Table 2.2: Parameter values and resulting frequencies for model AV node cells.

\(i_{si}\): This is one of the methods used by Michaels et al. in their study of the interaction of SA node cells [30]. Table 2.2 lists the scaling values of \(i_{si}\) used and the resulting cell frequencies. Figures 2.2 a-e show the resulting action potentials which are modifications to the action potentials of Figures 2.1a-e, respectively. In the top trace, with \(E_{\alpha p} = -6.7 \text{ mV}, \ E_{\beta p} = -65 \text{ mV},\) and \(\overline{i_{si}} = 0.99\) the resulting reduction in \(i_{si}\) produces a model for an AV node cell with a period of 793 msec which is slightly longer than the 753.25 msec period of the corresponding SA node cell (Figure 2.1a). There is also a small decrease in the maximum membrane potential which accompanies the scaling of \(i_{si}\). Similarly, lower traces show AV node cell models with intrinsic frequencies and maximum membrane potentials slightly less than that of the respective model SA node cells.

Purkinje fibre cells in a healthy adult heart have an intrinsic frequency between 20 and 40 cycles/min; however, this rate can increase significantly during many arrhythmias. Model cells with frequencies ranging from 40 to 120 cycles/min were produced by shifting the parameter, \(E_k\), of the pacemaker potassium current, \(i_{K2}\) (A.34). Figure 2.3 shows the corresponding action potentials for the various values of \(E_k\) given in Table 2.3. In the top trace, with \(E_k = -54.7 \text{ mV},\) the intrinsic period is 1506 msec. This corresponds to a firing frequency of approximately 40 cycles/min which is a typical
Figure 2.2: Model AV node cells (numbers indicate cell frequency in cycles/min).
Figure 2.3: Model Purkinje fibre cells (numbers indicate cell frequency in cycles/min).
Table 2.3: Parameter values and resulting frequencies for model Purkinje fibre cells.

<table>
<thead>
<tr>
<th>Figure 2.3</th>
<th>$E_k$ (mV)</th>
<th>Frequency (cycles/min)</th>
<th>Period (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>-54.7</td>
<td>39.84</td>
<td>1506.00</td>
</tr>
<tr>
<td>(b)</td>
<td>-45.0</td>
<td>60.27</td>
<td>995.50</td>
</tr>
<tr>
<td>(c)</td>
<td>-35.0</td>
<td>80.20</td>
<td>748.13</td>
</tr>
<tr>
<td>(d)</td>
<td>-25.0</td>
<td>100.71</td>
<td>595.75</td>
</tr>
<tr>
<td>(e)</td>
<td>-15.0</td>
<td>119.73</td>
<td>501.11</td>
</tr>
</tbody>
</table>

value for a Purkinje fibre cell in a healthy human heart. As $E_k$ is progressively shifted towards zero (lower traces) the frequency increases. As for the SA node cell, this increase is accompanied by a slight upward shift of the action potentials along the voltage axis. The five resulting models allow simulation of the electrical activity of Purkinje fibre cells with frequencies of approximately 40, 60, 80, 100, and 120 cycles/min.

It should be noted that similar control of pacemaker periodicity can be obtained by the application of an external current to each of the models. A hyperpolarizing (outward) current decreases, while a depolarizing (inward) current increases, cell frequency [30].

2.3 Modelling Adjacent Cell Interaction

Action potentials propagate within the heart by moving from cell to cell over regions of close membrane association called gap junctions which exist between adjacent cells (Figure 2.4). These junctions provide a low resistance pathway through which electric current can easily flow [17,30,39].

To describe the interaction of two adjacent cells, cell $i$ and cell $j$, it is assumed that coupling currents flow between the cells. For two neighbouring cells, these coupling currents simply describe the movement of action potentials over the gap junction between
Figure 2.4: Schematic diagram depicting the flow of an action potential between two adjacent cells across a gap junction (taken from [17], p.20).

the cells. This gap junction constitutes the entire propagation path for impulses travelling in both directions; therefore, the influence of one cell on the other will be almost immediate. This influence of cell $i$ on cell $j$ is described by a coupling current, $i_{cj}$, which is a function of intercell membrane conductance, $g$, and voltage difference as follows:

$$i_{cj} = g [E_j(t) - E_i(t)].$$  \hfill (2.9)

Similarly, the influence of cell $j$ on cell $i$ is given by:

$$i_{ci} = g [E_i(t) - E_j(t)].$$  \hfill (2.10)

These currents, (2.9) and (2.10), are included in the models for cell $j$ and cell $i$, respectively, and integrated along with the other ionic currents. Also, (2.9) and (2.10) have the same magnitude but are of opposite sign implying that, for two adjacent cells, the same current that flows out of one cell flows in to the other. This is the form of the coupling currents employed in the previous studies by both Michaels et al. [30] and Lambert and Chay [5] where only adjacent cell interactions were modelled.

2.4 Modelling Nonadjacent Cell Interaction

Certain types of cardiac cells, e.g., an SA node cell and a Purkinje fibre cell, are never physically adjacent. Even two cells of the same type, such as two ventricular muscle
cells, may be located some distance from each other. For two such nonadjacent cells, cell $i$ and cell $j$, the time required for action potential propagation between them will be significant relative to the duration of their action potentials. Furthermore, the path taken by an impulse from one to the other may not be the same as the path taken in the reverse direction. Consequently, in this case, the cells may not exert equal influences on each other and the coupling currents must be direction dependent.

An impulse originating at a particular cell, cell $i$, eventually reaches another distant cell, cell $j$, by travelling cell-to-cell crossing gap junctions over a path from cell $i$ to cell $j$. Finally, the impulse will arrive at cell $j$ from an adjacent cell denoted cell $j-1$ (Figure 2.5).

The coupling current flowing between the adjacent cells, cell $j-1$ and cell $j$, is analogous to (2.9) with subscripts changed and is described by:

$$i_{cj} = g_{j-1,j} \left[ E_j(t) - E_{j-1}(t) \right]$$  \hspace{1cm} (2.11)
where \( g_{j-1,j} \) is a constant representing the conductance in mS/cm\(^2\) of the gap junction between cells \( j-1 \) and \( j \).

In describing the influence of cell \( i \) on cell \( j \) it is the electrical activities of these two cells which are of concern in the model; therefore, the coupling current flowing between cell \( i \) and cell \( j \) should be expressed in terms of parameters describing only these two cells. In order to accomplish this, it is assumed that the impulse generated at cell \( i \) is not affected by its propagation to cell \( j \) or, in other words, that the membrane potential at cell \( i \) reaches cell \( j \) through cell \( j-1 \), after a finite amount of time, without a change in magnitude. Mathematically,

\[
E_{j-1}(t) = E_i(t - \tau_{i,j-1})
\]

where \( \tau_{i,j-1} \) is a constant representing the time in msec required for the conduction of an impulse from cell \( i \) to cell \( j-1 \). With this assumption, (2.11) becomes:

\[
i_{c_j} = g_{j-1,j} \left[ E_j(t) - E_i(t - \tau_{i,j-1}) \right].
\]

To remove any reference to cell \( j-1 \) in the above expression we let \( g_{i,j} = g_{j-1,j} \) and \( \tau_{i,j} = \tau_{i,j-1} \). With this new notation, \( g_{i,j} \) should be interpreted as the conductance of the gap junction between cell \( j \) and the cell adjacent to it in the conductance path from cell \( i \) to cell \( j \). Similarly, \( \tau_{i,j} \) is the time required for an impulse to travel from cell \( i \) to the cell immediately preceding cell \( j \) along a path to cell \( j \). Consequently, the coupling current which represents the influence of cell \( i \) on cell \( j \) can be written:

\[
i_{c_j} = g_{i,j} \left[ E_j(t) - E_i(t - \tau_{i,j}) \right].
\]

This coupling current is included in the model for cell \( j \) and integrated along with the ionic currents. The governing equation for cell \( j \), (2.5), becomes:

\[
\frac{dE_j(t)}{dt} = -\frac{1}{C} (i_{\text{ionic}} + i_{c_j})
\]
with
\[ i_{c_j} = \sum_i g_{i,j} [E_j(t) - E_i(t - \tau_{i,j})] \] (2.15)
being the sum of coupling currents over all cells \( i \) which influence cell \( j \).

This form of the coupling currents for modelling nonadjacent cell interaction is consistent with (2.9) for adjacent cells. For two adjacent cells, cell \( i \) and cell \( j \), the gap junction between the cells constitutes the entire propagation path for impulses travelling in either direction; therefore, letting \( g \) be the conductance of this intercell membrane, the following is true:
\[ g = g_{i,j}. \]

Furthermore, the impulse propagation times between the cells will be negligible; therefore, the following assumption can be made:
\[ \tau_{i,j} = 0. \]

Then (2.13) which describes the influence of cell \( i \) on cell \( j \) becomes:
\[ i_{c_j} = g [E_j(t) - E_i(t)]. \] (2.16)
which is (2.9) given earlier.

2.5 Range of Coupling Conductances

Numerical computations of cell interaction were run over a range of coupling conductances from \( g_{i,j} = 0 \) mS/cm\(^2\) (no coupling) to \( g_{i,j} = 0.1 \) mS/cm\(^2\). Ypey [39], in a study of interactions between general cardiac cells uses a value of 0.003 mS/cm\(^2\) for the maximum coupling conductance while Lambert and Chay [5] use values as high as 3.5 mS/cm\(^2\) in coupling their simple 2-variable model cells. The upper limit used throughout this paper, \( g_{i,j} = 0.1 \) mS/cm\(^2\), corresponds to a gap junction membrane
resistance of 10 kΩ/cm² and is the value used by Michaels et al. [30] in their study of the interactions of SA node cells modelled using the same Yanagihara et al. equations [38] as are used here.

2.6 Propagation Time Delays

Propagation time delays appropriate to the types of cells coupled in a particular computation are incorporated into the coupling currents flowing between the cells. For example, for studies involving the influence of an SA node cell on an AV node cell, $\tau_{s,a}$ is assigned a value representative of the time required for impulse conduction from the SA node to the AV node. This is the time required for atrial depolarization which, according to Section 1.1.3, has an average value of between 80 and 120 msec in a healthy heart. Similarly, in a computation of normal behavior, $\tau_{a,p}$ might be assigned a value corresponding to the time required for the passage of an impulse through the AV node from which it emerges to the Purkinje fibre network. Under pathological conditions, such as with damaged tissue, the transmission times between different regions of the heart can be much longer than their average values and, in severe cases, the damaged tissue may create a blockage so that impulses are not conducted at all from one region to another. The propagation time delays can be chosen according to the particular situation being modelled.
Chapter 3

Phasic Interactions of Pacemaker Cells

3.1 Phase Resetting

When two pacemaker cells interact, impulses which originate at one cell may induce subthreshold depolarizations in another causing all subsequent action potentials of the latter cell to be advanced or delayed in comparison with its undisturbed oscillation [28,39]. These alterations, or phase shifts, in the rhythms of interacting cells are a prerequisite to entrainment and have been observed both experimentally and theoretically. Phase resetting has been demonstrated by Jalife and Antzelevitch [22] for rabbit SA node cells and by Guevara, Shrier, and Glass [13] for embryonic chick ventricular heart cell aggregates. Numerous computer simulations have also been done. Winfree [37] has studied phase resetting for a wide variety of biological oscillators. Michaels et al. [30] using the Yanagihara et al. [38] SA node cell model and McAllister, Noble, and Tsien [28] using their Purkinje fibre cell model have reproduced experimental results quite closely. These studies, however, have been based on the interactions of similar adjacent cells. For the present model, the phenomenon of phase resetting will be analyzed for various pairs of the three different types of pacemaker cells. Because these cells are not necessarily physically adjacent, the propagation time between them will be significant and the strength of the coupling will be direction dependent.

The effect of an incoming pulse on the cycle length of an oscillator depends not only on the intensity and duration of the stimulus but also on its timing. If the arrival of
the impulse occurs while the cell is in a refractory state, its next action potential will be delayed. If, on the other hand, the impulse arrives at a time when the membrane impedance is low, e.g., during phase 0 or the latter part of phase 4, then the subsequent action potential may be advanced. The arrival time of an impulse from one cell at another cell is determined by two factors: the relative frequencies of the cells and the impulse propagation time between them. In the remainder of this chapter, impulse propagation times will be systematically adjusted to study the effects of the arrival time of one cell’s action potentials on the firing times of another cell.

When a relatively fast cell (one with a shorter period of oscillation) is coupled to a slower cell, more than one action potential of the fast cell will occur in each cycle of the slow cell. Therefore, to study the effects of a single action potential of one cell on the cycle length of another cell, the two cells were permitted to interact only during a single action potential phase (Figure 1.1) of the cell providing the stimulus. The action potential phase of a cell is defined as the period beginning when the membrane potential crosses its threshold value during phase 0 depolarization and ending when the potential first reaches its minimum value. For consistency, this type of pulsed coupling was also used for studies of the effects of slow cells on fast cells. Continuous coupling (the continuous interaction of cells from the time of onset of the stimulus to the end of the computation), however, probably reflects the true physical situation in a real heart more closely. Michaels et al. [30] consider the influence of one cell on another as consisting of two parts: the “phasic” influence during the action potential phase and the continuous or “tonic” influence over the period of phase 4 depolarization. Using both pulsed and continuous coupling to study phase resetting of SA node cells, they found that, qualitatively, the results were similar for both types of coupling and concluded that the entrainment phenomena observed during continuous coupling were “primarily a function of the phasic influence”.... “of one pacemaker on the activity of the other”. The
primary method of coupling in this chapter will be pulsed coupling although continuous coupling will also be done to compare results.

### 3.2 Methods

To study the effects of a single action potential of model cell $i$ on the intrinsic cycle length of model cell $j$, the cells were coupled as follows. First, the influence of $j$ on $i$ was eliminated, i.e., the conductance $g_{j,i}$ was set to zero so that no coupling current would flow from $j$ to $i$. Thus $i$ would oscillate unperturbed. On the other hand, the coupling conductance $g_{i,j}$ was maintained at a sufficiently high value during the action potential phase of $i$ and set equal to zero otherwise. This achieved the desired pulsed coupling. The propagation time $\tau_{i,j}$ was then adjusted in steps so the action potential of $i$ was ‘felt’ at different times, or phases, $\phi_j$ within a cycle of $j$. A cycle of $j$ begins from the peak or maximum potential of one action potential and ends with the peak of the subsequent action potential. The phases, $\phi_j$, were measured relative to the time corresponding to the peak of the first action potential of the perturbed cycle of $j$. Denoting this time by $t_j$ and the time at which the potential of $i$ crosses its threshold value by $t_{i\text{threshold}}$, the phase $\phi_j$ satisfies:

$$\phi_j = (t_{i\text{threshold}} + \tau_{i,j}) - t_j \quad \text{where} \quad 0 \leq \phi_j \leq T_j.$$

Figure 3.1 indicates the terminology used to describe phase interactions and shows an action potential of $i$ which causes an abbreviation of the perturbed cycle of $j$. Computations were carried out for numerous values of the propagation time $\tau_{i,j}$ such that the resulting phases $\phi_j$ assumed values ranging from 0 to $T_j$, the intrinsic cycle length of $j$ ($\phi_j = 0$, indicates that the action potential of $i$ reached $j$ at exactly the time, $t_j$, corresponding to the peak of the first action potential of the perturbed cycle of $j$). In this way the effect of the arrival of an action potential from $i$ at any time within a cycle
Figure 3.1: Terminology used to describe the influence of an action potential of cell $i$ on cell $j$. Schematic on left shows unidirectional coupling from $i$ to $j$. Dashed trace indicates control action potential (no interaction). Solid traces indicate activity when cells are coupled. Cell $i$ oscillates unperturbed and stimulates cell $j$ causing its second action potential to be advanced. Terminology used for delays (not shown) is analogous.
of \( j \) could be analyzed. After each computation, it was possible to scan the cycle in which the stimulus occurred and measure the phase shift \( \Delta T_j \) in the cycle length. These phase shifts were measured as the perturbed cycle length minus the intrinsic length; therefore, a positive phase shift (positive \( \Delta T_j \)) corresponds to a delay while a negative phase shift (negative \( \Delta T_j \)) corresponds to an advance in the occurrence of the subsequent action potential of \( j \). The shifts \( \Delta T_j \) were then plotted against \( \phi_j \) (where both were expressed as percent of the intrinsic cycle length, \( T_j \)) in what is known as a phase response curve (PRC). Some sample PRCs were obtained for various values of coupling conductances between different types of cells with different intrinsic cycle lengths. The coupling conductance values were chosen from the range of conductances of this study (0.0-0.1 mS/cm\(^2\)) and were sufficiently high to cause a measurable phase shift in the perturbed cell's cycle length.

3.3 An SA Node Cell and a Purkinje Fibre Cell

Although in a real heart an SA node cell is never physically adjacent to a Purkinje fibre cell, the activity of one may affect the activity of the other through the cell-to-cell propagation of impulses. With the present model, this type of interaction is studied by the incorporation of propagation time delays in the coupling currents flowing between the cells. This form of coupling and the method of the preceding section were used to study the phasic interactions of a model SA node cell (s) and model Purkinje fibre cell (p). The intrinsic periods of the cells were \( T_s = 599.53 \) msec and \( T_p = 748.13 \) msec which correspond to frequencies of approximately 100 and 80 cycles/min, respectively. These values represent a normal healthy oscillation rate for an SA node cell and a significantly high oscillation rate for a Purkinje fibre cell. This is a situation which is common in arrhythmias such as ventricular tachycardia and fibrillation.
Chapter 3. Phasic Interactions of Pacemaker Cells

The phase response curves of Figure 3.2 summarize, for two different values of the coupling conductance $g_{p,s}$, the effects of an action potential of $p$ on the cycle length of $s$. Although PRCs were obtained for several values of $g_{p,s}$, only two have been included. These PRCs use values of $g_{p,s}$ which are large enough to induce measurable phase shifts in the cycle of $s$ and produce PRCs which demonstrate, by the differences in their shapes, the effect of the coupling conductance. For $g_{p,s} = 0.005 \text{ mS/cm}^2$, the PRC shows that action potentials from $p$ which arrive during approximately the first one-third of the cycle of $s$ cause a delay, whereas those which arrive later cause an advance of the subsequent firing of $s$. When the coupling conductance was decreased to $g_{p,s} = 0.002 \text{ mS/cm}^2$ the shape of the PRC was maintained. Also, during this first one-third of the cycle of $s$ where both curves indicate delays (positive $\Delta T_s$), they are less for the case of coupling with the smaller conductance. Similarly, where both curves show advances, the magnitudes of the phase shifts are less for weaker coupling. These results are expected, since with decreased conductance, $p$ has less influence on the cycle length of $s$. For this reason also, with the smaller conductance, delays occur over a larger portion of the cycle (up to 40%). With the larger value of $g_{p,s}$, an action potential of $p$ is able to cause an advancement of the excitation of $s$, but a weaker stimulus still may cause only subthreshold depolarizations. These subthreshold depolarizations do not excite the cell and are followed by a period of repolarization to a more negative membrane potential from which the increase to the threshold value must begin again. The time required for this depolarization and subsequent repolarization delays the occurrence of the next action potential of $s$. Conversely, a stronger stimulus will be capable of exciting $s$ while it is relatively more refractory which occurs early in its peak-to-peak cycle, thus advances occur for lower $\phi_s$ with a larger conductance.

The lower graph of Figure 3.2 shows the membrane potential of $s$ plotted as a function of percent of its intrinsic cycle length over a complete peak-to-peak cycle prior to
Figure 3.2: Upper graph shows phase response curves summarizing the effects of a single action potential from $p$ on the cycle length of $s$ for two values of $g_{p,s}$ (mS/cm$^2$). Lower graph shows the intrinsic electrical activity of $s$ over a complete peak-to-peak cycle.
coupling. This plot provides a means of associating the cell’s intrinsic electrical activity with any value of $\phi_s$ of the corresponding PRC. For example, it is clear that for both values of $g_{p,s}$ the earliest phase advance of the action potential of $s$ does not occur until $s$ is undergoing phase 4 depolarization and membrane impedance is low.

For the same two model cells, the PRCs of Figure 3.3 demonstrate the effect of an action potential of $s$ on the cycle length of $p$ for two values of the coupling conductance $g_{s,p}$. As for the previous case, PRCs were obtained for several values of $g_{s,p}$, however, only two have been included. The values shown are sufficiently high that, in both cases, $s$ induces a measurable influence on the cycle length of $p$, yet the effects are different enough in each case to demonstrate the effect of the coupling conductance on the shape of the PRC. Again, for smaller conductance, corresponding to a decrease in the influence of $s$ on $p$, the general shape of the PRC is maintained and, where either both curves show delays or both show advances, the corresponding phase shifts are smaller in magnitude for the smaller value of $g_{s,p}$. Also, as in the preceding case with stronger coupling, delays occur over a smaller portion of $p$’s cycle because the larger the conductance, the more easily and the earlier in $p$’s cycle an action potential of $s$ can cause the advancement of a subsequent action potential of $p$. Comparing the electrical activity of $p$ (lower graph of Figure 3.3) at various phases to its PRC indicates that the largest phase delays occur during phase 3 repolarization when the cell is in a highly refractory state following its excitation. Furthermore, the transition from maximal delay to maximal advance occurs near the end of phase 3 repolarization and beginning of phase 4 depolarization when the refractory period comes to an end. Action potentials of $s$ arriving early in $p$’s cycle, at a time corresponding to the initial rapid rate of repolarization from the peak (phase 1), cause slight delays. McAllister, Noble, and Tsien [28] suggest that these delays might be due to a delayed repolarization. Following this region, there is an interval over which the rate of decrease in the membrane potential of $p$ lessens and during which a stimulus
Figure 3.3: Upper graph shows phase response curves summarizing the effects of a single action potential from s on the cycle length of p for two values of $g_{s,p}$ (mS/cm²). Lower graph shows the intrinsic electrical activity of p over a complete peak-to-peak cycle.
from $s$ causes slight advances. The magnitude of these phase shifts which occur early in $p$'s cycle are small, in agreement with the fact that a cardiac cell is most immune to stimuli immediately after excitation when it is in its absolute refractory state.

The biphasic response curves obtained here are similar in shape to those obtained experimentally by, amongst others, Jalife et al. [22] and numerically by Michaels et al. [30]. When either $p$ stimulates $s$ or vice-versa, the resulting PRCs (Figures 3.2, 3.3) demonstrate that, as the interaction between the cells is strengthened by increasing the coupling conductance, the transition from maximal delays to maximal advances occurs over a narrower range of phase values. This behavior was also found experimentally by Guevara et al. [13] for embryonic chick ventricular heart cells. When aggregates of these cells were stimulated by increasingly strong current pulses, the transition from maximal delay to maximal advance occurred much more abruptly.

3.4 An SA Node Cell and an AV Node Cell

Phase response curves were also obtained for the case of interaction between an SA node cell ($s$) and an AV node cell ($a$) where the same model SA node cell with an intrinsic oscillation period given by $T_s = 599.53$ msec as in the preceding simulations was used and coupled to a model AV node cell with $T_a = 793.00$ msec. These cycle lengths correspond to frequencies of approximately 80 and 75 cycles/min, respectively and represent normal rates for healthy SA node and AV node cells. The PRC of Figure 3.4 summarizes the effects of an action potential of $s$ on the intrinsic cycle length of $a$ for $g_{s,a} = 0.05$ mS/cm$^2$ while the PRC of Figure 3.5 demonstrates, for the same two cells and $g_{a,s} = 0.05$ mS/cm$^2$, the effects of the excitation of $a$ on the cycle length of $s$ (this value of the coupling conductances is one of several values which causes measurable changes in the perturbed cell’s cycle length and for which PRCs were obtained). The PRCs are almost identical
Figure 3.4: Upper graph shows phase response curve summarizing the effects of a single action potential from $s$ on the cycle length of $a$. Lower graph shows the intrinsic electrical activity of $a$ over a complete peak-to-peak cycle.
Figure 3.5: Upper graph shows phase response curve summarizing the effects of a single action potential from $a$ on the cycle length of $s$. Lower graph shows the intrinsic electrical activity of $s$ over a complete peak-to-peak cycle.
in shape. This is not unexpected since, except for the slower rate of depolarization of the AV node cell, the action potentials of the two cells are very similar (Figure 1.2). In both cases, discharges arriving early prolong, while those arriving later shorten, the cycle in which the stimulus occurs. As for the preceding PRCs, the transition from delay to advance occurs early in the phase 4 depolarization portion of the cycles in both cases. A further observation is that Figure 3.5 which shows the effects of the action potentials of $a$ on $s$ is very similar to Figure 3.2 which shows the effects of action potentials of $p$ on $s$. This indicates, as one would expect, that the source of the stimulus is not as important in determining the form of the resulting PRC as the type of cell being stimulated.

3.5 Fast and Slow Cells

Previous studies [30, 39] have obtained phase response curves showing that slower cells were much more affected by depolarizing currents than faster cells and that the phase shifts induced in a slow cell by a faster cell were always greater than those induced in the fast cell by the slower cell. These studies also indicated that the common entrained period for coupled fast and slow pacemakers firing in synchrony was always closer to the intrinsic period of the fast cell than of the slow cell. Thus, the changes in cycle length and subsequent phase shifts of the PRC were necessarily greater for the slower cell. These results; however, were obtained for similar cells coupled using adjacent-cell-coupling (Section 2.3) where the same current flowing out of one cell flows in to the other. For the present model, which allows the coupling of nonadjacent cells, the coupling currents flowing between the cells are direction dependent and are characterized by values of the coupling conductances and propagation time delays. The PRCs obtained here indicate that, with this direction dependent coupling, the phase shifts are not necessarily greater for the slower cell.
Comparing Figure 3.2 with Figure 3.3 reveals that the maximal advance of the slower Purkinje fibre cell \( p \) may be larger or smaller than the maximal advance of the faster SA node cell. Similarly, the maximal delay of \( p \) may be greater or less than the maximal delay of \( s \). The shape of the PRCs, and subsequently the cell which shows the greater phase shifts, is dependent on the values of the conductances \( g_{p,s} \) and \( g_{s,p} \). Thus, either cell can exert the larger influence.

Behavior similar to that of previous studies was obtained when a particular cell with a fixed period was coupled to another cell whose period of oscillation was then altered. As an example, Figure 3.6 shows the phase dependent effects of an action potential of an SA node cell on the cycle lengths of two Purkinje fibre cells, one with a period of 748.13 msec and the other with a period of 995.50 msec. The coupling conductance \( g_{s,p} \) remained constant at 0.065 mS/cm\(^2\), a value that is sufficiently high that action potentials at \( s \) were able to cause measurable phase-shifts in \( p \)’s cycle in both cases. At any given phase, the phase shifts are greater in magnitude for the slower Purkinje fibre cell. Furthermore, both the maximal delay and maximal advance are greater for the slower cell (although the maximal delays of the two cells differ only very slightly).

### 3.6 Phase Response Curves and Zones of Entrainment

The phase response curve gives some insight into the synchronization properties of an excitable cell oscillator since it determines the limits of the zones of stable entrainment for unidirectional coupling [39]. An action potential of one pacemaker can only advance or delay an action potential of another cell by a maximum amount indicated by the PRC. If the periods of the two oscillators differ by more than the maximum possible phase shift, the cells will not be entrained to a common frequency. For example, if a relatively fast cell is providing the stimulus to a slower cell and the corresponding PRC
Figure 3.6: Phase response curves summarizing the effects of a single action potential from $s$ on two different Purkinje fibre cells with periods as shown.
predicts that the maximal advance of the slower cell is less than the difference in the cycle lengths of the cells then the slow cell cannot be entrained to beat synchronously to the fast cell. Thus, a phase response curve provides a means of determining bounds on the cycle lengths of the cells for which entrainment can occur.

3.7 Pulsed versus Continuous Coupling

When pacemaker cells of the heart interact, the interaction is not restricted to the action potential phase. Consequently, the pulsed coupling used in obtaining the preceding PRCs does not reflect the true physiological situation. However, it was mentioned earlier that previous studies have concluded that the phasic interactions during an action potential were most important in determining the ultimate shape of the phase response curve and, therefore, the ultimate rhythm of coupled cells. This section will investigate some of the differences in PRCs obtained under conditions of pulsed and continuous coupling. Continuous coupling refers to a simulation allowing the interaction of the cells from the time of onset of the stimulus until the occurrence of the subsequent action potential of the perturbed cell at which time the computation was usually terminated.

Figure 3.7a shows the phase shifts induced in an SA node cell with period $T_s = 599.53$ msec due to continuous stimulation by a Purkinje fibre cell with period $T_p = 748.13$ msec. The coupling conductance used was $g_{p,s} = 0.005$ mS/cm$^2$. This value of $g_{p,s}$ and the same two cells were also used to obtain one of the PRCs shown in Figure 3.2 under conditions of pulsed coupling. Qualitatively, the results are similar in both cases. The general shape of the PRCs is the same with delays occurring for action potentials arriving early and advances occurring for action potentials arriving late in the cycle of $s$. The striking similarity between the PRCs is expected because the slower Purkinje fibre cell fires only once during any cycle of the faster SA node cell and coupling only during
Figure 3.7: Phase response curves summarizing the effects of \( p \) on \( s \) (a) and \( s \) on \( p \) (b) under conditions of continuous coupling.
the action potential phase of $p$ simply eliminates the remaining weaker influence during phase 4 depolarization. Quantitatively, there are differences in the results obtained under conditions of pulsed and continuous coupling. Although the portion of the curves showing advances are almost identical, the delays are greater in magnitude for the case of continuous coupling. This is due to the continuous ‘pull’ of the slower Purkinje fibre cell on the faster SA node cell during phase 4 depolarization.

When a fast cell provides the stimulus for a slower cell, the results obtained for the two methods of coupling are somewhat different. Figure 3.7b shows, for the same SA node and Purkinje fibre cells, the effects of the activity of $s$ on the cycle length of $p$ under conditions of continuous coupling. The corresponding PRC obtained using pulsed coupling is shown in Figure 3.3 with $g_{s,p} = 0.05 \text{ mS/cm}^2$. As in the previous case, the portion of the curves after the transition from delay to advance are almost identical. However, for small values of $\phi_p$ the PRCs are quite different. When the coupling is continuous the cycle length of $p$ is significantly shortened, whereas under pulsed coupling the phase shifts were small for small values of $\phi_p$. These advances which occur for continuous coupling are due to the fact that if an action potential of the faster cell ($s$) arrives early in $p$’s cycle then a second action potential will also arrive within the same cycle of $p$. In addition, since $T_s = 599.53$ msec and $T_p = 748.13$ msec this second action potential of $s$ will occur for $\phi_p > 80\%$, at a time when $p$ is in the latter stages of phase 4 depolarization and membrane impedance is low. Consequently, the firing of $p$ will be advanced in comparison to its unperturbed oscillation. A further observation is that the phase delays under continuous coupling are smaller due to the ‘pull’ of the faster SA node cell during phase 4 of its cycle than under conditions of pulsed coupling.