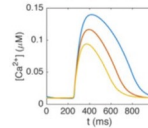
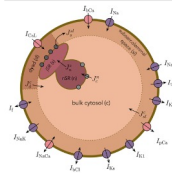
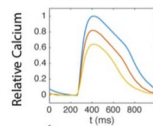


Computational inversion of optical data from cardiac MPS

SIMBER On-Site Kick-Off
Nick Forsch, Henrik Finsberg



Overview of the workshop

***Goal:** Understand the concepts involved with the inversion of MPS data for predicting drug targets and effects*

BACKGROUND	INVERSION IN MPS	DEMONSTRATION USING GRID SEARCH INVERSION
<ul style="list-style-type: none">• What is computational modeling?• The forward problem in modeling• The inverse problem• Examples in cardiac modeling with clinical applications	<ul style="list-style-type: none">• Steps of the inversion framework• Limitations and challenges	<ul style="list-style-type: none">• Explanation of algorithm• Hands-on demo with synthetic data• Hands-on demo with real data

These are not my ideas

IdentiPhy @ Simula Research Laboratory

Sam Wall

Aslak Tveito

Henrik Finsberg

Karoline Jæger

Kristian Hustad

Healy Lab

What is computational modeling?

The process of simulating physical, real-world systems using mathematics, physics, and computer science.

The bulk of the work:

- Constructing representations of systems using mathematical expressions
- Developing a computational framework that can simulate the system in time and/or space
- Validating the model to improve its accuracy and applicability

Important concepts in computational modeling

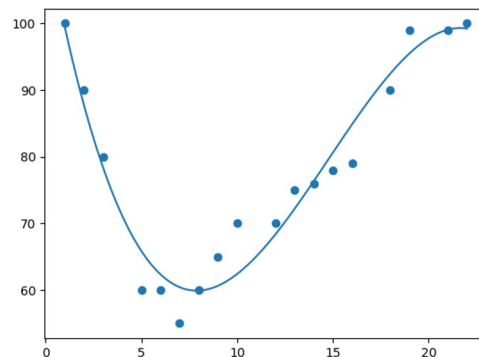
Model fidelity

- How well does the model represent the state and behavior of the system?
- Model may be suitable for studying a disease state but not a healthy state (or vice versa)

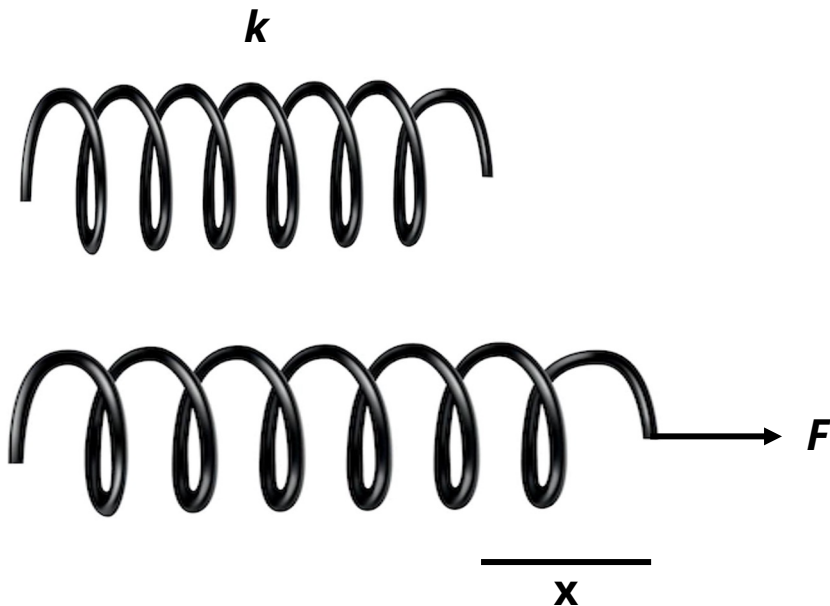


Data assimilation

- Estimating parameters of a mathematical model by fitting to data
- Most use of models involve this step since the mathematical expressions (the theory) is already determined



The forward problem in modeling



Hooke's Law:

$$F = kx$$

Observables: F, x

Parameters: k

If the material constant k is known, then by knowing x we can solve for F , or vice versa.

The inverse problem in modeling

What happens when we can only observe the force and the displacement of the spring and we know the underlying theory relating the observables?

For Hooke's Law, this is simple: $F/x = k$

The inverse problem is the process of calculating the factors that produce an observable set of information using a given model

The inverse problem in modeling

Cause → **Effect** is how the physical world typically operates

- We are given the effect (some observations) and we want to reveal the causes, both quantitatively and qualitatively
- Examples
 - Based on observable weather patterns (temperatures, wind speeds, precipitation, etc.) what are the causes (heat sources, sinks, atmospheric effects, etc.) so that we can make accurate forecasts?
 - If we want to launch a satellite into the atmosphere with a specific trajectory and orbit, what engine thrust magnitude and direction is needed?

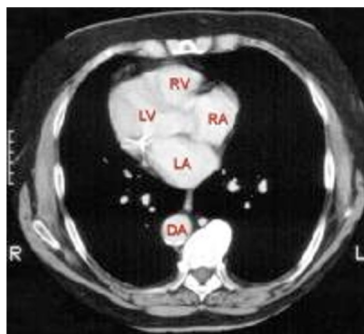
Examples of inverse problems with clinical applications

Measurements are clinically viable

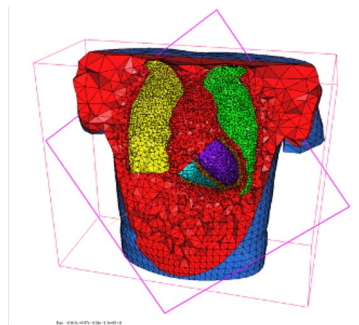
Imaging



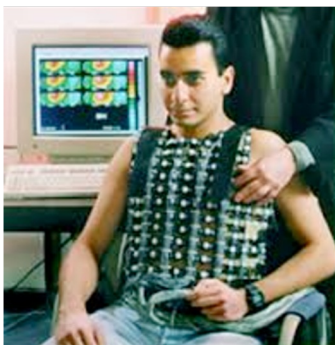
Segmentation



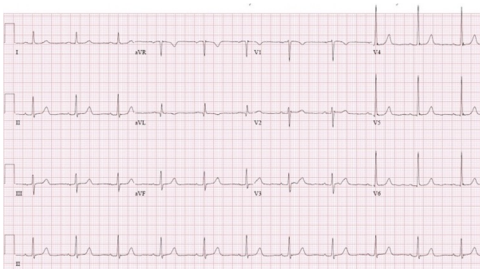
Meshing



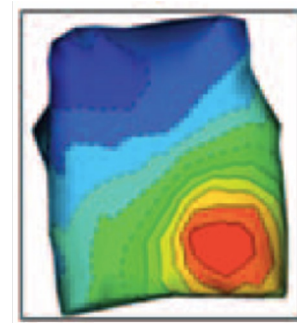
Body surface electrodes



Surface electrocardiogram



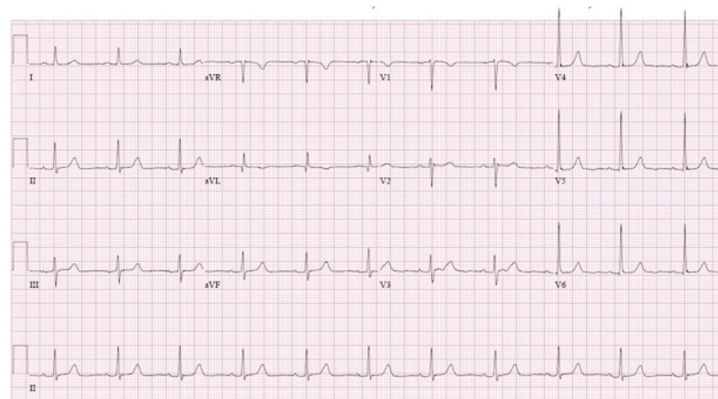
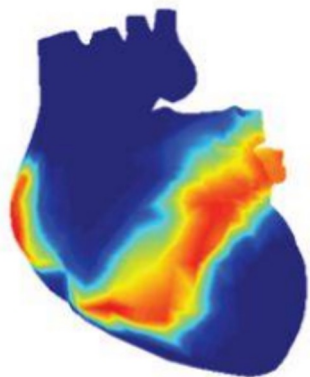
Body surface potentials



The inverse problem in cardiac electrophysiology

Cardiac electrophysiology: our model is 3D electrical propagation during an single beat in a 4-chamber geometry

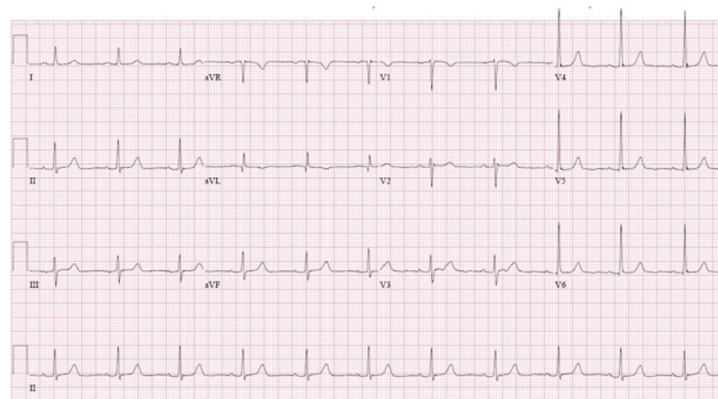
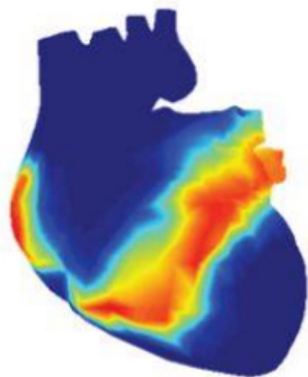
- The **forward** problem: using our model, simulate an infarct in a specific region of the heart and compute what the resultant surface ECG would look like



The inverse problem in cardiac electrophysiology

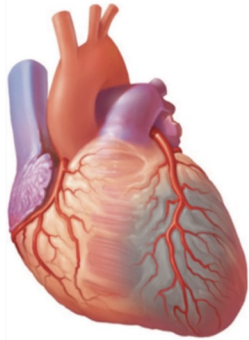
Cardiac electrophysiology: our model is 3D electrical wave propagation during an single beat in a 4-chamber geometry

- The **inverse** problem: given a measured ECG, determine what infarct size and location would have produced the ECG (*more clinically realistic*)



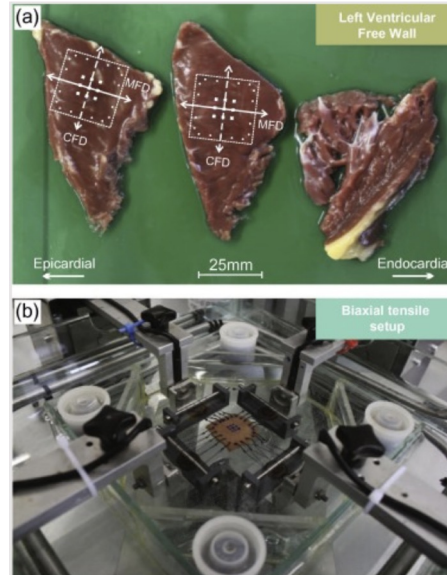
Assessing myocardial scarring in an infarcted heart

After myocardial infarction, tissue death leads to scarring and a change in material properties of the heart



A stiffer, scarred muscle does not function as well as the undamaged, healthy muscle

Material properties of the myocardium can be assessed through biaxial experiments



How do we determine the properties of the scarred heart *in vivo*?

The inverse problem in cardiac biomechanics

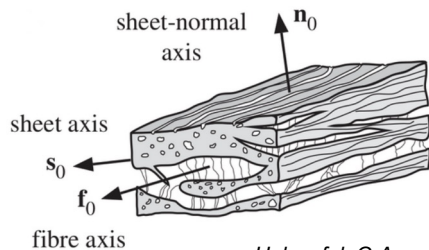
How do we determine the properties of the scarred heart *in vivo*?

Measurements/observables



Material model

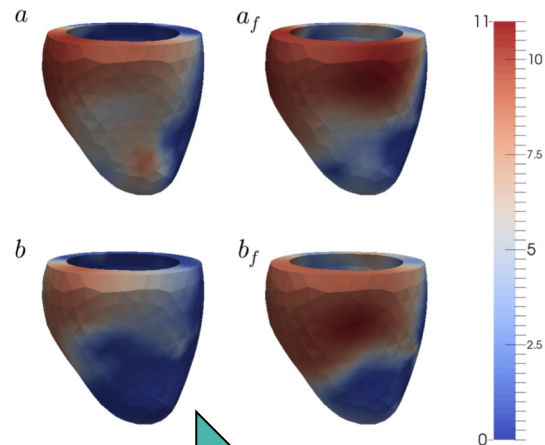
	Contribution from	Extracellular matrix
+	Contribution from	Fibers
+	Contribution from	Sheets
+	Contribution from	Angle between fibers and sheets



Relationship between material and observables

$$\sigma = J^{-1} \frac{\partial \Psi}{\partial \mathbf{F}} \mathbf{F}^T$$

(a few other things...)



Data assimilation

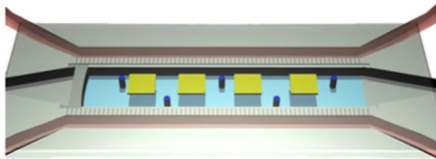
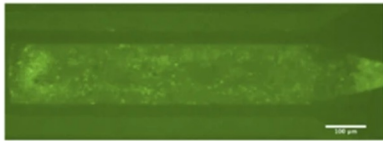
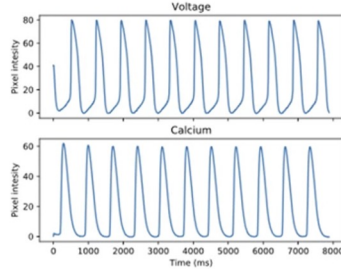
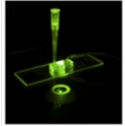
Common challenges with forward and inverse problems

1. Measurement error and uncertainty \rightarrow inversion error and uncertainty
2. Model fidelity
3. Underdetermined systems (the solution is non-unique)
4. Validation and verification of the solution to inverse problems

Inversion problems in cardiac microphysiological systems

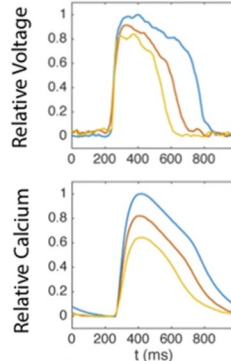
In vitro observation

Optical Action Potential Measurements

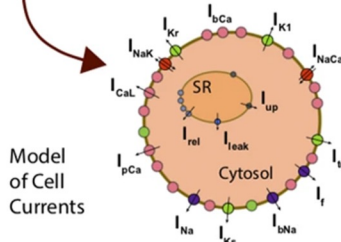


Computational inversion

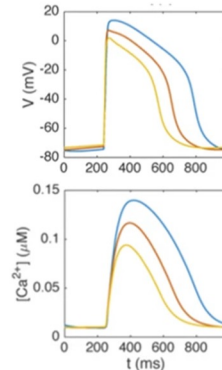
Measurements Under Drug



Model of Cell Currents



Optimized Mathematical Model



Base Model

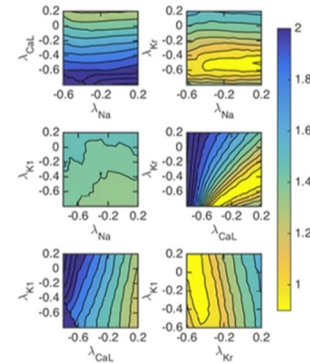
$$v_t = - \sum_i q_i I_i(v, s)$$

Drug Model

$$v_t = - \sum_i (1 + \lambda_i) q_i I_i(v, s)$$

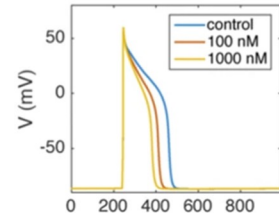


Predicting drug mechanism in mature cells



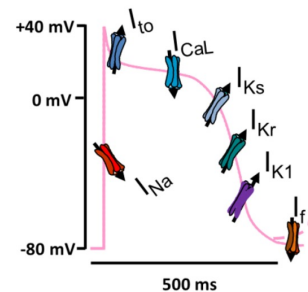
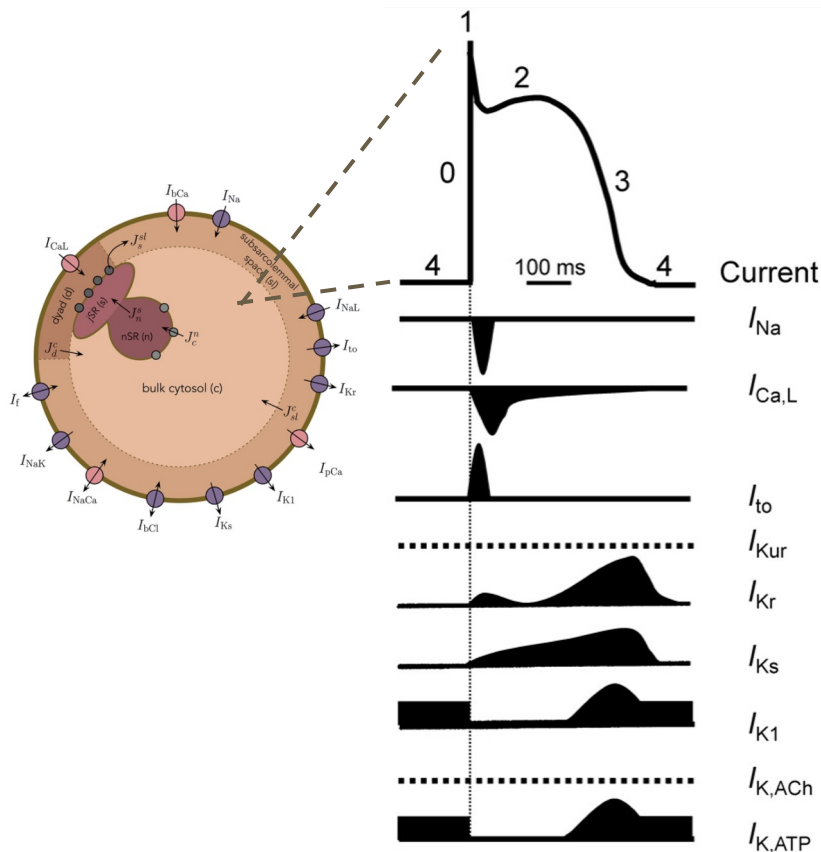
Detection of Channel Block

$$\begin{aligned} \lambda_{Na} &= -0.03 \\ \lambda_{CaL} &= -0.02 \\ \lambda_{Kr} &= -0.52 \\ \lambda_{K1} &= -0.00 \end{aligned}$$



Mapping Effect in Mature Cells

MPS forward problem



The standard model of the membrane potential of an excitable cell:

$$\frac{dv}{dt} = -\frac{1}{C_m} \sum_x N_x i_x$$

For voltage-gated ion channels, the average single channel current:

$$i_x = g_x o_x (v - E_x)$$

We parameterize the model by scaling the default conductance, g_x^0 :

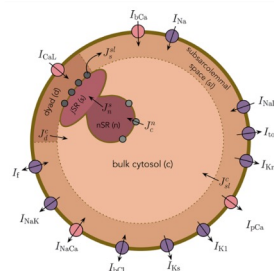
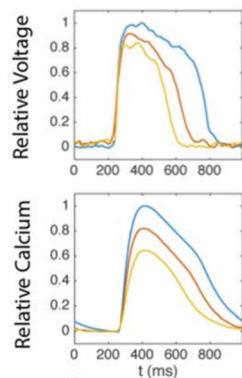
$$g_x^C = (1 + \lambda_x^C) g_x^0$$

$$g_x^D = (1 + \lambda_x^D) g_x^0$$

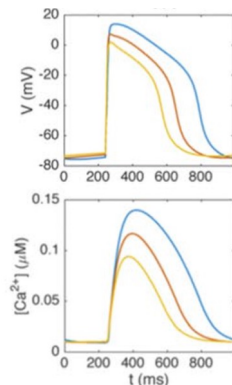
MPS inverse problem

- The inverse problem (i.e. inversion) is the process of estimating parameters of our biophysical mathematical model such that the outputs match the measured inputs (relative voltage and calcium)
- Through inversion we can reveal the relative change in the parameters of a mathematical cell AP model due to the introduction of a drug
- Differences in cell model parameters (e.g. maximal ionic channel conductances) represent a block or promotion of a specific ionic current

Measured inputs



Model outputs



The first step: Determine if the problem is solvable

$$f = x_1 + x_2$$

The concept of “well-posed” problems:

- The solution exists
- The solution is unique

The concept of “well-conditioned” problems

- Small changes to the input lead to small changes to the output

>>> *MPS inversion is often ill-posed and ill-conditioned*

Second step: construct or adapt a parameterized model

2 Examples of cardiac cell models

2.1 Purkinje cell models

- 2.1.1 Noble model (1962) [4 variables]
- 2.1.2 McAllister-Noble-Tsien model (1975) [10 variables]
- 2.1.3 DiFrancesco-Noble model (1985) [16 variables]
- 2.1.4 Karma model (1993) [2 variables]

2.2 Ventricular models

- 2.2.1 Generic models
 - 2.2.1.1 Beeler-Reuter model (1977) [8 variables]
 - 2.2.1.2 Fenton-Karma model (1998) [3 variables]
- 2.2.2 Guinea pig models
 - 2.2.2.1 Luo-Rudy 1 model (1991) [8 variables]
 - 2.2.2.2 Nordin model (1993) [14 variables]
 - 2.2.2.3 Luo-Rudy 2 model (1994) [15 variables]
 - 2.2.2.4 Luo-Rudy dynamic model (1995 -)
 - 2.2.2.5 Matsuoka-Sasai-Kuratomi-Ono-Noma model (2003) [45 variables]

2.2.3 Human models

- 2.2.3.1 Pribe-Beuckelmann model (1998) [17 variables]
- 2.2.3.2 Bernus-Wilders-Zemlin-Verschelde-Panfilov model (2002) [6 variables]
- 2.2.3.3 Ten Tusscher-Noble-Noble-Panfilov model (2004) [17 variables]
- 2.2.3.4 Iyer-Mazhari-Winslow model (2004) [67 variables]
- 2.2.3.5 Bueno-Orovio-Cherry-Fenton model [4 variables]

2.2.4 Canine models

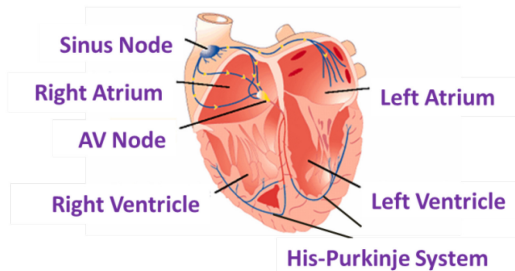
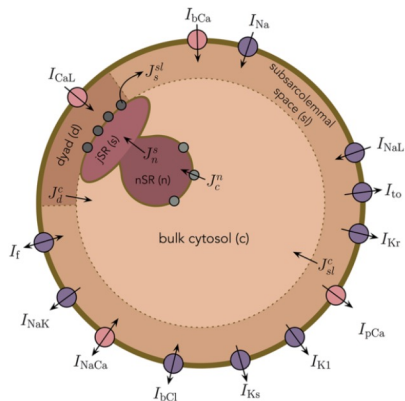
- 2.2.4.1 Winslow-Rice-Jafri-Marban-O'Rourke model (1999) [33 variables]
- 2.2.4.2 Fox-McHarg-Gilmour model (2002) [13 variables]
- 2.2.4.3 Cabo-Boyden model (2003) [16 variables]
- 2.2.4.4 Hund-Rudy model (2004) [29 variables]
- 2.2.4.5 Greenstein-Winslow model (2002)

2.2.5 Rabbit models

- 2.2.5.1 Puglisi-Bers model (2001) [20 variables]
2.2.5.2 Shannon-Wang-Puglisi-Weber-Bers model (2004) [45 variables]
2.2.5.3 Mahajan-Shiferaw et al. model (2008) [27 variables]

2.2.6 Rat models

- 2.2.6.1 Pandit-Clark-Giles-Demir model (2001) [26 variables]
- 2.2.7 Mouse models
- 2.2.7.1 Bondarenko-Szigeti-Bett-Kim-Rasmusson model (2004) [44 variables]



2.3 Atrial cell models

2.3.1 Rabbit models

- 2.3.1.1 Hilgemann-Noble model (1987)

2.3.2 Bullfrog models

- #### 2.3.2.1 Rasmusson-Clark-Giles-Robinson-Clark-Shibata-Campbell model (1990) [16 variables]

2.3.3 Human models

- 2.3.3.1 Nygren-Fiset-Firek-Clark-Lindblad-Clark-Giles model (1998) [29 variables]
2.3.3.2 Courtemanche-Ramirez-Nattel model (1998) [21 variables]
2.3.3.3 Simitev-Biktashev model (2006) [3 variables]

2.3.4 Canine models

- 2.3.4.1 Ramirez-Nattel-Courtemanche model (2000) [26 variables]
2.3.4.2 Cherry-Ehrlich-Nattel-Fenton model (2007) [4 variables]

2.4 Sinoatrial node cell models

2.4.1 Rabbit models

- 2.4.1.1 Yanagihara-Noma-Irisawa model (1980)
- 2.4.1.2 Bristow-Clark model (1982) [7 variables]
- 2.4.1.3 Irisawa-Noma model (1982)
- 2.4.1.4 Noble-Noble model (1984)
- 2.4.1.5 Noble-DiFrancesco-Denyer model (1989)
- 2.4.1.6 Wilders-Jongsma-van Ginneken model (1991) [15 variables]
- 2.4.1.7 Demir-Clark-Murphey-Giles model (1994) [27 variables]
- 2.4.1.8 Dokos-Celler-Lovell model (1996) [18 variables]
- 2.4.1.9 Zhang-Holden-Kodama-Honjo-Lei-Varghese-Boyett model (2000) [12 variables]
- 2.4.1.10 Kurata-Hisatome-Imanishi-Shibamoto model (2002) [30 variables]
- 2.4.1.11 Sarai-Matsuoka-Kuratomi-Ono-Noma model (2003) [50 variables]

2.4.2 Bullfrog models

- #### 2.4.2.1 Rasmusson et al. model (1990) [14 variables]

2.4.3 Mouse models

- #### 2.4.3.1 Mangoni et al. model (2006) [22 variables]

2.5 Atrioventricular node cell models

http://www.scholarpedia.org/article/Models_of_cardiac_cell

Third step: Select an optimization method for fitting the model to data

Iterative methods

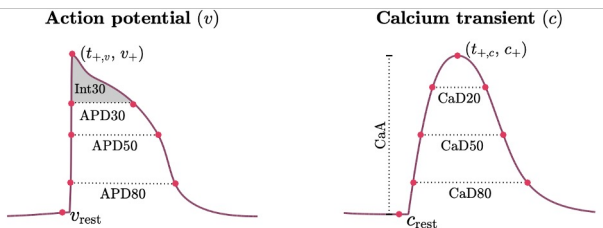
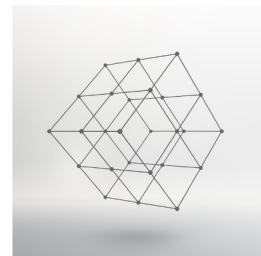
- Newton's method
- Gradient descent
- Pattern search

Heuristic methods

- Differential evolution
- Genetic algorithm
- Particle swarm optimization

Grid search optimization

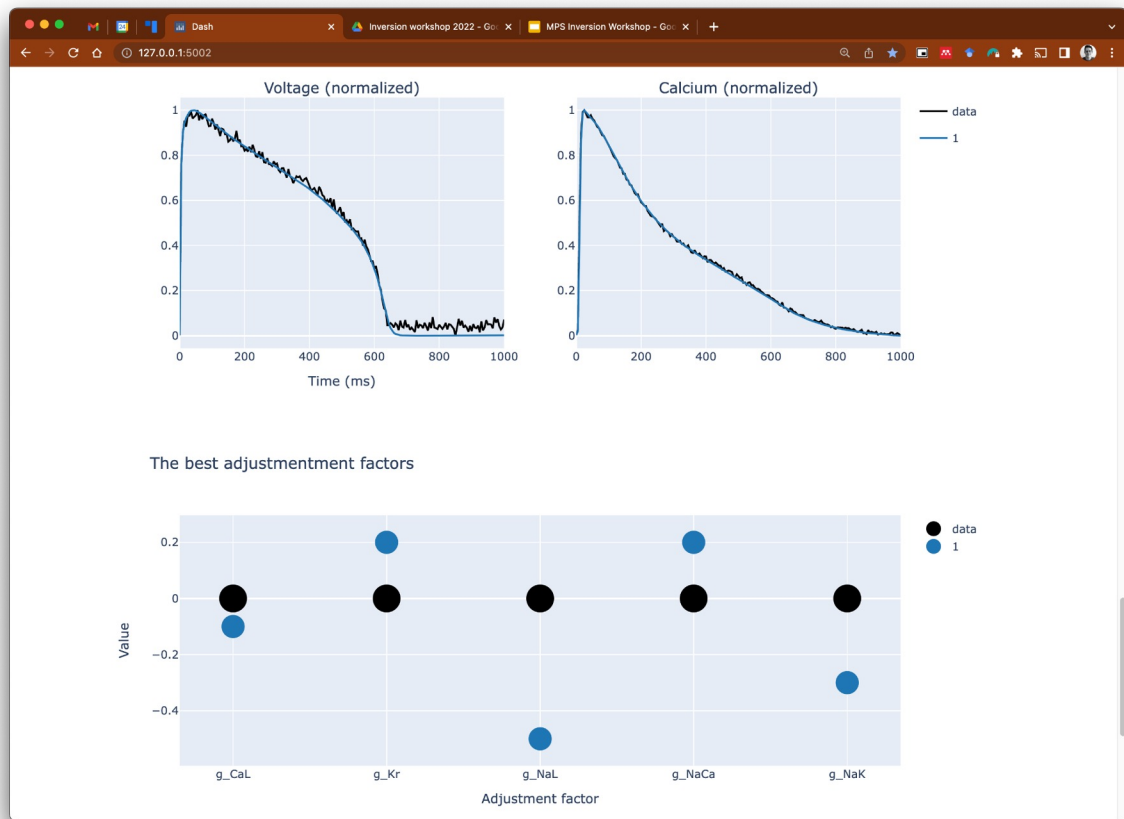
- Pre-compute many possible solutions by running the cell model with random or structured parameter sets
- Define features of the model output and measured input that can be used to quantify errors
- For data you want to invert, compute a cost function value for every point in your grid
- Sort all points in the grid by cost function and analyze the top N parameter sets



Cost function

$$J(\lambda) = \sum_i w_{i,v} (f_{i,v}^{\text{model}}(\lambda) - f_{i,v}^{\text{data}}(\lambda))^2 + w_{i,c} (f_{i,c}^{\text{model}}(\lambda) - f_{i,c}^{\text{data}}(\lambda))^2$$

Final step: solve the inverse problem



Demonstration of inversion using grid search optimization

- Demonstration of MPS inversion using synthetic data: `python app.py`
- Demonstration using real data: `python app_real_data.py`