Fast Parameterization of Human Ventricular Ionic Models Using CardioFit

Maxfield R Comstock[1], Flavio H Fenton[2], Elizabeth M Cherry[1]

[1] School of Computational Science and Engineering, Georgia Institute of Technology, Atlanta, GA, USA

[2] School of Physics, Georgia Institute of Technology, Atlanta, GA, USA

Abstract

Ionic models of cardiac action potentials (APs) may not reproduce all relevant datasets using their default settings, and tuning parameter values to improve fits is often difficult. To facilitate this task, we present CardioFit, a tool to fit cardiac AP model parameters to time-series data using particle swarm optimization (PSO). CardioFit quickly finds conductance parameter values for detailed human ventricular models, including those of ten Tusscher et al. (2006) and O'Hara et al., that match experimental data, within the capabilities of the models. CardioFit is implemented as a web-based tool using JavaScript and the WebGL graphics API, allowing PSO to take advantage of any available graphics-processing unit hardware to run in parallel. As the PSO algorithm requires the simultaneous evaluation of many candidate parameterizations when searching for the best fit, this method is well-suited to large-scale parallelism. Due to its fast parallel implementation, CardioFit obtains conductance parameters of detailed ionic models to match a given dataset in a few minutes on consumer-grade hardware, even though tens of thousands of model runs typically are required.

1. Introduction

Models of human heart tissue are important for understanding and predicting outcomes in a clinical setting. However, the electrical properties of human heart tissue vary even in healthy tissue and may be altered further due to cardiac disease. In order to account for this variability and provide patient-specific predictions, cardiac models incorporate parameters which may be tuned to achieve desired adjustments to the model behavior. However, as these parameters are numerous and have complex, interacting, and nonlinear effects, manually adjusting these parameters is a difficult process which is often impractical even for experts in a given model.

Many automated approaches have been developed for the task of parameter fitting; however, these approaches are often computationally expensive and may require a detailed understanding of the parameter fitting method in question. Additionally, they may be laborious to implement and difficult to validate for a specific model. To facilitate fast and easy parameter fitting of cardiac models to data, we have developed a fast, interactive tool, CardioFit, which uses the particle swarm optimization (PSO) algorithm to find parameterizations of cardiac models that reproduce the features of user-provided data sets [1]. We have previously demonstrated the effectiveness of CardioFit for fitting phenomenological models to both human data [2] and data from more complex models [3].

Although phenomenological models are sufficient to study cardiac dynamics in many cases, in scenarios like studying effects of drugs or calcium dynamics, more physiologically detailed models are necessary. In addition, even detailed models may not provide good fits to experimental data using their original parameter values and may require tuning [4]. To that end, we have incorporated into CardioFit two popular human cell models: the ten Tusscher-Noble-Noble-Panfilov 2006 (TNNP) model [5] and the O'Hara-Virág-Varró-Rudy (OVVR) model [6]. In this manuscript, we present results from fitting these models to human data, both synthetic and experimental, using CardioFit.

2. Methods

Models: Two mechanistic human ionic models were integrated into CardioFit. The first model added is the TNNP model [5], which includes 19 state variables and 12 currents with conductance or scaling parameters that can be fit using PSO. The second model added is the OVVR model [6], which includes 41 state variables and 14 currents. As four of these, I_{Na}, I_{CaL}, I_{CaNa}, and I_{CaK} are split into two components with separate conductance values, there are 18 total current conductance and scaling parameters that can be fit for this model. Notably, the I_{NaK} current does not have an explicit scaling parameter in the original formulation of the model, but the provided factor of 30 in the original equation is replaced in CardioFit using the new scaling parameter $\overline{G_{\mathrm{NaK}}}$. The default bounds

for each parameter value use $50\,\%$ and $200\,\%$ of the default value provided in the original model formulation as the minimum and maximum, respectively.

Models are integrated using the Rush-Larsen method for gating variables, explicit Euler integration for non-gating variables, and a calcium buffering approach described in Appendix A of Ref. [7] for intracellular calcium concentrations in the TNNP model. A fixed time step size of $0.02\,\mathrm{ms}$ is used for both models. For equations that are only dependent on voltage, values of the equation over a range of reasonable voltage values are pre-computed at the start of each simulation and stored in tables, which are then accessed during the simulation run to improve efficiency.

Particle swarm optimization: The PSO algorithm searches the parameter space for a given optimization problem by maintaining a pool of candidate parameterizations, referred to as "particles," which are iteratively updated based on low-error solutions from previous iterations. At each iteration, the parameter values associated with each particle are evaluated by running a simulation of the model using those parameters and measuring the error relative to the input data. The particle positions and velocities are then updated, with the velocities influenced to move in random degrees toward previously identified good solutions. The formulation of the PSO algorithm used in CardioFit is described in detail in Ref. [1]. For the time-series data used in the results presented here, mean absolute error between the data set and the model output is used as the error metric. When fitting multiple data sets simultaneously, a weighted sum of the error for each data set (with weights specified by the user) is used.

One of the main advantages of PSO is that it does not require any assumptions or transformation of the model being fit; CardioFit requires only an implementation of the model itself so that a simulation can be run for a provided set of parameters and the output can be compared with the data. The main limitations of PSO are that it is not guaranteed to find an optimal solution and that it has a high computational cost due to the need to run a full simulation of the model for every particle at every iteration. To improve performance, CardioFit uses a parallel implementation of the PSO algorithm in which the simulation and corresponding error for each particle during a single iteration are computed independently. As CardioFit allows thousands of particles to be used, and more particles generally decrease error [1], CardioFit uses graphics for large-scale parallelism, resulting in improved performance on machines with more powerful graphics-processing units (GPUs). All fits included here were performed using 50 iterations with 4096 particles.

CardioFit interface: In order to integrate an interactive user experience with the fast parallel performance provided by graphics hardware, CardioFit is implemented in JavaScript using the WebGL API for interaction with GPUs. A key benefit of this approach is that the software can be distributed as a web page and run in a web browser without the need for the user to manually install or compile the program to see the full benefits of GPU parallelism. Effective use of CardioFit does not require a detailed understanding of the PSO algorithm or the specific model being optimized, although expert users have the option to tune hyperparameters of the PSO algorithm and manually adjust the bounds and number of the parameters to be fit.

As the PSO algorithm is random in its nature, multiple runs of CardioFit, even with identical settings, will produce different results. The results for a run can be saved for use of the generated parameters in other applications.

3. Results

An important test of the capabilities of CardioFit is the model recovery case, where a model is fit to data taken from itself in an attempt to reproduce the behavior as closely as possible. Figure 1 shows the results of five fits for each of three types of fittings in the self-recovery case for the TNNP model fit to its own data paced at $1\,\mathrm{s}$ using the parameters from the original paper [5]. When fitting to voltage data only, the voltage characteristics are closely recovered (panel (A)), but the behavior of the intracellular calcium concentration is not well constrained (panel (B)), indicating that fitting to calcium data is important to adequately constrain the model behavior. Conversely, when only calcium data is fit, the fitted calcium reproduces the calcium data well (panel (D)), but the voltage values show increased error, particularly in the initial upstroke and the final stages of repolarization (panel (C)). By fitting both voltage and calcium data simultaneously, good reproduction of both types of data is acheived (panels (E–F)).

In addition to model recovery, fits of one model to another were performed in order to test the capabilities of the models to reproduce the behavior of other models. Figure 2 shows the result of fitting the OVVR model to the TNNP model using the same data sets as in the self-recovery case. Although exact reproduction of the data is not possible in this case, when only voltage data is fit, the OVVR model is capable of closely reproducing the voltage time series (panel (A)), but the intracellular calcium concentration shows large differences (panel (B)). When only the calcium data is fit, the voltage data shows increased triangulation (panel (C)) although the fitted calcium behavior is much more accurate to the data (panel (D)). As with the model recovery case, fitting both voltage and calcium data results in good recovery of both data sets (panels (E–F)).

The OVVR and TNNP models were also fit to data recorded from an explanted human heart during an optical-mapping experiment, as shown in Figure 3. The tissue was paced at intervals of $1\,\mathrm{s}$ and the shape of the action

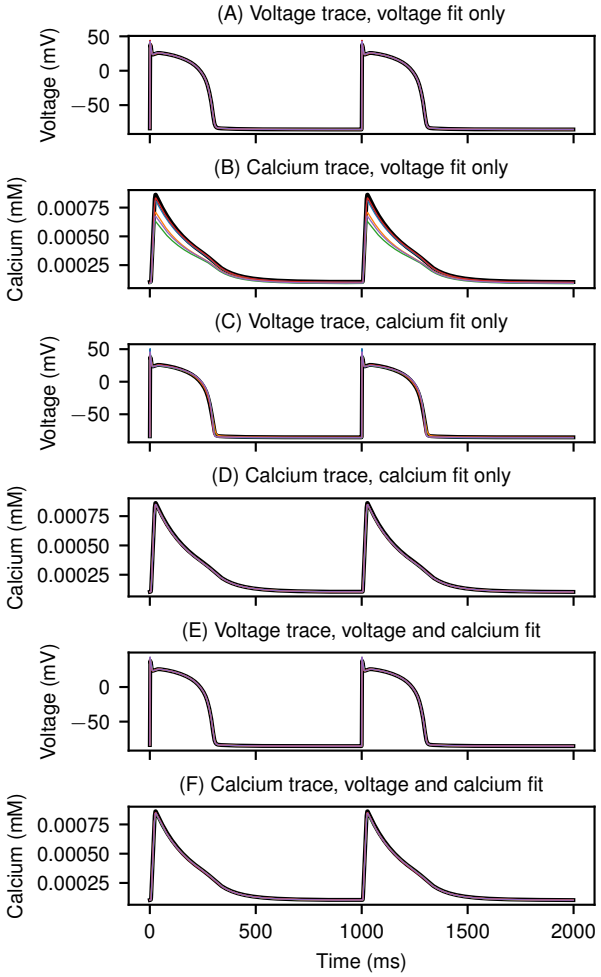

Figure 1. Fittings of the TNNP model to data taken from the same model using various combinations of voltage and intracellular calcium data. (A-B) Voltage and calcium traces from fitting to voltage data only. (C-D) Voltage and calcium traces from fitting to calcium data only. (E-F) Voltage and calcium traces from fitting both voltage and calcium data. Five fits are plotted in each case in various colors with the target data plotted in black.

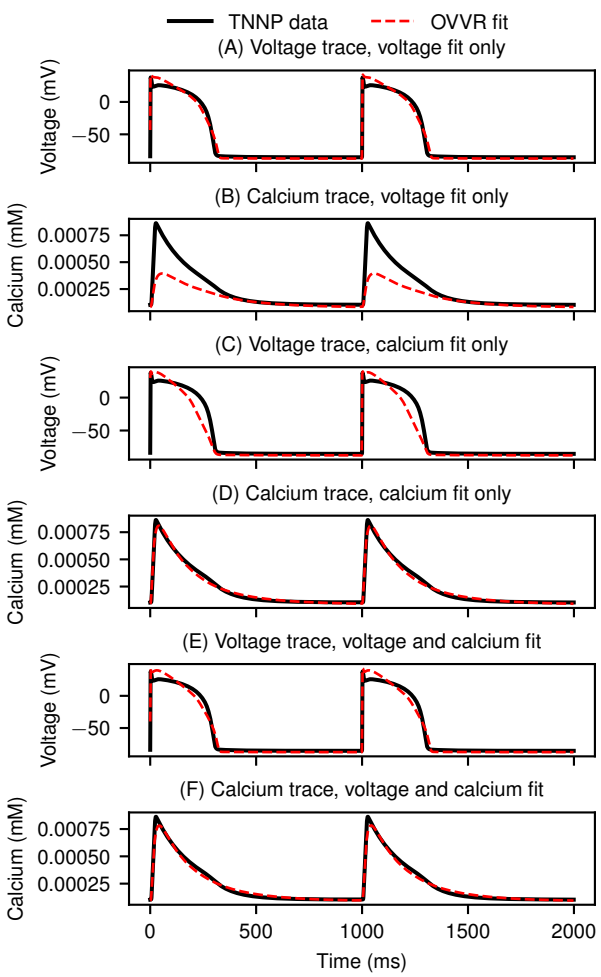

Figure 2. Fittings of the OVVR model to the TNNP model using various combinations of voltage and intracellular calcium concentration data. (A-B) Voltage and calcium traces from fitting to voltage data only. (C-D) Voltage and calcium traces from fitting to calcium data only. (E-F) Voltage and calcium traces from fitting both voltage and calcium data.

potential exhibited behavior bordering on Brugada syndrome, notably in the delayed development of the plateau. As neither model was formulated to recover this property, this aspect of the action potential is not reproduced by the models, although other features of the action potential are closely reproduced by both models, with the exception of the final repolarization stages for the OVVR model.

4. Discussion

The CardioFit tool is able to fit parameters of detailed human action potential models to both voltage and intracellular calcium concentration data. As demonstrated in the model self-recovery case and the model-to-model fit, fitting exclusively to voltage or calcium concentration is often not sufficient for constraining the other component. Consequently, fitting to both types of data simultaneously allows for superior reproduction of the recorded dynamics. For the sake of brevity, several cases are not shown such as the simultaneous fitting of multiple cycle lengths of data, model self-recovery for the OVVR model, and fittings of the TNNP model to OVVR data. The cases shown are indicative of typical results in these cases.

We believe that CardioFit provides researchers with a fast, easy-to-use method of fitting cardiac model parame-

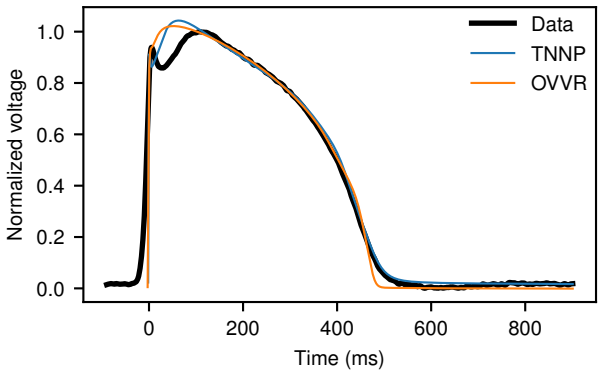

Figure 3. Fittings of the TNNP and OVVR models to optical mapping data recorded from a human heart displaying an AP morphology bordering on Brugada syndrome.

ters to data sets to facilitate the computational study of observed phenomena. Nevertheless, the work presented here has several limitations. Although CardioFit is designed to produce parameterizations quickly on consumer-grade hardware, the nature of the PSO algorithm requires a large amount of computation, particularly for complicated models such as TNNP and OVVR. Computers with insufficient hardware, particularly those without dedicated GPUs, may not be able to run the program or may be prohibitively slow, although all fittings presented here completed within a few minutes on a machine with a dedicated GPU. Additionally, fitting to more or longer data sets simultaneously requires relatively more computation. This limitation imposes a challenge for avoiding the effects of transient initial conditions, which requires pacing the model for several beats before comparison with the data. All fittings presented in this work used 80 beats of simulation before comparison with the data in an attempt to mitigate these transient effects. A possible future improvement to CardioFit would be find ways to reduce the requirement for long simulations, such as beginning with initial conditions that may be closer to the steady-state behavior of a given parameterization. Furthermore, reproducing detailed Brugada action potential features may require fitting additional parameters, such as time constant scale factors.

As both voltage and intracellular calcium concentration data can be recorded simultaneously from optical-mapping experiments [8], an important next step for the improvement of CardioFit is the capability to fit to recorded calcium concentration data. As CardioFit is already able to fit to calcium data taken from models, the only further addition required is the capability to normalize calcium data. A complexity of normalization is that many models (including TNNP and OVVR) incorporate significantly different expected ranges of calcium concentrations in their formulations, meaning that choosing reasonable values to normalize the calcium data may pose a challenge. The addition of calcium normalization to CardioFit and a corresponding investigation of fits of these models to human voltage and calcium data is currently in progress.

Acknowledgments

This study was supported by NSF grant CNS-2028677 and by NIH grants T32GM142616 and 2R01HL143450.

References

[1] Cairns DI, Comstock MR, Fenton FH, Cherry EM. CardioFit: a WebGL-based tool for fast and efficient parametrization of cardiac action potential models to fit user-provided data. Royal Society Open Science 2025; 12(8):250048.

[2] Cairns DI, Comstock MR, Fenton FH, Cherry EM. Automated customization of cardiac electrophysiology models to facilitate patient-specific modeling. In 2023 Computing in Cardiology (CinC), volume 50. IEEE, 2023; 1–4.

[3] Rheaume E, Velasco-Perez H, Cairns D, Comstock M, Rheaume E, Kaboudian A, Uzelac I, Cherry EM, Fenton FH. A modified Fitzhugh-Nagumo model that reproduces the action potential and dynamics of the ten Tusscher et al. cardiac model in tissue. In 2023 Computing in Cardiology (CinC), volume 50. IEEE, 2023; 1–4.

[4] Uzelac I, Ji YC, Hornung D, Schröder-Scheteling J, Luther S, Gray RA, Cherry EM, Fenton FH. Simultaneous quantification of spatially discordant alternans in voltage and intracellular calcium in langendorff-perfused rabbit hearts and inconsistencies with models of cardiac action potentials and ca transients. Frontiers in Physiology 2017;8:819.

[5] Ten Tusscher KH, Panfilov AV. Alternans and spiral breakup in a human ventricular tissue model. American Journal of Physiology Heart and Circulatory Physiology 2006; 291(3):H1088–H1100.

[6] O'Hara T, Virág L, Varró A, Rudy Y. Simulation of the undiseased human cardiac ventricular action potential: model formulation and experimental validation. PLoS computational biology 2011;7(5):e1002061.

[7] Zeng J, Laurita KR, Rosenbaum DS, Rudy Y. Two components of the delayed rectifier K+ current in ventricular myocytes of the guinea pig type: theoretical formulation and their role in repolarization. Circulation Research 1995; 77(1):140–152.

[8] Uzelac I, Crowley CJ, Iravanian S, Kim TY, Cho HC, Fenton FH. Methodology for cross-talk elimination in simultaneous voltage and calcium optical mapping measurements with semasbestic wavelengths. Frontiers in Physiology 2022; 13:812968.

Address for correspondence:

Elizabeth M. Cherry
756 West Peachtree Street NW, Atlanta, GA 30332
elizabeth.cherry@gatech.edu