Parametrizing Drug Effects with Machine Learning in a New Resonant Model of Cell Electrophysiology

Sucheta Sehgal¹, Nitish D Patel¹, Mark L Trew²

¹ The University of Auckland, Auckland, New Zealand

² Auckland Bioengineering Institute, The University of Auckland, Auckland, New Zealand

Abstract

Drugs often alter the action potential morphologies of cardiac cells. These changes can induce life-threatening arrhythmias. Although models of cellular electrophysiology (EP) are widely available, we have developed a promising alternative: a novel resonant model (RM) designed around the computational strengths of non-CPU platforms such as GPU and FPGA. However, like most models, the RM requires parameterization. To effectively parameterize the RM to capture drug effects on the action potential, we have investigated a machine learning algorithm using a Feed-Forward Neural Network (FFNN). We first designed the FFNN architecture and then found its hyperparameters using a random space search algorithm. The FFNN was trained on data obtained by blocking the 'funny current' in a detailed EP model of the human sinoatrial node (SAN). We used unseen current blockage data as an input to the FFNN for validation. The correlation coefficients between all predicted and reference AP waveform morphologies was above 0.97, with zero and close to zero p-values, indicating significant predictions. Parameters of the RM obtained from FFNN can be used to capture or predict changes in AP morphologies due to drug effects.

1. Introduction

The mechanisms of drug interaction with the EP of various organs are very complex and the effects span from the ion channel to the whole organ level. This makes an investigation of the drugs using solely experimental techniques very difficult and leads to incompatibility of prescription drugs with precision health. Computational models have provided insights into the mechanisms of the life-threatening phenomena, such as cardiac arrhythmogenesis [1]. Therefore, these models represent a powerful tool in investigating drug effects [2]. Also, promotion of computational models to quantify the effects of drugs has been recommended by CiPA [3]. Recently, we have developed a new high-fidelity computational model of AP of biolog-

ical cells [4]. In this paper, we propose a neural network model that can predict the parameters of the RM that correspond to a specific value of a current blockage. We show the efficacy of the proposed RM parameterization to predict changes in AP morphologies and we quantify the validity of the predicted AP waveforms by correlating them to the reference AP waveforms. Also, the comparison has been made between the FFNN fits and other parameterization methods (piecewise linear fits (PLF) and mixed fits (MF)) developed in our previous work [4].

2. Methods

Our objective is to develop an artificial neural network that predicts the RM coefficients with alterations in the ionic channel due to the effects of drugs. In this section, we describe the RM, general neural network architecture and the selection of the hyperparameters of the proposed architecture.

Resonant model of a biological cell (as detailed in [4]) uses finite trigonometric series in Equation (1) to generate the electrical pulse output of a cell $V(t, \beta)$.

$$V(t, \beta) = a_0(\beta) + \sum_{i=1}^n c_i(\beta) \cos(i\omega(\beta)t - \phi_i(\beta)) \quad (1)$$

Here, β represents the percentage reduction in an ion channel conductivity by the administration of a drug. The dynamic parameters (a_0, c_i, ω, ϕ_i) of the RM capture the change in the electrical pulse output due to the influence of a drug. As shown in Figure 1A, the FFNN generates these parameters and feed to the waveshape generator (WG). A WG consisting of n oscillators then produces an action potential (AP) waveshape corresponding to a value of β .

The reference data to train and test the FFNN was obtained using the Fabbri et al. model of human SAN [5]. The model was simulated by varying the maximum funny current (I_f) conductance g_f with β lying between 0 and 1 such that $g'_f = \beta * g_f$. For training, eleven different AP waveshapes were obtained corresponding to eleven equally spaced values of β . The coef-

Figure 2. Profiles of the Resonant model parameters with changing ‘funny current’. The blue traces are the training data obtained by parameterizing the detailed model wavelshapes. The orange traces are the predictions of FFNN with 2 neurons.

Figure 3. Percentage root mean squared error (RMSE) comparison of different Resonant model parameterization techniques for 20 I_f blockage percentage values. The coefficients were fitted with: 1) feed-forward neural network (light blue), 2) minimum RMSE fits (white dotted), and 3) minimum piecewise linear fits (dark blue).

RM was parameterized with PLF (dark blue bars) and MF (white dotted bars) as detailed in our previous work [4]. The figure shows that for most of the funny current blockage levels, the FFNN predictions outperform PLF and MF. At some blockage ranges (e.g 27%-37%), MF performs slightly better.

Figure 4 shows the predicted AP waveforms by the FFNN and PLF parameterized RM, RM_{NN} and RM_{PL} , respectively, for the four different I_f blockage values. The waveforms are compared to the corresponding I_f blockage simulations using the detailed (Fabbri et al.) EP model of the human SAN. Note here that the correlation coefficients CC_{NN} (between detailed model’s and FFNN parameterized

RM’s AP waveforms) and CC_{PL} (between detailed model’s and PLF parameterized RM’s AP waveforms) for all the predicted AP waveforms are above 0.97 and approaching the ideal value of 1. All the predicted AP waveforms and those obtained from Fabbri et al. model are significantly correlated ($p = 0$). Figure 5 draws out a comparison of predicted AP waveform CL metric and shows that the CL closely tracks the Fabbri et al. model. The quantitative effect of the total block of I_f in the FFNN parameterized RM led to an increase in CL of 27.6%. This was in good accordance with the 26% increase in the CL that was experimentally observed by Verkerk et al. [6] upon the complete

Table 2. Cost comparison of the RM parameterization methods.

	PLF ¹	MF ²	FFNNF ¹
Coefficients	170	189	96
Additions	22	143	65
Multiplications	22	644	45
Conditionals	85	10	6

¹ Piecewise linear fits, ²Mixed fits, ³ Feed-forward neural network fits

Figure 4. AP waveforms simulated in human SAN cell detailed EP model and parameterized Resonant model (prediction results) upon A: 97%, B: 84%, C: 47%, and D: 4% block of I_f . The correlation coefficients (CC_{NN} and CC_{PL}) between the reference and parameterized RM AP waveforms are also shown.

Figure 5. Predicted effects of I_f blockage on cycle length (CL).

blockage of I_f by the administration of a 2mM Cs⁺.

Table 2 shows the number of floating-point operations required to generate the RM coefficients with the different fit types and the number of coefficients to be stored in the memory. Even after accounting the capabilities of various implementation platforms such as CPU, FPGA, and GPU, the computational cost of MF far exceeds the accuracy benefits.

4. Conclusion

A machine learning algorithm is effective for parameterizing a new resonant model of cell electrical behaviour, enabling the capture of current blockage effects. With these parameterizations, the computational strengths of RM models can be applied to study and predict the effects of drugs on large scale simulations of cardiac electrical activity. In future, we hope to develop more complex neural network models to capture multiple ion channel blockage effects.

References

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Address for correspondence:

Nitish D. Patel
20 Symonds Street, Faculty of Engineering, Building 401
The University of Auckland, Auckland 1010, New Zealand
nd.patel@auckland.ac.nz