Parameter Estimation of a 3D Cardiac Electrophysiology Model Including the Restitution Curve Using Optical and MR Data

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PARAMETER ESTIMATION OF A 3D CARDIAC ELECTROPHYSIOLOGY MODEL INCLUDING THE RESTITUTION CURVE USING OPTICAL AND MR DATA

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ABSTRACT

Personalisation of a cardiac electrophysiology model is crucial not only to understand and simulate the actual dynamics of pathologies such as arrhythmia, but also to predict the behaviour of the heart in a therapeutic environment. In this paper, we present personalisation of a simplified ionic 3D cardiac electrophysiology model, the Mitchell-Schaeffer model (2003), for single and multiple heart rates. The personalisation is performed using the epicardial depolarisation and repolarisation maps obtained *ex-vivo* from optical imaging of large porcine healthy heart. First, we present a method to personalise the model to a constant heart rate, thus estimating the model parameters that could result in model predictions similar to the actual clinical data at the given heart rate used for personalisation. Next, we show a method to personalise the model to the observed actual spatial dispersion of the action potential duration restitution property in order to have model predictions more similar to the clinical data also at multiple heart rates.

1. INTRODUCTION

Building computational models of the human body has been an important research topic for the last few decades. In order to have sufficiently accurate model predictions in the clinical applications, there is a huge need of model personalisation, which is defined as the estimation of the model parameters that gives model simulations similar to the actual clinical data. Cardiac electrophysiology model personalisation is essential to develop predictive models that can be used to improve therapy planning and guidance. For instance, Radiofrequency (RF) ablation therapy on patients suffering from atrial fibrillation (AF) and ventricular tachycardia (VT) has only 50% success rate due to non availability of clinical consensus on optimum RF ablation patterns. Whereas personalised cardiac electrophysiology models could help understand the actual underlying mechanisms and dynamics involved in the formation of the wavebreaks causing AF and VT. Hence it could provide optimum RF ablation patterns leading to an increase in the success rate of RF ablation therapy. In this paper, we propose one personalisation method for cardiac electrophysiology model at a constant heart rate and an extended personalisation approach to the actual spatial dispersion of the action potential duration (APD) restitution at multiple heart rates. APD restitution is defined as the relationship of the succeeding APD with the preceeding diastolic interval (DI). The spatial dispersion, heterogeneity and slope of the APD restitution is one of the cause leading to the maintenance and stability of arrhythmia [1]. The personalisation is done using the fusion of high quality *ex-vivo* optical and MR imaging data.

A variety of mathematical models describing the cardiac electrophysiology have been developed and simulated at various scales. These models can be categorised into three main categories: Ionic models (IM), Phenomenological models (PM) and Eikonal models (EM). IM [2] characterise ionic currents flowing through the cardiac cell membrane and usually involve many parameters and variables, making it not well suited to solve inverse problem. However they do have analytic biological interpretation of the parameters and their influence on the behaviour of the model. EM [3] are very simple, describing only the time at which a depolarisation wave reaches a given point and does not precisely model the reaction parts of the cardiac electrical phenomenon. At the intermediate level are PM [4], which describe the action potential generation and propagation along the cell membrane, and are divided into mono-domain, modeling the transmembrane potential variable, and bi-domain modeling the intra- and extra-cellular potential variables. Authors have focused recently on estimation of parameters using EM [5] and PM [6], on 2D surface, using PM on 3D volume [7]. In this paper, we personalise one simplified IM, the Mitchell-Schaeffer (MS) model [9], described by two nonlinear ordinary differential equations for transmembrane potential variable and a gating variable for sodium current depicting the repolarisation phase. We chose to use this model because of the following reasons: (i) It has benefits of an ionic model, (ii) It has a few number of parameters to estimate, (iii) It is more efficient for personalisation compared to the PM model [8] and (iv) It has explicit formulae for maximum APD and APD restitution, which is later proven to be highly beneficial in parameter estimation. In our approach, the electrophysiology model is spatially integrated using a 3D tetrahedral mesh of the myocardium created from MR images taking into account the fibre orientation as well, and is temporally integrated using an optimum time integration scheme.

In summary, the main contributions of this paper are: (i) a personalisation method for a 3D cardiac electrophysiology model to constant heart rate, and (ii) an extended personalisation approach to multiple heart rates taking into account the actual spatial dispersion of APD restitution.

2. ELECTROPHYSIOLOGY MODEL SIMULATION

MS Model MS model [9] is a simplified ionic model derived from the Fenton Karma (FK) ionic model. FK model [9] has three ordinary differential equations corresponding to sodium, potassium and calcium currents, but the MS model contains two ODEs correspond-

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ing to sodium and potassium currents:

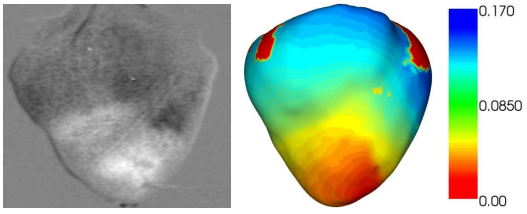
$$\left\{ \begin{array}{rcl} \partial_t u & = & div(D\nabla u) + \frac{zu^2(1-u)}{\zeta_{in}} - \frac{u}{\zeta_{out}} + J_{stim}(t) \\ \partial_t z & = & \left\{ \begin{array}{ll} \frac{(1-z)}{\zeta_{open}} & if \quad z < z_{gate} \\ \frac{-z}{\zeta_{close}} & if \quad z > z_{gate} \end{array} \right. \end{array} \right. \tag{1}$$

u is a normalised transmembrane potential, and z is the gating variable for sodium ion influx which depicts the repolarisation phase. $J_{in} = (zu^2(1-u))/\zeta_{in}$ represents the combination of inward sodium current which raises the action potential voltage and $J_{out} = -u/\zeta_{out}$ represents the outward potassium current that decreases the action potential voltage describing repolarisation. J_{stim} is the stimulation current, at the pacing location. The parameters ζ_{open} and ζ_{close} control the repolarisation variable, with ζ_{close} directly related to the APD.

The diffusion term in the model is controlled by the diffusion tensor D. This spatial diffusion can be related to a pseudo-conductivity. In the longitudinal direction of the fibre, this pseudo-conductivity is set to d which is one of the parameters we adjust, and to $d/2.5^2$ in the transverse directions. The electrophysiology model is solved spatially over a volumetric tetrahedral mesh of the left and right ventricles using the finite elements method, and in time using an optimum time integration scheme as Modified Crank-Nicolson/Adams-Bashforth (MCNAB) scheme, which is evaluated in terms of accuracy, stability and computational time [8].

3. OPTICAL AND MR IMAGE DATA

In this paper we performed the adjustments using optical recordings obtained on a healthy porcine heart. The explanted hearts were attached to a Langendorff perfusion system which permits to maintain the electrophysiological integrity of the hearts over 1-2 hours. The



(a) (b)

Fig. 1. (a) Raw optical signal (anterolateral view) showing action potential wave (white) and (b) Volumetric myocardial mesh generated from MR data, with projected depolarisation time isochrones (in s) derived from filtered optical data.

fluorescence dye (reflecting directly the changes of transmembrane potential) and the electro-mechanical uncoupler were injected into the perfusion line (more details are given in [10]). The heart was paced with an electrode by delivering square pulses of duration 5 ms, near the apex. The fluorescence signals are captured with high temporal (270 fps) and spatial ($< 1mm$) resolution, using a pair of CCD cameras (BrainVision Jp). At the completion of the optical experiment, the hearts were imaged using MR imaging for anatomy. A volumetric mesh was generated from the images with the INRIA softwares CGAL and GHS3D, resulting in a tetrahedral geometry. Diffusion Tensor Imaging was also used to estimate the fiber directions. The optical images recorded by the 2 CCD cameras were used to reconstruct a 3D stereoscopic surface of the heart. Several opaque markers were glued onto the epicardium to provide a way to register the optical images with the surface of the model generated from MR images. We estimated a rigid transformation between the optical and MR markers by minimising the least-square differences. We then projected the isochronal maps onto the registered volumetric mesh from MR Imaging with an interpolation from the triangular stereoscopic surface. For the adjustment to multiple heart rates, we used the similar optical data of another healthy porcine heart but recorded with a range of pacing frequencies f $(0.5, 0.7, 0.9, 1.1$ and 1.2 Hz)

4. PERSONALISATION METHOD

Estimation of the model parameters that result in a simulation which is similar to the measured data is defined as personalisation. Firstly, we present a method to personalise the model to a single heart rate and next, we present an extended personalisation approach to the multiple heart rates.

4.1. Personalisation to single heart rate

Here, we match the depolarisation and repolarisation time isochrones derived from the optical data to those obtained from the model simulation by optimising two model parameters. The adjustment of d in order to match the depolarisation isochrones is achieved in two successive phases (Calibration and Iterative Adjustment) while ζ_{close} is estimated in a direct manner.

Calibration. This step is used to initialise the model parameter values using analytical relationships between the measures and the parameters. The calibration function used here is similar to [7] and is given as $c(d) = \alpha\sqrt{d} + \beta$, where c is the conduction velocity and the constants α and β are determined by performing several model simulations for a range of d and computing corresponding c, and then fitting the function in non-linear least squares sense to the measures c. Once the relationship is estimated, it is used to determine the initial parameter value d for the median value of c computed for the actual reference data.

Iterative Adjustment. This step is used to optimise the d parameters with calibration result as initial guess. In order to keep computations reasonable, we divide the left ventricle into 17 zones as defined by American Heart Association and a similar division of 9 zones for the right ventricle, when an iterative adjustment is performed. The algorithm used here is a trust region method which finds the minimum of a subproblem, such as a quadratic model created using gradient and approximate hessian matrix at the current search point, and which is implemented using the Trilinos solver package. Here we use an objective function that minimises the difference between the simulated and measured depolarisation times by iteratively adjusting the d parameter value for each zone.

For ζ_{close}, the maximum action potential duration for a single cardiac cycle is directly given by the model [9] as follows: $APD = \zeta_{close}\log(1/h_{min})$ where $h_{min} = 4\zeta_{in}/\zeta_{out}$. As we only have one measured apd available from the data, we choose to adjust ζ_{close}, while keeping the other parameter values from the literature [9]. It is defined by the model that c has no relationship with ζ_{close}, which provides no coupling between the action potential duration and the conduction velocity. Thus we can simultaneously adjust parameter d and ζ_{close}. The defined relationship between ζ_{close} and APD remains valid also in 3D thus allowing us to directly estimate locally at each vertex, the parameter ζ_{close} without calibration and iterative adjustment.

4.2. Personalisation to multiple heart rates

In order to have valid model predictions for different heart rates, it is important to adjust the model conduction velocity and APD restitution to the actual restitution of the heart. Parameter estimation using the ECG-based restitution curves have been studied for the MS model [11]. Here, we present a method to personalise the cardiac electrophysiology model to the observed APD restitution phenomenon from the optical data. Thus we can have the model predict similar APD results to the actual data at different pacing frequencies. One of the advantages of the MS model is that it has an explicit formula for the APD restitution curve derived from the model, and is given as follows:

$$f(DI_n) = APD_{n+1} = \zeta_{close} \ln \left(\frac{1-(1-h_{min})e^{-\frac{DI_n}{\zeta_{open}}}}{h_{min}} \right) \quad (2)$$

where APD_{n+1} is the succeeding action potential duration and DI_n is the preceding diastolic interval at time instant n. Using the optical data of one pacing frequency f, we extract APD_{n+1} and DI_n for all pixels M having valid data. Each extracted pixel i has the APD_{n+1} - DI_n relationship given as: $APD^i_{n+1} = CL - DI^i_n$ where cycle length $CL = 1/f$. The same is done for all given pacing frequencies $N = 4$ (except 0.9 Hz). This relationship is shown by the negative slope of APD_{n+1} for all pixels at each f as shown in Fig.5. Next, for each corresponding pixel i over the range of pacing frequencies $j = 1$ to N, we fit the analytical restitution curve using the nonlinear least squares method which minimises the error between $f(DI^j_n)$ computed using (2) and APD^j_{n+1} extracted from the optical data. The objective function is defined as,

$$\min_{\theta} \sum_{j=1}^{N} (f(DI^j_n, \theta) - APD^j_{n+1})^2 \quad (3)$$

where $f(DI^j_n, \theta)$ corresponds to (2) and $\theta = [\zeta_{close}, h_{min}, \zeta_{open}]$ is the estimated parameter vector.

5. RESULTS

Before personalisation of the model, the simulations are computed with the parameter values given from literature.

Action Potential Duration. The mean absolute error on apd before personalisation is $159.5ms$ ($\approx$ 40% of apd), reduced to $8.72ms$ ($\approx$ 2%) after personalisation to single heart rate and with direct estimation of the parameter ζ_{close} locally, as shown in Fig.2.

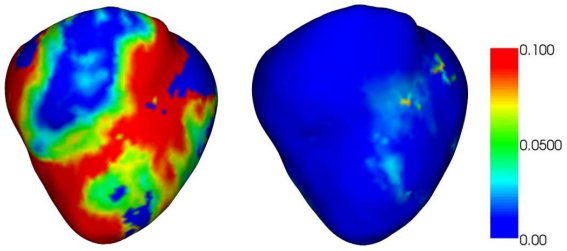


Fig. 2. Action potential duration error maps (in s) (a) before and (b) after personalisation to single heart rate

Depolarisation time. Before personalisation, the mean absolute error on the depolarisation time is $58.9ms$ ($\approx$ 30% of depolarisation duration), which reduces to $5.1ms$ ($\approx$ 2%) with adjustment of the parameter d for single heart rate.

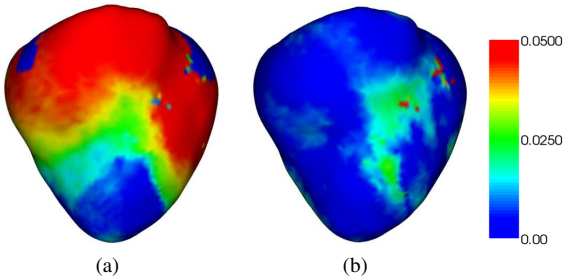


Fig. 3. Depolarisation time error maps (in s) (a) before and (b) after personalisation to single heart rate

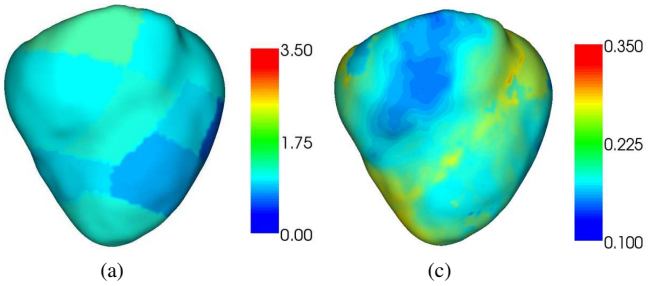


Fig. 4. Maps of estimated (a) parameter d and (b) parameter ζ_{close} with personalisation to single heart rate

APD Restitution. The absolute mean square error over all pixels, after personalisation to multiple heart rates is $0.58ms$, which implies a good fit of the restitution curves as shown in Fig.5. The parameters estimated using the optical data are then projected on the volumetric mesh for further analysis as given in Table.1 and in Fig.7 With these parameter values, we predict the steady-state APD for another pacing frequency 0.9 Hz, which is not used for personalisation to multiple heart rates. Fig.6 shows the mean steady-state APD for LV and RV with pacing frequency 0.9 Hz. Whereas Fig.8 shows a comparison of the APD error map for steady-state APD prediction at heart rate 0.9 Hz, with personalisation to multiple heart rates and with personalisation to a single heart rate.

Parameter	LV		RV	
	Mean	Std.Dev.	Mean	Std.Dev.
ζ_{close}	0.1880	$\pm$0.0012	0.1808	$\pm$0.0006
h_{min}	0.2406	$\pm$0.0006	0.2301	$\pm$0.002
ζ_{open}	0.4477	$\pm$0.0104	0.6188	$\pm$0.0267

Table 1. Mean and standard deviation of estimated parameter values with personalisation to multiple heart rates (0.5, 0.7, 1.1, 1.2 Hz)

6. DISCUSSION AND CONCLUSION

The first part of this work presented personalisation of the model to a single heart rate. This approach helps us simultaneously estimate two parameters d and ζ_{close} controlling the conduction velocity and the APD respectively. The model simulations using these estimated parameters would be similar to the actual clinical data but only for that particular heart rate, which was used to personalise the model.

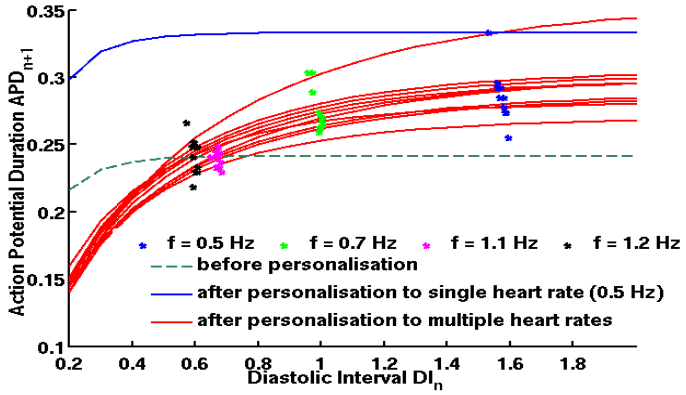


Fig. 5. Extracted APD-DI values (crosses, for 10 pixels) and analytical restitution curves before and after personalisation to single and multiple heart rates , values in s

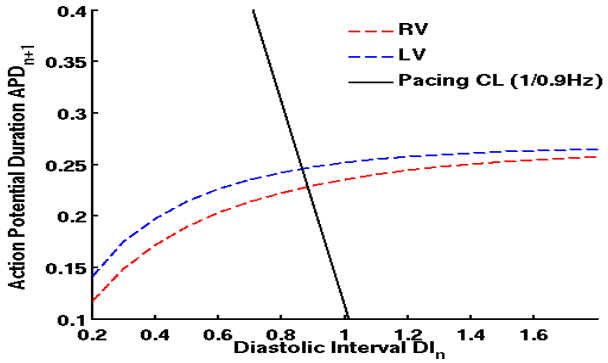


Fig. 6. Mean analytical restitution curves for LV and RV using the parameters (Table.1), and Cycle Length (CL) for heart rate 0.9 Hz

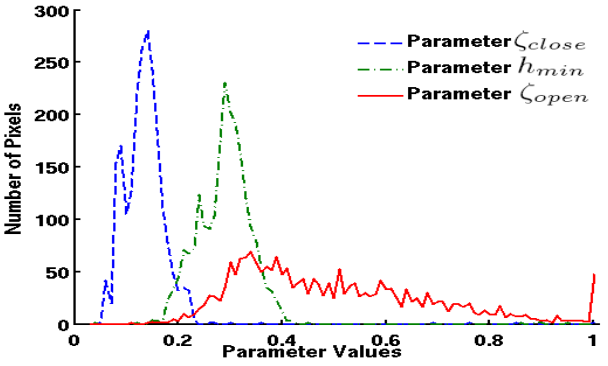


Fig. 7. Histogram of parameter values over both ventricles

However in order to adapt the model to the actual APD restitution property of the cardiac cells and have valid model predictions for different heart rates, the second part of this work presented an extended approach which estimates three parameters ζ_{close}, ζ_{open} and h_{min}. Estimated parameters ζ_{close} and h_{min} have a quite homogenous distribution over LV and RV. Whereas parameter ζ_{open} which controls the slope of APD restitution, is different for LV and RV, thus causing APD difference for LV (longer) and RV (shorter), also shown by Fig.6. Adapting the simulated restitution curve to the actual restitution curve is crucial to understand the mechanisms and dynamics of pathologies such as arrhythmia and ventricular tachycardia. Also it could produce model predictions similar to the actual pathological data. Future steps would be to study the correlation between the spatial heterogenity of APD restitution and electrical alternans and to adjust the parameters to the actual conduction velocity restitution, in order to have better model predictions.

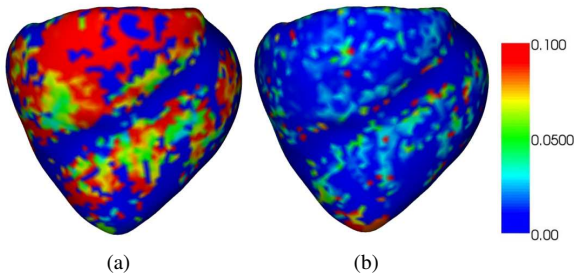


Fig. 8. Action potential duration error maps (in s) for steady-state APD prediction at pacing frequency 0.9 Hz, (a) with personalisation to single heart rate (0.5 Hz) and (b) with personalisation to multiple heart rates (0.5, 0.7, 1.1, 1.2 Hz)

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