# Electrophysiological Parameters in the Electrical Propagation During Atrial Fibrillation: A Population of Models Study

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## Abstract

*Cardiac tissue conduction velocity (CV) is a relevant variable in the maintenance and stability of atrial fibrillation (AF). The main goal of this work is to investigate modulation of CV in human chronic AF by inter-subject variability in ionic channel properties, cellular environmental factors and tissue coupling, by using a population of mathematical models. A monodomain tissue model was developed on the basis of the Skibsbye human atrial cell model. In this model, nine parameters are varied leading to a total number of 500 tissue models (8x156 cells). Among these simulations, 126 models are found within the experimental physiological range of biomarkers obtained from 149 chronic AF patients. The resulting population of 126 tissue models covers the variability in the biomarkers observed in the experimental recordings. The specific balance between sodium current and diffusion coefficient modulates the CV, critical for arrhythmia inducibility. The developed population of tissue models establishes the basis for further research in ionic mechanisms that facilitate AF maintenance and in-silico evaluation of personalised drug treatments.*

## 1. Introduction

Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia encountered in the clinical practice [1]. Moreover, the efficacy of current therapies to restore sinus rhythm is limited, especially in patients suffering chronic AF [1]. A deep understanding of the mechanisms responsible for the initiation and maintenance of the arrhythmia is essential for the increase of treatment efficacy [2].

Modifications in electrophysiological characteristics, known as atrial remodeling, facilitate reentrant stability thanks to the shortening of action potential (AP) and the reduction in conduction velocity (CV). According to other biological properties, this remodeling process is highly dependent on the genetics and clinical scenario of each patient, which explains the differences in the efficacy of treatments depending on the patient [2, 3].

Populations of models aim to overcome and prevent from unexpected responses and secondary effects associated with electrophysiological inter-subject variability during the implementation of new drugs [2]. Previous inter-subject variability studies have focused on the differences observed in representative biomarkers at the cellular level but, when studying mechanisms responsible for the initiation and maintenance of AF, it is crucial to consider the effect of neighboring cells and alterations in CV. The organization and structure of atrial tissue has been associated with atrial conduction abnormalities, presenting a substrate for atrial reentry [4].

In this work, we propose a population of 2D atrial tissue models, calibrated against human recordings in chronic AF (cAF), to investigate modulation of human atrial CV by inter-subject variability in ionic current densities, environmental factors, and tissue coupling.

## 2. Materials and methods

### 2.1. Experimental dataset and biomarkers

A set of experimental recordings were used to calibrate the population of models. Specifically, measurements on right atrial appendages from 149 patients diagnosed with cAF were employed [2,5]. A total of six biomarkers were used to quantify variability in APs (Figure 1B): AP duration at 20, 50, and 90% of repolarization (APD20, APD50, APD90 respectively), AP amplitude (APA), resting membrane potential (RMP) and AP plateau potential at 20% of APD90 (V20). The maximum and minimum values of these biomarkers at a pacing frequency of 1Hz are presented in Table 1.

### 2.2. Electrophysiological cellular model

The Skibsbye 2016 model was implemented and used in this work [6], whose schematic is depicted in Figure 1A. The model provides a detailed description of the transmembrane ionic currents and intracellular calcium handling, as an extension of the Koivumaki model [7].

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Table 1. Human atrial AP biomarker ranges in cAF.

| | Minimum Value | Maximum Value |
|---|---|---|
| **APD90 (ms)** | 140 | 330 |
| **APD50 (ms)** | 30 | 180 |
| **APD20 (ms)** | 1 | 75 |
| **APA (mV)** | 80 | 130 |
| **RMP (mV)** | –85 | –65 |
| **V20 (mV)** | –30 | 20 |

Some changes were incorporated to the cAF model variant to introduce disease-related remodeling: cell dilation (+10%), INa (-18%), ICaL (–55%), Ito (–62%), IKur (–38%), IKs (+145%), IK1 (+ 68%), INCX (+ 50%), expression of SERCA (–16%), PLB to SERCA (+ 18%), SLN to SERCA (–40%), baseline phosphorylation (+100%), ryanodine receptors (+100%) and calcium-activated potassium current IKCa (-50%) [7].

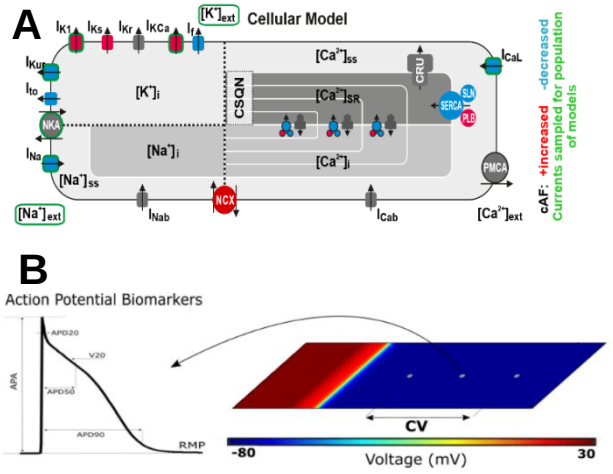


Figure 1. Cell electrophysiological model and electrical wavefront propagation along a 2D plane. Panel A represents Skibsbye's model. Red and blue marks represent the modifications introduced to account for AF remodeling. The currents that were sampled are rounded in green. Panel B shows wavefront propagation along a 2D plane. CV parameter is measured between two middle cells of the plane. APs biomarkers associated to an isolated cell are shown: APD20, APD50, APD90, APA, RMP and V20.

## 2.3. Tissue simulation and electrical propagation

Once the electrophysiological model for a cell was implemented, it was extended to the 2D level. A rectangular plane of 8 by 156 cells (representing width and length respectively) was generated. The total dimension of the plane was 0.8 by 15.6 mm.

Regarding the mathematical modeling, the reaction-diffusion equation (1) was used to introduce intercellular communication [8].

$$\frac{\partial V_m}{\partial t} = \nabla \cdot (D \nabla V_m) - \frac{I_{ion} + I_{applied}}{C_m} \qquad (1)$$

where $\nabla$ is the gradient operator and D is a diffusion coefficient with units of $\text{distance}^2\ \text{time}^{-1}$. A reference diffusion coefficient of D = $0.8 \cdot 10^5$ $\mu m^2/ms$ was used in this study. The ordinary differential equations were solved by applying the Forward Euler method.

Electrical propagation effects were analyzed by measuring CV. CV was calculated by dividing the distance between the measured points into the difference between activation times. Cell activation was detected by identifying the highest peak in voltage time-derivative. In Figure 1B, the wavefront propagation along a 2D plane is represented together with CV. The two selected cells for CV measurements were situated in the middle of the plane ((7.5, 0.4 mm) and (14.4, 0.4 mm) coordinates).

## 2.4. Construction of the population of models

To construct the population of models, a set of parameters was varied from -50% to +100% of their original value: $g_{Na}$, $I_{NaK}$, $g_{K1}$, $g_{CaL}$, $g_{Kur}$, $I_{KCa}$, $[Na^+]_o$, $[K^+]_o$ (marked in green in Figure 1.A) and the diffusion coefficient D.

Note that, apart from the variation in ionic currents that are commonly used when implementing a population of models in isolated cells, this study includes variability in the diffusion coefficient along with variations in $Na^+$ and $K^+$ extracellular concentrations. These parameters were varied in the population of models due to their role as modulators of the CV [4]. The rest of varied parameters ($g_{Na}$, $I_{NaK}$, $g_{K1}$, $g_{CaL}$, $g_{Kur}$) were chosen due to their strong correlation with the AP biomarkers in previous sensitive analyses [2]. Finally, the new current $I_{KCa}$ was included, whose effects have not been studied before in atrial population of models studies.

A total number of 500 different combinations of the aforementioned parameters were generated by using Latin Hypercube Sampling [3]. The number of models was selected according to the available computational time. The models were simulated by pacing with a train of 15 periodic stimuli at 1Hz (3 ms stimulus duration, twice diastolic threshold amplitude). The APs of three cells along the plane were analyzed for the last 5 periodic

stimuli. A cardiac simulation GP-GPU platform was used to perform the mathematical simulations. Biomarkers for the 500 tissue models were evaluated, and only those satisfying all the experimental constrains were included in the population of models.

Partial correlation was used to find correlations between electrophysiological parameters and biomarkers, after accounting for the linear effects of one or more additional variables [2, 3].

## 3. Results

### 3.1 Generation of the population of models

126 of the total 500 models (25.2%) presented all the biomarkers within the experimental range (Table 1). Only this set of experimentally calibrated population can be considered physiologically acceptable. The physiological population of models and experimental data are presented in Figure 2. Experimental recordings (orange dots) are compared with model predictions (blue dots) showing a good agreement between them. In addition, baseline AF model predictions are shown with green dots.

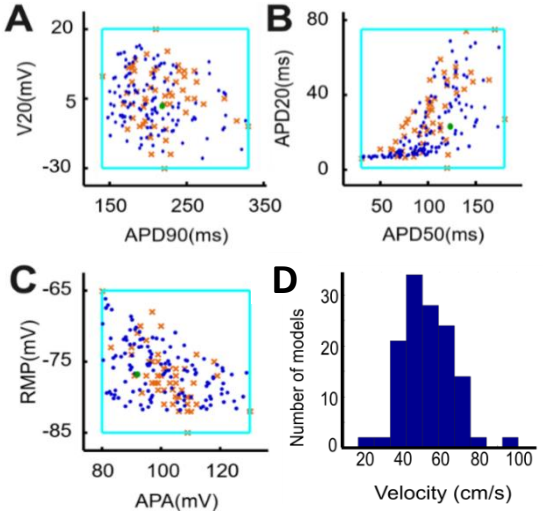


Figure 2. Population of tissue models calibration and distribution of CVs. Panels A, B and C show the values of the biomarkers –V20, APD20, APD50, APD90, RMP and APA– for the experimentally calibrated models. Blue marks correspond to the 'physiological population' (N=126). Orange marks correspond with experimental recordings. Baseline values are marked in green. Upper and lower bounds for 1 Hz biomarkers are marked in light blue. Panel D illustrates the distribution in CV of the physiological acceptable models.

Figure 2D shows the distribution of CV values in the physiological population. The obtained CVs ranges from 18.06 cm/s to 100.77 cm/s, covering similar values than those presented in previous studies [9].

The results illustrate how the population of models in tissue is able to reproduce the inter-subject variability found in patients (every experimental value has a neighboring model). Furthermore, the biomarkers corresponding to the baseline AF model were located inside experimental constraints.

Box plots in Figure 3A show the range of the varied parameters and the median physiological values. Edges of the boxes represent the 1st and 3rd quartiles. Note that most of the median values do not coincide with the baseline model value ($g_{Na}$, $I_{NaK}$, $g_{CaL}$, $I_{KCa}$, $[Na^+]_o$ and D) that is represented by the green line. These results indicate that the original model is not representative of median values. A wide range of values for the diffusion coefficient, ionic conductances and concentrations is covered. Most of the parameters admitted to be varied from -50% up to +90%, or even 100% of the basal value.

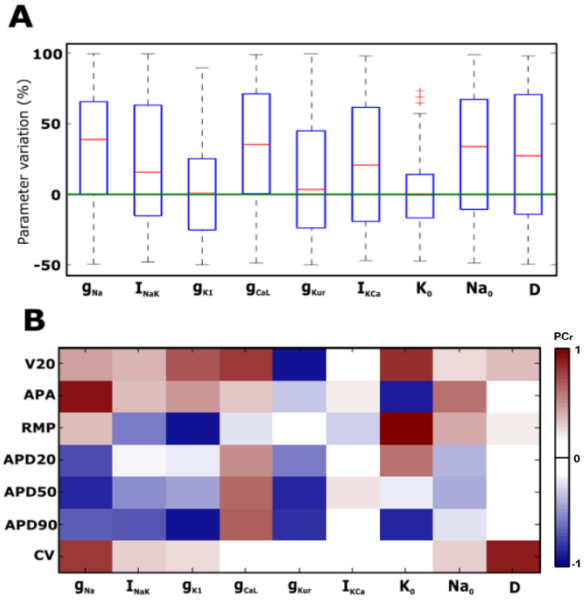


Figure 3. Box plot and partial correlation analysis. Box plot of Panel A shows the range and mean value of the varied parameters. Panel B shows partial correlation results where each correlation represents the effect of a specific parameter on each biomarker. Positive and negative correlations are marked in red and blue, respectively.

The results obtained after partial correlation analysis are presented in Figure 3B. Each correlation represents the effect of a specific parameter on each biomarker and the intensity of the color shows the intensity of the

correlation. Positive and negative correlations are marked in red and blue, respectively. Most of the parameters have a strong effect on various biomarkers. However, $I_{KCa}$ and $[Na^+]_o$ present weaker correlations with the biomarkers. Regarding CV, the presented study demonstrates a strong direct correlation of $g_{Na}$ and D with CV, whereas weaker correlations are established with $I_{NaK}$, $g_{k1}$ and $[Na^+]_o$.

On the other hand, D slightly affects V20 and RMP but no correlation was found with the rest of biomarkers. The analysis also concludes that an increase in sodium conductivity is directly related to APA and CV, and inversely related with APD20, APD50 and APD90. APD90 was found to be inversely related to potassium and sodium currents while it is directly related with $g_{CaL}$. Finally, $[K^+]_o$ was found to be strongly related with RMP and inversely related to APA and APD90.

## 4. Discussion

In this study, the effects of tissue inter cellular coupling on atrial propagation have been investigated in a subset of parameters, based in previous populations of models analysis [2, 3, 5] with other parameters underlying electrical propagation. The results obtained in this work are consistent with previous studies carried out at cellular level. Taking this as a sign of fidelity, the tissue level model has been used to analyze the problem in a deeper way by taking into account other features like CV and electrical propagation.

As a result, we have demonstrated that populations of models are affected by inter-cellular coupling that, together with the sodium current, modulates CV. Consequently, alteration of these parameters is highly relevant when studying the maintenance and stability of AF. Specifically, CV is predominantly governed by the specific balance between D and $g_{Na}$. However, although $g_{k1}$ is strongly correlated with RMP, we did not observe a strong relation between $g_{k1}$ and CV at the examined pacing frequency. Furthermore, the included parameter $I_{KCa}$, does not strongly affect any biomarker. Finally, it will be important for future studies to consider the population at different frequencies to ensure that the population reproduces rate dependent properties.

## 5. Conclusion

The use of populations of models at the cardiac tissue level can help in future investigations in the identification of the different mechanisms underlying AF initiation and termination, and thus a better classification of patients according to their most prominent mechanism. The development of populations of models accounting for diffusion properties can serve as a basis for further research in the evaluation of personalized anti-AF pharmacological therapies.


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