Mathematical Model of an Adult Human Atrial Cell
The Role of K⁺ Currents in Repolarization

A. Nygren, C. Fiset, L. Firek, J.W. Clark, D.S. Lindblad, R.B. Clark, W.R. Giles

Abstract—We have developed a mathematical model of the human atrial myocyte based on averaged voltage-clamp data recorded from isolated single myocytes. Our model consists of a Hodgkin-Huxley–type equivalent circuit for the sarcolemma, coupled with a fluid compartment model, which accounts for changes in ionic concentrations in the cytoplasm as well as in the sarcoplasmic reticulum. This formulation can reconstruct action potential data that are representative of recordings from a majority of human atrial cells in our laboratory and therefore provides a biophysically based account of the underlying ionic currents. This work is based in part on a previous model of the rabbit atrial myocyte published by our group and was motivated by differences in some of the repolarizing currents between human and rabbit atrium. We have therefore given particular attention to the sustained outward K⁺ current (I\textsubscript{sust}), which putatively has a prominent role in determining the duration of the human atrial action potential. Our results demonstrate that the action potential shape during the peak and plateau phases is determined primarily by transient outward K⁺ current, I\textsubscript{to}, and L-type Ca\textsuperscript{2+} current (I\textsubscript{Ca,L}) and that the role of I\textsubscript{sust} in the human atrial action potential can be modulated by the baseline sizes of I\textsubscript{Ca,L}, I\textsubscript{to}, and the rapid delayed rectifier K⁺ current. As a result, our simulations suggest that the functional role of I\textsubscript{sust} can depend on the physiological/disease state of the cell. (Circ Res. 1998;82:63-81.)

Key Words: human atrium ▪ repolarization ▪ sustained outward current ▪ computer modeling ▪ cardiac action potential

Within the past 5 years, quite extensive voltage-clamp and action potential data from human atrial myocytes have been published from a number of laboratories. In most cases the human atrial tissue was obtained during open heart surgery, in which small pieces of the right atrial appendage are excised as part of the cannulation procedure for cardiopulmonary bypass. However, cardiac tissue can also be obtained from the free wall of the atrium during valve replacement procedures, from explanted failing hearts during heart transplantations, or from donor hearts that cannot be used for transplantation. Once a specimen of cardiac tissue is obtained, enzymatic dispersion techniques are used to isolate single cardiac cells, from which action potential and voltage-clamp data can be recorded. We have made recordings of the outward K⁺ currents, which are responsible for repolarization in human atrial myocytes.1,2 On the basis of these data, as well as other published results, we have developed the first comprehensive mathematical model of the electrophysiological responses of a representative human atrial cell.

There are a number of published mathematical models that simulate the electrophysiological responses in several different species and cardiac cell types. Examples include the Purkinje fiber model of DiFrancesco and Noble,3 the Hilgemann and Noble atrial model,4 the Earm and Noble model of the single atrial cell,5 the bullfrog atrial and sinus venosus models of Rasmussen and colleagues,6,7 the ventricular cell models of Luo and Rudy,8-11 the rabbit sinoatrial node cell model of Demir et al,12 and the rabbit atrial cell model of Lindblad et al.13 Recently, the emphasis has shifted from general models, based on voltage-clamp data from several species,3,4 to more detailed models based on data from single isolated cells from a particular species. This is a direct reflection of the progress made in experimental work and the resulting availability of more comprehensive data. Our goal was to develop a model that is sufficiently accurate to have predictive capabilities for selected aspects of the electrophysiological responses in human atrium. Emphasis has been placed on the functional roles of the K⁺ currents during repolarization.

Materials and Methods

Basic Assumptions

Our model is of the general type first introduced by DiFrancesco and Noble3 and is based, in part, on the rabbit atrial model of Lindblad, Murphey, Clark, and Giles13 (hereafter referred to as the LMCG model). As shown in Fig 1, the model consists of a Hodgkin-Huxley–type electrical equivalent circuit for the sarcolemma coupled with a fluid compartment model. The dimensions of the human atrial myocyte are assumed identical to those of the rabbit atrial cell in the LMCG model. These dimensions (cylindrical geometry of 130-μm length and 11-μm diameter) are very close to the dimensions of human atrial myocytes (eg, 120-μm length and 10- to 15-μm diameter6,7). In addition, we have used a total cell capacitance of 50 pF, which agrees very well with our experimental observations for human atrial myocytes (51.9±3.5 pF, n=52).
Membrane Currents

Fig 1A shows the electrical equivalent circuit for the sarcolemma of the human atrial cell. It includes each of the ionic currents that are known to contribute to the action potential in human atrial myocytes (I\textsubscript{Na}, I\textsubscript{Ca,L}, I\textsubscript{K,R}, I\textsubscript{K,S}, I\textsubscript{K1}, I\textsubscript{Na}, and I\textsubscript{NaC}). The Ca\textsuperscript{2+} and Na\textsuperscript{+}-K\textsuperscript{+} pump and Na\textsuperscript{+}-Ca\textsuperscript{2+} exchanger currents responsible for maintaining intracellular ion concentrations (I\textsubscript{E-Ca}, I\textsubscript{Na-K}, and I\textsubscript{Na-Ca}), and the Na\textsuperscript{+} and Ca\textsuperscript{2+} background (leakage) currents (I\textsubscript{Leak} and I\textsubscript{leak}). Mathematical expressions describing the time and voltage dependence of the ionic currents have been developed on the basis of published voltage-clamp data recorded predominantly from human atrial myocytes. (See “Glossary” after Appendix 2 for terms used in text, figures, and tables.)

Na\textsuperscript{+} Current: I\textsubscript{Na}

Voltage-clamp data for I\textsubscript{Na} in human atrial and ventricular myocytes, recorded at 17°C have been published by Sakakibara and colleagues.\textsuperscript{13,14} These data suggest that the activation threshold is very close to the resting potential (≈−75 mV), which seems unrealistic, given that atrial and ventricular cells exhibit stable resting potentials and thresholds for activation near −55 mV. Moreover, the steady-state inactivation curves measured by Sakakibara and colleagues\textsuperscript{13,14} are such that I\textsubscript{Na} would be completely inactivated (ie, no current available) at the resting potential. As pointed out by these authors, this is probably a result of time- and/or temperature-dependent shifts in the steady-state inactivation characteristics. Other results, such as the data from rabbit atrium published by Wendt et al\textsuperscript{17} (on which the I\textsubscript{Na} description in the LMCG model is based) yield more positive (depolarized) steady-state activation and inactivation curves.

In developing a model of I\textsubscript{Na} under physiological conditions, we have found it necessary to use indirect information about I\textsubscript{Na} provided by action potential data in addition to voltage-clamp data. Thus, we have adjusted the steady-state activation curve (m\textsuperscript{2}) for I\textsubscript{Na} so that the threshold at which an action potential is elicited agrees with experimental observations. Furthermore, the peak magnitude of I\textsubscript{Na} was adjusted to match the maximum upstroke velocity of the action potential. (For a discussion of the relation between I\textsubscript{Na} and action potential upstroke velocity, refer to Cohen and Strichartz.)\textsuperscript{19} Fig 2A shows the steady-state activation curve (m\textsuperscript{2}) and inactivation (h) curves used to model I\textsubscript{Na}. Compared with the data from human atrial myocytes obtained by Sakakibara et al\textsuperscript{15} (Fig 2A), there are significant positive shifts in both the m\textsuperscript{2} (+22.8 mV) and h (+32.2 mV) curves. Fig 2B shows a simulated peak current-voltage relationship (steps from a holding potential of −80 mV) for I\textsubscript{Na}. The mathematical expressions for the kinetics of activation (τ\textsubscript{a}) and inactivation (τ\textsubscript{h1} and τ\textsubscript{h2}) are very similar to those of the LMCG model, as shown in Figs 2C and 2D. The processes of inactivation and recovery from inactivation are both described by the sum of a fast and a slow exponential. At plateau potentials, the fast component of inactivation has a time constant of 0.3 ms. The slow component of inactivation accounts for 10% of the total current and has a time constant of 3.0 ms at plateau potentials; i.e., it is 10 times slower than the fast component, in agreement with the data of Sakakibara et al.\textsuperscript{15}

L-Type Ca\textsuperscript{2+} Current: I\textsubscript{Ca,L}

Several quite comprehensive studies of I\textsubscript{Ca,L} in human atrial myocytes have been published.\textsuperscript{16–25} Overall, the results are quite consistent: I\textsubscript{Ca,L} has an activation threshold near −40 mV, its peak at ≈0 mV, and an apparent reversal potential of +50 to +60 mV. The current density for I\textsubscript{Ca,L} varies considerably among these studies, however, and is also known to be reduced in diseased or dilated cells.\textsuperscript{22,23} Table 1 shows published I\textsubscript{Ca,L} densities compared with those used in the present model. The inactivation process for I\textsubscript{Ca,L} is usually described as the sum of a fast and a slow component.\textsuperscript{20–21} In order to accurately measure the steady-state voltage dependence of inactivation, the duration of the “conditioning” prepulse in the voltage-clamp protocol (eg, see Li and Nattel)\textsuperscript{20} must be at least four to five times the time constant of the slower component of inactivation. If the prepulse duration is shorter, the slower component will not have reached its steady state when the availability of current is measured (second voltage-clamp pulse), and inactivation will appear incomplete. Ouadid et al\textsuperscript{21} measured inactivation at room temperature (where the slower time constant exceeds

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<th>Table 1. Peak I\textsubscript{Ca,L} Values From the Literature Compared With the Model</th>
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<td>Li and Nattel\textsuperscript{20}</td>
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<td>Ouadid et al\textsuperscript{21}</td>
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<td>Le Grand et al\textsuperscript{22}</td>
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<td>Model</td>
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100 ms) and found that inactivation was incomplete (U-shaped inactivation curve) when the prepulse duration was 150 ms but that it became more complete if the prepulse duration was increased to 400 ms. The data obtained by Li and Nattel at 36°C yield almost complete inactivation characteristics for a prepulse duration of 150 ms, consistent with faster kinetics at this temperature. However, these authors also note that prolonging the prepulse results in more complete inactivation curves. On the basis of these results, we have modeled inactivation of $I_{\text{Ca,L}}$ as a process involving two components with different time constants but identical, fully inactivating, steady-state voltage dependence. This formulation differs from the LMCG model\(^\text{11}\) as well as the Luo-Rudy model,\(^\text{7}\) which both use a single (voltage-dependent) component of inactivation with incomplete steady-state voltage dependence.

Ouadid et al\(^\text{20}\) also report that the inactivation process is slowed considerably when Ba\(^{2+}\) is substituted for Ca\(^{2+}\) as charge carrier, indicating that inactivation is also Ca\(^{2+}\) dependent. This phenomenon is included in the Luo-Rudy model\(^\text{7}\) but not in the LMCG model.\(^\text{11}\) Our formulation differs from that of Luo and Rudy, however, in order to incorporate recent experimental results. First, there is now evidence that there exists a small restricted subsarcolemmal domain between the L-type Ca\(^{2+}\) channels and the peripheral junctional sarcoplasmic reticulum (SR) where Ca\(^{2+}\) concentration ([Ca\(^{2+}\)]\(_{\text{SR}}\)) may transiently reach much higher levels than in the cytosol as a whole.\(^\text{27}\) This subsarcolemmal domain is not included in the Luo-Rudy model, which models Ca\(^{2+}\)-dependent inactivation as a function of total cytosolic Ca\(^{2+}\) concentration. We have included such a subsarcolemmal domain and have modeled Ca\(^{2+}\)-dependent inactivation as a function of [Ca\(^{2+}\)]\(_{\text{SR}}\). Second, there is recent evidence to suggest that [Ca\(^{2+}\)]\(_{\text{SR}}\) modulates $I_{\text{Ca,L}}$, inactivation by promoting a rapid mode of inactivation.\(^\text{24,25}\) Therefore, in our model, [Ca\(^{2+}\)]\(_{\text{SR}}\) determines the fraction of L-type channels that are in the rapidly inactivating mode, i.e., the ratio of the fast to slow components of inactivation discussed above. Thus, in this model, an experiment with Ba\(^{2+}\) as charge carrier shifted this equilibrium so that all L-type channels were in the slow mode. With Ca\(^{2+}\) as charge carrier, however, the equilibrium is shifted toward the faster mode of inactivation by an amount determined by [Ca\(^{2+}\)]\(_{\text{SR}}\). Hence, the inactivation of the total $I_{\text{Ca,L}}$ follows a biexponential time course, where the relative contributions of the fast and slow exponentials are determined by [Ca\(^{2+}\)]\(_{\text{SR}}\). We have chosen to model this [Ca\(^{2+}\)]\(_{\text{SR}}\) dependence as an instantaneous function of [Ca\(^{2+}\)]\(_{\text{SR}}\), assuming that the shift between the two modes is rapid compared with the diffusion of Ca\(^{2+}\) out of the restricted domain.

Fig 3A shows the steady-state activation ($\delta_L$) and inactivation ($\gamma_L$) curves used to model $I_{\text{Ca,L}}$. Assuming that activation can be measured more accurately at room temperature than at physiological temperature, we have used the activation curve ($\delta_L$) measured by Mewes and Ravens.\(^\text{28}\) However, in order to fit the voltage-clamp data (peak currents) of Li and Nattel\(^\text{25}\) (Fig 3B), we found it necessary to shift this activation curve by +3 mV. The expression for the inactivation curve ($\gamma_L$) is identical to that reported by Li and Nattel for human atrial myocytes at physiological temperature. Furthermore, the reversal potential for $I_{\text{Ca,L}}$ is set to a constant value of +60.0 mV, as measured by Li and Nattel, rather than to the Nerst potential for Ca\(^{2+}\) ions. As shown in Fig 3B, the simulated peak current-voltage relationship (steps from a holding potential of −80 mV) agrees well with voltage-clamp data. Figs 3C and 3D show the time constants of activation ($\tau_{\text{fL1}}$ and $\tau_{\text{fL2}}$) and inactivation ($\tau_{\text{rL1}}$ and $\tau_{\text{rL2}}$) plotted against membrane voltage. We have used the inactivation and recovery time constant data obtained by Li and Nattel to formulate the expressions for $\tau_{\text{rL1}}$ and $\tau_{\text{rL2}}$ (see Fig 3D). These data were obtained in human atrial myocytes at physiological temperature. The expression for $\tau_{\text{rL1}}$ (Fig 3C) is similar to that of the LMCG model.

**Transient and Sustained Outward K\(^{+}\) Currents: $I_{\text{K,trans}}$ and $I_{\text{K,sus}}$**

Voltage-clamp experiments designed to study the outward currents responsible for repolarization in human atrial myocytes have identified a transient outward K\(^{+}\) current (denoted $I_{\text{K,trans}}$), which activates rapidly on depolarization.\(^\text{12,19}\) In addition to this (Ca\(^{2+}\)-independent) transient K\(^{+}\) current, a Ca\(^{2+}\)-dependent transient outward current, which is activated by relatively large increases in [Ca\(^{2+}\)]\(_{\text{SR}}\), is sometimes observed.\(^\text{31}\) We have chosen not to include this Ca\(^{2+}\)-dependent current, since it has never been observed in our experimental work. After $I_{\text{K,trans}}$ has decayed (inactivated), a more slowly inactivating, “sustained,” outward K\(^{+}\) current (denoted $I_{\text{K,sus}}$) is observed.\(^\text{22,23,25}\) The available data suggest that $I_{\text{K,trans}}$ is a separate current from $I_{\text{K,sus}}$ and that it is also carried mainly by K\(^{+}\) ions.\(^\text{24,25}\)

The literature regarding the voltage dependence of $I_{\text{K,sus}}$ is somewhat inconsistent. In particular, the results regarding steady-state activation vary considerably. Shibata et al\(^\text{38}\) report a half-activation voltage ($V_{1/2}$) of +1.0 mV for $I_{\text{K,sus}}$ in human atrium, whereas Nåbauer et al,\(^\text{26}\) Wettwer et al\(^\text{36}\) (both in studies of human ventricle), and Le Grand et al\(^\text{22}\) (human atrium) report values of +16.7, +20.6, and +33.3 mV, respectively. These results seem unrealistic, since $I_{\text{K,sus}}$ is known to have a strong influence on early repolarization,\(^\text{1,2}\) and these values of $V_{1/2}$ would result in only a small amount of $I_{\text{K,sus}}$ being activated during a normal action potential (peak at +20 to +30 mV). Among the possible explanations for this variability in $V_{1/2}$ are the sensitivity of this parameter to the concentration of divalent cations (Ca\(^{2+}\) and Co\(^{2+}\)) used to block $I_{\text{Ca,L}}$ and the possibility of a difference between human atrial and ventricular $I_{\text{K,sus}}$. Therefore, we have based our model on the data of Shibata et al,\(^\text{38}\) which were recorded from human atrium in the presence of a low (100 μmol/L) Ca\(^{2+}\). The data regarding the voltage dependence of steady-state inactivation are also variable between different studies. Fig 4A shows the steady-state activation ($\delta_I$) and inactivation ($\gamma_I$) curves used to model $I_{\text{K,sus}}$. The $\delta$ curve is based on a fit to data from Shibata et al (○ in Fig 4A), and the $\gamma$ curve is that reported by Firek and Giles.\(^\text{27}\) Time constants of activation ($\tau_{\text{fI}}$) and inactivation ($\tau_{\text{rI}}$) are plotted against voltage in Fig 4C and 4D, respectively. Data regarding the time constant of inactivation indicate that $\tau_{\text{rI}}$ is ~13 ms (at 33°C) at membrane voltages positive to 0 mV. At hyperpolarized potentials, the recovery of $I_{\text{K,sus}}$ from inactivation as measured in our laboratory appears to follow an exponential time course with a strongly voltage-dependent time constant, increasing from 15 ms at −100 mV to 387 ms at −60 mV. Our formulation for $\tau_{\text{rI}}$ is based on a fit to experimentally obtained recovery time constant values at negative potentials and inactivation time constant values at positive potentials. The recovery of $I_{\text{K,sus}}$ from inactivation in human atrial cells has been shown to be considerably more rapid than in rabbit atrial cells.\(^\text{12}\) As a result, $I_{\text{K,sus}}$ magnitude and action potential waveform are much less rate dependent in human atrial cells.
Repolarization in a Model of a Human Atrial Cell

Our model of \( I_{Ks} \) is based on the data of Wang et al.\(^{35} \) Fig 4B and 4D show the steady-state activation curve \( (I_{ss}) \) and time constant of activation \( (\tau_a) \) for this current. On the basis of our recent data, we have also included a slow \((\tau=300.0\,\text{ms})\) partial \((40\%)\) inactivation. The time constant for this inactivation process was obtained by fitting a biexponential function to the decaying outward current waveforms as described by Koidl et al.\(^{39} \) In addition to providing an estimate of \( \tau_{inact} \), this method also provides a more accurate separation of \( I_r \) and \( I_{Ks} \) than when \( I_{ss} \) is estimated as the current at the end of the pulse.\(^{2,40} \) By combining our models of \( I_r \) and \( I_{Ks} \), we are able to produce current waveforms closely resembling those recorded from human atrial myocytes in response to voltage-clamp pulses. Fig 5 shows how \( I_r \) (panel A) and \( I_{Ks} \) (panel B) combine (panel C) to produce waveforms similar to experimental results (panel D). In our experience, the size of these currents varies considerably between individual cells, and as reported by Amos et al.,\(^{40} \) there is also considerable variability in the ratio of \( I_r \) to \( I_{Ks} \). The sizes of \( I_r \) and \( I_{Ks} \) in the model were chosen to provide good fits to action potential data and are well within this experimental variability. Table 2 compares \( I_r \) and \( I_{Ks} \) densities reported in the literature with those used in this model.

**Delayed Rectifier \( K^+ \) Currents: \( I_{K,r} \) and \( I_{K,s} \)**

Recent studies of the delayed rectifier \( K^+ \) currents in human and rabbit atrial myocytes show that in both species the delayed rectifier current is generated by two distinct \( K^+ \) conductances. These “rapid” \((I_{K,r})\) and “slow” \((I_{K,s})\) conductances have significantly different properties and can be separated experimentally on the basis of, for example, the sensitivity of \( I_{K,s} \), but not \( I_{K,r} \), to the antiarrhythmic drug E-4031.\(^{41–43} \) Since \( I_{K,s} \) is believed to contribute only a small fraction of the total delayed rectifier current during a normal atrial action potential,\(^{41} \) one could produce an acceptable fit to nominal action potential data using a model incorporating only \( I_{K,r} \). However, because of the very slow activation characteristics of \( I_{K,s} \), this current would be expected to be more significant at high heart rates, where it could build up progressively from cycle to cycle as a result of residual activation, i.e., failure to decay completely between cycles. Therefore, we have chosen to include both \( I_{K,r} \) and \( I_{K,s} \) in our model, thus enabling it to simulate specific effects of antiarrhythmic drugs on \( I_{K,s} \), the buildup of \( I_{K,s} \) at elevated heart rates, and the resulting changes, such as those in action potential duration (APD) and refractoriness.

![Figure 4. Parameters for \( I_r \) and \( I_{K,s} \). A, Steady-state activation and inactivation curves for \( I_r \) (\( \phi \) and \( \delta \), respectively) (\( \bigcirc \) represents data from Shibata et al\(^{1} \)). B, Steady-state activation and inactivation curves for \( I_{K,s} \) (\( \phi_{ss} \) and \( \delta_{ss} \), respectively) (\( \bigtriangledown \) represents data from Wang et al\(^{35} \)). C, Activation and inactivation time constants for \( I_r \) (\( \tau_{rr} \) and \( \tau_{sr} \), respectively). D, Activation and inactivation time constants for \( I_{K,s} \) (\( \tau_{rss} \) and \( \tau_{ss} \), respectively) (\( \bigtriangleup \) represents data from Wang et al\(^{35} \)).](Image 67x514 to 283x718)

![Figure 5. \( I_r \) and \( I_{K,s} \) in response to the voltage-clamp protocol shown in the inset, normalized to cell capacitance. A, Simulated \( I_r \) waveforms. B, Simulated \( I_{K,s} \) waveforms. C, Sum of the \( I_r \) and \( I_{K,s} \) waveforms in panels A and B. D, Outward currents recorded from a human atrial myocyte.](Image 334x513 to 532x718)

<table>
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<tr>
<th>Reference</th>
<th>( I_r )</th>
<th>( I_{K,s} )</th>
<th>Temperature</th>
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<tr>
<td>Koidl et al(^{39*} )</td>
<td>8 pA/pF</td>
<td>13 pA/pF</td>
<td>36°C to 37°C</td>
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<tr>
<td>Amos et al(^{40} )</td>
<td>5 pA/pF</td>
<td>6 pA/pF</td>
<td>22°C</td>
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<tr>
<td>Wang et al(^{41} )</td>
<td>. .</td>
<td>4 pA/pF</td>
<td>25°C</td>
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<tr>
<td>Our data(^* )</td>
<td>13.4 pA/pF</td>
<td>6.0 pA/pF</td>
<td>33°C</td>
</tr>
<tr>
<td>Model</td>
<td>11.1 pA/pF</td>
<td>6.7 pA/pF</td>
<td>33°C</td>
</tr>
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* \( I_r \) and \( I_{K,s} \) separated by curve-fitting.
† \( I_r = I_{K,s} \).
‡ Mean \( I_{K,s} \) \((\sim 300\,\text{pA})\) divided by mean capacitance \((74.3\,\text{pF})\).

In the absence of reliable published data from human atrial cells for these currents, we have used expressions from the LMCG model with only minor scaling adjustments. One exception is the inward...
rectifier current, where we have found it necessary to make minor modifications to the rectifying characteristics in order to fit action potential data (slightly narrower outward “hump”). We have also adjusted the $[K^+]_c$ dependence of $I_{K_{Ca}}$ to agree with data from our laboratory. Table 3 lists the changes made in the time-independent currents compared with those in the LMCG model.

### Material Balance

As in the LMCG model, we have included a fluid compartment formulation to monitor and account for changes in ion concentrations. These concentration changes can be a result of current flow across the cell membrane or of redistribution of ions within the cell (eg, uptake by the SR or binding of Ca$^{2+}$ to an intracellular buffer). Our fluid compartment model is similar to the one in the LMCG model. It includes descriptions of extracellular and intracellular spaces, formulations for Ca$^{2+}$ uptake and release and the buffering action of calsequestrin, and troponin and calmodulin buffers in the intracellular medium. Compartment volumes and other ultrastructural properties, as well as expressions describing the binding of Ca$^{2+}$ to intracellular troponin and calmodulin buffers and to calsequestrin in the SR release compartment, are identical to those of the LMCG model, except as noted in the following sections.

### Cleft Space

We have included a “cleft space” in our fluid compartment formulation, ie, a small restricted space surrounding the cell, in which accumulation or depletion of ions may occur (see Demir et al$^{25}$). The cleft space is modeled as an unstirred fluid layer; ie, ions can be exchanged between the cleft space and the extracellular medium (in which all concentrations are assumed constant) only through diffusion as a result of a concentration gradient. Ratios between diffusion time constants for the ions involved ($\tau_{Ca}$, $\tau_{K}$, and $\tau_{Na}$) were calculated from values for ionic conductivity$^{46}$ and the composition of the extracellular solution ($[Cl^-]=140 \text{ mmol/L}$, $[Na^+] = 130 \text{ mmol/L}$, $[K^+] = 5.4 \text{ mmol/L}$, and $[Ca^{2+}] = 1.8 \text{ mmol/L}$). We have adjusted the size and diffusion properties of the cleft space so as to produce oscillations in cleft space $[K^+]_c$ similar to experimental data.$^{25,48}$

### Electroneutral Na$^+$ Influx

In order to achieve long-term stability in the ionic concentrations in the model, we have found it necessary to add a small ($1.68\text{-pA}$) electroneutral inward flux of Na$^+$, denoted $I_{NaCa}$. This flux could, for example, be accounted for in terms of electroneutral coupled transport mechanisms, such as Na$^+$-H$^+$ exchange and Na$^+$-K$^+$-2Cl$^-$ cotransport. Modeling of these mechanisms, however, is beyond the scope of this work.

There are two major reasons for including this flux: First, the fact that long-term ionic homeostasis can be achieved with the addition of this small flux demonstrates that the sizes and other characteristics of the model elements are such that ionic homeostasis can reasonably be maintained. Second, if the ionic concentrations were allowed to change slowly from cycle to cycle (which would be the result if this flux were not included), the model would only be valid for short simulation times (seconds), for which this drift can safely be ignored. By ensuring long-term stability of the ionic concentrations, longer simulation times (minutes) become feasible and meaningful. Only with stable ionic concentrations can the model be used to simulate concentration changes as a result of rate changes or other interventions.

### Sarcoplasmic Reticulum

Our formulation for the SR is very similar to that of the LMCG model. However, we have made one important modification in accordance with recent evidence demonstrating that Ca$^{2+}$ can accumulate in a small domain between the sarcolemma and the peripheral junctional SR and trigger Ca$^{2+}$ release.$^{27,49}$ Specifically, we have removed the voltage-dependent term in the formulation for activation of SR Ca$^{2+}$ release and replaced it with a term dependent on Ca$^{2+}$ concentration in the restricted subsarcolemmal domain, $[Ca^{2+}]_d$. The sole mechanism for SR Ca$^{2+}$ release in our model is therefore Ca$^{2+}$-induced Ca$^{2+}$ release (CICR). Fig 1B includes a schematic representation of the model of the SR.

Stern$^{25}$ has shown that in order for a CICR model to be stable, ie, capable of producing a response that is graded by the amount of Ca$^{2+}$

**Table 3. Time-Independent Current Formulations Compared With the LMCG Model**

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<thead>
<tr>
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<th>Changes From LMCG Formulation</th>
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<tr>
<td>$k_1$</td>
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<tr>
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<td>5% reduction in $g_{Na}$</td>
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<tr>
<td>$k_{Ca}$</td>
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<tr>
<td>$k_{K}$</td>
<td>10% increase in $g_{K}$</td>
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<tr>
<td>$k_{CaP}$</td>
<td>87% increase in $g_{CaP}$</td>
</tr>
<tr>
<td>$k_{CaK}$</td>
<td>58% reduction in $g_{CaK}$</td>
</tr>
</tbody>
</table>

LMCG indicates the model of Lindblad et al.$^{15}$

Figure 6. Parameters for $k_{Ca}$ and $k_{CaS}$. A, Steady-state activation and inactivation curves for $k_{Ca}$ ($\beta_a$ and $\beta_p$, respectively). Data are from Wang et al$^{44}$ ($\Delta$), Muraki et al$^{41}$ ($\bigcirc$), and Sanguinetti et al$^{45}$ ($\square$). B, Steady-state activation curve for $k_{CaS}$ ($\theta$). Data are from Wang et al$^{44}$ ($\Delta$) and Muraki et al$^{41}$ ($\bigcirc$). C, Activation time constant for $k_{Ca}$ ($\tau_a$). Data are from Wang et al$^{44}$ ($\Delta$) and Muraki et al$^{41}$ ($\bigcirc$). D, Activation time constant for $k_{CaS}$ ($\tau_s$). Data are from Wang et al$^{44}$ ($\Delta$).

Figure 7. Current-voltage relationship for $I_{K_{Ca}}$ and $I_{K_{CaS}}$, normalized to peak $I_{K_{Ca}}$ ($\approx 0.6 \text{ pA/pF}$) ($\bigcirc$ and $\bullet$ represent data from Muraki et al$^{41}$). The $I_{K_{Ca}}$ waveform is the response to an 0.8-V/s “ramp” repolarization from an action potential peak potential down to $-30 \text{ mV}$.$^{41}$
that enters the cell through \( I_{Na} \), the trigger \( Ca^{2+} \) has to be separated from that released from the SR. Anatomically, this can be understood in terms of the concept of “release units” discussed, for example, by Isenberg and Han.51 According to this concept, \( Ca^{2+} \) release from the SR is recruited stepwise by the all-or-none activation of individual release units, consisting of one or more L-type \( Ca^{2+} \) channel and associated SR release channels. The activation of a release unit results in CICR within that unit only. The released \( Ca^{2+} \) then diffuses into the myoplasm, without directly affecting other units. This phenomenon has been included in our model as a lumped mechanism, where the SR release channel senses \([Ca^{2+}]_{e}\) in the restricted domain \( ([Ca^{2+}]_{e}) \) but releases \( Ca^{2+} \) directly to the cytosol (Fig 1B), thus separating trigger \( Ca^{2+} \) from that released from the SR.

**Parameter Values**

A model of this type contains a large number of parameters that must be assigned values based on the available data. We have approached this part of the model development process in a two-step fashion, where the majority of the parameter values have been assigned in the first step, based on experimental studies of individual model components. This has the advantage that most of the parameters associated with an individual membrane current can be justified and assigned independently. Once the descriptions of individual membrane currents has been completed, one is left with a limited number of free parameters, most of which are scaling factors, such as the maximum conductance values for each ionic current. These remaining free parameters can then be determined using data for whole-cell responses (eg, action potential waveforms) or other constraints as indicated previously (eg, ionic homeostasis). It should be emphasized, however, that model development is very much an iterative process and that it has been necessary in some cases to modify individual current expressions to obtain acceptable fits to action potential data or (as in the case of \( I_{Ca} \)) to use information from action potential recordings to resolve ambiguities in ion channel current data. The following sections describe the constraints and criteria used in order to assign values for the remaining free parameters.

**The Quiescent Human Atrial Myocyte**

In the absence of an external stimulus, a healthy human atrial cell is quiescent (does not contract or produce an action potential). In this quiescent state, the membrane potential comes to an equilibrium, “resting,” potential at which the net ion flux across the sarcolemma is zero. The resting membrane potential varies somewhat among individual cells, ranging from \( -70 \) to \( -80 \) mV. The resting membrane potential is the result of a precise balance between the time-independent background, pump, and exchanger currents (\( I_{Na}, I_{K}, I_{Ca}, I_{Na}, I_{Ca}, I_{Na}, I_{Ca}, and I_{Ca} \)). Although the resting state of the cell may seem less interesting than the active state during an action potential, an accurate description of the resting conditions is, in our experience, essential for successful modeling of the action potential. Moreover, the model of the resting state of the cell determines very important threshold characteristics and subthreshold properties, such as the input resistance of the cell. Very accurate simulation of these passive characteristics is essential before the cell model is to be used for comparison with experimental data that is obtained from single cells and in multicellular preparations from the human atrium. By establishing this “nominal model,” we have obtained a starting point from which the sensitivity of the action potential waveform to parameter perturbations may be studied (see “Results”). In addition to dictating the action potential waveform, the sizes (maximum conductance parameters) of the ionic currents also affect ionic homeostasis. The membrane currents involved in shaping the action potential therefore have to act in concert with those involved in the resting state to maintain constant ion concentrations at nominal stimulation rates. We have “tuned” our model so that ion concentrations remain constant from cycle to cycle at a stimulus frequency of 1 Hz.

**Results**

There are two major aims of the simulations presented in the following sections: (1) to establish the validity and usefulness of our model by demonstrating that the expressions that are based on fits to voltage-clamp data for individual ionic currents also are able to accurately reconstruct action potential data and (2) to use the model to investigate the functional roles of different ionic currents, to study the sensitivity of the action potential waveform to the sizes of those currents, and, finally, to predict the whole-cell response to, for example, selected channel blocking drugs.

**Simulated Action Potential Waveform**

Fig 8A shows a simulated action potential waveform (solid line) compared with recorded data (dotted line). B and C, Model-generated waveforms for the ionic currents during the action potential (note the difference in scale between panels B and C). Most often recorded from isolated human atrial cells in our laboratory. By establishing this “nominal model,” we have obtained a starting point from which the sensitivity of the action potential waveform to parameter perturbations may be studied (see “Results”). In addition to dictating the action potential waveform, the sizes (maximum conductance parameters) of the ionic currents also affect ionic homeostasis. The membrane currents involved in shaping the action potential therefore have to act in concert with those involved in the resting state to maintain constant ion concentrations at nominal stimulation rates. We have “tuned” our model so that ion concentrations remain constant from cycle to cycle at a stimulus frequency of 1 Hz.

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**Figure 8.** Model-generated action potential and membrane current waveforms. A, Model-generated action potential (solid line) compared with recorded data (dotted line). B and C, Model-generated waveforms for the ionic currents during the action potential (note the difference in scale between panels B and C). There are two major aims of the simulations presented in the following sections: (1) to establish the validity and usefulness of our model by demonstrating that the expressions that are based on fits to voltage-clamp data for individual ionic currents also are able to accurately reconstruct action potential data and (2) to use the model to investigate the functional roles of different ionic currents, to study the sensitivity of the action potential waveform to the sizes of those currents, and, finally, to predict the whole-cell response to, for example, selected channel blocking drugs.
combination with the previously demonstrated fits to voltage-clamp data, lends credibility to the model.

In Fig 8, panels B and C show the behavior of the membrane currents during an action potential. The first current to respond to a depolarizing stimulus pulse (delivered at time=$100 \text{ ms}$) is $I_{Na}$, which activates rapidly, resulting in a very large but transient inward current. Note that $I_{Na}$ is too large to be shown on the scale of Fig 8B; its peak magnitude is $\approx 5.8 \text{ nA}$, which corresponds to a maximum upstroke velocity of $116 \text{ V/s}$. $I_{Na}$ is primarily responsible for the upstroke (phase 0) of the action potential, but as seen from Fig 8B, a substantial amount of $I_{Na}$ remains during the early peak phase of the action potential as a result of the second slower component of $I_{Na}$ inactivation.

On depolarization of the cell, $I_c$, $I_{Na}$, and $I_{Ca,L}$ are also activated. However, $I_c$ and $I_{Na}$ reach their peak magnitude faster than $I_{Ca,L}$, and their combined magnitude is thus larger than that of $I_{Ca,L}$ early in the action potential. (This is because the peak of the action potential is close to the reversal potential for $I_{Ca,L}$.) The initial result on the action potential waveform is therefore a period of relatively rapid repolarization (phase 1), dominated by $I_c$. Since the time course of inactivation of $I_{Ca,L}$ is slow compared with that of $I_c$, the net current gradually becomes dominated by $I_{Ca,L}$ and $I_{Na}$. A situation where the repolarizing effect of $I_{Na}$ (and the remaining $I_c$) is balanced by the depolarizing effect of $I_{Ca,L}$ results. In the action potential waveform, the initial rapid repolarization (phase 1) is followed by a period during which the membrane potential levels off, forming a plateau (phase 2). Finally, as $I_{Ca,L}$ slowly inactivates, the repolarizing effects of $I_{Na}$ become dominant, and the action potential enters its final repolarization phase (phase 3). During this phase, $I_{Na}$ is aided by the inward rectifier current, $I_{K1}$, and the delayed rectifier currents, $I_{K,Ca}$ and $I_{K,L}$, in repolarizing the cell membrane back to the resting potential (phase 4).

### Simulated Ionic Fluxes

The fluid compartment part of this model monitors ion concentrations in the intracellular and cleft spaces. Valid modeling of the action potential requires not only the reconstruction of the action potential waveform but also a demonstration that this can be accomplished under conditions of ionic homeostasis at nominal heart rates. Table 4 shows how our model has been tuned to achieve homeostasis at 1 Hz. The average charge transported across the sarcolemma for each ionic current has been computed by integrating each current over one cycle (1 s in the case of a quiescent, nonstimulated cell). Note that the sums of these average charges are zero for all ionic species at a stimulus rate of 1 Hz (Table 4). When the cell is quiescent, there is a small net loss of intracellular $Na^+$ and gain of intracellular $K^+$. The existence of such an ionic imbalance at quiescence is supported by the observation by Bénard et al that trains of depolarizing pulses that activate $I_{Na}$ can be used to hyperpolarize the resting potential of human atrial cells after a period of quiescence. As suggested by these authors, the hyperpolarization and stabilization of the resting potential may be caused by activation of the $Na^+-K^+$ pump after $Na^+$ entry during the train of pulses. In our model, at a 2-Hz stimulus rate there will be a net gain of intracellular $Na^+$ and loss of $K^+$.

![Simulated Ionic Fluxes](image)

**TABLE 4. Current Integrals Over 1 s at Quiescence and at Stimulus Rates of 1 and 2 Hz**

<table>
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<th>2 Hz</th>
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<td>0.00</td>
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</tr>
</tbody>
</table>

For quiescent and 2-Hz rates, the integrals were computed 20 s after leaving the nominal 1-Hz rate. All values are pC/s.
seen in Fig 9C, the occupancies on these buffers increase rapidly as Ca\(^{2+}\) is released from the SR, thus “removing” large amounts of free Ca\(^{2+}\) from the cytosol. The uptake of Ca\(^{2+}\) by the SR also has a pronounced effect on the shape of the Ca\(^{2+}\) transient. This is also the primary pathway for actual removal of Ca\(^{2+}\) from the cytosol (as opposed to the “temporary storage” provided by the buffers), taking up intracellular Ca\(^{2+}\) as it dissociates from the buffers. In addition, some Ca\(^{2+}\) is removed from the cytosol via the Na\(^{+}\)-Ca\(^{2+}\) exchanger, \(I_{\text{NaCa}}\), and the Ca\(^{2+}\) pump, \(I_{\text{CaP}}\). As seen in Table 4, \(I_{\text{NaCa}}\) and \(I_{\text{CaP}}\), on average, remove the amounts of Ca\(^{2+}\) that were brought into the cell via \(I_{\text{Lx}}\) and \(I_{\text{CaL}}\), and thereby prevent a progressive buildup of cytosolic Ca\(^{2+}\) during repetitive stimulation.

Increasing the stimulus rate from the baseline (1 Hz) results in a change in ion concentrations in the intracellular medium (Table 4) as well as in the cleft space surrounding the cell. For the ionic species that exist in relatively low concentrations in the extracellular medium (Ca\(^{2+}\) and K\(^{+}\)), these changes can be significant. Fig 10 shows how the intracellular and cleft space concentrations change when the stimulus rate is increased abruptly from 1 to 2 Hz. Note the progressive shift in [K\(^{+}\)]i, of \(\approx 1\) mmol/L.\(^{47,48}\) In contrast, the change in [Na\(^{+}\)], is negligible because of its high baseline value of 130 mmol/L. If the simulation in Fig 10 is continued beyond the 20 s shown, [K\(^{+}\)]i begins to decline as a result of increased \(I_{\text{NaK}}\) activity due to increased [Na\(^{+}\)], and [K\(^{+}\)], (simulation not shown). The asymptotic values for [K\(^{+}\)]i and [Na\(^{+}\)]i are 5.6 and 10.0 mmol/L, respectively (reached after \(\approx 10\) minutes). This behavior is consistent with experimental observations.\(^{47}\)

Parameter Sensitivity of the Action Potential Shape

As mentioned in the previous section, there is considerable variation in action potential shape among individual cells from the human atrium. Our working hypothesis is that many of these differences in action potential wave shape can be explained in terms of differences in the magnitudes of the ionic currents (caused by previous drug treatment and/or natural variability). In order to investigate possible mechanisms of action potential shape variability, it is therefore necessary to have an understanding of how changes in the magnitudes of different ionic currents affect the action potential shape. Such an understanding is equally important, of course, in identifying suitable “targets” for drug action aimed at modifying the action potential shape.

A valid mathematical model provides a method for this sensitivity analysis;\(^{53}\) ie, it provides a method for studying how sensitive the state variables (eg, membrane voltage) are to perturbations in model parameters. We will restrict this analysis to a study of the sensitivity of the action potential waveform to changes in the sizes (maximum conductances) of the currents involved in shaping the action potential, although this type of analysis in principle can be used to study the sensitivity of any state variable to perturbations in any model parameter. Briefly, sensitivity analysis involves the computation of the partial derivative of the state variable of interest (in this case, membrane voltage) with respect to a model parameter. We will present the results in terms of sensitivity functions, defined as:

\[
\epsilon_s = \frac{\partial \nu}{\partial x}
\]
which can be interpreted as a proportionality factor relating a relative change in a model parameter to a resulting change in membrane voltage. The computational aspects of this method are outlined in Appendix B (see also Paulsen et al11).

Fig 11 shows the result of the sensitivity analysis, ie, the sensitivity functions for the membrane voltage (action potential) with respect to the parameters of interest. Sensitivity functions were computed for all maximum conductance parameters in the model as well as for the scaling parameters for $I_{NaK}$ and $I_{NaCa}$. The sensitivity functions for $I_{Na}$ and $I_{K}$ have been omitted from Fig 11, since these currents were found to have negligible influence on the action potential shape (small sensitivity functions), except for the obvious importance of $I_{Na}$ during the upstroke. Several of the sensitivity functions have maximum absolute values of $\approx 50$ mV during the late repolarization phase of the action potential. In other words, a 10% change in either one of these parameters would alter the membrane voltage by $\approx 5$ mV during this phase of the action potential. Although this estimate is based on a linearization around the nominal parameter value and thus is most accurate for small perturbations, it can provide an indication of the approximate change expected for larger perturbations. Overall, we can anticipate that changes in these parameters in the $\pm 50%$ range will produce significant changes in the action potential waveform.

Perhaps more important than the absolute sensitivity values, however, is the information provided by the time course of the sensitivity functions. As the ionic conductances change during the action potential, the sensitivity functions indicate which currents have the greatest influence on the action potential shape at each point in time. For example, it is clear that the action potential waveform is sensitive to $g_{Na}$ primarily early in the peak phase of the action potential but that $g_{Na}$ and $g_{Ca}$ rapidly become more important early in the plateau phase. Throughout the plateau phase, $|\epsilon_{Na}|$ (absolute value) and $|\epsilon_{Ca,Na}|$ are larger than $|\epsilon_{g}|$, and this portion of the action potential waveform is therefore particularly sensitive to perturbations in $g_{Na}$ and $g_{Ca,Na}$. Toward the end of repolarization, the action potential becomes very sensitive to the size of the time-independent currents involved in maintaining the resting potential. This analysis shows that (under the hypothesis that action potential changes can be explained in terms of changes in the magnitudes of ionic currents) $g_{Na}$, $g_{Na}$, and $g_{Ca,Na}$ are the most important model parameters in determining the action potential waveform during the peak and plateau phases of the action potential.

### Roles of $I_{Na}$ and $I_{Ca}$ in Repolarization

The effects on the human atrial action potential of blocking $I_{Na}$ with agents such as 4-aminopyridine, flecainide, and quinidine have been described in the literature. Partial block of $I_{Na}$ results in a slowing of the rate of repolarization of the action potential, particularly during the early repolarization phase (phase 1). This is, of course, consistent with the characteristics of $I_{Na}$ and its role in the generation of the action potential as indicated by sensitivity analysis. In a recent study of the effects of some antiarrhythmic agents on $I_{Na}$ and $I_{Ca}$, Wang et al.6 found that quinidine, in addition to blocking $I_{Na}$, has a pronounced effect on $I_{Ca}$ at clinically relevant concentrations. Considering that our sensitivity analysis indicates a prominent role for $I_{Ca}$ in repolarization, the APD is expected to be quite sensitive to modulation of $I_{Ca}$ magnitude. A detailed account of the role of $I_{Na}$ and $I_{Ca}$ in the repolarization of the human atrial action potential is therefore essential for understanding the antiarrhythmic actions of quinidine.

Since pharmacological blocking agents used in experimental work usually affect more than one current and since their effects are often rate dependent, it is difficult to gain a quantitative understanding of the importance of a particular current ($I_{Na}$ or $I_{Ca}$) in repolarization from experimental results alone. In a computer model, however, it is possible to alter the characteristics of one ionic current in a controlled fashion, while leaving all other currents unaffected. Such simulations can be a valuable complement to experimental work. Given that drugs that prolong the APD (class III drugs) have been shown to be effective in the treatment of atrial arrhythmias, a thorough understanding of the influence of different ionic currents on the APD is needed.

Fig 12A shows the effects on the action potential of various degrees of block ($30\%, 60\%,$ and $90\%$) of block of $I_{Na}$. (In the present study, an $x\%$ block of $I_{Na}$ is simulated as an $x\%$ reduction in the maximum conductance, $g_{Na}$.) As observed experimentally, $I_{Na}$ block results in a broadening of the action potential peak during phase 1 of repolarization (refer to Fig 2 in Firek and Giles8). In addition, because of the elevation of the action potential peak and plateau levels, the contribution of $I_{Ca}$ to repolarization is increased. The resulting prolongation of the APD is therefore only moderate, even for substantial reductions of $I_{Na}$ size. Fig 12B shows the effects of various degrees of block ($15\%, 30\%,$ and $45\%$) of block of $I_{Ca}$ on the action potential. In contrast to $I_{Na}$ block, inhibition of $I_{Ca}$ primarily affects the plateau phase of the action potential, with little or no effect on...
the action potential peak. As a result, $I_{\text{m}}$ block produces a more pronounced prolongation of the action potential than does $I_t$ block. For example, 30% block of $I_{\text{m}}$ results in a 15% increase in APD at 90% repolarization (APD$_{90}$) compared with the 5% increase in APD$_{90}$ resulting from 30% $I_t$ block. Many antiarrhythmic agents have effects on several ion channels. For example, according to Wang et al.,$^{56}$ quinidine blocks both $I_t$ and $I_{\text{m}}$ (in addition to its effects on Na$^+$ channels). It is therefore of interest to study the effects on the action potential of combined $I_t$ and $I_{\text{m}}$ block. Fig 12C shows the result of a simulation in which both $I_t$ and $I_{\text{m}}$ have been reduced by 40% (approximately corresponding to the effect of 5 μmol/L quinidine at a stimulus rate of 1 Hz$^3$). As expected, the result is essentially a combination of the previously demonstrated effects of $I_t$ and $I_{\text{m}}$ block, i.e., a widened peak, an elevated action potential plateau, and a prolongation of APD$_{90}$ of 27%.

**Modulation of the Role of $I_{\text{m}}$ by Baseline $I_{Ca,L}$, $I_{\text{m}}$, and $I_{K,r}$ Sizes**

As discussed in “Model Development,” published data regarding the size of $I_{Ca,L}$ and $I_{\text{m}}$ are quite variable. Both these currents (as well as $I_t$) are known to be depressed in diseased human atrial cells$^{26,28}$ and modulated by adrenergic stimulation.$^{26,30}$ Furthermore, a recent study$^{39}$ shows that the size of $I_{\text{m}}$ is significantly reduced in cells obtained from patients in chronic atrial fibrillation compared with patients in normal sinus rhythm. It is therefore likely that a range of sizes of these two currents contributes to the physiological (and pathophysiological) behavior of the human atrial cell. Similarly, $I_{K,r}$ in our nominal model is very small, which is consistent with observations from our laboratory. Since results in other species$^{60}$ indicate that this may be a consequence of the cell isolation techniques used for human atrial myocytes,$^7$ this current may be considerably larger in vivo. Given these uncertainties in the actual sizes of several of the ionic currents, it is appropriate to investigate how the conclusions reached above are affected by our assumptions for these current sizes. We have chosen to focus on the role of $I_{\text{m}}$ in repolarization, since this current is an important determinant of APD. Starting from our nominal model, we have performed a large number of simulations for different combinations of increased/decreased $I_{Ca,L}$, $I_{\text{m}}$, and $I_{K,r}$. All simulations were performed at a stimulation rate of 1 Hz, and 20 cycles were allowed after each change of parameter values in order for any initial transient behavior to die out before the APD prolongation was evaluated. Fig 13 shows how the APD prolongation resulting from a 50% reduction of $I_{\text{m}}$ depends on the baseline sizes of $I_{Ca,L}$ and $I_{K,r}$. $I_{Ca,L}$ and $I_{K,r}$ sizes are expressed as percentages of those in the nominal model; i.e., the nominal model corresponds to 100% of both currents. A 7-fold (700%) increase in $I_{K,r}$ corresponds approximately to the size of $I_{K,s}$ observed in rabbit atrial myocytes.$^4$ It is clear from Fig 13 that the role of $I_{\text{m}}$ as a major determinant of APD depends strongly on the size of $I_{K,r}$ current. The action potentials shown in the insets in Fig 13 provide an indication of the underlying mechanism. When $I_{\text{m}}$ is partially blocked, the action potential plateau is depolarized, which in turn increases the amount of $I_{K,s}$ (and $I_{K,r}$) that is activated. This effect, which counteracts the APD-prolonging effect of $I_{\text{m}}$ block, becomes stronger as the size of $I_{K,r}$ is increased. Similarly, Fig 14 shows how the APD prolongation as a result of 50% $I_{\text{m}}$ block depends on the baseline sizes of $I_{Ca,L}$ and $I_{\text{m}}$. Again, the APD-prolonging effect of $I_{\text{m}}$ block is strongly dependent on the baseline current densities. Generally, the APD prolongation as a result of partial $I_{\text{m}}$ block becomes larger as the baseline size of $I_{Ca,L}$ increases, provided that the increase.

**Figure 12. Effects of partial block of $I_t$ and $I_{\text{m}}$. A, $I_t$ block (30%, 60%, and 90%) has its main effect on the peak and produces only a moderate prolongation of the action potential. B, $I_{\text{m}}$ block (15%, 30%, and 45%) has a strong effect on the action potential duration. C, Combined block (40%) of $I_t$ and $I_{\text{m}}$ widens the peak and prolongs the action potential, in a way similar to the effect of 4-aminopyridine (4-AP). D, Recorded action potential under control conditions and in the presence of 4-AP (data from Firek and Giles$^2$).**

**Figure 13. Prolongation of action potential duration at 90% repolarization (APD$_{90}$) as a result of 50% reduction of $I_{\text{m}}$ size, plotted as a function of the baseline $I_{Ca,L}$ and $I_{K,r}$ sizes. (100% denotes the nominal sizes of $I_{Ca,L}$ and $I_{K,r}$.) Insets show examples of action potentials (before and after $I_{\text{m}}$ block) corresponding to three points in the graph (middle inset is for the nominal model).**
Discussion

Mathematical models form an important complement to experimental work in attempts to elucidate the ionic mechanisms underlying the action potential and other electrophysiological phenomena in cardiac cells. At a minimum, these models can provide a means of integrating data obtained from many different experiments and laboratories so that biophysically based explanations of complex nonlinear phenomena such as action potential initiation (excitation) and repolarization can be given. Mathematical models also provide a way of reviewing data in the context of the normal behavior of a cell (during an action potential), even when some of the data may have been obtained under completely different experimental conditions, eg, a voltage-clamp experiment. Moreover, as illustrated in the last few sections of “Results,” mathematical models can also have considerable predictive capabilities. After a model has been developed and carefully validated, it can be used to predict the response of the cell to selected drugs, experimental protocols, etc. Ideally, experimental work and model development should be carried out in close association, using the model to design and evaluate experiments and using experimental results to improve the model.

We have developed a mathematical model of the human atrial cell based primarily on data recorded from enzymatically isolated single human atrial cells. Our model is capable of accurately reconstructing a recorded human atrial action potential and illustrates the functional roles of the ionic currents. In addition, our model maintains ionic homeostasis at a nominal stimulus rate, demonstrating that the reconstruction of the action potential is accomplished using plausible current densities. We used the LMCG rabbit atrial model as a “starting point” for the model development. As a result, these two formulations are very similar in some aspects, particularly for the membrane currents where incomplete (or no) data from human atrial cells are available. However, there are some important differences between the electrophysiological responses of rabbit and human atrial cells; these provided the motivation for the development of this human atrial cell model. Perhaps most striking is the small rate dependence of I,

Roles of I, and I, in Repolarization

Both I, and I, have important roles in the repolarization of the action potential of human atrium. In particular, I, because of its noninactivating characteristics, is necessary for repolarization to the resting potential. This important role in repolarization makes I, and I, potential targets for class III antiarrhythmic drugs, which are designed to prolong the APD. Indeed, a recent study of flecainide and quinidine, both known to prolong the human atrial action potential, shows that both these drugs produce a partial block of I. Quinidine also blocks I, which could explain its greater efficacy (compared with flecainide) in prolonging the APD. Our simulations of partial I, and I, block (see “Results”) produce prolongations of the APD that are comparable to experimentally observed effects of flecainide and quinidine, ie, a 27% prolongation of APD when I, and I, are both reduced by 40%. For comparison, Wang et al reported that 2.25 μmol/L quinidine increased APD by 33% in human atrial cells at a stimulation rate of 1 Hz. It should be noted that only some of the known effects of quinidine have been modeled; therefore, our results cannot be directly compared with these experimental observations. For example, the effects of quinidine on I, as well as the state dependence of I, block by quinidine, would have to be included in a more comprehensive treatment of quinidine effects. Nevertheless, the experimental observations

Figure 14. Prolongation of action potential duration at 90% repolarization (APD90) as a result of 50% reduction of I, size, plotted as a function of the baseline I,Ca and I,sus sizes. Insets show examples of action potentials (before and after I,sus block) corresponding to three points in the graph (middle inset is for the nominal model).
agree very well with our model predictions and provide an independent “test” of how well our model describes the roles of \( I_\text{Kf} \) and \( I_\text{Ks} \) in repolarization.

Action potential generation involves a complex interaction among the ionic currents in a given cell type. The role of a particular ionic current in the action potential is therefore not determined solely by the characteristics of that current. We have investigated how the role of \( I_\text{Kf} \) in repolarization is affected when the baseline densities of \( I_\text{Ca,L} \), \( I_\text{Kf} \) and \( I_\text{Ks} \) are varied within ranges that are relevant to the physiological and pathophysiological behavior of the human atrial cell. Our results demonstrate that \( I_\text{Kf} \) block will, in general, result in a prolongation of the action potential. The amount of prolongation, however, depends quite strongly on the baseline current densities. If the human atrial cell is assumed to have an \( I_\text{Kf} \) density comparable to that observed in the rabbit atrium\(^{40} \) or if the \( I_\text{Ca,L} \) and \( I_\text{Kf} \) densities are reduced as observed in diseased cells\(^{22,26} \), the APD prolongation resulting from \( I_\text{Kf} \) block may be considerably smaller than indicated by our nominal model. The efficacy of a drug targeting \( I_\text{Kf} \) would therefore be expected to depend critically on the disease state of the tissue. For example, based on the recent observation by Van Wagoner et al.\(^{59} \) that \( I_\text{Kf} \) density is reduced in cells obtained from patients in chronic atrial fibrillation, the efficacy of an \( I_\text{Kf} \)-blocking drug may be limited in these patients.

Limitations of the Model

When using our model to gain insight into the electrophysiological responses of the human atrial cell, it is important to be aware of certain limitations, which are summarized by the following items:

1. The Hodgkin-Huxley formalism along with its concept of independent activation and inactivation “gating” variables has some important limitations. Notably, the processes of inactivation and recovery from inactivation (and analogously activation and deactivation) are governed by a single time constant. Experimental observations, however, often indicate that inactivation and recovery from inactivation occur with different time constants, even at the same membrane potential. In order to overcome this problem, one would have to use a more complicated modeling formalism that treats inactivation and recovery as two separate processes. To reduce the computational requirements of the model, we have chosen a “compromise” solution, in which time constant values are determined by measured inactivation kinetics at depolarized membrane potentials and by measured recovery kinetics at hyperpolarized potentials. In cases in which the time constants of inactivation and recovery are very different, this compromise results in unconventional time constant expressions, such as those for \( I_\text{Kf} \) in Fig 2D.

2. The available data regarding the intracellular Ca\(^{2+}\) transient and the Ca\(^{2+}\) handling in the SR have, with few exceptions\(^{52,58} \), been recorded in cells from species other than humans. In addition, the understanding of the exact mechanisms involved in these phenomena is incomplete, and a quantitative model of SR Ca\(^{2+}\) release and uptake has not yet been developed. Our Ca\(^{2+}\)-dependent formulation for SR Ca\(^{2+}\) release replaces the voltage-dependent formulation used in earlier models\(^{4,12,13} \) but is nevertheless only a qualitative description of this phenomenon. Other features of the SR function are the same as those in the LMCG model.\(^ {13} \) Our SR formulation is therefore not based on human data.

3. The shape of the action potentials recorded from enzymatically isolated human atrial cells is variable, even at a fixed stimulus frequency. There are several reasons for this variability, including genuine heterogeneity between cells from different parts of the atrium, the disease states of the patients from whom the specimens are obtained, and the use of various drugs (eg, Ca\(^{2+}\) channel blockers and β-blockers) by the donors. It is important to acknowledge that this variability exists and that the exact action potential waveform in the model is chosen because it is representative of the action potential shapes that are most often observed in our single cell records. As indicated by sensitivity analysis, the shape of the human atrial action potential as described by our model is quite sensitive to variations in the strengths of three ionic currents (\( I_\text{Kf} \), \( I_\text{L} \) and \( I_\text{Ca,L} \)). Under the assumption that the currents involved and their kinetic properties are unchanged, our results therefore suggest that the experimentally observed variation in action potential shape is caused mainly by variations in these currents and can be explained within the framework of our model. However, it is also conceivable that regional diversity in the molecular basis of the currents in human atrium could give rise to regional differences in kinetics and pharmacological sensitivity. Most of the data on human atrial electrophysiology to date have been obtained from samples of the atrial appendage, and there are therefore little experimental data available regarding regional differences in human atrium. If and when data to suggest regional diversity become available, our model should provide a useful framework for predicting the consequences.

4. Our model of Ca\(^{2+}\)-dependent inactivation of \( I_\text{Ca,L} \) uses a single lumped subsarcolemmal compartment in which Ca\(^{2+}\) accumulates and is therefore limited in its ability to simulate the effect of Ca\(^{2+}\) accumulation in restricted spaces close to each L-type Ca\(^{2+}\) channel. In contrast to voltage-dependent gating, where it is reasonable to assume that the controlling variable (membrane voltage) is spatially uniform (space-clamp conditions), this is in all likelihood not the case for subsarcolemmal Ca\(^{2+}\). Since inactivation is a nonlinear function of \([Ca^{2+}]_\text{s}\), it is not strictly correct to use a formulation in which all channels are subject to one (average) Ca\(^{2+}\) concentration.

Notwithstanding these limitations, this model provides the most complete description available of the ionic mechanisms underlying the human atrial action potential, and it is based on the available data. As a result, it provides a very useful tool for investigating fundamental electrophysiological responses of the human atrial cell, such as excitability, refractoriness, and the action of channel blocking drugs.

Appendix 1: Model Equations

Tables 5 through 19 contain all the equations, parameter values, and initial conditions necessary to carry out the simulations presented in this article. Unless otherwise noted, the units are as follows: time in seconds (s), voltage in millivolts (mV), concentration in millimoles/liter (mmol/L), current in picoamperes (pA), conductance in nanomhos (nS), capacitance in nanofarads (nF), volume in nanoliters (nL), and temperature in kelvin (K). The stimulus used to evoke an action potential consists of a rectangular current pulse (\( I_{\text{stim}} \)) with an amplitude of 280 pA and duration of 6 ms.
TABLE 5. Membrane Voltage: V

\[
\frac{dV}{dt} = \frac{I_{Kt} + I_{Ca,L} + I_i + I_{in} + I_{K1} + I_{B,Na} + I_{B,Ca} + I_{NaK} + I_{CaP} + I_{NaCa} - I_{stim}}{-C_m}
\]

TABLE 6. Na⁺ Current: \( I_{Na} \)

\[
I_{Na} = P_{Na,m} m^3(0.9h_1 + 0.1h_2)[Na^+]_V \frac{F}{RT} e^{\frac{E_N - E_{Na}}{RT}} - 1.0 e^{\frac{E_V - E_{Na}}{RT}} - 1.0
\]

\[
\frac{d\bar{m}}{dt} = \frac{1.0}{1.0 + e^{\frac{V-25.21}{8.21}}} - m
\]

\[
\frac{d\bar{h}}{dt} = \frac{1.0}{1.0 + e^{\frac{V+65.89}{5.3}}} - h
\]

\[
\tau_m = 0.000042 e^{-((V+25.57)/28.81)^2} + 0.000024
\]

\[
\tau_h = 0.03 + 0.00003
\]

\[
E_{Na} = \frac{RT}{F} \log \frac{[Na^+]_V}{[Na^+]_I}
\]

TABLE 7. Ca²⁺ Current: \( I_{Ca,L} \)

\[
I_{Ca} = \frac{1.0}{1.0 + e^{\frac{V+27.4}{8.21}}}
\]

\[
\frac{d\bar{f}_1}{dt} = \frac{\bar{f}_1 - f_1}{\tau_{f_1}}
\]

\[
\frac{d\bar{f}_2}{dt} = \frac{\bar{f}_2 - f_2}{\tau_{f_2}}
\]

\[
\tau_{f_1} = 0.0027 e^{-((V+35.0)/30.0)^2} + 0.002
\]

\[
\tau_{f_2} = 0.161 e^{-((V+40.0)/14.4)^2} + 0.010
\]

\[
\tau_{f_1} = 1.3323 e^{-((V+40.0)/14.2)^2} + 0.0626
\]

\[
f_{Ca} = \frac{[Ca^{2+}]_d}{[Ca^{2+}]_d + k_{Ca}}
\]
### TABLE 8. Transient and Sustained Outward K\(^+\) Currents: \(I_t\) and \(I_{sus}\)

\[
I_t = \mathfrak{g}_{rs}(V - E_K)
\]

\[
\tau = \frac{1.0}{1.0 + e^{V-1.0/-11.0}}
\]

\[
\frac{dr}{dt} = \frac{\tau - r}{\tau}
\]

\[
\tau = 0.0035e^{-(V/30.0)^2} + 0.0015
\]

\[
I_{sus} = \mathfrak{g}_{sus}(V - E_K)
\]

\[
\tau = \frac{1.0}{1.0 + e^{(V+40.0)/11.5}}
\]

\[
\frac{dr}{dt} = \frac{\tau - r}{\tau}
\]

\[
\tau = 0.4812e^{-(V+52.45)/14.97} + 0.01414
\]

### TABLE 9. Delayed Rectifier K\(^+\) Currents: \(I_{k,s}\) and \(I_{k,r}\)

\[
I_{k,s} = \mathfrak{g}_{k,s}(V - E_K)
\]

\[
\tau_{s} = \frac{1.0}{1.0 + e^{V+4.31/-2.8}}
\]

\[
\frac{d\tau_{s}}{dt} = \frac{\tau_{s} - \tau_{s}}{\tau_{s}}
\]

\[
\tau_{s} = 0.4109 + 0.6e^{-(V+20.00)/10.0}
\]

\[
I_{k,r} = \mathfrak{g}_{k,r}(V - E_K)
\]

\[
\tau_{r} = \frac{1.0}{1.0 + e^{V+8.0/-12.5}}
\]

\[
\frac{d\tau_{r}}{dt} = \frac{\tau_{r} - \tau_{r}}{\tau_{r}}
\]

\[
\tau_{r} = 0.009 + 0.0005e^{-(V+8.00)/12.5}
\]

### TABLE 10. Inward Rectifier K\(^+\) Current: \(I_{k1}\)

\[
I_{k1} = \mathfrak{g}_{k1}(V - E_K)\left[V - E_K\right]
\]

\[
E_K = \frac{RT}{F}\log\left[K^+\right]/\left[K^+\right]
\]

### TABLE 11. Background Inward Currents: \(I_{B,Na}\) and \(I_{B,Ca}\)

\[
I_{B,Na} = \mathfrak{g}_{B,Na}(V - E_{Na})
\]

\[
I_{B,Ca} = \mathfrak{g}_{B,Ca}(V - E_{Ca})
\]

\[
E_{Na} = \frac{RT}{F}\log\left[Na^+\right]/\left[Na^+\right]
\]

\[
E_{Ca} = \frac{RT}{2F}\log\left[Ca^{2+}\right]/\left[Ca^{2+}\right]
\]
\[
\begin{align*}
\text{TABLE 12. Pump and Exchanger Currents: } & I_{\text{NaK}}, I_{\text{CaP}}, \text{ and } I_{\text{NaCa}} \\
I_{\text{NaK}} &= I_{\text{NaK}} \frac{[K^+]_i}{[K^+]_o} - \frac{[Na^+]_i}{[Na^+]_o} \times V + 150.0 + \frac{2}{V} + 200.0 \\
I_{\text{CaP}} &= I_{\text{CaP}} \frac{[Ca^{2+}]_i}{[Ca^{2+}]_o} + k_{\text{CaP}} \\
I_{\text{NaCa}} &= k_{\text{NaCa}} \frac{[Na^+]_i}{[Na^+]_o} \times \frac{[Ca^{2+}]_i}{[Ca^{2+}]_o} - \frac{[Na^+]_i}{[Na^+]_o} \times \frac{[Ca^{2+}]_i}{[Ca^{2+}]_o} \\
&+ 1.0 + d_{\text{NaCa}} \frac{[Na^+]_i}{[Na^+]_o} \times \frac{[Ca^{2+}]_i}{[Ca^{2+}]_o} \\
\end{align*}
\]

\[
\begin{align*}
\text{TABLE 13. Intracellular Ion Concentrations: } & [Na^+]_i, [K^+]_i, \text{ and } [Ca^{2+}]_i \\
\frac{d[Na^+]}{dt} &= -I_{\text{Na}} + I_{\text{B}\text{Na}} + 3I_{\text{NaK}} + 3I_{\text{NaCa}} + \Phi_{\text{Na,mem}} \\
\frac{d[K^+]}{dt} &= \frac{I_{\text{in}} + I_{\text{K}} + I_{\text{F}} + I_{\text{Ca}} - 2I_{\text{NaK}}}{V_{\text{ol,F}}} \\
\frac{d[Ca^{2+}]}{dt} &= \frac{-I_{\text{b}} + I_{\text{b,Na}} + I_{\text{CaP}} - 2I_{\text{NaCa}} + I_{\text{Ca}} - I_{\text{d}}}{2.0 \cdot V_{\text{ol,F}}} \\
\frac{dO}{dt} &= 20.0 \frac{dO_{\text{TC}}}{dt} + 0.16 \frac{dO_{\text{TMG}}}{dt} + 0.045 \frac{dO}{dt} \\
I_{\text{b}} &= \left( [Ca^{2+}]_i - [Ca^{2+}] \right) \frac{2F \cdot Vol_{\text{f}}}{\tau_{\text{rel}}} \\
\end{align*}
\]

\[
\begin{align*}
\text{TABLE 14. Cleft Space Ion Concentrations: } & [Na^+]_c, [K^+]_c, \text{ and } [Ca^{2+}]_c \\
\frac{d[Na^+]}{dt} &= \frac{[Na^+]_o - [Na^+]_c}{\tau_{\text{ns}}} \\
&+ \frac{I_{\text{Na}} + I_{\text{B}\text{Na}} + 3I_{\text{NaK}} + 3I_{\text{NaCa}} + \Phi_{\text{Na,mem}}}{V_{\text{ol,F}}} \\
\frac{d[K^+]}{dt} &= \frac{[K^+]_o - [K^+]_c}{\tau_{\text{k}}} \\
&+ \frac{I_{\text{in}} + I_{\text{K}} + I_{\text{F}} + I_{\text{Ca}} - 2I_{\text{NaK}}}{V_{\text{ol,F}}} \\
\frac{d[Ca^{2+}]}{dt} &= \frac{[Ca^{2+}]_o - [Ca^{2+}]_c}{\tau_{\text{ca}}} \\
&+ \frac{I_{\text{CaL}} + I_{\text{b,Na}} + I_{\text{CaP}} - 2I_{\text{NaCa}}}{2.0 \cdot V_{\text{ol,F}}} \\
\end{align*}
\]

\[
\begin{align*}
\text{TABLE 15. Intracellular Ca^{2+} Buffering} \\
\frac{dO_{\text{C}}}{dt} &= 200.0 \times [Ca^{2+}]_i (1.0 - O_{\text{C}}) - 476.0O_{\text{C}} \\
\frac{dO_{\text{TC}}}{dt} &= 78400.0 \times [Ca^{2+}]_i (1.0 - O_{\text{TC}}) - 392.0O_{\text{TC}} \\
\frac{dO_{\text{TMG}}}{dt} &= 200000.0 \times [Ca^{2+}]_i (1.0 - O_{\text{TMG}}) - 6.6O_{\text{TMG}} \\
\frac{dO_{\text{TMG}}}{dt} &= 666.0O_{\text{TMG}} \\
\end{align*}
\]

\[
\begin{align*}
\text{TABLE 16. Ca^{2+} Handling by the Sarcoplasmic Reticulum} \\
I_{\text{up}} &= I_{\text{up}} \frac{[Ca^{2+}]_i/k_{\text{yec}} - k_{\text{yec}} [Ca^{2+}]_i/k_{\text{yec}}}{[Ca^{2+}]_i} \\
I_{\text{rel}} &= \alpha_{\text{rel}} \left( \frac{F_3}{F_2 + 0.25} \right)^2 \left( [Ca^{2+}]_i - [Ca^{2+}] \right) \\
\frac{dO_{\text{Cabr}}}{dt} &= 480.0 \times [Ca^{2+}]_i (1.0 - O_{\text{Cabr}}) - 400.0O_{\text{Cabr}} \\
\frac{d[Ca^{2+}]_i}{dt} &= \frac{I_{\text{up}} - I_{\text{rel}}}{2 \cdot V_{\text{ol,F}}} \\
\frac{dO_{\text{Cabr}}}{dt} &= \frac{I_{\text{up}} - I_{\text{rel}}}{2 \cdot V_{\text{ol,F}}} \\
\frac{dF_3}{dt} &= r_{\text{rec}} (1.0 - F_1 - F_2) - r_\text{f,F1} \\
\frac{dF_2}{dt} &= r_\text{f,F1} - r_\text{rel,F2} \\
r_{\text{rec}} &= 203.8 \left( \left( \frac{[Ca^{2+}]_i}{k_{\text{rel}}} \right)^4 + \frac{[Ca^{2+}]_i}{k_{\text{rel}}} \right) \\
r_{\text{rel}} &= 33.96 + 339.6 \left( \left( \frac{[Ca^{2+}]_i}{k_{\text{rel}}} \right)^4 + \frac{[Ca^{2+}]_i}{k_{\text{rel}}} \right)
\end{align*}
\]
TABLE 17. Parameter Values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\text{Na}^+]_o$</td>
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</tr>
<tr>
<td>$[\text{K}^+]_i$</td>
<td>5.4 mmol/L</td>
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</tr>
<tr>
<td>$[\text{Ca}^{2+}]_i$</td>
<td>1.8 mmol/L</td>
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</tr>
<tr>
<td>$E_{\text{Clabs}}$</td>
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</tr>
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<td>$k_0$</td>
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<td>$R$</td>
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<td>$T$</td>
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<td>$F$</td>
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</tr>
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<td>$C_m$</td>
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<td>$V_{0l}$</td>
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</tr>
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<td>$\tau_f$</td>
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<td>$\tau_a$</td>
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</tr>
<tr>
<td>$\tau_t$</td>
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<td>$\tau_{C}$</td>
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<td>$\tau_{H}$</td>
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<td>$\tau_{Ca}$</td>
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<tr>
<td>$\tau_{Ca}$</td>
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TABLE 18. Maximum Conductance Values

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<th>Parameter</th>
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<tr>
<td>$p_{Na}$</td>
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<td>$p_{Ca}$</td>
<td>6.75 nS</td>
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<td>$p_{K}$</td>
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<tr>
<td>$p_{A}$</td>
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<td>$p_{C}$</td>
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</tr>
<tr>
<td>$p_{Ca}$</td>
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TABLE 19. Initial Conditions

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</tr>
<tr>
<td>$[\text{K}^+]_i$</td>
<td>5.3581 mmol/L</td>
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<tr>
<td>$[\text{Ca}^{2+}]_i$</td>
<td>1.8147 mmol/L</td>
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<tr>
<td>$[\text{Na}^+]_o$</td>
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<td></td>
</tr>
<tr>
<td>$[\text{K}^+]_i$</td>
<td>129.4505 mmol/L</td>
<td></td>
</tr>
<tr>
<td>$[\text{Ca}^{2+}]_i$</td>
<td>6.7290 $\times 10^{-3}$ mmol/L</td>
<td></td>
</tr>
<tr>
<td>$[\text{Ca}^{2+}]_i$</td>
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<td>$p_{Na}$</td>
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<td>$h$</td>
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<tr>
<td>$b$</td>
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</tr>
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<td>$d$</td>
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<tr>
<td>$f_a$</td>
<td>0.9986</td>
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</table>

All simulations were performed by forward integration of the coupled system of differential equations using the CVODE solver package for ordinary differential equations. CVODE was developed by S.D. Cohen and A.C. Hindmarsh at Lawrence Livermore National Laboratories, Livermore Calif. Sufficient accuracy was ensured by adjusting the temporal step size of the integration so that the local error in all state variables (as estimated by the CVODE algorithm) satisfied a relative error bound. Computer programs for the simulations were written in the C programming language under the UNIX operating system. Simulations were performed on Sun Microsystems Sparc workstations (Sparc 2, IPX) and on a Micron Millennia Pentium 166 PC running the Linux operating system. At a stimulus frequency of 1 Hz, one cycle (i.e., 1 s of data) requires ~0.9 s of CPU time on the Pentium 166 platform.

Appendix 2: Sensitivity Analysis

This Appendix contains a brief derivation of the method used to study the parameter sensitivity of the action potential waveform. The reader is referred to Reference 53 for more detailed information.

Starting from a system of the general form,

$$\frac{dx}{dt} = f(x, \alpha, t)$$

we take the partial derivative of Equation 1 with respect to a parameter $\alpha_i$ to obtain the following equation:

$$\frac{\partial}{\partial \alpha_i} \left( \frac{dx}{dt} \right) = \frac{\partial}{\partial \alpha_i} f(x, \alpha, t) = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \cdots & \frac{\partial f_1}{\partial x_N} \\
\vdots & \ddots & \vdots \\
\frac{\partial f_N}{\partial x_1} & \cdots & \frac{\partial f_N}{\partial x_N} \end{bmatrix} \begin{bmatrix} \frac{\partial x_1}{\partial \alpha_i} \\
\vdots \\
\frac{\partial x_N}{\partial \alpha_i} \end{bmatrix}$$

$$J_k^f \frac{\partial x}{\partial \alpha_i} + \frac{\partial f}{\partial \alpha_i}$$

The time derivative of the state vector $x(\alpha, t)$ can be written as follows:

$$\frac{dx}{dt} x(\alpha, t) = J_k^f \frac{\partial x}{\partial \alpha_i} + \frac{\partial x(\alpha, t)}{\partial t} = \frac{\partial x}{\partial t} x(\alpha, t)$$

where the time derivative of $x$ vanishes, since all parameters are assumed to be time invariant. Thus, from Equation 1, we have the following:

$$\frac{\partial}{\partial \alpha_i} \left( \frac{\partial x}{\partial t} \right) = J_k^f \frac{\partial x}{\partial \alpha_i} + \frac{\partial f}{\partial \alpha_i}$$

Interchanging the order of integration, we obtain the following equation:

$$\frac{\partial}{\partial \alpha_i} \left( \frac{\partial x}{\partial t} \right) = \frac{\partial}{\partial t} \epsilon_i = J_k^f \frac{\partial x}{\partial \alpha_i} + \frac{\partial f}{\partial \alpha_i}$$

where $\epsilon_i$ is the sensitivity of the state $x$ to the parameter $\alpha_i$, i.e.,

$$\epsilon_i = \frac{\partial}{\partial t} x(\alpha, t)$$

Note, finally, that Equation 5 defines a costate system\(^{13}\) of the same general form as Equation 1, i.e.,

$$\frac{\partial}{\partial t} \epsilon_i = f_i(\alpha, x, t)$$

where

$$f_i(\alpha, x, t) = J_k^f \frac{\partial x}{\partial \alpha_i} + \frac{\partial f}{\partial \alpha_i}$$

The costate system for each parameter of interest can be integrated along with the original system, yielding the desired sensitivity functions.
Glossary

$I_{\text{Na}}$ Na$^+$ current

$I_{\text{Ca,L}}$ L-type Ca$^{2+}$ current

$I_{\text{K}}$ Transient outward K$^+$ current

$I_{\text{K,R}}$ Sustained outward K$^+$ current

$I_{\text{K,S}}$ Slow delayed rectifier K$^+$ current

$I_{\text{K,D}}$ Inwardly rectifying K$^+$ current

$I_{\text{Na,NO}}$ Background Na$^+$ current

$I_{\text{Ca,O}}$ Background Ca$^{2+}$ current

$I_{\text{Na,K}}$ Na$^+$-K$^+$ pump current

$I_{\text{Ca,P}}$ Sarcolemmal Ca$^{2+}$ pump current

$I_{\text{Na,E}}$ Na$^+$-Ca$^{2+}$ exchange current

$\Phi_{\text{Na,em}}$ Electroneutral Na$^+$ influx

$I_{\text{K}}$ Ca$^{2+}$ diffusion current from the diffusion-restricted subsarcolemmal space to the cytosol

$I_{\text{sp}}$ Sarcoplasmic reticulum Ca$^{2+}$ uptake current

$I_{\text{sp}}$ Sarcoplasmic reticulum Ca$^{2+}$ translocation current (from uptake to release compartment)

$I_{\text{sl}}$ Sarcoplasmic reticulum Ca$^{2+}$ release current

$[\text{Na}^+]_b$ Na$^+$ concentration in bulk (bathing) medium

$[\text{K}^+]_b$ K$^+$ concentration in bulk (bathing) medium

$[\text{Ca}^{2+}]_b$ Ca$^{2+}$ concentration in bulk (bathing) medium

$[\text{Na}^+]_c$ Na$^+$ concentration in the extracellular cleft space

$[\text{K}^+]_c$ K$^+$ concentration in the extracellular cleft space

$[\text{Ca}^{2+}]_c$ Ca$^{2+}$ concentration in the extracellular cleft space

$[\text{Na}^+]_{\text{int}}$ Na$^+$ concentration in the intracellular medium

$[\text{K}^+]_{\text{int}}$ K$^+$ concentration in the intracellular medium

$[\text{Ca}^{2+}]_{\text{int}}$ Ca$^{2+}$ concentration in the intracellular medium

$[\text{Mg}^{2+}]_{\text{int}}$ Mg$^{2+}$ concentration in the intracellular medium

$[\text{Ca}^{2+}]_{\text{dl}}$ Ca$^{2+}$ concentration in the restricted subsarcolemmal space

$[\text{Ca}^{2+}]_{\text{sp}}$ Ca$^{2+}$ concentration in the sarcoplasmic reticulum uptake compartment

$[\text{Ca}^{2+}]_{\text{sl}}$ Ca$^{2+}$ concentration in the sarcoplasmic reticulum release compartment

$E_{\text{Na}}$ Equilibrium (Nernst) potential for Na$^+$

$E_{\text{K}}$ Equilibrium (Nernst) potential for K$^+$

$E_{\text{Ca}}$ Equilibrium (Nernst) potential for Ca$^{2+}$

$E_{\text{Ca,app}}$ Apparent reversal potential for $I_{\text{Ca,L}}$ (differs from $E_{\text{Ca}}$)

$P_{\text{Na}}$ Permeability for $I_{\text{Na}}$

$g_{\text{Ca,L}}$ Maximum conductance for $I_{\text{Ca,L}}$

$g_{\text{K}}$ Maximum conductance for $I_{\text{K}}$

$g_{\text{Na,K}}$ Maximum conductance for $I_{\text{Na,K}}$

$g_{\text{K,S}}$ Maximum conductance for $I_{\text{K,S}}$

$g_{\text{K,D}}$ Maximum conductance for $I_{\text{K,D}}$

$g_{\text{Na,NO}}$ Maximum conductance for $I_{\text{Na,NO}}$

$g_{\text{Ca,O}}$ Maximum conductance for $I_{\text{Ca,O}}$

$m$ Activation gating variable for $I_{\text{Na}}$

$h_{1,2}$ Fast and slow inactivation gating variables for $I_{\text{Na}}$

$d_{1}$ Activation gating variable for $I_{\text{Ca,L}}$

$f_{1,2}$ Fast and slow inactivation gating variables for $I_{\text{Ca,L}}$

$f_{\text{Ca}}$ [Ca$^{2+}]_0$-dependent ratio of fast ($f_1$) to slow ($f_2$) inactivation of $I_{\text{Ca,L}}$

$k_{\text{Ca}}$ Half-maximum Ca$^{2+}$ binding concentration for $I_{\text{Ca,L}}$

$r$ Activation gating variable for $I_{\text{K}}$

$s$ Inactivation gating variable for $I_{\text{K}}$

$s_{1,2}$ Rapidly and slowly recovering inactivation gating variables for $I_{\text{K}}$

$t_{\text{ms}}$ Activation gating variable for $I_{\text{ms}}$

$s_{\text{ms}}$ Inactivation gating variable for $I_{\text{ms}}$

$v$ Activation gating variable for $I_{\text{K}}$

$p$ Inactivation gating variable (instantaneous) for $I_{\text{K}}$

$m, h_1, \ldots$ Steady-state value of $m$, $h_1$, etc

$F_1$ Relative amount of “inactive precursor” in the $I_{\text{Na}}$ formulation

$F_2$ Relative amount of “activator” in the $I_{\text{Na}}$ formulation

$\tau_{h_1, h_2}$ Fast and slow inactivation time constants for $I_{\text{Na}}$

$\tau_1$ Activation time constant for $I_{\text{Na}}$

$\tau_1$ Activation time constant for $I_{\text{Ca,L}}$

$\tau_{h_1, h_2}$ Fast and slow inactivation time constants for $I_{\text{Ca,L}}$

$\tau_1$ Activation time constant for $I_{\text{Ca,L}}$

$\tau_{h_1, h_2}$ Rapidly and slowly recovering inactivation time constants for $I_{\text{K}}$

$\tau_{h_1, h_2}$ Activation time constant for $I_{\text{K}}$

$\tau_1$ Activation time constant for $I_{\text{K}}$

$\tau_1$ Activation time constant for $I_{\text{K}}$

$\tau_1$ Activation time constant for $I_{\text{K}}$

$O$ Buffer occupancy

$O_C$ Fractional occupancy of the calmodulin buffer by Ca$^{2+}$

$O_{TC}$ Fractional occupancy of the troponin-Ca$^{2+}$ buffer by Ca$^{2+}$

$O_{TMBG}$ Fractional occupancy of the troponin-Mg$^{2+}$ buffer by Ca$^{2+}$

$O_{TMBG}$ Fractional occupancy of the troponin-Mg$^{2+}$ buffer by Mg$^{2+}$

$O_{Calse}$ Fractional occupancy of the calsequestrin buffer (in the sarcoplasmic reticulum release compartment) by Ca$^{2+}$

$R$ Universal gas constant

$T$ Absolute temperature

$F$ Faraday’s constant

$C_{\text{mem}}$ Membrane capacitance

$V$ Membrane voltage

$V_{\text{el}}$ Volume of the extracellular cleft space

$V_{\text{ols}}$ Total cytosolic volume

$V_{\text{d}}$ Volume of the diffusion-restricted subsarcolemmal space

$V_{\text{sp}}$ Volume of the sarcoplasmic reticulum uptake compartment

$V_{\text{sl}}$ Volume of the sarcoplasmic reticulum release compartment
Repolarization in a Model of a Human Atrial Cell

\[ \tau_{Na}, \tau_K, \tau_C \]

\[ \tau_D \]

Time constant of diffusion of Na\(^{+}\), K\(^{+}\), and Ca\(^{2+}\) from the bulk medium to the extracellular cleft space

\[ \tau_{Ik} \]

Time constant of diffusion from the restricted subsarcomemmal space to the cytosol

\[ \bar{I}_{Na,K} \]

Maximum Na\(^{+}\)-K\(^{+}\) pump current

\[ k_{Na,K} \]

Half-maximum K\(^{+}\) binding concentration for \( I_{Na,K} \)

\[ k_{Na,K,Na} \]

Half-maximum Na\(^{+}\) binding concentration for \( I_{Na,K} \)

\[ I_{Ca} \]

Maximum Ca\(^{2+}\) pump current

\[ k_{Ca} \]

Half-maximum Ca\(^{2+}\) binding concentration for \( I_{Ca} \)

\[ k_{Na} \]

Scaling factor for \( I_{Na} \)

\[ \gamma \]

Position of energy barrier controlling voltage dependence of \( I_{Na} \)

\[ d_{Na,Ca} \]

Denominator constant for \( I_{Na,Ca} \)

\[ I_{op} \]

Maximum sarcoplasmic reticulum uptake current

\[ k_{sys} \]

Half-maximum binding concentration for [Ca\(^{2+}\)] to \( I_{op} \)

\[ k_{sys} \]

Half-maximum binding concentration for [Ca\(^{2+}\)] to \( I_{op} \)

\[ k_{rel} \]

Ratio of forward to back reactions for \( I_{op} \)

\[ \tau_L \]

Time constant of diffusion (“translocation”) of Ca\(^{2+}\) from sarcoplasmic reticulum uptake to release compartment

\[ \alpha_{rel} \]

Scaling factor for \( I_{rel} \)

\[ k_{rel} \]

Half-activation [Ca\(^{2+}\)]\(^{1/2}\) for \( I_{rel} \)

\[ k_{rel} \]

Half-activation [Ca\(^{2+}\)]\(^{1/2}\) for \( I_{rel} \)

\[ t_{recov} \]

Recovery rate constant for the sarcoplasmic reticulum release channel

\[ 7. \quad \text{Rasmusson RL, Clark JW, Giles WR, Shibata EF, Campbell DL. A mathematical model of a bullfrog cardiac pacemaker cell. Am J Physiol. 1990;259:H352–H369.} \]

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