

# The Effects of Long- and Short-term Memory on Action Potential Duration for Atrial Cellular Automata

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## Abstract

*Biophysical atrial simulation can improve therapies by simulating ablative and pharmacological strategies, although their use is limited by their high computational cost. Simpler cardiac automata can achieve acceptable timeframes, calculating the Action Potential Duration (APD) from the previous Diastolic Interval (DI), although it is necessary to question whether this approach is sufficient for short- and long-term simulations.*

*The analysis of 992 simulated activation protocols showed an expected increase of the APD with the previous DI interval. Short-term memory at long-term simulations was showed as the dependency of  $APD^{+1}$  with the previous activation ( $APD^0$ ): shorter  $APD^0$  provoked shorter  $APD^{+1}$ , and this effect was comparable to the effect of previous DI. Independent prediction based on both  $APD^0$  and DI allowed better estimation of  $APD^{+1}$  values ( $14 \pm 10$  ms), compared to using DI alone ( $29 \pm 19$  ms,  $p=0.029$ ).*

*Atrial automata should consider short term memory, as duration of previous activations, to accurately estimate posterior APD in long-term simulations, to mimic the natural electrophysiological response.*

## 1. Introduction

Cardiac arrhythmias at atrial or ventricular level are among the main causes of disease and mortality. Atrial fibrillation (AF) is the most prevalent cardiac pathology, affecting >10% of the elderly population [1]. Due to the lack of knowledge about the specific mechanisms initiating and perpetuating AF, choosing specific treatment for each patient is still a major clinical and economic problem. In silico models represent a great tool for guiding personalized medicine as they provide interesting insights on the individual AF manifestation. In particular, they were confirmed to be especially useful in diagnosing pathological situations [2], and in evaluating ablative [3] and pharmacological [4] strategies results. Numerous mathematical models describe cardiac functions in detail from both an electrophysiological [5] and a hemodynamic

[6] point of view.

Atrial simulations can be used to quantify the response of the patient electrophysiology against different scenarios, such as changes in activation location or frequency, ionic concentration, temperature, pH or drug effects [1]. These simulations are characterized through standard electrophysiological metrics, namely the Action Potential Duration (APD). In this regard, biophysical modelling [8] is among the most widely used and has been implemented by several solvers, for instance ELVIRA [9] and openCARP [10], that manage to accurately describe the transmembrane potential (TP), ionic concentrations or gating variables. However, this precision brings with it a high computational cost and long simulation times, due to the huge use of parameters and to the large number of systems of ordinary differential equations to be solved, that can compromise clinical diagnostic times. For this reason, the use of electrophysiological solvers with compatible diagnostic times are demanded, such as solvers describing the cardiac electrical characteristics by discrete states, so called cellular automata (CA) [11].

The aim of this work is to extend the use of a ventricular CA [12] to the atrial electrophysiology, by developing a new CA describing the specific atrial electrical activity. This atrial CA will be calibrated against classic and validated atrial biophysical simulations [5] in different stimulus scenarios.

## 2. Materials and Methods

### 2.1. Biophysical model

Atrial biophysical simulations were performed with ELVIRA software using the Coutermanche atrial model [13] on a rectangular atrial tissue ( $0.3 \times 20 \times 0.025$  cm, 2106 cells, 0.25 mm inter-node distance, 0.01 ms of temporal interval) activated from the inferior front, see Fig. 1a. Fiber direction was included in the model along the large axis of the model with a longitudinal diffusion of 0.0035 S/cm-pF and a longitudinal vs transversal relation of 0.35. For the analysis, three midline points of the slab of tissue were considered: one for the analysis of the Transmembrane

Potential curve (TP) and two for the measurement of Conduction Velocity (CV), as shown in Fig. 1a.

Long-term S1-S2 pacing protocols were performed, corresponding to sequences of S1 intervals (340ms to 1000ms,  $N=31$  values), repeated 15 or 16 times before an S2 stimulus with values between 100ms and 1000ms ( $N=32$  values). A total of 992 S1-S2 training protocols were simulated in 31 long-term simulations for a total of 3720 simulated minutes ( $120\pm 30$  minutes per simulation), in which the order and combination of S1 and S2 values were randomly selected.

Transmembrane Potential (TP) curves were used to measure the APD and the Diastolic Interval (DI). APD was measured as the difference between the activation time (instant of maximal positive  $dV/dt$ ) and the 90% of repolarization, the so-called  $APD_{90}$ .  $APD^0$  and  $APD^{+1}$  denote the last S1 and S2 activations respectively (see Fig 1b). The DI was measured as the interval from end of  $APD^0$  and the beginning of  $APD^{+1}$ . Fig. 1b pinpoints exactly their corresponding values.

Conduction velocity was measured as the space separating the measuring points (6 mm) divided by the difference in their activation times, see Fig. 1b.

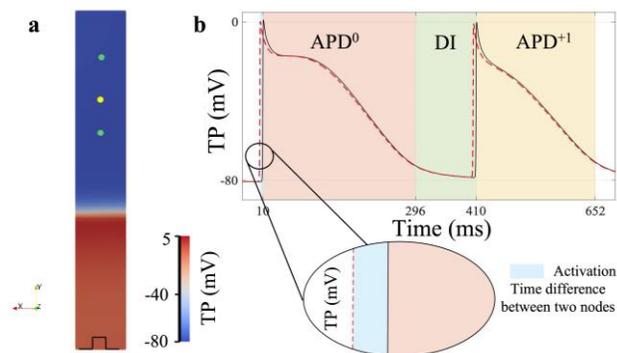


Figure 1. a) Rectangular atrial tissue used for biophysical simulations. Yellow and green nodes were used to measure APD and CV respectively; b) Transmembrane Potential curve of two nodes (red and black lines) with highlighted sections:  $APD^0$  (red), DI (green),  $APD^{+1}$  (yellow), and activation time difference between node (blue).

## 2.1. Cellular Automata

The biophysical simulations just described demonstrate accuracy and ease in analyzing the results. However, the computational time they require is high and therefore they cannot be used in the clinical field. Serra's [12] presents an alternative method for modelling cardiac tissue electrophysiology, which is a spatially extended, event based, asynchronous cellular automaton, prepared for the analysis of ventricular tissues and geometries.

Cellular Automata (CA), unlike biophysical models, consider only two main states for each piece of cardiac

tissue: 0 (inactive, i.e., repolarized, and excitable) and 1 (active, i.e., able to activate the neighbors). Each event simulated (activation, repolarization) is processed at the exact time when they occur and therefore there is no need of a granular time step.

Transition from state 0 to 1 (activation) is triggered by previous activations of immediate neighboring nodes (26 neighbors for hexahedral meshes). The exact instant of activation is calculated using the Fast-Marching algorithm [14] considering propagation velocity of a planar wave. The CV for this activation, as well as the  $APD^{+1}$  of the subsequent active state, is calculated from the previous states and DI of the calculated node. Transition from state 1 to 0 (repolarization) is automatically triggered once the calculated  $APD^{+1}$  is over. Propagation waves are initiated by manually activating specific nodes.

Calculation of individual values of CV and  $APD^{+1}$  for each activation is one of the most important steps of CA, and they are usually tuned summarizing experimental data into numerical functions. This work compares two strategies for CV and  $APD^{+1}$  calculation using experimental data from biophysical simulations: considering only previous DI value and summarizing the  $APD^{+1}$  values into restitution curves or considering both previous DI and  $APD^0$  values and summarizing the  $APD^{+1}$  values into restitution surfaces.

## 3. Results

### 3.1. Biophysical model characterization

Characterization of the APD metrics for the biophysical simulation can be observed in Figure 2a, where the  $APD^{+1}$  is represented as a function of the previous DI. Single curve fitting produced an error of  $23\pm 21$  ms. This was provoked by the increase of the  $APD^{+1}$  with the previous  $APD^0$ , as can be observed by the different curves fitted for each  $APD^0$  (color-coded). When  $APD^{+1}$  is summarized using both DI and  $APD^0$  (Fig. 2b), and therefore constructing a restitution surface, the error fitting was considerably lower ( $10\pm 14$  ms,  $p < 0.001$ ).

Panel 2c shows the biophysical simulation characterization for the CV metric. In this case, the effect of the previous  $APD^0$  was almost inappreciable, and the simpler curve fitting showed similar error ( $2.9\pm 4.6$  cm/s) than the surface fitting using both DI and  $APD^0$  ( $3.0\pm 5.6$  cm/s,  $p=0.87$ ).

### 3.2. Cellular automata simulations

Using the CA we reproduced the simulations performed with the biophysical model. Computational time using the CA was in average 30 times faster than the equivalent biophysical solver: 10,9 vs. 327,3 seconds of computation time per second of simulated time, respectively. Analysis

of the biophysical simulations took five times longer than in CA due to the need to calculate APA-related values: 300 sec compared to 60 sec.

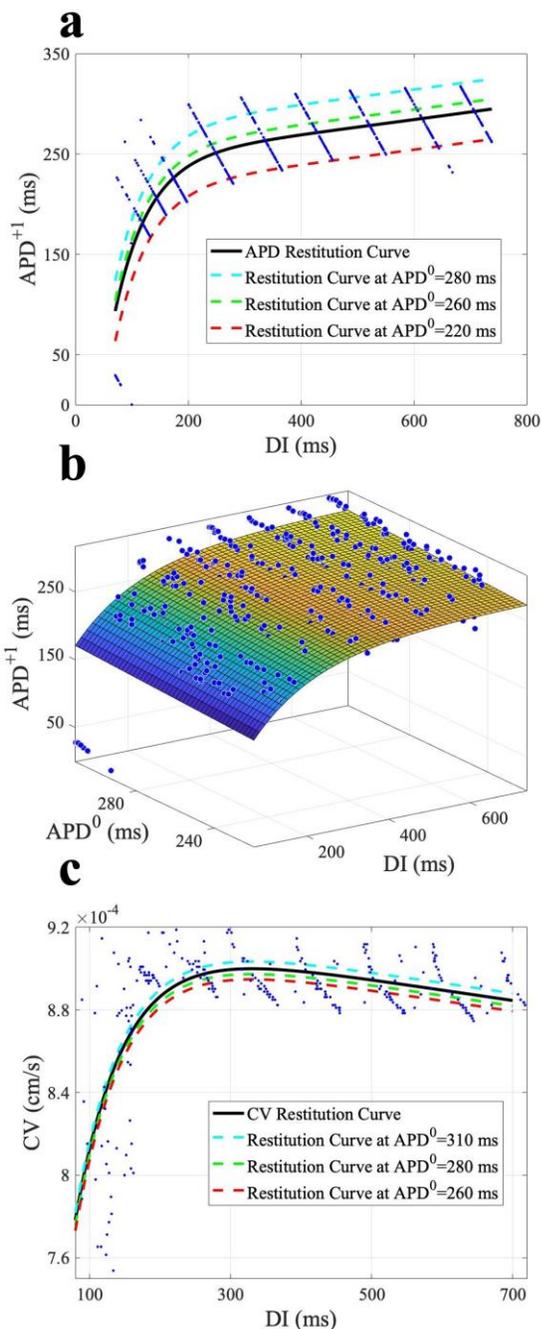


Figure 2. a) APD Restitution Curve highlighted for different values of  $APD^0$ ; b) APD Restitution Surface; c) CV Restitution Curve.

Figure 3 shows an example of a biophysical simulation (panel a) reproduced by the atrial CA using both strategies: calculating  $APD^{+1}$  from previous DI (restitution curve,

panel b) and calculating  $APD^{+1}$  from previous DI and  $APD^0$  (restitution surface, panel c). Whereas the APD value of the CA using the APD curve change for each activation, the automata with APD surface showed better correspondence in each simulated stimulus.

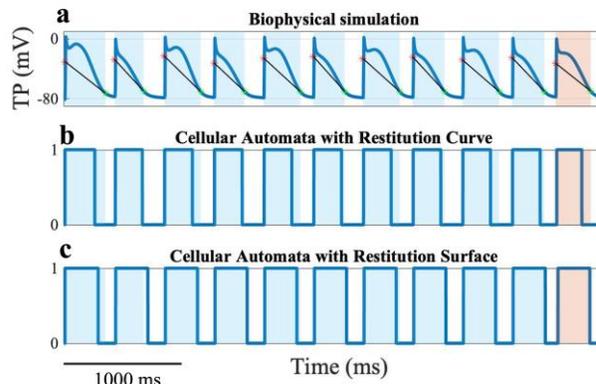


Figure 3. Comparison of biophysical and CA simulations. a) Transmembrane Potential (TP) curve. Red dots: activation instant; green dots: 90% repolarization time. b) Atrial CA using restitution curve. c) Atrial CA using restitution surface.

To confirm this individual finding on multiple simulations, two different analyses were performed. The initial theoretical deviation is shown in Figure 4a, indicating the deviation produced by the biophysical model characterization. This was calculated as the difference between the  $APD^{+1}$  values extracted from the biophysical simulations and the equivalent values obtained using the interpolation of the restitution surface or curve. As expected, considering both  $APD^0$  and DI, the  $APD^{+1}$  error resulted in values of  $10 \pm 14$  ms, less than when considering DI alone, which was  $23 \pm 21$  ms ( $p < 0.001$ ), see Fig. 4a.

Second validation strategy consisted of new simulations, not used for calculating the restitution surfaces/curves, with both the biophysical and CA solvers. New simulations performed ( $N=15$ ) reproduced S1-S2 protocols with ten S1s followed by one S2. S1 values were taken randomly between 300 ms and 1000 ms and S2 values between 200 ms and 500 ms. Same pacing protocols were reproduced with the biophysical and CA solvers (surface and curve-based), in the case of CA solvers using the restitution surface/curves from the  $N=992$  training data. These simulations considered cumulated deviations from consecutive beats.

This experimental verification confirmed the difference between the two CA strategies: considering both  $APD^0$  and DI the mean error was  $14 \pm 10$  ms, while considering DI alone, the mean error was  $29 \pm 19$  ms, with  $p=0.029$ , see Fig. 4b. This implies that considering the value of earlier APDs improves the estimation of later APDs, and therefore in simulations of long duration it is necessary to consider the short-term memory of the simulator.

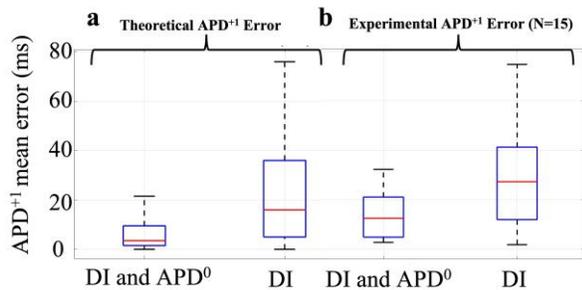


Figure 4. Theoretical (a) and Experimental (N=15) (b) error in APD by the atrial CA.

#### 4. Discussion and Conclusions

This study reports on the developing of a cellular automaton able to reproduce the atrial electrophysiological activity [12]. The results of biophysical simulations on a rectangular piece of atrial tissue were characterized using DI, APD and CV values. These markers showed a difference in the dependence of APD<sup>+1</sup> and CV on APD<sup>0</sup> which represents the short-term memory effect of the simulation. APD<sup>+1</sup> varies as a function of the APD<sup>0</sup> value, while CV does not change with it. Thus, it was decided to consider APD<sup>+1</sup> as a function of DI and APD<sup>0</sup> and CV as a function of DI alone. This reduced the error on the estimated APD<sup>+1</sup> value by more than half, making it closer to the results of biophysical simulations.

The results obtained make it possible to have a simulator with reduced computational time (x30) and with high precision in the simulated parameters, making it interesting for clinical use due to the possibility of predicting results in clinical diagnostic times.

However, our investigations so far have only been applied to a piece of atrial tissue. They need to be extended to more realistic tissues including three-dimensional atrial geometries. Furthermore, the study was conducted by pacing protocols of different but constant values, and cases of irregular rhythms such as atrial fibrillation and tachycardia should be considered.

Simulating the atria electrophysiological aspects is of great interest to diagnose pathological situations or to evaluate ablative or pharmacological strategies. Doing this in reasonable computational times compatible with diagnostic times is necessary. This work presented an atria cellular automata that allows APD prediction errors in clinical ranges, thanks to a careful analysis of the parameters and the simulation short-term effects, thus approaching the results of biophysical models. This improvement in prediction is accompanied by a thirty-fold decrease in computing time.

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