Reproducing Cardiac Ionic Model Properties Using a Discrete-Time Model

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Abstract

Typical differential equations-based models of cardiac action potentials (APs) may be inefficient for studying processes that occur over long time scales, such as heart rate variability and electrophysiological remodeling due to atrial fibrillation or heart failure. A discrete-time model of cardiac APs and intracellular calcium cycling may offer advantages in such settings, but correlations between continuous- and discrete-time models so far have not been developed. We used particle swarm optimization to fit the parameters of the Qu et al. discrete-time model to AP duration (APD) values over a wide range of periods for the ten Tusscher et al. (2006), Beeler-Reuter, and Fox et al. models. We found that the discrete model is capable of reproducing the APD dynamics of each model over a wide range of pacing periods including the alternans regions. Unlike the detailed ionic models, the discrete model requires only a single update step for each APD value and retains information about calcium dynamics, such as peak intracellular calcium and sarcoplasmic reticulum calcium load during the AP. Using these fittings, the discrete model may offer advantages for studying aspects of cardiac APs or calcium dynamics normally investigated through detailed ionic models at a fraction of the computational cost.

1. Introduction

Detailed models of cardiac action potentials are typically described using differential equations, with many time steps required to accurately simulate a single action potential and many equations required to be solved for a single time step update. Due to this computational requirement, simulations of cardiac cells using these models can be slow, especially when many action potentials are required to study long-term behaviors like cardiac tissue remodeling or the effects of circadian rhythms over days, weeks, or months. Although relatively simple differential equations-based ionic models may partially alleviate this computational requirement [1–3], they still require small time steps for accurate solutions and often omit important state components such as intracellular ion concentrations.

A possible alternative to differential equations-based action potential models is the use of a discrete model, such as the model developed by Qu et al. [4], which uses state variables such as action potential duration (APD) to represent the state of an entire action potential. A single iteration of this model therefore computes the behavior of an entire action potential using only the values from the previous action potential, including calcium concentrations, as an input, allowing rapid simulation of many action potentials. However, as this model differs from differential equations models in many ways, its capability to reproduce the important characteristics of cardiac cells found in other models must be established if the model is to be used in a predictive manner. The model's behavior can be adjusted using its parameters, but manually tuning the parameter values is challenging, as the model equations are highly nonlinear and the model contains many parameters.

To identify parameter regimes of the discrete model that reproduce the characteristics of popular ionic models, we used the particle swarm optimization (PSO) algorithm to fit the discrete model parameters to data taken from several such models. The resulting fits demonstrate that the discrete model can capture the rate-dependent dynamics of these models, including bifurcations to alternans.

2. Methods

Action potential duration (APD) data was recorded from the ten Tusscher et al. (2006) model [5], the Beeler-Reuter model [6], and the Fox et al. model [7]. Each model was paced using a dynamic pacing protocol in which 150 beats were simulated per cycle length, with the next cycle length set to $10\,\mathrm{ms}$ less than the previous without resetting the model state until a cycle length of $100\,\mathrm{ms}$ or block was reached. For each cycle length, APD_{90} values from the last 4 beats were recorded for fitting. All three models produced alternans for certain cycle lengths.

The discrete model proposed by Qu et al. [4] uses three state variables to represent the state of the model for each action potential: APD, sarcoplasmic reticulum calcium load, and total calcium in the cell. Other important values, such as the peak intracellular calcium concentration,

can be derived from these quantities. The model includes 22 parameters, all of which were fit for the ten Tusscher et al. and Fox et al. models. For the Beeler-Reuter model, the secondary restitution function term of the discrete model was not used by setting the parameters $A_1 = 0$, $D_1 = 1$, and $\tau_1 = 1$; the other 19 parameters were then fit.

To enable fast fittings of many data sets, we extended the CardioFit program [8] to support fitting the Qu et al. model to APD data. The PSO formulation remained unchanged from CardioFit, with the sum of relative error between the model APD output and each input APD used as the error metric. Fits were generated for entire APD rate-adaptation curves, so that a single parameterization of the discrete model was generated to fit the entire rate-adaptation curve for a given differential equations-based model.

3. Results

Fittings of the Qu et al. model were generated for three detailed ionic models using CardioFit and are shown in Figure 1, with the APD data from the ionic model in black and the fitted discrete model APDs in orange. The discrete model closely reproduces the trend of the APD data as a function of cycle length in all cases, notably reproducing the bifurcation points and APDs during alternans. Thus, the discrete model can faithfully reproduce both quantitative and qualitative aspects of the APD rate-dependence data for these three models. This result also demonstrates the utility of the PSO approach used by CardioFit for identifying such parameterizations using only the output of the ionic model.

A key concern when fitting models to data is identifiability, which is the ability for both the model and target data to constrain the optimal parameter set. Many cardiac models have poor identifiability with commonly-used types of data [9, 10]. To demonstrate how well the parameters of the Qu et al. model were constrained by the model data, Figure 2 shows the distribution of each parameter value over 50 fits to each set of model data. The parameter values were normalized over their respective bounds to facilitate comparisons; the bounds along with the means and standard deviations for all parameters are given in Table 1. Many parameters have a wide distribution in the parameter space, implying low identifiability for these parameters. On the other hand, some parameters, such as τ_0 and D_0 (which govern the steepness of the restitution curve and the location of the steep region, respectively), are constrained to small ranges of values in each fitting. The values of such parameters may be essential to reproducing the desired behavior in each case, with the other parameters possibly having little effect or having interacting effects that allow a change in one parameter value to compensate for the effect of another.

To determine which parameters had statistically significant differences in their distributions between models, we determined the p-values for each pair of parameter distributions among the models using the independent t-test. Values of $p < 0.001$ were considered significant. Only the parameters A_0 (which influences the maximum APD), D_0, and τ_0 produced distinct distributions with a high degree of confidence for every pair of models, indicating that these parameters may be the most important to capture the specific behavior of each model. Some parameters distinguished certain data sets and not others; for example, A_1 and D_1 (secondary restitution parameters) showed significant difference when comparing the ten Tusscher et al. and Fox et al. model data, while γ (Ca-to-APD coupling), κ (strength of Ca period dependence) and η (APD-to-Ca coupling) only distinguished the Beeler-Reuter model data

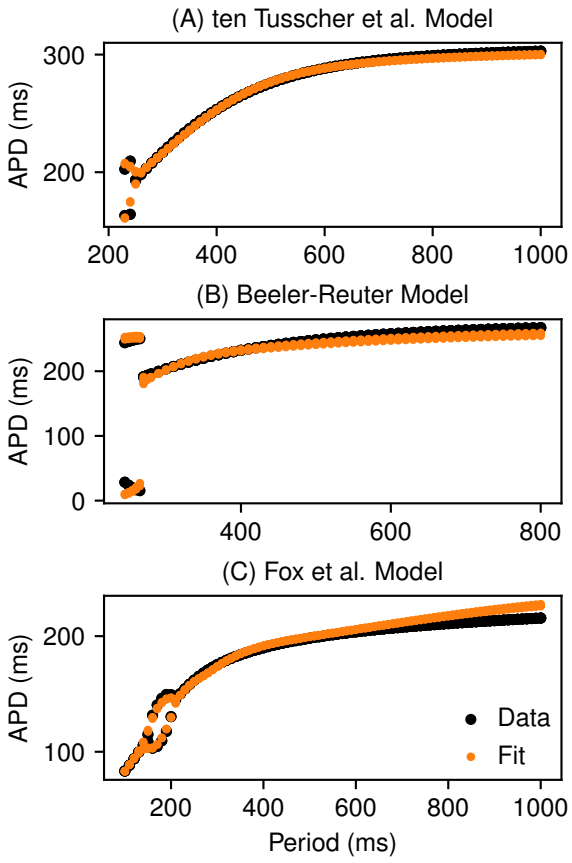

Figure 1. Fits of the Qu et al. discrete action potential model (orange) to three differential-equations models (black). 50 fits were generated using CardioFit, with the lowest-error result shown. Each fitting used 65 536 particles and 128 iterations. The discrete model was paced for 100 beats, with the last four APDs plotted. The discrete model closely reproduces the APD dynamics of the differential equations models including the alternans regions.

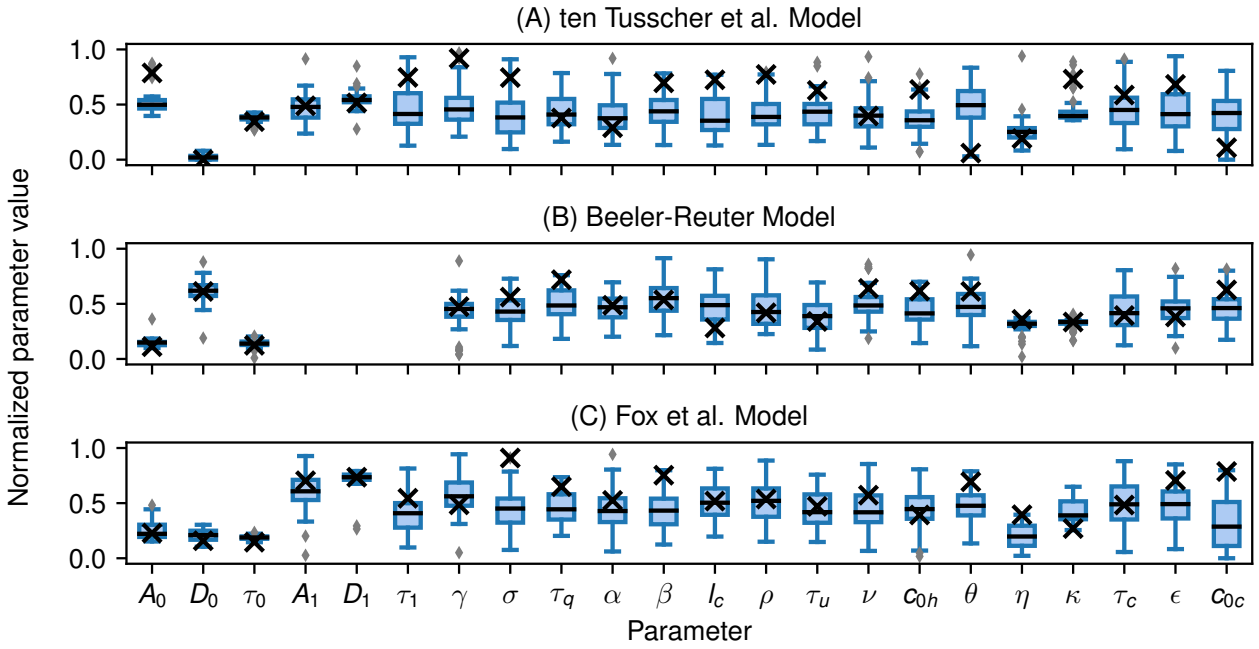

Figure 2. Distributions of parameter values from CardioFit-generated parameter sets. The value of each parameter is normalized over its range within the bounds of the parameter search space. 50 fits were generated for each differential-equations model using 65 536 particles. The normalized parameter values of the best fit parameter set are marked with a black "×". For the Beeler-Reuter model A_1, D_1, τ_1 were not fit and a lower bound of 0 was used for τ_0.

Table 1. Parameter bounds and mean values ± standard deviations (s.d.) obtained for the three datasets. For the Beeler-Reuter (BR) fits A_1, D_1, and τ_1 were set to constants and a lower bound of 0 was used for τ_0.

Parameter	Bounds	(A) ten Tusscher et al. Model	(B) Beeler-Reuter Model	(C) Fox et al. Model
A_0	100, 400	261.851 ± 37.478	143.880 ± 11.290	175.035 ± 23.294
D_0	0, 80	1.751 ± 1.638	49.448 ± 8.172	16.855 ± 3.893
τ_0	30 (BR: 0), 150	74.849 ± 3.878	46.978 ± 3.811	52.387 ± 2.295
A_1	0, 10	4.678 ± 1.224	0.000	6.055 ± 1.714
D_1	10, 100	59.361 ± 7.023	1.000	74.687 ± 8.595
τ_1	300, 800	529.238 ± 95.640	1.000	499.129 ± 81.123
γ	0, 0.01	0.005 ± 0.002	0.004 ± 0.002	0.006 ± 0.002
σ	0.4, 0.6	0.480 ± 0.036	0.488 ± 0.027	0.489 ± 0.033
τ_q	60, 100	77.156 ± 7.038	79.936 ± 5.558	78.326 ± 5.648
α	0.018, 0.054	0.032 ± 0.006	0.035 ± 0.004	0.034 ± 0.006
β	2.5, 7.5	4.700 ± 0.785	5.234 ± 0.832	4.722 ± 0.865
l_c	70.125, 150	102.851 ± 14.828	106.960 ± 12.227	111.112 ± 13.645
ρ	0, 0.75	0.312 ± 0.126	0.347 ± 0.125	0.383 ± 0.139
τ_u	150, 250	193.269 ± 15.374	189.577 ± 14.475	194.579 ± 16.381
ν	0.3, 0.5	0.380 ± 0.032	0.399 ± 0.030	0.386 ± 0.036
c_{0h}	37.5, 62.5	46.924 ± 3.740	48.392 ± 3.508	48.665 ± 4.409
θ	0, 25	12.166 ± 4.416	12.121 ± 3.978	11.894 ± 3.793
η	-0.075, 0.125	-0.024 ± 0.025	-0.014 ± 0.013	-0.034 ± 0.021
κ	-0.075, 0.125	0.017 ± 0.028	-0.011 ± 0.009	0.010 ± 0.020
τ_c	225, 375	292.962 ± 25.511	291.197 ± 23.876	301.157 ± 28.873
ϵ	1.5, 2.5	1.936 ± 0.187	1.945 ± 0.141	1.984 ± 0.171
c_{0c}	-21, 35	1.073 ± 11.713	4.471 ± 7.425	-2.526 ± 13.673

from the Fox et al. data. Additionally, η showed significant difference between the ten Tusscher et al. and Beeler-Reuter model data.

Table 2 gives information about the sum of relative APD errors found for each model. Note that these values cannot be directly compared across models, as each used a different number of data points.

Table 2. Statistics on the sum of relative APD error in ms for the 50 fits generated for each model.

Model	Min	Max	Mean $\pm$ s.d.
ten Tusscher et al.	0.891	2.031	1.138 ± 0.156
Beeler-Reuter	6.236	12.982	7.723 ± 1.342
Fox et al.	1.733	5.772	3.539 ± 0.663

4. Discussion

This work demonstrates the capability of a discrete model to quantitatively reproduce APD rate-dependence data of detailed differential equations-based cardiac models including alternans dynamics, as shown in Figure 1, using parameter-fitting approaches such as PSO. The discrete model thus has the potential to drastically speed up cardiac simulation when estimation of physiological values such as APD or peak intracellular calcium concentration are needed, but the fine-grained time resolution of continuous models is not required.

Although the Qu et al. model used in this study is capable of accurately reproducing many features of the APD rate-dependent behavior from differential equations-based models, this model has several limitations to consider. The discrete model uses 22 parameters, with many parameter changes leading to qualitative changes not thoroughly discussed in its original formulation [4]. While such parameter regimes may lead to useful model behavior, it is also possible that certain parameterizations may encounter non-physical behavior or numerical instability in certain state components. As seen in Figure 2, many parameters are not well-constrained by the current data, and may be impossible to constrain in the current formulation due to structural limitations of the model, although this limitation does not prevent CardioFit from finding parameterizations that closely reproduce the input data. Additionally, the discrete model does not include a mechanism to account for conduction block, although the model could be augmented to handle this case.

A potential future improvement to the current fitting scheme would be to include data such as peak intracellular calcium concentration, which may further constrain certain parameters. The PSO algorithm allows arbitrary error metrics, making additional types of data simple to incorporate. A challenge of this approach, particularly when fitting to model data, arises from the fact that many models produce very different calcium dynamics, which the Qu et al. model may have difficulty reproducing.

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