Parameter Identification for a Cardiac Electrophysiology Model

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Introduction

Several ionic models are available to describe the evolution of the electrical potential across cardiac cell membranes. These models usually read as a systems of coupled highly nonlinear differential equations with many adjustable parameters. The adjustment of parameters becomes increasingly important to be able to personalise these models using medical data or to compare models with each other in the best possible way.

We propose numerical methods to optimally adjust the parameters in ionic models, in particular when these models involve terms (ionic currents or gating source terms) that are not continuous or stiff in the state variables. Our methods are based on the numerical solution of optimal control problems with least-square objective functions. Two types of least-square functions will be used. The first one attempts to fit the main features of the cardiac action potential (AP), namely the action potential duration (APD), the depolarization time (DT), recovery time (RT), etc. The second function attempts to fit the trans-membrane potential predicted by the model to experimental recording on a single cell.

Mitchell-Schaeffer model

Single-cell model: $u = u(t)$ and $v = v(t)$, $t > 0$, are solutions of:

$$\frac{du}{dt} = f(u,v) + I_{stim}(t), \quad \text{with} \quad f(u,v) = \frac{1}{\tau_{in}} vu^2(1-u) - \frac{1}{\tau_{out}} u, \tag{1}$$

$$\frac{dv}{dt} = g(u,v), \quad \text{with} \quad g(u,v) = \begin{cases} \dfrac{1-v}{\tau_{open}}, & \text{if} \quad u < u_{gate}, \\ \dfrac{-v}{\tau_{close}}, & \text{if} \quad u \geq u_{gate}. \end{cases} \tag{2}$$

The functions f and g depend on the parameters $\tau = [\tau_{in}, \tau_{out}, \tau_{open}, \tau_{close}]$.

Equations (1)-(2) are solved using the initial condition

$$[u(0), v(0)] = [0, 1] \tag{3}$$

and a stimulating current I_{stim} that looks like

$$I_{stim}(t) = \begin{cases} A & \text{if } t \in [n \cdot BCL, n \cdot BCL + \Delta t], \ n \in \mathbb{N} \\ 0 & \text{otherwise ,} \end{cases}$$

where the amplitude A depends on the stimulation rate BCL, the stimulation duration Δt and the model parameters.

Optimal control problem I

Least square fit on the phase durations: Consider the four phase durations ΔT_i^*, $i = 1,2,3,4$, (depolarization, plateau, repolarization and recovery phases) obtained experimentally.

Find τ^* minimizing the following least square function

$$J(\tau) = \frac{1}{2} \sum_{i=1}^{4} \omega_i (\Delta T_i - \Delta T_i^*)^2,$$

where

- $\omega_i \geq 0$, $i = 1,2,3,4$, are weight constants;
- u and v are solution of (1)-(3);
- I_{stim} is adjusted to stimulate the cell only once;
- the times $T_i = T_i(\tau)$, $T_1 < T_2 < \ldots < T_5$, are such that

$$\begin{cases} u(T_i) = \gamma_i, \quad i = 1,3,4, \quad \gamma_i \ \text{ thresholds given,} \\ u(T_2) = \max_t(u(t)), \\ v(T_5) = \gamma_5, \quad \gamma_5 \ \text{ given;} \end{cases}$$

- $\Delta T_i = T_{i+1} - T_i$;
- the thresholds γ_i are characteristic values of the potential u (or v for γ_5) indicating the beginning or the end of the phases.

Optimal control problem II

Least square fit of the potential: Consider a trans-membrane potential $\tilde{u}_i = \tilde{u}_i(t,s)$, $t \in [0,T]$, $s \in (0,1)$, $i \in \mathbb{N}$, measured experimentally and that has been rescaled using a scaling factor s .

Define $J_i = J_i(\tau, s)$

$$J_i(\tau, s) = \int_0^T | u(t,\tau) - \tilde{u}_i(t,s) |^2 \, dt,$$

where u and v are solution of (1)-(3) with I_{stim} adjusted to match the stimulation pattern of $\tilde{u}_i$.

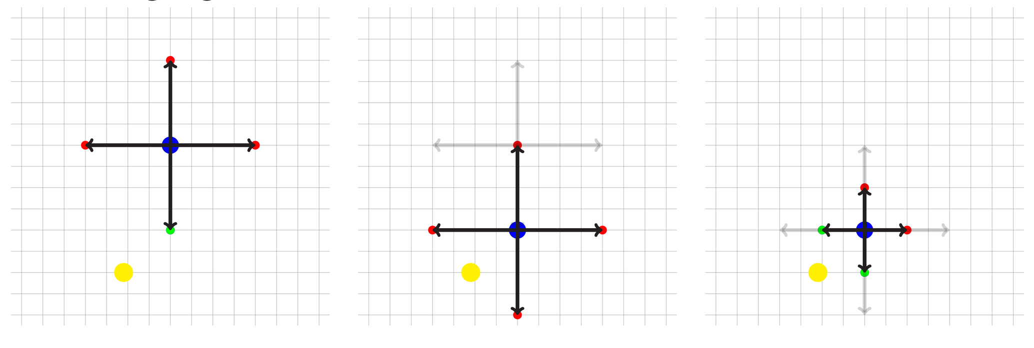
Consider multiple different $\tilde{u}_i$, $i = 1, \ldots, N$, obtained by stimulating the same heart at different frequencies and find $[\tau^*, S^*]$ minimizing

$$J(\tau, S) = \sum_{i=1}^{N} J_i(\tau, s_i)$$

where $S = (s_1, \ldots, s_N)$ are the scaling factors for the $\tilde{u}_i$'s

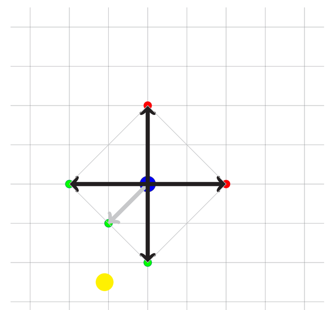
Solving the optimization problem

- Previous work hints towards the need for non-differentiable optimization, since deriving the cost function J *w.r.t.* τ or $[\tau, S]$ is difficult.
- First method tried is Compass Search [1]. From this basic idea, 3 variations were proposed and tested: Golden Compass Search, Hybrid Compass Search and FrontTrack Compass Search.
- As seen in the following figures, these methods resemble each other in a few ways



(a) initial D (b) next iteration (c) contraction

An example of the first 3 iterations of Compass Search in $\mathbb{R}^2$.



An example of an iteration of Hybrid Compass Search in $\mathbb{R}^2$

- Despite the similarities in these methods, the latter two usually reach better accuracy in less function evaluations.

Application to three cardiac tissues using Problem I

Experimental durations (ms)

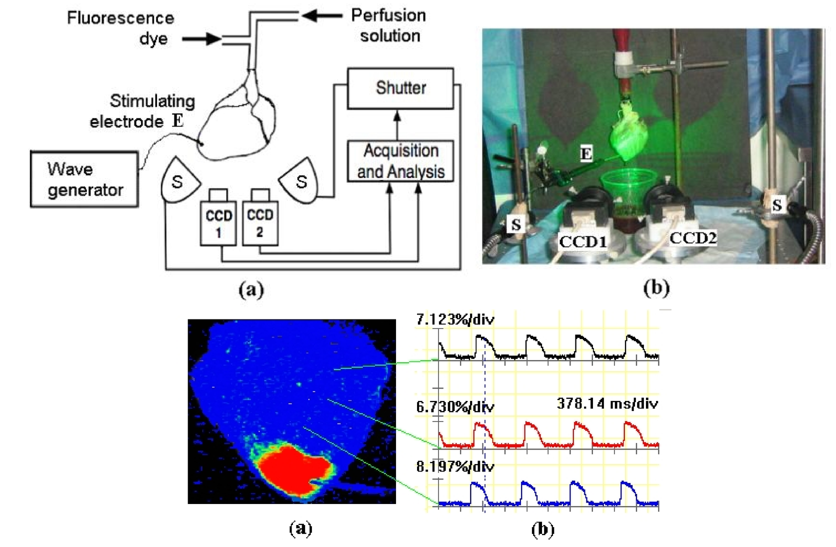
Tissues	ΔT_1^*	ΔT_2^*	ΔT_3^*	ΔT_4^*
Left ventricle (LV)	8	250	30	260
Purkinje fibers (PF)	8	380	65	320
Right atria (RA)	$4-5$	100	20	250

Results using FrontTrack Compass Search

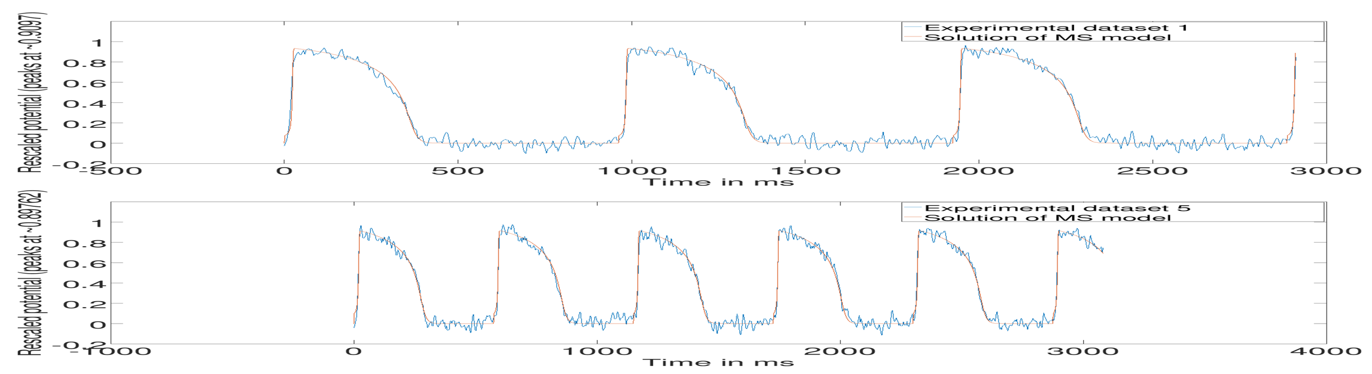
Tissue	ΔT_1	ΔT_2	ΔT_3	ΔT_4	τ_{final}	$J(\tau_{final})$	evals
LV	7.998	250.171	29.917	259.997	$[0.311, 4.58, 129.47, 189.17]$	$8.65x10^{-6}$	269
PF	7.998	380.23	64.978	320.072	$[0.381, 13.35, 152.09, 165.35]$	$6.17x10^{-7}$	232
RA	3.998	99.901	20.039	250.499	$[0.182, 4.24, 116.97, 53.71]$	$9.05x10^{-6}$	268

Adjusting models to experimental data using Problem II

Data acquisition using voltage-based optical fluorescence imaging [2]

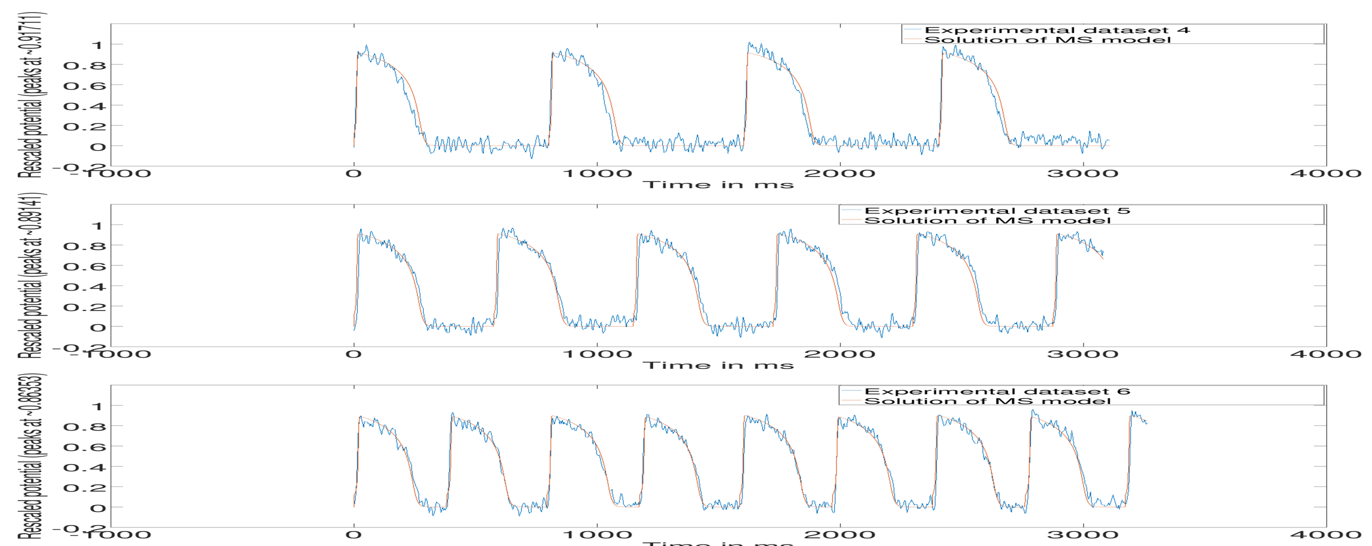


Problem II is used to fit the MS model to datasets individually



The model fitted to two different data sets individually

Problem II is used to fit the model to multiple data sets simultaneously



The model is fitted to three different datasets at once

Conclusions

- When compared to other optimisation methods used in previous work done on problem I, Compass Search and its variations perform better [3].
- When fitting a single set of experimental data, these methods work well to fit the model. However, fitting multiple data sets at once is still difficult and needs more thinking to optimize he methods.
- Future work on these problems includes trying to match data obtained from faster stimulations as these induce a different kind of response that the model will need to account for and focusing on improving multiple data fitting.

References

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