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DIFFERENTIAL MODEL OF EXCITATION – CONTRACTION COUPLING IN A CARDIAC CELL FOR MULTICYCLE SIMULATIONS

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Abstract: We present a differential model of excitation – contraction coupling in a cardiac cell intended to be used in simulations of one or many heart cycles on the cell or the heart scales. It takes into account the dynamics of the main ionic currents flowing through the membrane channels (fast sodium, L-type calcium and outward potassium) and Na^+/Ca^{2+} exchangers and Na^+/K^+ pumps. The model includes also a description of the dynamics of the main calcium buffers in the bulk cytosol and in the sarcoplasmic reticulum. With thirteen state variables, its complexity is between that of FitzHugh-Nagumo type models of the action potential (two state variables) and that of the more complex ionic channels models (up to sixty state variables for some of them). It allows realistic modelling of action potential, total ionic current, current gating, intracellular calcium transients, in particular for calcium bound on troponin C, and multicycle effects, like restitution curves for the action potential duration, CICR dependence on intracellular calcium concentration, positive staircase effect for the heart rate. Due to its sound asymptotic behavior without drifts of the state and its medium complexity, this model can be used in multi-beat simulations from the cell to the heart scales.

Introduction

Mathematical models of the cardiac electromechanical activity are used from the molecular scale to the whole heart, with a special focus on the ventricular cell behavior during a heart cycle. On this pivot scale, model complexity varies as the number of state variables (action potential, intracellular ion concentrations, gate variables of ionic channels), from two to more than sixty [1][2][3]. An appropriate model has to be chosen for each particular task, depending in particular upon the spatial dimension or number of heart cycles considered, to limit the computational load for direct problems (computing state evolution from initial state and parameters) or ill posedness of inverse problems (estimating state and parameters from measurements).

In a study of the control mechanisms of excitation-contraction (EC) coupling including heart-rate effects, we need to combine a detailed model of sub cellular calcium dynamics with an ionic-currents model. We present the resulting model that avoids the simple union of the state-

variable sets and has a sound asymptotic behavior without drifts of the state for multi-beat simulations.

The proposed model of EC coupling is a differential equation linking a stimulation current to the concentration of Calcium fixed on Troponin-C that controls the contraction of the sarcomere. The ubiquitous messenger in this coupling is the free intracellular Calcium [4]: its concentration is one of the state variables[5].

The electrical excitation is taken into account by a membrane model built using the charge conservation principle as in [6] and involving three state variables: the intracellular concentrations of free Calcium, Sodium and Potassium. Two gate variables are used for five membrane currents as in [7]. The action potential (AP) is then given by an algebraic formula in terms of differences between these concentrations and the corresponding extracellular ones. The ionic currents flowing through channels, exchangers and electrogenic pumps are expressed in term of AP and the previous state variables. As in [7], the Na^+/Ca^{2+} exchange transport, which is sodium dependent and regulated by calcium and the $Na^+/K^+ - ATPase$, which is responsible for active transport of sodium and potassium, are taken into account.

Our model for Calcium dynamics is derived from [7][5][8]. It takes into account the main processes that regulate intracellular Calcium concentration: release and uptake by the sarcoplasmic reticulum (SR), buffering in the SR [8] and in the bulk cytosol [5] where several buffers of Calcium are in competition with the myofilament protein troponin-C which regulates the contractile activity. Seven buffers have been selected for their capacity. We assume that the diffusion phenomena between the cell compartments are very fast so that there is only one free intracellular Calcium concentration in the bulk cytosol.

The proposed model of EC coupling has thirteen state variables. As its parent models it is able to reproduce realistic action potential, intracellular calcium transients, total ionic current and restitution curves (functions of the diastolic interval) for the action potential duration (APDR). The buffer model structure ensures various properties: positivity, boundedness (due to maximal binding capacities) and quasi steady state (in the case of a constant heart rate) for all concentrations; heart rate effects like the positive staircase (due to the asymmetry of Calcium binding and unbinding rates).

Materials and Methods

The trans-membrane voltage, V , of a single cell can be described with the following differential equation, [8],

$$\frac{dV}{dt} = -\frac{I_{ion} + I_{ext}}{C_m} \quad (1)$$

Where I_{ext} is the externally applied stimulus current, C_m the membrane capacitance and I_{ion} the sum of all trans-membrane ionic currents given by (see table 1)

$$I_{ion} = I_{Na} + I_{bNa} + I_{NaK} + I_{CaL} + I_{pCa} + I_{bCa} + I_{NaCa} + I_{K1} + I_{Kr} + I_{Ks} + I_{to} + I_{pK} \quad (2)$$

The electrical activity is described by five currents, $I_{K,t}$, $I_{Na,t}$, $I_{Ca,t}$, the sums of all the currents in the Panvilov's model through the K^+ , Na^+ , Ca^{2+} channels respectively [6], and the exchanger and the pump currents.

$$\begin{cases} I_{Na,t} = I_{Na} + I_{bNa} \\ I_{Ca,t} = I_{CaL} + I_{pCa} + I_{bCa} \\ I_{K,t} = I_{K1} + I_{to} + I_{Kr} + I_{Ks} + I_{pK} \end{cases} \quad (3)$$

The models for these currents, derived from basic physical principles [7], are given below.

$$I_{K,t} = \bar{I}_K \cdot G_K \cdot \sinh\left(\frac{z_K(V - V_K)}{2RT/F}\right) + \bar{I}_{b,K} \quad (4)$$

$$I_{Na,t} = \bar{I}_{Na} \cdot G_{Na} \cdot m_\infty \cdot \sinh\left(\frac{z_{Na}(V - V_{Na})}{2RT/F}\right) \quad (5)$$

$$I_{Ca,t} = [\bar{I}_{Ca}(1 - G_K)d_\infty + \bar{I}_{b,Ca}] \sinh\left(\frac{z_{Ca}(V - V_{Ca})}{2RT/F}\right) \quad (6)$$

$$I_{NaK} = \bar{I}_{NaK} \tanh\left(\frac{V + 2V_K - 3V_{Na} - V_{ATP}}{2RT/F}\right) \quad (7)$$

$$I_{NaCa} = \bar{I}_{NaCa} \sinh\left(\frac{V + 2V_{Ca} - 3V_{Na}}{2RT/F}\right) \quad (8)$$

$$V_X = \frac{RT}{z_X F} \log \left| \frac{X_e}{X_i} \right|, \quad X \in \{Ca, Na, K\} \quad (9)$$

$$z_X = \begin{cases} 1 & \text{if } X \in \{Na, K\} \\ 2 & \text{if } X \in \{Ca\} \end{cases} \quad (10)$$

Where G_K and G_{Na} , the probabilities that the channels are open (activation/inactivation mechanisms), verify

$$\frac{dG_K}{dt} = \frac{1}{\tau_K} \cosh\left(\frac{V - V_{G_K}}{RT/2F}\right) \left\{ \frac{1}{2} \left[1 + \tanh\left(\frac{V - V_{G_K}}{RT/2F}\right) \right] - G_K \right\} \quad (11)$$

$$\frac{dG_{Na}}{dt} = \frac{1}{\tau_{Na}} \cosh\left(\frac{V - V_{G_{Na}}}{RT/2F}\right) \left\{ \frac{1}{2} \left[1 - \tanh\left(\frac{V - V_{G_{Na}}}{RT/2F}\right) \right] - G_{Na} \right\} \quad (12)$$

d_∞ and m_∞ are the steady states fraction of open channels for these very fast gates,

$$d_\infty = \frac{1}{2} \left[1 + \tanh\left(\frac{V - V_d}{RT/2F}\right) \right] \quad (13)$$

$$m_\infty = \frac{1}{2} \left[1 + \tanh\left(\frac{V - V_m}{RT/2F}\right) \right] \quad (14)$$

The differential equations for V and the conservation laws for intracellular ionic concentration are then [6], [7],

$$\frac{dV}{dt} = -\frac{(I_{K,t} + I_{Na,t} + I_{Ca,t} + I_{NaK} + I_{NaCa} + I_{ext})}{C_m} \quad (15)$$

$$\frac{dK_i}{dt} = \frac{2I_{NaK} - I_{K,t} - I_{ext}}{FV_C} \quad (16)$$

$$\frac{dNa_i}{dt} = \frac{-I_{Na,t} - 3I_{NaK} - 3I_{NaCa}}{FV_C} \quad (17)$$

$$\frac{dCa_i}{dt} = \frac{2I_{NaCa} - I_{Ca,t}}{2FV_C} + J_{leak} + J_{rel} - J_{up} - \sum_{b \in I_B} \frac{dCa_{ib}}{dt} \quad (18)$$

Where $I_B = \{Tn, Tn - Ca, Tn - Mg, M - Ca, M - Mg, Cal, SR\}$. Equations (16-17) can be solved for $I_{K,t}$, $I_{Na,t}$ and $I_{Ca,t}$:

$$I_{K,t} = -FV_C \frac{dK_i}{dt} + 2I_{NaK} - I_{ext} \quad (19)$$

$$I_{Na,t} = -FV_C \frac{dNa_i}{dt} - 3I_{NaK} - 3I_{NaCa} \quad (20)$$

$$I_{Ca,t} = 2I_{NaCa} - 2FV_C \left(\frac{dCa_i}{dt} + \sum_{b \in I_B} \frac{dCa_{ib}}{dt} - J_{leak} - J_{rel} + J_{up} \right) \quad (21)$$

The equation above can be rewritten as follows,

$$I_{Ca,t} = 2I_{NaCa} - 2FV_C \frac{dCa_T}{dt} \quad (22)$$

Let $I_B' = I_B \cup \{JCT\}$ be the set of all cytosolic calcium buffers, then the following equations define $I_{Ca,t}$.

$$Ca_T = Ca_i + \sum_{b \in I_B'} Ca_{ib} + \frac{V_{SR}}{V_C} Ca_{SRT} \quad (23)$$

$$\frac{dCa_{SRT}}{dt} = \frac{V_C}{V_{SR}} (-J_{leak} - J_{rel} + J_{up}) \quad (24)$$

$$J_{up} = Q_{up} J_{max} \frac{\left| \frac{Ca_i}{K_{mf}} \right|^H - \left| \frac{Ca_{SR}}{K_{mr}} \right|^H}{1 + \left| \frac{Ca_i}{K_{mf}} \right|^H + \left| \frac{Ca_{SR}}{K_{mr}} \right|^H} \quad (25)$$

$$J_{rel} = K_{rel} \cdot d_\infty \cdot (Ca_{SR} - Ca_{iJCT}) \quad (26)$$

$$J_{leak} = K_{leak} (Ca_{SR} - Ca_{iJCT}) \quad (27)$$

Substituting in (15), yields

$$\frac{dV}{dt} = \frac{FV_C}{C_m} \left(\frac{dNa_i}{dt} + \frac{dK_i}{dt} + 2 \frac{dCa_T}{dt} \right) \quad (28)$$

$$\frac{d}{dt} \left[V - \frac{FV_C}{C_m} (Na_i + K_i + 2Ca_T) \right] = 0 \quad (29)$$

which is integrated to give an algebraic equation,

$$V - \frac{FV_C}{C_m} \{Na_i + K_i + 2Ca_T\} = V_{ext} \quad (30)$$

Then,

$$Ca_T = \frac{1}{2} \left(\frac{C_m}{FV_C} (V - V_{ext}) - Na_i - K_i \right) \quad (31)$$

With,

$$V_{ext} = -\frac{FV_C}{C_m}(Na_e + K_e + 2Ca_e) \quad (32)$$

Calcium buffering in the cytosol by troponin-C, troponin-C ($Ca^{2+} - Mg$), calmodulin, myosin ($Ca^{2+} - Mg$), SR and junction, is modeled as follows, where we use the function $|x|_+ = \max(x, 0)$ so that the set $[0, B_b]$ is an attractor for each Ca_{ib} (in particular $Ca_{ib} \in [0, B_b]$ if this is true for some initial time):

$$\frac{dCa_{ib}}{dt} = k_{onb}|Ca_i|_+(B_{ib} - Ca_{ib}) - k_{offb}Ca_{ib}, \quad b \in I_B \quad (33)$$

Buffering in the junction and in the SR is fast, so that

$$Ca_{iJCT} = \frac{B_{JCT}|Ca_i|_+}{|Ca_i|_+ + K_{JCT}} \quad (34)$$

$$Ca_{SRT} = Ca_{SR} + Ca_{SRb} \quad \text{with} \quad Ca_{SRb} = \frac{B_{SR}|Ca_{SR}|_+}{|Ca_{SR}|_+ + K_{SR}} \quad (35)$$

Relations (35) and (23) lead to a wellposed equation for Ca_{SR} as a function of the state variables (with (31)),

$$Ca_{SR} + \frac{B_{SR}|Ca_{SR}|_+}{|Ca_{SR}|_+ + K_{SR}} = \frac{V_C}{V_{SR}} \left(Ca_T - Ca_i - \sum_{b \in I_{b'}} Ca_{ib} \right) \quad (36)$$

Model summary:

$$\left\{ \begin{array}{l} \frac{d}{dt} V = \frac{I_{K,t} + I_{Na,t} + I_{Ca,t} + I_{NaK} + I_{NaCa} + I_{ext}}{C_m} \\ \frac{d}{dt} K_i = \frac{2I_{NaK} - I_{K,t} - I_{ext}}{FV_C} \\ \frac{d}{dt} Na_i = \frac{-I_{Na,t} - 3I_{NaK} - 3I_{NaCa}}{FV_C} \\ \frac{d}{dt} Ca_i = \frac{1}{2FV_C} (2I_{NaCa} - I_{Ca,t}) + J_{leak} + J_{rel} - J_{up} \\ \quad - |Ca_i|_+ \sum_{b \in I_B} k_{onb}(B_{ib} - Ca_{ib}) + \sum_{b \in I_B} k_{offb}Ca_{ib} \\ \frac{d}{dt} Ca_{ib} = k_{onb}|Ca_i|_+(B_{ib} - Ca_{ib}) - k_{offb}Ca_{ib}, \quad b \in I_B \\ \frac{d}{dt} G_K = \frac{1}{\tau_K} \cosh\left(\frac{V - V_{GK}}{RT/2F}\right) \\ \quad \times \left\{ \frac{1}{2} \left[1 + \tanh\left(\frac{V - V_{GK}}{RT/2F}\right) \right] - G_K \right\} \\ \frac{d}{dt} G_{Na} = \frac{1}{\tau_{Na}} \cosh\left(\frac{V - V_{GNa}}{RT/2F}\right) \\ \quad \times \left\{ \frac{1}{2} \left[1 - \tanh\left(\frac{V - V_{GNa}}{RT/2F}\right) \right] - G_{Na} \right\} \end{array} \right. \quad (37)$$

Results

For one-beat simulations, the pacing protocol uses a current stimulus, with a duration of 10ms and an amplitude of $-1.0nA$. The stimulus is assumed to carry K^+ ions and is added to $I_{K,t}$ before calculation of K_i^+ using equations (15) and (16). Fig 1 shows the response to this stimulus of the two main outputs of our ECC model, V and Ca_{iTn} and Fig 2 the responses of the various concentrations and currents. Concerning the action potential and the ionic currents, these results are very similar to those obtained e.g. in [8].

Fig 3 shows an example of response to a sequence of external stimuli. A quasi steady-state is reached in a few periods for V and the ionic currents. Remark that the sequence of stimuli is non conservative for the potassium, so that we can observe a ramp for K_i and Na_i due to the NaK pump and a slow variation of Ca_i .

Table 1: Abbreviations used in the text

| Abbrev. | Definition |
|---------------|---|
| V | Action potential |
| V_{ext} | External stimulus voltage |
| I_{ext} | External stimulus current |
| $I_{X,t}$ | Total X current through all channels |
| I_{NaCa} | $Na^+ - Ca^{2+}$ exchanger current |
| I_{NaK} | $Na^+ - K^+$ pump current |
| g_K | Potassium activation gating |
| g_{Na} | Sodium inactivation gating |
| d_∞ | Calcium activation gating |
| m_∞ | Sodium activation gating |
| J_{rel} | Calcium-Induced Calcium Release current |
| J_{up} | Pump current taking up calcium in the SR |
| J_{leak} | Leakage current from SR to the cytoplasm |
| X_i | Intracellular concentration of the free ion X |
| X_e | External concentration of the ion free X |
| Ca_T | Total calcium concentration in the cell |
| Ca_{SRT} | Total calcium concentration in the SR |
| Ca_{SRb} | Concentration of Ca buffered in the SR |
| Ca_{SR} | Free calcium concentration in the SR |
| Ca_{iTn} | Ca buffered in Troponin-C |
| Ca_{iTn-Ca} | Ca buffered in Troponin-C Ca-Mg (Ca) |
| Ca_{iTn-Mg} | Ca buffered in Troponin-C Ca-Mg (Mg) |
| Ca_{iM-Ca} | Myosin (Ca) Ca-buffered in the cytosol |
| Ca_{iM-Mg} | Myosin (Mg) Ca-buffered in the cytosol |
| Ca_{iCal} | Calmodulin Ca-buffered in the cytosol |
| Ca_{iSR} | SR Ca-buffered in the cytosol |
| Ca_{iJCT} | SR Calcium buffered in the junction |

Discussion

Our model is a set of eleven conservation equations for the total electrical charge (V , up to some capacitance factor), potassium, sodium, free calcium in the cytosol (K_i , Na_i , Ca_i), calcium bound in seven intracellular buffers (Ca_{ib} , $b \in I_B$), plus two gate equations. It is based on three models. Ionic channel gating is modeled as in Endresen [7] by first order kinetics for the fluctuations between the "closed" and "open" states, leading to the state variables G_K and G_{Na} with $G_{Ca} = 1 - G_K$. From this work is also borrowed the invariant expression linking V to the surplus of charge inside the cell (from (30), (32)): $V = \frac{FV_C}{C_m} \{ (Na_i - Na_e) + (K_i - K_e) + 2(Ca_T - Ca_e) \}$. This algebraic relation shows some possible choices for the state

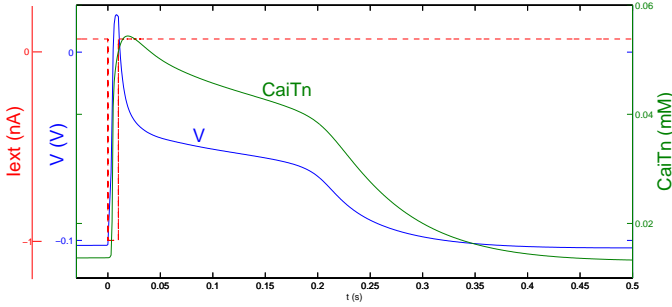


Figure 1: The external stimulation current I_{ext} and the main outputs: action potential V and concentration of calcium buffered on $Tn - Ca$

variables, in particular the possibility to eliminate V . This is sometime called the “algebraic method” [6]. Here we prefer to keep V and to replace Ca_T by a more detailed description of calcium storage (Ca_i , Ca_{ib}). So, it is still a “differential method” but the invariant is used to represent the calcium concentration in SR ((31), (32)). The respect of this invariant is important for a sound asymptotic behavior of the differential model.

The structure of the calcium dynamics model is borrowed from Shannon [5]. Some buffers of weak capacities have been omitted when in parallel with buffers of similar dynamic characteristics. Keeping both Ca_i and Ca_{iCT} to describe free intracellular calcium, has allowed to adapt the Ten Tusscher’s model of CICR [8] to give the expression (26), that is also a simplification of the mechanism in [5]. Remark that it takes into account a CICR dependence on intracellular calcium concentration.

Our final model of EC coupling is still complex for some applications (e.g. imbedding in distributed models of the heart). Also it is probably not a minimal state-space realization having the mentioned properties of the input-output relation, primarily interesting us, between I_{ext} , V_{ext} and V , Ca_{Tn} . In fact it would be useful to have a consistent hierarchy of state-space realizations of this input-output map with the corresponding properties of each model. This will be the object of future works.

Conclusion

We have presented a differential model of the membrane potential and of the calcium bound to the troponin C that is in good agreement with more complete models of the ionic currents and calcium dynamics in a ventricular cell. Due to its sound asymptotic behavior without drifts of the state and its medium complexity, this model of excitation-contraction coupling can be used in multi-beat simulations from the cell to the heart scales.

Table 2: Initial conditions

| Variable | Initial value | Unit |
|----------------|---------------------|------|
| V_0 | $-89 \cdot 10^{-3}$ | V |
| K_{i0} | 127.8028 | mM |
| Na_{i0} | 20.6954 | mM |
| Ca_{i0} | 0.0010 | mM |
| Ca_{iTn0} | 0.0451 | mM |
| $Ca_{iTn-Ca0}$ | 0.1389 | mM |
| $Ca_{iTn-Mg0}$ | 0.0003 | mM |
| Ca_{iM-Ca0} | 0.1362 | mM |
| Ca_{iM-Mg0} | 0.1033 | mM |
| Ca_{iCa0} | 0.0031 | mM |
| Ca_{iSR0} | 0.0121 | mM |
| G_{K0} | 0.0737 | |
| G_{Na0} | 0.0293 | |

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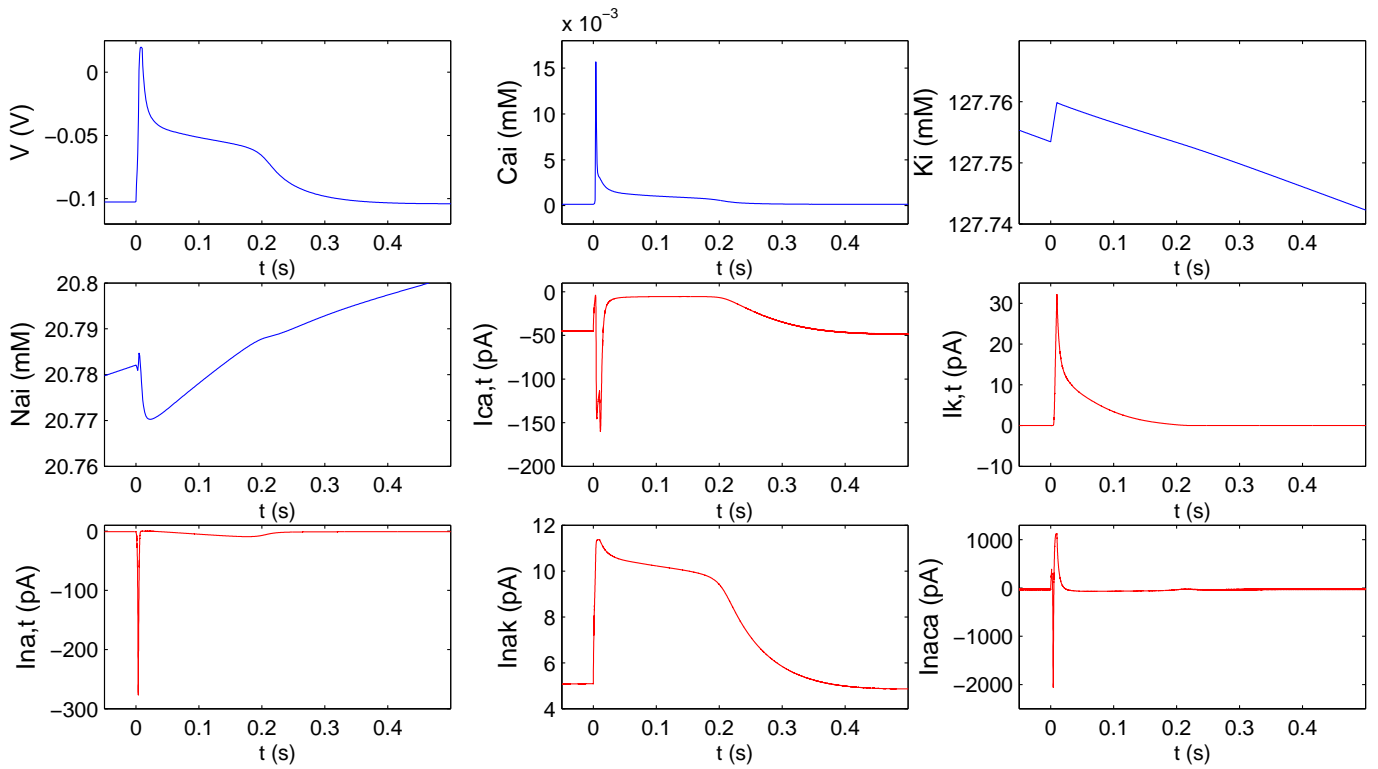


Figure 2: Action potential V ; concentrations of Ca_i , Na_i , K_i and ionic currents $I_{Ca,t}$, $I_{K,t}$, $I_{Na,t}$, I_{NaK} , I_{NaCa} in response to an external stimulus I_{ext}

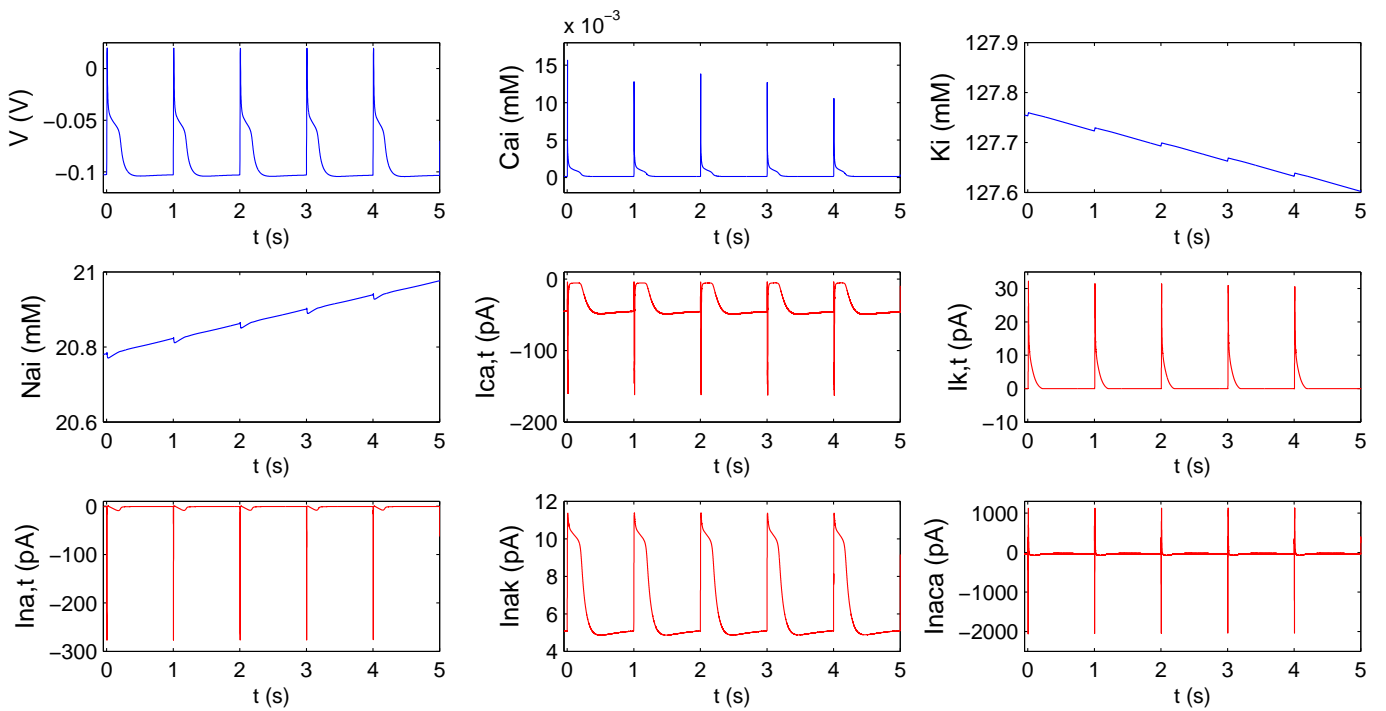


Figure 3: Response to a sequence of external stimuli, I_{ext} , of the action potential V , concentrations of Ca_i , Na_i , K_i and ionic currents $I_{Ca,t}$, $I_{K,t}$, $I_{Na,t}$, I_{NaK} , I_{NaCa}

Table 3: Model parameters

| Parameter | Value | Unit |
|----------------------|------------------------|--------------------|
| V_C | 16.404 | pL |
| V_{SR} | 1.094 | pL |
| F | 96.486 | $Cmmol^{-1}$ |
| V_m | $-56.86 \cdot 10^{-3}$ | V |
| V_d | $-5 \cdot 10^{-3}$ | V |
| V_{GK} | $-26 \cdot 10^{-3}$ | V |
| V_{GNa} | $-71.55 \cdot 10^{-3}$ | V |
| C_m | 65.616 | pF |
| R | $8.314 \cdot 10^{-3}$ | $Jmmol^{-1}K^{-1}$ |
| T | 310 | K |
| V_{ATP} | $-450 \cdot 10^{-3}$ | V |
| \bar{I}_{Na} | 112.7 | pA |
| \bar{I}_K | 32.9 | pA |
| $\bar{I}_{b,K}$ | 70 | pA |
| \bar{I}_{Ca} | 26.2 | pA |
| $\bar{I}_{b,Ca}$ | 0.01645 | pA |
| \bar{I}_{NaK} | 11.46 | pA |
| \bar{I}_{NaCa} | 1400 | pA |
| K_e | 5.4 | mM |
| Na_e | 140 | mM |
| Ca_e | 2 | mM |
| $\tau_K = \tau_{Na}$ | 0.2 | s |
| K_{leak} | 0.005 | s^{-1} |
| H | 1.787 | |
| K_{mf} | $0.246 \cdot 10^{-3}$ | mM |
| K_{mr} | 1.7 | mM |
| J_{max} | $286 \cdot 10^{-3}$ | mMs^{-1} |
| Q_{up} | 2.6 | |
| K_{rel} | $25 \cdot 10^3$ | s^{-1} |

Table 4: Model parameters (Continued)

| Parameter | Value | Unit |
|----------------|---------------------|-----------------|
| k_{onTn} | $32.7 \cdot 10^3$ | $mM^{-1}s^{-1}$ |
| k_{offTn} | 19.6 | s^{-1} |
| B_{iTn} | $70 \cdot 10^{-3}$ | mM |
| $k_{onTn-Ca}$ | $2.37 \cdot 10^3$ | $mM^{-1}s^{-1}$ |
| $k_{offTn-Ca}$ | 0.032 | s^{-1} |
| B_{iTn-Ca} | $140 \cdot 10^{-3}$ | mM |
| $k_{onTn-Mg}$ | $0.003 \cdot 10^3$ | $mM^{-1}s^{-1}$ |
| $k_{offTn-Mg}$ | 3.33 | s^{-1} |
| B_{iTn-Mg} | $140 \cdot 10^{-3}$ | mM |
| k_{onM-Ca} | $13.8 \cdot 10^3$ | $mM^{-1}s^{-1}$ |
| $k_{offM-Ca}$ | 0.46 | s^{-1} |
| B_{iM-Ca} | $140 \cdot 10^{-3}$ | mM |
| k_{onM-Mg} | $0.0157 \cdot 10^3$ | $mM^{-1}s^{-1}$ |
| $k_{offM-Mg}$ | 0.057 | s^{-1} |
| B_{iM-Mg} | $140 \cdot 10^{-3}$ | mM |
| k_{onCal} | $34 \cdot 10^3$ | $mM^{-1}s^{-1}$ |
| k_{offCal} | 238 | s^{-1} |
| B_{iCal} | $24 \cdot 10^{-3}$ | mM |
| k_{onSR} | $100 \cdot 10^3$ | $mM^{-1}s^{-1}$ |
| k_{offSR} | 60 | s^{-1} |
| B_{iSR} | $19 \cdot 10^{-3}$ | mM |
| K_{JCT} | $13 \cdot 10^{-3}$ | mM |
| B_{JCT} | $4.6 \cdot 10^{-3}$ | mM |
| K_{SR} | 0.0065 | mM |
| B_{SR} | 0.14 | mM |