Parameterizing Cardiac Models for Medical Cyber-physical Systems

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Context

This project is a component of a larger effort is to develop the foundations of modeling, synthesis and development of verified medical device software and systems from verified closed-loop models of the device and organ(s). This research spans both implantable medical devices such as cardiac pacemakers and physiological control systems such as drug infusion pumps which have multiple networked medical systems. Here we focus on advancing two aspects of this work: (1) development of patient-specific models and therapies and (2) multi-scale modeling of complex physiological phenomena.

Challenges and Approach

Mathematical models, generally posed as a system of differential equations, are an important tool for studying phenomena in cardiac electrophysiology ranging from cellular and subcellular mechanisms to tissue-level properties of arrhythmias and defibrillation. However, finding parameters for these models that fit experimental data is challenging because of the large number of parameters, biological variability, and the highly nonlinear nature of the problem. Because it may be necessary to perform multiple parameterizations for a single experiment, computational efficiency is also important. For this work we use the following models and parameter-fitting algorithms.

- **Two flexible models**
  - ***Fenton-Karma (FK) model:*** 3 coupled differential equations, 13 parameters, cannot reproduce action potential shape.

$$\partial_t u(t,\mathbf{x}) = -\left(I_{fi}(u,v) + I_{so}(u) + I_{si}(u,w)\right)$$

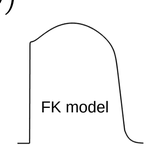
$$\partial_t v(t,\mathbf{x}) = \begin{cases} -v/\tau_v^+ & u \geq u_c \\ (1-v)/\tau_{v2}^- & u_c > u \geq u_v \\ (1-v)/\tau_{v1}^- & u < u_v \end{cases}$$

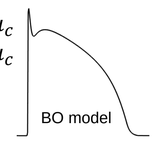
$$\partial_t w(t,\mathbf{x}) = \begin{cases} -w/\tau_w^+ & u \geq u_c \\ (1-w)/\tau_w^- & u < u_c \end{cases}$$

$$I_{fi}(u,v) = \begin{cases} -v(u-u_c)(1-u)/\tau_d & u \geq u_c \\ 0 & u < u_c \end{cases}$$

$$I_{so}(u) = \begin{cases} 1/\tau_r & u \geq u_c \\ u/\tau_o & u < u_c \end{cases}$$

$$I_{si}(u,w) = -w\left(1+\tanh\left(k\left(u-u_c^{si}\right)\right)\right)/(2\tau_{si})$$



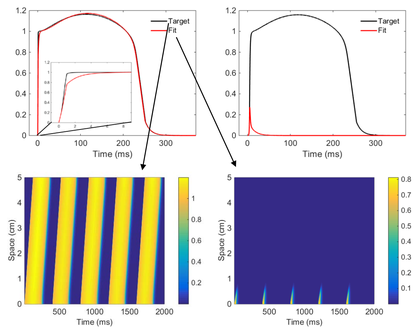


  - ***Bueno-Orovio et al. (BO) model:*** Extension of the FK model with 4 differential equations, 28 parameters, can reproduce action potential shape.
- **Two parameter-fitting algorithms:**
  - ***Genetic algorithm:*** Different areas of parameter space are explored; fitness metric includes curve error as well as action potential duration.
  - ***Data assimilation:*** Fitting performed in conjunction with state estimation. One or more parameters are introduced for estimation as additional differential equations with time derivatives of zero; nevertheless, the model parameters being estimated receive corrections indirectly when the ensemble members are updated. Results here are for one spatial dimension.

We consider finding parameterizations to fit the models to data generated from models, including model recovery cases, as well as experimental data from microelectrode recordings.

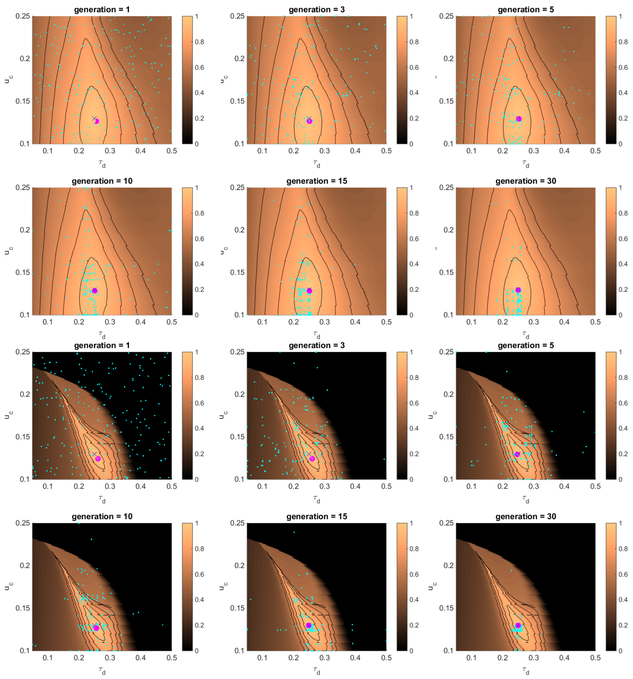
Genetic Algorithm: Model Recovery

We solve the model differential equations for a single cell only to speed up calculations by two orders of magnitude and aim to overcome known differences between single-cell and tissue dynamics through use of a biphasic stimulus current derived from an intercellular coupling current in 1d.



Biphasic stimulus current with the FK model. Top left: representative 0d fitting using a square stimulus. Despite problems fitting the upstroke (inset), curve error remains small. Top right: 0d simulation using the parameters from the fit at the left but with a biphasic stimulus: no action potential results. Bottom left: Target parameters produce wave propagation in 1d. Bottom right: parameter values from the 0d fit (top left) fail to produce wave propagation in 1d.

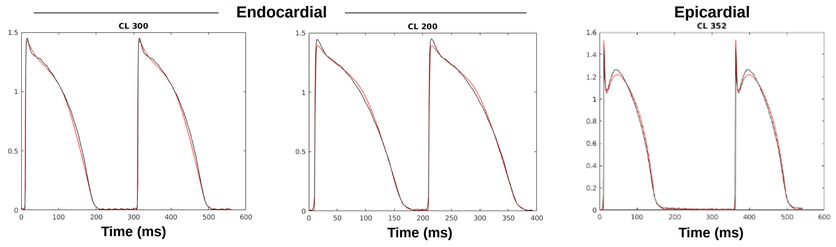
Algorithm performance for the FK model using a *square stimulus* with two parameters being fit, with visualization of the fitness landscape. Because the landscape is fairly flat, the GA has difficulty improving after finding an area of good fitness.



Algorithm performance for the FK model using a *biphasic stimulus* with two parameters being fit, with visualization of the fitness landscape. The fitness landscape is significantly less flat than for the square stimulus, and population members move quickly toward the correct parameter values.

Genetic Algorithm: Experimental Data

For experimental data, we permitted the algorithm to vary 18 parameters. The algorithm was able to find good parameterizations for endocardial microelectrode data (two CLs fit simultaneously) and for epicardial microelectrode data.



References

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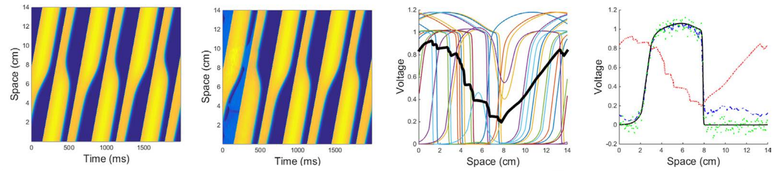
Data Assimilation: Model Recovery

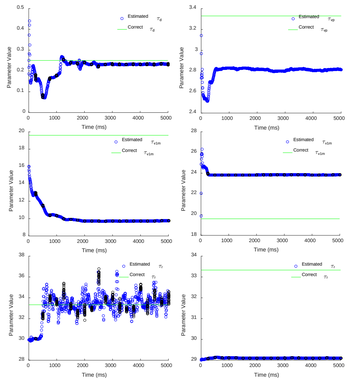
We also consider estimating parameters as part of state estimation through data assimilation. We use the Local Ensemble Transform Kalman Filter (LETKF), which has been used previously for cardiac state reconstruction and includes an ensemble of states to characterize uncertainty.



Discordant alternans truth state and reconstruction. Ensemble is initialized to random model states and the initial state estimate is the ensemble average. Corrections from noisy data quickly correct to a wave shape.

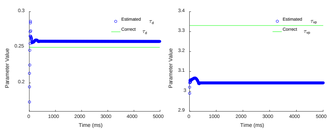
Parameters are added as extra differential equations with time derivatives of zero and receive corrections indirectly when the ensemble members are updated. Results here are for one spatial dimension.

Many parameters cannot be fit robustly because the model is relatively insensitive to them; their effects are not large enough over the typical assimilation interval. The algorithm can account for the small differences evident in wave properties over that time interval when observations are assimilated, thereby making it unnecessary to adjust the parameter value.



Estimates of different single parameters in the Fenton-Karma model using data assimilation. Each shows the parameter estimate as a function of time. Top left: τ_d is fit well. Top right: τ_v^+ is not fit well. Middle row: τ_{v1}^- is not fit well from over- or underestimates. Bottom row: τ_r sometimes can be fit and sometimes cannot depending on initial conditions and algorithm parameters.

Fitting sensitive parameter τ_d and insensitive parameter τ_v^+ together yields the same results as fitting both separately.



Conclusions

Genetic Algorithm	Data Assimilation
+ Can find acceptable values for many parameters for the FK and BO models; sensitive to many parameters.	+/- Can find acceptable values for a limited number of parameters for the FK model; sensitive to a small number of parameters.
+ Use of biphasic current gives results closer to those from 1d using 0d, aiding in efficiency.	+ If state estimation is performed, parameter estimation adds little to the computational cost.
+ Many parameters can be fit simultaneously.	+/- A few parameters can be fit simultaneously
- Fairly good bounds are needed to avoid long runtimes.	- Fairly good initial estimates are needed.
- Algorithm can fit some experimental data but has trouble with other types.	- Algorithm has not been tested with experimental data.

Both approaches show promise for finding model parameterizations and will help in producing personalized models, which can lead to more accurate and robust results in simulating interactions between organs and devices.

Acknowledgements

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