SUPPRESSING CHAOS IN CARDIAC MODELS USING OVERDRIVE PACING

L.S.Averyanova, G.V.Osipov, C.K.Chan and J.Kurths

***Abstract*— Recent findings indicate that ventricular fibrillation can arise from spiral wave chaos. Our objective in this computational study was to investigate wave interactions in excitable media and to explore the feasibility of using overdrive pacing to suppress spiral wave chaos. This work is based on the finding that in excitable media, propagating waves with the highest excitation frequency eventually overtake all other waves. It was analyzed the effects of two simultaneously applied low-amplitude forces: (i) constant current and (ii) high-frequency pacing in one-dimensional and two-dimensional networks of coupled, excitable cells governed by the Luo-Rudy model. In the one-dimensional cardiac model, it was founded narrow high-frequency regions of 1:1 synchronization between the input stimulus applied to single cell and the whole system's response. Importantly, the frequencies in this region were higher than those present in fibrillation episodes. When it was locally paced the two-dimensional cardiac model with frequencies from this region, it was founded that spiral wave chaos could be suppressed. As a result of such doubled force, spiral waves behavior becomes more regular. This allows to suppress the spiral chaos more effectively. These findings suggest that low-amplitude, high-frequency overdrive pacing, in combination with low-amplitude positive constant current may be useful for eliminating fibrillation.**

I. INTRODUCTION

Cardiovascular diseases are the root cause of mortality in economically developed countries. That's why propagation mechanisms of arrhythmia study, diagnostic technique development and methods of their prevention and treatment are all-important today. Physicians, biologists, physicists and specialists in the area of mathematical modeling perform research heart arrhythmias. Heart is a dynamic system: processes toward here are able to describe as evolution of some state variables: electric membrane potentials, conductivities of ion channels, ion currents. Cardiac tissue is able to consider as medium consists of stable and excitable elements-cells. And a mathematical model of a heart is a system of a great number of ordinary differential equation. It is necessary to use methods of parallel computing and modern computer engineering.

Under sinus rhythm, waves of electrical activity propagate throughout the heart, eliciting a simultaneous contraction of the ventricles. It is known that a spiral wave arise from one of arrhythmias in cardiac muscle - tachycardia. Its rotation frequency is higher than a frequency of normal sequence of dirge pulse. That spiral waves break up into spiral waves chaos. And ventricular fibrillation might arise.

Today is only one clinical method of treating a heart in ventricular fibrillation - applying a large voltage shock to the heart. That shock is defibrillation. It may be realized with the help of outside or implanted defibrillators. Once the heart cells repolarize in synchrony, it reduces to recommencement of normal cardiac contraction. Although the shock is sufficient energy to annihilate fibrillation, it is also of sufficient strength to damage the underlying cardiac tissue, cause pain to the patient. However, means of management of processes with the help of light signals is known at nonlinear dynamics. The development and adaptation these methods with low - amplitude signals is the important modern problem.

Current ventricular defibrillation techniques rely on the application of a large voltage shock to the heart. This forces the entire medium into an absolute refractory period, which serves to prevent local re-excitation. Once the heart cells repolarize in synchrony, electrical waves from the sinoatrial node take over and a sinus rhythm resumes. However, the energy necessary for successful defibrillation using this technique is quite painful and often large enough to damage the tissue.

The one of alternatives methods of annihilate spiral waves chaos were propose [1-6]. It was basis on the property that the wave with the highest frequency will eventually overtake all other waves.

It was propose to apply a localized outside impact, which frequency must be higher than medium frequency of spiral waves chaos. The effect of this impact is not successfully always because it is the effect of bistability. It was shown that the pacing can be optimized if it is used in conjunction with antiarrhythmic drugs , especially those which block calcium channels [7].

Although, it was study a collective phenomena in nonhomogeneous chain and lattices of coupled models of cardiac cells.

We analyze the effects of two simultaneously applied low-amplitude forces: (i) constant current and (ii) high-frequency pacing in one-dimensional and two-dimensional networks of coupled excitable cells governed by the Luo-Rudy model. In the one-dimensional case, we found high-frequency regions of $1:1$ synchronization between the input stimulus applied to single cell and the whole system's response. Importantly, the frequencies in this region were higher than those present in fibrillation episodes. When we locally paced the two-

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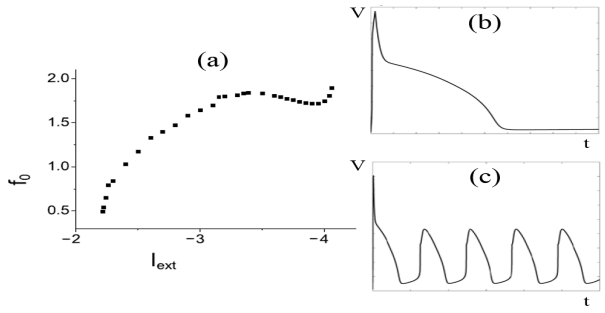

Fig. 1. One isolated Luo-Rudy cell - (a)frequencies of oscillations (Hz) versus the constant depolarizing current I_{ext} (mA/cm^2); the evolution of the membrane potential (b) for the excitable cell, (c) for the oscillatory cell.

dimensional cardiac model with frequencies from this region, it was founded that spiral wave chaos could be suppressed.

As a result of such doubled force, spiral waves behavior becomes more regular. This allows to suppress the spiral chaos more effectively. These findings suggest that low-amplitude, high-frequency overdrive pacing, in combination with low-amplitude positive constant current may be useful for eliminating fibrillation.

II. Methods

A. Cardiac Model

We conducted all of our computational experiments with a monophasic description of ventricular myocardium. The model [8] is given by the expression:

$$C_m \frac{\partial V}{\partial t} = -(I_i + I_{st} + I_{ext}) + C_m D \nabla^2 V \qquad (1)$$

where V is the membrane voltage,C_m = 1 mF/cm^2 is the membrane capacitance, D = 1.25 $cm^2/msec$ is the diffusion coefficient, I_{st} and I_{ext} are the input stimulus, andI_i is the sum of six ionic currents:

$$I_i = I_{Na} + I_{si} + I_K + I_{K1} + I_{Kp} + I_b \qquad (2)$$

as specified in the Luo-Rudy phase I model. The form of the sodium current I_{Na} , the slow inward calcium current I_{si}, and the potassium current I_K, is given by:

$$I_i = \overline{G_i} g_i(V,t)(V - E_i) \qquad (3)$$

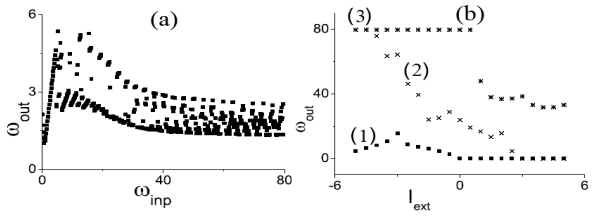

Fig. 2. (a) Output frequency (Hz) of oscillations of an isolated Luo-Rudy cell versus the input frequency (Hz). $I_{ext} = -1.5 mA/cm^2$. Input periodic signal is 50% duty cycle, amplitude $A = -2 mA/cm^2$. (b) Maximal output frequencies (Hz) versus the input constant current (mA/cm^2). Amplitudes of input high-frequency current are (1) $A = -2$; (2) $A = -5$; (3) $A = -10$ mA/cm^2

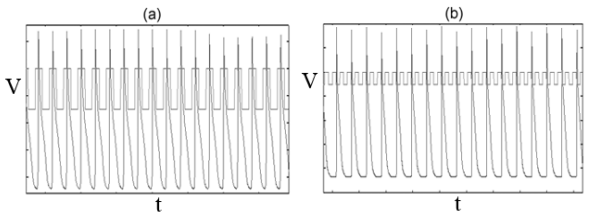

Fig. 3. Examples of (a) 1:1 synchronization and (b) 2:1 synchronization for the chain of 10 cells with the schematic image of the input signal. We paced the first cell in the chain.

where $\overline{G_i}$ is the maximum constant conductance of the ion, g_i is the product of one or more gating variables, and E_i is the reversal potential of the ion. The dynamics of each gating variable is modeled as:

$$\frac{dg_i}{dt} = \frac{g_\infty - g_i}{\tau_{gi}} \qquad (4)$$

where $g_\infty = \frac{\alpha_{gi}}{\alpha_{gi}+\beta_{gi}}$ is the steady-state value, $\tau_{gi} = \frac{1}{\alpha_{gi}+\beta_{gi}}$ is the time constant, and the α's and β's are functions of the membrane voltage. The form of the time-independent potassium current I_{K1}, the plateau potassium current I_{Kp}, and the background current I_b, is given by:

$$I_i = \overline{A_i}(V - E_i) \qquad (5)$$

where E_i is the reversal potential of the ion and $\overline{A_i}$ is a scaling factor. Note that $\overline{A_i}$ is a function of voltage for I_{K1} and I_{Kp}. The conductances and reversal potentials used in the simulations are: G_{Na} = 23.0; E_{Na} = 54.44; G_{si} = 0.705; E_{si} = 7.7-13.0287ln($[Ca]$); G_K = 0.705; E_K = -77; G_{ca_b} = 0.06; G_{K1} = -87.23; E_{K1} = -87.23; G_{Kp} = 0.0183; E_{Kp} = -87.23; G_b = 0.03921; E_b = -59.87.

B. Theoretical Basis of our Approach

The behavior of interacting waves in excitable media is governed by the following fundamental properties:

1) The wave with the highest frequency will eventually overtake all other waves [7]. This is due to the fact that slower waves are progressively invaded by faster waves.

2) A given medium supports spiral waves of a single frequency [7]. This characteristic arises from general properties of the system's action potential, in particular, its refractory period. The spiral wave frequency varies from medium to medium, even though a unique frequency exists for every medium.

3) The time to suppression of colliding periodic waves depends inversely on two factors: (i) the frequency difference between the waves, and (ii) the velocity of the wave with the highest frequency. Thus, a slower wave is more quickly invaded by a faster wave as the frequency and/or velocity of the faster wave increases [7].

It was used the above properties to guide experiments. For example, it was explored stimulation frequencies greater than those present in fibrillating cardiac tissue, we utilized the highest input frequencies supported by the medium.

In order to find the highest frequencies supported by the medium, it was characterized the frequency response

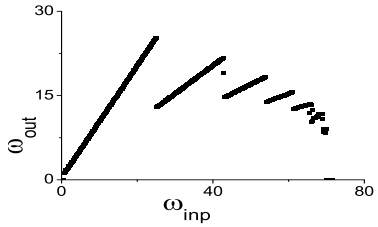

Fig. 4. The example of output frequency (Hz) of oscillations in the chain of 10 Luo-Rudy cells (from the last cell) versus the input frequency (Hz). We paced only the first cell in the chain. Input periodic signal is 50% duty cycle, amplitude is $A = -30mA/cm^2$, $I_{ext} = 3mA/cm^2$.

of the system by examining the synchronization between the applied stimulation and the resulting action potentials of the medium. Note that high-frequency stimulus in excitable media typically do not result in 1:1 synchronization between the input (pulse stimulus) and the response (action potential). This effect is due to the system's refractory period.

III. Results

A. One cell

When the value of I_{ext} in an isolated cell is increased above a bifurcation value approximate equal to 2.21 mA/cm^2 at the chosen values of parameters, a limit cycle appears in the phase space of the model, thus the cell becomes oscillatory.

Though this approach might not account for real physiological mechanisms of cell oscillation, the development of a more adequate model is hindered by the lack of understanding of the mentioned mechanisms in in-vitro experiments. However, in real situations, it is known that the leakage (depolarization) current of the non-pacemaker cells can increase turning them into oscillatory cells when they are dissociated from the heart tissues.

The measured dependence of the oscillation frequency of the cell upon the value of the depolarizing current is presented in Fig.1(a).

So, it may be different regimes for both kinds of cells under external forse: (i) synchronization for oscillatory cells or (ii) stimulated oscillations for excitable cells. (The evolution of the membrane potential of the excitable cell and the oscillatory cell is presented in Fig.1(b,c).)

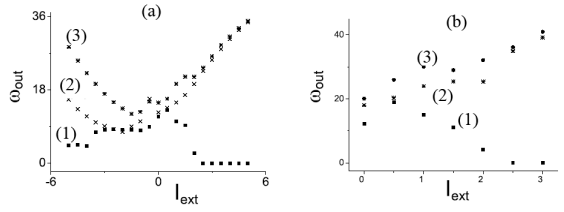

Fig. 5. Maximal output frequencies (Hz) (from the last cell in the chain) versus the input constant current (mA/cm^2). For the chain of 10 cells. Amplitudes of the input high-frequency current are (1) $A = -10$; (2) $A = -30$; (3) $A = -50$ mA/cm^2. Where (a) is for 50% duty cycle and (b) is for 14% duty cycle.

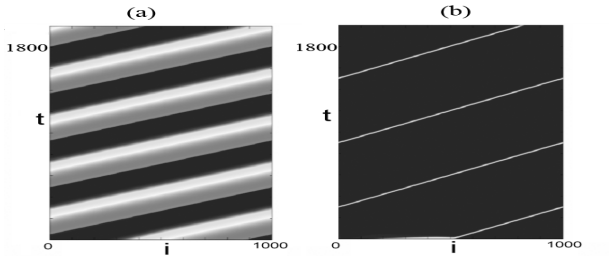

Fig. 6. Propagation of the pulse in the chain of 1000 cells for (a) $I_{ext} = -2.4$ and (b) $I_{ext} = 5$ mA/cm^2. The initial conditions are equivalent.

We periodically paced the one isolated Luo-Rudy cell with a square-wave stimulus (amplitude A= -2, -5, -10mA/cm^2). The example of input-output frequency characterization for the $I_{ext} = -1.5mA/cm^2$ is shown in Fig.2(a).

The results are presented in Fig.2(b). It is presented the maximal values output frequencies versus the input values of high-frequency current.

So, the most perspective amplitudes of input high-frequency current are:

1) For amplitude of I_{st}: $A = -2mA/cm^2$ it is the area which corresponds to oscillatory cell;

2) For $A = -5mA/cm^2$ and $A = -10mA/cm^2$ it may be the positive values of input high-frequency current.

B. One-Dimensional Simulations

We periodically paced the first cell in the chain of 10 cells with a square-wave stimulus - 50% duty cycle (amplitudes of input high- frequency current $A = -10, -30, -50mA/cm^2$). There are synchronization 1:1, 2:1, 3:1 and other (Two examples of synchronization are presented in Fig.3).

The example of output frequencies from the last cell for the $I_{ext} = -30mA/cm^2$ in the chain is presented in Fig.4.

Discussion:

1) The amplitude of input high-frequency current $= -10mA/cm^2$ for 10 cells is insufficient for high-frequency response of the last cell in chain. Maximal frequency is 13.0764 Hz.

2) Values of input high-frequency current $= -30mA/cm^2$, $= -50mA/cm^2$ allow to get frequencies 20-35 Hz, synchronization 1:1.

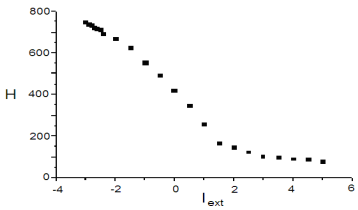

Fig. 7. Pulse width $(msec)$ versus the input current (mA/cm^2) for the chain of 1000 Luo - Rudy cells.

Results are presented in Fig.5. It is the maximal values output frequencies versus the I_{ext} for two types of input periodic signal - with 50% and 14% duty cycle.

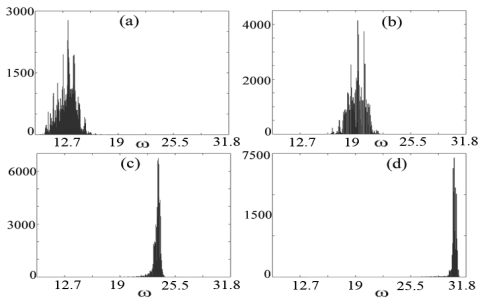

Fig. 8. Histograms of mean frequencies of oscillations of all cells for the grid 300 to 300 cells. For (a) $I_{ext} = 0$, (b) $I_{ext} = 0.5$, (c) $I_{ext} = 1$, (d) $I_{ext} = 2\ mA/cm^2$.

The most perspective amplitudes of input high-frequency current are: (i) For minimal amplitude of input high-frequency current $= -10mA/cm^2$ it is the area of values of low constant current from $0.5mA/cm^2$ to $1.5mA/cm^2$;(ii) for $= -30mA/cm^2$ it is values of I_{ext} higher than $2mA/cm^2$;(iii) for $= -50mA/cm^2$ it is values of I_{ext} higher $4mA/cm^2$.

For the 1000 cells it was shown that the application of positive current leads to decrease of pulse width, if the initial conditions are equivalent. Propagation of the pulse in the chain of 1000 cells for different values of I_{ext} is presented in Fig.6. And the results (pulse width versus the input current) are presented in Fig.7.

C. Two-Dimensional Simulations

First, we try to get time-dependent characteristics for the different values of constant current in the grid 300 to 300 cells. We make histograms of the mean frequencies of oscillations from every cells in the grid (Fig.8). One can tell, that the width of histogram in Fig.8(a) and Fig.8(b) is sufficiently great. After increasing constant current to 1 and 2 mA/cm^2 the width of histogram became more narrow (Fig.8(c) and Fig.8(d)). It is possible to say, that in 2D simulation the increase of external current leads to more regular behavior in the lattice coupled cells. Our numerical experiments show the nonprogressive suppression of spiral waves chaos without using constant current. When the collective behavior is more regular (e.g. $I_{ext} = 1; 2mA/cm^2$) the suppressing chaos can be archived using overdrive pacing with correctly chosen external frequency. Note, that the signal with 50% duty cycle don't allows to get the response of the system with the required frequency for suppressing chaos(Fig.5(a)), and we used the periodic signal with 14% duty cycle (Fig.5(b)) for suppressing.

Using the previous results, we try to suppress chaos,if we add the external current equal 1 mA/cm^2. The frequency sufficient to annihilating chaos is 23.8 Hz, which is seen in Fig.10(c). We periodically paced the two-dimensional grid of 300 to 300 Luo - Rudy cells with a square-wave stimulus (amplitude $A = -30mA/cm^2$). The area of pacing is the central rectangle of the grid. Constant current applied to all cells in the grid.

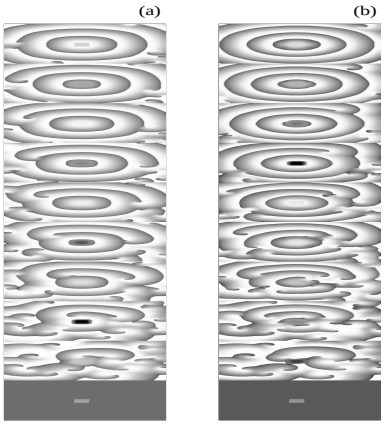

Fig. 9. Suppressing spiral waves chaos. Grid 300 x 300 cells. $I_{ext} = 1mA/cm^2$ $A = -30mA/cm^2$, frequencies are (a) $\omega = 23.8$ Hz; (b) $\omega = 25.5$ Hz.Time axis is vertically. The first bar shows the input signal.

It was shown that the method is successfully for suppressing spiral waves chaos (Fig.9).

The spiral waves chaos was eliminated after 4.00 sec pacing.

IV. Conclusion

The application of positive current leads to more regular behavior in the lattice coupled cells, which helps to annihilate spiral waves chaos.In 2D simulations it was found that the increase of external current leads to more regular behavior in the lattice of coupled cells.It was shown that overdrive pacing method ia able to annihilate spiral waves chaos. (Note, that the most perspective area of values of constant low amplitude current stands over $0mA/cm^2$).

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