A Machine Learning Approach to the Personalization of Atrial Electrophysiological Models

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Abstract

Atrial Fibrillation (AF) is the most prevalent form of cardiac arrhythmia, affecting 2% of the total population. Despite its prevalence, the most common general treatments for AF show a high recurrence rate possibly due to high inter-subject variability. Personalized simulations can be used to simulate the effects of treatments in different patients, but the resources needed to develop a personalized model are very high. This work aimed to develop a machine learning-based workflow to accelerate the development of personalized models.

A rectangular tissue model was used to simulate cardiac rhythm for 2100 different ionic profiles, obtaining their biomarkers. Three neural networks were trained to estimate ionic currents from biomarkers, propagability from ionic profiles and biomarkers from ionic currents. When estimating biomarkers from ionic currents (R2: 0.98±0.02, N=6), results were more accurate than the opposite estimation (R2: 0.48± 0.38, N=8).

Machine learning can accelerate the implementation of personalized ionic profiles by estimating biomarkers quickly and in mass for a wide range of currents and selecting those more representative for the patient.

1. Introduction

Atrial Fibrillation (AF) is one of the most prevalent forms of cardiac arrhythmia with clinical repercussions, being the reason for the highest number of emergency medical service interventions among cardiac arrhythmias. Its prevalence increases with age, ranging from 1-2% among general population to over 5% of the population over 65 years old [1].

Despite its prevalence, the general treatments for AF, being anti-arrhythmic drug therapies and catheter ablation therapies, show a rather high recurrence rate, with a recurrence of approximately 59% with drug therapy and 36% with catheter therapy on the first year [2]. A more accurate diagnosis and treatment by adjusting for inter-subject variability can help reduce this recurrence rate [3].

Personalized biophysical atrial simulations can be used to simulate the effect of different treatments in specific patients, but the computational cost of such strategies limits their use cases [4].

The primary objective of this study is to design and evaluate a machine learning-based workflow to accelerate the development of personalized electrophysiological models. The study involves the simulation of a population of models using traditional methods to use their data for the training of two machine learning networks to predict ionic currents from biomarkers and vice versa, along with classification models to differentiate whether a certain combination of ionic currents will produce biomarkers. Then the networks were used to estimate biomarkers in mass, selecting those closest to a target example patient.

2. Material and methods

2.1. Population of models

The electrophysiological model used in this project is the model of Koivumäki [5], applied in a rectangular atrial tissue sample (0.3x2x0.025 cm, 2106 cells, 0.25 mm inter-node distance, 0.01 ms of temporal interval, 0.24 μm^2/ms isotropic diffusion, Figure 1.a) activated from the bottom front with a frequency of 1Hz. The point depicted in white was dedicated to obtaining the transmembrane action potential curve, other two points were used to calculate conduction velocity.

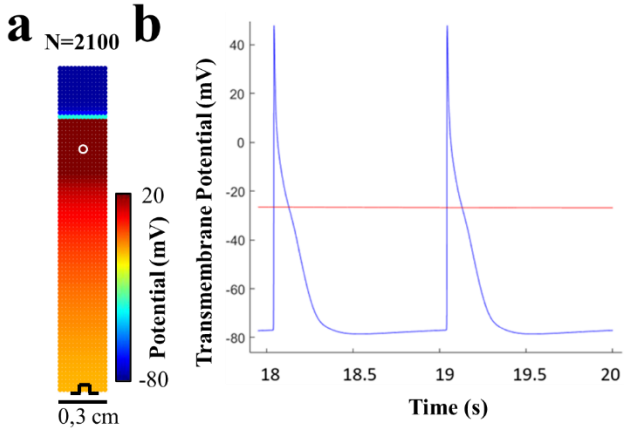

Figure 1: a) Rectangular atrial tissue used for biophysical simulations, actions potentials from white dot were analized, stimulation comes from bottom. b) Example of combination of ionic currents resulting in Action Potential propagation (blue) or non-propagation (red)

Latin hypercube sampling [6,7] was used to obtain a total of 2100 ionic profiles. Eight ionic currents (I_{Na}, I_{CaL}, I_{NaK}, I_{K1}, I_{To}, I_{Kr}, I_{Ks} and I_{Kur}) were sampled in a range from -75% to 150% of a chronic atrial fibrillation (cAF) model, obtained as a result of applying the following modifications on the sinus rhythm model presented in [6]: 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%). Do note that some of the generated ionic profiles are not capable of propagating the action potential (Figure 1.b).

2.2. Machine learning

Two different approaches have been devised for the personalization of models: (1) to predict ionic currents from biomarkers and (2) to predict biomarkers from ionic currents. Action potential biomarkers (RMP, APA, APD90, APD50, APD20 and V20) and the eight ionic currents described before have been considered. All data was distributed using a training (70%) and validation (30 %) split.

The first approach uses a single network to directly estimate ionic profiles from biomarkers. The network consists of two hidden layers, each containing 128 neurons and a dropout of 0.1.

The second approach consists of generating a massive amount of randomised ionic profiles, classifying them according to whether or not they can propagate, and predicting biomarkers from said ionic profiles. Afterwards, the filtered ionic currents are fed into a second network that will estimate biomarker values for them, skipping the need for simulation. This requires the use of two networks, a classifier and a predictor. The classifier used is a single layered perceptron with 128 neurons, while the predictor is a similar network to the one used in the first approach.The models were chosen by comparing error rates among other ML algorithms, including classification and regression trees, random forests and support vector machines.

3. Results

3.1. Population of models

Out of the 2100 simulated models, a total of 864 (~41.14%) were deemed able to propagate the action potential (Figure 2.a). I_{Na} current cannot produce a viable biomarker when under 0.4, and I_{K1} cannot produce it when over 2.0 (Figure 2.b). These are also the ionic currents with highest statistical significance in their difference between propagation and non-propagation, suggesting a high correlation between the two currents' values and propagation viability.

While some biomarkers tend to correlate (Figure 2.d), generated biomarkers still reach most if not all the range of physiologically possible values (Figure 2.c).

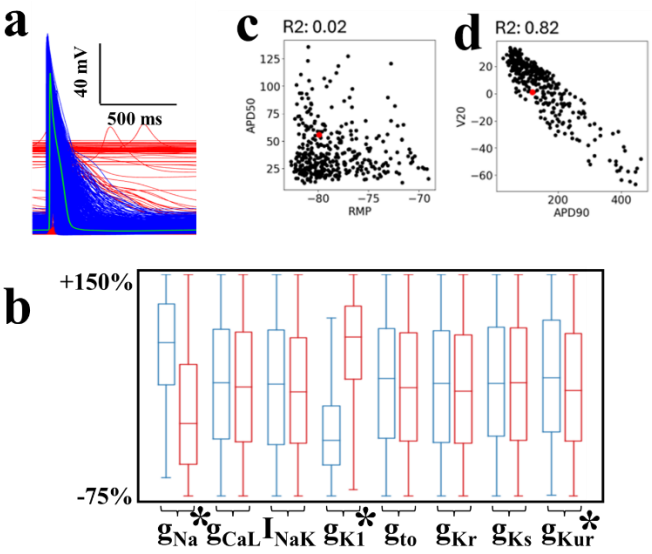

Figure 2: Population of models analysis. a) Action potential curves obtained from simulations. Basal model in green, propagating curves in blue, non-propagating curves in red. b) Comparative boxplot of propagation viability for each ionic current. c) Biomarkers with least correlation d) Biomarkers with most correlation

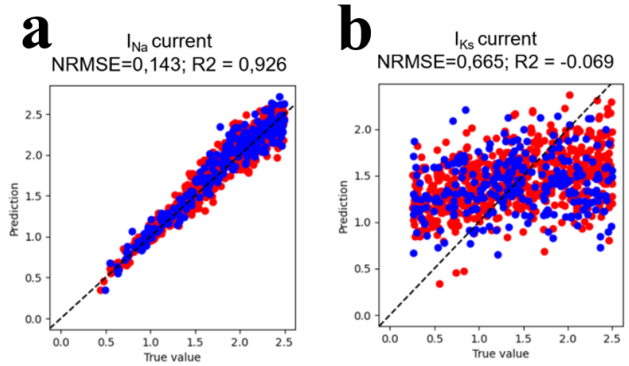

Figure 3: Predicting ionic currents from biomarkers. a) Best prediction (I_{Na}). b) Worst prediction (I_{Ks}). Training samples in red, test samples in blue.

3.2. Machine Learning results

While some ionic currents can be predicted relatively accurately from biomarkers, such as I_{Na} with an R^2 score of 0.926 (Figure 3.a), the struggles with predicting several currents such as the I_{Kr} and I_{Ks} currents or the I_{NaK} exchanger, with I_{Ks} having an R^2 score of -0.069. The network corresponding to the first approach averages an R^2 score of 0.48 with a standard deviation of 0.38 when taking all currents into account. For that reason, a second approach is needed.

The second approach proves to obtain more reliable predictions. The classifier network for propagability has a sensitivity of 0.97 and a specificity of 0.98 (Figure 4.a), while the prediction network averages at an R^2 score of 0.96 with a standard deviation of 0.02, with APA being the highest scored biomarker prediction at 0.984 (Figure 5.b) and APD90 being the lowest scored at 0.934 (Figure 5.c).

An example use case was done to test the second approach. 100.000 ionic current combinations was generated as described for the training data, the combinations were classified, and the biomarkers estimated to those models able to generate an action potential.

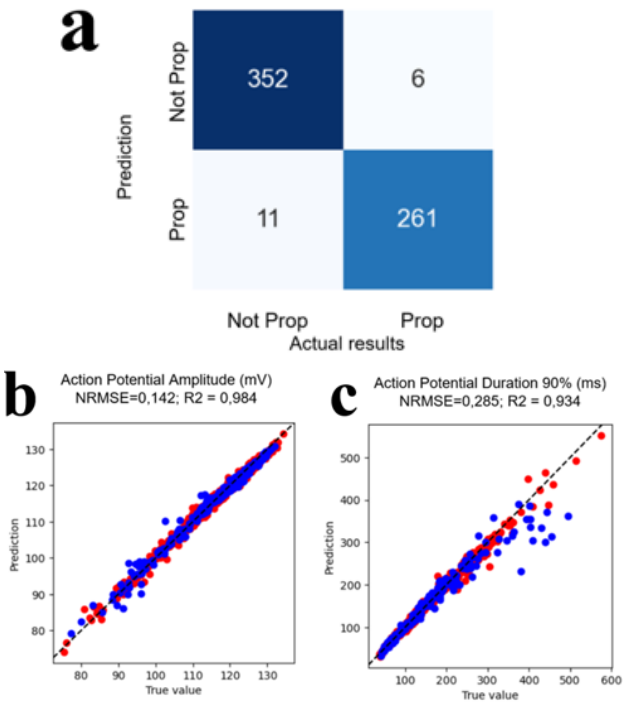

Figure 4: Predicting biomarkers from ionic currents. A) Confusion matrix for propagability classification. B) Best prediction (APA). C) Worst prediction (APD90). Training samples in red, test samples in blue.

After choosing an example patient's biomarker data (RMP = -75 mV, APA = 105 mV, APD90 = 200 ms, APD50 = 35 ms), biomarker values were normalized ($X_N = (X-\mu)/\sigma$) with reference to the original 2100 population results. The 25 ionic current combinations presenting the biomarkers with a smaller Euclidean distance to the example patient were chosen. The ionic currents corresponding to the 25 models chosen are depicted in Figure 5.a presenting high variabilities in most currents, note that I_{K1} and I_{Na} presented lower deviations. Figure 5.b describes the action potentials for the 25 combinations, and Figure 5.c shows the 6 normalized biomarkers.

It is important to note that simulating a population of 100,000 models on a GPU platform [8] would take approximately 30 days, whereas the same ionic currents fed into the second network returned results almost instantly.

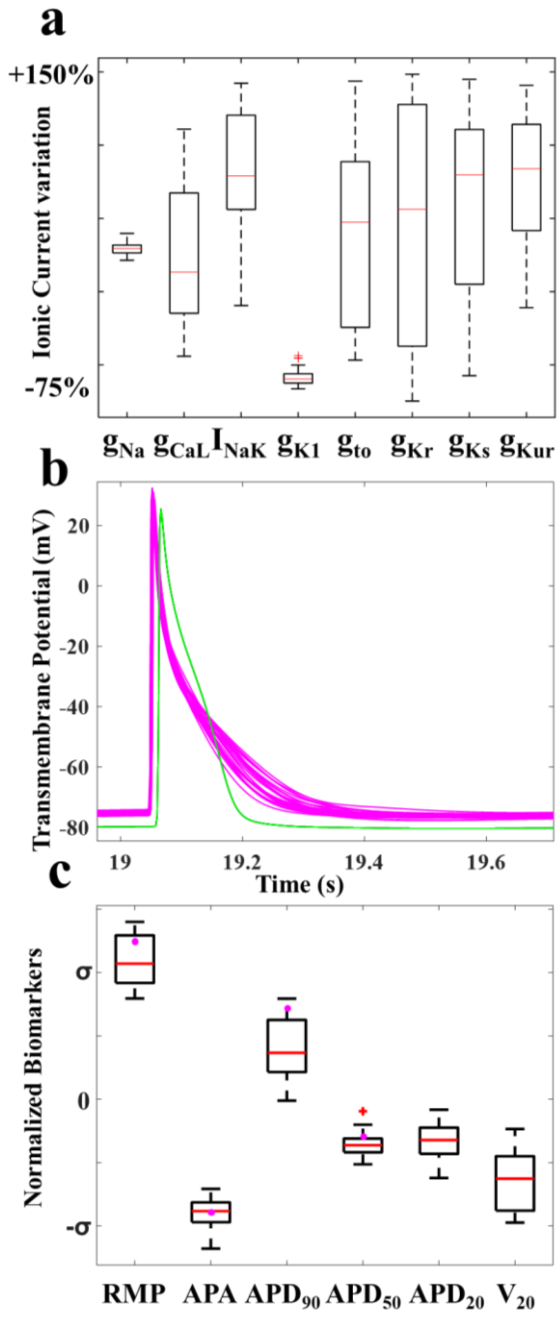

Figure 5: Finding the 25 most similar action potentials to an example case (RMP = -75 mV, APA = 105 mV, APD90 = 200 ms, APD50 = 35 ms) a) Boxplot of the ionic current variations obtained. b) Transmembrane potential traces simulated with the 25 combinations (magenta) and chronic AF baseline model (green). c) Boxplot of obtained biomarkers, normalized objective values are depicted in magenta.

4. Discussion

This project successfully developed Machine learning-based workflow to accelerate the development of personalized atrial electrophysiological models with the use of neural networks to predict biomarkers from a population of generated ionic currents, removing the time cost of running simulations.

However, several limitations can be identified in this work. Firstly, all predictions are based on a single stimulation protocol at 60 bpm and in a bidimensional tissue model, using different pacing protocols or simulating fibrillatory behaviours could enhance the clinical relevance of the strategy presented. Secondly, the biomarkers predicted in this work are not commonly available in clinical practice. Therefore, exploring the prediction of biomarkers derived from intracavitary or ECG recordings, among others, should be considered. Finally, 2100 models were simulated to train the networks, the number of models needed to be simulated for future predictions should be evaluated as it will be determinant in the time needed to complete a whole population of models.

5. Conclusion

A machine learning workflow was successfully developed to obtain personalized atrial electrophysiological models, and the implementation of personalized ionic profiles has been greatly accelerated by estimating biomarkers quickly and in mass for a wide range of currents and selecting those more representative for the target patient.

A population of 2100 ionic currents was simulated, enabling the training and validation of machine learning models to predict ionic currents and biomarkers. The approach predicting biomarkers from ionic currents was much more effective than the on predicting ionic currents from biomarkers, and this approach may be extended further based on biomarkers available in the clinical practice.

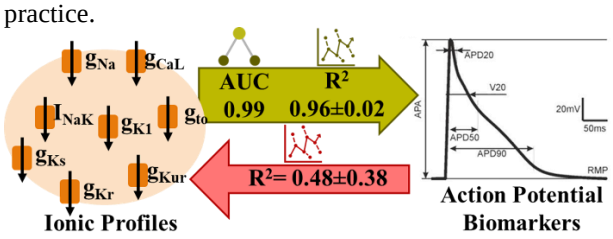

Figure 6: Summary of the results presented in the work. Note how predicting biomarkers from currents (second approach, green) presented more reliable results than predicting currents from biomarkers (first approach, red).

Regarding efficiency increase, a 20 second simulation of 100.000 ionic currents to obtain their biomarkers would take in the order of 30 days, when the use of a trained network eliminates the time cost completely. This allows for the generation of ionic currents in massive quantities to then find the ones most fitting for the patient, obtaining the personalized models.

Acknowledgments

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