

# Personalization of Atrial Electrophysiology Models from Decapolar Catheter Measurements

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**Abstract.** A novel method to characterize biophysical atria regional ionic models from multi-electrode catheter measurements and tailored pacing protocols is presented. Local atria electrophysiology was described by the Mitchell and Schaeffer 2003 action potential model. The pacing protocol was evaluated using simulated bipolar signals from a decapolar catheter in a model of atrial tissue. The protocol was developed to adhere to the constraints of the clinical stimulator and extract the maximum information about local electro-physiological properties solely from the time the activation wave reaches each electrode. Parameters were fitted by finding the closest parameter set to a data base of 3125 pre computed solutions each with different parameter values. This fitting method was evaluated using 243 randomly generated in silico data sets and yielded a mean error of  $\pm 10.46\%$  error in estimating model parameters.

**Keywords:** Electrograms · Computational models personalization · Multi-electrode catheters

## 1 Introduction

Computational models represent a novel framework for studying pathologies of the human atria and offer a pathway for selecting patients and personalizing treatment, [1, 2]. Of particular interest is the study of atrial fibrillation (AF), a pathology where the underpinning mechanisms triggering and maintaining the arrhythmia are not known. The use of increasingly sophisticated electro anatomical mapping systems, high fidelity imaging techniques and inverse ECG methods has significantly improved patient outcomes [3]. These improved diagnostic modalities are still only able to provide information on the current state of the patient and are unable to provide predictions of the outcome of treatments.

Biophysical modeling provides a formal framework that combines our understanding of atria physiology, physical constraints and patient measurements to make quantitative predictions of patient response to treatment. These models have provided fundamental insight into the mechanisms that underpin arrhythmia's in the ventricle and the atria, [4] but their potential to inform clinical procedures had been limited by their inability to capture the significant variability in physiology inherent both between and within AF patients.

The aim of this study is to develop and test a robust and rapid pacing protocol and a model fitting method that allow for local characterization of cellular biophysical parameters and electrophysiology restitution within patients atria. Validation of the pacing protocol will be presented in Sect. 3. Validation of the method proposed here is purely based on synthetic data. Application to experimental data will be a topic of a future work.

## 2 Method

### 2.1 Computational Model

The first step of the method proposed is to build a data set of restitution curves for each permutation of a set of parameters known a priori. A numerical model describing the action potential propagation across the left atrium tissue is implemented. The model is then used to reproduce electrogram signals from the poles of a decapolar catheter when an ectopic pacing stimulus is applied to the central poles. The procedure for building the restitution curves is described in Sect. 2.2.

Atria tissue electrophysiology was modeled by the mono-domain equations [5], a simplification of the bi-domain model, [6] when intra- and extra-cellular conductivities are considered proportionals up to a constant,  $\lambda$ . Due to assumed local symmetry and negligible thickness in the atrium the model was reduced to a 1D fiber model as follows:

$$\frac{\partial v_m}{\partial t} - \sigma_m \frac{d^2 v_m}{dx^2} = I_{\text{ion}} + I_{\text{app}} \quad (1)$$

$$\sigma_m = \frac{\lambda}{1 + \lambda} \quad (2)$$

where  $I_{\text{ion}}$  is an external applied stimulus, while  $I_{\text{ion}}$  characterize the ionic currents defined by the ionic model, [7].

Substituting the mono-domain approximation into the extra-cellular potential equilibrium equation, and simplifying the conductivity it follows that:

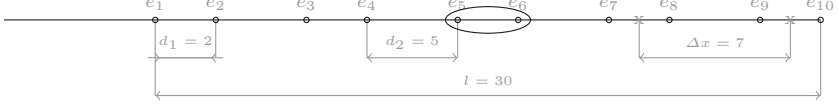
$$\begin{aligned} \sigma_i \frac{d^2 v_m}{dx^2} + (\sigma_i + \sigma_e) \frac{d^2 \phi_e}{dx^2} &= 0 & \sigma_e &= \lambda \sigma_i \\ \sigma_i \frac{d^2}{dx^2} (v_m + (1 + \lambda) \phi_e) &= 0 & & \\ \frac{d}{dx} (v_m + (1 + \lambda) \phi_e) &= \text{const} & & \end{aligned} \quad (3)$$

where  $\phi_e$  represents the extra-cellular potential,  $v_m$  the trans-membrane potential,  $\sigma_i$  the intra-cellular conductivity and  $\sigma_e$  the extra-cellular conductivity. The constant term appearing on the right-hand side of (3) is fixed by imposing a zero spatial mean on the extra-cellular potential:

$$\phi_e = -\frac{1}{1 + \lambda} (v_m - \bar{v}_m)$$

where  $\bar{v}_m$ , denotes the spatial mean of the trans-membrane potential.

The catheter configuration and the catheter dimensions are depicted in Fig. 1; bipolar signals were evaluated as the difference of the extra-cellular potentials between a pair of electrodes spaced by a distance  $d_1$ .



**Fig. 1.** Decapolar catheter configuration and dimensions. Dimensions are expressed in mm. The pacing stimulus is applied to the central poles, highlighted by the gray ellipse. Bipolar poles are determined by the pairs:  $(e_1, e_2)$ ,  $(e_3, e_4)$ ,  $(e_5, e_6)$ ,  $(e_7, e_8)$ ,  $(e_9, e_{10})$

Ionic currents were described using the Mitchell Schaefer 2003 (MS), [7] ionic current model. Despite its simplicity, the MS model captures the Effective Refractory Period (ERP) and the Conduction Velocity (CV) restitution with a minimal number of parameters. The MS model has four parameters that describe the opening ( $\tau_{\text{open}}$ ,  $\tau_{\text{in}}$ ) and closing ( $\tau_{\text{close}}$ ,  $\tau_{\text{out}}$ ) rate of the fast activation and slow repolarization currents respectively.

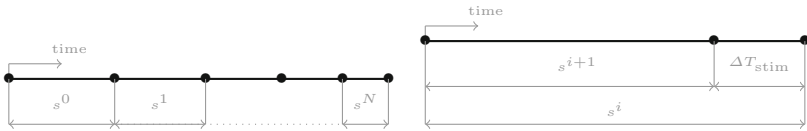
## 2.2 Pacing Protocol and Restitution Curves

Atria were paced from the central poles  $(e_5, e_6)$  of the decapolar catheter depicted in Fig. 1; activations were measured at proximal and distal poles,  $(e_1, e_2)$ ,  $(e_3, e_4)$ ,  $(e_7, e_8)$ ,  $(e_9, e_{10})$ .

The initial (maximum) inter-beat interval was fixed at  $s^0 = 700$  ms and the minimum inter-beat interval  $s_{\text{min}} = 200$  ms, for each decrement step  $\Delta T_{\text{stim}}$  the inter-beat delay  $s^{i+1}$  is defined recursively as:

$$\begin{aligned} s^{i+1} &= s^i - \Delta T_{\text{stim}}, & i &= 1, \dots, N \\ (s^N - s_{\text{min}}) &= \min(s^i - s_{\text{min}}, (s^i - s_{\text{min}}) \geq 0 \end{aligned} \quad (4)$$

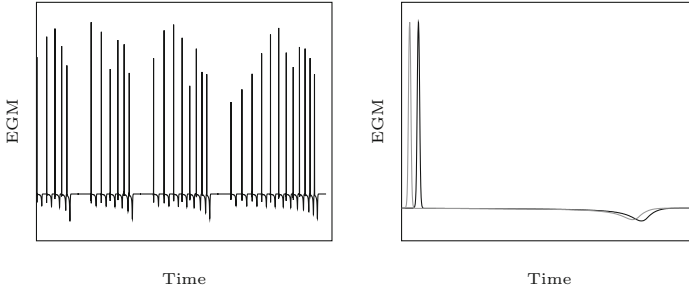
and depicted graphically in Fig. 2.



**Fig. 2.** Inter-beat sequence. Left: the sequence generated by the recursion defined in (4). Right: definition of the  $(i + 1)$ -th pacing interval as a function of the previous one.

In this work, values of  $\Delta T_{\text{stim}} = (100, 80, 60, 40, 20, 10)$  ms were chosen.

For each bipolar pair the Non-Linear Energy Operator (NLEO), [8], was evaluated between two subsequent stimulations. In Fig. 3 (left) the output of a bipolar electrode is depicted; in the same Figure (right) activations are showed.



**Fig. 3.** Example of output of a bipolar electrode (left) and particular for two subsequent electrodes. Peaks corresponds to activations.

The time of maximal NLEO was defined as the activation time. We have assumed that we do not have access to repolarization times as these can not be observed reliably in an atria electrogram. Repolarization times were available in [9], when a mono phasic action potential catheter was used to make recordings. In the absence of repolarization times we estimate the ERP by identifying when activation fails to propagate for a given inter-beat interval.

CV was evaluated as the ratio between the distance  $\Delta x$  defined in Fig. 1 and the time elapsed during which the activation front propagates from one electrode to the subsequent one.

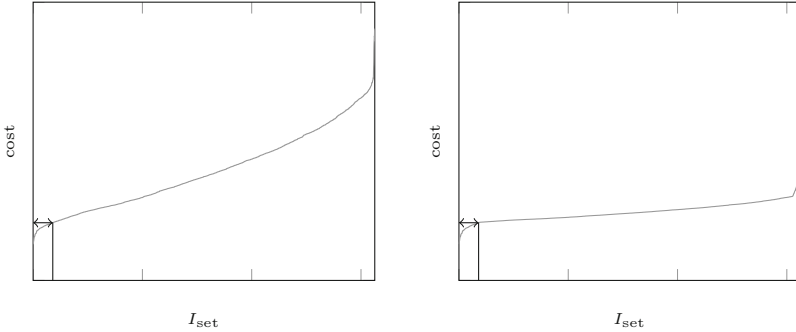
### 2.3 Parameter Fitting

A data base of simulation results for 3125 combinations of model parameters was created for the pacing protocol described above. The data base was created once on an HPC in approximately one hour and a half. The range of parameter values explored in the data set are described in Table 1. Restitutions were then evaluated for each member of the data base.

The parameter fitting is performed in two steps. First, for each member of the data set a cost  $C_1$  is evaluated as the sum of the mean square difference of the “measured” and the data base CV on each electrode and for each pacing decrement. A monotone  $C_1$  cost function is then obtained by re-ordering the data set. A subset of  $N_1$  solutions is chosen that have a  $C_1$  cost below a cut off value. The cut off is the minimum of a defined cost function value (Fig. 4 left panel) or the cost function where the derivative is less than the modulus of the cost function derivative, to avoid plateau regions (Fig. 4 right panel).

**Table 1.** Parameter values used for building the data set

	Conductivity (S/cm)	$\tau_{in}$ (ms)	$\tau_{out}$ (ms)	$\tau_{open}$ (ms)	$\tau_{close}$ (ms)
Min	0.001	0.225	4.5	75	120
Max	0.003	0.375	7.5	125	180
Step	0.0005	0.0375	0.75	12.5	15



**Fig. 4.** Example of cost function and choice of candidate subset. Left panel: cost criteria determined by a maximum cost value; this happens when the cost as a function of  $I_{set}$  is enough steeper. If this is not the case, the selection of  $I_{set}$  is performed using the derivative of the cost function (right panel)

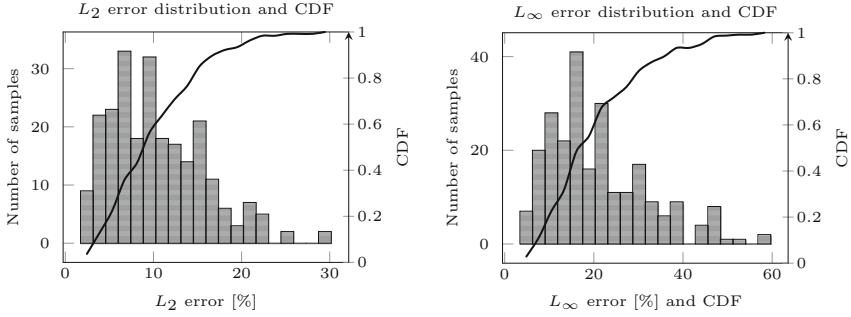
On the set of  $N_1$  candidates a new cost  $C_2$  is evaluated as the sum of the mean square difference between the “measured” and data base ERP on each electrode and with each pacing decrement.

A new sub-set of  $N_2$  candidates is then chosen as the sub-set yielding an ERP-related cost smaller than a fixed tolerance. From these available parameter sets, the one that best fits the CV was chosen as the CV measurement had the highest fidelity. The application of the estimation procedure was performed in less than one minute on 2.66 Ghz Xeon desktop machine.

### 3 Results

To evaluate the error properties and robustness of our approach a set of 243 combination models was generated by choosing parameter randomly in the  $[\min, \max]$  interval reported in Table 1. For each combination, the parameter set determined from the fitting process was compared with the known true solution and the  $L_2$  (mean error on the 5 parameters) and the  $L_\infty$  error (maximum error between the 5 parameters) were then evaluated as a percentage of the known true solution. Figure 5 shows the  $L_2$  and  $L_\infty$  error distributions and the corresponding cumulative distribution function (CDF). For the  $L_2$  error, a maximum value of 29.45 % was found with a mean error of 10.46 % and a standard deviation on the error of 5.4 %. As depicted by the CDF, 95 % of the estimated parameters analyzed here have a  $L_2$  error not greater than 20 %.

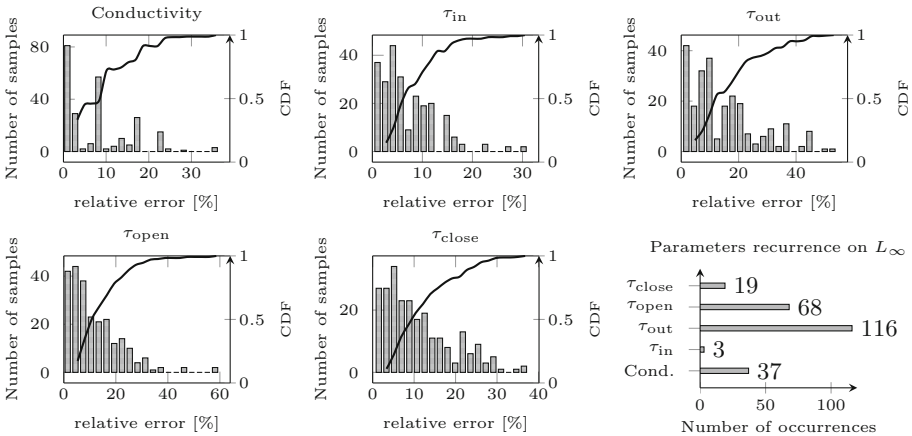
Figure 6 shows the error distribution for each parameter together with its CDF. Higher relative errors occur when the value of the parameter to estimate is close to the minimum value adopted for building the data base of Table 1. The best performances are obtained in estimating the conductivity and  $\tau_{in}$  parameters.



**Fig. 5.** Left:  $L_2$  error distribution (bars) and cumulative distribution (thick line) evaluated for 243 set of randomly chosen parameters. Right:  $L_\infty$  error distribution (bars) and cumulative distribution (thick line) evaluated for 243 set of randomly chosen parameters.

According to [11],  $\tau_{open}$ ,  $\tau_{close}$  parameters characterize ERP restitution: a poorer approximation of these two parameters was expected, since the available data is best able to constrain parameters affecting CV restitutions.

The parameter  $\tau_{out}$  is constrained by both CV and ERP restitution. This parameter characterizes the outward repolarization current, [7]. The inability to accurately measure ERP through activation times alone means that this parameter is often poorly constrained leading to it often being the worst fit parameter (see Fig. 6, bottom right).



**Fig. 6.** Error distribution and CDF for each parameter; Recurrence of the maximum error for each parameter

Figure 6 (bottom, right) shows the number of occurrences each parameter defines the  $L_\infty$  error. The  $\tau_{\text{out}}$  and  $\tau_{\text{open}}$  parameters appear to be the least well constrained (116 occurrences for  $\tau_{\text{out}}$ , 68 for  $\tau_{\text{open}}$ ).

Robustness with respect to noise was evaluated by adding a white noise signal to each of the bipolar electrograms with an intensity equal to the 10% of the maximum absolute value of the electrode output. For the  $L_2$  error, a maximum value of 29.45% was found with a mean error of 10.72% and a standard deviation on the error of 5.5%. This result is not surprising since the proposed method fits the model parameters using activation time values, i.e. where the signal to noise ratio is maximum.

## 4 Discussion

A pacing protocol designed to constrain the biophysical parameters of a cellular ionic model from a multi-electrodes catheter bipolar electrograms was derived and tested. The simplified model used in this study reflects the level of complexity available from clinical data where only endocardial surface activation times can be recorded. Differently from [10], the same catheter is used to both pacing and measuring the activation times, reducing uncertainty in the relative orientation of the wave propagation and the catheter. The CV and ERP restitutions with respect to the pacing decrement were determined only using the activation times. The robustness of the method was tested on a set of 243 combination of randomly chosen parameters.

In the test performed, higher relative errors occurred when the value of parameter to estimate was close to the minimum value adopted for building the data base. The best performances were obtained in the estimation of the conductivity and  $\tau_{\text{in}}$  parameters. These parameters mainly characterize the CV restitution, the measurements which are well represented by the data set. Conversely,  $\tau_{\text{open}}$  and  $\tau_{\text{close}}$  characterize ERP restitution. The accuracy in determining ERP depends on  $\Delta T_{\text{stim}}$ , thus a poorer approximation on ERP could lead to a poorer approximation on  $\tau_{\text{open}}$  and  $\tau_{\text{close}}$ .

The  $\tau_{\text{out}}$  parameter appears to be the least well constrained (116 occurrences in determining the  $L_\infty$  error); and poorly approximated. This parameter characterizes the outward current, and thus the repolarization: a possible reason of the poor performances in constraining  $\tau_{\text{out}}$  could be ascribed to a greater influence of this parameter on the ERP restitution than the CV restitution.

Another limitation on the accuracy of the proposed methods depends on the number of values adopted for each parameter in building the data set.

The proposed method represents a first step in personalizing atrial electrophysiology models to individual patient physiology and pathology on clinical time scales.

## 5 Conclusions

In this work were introduced a robust and potentially clinically tractable protocol and fitting algorithm for characterizing local tissue electro-physiology properties by biophysical ionic cell models.

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