Investigation of Cardiac Cell Recovery Processes in Luo and Rudy Model

Boris Y. Kogan, Simon D. Shpilfoygel

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Abstract

The cell recovery processes play a significant role in circular and spiral wave propagation in cardiac tissue. The study of the Luo-Rudy sophisticated mathematical model based on the up to date physiological data shows that these processes are determined by the time course of the gate variables after the completion of cell membrane repolarization. It is found that only three gate variable, namely f, j and X make the basic contribution. Moreover, the gate variables f and X affect the action potential duration while gate variable j determines the $\frac{dV}{dt}_{max}$ restitution. The gate variables j and f reach their stationary values during the first $75 - 150$ msec after the termination of the cell repolarization processes but gate variable X acts during almost the whole diastolic interval.

1 Introduction

Currently there exist a wide variety of mathematical models for membrane action potential of myocardium. Some of these models, such as Beeler-Reuter [1] and Luo-Rudy [2, 3, 4] provide accurate enough and detailed representation of processes that occur inside a heart muscle cell. However, they are so complicated and computationally expensive that even modern massively parallel computer systems are not fast enough to permit interactive simulations, especially for 2 or 3-dimensional wave propagation. The simplified models were introduced to overcome the computational difficulties and at the same time to provide possibilities for an analytical solution (a piece-wise approximation of the Fitzhugh-Nagumo model [5]). Most of the simplified models (Fitzhugh-Nagumo [6], Van Capelle-Durrer [7] and Karma [8]) reproduce the decreased maximal rate of depolarization and do not reproduce the cell recovery processes properly. Moreover, they are based on the old physiological data implemented in the Noble model of Purqinje fiber [9].

In order to simulate correctly the action potential propagation a smplified model must provide accurate cell recovery processes which determine the restitution of action potential duration and the restitution of the maximum of the action potential depolarization rate (hereafter referred to as APD and $\frac{dV}{dt}_{max}$ restitution respectively).

The major objective of this study is to investigate the relations between variables of the most complete up to date cell mathematical model, and the restitution of action potential duration and maximal depolarization rate. For this purpose we use the first version of the Luo-Rudy mathematical model [2] based on up-to-date physiological data and its computer implementation described in [10]. The equations and parameters of the implemented Luo-Rudy model are described in the Appendix.

2 The Variables Of Luo-Rudy Model and Recovery Processes

As it was already mentioned, the cell recovery processes are observed after the repolarization of the cell membrane is accomplished. Because in this phase of the action potential (hereafter referred to as AP) the membrane potential already had returned to its rest value and all of the ionic currents to their steady states, the only variables that can continue to change in time are the gate variables. The time course of all six gating variables and Calcium uptake obtained by computer simulation are plotted in Fig. 1, 2.

The only three variables that do not achieve their rest values at the end-moment of the AP are X, f and j. The gate variables j and f reach their stationary values during first 75–150 msec after the termination of the cell repolarization processes while X acts during almost the whole diastolic interval. The other three variables and Calcium uptake achieve their steady state values at the end moment of repolarization processes and therefore cannot affect the parameters of the next excited action potential in any way. When the next stimulus is applied, gating variables X, f and j have some initial values that differ from the steady state ones that, in turn, may change the parameters of the AP excited by this stimulus.

That allows us to focus this study on an investigation of the effects caused by these three variables. In order to study these effects one may either simulate a repeatedly excited medium or reproduce the action potential with varying initial conditions for each gate variable under consideration. That allows us to observe the changes in action potential parameters under the influence of each gate variable separately.

The effects of the gate variable on AP parameters determine the well-known APD and maximum depolarization rate restitution characteristics of the cell.

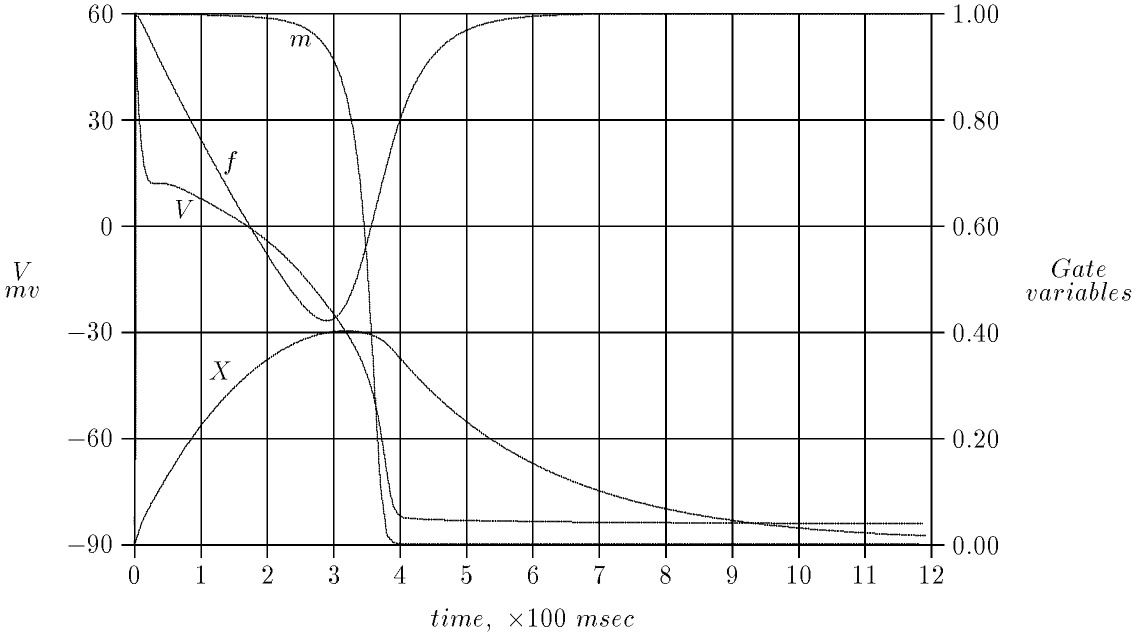

Figure 1: The AP and gate variables f, m and X

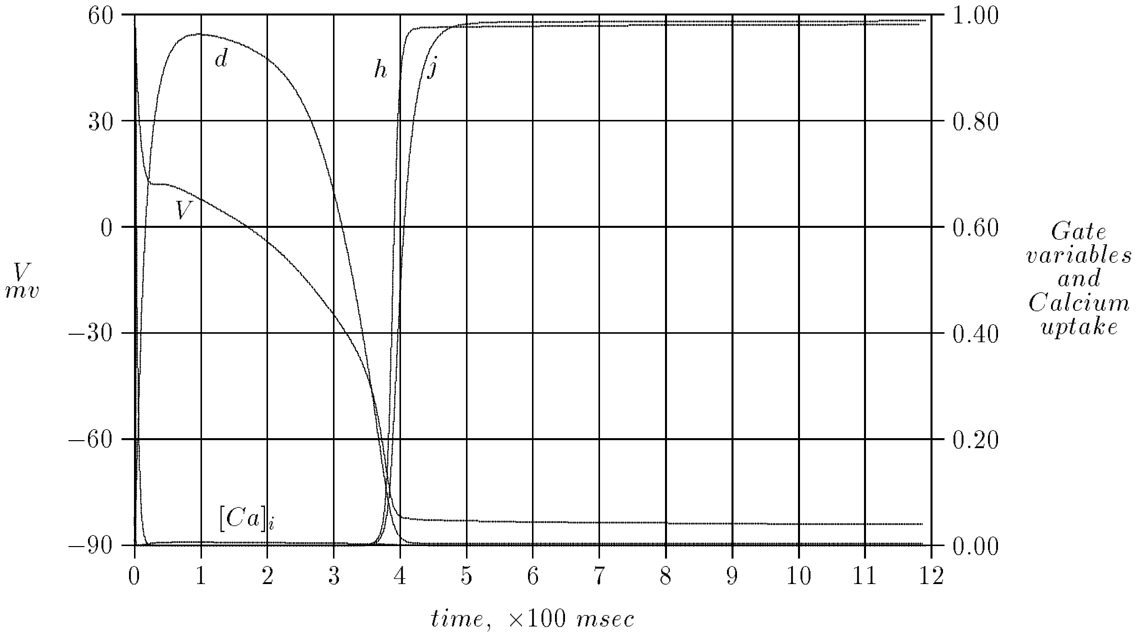

Figure 2: The AP, gate variables j, h and d and Calcium uptake $[Ca]_i$

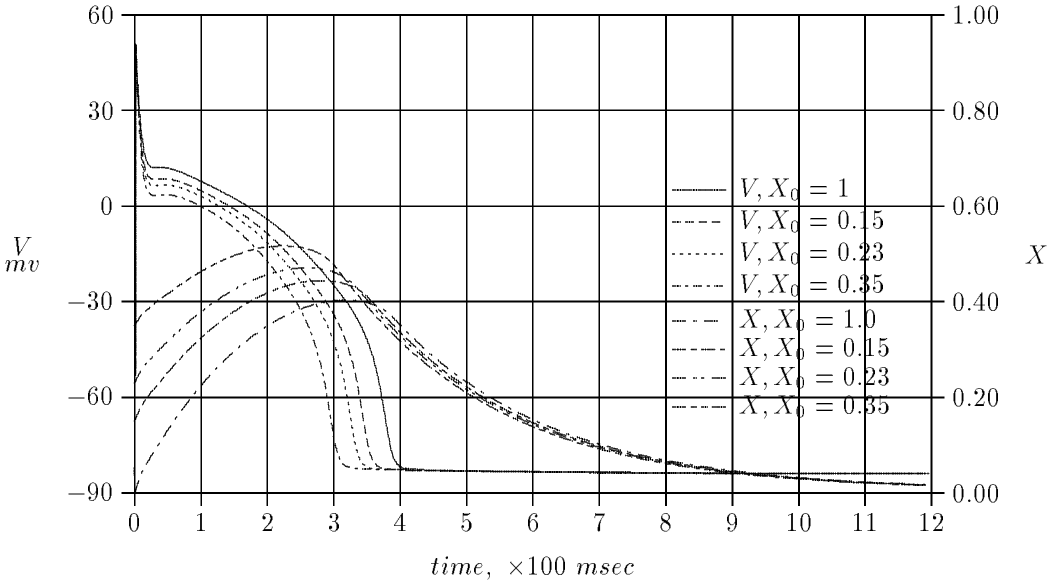

Figure 3: The AP and gate variable X under various initial conditions for X

3 The Effect of gate variable X on $\frac{dV}{dt}_{max}$ and APD

The initial values of the gating variable X were set equal to 0 (the steady state value), 0.07, 0.15, 0.23, 0.29 and 0.35. They correspond respectively to the values that X reaches at 791, 605, 503, 450 and 400 msec after the beginning of the application of the first stymulae in case of repeatable excitation. From the Fig. 3 one can draw a conclusion that the gating variable X effects both the duration and the shape of the AP significantly. The values of APD achieved under these initial conditions for X are plotted on Fig. 8 versus the diastolic interval corresponding to these initial values.

In the whole range of initial values for X the changes in the maximum depolarization rate do not exceed 0.626 V/sec (see Fig. 6) or approximately 0.2 % of the $\frac{dV}{dt}_{max}$ and therefore can be considered insignificant.

Thus the recovery processes of gate variable X affect the APD significantly.

4 The Effect of gate variable j on $\frac{dV}{dt}_{max}$ and APD

In computer simulations of the Luo and Rudy model the initial conditions for the gate variable j were chosen equal to 0.9887 (the steady state value), 0.95, 0.9, 0.8, 0.7, 0.6, 0.5 and 0.4. These values of initial conditions correspond respectively to the values of j at 452, 435, 420, 411, 405, 401 and 397 msec after the application of the first stymulae. Fig. 6 shows clearly that j significantly affects the maximum of the depolarization rate. Figure 7 provides another presentation of the effects that the gating variable j have on the maximum of the depolarization rate. It can be seen from this figure that the gate variable j has significant effect on the $\frac{dV}{dt}_{max}$ if and only if the diastolic interval does not exceed 75 msec. In the other case the change of the maximum of the depolarization rate does not exceed 1 % of the absolute value and thus could be considered insignificant.

At the same time j does not affect the APD at all but affects the spike amplitude, according to Fig. 4.

The results obtained in this simulation show that the gate variable j plays a significant role when a repeated excitation is applied at the first 100 msec after the completion of the first AP.

5 The Effect of gate variable f on $\frac{dV}{dt}_{max}$ and APD

In order to find those effects the initial values of f were set to 1.0 (the steady state value) 0.95, 0.9 and 0.8 which correspond respectively to the values of f at 474, 437 and 398 msec. It was discovered that f affects the APD as it can be seen in Fig. 5. From Figure 8 it can be seen that f effects the APD if and only if the diastolic interval does not exceed 200 msec. As well, it can be seen

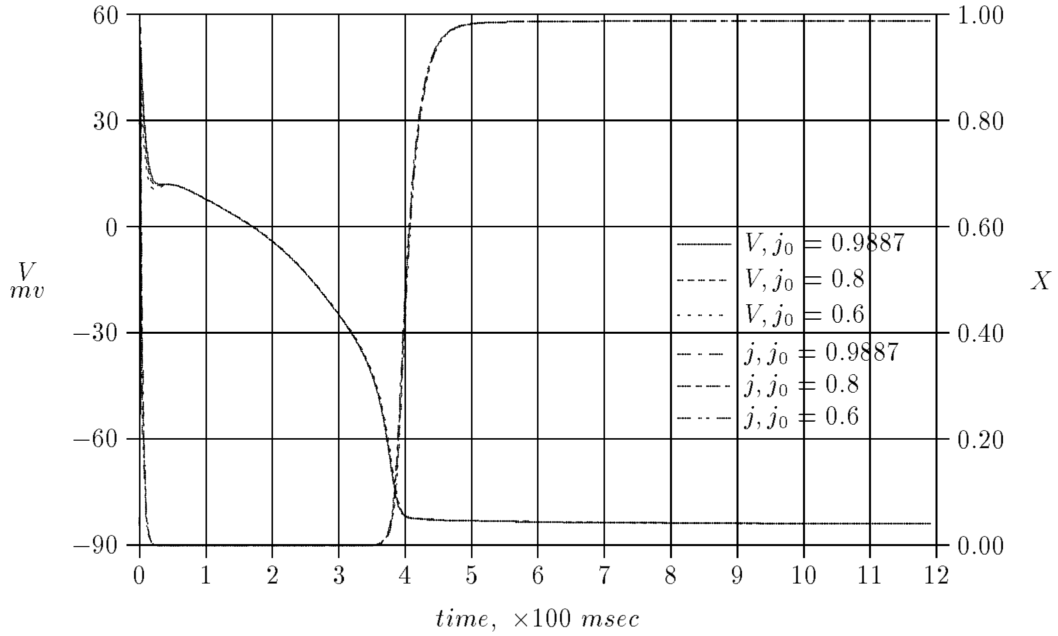

Figure 4: The AP and gate variable j under various initial conditions for j.

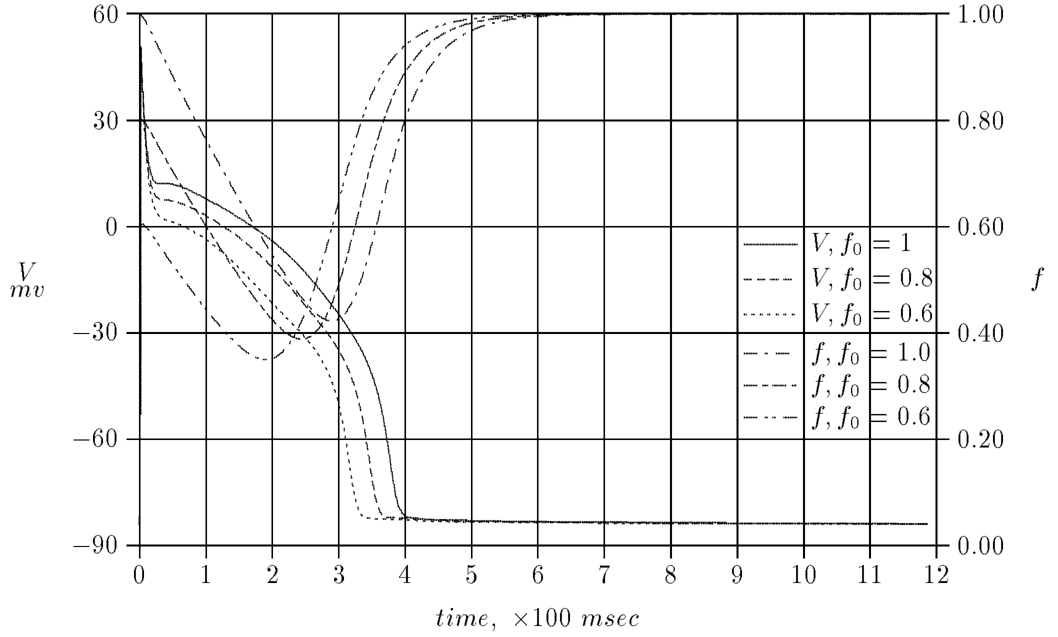

Figure 5: The AP and gate variable f under various initial conditions for f.

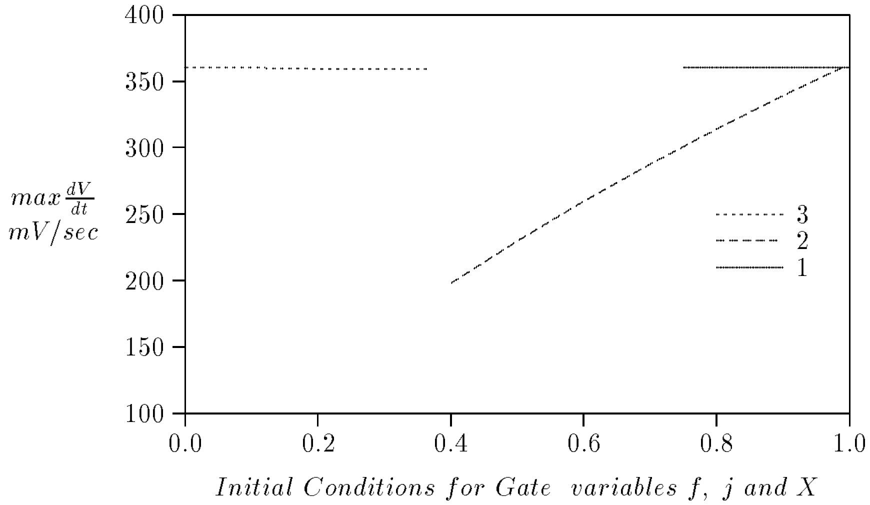

Figure 6: The maximum of $\frac{dV}{dt}$ under variuos initial conditions independently applied to gate variables f (curve 1), j (curve 2) and X (curve 3).

that the changes of the APD induced by f, form approximately one third of the changes induced by X. It means that X keeps it effects on the APD for a longer time than f and the magnitude of those effects is larger.

However, f does not affect the value of $\frac{dV}{dt}_{max}$ as it can be seen from the Figures 6 and 7.

It should be mentioned that the effects of f coincise with the ones of X. The combined effect of gate variables X and f is represented in Fig. 7 and gives the APD restitution characteristic of Luo-Rudy model. The effects of gate variables are separated: f and X affect the APD while j affects the maximum of the depolarization rate. It means that it should be possible to simulate the effects of f by modifying the parameters that controls the time course of X. That allows a future simplified model to retain only two gate variables, one of which affects the APD while the other one - $\frac{dV}{dt}_{max}$.

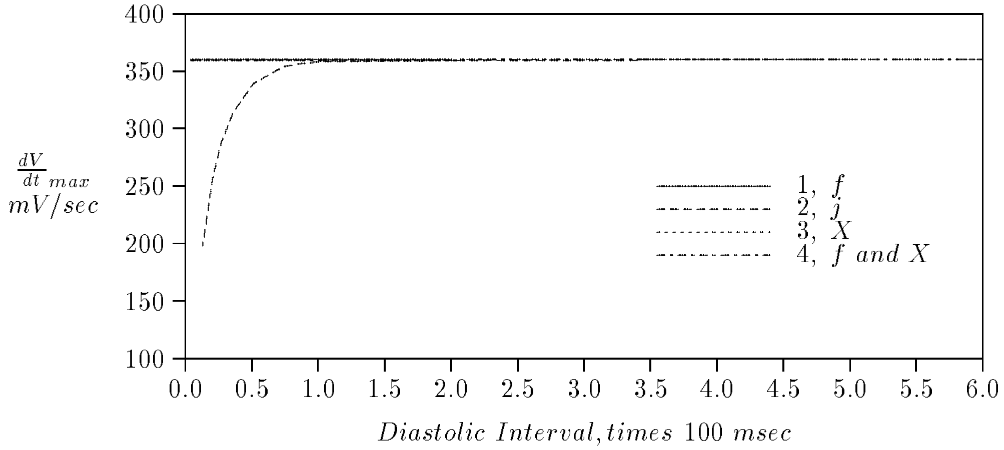

Figure 7: The maximum of $\frac{dV}{dt}$ under various diastolic intervals that are presented by different initial conditions applied independently to the following gate variables: f (curve 1), j (curve 2), X (curve 3) and applied jointly to f and X gate variables (curve 4).

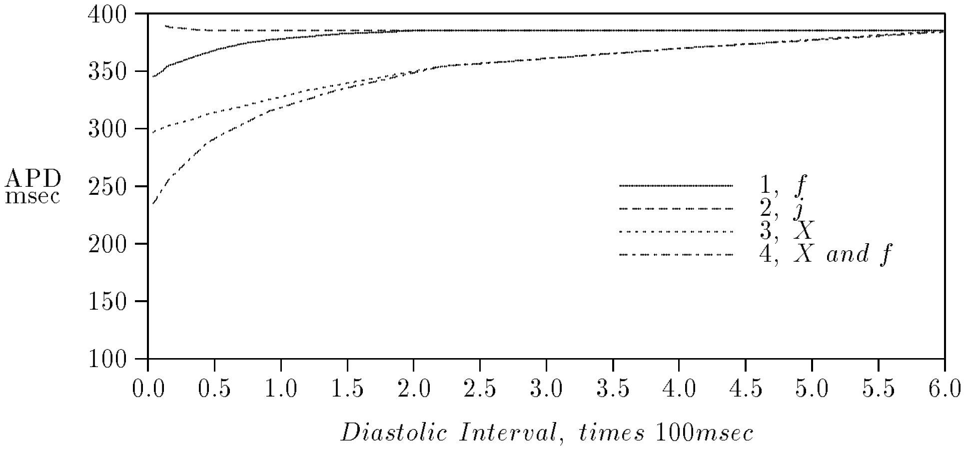

Figure 8: The action potential duration under various diastolic intervals that are expressed by different initial conditions applied independently to the following gate variables: f (curve 1), j (curve 2), X (curve 3) and applied jointly to f and X gate variables (curve 4).

6 Conclusion

- Among seven gating variables of the LR model only three affect the cell recovery processes or determine the restitution characteristics of wave propagation process. Two of them, namely X and f affect only the APD while j affects the maximum of the depolarization rate only.

- A simplified model that employs one gate variable can not provide precise restitution of APD and the maximum depolarization rate simultaneously. To accomplish that, it must include at least two gate variables, namely j and a generalized gate variable that summarizes the effects of both X and f on APD restitution.

Appendix. General Description Of The Luo-Rudy Model

A mathematical model for the membrane action potential of myocardium recently introduced by Luo and Rudy [2] improves in a number of ways the widely used Beeler-Reuter [1] model. The Luo-Rudy model (hereafter referred to as L-R model) incorporates more, in comparison with the Beeler-Reuter model, accurate ionic descriptions from the Ebijara-Johnson [11] model and the data from the most recent physiological experiments. Computer implementation, validation, and controllability studies showed [2, 10] that the model can be considered the most accurate and complete one available.

The L-R model is based upon the Hodgkin-Huxley [12] type formalism, where the rate of change of membrane action potential is given by

$$\frac{dV}{dt} = -\frac{1}{C}(I_i + I_{stim})$$

where V is the membrane action potential, C is the membrane capacitance , I_{stim} is a stimulus current and I_i is the sum of six ionic currents into and from the cell.

Each ionic current corresponds to an ion channel the conductance of which is determined by a gating variable. The equations for the gate variables are of the form

$$\frac{dy}{dt} = \frac{(y_\infty - y)}{\tau_y}$$

where

$$\tau_y = 1/(\alpha_y - \beta_y)$$

and

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

Here y represents a gating variable, τ_y is its time constant, y_∞ is the steady-state value of y, while α_y and β_y are voltage-dependent "opening" and "closing" rate constants.

The Luo-Rudy model considers the sum of ion currents I_i to include the following 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 (also known as leakage) current

and gating variables h, j, m, d, f and X.

The said currents are described by the following expressions:

Fast sodium current:

$$I_{Na} = 23m^3hj(V - V_{Na})$$

For V $\geq$ -40mV:

$\alpha_h = \alpha_j = 0.0$

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

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

For V $<$ -40mV:

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

$\alpha_j = [-1.2714 \cdot 10^5 exp(.2444V) - 3.474 \cdot 10^{-5} exp(-.04391V)]/\{+exp[.311(E + 79.23)]\}$

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

$\beta_j = [0.1212 \cdot exp(-0.01052V)]/\{1 + exp[-0.1378(V + 40.14)]\}$

For all V:

$\alpha_m = [0.32(V + 47.13)]/\{1 - exp[-0.1(V + 47.13)]\}$

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

Slow inward current:

$$I_{si} = 0.09df(V - Vsi)$$

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

$\alpha_d = (0.095exp[-0.01(V-5)])/(1+exp[-0.72(V-5)])$

$\beta_d = (0.07exp[-0.017(V+44)])/(1+exp[0.5(V+44)])$

$\alpha_f = (0.012exp[-0.008(V+28)])/(1+exp[0.15(V+28)])$

$\beta_f = (0.0065exp[-0.02(V+30)])/(1+exp[-0.2(V+30)])$

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

Time dependent potassium current:

$$I_K = \overline{G}_K X X_i (V - V_K)$$

$\overline{G}_K = 0.282 \cdot \sqrt{[K_0/5.4}$

For V$> -100mV : X_i = 2.837\{exp[0.04(V+77)]-1\}/\{(V+77)\cdot exp[0.04(V+35)]\}$

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

$\alpha_X = 0.0005 \cdot exp[0.083(V+50)]/\{1+exp[0.057(V+50)]\}$

$\beta_X = 0.0013 \cdot exp[-0.06(V+20)]/\{1+exp[-0.04(V+20)]\}$

Time-dependent potassium current:

$$I_{K1} = \overline{G}_{K1} K1_\infty (V - E_{K1})$$

$\overline{G}_{K1} = 0.6047/\sqrt{[K_0/5.4}$

$\alpha_{K1} = 1.02/\{1+exp[0.2385 \cdot (V - E_{K1} - 59.215)]\}$

$\beta_{K1} = \{0.49214exp[0.08032(V - E_{K1} + 5.476)] + exp[0.06175(V - E_{K1} - 594.31)]\}/$
$\{1+exp[-0.5143(V - E_{K1} + 4.753)]\}$

Plateau potassium current:

$$I_{Kp} = 0.0183 \cdot Kp \cdot (V - E_{Kp}),\ E_{Kp} = E_{K1}$$

$K_p = 1/\{1+exp[(7.488 - V)/5.98]\}$

Background current:

$$I_b = 0.03921(V + 59.87)$$

Total time-independent potassium current:

$$I_{K1(T)} = I_{K1} + I_K + Ib$$

The Luo-Rudy model consists of 8 ordinary differential equations: one for the action potential, six for 6 gating variables and one for the Calcium uptake and seventeen nonlinear functions of the membrane potential.

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