Mathematical models of the electrical action potential of Purkinje fibre cells

BY PHILIP STEWART, OLEG V. ASLANID, DENIS NOBLE, PENELLOPE J. NOBLE, MARK R. BOYETT AND HENGGUI ZHANG

School of Physics and Astronomy, and Faculty of Medical and Human Sciences, University of Manchester, Manchester M13 9PL, UK
Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford OX1 3PT, UK

Early development of ionic models for cardiac myocytes, from the pioneering modification of the Hodgkin–Huxley giant squid axon model by Noble to the iconic DiFrancesco–Noble model integrating voltage-gated ionic currents, ion pumps and exchangers, Ca$^{2+}$ sequestration and Ca$^{2+}$-induced Ca$^{2+}$ release, provided a general description for a mammalian Purkinje fibre (PF) and the framework for modern cardiac models. In the past two decades, development has focused on tissue-specific models with an emphasis on the sino-atrial (SA) node, atria and ventricles, while the PFs have largely been neglected. However, achieving the ultimate goal of creating a virtual human heart will require detailed models of all distinctive regions of the cardiac conduction system, including the PFs, which play an important role in conducting cardiac excitation and ensuring the synchronized timing and sequencing of ventricular contraction. In this paper, we present details of our newly developed model for the human PF cell including validation against experimental data. Ionic mechanisms underlying the heterogeneity between the PF and ventricular action potentials in humans and other species are analysed. The newly developed PF cell model adds a new member to the family of human cardiac cell models developed previously for the SA node, atrial and ventricular cells, which can be incorporated into an anatomical model of the human heart with details of its electrophysiological heterogeneity and anatomical complexity.

Keywords: model; Purkinje; cardiac; conduction; electrophysiology

1. Introduction

Purkinje fibre (PF) cells are tertiary pacemakers of the heart, normally suppressed by the primary pacemaker, the sino-atrial (SA) node (Vassalle 1970, 1977). The PF network is an important part of the cardiac conduction system, responsible for ensuring the synchronized timing and sequencing of ventricular contraction (Fozzard et al. 1991). It can also be a major source for generating life-threatening ventricular arrhythmias (Nattel & Quantz 1988; Nibley & Wharton 1995; Asano et al. 1997; Berenfeld & Jalife 1998). Under

One contribution of 15 to a Theme Issue ‘The virtual physiological human: tools and applications II’.
normal conditions, the PF network serves as a fast conduction pathway to conduct electrical excitation waves, originating from the SA node, into the ventricles. In some abnormal conditions, the PF network may produce a series of ectopic focal activities that rapidly drive the surrounding ventricular tissue, leading to ventricular tachycardia and fibrillation (Pogwizd & Corr 1992; Arnar et al. 1997, 2001; Chung et al. 1997; Pogwizd et al. 1998; Arnar & Martins 2002). Conduction block in either the left or right bundle branches of the PFs can lead to uncoordinated ventricular excitation and contraction (Fantoni et al. 2005; Imanish et al. 2006; Niu et al. 2006). Additionally, under some circumstances, a localized temporal functional conduction block in the PF network can generate re-entrant excitation waves giving rise to ventricular fibrillation (Arnar et al. 1997, 2001; Xing & Martins 2004).

The PF network is a distinctive tissue of the heart with intrinsic electrical properties remarkably different from other cardiac tissues including that of the ventricle (Tseng & Boyden 1989; Yu et al. 1995; Cordeiro et al. 1998; Han et al. 2001a, 2002; Dumaine & Cordeiro 2007). In many species, the PF cell action potentials (APs) have unique features, including a larger upstroke velocity, lower plateau and longer AP duration (APD; Baláti et al. 1998; Burashnikov & Antzelevitch 1999; Schram et al. 2002; Lu et al. 2005). Importantly, PF cells can present automaticity due to slow spontaneous diastolic depolarization (Yu et al. 1995; Baláti et al. 1998). Such differences in electrical APs are associated with different kinetics and current densities in a number of major ion channels (Han et al. 2001a, 2002; Dumaine & Cordeiro 2007). Considering both the important role of the PF system in ensuring normal ventricular excitation and generating life-threatening ventricular arrhythmias, and their distinctive properties in ion channel kinetics, it is necessary to develop a biophysically detailed model for the electrical APs of PF cells that can be incorporated into a realistic model of the human heart.

(a) Half a century of progress

The seminal work by Hodgkin & Huxley (1952), in which they derived a quantitative description of the ionic currents and hence the AP of the giant squid axon, began what is now more than half a century of development in mathematical models describing the electrophysiology of biologically excitable cells. A decade later, Noble (1962) pioneered the application of the work of Hodgkin & Huxley (1952) to cardiac myocytes, proposing modifications that would result in a simple ionic model of a mammalian PF cell, reproducing the much longer APD and pacemaker potential of the PF. The model retained a single fast sodium current, but split the potassium current into two components, \( I_{K1} \) (note \( I_{K1} \) here differs from the inward rectifier potassium current referred to later) and \( I_{K2} \), with the conductance of \( I_{K1} \), \( g_{K1} \), instantaneously dependent on membrane potential, and \( g_{K2} \), the conductance of \( I_{K2} \), rising slowly as the membrane depolarizes.

The advent of the first successful voltage-clamp measurements by Deck & Trautwein (1964), discoveries of the cardiac calcium current by Reuter (1967) and multiple components of the potassium current, \( I_{K} \), by Noble & Tsien (1969) resulted in a need for a successor to the Noble (1962) model. In response to the growing wealth of experimental data (Noble & Tsien 1968, 1969) and knowledge at the time, McAllister et al. (1975) developed a model to reproduce the AP of

Phil. Trans. R. Soc. A (2009)
the cardiac PF using nine ionic currents. Their model added a new secondary inward calcium current, $I_{Ca}$, a transient outward chloride current, $I_{Cl}$, and fast and slow potassium currents, $I_{x1}$ and $I_{x2}$. The resultant model could reproduce a much wider range of experimental observations known at the time, some with a high degree of accuracy.

The model of McAllister et al. (1975) was superseded by the DiFrancesco & Noble (1985) PF cell model. DiFrancesco (1981) had already shown that what was previously called $I_{K2}$ was actually an inward, hyperpolarization-activated pacemaker current, $I_f$, as opposed to an outward, depolarization-activated current, as described by McAllister et al. (1975) in their model. In addition to the incorporation of $I_f$, the model of DiFrancesco & Noble (1985) included dynamic changes of intra- and extracellular ion concentrations, ionic pumps and exchangers that are necessary to restore and maintain the transmembrane ion concentration gradients, and a description of the Ca$^{2+}$ handling in the sarcoplasmic reticulum (SR). The depletion of potassium ions in the extracellular spaces made the inclusion of the sodium–potassium ($I_{NaK}$) pump a necessity, otherwise $I_f$ would not resemble a potassium current. As a consequence of introducing the Na$^+$–K$^+$ pump and hence changes in the potassium concentration, it also became necessary to include concentration changes for sodium and calcium, leading to the introduction of the sodium–calcium exchanger ($I_{NaCa}$) and a description of calcium release from the SR, including calcium-induced calcium release, described by Fabiato & Fabiato (1975). The DiFrancesco & Noble (1985) model had thus become the first electrophysiologically detailed model capable of describing both ionic currents and concentration changes.

Building on the successes of these models, development shifted towards different cardiac tissues across a variety of species, notably including the mammalian ventricular models of Luo & Rudy (1991, 1994a,b) and the human models for atrial (Courtemanche et al. 1998; Nygren et al. 1998) and ventricular cells (Iyer et al. 2004; ten Tusscher et al. 2004; ten Tusscher & Panfilov 2006). During this time, the development of further PF models has largely been neglected (Boyett et al. 2005).

(b) The virtual human heart

We are fast approaching the ultimate goal of constructing a virtual human heart with detailed ionic models of all distinctive regions of the cardiac conduction system already available, including the atria (Courtemanche et al. 1998; Nygren et al. 1998) and the ventricles (Iyer et al. 2004; ten Tusscher et al. 2004; ten Tusscher & Panfilov 2006). A simple caricature model for the human SA node has been developed (Seemann et al. 2006) as has been a detailed anatomical geometry of the whole human heart (Sachse et al. 2000). The human PF cell is one of the remaining missing models for the human cardiac conduction system. Minor modifications to the maximum conductance of $I_{Ks}$ and $I_{Na}$ in the ten Tusscher et al. (2004) and ten Tusscher & Panfilov (2006) human ventricle model were proposed by ten Tusscher & Panfilov (2008), which resulted in a simple human PF model and allowed them to simulate the cardiac conduction system in the ventricles. However, their resultant AP lacks many of the characteristics observed experimentally in human PF cells (Dangman et al. 1982;
Lee et al. 2004). We therefore aim to develop a biophysically detailed model of the human PF cell AP to fulfil the impending requirement to build a virtual human heart.

2. Methods

The dynamics of the membrane potential in a cardiac cell are described by the following differential equation:

$$C_m \frac{dV}{dt} = -(I_{ion} + I_{stim}),$$

(2.1)

where $C_m$ is the membrane capacitance; $V$ is the membrane potential; $t$ is the time; $I_{ion}$ is the sum of the transmembrane ionic currents; and $I_{stim}$ is an externally applied stimulus current (Hodgkin & Huxley 1952). Numerous biophysically detailed descriptions of $I_{ion}$ have already been developed for many different cardiac tissue types, in a variety of species.

(a) Human Purkinje fibre model

We developed a description of $I_{ion}$ for the human PF cell based on the model of the human endocardial cell by ten Tusscher et al. (2004) and ten Tusscher & Panfilov (2006). We modified their model based on the experimental data of Han et al. (2002) describing the properties of potassium currents in human PF cells. Our description of $I_{ion}$ required the addition of two currents: a hyperpolarization-activated current, $I_f$, and a sustained potassium current, $I_{sus}$, resulting in a total of 14 ionic currents, as given in equation (2.2). In addition to the introduction of the new currents, the descriptions for the inward rectifier current, $I_{K1}$, and the transient outward current, $I_{to}$, were reformulated, and the maximum conductance of the rapid and slow delayed rectifier potassium currents, $I_{Kr}$ and $I_{Ks}$, and the fast sodium current, $I_{Na}$, were altered because these channels are distinctively different in channel kinetics and current densities between PF and ventricular cells:

$$I_{ion} = I_{Kr} + I_{Ks} + I_{K1} + I_{to} + I_{sus} + I_{Na} + I_{b,Na} + I_{Ca,L} + I_{b,Ca} + I_{NaK}$$

$$+ I_{NaCa} + I_{p,Ca} + I_{p,K} + I_f.$$  

(2.2)

A detailed listing of all equations and parameters for the developed human PF cell AP can be found in appendices A and B, respectively. The model is available online from the CellML repository (http://www.cellml.org/) and was developed with CELLULAR OPEN RESOURCE (Garny et al. 2003). Below we describe details of modifications made to the ten Tusscher et al. (2004) and ten Tusscher & Panfilov (2006) model of endocardial cells for each individual current.

(i) Transient outward current, $I_{to}$, and sustained current, $I_{sus}$

The transient outward potassium current, $I_{to}$, and the sustained potassium current, $I_{sus}$, are both present in human PF and ventricular cells; however, their channel properties (i.e. channel kinetics and current densities) are different between the two cell types (Han et al. 2002). In the PF cells, it was observed that
$I_{to}$ is significantly smaller in current density and slower in inactivation and recovery, but $I_{sus}$ current density is substantially larger (Han et al. 2002). The clear difference between the PF and ventricular cells in their sensitivities to potassium channel blocks (e.g. 4AP and tetraethylammonium) may be due to a different molecular basis forming the $I_{to}$ and $I_{sus}$ channels in the two cell types as seen in canines (Han et al. 2000, 2001b).

To reflect the fundamental differences in the $I_{to}$ and $I_{sus}$ channel properties, the equations of the ten Tusscher et al. (2004) model for the steady-state activation variable, $r_N$, and inactivation variable, $s_N$, of $I_{to}$ were reformulated based on the experimental data of Han et al. (2002) on human PF cells. This resulted in an increase in slope factor of $r_N$ and $s_N$ from 6 and 5 mV, respectively, to 13 mV, and an additional shift in the half-inactivation (figure 1a) by $K_{1}$ mV. Equations for the activation and inactivation time constants, $\tau_r$ and $\tau_s$, were also reformulated to fit the experimental data of Han et al. (2002). The resultant $\tau_r$ and $\tau_s$ are significantly larger than in the ventricle model (a maximal increase by 72 and 1300% for $\tau_r$ and $\tau_s$, respectively; figure 1b). Maximum conductance, $G_{to}$, was determined by fitting the current–voltage ($I–V$) relationship (figure 1c) to the experimental data of Han et al. (2002), resulting in an increase of 12 per cent with respect to the endocardial model of ten Tusscher et al. (2004).

In the original ten Tusscher et al. (2004) and ten Tusscher & Panfilov (2006) model, there is no formulation for the sustained potassium current, $I_{sus}$. Experimental data from both animal and human studies suggested the presence of the current in PF cells, which is distinctively different in molecular basis from its ventricular counterpart (Han et al. 2000, 2001a,b). Based on the experimental data of Han et al. (2002), $I_{sus}$ was introduced with a single instantaneous activation variable, $a$, described by a single exponential sigmoid function. To determine the maximum conductance, $G_{sus}$, the simulated $I–V$ relationship (figure 1d) obtained using the same voltage-clamp protocol used experimentally was fitted to the experimental data of Han et al. (2002). Model parameters and equations were validated by the consistency of the resulting simulated current traces of $I_{to} + I_{sus}$ (figure 1e) and the $I–V$ relationship with those observed experimentally (Han et al. 2002).

(ii) Hyperpolarization-activated current, $I_f$

The hyperpolarization-activated current, $I_f$, is believed to play an important role in producing spontaneous diastolic depolarization leading to automaticity in some cardiac tissues, such as the SA node and PF cells (DiFrancesco 2006). $I_f$ has been recorded from both animal and human PF cells (Callewaert et al. 1984; Cerbai et al. 1997; Shi et al. 1999; Han et al. 2002). In the absence of a description of $I_f$ in the ten Tusscher et al. (2004) and ten Tusscher & Panfilov (2006) model, we introduced $I_f$ based on the model of Zhang et al. (2000) for the rabbit SA node. The model equations for the steady-state activation variable, $y_\infty$, and the voltage-dependent time constant of activation, $\tau_{y^f}$, were reformulated based on the experimental data on the channel kinetics of human PF $I_f$ (Han et al. 2002). The maximal channel conductance, $G_{f}$, was determined by fitting the simulated $I–V$ relationship to the experimental data (Han et al. 2002). The model equations and parameters were validated by the agreement of the simulated $I_f$ current traces (figure 2a) and $I–V$ relationship (figure 2b) during voltage clamp with experimental data (Han et al. 2002).
Experimental data suggested a different $I_{K1}$ current density between the PF and ventricular cells (Han et al. 2002). In rabbit hearts, it was shown that the measured $I_{K1}$ density was much smaller than in ventricular myocytes.

(iii) **Inward rectifier current, $I_{K1}$**

Experimental data suggested a different $I_{K1}$ current density between the PF and ventricular cells (Han et al. 2002). In rabbit hearts, it was shown that the measured $I_{K1}$ density was much smaller than in ventricular myocytes.

*Phil. Trans. R. Soc. A* (2009)
Based on the experimental data of human PF cells (Han et al. 2002), the endocardial description (ten Tusscher et al. 2004) of the time-independent inward rectification factor, $x_{K1\infty}$, of $I_{K1}$ was reformulated. The maximum conductance, $G_{K1}$, was determined by fitting the simulated $I$–$V$ relationship (figure 2c) to the experimental data (Han et al. 2002).

(b) All-or-nothing repolarization

Following the methods of Vassalle (1966) and McAllister et al. (1975), the phenomenon of all-or-nothing repolarization (Weidmann 1951) can be used as a method of validating qualitatively the behaviour of the AP model. APs are elicited by a suprathreshold stimulus at a time interval of 1 s and remain unperturbed during the resultant AP. During the 10th AP, at times of 40, 60 and 80 ms after the AP has been elicited, the membrane potential, $V$, is clamped for 20 ms to a holding potential, $V_{\text{hold}}$, and then released. The response to varying $V_{\text{hold}}$ is determined by whether the AP repolarizes earlier than a normal AP. If $V_{\text{hold}}$ is above a threshold value, the membrane will depolarize and the AP will repolarize later than normal. If $V_{\text{hold}}$ is at or below the threshold, the membrane will repolarize earlier than usual.
Overdrive suppression

Rapid stimulation of PF cells can result in a phenomenon called overdrive suppression (Vassalle 1970; Valenzuela & Vassalle 1983; Boyett & Fedida 1984), where the pacemaker activity of the PF cells is suppressed for a period of time following high-frequency stimulation after which it restarts again. Under normal sinus rhythm in the heart, the pacemaking of the PF cells is usually suppressed by the SA node. Overdrive suppression was simulated using the following protocol: no external stimulus was applied for the first 100 s, after which the cell was paced by a series of periodic suprathreshold stimuli (with an amplitude of $-52 \text{ pA pF}^{-1}$ and a duration of 1 ms) at frequencies of 1.5, 2.0 or 2.5 Hz, before the external stimulation was stopped 10 min later.

3. Results

(a) Simulated action potential of human Purkinje fibre cells

The simulated time course of the autorhythmic human PF APs (figure 3a), major underlying ionic channel currents (figure 3b–j) and the transient of intracellular Ca$^{2+}$ concentration (figure 3k) are shown in figure 3. The simulated AP begins with a rapid phase-0 depolarization upstroke, accompanied by the activation of $I_{\text{Na}}$ (figure 3b). Following the rapid depolarization, there is a rapid phase-1 repolarization caused by the activated $I_{\text{to}}$ (figure 3d), producing a sharp spike and notch. The phase-2 plateau is maintained by the activation of $I_{\text{CaL}}$ (figure 3c), which is followed by the phase-3 repolarization as a consequence of an integral action of $I_{\text{Kr}}$, $I_{\text{Ks}}$ and $I_{\text{K1}}$ (figure 3e–g). Activation of $I_{\text{f}}$ (figure 3h) produces a phase-4 diastolic depolarization leading to automaticity. During the time course of APs, activation of $I_{\text{NaK}}$ (figure 3i) and $I_{\text{NaCa}}$ (figure 3j) contributes to dynamic changes of ion concentrations and also to the morphology of the APs. The reconstructed sharp spike/notch and the phase-4 diastolic depolarization leading to automaticity are features of PF cells that are distinctive compared with ventricular myocytes.

The simulated AP has characteristics comparable to the experimental data of human PF cells. Experimentally measured maximal diastolic potential (MDP) of PF APs is between $-79$ and $-85$ mV (Dangman et al. 1982; Lee et al. 2004). In simulations, the computed MDP is $-75.53$ mV. The experimentally measured amplitude of APs (APA, measured from the MDP to the overshoot of the AP) for human PF cells is between 107 and 114 mV (Dangman et al. 1982; Lee et al. 2004). In the model, the computed APA is 123.13 mV. PF cells have a larger upstroke velocity than ventricular myocytes. The measured maximal upstroke velocity from human PF cells is from 207 to 387 V s$^{-1}$ (Dangman et al. 1982; Lee et al. 2004). In the model, the computed maximal upstroke velocity is 327.42 V s$^{-1}$. The experimentally measured APD$_{90}$ is 319 ± 23 ms (Lee et al. 2004), while the computed value is approximately 293 ms. The measured slope of the diastolic potential from paced PF cells is 3.7 ± 1.0 mV s$^{-1}$ (Lee et al. 2004). In automatic cells, it is expected that there will be a larger slope of the diastolic potential. In the model, the simulated APs are automatic with a computed slope of diastolic potential of 10 mV s$^{-1}$. The computed cycle length for spontaneous APs is approximately 1.1 s, which is close to the experimentally observed range of 1.3–3.0 s (Schmidt & Thews 1993; Lee et al. 2004).
Figure 3. (a) Simulated autorhythmic APs. Inset: comparison between APs evoked by an external stimulus from uncorrected (black) and corrected (grey) parameters for heart failure-induced electrical remodelling. (b–j) Time traces for major ionic currents and (k) calcium transient.

Phil. Trans. R. Soc. A (2009)
All-or-nothing repolarization and overdrive suppression

Figure 4a,b shows the simulated all-or-nothing repolarization results obtained using the model. In figure 4a, time courses of repolarized APs clamped 80 ms after the AP was elicited to various potentials for 20 ms are shown. When the clamp potential is above \(-25\,\text{mV}\), the model response is a secondary depolarization that extends the AP repolarization duration and increases the APD. However, when the clamp potential is at or below \(-25\,\text{mV}\), the model response results in successive repolarization that shortens the AP repolarization duration. Thus, the model presents the existence of a threshold \((-25\,\text{mV})\) at which repolarization can be accelerated. Figure 4b shows the computed threshold for all-or-nothing repolarization at 40, 60 and 80 ms after the AP was elicited. The computed threshold is dynamical, which shifts towards the plateau potential with time. The simulated all-or-nothing repolarization and dynamical shift of the determined threshold for forcing repolarization with varied refractory timing are consistent with experimental observations on PF tissues (Weidmann 1951; Vassalle 1966).

Rapid stimulation of PF cells can result in overdrive suppression (Vassalle 1970; Valenzuela & Vassalle 1983; Boyett & Fedida 1984), a phenomenon that is reproduced by the model (figure 4c). During the first 100 s period, the PF cell model is stably autorhythmic. In the following 10 min period, the PF model is stimulated by a series of rapid stimuli at 2.5 Hz, each of which evokes an AP. When the external stimulus is switched off, there is a period of quiescence before stable automaticity resumes (figure 4c(i)). The characteristics of the simulated overdrive suppression are similar to the experimental observations by Boyett et al. (1987).

To investigate possible mechanisms underlying the genesis of overdrive suppression, time courses of intracellular Na\(^{+}\) concentration and the Na\(^{+}\)–K\(^{+}\) pump current are considered (figure 4c(ii)(iii)). During the period of rapid stimulation, the intracellular Na\(^{+}\) concentration rises slowly towards an asymptotic level, approximately 4 mM higher than the initial value. Associated with the increased intracellular Na\(^{+}\) concentration is a monotonic increase in the Na\(^{+}\)–K\(^{+}\) pump current. This increase in Na\(^{+}\)–K\(^{+}\) pump current suppresses the spontaneous pacemaking activity when the external stimulus is switched off, leaving the cell model in a quiescent state. During the quiescent period, intracellular Na\(^{+}\) falls comparatively quickly to the initial value (figure 4c(ii)), resulting in decreased Na\(^{+}\)–K\(^{+}\) pump current. When the Na\(^{+}\)–K\(^{+}\) pump current decreases to a critical amplitude, comparable with the amplitude of \(I_{\text{NaK}}\) during the diastolic phase of the AP before rapid stimulation, the spontaneous pacemaking activity of the PF cell model resumes.

An increase in intracellular Na\(^{+}\) during rapid pacing has been observed experimentally (Boyett et al. 1987) and is believed to be responsible for suppression of automaticity following prolonged periods of rapid stimulation (Valenzuela & Vassalle 1983), as it produces a rate-dependent increase in the Na\(^{+}\)–K\(^{+}\) pump activity (Kline & Kupersmith 1982; Boyett & Fedida 1984). The simulations presented support this hypothesis (figure 4c). The link between overdrive suppression and the rate-dependent increase in the Na\(^{+}\)–K\(^{+}\) pump current due to intracellular Na\(^{+}\) overload can be further studied by removing the contribution of \(I_{\text{NaK}}\) to cell membrane potential (i.e. it is removed from...
equation (2.2)), while retaining the Na\(^+\)–K\(^+\) pump function in sustaining the homoeostasis of Na\(^+\) and K\(^+\) ions. The removal of the Na\(^+\)–K\(^+\) pump current from equation (2.2) results in a relatively small intracellular Na\(^+\) overload and negligible increase in Na\(^+\)–K\(^+\) pump current, and as a result abolishes the period

\[ f(\text{Hz}) \]

\[ T_q(s) \]

Figure 4. Reproduction of experimental phenomena. All-or-nothing repolarization: (a) 80 ms after the AP is elicited, the membrane is clamped to a holding potential for 20 ms and then released, resulting in either successive depolarization and a prolongation of the APD or repolarization and a shortening of the APD. (b) The threshold for repolarization approaches the plateau potential as the time after the AP is elicited, at which the membrane is clamped, increases. (c) Overdrive suppression of the pacemaker after a period of rapid stimulation. (i) The cell is autorhythmic before rapid stimulation at 90, 120 or 150 beats per minute for 10 min, after which a period of quiescence occurs, the pacemaker recovers and eventually resumes spontaneous activity. Slow rises in both (ii) \([\text{Na}^+]_i\) and (iii) \(I_{\text{NaK}}\) occur during rapid pacing, returning to normal levels shortly after automaticity resumes. (d) Removal of \(I_{\text{NaK}}\) from equation (2.2) while retaining the Na\(^+\)–K\(^+\) pump function resulted in no period of quiescence after rapid pacing. (e) Effect of pacing frequency, \(f\), on period of quiescence, \(T_q\).

Phil. Trans. R. Soc. A (2009)
of quiescence after the rapid stimulation (figure 4d). This provides further support for the hypothesis that the overloading of intracellular Na\(^+\) concentration is responsible for the genesis of overdrive suppression (Vassalle 1970).

Boyett & Fedida (1984) demonstrated that overdrive suppression is rate dependent and the period of quiescence, \(T_q\), is longer at higher stimulation frequencies. Such a rate-dependent prolongation of the suppression period is reproduced by the model for stimulation frequencies greater than 1.5 Hz. The model was paced at 1.5, 2 and 2.5 Hz (corresponding to pacing rates of 90, 120 and 150 beats per minute, respectively) and with the increasing frequency, the measured \(T_q\) increased from 50 to 83 s (figure 4e).

(c) Ionic mechanisms underlying human Purkinje fibre cells

Simulations were performed to elucidate the role of each major individual ionic current in generating autorhythmic human PF APs (figure 5), especially the genesis of diastolic depolarization leading to automaticity.

(i) Effect of \(I_{Na}\) on the action potential

The role of \(I_{Na}\) was investigated by blocking \(I_{Na}\) either partially or completely (figure 5b). Blocking \(I_{Na}\) by 50 per cent slows down the automatic activity. Compared with the control condition, the measured cycle length increases from 1.1 to 2.6 s, while the overshoot is decreased from 30 to 18 mV, as is the maximal upstroke velocity, which decreases to 24 V s\(^{-1}\). There is no noticeable change in the MDP or the APD. Blocking \(I_{Na}\) by 100 per cent results in the abolition of automaticity with the membrane potential resting at \(-66.5\) mV.

(ii) Effect of \(I_{CaL}\) on the action potential

The role of \(I_{CaL}\) was determined by blocking \(I_{CaL}\) either partially or completely (figure 5a). Blocking \(I_{CaL}\) by 50 per cent resulted in a slowing of the automaticity, increasing the cycle length to 1.4 s. Additionally, it decreases the overshoot, shortens APD and also decreases the plateau potential of the APs. There was no noticeable change in the MDP. However, blocking \(I_{CaL}\) further to 100 per cent accelerates, rather than decelerates, the automaticity. In this condition, the measured CL decreases to 0.9 s. The accelerated automaticity is due to a shortening of the APD as a consequence of the loss of the AP plateau, similar to previous experimental observations in peripheral rabbit SA node cells, in which the application of nifedipine, an inhibitor of \(I_{CaL}\), shortened the rabbit SA node APD and accelerated its pacemaking activity (Kodama et al. 1997).

(iii) Effect of \(I_{Kr}\) on the action potential

Blocking \(I_{Kr}\) by 50 or 100 per cent produces a prolonged APD and a reduction in the rate of automaticity (figure 5c). However, it has negligible effect on the overshoot and MDP. The slowing down in the automaticity can be attributed to the prolonged APD as observed in rabbit SA node cells (Kodama et al. 1997).

Phil. Trans. R. Soc. A (2009)
(iv) **Effect of I\textsubscript{Ks} on the action potential**

Blocking I\textsubscript{Ks} by 50 or 100 per cent produces negligible effects on the overshoot, MDP, maximal upstroke velocity and the automaticity of the APs (figure 5d). It does, however, prolong the measured APD\textsubscript{50} from 231 to 309 ms with a 100 per cent block.

(v) **Effect of I\textsubscript{to} on the action potential**

Blocking I\textsubscript{to} by 50 or 100 per cent produces negligible effects on the overshoot, MDP, maximal upstroke velocity and the automaticity of APs (figure 5e). However, it has remarkable effects on the phase-1 repolarization. Blocking I\textsubscript{to}
slows down the phase-1 repolarization producing an elevated plateau potential and a less marked phase-1 spike/notch. By blocking $I_{to}$ by 100 per cent, the unique feature of the phase-1 notch of the PF cell AP disappears.

(vi) **Effect of $I_f$ on the action potential**

Blocking $I_f$ has the most dramatic effect on the automaticity of the PF cell model, though its effect on the overshoot, MDP, maximal upstroke velocity and APD is negligible (figure 5f). Blocking $I_f$ by 30 per cent increased the measured cycle length of APs from 1.1 to 1.7 s under the control condition. Blocking $I_f$ by 100 per cent abolished the automaticity with the membrane potential resting at $-75.5 \text{ mV}$, close to the MDP. However, the cell model remains excitable and with an external suprathreshold stimulus, a full AP can be evoked.

(d) **Comparison between human and canine Purkinje fibre cell action potential models**

The electrical properties of PF cells are species dependent (Lu et al. 2001). Experimental data indicate dramatic differences in the morphology of human and canine PF APs. Primarily, canine PF cells have a much lower AP plateau and more predominant notch (Dumaine & Cordeiro 2007) than human PF cells (Lee et al. 2004). It is possible that such differences in their APs are due to different properties of ion channels in the two species. Using the model we developed for canine PF cells (O. V. Aslanidi et al. unpublished data) and the present model, we have identified $I_{to}$ as the main factor contributing to differences between human and canine PF APs. There are experimental data suggesting that the current density of $I_{to}$ measured at 20 mV from canine PF cells is significantly larger than from human PF cells (figure 6a). Blocking $I_{to}$ in the canine PF cell model produces APs with substantially changed morphology (figure 6b): an elevated plateau and less marked notch as seen in human PF cells (Han et al. 2002). Therefore, we conclude that the large differences in the AP plateau potential and notch between the canine and human PF cells seen experimentally (Lee et al. 2004; Dumaine & Cordeiro 2007) can be explained by significant differences in the transient outward current between the two species (Han et al. 2001a, 2002).

4. **Discussion**

In this study, we have developed a biophysically detailed model for the electrical AP of the human PF cell based on modifications to the ten Tusscher et al. (2004) and ten Tusscher & Panfilov (2006) model of human ventricular myocytes, which incorporate extant voltage-clamp data recorded from human PF cells (Han et al. 2002). Conductance, steady-state activation and inactivation curves and time constants for $I_{to}$, $I_{Kr}$, $I_{Ks}$ and $I_{K1}$ were updated, and two additional currents were introduced: a hyperpolarization-activated pacemaking current, $I_f$, and a sustained potassium current, $I_{sus}$, absent in the ventricular cell models but present in PF cells, which we fitted to the experimental data of Han et al. (2002). The resultant model reproduces the PF...
cell AP with characteristics consistent with experimental recordings (Dangman et al. 1982; Lee et al. 2004). Inclusion of $I_f$ in the model produces autorhythmic APs with a cycle length of approximately 1.1 s, which is consistent with experimental data (Schmidt & Thews 1993; Lee et al. 2004). The model is also validated by its ability to reproduce the all-or-nothing repolarization phenomenon observed in PF tissues (Wiedmann 1951; Vassalle 1966), and the well-known physiological phenomenon of overdrive suppression (Vassalle 1970; Valenzuela & Vassalle 1983; Boyett & Fedida 1984). Using the model, we compute the functional role of several major ionic currents ($I_{Na}$, $I_{CaL}$, $I_{to}$, $I_{Kr}$, $I_{KS}$ and $I_f$) in producing the unique features of human PF APs, especially the fast phase-1 repolarization, the phase-4 diastolic depolarization and the automaticity. It is shown that while $I_{to}$ plays an important role in producing the phase-1 notch, $I_{Na}$, $I_{CaL}$ and $I_f$ all play an important role in controlling the automaticity of PF cells.

(a) Comparison to other species

In contrast to many other species including canine (Dumaine & Cordeiro 2007), rabbit (Dumaine & Cordeiro 2007) and sheep (Boyett 1981), the human PF AP lacks a number of characteristics, such as a longer APD, lower plateau potential and less marked phase-1 notch than its ventricular counterpart. The human PF AP is, in fact, more ventricular-like than other species (Dangman et al. 1982; Lee et al. 2004). The presented human PF model reproduces this observation. It is of scientific interest to investigate the ionic mechanisms underlying such differences in the AP characteristics between human and animal models. Using the present model and the model we developed for canine PF cells (O. V. Aslanidi et al. unpublished data), we have shown that the marked differences in the morphology of PF APs between the human and canine hearts can be explained by the different $I_{to}$ densities of PF cells measured in the two species, as observed experimentally.
Adjustment of model parameters due to heart failure-induced ion channel remodelling

The experimental data of Han et al. (2002) on properties of potassium currents of human PF cells were obtained from explanted failing human hearts. It is well known that heart failure induces changes in channel properties of several major ion channels (i.e. ion channel remodelling) responsible for electrical APs in both PF and ventricular cells (Priebe & Beuckelmann 1998; Han et al. 2001). Experimental data also suggested that heart failure-induced ion channel remodelling is comparable between PF and ventricular cells (Han et al. 2001). In human ventricular cells, it was shown that the AP is prolonged in patients with heart failure (Priebe & Beuckelmann 1998). Associated with the changes in the AP is the downregulation of $I_{K1}$ (Beuckelmann et al. 1993; Koumi et al. 1995) and $I_{to}$ (Beuckelmann et al. 1993; Nébauer et al. 1993). There is no evidence for heart failure-induced remodelling on other potassium channels, such as $I_{Kr}$ and $I_{Ks}$, nor on the fast sodium current $I_{Na}$ (Priebe & Beuckelmann 1998; Han et al. 2001). However, there is evidence that the current densities and kinetics of $I_{Ca}$ are unaltered (Beuckelmann et al. 1993; Mewes & Ravens 1994; Ouedid et al. 1995), though Ca$^{2+}$ handling is altered and the activity of the Na$^{+}$—Ca$^{2+}$ exchanger is enhanced (Gwathmey et al. 1987; Beuckelmann et al. 1992; Flesch et al. 1996; Reinecke et al. 1996) in the failing hearts. Data obtained from canine studies suggested that congestive heart failure (CHF) produced compatible ion channel remodelling between PF and ventricular myocytes, with the main changes involving downregulation of both $I_{K1}$ and $I_{to}$ densities and slowed inactivation of $I_{CaL}$, but no change in other currents such as $I_{Ks}$, $I_{Kr}$, $I_{NaCa}$ and $I_{CaT}$ (Priebe & Beuckelmann 1998; Tomasselli & Marban 1999; Han et al. 2001, 2002).

The present PF cell model is based on the experimental data of Han et al. (2002) obtained from failing human hearts. Some major ion channels, including $I_{K1}$ and $I_{to}$, may be affected by heart failure-induced ion channel remodelling. Thus, it is necessary to adjust some channel parameters in order to model a normal human PF cell. We assumed heart failure-induced ion channel remodelling to be consistent across PF and ventricular myocytes and followed the approach of Priebe & Beuckelmann (1998). Namely, heart failure would produce a 36 per cent reduction in $I_{to}$ and a 20 per cent reduction in $I_{K1}$ current densities. Therefore, in the normal PF cell model, $G_{to}$ and $G_{K1}$ were increased by 36 and 20 per cent, respectively. As equations and parameters for $I_{NaCa}$ and Ca$^{2+}$ handling were inherited from the original ten Tusscher et al. (2004) and ten Tusscher & Panfilov (2006) model, we assumed they are for healthy cells, and therefore did not require adjustment.

In the model with adjusted parameters to compensate for heart failure-induced ion channel remodelling of $I_{to}$ and $I_{K1}$, the simulated PF APs (the grey line in the inset of figure 3a) evoked by an external stimulus are similar to those of the uncorrected model, except for a more marked phase-1 repolarization. This is consistent with the experimental observation of Han et al. (2001) on canine PF cells: the characteristics of canine PF cells are very close between normal hearts and hearts with CHF, except a less marked phase-1 repolarization and higher plateau voltage in CHF. There were no significant differences in resting potential, AP amplitude or APD between control and CHF cells.


(c) Limitations

The model was constructed based on the experimental data of Han et al. (2002) on properties of potassium currents in human PF cells isolated from failing hearts, which were treated by a variety of medications. As both disease and medication can change the kinetics and current density of ion channels (Han et al. 2001a), it is possible that the data of Han et al. (2002) may not truly reflect the electrical properties of healthy human PF cells. These are well-recognized limitations for virtually all electrophysiological studies of human cardiac cells in the literature, based on which all other models for human cardiac cells were developed. Though we have adjusted possible electrical remodelling induced by heart failure for $I_{to}$ and $I_{K1}$ based on experimental studies in canine and humans (Priebe & Beuckelmann 1998; Han et al. 2001a), the adjustment for parameters may be incomplete, as other channels, such as $I_{Kr}$ and $I_{Ks}$, may also be remodelled by heart failure.

In the absence of detailed experimental data, a number of major currents including $I_{Na}$ and $I_{CaL}$, and intracellular Ca$^{2+}$ handling, were inherited from the ten Tusscher et al. (2004) and ten Tusscher & Panfilov (2006) models. It is possible that these inherited descriptions, notably the Ca$^{2+}$ handling mechanisms, are different between PF and ventricular cells (e.g. due to a lack of t-tubules in PF cells; Sommer & Johnson 1968; Boyden et al. 2000). These limitations must be addressed in the future when more experimental data are available and can be used to improve the validity of the current model. The present model is quiescent following rapid stimulation at pacing rates over 90 beats per minute (i.e. stimulus frequency higher than 1.5 Hz), faster than an average adult human heart rate at normal physiological conditions, potentially due to the inheritance of ventricle data.

Additionally, recent studies have identified a number of currents absent in the model which are believed to play an important role in AP morphology of PF cells, notably $I_{K(ACH)}$, $I_{CaT}$ and $I_{NaL}$ (Gaborit et al. 2007; Dun & Boyden 2008). Though identified in human PF cells, a lack of experimental data on $I_{K(ACH)}$ and $I_{CaT}$ prevents their inclusion in the current model, while the presence of $I_{CaT}$ in human PF cells has yet to be observed (Dun & Boyden 2008). The role of $I_{NaL}$ and $I_{CaT}$ has been studied in more detail in canine PF cells (O. V. Aslanidi et al. unpublished data), which revealed that $I_{CaT}$ and $I_{K(ACH)}$ played a minor role, whereas the effect of $I_{NaL}$ on the APD was much more prominent. Future models of human PF cells should incorporate effects of the latter, subject to availability of experimental data. The developed model can however reproduce the typical features of APs in human PF cells, such as the marked phase-1 notch, automaticity, all-or-nothing repolarization and overdrive suppression; thus, it can be used to simulate the conduction system of PF network in the whole heart model.

(d) Role of $I_f$ in pacemaking activity of Purkinje fibre cells

Controversy still surrounds the mechanism underlying the genesis of automaticity in cardiac pacemaking cells including the SA node and PF cells. Blocking $I_f$ in the present model abolishes the automaticity of the PF cells (figure 5f), providing evidence to support the hypothesis that $I_f$ is the primary factor responsible for generating pacemaking activity (DiFrancesco 1981, 2006). However, experimental studies have also suggested an alternative hypothesis.
that reverse excitation–contraction (EC) coupling (Dangman & Miura 1987; Boyden et al. 2000; Lakatta et al. 2003; ter Keurs & Boyden 2007) may play a critical role underlying cardiac automaticity. The present model is not sufficient to investigate the possible role of the major mechanisms of reverse EC coupling—Ca$^{2+}$ sparks and waves—in initiating PF cell automaticity, since the model lacks consideration of spatially extended features of Ca$^{2+}$ handling and diffusion (Tao et al. 2008). Such an approach would involve considering spatio-temporal dynamics of subcellular variables, which is beyond the scope of the present paper.

(e) Looking forward

By combining a geometric model with suitable models of the AP in single cells, it is possible to reconstruct the electrical activity and activation sequence of the whole heart. The newly developed PF cell model adds a new member to the family of human cardiac cell models developed in previous studies for the SA node (Seemann et al. 2006), atrial (Courtemanche et al. 1998; Nygren et al. 1998) and ventricular (Iyer et al. 2004; ten Tusscher et al. 2004; ten Tusscher & Panfilov 2006) cells, which can be incorporated into an anatomical model of the human heart (Sachse et al. 2000) with details of its electrophysiological heterogeneity and anatomical complexity.

P.S. is supported by a UK EPSRC DTA studentship. O.V.A., M.R.B. and H.Z. are supported by the UK BBSRC (BBS/B/1678X) project grant.

Appendix A. Model equations

(a) Inward rectifier current, $I_{K1}$

\[ I_{K1} = G_{K1} x_{K1\infty} (V - 8 - E_K), \]

\[ x_{K1\infty} = \frac{1}{1 + e^{0.1(V+75.44)}}, \]

(b) Transient outward current, $I_{to}$

\[ I_{to} = G_{to} r_s (V - E_K), \]

\[ r_s = \frac{1}{1 + e^{(20-V)/13}}, \]

\[ \tau_r = 10.45 e^{-(V+40)^2/1800} + 7.3, \]

\[ s_{\infty} = \frac{1}{1 + e^{(V+27)/13}}, \]

\[ \tau_s = 85 e^{-(V+25)^2/320} + \frac{5}{1 + e^{(V-40)/5}} + 42. \]
(c) Sustained current, $I_{\text{sus}}$

\[
I_{\text{sus}} = G_{\text{sus}} a(V - E_K), \quad (A8)
\]

\[
a_\infty = \frac{1}{1 + e^{(5-V)/17}}. \quad (A9)
\]

(d) Hyperpolarization-activated current, $I_f$

\[
I_f = i_{f,K} + i_{f,Na}, \quad (A10)
\]

\[
i_{f,K} = G_{f,K} y(V - E_K), \quad (A11)
\]

\[
i_{f,Na} = G_{f,Na} y(V - E_{Na}), \quad (A12)
\]

\[
y_\infty = \frac{1}{1 + e^{(V+80.6)/6.8}}, \quad (A13)
\]

\[
\alpha_y = e^{-2.9 - (0.04V)}, \quad (A14)
\]

\[
\beta_y = e^{3.6 + (0.11V)}, \quad (A15)
\]

\[
\tau_y = \frac{4000}{\alpha_y + \beta_y}. \quad (A16)
\]

(e) Fast sodium current, $I_{Na}$

\[
I_{Na} = G_{Na} m^3 h j (V - E_{Na}), \quad (A17)
\]

\[
m_\infty = \frac{1}{\left[1 + e^{-(-56.86-V)/9.03}\right]^2}, \quad (A18)
\]

\[
\alpha_m = \frac{1}{1 + e^{(-60-V)/5}}, \quad (A19)
\]

\[
\beta_m = \frac{0.1}{1 + e^{(V+35)/5}} + \frac{0.1}{1 + e^{(V-50)/200}}, \quad (A20)
\]

\[
\tau_m = \alpha_m \beta_m, \quad (A21)
\]

\[
h_\infty = \frac{1}{\left[1 + e^{(V+71.55)/7.43}\right]^2}, \quad (A22)
\]

\[
\alpha_h = 0 \quad \text{if } V \geq -40, \quad (A23)
\]

\[
\alpha_h = 0.057 e^{- (V+80)/6.8} \quad \text{otherwise,}
\]

Phil. Trans. R. Soc. A (2009)
\[ \begin{align*}
\beta_h &= \frac{0.77}{0.13[1 + e^{-(V+10.66)/11.1}]} \quad \text{if } V \geq -40, \\
\beta_h &= 2.7 e^{0.079V} + 3.1 \times 10^5 e^{0.3485V} \quad \text{otherwise,}
\end{align*} \] (A 24)

\[ \tau_h = \frac{1}{\alpha_h + \beta_h}, \] (A 25)

\[ j_\infty = \frac{1}{[1 + e^{(V+71.55)/7.43}]^2}, \] (A 26)

\[ \alpha_j = 0 \quad \text{if } V \geq -40, \] (A 27)

\[ \alpha_j = \frac{(-2.5428 \times 10^4 e^{0.2444V} - 6.948 \times 10^{-6} e^{-0.04391V})(V + 37.78)}{1 + e^{0.311(V+79.23)}} \quad \text{otherwise,} \] (A 28)

\[ \begin{align*}
\beta_j &= \frac{0.6 e^{0.057V}}{1 + e^{-0.1(V+32)}} \quad \text{if } V \geq -40, \\
\beta_j &= \frac{0.02424 e^{-0.01052V}}{1 + e^{-0.1378(V+40.14)}} \quad \text{otherwise,}
\end{align*} \] (A 29)

\[ \tau_j = \frac{1}{\alpha_j + \beta_j}. \] (A 30)

\( (f) \) \textit{L-type calcium current, } I_{CaL}

\[ I_{CaL} = G_{CaL} d_{\infty} f 2 f_{Cass}^4 \frac{(V - 15)F^2}{RT} \frac{0.25[Ca^{2+}]_{ss} e^{2(V-15)F/RT} - [Ca^{2+}]_o}{e^{2(V-15)F/RT} - 1}, \] (A 31)

\[ d_{\infty} = \frac{1}{1 + e^{(-8-V)/7.5}}, \] (A 32)

\[ \alpha_d = \frac{1.4}{1 + e^{(-35-V)/13}} + 0.25, \] (A 33)

\[ \beta_d = \frac{1.4}{1 + e^{(V+5)/5}}, \] (A 34)

\[ \gamma_d = \frac{1.4}{1 + e^{(50-V)/20}}. \] (A 35)
Models of Purkinje fibre cells

\[ \tau_d = \alpha_d \beta_d + \gamma_d, \quad (A\ 36) \]

\[ f_\infty = \frac{1.4}{1 + e^{(V+20)/7}}, \quad (A\ 37) \]

\[ \alpha_f = 1102.5 \ e^{(-(V+27)/15)^2}, \quad (A\ 38) \]

\[ \beta_f = \frac{200}{1 + e^{(13-V)/10}}, \quad (A\ 39) \]

\[ \gamma_f = \frac{180}{1 + e^{(V+30)/10}} + 20, \quad (A\ 40) \]

\[ \tau_f = \alpha_f + \beta_f + \gamma_f, \quad (A\ 41) \]

\[ f_{2\infty} = \frac{0.67}{1 + e^{(V+35)/7}} + 0.33, \quad (A\ 42) \]

\[ \alpha_{f2} = 600 \ e^{-(V+25)^2/170}, \quad (A\ 43) \]

\[ \beta_{f2} = \frac{31}{1 + e^{(25-V)/10}}, \quad (A\ 44) \]

\[ \gamma_{f2} = \frac{16}{1 + e^{(V+30)/10}}, \quad (A\ 45) \]

\[ \tau_{f2} = \alpha_{f2} + \beta_{f2} + \gamma_{f2}, \quad (A\ 46) \]

\[ f_{Ca_\infty} = \frac{0.6}{1 + \left(\frac{[Ca^{2+}]_{ss}}{0.05}\right)^2} + 0.4, \quad (A\ 47) \]

\[ \tau_{fCa_{ss}} = \frac{80}{1 + \left(\frac{[Ca^{2+}]_{ss}}{0.05}\right)^2} + 2. \quad (A\ 48) \]

\( g \) Slow delayed rectifier current, \( I_{Ks} \)

\[ I_{Ks} = G_{Ks} x_s^2 (V - E_{Ks}), \quad (A\ 49) \]

\[ x_{ss} = \frac{1}{1 + e^{(-5-V)/14}}, \quad (A\ 50) \]
\[ \alpha_{zs} = \frac{1400}{\sqrt{1 + e^{(5-V)/6}},} \quad (A\ 51) \]

\[ \beta_{zs} = \frac{1}{1 + e^{(V-35)/15}}, \quad (A\ 52) \]

\[ \tau_{zs} = \alpha_{zs} \beta_{zs} + 80. \quad (A\ 53) \]

(h) Rapid delayed rectifier current, \(I_{Kr}\)

\[ I_{Kr} = G_{Kr} \sqrt{\frac{[K^+]_o}{5.4}} x_{r1} x_{r2} (V - E_K), \quad (A\ 54) \]

\[ x_{r1\infty} = \frac{1}{1 + e^{(-26-V)/7}}, \quad (A\ 55) \]

\[ \alpha_{xr1} = \frac{450}{1 + e^{(-35-V)/10}}, \quad (A\ 56) \]

\[ \beta_{xr1} = \frac{6}{1 + e^{(V+30)/11.5}}, \quad (A\ 57) \]

\[ \tau_{xr1} = \alpha_{xr1} \beta_{xr1}, \quad (A\ 58) \]

\[ x_{r2\infty} = \frac{1}{1 + e^{(V+88)/24}}, \quad (A\ 59) \]

\[ \alpha_{xr2} = \frac{3}{1 + e^{(-60-V)/20}}, \quad (A\ 60) \]

\[ \beta_{xr2} = \frac{1.12}{1 + e^{(V-60)/20}}, \quad (A\ 61) \]

\[ \tau_{xr2} = \alpha_{xr2} \beta_{xr2}. \quad (A\ 62) \]

(i) \(Na^+/Ca^{2+}\) exchange current, \(I_{NaCa}\)

\[ I_{NaCa} = k_{NaCa} \frac{e^{\gamma VF/RT}[Na^+]_o [Ca^{2+}]_\infty - e^{(\gamma-1)VF/RT}[Na^+]_o [Ca^{2+}]_{\infty}}{(K_{mNa}^3 + [Na^+]_o) (K_{mCa} + [Ca^{2+}]_\infty) (1 + k_{sat} e^{(\gamma-1)VF/RT})}. \quad (A\ 63) \]
(j) Na\(^+\)/K\(^+\) pump current, \(I_{NaK}\)

\[
I_{NaK} = \frac{P_{NaK}[K^+]_o[Na^+]_i}{([K^+]_o + K_{mK})([Na^+]_i + K_{mNa})(1 + 0.1245 e^{-0.1V_F/R_T} + 0.0353 e^{-V_F/R_T})},
\]

(A 64)

\[
I_{pCa} = G_{pCa} \frac{[Ca^{2+}]_i}{K_{pCa} + [Ca^{2+}]_i},
\]

(A 65)

\[
I_{pK} = G_{pK} \frac{V - E_K}{1 + e^{(25-V)/5.98}},
\]

(A 66)

(k) Background current, \(I_b\)

\[
I_{bNa} = G_{bNa}(V - E_{Na}),
\]

(A 67)

\[
I_{bCa} = G_{bCa}(V - E_{Ca}).
\]

(A 68)

(l) Calcium dynamics

\[
I_{leak} = V_{leak}([Ca^{2+}]_{sr} - [Ca^{2+}]_i),
\]

(A 69)

\[
I_{up} = \frac{V_{\text{maxup}}}{1 + K_{up}^2/[Ca^{2+}]_i},
\]

(A 70)

\[
I_{rel} = V_{rel}O([Ca^{2+}]_{sr} - [Ca^{2+}]_{ss}),
\]

(A 71)

\[
I_{xfer} = V_{xfer}([Ca^{2+}]_{ss} - [Ca^{2+}]_i),
\]

(A 72)

\[
O = \frac{k_1[Ca^{2+}]_{ss}^2 \bar{R}}{k_3 + k_4[Ca^{2+}]_{ss}^2},
\]

(A 73)

\[
\frac{d\bar{R}}{dt} = -k_2[Ca^{2+}]_{ss} \bar{R} + k_4(1 + \bar{R}),
\]

(A 74)
\[ k_1 = \frac{k_{1'}}{k_{\text{Ca}_{sr}}} , \]  
(A 75)

\[ k_2 = k_2' k_{\text{Ca}_{sr}} , \]  
(A 76)

\[ k_{\text{Ca}_{sr}} = \max_{\text{sr}} \frac{\max_{\text{sr}} - \min_{\text{sr}}}{1 + (\text{EC}/[\text{Ca}^{2+}]_{\text{sr}})^2} , \]  
(A 77)

\[ [\text{Ca}^{2+}]_{i \text{ Bufc}} = \frac{[\text{Ca}^{2+}]_i \times \text{Bufc}}{[\text{Ca}^{2+}]_i \times K_{\text{Bufc}}} , \]  
(A 78)

\[ \frac{d[\text{Ca}^{2+}]_{i \text{ total}}}{dt} = - \frac{I_{\text{bCa}} + I_{\text{pCa}} - 2 I_{\text{NaCa}}}{2 V_c F} + \frac{V_{\text{sr}}}{V_c} (I_{\text{leak}} - I_{\text{up}}) + I_{\text{xfer}}, \]  
(A 79)

\[ [\text{Ca}^{2+}]_{\text{sr Bufsr}} = \frac{[\text{Ca}^{2+}]_{\text{sr}} \times \text{Buf}_{\text{sr}}}{[\text{Ca}^{2+}]_{\text{sr}} + K_{\text{Bufsr}}} , \]  
(A 80)

\[ \frac{d[\text{Ca}^{2+}]_{\text{sr total}}}{dt} = - I_{\text{leak}} + I_{\text{up}} - I_{\text{rel}}, \]  
(A 81)

\[ [\text{Ca}^{2+}]_{\text{ss Bufsr}} = \frac{[\text{Ca}^{2+}]_{\text{ss}} \times \text{Buf}_{\text{ss}}}{[\text{Ca}^{2+}]_{\text{ss}} + K_{\text{Bufss}}} , \]  
(A 82)

\[ \frac{d[\text{Ca}^{2+}]_{\text{ss total}}}{dt} = - \frac{I_{\text{CaL}}}{2 V_{\text{ss}} F} + \frac{V_{\text{sr}}}{V_{\text{ss}}} I_{\text{rel}} - \frac{V_c}{V_{\text{ss}}} I_{\text{xfer}}, \]  
(A 83)

\[(m) \text{ Sodium and potassium dynamics} \]

\[ \frac{d[\text{Na}^+]_i}{dt} = - \frac{I_{\text{Na}} + I_{\text{bNa}} + i_{\text{fNa}} + 3 I_{\text{NaK}} + 3 I_{\text{NaCa}}}{V_c F} , \]  
(A 84)

\[ \frac{d[\text{K}^+]_i}{dt} = - \frac{I_{\text{K1}} + I_{\text{lo}} + I_{\text{Kr}} + I_{\text{Ks}} + i_{\text{fK}} + I_{\text{sus}} - 2 I_{\text{NaK}} + I_{\text{pK}} + I_{\text{stim}}}{V_c F} . \]  
(A 85)
## Appendix B. Model parameters

*(a) Parameters*

<table>
<thead>
<tr>
<th>parameter</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$G_{K1}$</td>
<td>0.065 nS pF$^{-1}$</td>
</tr>
<tr>
<td>$G_{t_o}$</td>
<td>0.0814 nS pF$^{-1}$</td>
</tr>
<tr>
<td>$G_{sus}$</td>
<td>0.0227 nS pF$^{-1}$</td>
</tr>
<tr>
<td>$G_{t_K}$</td>
<td>0.0234346 nS pF$^{-1}$</td>
</tr>
<tr>
<td>$G_{t_Na}$</td>
<td>0.0145654 nS pF$^{-1}$</td>
</tr>
<tr>
<td>$G_{Kr}$</td>
<td>0.0918 nS pF$^{-1}$</td>
</tr>
<tr>
<td>$G_{Ks}$</td>
<td>0.2352 nS pF$^{-1}$</td>
</tr>
<tr>
<td>$G_{Na}$</td>
<td>130.5744 nS pF$^{-1}$</td>
</tr>
<tr>
<td>$R$</td>
<td>8.3143 J K$^{-1}$ mol$^{-1}$</td>
</tr>
<tr>
<td>$T$</td>
<td>310 K</td>
</tr>
<tr>
<td>$F$</td>
<td>96.4867 C mmol$^{-1}$</td>
</tr>
<tr>
<td>$C_{m}$</td>
<td>2.0 μF cm$^{-2}$</td>
</tr>
<tr>
<td>$S$</td>
<td>0.2 μm$^{-1}$</td>
</tr>
<tr>
<td>$ρ$</td>
<td>162 Ω cm</td>
</tr>
<tr>
<td>$V_c$</td>
<td>16.404 μm$^3$</td>
</tr>
<tr>
<td>$V_{sr}$</td>
<td>1.094 μm$^3$</td>
</tr>
<tr>
<td>$V_{ss}$</td>
<td>0.05468 μm$^3$</td>
</tr>
<tr>
<td>$[K^+]_o$</td>
<td>5.4 mM</td>
</tr>
<tr>
<td>$[Na^+]_o$</td>
<td>140 mM</td>
</tr>
<tr>
<td>$[Ca^{2+}]_o$</td>
<td>2 mM</td>
</tr>
<tr>
<td>$p_{KNa}$</td>
<td>0.03 (dimensionless)</td>
</tr>
<tr>
<td>$G_{CaL}$</td>
<td>3.980$^{-5}$ cm ms$^{-1}$ μF$^{-1}$</td>
</tr>
<tr>
<td>$k_{NaCa}$</td>
<td>1000 pA pF$^{-1}$</td>
</tr>
<tr>
<td>$γ$</td>
<td>0.35 (dimensionless)</td>
</tr>
<tr>
<td>$K_{NaCa}$</td>
<td>1.38 mM</td>
</tr>
<tr>
<td>$K_{mNaI}$</td>
<td>87.5 mM</td>
</tr>
<tr>
<td>$k_{sat}$</td>
<td>0.1 (dimensionless)</td>
</tr>
<tr>
<td>$α$</td>
<td>2.5 (dimensionless)</td>
</tr>
<tr>
<td>$P_{NaK}$</td>
<td>2.724 pA pF$^{-1}$</td>
</tr>
<tr>
<td>$K_{mK}$</td>
<td>1 mM</td>
</tr>
<tr>
<td>$K_{mNa}$</td>
<td>40 mM</td>
</tr>
<tr>
<td>$G_{pK}$</td>
<td>0.0146 nS pF$^{-1}$</td>
</tr>
<tr>
<td>$G_{pCa}$</td>
<td>0.1238 nS pF$^{-1}$</td>
</tr>
<tr>
<td>$K_{pCa}$</td>
<td>0.0005 mM</td>
</tr>
<tr>
<td>$G_{iNa}$</td>
<td>0.000290 nS pF$^{-1}$</td>
</tr>
<tr>
<td>$G_{iCa}$</td>
<td>0.000592 nS pF$^{-1}$</td>
</tr>
<tr>
<td>$V_{maxup}$</td>
<td>0.006375 mM ms$^{-1}$</td>
</tr>
<tr>
<td>$K_{up}$</td>
<td>0.00025 mM</td>
</tr>
<tr>
<td>$V_{rel}$</td>
<td>40.8 mM ms$^{-1}$</td>
</tr>
<tr>
<td>$k_1'$</td>
<td>0.15 mM$^{-2}$ ms$^{-1}$</td>
</tr>
<tr>
<td>$k_2'$</td>
<td>0.045 mM$^{-1}$ ms$^{-1}$</td>
</tr>
</tbody>
</table>

(Continued.)
### Initial conditions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_3$</td>
<td>$0.060,\text{ms}^{-1}$</td>
</tr>
<tr>
<td>$k_4$</td>
<td>$0.000015,\text{ms}^{-1}$</td>
</tr>
<tr>
<td>EC</td>
<td>1.5 mM</td>
</tr>
<tr>
<td>$\max_{sr}$</td>
<td>2.5 (dimensionless)</td>
</tr>
<tr>
<td>$\min_{sr}$</td>
<td>1 (dimensionless)</td>
</tr>
<tr>
<td>$V_{\text{leak}}$</td>
<td>$0.00036,\text{mM},\text{ms}^{-1}$</td>
</tr>
<tr>
<td>$V_{\text{xfer}}$</td>
<td>$0.0038,\text{mM},\text{ms}^{-1}$</td>
</tr>
<tr>
<td>$\text{Buf}_c$</td>
<td>0.2 mM</td>
</tr>
<tr>
<td>$K_{\text{Buf}_c}$</td>
<td>0.001 mM</td>
</tr>
<tr>
<td>$\text{Buf}_{sr}$</td>
<td>10 mM</td>
</tr>
<tr>
<td>$K_{\text{Buf}_{sr}}$</td>
<td>0.3 mM</td>
</tr>
<tr>
<td>$\text{Buf}_{ss}$</td>
<td>0.4 mM</td>
</tr>
<tr>
<td>$K_{\text{Buf}_{ss}}$</td>
<td>0.00025 mM</td>
</tr>
</tbody>
</table>

### Parameter values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V$</td>
<td>$-74.7890522727$</td>
</tr>
<tr>
<td>$[\text{Na}^+]_i$</td>
<td>8.5447311020</td>
</tr>
<tr>
<td>$[\text{K}^+]_i$</td>
<td>136.9896086978</td>
</tr>
<tr>
<td>$[\text{Ca}^{2+}]_i$</td>
<td>0.0001720623</td>
</tr>
<tr>
<td>$[\text{Ca}^{2+}]_{sr}$</td>
<td>3.2830723338</td>
</tr>
<tr>
<td>$[\text{Ca}^{2+}]_{ss}$</td>
<td>0.0006146554</td>
</tr>
<tr>
<td>$m$</td>
<td>0.0145766758</td>
</tr>
<tr>
<td>$h$</td>
<td>0.2979720207</td>
</tr>
<tr>
<td>$j$</td>
<td>0.0692509548</td>
</tr>
<tr>
<td>$x_{r,1}$</td>
<td>0.4663168269</td>
</tr>
<tr>
<td>$x_{r,2}$</td>
<td>0.3657472179</td>
</tr>
<tr>
<td>$x_s$</td>
<td>0.0486609588</td>
</tr>
<tr>
<td>$r$</td>
<td>0.0006830833</td>
</tr>
<tr>
<td>$s$</td>
<td>0.9717098312</td>
</tr>
<tr>
<td>$d$</td>
<td>0.0001356656</td>
</tr>
<tr>
<td>$f_1$</td>
<td>0.5943228461</td>
</tr>
<tr>
<td>$f_2$</td>
<td>0.8265709174</td>
</tr>
<tr>
<td>$f_{\text{Cass}}$</td>
<td>0.9767040566</td>
</tr>
<tr>
<td>$R$</td>
<td>0.8199969443</td>
</tr>
<tr>
<td>$O$</td>
<td>0.0000006152</td>
</tr>
<tr>
<td>$y$</td>
<td>0.0184308075</td>
</tr>
</tbody>
</table>
Models of Purkinje fibre cells

References


*Phil. Trans. R. Soc. A* (2009)


Fabiato, A. & Fabiato, F. 1975 Contractions induced by a calcium-triggered release of calcium from the sarcoplasmic reticulum of single skinned cardiac cells. *J. Physiol.* 249, 469–495.


Han, W., Chartier, D., Li, D. & Nattel, S. 2001 The ionic remodeling of canine Purkinje cells by congestive heart failure. *Circulation* 104, 2095–2100. (doi:10.1161/01.heart.4201.097134)

Han, W., Wang, Z. & Nattel, S. 2001b Expression profile of ion channel mRNA in canine cardiac Purkinje fibers—a basis for electrophysiological specificity? *Circulation* 104(Suppl. II), I1-133.


*Phil. Trans. R. Soc. A* (2009)
Models of Purkinje fibre cells


Phil. Trans. R. Soc. A (2009)


