Parameter estimation for a phenomenological model of the cardiac action potential

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Abstract

The action potential (AP) of a cardiac cell is made up of a complex balance of ionic currents which flow across the cell membrane in response to electrical excitation of the cell. Mathematical models of the action potential have grown increasingly complex and include many subcellular phenomena such as calcium handling and complex Markov formulations of the gating dynamics of the ion channels. The fitting of parameters to such models has seen a large degree of parameter and module re-use from earlier models. An alternative method for modelling electrically exciteable cardiac tissue is a phenomenological model, which reconstructs tissue level AP wave behaviour without subcellular details.

We use some techniques for parameter estimation to fit the morphology of the AP in the four variable Bueno-Orovio phenomenological model. We establish an approximation of a nonlinear ordinary differential equation model that corresponds to the given phenomenological model of the cardiac action potential. The parameter estimation problem is converted into a minimisation problem for the unknown parameters. A modified hybrid Nelder-Mead simplex search and particle swarm optimization is then used to solve the minimisation problem for the unknown parameters. We demonstrate the successful fitting of data generated from a well known biophysically detailed model. We also show that we can produce a successful fit to an experimental AP recording that contains both noise and experimental artefacts. The

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parameter estimation method's ability to fit a complex morphology to a model with substantially more parameters than previously used is established.

Contents

1 Introduction

Constructing and fitting parameters to a model of the electrical activity of a cardiac cell is a highly complex and difficult process. The action potential (AP) of a cardiac cell is made up of a balance of voltage sensitive ionic currents that flow across the cell membrane in response to electrical excitation of the cell. Mathematical models of the AP of a ventricular myocyte, the most common electrically active cell in the heart, may feature as many as 67 variables [4] and include many subcellular phenomena such as calcium handling and complex Markov formulations for the gating kinetics of the ion channels. The fitting of parameters to large biophysically detailed models has increasingly seen a large degree of parameter and module re-use from earlier models [10] which may be inconsistent in factors such as species or the temperature of the experiment performed. Often the data required to parameterize and validate a model for a particular current in the species in question cannot be found within the literature as it is either difficult or impossible to obtain, too time consuming to generate or of insufficient interest to experimentalists. Given a valid parameter set, such models often need to be refitted to different regions of the same heart which can exhibit heterogenetity electrophysical properties, such as the conductances of various currents and the overall morphology of the AP. This refitting is problematic, given that the number of unknown parameters may be large.

An alternative method for modelling cardiac tissue is a phenomenological model [1, 3], which seeks to reconstruct the behaviour of the AP without resorting to the use of a biophysically detailed model. Properties such as AP morphology, dynamic restitution (the change in AP duration in response to stimulus frequency) and conduction velocity restitution (the change in AP velocity with stimulus frequency when propagating through tissue) may all be fitted using this approach given appropriate experimental data from microelectrode or optical mapping experiments. The resulting model may then be used to investigate tissue level phenomena such as spiral waves during ventricular fibrillation.

We will propose a new parameter estimation technique to fit the morphology of the AP in the four variable Bueno-Orovio phenomenological model [1]. The problem is of interest from the perspective of parameter estimation extimation as well as cardiac modelling. We have a parameter space of large dimension (29 parameters) over a wide range which have effects at different time points during the action potential. In published parameter sets such as those in [1, 11] we see large ranges in the values of parameters. Furthermore, some parameters have a well defined role in defining the AP morphology, whereas others control other properties such as dynamic restitution and thus have little effect on morphology. The parameter surface of the model therefore has regions of low and high sensitivity which vary with dimension and size of the parameter. The ordinary differential equations themselves are stiff with a large gradient in potential at the upstroke where a stimulus current is applied.

The parameter estimation of the model is converted into a minimisation problem for the unknown parameters. A modified hybrid Nelder-Mead simplex search and particle swarm optimization is then used to minimise the objective function. This is discussed further in Section 3. Finally, we use both data generated from the Luo-Rudy model [6] paced at both 500ms and 1000ms cycle lengths, and also experimental recorded AP from an isolated guinea pig ventricular myocyte [11] as target data for our minimisation process and assess the success of the procedure by reference to a least squares objective function.

2 Model structure

The work presented in this section is based on the [1] phenomenological model of the ventricular AP. We have chosen this form of the Fenton-Karma type phenomenological models as the additional fourth variable provides the flexibility required to fit a wide variety of experimentally observed AP mor-

phologies, whereas earlier versions such as [3] were unable to reproduce AP morphology satisfactorily. As we focus on AP morphology this fidelity is our overriding concern.

We describe the model [1] in its entirety here. The model consists of a total of four variables, u, v, w and s. u is the dimensionless voltage variable which is rescaled to dimensions of mV using the formula $V_{mV} = Vu + R$. As u generally takes the value 0 at rest, R is in effect the rest potential of the data, that is to say the transmembrane potential at which the cell sits at steady state when exposed to no external stimulus at physiological extracellular ionic concentrations. The model equations are as follows:

$$\frac{\partial u}{\partial t} = \nabla\big(D\nabla u\big) - (J_{fi} + J_{so} + J_{si} + J_{stim}), \tag{1}$$

$$\frac{\partial v}{\partial t} = (1 - H(u - \theta_v))(v_\infty - v)/\tau_v^- - H(u - \theta_v)v/\tau_v^+, \tag{2}$$

$$\frac{\partial w}{\partial t} = (1 - H(u - \theta_w))(w_\infty - v)/\tau_w^- - H(u - \theta_w)w/\tau_w^+, \tag{3}$$

$$\frac{\partial s}{\partial t} = ((1 + \tanh(k_s(u - u_s)))/2 - s)/\tau_s, \tag{4}$$

where H is the Heaviside function. The currents J_{fi}, J_{so} and J_{si} are given as follows:

$$J_{fi} = - vH(u - \theta_v)(u - \theta_v)(u_u - u)/\tau_{fi}, \tag{5}$$

$$J_{so} = (u - u_o)(1 - H(u - \theta_w))/\tau_o + H(u - \theta_w)/\tau_{so}, \tag{6}$$

$$J_{si} = - H(u - \theta_w)ws/\tau_{si}, \tag{7}$$

and J_{stim} is the applied stimulus current. Furthermore, some of the time constants themselves depend on the membrane potential as follows

$$\tau_v^- = (1 - H(u - \theta_v^-))\tau_{v1}^- + H(u - \theta_v^-)\tau_{v2}^-, \tag{8}$$

$$\tau_w^- = \tau_{w1}^- + (\tau_{w2}^- - \tau_{w1}^-)(1 + \tanh(k_w^-(u - u_w^-)))/2, \tag{9}$$

$$\tau_{so} = \tau_{so1} + (\tau_{so2} - \tau_{so1})(1 + \tanh(k_{so}(u - u_{so})))/2, \tag{10}$$

$$\tau_s = (1 - H(u - \theta_w))\tau_{s1} + H(u - \theta_w)\tau_{s2}, \tag{11}$$

$$\tau_o = (1 - H(u - \theta_o))\tau_{o1} + H(u - \theta_o)\tau_{o2}. \tag{12}$$

The steady state values are given as

$$v_\infty = \begin{cases} 0, & u < \theta_v^- \\ 1, & u \geq \theta_v^- \end{cases} \tag{13}$$

$$w_\infty = (1 - H(u - \theta_o))(1 - u/\tau_{w\infty}) + H(u - \theta_o)w_\infty^*. \tag{14}$$

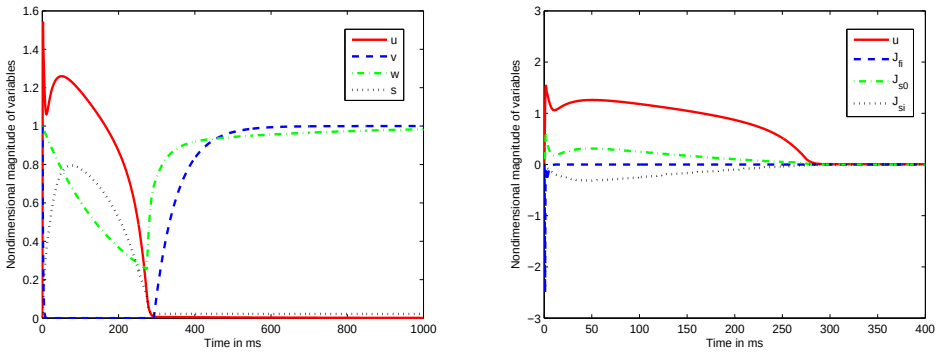

Figure 1: Simulated data using the epicardial data set provided by [1] after 5 stimuli to reach steady state at a pacing frequency of 1000ms. The values of the variables of the model u, v, w and s and the values of the currents J_{fi}, J_{so} and J_{si} over the same AP are shown. Note that the x axis on the right hand plot has been rescaled to enhance visibility of the current morphologies.

The model employs a diffusion term in Equation (1) and so is similar to the monodomain equations used to simulate cardiac electrophysiology for biophysically detailed models. However, in the course of simulation in [1], diffusion is taken to be constant at $1.171\text{cm}^2/\text{s}$, based on experimental measurements of human ventricular cell size and conductances. Thus, the relation in (1) becomes the Laplacian as we can move the constant diffusion coefficient outside of the gradient operator. It should be noted that this model can equally well take into account factors such as fibre orientation by setting the diffusion parameter D to be a conductivity tensor, at which point this property will no longer hold [3]. As we are concerned only with AP morphology in this paper we set $D = 0$.

The currents represent an approximation to groups of currents observed in the cell rather than having any definite biophysical meaning. The behaviour of the model is shown in Fig. 1 using the human epicardial cell parameter set from [1] in response to a stimulus current of non-dimensional magnitude -0.5 and of duration 2ms. We show the behaviour of the potential u, the gating variables v, w and s and the currents J_{fi}, J_{so} and J_{si}. We use the same stimulus magnitude and duration for the parameter fitting process.

Most parameters in the model have well defined meanings in the context of the shape of the action potential.

This model is able to reproduce physiological properties such as maximum velocity of upstroke, threshold of excitation, action potential morphology, dynamic restitution curves and conduction velocity restitution curves.

3 Parameter estimation technique

In science and engineering applications there are broad classes of inverse problems that can be described as problems that seek to go backwards from measurement data sets to estimated parameter values, such as, for example, specific rates of reactions for compounds. The parameter estimation literature features many papers by researchers seeking the rates of some chemical reactions or to determine approximate values of the coefficients in the differential equations governing a particular phenomenon [1]. Nonlinear differential algebraic equations are an important class of models for dynamical processes. To establish models that describe the process behavior in a quantitatvely correct way, parameters in the model often have to be determined from observations or measurements of the processes [1].

Some nonlinear programming methods have been applied to solve the global optimization of continuous-variable functions. For example, Gauss-Newton method [8]. Searching a continuous-variable function under a given search domain must locate global optimum without being trapped in local solutions. Optimization techniques can be classified into two broad categories: traditional direct search techniques (such as simplex search methods) and evolutionary techniques (such as the particle swarm optimization). The Nelder-Mead (NM) method [9] is a simple direct search technique that has been widely used in various unconstrained optimization scenarios. One of the reasons for its popularity is that the method is easy to implement and does not need the derivatives of the function under exploration. However, one has to be very careful when using the NM method since it can be sensitive to the choice of initial points and is not guaranteed to attain the global optimum. Eberhart and Kennedy [2] proposed a new heuristic algorithm called particle swarm optimization (PSO). The theory of PSO lets each particle fly through a multidimensional search space while the particles' velocity and position are constantly updated based on the best previous performance of the particle and of the particles' neighbours, as well as the best performance of particles in the entire population. PSO has been successful in optimizing various continuous nonlinear functions, including nonlinear unknown parameters and unknown domains of parameters.

In this section, we propose a new parameter estimation techniques, i.e., a modified hybrid Nelder-Mead simplex search and a particle Swarm optimization method to fit the morphology of the AP in the four variable Bueno-Orovio phenomenological model.

The governing deterministic dynamical system can be written as the following differential algebraic equations with m unknown parameters of the

form:

$$\frac{dy(t)}{dt} = f(t, y, \lambda_1, \lambda_2, \cdots, \lambda_m), 0 \leq t \leq T, \quad (15)$$

$$y(0) = y^0, \quad (16)$$

where $y = (y_1, y_2, \cdots, y_n)^T$ and $f = (f_1, f_2, \cdots, f_n)^T$ are n-dimensional vector functions, f_i $(i = 1, 2, \cdots, n)$ may be nonlinear with respect to the unknown parameters $\lambda_i, (i = 1, \cdots, m)$, m is the number of parameters, n is the number of species.

In this work, we used the differential/algebraic system solver (DASSL) [5] as our ODE solver. DASSL is based on the backward difference formulas (BDF). DASSL approximates the derivatives using the k^{th} order BDF, where k ranges from one to five. At every step it chooses the order k and stepsize based on the behaviour of the solution.

We assume that $(\lambda_1, \lambda_2, \cdots, \lambda_m) \in R$, where R is a bounded domain of the form:

$$R = [\lambda_1^{(min)}, \lambda_1^{(max)}] \times [\lambda_2^{(min)}, \lambda_2^{(max)}] \times \cdots \times [\lambda_m^{(min)}, \lambda_m^{(max)}]. \quad (17)$$

Let $y_i(t_k)$ be given target solutions of (15) and (16), while the $y_{i,k}$ are numerical solutions of (15) and (16) using DASSL for given $\lambda = (\lambda_1, \lambda_2, \cdots, \lambda_m)$ $\in R$. The error of the given parameter vector $\lambda^* = (\lambda_1^*, \lambda_2^*, \cdots, \lambda_m^*) \in R$ of (15) is determined by

$$\underline{g}(\lambda^*) = \underbrace{\min}_{\lambda \in R} \underline{g}(\lambda) = \underbrace{\min}_{\lambda \in R} \left\{ \frac{1}{n} \sum_{i=0}^{n} \left[\sqrt{\frac{\sum_{k=0}^{N} (y_i(t_k) - y_{i,k})^2}{N+1}} \right] \right\} \quad (18)$$

where $T = N\tau$, τ is a time step.

We focus on a modified hybrid Nelder-Mead simplex search and a particle Swarm optimization method that tries to find a potential global minimum $\underline{g}(\lambda^*)$ of a multimodal, continuous-variable function in (15).

The novel MH-NMSS-PSO is based on the Nelder-Mead simplex search method (NMSS) [9] and the particle swarm optimization (PSO) algorithm [2] for the optimization of multimodal functions. The NMSS focuses on "exploitation"; the PSO focuses on "exploration". The first major difference between NMSS and PSO is the choice of initial points. In the NMSS, the initial points are pre-determined, but they are a set of random points in PSO. The second difference is with the directions and conditions of the preceding steps. The PSO proceeds by moving towards those points that have better (objective) function values, whereas the NMSS evolves by moving away from a point that has the worst performance.

Taking the better characteristics of each method, we propose a modified hybrid Nelder-Mead simplex search and particle swarm optimization method.

An initial population, $3m+1$ particles, is constructed in two parts. Firstly, the standard starting point is used in the NMSS to form an initial simplex of $m+1$ particles, and an additional $2m$ particles are randomly generated in the PSO part. The population of $2m$ particles in the PSO part may be a worthy investment as they may bring about an early convergence to the vicinity of the global optimum.

A total of $3m+1$ particles are sorted by their objective function value $\underline{g}(\lambda^*)$ in (18), and the best m particles are saved for subsequent use in the simplex search part of the hybrid method. Joined by the m best particles and the $(m+1)^{th}$ particle, the last $2m$ particles are adjusted by the PSO method (i.e., selection and velocity update). The procedure for adjusting the last $2m$ particles involves selection of the global best particle, selection of the neighborhood best particles, and finally velocity updates.

The modified hybrid Nelder-Mead simplex search and particle Swarm optimization (MH-NMSS-PSO) algorithm can be summarized in Algorithm 3.1.

Input: Intervals $R = [\lambda_1^{(min)}, \lambda_1^{(max)}] \times [\lambda^{(min_2, \lambda_2^{(max)}]}$ $\times \cdots \times [\lambda_m^{(min)}, \lambda_m^{(max)}]$ to seach for solution within, initial velocities, given targe solutions $y_i(t_k)$, $(i = 1, \cdots, m;\ k = 1, \cdots, n)$, the error parameter ϵ and the number of iterations N_{iter}.

Output: The best parameter estimation values $\lambda^* = (\lambda_1^*, \lambda_2^*, \cdots, \lambda_m^*)$.

Generate a population of size $3m+1$;

for $IT = 1 : N_{iter}$ **do**

(i) Evaluation and Ranking: evaluate the objective function value $\underline{g}(\lambda)$ in (18) of each particle;

(ii) Nelder-Mead simplex search method: apply a NMSS operator to the best $m+1$ particles and replace the $(m+1)^{th}$ particle with the update;

(iii) Particle Swarm Optimization: apply the PSO operator for updating $2m$ particles with the worst objective function value;

if *the stopping criterion* $S_c < \epsilon$ **then**

break;

end

end

Algorithm 3.1: MH-NMSS-PSO.

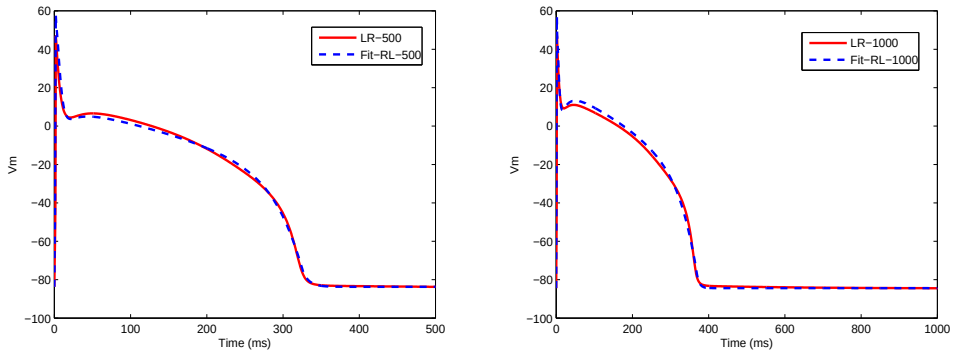

Figure 2: A comparison of the deterministic model obtained by refitting the parameters of the original model [1] to a sample action potential generated by the Luo-Rudy model at cycle lengths of 500ms and 1000ms.

The stopping criterion is then defined by

$$S_C = \left[\sum_{i=1}^{m+1} \frac{(\bar{g} - \sqrt{g_i})^2}{m+1} \right]^{\frac{1}{2}} < \epsilon, \tag{19}$$

where $g_i^* = \underline{g}(P_i) = \sqrt{g_i} = \sqrt{g_i(\lambda_{1,i}, \lambda_{2,i}, \cdots, \lambda_{m,i})}$; $\bar{g} = \sum_{i=1}^{m+1} \frac{g_i^*}{m+1}$ and ϵ is a small error parameter.

All numerical methods and MH-NMSS-PSO have been implemented in Fortran 77 on a PC.

4 Application to parameter estimation for a phenomenological model of the cardiac action potential

In this section, the MH-NMSS-PSO algorithm and numerical technique are employed to estimate the parameters for the phenomenological model of the AP described in Section 2. We give the ranges for our parameter estimation based on [1].

Example 1: Fitting Luo-Rudy 500ms data and Luo-Rudy 1000ms data

Using the MH-NMSS-PSO algorithm and numerical technique, we obtain parameter estimates to fit the phenomenological model to data generated by the Luo-Rudy model [6] paced at both 500ms and 1000ms cycle lengths. The dimensionless voltage variable u is rescaled to dimensions of mV using the equation $V_{mV} = Vu + R$ to produce the final fits to the data that are shown

Table 1: Fitted parameter values

Pa	LR 500	LR 1000	GP	Pa	LR 500	LR 1000	GP
θ_v	0.4509	0.3647	0.3200	θ_w	0.0917	0.1265	0.1300
θ_v^-	0.0000	0.0060	0.1900	θ_0	0.0000	0.0003	0.0060
u_s	0.9185	0.9324	0.9800	u_w	0.0000	0.0251	0.0175
u_{s0}	0.7785	0.6324	0.7072	u_u	1.9180	1.7530	1.6200
u_0	0.0000	0.0000	0.0000	τ_w^∞	0.09323	0.0865	0.0410
τ_{01}	571.000	521.2769	456.3476	τ_{02}	8.8481	6.6474	6.1000
τ_{s1}	4.1762	2.7342	3.0600	τ_{s2}	12.5582	13.2947	2.1900
τ_{s01}	44.1989	56.4735	30.9000	τ_{s02}	1.3781	1.2295	1.2874
τ_{w1}	58.2595	53.2368	6.1828	τ_{w2}	18.2595	125.8942	140.000
τ_{v1}	85.8577	71.7017	76.0000	τ_{v2}	973.0652	13.4584	10.300
τ_{si}	5.0682	3.8715	2.7844	τ_v^+	2.5500	2.1623	1.3500
τ_w^+	371.0585	348.6196	276.000	τ_{fi}	0.2369	0.1809	0.1100
w_∞^*	0.8523	0.8266	0.8430	k_{s0}	2.2857	2.0647	2.0100
k_w	61.9641	152.3928	206.9896	k_s	2.0874	2.0952	2.8100
V	77.5000	81.6499	276.000	R	-83.720	-84.400	-76.100

in Fig. 2. The estimated parameter values are listed in Table 1. Here Pa denotes parameter and GP denotes Guinea Pig.

Example 2: Fitting to experimental data

Using the MH-NMSS-PSO algorithm and numerical technique, we obtain parameter values to fit the phenomenological model to an experimentally recorded AP from an isolated guinea pig ventricular myocyte paced at a cycle length of 1000ms. The experiment was conducted in accordance with the UK Home Office guidance on the Operation of Animals (Scientific Procedures) Act of 1986. For further details of the experimental protocol used see [11]. The estimated parameter values are shown in Table 1. The dimensionless voltage variable u is rescaled to dimensions of mV using the equation $V_{mV} = Vu + R$ to produce the final fit to the experimental data, shown together with nondimensional magnitude of current variables in Fig. 3.

The simulations produced give an excellent agreement with both the generated AP morphologies from the Luo-Rudy model and the experimental data.

5 Conclusions

We have demonstrated that the modified hybrid Nelder-Mead simplex search and particle swarm optimization is valid for the fitting of AP morphology in a cardiac electrophysiology tissue model. We have shown the closeness of fit

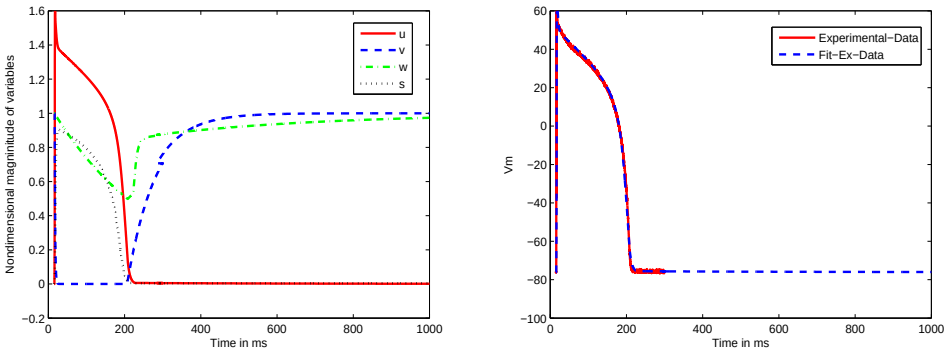

Figure 3: A comparison of the deterministic model obtained by refitting the parameters of the original model to a sample action potential drawn from the experimental data for a guinea pig isolated ventricular myocyte.

achieved by the model to data both artificially generated from a biophysically detailed cardiac electrophyslogy model and experimental data taken from ventricular myocytes both in isolation and in tissue. Restitution is not recovered adequately, but we did not set out to achieve this. This is shown by the variation in parameters between the 500ms and 1000ms columns in Table 1. We would ideally seek one set of parameters to describe both sets of data. The different results obtained indicate that fitting the model to an AP morphology derived from one cycle length is insufficient to fully parameterise all aspects of the model using this method. Extra data at different cycle lengths will be required to do this. We observe that the program runs to a successful completion in a few minutes for the initial parameter ranges. However, the efficacy of our approach is very much dependent on how we choose our initial ranges for the parameters. These techniques can be applied to the parameter estimation of other kinds of differential algebraic equations.

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