Quantifying Distributions of Parameters for Cardiac Action Potential Models Using the Hamiltonian Monte Carlo Method

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Abstract

Cardiac action potential (AP) models are typically given with a single set of parameter values; however, this approach does not consider variability and uncertainty across individuals and experimental conditions. As an alternative to single-value parameter fitting, we used a Bayesian approach, the Hamiltonian Monte Carlo (HMC) algorithm, to find distributions of physiological parameter values for the Mitchell-Shaeffer (MS) and Fenton-Karma (FK) cardiac AP models across a range of cycle lengths (CLs), some of which included alternans. We also calculated parameter distributions for both models using microelectrode recordings of zebrafish APs from a range of CLs. For synthetic APs generated from three CLs using the MS (FK) models, HMC produced unimodal quasi-symmetric distributions for all five (13) parameters. APs generated by setting all parameters in the MS (FK) model to the modes of their corresponding marginal distributions yielded errors in voltage traces below 5.0% (0.6%). We also obtained distributions for the MS (FK) model parameters using zebrafish data to construct the first minimal model of the zebrafish AP, with voltage trace errors below 4.8% (3.4%). Thus, we have shown that HMC can identify not only a single set of parameter values but also viable distributions for cardiac AP model parameters using synthetic and experimental data.

1. Introduction

Fitting cardiac action potential (AP) models to reproduce the dynamics of experiments is a critical task for producing trustworthy model predictions. However, experimental data are accompanied by uncertainty and variability both within and across individuals. In general, models do not account for such uncertainty in parameter values and instead use various parameter-fitting methods to obtain a single value for each parameter being fit.

Modern statistical methods approach the problem differently by seeking to obtain a multivariate distribution of the parameter values consistent with the available data. Typically, Bayesian methods are used to iteratively evolve a population of parameterizations given by a prior to obtain the target posterior distribution conditioned on the data. Markov Chain Monte Carlo (MCMC) methods are a standard approach, but traditional MCMC approaches, like Metropolis-Hastings or Gibbs sampling, become computationally infeasible as the number of parameters increases beyond a small number. One alternative is the use of an approximate Bayesian computation (ABC) method [1], where the computationally expensive step of calculating the likelihood is not needed and the target distribution obtained is an approximation of the true distribution being sought.

Although ABC approaches significantly reduce computation time compared to standard MCMC methods, it would be useful to obtain the true distribution while retaining computational efficiency. The Hamilton Monte Carlo (HMC) method [2] was developed for this purpose, but to date it has not been applied to cardiac electrophysiology data. Here we show that HMC can be used to produce a set of samples from the true distribution of parameter values for cardiac AP models in a manner that remains computationally efficient even with a moderate number of parameters.

2. Methods

We used the two-variable Mitchell-Schaeffer (MS) AP model [3] with HMC to obtain distributions for its five parameters; we also obtained distributions for the 13 parameters of the Fenton-Karma model [4]. Each model was integrated using forward Euler with an adaptive time step (0.1 ms for the first 4 ms after each stimulus, 0.5 ms otherwise). We considered both synthetic data and experimental data. To obtain the synthetic data, first, the true model parameters ($\tau_{in} = 0.3, \tau_{out} = 6, \tau_{open} = 150, \tau_{close} =$

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$120, v_{gate} = 0.13$ for MS and $\tau_r = 89, \tau_{si} = 276, \tau_d = 0.48, \tau_w^+ = 200, k = 4.5, u_c^{si} = 0.37, \tau_w^- = 215, u_v = 0.01, \tau_0 = 26, u_c = 0.17, \tau_v^+ = 44, \tau_{v1}^m = 82, \tau_{v2}^- = 589$ for FK) were perturbed by adding Gaussian noise with a mean of 0 and standard deviation of 0.1. After that, the model with the perturbed parameters was paced for 1 ms at three different cycle lengths (CLs) until reaching steady state (last 2 beats in a series of 6), one (350 ms) at a longer CL with no alternans and two (300 and 276 ms) within the alternans regime. Finally, Gaussian noise (mean zero, standard deviation 0.03) was added to the last two APs from each of the three CLs to obtain the synthetic dataset. Experimental voltage time series were obtained from zebrafish hearts following methods described previously [5]. Hearts were stimulated for a series of CLs until steady-state dynamics were achieved and included transitions to alternans. The last two APs from the same three CLs of 350 ms, 300 ms, and 276 ms were included in the final experimental dataset, with the smaller two producing alternans. Measurements were considered to include random Gaussian error with mean 0 and standard deviation σ (which was the standard deviation of added noise for the synthetic dataset and which represents uncertainty for the experimental dataset). Data points were spaced every 0.1 ms (0.5 ms) for the first 4 ms of each AP and otherwise every 15 ms (10 ms) when using the MS model with the synthetic (experimental) dataset. With the FK model, data points were 0.5 ms apart for the first 4 ms of each AP and 1 ms apart for the next 3 ms, with a spacing of 15 ms otherwise, for both datasets.

To sample from the final distribution using a full Bayesian model, we applied HMC, an MCMC method that explores the parameter space more efficiently than conventional MCMC methods like Metropolis-Hastings or Gibbs sampling; such methods typically suffer from poor scalability, random-walk behavior and correlated samples [2]. HMC uses the gradient of the posterior distribution to construct a Hamiltonian system by taking the parameters as the position variables and adding momentum variables. For this work, HMC was implemented through the No-U-Turn Sampler (NUTS) using Stan [6]. Folded normal priors were selected to avoid negative values and were centered at the true value with standard deviations of 30 percent of the true value. For all cases, we used a sample size of 500 and a warm-up period of 1000. In addition, the true values of the model used for the synthetic dataset were provided as initial points in Stan for both datasets when using the MS model; for the FK model, the initial points were $\tau_r = 110, \tau_{si} = 280, \tau_d = 0.3, \tau_w^+ = 200, k = 5, u_c^{si} = 0.45, \tau_w^- + 200, u_v = 0.01, \tau_0 = 20, u_c = 0.2, \tau_v^+ = 27, \tau_{v1}^m = 80$, and $\tau_{v2}^- = 350$.

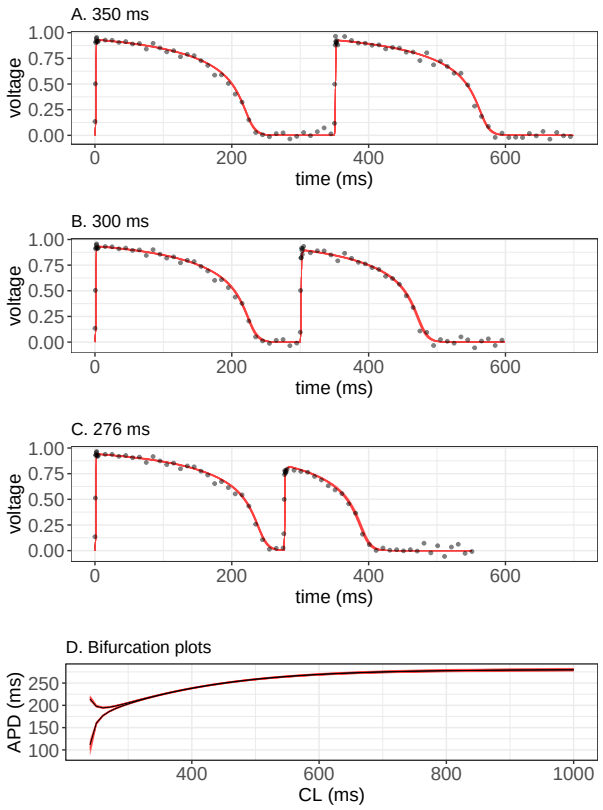

Figure 1. A-C: MS model-derived synthetic action potentials (black) and 100 action potentials obtained using MS model parameterization samples from the HMC population (red) for three CLs. D: Bifurcation plots showing APDs as a function of cycle length for the synthetic data (black) and the same samples (red) as above.

3. Results

Figure 1A-C show results for the synthetic dataset using the MS model. APs using the true values for the three CLs included in the dataset (350 ms, 300 ms, and 276 ms) are shown along with superimposed AP traces of 100 randomly selected parameter samples from the 500 samples generated using HMC. APs generated using those samples closely match the true APs well, with very little variation in AP shape and repolarization timing. A bifurcation plot using the true values for the MS model is shown in Figure 1D in black along with 100 bifurcation plots obtained using the same parameter samples as in the AP plots (red); all cases considered a minimum CL of 150 ms. Little variability is observed for CLs that were not made available to HMC, including long CLs and short CLs past the bifurcation point.

The marginal distributions of the five MS parameters are shown in Figure 2. Each distribution is unimodal and

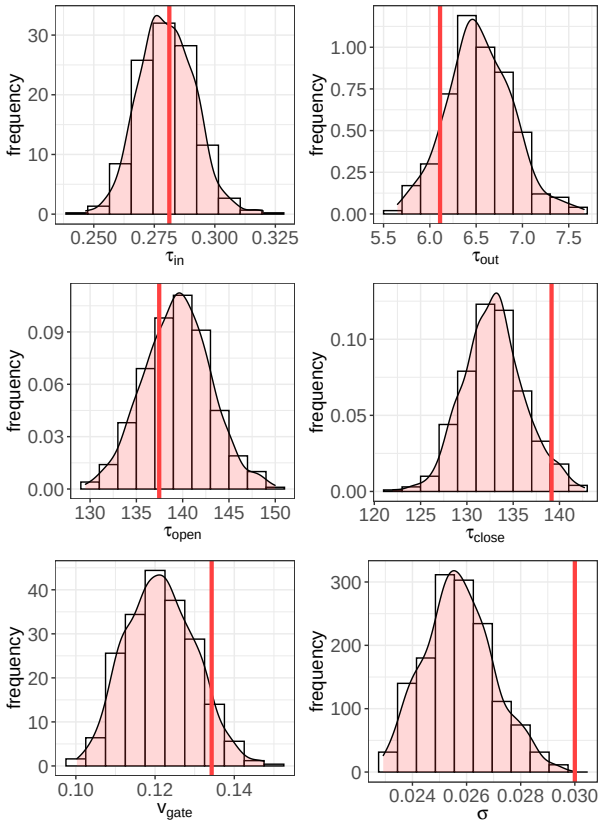

Figure 2. Distributions obtained for all five MS model parameters using HMC for the synthetic dataset along with the standard deviation σ of the noise.

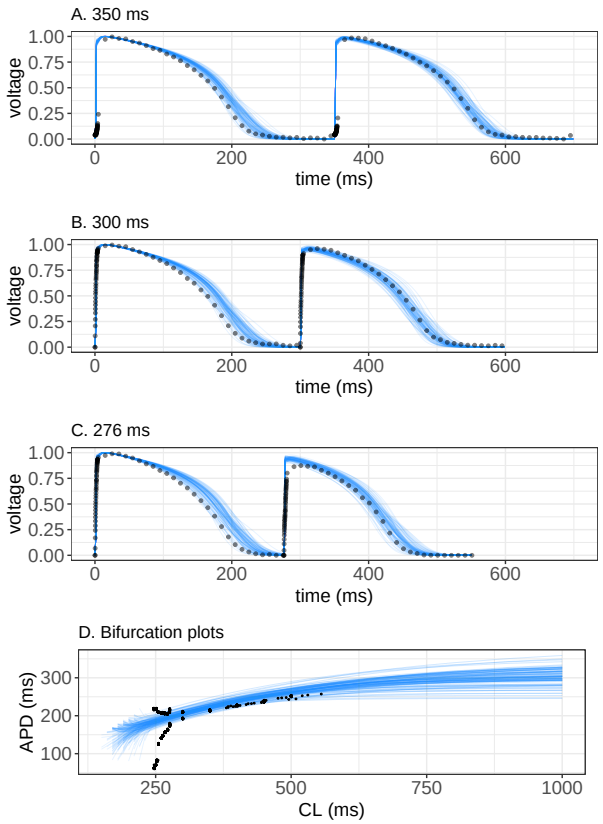

Figure 3. A-C: Normalized zebrafish action potentials (black) and 100 action potentials obtained using MS model parameterization samples from the HMC population (blue) for three CLs. D: Bifurcation plots showing APDs as a function of CL for the synthetic data (black) and the same samples as above (blue).

tightly centered around values very close to the true parameter values; the use of the same model for generating the data and for fitting, together with the simple structure of the model, cause HMC to behave more like a parameter fitting-algorithm. In addition, the standard deviation of the Gaussian noise in the observations, as estimated through HMC, is quite small, with a mean of about 0.025. HMC is able to recover the true parameters with a high level of accuracy; the mean posterior predictive values lie between the 2.5 and 97.5 percentiles. Thus, HMC is capable of recovering parameters for a model-derived dataset with a high degree of accuracy, even with multiple sources of noise included. The modes of the distributions displayed have a maximum error of 9%.

HMC's contributions beyond simple parameter fitting become more evident when considering experimental data, which may not be as well fit by the simple MS model. Figure 3A-C show zebrafish APs from three CLs (350 ms, 300 ms, and 276 ms) along with APs generated from the MS model using 100 of the 500 parameter samples generated using HMC. As in the synthetic data, alternans is present for CLs of 300 ms and 276 ms. Here good agreement is obtained but with greater variations; for example, repolarization times differ by as much as 30 ms. Figure 1D shows the bifurcation plot of the experimental data together with bifurcation plots obtained using the same parameterization samples (down to a minimum CL of 150 ms). Here again, greater variability can be seen than was observed for the model-derived dataset, especially at the longest and shortest CLs.

Marginal distributions obtained using HMC for all five MS parameters are shown in Figure 4. As with the synthetic dataset, each distribution is unimodal, but now the values are spread across a broader range. In addition, the noise standard deviation σ is about an order of magnitude larger than it was estimated to be for the synthetic dataset.

We also considered use of the FK model within HMC (results not shown) for fitting an FK model-derived dataset with APs from three CLs that included alternans as well as the same zebrafish dataset. Results were similar, with errors in voltage traces obtained using the modes of the

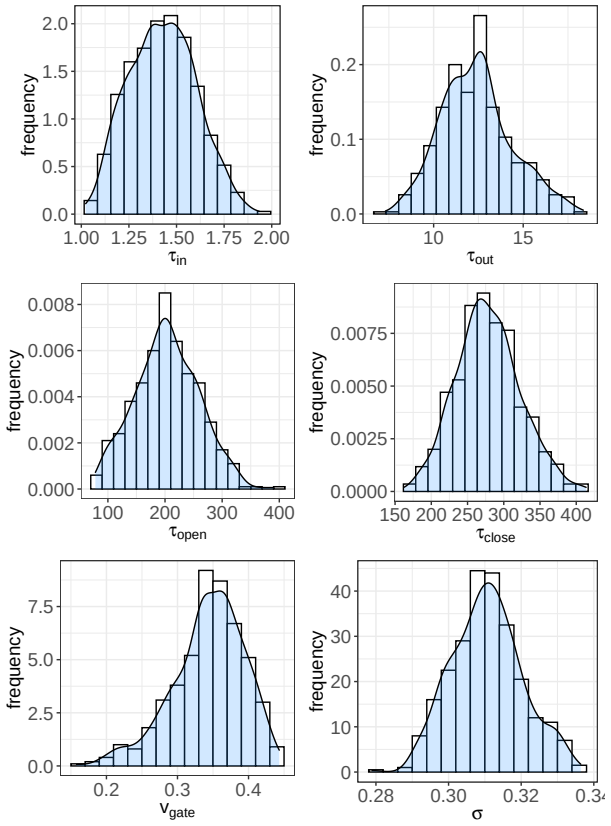

Figure 4. Distributions obtained for all five MS model parameters using the zebrafish data along with the standard deviation σ of the noise.

13 parameter distributions less than 0.6 percent. Fitting the experimental dataset in HMC with the FK model also resulted in a low level of error of 3.4%.

4. Conclusions and Future Work

In this study, we have shown that HMC can produce probability distributions of model parameters that can reproduce the shapes and dynamics of cardiac APs, including during alternans, with good fidelity. When obtaining parameter distributions for a dataset derived from the same model used by HMC, narrow distributions that include the true values within a 95 percent confidence interval were obtained, demonstrating the accuracy of the approach. For the experimental dataset, HMC also recovers unimodal distributions, but in this case they are much broader, reflecting a greater level of uncertainty. In addition, the dynamics obtained using the samples within the distribution show greater variability, especially for CLs well beyond those included in the dataset. HMC also estimated the standard deviation of the noise in the datasets, which agreed with the known value for the synthetic data and was estimated about ten times larger for the experimental dataset. We believe the larger standard deviation for the experimental dataset, despite its smoother appearance compared to the synthetic dataset, arises because the model is not a complete description of zebrafish AP dynamics. In the future, we aim to apply HMC to describe variability in the shape and duration of synthetic and experimental APs among individuals and in space and time within a single individual.

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