Phase response characteristics of sinoatrial node cells


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Abstract

In this work, the dynamic response of the sinoatrial node (SAN), the natural pacemaker of the heart, to short external stimuli is investigated using the Zhang et al. model. The model equations are solved twice for the central cell and for the peripheral cell. A short current pulse is applied to reset the spontaneous rhythmic activity of the single sinoatrial node cell. Depending on the stimulus timing either a delay or an advance in the occurrence of next action potential is produced. This resetting behavior is quantified in terms of phase transition curves (PTCs) for short electrical current pulses of varying amplitude which span the whole period. For low stimulus amplitudes the transition from advance to delay is smooth, while at higher amplitudes abrupt changes and discontinuities are observed in PTCs. Such discontinuities reveal critical stimuli, the application of which can result in annihilation of activity in central SAN cells. The detailed analysis of the ionic mechanisms involved in its resetting behavior of sinoatrial node cell models provides new insight into the dynamics and physiology of excitation of the sinoatrial node of the heart.

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Keywords: Heart; Sinoatrial node; Mathematical models; Cardiac models; Phase resetting; Three-dimensional phase transition curves; Regional differences

1. Introduction

Auto-rhythmic excitation in the cardiac muscle is driven by the sinoatrial node (SAN), the natural pacemaker of the heart. Under physiological or pathological conditions during clinical interventions, such as defibrillation of cardiac muscle or accidental situations like electrocution, the pacemaker of the heart is subjected to external stimulation [1].

Experimental [2,3] and numerical [4–6] studies indicate that the application of short current pulses to sinoatrial pacemaker cells result in changes in the cell’s cycle length which depend on both the phase and the amplitude of the stimulus [3,7–31]. In most cases, the applied perturbation does not affect the amplitude or the configuration of the pacemaker cell action potential. The magnitude and direction of the phase shift resulting from the alteration of the beat-to-beat interval depends on the timing as well as on the strength of the stimulus. In terms of the resetting effect, the total charge injected into the cell seems to be the crucial factor. Thus, any combinations of various pulse amplitudes and durations, which result in the injection of the same amount of current, are equivalent [5].

The response of biological oscillators to external perturbations has been extensively studied using both theoretical and experimental approaches (reviewed in [32]). Using topological arguments, Winfree [33] greatly contributed to the qualitative understanding of phase resetting responses in biological oscillators and pointed out that, in a spatially extended system like cardiac tissue, such responses play a crucial role in the initiation of arrhythmias. Stimuli of critical amplitude and phase might lead to annihilation of normal rhythmic activity and the initiation of complex spiral wave arrhythmias.

Mathematical models which describe the electrical activity of SAN have been presented by various research groups [1]. The first models produced by Yanagihara et al. [34] and Noble and Noble [35], where the basis for models presented later [36,37].
The analysis of phase response characteristics provides new insight into the dynamics of the mathematical models, of the electrical activities of SAN, and an experimentally verifiable test for the accurate reconstruction of SAN tissue dynamics. Simulation of the spatial variation in the electrical properties of SAN cells and their phase response profiles is necessary for reconstruction of the complex dynamics of the SAN tissue. Zhang et al. [38] recently presented one-dimensional model which describes all of the above.

In this work, we investigate and characterize the effects of external stimulation on central and peripheral SAN cells using the Zhang et al. model [38]. The equation of the model along with the appropriate initial conditions are solved using the Runge–Kutta method. Short (0.5 ms) depolarizing and hyperpolarizing electrical current pulses of varying amplitude and of timing spanning the whole period are applied and the phase transition curves (PTC) are obtained [22]. Three-dimensional PTC [4], relating old phase and stimulus amplitude to the new phase after stimulation, are generated in order to locate critical stimuli and singularities in the models. Numerical simulations for the electrical activity of the transitional cells lying between the center and the periphery of the SAN [38] are carried out. Simulations are conducted when specific ionic currents vary.

The application of a critical depolarizing stimulus (about 0.4 nA) during the late repolarization phase of action potential resulted in annihilation of the activity in central SAN cells, revealing the existence of a stable singularity in the corresponding model configuration [22]. Detailed analysis of the phase response characteristics of the peripheral cells failed to show a similar singularity and annihilation of normal activity. This difference in phase response behavior of central and peripheral cells is portrayed in the structure of the corresponding PTC.

2. Methods

We assume that we apply a short pulse at the SAN and we obtain the PTC using the model proposed by Zhang et al. [38]. The spatial effects are ignored and the problem is reduced to a time dependent problem which is described by the set of ordinary differential equations.

2.1. Model equations

The electrical activity of central and peripheral SAN cells is simulated using the model proposed by Zhang et al. [38] which was developed using experimental data. The model includes formulations for the ionic currents \( I_{Na}, I_{CaL}, I_{CaT}, I_{to} \), sensitive sustained current \( I_{sus}, I_{K,t}, I_{K,s}, I_t \) and background currents \( I_{b,Na}, I_{b,Ca}, I_{b,K}, I_p, I_{NaCa} \). Table 1 shows the parameters entering the model. The total ionic current \( I_{tot} \) appearing in the differential equation which models the membrane potential \( V \) is comprised of the currents: \( I_{Na}, I_{CaL}, I_{CaT}, I_{to}, I_{sus}, I_{K,t}, I_{K,s}, I_t, I_{b,Na}, I_{b,Ca}, I_{b,K}, I_{NaCa} \) and \( I_p \). The total membrane potential is modelled as

\[
\frac{dV}{dt} = \frac{-1}{C} I_{tot},
\]

where \( V \) is the membrane potential, \( t \) is the time, \( C \) is the membrane capacitance of SAN and

\[
I_{tot} = (I_{Na} + I_{CaL} + I_{CaT} + I_{to} + I_{sus} + I_{K,t} + I_{K,s} + I_t + I_{b,Na} + I_{b,Ca} + I_{b,K} + I_{NaCa} + I_p).
\]

The transition from central to peripheral SAN activity was modelled as in [38], using a scaling factor which depends on the distance of each cell from the center of the SAN. The set of differential Eqs. (1)–(16) given in Tables 2–9 is solved using a fourth order Runge–Kutta method with time step 0.1 ms. Further details for the formulation of the equations described in Tables 2–9 and the experimental background behind the equations are sited in [38]. The set of differential Eqs. (1)–(16) are solved twice: first the set of equations is solved for the central cell with initial conditions shown in the left column of Table 9 and second for the peripheral cell with initial conditions shown in the right column in Table 9. The model equations for central, peripheral and transitional cell configurations are integrated until a stable limit cycle is obtained. The minimum diastolic potential is determined on the stable limit cycle and the vector of dynamic variables at this point is recorded and used as the initial condition in the subsequent simulations. For each of the configurations examined, a single 0.5 ms depolarizing or hyperpolarizing current stimulus of a given amplitude is applied at several time steps during the whole period of integration. The starting reference point is selected at the membrane potential level of \((-10 mV)\) during the depolarization phase of the action potential and at each subsequent run the stimulus timing increases by 1 ms. The stimulation current amplitude varies from 0 to 7.5 nA. For a given stimulus amplitude, the corresponding PTC are obtained [22], for the whole range of stimulus amplitudes, three-dimensional PTC are also obtained [4].

3. Results

The normal electrical activity of central, peripheral, and transitional SAN cells is shown in Fig. 1. The membrane potential \( V \) of central (dark line—in Fig. 1(a)) and peripheral (dark line—in Fig. 1(c)) SAN cells is plotted vs time. The gray lines indicate the electrical activity of the transitional cells. The duration of the simulation is 1 s. The transition between central and peripheral activity is modelled using a scaling factor (ranging from 0 to 1) which depends on the distance of the cell from the center of the SAN (see Eqs. (80) and (81) in Ref. [38] and Ref. [39]). The scaling factor is used in order to calculate the capacitance and the ionic conductances of the transitional cells given their corresponding values at the center and the periphery of the SAN.

For the transitional cell activity shown in Fig. 1 the scaling factor values (0.04 in Fig. 1(a) and 0.13 in plot Fig. 1(c)) SAN cells is plotted vs time. The gray lines indicate the electrical activity of the transitional cells. The duration of the simulation is 1 s. The transition between central and peripheral activity is modelled using a scaling factor (ranging from 0 to 1) which depends on the distance of the cell from the center of the SAN (see Eqs. (80) and (81) in Ref. [38] and Ref. [39]). The scaling factor is used in order to calculate the capacitance and the ionic conductances of the transitional cells given their corresponding values at the center and the periphery of the SAN.

For the transitional cell activity shown in Fig. 1 the scaling factor values (0.04 in Fig. 1(a) and 0.13 in plot Fig. 1(c)) were selected to indicate the point where a sharp change in membrane potential configuration is evident. Thus, in Fig. 1(c) the transitional cell appears to have the characteristic spike-and-dome configuration of peripheral cells.

The total ionic current \( I_{tot} \) is plotted vs membrane potential \( V \) for each of the corresponding simulations Fig. 1(b) and (d).
Fig. 1. Normal electrical activity in central (a,b), peripheral (c,d) and transitional sinoatrial node cells (gray lines in a–d). In figures (b) and (d) the total ionic current $I_{\text{tot}}$ is plotted vs the membrane potential $V$ shown in figures (a) and (c). Figures (a) and (c) indicate the variations of membrane potential $V$ with time $t$.

Fig. 2. (a) Single pulse perturbation protocol for the central sinoatrial node cell. A depolarizing stimulus of 0.45 nA is applied with a time delay $\Delta$ after the detection (at $V = -10$ mV during the depolarization phase) of the second action potential. The gray trace corresponds to the unperturbed activity. (b) The total ionic current $I_{\text{tot}}$ vs the membrane potential $V$. The difference in $I_{\text{tot}}$ amplitude between central and peripheral cells is mainly due to the contribution of $I_{\text{Na}}$ which is not present in central cells. The $I_{\text{tot}}$–$V$ plots provide a means to visualize the effects of external perturbation on the SAN cell activity (see Fig. 2) and can be considered as a representation of the complete multi-dimensional phase space of the model.

The single pulse perturbation protocol used is shown in Fig. 2. The gray solid line represents the normal unperturbed electrical activity of central SAN cell with a period $T_0 = 334$ ms. The onset of the action potential is marked at $V = -10$ mV (depolarization phase). At a time interval $\Delta$ after the onset of the action potential a short (0.5 ms) depolarizing current pulse is applied resulting in early depolarization of the cell membrane (dark line). The phase $\phi$ of the stimulus is $\Delta / T_0$, while the new phase of the perturbed oscillator is $\phi' = \phi + 1 - T / T_0$ where $T$ is the period of the perturbed cycle [22]. The electrical activity resumes immediately after the first perturbed cycle as is evident from the $I_{\text{tot}}$–$V$ plot (Fig. 2(b)) in which both simulations are shown (gray line corresponds to the unperturbed limit cycle oscillation of the central SAN cell and the black line corresponds to the limit cycle oscillation of the SAN).

The individual ionic currents comprising $I_{\text{tot}}$ in both the central and peripheral SAN cell models are shown in Fig. 3(a), (b). Current traces of 1 s of spontaneous activity are plotted.
A comparison of the two plots reveals the contribution of each ionic current in \( I_{\text{tot}} \). The sodium current \( I_{Na} \) is the principal component of \( I_{\text{tot}} \) in peripheral while it is absent in central SAN cells.

In the central cell model, the maximum upstroke velocity of the action potential is 6 V s\(^{-1}\), the minimum diastolic potential is −68 mV and the maximum systolic potential is 22 mV, while in the peripheral cell model the maximum upstroke velocity of the action potential is 86 V s\(^{-1}\), the minimum diastolic potential is −81 mV and the maximum systolic potential is 25 mV.

For each one of the experiments shown in Fig. 1(a) and (c), we repeat those with \( \Delta \) from 0 to \( T_0 \) (correspondingly \( 0 < \phi < 1 \) and current stimulus amplitudes from 0 to 7.5 nA. The results are shown in Fig. 4 where representative PTC are depicted. Fig. 4(a)–(d) correspond to low amplitude stimuli (−0.3 nA) while Fig. 4(e)–(g),(j) traces correspond to high amplitude stimuli. Fig. 4(a)–(d), (j) correspond to central and peripheral cells while the Fig. 4(b), (c), (f), (g) correspond to the transitional cell configurations shown in Fig. 1 (gray lines in Fig. 1(a) and (c), respectively).

The advance or delay in the occurrence of the first action potential after perturbation for a set of experiments for which the stimulus phase varies from 0 to 1 can be visualized by plotting the ratio of the corresponding period \( T_1 \) (during which the stimulus was applied) to the period \( T_0 \) of the unperturbed cycle over the stimulus phase \( \phi \). Such plots were obtained for the central and peripheral SAN (Fig. 5).

Low amplitude stimulation shown in Fig. 5(a), (b), in both the central and peripheral SAN cells, produces only minimal advances (\( T_1/T_0 < 1 \)) or delays (\( T_1/T_0 > 1 \)) for most of the cycle excluding a small region around \( \phi = 0.4 \) where a significant advance is observed. At this region the membrane is in the absolute refractory period and the stimulus amplitude is sufficient to initiate an action potential and thus to shorten \( T_1 \). Increasing the stimulation amplitude extends the \( \phi \) region where an advance is observed. In central cells the delay in the occurrence of the action potential at intermediate stimulus levels observed close to \( \phi = 0.6 \) is associated with the approximation of a singularity in the phase space. Around this singularity \( T_1 \) becomes close to \( 2 \times T_0 \) (Fig. 5(c)) while for \( 0.4 < \phi < 0.6 \) approaching \( T_1/T_0 = 2 \), there are missing points which correspond to \( T_1/T_0 \to \infty \).

The PTC shown in Fig. 4 indicate that, in central, peripheral, and transitional SAN cells, both Type 0 (Fig. 4(a)–(d)) and Type 1 (Fig. 4(e)–(j)) phase resetting is obtained. Low amplitude stimuli produce continuous PTC since the effect of the external perturbation on the phase of the limit cycle oscillator is less pronounced. The discontinuities of the PTC for stronger
stimuli (Type 1 phase resetting) are indicative of the existence of a singularity in the limit cycle.

Each of the PTC in Fig. 4 represents a set of experiments like the one shown in Fig. 2 where the stimulus amplitude is constant while the interval $\Delta t$ varies. A set of such curves for various stimulus amplitudes produces a three-dimensional phase transition surface [4] relating both $\phi$ and stimulus amplitude to the new phase $\phi'$ of the perturbed oscillator. Such three-dimensional phase transition plots allow further investigation of the phase resetting behavior of an oscillator. Moreover, such PTC can help in finding the exact stimulus phase and amplitude combination which brings the oscillator close to the singularity range.

The three-dimensional phase transition plots for the central, transitional and peripheral SAN cells are shown in Fig. 6 as contour plots with the new phase $\phi'$ is color-coded.
Fig. 5. Alteration of the timing of the first action potential after stimulation is plotted $T_1/T_0$ vs $\phi$ for various stimulation amplitudes. (a) Peripheral cell at $-0.5$ nA, (c) peripheral cell at $-2.5$ nA, (e) peripheral cell at $-5$ nA, (g) peripheral cell at $-6.5$ nA and (b) central cell at $-0.2$ nA, (d) central cell at $-0.4$ nA, (f) central cell at $-0.6$ nA ($T_0$, central = 320 ms, $T_0$, peripheral = 160 ms).

on a gray scale from 0 to 1. The ordering of the plots is similar to that of Fig. 4 and the corresponding PTC of Fig. 4 can be considered as horizontal “slices” of the data at the corresponding current stimulus amplitude ($I_{stim}$). The difference in the stimulus amplitude for the corresponding plots is due to the difference in the amplitude of the corresponding total membrane current (a stronger stimulus is required to produce Type 1 phase resetting behavior of Fig. 1).

In the three-dimensional phase transition plots shown in Fig. 6, there exist regions where the new phase $\phi'$ is very dense
Fig. 6. Three-dimensional contour plots of the new phase vs old phase and amplitude: for (a) central, (b) peripheral, and (c), (d) transitional SAN cell.

Fig. 7. A critical stimulus of $-0.4\ nA$ applied at $t = 0.53\ s$ resulting in permanent annihilation of sinoatrial node repetitive activity.

(e.g. for $\phi = 0.55$ and $I_{\text{stim}} = -0.4\ nA$). Such regions indicate the existence of a singularity and should be further investigated by fine-tuning of both $\Delta$ interval and $I_{\text{stim}}$ amplitude.

Further experimentation with finer values for $\Delta$ and $I_{\text{stim}}$ within those regions revealed the existence of a stable singularity for the central SAN cell. In the simulation shown in Fig. 7a...
critical stimulus of $-0.4 \text{nA}$ is applied at $t = 0.53 \text{s}$ resulting in permanent annihilation of the normal repetitive activity. Transitional and the peripheral cells do not exhibit similar behavior.

The application of stimulus of appropriate amplitude and phase (e.g. $\phi = 0.4$ and $I_{\text{stim}} = -5.4$) results in a series of low amplitude oscillations of the membrane potential with normal limit cycle behavior resuming after 2–3 cycles.

4. Discussion

Investigation of the dynamic behavior of biological oscillators and their response to external perturbation is of great importance in biological research since biological oscillations are involved in many vital processes in living systems [32,33]. Understanding the dynamic response of the SAN to external perturbations is important in elucidating its behavior under normal and pathological conditions [33]. Studies in the past have concentrated on the elucidation of the phase resetting dynamics of the SAN using biophysical ionic models [15,29,5] but did not address the issue of regional differences between central and peripheral node cells (the corresponding ionic models described central cell behavior).

The SAN is a complex structure and regional differences in the electrical activity of regional cells seem to be important in the behavior of the natural pacemaker of the heart [39,40,30]. The Zhang et al. model [38] used in this study accounts for regional differences and can be used to model the electrical activity of central, peripheral, and transitional cells.

In this work, the analysis of phase resetting characteristics of each type of SAN cell by means of three-dimensional phase transition plots, revealed important differences in their response to external electrical stimuli (see Fig. 6). Although all types of cells display both Type 0 and Type 1 phase resetting behavior, the stimulus amplitude at which Type 1 phase resetting behavior first appears varies. This is a result of the regional differences in $I_{\text{tot}}$ amplitude (see Fig. 1): $I_{\text{tot}}$ is higher in the periphery of SAN (mainly due to the dominance of $I_{\text{Na}}$) and thus a higher amplitude of external stimulus is required in order to significantly affect the normal limit cycle behavior. We have produced $I_{\text{tot}}-V$ plots to provide a means to visualize the effects of external perturbation on the SAN cell electrical activity (Fig. 2).

Our simulations show the existence of a critical stimulus amplitude-phase combination which is capable of annihilating the electrical activity of the central SAN cells (Fig. 7). So far, there is no reference in the literature describing and proofing the existence of such a combination in Zhang model. It is believed that such critical stimuli are involved in the generation of certain cardiac arrhythmias [33] and gives new insights into the investigation of cardiac models.

In a complex structure like the SAN, regional differences and spatiotemporal interactions could play an important role in its pathophysiological response to external perturbations and should be further investigated. This must be included in our next set of experiments targeting one-dimensional cells. However, the use of the finite element method might help in the analysis of two- and three-dimensional structures. The comparison of phase resetting characteristics of other models will be included too.

Investigation of the effects of increases of various concentration on annihilation of SAN activity must be further studied.

5. Summary

In the present work, we use the model proposed from Zhang et al. [38] and we examine the dynamic response of the SAN to external stimulus. We apply a short current to reset the spontaneous rhythmic activity of the single SAN. This application of the external stimulus results in the prolongation of the normal activity and a new phase is obtained. This resetting behavior is quantified in terms of phase transition curves (PTCs) for short electrical current pulses of varying amplitude which span the whole period. Discontinuities, as we show in the figures, reveal critical stimulus. The application of this critical stimulus can result in annihilation of activity on SAN cells. Detailed analysis of the ionic mechanisms which involved in the resetting behavior could be useful and provide new insight into the physiology of the excitation in SAN cell. Our work, is a step forward to a future work on higher dimensionality model were we believe the resetting techinc can be more significant.

Acknowledgements

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Appendix

The parameters used in the model are given in Table 1. The set of differential equations (1)–(16) given in Tables 2–9 was solved using a fourth order Runge–Kutta method with time step 0.1 ms.

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<th>Table 1 Parameters of the model</th>
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<td>4-AP</td>
</tr>
<tr>
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</tr>
<tr>
<td>APD</td>
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<tr>
<td>CL</td>
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<tr>
<td>$C_m$</td>
</tr>
<tr>
<td>$C_m' (x)$, $C_m'' (x)$</td>
</tr>
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<td>$d_{\text{ICa,L}}$, $d_{\text{ICa,T}}$</td>
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<td>$d_{\text{Na,Ca}}$</td>
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<td>$F$</td>
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<td>$F_{Na}$</td>
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Table 1 (continued)

<table>
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<th>Symbol</th>
<th>Definition</th>
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<td>( f_L, f_I )</td>
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<td>( \theta, \gamma )</td>
<td>Conductance of a current in peripheral or central SA node cell models</td>
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<td>( g^{a}(x), g^{s}(x) )</td>
<td>Conductance of a current in atrial muscle cell or SA node cell in one-dimensional model of intact SA node at distance ( x ) from center of SA node</td>
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<td>( g_{Na} )</td>
<td>Conductance of ( I_{Na} )</td>
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<tr>
<td>( g_{Na}, g_{Kas} )</td>
<td>Conductance of ( I_{Na} ) and ( I_{Kas} )</td>
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<td>( g_{K1}, g_{Ks} )</td>
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<td>( g_{Na}, g_{Na1} )</td>
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<td>Transient and sustained components of 4-AP-sensitive current</td>
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<tr>
<td>( L^a )</td>
<td>Length of string of SA node tissue in one-dimensional model of intact SA node</td>
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<tr>
<td>( m )</td>
<td>Activation variable for ( I_{Na} )</td>
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<td>( \lambda )</td>
<td>Space constant</td>
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Table 2

Formulation of the equations of \( Na^+ \) current \( (I_{Na}) \)

The sodium current \( I_{Na} \) is given by the equation

\[
I_{Na} = \frac{g_{Na}(m)^{3}h_{Na}^{2}(F)^{2}RT}{RT + \left(F(V^{E_{Na}})RT - 1.0\right)} \frac{F}{V}
\]

Sodium current \( m \) gate

\[
\frac{dm}{dt} = \left( m_{∞} - m \right) \frac{1}{\tau_{m}}
\]

\[
m_{∞} = \left( \frac{1.0}{1.0 + e^{-V/5.46}} \right)^{1.0/3.0}
\]

\[
\tau_{m} = \frac{0.0006247}{(0.832e^{-0.335V}+66.71)e^{0.627e^{-0.082(V+65.01)}}} + 0.000004
\]

Sodium current \( h \) gate

\[
h = (1.0 - F_{Na})h_{1} + F_{Na}h_{2}
\]

\[
\frac{dh_{1}}{dt} = \frac{\left(h_{1,∞} - h_{1}\right)}{\tau_{h_{1}}}
\]

\[
\frac{dh_{2}}{dt} = \frac{\left(h_{2,∞} - h_{2}\right)}{\tau_{h_{2}}}
\]

\[
h_{1,∞} = \frac{1.0}{(1.0 + e^{V+66.71}/8.3)}
\]

\[
h_{2,∞} = h_{1,∞}
\]

\[
\tau_{h_{1}} = \frac{0.000003171e^{-0.2815(V+17.11)} + 0.0005977}{(1.0 + 0.0005732e^{-0.3429(V+27.75)})}
\]

\[
\tau_{h_{2}} = \frac{0.000003186e^{-0.6219(V+18.8)}}{(1.0 + 0.00007189e^{-0.6683(V+34.07)})} + 0.003556
\]
Table 3
Formulation of the equations of L-type Ca\(^{2+}\) current, \(I_{Ca,L}\)

\[ I_{Ca,L} = g_{Ca,L} \left( f_{L} d_{L} + \frac{0.006}{1 + e^{-(V+14.1)/6.0}} \right) (V - E_{Ca,L}) \]

L-type Ca channel \(d\) gate

\[ \frac{dd_{L}}{dt} = \left( d_{L,\infty} - d_{L} \right) \tau_{d,L} \tag{5} \]

\[ \tau_{d,L} = \frac{1.0}{\tau_{d,L} + \beta_{d,L}} \]

\[ d_{L,\infty} = \frac{1.0}{1 + e^{-(V+23.1)/6.0}} \]

L-type Ca channel \(f\) gate

\[ \frac{df_{L}}{dt} = \left( f_{L,\infty} - f_{L} \right) \tau_{f,L} \tag{6} \]

\[ \tau_{f,L} = \frac{1.0}{\tau_{f,L} + \beta_{f,L}} \]

\[ f_{L,\infty} = \frac{1.0}{1 + e^{(V+45.5)/3.0}} \]

T-type Ca channel \(I_{Ca,T}\)

\[ I_{Ca,T} = g_{Ca,T} d_{T} f_{T} (V - E_{Ca,T}) \]

T-type Ca channel \(d\) gate

\[ \frac{dd_{T}}{dt} = \left( d_{T,\infty} - d_{T} \right) \tau_{d,T} \tag{7} \]

\[ \tau_{d,T} = 1068.0 e^{-(V+26.3)/30.0} \]

\[ \beta_{d,T} = 1068.0 e^{-(V+26.3)/30.0} \]

T-type Ca channel \(f\) gate

\[ \frac{df_{T}}{dt} = \left( f_{T,\infty} - f_{T} \right) \tau_{f,T} \tag{8} \]

\[ \tau_{f,T} = \frac{1.0}{\tau_{f,T} + \beta_{f,T}} \]

\[ f_{T,\infty} = \frac{1.0}{1 + e^{(V+71.7)/9.0}} \]

Table 4 (continued)

\[ \tau_{d,T} = \frac{1.0}{\tau_{d,T} + \beta_{d,T}} \]

\[ d_{T,\infty} = \frac{1.0}{1 + e^{-(V+23.1)/6.8}} \]

\[ \tau_{f,T} = \frac{1.0}{\tau_{f,T} + \beta_{f,T}} \]

\[ f_{T,\infty} = \frac{1.0}{1 + e^{(V+71.7)/9.0}} \]

Table 5
Formulation of the equations for sensitive currents \(I_{s}\) and delayed rectifying current \(I_{K,r}\)

\[ I_{s} = g_{s} q r (V - E_{K}) \]

\[ I_{s,\infty} = g_{s} q r (V - E_{K}) \]

\[ q\) gate

\[ \frac{dq}{dt} = \frac{(q_{\infty} - q)}{\tau_{q}} \tag{9} \]

\[ q_{\infty} = \frac{1.0}{1 + e^{(V+59.37)/13.1}} \]

\[ \tau_{q} = \left( 0.0101 + \frac{0.06517}{0.57 e^{-0.09(V+50.61)} + 0.000024 e^{0.1(V+59.93)}} \right) \]

4-AP sensitive currents \(r\) gate

\[ \frac{dr}{dt} = \frac{(r_{\infty} - r)}{\tau_{r}} \tag{10} \]

\[ r_{\infty} = \left( 1.0 + e^{-(V+80.93)/19.7} \right) \]

\[ \tau_{r} = \left( 0.00298 + \frac{0.01559}{1.037 e^{0.09(V+50.61)} + 0.369 e^{-0.12(V+23.84)}} \right) \]
Table 5 (continued)

Rapid delayed rectifying potassium current $I_{K,d}$

$$I_{K,d} = g_{K,d} p_a p_b (V - E_K)$$

$$p_a = ((1.0 - F_{K,d}) p_{a,t} + F_{K,d} p_{a,s})$$

Rapid delayed rectifying potassium current $p_{a,t}$ gate

$$\frac{dp_{a,t}}{dt} = \frac{(p_{a,t,\infty} - p_{a,t})}{\tau_{p_{a,t}}}$$

$$p_{a,t,\infty} = \frac{1.0}{(1.0 + e^{-(V+14.27)/10.5})}$$

$$\tau_{p_{a,t}} = \frac{1.0}{(37.2e^{(-V-9.00)/15.9} + 0.96e^{-(V-9.90)/21.5})}$$

Rapid delayed rectifying potassium current $p_{a,s}$ gate

$$\frac{dp_{a,s}}{dt} = \frac{(p_{a,s,\infty} - p_{a,s})}{\tau_{p_{a,s}}}$$

$$p_{a,s,\infty} = P_{a,t,\infty}$$

$$\tau_{p_{a,s}} = \frac{1.0}{(4.2e^{(-V-9.00)/17.0} + 0.15e^{-(V-9.90)/21.6})}$$

Rapid delayed rectifying potassium current $p_t$ gate

$$\frac{dp_t}{dt} = \frac{(p_{t,\infty} - p_t)}{\tau_{p_t}}$$

$$p_{t,\infty} = \frac{1.0}{(1.0 + e^{(V+14.67)/10.1})}$$

Table 6 (continued)

Formulation of the equations for slow delayed rectifying current ($I_{K,s}$) and hyperpolarization current ($I_t$)

Slow delayed rectifying potassium current $I_{K,s}$

$$I_{K,s} = g_{K,s} (x_s)^2 (V - E_{K,s})$$

Slow delayed rectifying potassium current $x_s$ gate

$$\frac{dx_s}{dt} = \frac{(x_{s,\infty} - x_s)}{\tau_{x_s}}$$

$$x_{s,\infty} = \frac{x_s}{(x_s + \beta_{x_s})}$$

$$\tau_{x_s} = \frac{1.0}{(x_s + \beta_{x_s})}$$

Hyperpolarization activated current $I_t$

$$I_t = (I_{t,Na} + I_{t,K})$$

$$I_{t,Na} = g_{t,Na} (V - E_{Na})$$

$$I_{t,K} = g_{t,K} (V - E_K)$$

Hyperpolarization activated current $y$ gate

$$\frac{dy}{dt} = \frac{(y_{\infty} - y)}{\tau_y}$$

$$y_{\infty} = \frac{y}{(y + \beta_y)}$$

$$\tau_y = \frac{1.0}{(y + \beta_y)}$$
Table 7
Formulation of the equations for background, pump and exchanger currents

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{h,Na}$</td>
<td>$g_{h,Na}(V - E_{Na})$</td>
</tr>
<tr>
<td>$I_{p,Na}$</td>
<td>$g_{p,Na}(V - E_{Na})$</td>
</tr>
<tr>
<td>$I_{h,K}$</td>
<td>$g_{h,K}(V - E_K)$</td>
</tr>
<tr>
<td>$I_{p,K}$</td>
<td>$g_{p,K}(V - E_K)$</td>
</tr>
<tr>
<td>$I_{h,Na}$</td>
<td>$g_{h,Na}(V - E_{Na})$</td>
</tr>
<tr>
<td>$I_{p,Na}$</td>
<td>$g_{p,Na}(V - E_{Na})$</td>
</tr>
<tr>
<td>$I_{h,K}$</td>
<td>$g_{h,K}(V - E_K)$</td>
</tr>
<tr>
<td>$I_{p,K}$</td>
<td>$g_{p,K}(V - E_K)$</td>
</tr>
</tbody>
</table>

Sodium background current $I_{h,Na} = g_{h,Na}(V - E_{Na})$

Potassium background current $I_{p,Na} = g_{p,Na}(V - E_{Na})$

Calcium background current $I_{h,Na} = g_{h,Na}(V - E_{Na})$

Sodium calcium exchanger $I_{NaCa}$

Calcium exchanger $I_{Ca}$

Sodium calcium exchanger $I_{NaCa}$

Sodium potassium pump $I_{p}$

$I_{p} = I_{p,max} \left( \frac{[Na^+]_{i}}{[K^+]_{o} \times (1.5 + e^{-(V+60.0)/40.0})} \right)$

$E_{Na} = \frac{RT}{F} \ln \frac{[Na^+]_{o}}{[Na^+]_{i}}$

$E_{K} = \frac{RT}{F} \ln \frac{[K^+]_{i}}{[K^+]_{o}}$

$E_{Ca} = \frac{RT}{2F} \ln \frac{[Ca^{2+}]_{o}}{[Ca^{2+}]_{i}}$

$E_{K,s} = \frac{RT}{F} \ln \frac{([K^+]_{o} + 0.12[Na^+]_{i})}{([K^+]_{o} + 0.12[Na^+]_{i})}$

Table 8
Formulation of the equations for reversal and equilibrium potentials

Reversal and equilibrium potentials

<table>
<thead>
<tr>
<th>Equation</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{Na} = \frac{RT}{F} \ln \frac{[Na^+]<em>{o}}{[Na^+]</em>{i}}$</td>
<td></td>
</tr>
<tr>
<td>$E_{K} = \frac{RT}{F} \ln \frac{[K^+]<em>{i}}{[K^+]</em>{o}}$</td>
<td></td>
</tr>
<tr>
<td>$E_{Ca} = \frac{RT}{2F} \ln \frac{[Ca^{2+}]<em>{o}}{[Ca^{2+}]</em>{i}}$</td>
<td></td>
</tr>
<tr>
<td>$E_{K,s} = \frac{RT}{F} \ln \frac{([K^+]<em>{o} + 0.12[Na^+]</em>{i})}{([K^+]<em>{o} + 0.12[Na^+]</em>{i})}$</td>
<td></td>
</tr>
</tbody>
</table>

Table 9
Initial conditions for central and peripheral cell

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Central</th>
<th>Peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V$</td>
<td>-55,443</td>
<td>-78,4021</td>
<td></td>
</tr>
<tr>
<td>$m$</td>
<td>0.15876</td>
<td>0.0531058</td>
<td></td>
</tr>
<tr>
<td>$b$</td>
<td>0.0365616</td>
<td>0.341077</td>
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</tr>
<tr>
<td>$h_1$</td>
<td>0.0515223</td>
<td>0.0207796</td>
<td></td>
</tr>
<tr>
<td>$d_1$</td>
<td>0.00328396</td>
<td>0.00010931</td>
<td></td>
</tr>
<tr>
<td>$f_1$</td>
<td>0.853578</td>
<td>0.97761</td>
<td></td>
</tr>
<tr>
<td>$d$</td>
<td>0.0022651</td>
<td>0.00226369</td>
<td></td>
</tr>
<tr>
<td>$f$</td>
<td>0.129637</td>
<td>0.278358</td>
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</tr>
<tr>
<td>$y$</td>
<td>0.0230307</td>
<td>0.0215392</td>
<td></td>
</tr>
<tr>
<td>$r$</td>
<td>0.0234583</td>
<td>0.0110545</td>
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</tr>
<tr>
<td>$q$</td>
<td>0.288777</td>
<td>0.435506</td>
<td></td>
</tr>
<tr>
<td>$s$</td>
<td>0.137793</td>
<td>0.0950833</td>
<td></td>
</tr>
<tr>
<td>$p_{d,s}$</td>
<td>0.29045</td>
<td>0.313397</td>
<td></td>
</tr>
<tr>
<td>$p_{d,s}$</td>
<td>0.561665</td>
<td>0.3783</td>
<td></td>
</tr>
<tr>
<td>$p_{m}$</td>
<td>0.973981</td>
<td>0.991546</td>
<td></td>
</tr>
</tbody>
</table>