Evaluation of Automata-based Simulations for Atrial Fibrillation in 2D/3D Geometries Reproducing Disease Progression

Giada S. Romitti, Alejandro Liberos, María Termenón-Rivas, Javier Barrios-Álvarez de Arcaya, Pau Romero, Dolors Serra, Ignacio García-Fernandez, Miguel Lozano, Rafael Sebastian, Miguel Rodrigo

CoMMLab, Universitat de València, València, Spain

Abstract

Atrial biophysical simulations demand high computational resources due to the large number of equations that must be solved, and small space and time discretization required, which make them impractical for clinical use. Cellular Automaton (CA), by taking a finite number of states, reduces computational time and can provide interesting insights for subsequent digital twin models. This study explores the potential of a CA that successfully simulates atrial electrophysiology in healthy and pathological conditions, when compared with biophysical simulations.

CA was trained at cellular and tissue level from biophysical simulations in tissue slabs under controlled pacing conditions. Then, trained CA was used to simulate complex AF patterns in a 2D sheet of atrial tissue and a complete 3D atrial geometry that were compared against biophysical simulations. In the former, self-sustained arrhythmia under different degrees of electrophysiological remodeling gave a mean difference error of 6.25±2.87ms in cycle length. In the 3D geometry, the value of local activation times differed by 9.6±7.6ms for sinus rhythm and provided comparable patterns for chronic AF. All results are accompanied by a reduction in computational times approaching real times (21 times faster than biophysical simulations on GPUs cards).

These findings suggest that CA models have the potential to provide a more efficient tool for reproducing patient-specific atrial electrophysiology in clinical times.

1. Introduction

Among cardiac arrhythmias, atrial fibrillation (AF) is the prevalent one [1]. Since the early twentieth century, the mechanisms underlying the initiation and maintenance of AF have been the subject of ongoing debate, as they are not yet fully comprehended. Therefore, choosing specific treatment is still a major and clinical problem, which makes pharmacological and ablative treatments sub-optimal [2].

Digital twin technology has the potential to refine personalized medicine and improve patient outcomes by creating a virtual tool that merges personal clinical data using mechanistic and statistical models. In the context of AF they can predict disease development helping to design customised treatments, monitoring their effectiveness and patient response [3].

Cardiac digital twin simulations are mainly based on biophysical models [4], which reproduces the electrophysiological behaviour using dozens of ionic channel expression, which results in a high computational cost. It is therefore necessary to ask whether this high precision is necessary, especially if those models are thought to be used in everyday diagnostics. A possible compromise may be to decrease the number of parameters, but care must be taken with the accuracy of the results generated. In this direction, Cellular Automaton (CA) have been developed to describe complex systems by summarising them with a discrete set of states [5]. Recent evidence [6] present simulations of healthy and pathological conditions in real ventricular geometries using CA with two unique excitation states dependent of restitution properties. This approach has succeeded in keeping computational times short.

The aim of this work is to validate a CA able to simulate the atrial electrophysiological activity in affordable timeframes. To achieve this, biophysical simulations were first conducted to derive restitution properties necessary for the CA to function. Then, the CA was compared against biophysical simulations in realistic healthy and fibrillatory scenarios on 2D domains and complete atrial 3D geometry.

2. Materials and Methods

2.1. Biophysical model

Biophysical simulations were carried out with Koivumäki's atrial model [7]. This was solved using a combination of forward Euler and Rush-Larsen methods and implemented in a Global Purpose GPU platform [8].

The domains of the simulations are three. The first is a small rectangular slab of atrial tissue (0.3x2x0.025cm, 2106 cells, hexahedral mesh, 0.25 mm inter-node distance) activated from the inferior front, see Fig. 1a. On this, a total of 3000 S1-S2 pacing-protocols (random $S1 \in \{100,\ldots,1000\}$ms repeated 15/16 times before a

S2∈{100,…,1000}ms) were given. This was replicated under {0, 33, 66, 100, 135}% of electrical remodeling. A zero-remodeling percentage represents healthy atrial conditions, while 100% of remodeling represents the atrial substrate of average chronic AF (cAF) patients. The latter was created by modifying the sinus rhythm model presented in [7]: SERCA expression (-16%), PLB to SERC ratio (+18%), SLN to SERCA ratio (-40%), maximal I_{NCX} (+50%), sensitivity of RyR to $[Ca^{2+}]_{SR}$ (+100%), conductance of I_{CaL} (-59%), conductance of I_{to} (-44%), conductance of I_{Kur} (-22%) and conductance of I_{K1} (+100%). Note that modifications in I_{to}, I_{Kur} and I_{K1} have been altered from the original cAF model [7]. Time discretization was set to 20µs for all the simulations.

From simulations' results, the values of action potential duration (APD), conduction velocity (CV) and diastolic interval (DI), see Fig. 1b, were obtained. APD was measured as the difference between the activation time (instant of maximal positive dV/dt) and the time at which 90% of repolarization is reached, the so-called APD_{90}. APD^0 and APD^{+1} denote the last S1 and S2 activations, respectively. The values acquired were used to characterize the restitution properties of the model.

Simulations of self-sustained arrhythmia and healthy conditions were also reproduced in a square slab of atrial tissue (7.0x7.0x0.03 cm, 109512 cells, hexahedral mesh, 0.30 mm inter-node distance, see Fig. 3a-3b) and in a volumetric 3D model of the human atria constructed from medical images [9] (284578 vertices connected in 1353783 tetrahedra, with distance between nodes of 673.38µm, isotropic tissue, see Fig. 4). In both domains, a functional reentry was obtained from the interaction between consecutive wavefronts from different regions, which physiologically created a reentrant source [1]. Cycle length (CL) and local activation time (LAT) values were calculated for this group of simulations.

2.2. Cellular Automata

An alternative approach to model cardiac tissue electrophysiology was proposed in a previous study [6, 10]. This approach used a spatially extended, event-based, asynchronous CA that is specifically designed for analysing ventricular tissues and geometries.

The CA considered uses two main states: 0 (inactive or repolarized) and 1 (active or able to activate the neighbours). In order to be activated, a node must be stimulated by its neighbours. This stimulation follows the Fast-Marching method [11], which takes the neighbours reached with the plane wave going at CV speed. Subsequently, a node finishes being activated when a time interval equal to its assigned APD has passed since it was activated.

The APD, as well as the CV value, must be calculated for each activation. To do this, restitution properties from biophysical simulations are used. Note that these properties are derived only once for each type of substrate, and will then be valid for each geometry simulated with the CA. However, the CA also incorporates electrotonic effects from neighbouring cells, and short memory from previous AP for each node.

CA is implemented in Processing [12], which uses the Java language, and can be used in any type of computer without the need for parallelization. The simulations done with the CA use the same domain and pacing conditions as those done with the biophysical model, in order to make an accurate and fair comparison analysis.

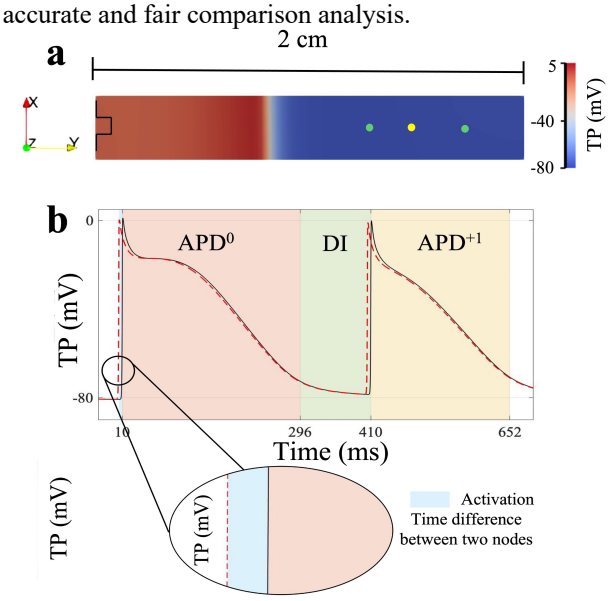

Figure 1. a) Rectangular atrial tissue used for CA training to biophysical simulations; b) Transmembrane Potential curve of two nodes (red and black lines) with highlighted sections: APD^0 (red), DI (green), APD^{+1} (yellow), and activation time difference between node (blue).

3. Results

3.1. Biophysical Model Characterization

From the simulations performed on the sheet of atrial tissue, the experimental values of APD, DI and CV were derived. These must be summarized in numerical functions that relate them to each other. Whereas [6] describes APD and CV as a function of DI (thus creating two restitution curves), it is necessary to ask whether this single dependency is sufficient for the description of our biomarkers. An interesting aspect to consider is the influence that short-term memory (in this work summarized as the APD^0) of the simulation has on the values considered from the last stimulation.

An analysis of the dependence APD^{+1} with previous activations showed that, regarding the APD^{+1} value, fitting a single curve based on previous APD produced a greater error (100% remodeling case: 2.12±1.33 ms, Fig. 2a)

respect to by considering a surface fitting including previous APD and DI (1.41±2.12 ms, p=0.0052, Fig. 2b).

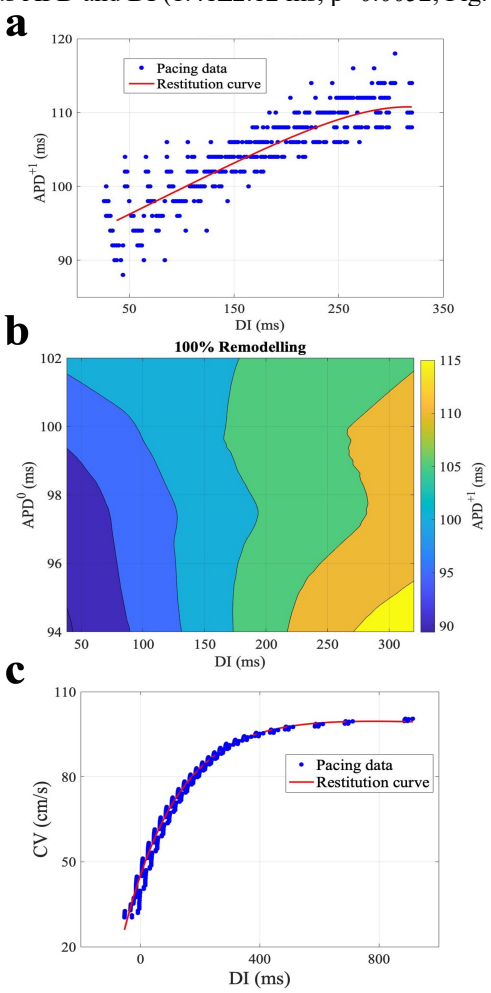

Figure 2. a) APD Restitution Curve; b) Contour map describing APD^{+1} as a function of DI and APD^{0}; c) CV Restitution Curve.

This was not observed in the CV case (Fig. 2c): fitting a single curve produced an error equal to the one obtained by considering a surface fitting. This could be explained by the model's memory or inertias of the different ionic concentrations and variables associated with the channels. For this reason, it was decided to consider a restitution surface for APD values and a restitution curve for CV values.

3.2. Cellular Automata Validation

Simulation of complex rhythms conducted by the trained CA were evaluated against the corresponding biophysical simulations. Three cases were considered for comparison: self-sustained arrhythmia in the square slab of tissue (Fig.3a-3b), sinus rhythm conduction in the 3D geometry (Fig. 4a-4b) and self-sustained arrhythmia in the 3D geometry (Fig. 4c-4d).

Simulations of self-sustained arrhythmia in the sheet of tissue were repeated for {33, 66, 100, 135}% remodeled fractions. By producing S1-S2 protocols at the same nodes and comparing CL values between biophysical and CA, it was noted that the mean difference between values obtained was 6.25±2.87ms (<5%), see Fig. 3c, as well as the same rotor propagation pattern, see Fig. 3a-3b.

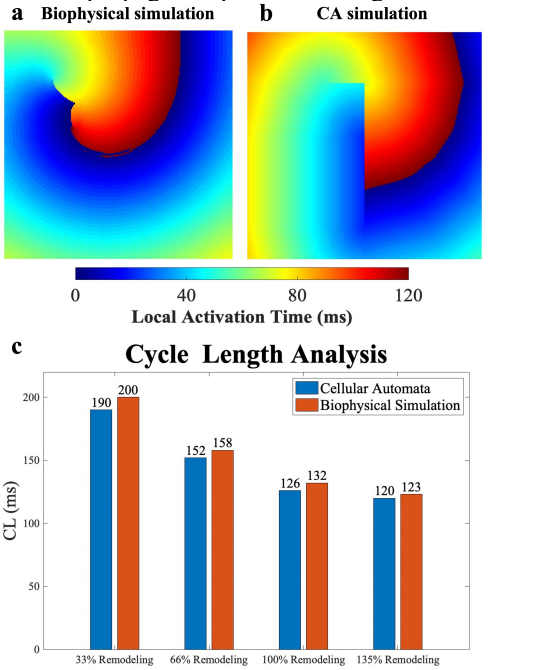

Figure 3. a) Functional reentry simulated with 100% remodeling and biophysical model; b) Functional reentry simulated with 100% remodeling and CA; c) analysis of differences between rotor CLs obtained with CA and biophysical model at different remodeling levels.

As far as 3D complete geometry is concerned, the first simulations were carried out in a healthy case (0% remodeling, with fiber direction), producing a sinus activation. The depolarization time was adjusted with that of the corresponding biophysical model (110 ms, Fig. 4a-b). On average the difference between CA and biophysical simulation in local activation times of each node differ by 9.6±7.6ms. Finally, a self-sustained reentry was also reproduced in the complete geometry in chronic AF conditions (100% remodeling), reproducing an 8-figure reentry. In this case, the CA reproduced a comparable re-entrant behavior, as shown in Fig. 4c-4d, with slight differences in the propagation patterns in RA.

Besides, a strong evidence of computational time decrease was found. CA was in average 21 times faster than the equivalent biophysical solver: 17 vs. 360 seconds of computation time per second of simulated time, respectively. It is important to emphasize that this result was obtained using a single core for CA and 3840 cores for biophysical simulations.

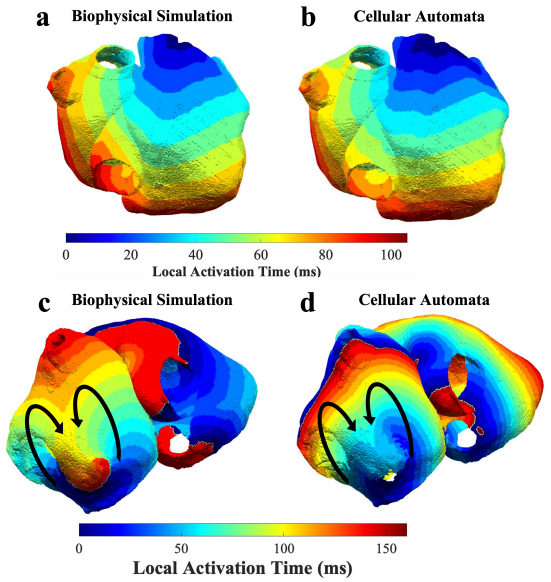

Figure 4. Simulation of a healthy case with a) biophysical model and b) CA. Functional reentry simulated with c) biophysical model and d) CA. Represented the local activation time.

4. Discussion and Conclusion

This study describes a CA able to simulate atrial electrophysiological activity in pathological conditions with high accuracy and reduced computational time. The CA was trained using the Koivumäki atrial model on a small rectangular piece of pacing atrial tissue. Then, CA was validated against biophysical simulations on a 2D reentrant pattern and finally on a complete 3D atrial geometry.

By analyzing the dependence of both CV and APD^{+1} on the short-term memory effect of the simulation (APD^{0}), it was found that APD^{+1} varied as a function of APD^{0} while CV remained unchanged. Therefore, APD^{+1} was considered as a function of DI and APD^{0}, while CV was considered a function of DI alone. This made it possible to create suitable restitution properties for the CA, which reduced the error in the estimated APD^{+1} value.

Simulations of re-entrant scenarios were carried out to approach AF situations, and the results were analyzed qualitatively and quantitatively for the square atrial tissue. The CA faithfully reproduced the activation wave pattern obtained with a biophysical model, both in the atrial tissue and in the complete atrial domain. Moreover, the differences concerning CL were minimal and consistent with the level of remodeling.

The results of the study indicate that it is possible to train CA by simulating a biophysical model on a limited domain, and then directly use CA for more complex and realistic simulations to achieve high precision and reduced computational time (x21).

Further studies, which take artificial intelligence into account instead of restitution properties, will need to be undertaken. Furthermore, integrating other cellular models for simulations would allow further validations of the efficiency of CA. Finally, simulating treatments such as ablative and pharmacological should be added to the study to assess the sensitivity of the results in those scenarios.

Acknowledgments

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Address for correspondence:

Miguel Rodrigo Bort.
Av. de la Universidad s/n, 46100, Burjassot, Valencia, Spain.
miguel.rodrigo@uv.es.