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# COMPUTER SIMULATION OF THE JAFRI-WINSLOW ACTION POTENTIAL MODEL

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# Computer Simulation of the Jafri-Winslow Action Potential Model

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## Abstract

Computer simulation of the Jafri-Winslow action potential mathematical model reveals that this model does not provide the long term stability of the steady state regime.

Under normal conditions (basic cycle length 1000 *ms*) maximum values of membrane potential, calcium concentrations in different compartments, and the *L*-type calcium channel current are not consistent with that in the original Jafri-Winslow's paper. The action potential duration restitution curve (*S1-S2* protocol) is non-monotonous unlike one in original paper.

Under periodic pacing (from 0.5 *Hz* to 5 *Hz*), it was impossible to get a stable behavior of the model after 30 s of stimulation unlike to the results presented in the original paper.

## 1. Introduction

The recent advances in physiological techniques (such as laser scan confocal microscopy, single channel current recording) allow to get more accurate information about intracellular calcium dynamics. Particularly, it was found that free intracellular calcium concentration not only participates in the cardiac cell contraction process, but also affects the shape and duration of the action potential (AP).

For last ten years, various mathematical models of isolated atrial [1-4] and ventricular [5-8] cardiac cells were formulated. Among these models, the Jafri-Winslow model[8] can be considered as a most advanced.

Despite the extremely high complexity of the model (described by 30 nonlinear differential equations), its application for computer simulation of different electro-physiological processes in the heart tissue is assumed to be very attractive. Such model, if it works properly, may serve as an standard for comparison with other more simplified models.

In this report, we present the results of our computer simulation which cover the behavior of the Jafri - Winslow model in steady state, normal, and high pacing rate regimes.

## 2. Equations and initial conditions

The Jafri-Winslow model [8] is one of the recently proposed mathematical model of the cardiac action potential which includes developed calcium dynamics. The distinctive features of this model are:

- Novel description of the *L*-type $Ca^{2+}$ channel,
- Employment of the Keizer - Levine model [9] for ryanodine receptors (*RyR*s) which provide adaptation at elevated $Ca^{2+}$,
- Introduction of restricted intracellular subspace (cleft) into which the *RyR*s and the *L*-type $Ca^{2+}$ channel empty and through which they interact,
- The non-fixed intracellular concentrations of $Na^{+}$ and $K^{+}$ ions. Its time changes are determined by reaction kinetics differential equations,
- The time dependent buffering is provided only for troponin buffer,

All other cell processes are described according to the Luo and Rudy [5].

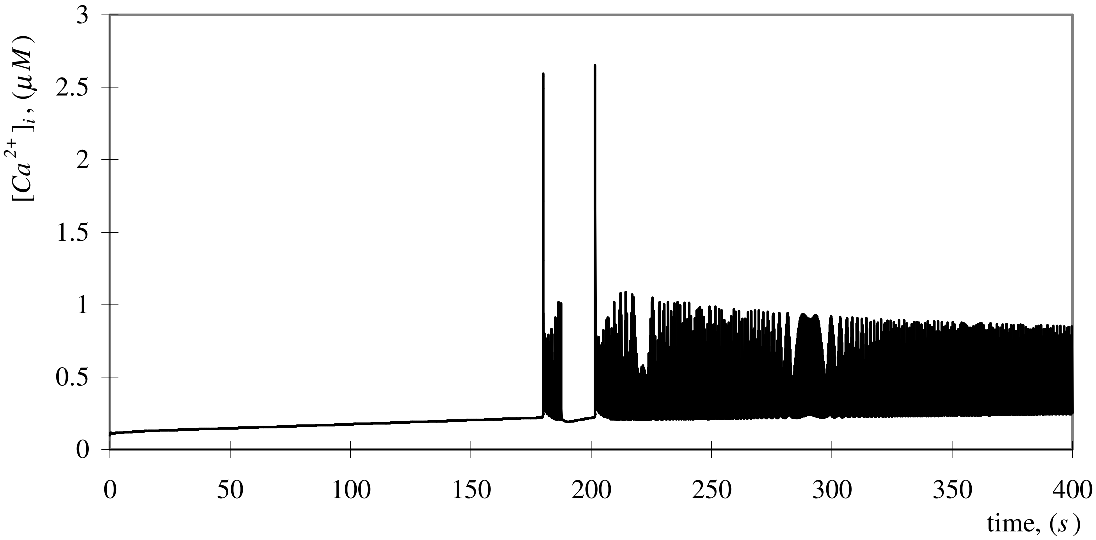
For this model, the full set of differential equations, values of parameters, and initial conditions are presented in Appendix 1. They are taken from web-site [10] and obtained after numerous corrections of the original paper [8].

## 3. Stability of steady state regime

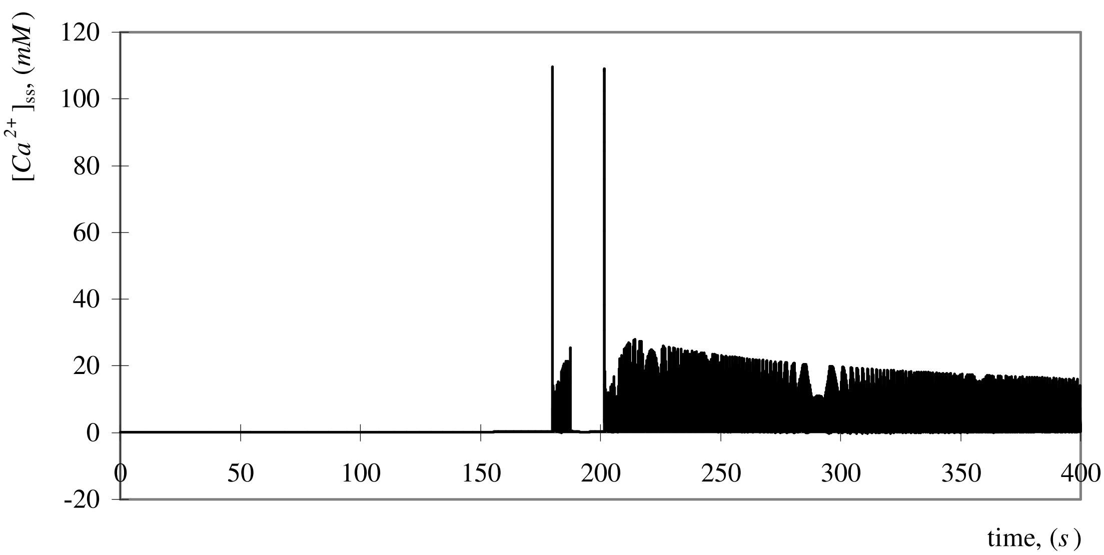
In correct cell model, the stability of the steady state regime must be provided. It means that all model variables have to reach its rest values after some comparatively short time interval, being running with small perturbation of initial conditions and without external stimulation. In order to check the stability of steady state regime for the Jafri-Winslow model [8], the full set of 30 ordinary differential equations with given initial conditions (see Appendix 1) was solved on computer without any stimulation ( $I_{stim}$ = 0). This computation was done during 400 *s* using both the Runge-Kutta 4$^{th}$-Order method and the Euler method with a variable time step not exceeded 0.1 *ms*. The discrepancy between the results found using these two numerical integration methods were negligibly small. The computation results are presented in Fig. 1a,b, 2a,b, and 3a,b.

At the time interval from 0 to 179.9 *s*, a calcium concentration increases in all compartments. Namely, the $[Ca^{2+}]_i$ and $[Ca^{2+}]_{ss}$ concentrations increase more than two times and reach values 0.22 $\mu M$ and 0.29 $\mu M$, respectively (see Fig. 1a, 1b); the $[Ca^{2+}]_{JSR}$ and $[Ca^{2+}]_{NSR}$ concentrations increase about four times and reach values 4.5 *mM* and 4.7 *mM*, correspondingly (see Fig. 2a, 2b). Let us note that the $[Ca^{2+}]_i$ rest concentrations measured in experimental study are 0.136 μM [11] and 0.12 $\mu M$ [12].

The sodium concentration $[Na^+]_i$ (see Fig. 3a) increases monotonously as a smooth function of time till t = 179.9 *s*. Then it continues to increase undergoing small oscillations. Extrapolating $[Na^+]_i$ graph for $t \to \infty$ , it is possible to get an asymptotic value of the sodium concentration about 22.9 *mM*. This value is more than two times as much as the one in the Luo-Rudy model where $[Na^+]_i$ = 10.0 *mM* . The potassium concentration $[K^+]_i$ (see Fig. 3b) decreases after 179.9 *s* up to 400 *s* with small oscillations. Extrapolating $[K^+]_i$ graph for $t \to \infty$, it is possible to get an equilibrium potassium concentration about 132.0 *mM* ( instead 145.0 *mM* in the Luo-Rudy model ).




(a)

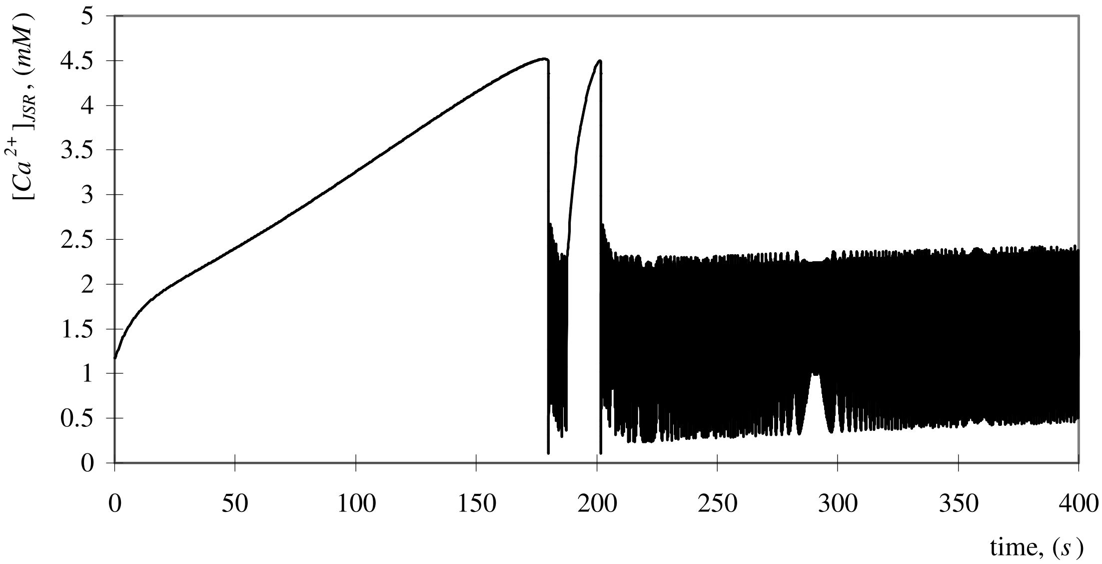



(b)

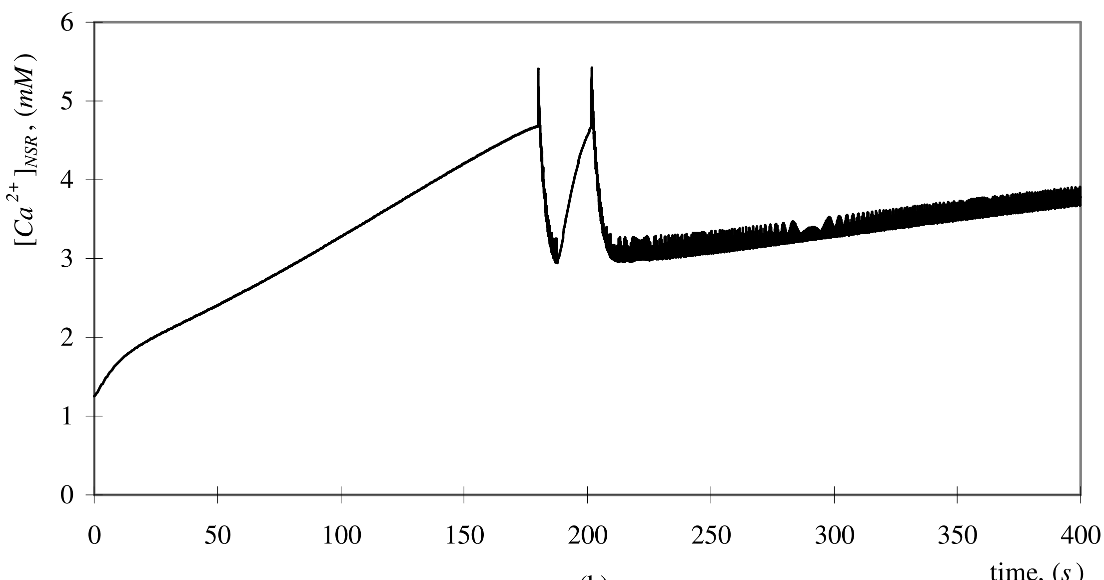
Fig.1 Changes of calcium concentrations in time:

(a) - in cytoplasma $[Ca^{2+}]_i$

(b) - in subspace $[Ca^{2+}]_{ss}$




(a)

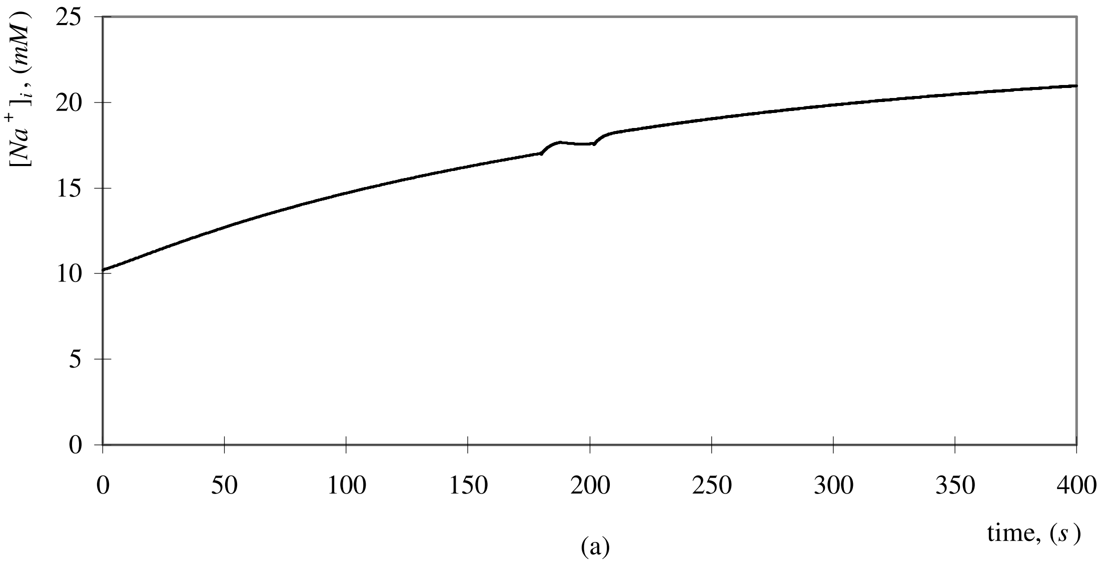



(b)

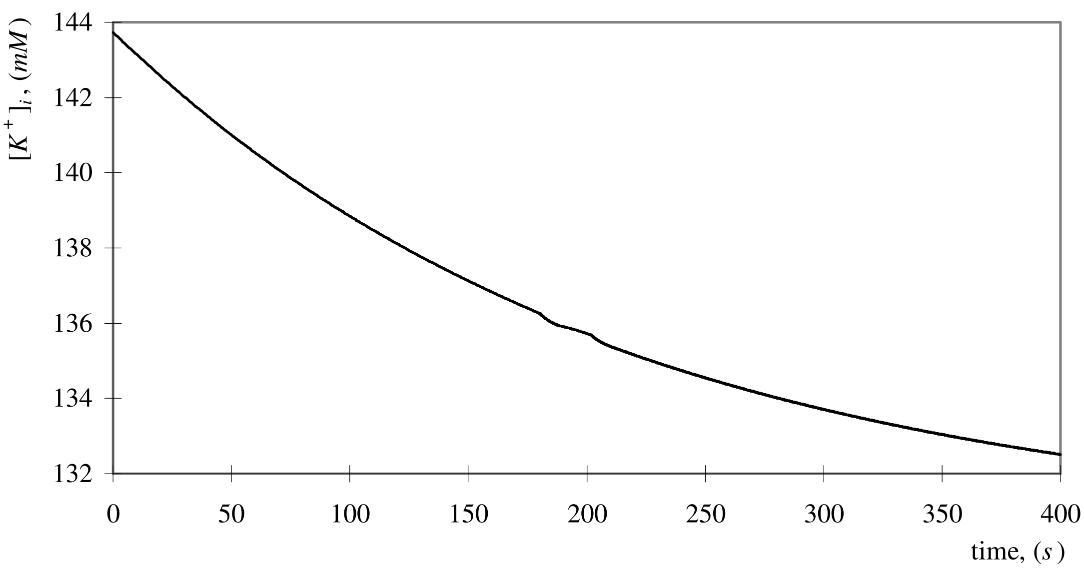
Fig. 2. Changes of calcium concentrations in time:

(a) - in *JSR*

(b) - in *NSR*




(a)

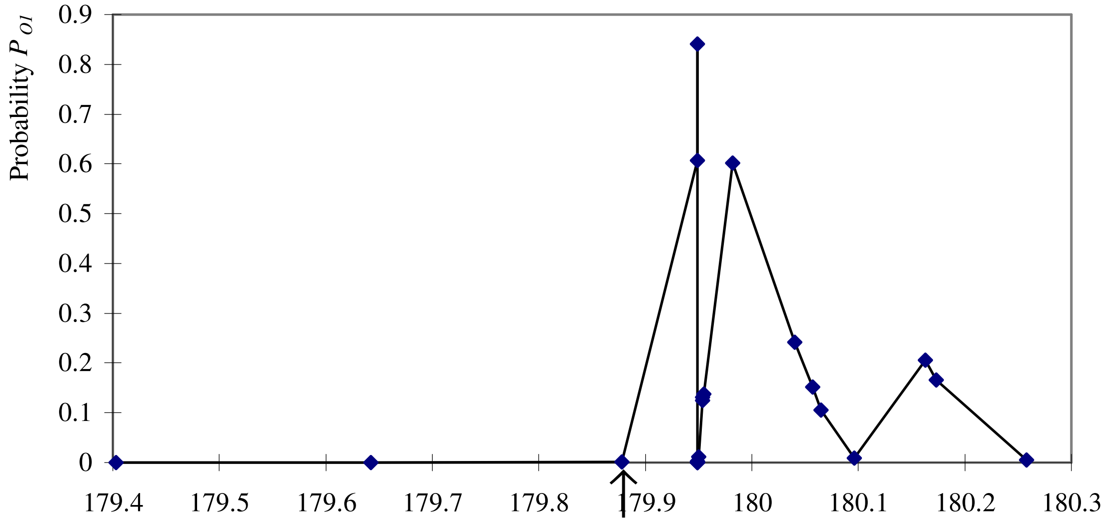



(b)

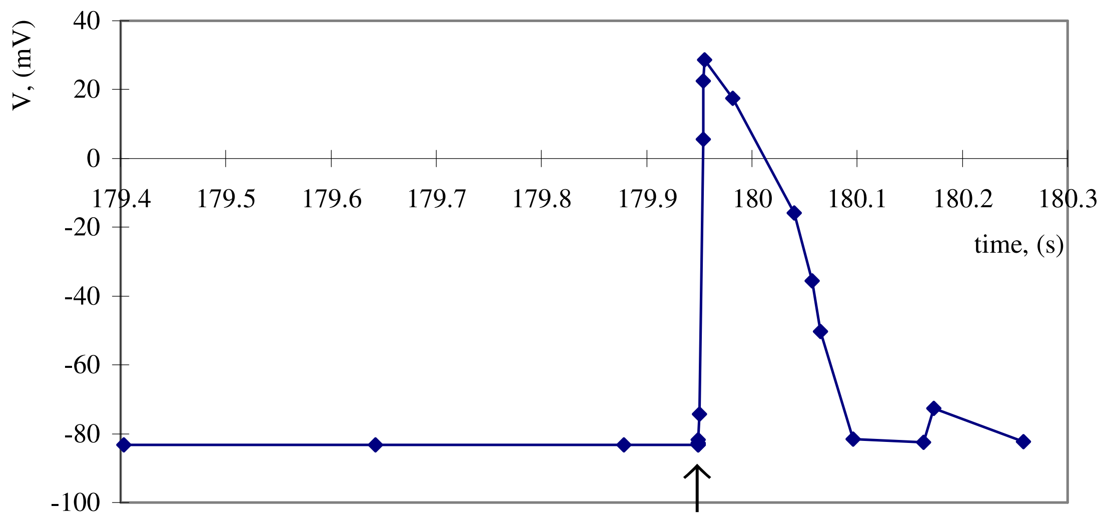
Fig. 3. Changes of sodium and potassium concentrations in time:

(a) - sodium concentration $[Na^+]_i$

(b) - potassium concentration $[K^+]_i$




(a)




(b)

Fig. 4. Changes of the variable $P_{O1}$ and the action potential $V$ in time interval included distortion of the steady state regime. The arrows show the moments of stability violation.

The steady state regime is violated after 179.9 *s* (see Fig. 1, 2, 3). Among the model variables, the variable $P_{O1}$ first begins rapidly to change (see Fig. 4a). When it reaches the value $P_{O1}$ = 0.61, the *AP* spontaneously appears (see Fig. 4b) and then the steady state regime is disturbed.

To make sure that these data are not computational errors, the asymptotic solution was found for the set of equations (10),(43), and (44). For $t \rightarrow \infty$, all transfer fluxes in these equations $J_{leak}$, $J_{xfer}$, $J_{up}$, and $J_{trpn}$, as well as the fast $Na^+$ current ($I_{Na}$) can be assumed to be equal zero. Additionally, the nonspecific $Ca^{2+}$-activated currents $I_{ns,Na}$ and $I_{ns,K}$ are also equal zero because $P_{ns(Ca)} = 0$. In the steady state, the $I_{Ca,K}$ current can be neglected as well because both variables $O \cong 0$ when the *L*-type $Ca^{2+}$ channel is closed and $O_{Ca}$ is equal zero permanently. Therefore, the set of the equations (10),(43), and (44) can be reduced to:

$$I_{Ca,b} - 2\, I_{NaCa} + I_{p(Ca)} = 0$$

$$I_{Na,b} + 3\, I_{NaCa} + 3\, I_{NaK} = 0$$

$$I_K + I_{K1} + I_{Kp} - 2\, I_{NaK} = 0$$

The currents in the first and in the second equations are nonlinear functions of the calcium and sodium intracellular concentration, and of the membrane rest potential $V_r$. Numerical solution of this nonlinear system of algebraic equations was found in relation to the values of $[Ca^{2+}]_i$ and $[Na^+]_i$ for different fixed values $V_r$. In the third equation, the $I_{K1}$ and $I_{Kp}$ currents are functions of the values $[K^+]_i$ and $V_r$. The $I_K$ current depends additionally on the gate variable $x$ that can be found for steady state as $x_\infty = \alpha_x(V_r)/(\alpha_x(V_r) + \beta_x(V_r))$. Thus, the potassium concentration was found from the third equation for different sets of values $[Na^+]_i$, and $V_r$. The results of computations are given in the table 1.

**Table 1**

| $V$, $mV$ | $[Ca^{2+}]_i$, $\mu M$ | $[Na^+]_i$, $mM$ | $[K^+]_i$, $mM$ |
|---|---|---|---|
| -82.0 | 0.387 | 21.994 | 125.137 |
| -83.0 | 0.400 | 22.596 | 129.845 |
| -84.0 | 0.413 | 23.198 | 134.725 |
| -85.0 | 0.427 | 23.826 | 139.780 |

The concentrations of sodium and potassium ions agree very well with the ones received by extrapolating the solution of the full set of the Jafri-Winslow model differential equations to $t \rightarrow \infty$. Unfortunately, it is impossible to find the $[Ca^{2+}]_i$ concentration by extrapolating due to a significant amplitude of its oscillations (see Fig. 1a). However, good agreement of the results for sodium and potassium concentration for $t \rightarrow \infty$, received using two different approaches, allow to assume that these results are correct. Moreover, these results show that the Jafri-Winslow model equations give the excessive steady state values of $[Ca^{2+}]_i$ and $[Na^+]_i$.

Assuming that main mismatch is connected with the differential equation for the sodium concentration, the set of equations of the Jafri-Winslow model was solved with given initial conditions keeping constant both the $[Na^+]_i = 10.242$ $mM$ and $[K^+]_i = 143.727$ $mM$ concentrations during the whole computation time. In this case, all variables reach its stable steady state values for the time approximately equals to 50 $s$.

Additional computation of the full set of the Jafri-Winslow model equations was performed with initial values of both sodium and potassium concentration $[Na^+]_i = 22.9$ $mM$ and $[K^+]_i = 132.0$ $mM$ that were previously found by extrapolating to $t \rightarrow \infty$. In this case, the steady state regime was violated essentially earlier (at time $t = 10$ $s$). The process of the steady state instability develops faster because the excessive $[Na^+]_i$ and $[K^+]_i$ concentrations were used at the very beginning of the simulation.

These computations allow to explain why the oscillations occur. The Jafri-Winslow model does not provide the correct value for the steady state $[Na^+]_i$ concentration. In the reverse mode, the $Na^+$-$Ca^{2+}$ exchanger current contributes to increasing an intracellular calcium concentration. The system becomes overloaded with calcium. Conditions appear for increasing the transfer fluxes $J_{rel}$, $J_{xfer}$, and $J_{tr}$ . At the moment of time t = 179.9 $s$, these fluxes become 40-60 times as much as in a vicinity of $t = 0$. The significant rise of these fluxes causes the distortion of the steady state regime.

## 4. Model in normal conditions

The shape and basic characteristics of the AP and intracellular calcium dynamics were obtained by application of a stimulation current $I_{stim} = 100$ $\mu A/cm^2$ with duration 0.5 $ms$ (the same as in paper [8]).

The characteristics in normal conditions were defined after a preconditioning during 10.0 *s* with period of 1.0 *s* (the stimulation frequency $f_{stim}$ = 1 *Hz*). Some computation results are presented in Table 2 and in Fig. 5a,b. The action potential duration (*APD*) was defined at the level of the membrane potential $V = -80.0$ *mV*. The *APD* and the maximum values of some variables are presented in table 2 with the corresponding data from the paper [1], for comparison.

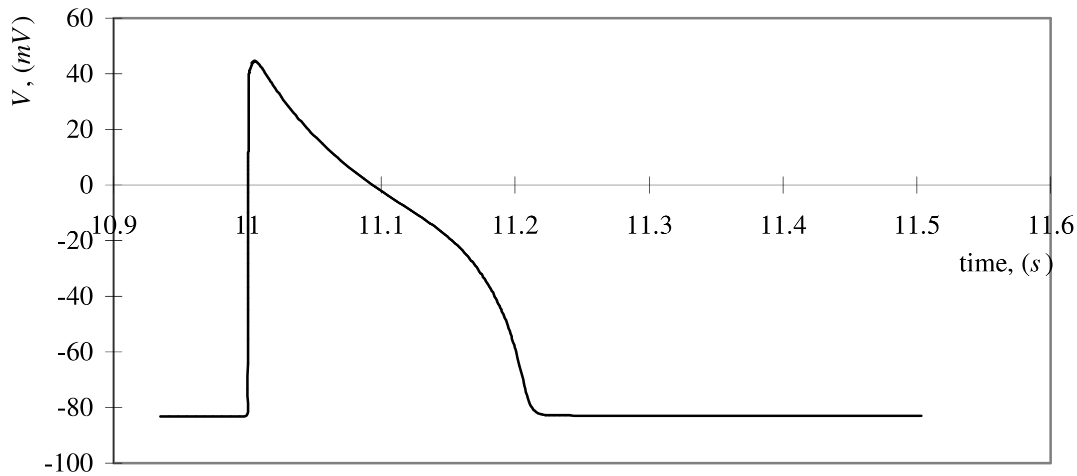
**Table 2**

| $V$ <br> $mV$ | $[Ca^{2+}]_i$ <br> $\mu M$ | $[Ca^{2+}]_{ss}$ <br> $\mu M$ | $[Ca^{2+}]_{JSR}$ <br> $mM$ | $I_{Ca}$ <br> $\mu A/cm^2$ | $APD$ <br> $ms$ | Note |
|---|---|---|---|---|---|---|
| | | | Our computer simulation results | | | |
| 44.52 | 1.36 | 40.65 | 2.21 | -4.55 | 212.54 | With preconditioning, $t$ = 11.0 *s* |
| 50.33 | 0.84 | 22.50 | 1.31 | -5.57 | 217.42 | Without preconditioning, $t$ = 0 *s* |
| | | | Data from the paper [1] | | | |
| 50.4 | 0.84 | 22.30 | 1.175 | -6.46; -6.0 | 183 | With preconditioning, $t$ = 10 *s* |

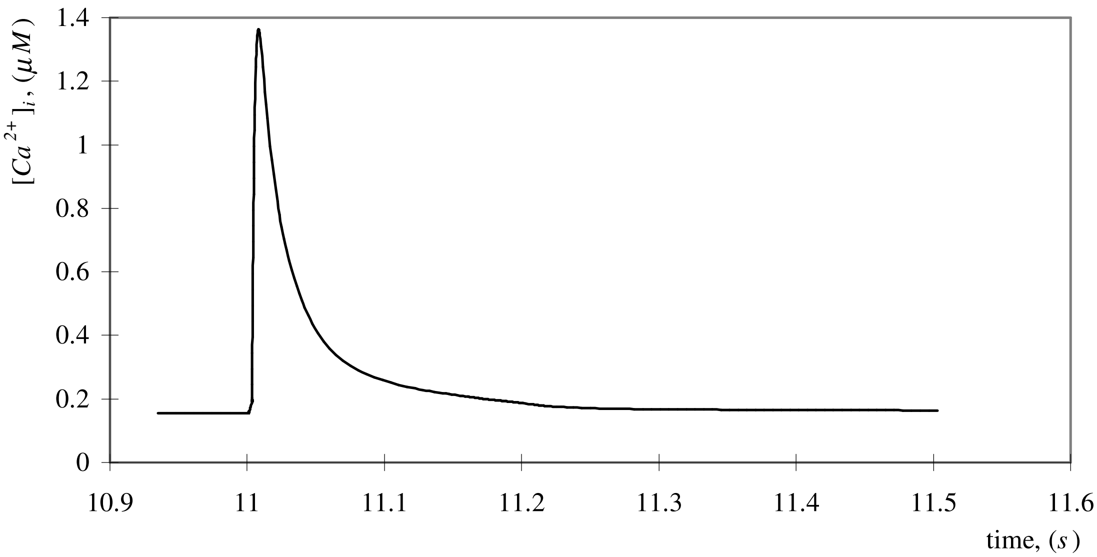
The computation results, except the APD, obtained without preconditioning agree with that of the paper [8] with preconditioning. Some disagreement of data with preconditioning exists between the results of our simulations and data from the paper [8]. It is worthwhile to note that a steady state regime is not reached after preconditioning time t = 10.0 *s*.

The APD restitution was determined in according to the *S1-S2* protocol. After the 10 *s* preconditioning, the *S2* stimulus was applied with different diastolic intervals (*DI*). Both the *APD* values and the maximum values of the membrane potential were defined as functions of the diastolic interval. The results are presented in Fig. 6a,b,c.

The *APD* restitution curve has the maximum *APD* = 212.2 *ms* at the *DI* = 1.0 *s* and then decreases to the *APD* = 207 *ms* at the *DI* = 5 *s* (see Fig. 6a). This differs in respect to the results of the paper [8] where




(a)




(b)

Fig. 5. The shape of the action potential $V$ and the intracellular calcium concentration $[Ca^{2+}]_i$ in normal conditions

(a) - $V$

(b) - $[Ca^{2+}]_i$

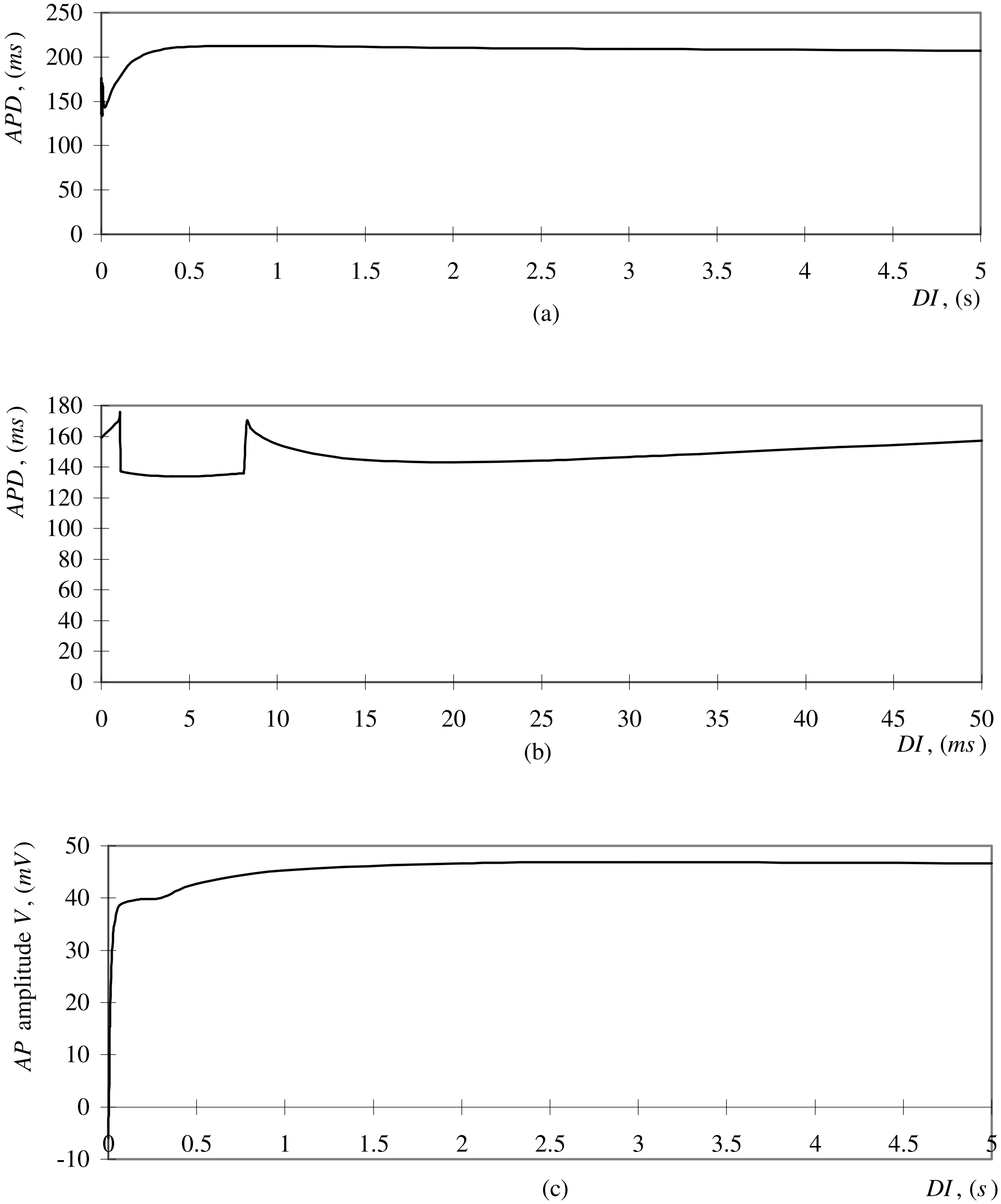



Fig. 6. *APD* and *AP* maximum restitution curves:

(a) - for *DI* range from 0 to 5.0 *s*

(b) - for *DI* range from 0 to 50.0 *ms*

(c) - maximum restitution curve for *DI* from 0 to 5.0 *s* the *APD* restitution is a monotonous function of the *DI* and tends to the *APD* value 189 *ms* with the increase of the *DI*.

In the region of the *DI* from 1.0 *s* to 20.0 *ms*, the *APD* restitution curve monotonously changed up to the *APD* = 143.1 *ms*. Then, the *APD* restitution curve became non-monotonous (see Fig.6b) and has two maximums: 169.8 *ms* for *DI* = 8.25 *ms* and 175.3 *ms* for *DI* = 1.05 *ms*. This complex behavior can be explained by specific formulation of the CICR mechanism used in this model.

In contradictory with the results of the paper [8] for the $DI > 3.0$ *s*, the *AP* amplitude values decreased like the *APD* values when the *DI* increased (Fig. 6c). It can be explained by the instability of the Jafri-Winslow model steady state regime.

Thus, the obtained simulation results in normal conditions are not consistent with that in the original paper [8].

## 5. Model under repetitive excitation

Some additional evidences of the Jafri-Winslows model instability were found by studying the behavior of this model under periodical pacing with frequencies of stimulation $f_{stim}$ in the range from 0.5 *Hz* to 6.6 *Hz*. The behavior was observed during first 30.0 *s* of stimulation.

For stimulation with frequencies 0.5 *Hz* and 1.0 *Hz*, the shape of the *AP* is not changed, but the decrease of the AP amplitudes (which does not exceed 10%) is observed. At the same time, the maximum values of calcium concentrations are increased in all compartments almost twice accompanied by the rise of the $J_{rel}$ flux. These changes were considered in the Section 1 as a precursor of instability. Indeed, when the simulation frequency is increased to 1.4 *Hz*, the additional undertreshold voltage pulses are observed between the normal *AP*. These additional voltage pulses arise after 19.3 *s* of stimulation (see Fig. 7).

When the stimulation frequencies are in the range from 1.4 *Hz* to 5.0 *Hz*, the moment of time of the first appearance of the additional voltage pulses is shifted from 19 *s* to 11.4 *s*.

When the frequency of stimulation is equal to 6.6 *Hz*, each odd stimulus causes the *AP*, whereas each even one produces some spike on the repolarization phase of the *AP* (see Fig. 9a). This leads to the *APD*

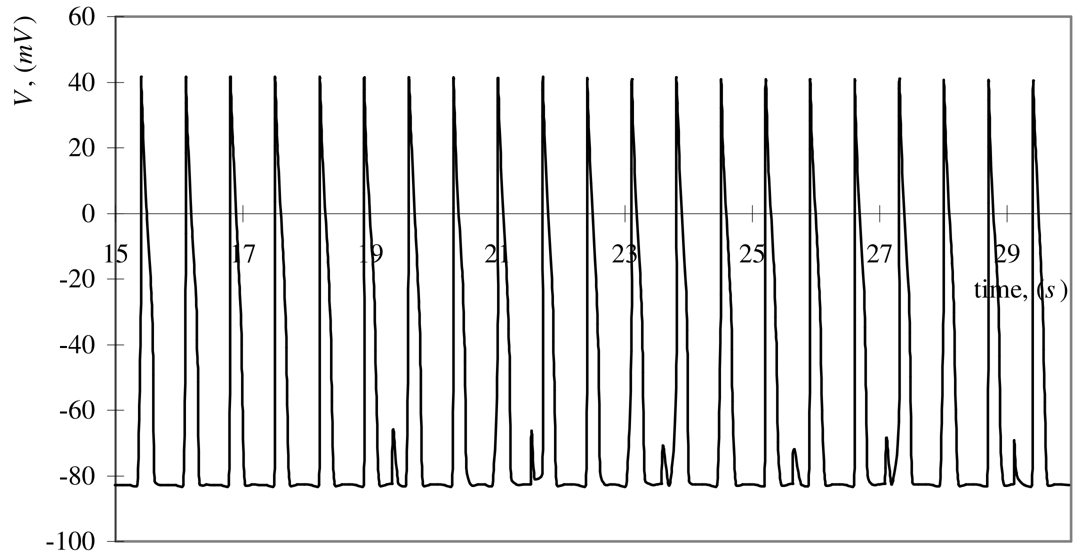



Fig. 7. Appearance of additional pulses for $f_{stim}$ = 1.4 $Hz$

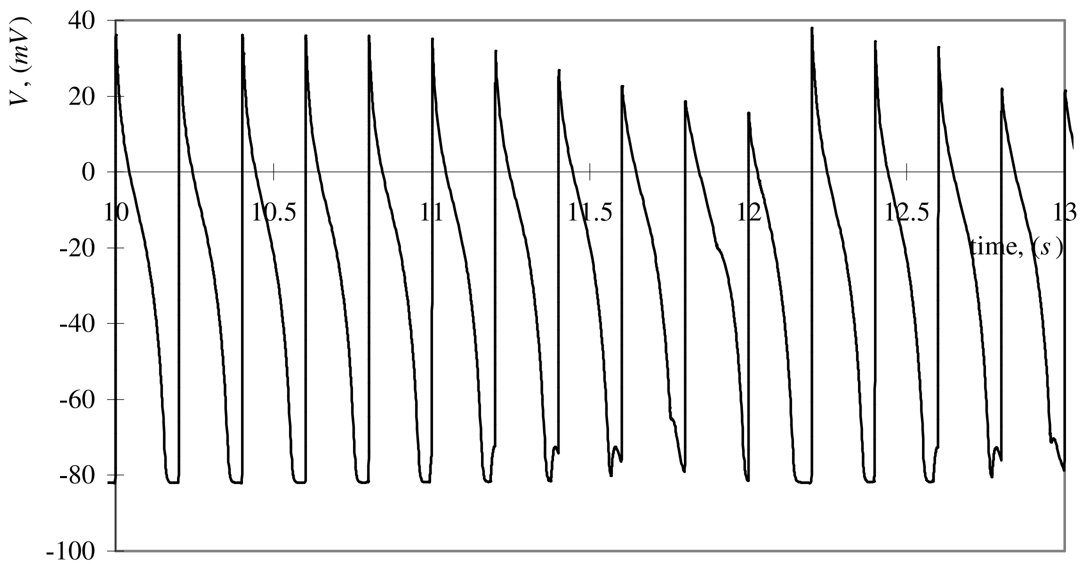
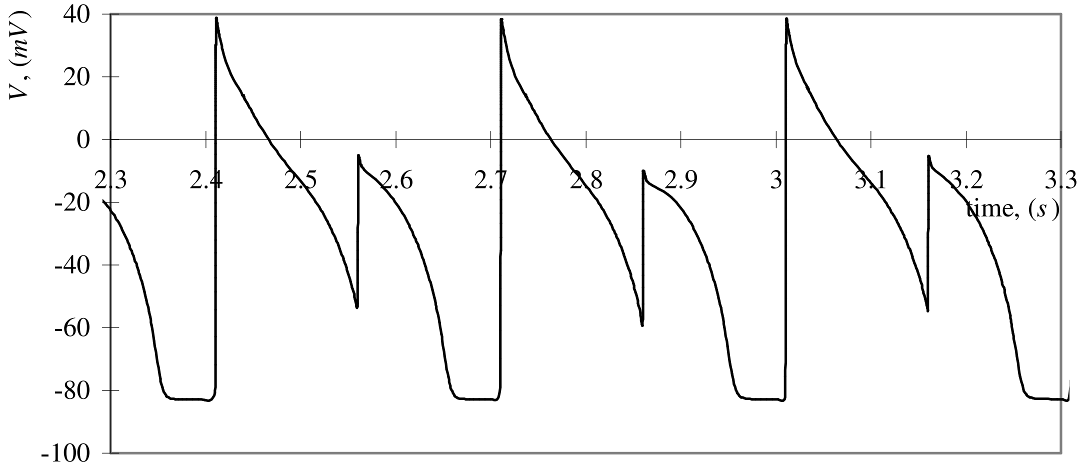
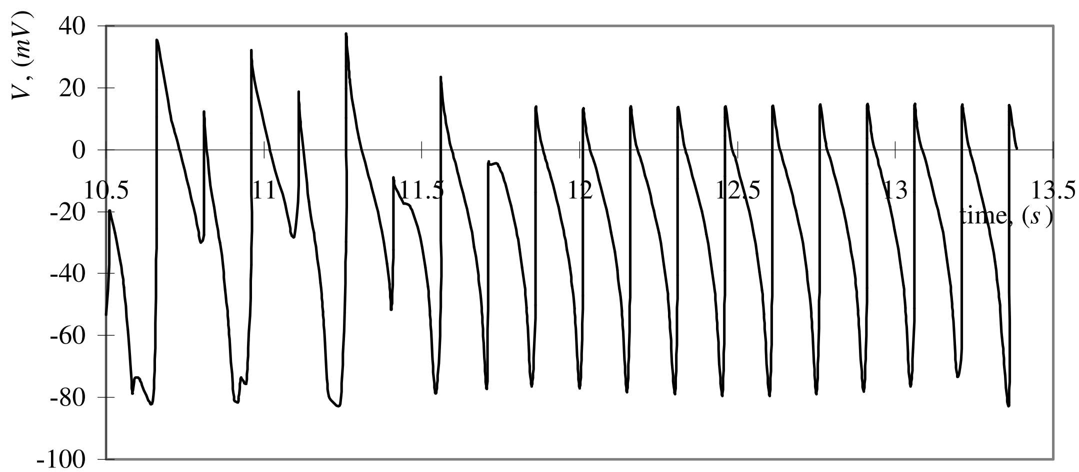



Fig. 8. The shift of additional pulses appearance for $f_{stim}$ = 5 $Hz$




(a)

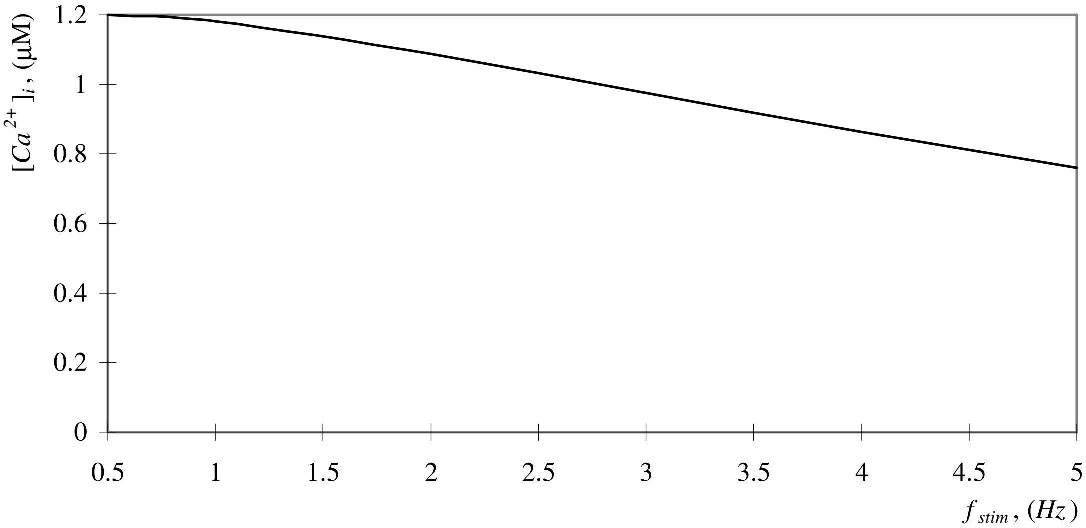



(b)

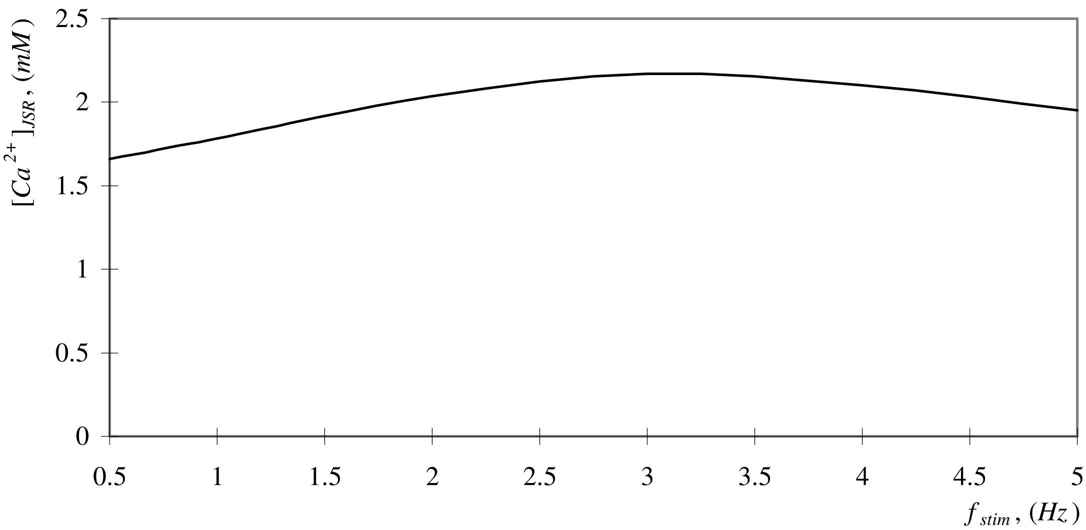
Fig. 9. The shape of the *AP* when $f_{stim}$ = 6.6 *Hz*

(a) - after 2.4 *s* from the beginning of pacing

(b) - after 10.5 *s* from the beginning of pacing




(a)




(b)

Fig. 10. Variations of calcium concentrations in different compartments as a function of the simulation frequency:

(a) - $[Ca^{2+}]_i$

(b) - $[Ca^{2+}]_{JSR}$

prolongation. After 12 *s* from the beginning of stimulation, the model reacts on each stimulus (see Fig. 9b) and stationary *AP*s are generated with the basic cycle length $BCL$ = 150 *ms*.

The dependence of the maximum values of both the calcium concentrations $[Ca^{2+}]_i$ and $[Ca^{2+}]_{JSR}$ on the frequency of stimulation $f_{stim}$ is presented in Fig. 10a,b. The data were taken at the moment of time $t$ = 5.0 *s* from the beginning of stimulation. The curve for $[Ca^{2+}]_i$ monotonously decreases with the increase of the stimulation frequency $f_{stim}$ (see Fig. 10a) while in the paper [8] it has a maximum at $f_{stim}$ = 2 *Hz*. The curve for $[Ca^{2+}]_{JSR}$ has a maximum at $f_{stim}$ = 3 *Hz* (see Fig. 10b) while in [8] it rises monotonously to the value $[Ca^{2+}]$ = 2.5 *mM*.

## Conclusion

- The Jafri-Winslow model is a very detailed model that related to the second generation cardiac AP mathematical models. It requires comparatively big computational power for implementation.
- Due to small dimensions of introduced cleft compartment, a very small integration time steps are required during some phase of computation.
- The presented in [8] version of the model with correction given in web-site [10] did not eliminate the instability of steady state regime and abnormal behavior of the CICR mechanism, under high pacing rate conditions.
- Even if these drawbacks of the model would be eliminated, it remained not clear immediately what kind of advantage this model offers. The $Ca^{2+}$ release mechanism is unable to account for the graded $Ca^{2+}$ release and does not provide partial depletion of the sarcoplasmic reticulum. Thus, the use of this model is supposed to be premature without correction of parameters and serious modification.

We thank Eugene Chudin for useful discussions.

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