Computer models of canine ventricular action potentials

The mHR model is described by 30 ordinary differential equations (ODEs): one equation describing $V_m$, six equations describing sarcoplasmic and sarcoplasmic-reticulum ion concentrations and 23 equations describing channel gating. Unless otherwise noted, all equations and parameter values are identical to those in the HR model\(^1\) (note that variable initial conditions can be found online at rudylab.wustl.edu).

All computations were done using the MATLAB\(^\circledR\) mathematical programming environment (see www.mathworks.com). Code was written that preserved accuracy and avoided computational singularities, cf., in the evaluation of $z/(e^z - 1)$ when $|z| \approx 0$.

Two programs were written: one simulating an isolated myocyte (membrane model), and one simulating a one-dimensional ring of ventricular tissue (propagated model).

Numerical solution of the membrane model

The mHR-model ODEs are stiff, with time constants of $I_{Na}$ being $< 1$ ms, while time constants of changes in sarcoplasmic concentrations being $> 10$ s. Integration of the equations was performed using the MATLAB\(^\circledR\) library routine ode15s, a program that excels in solving stiff initial-value problems. The program is an adaptive algorithm that automatically adjusts integration time increments to maintain a relative tolerance of better than $10^{-3}$, or an absolute tolerance of better than $10^{-6}$.
Action potentials were elicited by imposing a brief (typically 0.5-ms) depolarizing current pulse (typically $-100 \, \mu A/\mu F$) at time $t = 0$. After any change in a model parameter or condition, the model was “paced” (1 Hz) to a steady state, whereby equation values following a pacing cycle were supplied as initial conditions to the next cycle. Pacing to a steady state, as assessed by successive identical voltage traces, typically required between 40 and 100 cycles.

Supplement Figure 1 shows membrane model action potentials comparing the HR and mHR models, with action potentials elicited by a $-80 \, \mu A/cm^2$ current pulse of 1 ms duration. The action potentials superimpose. The midpoint of $h_n j_v$ in the HR model occurs at $-70.3 \, mV$, while in the mHR model, the midpoint was shifted to $-74.0 \, mV$, a value more typical for a normal ventricular myocyte (see Table 1A). The two plots superimpose when the maximum Na$^+$ conductance $\bar{g}_{Na}$ was increased by 15% from 8.25 mS/$\mu F$ (HR) to 9.49 mS/$\mu F$ (mHR), reflecting the fact that the 3.7-mV left-shift in the $h_n j_v$ curve resulted in slightly less inward Na$^+$ current. In both models, $\dot{V}_{max}$ was 193 V/s, a value less than is seen experimentally where typical values are closer to ~300 V/s. As such, in subsequent simulations using the mHR model, we increased $\bar{g}_{Na}$ by and additional 50% to 14.2 mS/$\mu F$, which produced a $\dot{V}_{max}$ of 289 V/s. Finally, the inset of Figure 1 compares the two superimposed action potentials quantitatively (see legend for description of the symbols).

Numerical solution of the propagated model
To determine conduction velocity and to investigate action-potential shape and duration of a propagating action potential, the 30 ODEs describing the membrane action potential were inserted into the cable equation, which resulted in a partial differential equation describing membrane potential as a function of time ($t$) and one-dimensional space ($x$):

$$\frac{\partial V_m}{\partial t} = \frac{1}{S_V R_a C_m} \frac{\partial^2 V_m}{\partial x^2} - \frac{I_m(x)}{C_m}. \quad (1)$$

$S_V$ is the cell surface-to-volume ratio and was set to 4037 cm$^2$/cm$^3$, the ratio of capacitive membrane area ($A_{cap}$) to cell volume ($V_{cell}$) reported for the HR model. $R_a$ is the axial resistance and was set to 280 $\Omega$cm, a value intermediated between values measured in different myocardial preparations ranging from 180 $\Omega$cm to 470 $\Omega$cm.$^{2-4}$ Note that $R_a$ reflects not only the sarcoplasmic resistivity (~100 $\Omega$cm), but also the resistance through gap junctions. $C_m$ is the cell membrane capacitance, and $I_m$ is the total membrane ionic current generated by the membrane action potential. Although the model computes values for some sarcoplasmic ion concentrations, it was assumed that the axial currents during a propagating action potential result in negligible changes in intracellular solute composition.

The geometry of the interconnected fibers used in our solution of Supplement equation (1) consists of a closed one-dimensional ring of electrically coupled cells with circumference $\ell$, and this results in the (Dirichlet) boundary condition $V(x=0) = V(x=\ell)$. The ring is broken into discrete segments (nodes), each with length significantly less than the resting length constant. We used 101 nodes of length $\Delta x = 0.02$ cm, for a total circumference $\ell = 2.02$ cm. The membrane action potential in each node is described
by the 30 ODEs discussed above, resulting in a total of $101 \times 30 = 3030$ equations that must be integrated.

Integration of Supplement equation (1) was done using Strang splitting\(^6\), an algorithm that integrates the diffusion equation using the Crank-Nicolson method\(^5\), coupled with a two-point Runge-Kutta algorithm\(^5\) for integrating the membrane model at each node. The combined algorithm is “second order” both in time and space. We verified the accuracy of the algorithm by comparing results computed with $\Delta t = 0.005$ ms with the same integration with $\Delta t = 0.002$ ms. To improve computational speed, we pre-computed a look-up table for all model equations that were time independent ($V_m$ resolution of 0.001 mV).

Initial conditions for each of the 101 nodes of the ring were set to values determined by pacing the membrane model to steady state. Action potentials were initiated at time $t = 0$ using a brief (typically 0.5 ms) depolarizing current pulse (typically $-200 \mu A/\mu F$) applied simultaneously at nodes 1 and 101. This produced two propagating action potentials in the ring: one propagating in the clockwise direction from nodes 1 to 50 (0 to 1 cm), and the other propagating in the counterclockwise direction from nodes 101 to 50 (2.02 to 1 cm).

Supplement Figure 2 shows propagating action potentials (midpoint of $h, j_e$ at $-74.0$ mV and $g_{Na}$ equal to 14.2 mS/\mu F) where $V_m(x)$ is plotted as a function of time at the following distances ($x$): 0, 0.2, 0.4, 0.6, 0.8 and 1.0 cm (left to right, respectively). The action potential at 0 cm (leftmost trace) is distorted by the depolarizing current pulse. The action potential at 1.0 cm (rightmost trace) is distorted due to the “collision” of the two action potentials arriving from the clockwise and counterclockwise directions;
the resulting larger axial current thus elicits a larger inward current. At distances between 0.2 cm and 0.8 cm (and between 1.8 cm and 1.2 cm, not shown), the action potentials appear nearly identical in shape, reflecting uniform conduction at these regions of the tissue ring. This is also seen in the inset to Supplement Figure 2, which shows the “foot” of the propagating action potential at 0.6 cm plotted in an expanded time scale; one observes the expected exponentially rising potential as the axial current charges \( C_m \). Conduction velocity was computed from the difference of the times at peak amplitude measured at 0.4 cm and 0.6 cm, and equals 46.0 cm/s.

**References**


Figure Legends:

Figure 1. Two steady-state action potentials (paced at 1 Hz) comparing the HR and mHR models. The two plots superimpose. Inset: $APD_{90}$ action-potential onset time to 90% repolarization; $APO$, overshoot potential; $APA$, action-potential amplitude; $EDP$, end-diastolic potential; $V_{\text{max}}$, maximum upstroke velocity; $h_{\text{midpt.}}$, potential where $h_x, j_x$ equals 0.5; $g_{Na}$, maximum Na$^+$ conductance.

Figure 2. Propagating action potentials in mHR model showing $V_m(x)$ at distances 0, 0.2, 0.4, 0.6, 0.8 and 1.0 cm (left to right). The action potentials are elicited by a brief depolarizing current pulse administered at nodes 1 and 101 (0 and 2.02 cm) at time $t = 0$. Inset: action potential at 0.6 cm plotted on an expanded time scale (10–15 ms). Conduction velocity is 46.0 cm/s.
Supplement Figure 1

- $V_m$ (mV)
- time (ms)
- $\dot{V}_{max}$
- hj midpt.
- $\bar{g}_N$ (mS/\mu F)

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