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Simulation of Ion Currents and Action Potential in Cardiac and Induction of Acute Hypoxia

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Abstract

Sudden cardiac death describes the unexpected natural death from a cardiac cause within a short time period, generally ≤1 hour from the onset of symptoms, in a person without any prior condition that would appear fatal.

This study describes a computer model of electrical propagation in a cardiac in order to investigate the factors affecting the cardiac activity. The basic elements of this model are a set of identical excitable cables connected together and a dynamic representation of the cardiac cellular membrane. The membrane model incorporates ionic components of the cardiac cells which include fast sodium current, a slow inward current, a set of potassium currents and a membrane capacitance. The intracellular calcium concentration increases as a function of the calcium membrane current at the onset of the action potential and returns to its resting level at the end of repolarization phase. The gating model describes the non-linear currents of the membrane model. The formulation of these currents follows the Hodgkin-Huxley type model and we investigated the net effects of acute hypoxia and catecholamine's on the cardiac action potential. Variability in delivery of oxygen can lead to electric instability in the myocardium

and the generation of arrhythmias. In addition ischemic heart disease, angina and sudden cardiac death.

CHAPTER I

Historical Introduction

1.1 History of Modeling the Spread:

Described a method for simulating a cable demonstrating the ability of its approach to produce more information than experimental methods. Weidman [1] proposed the application of the theory of one-dimensional cable of cardiac muscle. Assuming that the fibers are considered continuous and behave as a functional syncytium, he analyzed the spread of passive current in Purkinje fibers and calculated constants of space and time of these fibers. These results show that the space constant is relatively long compared to the length of the cell and the decrease in electronic potential follows an exponential pace. After Weidmann, several researchers have used the theory of continuous cable in experimental studies to extract the passive parameters [2, 3]. Clerc [4] studied conduction velocity values as a function of the axial strength in the longitudinal and transverse directions in the ventricular muscle tissue. These findings show that the variations in the speed of conduction depends on the effect of cytoplasmic resistance and the resistance of intercellular junctions , which are represented by an effective axial strength with different values in both directions. Saffitz et al. [5] do not agree with these results.

1.2 Model Development:

1.2.1 Hodgkin–Huxley model 1952: [6]

The Hodgkin–Huxley model (or "conductance-based model") is a mathematical model (a type of scientific model) that describes how action potentials in neurons are initiated and propagated. It is a set of nonlinear differential equations that approximates the electrical characteristics of excitable cells such as neurons and cardiac myositis. Alan Lloyd Hodgkin and Andrew Huxley described the model in 1952 to explain the ionic mechanisms underlying the initiation and propagation of action potentials in the squid giant axon.

- **The ionic current:**

A further subdivision of the membrane current can be made by splitting the Ionic current into components carried by sodium ions (INa), potassium ions (IK) and other ions (I): I=INa + IK + It

The individual ionic currents in the third paper of this series (Hodgkin & Huxley, 1952 b), we showed that

The ionic permeability of the membrane could be satisfactorily expressed in

Terms of ionic conductance's (gNa, I and gl). The individual ionic currents are Obtained from these by the relations

INa =gNa (E - ENa), IK=gK (E - EK), It=gt (E - El),

Where ENa and EK are the equilibrium potentials for the sodium and potassium Ions. El is the potential at which the 'leakage current' due to chloride and other ions is zero. For practical application it is convenient to write these.

Equations in the form:

- **I Na=gNa (V-VNa),**
- **IK=gEK (V-VK),**
- **It= gt (V-Vt)**

The Hodgkin–Huxley model is regarded as one of the great achievements of 20th-century biophysics.

1.2.2 FITZHUGH, R.A. (1961): [7]

The FitzHugh-Nagumo model explained the dynamical mechanism of *spike accommodation* in HH-type models. When stimulation strength *I* increases slowly, the neuron remains quiescent. The resting equilibrium of the FitzHugh-Nagumo model shifts slowly to the right, and the state of the system follows it smoothly without firing spikes. In contrast, when the stimulation is increased abruptly, even by a smaller amount, the trajectory could not go directly to the new resting state, but fires a transient spike; see figure. Geometrically, this phenomenon is similar to the post-inhibitory (rebound) response.

The FitzHugh-Nagumo model is a simplification of the Hodgkin-Huxley (1952) model [1]. The number of equations is reduced to two: a cubic equation representing the fast variable (u) and linear equation for the slow variable (v).

- $V^{\cdot} = f(V) - W + I + Vxx$
- $W = a(bV - cW)$

1.2.3 BBEELER, G.W. et REUTER H. (1977): [8]

The model is used to simulate mammalian ventricular action potentials. It formulates ionic current gating in terms of Hodgkin-Huxley type equations. This model describes four ionic currents: fast inward sodium current, slow (calcium-carried) inward current, time-dependent outward potassium current, and time-independent (predominantly potassium) outward current. This model includes basic intracellular calcium concentration handling.

$$J_{ion} = J_{K_1} + J_{x_1} + J_{Na} + J_{Ca}$$ ion current

$$J_{K_1} = 0.35\left\{\frac{4\{\exp[0.04(V_m+85)]-1\}}{\exp[0.08(V_m+53)]+\exp[0.04(V_m+53)]} + \frac{0.2(V_m+23)}{1-\exp[-0.04(V_m+23)]}\right\}$$

time-independent K^+ current

$$J_{x_1} = x_1 \cdot 0.8\left\{\frac{\exp[0.04(V_m+77)]-1}{\exp[0.04(V_m+35)]}\right\}$$ time- and voltage-dependent K^+ current

$$J_{Na} = (\bar{g}_{Na} \cdot m^3 \cdot h \cdot j + g_{NaCa})(V_m - E_{Na})$$ two Na^+ currents (fast and background)

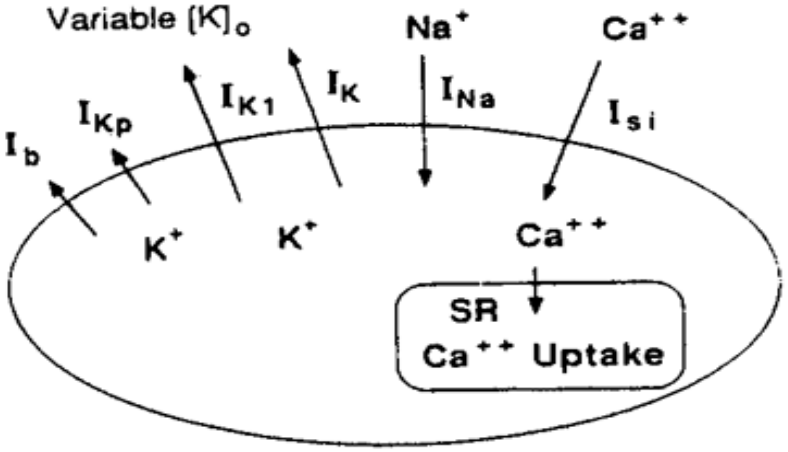
$$J_{Ca} = \bar{g}_{Ca} \cdot d \cdot f \cdot (V_m - E_{Ca})$$ slow Ca^{2+} current

1.2.4 LR1991 [9]:

A mathematical model of the membrane action potential of the mammalian ventricular cell is introduced. The model is based, whenever possible, on recent single-cell and single-channel data and incorporates the possibility of changing extracellular potassium concentration [K] o. Physiological simulations focus on the interaction between depolarization and repolarization (i.e., premature stimulation). First formulation by Luo and Rudy, inspired by Beeler & Reuter (1977). The model implements six transmembrane currents and, like the Beeler-Reuter model, takes into account concentration changes of intracellular Ca2+ only.

The transmembrane currents are:

1. **INa:** Na+ inward current. Formulation according to Beeler & Reuter, with modifications proposed by Haas et al. (1971) and Ebihara & Johnson (1980), with adjustments.
2. **Isi:** Slow (Ca2+) inward current. Formulation of Beeler & Reuter.
3. **IK:** Time-dependent K+ current (delayed rectifier). Formulation of Beeler & Reuter, with modifications.
4. **IK1:** Time-independent K+ current. Original formulation.
5. **IKp:** Plateau K+ current. Original formulation.
6. **Ib:** Background current. Original formulation.



$I_{Na} = \bar{G}_{Na} \cdot m^3 \cdot h \cdot j \cdot (V - E_{Na})$ $\tau_m = 0.03;\ \tau_h = 9.7;\ \tau_j = 79$ (msec)

$I_{si} = \bar{G}_{si} \cdot d \cdot f \cdot (V - E_{si})$ $d[Ca]_i/dt = -10^{-4} \cdot I_{si} + 0.07(10^{-4} - [Ca]_i)$

$I_K = \bar{G}_K \cdot X \cdot X_i \cdot (V - E_K)$ $\bar{G}_K = 0.282 \cdot \sqrt{[K]_o / 5.4}$

$I_{K1} = \bar{G}_{K1} \cdot K1_\infty \cdot (V - E_{K1})$ $\bar{G}_{K1} = 0.647 \cdot \sqrt{[K]_o / 5.4}$

$I_{Kp} = \bar{G}_{Kp} \cdot Kp \cdot (V - E_{Kp})$

Figure 1.1 LR 1991 equation.

1.2.5 LRd1994 [9]:

A dynamic model of the cardiac ventricular action potential. Afterdepolarizations, triggered activity, and potentiation. Major extension of the LR91 model. Focuses on processes that regulate intracellular calcium and depend on its concentration. This model for the mammalian ventricular action potential is based mostly on the guinea pig ventricular cell. However, it provides the framework for modeling other types of ventricular cells with appropriate modifications made to account for species differences. The model provides the basis for the study of arrhythmogenic activity of the single myocyte including after depolarization's and triggered activity. It can simulate cellular responses under different degrees of calcium overload.

Serves as a basis for all subsequent studies. Includes formulation for most of the sarcolemmal currents, pumps and exchangers. Implements cell compartmentalization (myoplasm, junctional and nonjunctional sarcoplasmic reticulum), Ca2+ buffers in the myoplasm (troponin, calmodulin) and in the junctional sarcoplasmic reticulum (calsequestrin), and calcium-inducedCa2+ release. It takes into account myoplasmic concentration changes of Na+ and K+ as well as Ca2+ concentration changes in all three compartments. Sarcolemmal currents are normalized to cell membrane capacitance and expressed in μA/μF, not in μA/cm2 (as in LR91 and Beeler-Reuter models). In the initial work, Ca2+ buffering was computed using Steffens's iterative method. Later, buffering was computed analytically (see LRd95).

- **Sarcolemmal currents:** Currents from LR91 and specific changes:
- INa: Reduction of g Na max from 23 mS/cm2 to 16 mS/μF.
- ICa, L: L-type Ca2+ inward current. Replaces I is (which becomes obsolete) used in LR91. Original new formulation. Note erratum below.
- IK: Square-dependence on activation gate x was incorporated.

- IK1: gK1 max at [K+] o = 5.4 mmol/L was increased from 0.6047 mS/cm2 to 0.75 mS/µF.
- IKp: No changes
- Ib: Replaced by INa, b and ICa, b (see "New currents" below) and therefore becomes obsolete.

- **New currents:**
- INaCa: Na+ /Ca2+ exchanger current. Formulation according to Di Francesco & Noble (1985), with adjustments.
- INaK: Na+ /K+ ATPase current. Original formulation, inspired by Di Francesco & Noble (1985) and Rasmusson et al. (1990).
- IpCa: Ca2+ pump. Original formulation.
- ICa, b: Ca2+ background current. Together with INa, b, replaces Ib from LR91, which becomes obsolete. Original formulation.
- INa, b: Na+ background current. Together with ICa, b, replaces Ib from LR91, which becomes obsolete. Original formulation.

- **Intracellular calcium fluxes:**
- Irel, CICR: Ca2+ -induced Ca2+ release (CICR) from the junctional sarcoplasmic reticulum (JSR). Original formulation. Triggered by Ca2+ entry during 2 MS starting from the time of occurrence of dV/dtmax. CICR is graded (increases with increasing Ca2+ entry) but involves a threshold (no release for small entry of Ca2+, below a given threshold).
- Iup: Ca2+ uptake into the nonjunctional sarcoplasmic reticulum (NSR). Original formulation.
- Ileak: Ca2+ leakage from the NSR. Original formulation.
- Itr: Translocation of Ca2+ from the NSR to the JSR. Original formulation.

- Processes specifically used to model pathophysiological conditions (not used in other studies unless explicitly stated):
- Used to model cell behavior under Ca2+-overload conditions (resting diastolic
- [Ca2+] myoplasmic, free >0.3 µmol/L):
- Ins (Ca): Nonspecific Ca2+-activated sarcolemmal current. Original formulation.
- Irel, spont: Spontaneous Ca2+ release from the JSR. Original formulation. Triggered by a level of buffered Ca2+ in the JSR exceeding a given threshold.

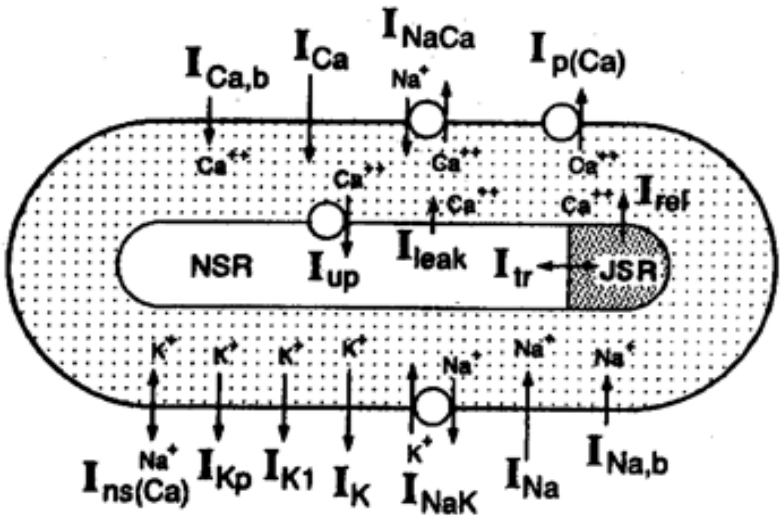


Figure 1.2 a dynamic model of the cardiac cell action potential LR94.

1.2.6 LRd1995 [9]:

Two components of the delayed rectifier K+ current in ventricular myositis of the guinea pig type. Theoretical formulation and their role in repolarization. Incorporation of the two components (rapid and slow) of the delayed rectifier K+ current. Introduction of an analytical method to compute Ca2+ buffering (based on solving polynomial equations of 2nd and 3rd degrees), replacing Steffensen's iterative method used in LRd94.

- **<u>Specific changes compared with LRd94:</u>**

- IK: IK from LRd94 is replaced with IKr and IKs (see "New currents" below) and therefore becomes obsolete.
- IKp: gKpmax decreased from 0.0183 to 0.00552 mS/µF.
- ICa, L: Hill coefficient (exponent) in gate Ca changed from 2 to 1.

- **New currents:**
- IKr: Rapid component of the delayed rectifier K+ current. Original formulation. Maximal conductance is [K+] o -dependent.
- IKs: Slow component of the delayed rectifier K+ current. Original formulation. Maximal conductance is Ca2+ -dependent.
- ICa, T: T-type Ca2+ current. Original formulation.

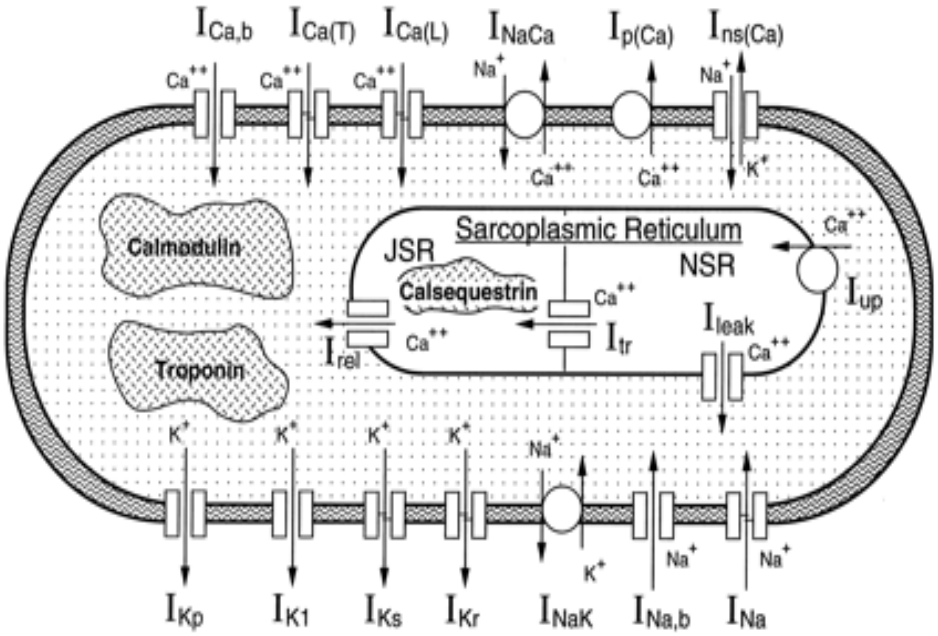


Figure 1.3 a dynamic model of the cardiac cell action potential LR95.

1.2.7 LRd1999 [9]:

Effects of IKr and IKs heterogeneity on action potential duration and its rate dependence: a simulation study.

A growing body of evidence suggests that heterogeneity of ion channel expression and electrophysiological characteristics is an important property of the ventricular myocardium. The 2 components of the delayed rectifier potassium current, IKr (rapid) and IKs (slow), play a dominant role in the repolarization of the action potential and are important determinants of its duration. The effects of heterogeneities of IKr and IKs on action potential duration (APD) and its rate dependence (adaptation) are studied with the use of the LRd model of a mammalian ventricular cell. The clinical significance of this study is in the context of repolarization abnormalities and associated arrhythmias (e.g., long QT syndrome and torsade de pointes).

Refinement of IKs, CICR (graded release without threshold) and formulation for three different cell types: epi-, mid- and endocardial. The default model cell (control), used in subsequent studies, is pericardial unless stated otherwise.

Specific changes compared with LRd95 (for the control epicedial cell):

IKs: Incorporation of a second xs gate (xs2). The first xs gate (xs1) is the same as the xs gate in LRd95. Reformulation of gKs max and its Ca2+ -dependence.

Irel, CICR: Reformulation of Gruel by adding a cubic tail to its initial formulation which involved a threshold (no CICR at all for a small entry of Ca2+). With this formulation, CICR always occurs (graded response even for a small entry of Ca2+).

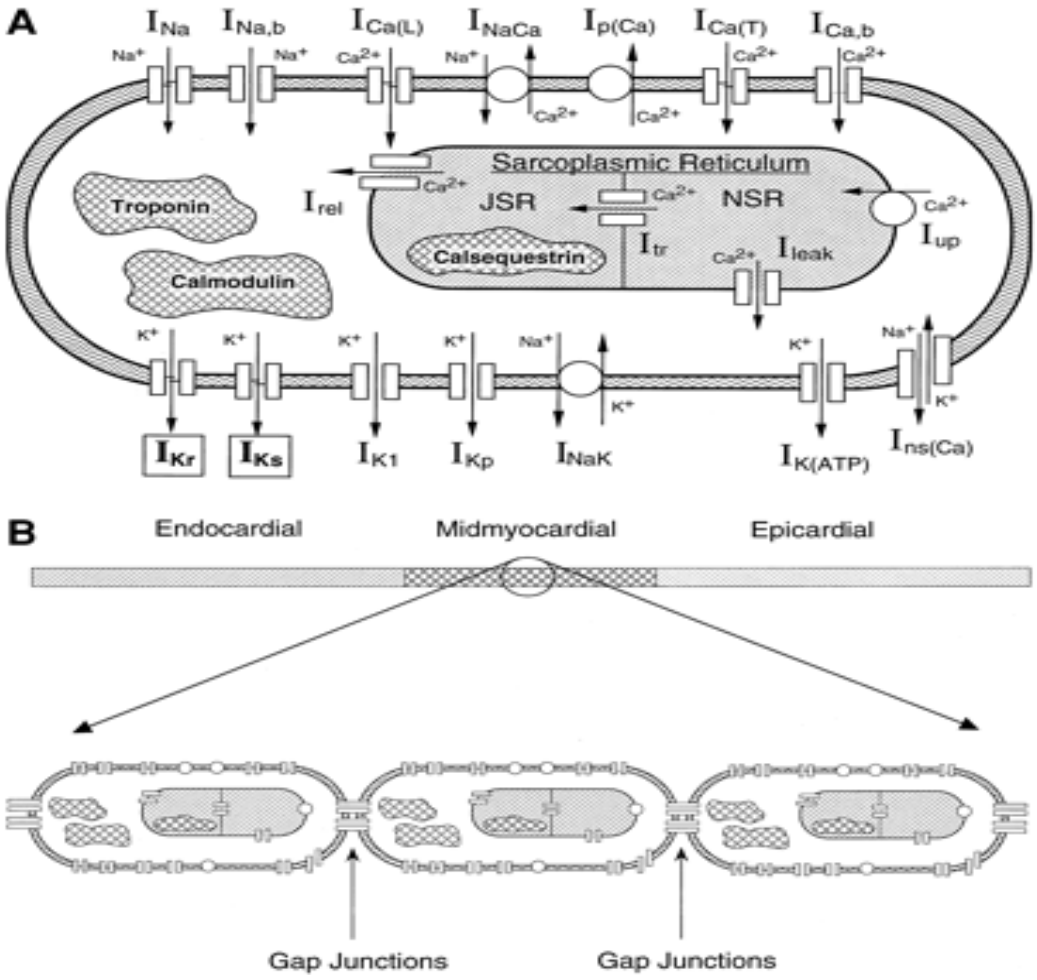


Figure 1.4 Effects of IKr and IKs on action potential in LR99 cell model.

1.2.8 LRd2000 [9]:

Action potential and contractility changes in [Na (+)] overloaded cardiac myositis: a simulation study. Biophys J 78:2392-404, 2000. The investigate show effects of elevated intracellular sodium on the cardiac action potential (AP) and on intracellular calcium using the Luo-Rudy model of a mammalian ventricular motet. By slowing AP depolarization (hence velocity) and shortening APD, Na+-overload acts to enhance indelibility of reentrant arrhythmias. Shortened APD with elevated [Ca2+] i (secondary to Na+-overload) also predisposes the myocardium to arrhythmogenic delayed after depolarization's.. Reformulation of CICR and INaCa. Formulation of the Na+ -activated K+ current, used to model cell behavior under Na+ overload conditions.

- **<u>Specific changes compared with LRd99:</u>**

  INaCa: Reformulation according to Varghese & Sell (1997).

  INaK: Increase of INa, K max from 2 to 2.25 µA/µF.

  Iup: Iup max increased from 0.005 to 0.00875 mmol/L/Ms.

  Irel, CICR: Original reformulation. Triggered by Ca2+ entry starting from the time of occurrence of dV/dtmax. CICR is graded, without threshold.

  Used to model cell behavior under Na+ -overload conditions ([Na+] i >10 mmol/L):

  IK (Na): Na+ -activated K+ current. Original formulation.

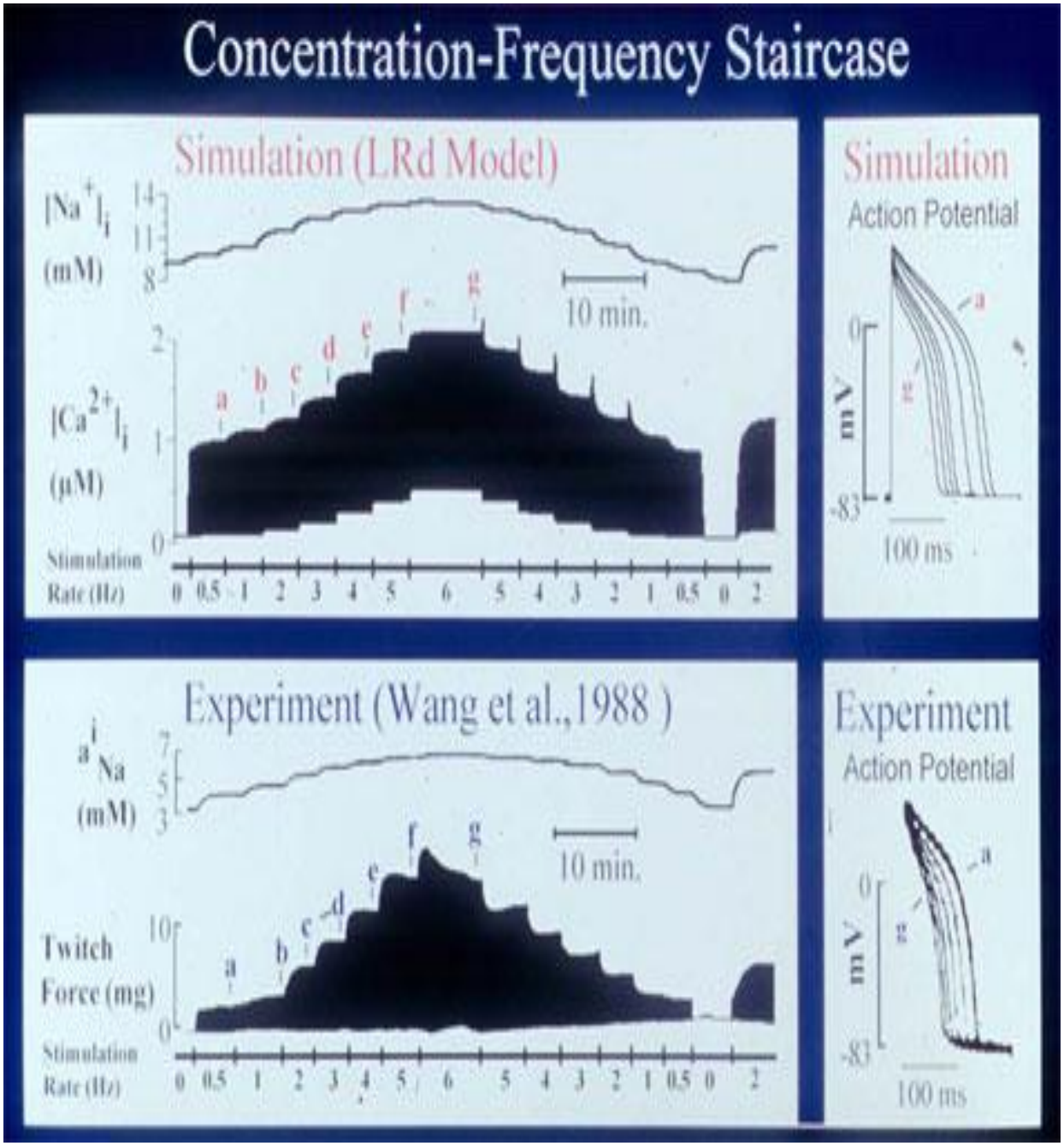


Figure 1.5 Effects of elevated intracellular sodium on
The cardiac action potential

1.2.9 LRd2007 [9]:

Regulation of Ca2+ and electrical alternans in cardiac myositis: role of CaMKII and repolarizing currents.

Livshitz and Rudy modified LRd, incorporating new findings in the relationship between Ca-transient, ICa (L) and SR Ca loading. This version of LRd shows AP and Ca-transient alternant at very fast pacing.

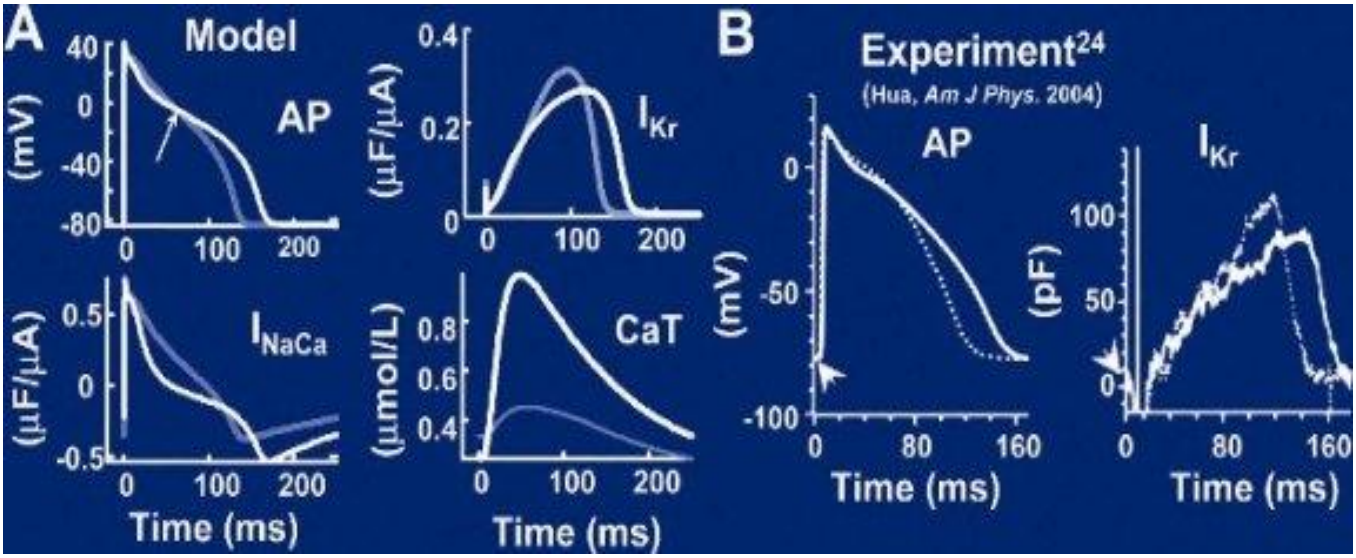


Figure 1.6 Alternant oscillation of the action potential (AP)
And possibly Ca2+ transient (CaT).

Alternant of cardiac repolarization is associated with arrhythmias and sudden death. At the cellular level, alternant involves beat-to-beat oscillation of the action potential (AP) and possibly Ca2+ transient (CaT). Because of experimental difficulty in independently controlling the Ca2+ and electrical subsystems, mathematical modelling provides additional insights into mechanisms and causality. Pacing protocols were conducted in a canine ventricular motet model with the following results: (I) CaT alter nans results from refractoriness of the SR Ca2+ release system; alternation of the L-type Ca2+ current (ICa(L)) has a negligible effect; (II) CaT-AP coupling during late AP occurs through the Na+/Ca2+ exchanger (INaCa) and underlies APD alter nans; (III) Increased Ca2+/calmodulin-dependent protein kinase II (CaMKII) activity extends the

range of CaT and APD alter nans to slower frequencies and increases alter nans magnitude; its decrease suppresses CaT and APD alter nans, exerting an antiarrhythmic effect; (IV). Increase of the rapid delayed rectifier current (IKr) also suppresses APD alter nans, but without suppressing CaT alternans. Thus, CaMKII inhibition eliminates APD alter nans by eliminating its cause (CaT alter nans), while IKr enhancement does so by weakening CaT-APD coupling. The simulations identify combined CaMKII inhibition and IKr enhancement as a possible antiarrhythmic intervention.

1.2.10 Gaur N, Rudy Y 2009 [9] :

Contributions of Ion Channel Currents to Ventriculart Action Potential Changes and Induction of Early Afterdepolarizations during Acute Hypoxia Variability in delivery of oxygen can lead to electric instability in the myocardium and the generation of arrhythmias increases the risk of developing ventricular

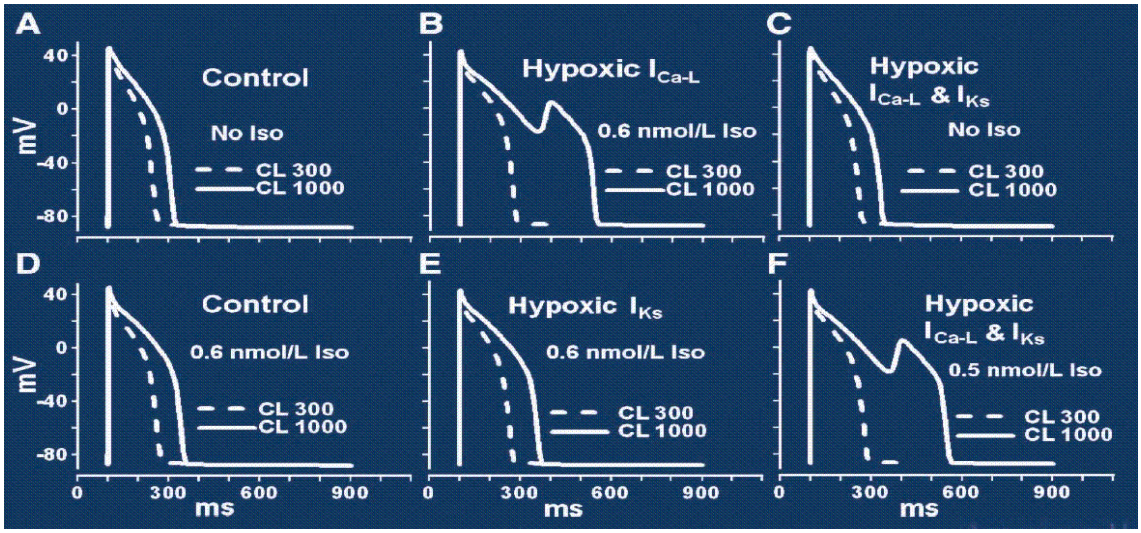


Figure 1.7 Effects of acute hypoxia and catecholamine's on The cardiac action potential**.**

CHAPITRE II

Methods and Materials

The cardiac myocyte is responsible for the coupling of electrical impulse to mechanical function, a process with so-called “excitation-contraction Coupling”. [10] Among the ions participating in the complex processes of the cardiac myocyte, Ca2+ may be the most important because it is directly involved in both electricity and mechanics. In the cardiac myocyte, dynamic change of ionic concentrations (Na+, K+, Ca2+,and Cl-), membrane voltage, time sequence and various regulatory Pathways determine the ion channel kinetics, which can be expressed as Mathematical formalisms.

There are several ion channels integrated in a Single cell, and their Interactions are intricate and nonlinear processes, making the single Cardiac cell an interacting system with high synergism and integration. These properties make it feasible to use the computational approach to analyze and elucidate the underlying mechanisms of the whole cardiac Cell.

This chapter describes the different approaches used to model the propagation and reentrant excitation in a multidimensional model of Cardiac tissue. The purpose of propagation models is to describe the activation and recovery of electrical activity in the heart.

The majority of these models are developed to understand the factors that contribute to conduction problems and the mechanisms associated with cardiac arrhythmias. They are considered as an approximate representation of the real physical system. The choice of model is based on several criteria. This study consists of two main parts: the first gives an overview of different approaches to simulate the propagation and the second discusses the approaches used to study the reentry.

The proposed Methods for studying the electrical activity can be divided into two parts:

1. Description of the kinetics of transmembrane ion currents.
2. Representation of the electrical properties of tissues.

The kinetics of ion currents describes the flow of ions between the Intracellular environment and the extracellular environment through the cell membrane. The flow associated with each ionic species is through Special channels. The mathematical representation of all ion currents constitutes the membrane model .Membrane models Contain three sub-models:

1. The analogy model wherein the model components of the Membrane are represented by electrical components.
2. The model of the door wherein the conductance of each channel is controlled by a number of separate doors.
3. The model of ion concentration that characterizes the concentration of certain ions between the intracellular and extracellular compartments.

2.1 CELL MEMBRANE POTENTIALS

2.1.1 Resting Membrane Potentials:

Cardiac cells, like all living cells in the body, have an electrical potential across the cell membrane. The outside of the cell is considered 0 mV. If measurements are taken with a resting ventricular myocyte, a membrane potential of about –90 mV will be recorded. This **resting membrane potential (Em)**

ION	Inside(mM)	Outside(mM)
Na+	20	145
K+	150	4
Ca++	0.0001	2.5
Cl-	25	140

Table 2.1 ion concentration inside and outside of resting myositis

The resting membrane potential (Em) is determined by the Concentrations of Positively and negatively charged ions across the cell membrane, the relative permeability of the cell Membrane to these ions, and the ionic pumps that transport ions across the cell membrane. [11]

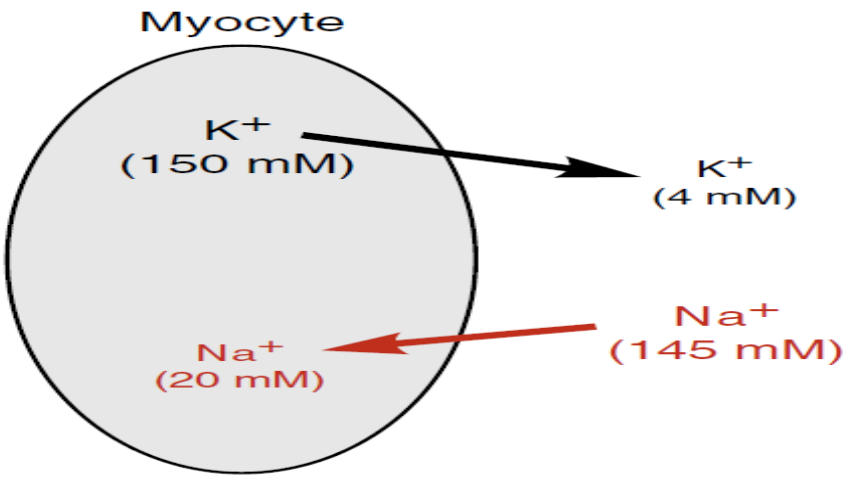


Figure 2.1 Concentrations of Na+ and K+ inside and Outside a cardiac myocyte.

2.1.2 Action Potentials:

The cardiac action potential is a short-lasting event in which the difference of potential between the interior and the exterior of each cardiac cell rises and falls following a consistent trajectory.[12] Action potentials are generated by the movement of ions through the transmembrane ion channels in the cardiac cells.[13] The cardiac action potential differs significantly in different portions of the heart. The heart is provided by a special excitatory system and a contractile system necessary to perform this function.

This differentiation of the action potentials allows the different electrical characteristics of the different portions of the heart. Action potentials occur when the membrane potential suddenly

Depolarizes and then repolarizes back to its resting state. The two general types of cardiac action potentials include no pacemaker and pacemaker action potentials. Nonpacemaker action potentials are triggered by depolarizing currents from adjacent cells, whereas pacemaker cells are capable of spontaneous action potential generation. Both types of action potentials in the heart differ considerably from the action potentials found in neural and skeletal muscle cells.

One major difference is the duration of the action potentials. In a typical nerve, the action potential duration is about 1 millisecond. In skeletal muscle cells, the action potential duration is approximately 2-5 ms. In contrast, the duration of ventricular action potentials ranges from 200 to 400 milliseconds. These differences among nerve, skeletal muscle, and cardiac myocyte action potentials relate to differences in the ionic conductances responsible for generating the changes in membrane potential. [14]

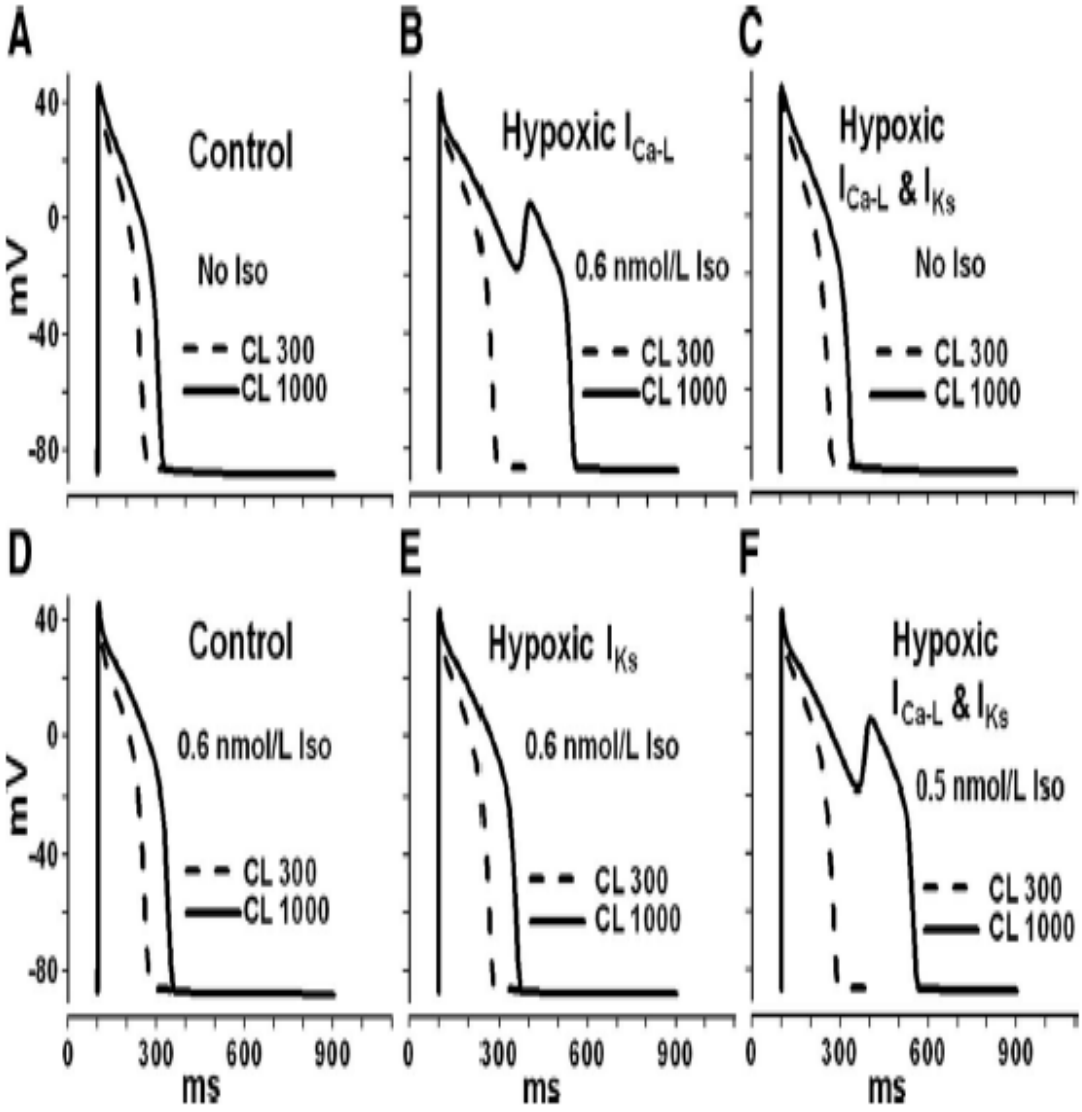


Figure 2.2 The effect of hypoxia and Iso on the AP.

2.1.3 Ion Channels:

As explained above, action potential is due to ion's motion inward and outward the cell. This ion current happens through the so-called Ion channels. Ion channels are proteins that reside in the cell membrane.

In response to external stimuli, such as changes in potential across the cell membrane, ion channels can form a pore, which allows movement of ions into or out of cells. The integrated behavior of thousands of ion channels in a single cell results in an ion current, and the integrated behavior of many ion currents makes up the characteristic cardiac

action potential. Thus, ion channels are the fundamental building blocks that determine the electrical activity of cardiac tissue.

Each ion has his specific channel or channels. On the other hand, each channel has gates which open and close under multiple triggering events. These channels are proteins composed by several subunits and under a stimulus these subunits open a gate creating an aqueous channel which permits the ion fast move through it. Without this aqueous medium ion's movement would be slow, crossing the lipid bilayer cellular membrane.[15]

These channels are selective for ions so there are Na^+, K^+, Ca^{2+}, and Cl^- channels, among others. And each ion can have some different channels which are used in different situations. Most of them are controlled by the membrane potential and are the so-called voltage-gated ion channels. Others, are ligand-gated channels what means they need the presence of a chemical ligand to open its gate.

Voltage-gated ion channels have transmembrane voltage sensors. Ligand-gated channels have receptors where the ligand will be bound to unleash an action.

Ion	Current (I)	α subunit protein	α subunit gene	Phase / role
Na+	Ina	NaV1.5	SCN5A[19]	0
Ca2+	ICa(L)	CaV1.2	CACNA1C[20]	0-2
K+	Ito1	KV4.2/4.3	KCND2/KCND3	1, notch
K+	IKs	KV7.1	KCNQ1	2,3
K+	IKr	KV11.1 (hERG)	KCNH2	3
K+	IK1	Kir2.1/2.2/2.3	CNJ2/KCNJ12/KCNJ4	3,4
a+, Ca2+	INaCa	3Na+-1Ca2+-exchanger	NCX1 (SLC8A1)	ion homeostasis
Na+, K+	INaK	3Na+-2K+-ATPase	ATP1A	ion homeostasis
Ca2+	IpCa	Ca2+-transporting ATPase	ATP1B	ion homeostasis

Table 2.2 Major currents during the cardiac ventricular Action potential

Everything is regulated by genes. Most of these mechanisms are yet under research and belong to molecular biology. The complexity of this subject is enormous and here is not the right place to discuss it.[13]

As an example here is a table with the major ion currents their subunit proteins, some of their controlling genes and the action potential phase where they act.

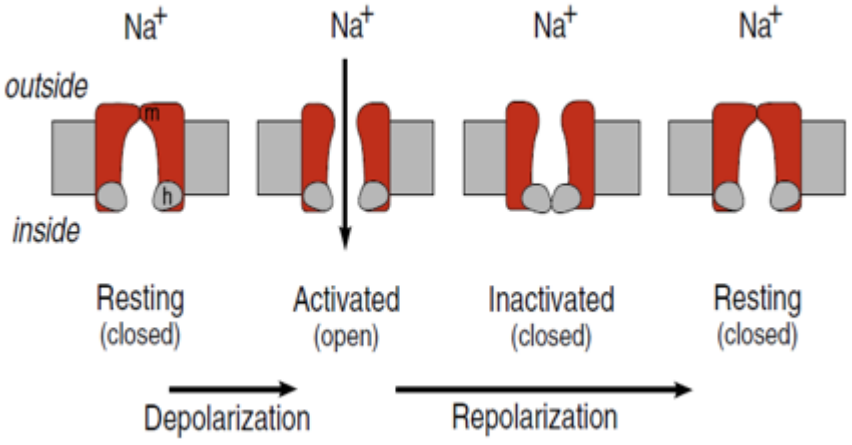


Figure 2.3 open and closed states of fast sodium channels in Cardiac myocytes.

The flow of the Ionic currents across the membrane is introduced to each segment. Type reaction diffusion equation was used to describe the propagation in cables. By this method, it aims to simulate the spread and re-entry to identify factors that play a key role in the generation and maintenance of cardiac arrhythmias. We will describe the membrane model used with the electrical Analogy and kinetics of the doors. And the model used to Study the propagation including defined assumptions, Conditions at the borders

- **Effects of Hypoxia on Ion Channels**

Hypoxia decreases INa and increases INa-L in ventricular myocytes. 14–16 The effect of hypoxia on the sodium current was modeled by reducing conductance of INa by 10% and increasing the conductance of INa-L so that current was in the range of 0.1 to 0.5% of INaas seen experimentally. 15 Hypoxia decreases basal ICa-L and IKs in the absence of _-AR stimulation.

10, 11 Hypoxia also decreases K0.5for activation of ICa-L and IKs by Iso. 10, 11 both of these effects were included in the model. These responses are reversible with an increase in oxygen tension to normoxia (room oxygen).

2.1.4 Cell MODEL:

The membrane model describes the flow of the Ionic currents between the intracellular and extracellular environments.

- **Cell Model:**

The theoretical dynamic model of a mammalian ventricular AP, the Luo–Rudy model, provides the basis for the simulations. The model is predominantly based on guinea pig experimental data.

The membrane ionic channel currents are formulated mathematically using Hodgkin–Huxley formalism. Ionic pumps and exchangers are also included in the model. The model accounts for processes that regulate intracellular ionic concentration changes of Na, K, and Ca. Intracellular processes represented in the model include Ca uptake and Ca release by the sarcoplasmic reticulum (SR) and the buffering of Ca by calmodulin and troponin (in the myoplasm) and calsequestrin (in the SR). For the Na–Ca exchanger, the model uses a formulation based on conservation principle.

Experimental data on voltage dependence of conductance and open time duration14, 16 were used to formulate and include a model of INa-L in the model. β-AR effects were included in the model by using the K0.5 for enhancement of ICa-L and IKs caused by Iso as observed experimentally 10,11 and by up regulation of SR Ca uptake. Iso effect on inward rectifying potassium current (IK1)25 was also considered in simulations of the progressive effect of hypoxia on APs.

2.1.5 Equations for Theoretical Modeling:

A complete list of model equations and definitions of the Luo-Rudy Model Equivalent circuit of the cable. The extracellular medium is an Infinite medium of very low resistivity $_R$. R_I is the axial Resistance of the intracellular environment. V is the transmembrane potential. I_{ax} is the axial current I_C is the capacitive current, I_m is the current membrane and I_{ion} the ion current. In this study, we used the model membrane developed by Luo and Rudy phase 1. It is based on the digital reconstruction of ventricular action potentia. The dynamics of the membrane potential is described by the following equation:

$$I_{stim} = C_m \frac{dV}{dt} + I_{ion} \qquad \text{(Equation 1)}$$

Where: C_m represents the specific capacity of the membrane inpF/cm^2,

I_{stim} The stimulation current inμA/cm^2,

V is the membrane potential in mV.

The first term of (equation 1) right corresponds to the membrane capacitive current in□A/cm^2, is the total ion current en□A/cm^2. It is equal to the sum of the currents representing each ionic species. The wording of each of these currents is in annex 1.

I_{ion} = ina+ inap+ ical+ icat+ ikr+ iks+ iki+ ikp+ ikna+ ikatp+ ito+ inaca+ inak+ insca+ ipca+ icab+ inab *(Equation 2)*

Nonlinear currents in the membrane model are described by the model of doors. These currents are expressed according to the formulation of Hodgkin-Huxley [28]. Conductance of each channel is controlled by a number of independent doors. These doors are in a State of open or closed state. Ions pass through the channels when all doors are in the open State. The average proportion of door which is located in the open State is written:

$$\frac{dy}{dt} = (y_\infty - y)/\tau_y = \alpha_y(1-y) - \beta_y y \qquad (3)$$

With

$$y_\infty = \alpha_y/(\alpha_y + \beta_y)$$
$$\tau_y = 1/(\alpha_y + \beta_y) \qquad (4)$$

Where: y is the proportion of door in the open State,

Y_∞ is the value of y to the stable State which depends on the potential

τ_Y is the time constant

α_y And β_y are functions that depend on the potential V.

α_y

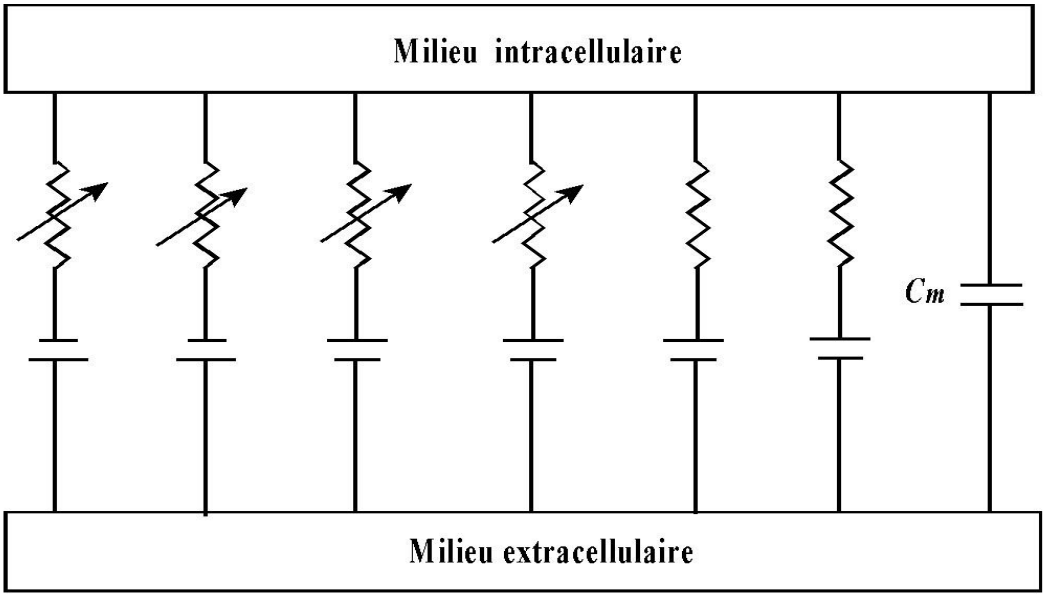


Figure 2.4 Equivalent circuit of the membrane model of Luo-Rudy.

Each ionic species is represented by a battery in series with a Conductance. The membrane is represented by a set of ionic species in Parallel with the capacity of the membrane. The intracellular and Extracellular potassium and Sodium concentrations are $[Na]_i$, $[K]_i$, $[Na]_e$, $[K]_e$ respectively. The nominal values of the parameters of the Membrane are listed in table 3.1. The current sodium I_{Na} is controlled by an activation gate *m* as well as two doors of inactivation *h* and *j*.

The slow current returning $_{If}I$ is characterized by an activation gate *d* and an inactivation gate *f*. Time dependent potassium current I_k depends on the variable x.

Parameter	**Definition**	**Nominal Value**
C_m	Membrane capacity	1.0 F/cm^2
$\overline{g}_{Na}$	Maximum conductance for I_{Na}	23 mS/cm^2
$\overline{g}_{si}$	Maximum conductance for $_{If}I$	0.09 mS/cm^2
$\overline{g}_K$	Maximum conductance for I_K	0.282 mS/cm^2

$\bar{g}_{K1}$	Maximum conductance for I_{K1}	0.6013 mS/cm^2
$\bar{g}_{Kp}$	Maximum conductance for I_{Kp}	0.0184 mS/cm^2
$\bar{g}_b$	Maximum conductance for $_b I$	0.02438 mS/cm^2
E_{Na}	I_{Na} reversal potential	54.00 mV
E_K	Reversal potential of I_K	-77.00 mV
E_{K1}	Reversal potential of I_{K1}	-238.26 mV
V_r	Resting potential	-84.00 mV
[$[Na]_i$	Intracellular Sodium concentration	18 mM
[$[Na]_e$	Extracellular Sodium concentration	140 mM
[$[K]_i$	Intracellular Potassium concentration	145 mM
$[K]_e$	Extracellular Potassium concentration	.4 mM

Table 2.3 Nominal values of the parameters of the membrane with the Intracellular concentrations and extracelluaires and their respective Reversal potentials.

2.1.6 INPUT CURRENT:

The sodium current is responsible for depolarization of the membrane during the rise of the action potential. It is expressed by the following equation:

$$I_{Na} = \bar{g}_{Na}.m^3.h.j.(V - E_{Na}) \qquad (5)$$

Where $\bar{g}_{Na}$ the maximum conductance of the sodium channel and V is the membrane potential. *M* is the variable of activation, *h* and *j* are the variables of inactivation. E_{Na} is the reversal potential of sodium which is calculated by the following equation:

$$E_{Na} = \frac{RT}{F}.\ln(\frac{[Na]_e}{[Na]_i}) \qquad (6)$$

Where R is the Boltzmann constant, T is the absolute temperature, and F is the Faraday constant. $[Na]_i$ and $[Na]_e$ are intracellular and extracellular sodium ion concentrations respectively. The current I_{If} is an inward slow which is associated with the ion current Na^+ and Ca^{2+}. This current is responsible for the formation of the plateau of the action potential. It is given by the following expression:

$$I_{si} = \bar{g}_{si}.d.f.(V - E_{si}) \qquad (7)$$

$\bar{g}_{si}$ Is the maximum conductance of calcium channel? D and f are the dynamic variables of activation and inactivation and E_{If} is the reversal potential is given by the following expression:

$$E_{si} = 7.7 - 13.0287.\ln([Ca]_i) \qquad (8)$$

$$\frac{d[Ca]_i}{dt} = -10^{-4}.I_{si} + 0.07(10^{-4} - [Ca]_i) \qquad (9)$$

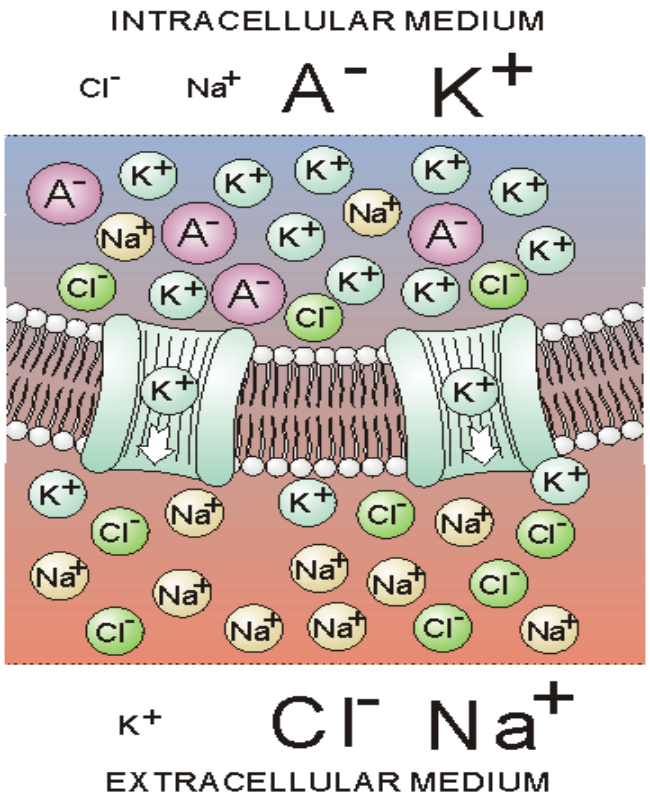


Figure 2.5 Intracellular and extracellular ions in the medium.

2.1.7 OUTPUT CURRENT:

The dependent potassium current of time is controlled by a gate of activation X depending on time and an independent inactivation X_i door of time. It is given by the following expression:

$$I_K = \overline{G}_K . X . X_i . (V - E_K) \qquad (10)$$

X_I introduces the property of rectification of the current I_K. And E_K are given by:

$$\overline{G}_K = 0.282 . \sqrt{[K]_e / 5.4} \qquad (11)$$

$$E_K = \frac{RT}{F} . \ln\left(\frac{[K]_e + PR_{NaK} . [Na]_e}{[K]_i + PR_{NaK} . [Na]_i} \right) \qquad (12)$$

PR_{NaK} is the ratio of permeability of Na / K. The independent potassium current of time I_{K1} depends on the potential membrane E_{K1} and $_e\,[K]$. It is given by:

$$I_{K1} = \overline{G}_{K1} . K1_\infty . (V - E_{K1}) \qquad (13)$$

$\overline{G}_{K1}$ Is the conductance of the current I_{K1}, K_1 □ is the inactivation gate and E_{K1} is the potential for reversal for this channel. These expressions are given by:

$$E_{K1} = \frac{RT}{F} . \ln\left(\frac{[K]_o}{[K]_i}\right) \qquad (14)$$

$$K1_\infty = \frac{\alpha_{K1}}{\alpha_{K1} + \beta_{K1}} \qquad (15)$$

$$\overline{G}_{K1} = 0.6047 . \sqrt{[K]_o / 5.4} \qquad (16)$$

The potassium current of the tray I_{Kp} and leakage I_b are given by:

$$I_{Kp} = \overline{g}_{Kp} . K_p . (V - E_{Kp}) \qquad (17)$$

$$I_b = \overline{g}_b . K_p . (V - E_b) \qquad (18)$$

Below are the equations that are added and/or modified for the simulations in this article.

Definitions of Variables and Parameters:

K50Iso: K0.5 of activation of L-type Ca channel current (ICa-L) or slowly activated delayed rectifier potassium current (IKs) in response to Isoproterenol (Iso) in nmol/L

Isofactor: change factor of ICa-L or IKs due to Iso

Iso: concentration of Iso (nmol/L)

ilca: calcium (Ca2+) current through L-type channels (μA/μF)

ilcana: sodium (Na+) current through L-type channels (μA/μF)

ilcak: potassium (K+) current through L-type channels (μA/μF)

ilcatot: total current through L-type channels (μA/μF)

d: voltage dependent activation gate of ICa-L

f: voltage dependent inactivation gate of ICa-L

fca: Ca2+ dependent inactivation gate of ICa-L

ibarca: max. Ca2+ current through L-type channels (μA/μF)

ibarna: max. Na+ current through L-type channels (μA/μF)

ibark: max. K+ current through L-type channels (μA/μF)

iks: current through slowly activated delayed rectifier K+ channels (μA/μF)

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gks: max. conductance of *I*Ks (mS.μF-1)

xs1: fast activation gate of *I*Ks

xs2: slow activation gate of *I*Ks

eks: reversal potential of *I*Ks (mV)

ainap: rate of activation of late Na+ current (*I*Na-L) (ms-1)

binap: rate of deactivation of *I*Na-L (ms-1)

p: activation gate of *I*Na-L

pss: steady state value of activation gate of *I*Na-L

taup: time constant of activation gate of *I*Na-L

gna: max. conductance of fast Na+ current (mS.µF-1)

inap: late Na+ current (µA.µF-1)

ina: fast Na+ current (µA.µF-1)

v: membrane potential (mV)

ena: reversal potential of Na+ current (mV)

iup: rate of Ca2+ uptake from myoplasm to network sarcoplasmic reticulum (NSR) (mmol.L-1.ms-1)

iupbar: max. rate of Ca2+ uptake from myoplasm to NSR (mmol.L-1.ms-1)

cai: myoplasmic Ca2+ concentration (µmol.L-1.µF-1)

kmup: half saturation concentration of iup (mmol.L-1)

iki: current through inward rectifier K+ channels (IK1) (µA.µF-1)

gki: max. conductance of *iki* (mS.µF-1)

eki: reversal potential of K+ currents (mV)

kin: inactivation gate of *I*K1

Model Equations:

L-Type Calcium Current, *I*Ca-L

K50Iso = 5.3 for Control Conditions

K50Iso = 1.6 for Hypoxic Conditions

$$Isofactor = 1 + \frac{3}{1+10^{\log_{10}(k50Iso)-\log_{10}(Iso)}} \quad \text{for Control Conditions}$$

$$Isofactor = 0.75 + \frac{3}{1+10^{\log_{10}(k50Iso)-\log_{10}(Iso)}} \quad \text{for Hypoxic Conditions}$$

(19)

*ilca = Isofactor*d*f*fca*ibarca*

*ilcana = Isofactor*d*f*fca*ibarna*

*ilcak = Isofactor*d*f*fca*ibark*

ilcatot = ilca + ilcana + ilcak

Iso = 0.0001 (~0) for non β-adrenergic conditions

Slowly Activating Delayed Rectifier Potassium Current, *I*Ks

K50Iso = 15 for Control Conditions

K50Iso = 1.5 for Hypoxic Conditions

$$Isofactor = 0.3 + \frac{0.6}{1+10^{\log_{10}(k50Iso)-\log_{10}(Iso)}} \text{ for Control Conditions}$$

$$Isofactor = 0.22 + \frac{0.6}{1+10^{\log_{10}(k50Iso)-\log_{10}(Iso)}} \text{ for Hypoxic Conditions}$$

(20)

*iks = Isofactor*gks*xs1*xs2*(v-eks)* (21)

Iso = 0.0001 (~0) for non β-adrenergic conditions

Late Sodium Current, *I*NaL

$$ainap = 19^{*}\exp\left(\frac{v}{16.5}\right)$$

$$binap = 0.2^{*}\exp\left(\frac{-v}{20}\right)$$

$$pss = \left(\frac{ainap}{ainap+binap}\right)$$

$$taup = \left(\frac{1}{ainap+binap}\right)$$

$$p = pss - (pss\text{-}p)^{*}\exp\left(\frac{-dt}{taup}\right)$$

*inap = 0.00007*gna*p3 *(v-ena)* for Control Conditions

*inap = 0.00018*gna*p3 *(v-ena)* for Hypoxic Conditions

Fast Sodium Current, *I*Na

gna = 16 for Control Conditions

gna = 14.4 for Hypoxic Conditions

Transient Outward K+ current, *I*to1

A recently published model of Ito1

1 was used in the simulations when looking

Into the effects of Hypoxia and Iso in the presence of *I*to1.

SR Ca2+ Uptake

$$iup = 1.5*iupbar*\left(\frac{cai}{cai + kmup}\right) \text{ for β-adrenergic conditions}$$

$$iup = iupbar*\left(\frac{cai}{cai + kmup}\right) \text{ for non β-adrenergic conditions}$$

Experiments by Koumi *et al.*2 indicates that the open probability of *I*K1

Channels decreases to 21±4% of its normal value during exposure to Iso.

We incorporate this effect in the model by reducing *I*K1 to 25% of its normal value.

*iki = 0.25*gki*kin*(v-eki)*

Time-dependent changes of *I*Ca-L and *I*Ks due to Iso

For less than 50 beats

Isofactor = Isofactor(i/50)*, where i is the beat number

For more than 50 beats

Isofactor = Isofactor

	Modeled data						Experimental data		
	normoxia	hypoxia (all)	normoxia +iso	hypoxia + iso (I_{Ca-L})	hypoxia + iso (I_{Ks})	hypoxia + iso (I_{Ca-L}+I_{Ks})	normoxia	hypoxia	hypoxia + 3nM iso
RMP (mV)	-88	-88	-88	-87	-88	-87	-82 ± 1.5	-81.2 ± 1.9	-82.1 ± 2.9
APP (mV)	47	45	46	44	44	44	42.3 ± 1.8	42.5 ± 1.1	42.3 ± 1.4
APD (ms)	225	219	244	445	284	457	226 ± 12.8	213 ± 13.1	291.8 ± 12.2#
MRD (mV/ms)							138 ± 8	136 ± 9	135 ± 13
EAD formation	no	no	no	yes	no	yes	no	no	yes (3 cells)
n							10	10	7

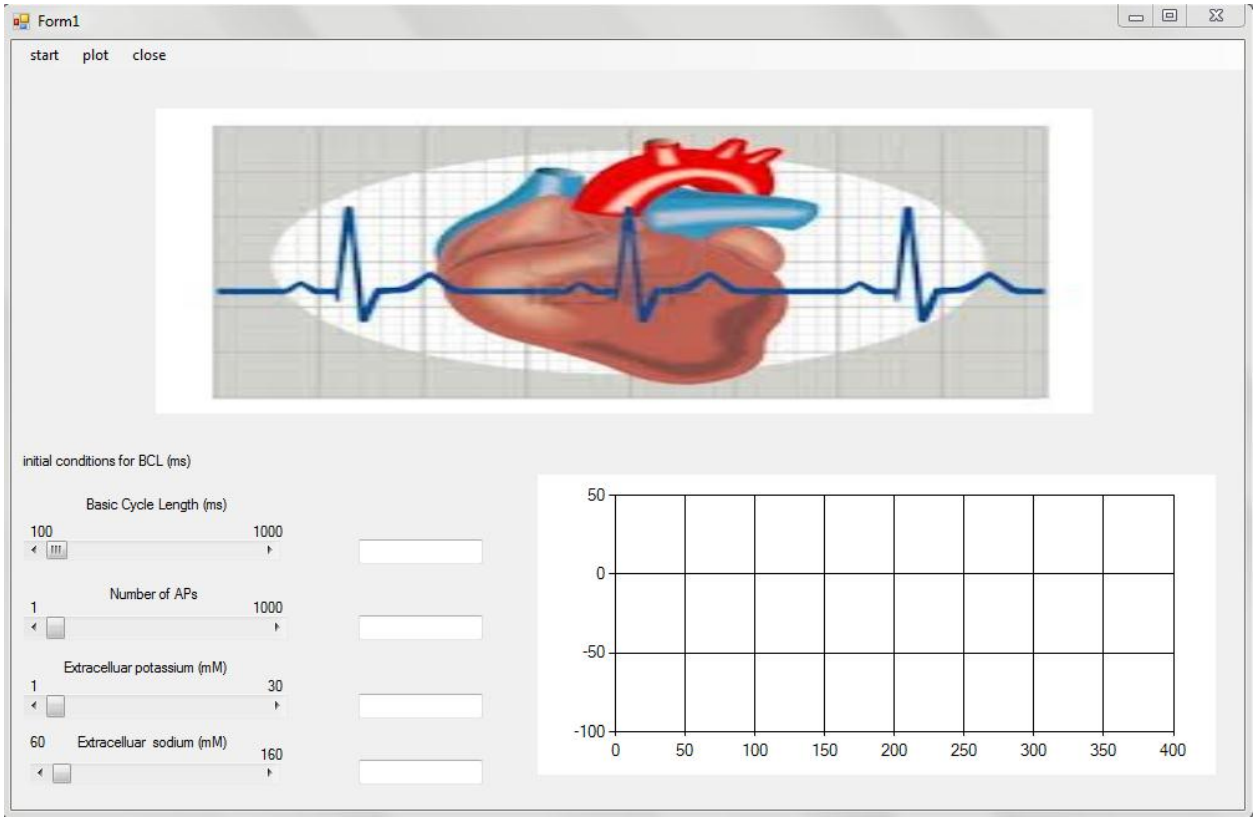
Table 2.4 the effect of hypoxia on action potential parameters

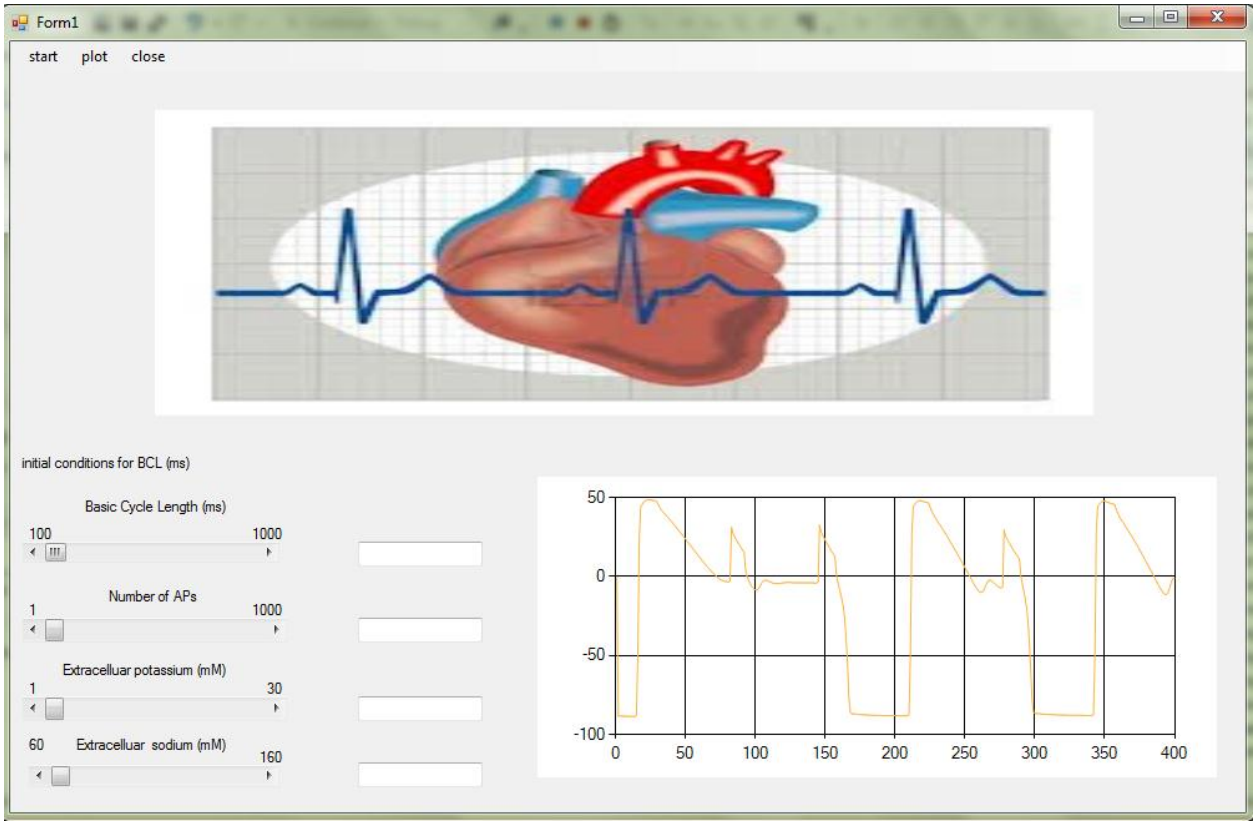
Results

We incorporated all published data on the effects of hypoxia on the late Na_ current (*I*Na-L), the fast Na_ current (*I*Na), the basal L-type Ca2_ channel current (*I*Ca-L), and the slow (*I*Ks) and rapid components of the delayed rectifier K_-current (*I*Kr) into the Luo–Rudy model of the action potential.

However in the presence of AR stimulation, hypoxia caused a prolongation of the action potential and early after depolarization's (EADs) and spontaneous tachycardia were induced. Experiments performed in guinea pig ventricular myocytes confirmed the modeling results.

Our interface with result:





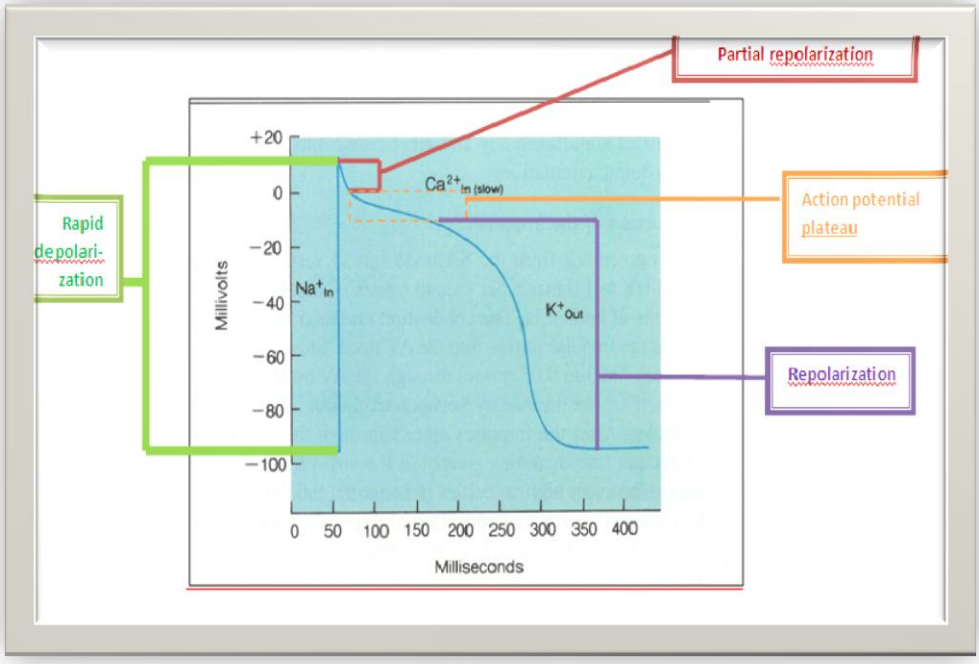


Figure 2.6 action potential.

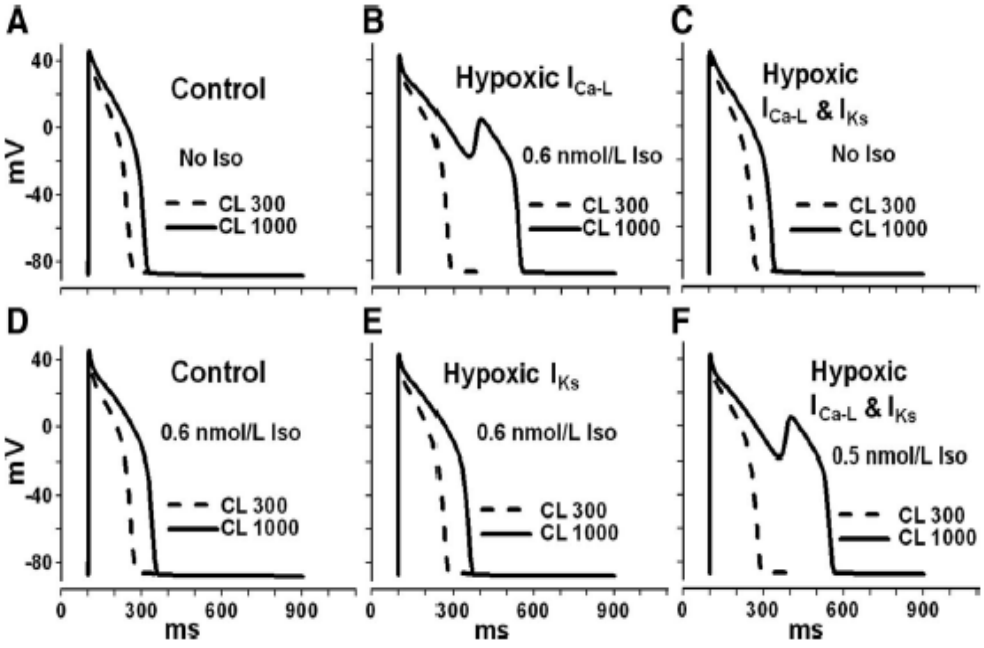


Figure 2.7 The effect of hypoxia on the AP.

t	v	inap	ical	ikp
6.9	-88.1906	-0.00139042	2.39955e-017	1.5436e-009
14.4	-88.2248	-0.000353228	6.77529e-015	1.54407e-009
21.9	-88.2664	-8.97884e-005	6.92564e-015	1.56682e-009
29.4	-88.3046	-2.28332e-005	7.04385e-015	1.585e-009
36.9	-88.339	-5.80844e-006	7.13883e-015	1.59948e-009
44.4	-88.3701	-1.47797e-006	7.21433e-015	1.61091e-009
51.9	-88.398	-3.76148e-007	7.27348e-015	1.61982e-009
59.4	-88.4231	-9.5746e-008	7.31898e-015	1.62665e-009
66.9	-88.4456	-2.43744e-008	7.35311e-015	1.63176e-009
74.4	-88.4658	-6.20563e-009	7.37779e-015	1.63545e-009
81.9	-88.4839	-1.58003e-009	7.39466e-015	1.63799e-009

89.4	-88.5001	-4.02309e-010	7.40509e-015	1.63956e-009
96.9	-88.5147	-1.02439e-010	7.41022e-015	1.64034e-009
100.01	-87.7209	-2.60839e-011	7.411e-015	1.64049e-009
100.51	-49.1102	-6.64169e-012	7.40821e-015	1.6401e-009
101.01	23.208	-1.69114e-012	7.40251e-015	1.63928e-009
101.51	44.0161	-4.30596e-013	7.39445e-015	1.63811e-009
102.01	45.4795	-1.09635e-013	7.38447e-015	1.63665e-009
102.51	46.7364	-2.79135e-014	7.37295e-015	1.63497e-009
103.01	47.7466	-7.10661e-015	7.36017e-015	1.63309e-009
103.51	48.3894	-1.80923e-015	7.34641e-015	1.63106e-009
104.01	48.6458	-4.6058e-016	7.33186e-015	1.62891e-009
104.51	48.6225	-1.17246e-016	7.31669e-015	1.62667e-009
105.01	48.47	-2.98448e-017	7.30104e-015	1.62435e-009
105.51	48.2888	-7.5966e-018	7.28502e-015	1.62197e-009
106.01	48.1237	-1.93352e-018	7.26874e-015	1.61955e-009
106.51	47.9866	-4.92102e-019	7.25227e-015	1.6171e-009
107.01	47.8759	-1.25239e-019	7.23566e-015	1.61462e-009
114.51	46.6131	-3.18714e-020	7.21898e-015	1.61212e-009
122.01	44.8115	-8.11038e-021	7.20226e-015	1.60962e-009
129.51	43.2234	-2.06376e-021	7.18554e-015	1.60711e-009
137.01	41.9543	-5.25113e-022	7.16884e-015	1.6046e-009
144.51	40.8734	-1.33605e-022	7.15219e-015	1.60209e-009
152.01	39.8779	-3.39917e-023	7.13561e-015	1.59959e-009
159.51	38.9099	-8.64768e-024	7.1191e-015	1.5971e-009
167.01	37.9394	-2.1999e-024	7.10269e-015	1.59462e-009
174.51	36.9524	-5.59609e-025	7.08639e-015	1.59215e-009
182.01	35.9436	-1.42346e-025	7.07019e-015	1.58969e-009
189.51	34.9124	-3.6206e-026	7.0541e-015	1.58724e-009
197.01	33.8602	-9.20864e-027	7.03814e-015	1.58481e-009

200.02	34.2095	-2.34201e-027	7.0223e-015	1.5824e-009

Table 3.1 *Some values for time (t), v, and some of currents*

Discussion and Future Research

Although it is well recognized that arrhythmias are a significant cause of death in ischemic heart disease, the role of acute hypoxia in induction of arrhythmia is not well understood.

A published data reporting the effects of acute hypoxia on INa, INa-L, ICa-L, IKs, and IKr into the Luo–Rudy model of a cardiac ventricular AP are incorporated and have been determined the effect on AP morphology and APD. In the absence of β-AR stimulation, hypoxia has little effect on the AP even when we modeled the effects of hypoxia on INa-L and INa at twice the rates reported in published studies. In the presence

of β-AR stimulation in a paced cell, EADs are generated only at CL of 1000 ms when the effects of hypoxia on ICa-L are modeled alone or together with hypoxic IKs.

Experimental results confirm the modeling results similar results were obtained for pause-induced EADs at a shorter CL of 300 ms. EADs quickly degenerate into spontaneous tachycardia only in a hypoxic cell in the presence of 1 nmol/L Iso when we also include the effect of Iso on IK1. Oxygen is the substrate for the production of reactive oxygen species. A rapid decrease in oxygen tension that is not energy limiting (and not ATP depleting; thus, ATP-dependent potassium current [IKATP] is not activated) is associated with a decrease in cellular reactive oxygen species and a more reduced cellular redox state. Electrophysiological effects of acute myocardial ischemia where there is complete cessation of perfusion and IKATP plays an important role have been investigated elsewhere. The increase in sensitivity of ICa-L to Iso during hypoxia occurs as a result of modification of thiol groups on the channel or a regulatory protein such as protein kinase A because exposing myocytes to dithiothreitol and intracellular perfusion with catalase mimic the effect of hypoxia.

Our results suggest that a reduced redox state is protective with respect to cellular excitability because we could not induce EADs in a native cell during hypoxia or when modeling hypoxia alone. However, in the presence of β-AR stimulation, an increase in calcium influx through ICa-L prolongs APD and triggers EADs. The frequency of EADs is influenced by the modal gating of ICa-L. Increased ratios of channels gating in mode 2 (that occurs with β-AR stimulation) Are associated with increased frequency of EADs.

Sympathetic stimulation increases the risk of arrhythmia.

B-Blockers are the only class of antiarrhythmic that have been demonstrated to decrease mortality. The results of this study are consistent with previously published data indicating that decreasing calcium influx through the channel or decreasing adrenergic stimulation can reduce the incidence of EADs. Cacalmodulin– dependent protein kinase II inhibitory peptide can eliminate EADs and ventricular tachycardia, 38 as can protein kinase an inhibitors and β-AR antagonists. We conclude that ICa-L is the primary initiator of EADs

and spontaneous tachycardia occurs during hypoxia as a result of increased sensitivity of the channel to β-AR stimulation.

The results obtained in our model is comparable to those published before and we change any parameter of the currents via the interface that we build. This interface simplify the simulation instead of going through the code and change the parameters manually.

This research is first step in simulation of one cardiac cell and the effects of the hypoxia on the ion currents and action potential.

It can continue to simulate more than one cell "cardiac tissue" or the all cells of the cardiac and do a 2D or 3D model of it to see the effects of hypoxia on the cardiac activity.

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Appendix 1:

Code of the project:

// wfa.cpp: main project file.

```
#include "stdafx.h"
#include "Form1.h"
#include <iostream>
#include <iomanip>
#include <math.h>
#include <fstream>
#include <cstdlib>
#include <stdio.h>
#include <iostream>
```

```
#include <string>
using namespace std;
using namespace wfa;
double  bcl ;       // Basic Cycle Length (ms)
#define beats  10  // Number of Beats



/* List of variables and parameters (this code uses all global variables) */
void prttofile ();
int printdata;
int printval;



//saved data
int counter = 0;
double saveValuesTime[2000];
double saveValuesVolt[2000];
double saveValuesCa[2000];
double saveValuesK[2000];
double saveValuesNa[2000];

/* Cell Geometry */
const double l = 0.01; // Length of the cell (cm)
const double a = 0.0011; // Radius of the cell (cm)
const double pi = 3.141592; // Pi
double vcell; // Cell volume (uL)
double ageo; // Geometric membrane area (cm^2)
double acap; // Capacitive membrane area (cm^2)
double vmyo; // Myoplasm volume (uL)
double vmito; // Mitochondria volume (uL)
double vsr; // SR volume (uL)
double vnsr; // NSR volume (uL)
```

```
double vjsr; // JSR volume (uL)
double vcleft; // Cleft volume (uL)



/* Voltage */
double v; // Membrane voltage (mV)
double vnew; // New Voltage (mV)
double dvdt; // Change in Voltage / Change in Time (mV/ms)
double dvdtnew; // New dv/dt (mV/ms)
double flag; // Flag condition to test for dvdtmax



/* Time Step */
double dt; // Time step (ms)
double t; // Time (ms)
double udt; // Universal Time Step
int utsc; // Universal Time Step Counter
int nxstep; // Interval Between Calculating Ion Currents
int steps; // Number of Steps
int increment; // Loop Control Variable



/* Action Potential Duration and Max. Info */
double vmax [beats] ; // Max. Voltage (mV)
double dvdtmax [beats] ; // Max. dv/dt (mV/ms)
double apd [beats] ; // Action Potential Duration
double toneapd [beats] ; // Time of dv/dt Max.
double ttwoapd [beats] ; // Time of 90% Repolarization
double rmbp [beats] ; // Resting Membrane Potential
double nair [beats] ; // Intracellular Na At Rest
```

```
double cair [beats] ; // Intracellular Ca At Rest
double kir [beats] ; // Intracellular K At Rest
double caimax [beats] ; // Peak Intracellular Ca
int i; // Stimulation Counter


/* Total Current and Stimulus */
double st; // Constant Stimulus (uA/cm^2)
double tstim; // Time Stimulus is Applied (ms)
double stimtime; // Time period during which stimulus is applied (ms)
double it; // Total current (uA/cm^2)


/* Terms for Solution of Conductance and Reversal Potential */
const double R = 8314; // Universal Gas Constant (J/kmol*K)
const double frdy = 96485; // Faraday's Constant (C/mol)
const double temp = 310; // Temperature (K)


/* Ion Valences */
const double zna = 1; // Na valence
const double zk = 1; // K valence
const double zca = 2; // Ca valence


/* Ion Concentrations */
double nai; // Intracellular Na Concentration (mM)
double nao; // Extracellular Na Concentration (mM)
double nabm; // Bulk Medium Na Concentration (mM)
```

```
double dnao; // Change in Cleft Na Concentration (mM)
double ki; // Intracellular K Concentration (mM)
double ko; // Extracellular K Concentration (mM)
double kbm; // Bulk Medium K Concentration (mM)
double dko; // Change in Cleft K Concentration (mM)
double cai; // Intracellular Ca Concentration (mM)
double cao; // Extracellular Ca Concentration (mM)
double cabm; // Bulk Medium Ca Concentration (mM)
double dcao; // Change in Cleft Ca Concentration (mM)
double cmdn; // Calmodulin Buffered Ca Concentration (mM)
double trpn; // Troponin Buffered Ca Concentration (mM)
double nsr; // NSR Ca Concentration (mM)
double jsr; // JSR Ca Concentration (mM)
double csqn; // Calsequestrin Buffered Ca Concentration (mM)
const double taudiff = 1000; // Diffusion Constant for Ion Movement from Bulk Medium to Cleft Space


/* Myoplasmic Na Ion Concentration Changes */
double naiont; // Total Na Ion Flow (uA/uF)
double dnai; // Change in Intracellular Na Concentration (mM)


/* Myoplasmic K Ion Concentration Changes */
double kiont; // Total K Ion Flow (uA/uF)
double dki; // Change in Intracellular K Concentration (mM)


/* NSR Ca Ion Concentration Changes */
double dnsr; // Change in [Ca] in the NSR (mM)
double iup; // Ca uptake from myo. to NSR (mM/ms)
double ileak; // Ca leakage from NSR to myo. (mM/ms)
```

```
double kleak; // Rate constant of Ca leakage from NSR (ms^-1)
const double kmup = 0.00092; // Half-saturation concentration of iup (mM)
const double iupbar = 0.00875; // Max. current through iup channel (mM/ms)
const double nsrbar = 15; // Max. [Ca] in NSR (mM)



/* JSR Ca Ion Concentration Changes */
double djsr; // Change in [Ca] in the JSR (mM)
const double tauon = 0.5; // Time constant of activation of Ca release from JSR (ms)
const double tauoff = 0.5; // Time constant of deactivation of Ca release from JSR (ms)
double tcicr; // t=0 at time of CICR (ms)
double irelcicr; // Ca release from JSR to myo. due to CICR (mM/ms)
const double csqnth = 15; // Threshold for release of Ca from CSQN due to JSR overloa(mM)
double gmaxrel = 150; // Max. rate constant of Ca release from JSR due to overload (ms^1)
double grelbarjsrol; // Rate constant of Ca release from JSR due to overload (ms^-1)
double greljsrol; // Rate constant of Ca release from JSR due to CICR (ms^-1)
double tjsrol; // t=0 at time of JSR overload (ms)
double ireljsrol; // Ca release from JSR to myo. due to JSR overload (mM/ms)
const double csqnbar = 10; // Max. [Ca] buffered in CSQN (mM)
const double kmcsqn = 0.8; // Equilibrium constant of buffering for CSQN (mM)
double bjsr; // b Variable for analytical computation of [Ca] in JSR (mM)
double cjsr; // c Variable for analytical computation of [Ca] in JSR (mM)
double on; // Time constant of activation of Ca release from JSR (ms)
double off; // Time constant of deactivation of Ca release from JSR (ms)
double magrel; // Magnitude of Ca release
double dcaiont; // Rate of change of Ca entry
double dcaiontnew; // New rate of change of Ca entry
double caiontold; // Old rate of change of Ca entry



/* Translocation of Ca Ions from NSR to JSR */
double itr; // Translocation current of Ca ions from NSR to JSR (mM/ms)
```

```
const double tautr = 180; // Time constant of Ca transfer from NSR to JSR (ms)



/* Myoplasmic Ca Ion Concentration Changes */
double caiont; // Total Ca Ion Flow (uA/uF)
double dcai; // Change in myoplasmic Ca concentration (mM)
double catotal; // Total myoplasmic Ca concentration (mM)
double bmyo; // b Variable for analytical computation of [Ca] in myoplasm (mM)
double cmyo; // c Variable for analytical computation of [Ca] in myoplasm (mM)
double dmyo; // d Variable for analytical computation of [Ca] in myoplasm (mM)
double gpig; // Tribute to all the guinea pigs killed for the advancement of knowledge
const double cmdnbar = 0.050; // Max. [Ca] buffered in CMDN (mM)
const double trpnbar = 0.070; // Max. [Ca] buffered in TRPN (mM)
const double kmcmdn = 0.00238; // Equilibrium constant of buffering for CMDN (mM)
const double kmtrpn = 0.0005; // Equilibrium constant of buffering for TRPN (mM)



/* Fast Sodium Current (time dependent) */
double ina; // Fast Na Current (uA/uF)
double gna; // Max. Conductance of the Na Channel (mS/uF)
double ena; // Reversal Potential of Na (mV)
double am; // Na alpha-m rate constant (ms^-1)
double bm; // Na beta-m rate constant (ms^-1)
double ah; // Na alpha-h rate constant (ms^-1)
double bh; // Na beta-h rate constant (ms^-1)
double aj; // Na alpha-j rate constant (ms^-1)
double bj; // Na beta-j rate constant (ms^-1)
double mtau; // Na activation
double htau; // Na inactivation
double jtau; // Na inactivation
double mss; // Na activation
double hss; // Na inactivation
```

```
double jss; // Na inactivation
double m; // Na activation
double h; // Na inactivation
double j; // Na inactivation



/* Persistent Sodium Current (time dependent) */
double inap,gnap;
double ainap,binap,p,taup,pss;



/* Current through L-type Ca Channel */
double ilca; // Ca current through L-type Ca channel (uA/uF)
double ilcana; // Na current through L-type Ca channel (uA/uF)
double ilcak ; // K current through L-type Ca channel (uA/uF)
double ilcatot; // Total current through the L-type Ca channel (uA/uF)
double ibarca; // Max. Ca current through Ca channel (uA/uF)
double ibarna; // Max. Na current through Ca channel (uA/uF)
double ibark; // Max. K current through Ca channel (uA/uF)
double d; // Voltage dependant activation gate
double dss; // Steady-state value of activation gate d
double taud; // Time constant of gate d (ms^-1)
double f; // Voltage dependant inactivation gate
double fss; // Steady-state value of inactivation gate f
double tauf; // Time constant of gate f (ms^-1)
double fca; // Ca dependant inactivation gate
const double kmca = 0.0006; // Half-saturation concentration of Ca channel (mM)
double pca = 0.00054; // Permeability of membrane to Ca (cm/s)
const double gacai = 1; // Activity coefficient of Ca
const double gacao = 0.341; // Activity coefficient of Ca
double pna = 0.000000675; // Permeability of membrane to Na (cm/s)
```

```
const double ganai = 0.75; // Activity coefficient of Na
const double ganao = 0.75; // Activity coefficient of Na
double pk = 0.000000193; // Permeability of membrane to K (cm/s)
const double gaki = 0.75; // Activity coefficient of K
const double gako = 0.75; // Activity coefficient of K


/* Current through T-type Ca Channel */
double icat; // Ca current through T-type Ca channel (uA/uF)
double gcat; // Max. Conductance of the T-type Ca channel (mS/uF)
double eca; // Reversal Potential of the T-type Ca channel (mV)
double b; // Voltage dependant activation gate
double bss; // Steady-state value of activation gate b
double taub; // Time constant of gate b (ms^-1)
double g; // Voltage dependant inactivation gate
double gss; // Steady-state value of inactivation gate g
double taug; // Time constant of gate g (ms^-1)


/* Rapidly Activating Potassium Current */
double ikr; // Rapidly Activating K Current (uA/uF)
double gkr; // Channel Conductance of Rapidly Activating K Current (mS/uF)
double ekr; // Reversal Potential of Rapidly Activating K Current (mV)
double xr; // Rapidly Activating K time-dependant activation
double xrss; // Steady-state value of inactivation gate xr
double tauxr; // Time constant of gate xr (ms^-1)
double r; // K time-independent inactivation


/* Slowly Activating Potassium Current */
double iks; // Slowly Activating K Current (uA/uF)
```

```
double gks; // Channel Conductance of Slowly Activating K Current (mS/uF)
double eks; // Reversal Potential of Slowly Activating K Current (mV)
double xs1; // Slowly Activating K time-dependant activation
double xs1ss; // Steady-state value of inactivation gate xs1
double tauxs1; // Time constant of gate xs1 (ms^-1)
double xs2; // Slowly Activating K time-dependant activation
double xs2ss; // Steady-state value of inactivation gate xs2
double tauxs2; // Time constant of gate xs2 (ms^-1)
const double prnak = 0.01833; // Na/K Permeability Ratio



/* Potassium Current (time-independent) */
double iki; // Time-independent K current (uA/uF)
double gki; // Channel Conductance of Time Independant K Current (mS/uF)
double eki; // Reversal Potential of Time Independant K Current (mV)
double aki; // K alpha-ki rate constant (ms^-1)
double bki; // K beta-ki rate constant (ms^-1)
double kin; // K inactivation
double ikifactor;



/* Plateau Potassium Current */
double ikp; // Plateau K current (uA/uF)
double gkp; // Channel Conductance of Plateau K Current (mS/uF)
double ekp; // Reversal Potential of Plateau K Current (mV)
double kp; // K plateau factor



/* Na-Activated K Channel */
double ikna; // Na activated K channel
double pona; // Open probability dependant on Nai
```

```
double pov; // Open probability dependant on Voltage
double ekna; // Reversal potential
const double gkna = 0.12848; // Maximum conductance (mS/uF)
const double nkna = 2.8; // Hill coefficient for Na dependance
const double kdkna = 66; // Dissociation constant for Na dependance(mM)



/* ATP-Sensitive K Channel */
double ikatp; // ATP-sensitive K current (uA/uF)
double ekatp; // K reversal potential (mV)
double gkbaratp; // Conductance of the ATP-sensitive K channel (mS/uF)
double gkatp; // Maximum conductance of the ATP-sensitive K channel (mS/uF)
double patp; // Percentage availability of open channels
const double natp = 0.24; // K dependence of ATP-sensitive K current
const double nicholsarea = 0.00005; // Nichol's area (cm^2)
const double atpi = 3; // Intracellular ATP concentraion (mM)
const double hatp = 2; // Hill coefficient
const double katp = 0.250; // Half-maximal saturation point of ATP-sensitive K (mM)



/* Ito Transient Outward Current (Dumaine et al. Circ Res 1999;85:803-809) */
double ito; // Transient outward current
double gitodv; // Maximum conductance of Ito
double ekdv; // Reversal Potential of Ito
double rvdv; // Time independent voltage dependence of Ito
double zdv; // Ito activation
double azdv; // Ito alpha-z rate constant
double bzdv; // Ito beta-z rate constant
double tauzdv; // Time constant of z gate
double zssdv; // Steady-state value of z gate
double ydv; // Ito inactivation
double aydv; // Ito alpha-y rate constant
```

```
double bydv; // Ito beta-y rate constant
double tauydv; // Time constant of y gate
double yssdv; // Steady-state value of y gate
double yydv;
double ayydv;
double byydv;
double tauyydv;
double yyssdv;



/* Sodium-Calcium Exchanger V-S */
double inaca; // NaCa exchanger current (uA/uF)
const double c1 = .00025; // Scaling factor for inaca (uA/uF)
const double c2 = 0.0001; // Half-saturation concentration of NaCa exhanger (mM)
const double gammas = .15; // Position of energy barrier controlling voltage dependence
of inaca



/* Sodium-Potassium Pump */
double inak; // NaK pump current (uA/uF)
double fnak; // Voltage-dependence parameter of inak
double sigma; // [Na] o dependence factor of fnak
const double ibarnak = 2.25; // Max. current through Na-K pump (uA/uF)
const double kmnai = 10; // Half-saturation concentration of NaK pump (mM)
const double kmko = 1.5; // Half-saturation concentration of NaK pump (mM)



/* Nonspecific Ca-activated Current */
double insna; // Non-specific Na current (uA/uF)
double insk; // Non-specific K current (uA/uF)
double ibarnsna; // Max. Na current through NSCa channel (uA/uF)
```

```
double ibarnsk; // Max. K current through NSCa channel (uA/uF)
const double pnsca = 0.000000175; // Permeability of channel to Na and K (cm/s)
const double kmnsca = 0.0012; // Half-saturation concentration of NSCa channel (mM)



/* Sarcolemmal Ca Pump */
double ipca; // Sarcolemmal Ca pump current (uA/uF)
const double ibarpca = 1.15; // Max. Ca current through sarcolemmal Ca pump (uA/uF)
const double kmpca = 0.0005; // Half-saturation concentration of sarcolemmal Ca pump (mM)



/* Ca Background Current */
double icab; // Ca background current (uA/uF)
double gcab; // Max. conductance of Ca background (mS/uF)
double ecan; // Nernst potential for Ca (mV)



/* Na Background Current */
double inab; // Na background current (uA/uF)
double gnab; // Max. conductance of Na background (mS/uF)
double enan; // Nernst potential for Na (mV)



/* b-adrenergic effects */
double isofactor,base_ical, base_iks, gupiso;
double iso, k50isoical,k50isoiks,gksiso;



/* Ion Current Functions */
void comp_ina (); // Calculates Fast Na Current
```

```
void comp_inap(); // Persistent Na current
void comp_ical (); // Calculates Currents through L-Type Ca Channel
void comp_icat (); // Calculates Currents through T-Type Ca Channel
void comp_ikr (); // Calculates Rapidly Activating K Current
void comp_iks (); // Calculates Slowly Activating K Current
void comp_iki (); // Calculates Time-Independent K Current
void comp_ikp (); // Calculates Plateau K Current
void comp_ikna (); // Calculates Na-activated K Current
void comp_ikatp (); // Calculates ATP-Sensitive K Current
void comp_ito (); // Calculates Transient Outward Current
void comp_inaca (); // Calculates Na-Ca Exchanger Current
void comp_inak (); // Calculates Na-K Pump Current
void comp_insca (); // Calculates Non-Specific ca-Activated Current
void comp_ipca (); // Calculates Sarcolemmal Ca Pump Current
void comp_icab (); // Calculates Ca Background Current
void comp_inab (); // Calculates Na Background Current
void comp_it (); // Calculates Total Current



/* Ion Concentration Functions */
void conc_nai (); // Calculates new myoplasmic Na ion concentration
void conc_ki (); // Calculates new myoplasmic K ion concentration
void conc_nsr (); // Calculates new NSR Ca ion concentration
void conc_jsr (); // Calculates new JSR Ca ion concentration
void calc_itr (); // Calculates Translocation of Ca from NSR to JSR
void conc_cai (); // Calculates new myoplasmic Ca ion concentration
void conc_cleft (); // Calculates new cleft ion concentrations
```

```
int main(array<System::String ^> ^args)
{
	// Enabling Windows XP visual effects before any controls are created
	Application::EnableVisualStyles();
	Application::SetCompatibleTextRenderingDefault(false);

	// Create the main window and run it
	Application::Run(gcnew Form1());
printdata = 60;


/* Cell Geometry */
vcell = 1000*pi*a*a*l; // 3.801e-5 uL
ageo = 2*pi*a*a+2*pi*a*l; // 7.671e-5 cm^2
acap = ageo*2; // 1.534e-4 cm^2
vmyo = vcell*0.68;
vmito = vcell*0.26;
vsr = vcell*0.06;
vnsr = vcell*0.0552;
vjsr = vcell*0.0048;
vcleft = vcell*0.12/0.88;


/* Time Loop Conditions */
t = 0.0; // Time (ms)
udt = 0.01; // Time step (ms)
steps = (bcl*beats)/udt;  // Number of ms
st = -0.0; // Stimulus
tstim = 100.0; // Time to begin stimulus
stimtime = 10.0; // Initial Condition for Stimulus
v = -88.3; // Initial Voltage (mv)
```

```
/* Beginning Ion Concentrations */
nai = 12.11; // Initial Intracellular Na (mM)
nao = 140; // Initial Extracellular Na (mM)
nabm = 140; // Initial Bulk Medium Na (mM)
ki = 134.88;// Initial Intracellular K (mM)
ko = 4.5; // Initial Extracellular K (mM)
kbm = 4.5; // Initial Bulk Medium K (mM)
cai = 8.72e-5; // Initial Intracellular Ca (mM)
cao = 1.8; // Initial Extracellular Ca (mM)
cabm = 1.8; // Initial Bulk Medium Ca (mM)


/* Initial Gate Conditions */
m = 0.000838;
h = 0.993336;
j = 0.995484;
d = 0.000003;
f = 0.999745;
xs1 = 0.004503;
xs2 = 0.004503;
xr = 0.000129;
b = 0.000994;
g = 0.994041;
zdv = 0.0120892;
ydv = 0.999978;

/* Initial Conditions */
grelbarjsrol = 0;
tjsrol = 1000;
tcicr = 1000;
jsr = 1.17;
nsr = 1.17;
trpn = 0.0143923;
```

```
cmdn = 0.00257849;
csqn = 6.97978;
flag = 0;
dt = udt;
utsc = 50;
dcaiont = 0;
i=-1;


// Hypoxic conditions
gna = 0.9*16;
gnap = 0.00018;
k50isoical = 1.5;
base_ical = 0.75; //for hypoxic simulation without b-adrenergic stimulation
k50isoiks = 1.5;
base_iks = 0.22;
ikifactor = 1;


//b-adrenergic stimulation
iso = 0.5;
gupiso = 1.5;
st = -80;


/* Beginning of Time Loop */
//Main loop
for (increment = 0; increment < steps; increment++)
{
if(abs(dvdt)<0.25 && v<0)
{nxstep = 50;}
else
{nxstep = 50;}
if(utsc>=nxstep || dvdt>5 || irelcicr>0.01 || (t>=(tstim-udt) && t<=(tstim+udt))
```

```
|| (stimtime>=0 && stimtime<=0.5))
{

/* List of functions called for each timestep, currents commented out are only used when modeling
pathological conditions */
comp_ina ();
comp_inap();
comp_ical ();
comp_icat ();
comp_ikr ();
comp_iks ();
comp_iki ();
comp_ikp ();
comp_ikna ();
comp_ikatp ();
comp_ito ();
comp_inaca ();
comp_inak ();
comp_insca ();
comp_ipca ();
comp_icab ();
comp_inab ();
comp_it ();
conc_nai ();
conc_ki ();
calc_itr ();
conc_jsr ();
conc_nsr ();
conc_cai ();

/* Cleft Space disabled, if you want to use cleft space, make sure the initial conditions
of ion concentrations in the bulk medium are the same as the extracellular concentrations */
stimtime = stimtime+dt;
vnew = v-it*dt;
```

```
dvdtnew = (vnew-v)/dt;
if(i>=0)
{
if (vnew>vmax [i] )
vmax [i] = vnew;
if (cai>caimax [i] )
caimax [i] = cai;
if (dvdtnew>dvdtmax [i] )
{dvdtmax [i] = dvdtnew;
toneapd [i] = t;}
if (vnew>=(vmax [i] -0.9*(vmax [i] -rmbp [i] )))
ttwoapd [i] = t;
}
if(csqn>=csqnth && tjsrol>50)
{grelbarjsrol = 4;
tjsrol = 0;

// mention the time spontaneous release occured
//cout << "Spontaneous Release occurred at time " << t << endl;
}
utsc = 0;
dt = 0;
}
if(dvdt>3 || irelcicr>.01)
{printval = 50;}
else
{printval = 750;}
if(printdata>=printval)
{prttofile();
printdata = 0;}
printdata = printdata+1;
v = vnew;
dvdt = dvdtnew;
caiontold = caiont;
```

```
dcaiont = dcaiontnew;
dt = dt+udt;
utsc = utsc+1;
t = t+udt;
}

for(i=0;i<beats;i++)
{apd [i] = ttwoapd [i] -toneapd [i] ;
}

for(i=0;i<2000;i++){
}
Application::Run(gcnew Form1());
return(1);
}


/* Functions that describe the currents begin here */
// ina current
void comp_ina ()
{
ena = ((R*temp)/frdy)*log(nao/nai);
am = 0.32*(v+47.13)/(1-exp(-0.1*(v+47.13)));
bm = 0.08*exp(-v/11);
if (v < -40)
{ah = 0.135*exp((80+v)/-6.8);
bh = 3.56*exp(0.079*v)+310000*exp(0.35*v);
aj = (-127140*exp(0.2444*v)-0.00003474*exp(-0.04391*v))*((v+37.78)/(1+exp(0.311*(v+79.23))));
bj = (0.1212*exp(-0.01052*v))/(1+exp(-0.1378*(v+40.14)));}
else
{ah = 0;
bh = 1/(0.13*(1+exp((v+10.66)/-11.1)));
aj = 0;
aj = (0.3*exp(-0.0000002535*v))/(1+exp(-0.1*(v+32)));}
```

```
mtau = 1/(am+bm);
htau = 1/(ah+bh);
jtau = 1/(aj+bj);
mss = am*mtau;
hss = ah*htau;
jss = aj*jtau;
m = mss-(mss-m)*exp(-dt/mtau);
h = hss-(hss-h)*exp(-dt/htau);
j = jss-(jss-j)*exp(-dt/jtau);
ina = gna*m*m*m*h*j*(v-ena);
}
```

// inap current

```
void comp_inap()
{
ainap = 19*exp(v/16.5);
binap = 0.2*exp(-v/20);
pss = ainap/(ainap+binap);
taup = 1/(ainap+binap);
p = pss - (pss-p)*exp(-dt/taup);
inap = gnap*ina*p*p*p*(v-ena);
saveValuesNa[counter]=inap;
}
```

// ical current "ca L type"

```
void comp_ical ()
{
dss = 1/(1+exp(-(v+10)/6.24));
taud = dss*(1-exp(-(v+10)/6.24))/(0.035*(v+10));
```

```
dss = dss/(1+exp(-(v+60)/0.24));
fss = (1/(1+exp((v+32)/8)))+(0.6/(1+exp((50-v)/20)));
tauf = 1/(0.0197*exp(-pow(0.0337*(v+10),2))+0.02);
d = dss-(dss-d)*exp(-dt/taud);
f = fss-(fss-f)*exp(-dt/tauf);
ibarca = pca*zca*zca*((v*frdy*frdy)/(R*temp))
*((gacai*cai*exp((zca*v*frdy)/(R*temp))-gacao*cao)/(exp((zca*v*frdy)/(R*temp))-1));
ibarna = pna*zna*zna*((v*frdy*frdy)/(R*temp))
*((ganai*nai*exp((zna*v*frdy)/(R*temp))-ganao*nao)/(exp((zna*v*frdy)/(R*temp))-1));
ibark = pk*zk*zk*((v*frdy*frdy)/(R*temp))
*((gaki*ki*exp((zk*v*frdy)/(R*temp))-gako*ko)/(exp((zk*v*frdy)/(R*temp))-1));
fca = 1/(1+cai/kmca);
isofactor = 1 + 3/( 1 + pow(10,(log(k50isoical) - log(iso))));
ilca = isofactor*d*f*fca*ibarca;
ilcana = isofactor*d*f*fca*ibarna;
ilcak = isofactor*d*f*fca*ibark;
ilcatot = ilca+ilcana+ilcak;
saveValuesCa[counter]=ilcatot ;
}
}
```

// icalt current " ca T type"

```
void comp_icat ()
{
bss = 1/(1+exp(-(v+14.0)/10.8));
taub = 3.7+6.1/(1+exp((v+25.0)/4.5));
gss = 1/(1+exp((v+60.0)/5.6));
if (v<=0)
taug = -0.875*v+12.0;
else
taug = 12.0;
b = bss-(bss-b)*exp(-dt/taub);
g = gss-(gss-g)*exp(-dt/taug);
gcat = 0.05;
```

```
eca = (R*temp/(2*frdy))*log(cao/cai);
icat = gcat*b*b*g*(v-eca);
}
```

// ike current

```
void comp_ikr ()
{
gkr = 0.02614*sqrt(ko/5.4);
ekr = ((R*temp)/frdy)*log(ko/ki);
xrss = 1/(1+exp(-(v+21.5)/7.5));
tauxr = 1/(0.00138*(v+14.2)/(1-exp(-0.123*(v+14.2)))+0.00061*(v+38.9)/(exp(0.145*(v+38.9))-1));
xr = xrss-(xrss-xr)*exp(-dt/tauxr);
r = 1/(1+exp((v+9)/22.4));
ikr = gkr*xr*r*(v-ekr);
}
```

// iks current

```
void comp_iks ()
{
gks = 0.433*(1+0.6/(1+pow((0.000038/cai),1.4)));
eks = ((R*temp)/frdy)*log((ko+prnak*nao)/(ki+prnak*nai));
xs1ss = 1/(1+exp(-(v-1.5)/16.7));
xs2ss = xs1ss;
tauxs1 = 1/(0.0000719*(v+30)/(1-exp(-0.148*(v+30)))+0.000131*(v+30)/(exp(0.0687*(v+30))-1));
tauxs2 = 4*tauxs1;
xs1 = xs1ss-(xs1ss-xs1)*exp(-dt/tauxs1);
xs2 = xs2ss-(xs2ss-xs2)*exp(-dt/tauxs2);
gksiso = base_iks + 0.6/(1+pow(10,(log(k50isoiks) - log(iso))));
iks =gksiso*gks*xs1*xs2*(v-eks);
}
```

// iki current

```
void comp_iki ()
{
gki = 0.75*(sqrt(ko/5.4));
eki = ((R*temp)/frdy)*log(ko/ki);
aki = 1.02/(1+exp(0.2385*(v-eki-59.215)));
bki = (0.49124*exp(0.08032*(v-eki+5.476))+exp(0.06175*(v-eki-594.31)))/(1+exp(-0.5143*(v-
eki+4.753)));
kin = aki/(aki+bki);
gki = 0.75*(sqrt(ko/5.4));
eki = ((R*temp)/frdy)*log(ko/ki);
aki = 1.02/(1+exp(0.2385*(v-eki-59.215)));
bki = (0.49124*exp(0.08032*(v-eki+5.476))+exp(0.06175*(v-eki-594.31)))/(1+exp(-0.5143*(v-
eki+4.753)));
kin = aki/(aki+bki);
iki = ikifactor*gki*kin*(v-eki);
}
```

// ikp current

```
void comp_ikp ()
{
gkp = 0.00552;
ekp = eki;
kp = 1/(1+exp((7.488-v)/5.98));
ikp = gkp*kp*(v-ekp);
saveValuesK[counter]=ikp;

}
```

// ikna current

```
void comp_ikna ()
{
ekna = ((R*temp)/frdy)*log(ko/ki);
```

```
pona = 0.85/(1+pow((kdkna/nai),2.8));
pov = 0.8-0.65/(1+exp((v+125)/15));
ikna = gkna*pona*pov*(v-ekna);

}
// ikatp current
void comp_ikatp ()
{
ekatp = ((R*temp)/frdy)*log(ko/ki);
gkatp = 0.000195/nicholsarea;
patp = 1/(1+(pow((atpi/katp),hatp)));
gkbaratp = gkatp*patp*(pow((ko/4),natp));
ikatp = gkbaratp*(v-ekatp);
}


// ito current
void comp_ito ()
{
gitodv = 0.4975;
ekdv = ((R*temp)/frdy)*log((ko)/(ki));
rvdv = exp(v/550);
azdv = 1/(1.2089*(1+exp((v-18.4099)/-29.3814)));
bzdv = 3.5/(1+exp((v+100)/29.3814));
aydv = 0.025/(1+exp((v+58)/5));
bydv = 1/(9.7953*(1+exp((v+19)/-9)));
ayydv = 1/(250*(1+exp((v+60)/5)));
byydv = bydv;
zssdv = 1/(1+exp((v+9.437)/-7.133));
tauzdv = 1/(azdv+bzdv);
yssdv = aydv/(aydv+bydv);
tauydv = 1/(aydv+bydv);
yyssdv = ayydv/(ayydv+byydv);
tauyydv = 1/(ayydv+byydv);
```

```
zdv = zssdv -(zssdv-zdv)*exp(-dt/tauzdv);
ydv = yssdv -(yssdv-ydv)*exp(-dt/tauydv);
yydv = yyssdv -(yyssdv-yydv)*exp(-dt/tauyydv);
ito = gitodv*zdv*zdv*zdv*ydv*yydv*rvdv*(v-ekdv);
ito = 0;
}
```

// inaca current

```
void comp_inaca ()
{
inaca = c1*exp((gammas-1)*v*frdy/(R*temp))
*((exp(v*frdy/(R*temp))*nai*nai*nai*cao-nao*nao*nao*cai)
/(1+c2*exp((gammas-
1)*v*frdy/(R*temp))*(exp(v*frdy/(R*temp))*nai*nai*nai*cao+nao*nao*nao*cai)));
}
```

// inak current

```
void comp_inak ()
{
sigma = (exp(nao/67.3)-1)/7;
fnak = 1/(1+0.1245*exp((-0.1*v*frdy)/(R*temp))+0.0365*sigma*exp((-v*frdy)/(R*temp)));
inak = ibarnak*fnak*(1/(1+pow(kmnai/nai,2)))*(ko/(ko+kmko));
}
```

// insca current

```
void comp_insca ()
{
ibarnsna = pnsca*zna*zna*((v*frdy*frdy)/(R*temp))
*((ganai*nai*exp((zna*v*frdy)/(R*temp))-ganao*nao)/(exp((zna*v*frdy)/(R*temp))-1));
ibarnsk = pnsca*zk*zk*((v*frdy*frdy)/(R*temp))
```

```
*((gaki*ki*exp((zk*v*frdy)/(R*temp))-gako*ko)/(exp((zk*v*frdy)/(R*temp))-1));
insna = ibarnsna/(1+pow(kmnsca/cai,3));
insk = ibarnsk/(1+pow(kmnsca/cai,3));
}
```

// ipca current

```
void comp_ipca ()
{
ipca = (ibarpca*cai)/(kmpca+cai);
}
```

// icab current

```
void comp_icab ()
{
gcab = 0.003016;
ecan = ((R*temp)/(2*frdy))*log(cao/cai);
icab = gcab*(v-ecan);
}
```

//inab current

```
void comp_inab ()
{
gnab = 0.004;
enan = ena;
inab = gnab*(v-enan);
}
```

// it current

```
void comp_it ()
{
naiont = inap+ina+inab+ilcana+insna+3*inak+3*inaca;
kiont = ikr+iks+iki+ikp+ilcak+insk-2*inak+ito+ikna+ikatp;
```

```
caiont = ilca+icab+ipca-2*inaca+icat;
if (dvdtnew > 10 && tcicr > 10 && flag == 1)
{flag = 0;}
if ( (t>=tstim && t<(tstim+dt)))
{stimtime = 0;
i = i+1;
tstim = tstim + bcl;
rmbp [i] =v;
nair [i] = nai;
kir [i] = ki;
cair [i] = cai;
}
if(stimtime>=0 && stimtime<=0.5)
{it = st+naiont+kiont+caiont;}
else
{it = naiont+kiont+caiont;}
}
/* Functions that calculate intracellular ion concentrations begins here */
void conc_nai ()
{
dnai = -dt*(naiont*acap)/(vmyo*zna*frdy);
nai = dnai + nai;
}
```

// ki current

```
void conc_ki ()
{
if(stimtime>=0 && stimtime<=0.5)
{dki = -dt*((kiont+st)*acap)/(vmyo*zk*frdy);}
else
{dki = -dt*(kiont*acap)/(vmyo*zk*frdy);}
ki = dki + ki;
}
```

// itr current

```
void calc_itr ()
{
itr = (nsr-jsr)/tautr;
}
```

//calculate jsr factor

```
void conc_jsr ()
{
kleak = iupbar/nsrbar;
ileak = kleak*nsr;
iup = (gupiso+0.5)*iupbar*cai/(cai+kmup);
dcaiontnew = (caiont-caiontold)/dt;
if(v>-35 && dcaiontnew>dcaiont && flag==0)
{flag = 1;
tcicr = 0;}
on = 1/(1+exp((-tcicr+4)/tauon));
off = (1-1/(1+exp((-tcicr+4)/tauoff)));
magrel = 1/(1+exp(((ilca+icab+ipca-2*inaca+icat)+5)/0.9));
irelcicr = gmaxrel*on*off*magrel*(jsr-cai);
tcicr = tcicr+dt;
greljsrol = grelbarjsrol*(1-exp(-tjsrol/tauon))*exp(-tjsrol/tauoff);
ireljsrol = greljsrol*(jsr-cai);
tjsrol = tjsrol+dt;
csqn = csqnbar*(jsr/(jsr+kmcsqn));
djsr = dt*(itr-irelcicr-ireljsrol);
bjsr = csqnbar-csqn-djsr-jsr+kmcsqn;
cjsr = kmcsqn*(csqn+djsr+jsr);
jsr = (sqrt(bjsr*bjsr+4*cjsr)-bjsr)/2;
}
```

// clacuate the nsr factor

```
void conc_nsr ()
{
dnsr = dt*(iup-ileak-itr*vjsr/vnsr);
nsr = nsr+dnsr;
}
```

// cai current

```
void conc_cai ()
{
dcai = -dt*(((caiont*acap)/(vmyo*zca*frdy))+((iup-ileak)*vnsr/vmyo)
-(irelcicr*vjsr/vmyo)-(ireljsrol*vjsr/vmyo));
trpn = trpnbar*(cai/(cai+kmtrpn));
cmdn = cmdnbar*(cai/(cai+kmcmdn));
catotal = trpn+cmdn+dcai+cai;
bmyo = cmdnbar+trpnbar-catotal+kmtrpn+kmcmdn;
cmyo = (kmcmdn*kmtrpn)-(catotal*(kmtrpn+kmcmdn))+(trpnbar*kmcmdn)+(cmdnbar*kmtrpn);
dmyo = -kmtrpn*kmcmdn*catotal;
gpig = sqrt(bmyo*bmyo-3*cmyo);
cai = (2*gpig/3)*cos(acos((9*bmyo*cmyo-2*bmyo*bmyo*bmyo-27*dmyo)
/(2*pow((bmyo*bmyo-3*cmyo),1.5)))/3)-(bmyo/3);
}
```

```
void conc_cleft()
{
dnao = dt*((nabm-nao)/taudiff+naiont*acap/(vcleft*frdy));
nao = dnao+nao;
if(stimtime>=0 && stimtime<=0.5)
{dko = dt*((kbm-ko)/taudiff+(kiont+st)*acap/(vcleft*frdy));}
else
{dko = dt*((kbm-ko)/taudiff+kiont*acap/(vcleft*frdy));}
ko = dko+ko;
```

```
dcao = dt*((cabm-cao)/taudiff+caiont*acap/(vcleft*frdy*2));
cao = dcao+cao;
}


// to print values of the current
void prttofile()
{ if (i> (beats-5))
        t = t-(bcl*(beats-4))-100;
        saveValuesTime[counter] = t;
        saveValuesTime[counter] = v;
        counter++;

}
```