A Modified FitzHugh-Nagumo Model that Allows Control of Action Potential Duration and Refractory Period

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Abstract

To investigate complex electrophysiological behaviour (such as reentrant cardiac arrhythmias) in the setting of the complex anatomy of the heart, the use of a simplified model is computationally more effective. In this study, the Rogers-modified FitzHugh-Nagumo model was further modified to allow control of action potential upstroke velocity, conduction velocity, action potential duration and refractory period. Model parameters were chosen to simulate the action potentials in rabbit sinoatrial node (SAN), atrioventricular node (AVN), atrial muscle and His bundle. The resulting action potential waveforms were a reasonable resembling to experimental data. We have successfully used the models to simulate normal action potential conduction through our rabbit right atrium model. Using a S1-S2 protocol, we were able to simulate an atrial reentrant arrhythmia, reentry occurred around the superior vena cava and the high frequency activity was filtered by the AVN, as observed experimentally.

1. Introduction

Many models have been proposed to simulate the cardiac action potential. They can be classified into two groups: biophysically-detailed (ionic) models and mathematical caricatures (simplified models). To investigate complex electrophysiological behaviour in the setting of the complex anatomy of the heart, the use of a simplified model is computationally more effective – it enables testable predictions about heart behaviour to be made with relatively low computational resource requirements. In this study, the Rogers-modified FitzHugh-Nagumo model [1] was further modified to allow control of action potential upstroke velocity, conduction velocity, duration and refractory period. Model parameters were chosen to simulate the action potentials in rabbit sinoatrial node (SAN), atrioventricular node (AVN), atrial muscle and His bundle.

2. Methods

Instead of ionic models, the model we used to simulate the action potential is based on the Rogers modified FitzHugh-Nagumo model.

$$\begin{aligned} \frac{\partial u}{\partial t} &= \nabla \cdot \boldsymbol{D}\nabla u + c_1 u(u-\alpha)(1-u) - c_2 uv \\ \frac{\partial v}{\partial t} &= b(u - dv) \end{aligned} \tag{1}$$

where u is the excitation variable, which is analogous to transmembrane potential, v is the recovery variable, $\boldsymbol{D}$ is the diffusion tensor, and a, b, c_1, c_2, and d are "membrane" parameters that define the shape of action potential pulse. Four key factors which were chosen to define the parameters are upstroke velocity, refractory period, action potential duration and action potential conduction velocity. The Rogers modified FitzHugh-Nagumo model was modified further for this purpose. For sinoatrial node, we modified original FitzHugh-Nagumo model instead.

$$\frac{\partial u}{\partial t} = \nabla \cdot \boldsymbol{D}\nabla u + c(u(u-\alpha)(1-u) - uv)$$

$$\text{for SAN, use :}$$

$$\frac{\partial u}{\partial t} = \nabla \cdot \boldsymbol{D}\nabla u + c(u(u-\alpha)(1-u) - v) \tag{2}$$

$$\begin{cases} c = c_1 & \dfrac{\partial u}{\partial t} \geq 0 \\ c = c_2 & \dfrac{\partial u}{\partial t} < 0 \end{cases}$$

$$\frac{\partial v}{\partial t} = b(u - dv)$$

When defining model parameters, a 5x5x50 elements model of a strand of SAN, AVN, atrial muscle or His bundle tissue was used. A stimulus was given to the first three sets of elements at one end of the strand (3x5x5). The action potential waveform was recorded from the middle of the strand (point 25, 3, 3). The conduction velocity was measured as the average conduction velocity from the 10th set of elements to the 40th set of elements. Action potential duration was measured at 90% repolarization. A standard S1-S2 protocol was used to measure the refractory period. Figure 1 shows the elements model of a strand.

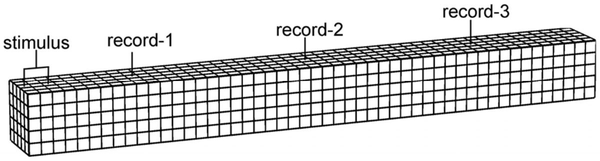

Figure 1. The elements model of a strand for defining parameters. 'stimulus' is the location where a stimulus was given; 'record-2' is the location where the action potential waveform was recorded. 'record-1' and 'record-3' were locations where the propagation times were recorded to calculate the average conduction velocity.

The conduction velocity is mainly controlled by the diffusion tensor ***D***. The upstroke velocity is mainly controlled by the parameter c_1, which also contributes to the conduction velocity.

To find out which parameters contribute to the action potential duration and refractory period, we did some experiments. To exam how parameters *b, d* contribute to the action potential duration and refractory period; the conduction velocity and upstroke velocity were kept same by using same ***D*** (=5), *c* ($c_1=c_2=10$) and α (=0.1), parameter *b* changed from 0.004 to 0.028, parameter *d* changed from 1 to 2.6. Figure 2 shows that action potential duration as function of parameter *d* (1~2.6) at different parameter *b* (0.004~0.028). The results show that action potential duration increases with parameter *d* and decreases with parameter *b*. It means that decreasing *b*, or increasing *d* can increase action potential duration.

Figure 3 shows that refractory period as function of the parameter *d* at different parameter *b*. The results show that refractory period decrease with *b*. But the refractory period is not a monotonically function of parameter *d*. The refractory period decrease with *d* when *d* is smaller than *1.9* and increase with *d* when *d is* larger than *1.9.* The refractory period is shortest when *d* is around *1.9*.

From Figure 2 and Figure 3, it was also found that the refractory period is not a monotonically increase function of action potential duration.

Hence, it is possible to define the action potential duration and refractory period by choose suitable parameter *b* and *d*.

To control action potential duration, the parameter *c* was set to two values: c_1 for depolarization and c_2 for repolarization. The action potential duration increase when c_2 decreases. Figure 4 shows that action potential duration and refractory period as function of parameter c_2 at same c_1 (=10) and parameter *b* (=0.1), *d* (=2.). The result shows that the action potential duration and refractory period increase when parameter c_2 decrease.

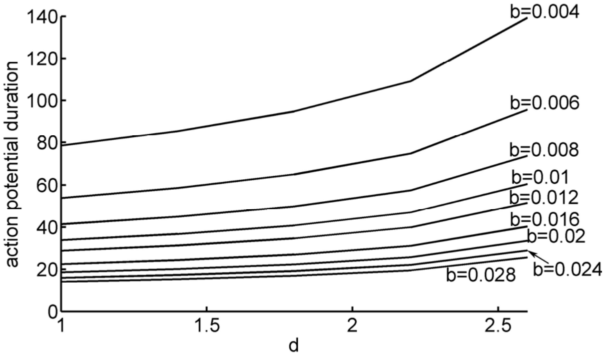

Figure 2. Action potential duration as function of parameter *d* at different parameter *b* and same parameters: ***D****=5, $c_1=c_2=10$, α=0.1.*

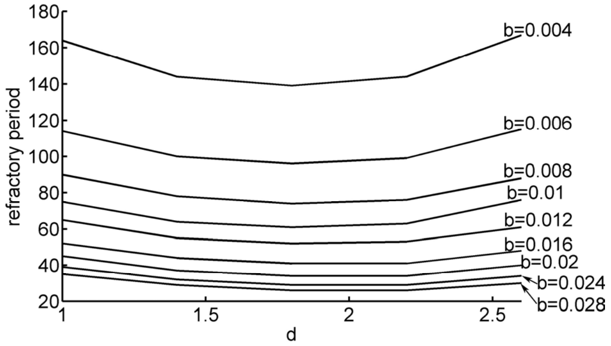

Figure 3. Refractory period as function of parameter *d* at different parameter *d* and same parameters: ***D****=5,c1=c2=10, α=0.1.*

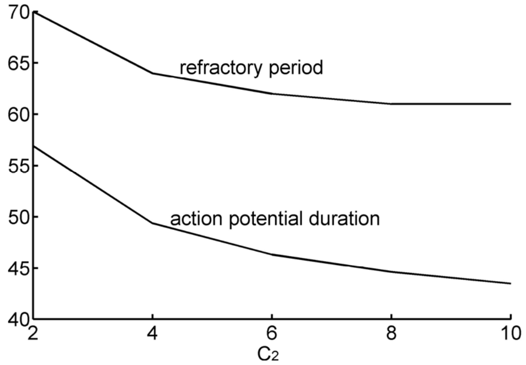

Figure 4. Refractory period and action potential duration as function of parameter c_2 at same parameters (***D****=5, c1=10, b=0.01, d=2, α=0.1*)

Figure 5 shows the action potential waveforms at different parameters. These three waveforms have same upstroke velocity and action potential duration. The result shows that it is possible to define the waveform by choosing different parameters combination.

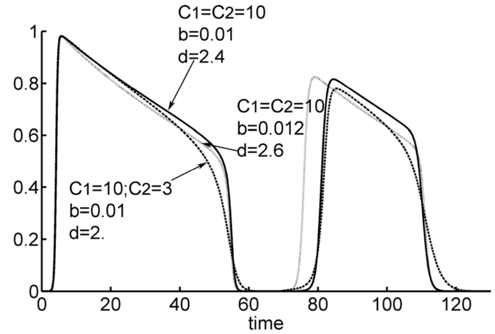

Figure 5. The action potential waveforms at different parameters c2, b, d and same parameters ***D***=5, c_1=10, α=0.1.

3. Results

Table 1. Parameters for sinoatrial node, atrial muscle and atrioventricular node.

parameters	sinoatrial node	atrium muscle	atrioventricular node
D	2	7	2
c_1	0.5	12.7	1.45
c_2	0.22	1.84	1
B	0.003	0.01	0.013
D	3.5	2.475	2.5

Table 2. Simulation results of conduction velocity, upstroke velocity, action potential duration and refractory period of sinoatrial node, atrial muscle and atrioventricular node.

results	sinoatrial node	atrium muscle	atrioventricular node
conduction velocity (mm/ms)	0.0673	0.533	0.0949
upstroke velocity (ms^{-1})	0.0591	1.583	0.158
action potential duration (ms)	181	75	94
refractory period (ms)	273 273	82 82	91 91

Let the size of element in the elements model (Figure 1) is *0.06 mm* and the time unit in equation (2) is *1 ms*. We defined a series parameter for sinoatrial node, atrial muscle, atrioventricular node and His bundle. Table 1 list the parameters we defined for sinoatrial node, atrial muscle and atrioventricular node using the methods introduced above. Table 2 list the simulation results of four key factors: conduction velocity, upstroke velocity, action potential duration and refractory period of sinoatrial node, atrial muscle and atrioventricular node using a strand elements model.

Figure 6 shows the action potential waveforms of simulation (left) and experiment (right). It shows that the resulting action potential waveforms were a reasonable resembling to experimental waveforms.

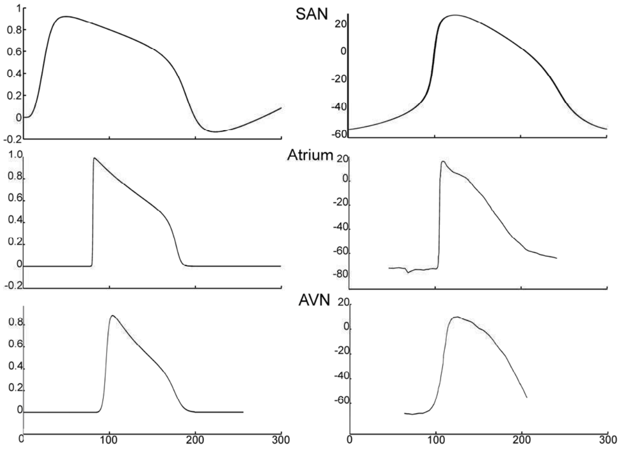

Figure 6 Action potential waveforms. Left: simulation waveforms using our model. Right: experimental waveforms

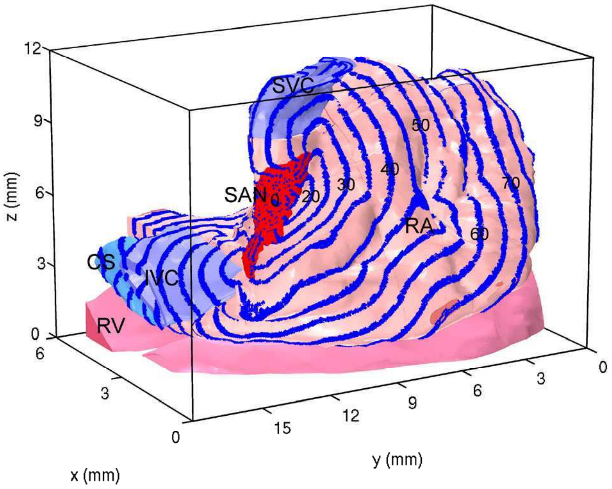

Figure 7. Outside view of normal action potential propagation time sequence through the rabbit right atrium model. SAN: sinoatrial node; SVC: superior vena cava; IVC: inferior vena cava; CS: coronary sinus; RA: right atrial free wall; RV: right ventricle. Time unit is ms.

The model with the parameters defined (Table 1) was used to simulate normal action potential propagation through our rabbit right atrium model[2]. The model has around 1.6 million elements. The simulations were carried out on our 40 nodes High-performance Computing Cluster. Figure 7 shows the normal action potential propagation time sequence viewing from outside of rabbit right atrium. Figure 8 shows the normal action potential propagation time sequence viewing from the inside of right atrium.

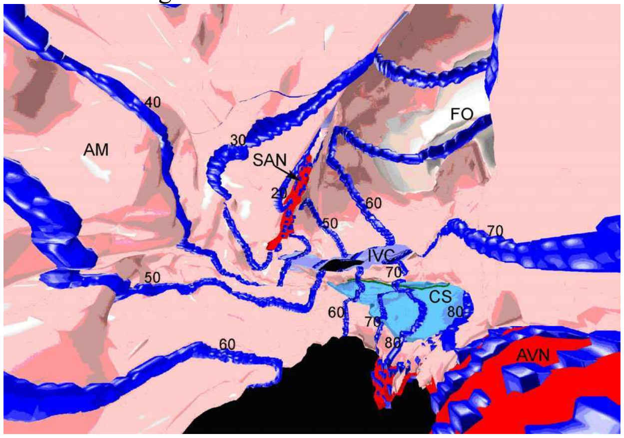

Figure 8 Inside view of the normal action potential propagation time sequence through the rabbit right atrium model. SAN: sinoatrial node; IVC: inferior vena cava; CS: coronary sinus; AM: atrial muscle; FO: fossa ovalis. Time unit is ms.

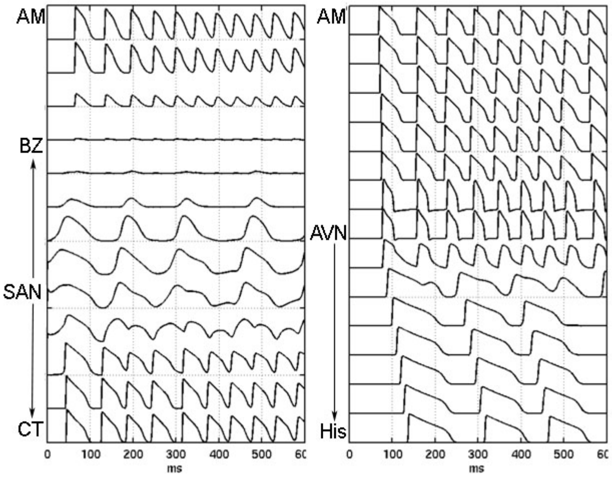

Figure 9. Action potential traces recording from various locations. SAN: sinoatrial node; AVN: atrioventricular node; AM: atrial muscle; CT: crista terminalis; BZ: block zone; His: His bundle.

S1-S2 protocol was used to simulate an atrial reentrant arrhythmia. S1 is normal sinoatrial beat; S2 was stimulus from superior vena cava. The reentry occurred around the superior vena cava and the high frequency activity was filtered by the atrioventricular node, as observed experimentally. Figure 9 shows action potential traces recording from various locations. Left panel shows the action potential propagation started from sinoatrial node, then propagate to both direction, the wave front was blocked by block zone. Right panel shows the action potential wave front propagate through atrioventricular node. The high frequency action potential was filtered by the atrioventricular node.

4. Discussion and conclusions

In this work, we further modified the FitzHugh-Nagumo type model by considering four key factors of action potentials: the conduction velocity, upstroke velocity, action potential duration and refractory period. The conduction velocity and upstroke velocity are easy defined using diffusion tensor ***D*** and membrane parameter c_1 in equation (2).

The action potential duration and refractory period can be controlled by choosing suitable parameters c_2, *b* and *d* in equation (2). The action potential duration increases with parameter *d* and decreases with parameter *b*. The refractory period decreases with parameter *b*. But the refractory period is not monotonically function of *d*.

The modified model was successfully implemented to simulate normal action potential conduction through our rabbit right atrium model [2]. Using a S1-S2 protocol, we were able to simulate an atrial reentrant arrhythmia, reentry occurred around the superior vena cava and the high frequency activity was filtered by the AVN, as observed experimentally.

The FitzHugh-Nagumo type model is a good simple model to investigate complex electrophysiological behaviour (such as reentrant cardiac arrhythmias) in the setting of the complex anatomy of the heart.

Acknowledgements

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References

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