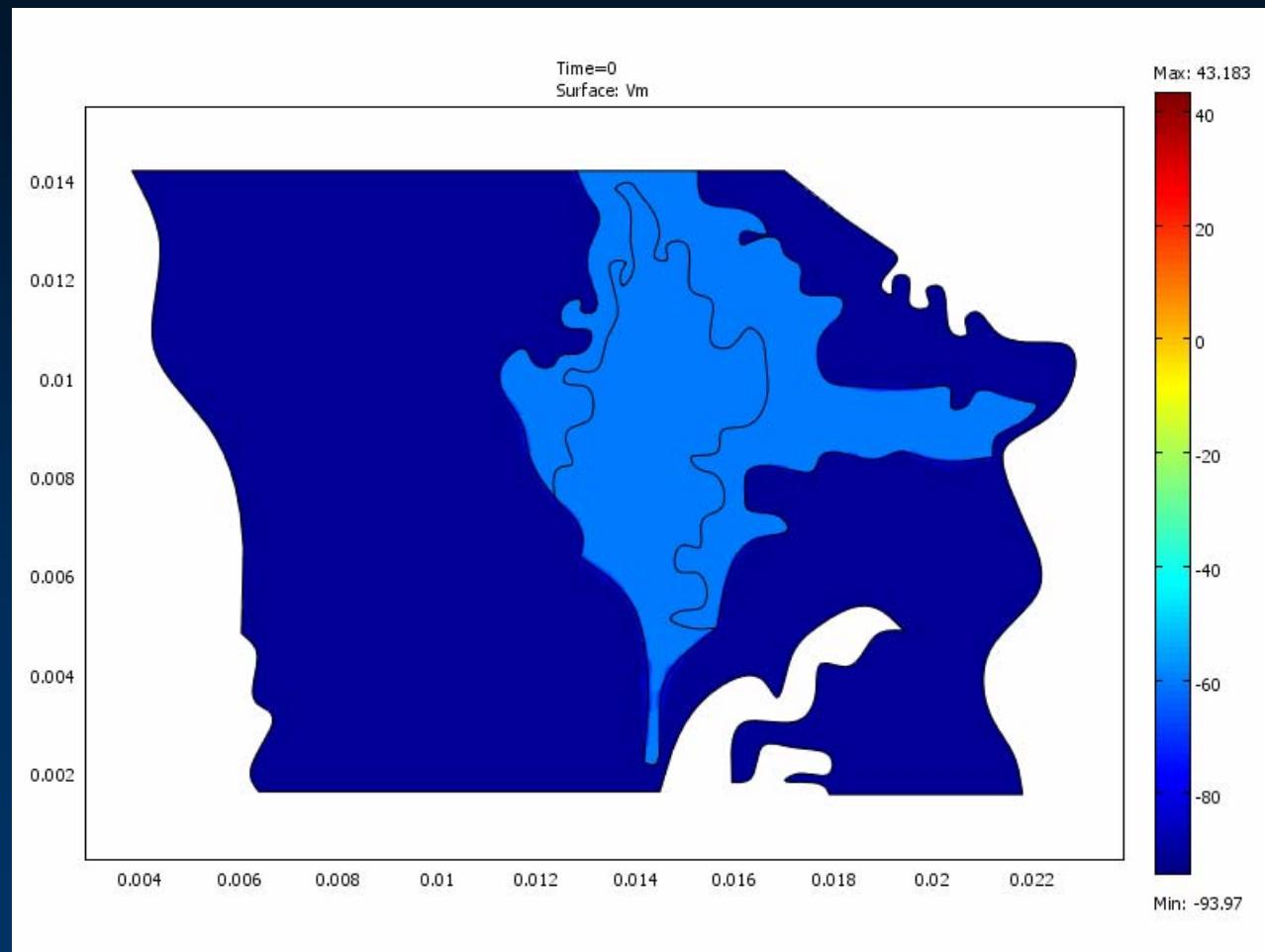
# ModelML <import>

- <import>
- Currently support FML and CellML
- For CellML, need to declare
  - Dependent variable
  - Time variable
- CellML modifications
  - Variable value overrides
  - Attach/Modify equations from CellML

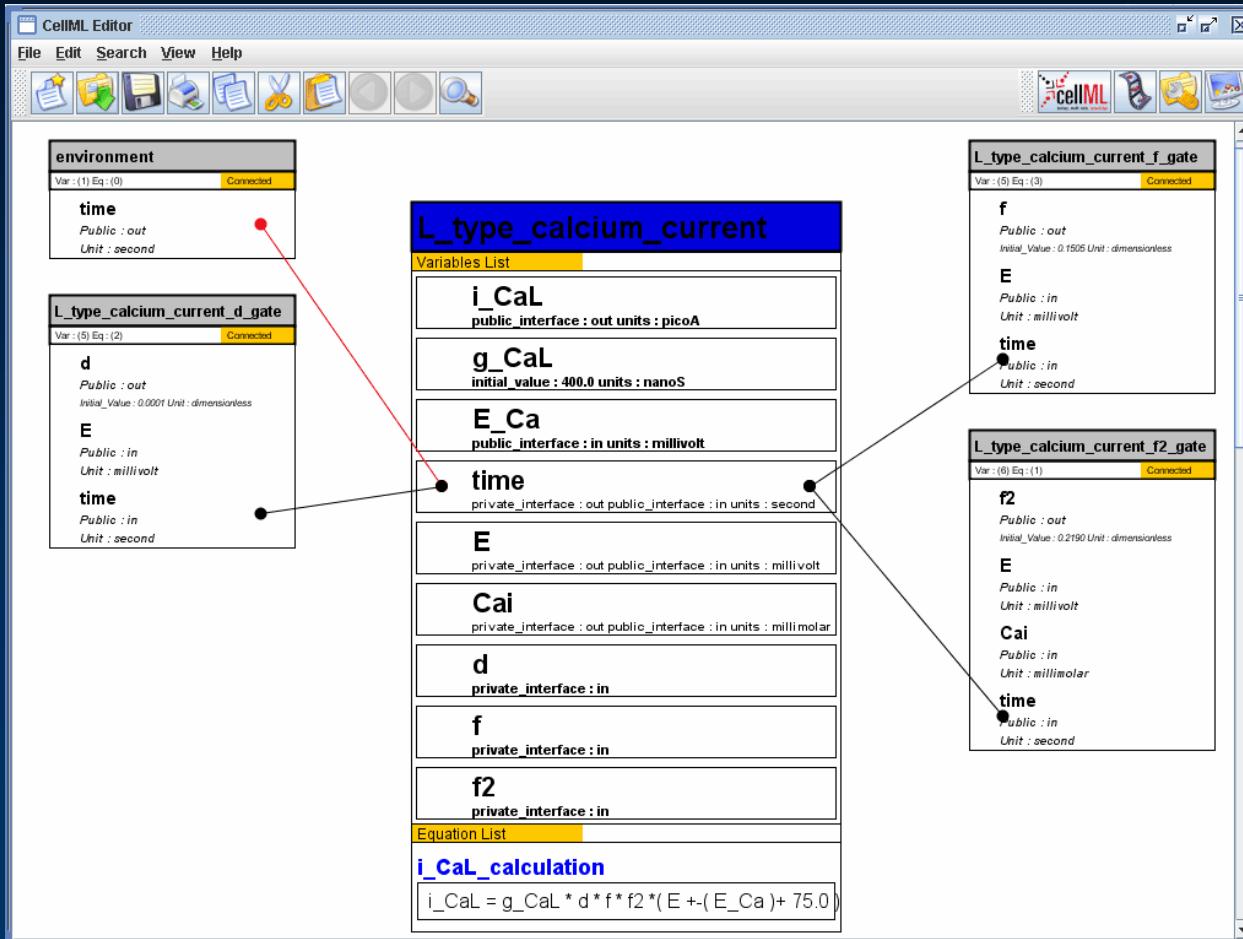
# ModelML <system>

- Describes an ODE system
- can be fully described from one CellML model, or from a subset of ODE equations from a CellML model
- Allows us to combine/utilise different CellML models together.

# 2D Cardiac Pacemaker Using FML/ModelML



# Development of a CellML Editor, Incorporating Component Visualization



# Acknowledgements

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