Identification of Parameters describing Phenomenological Cardiac Action Potential Models using Sigma-Point Methods

Jesus Fernandez-Bes[1,2], David Adolfo Sampedro-Puente[1,2], Esther Pueyo[1,2]

[1] BSICoS group, I3A, IIS Aragón, University of Zaragoza, Zaragoza, Spain
[2] CIBER-BBN, Zaragoza, Spain

Abstract

Phenomenological action potential (AP) models allow reproducing characteristic features of cardiomyocytes' electrical activity without fully describing the underlying biophysics, thus being very useful for whole-heart electrophysiological simulations. Methods to identify the parameter values of phenomenological models commonly attempt to reproduce specific AP properties rather than the whole AP waveform. In this work we propose the use of a sequential estimation approach based on sigma-point filters to adjust such parameters. The proposed methodology has been tested in estimating the parameters of the phenomenological Bueno-Cherry-Fenton model to replicate the APs generated with in silico models as well as experimentally measured APs. With the new method the whole AP waveforms can be reproduced more accurately than with previous parameter fitting methods and the AP duration restitution curves are in better agreement with available experimental data.

1. Introduction

In recent years, there has been a growing interest in the use of computational models in cardiac research to complement experimental and clinical investigations. Some of these models aim at providing detailed descriptions of cellular electrophysiology [1, 2], but they are computationally expensive, particularly for large-scale simulations of whole-heart electrophysiology. On the other hand, phenomenological action potential (AP) models [3] allow reproducing characteristic features of cardiomyocytes' electrical activity without fully describing the underlying biophysics, hence being more suitable for simulations with high computational demand. Additionally, by adjusting a number of parameters, phenomenological AP models can be used to represent different cell characteristics.

Current methods used to fit the parameter values of phenomenological models make use of non-linear optimization methods [3, 4] and attempt to replicate specific experimentally measured AP properties like duration, amplitude, upstroke velocity or restitution. In this study a novel methodology is proposed that allows identifying the parameter values of phenomenological AP models to reproduce the whole morphology of AP waveforms. We hypothesize that with this methodology not only can cellular behavior be described more accurately but also the variability among cells can be better represented.

The proposed methodology uses a sequential estimation approach based on sigma-point filters. To the best of our knowledge this is the first time that this approach is used to fit cardiac AP models, yet there has been some related research in the literature. In [5, 6] Markov Chain Monte Carlo (MCMC) methods were used to estimate the ionic conductances of AP models. Our proposed methodology involves lower computational complexity than that used in [5, 6] and additionally provides an estimation of the hidden states together with the model parameters. Other approaches based on global optimization methods, like genetic algorithms, have also been considered [7]. However, those schemes do not take into account the sequential nature of the AP data and provide no information about the underlying model dynamics. Furthermore, they do not offer confidence measurements for the estimates, as can be obtained with our proposed method.

2. Methods

2.1. Action potential data

The Bueno-Cherry-Fenton (BCF) phenomenological AP model was taken as a basis for our study [3]. It is formulated as a four-variable ordinary differential equation (ODE) system (variables u,v,w,s) with 27 free parameters that can be adapted to different cell characteristics.

In this study AP traces generated with the ten Tusscher-Noble-Noble-Panfilov (TNNP) [1] and the O'Hara-Virág-Varró-Rudy (OVVR) [2] human ventricular models were used to assess the performance of our proposed method. 50 cycles of steady-state AP data were calculated with each of the models while stimulating at 1 Hz pacing frequency.

 ISSN: 2325-887X DOI:10.22489/CinC.2017.060-109

Forward-Euler with a time step $\delta_t = 0.02$ ms was used for numerical integration.

On top of simulated data, the method was tested on experimental AP traces from an isolated human ventricular myocyte (see [8] for details on the experimental methods).

2.2. Parameter identification

The system of ODEs was casted into a non-linear discrete-time state-space model. The state-space model has the following form [9]:

$$\mathbf{x}_k = f(\mathbf{x}_{k-1}, \boldsymbol{\omega}) + \mathbf{q}_k \quad (1)$$

$$y_k = u_k + r_k \quad (2)$$

where four types of variables are involved: state variables in the vector $\mathbf{x}_k = [u_k, v_k, w_k, s_k]^T$, noise variables (process noise $\mathbf{q}_k$ and observation noise r_k), observed variable y_k (in this case the normalized AP u_k, corrupted by observation noise) and static parameters in vector $\boldsymbol{\omega}$, with elements $\omega^{(i)}$, $i \in \{1, ..., 22\}$. The observation noise r_k was assumed to be zero-mean Gaussian with variance σ_r^2. The process noise vector $\mathbf{q}_k$ was assumed to be 0. If this method were used to estimate the parameter values of a stochastic model, e.g. [4], $\mathbf{q}_k$ could be defined accordingly to represent the underlying noise process.

The Unscented Kalman Filter (UKF) [10] was used to jointly infer the state vector $\mathbf{x}_k$ and parameter vector $\boldsymbol{\omega}$. UKF belongs to the so-called Sigma-Point Filters. Compared to other methods, such as the Extended Kalman Filter, UKF is able to better capture higher order moments and, importantly, does not require differentiability of the model functions. On the other hand, UKF is less computationally intensive than techniques based on random simulation, such as MCMC methods [11]. In this study the parameters of the AP model and the hidden states that generate the data were jointly inferred by following an *state augmentation approach* (see e.g. [11, Chapter 12]). Specifically, the parameters were added to the state vector and that augmented vector was estimated. To avoid singularities in the estimation a small noise term $\boldsymbol{\epsilon}_k$ was added to the parameter vector:

$$\mathbf{x}_k = f(\mathbf{x}_{k-1}, \boldsymbol{\omega}_{k-1}) + \mathbf{q}_k \quad (3)$$

$$\boldsymbol{\omega}_k = \boldsymbol{\omega}_{k-1} + \boldsymbol{\epsilon}_k \quad (4)$$

$$y_k = u_k + r_k \quad (5)$$

The noise $\boldsymbol{\epsilon}_k$ was assumed to be Gaussian with zero mean and standard deviations $\boldsymbol{\sigma}_{\boldsymbol{\omega}}$. As parameters have very different dynamic ranges (see Table 1), the standard deviations in vector $\boldsymbol{\sigma}_{\boldsymbol{\omega}}$ were taken to be proportional to the parameter values: $\sigma_{\omega^{(i)}} = \gamma\omega^{(i)}$, where γ is selected to trade off a good learning rate and small steady-state oscillations.

2.3. Performance assessment

The ability of the method to fit an input AP trace was evaluated in terms of the Root Mean-Squared-Error (RMSE), defined as:

$$\text{RMSE} = \sqrt{\frac{1}{N}\sum_{n=0}^{N-1}\left[V(n) - \widehat{V}(n)\right]^2} \quad (6)$$

where N is the number of samples, V is the input AP and $\hat{V}$ is the AP calculated with the estimated values of the BCF model parameters.

Additionally, the performance of the method was assessed by comparing the S1-S2 AP duration (APD) restitution curve calculated with the estimated parameter values for the BCF model and the experimental restitution data measured in [12]. The S1-S2 APD restitution curves calculated with the TNNP model [1] and with the BCF model using the parameter values derived in a previous study [3] were also evaluated for comparison purposes.

3. Results

3.1. AP shape

The values of the BCF model parameters that led to best fitting of the AP traces generated with the TNNP [1] and OVVR [2] models as well as obtained experimentally from an isolated cell [8] are presented in Table 1 (third, fourth and fifth columns). In the second column, the parameters values estimated in [3] for the TNNP model are reproduced as a reference for comparison with our proposed model. As can be seen, there are significant differences between our method and the method proposed in [3] for some parameters, e.g. τ_{fi} or τ_{o1}, whereas other parameters are only slightly different. While in Table 1 the mean value of the parameters estimated with our UKF-based method are presented, an additional advantage of this method is that it provides uncertainty measures reflecting the confidence of the algorithm in those values.

The AP traces calculated with the BCF model using our estimated parameter values are presented in Fig. 1 (a)-(c) for the three sets of tested input data. Corresponding RMSE values are shown in Table 2. For the input AP data generated with the TNNP model, the RMSE associated with the method proposed in this study is notably lower than the RMSE of the method used in [3]. These differences can be appreciated in Fig. 1 (a), where our method provides a more reliable estimate of the input AP shape.

3.2. APD restitution

Fig. 2 presents the S1-S2 APD restitution curves calculated with the BCF model using the sets of parame-

Table 1. Parameter values of the BCF model estimated for different sets of input data.

Input Data	TNNP AP		OVVR AP	Experim. AP
Estimation	Study [3]	This study	This study	This study
τ_{v1}^-	60	59.11	60.19	37.257
τ_{v2}^-	1150	1078	1150	1.0263
τ_v^+	1.4506	2.442	2.7842	1.8218
τ_{w1}^-	70	61.686	59.024	53.268
τ_{w2}^-	20	20.1	15.05	13.089
τ_w^+	280	126.172	108.47	290.83
k_w^-	65	66.41	64.8	83.227
u_w^-	0.03	0.03	0.011	0.042
τ_{fi}	0.11	0.98	0.754	0.987
τ_{o1}	6	307.884	303.31	309.87
τ_{o2}	6	9.532	9.967	9.883
τ_{so1}	43	36.018	47.97	197.694
τ_{so2}	0.2	0.163	0.101	0.122
k_{so}	2	3.397	2.21	1.064
u_{so}	0.65	0.988	0.998	0.375
τ_{s1}	2.7343	2.88	3.01	4.486
τ_{s2}	3	19.619	19.94	2.14
k_s	2.0994	3.688	1.3885	1.775
u_s	0.9087	0.851	0.998	0.387
τ_{si}	2.8723	3.376	3.842	19.693
$\tau_{w\infty}$	0.07	126.172	0.009	0.471
w_∞^*	0.94	0.827	0.787	0.976

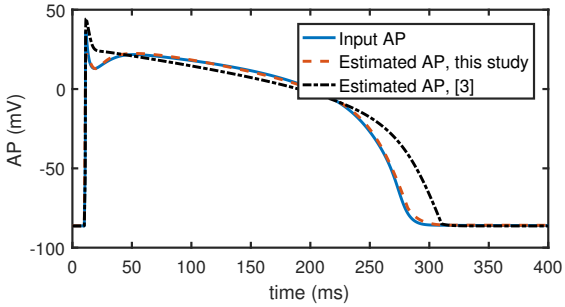
Table 2. RMSE of the reproduced potentials

	TNNP AP		OVVR AP	Experim. AP
	Study [3]	This study	This study	This study
RMSE	6.49 mV	1.115 mV	1.572 mV	2.9856 mV

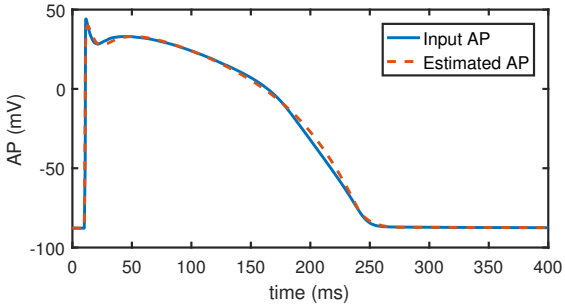
ter values estimated in this study and in [3] when fitting data generated with the TNNP model. Also, the restitution curve calculated with the TNNP model and the experimental data from Morgan *et al.* [12] used in [1] to fit their model are plotted for comparison. As can be observed, our UKF-based method reproduces the experimental APD restitution data more accurately than the method used in [3], especially for higher diastolic intervals (DIs).

4. Discussion

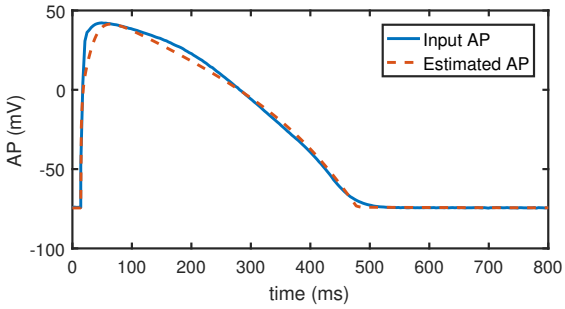
According to the results presented in this study, our proposed UKF-based method is able to identify the values of the relatively large number of BCF model parameters to reproduce specific AP shapes. Taking as input the AP trace generated with the TNNP model, our method notably outperforms a previously proposed approach based on nonlinear constrained optimization [3] in reproducing both the steady-state AP waveform and the APD restitution curve. Additionally, our method is able to reliably replicate the shapes of the APs generated with another human ventricular cell model, namely the OVVR model, as well as human ventricular APs recorded experimentally. In future studies, the proposed method can be used to fit data from a population of cells, thus allowing to have accurate representations of the characteristics of individual cells. Such *in silico* representations can be of great utility to perform realistic tissue and whole-heart simulations at an affordable cost for arrhythmia investigations.



(a) Fitting of AP trace generated with the TNNP model [1].



(b) Fitting of the AP trace generated with the OVVR model [2].



(c) Fitting of experimental AP data (see [8]).

Figure 1. Input AP traces of human ventricular cells (blue) and estimated AP traces using the BCF model with the parameter values calculated in this study (dashed red). In (a) the results of [3] are presented for comparison (dashed-dotted black).

In this work 22 out of the 27 parameters of the BCF model were estimated. The thresholding parameters u_u, θ_v, θ_w, θ_v^- and θ_0 were not estimated due to the lack of smoothness in the solution space. Future studies can deal with estimation of these parameters e.g. by using a method that iterates between MCMC methods or Genetic algorithms (not requiring any level of smoothness in the solutions) and UKF, rather than by using the *state augmentation approach* considered in this study [13]. This would,

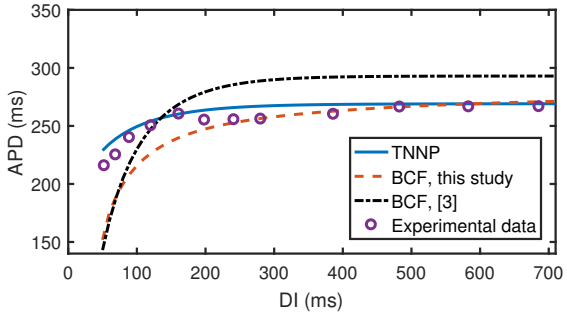


Figure 2. S1-S2 APD restitution curves for human ventricular cells calculated with the TNNP model (solid blue) and with the phenomenological BCF model using the parameter values estimated in [3] (dashed-dotted black) and in this study (dashed red). Experimental measurements from [12] are also included.

however, significantly increase the algorithm complexity.

Introduction of those additional thresholding parameters might lead to more accurate fitting of the left part of the S1-S2 restitution curve corresponding to very small DIs. Future studies should be undertaken to further investigate how the methodology proposed in this study could be extended to improve such fitting.

5. Conclusions

A novel methodology based on sigma-point filters has been proposed to identify the parameter values of phenomenological cardiac cell models, allowing to replicate whole AP waveform morphologies. The proposed methodology has been successfully tested using human ventricular APs generated with biophysically detailed models (TNNP and OVVR models) as well as recorded experimentally.

Acknowledgements

This work was supported by projects TIN2013-41998-R and DPI2016-75458-R from Spanish Ministry of Economy and Competitiveness (MINECO), Spain, MULTI-TOOLS2HEART from CIBER-BBN through Instituto de Salud Carlos III, Spain, European Social Fund (EU) and Aragón Government through BSICoS group (T96) and by the European Research Council (ERC) through project ERC-2014-StG 638284. The work of D. A. Sampedro-Puente is supported by a personal grant from Aragón Government and EU funds. Computations were performed using the ICTS NANBIOSIS, more specifically the High Performance Computing Unit of CIBER-BBN at the University of Zaragoza.

References

[1] ten Tusscher KH, Noble D, Noble PJ, Panfilov AV. A model for human ventricular tissue. Am J Physiol Heart Circ Physiol 2004;286(4):H1573–89.

[2] O'Hara T, Virág L, Varró A, Rudy Y. Simulation of the undiseased human cardiac ventricular action potential: Model formulation and experimental validation. PLoS Comput Biol 2011;7(5).

[3] Bueno-Orovio A, Cherry EM, Fenton FH. Minimal model for human ventricular action potentials in tissue. J Theoretical Biol 2008;253(3):544–560.

[4] Walmsley J, Mirams G, Bahoshy M, Bollensdorff C, Rodriguez B, Burrage K. Phenomenological modeling of cell-to-cell and beat-to-beat variability in isolated guinea pig ventricular myocytes. 2010 Int Conf IEEE Eng Med and Biol Soc EMBC10 2010;1457–1460.

[5] Johnstone RH, Chang ETY, Bardenet R, de Boer TP, Gavaghan DJ, Pathmanathan P, Clayton RH, Mirams GR. Uncertainty and variability in models of the cardiac action potential: Can we build trustworthy models? J Mol Cell Cardiology 2016;96:49–62.

[6] Johnstone RH, Bardenet R, Gavaghan DJ, Polonchuk L, Davies MR, Mirams GR. Hierarchical Bayesian modelling of variability and uncertainty in synthetic action potential traces. Comput in Cardiology 2017;43:1089–1092.

[7] Syed Z, Vigmond E, Nattel S, Leon LJ. Atrial cell action potential parameter fitting using genetic algorithms. J Med Biol Eng and Comput 2005;43(5):561–571.

[8] Pueyo E, Corrias A, Virág L, Jost N, Szél T, Varró A, Szentandrássy N, Nánási PP, Burrage K, Rodríguez B. A multiscale investigation of repolarization variability and its role in cardiac arrhythmogenesis. Biophysical J 2011;101(12):2892–2902.

[9] Wilkinson DJ. Stochastic modeling for systems biology. CRC press, 2011.

[10] Wan E, Van Der Merwe R. The unscented Kalman filter for nonlinear estimation. Proc IEEE 2000 Adapt Sys Signal Process Commun and Cont Symp 2002;153–158.

[11] Särkkä S. Bayesian filtering and smoothing, volume 3. Cambridge Univ. Press, 2013.

[12] Morgan JM, Cunningham D, Rowland E. Dispersion of monophasic action potential duration: Demonstrable in humans after premature ventricular extrastimulation but not in steady state. J Am Coll Cardiol 1992;19(6):1244–1253.

[13] Kokkala J, Solin A, Särkkä S. Expectation maximization based parameter estimation by sigma-point and particle smoothing. In 2014 17th Int. Conf. Inf. Fusion (FUSION). IEEE, 2014; 1–8.

Address for correspondence:

Jesus Fernandez-Bes
I3A, Edificio I+D [5.1.01b], c/ Mariano Esquillor
50018 Zaragoza, Spain.
jfbes@unizar.es