A Modified Fitzhugh-Nagumo Model that Reproduces the Action Potential and Dynamics of the Ten Tusscher et al. Cardiac Model in Tissue

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Abstract

The two-variable Fitzhugh-Nagumo (FHN) model is widely used due to its simplicity; however, it lacks many of the dynamics observed in cardiac experiments that can be reproduced by complex ionic cell models, such as the 19-variable Ten Tusscher et al. (TNNP) model. We aim to parameterize a modified version of the FHN model that reproduces the dynamics in space of more complex cardiac cell models. We combined a series of modifications that previously were applied to the FHN model — mainly, the addition of a nullcline at zero voltage for the fast variable, that eliminates the hyperpolarization of the traditional FHN model and the modification of the slow nullcline from linear to quadratic, which allows alternans behavior and a better fit to experiments and other models. This new model is fitted using particle swarm optimization (PSO) to fit the action potential for a large number of pacing periods so that the restitution of the action potential is matched between the two models. We created a modified FHN model that matches most of the action potential (AP) shape of the TNNP model for a large range of periods and dynamics in space. This model allows for faster proof of concept investigations that can then help guide the more time-consuming simulations from using complex ionic models.

1. Introduction

The 19-variable Ten Tusscher et al. (TNNP) model [1] is one of the most commonly used models for detailed electrophysiological studies as it reproduces many detailed properties from single human ventricular cells from ionic currents and intracellular calcium dynamics, and is able to closely reproduce properties of the wave propagation in human ventricular tissue such as the action potential duration (APD) and conduction velocity (CV) restitutions. However it can be very computationally demanding for large scale studies, such as those which simulate 3D ventricles[2].

In the realm of more simplistic models, the FHN model — a valuable precursor to more complex models — stands out due to its wide application in many studies of nerve, heart and general excitable media. However, it is deficient compared to focused cardiac models due to its simplicity, which includes the lack of “spike-and-dome” morphology of the cardiac action potential that appears in some types of cardiac cells such as epicardium and mid-miocardium. Perhaps more importantly, it cannot study the effects of drugs or mutations that interact with ion channels and FHN was not designed to fit experimental data or other numerical models.

However recent improvements on the FHN model such as those shown by Eq (1) have been made in order to more accurately describe the cardiac action potential and to enable the model to be fitted to experimental data [3]. With these modifications, even when the FHN model can not directly reproduce specific cardiac cell effects, it can be fitted to data resulting from changes to the ion channels. The resulting fit can be used to perform preliminary exploratory studies of various hypotheses, that are far less computational intensive, before using the more complex models for validation of these studies.

\[ \frac{\partial u}{\partial t} = D \nabla^2 u + \mu u(1 - u)(u - \alpha) - vu \]
\[ \frac{\partial v}{\partial t} = \epsilon((\beta - u)(u - \gamma) - \delta v - \theta) \]

(1)

This manuscript provides a blueprint for mapping the modified FHN model, Eqn (1), to the TNNP model. By doing so, we have created a parameter set which closely reproduces the APD restitution curve as well as the general shape of the AP for the TNNP model. This parameterization allows for faster computational investigation of
cardiac cells and tissues before embarking with the use of the more complex ionic cell models.

2. Methods

Two-dimensional TNNP simulations were run on an altered version of the code constructed in WebGL [2, 4, 5], which creates a spiral wave in tissue in accordance with the TNNP model. The alterations made allowed us to pace in a single cell, pace in tissue, record conduction velocity, and pace in the presence of an obstacle such as scar tissue. Additionally, we modified the code to record the AP signal at a chosen probed point as a function of time.

The properties of the AP morphologies and restitution curves were matched using the PSO (particle swarm optimization) [6] algorithm for several action potentials at different pacing frequencies. The PSO algorithm is derivative of swarming behavior seen in a flock of birds [7]. The algorithm works by beginning with a random set of initial conditions, in our case, initial voltages and searching for the global best fit to the data given. Each particle, or data point has both a best individual voltage and a best global voltage to track. Movements of these particles are guided by their best individual and global voltages as described by Zhang et. al. [8].

We supplied this algorithm with simulated data from the TNNP model. Once a fit is obtained, a new set of initial conditions are obtained and the fit is repeated recursively for increased accuracy. The PSO program we used employed increments of 32 iterations at a time. We then compared the modified FHN model to the original TNNP data fed into the algorithm. To ensure a good fit for cardiac tissue, we used data from multiple cycle lengths in our PSO algorithm.

After a fit was created by PSO it was tested in single cell pacing to see if the fit’s single cell restitution curve at 75% fit the TNNP model. Once a match was found here, we simulated the fit in WebGL, using Kaboudian’s library and TNNP code as a reference [2, 4, 5]. The action potentials of both the FHN fit and the TNNP model were recorded and compared. Once a fit passed these stages, the CV and APD of a plane wave were recorded in both TNNP and the FHN fit. This technique allowed us to make a restitution curve of the conduction velocity. Which allowed for appropriate adjustments to be made to the model parameters in order to replicate the TNNP CV, spiral wave behavior, and scar tissue reaction.

3. Results

The resulting fit can be seen in Equation 2:

$$\frac{\partial u}{\partial t} = D \nabla^2 u + 1.475 u(1 - u)(u - 0.203) - vu$$

$$\frac{\partial v}{\partial t} = 0.005((1.63 - u)(u - 0.325) - 1.403v + 0.095)$$

(2)

Figure 1. The single cell restitution curve of the TNNP and the modified FHN models.

The fit was made by PSO to match the restitution curve and AP shape in a single cardiac cell of the TNNP model as seen in Figure 1. The particular parameters that made this fit a good in tissue candidate were $\alpha$, $\beta$, $\mu$, and $\gamma$. These values correlate directly (except for $\alpha$ which correlates inversely) with the APD in tissue and the CV. Since the TNNP model has a larger action potential than typically seen in the FHN model and a faster conduction velocity, it was critical to match these variable with initial conditions starting at their maximum (or in the case of $\alpha$ the minimum) allowed values. The in-tissue results of the fit can be seen in Figures 4 and 5.

The accurate in-tissue results obtained by the fit allowed us to find the appropriate diffusion and time scale to allow the modified FHN model to mimic the TNNP model. To obtain the scaling factors we scaled the diffusion constant, $D$, up by a factor of 9 and the $dt$ down by a factor of $\frac{1}{9}$ to remain resolved in our simulations. This adjustment allowed for us to effectively zoom in on the correct scale of the modified HFN model so its variable speeds could match that of the TNNP model.

The adjustment resulted in the CV restitution curve seen in Figure 6 and the spiral wave seen in Figure 3. For the spiral wave the modified FHN model has a rotation period of approximately 252 ms while the TNNP model has a rotation period of approximately 231 ms.

Additionally, the new fit for TNNP was tested around scar tissue to validate the model behavior when compared to the TNNP model. The resulting test can be seen in Figure 7. The same characteristic double arch pattern seen in the TNNP model by Costa et. al. [9] and Figure 8 is seen in Figure 7. Furthermore, we included a representation of the border zone to demonstrate that the action
potential behaved the same in the border zone as well. The boarder zone in a naturally occurring regime of tissue around a scar where the APD is reduced by a damping coefficient, $\rho$. Here we use $\rho = 0.5$ as a proof of concept that the modified FHN fit will behave similarly to the TNNP. Within the boarder zone we are able to see the triangula-

4. Discussion

The modified FHN fit has strengths and limitations. It can be used to replicate the action potential of the TNNP model, ensuring that the fit makes a good restitution curve. However, the fit goes into conductance block at a cycle length of $300\,ms$, while the TNNP goes into conductor block at a cycle length of $320\,ms$. Both the fit and the TNNP model show bifurcation at a cycle length of $320\,ms$ in tissue and $360\,ms$ in single cell. The fit is additionally able to recreate the spiral wave dynamics close to the ones seen in the TNNP model as well as respond similarly to scar tissue.

The fitted modified FHN model is far from perfect though. Due to the large reduction in information on the ion channels that is inherit with the FHN mode. The main limitation of the modified FHN fit is the CV restitution. As seen in Figure 6, the CV of the TNNP model has a shal-
low slope. The modified FHN fit on the other hand has a steeper slope. Further more, with our particular fit, the alternans are more pronounced in the TNPP model than in the modified FHN model. However this restitution could be in the future fitted by changing values in the $\beta$ parameter.

Future studies with this simplified model could include to vary the different ion channels in the TNPP model and re-fit the FHN parameters to fit the corresponding dynamics. This study would allow for precursor computations of the FHN model to be run first in order to test hypotheses before a detailed investigation is made.

5. Conculsion

The TNPP fit of the modified FHN equations discussed in this paper is capable of replicating the action potential shape and restitution in single cell and in tissue dynamics. While our current fit is limited by its conduction velocity some how, it can mimic the dynamics of spiral waves and responds similarly as the TNPP model around scar tissue and within the boarder zone.

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References