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THE LUO-RUDY MODEL OF CARDIAC ACTION POTENTIAL: COMPUTER IMPLEMENTATION AND CONTROLLABILITY

B. S. Billett
B. Y. Kogan

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Abstract

Recent advances in single cell and single channel recording techniques have lead to the generation of more accurate descriptions of cardiac muscle cell ion channel kinetics, and the development of a new mathematical model of its action potential, the Luo and Rudy model. In order to study the propagation effects of drugs by spatial simulations, it is first necessary to develop a means to control some characteristics of action potential given by this model. Presented here are the results of computer implementation, validation, and controllability experiments of the Luo–Rudy model of cardiac action potential.

DESCRIPTION OF THE MODEL

One of the most recent and complete mathematical models for the membrane action potential of myocardium was published by Luo and Rudy [1] (hereafter referred to as the Luo–Rudy or L-R model). Based on the Hodgkin and Huxley [2] paradigm for action potential, this model updates the widely accepted and used Beeler–Reuter model [3] by incorporating more accurate ionic descriptions from the Ebijara–Johnson model [4], and the most recent available quantitative data from single cell and single channel experiments. Although, the model does not explicitly include some aspects of action potential, including the active sodium ion pump, it is now considered the most complete and accurate model available.

The important improvements from the Beeler–Reuter model include more accurate fast inward sodium ion and outward potassium ion kinetics. Also new is the facility for specifying the extracellular potassium ion concentration – $[K]_o$. The sodium channel modifications are particularly important because of the effect on the action potential depolarization and upstroke ($\dot{E}_{max}$, which influences propagation characteristics.

The L-R model is generally based upon the Hodgkin–Huxley type formalism. The rate of change of action potential is given by the equation:

$$dE/dt = -(1/C)(I_i + I_{stim}) \tag{1}$$

where E is the membrane potential, C is the membrane capacitance, I_{st} is a stimulus current, and I_i is the sum of ionic currents into the cell.

In order to explain and characterize changing ion kinetics, ion "gates" – variables that determine conductance of the membrane to specific ions, are used. These gating variables are determined by a system of coupled nonlinear ordinary differential equations. Each ion channel uses one or more gating variables to match the kinetics of real experimental data. Each channel is described by a differential equation of the form:

$$dy/dt = (y_\infty - y)/\tau_y \tag{2}$$

where

$$\tau_y = 1/(\alpha_y + \beta_y) \tag{3}$$

and

$$y_\infty = \frac{\alpha_y}{\alpha_y + \beta_y} \tag{4}$$

here y is the gating variable, τ_y is its time constant, and α_y and β_y are "opening" and "closing" rate constants, which are functions of E.

The Luo–Rudy model includes six ionic currents:

I_{Na} – the fast sodium current

I_{si} – a slow inward current

I_K – the time dependent potassium current

I_{K1} – the time independent potassium current

I_{Kp} – the plateau potassium current

I_b – the background or leakage current

Below is the complete description of the model currents:

Fast sodium current:

$$I_{Na} = 23m^3hj(E - E_{Na}) \tag{5}$$

For $E \geq -40$mV:

$\alpha_h = \alpha_j = 0.0$

$\beta_h = 1/(0.13(1 + \exp[(E + 10.66)/-11.1]))$

$\beta_j = 0.3\exp(-2.535 \cdot 10^{-7}E)/(1 + \exp[-0.1(E + 32)]))$

For $E < -40$mV:

$\alpha_h = 0.135\exp[(80 + E)/-6.8]$

$\beta_h = 3.56\exp(0.079E) + 3.1 \cdot 10^5\exp(0.35E)$

$\alpha_j = ([-1.2714{\cdot}10^5 \exp(0.2444E) - 3.474{\cdot}10^5 \exp(-0.044E))(E+37.38))/(1+\exp[.311(E+79.23)])$

$\beta_j = (0.1212 \exp(-0.01052E))/(1 + \exp[-.1378(E + 40.14)])$

For all E:

$\alpha_m = [0.32(E + 47.13)]/[1 - \exp[-.1(E + 47.13)]]$

$\beta_m = 0.08 \exp(-E/11)$

Slow inward current:

$$I_{si} = 0.09df(E - E_{si}) \tag{6}$$

$E_{si} = 7.7 - 23.0287 \ln([Ca]_i)$

$\alpha_d = (.095 \exp[-.01(E - 5)])/(1 + \exp[-.072(E - 5)])$

$\beta_d = (.07 \exp[-.017(E + 44)])/(1 + \exp[.05(E + 44)])$

$\alpha_f = (.012 \exp[-.008(E + 28)])/(1 + \exp[.15(E + 28)])$

$\beta_f = (.0065 \exp[-.02(E + 30)])/(1 + \exp[-.2(E + 30)])$

Calcium uptake: $d([Ca]_i)/dt = -10^{-4} I_{si} + 0.07(10^{-4} - [Ca]_i)i$

Time dependent potassium current:

$$I_K = \bar{G}_K X X_i (E - E_K) \tag{7}$$

$\bar{G}_K = 0.282\sqrt{[K]_o/5.4}$

For $E > -100$mV: $X_i = 2.837[\exp(.04(E + 77)) - 1]/[(E + 77)\exp[.04(E + 35)]]$

For $E \leq -100$mV: $X_i = 1$

$\alpha_X = 1.02/(.083(E + 50))/(1 + \exp(.057(E + 50)))$

$\beta_X = .0013 \exp(-0.06(E + 20))/(1 + \exp(-0.04(E + 20)))$

Time independent potassium current:

$$I_{K1} = \bar{G}_{K1} K1_\infty (E - E_{K1}) \tag{8}$$

$\bar{G}_{K1} = 0.6047\sqrt{[K]_o/5.4}$

$\alpha_{K1} = 1.02/(1 + \exp(.2385(E - E_{K1} - 59.215)))$

$\beta_{K1} = (.49 \exp(.24(E - E_{K1} + 5.48)) + \exp .062(E - E_{K1} - 594.3)))/(1 + \exp(-.5143(E -$

$E_{K1} + 4.75)))$

Plateau potassium current:

$$I_{Kp} = 0.0183 K_p (E - E_{Kp}) \tag{9}$$

$E_{Kp} = E_{K1}$

$K_p = 1/(1 + \exp((7.488 - E)/5.98))$

Background current:

$$I_b = 0.03921(E + 59.87) \tag{10}$$

Total time independent potassium current:

$$I_{K1(T)} = I_{K1} + I_{Kp} + I_b \tag{11}$$

IMPLEMENTATION OF THE LUO–RUDY MODEL

The basic equations for the point model were implemented on a Sun-4 computer in C. The equations were solved numerically by one of several algorithms, including Euler, second and fourth order Runge–Kutta, and a recently developed special algorithm for mildly stiff differential equations, the Ashour–Hanna method [5].

Rest Potential

The rest potential across a membrane is based on the Nernst equation, which describes the equilibrium potential due to ionic concentrations on each side of the membrane. This equilibrium potential is also known as the reversal potential. In the Luo–Rudy model, the extracellular potassium concentration $[K]_o$ is a parameter of the model, which directly affects the rest potential of the cell (E_{rest}).

For the Luo–Rudy model, initial values of gating variables have already been approximated from experimental data. This eliminates initial contributions of all but the time

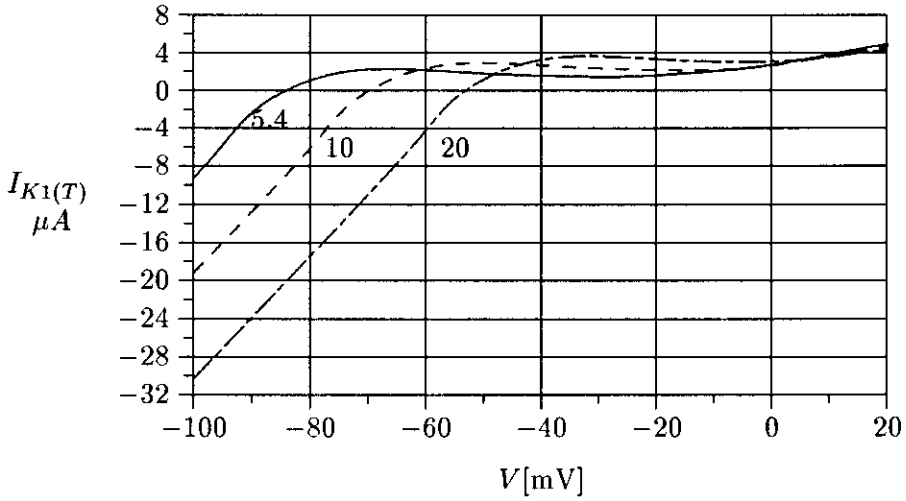

FIGURE 1. Current-voltage curves ($I_{K1(T)}$-E) for various $[K]_o$ levels: 5.4mM, 10mM, 20mM. E_{rest} is the solution to $I_{K1(T)} = 0$.

$[K]_o$	E_{K1}	E_{rest}
5.4	-87.25	-84.2
7.0	-80.37	-78.15
10.	-70.91	-69.76
15.	-60.16	-60.14
20	-52.53	-52.23

Table 1. Values of E_{rest} used as initial conditions for various levels of $[K]_o$.

independent potassium currents. Therefore, the rest potential can be approximated by solving the equation $I_{K1(T)} = 0$, where the total time independent potassium currents are zero. Figure 1 shows the current voltage characteristics for $[K]_o$. These curves were solved numerically by Newton's method to find E_{rest} for several values of $[K]_o$. For the normal value of $[K]_o$ = 5.4mM, $E_{rest} = -84.2$mV. Table 1 lists E_{rest} solutions for various levels of $[K]_o$.

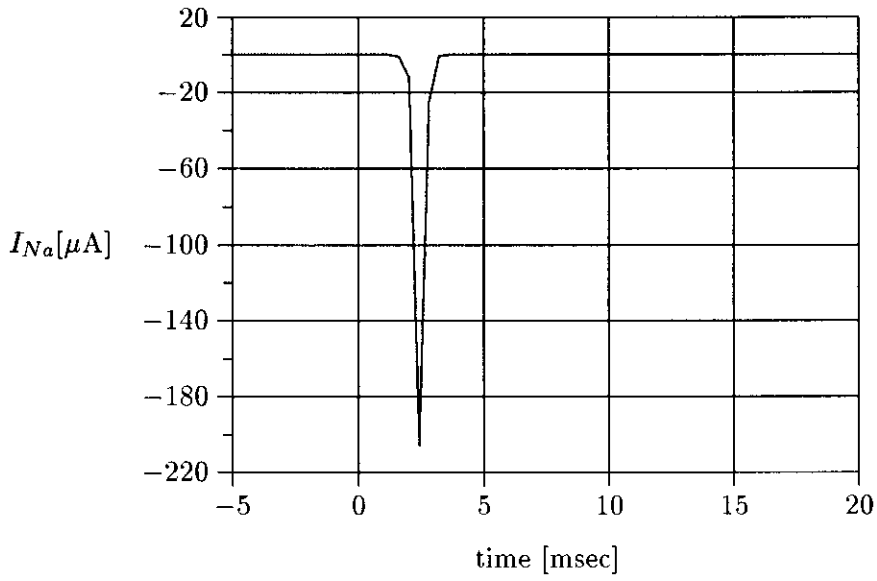

FIGURE 2. Sodium current (I_{Na}) generated by the Luo–Rudy model after $I_{stim} = -20\mu A$, $2msec$ is applied, and action potential results.

Sodium ion channel

The fast inward sodium current is responsible for the fast depolarization of the cell membrane. Since the reversal potential for sodium E_{Na} is much larger than the rest potential of the cell ($E_{Na} = 54.4$mV), sodium ions have a very strong tendency to enter the cell, and result in a fast inward current when the membrane becomes permeable to them, after the potential threshold is exceeded ("gating" variable > 0).

By first implementing only the sodium ion channel and background ion channel (necessary to balance currents), it was possible to check the accuracy of the implementation, as well as the separate effect of the sodium channel on the action potential. Figure 2 shows the time course of the fast inward sodium current $I_{stim} = -20\mu$A, for 2msec. Figure 3 shows the time course of an action potential resulting from only the effects of the sodium and background or leakage currents. The maximum rate of depolarization resulting from this inward current is $\dot{E}_{max} = 300$E/sec.

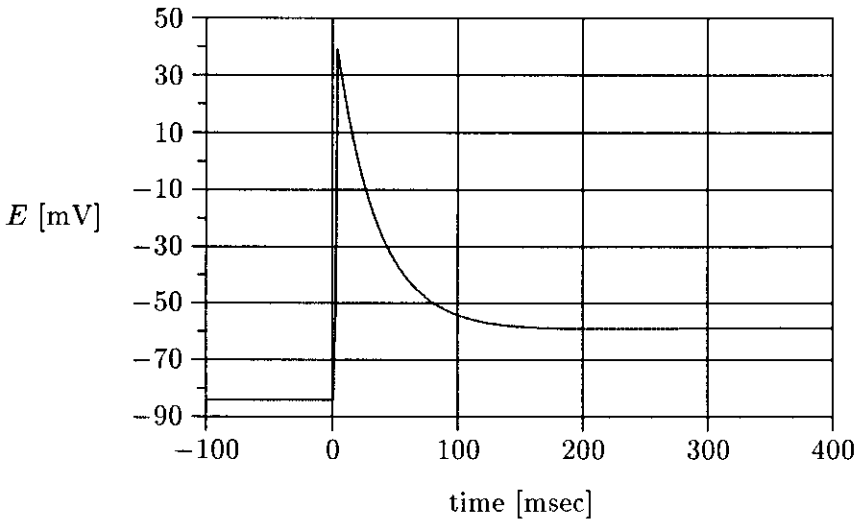

FIGURE 3. Action potential generated by the Luo–Rudy model by incorporating only the sodium and background currents, after $I_{stim} = -20\mu A$, $2msec$ is applied, and action potential results.

Potassium ion channel

The Luo–Rudy model divides the potassium current into three components, the time dependent potassium current I_K, the time independent potassium current I_{K1}, and the plateau potassium current I_{Kp}. By patch clamp experiments, Shibasaki [6] has hypothesized that the I_K channel is controlled by two gates, the time dependent X gate, and the time independent X_i gate. The Luo–Rudy model follows these suggestion, which are important in this work for the ability they provide for modifying the action potential duration and restitution characteristics. These potassium currents act to lengthen the action potential considerably by slowing repolarization process. Figure 4 shows the time course of the current I_K during a full action potential. When only the sodium, potassium, and leakage currents are summed in the model as I_i, it is possible to see their separated effects on the action potential, as shown in figure 5.

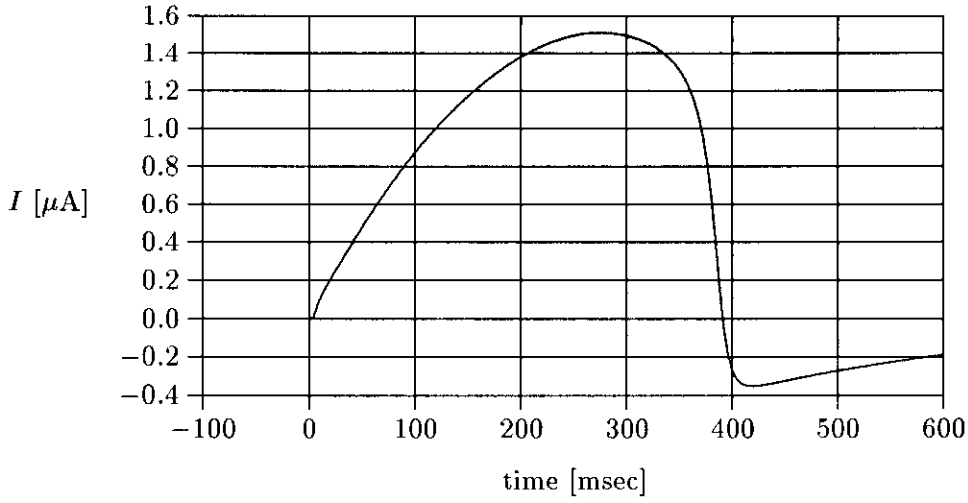

FIGURE 4. Time dependent potassium current I_K during full action potential in the Luo–Rudy model. $I_{stim} = -20\mu$A, duration 2msec.

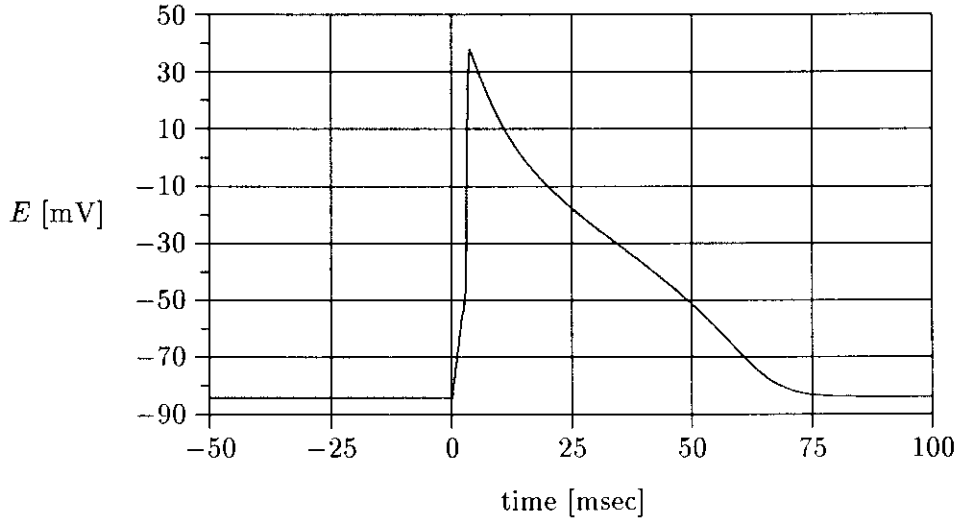

FIGURE 5. Action potential resulting from sodium I_{Na}, potassium I_K, I_{K1}, I_{Kp}, and leakage (background) currents I_b only in the Luo–Rudy model.

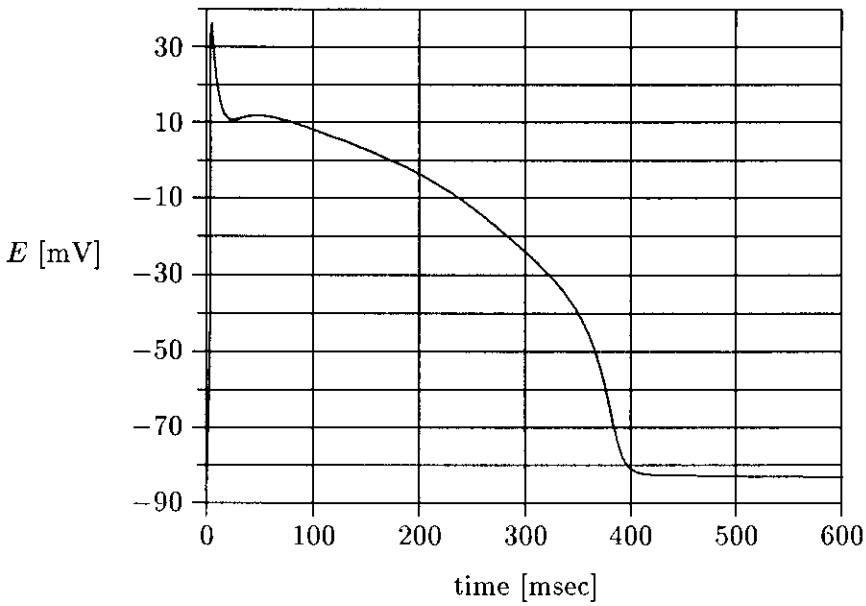

FIGURE 6. One normal action potential generated by the Luo–Rudy model. $I_{stim} = -20\mu A$, for 2.0msec

Normal action potential

Finally, by including the uptake of calcium ions into the cell $[Ca]_i$ and the so-called slow inward current (really a combination of several inward currents), one can obtain the complete action potential. As seen in figure 6, the calcium uptake accounts partly for the action potential "notch" immediately following the upstroke peak, and the slow inward current contributes to increasing the length of the action potential.

In specifying the action potential duration, the time difference between crossing the 10% point of the full action potential height on depolarization and repolarization is used. For the full action potential shown here, the action potential duration (APD) is measured to be 387.4 msec.

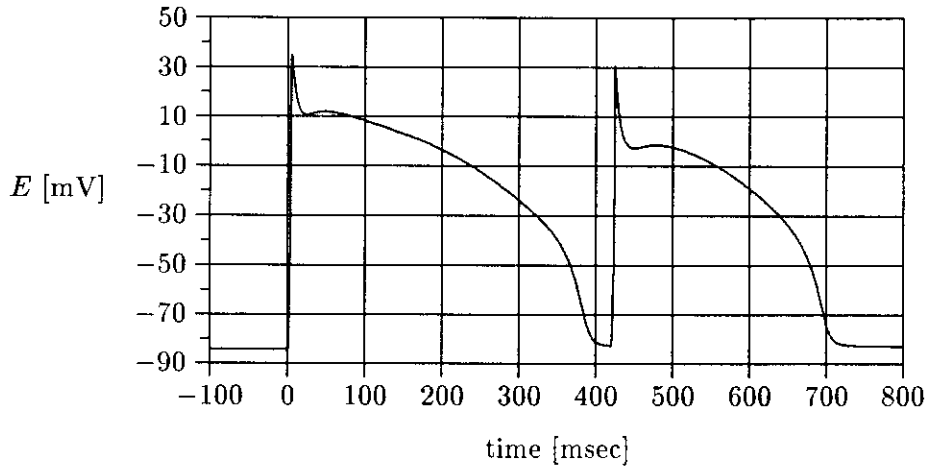

FIGURE 7. Two successive action potentials. I_{stim} = 20μA for both (S_1 and S_3), DI = 35msec

VALIDATION OF THE MODEL

Repeatable excitations

Cardiac action potentials exhibit a variety of important complex behaviors which must be reflected in the model for it to be useful and accurate. When repeated stimuli are presented to the membrane the action potential duration decreases depending on the cycle length or diastolic interval (DI), as described for the $\varepsilon 4$ modified FitzHugh–Nagumo model. Specifically, as the diastolic interval, or time between repolarization of one action potential, and the depolarization of the next one decreases, the action potential duration decreases. This is known as the action potential duration restitution (APDR). APDR has been linked to important phenomena including ventricular tachycardia/fibrillation [7, 8].

Figure 7 shows the time course of two action potentials ($S_1 - S_2$). I_{stim} for both action potentials is -20μA with duration of 2.0 msec. Here the DI is 35msec or T = 415msec. The first action potential duration APD_1 = 387msec, the second APD_2 = 284msec. Figure 8 shows the normal APDR curve produced by the Luo–Rudy model for stimulation period T of 200–1500msec (DI= 0–300msec).

Recently researchers have explored the importance of the $S_2 - S_3$ or double premature

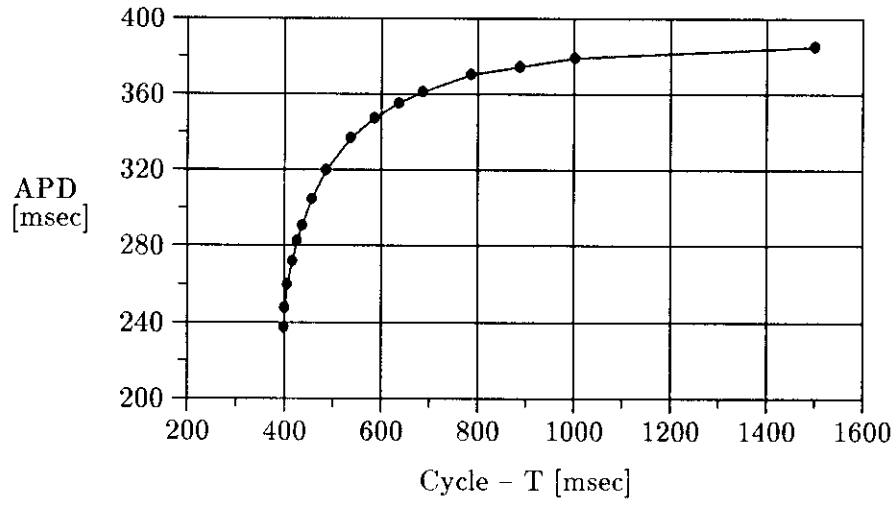

FIGURE 8. Normal action potential duration restitution curve for APD_2 for the Luo–Rudy model.

stimuli coupling interval [9]. In this experiment, the $S_1 - S_2$ diastolic interval is held constant, and the interval between the second and third action potentials is varied ($S_2 - S_3$). Figure 9 shows the difference between these two APDR curves. Here, the $S_1 - S_2$ interval is held constant at 50msec, while the $S_2 - S_3$ interval is varied from 50–700msec.

In the Luo–Rudy model, variations in the parameter $[K]_o$, which has a pronounced effect on the rest potential and action potential duration, should also have important effects on repeated excitations, including supernormal excitability [10]. Figure 10 shows the APDR curves for the actual values of APD and cycle time, for $[K_o]$ = 5.4, 7, 10mM. Figure 11 shows the same curves normalized for the original APD_1 values.

Strength–interval dependence

Related to the action potential duration restitution relationship is the strength–interval dependence. These two characteristics of action potential are the result of different elements of the cell's recovery properties. In the strength interval dependence, a phenomena which is known as rate–dependent block is characterized by the strength of applied stimuli, rather than by resulting action potential duration, as in APDR. At different rates of stimulation, or

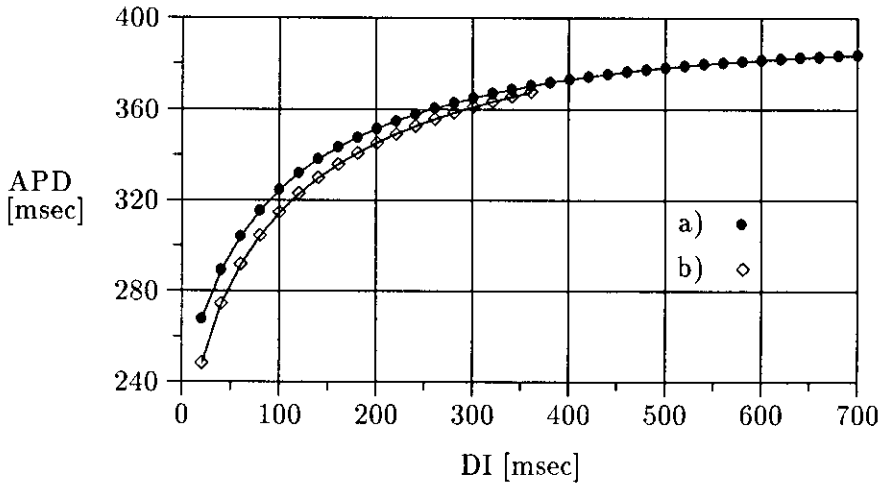

FIGURE 9. Action potential duration restitution curves. a) The standard $S_1 - S_2$ APDR where the interval is varied from 50–700msec. b) $S_1 - S_2$ is held constant at 50msec, $S_2 - S_3$ is varied from 50–700msec — shown is the APDR for the third action potential.

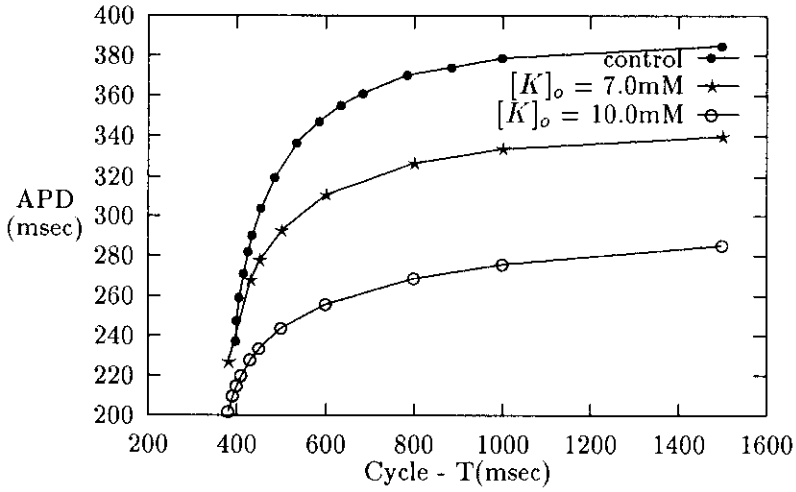

FIGURE 10. Comparison of APD restitution curves for normal ($[K]_o$ = 5.4mM) and ischemic ($[K]_o$ = 7,10mM). APD values and periods are absolute.

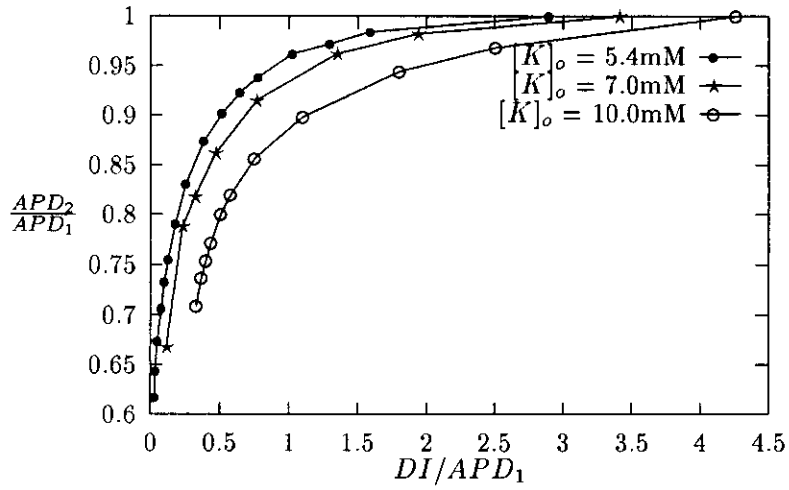

FIGURE 11. Comparison of APD restitution curves for normal ($[K]_o$ = 5.4mM) and ischemic ($[K]_o$ = 7,10mM). APD values and periods are normalized.

diastolic intervals, stimuli are applied until an action potential is produced. This establishes the critical value of stimulus current (threshold) at that rate or diastolic interval. As the stimulus is applied closer to the absolute refractory period of the action potential, the stimulus threshold approaches infinity. Figure 12 graphs this relationship as exhibited by simulation of the Luo–Rudy model. I_{stim} currents were applied for 2msec.

CONTROLLABILITY OF THE LUO–RUDY MODEL

Action potential duration

The model Luo–Rudy has been designed by carefully matching the results of numerous patch clamp experiments to quantitative representations of ion channel kinetics represented in the model. It is desirable to explore the effects of altered action potential duration, action potential duration restitution, and membrane excitability, while having no or minimized altering effects to the underlying ion channel kinetics.

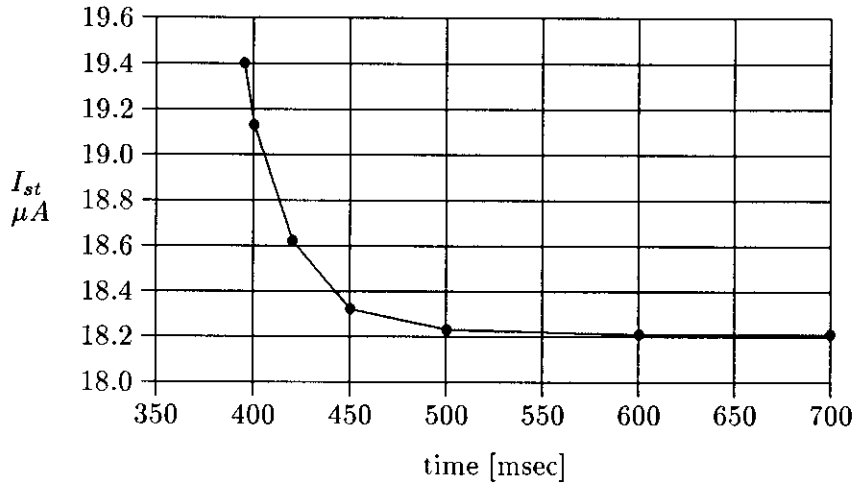

FIGURE 12. Strength–interval relationship in the Luo–Rudy model. I_{stim} applied for 2msec.

This section outlines a method and results for controlling these macro characteristics of the Luo–Rudy model, so as to match experimental data from drug intoxicated preparations, and simulate action potential behavior. Eventually this method will allow higher dimensional simulation of these effects.

The most obvious characteristic of action potential to control is the action potential duration (maximum). It is important, however, to minimize the impact on underlying ion channel kinetics and keep the exponential nature of the APDR curve unchanged.

To accomplish this goal, a variable parameter ϕ_{xi} was inserted into the equation 7 for time dependent potassium current. This current is partly responsible for the repolarization phase of the action potential, so it is a logical choice to modify. The membrane conductance to potassium $\bar{G}_K$ is controlled by two gating variables, the time dependent activation X, and the time independent inactivation gate X_i. It is the inactivation that controls repolarization of the membrane. By experimentation, it was found that the optimal new equation for X_i including the new parameter ϕ_{xi} is for $E > -100\text{mV}$:

$$X_i = \frac{2.837e^{[0.04(E+77)]-1}}{(E+77)e^{[0.04(E+\phi_{xi}35)]}} \tag{12}$$

and $X_i = 1$ for $E \leq -100\text{mV}$.

Figure 13 shows action potential duration results for ϕ_{xi} values of 0–1, and a linear fit

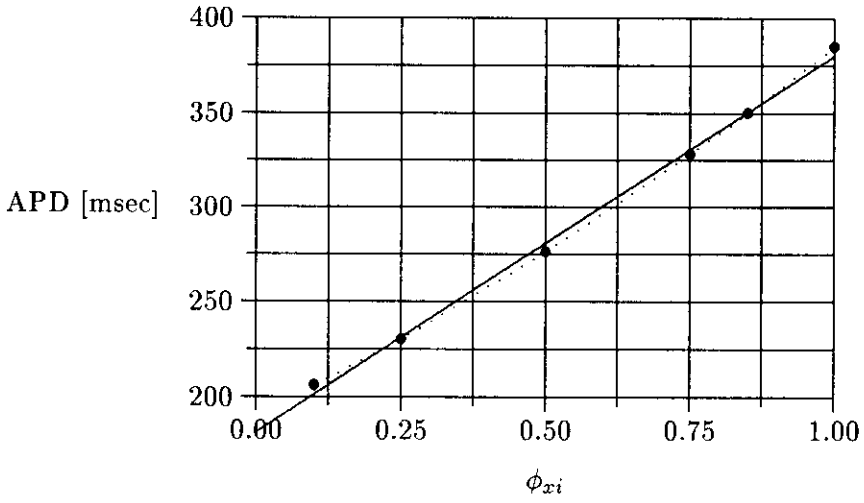

FIGURE 13. Action potential duration in Luo–Rudy model as a function of the controllable parameter ϕ_{xi}. Linear fit to simulation data gives the line shown $APD = 181.55 + 198.8\phi_{xi}$ with error $R^2 = .997$.

to the data. Experimental APD values can be matched to the modified Luo–Rudy model using this linear equation for ϕ_{xi}.

Figure 14 shows the APDR curves resulting for the same set of ϕ_{xi} values.

Action potential duration restitution

The characteristic of action potential duration restitution is a unique characteristic of the action potential, as it is exhibited *after* the action potential has completed, and the membrane is fully repolarized. The effect becomes apparent only upon the next action potential. It seems logical that it must be governed by a activation characteristic that has not fully recovered following the repolarization of the membrane. In the Luo–Rudy model, this is the time dependent potassium activation "gate" X. By using a logical expression to modify this gating variable only after the action potential is complete, modification of the APDR curve without altering any other aspects of the ion channel kinetic or action potential is possible.

By inserting the new parameter γ_x into the expression for τ_X, the time constant for X,

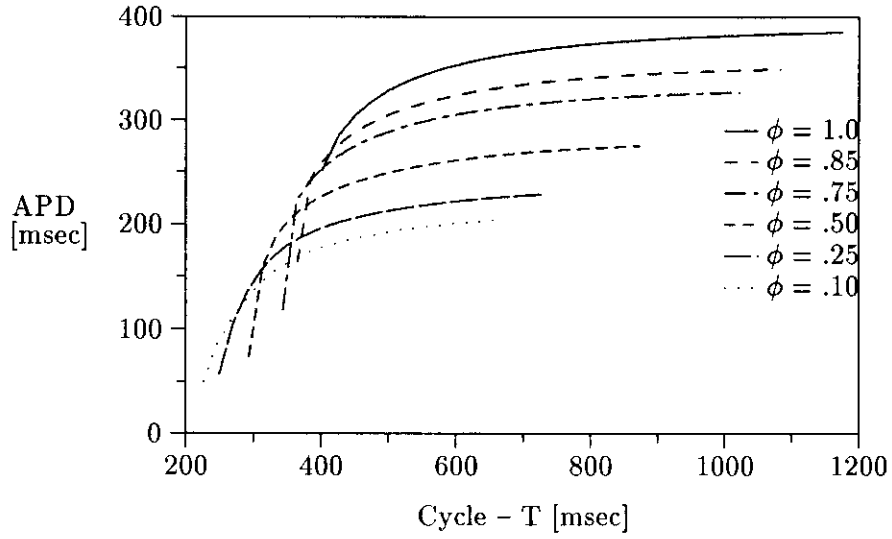

FIGURE 14. Action potential duration restitution curves for ϕ_{xi} = .1, .23, .5, .75, .85, 1.0.

and by altering this expression logically as a function of E, the needed effects on APDR are obtained. For $E \geq 0.01E_{min}$:

$$\tau_X = \frac{1}{\gamma_x(\alpha_x + \beta_x)} \tag{13}$$

For $E < 0.01E_{min}$:

$$\tau_X = \frac{1}{(\alpha_x + \beta_x)} \tag{14}$$

Figure 15 shows the time course of the gating variable X using the above logical expression for γ_x values of 1.0 and 3.0. Note the altered time course after the end of the normal action potential. Figure 16 shows the family of curves representing APDR curves resulting from γ_x values from 0.5 to 3.0.

In order to match experimental data to the model, first the exponential characteristic of the data β must be estimated, as done for the $\varepsilon 4$ modified FitzHugh–Nagumo model. Figure 17 shows the relationship of β to the parameter γ_x, and a linear fit to the data points: $\beta = 0.00436\gamma_x + 1.44 \cdot 10^{-4}$ with error $R^2 = 0.994$. For data from earlier mentioned canine control and Quinidine intoxicated experiments β = .0047 and .0055, respectively. This corresponds to γ_x values of 1.045 and 1.228, for the modified Luo–Rudy model.

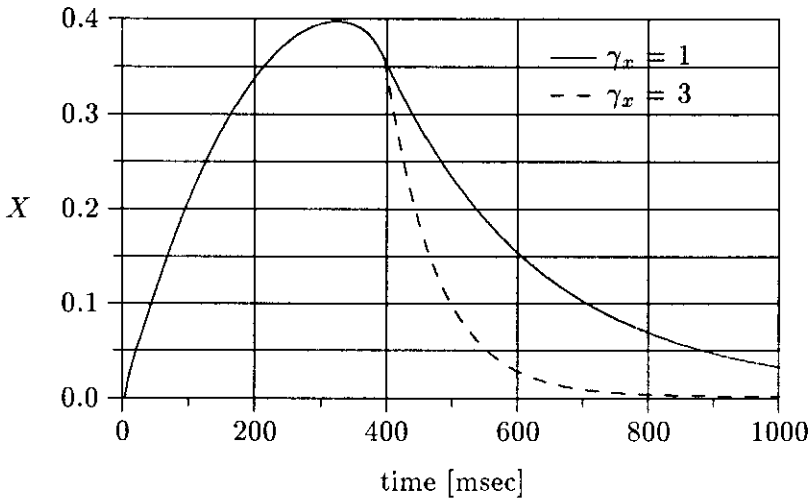

FIGURE 15. Time course of X during and after normal action potential for Luo–Rudy model, $\gamma_x = 1, 3$.

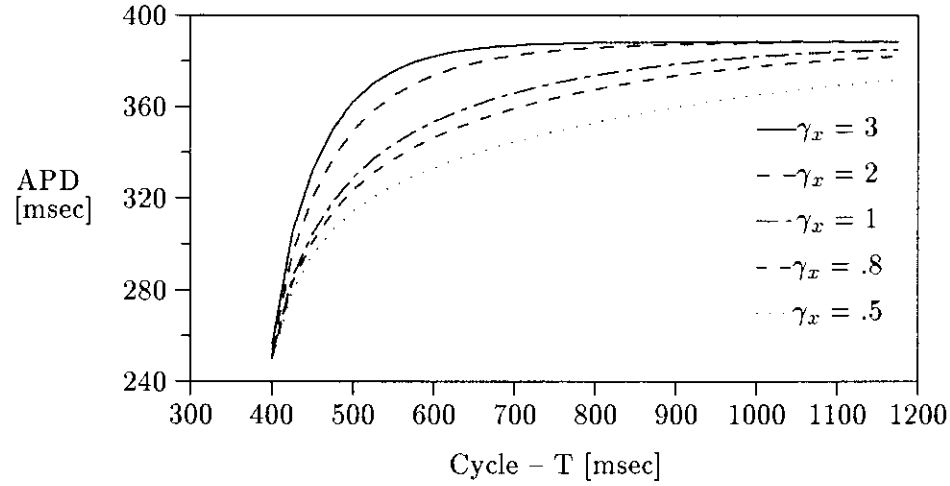

FIGURE 16. Action potential duration restitution curves for $\gamma_x = .5, .8, 1, 2, 3$.

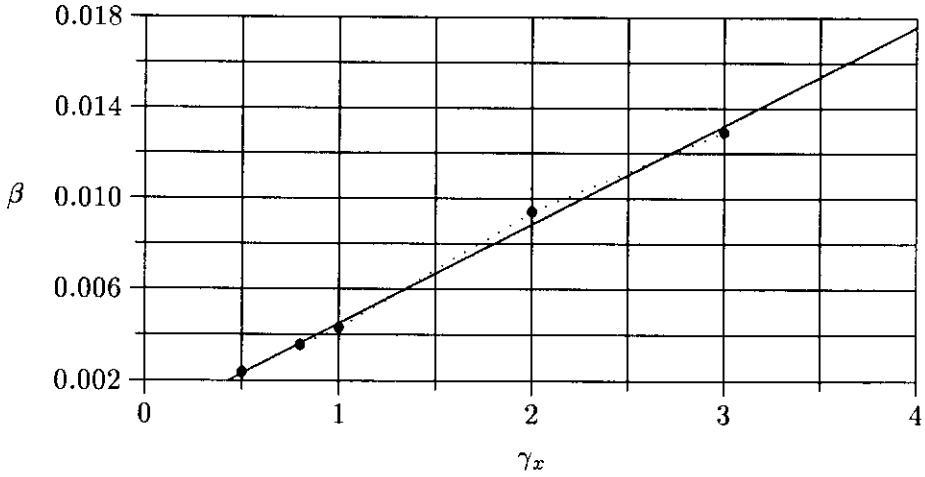

FIGURE 17. Determination of γ_x for Luo–Rudy model from experimental β data.Linear fit equation: $\beta = 0.00436\gamma_x + 1.44 \cdot 10^{-4}$

Excitability

Excitability is a measure of a tissue's responsiveness to stimuli. The lower the excitability, the greater is the stimulus strength needed to cause an action potential. This is also known as the action potential *threshold* of excitation. The excitability of real cardiac tissue undergoes marked changes soon and late after a myocardial infarction. Other situations may also alter the tissue excitability, including ischemia and drug infusion.

As mentioned earlier, the fast inward sodium current I_{Na} is responsible for the depolarization of the tissue. Altering the character of the activation "gate" for the sodium channel m is proposed for controlling the excitability of the tissue. The voltage offset value of 47.13 is replaced by the new parameter m_{th} in the equation for the activation gate opening rate constant α_m as follows:

$$\alpha_m = \frac{0.32(E + m_{th})}{1 - e^{-0.1(E+m_{th})}} \tag{15}$$

Values for the voltage threshold of excitability were computed by applying graduated I_{stim} currents for a given m_{th}, until an action potential was generated, then measuring the value of E_{th} from the plateau peak of the latent period before the onset of the action potential. Figure 18 graphs these results. $m_{th} = 47.13$ is the standard or control value.

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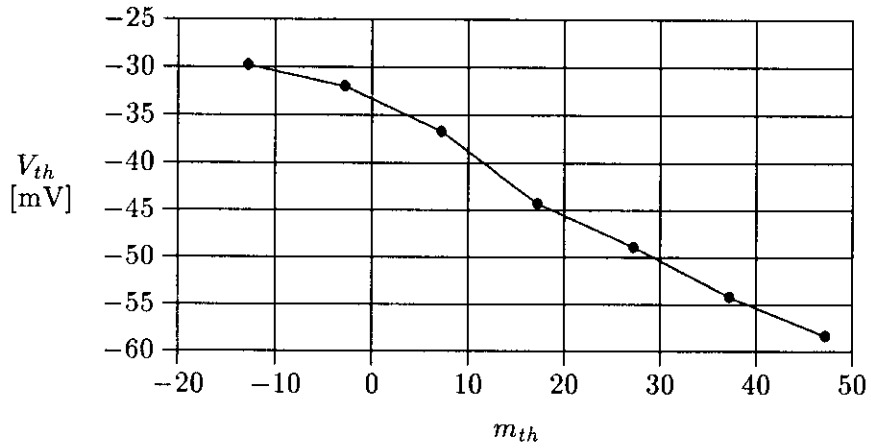

FIGURE 18. Action potential threshold in Luo–Rudy model as a function of the controllable parameter m_{th}.

CONCLUSION

The most recent and accurate model of cardiac action potential, the Luo–Rudy model, has presented an opportunity to study new facets of action potential generation and propagation in cardiac muscle cells. By carefully implementing and evaluating the effects of individual gating variables and ion channel kinetic descriptions, it was possible to develop methods for controlling characteristics of the action potential. Results were obtained which validated the mathematical model for repeated stimuli experiments. Results of controllability experiments showed that introduction of the new parameters ϕ_{xi}, γ_x, and m_{th}, provided a means for independently controlling the action potential characteristics mentioned, while minimizing impact on underlying ion channel kinetics.

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