Ensuring Stability in Models of Atrial Kinetics

A van Oosterom[1], V Jacquemet[2]

[1]Cardiomet, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[2]Signal Processing Institute, Ecole Polytechnique Fédérale de Lausanne, Switzerland

Abstract

The membrane kinetics of hunan atrial myocytes as formulated by Courtemanche, Ramirez and Nattel has been studied while focussing on its progression toward stationary solutions during long term repetitive stimulation. An algorithm is presented for finding the initial settings for all state variables on the basis of those assumed for the transmembrane potential V_{m} and the intracellular concentrations of the ions involved: [Na^+], [K^+], and [Ca^{2+}]. The algorithm may be used for testing the feasibility of yielding stationarity for any proposed combination of these values, as well as for any perturbation of the model parameters.

1. Introduction

The membrane kinetics of human atrial myocytes as formulated by Courtemanche, Ramirez and Nattel (CRN) [1] is a commonly used model in studies of the atrial electric activity, in particular those investigating the conditions leading up to –or terminating– atrial fibrillation [2]. A notorious problem in such models is the slow drift of all state variables. One of the explanations proposed in the literature attributes the drift to the accumulation of charge in the cell (numerical representation of a membrane patch) resulting from the applied stimulus current.

To study this hypothesis in the CRN model, simulations (real time: 1 h) were carried out during continuous stimulation, as well as during episodes with zero stimulus strength. The simulated variables V_{m}, $[\mathrm{Na}^+]_{\mathrm{i}}$, $[\mathrm{K}^+]_{\mathrm{i}}$, and $[\mathrm{Ca}^{2+}]_{\mathrm{i}}$ were monitored at 1 s intervals, each involving 10^5 time steps (10 μs intervals) of the numerical solution method. The results of the zero stimulus strength condition are shown in Fig. 1, presented as the percentage change relative to the initial values of the CRN paper. Note the changes of up to 1 %. These percentages are similar to those occurring during a single (stimulated) beat.

The question then arose if, in the absence of a stimulus, stable solutions might be feasible. This question has been addressed in a paper by Jacquemet [3] and the answer was affirmative. In fact an infinite number of stable solutions were identified, from which a unique version could

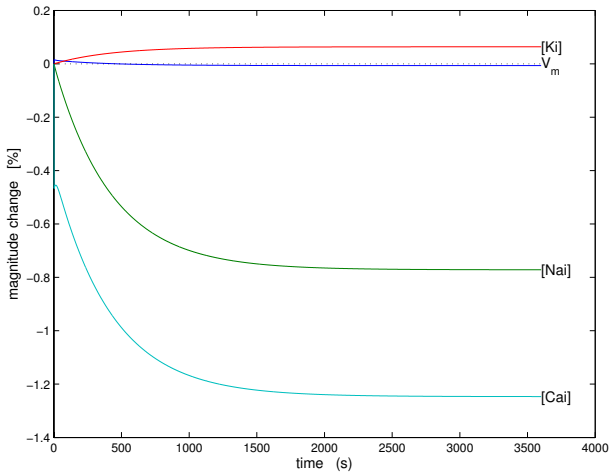

Figure 1. Time course of the change of the absolute values of the major state variables indicated, relative to their initial values; zero stimulus strength. Since V_{m} is negative, a positive change corresponds to a shift to more negative values.

be specified on the basis of prescribing a value for $[\mathrm{NS}]_{\mathrm{i}}$, the total (non-specific) intracellular charge concentration.

In this contribution an algorithm is presented for finding such combinations of initial settings for these four state variables that ensure a steady state in the absence of external stimuli on the basis of an assumed value of the intercellular charge density. In turn, these then specify initial values for the remaining ones of the total of the 21 state variables involved.

In the absence of a stimulus, all state variables remained constant with respect to their initial values. However, the response to periodic stimuli still exhibited a residual drift. This could be effectively solved by introducing a mild feed-back for $[\mathrm{Na}^+]$ and $[\mathrm{K}^+]$, which eases their values to the constant steady state values following the termination of the stimulation.

Below, full details of the algorithm for ensuring stability are presented, followed by an illustration of its effectiveness.

2. Methods

2.1. The CRN algorithm

For a complete description of the CRN model, its creation, justification and a documentation of its parameters the reader is referred to the original publication [1], as well as to the overview presented in [3]. A summary, attuned to the current discussion, is as follows.

The membrane kinetics of the CRN model describes the interaction of the transmembrane potential $V_{\rm m}$ and the intracellular concentrations of three ions: sodium $[{\rm Na}^+]_{\rm i}$ with gating variables m, h and j, potassium $[{\rm K}^+]_{\rm i}$ with gating variables $x_{\rm r}, x_{\rm s}, u_{\rm a}, u_{\rm i}, s_{\rm a}$ and $s_{\rm i}$, and calcium $[{\rm Ca}^{2+}]_{\rm i}$ with gating variables d, fca and f. These state variables control the individual currents across the membrane and the flux of each of the associated ions. In addition, there are exchanges of $[{\rm Ca}^{2+}]$ across the boundary between the intracellular compartment and the two compartments of an internal calcium store, the sarcoplasmic reticulum, its so-called uptake and release compartments (see Fig. 1 of [1] or Fig. 3 of [3]). The concentrations of $[{\rm Ca}^{2+}]$ within these compartments are denoted by $[{\rm Ca}^{2+}]_{\rm up}$ and $[{\rm Ca}^{2+}]_{\rm rel}$, respectively. The exchange between the internal compartment and the release compartment is specified by three gating variables: u, v and w. In all 21 state variables are involved: one voltage, five concentrations and 15 gating variables. At any moment in time the state of the system can be specified by a vector $\mathbf{x} = [\,V_{\rm m}\ \mathbf{c}\ \mathbf{y}]$, with $V_{\rm m}$ a scalar denoting the transmembrane potential, $\mathbf{c}$ a vector denoting the 5 concentrations and $\mathbf{y}$ a vector denoting the 15 gating variables. The dynamics of the system is that of 21 coupled first order non-linear differential equations.

The dynamics of this system is highly complex, but constant stationary solutions exist for specific sets of values of the state variables $V_{\rm m}$, $[{\rm Na}^+]_{\rm i}$, $[{\rm K}^+]_{\rm i}$ and $[{\rm Ca}^{2+}]_{\rm i}$ [3]. These then set the corresponding values of the remaining state variables.

2.2. Finding the (constant) state variables

In the following, the term "steady state" is used to refer to the situation where all state variables are constant over time. During steady state, the time derivatives of all state variables are zero and, hence, their values are constant. For the gating variables, these values are generally referred to as y_∞. Most of these depend (non-linearly) on $V_{\rm m}$. Exceptions are fca_∞, which depends on $[{\rm Ca}^{2+}]_{\rm i}$, and u_∞, v_∞ and w_∞, which depend on $F_{\rm n}$, a function switching the $[{\rm Ca}^{2+}]$ release from the intracellular calcium store. $F_{\rm n}$ is based on the balance between three ion currents involved in the release. These currents themselves are a function of other state variables.

In the CRN model various currents express the exchange

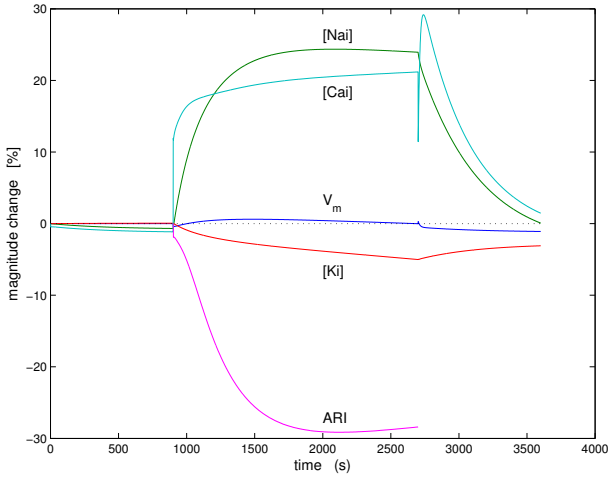

Figure 2. As in Fig. 1, now with a stimulus at 1 s intervals, applied from t=900 s till t=2700 s. The changes in the activation-recovery intervals (ARI) of the beats relative to that of the first beat are shown in the lower trace.

of ions across the membrane: $I_{\rm Na}$, $I_{\rm bNa}$, $I_{\rm NaK}$, $I_{\rm K1}$, $I_{\rm to}$, $I_{\rm Kur}$, $I_{\rm Kr}$, $I_{\rm Ks}$, $I_{\rm pCa}$, $I_{\rm Cal}$, $I_{\rm bCa}$ and $I_{\rm NaCa}$ [1].

The flux of specific ions across the membrane is directly linked to the combination of the above currents. During steady state, all individual intracellular ion concentrations are constant, which means that their total flux across the membrane is zero. Similarly, the total flux of $[{\rm Ca}^{2+}]$ to and the intracellular calcium store must be zero and, as a consequence, among $\mathbf{x}$ the five state variables, $[{\rm Ca}^{2+}]_{\rm up}$, $[{\rm Ca}^{2+}]_{\rm rel}$ and the associating state variables (u, v and w) gating the release of $[{\rm Ca}^{2+}]$, may be excluded while treating the ion flux across the membrane.

The zero flux condition across the membrane, applied to each of the 3 individual ions, forms the basis of the algorithm for finding the steady state values of the state variables involved. This demands the search of the values of the remaining 16 state variables such that all three fluxes are zero. As mentioned before, an infinite number of solutions exist[3]; the unique solution chosen heuristically here is the one that takes the total charge concentration in the intracellular space to be equal to that in the extracellular space.

2.3. The membrane state variables

The three individual ion fluxes across the membrane, F_{Na^+}, F_{K^+} and $F_{Ca^{2+}}$ are denoted by a column vector $\mathbf{f}$. These fluxes are expresses as a linear combination ($\mathbf{f} = \mathbf{W}\ \mathbf{i}$) of the 12 currents listed previously, also represented by a column vector $\mathbf{i}$. The matrix $\mathbf{W}$ reflects the valence of the ions and the stoechiometry of the reactions involved.

Under steady state conditions all elements of the current vector $\mathbf{i}$ are a function of the state vector $\mathbf{x}$, in which, as discussed in the previous subsection, for the gating vector $\mathbf{y}$ we may write $\mathbf{y} = \mathbf{y}(V_\mathbf{m}, \mathbf{c})$. Recall that, during steady state, $\mathbf{y} = \mathbf{y}_\infty$, and the elements $[\mathrm{Ca}^{2+}]_{\mathrm{up}}$ and $[\mathrm{Ca}^{2+}]_{\mathrm{rel}}$ of the vector $\mathbf{c}$ do not play a role in the transmembrane currents and fluxes. We now have

$$\mathbf{f} = \mathbf{W}\,\mathbf{i} = \mathbf{W}\,\mathbf{i}\,(V_\mathrm{m}, \mathbf{c}, \mathbf{y}(V_\mathrm{m}, \mathbf{c}))\,, \qquad (1)$$

and the elements of the vector $[\ V_m\ [Na^+]_\mathrm{i}\ [K^+]_\mathrm{i}\ [Ca^2+]_\mathrm{i}\ ]$ need to be found such that all elements of the vector $\mathbf{f}$ are zero.

Equation (1) poses the problem of finding zeros in the 4D parameter space on the basis of just three conditions (the zero fluxes). The solution was made unique by adding the constraint: $[Na^+]_\mathrm{i} + [K^+]_\mathrm{i} + 2[Ca^{2+}]_\mathrm{i} = [Na^+]_\mathrm{e} + [K^+]_\mathrm{e} + 2[Ca^{2+}]_\mathrm{e}$, demanding the total intracellular and extracellular charge density of the ions expressed in the CRN model to be equal.

An algorithm for solving (1) was devised, based on the Levenberg-Marquardt method (L-M method) [4], a non-linear parameter estimation procedure, which was applied to a parameter vector $\mathbf{p}$ with elements $p_i, i = 1 \ldots 4$, scaling the respective elements of $[\ V_m\ [Na^+]_\mathrm{i}\ [K^+]_\mathrm{i}\ [Ca^{2+}]\ ]$, the default values shown in Table 2 of [1] by 1.01^{p_i}. The initial parameter vector $\mathbf{p}$ was [0 0 0 0]. In this manner the numerical problems related to the widely differing scales of the actual individual parameters, $V_m, [Na^+]_\mathrm{i}, [K^+]_\mathrm{i}$ and $[Ca^{2+}]_\mathrm{i}$ are avoided. Moreover, their signs are saveguarded throughout the procedure.

The L-M method iteratively minimizes the squared norm (SSQ) of $\mathbf{f}$. The elements of the required gradient matrix of SSQ with respect to those of $\mathbf{p}$ were computed numerically, using a local parabolic approximation with step size: $\Delta p_i = 2\ 10^{-3}$. The search direction in parameter space is influenced by the value of a positive constant λ, whose value is adjusted after each iteration. For increasing values of λ the search direction tends more and more toward the local gradients of SSQ, accompanied by increasingly smaller step sizes. Conversely, for decreasing values of λ the search it tends toward the direction indicated by the Gauss-Newton method, while gradually lifting the constraint on the step size.

Starting from $\lambda = 1$, if after any iteration SSQ decreased, λ was reduced two-fold, else it was increased four-fold. When nit, the index of the iteration, exceeded 300, or when λ exceeded 100, the iteration process was stopped.If, at the final iteration, $SSQ > 10^{-6}$ the initial estimate of $[\ V_m\ [Na^+]_\mathrm{i}\ [K^+]_\mathrm{i}\ [Ca^{2+}]_\mathrm{i}]$ was rejected, and the combination found was deemed non-feasible.

2.4. State variables of the calcium store

The above procedure produces the steady initial values of all state variables except for the five involved in the $[Ca^{2+}]$ store: $[\mathrm{Ca}^{2+}]_{\mathrm{up}}$, $[\mathrm{Ca}^{2+}]_{\mathrm{up}}$ and the associating gating variables $u = u_\infty$, $v = v_\infty$ and $w = w_\infty$. In subsequent dynamic applications, their initial values need to be specified. In fact, only four need to be identified, since $w = w_\infty$ as specified in the CRN algorithm is a function of V_m only, the latter being identified during the L-M procedure.

The remaining four were computed on the basis of the condition (during steady state) of zero total calcium flux to the store, the ones related to I_{up}, $I_{\mathrm{leak}} = I_{\mathrm{up;leak}}$ and I_{rel}. The latter of these currents is gated by the state variables u, v and w. In addition the calcium flux between uptake and release compartment was taken into account, the latter represented by a transient current I_{tr}.

The key elements of the CRN formulation [1] that play a role in this computation during steady state are as follows. These are denoted such that all variables found in the first step (the L-M method) are treated as constants, while showing explicitly only the ones that remain to be found. They are, using a compact notation for the calcium concentrations: $[\mathrm{Ca}^{2+}] \rightsquigarrow C$, $I_{\mathrm{leak}}(C_{\mathrm{up}})$, $I_{\mathrm{tr}}(C_{\mathrm{up}}, C_{\mathrm{rel}})$, $I_{\mathrm{rel}}(u(F_\mathrm{n}), v(F_\mathrm{n}), C_{\mathrm{rel}})$, with $F_\mathrm{n} = F_\mathrm{n}(I_{\mathrm{rel}})$.

For zero flux we must have: I_{up}=I_{leak} + I_{rel}. Correspondingly, for the transient flux between the uptake and release compartments: I_{up}=I_{leak} + I_{tr}. The combination of the latter two expressions can be formulated as a system of two equations

$$\begin{aligned} I_{\mathrm{leak}}(C_{\mathrm{up}}) + I_{\mathrm{tr}}(C_{\mathrm{up}}, C_{\mathrm{rel}}) &= I_{\mathrm{up}} \\ I_{\mathrm{leak}}(C_{\mathrm{up}}) + I_{\mathrm{rel}}\,(u(F_\mathrm{n}), v(F_\mathrm{n}), C_{\mathrm{rel}}) &= I_{\mathrm{up}}. \end{aligned}$$

The relevant details of the functions indicated above, taken from the CRN formalism, are

$$\begin{aligned} I_{\mathrm{leak}}(C_{\mathrm{up}}) &= c_1 C_{\mathrm{up}}, \\ I_{\mathrm{tr}}(C_{\mathrm{up}}, C_{\mathrm{rel}}) &= c_2 \times (C_{\mathrm{up}} - C_{\mathrm{rel}}), \\ I_{\mathrm{rel}} &= k(F_\mathrm{n}) \times (C_{\mathrm{rel}} - C_\mathrm{i}), \text{with} \\ k(F_\mathrm{n}) &= krel\ u^2(F_\mathrm{n})\ v(F_\mathrm{n})\ w \ \text{ and} \\ F_\mathrm{n} &= a \times I_{\mathrm{rel}} - b. \end{aligned} \qquad (2)$$

The current I_{up} is a function of C_i only and hence, since the value of the latter is determined in the L-M procedure, here I_{up} can be treated as a constant. The same applies to b and w. The constants a, c_1 and c_2 denote compact forms of the CRN parameters.

Based on this notation the system (2) can be written as

$$\begin{bmatrix} c_1 + c_2 & -c_2 \\ c_1 & k(F_\mathrm{n}) \end{bmatrix} \begin{bmatrix} C_{\mathrm{up}} \\ C_{\mathrm{rel}} \end{bmatrix} = \begin{bmatrix} I_{\mathrm{up}} \\ I_{\mathrm{up}} + k(F_\mathrm{n})\ C_\mathrm{i} \end{bmatrix}.$$

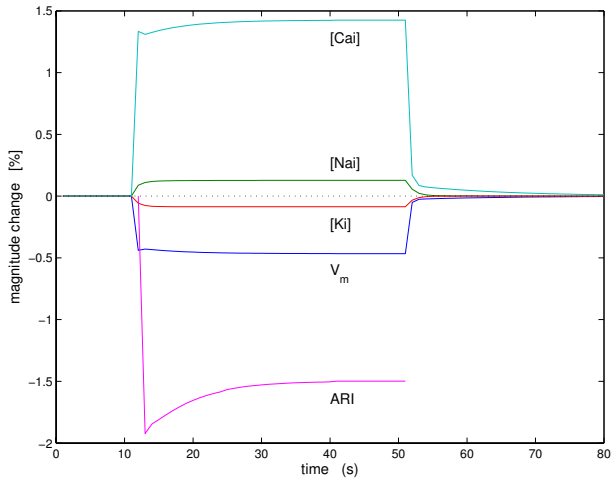

Figure 3. As in Fig. 2 but now using the initial state variables yielding a constant steady state. Note the expanded time base. $\alpha = 10^{-5}$. $[K^+]$ changes are shown magnified 10 fold; those of $[Ca^{2+}]$ are shown reduced 10 fold .

Any known value of $F_{\rm n}$ sets the values of u, v and, hence, of k. Generally, $F_{\rm n}$ cannot be assumed to be known. However, for any value of $F_{\rm n}$ in the CRN formalism, the resting state value of the product $u^2(F_{\rm n})v(F_{\rm n})$ is such that the resulting value of $I_{\rm rel}$ as in (2), is always several orders of magnitudes smaller than any of the other currents involved [3]. Using this approximation, solving (2), then reduced to a system of linear equations, yields

$$\begin{array}{rcl} C_{\rm up} & = & I_{\rm up}/c_1 \\ C_{\rm rel} & = & I_{\rm up}/c_1 \quad = \quad C_{\rm up}. \end{array} \qquad (3)$$

Finally, $F_{\rm n}$ is calculated from the standard expression of the CRN algorithm, while using $I_{\rm rel} \approx 0$: $F_{\rm n} = 10^{-13}(I_{\rm NaCa} - 2.5I_{\rm Cal})/F$, with F denoting Faraday's constant. This defines $u_\infty = u(F_{\rm n})$ and $v_\infty = u(F_{\rm n})$, and so all four remaining resting state variables are found.

2.5. Anchoring the solution

On the basis of the steady state variables identified by the algorithm described above, the CRN kinetics of a single unit was first applied at zero stimulus strength. Unlike what was observed resulting from using the default initial values specified in the CRN paper, all 21 state variables were found to remain constant over time as desired. However, upon initiation of a periodic stimulus (with strength twice the threshold), a residual, slow drift was observed. This was "cured" by introducing a feedback that eased the two state variables in which the drift was most pronounced, $[{\rm Na}^+]_{\rm i}$ and $[{\rm K}^+]_{\rm i}$, toward their constant resting values $[{\rm Na}^+]_{\rm i;rest}$ and $[{\rm K}^+]_{\rm i;rest}$, respectively. The feedback was implemented, directly following the update of the concentrations at each time step of 10μs, as

$$\begin{array}{rcl} [{\rm Na}^+]_{\rm i} & = & (1-\alpha)\,[{\rm Na}^+]_{\rm i} \quad + \quad \alpha\,[{\rm Na}^+]_{\rm i;rest} \\ [{\rm K}^+]_{\rm i} & = & (1-\alpha)\,[{\rm K}^+]_{\rm i} \quad + \quad \alpha\,[{\rm K}^+]_{\rm i;rest} \end{array} , \qquad (4)$$

with $0 <= \alpha <= 1$ setting the "pull" of the anchor. Its value was found empirically, aiming for it to be as small as possible while still removing long term, persistent drift. The value adopted was 10^{-5}.

3. Results

The time course over 1 h of the four major state variables of the CRN kinetics initiated at the default settings of the CRN paper is shown in Fig. 2. A stimulus (interval 1 s) was applied between 15 and 45 min. The initial stage depicts the drift as also documented in Fig. 1. During the next stages a more pronounced, persistent drift can be observed. In contrast, the corresponding response to onset or termination of the stimulus condition based on the algorithm presented, depicted in Fig. 3, exhibits much faster (compare Fig. 2) transition to the subsequent, respective steady state behavior.

4. Discussion

The results shown demonstrate that long term stability of the CRN formalism can be assured by tuning the initial state variables to the zero-flux condition of the individual ions. The same was found to hold true when using perturbations of the basic parameters of the CRN formalism such as the conductances of individual ions.

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Address for correspondence:

A. van Oosterom
Steegstraat 20, 5439NL, The Netherlands.
adriaan.vanoosterom@epfl.ch