Chapter 6

Discussion

6.1 Summary of the Heart Model

Various aspects of the electrophysiology of the heart, such as phase resetting and mutual entrainment, due to the initiation and conduction of cardiac action potentials have been investigated through the dynamic interactions of model cells representing the major components of the heart’s conduction system. These cells of the SA node, AV node, Purkinje fibre system, and ventricular myocardium were modelled using Hodgkin-Huxley-type oscillators. The electrical activities of the SA node, Purkinje fibre, and ventricular myocardial cells were simulated using the models devised by Yanagihara et al. [38], McAllister et al. [28], and Beeler and Reuter [1], respectively. Because the action potentials of an AV node cell are very similar to those of an SA node cell, the electrical activity of the AV node cell was simulated using a model derived from the Yanagihara et al. model for the SA node cell. In order that the model heart be capable of simulating the wide range of both normal and pathological functionings typical of a real heart, certain physiologically based parameters in the model equations were altered to produce model cells which exhibit a wide range of frequencies. The model allowed the coupling of any number of the four types of cells where the frequencies of the pacemaker cells were chosen from predetermined sets of values. Cell interaction was simulated by the addition of purely resistive coupling currents flowing between interacting cells where the form of the coupling current was dependent on whether or not the cells were assumed
to be physically adjacent. An action potential travelling from one cell to another non-adjacent cell will likely take a different path over the tissue separating the cells than an impulse travelling in the reverse direction. Furthermore, the time required for this impulse propagation between such nonadjacent cells is significant relative to the duration of the action potentials. These facts were incorporated into the model by means of direction dependent coupling conductances and conduction time delays. For adjacent cells, where the intercell membrane constitutes the entire propagation path, the conduction times are negligible and the coupling conductances simply represent the conductance of the gap junction membrane. Consequently, in this case, the coupling currents were reduced to the form used in previous studies of adjacent cell interaction [5,30,39] where the coupling currents flowing between two model cells were of opposite sign but equal magnitude. Then with the four types of model cells of varying frequencies and a method of coupling them, various aspects of cell interaction were investigated throughout the chapters of this thesis.

6.2 Discussion of Results

The changes in cycle length caused by the subthreshold depolarizations induced in one pacemaker by another are a prerequisite to the entrainment of the cells. This phase-resetting phenomenon was investigated in Chapter 3 through the use of phase-response curves for various pairs of interacting cells using pulsed-coupling. Biphasic response curves similar to those obtained experimentally were produced. As in previous studies, the shape of a PRC was maintained with a decrease in coupling conductance. Also, as expected, over most of the cycle, the phase shifts were less with weaker cell interaction. The exception was a small range of phase values where delays occur for lower conductances and the transition to advances had already been made with the stronger stimulus.
It also was found that with an increase in conductance the transition from maximal cycle prolongation to maximal cycle abbreviation occurred over a much narrower range of phases. This is analogous to previous experimental results obtained for chick heart cells [13]. The PRCs for fast and slow cells were also studied. In contrast to previous works studying interactions of similar cells, the phase shifts induced in a slow cell by a faster one were not necessarily larger than the corresponding phase shifts induced in the same fast cell by the slower one. Again this is due to the direction dependent coupling currents and the unequal influences exerted by different types of cells. Behavior demonstrating the greater sensitivity of a slower cell was obtained, however, when a particular cell was coupled to another cell whose intrinsic frequency was subsequently altered. In this case, the phase shifts were indeed greater at a given phase for the slower cell. Finally, comparisons were made between phase response curves obtained under conditions of pulsed and continuous coupling with expected results. PRCs summarizing the effects of a slower cell on a faster cell were similar for both methods of coupling. The differences lie in the size of the phase delays which were greater under continuous coupling due to the continuous 'pull' of the slower cell. For the case of a fast cell stimulating a slower one, the PRC obtained under continuous coupling was somewhat different from the corresponding pulsed-coupling PRC. This is due to the fact that for certain phases more than one discharge of the faster cell will occur during the perturbed cycle of the slower cell. Also, the continuous influence of the fast cell caused delays to be less for the PRC obtained under conditions of continuous coupling.

Most muscle cells are nonspontaneous and are only activated by the external stimulation of neighbouring cells. For ventricular muscle cells the external stimulation may be provided by Purkinje fibre cells. This activation of a nonpacemaker cell was computed for the present model in Chapter 4 and it was found that the level of activation of the muscle cell was dependent on the strength of the interaction. Also, as in an earlier study
by van Capelle [34] which uses a simple two-state variable model, the common cycle length at synchrony was somewhat lower than the intrinsic period of oscillation of the pacemaker cell.

A second property of a healthy heart is that the SA node acts as the primary pacemaker and other cells are entrained to its regular rhythm. Impulses generated at the SA node spread throughout the atria and then the ventricles causing first atrial and then ventricular contraction. This production of a heartbeat was mimicked for the present model in Chapter 4 by the coupling of one of each type of model cell with intrinsic frequencies and propagation time delays representative of those in a healthy heart. Results demonstrated that each impulse initiated at the SA node was transmitted from one model cell to another causing the excitation of each shortly after its stimulation. Each cell fired at the SA node rate. Also, the time between the activation of one cell and a succeeding cell in the conduction path was within milliseconds of the specified action potential propagation time between the same cells.

Both of the functions of a healthy heart discussed in Chapter 4 are possible because of the ability of cardiac cells to become entrained to a common frequency. Entrainment, however, can also be the cause of many irregular rhythms of the heart. A particular pathological situation known as modulated ventricular parasystole which is characterized by the formation of a ventricular ectopic focus (site of pacemaker activity other than the SA node) was studied in Chapter 5. A simple two-cell model in which an SA node cell (s) was coupled to a Purkinje fibre cell (p) was used throughout the computations. The results confirmed the well-known result that when two pacemakers of different intrinsic oscillation periods are coupled and the strength of the coupling increased, the ratio of their periods approaches unity [30,39]. Furthermore, around certain values of the coupling conductances, stable patterns of \( m:n \) entrainment (\( m \) cycles of one pacemaker
for every $n$ cycles of the other) which are common in the clinical analysis of electrocardiograms were observed. The results differed from previous studies of similar adjacent cell interaction, in that the faster cell did not always determine the cycle length at 1:1 entrainment. This is due to the fact that the coupling currents are characterized by direction dependent conductances, $g_{s,p}$ and $g_{p,s}$, and also that different cells do not exert equal influences on each other. For example, it was found that for equal values of $g_{s,p}$ and $g_{p,s}$ the Purkinje fibre cell exerts a much greater influence on the SA node cell than vice-versa. Cells of different intrinsic oscillation periods were made to interact for different values of the coupling conductances and regions of synchronous and asynchronous behavior plotted. It was found that when $g_{p,s}$ was greater than some minimum value and the ratio of the coupling conductances $g_{p,s}/g_{s,p}$ was sufficiently high (indicating that the influence of $p$ on $s$ was greater than the influence of $s$ on $p$), then $p$ became the lead cell and the common period at synchrony was closer to the intrinsic cycle length of $p$ than of $s$. Similarly, when $g_{s,p}$ was greater than some minimum value and the ratio $g_{s,p}/g_{p,s}$ was sufficiently high then 1:1 $s$ entrainment occurred and the common cycle length was closer to the intrinsic cycle length of $s$ than of $p$. For the case of interactions between similar adjacent cells, previous studies [30,39] have found that the common cycle length was, both closer to the intrinsic period of the faster cell, and always between the intrinsic periods of the two cells. For the present model, the common cycle length was always closer to the intrinsic oscillation period of the lead cell but was not restricted to values between the periods of the two cells. When the intrinsic period of $s$ was less than that of $p$ ($s$ firing at a faster rate than $p$) and the ratio $T_p/T_s$ decreased, the regions of 1:1 $s$ and 1:1 $p$ entrainment increased in size, supporting the general rule: the closer the intrinsic periods of interacting cells the less coupling is required for synchrony [39]. However, the increase in size of the region of entrainment to $p$ was greater than the increase in size of the 1:1 $s$ entrainment region. This exemplified the fact that the Purkinje fibre cell
exerts a stronger influence on the SA node cell than vice-versa. Further evidence of this was discovered when the ratio $T_p/T_s$ was decreased to a value less than 1. In this case, $p$ fires at a faster rate than $s$ and it was found that, over the range of conductances studied, $p$ was never 1:1 $s$ entrained.

6.3 Suggestions for Future Research

Due to the vast number of cardiac arrhythmias and entrainment phenomena readily observable in a real heart, the present study has only begun to explore the properties of impulse initiation and conduction among interacting cells. As a result, the following also are just a few of the ways the model can be used to investigate further the electrophysiology of the heart.

The AV node provides the only passage for impulses travelling between the atria and the ventricles; therefore, its malfunction may completely dissociate atrial and ventricular contraction. Studies of arrhythmias caused by the malfunction of the AV node have been done using simplified models, for example by Keener [25]. The present model which uses the more physiologically realistic Hodgkin-Huxley-type oscillators and provides a method of coupling nonadjacent cells could be used to study these arrhythmias which lead to the independent functioning of cells of the atria and ventricles.

Ventricular fibrillation, an arrhythmia which occurs under conditions of ventricular parasystole (at least two ventricular ectopic foci discharging independently of the SA node), has been of much interest in recent years. This arrhythmia, which leads to rapid death, has often been associated with aperiodic dynamics and chaos. There has been much controversy over the existence of chaotic modes separating the stable modes of $m:n$ entrainment [24,15]. Glass et al. [9], using circle maps to simulate ventricular parasystole, have theoretically predicted regions of aperiodic dynamics which also have
been observed experimentally. They claim that, even if experimental noise were not present, these regions would still exist. Ypey et al. [39]; however, state that their results on the mutual entrainment of pacemaker cells suggest that chaotic modes do not exist between the regions of stable \( m:n \) entrainment. For the present model, the existence of aperiodic dynamics, also could be investigated for ventricular parasystole. For the simple model of Chapter 6, this would require subdividing the regions of asynchronous behavior (labelled ‘not 1:1’) of the various synchrony diagrams into zones of \( m:n \) entrainment. The difficulty lies in the fact that some stable \( m:n \) entrainment patterns, such as, say, 1021 : 1019 entrainment, require long simulation runs to detect and may be mistakenly classified as aperiodic.

Simulations involving larger numbers of model cells would allow the study of the spread of the cardiac action potential over a tissue as well as provide some insight into the mechanisms which cause the mutual synchronization of small clusters of adjacent cells. However, the computational cost and time of such an endeavor could become exorbitant.

The use of the highly nonlinear Hodgkin-Huxley-type oscillators to represent the cells of the model meant that extensive numerical computations were required to solve the systems of equations. One of the long range objectives of this research is to reduce the system of cell model equations to a form which is more tractable analytically and yet retains physiological relevancy. A possible approach is to adapt the averaging technique employed by Ermentrout and Kopell [27] in their studies of coupled biological oscillators.

Finally, it was briefly mentioned that the phase response curve may be useful in predicting zones of entrainment for unidirectional interaction [39]. This, as well as its potential use in studies of mutual entrainment, is an area worthy of further investigation.
Bibliography


Bibliography


[35] van der Pol, B. and van der Mark, J. The heartbeat considered as a relaxation oscillation, and an electrical model of the heart. *Phil. Mag. (Series 7)*, 6, 763-775, 1928.


Appendix A

The Cell Models

The SA and AV nodes, Purkinje fibre, and ventricular myocardial cells have been modelled using the Hodgkin-Huxley formulation in which the rate of change of the transmembrane potential of a cell is described by a governing equation of the form:

\[
\frac{dE_j(t)}{dt} = -\frac{1}{C} i_{ionic}
\]  

(A.1)

where \( t \) is the time in msec, \( j \) denotes the cell type and is one of: \( s, a, p, \) or \( v \) indicating SA node, AV node, Purkinje fibre, and ventricular myocardial cells, respectively, \( E_j(t) \) is the membrane potential in mV (expressed as the inside potential minus the outside potential) of cell \( j \) at time \( t \), \( C \) is the membrane capacitance in \( \mu F/cm^2 \), and \( i_{ionic} \) is the total ionic current in \( \mu A/cm^2 \) flowing out of cell \( j \).

In the sections to follow, the equations describing the ionic current, \( i_{ionic} \), of each of the four types of cells are given in detail. The equations for the SA node, Purkinje fibre, and ventricular myocardial cells are, for the most part, exactly as they are in the original papers [1,2,8,38] with the exception of a few minor changes in notation. The equations for the AV node cell are a modification of the equations for the SA node cell. In each of the models, ionic current components which are time dependent include gating variables for activation and/or inactivation. Such a gating variable \( x \) follows the first-order kinetics:

\[
\frac{dx}{dt} = \alpha_x (1 - x) - \beta_x x
\]  

(A.2)
A.1 The Sinus Node Cell

Yanagihara et al. [38] describe the total ionic current of the SA node cell by:

\[ i_{\text{ionic}} = i_{s1} + i_{Na} + i_K + i_h + i_I. \]  \hspace{1cm} (A.3)

The individual components of the ionic current are given by the following equations where \( E_s \) is the transmembrane potential of the SA node cell at a particular time.

**Slow inward current:**

\[ i_{s1} = 12.5 \{ \exp[(E_s - 30)/15] - 1 \} (0.95d + 0.05)(0.95f + 0.05) \] \hspace{1cm} (A.4)

where the gating variables \( d \) and \( f \) satisfy (A.2) and the rate constants are given by:

\[ \alpha_d = \frac{1.045 \times 10^{-2}(E_s + 35)}{1 - \exp[-(E_s + 35)/2.5]} + \frac{3.125 \times 10^{-2}E_s}{1 - \exp(-E_s/4.8)}, \] \hspace{1cm} (A.5)

\[ \beta_d = \frac{4.21 \times 10^{-3}(E_s - 5)}{\exp[(E_s - 5)/2.5] - 1}, \] \hspace{1cm} (A.6)

\[ \alpha_f = \frac{3.55 \times 10^{-4}(E_s + 20)}{\exp[(E_s + 20)/5.633] - 1}, \] \hspace{1cm} (A.7)

\[ \beta_f = \frac{9.44 \times 10^{-4}|E_s + 60|}{1 + \exp[-(E_s + 29.5)/4.16]}, \] \hspace{1cm} (A.8)

**Sodium current:**

\[ i_{Na} = 0.5 \, m^3h \, (E_s - 30) \] \hspace{1cm} (A.9)

where the gating variables \( m \) and \( h \) satisfy (A.2) and the rate constants are given by:

\[ \alpha_m = \frac{E_s + 37}{1 - \exp[-(E_s + 37)/10]}, \] \hspace{1cm} (A.10)

\[ \beta_m = 40 \, \exp[-5.6 \times 10^{-2}(E_s + 62)]. \] \hspace{1cm} (A.11)
Appendix A. The Cell Models

\[ \alpha_h = 1.209 \times 10^{-3} \exp[-(E_s + 20)/6.534], \quad (A.12) \]
\[ \beta_h = \frac{1}{\exp[-(E_s + 30)/10] + 1}. \quad (A.13) \]

Hyperpolarization current:

\[ i_h = 0.4 \, q \, (E_s + 25) \quad (A.14) \]

where the gating variable \( q \) satisfies (A.2) and the rate constants are given by:

\[ \alpha_q = \frac{3.4 \times 10^{-4} (E_s + 100)}{\exp((E_s + 100)/4.4) - 1} + 4.95 \times 10^{-5}, \quad (A.15) \]
\[ \beta_q = \frac{5 \times 10^{-4} (E_s + 40)}{1 - \exp[-(E_s + 40)/6]} + 8.45 \times 10^{-5}. \quad (A.16) \]

Potassium current:

\[ i_K = \frac{0.7 \, p \{ \exp[0.0277(E_s + 90)] - 1 \}}{\exp[0.0277(E_s + 40)]} \quad (A.17) \]

where the gating variable \( p \) satisfies (A.2) and the rate constants are given by:

\[ \alpha_p = \frac{9 \times 10^{-3}}{1 + \exp[-(E_s - E_{\alpha_p})/9.71]} + 6 \times 10^{-4}, \quad (A.18) \]
\[ \beta_p = \frac{2.25 \times 10^{-4}}{(E_s - E_{\beta_p}) \{ \exp[(E_s - E_{\beta_p})/13.3] - 1 \}}. \quad (A.19) \]

Since slight changes in \( E_{\alpha_p} \) and \( E_{\beta_p} \) produce significant changes in the oscillation frequency of the SA node cell, these parameters were used to produce model cells with varying cycle lengths. The actual values used along with the resulting frequencies are given in Section 2.2.5.
Leak current:

\[ i_l = 0.8 \left\{ 1 - \exp\left[-\frac{(E_s + 60)}{20}\right] \right\}. \]  
(A.20)

### A.2 The AV Node Cell

A model for AV node cells was created from the equations for the SA node cells [38]. The total ionic current for the AV node cell is given by (A.3) where, with the exception of \( i_{si} \), the individual current components are described by the same equations as for the SA node cell. The slow inward current, \( i_{si} \), however, was scaled by the constant, \( \overline{i_{si}} \), to slow the rate of depolarization which is not as fast for AV node cells as it is for SA node cells (Figure 1.2). Thus, for the AV node cell, \( i_{si} \) is given by:

\[ i_{si} = \overline{i_{si}} \times 12.5 \left\{ \exp\left[\left(\frac{E_a - 30}{15}\right) - 1\right] \times (0.95d + 0.05) \times (0.95f + 0.05) \right\} \]  
(A.21)

where \( E_a \) denotes the cell membrane potential and the subscript \( a \) indicates that the cell is an AV node cell. The gating variables \( d \) and \( f \) and their rate constants are as for the SA node cell. The intrinsic oscillation frequency of the model AV node cell is determined by the value of the scaling constant \( \overline{i_{si}} \) and, as for the SA node cell, the values of the constants \( \overline{E_{\alpha_r}} \) and \( \overline{E_{\beta_r}} \) of \( i_K \). The actual values used for these three constants are reported in Section 2.2.5.

### A.3 The Purkinje Fibre Cell

The McAllister, Noble, and Tsien model for the Purkinje fibre cell [28] describes the membrane current by the following:

\[ i_{\text{ionic}} = i_{Na} + i_{si} + i_{qr} + i_{K_2} + i_{x_1} + i_{x_2} + i_{K_1} + i_{Na_b} + i_{Cl_b}. \]  
(A.22)
The ionic current components are described below where \( E_p \) denotes the membrane potential of the Purkinje fibre cell at a specific time.

**Excitatory Sodium current:**

\[
i_{Na} = m^3 h (E_p - 40) \quad (A.23)
\]

where the gating variables \( m \) and \( h \) satisfy \((A.2)\) and the rate constants are given by:

\[
\alpha_h = 1.13 \times 10^{-7} \exp[-(E_p + 10)/5.43], \quad (A.24)
\]

\[
\beta_h = \frac{2.5}{\exp[-0.082(E_p + 10)] + 1}, \quad (A.25)
\]

\[
\alpha_m = \frac{(E_p + 47)}{1 - \exp[-0.1(E_p + 47)]}, \quad (A.26)
\]

\[
\beta_m = 9.86 \exp[-(E_p + 47)/17.86]. \quad (A.27)
\]

**Secondary inward current:**

\[
i_{si} = 0.8 (E_p - 70) df + 0.04 (E_p - 70) d' \quad (A.28)
\]

where the gating variables \( d \) and \( f \) satisfy \((A.2)\) and the rate constants are given by:

\[
\alpha_d = \frac{0.002 (E_p + 40)}{1 - \exp[-0.1(E_p + 40)]}, \quad (A.29)
\]

\[
\beta_d = 0.02 \exp[-0.0888(E_p + 40)], \quad (A.30)
\]

\[
\alpha_f = 0.000987 \exp[-0.04(E_p + 60)], \quad (A.31)
\]

\[
\beta_f = \frac{0.02}{\exp[-0.087(E_p + 26)] + 1}, \quad (A.32)
\]

\[
d' = 1 + \exp[-0.15(E_p + 40)]^{-1}. \quad (A.33)
\]
Pacemaker potassium current:

\[ i_{K_2} = \overline{i_{K_2}} \cdot k \]  \hspace{1cm} (A.34)

where the gating variable \( k \) \(^1\) satisfies (A.2) and the rate constants are given by:

\[ \overline{i_{K_2}} = \frac{2.8 \left\{ \exp[0.04(E_p + 110)] - 1 \right\}}{\exp[0.08(E_p + 60)] + \exp[0.04(E_p + 60)]}, \]  \hspace{1cm} (A.35)

\[ \alpha_k = \frac{0.001(E_p - \overline{E}_k)}{1 - \exp[-0.2(E_p - \overline{E}_k)]}, \]  \hspace{1cm} (A.36)

\[ \beta_k = 0.00005 \exp[-0.067(E_p - \overline{E}_k)], \]  \hspace{1cm} (A.37)

where the variable \( \overline{E}_k \) is used to determine the oscillation frequency of the Purkinje fibre cell. The values used and the resulting oscillation frequencies are reported in Section 2.2.5.

Plateau potassium currents:

The first plateau potassium current is:

\[ i_{x_1} = \frac{1.2 \cdot x_1 \{ \exp[0.04(E_p + 95)] - 1 \}}{\exp[0.04(E_p + 45)]}, \]  \hspace{1cm} (A.38)

where the gating variable \( x_1 \) satisfies (A.2) and the rate constants are given by:

\[ \alpha_{x_1} = \frac{0.0005 \exp[(E_p + 50)/12.1]}{1 + \exp[(E_p + 50)/17.5]}, \]  \hspace{1cm} (A.39)

\[ \beta_{x_1} = \frac{0.0013 \exp[-(E_p + 20)/16.67]}{1 + \exp[-(E_p + 20)/25]}, \]  \hspace{1cm} (A.40)

\(^1\)In the original paper [28], the gating variable is denoted \( s \) rather than \( k \), however, in this study, \( s \) is reserved to indicate an SA node cell.
The second plateau potassium current is:

$$i_{x_2} = x_2 (25 + 0.385E_p)$$  \hspace{1cm} (A.41)

where the gating variable $x_2$ satisfies (A.2) and the rate constants are given by:

$$\alpha_{x_2} = \frac{0.000127}{1 + \exp[-(E_p + 19)/5]},$$  \hspace{1cm} (A.42)

$$\beta_{x_2} = \frac{0.0003 \exp[-(E_p + 20)/16.67]}{1 + \exp[-(E_p + 20)/25]}.$$  \hspace{1cm} (A.43)

**Transient chloride current:**

$$i_{q_r} = 2.5 q r (E_p + 70)$$  \hspace{1cm} (A.44)

where the gating variables $q$ and $r$ satisfy (A.2) and the rate constants are given by:

$$\alpha_q = \frac{0.008 E_p}{1 - \exp(-0.1E_p)},$$  \hspace{1cm} (A.45)

$$\beta_q = 0.08 \exp[-0.0888 E_p],$$  \hspace{1cm} (A.46)

$$\alpha_r = 0.00018 \exp[-0.04(E_p + 80)],$$  \hspace{1cm} (A.47)

$$\beta_r = \frac{0.02}{\exp[-0.087(E_p + 26)] + 1}.$$  \hspace{1cm} (A.48)

**Outward background current:**

$$i_{K_1} = (\frac{i_{K_2}}{2.8}) + \frac{0.2 (E_p + 30)}{(1 - \exp[-0.04(E_p + 30)])}.$$  \hspace{1cm} (A.49)

**Inward background current carried by sodium ions:**

$$i_{Na,b} = 0.105 (E_p - 40).$$  \hspace{1cm} (A.50)
Appendix A. The Cell Models

Background current carried by chloride ions:

$$i_{Cl,b} = 0.01 (E_p + 70).$$  \hspace{1cm} (A.51)

A.4 The Ventricular Myocardial Cell

The model, due to Beeler and Reuter [1], for the ventricular muscle cell describes the ionic current by:

$$i_{ionic} = i_{Na} + i_{K_1} + i_{x_1} + i_{si}. \hspace{1cm} (A.52)$$

The individual current components are described by the following equations where $E_v$ denotes the membrane potential of the ventricular muscle cell at a specific instance in time.

**Sodium current:**

$$i_{Na} = (4m^3hj + 0.003)(E_v - 50) \hspace{1cm} (A.53)$$

where the gating variables $m$, $h$, and $j$ satisfy (A.2) and the rate constants are given by:

$$\alpha_m = \frac{[E_v + 47]}{exp[-0.1(E_v + 47)] - 1}, \hspace{1cm} (A.54)$$

$$\beta_m = 40 \exp[-0.056(E_v + 72)], \hspace{1cm} (A.55)$$

$$\alpha_h = 0.126 \exp[-0.25(E_v + 77)], \hspace{1cm} (A.56)$$

$$\beta_h = \frac{1.7}{\exp[-0.082(E_v + 22.5)] + 1}, \hspace{1cm} (A.57)$$

$$\alpha_j = \frac{0.055 \exp[-0.25(E_v + 78)]}{\exp[-0.2(E_v + 78)] + 1}, \hspace{1cm} (A.58)$$

$$\beta_j = \frac{0.3}{\exp[-0.1(E_v + 32)] + 1}, \hspace{1cm} (A.59)$$
Time-independent potassium current:

\[
i_{K_1} = 0.35 \left\{ \frac{4\{\exp[0.04(E_v + 85)] - 1\}}{\exp[0.08(E_v + 53)] + \exp[0.04(E_v + 53)]} + \frac{0.2(E_v + 23)}{1 - \exp[-0.04(E_v + 23)]} \right\}.
\]  

(A.60)

Outward current:

\[
i_{x_1} = \frac{0.8 x_1 \{\exp[0.04(E_v + 77)] - 1\}}{\exp[0.04(E_v + 35)]}
\]  

(A.61)

where the gating variable \( x_1 \) satisfies (A.2) and the rate constants are given by:

\[
\alpha_{x_1} = \frac{0.0005 \exp[0.083(E_v + 50)]}{\exp[0.057(E_v + 50)] + 1},
\]  

(A.62)

\[
\beta_{x_1} = \frac{0.0013 \exp[-0.06(E_v + 20)]}{\exp[-0.04(E_v + 20)] + 1}.
\]  

(A.63)

Slow inward current:

\[
i_{si} = 0.09 df(E_v - E_{si})
\]  

(A.64)

where the gating variables \( d \) and \( f \) satisfy (A.2) and the rate constants are given by:

\[
\alpha_d = \frac{0.095 \exp[-0.01(E_v - 5)]}{\exp[-0.072(E_v - 5)] + 1},
\]  

(A.65)

\[
\beta_d = \frac{0.07 \exp[-0.017(E_v + 44)]}{\exp[0.05(E_v + 44)] + 1},
\]  

(A.66)

\[
\alpha_f = \frac{0.012 \exp[-0.008(E_v + 28)]}{\exp[0.15(E_v + 28)] + 1},
\]  

(A.67)

\[
\beta_f = \frac{0.0065 \exp[-0.02(E_v + 30)]}{\exp[-0.2(E_v + 30)] + 1},
\]  

(A.68)

\[
E_{si} = -82.3 - 13.0287 \ln[Ca_i]
\]  

(A.69)

\[
d[Ca_i]/dt = -10^{-7}i_{si} + 0.07\{10^{-7} - [Ca_i]\},
\]  

(A.70)
where this last equation models the movement of calcium which flows into the muscle cell and is subsequently removed by an uptake mechanism that reduces the intracellular calcium concentration to $10^{-7}$ M.