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A MODEL OF CARDIAC TISSUE AS AN EXCITABLE MEDIUM WITH TWO INTERACTING PACEMAKERS HAVING REFRACTORY TIME

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Abstract. A quite general model of the nonlinear interaction of two impulse systems describing some types of cardiac arrhythmias is developed. Taking into account a refractory time the phase locking phenomena are investigated. Effects of the tongue splitting and their interweaving in the parametric space are found. The results obtained allow us to predict the behavior of excitable systems with two pacemakers depending on the type and intensity of their interaction and the initial phase.

1. Introduction. Recent progress in the theory of dynamical systems showed that various nonlinear systems including excitable media can exhibit chaotic properties. Generally, an excitable medium can be considered as a set of interacting active elements. The simplest way to model such an individual active element is to describe it as a cellular automaton. Then, by this approach, the excitable medium can be constructed from the elements which have three possible states: of rest, excitation and refractoriness. Moved into an excited state, such an element stays there for a fixed time, then goes to the state

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of refractoriness and only after that returns to the state of rest. So, transitions into the excited state are possible only from the state of rest.

This transition is brought about by some external action. An element can be excited if one of the neighboring elements is excited. As a result, from the place of a supercritical external action a concentric excitation wave is propagated. A local periodically acting source is called a pacemaker. If in the medium there are two or several pacemakers then the activity of a low-frequency pacemaker will be suppressed by another pacemaker with a higher generation frequency [1–3].

In application to the cardiac tissue, appearance of several pacemakers leads to various disorders in the cardiac rhythm, i.e. arrhythmias [3–7]. Moreover, a few abnormal sources and spiral waves result in a fibrillation phenomenon (in fact, spatio-temporal cardiac chaos). Because cardiac arrhythmias are pathological states, their investigation is of great importance. Analysis of the spatio-temporal chaotic behavior can open a clue to the problem of controllability of the complex cardiac dynamics [8–10].

As is known, some cardiac arrhythmias can be represented by the interaction of spontaneous nonlinear sources. In the framework of such an approach analysis of the heart rhythms can be subdivided into two large groups: modeling on the basis of continuous time representations (i.e. using systems of ordinary differential equations) pioneered by van der Pol and van der Mark [11–15] (see also Refs. therein), and investigations via maps [4, 16–24]. Continuous models, in general, allow a quantitative and qualitative description of AV-blocks of various types (see, for example, [14]), whereas the discrete models are successfully used mainly for consideration of atrial and ventricular parasistole (see, e.g., [23]). In our investigations, a quite general model of sampled-data systems describing both types of such arrhythmias is constructed. Taking into account a refractory period, possible areas of the phase lockings are investigated. The model turns out to be a universal one in the sense that it does not depend on the specific form of interactions, i.e. on the phase response curve. Phenomena of the splitting of resonance tongues and superposition of the synchronization areas are found. Using the results obtained we can define dynamics of the excitable media with active pacemakers depending on their interaction intensity and the initial phase difference.

These facts allow us to use our model in applications, say for the description of arrhythmias occurring in the real cardiac tissues. Moreover, utilizing the principles of our construction one can develop a quite general theory of the excitable medium with interacting pacemakers under external actions. This can be of great practical importance because it leads to controlling rhythms by external stimuli.

2. Heart as a homogeneous excitable medium. In certain situations cardiac arrhythmias can be described as an interaction of two spontaneously oscillating nonlinear sources. Such an interaction can be considered as an influence of an external periodic perturbation (with the constant amplitude and frequency) on a nonlinear oscillator. As is known, in this case it is possible to use the well-known circle map [4, 23, 24]:

$$x_{n+1} = x_n + f(x_n) \pmod 1, \tag{1}$$

where x_n is a phase difference in oscillators, and the function $f(x)$ determines a change in the phase after the action of stimulus. This function is called a phase response curve (PRC).

Note that such an approach has certain restrictions. First of all, in the framework of a one-dimensional modeling one should neglect the propagation of excitation waves on the heart surface. The violations of the cardiac rhythm due to the absence of the pulse co-ordinations in all myocardium cannot be described on the basis of this approach.

For the further analysis of the dynamics of the constructed model it is necessary to find a proper analytical approximation of the experimentally obtained phase response curve. This allows us to investigate the basic features of the behaviour of the considered system.

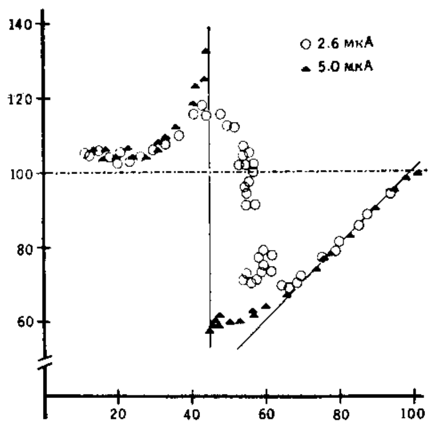

Fig. 1. The experimentally obtained phase response curve (redrawn from [13, 14]). The diagram shows the dependence of the duration of the perturbed cycle (in %) on the input phase

Experiments on the recording of phase shifts have been carried out for a quite large number of various systems. First of all, we are interested in the PRC experimentally recorded from the research of some cardiac tissues. In [25, 26] measurements on the duration of a cycle of spontaneous beating Purkinje fibres after stimulation by short electric current pulses have been performed. The obtained phase response curve is shown in Fig. 1. Taking into account this experimental material, it is possible to make the following general conclusions [4, 25–27].

1. Depending on a phase, the single input can lead to either increasing or decreasing in the period of the perturbed cycle.

2. After perturbation, the rhythm is usually restored (after some transient time) with the same frequency and amplitude, but the phase is shifted.

3. In the diagram in Fig. 1 one can see the obvious breaks which appear at some amplitudes of stimulus.

It is necessary to take into account that: i) The assumption of the immediate resetting of the pacemaker rhythm after the action of external stimulus is an idealization; ii) For the adequate description of the 3rd PRC feature we should fit such a parametrical function $f(x) = f_a(x)$ which undergoes the breaks at continuous change of the parameter a describing a stimulus amplitude. In the context of the circle map theory this means that the transformation (1) changes a topological degree. Unfortunately, consideration of such maps is a rather complex problem, and a continuous PRC approximation is usually used. In the present paper we also confine ourselves to this restriction.

The basic feature of any approximation of the PRC is the necessity of the dependence on two physical parameters: the amplitude of stimulus and the input phase. In the ideal case the other (so-called "internal") parameters can be reduced to them.

Taking into account the sinusoidal and polynomial functions as approximations of the PRC, we construct a model of two *bidirectionally* interacting active oscillators.

3. The analytical model with mutual influence of impulses. Let us consider system of two nonlinear interacting oscillators (Fig. 2). Suppose that the pulse of the

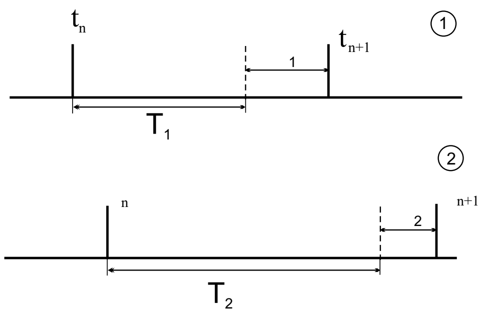

Fig. 2. Construction of the model of two nonlinearly interacting oscillators

first oscillator with period T_1 beats at time t_n, and the pulse of the second oscillator (with period T_2) beats at time τ_n. Then the next moments of the appearance of impulses are defined as

$$\begin{cases} t_{n+1} = t_n + T_1, \\ \tau_{n+1} = \tau_n + T_2. \end{cases}$$

Now, taking into account that the period of the first oscillator is changed under the influence of the second impulse by the value of $\Delta_1((\tau_n - t_n)/T_1)$ (where the expression in brackets means that this value depends only on the phase of the second impulse), one can get the appropriate expression for t_{n+1}: $t_{n+1} = t_n + T_1 + \Delta_1((\tau_n - t_n)/T_1)$. For the further analysis let us confine ourselves to the case when the pulses of the two oscillators strictly alternate [1]. Then for the second oscillator one can obtain: $\tau_{n+1} = \tau_n + T_2 + \Delta_2((t_{n+1} - \tau_n)/T_2)$. Dividing these expressions by T_1, one can find the corresponding values for the phases:

$$\begin{cases} \varphi_{n+1} = \varphi_n + \dfrac{1}{T_1}\Delta_1\left(\delta_n - \varphi_n\right), \\ \delta_{n+1} = \delta_n + \dfrac{T_2}{T_1} + \dfrac{1}{T_1}\Delta_2\left(\dfrac{t_n}{T_2} + \dfrac{T_1}{T_2} + \dfrac{1}{T_2}\Delta_1\left(\delta_n - \varphi_n\right) - \dfrac{\tau_n}{T_2}\right). \end{cases}$$

[1]The case when the pulses of the two oscillators do not intermittent remains to be explored [28].

Here $\varphi_n = t_n/T_1$ is the phase of the first perturbed oscillator with respect to the unperturbed one (with period T_1), and $\delta_n = \tau_n/T_1$ is the phase of the second perturbed oscillator with respect to the same first oscillator with period T_1. Using the parameters $a = T_2/T_1$ and $\Delta_1/T_1 = f_1$, $\Delta_2/T_1 = f_2$ one can obtain:

$$\begin{cases} \varphi_{n+1} = \varphi_n + f_1(\delta_n - \varphi_n), \\ \delta_{n+1} = \delta_n + a + f_2\left(\dfrac{1}{a}\left(\varphi_n + 1 + f_1\left(\delta_n - \varphi_n\right) - \delta_n\right)\right). \end{cases}$$

The final expression for the phase difference in the oscillators is as follows:

$$x_{n+1} = x_n + a + f_2\left(\frac{1}{a}(1 + f_1(x_n) - x_n)\right) - f_1(x_n) \pmod 1, \tag{2}$$

where $x_n = \delta_n - \varphi_n$.

It is obvious that the PRC changes its form depending on the amplitude of the external stimulus. In the simplest case this dependence can be considered as a multiplicative relation. Then the phase response curves can be written as follows:

$$f_1 = \gamma h(x), \qquad f_2 = \varepsilon h(x),$$

where $h(x)$ is a periodic function so that $h(x+1) = h(x)$. Under this assumption, transformation (2) takes the form:

$$x_{n+1} = x_n + a + \varepsilon h\left(\frac{1}{a}\left(1 + \gamma h\left(x_n\right) - x_n\right)\right) - \gamma h\left(x_n\right) \qquad (\mathrm{mod}\, 1)\,. \tag{3}$$

In the present paper we consider the map (3) with the sinusoidal and polynomial functions for $h(x)$. The obtained results are the continuation of our previous works concerning modeling certain cardiac arrhythmias [29, 30].

4. The phase diagrams for approximations of the PRC with refractoriness. First of all we consider a situation when permanent inputs act on the nonlinear oscillator, i.e. $f_2(x) \equiv 0$ or $\varepsilon = 0$. Suppose that $h(x) = \sin(2\pi x)$. Then the curve of phase response f_1 can be written as follows: $f_1(x) = \gamma \sin(2\pi x)$. In this case expression (3) has the form of a standard circle map. Its phase diagram is well studied both analytically and numerically (see, for example, [4, 31] and references therein). Our aim is to make bifurcation analysis taking into account the refractory period. It should be noted that the experimentally obtained PRC with the refractoriness on the example of chicken heart cells has been described in [32]. Moreover, in this paper the corresponding analytical model was proposed. The model was constructed in such a way that the experimental data were well fitted by smooth two-parametric exponential functions.

In our analysis we propose a quite simple approximation of the PRC including the refractory time. This time can be taking into consideration in the map (3) as follows:

$$x_{n+1} = \begin{cases} x_n + a, & 0 \le x_n \le \delta \pmod 1, \\ x_n + a - \gamma \sin\left(2\pi \dfrac{x_n - \delta}{1 - \delta}\right), & \delta < x_n \le 1 \pmod 1. \end{cases} \tag{4}$$

In this case the PRC is continuous (see Fig. 3, the solid line).

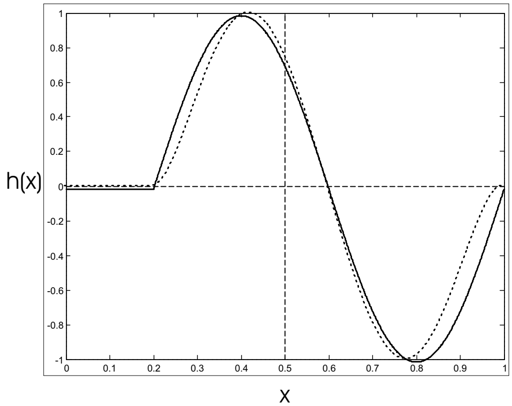

Fig. 3. Various approximations of the PRC: sinusoidal (solid line); polynomial (dotted line)

Suppose that $\delta = 0.1$ (note that the phase diagram is qualitatively the same for the other values of δ). In Fig. 4 the phase locking regions in the parametric space (a, γ) obtained by numerical analysis of the system (4) are shown. To reveal more important phase lockings, in this figure we choose $a \in [1, 2]$. The various saturation of the colour defines the phase locking areas with the multiplicity N:M, where N cycles of external stimulus correspond to M cycles of the nonlinear oscillator. One can see that "tails" of the main locking regions are slightly splitted and overlap each other at large γ. At the same time their boundaries are essentially diffused.

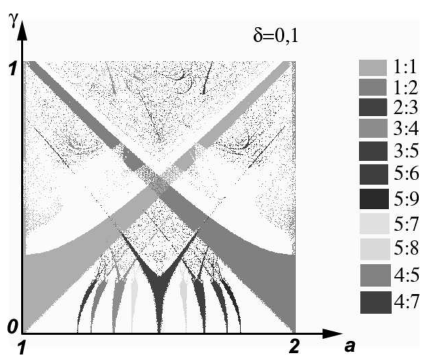

Fig. 4. The areas of the stable phase lockings for the system (4)

The authors of [32] have compared the phase diagram obtained on the basis of the proposed PRC approximation (of the exponential type) with the phase diagram of the sine map. They came to the conclusion that their model does not have some bifurcations which one can observe in the sine model. So, they assumed that when the amplitude of the external impulse increases there is a nonlinear growth of the extremum values of the PRC. In our model, the extrema grow in the same manner as for the sine model (linearly). Hence, we can suppose that our system has all bifurcations of the sine map but the forms and positions of phase-lockings vary due to the refractoriness.

Let us consider the polynomial function as the other approximation of the PRC. Then, taking into account the refractory time, the map (3) has the following form:

$$(5)\quad x_{n+1} = \begin{cases} x_n + a, & 0 \le x_n \le \delta, \\ x_n + a + 20\sqrt{5}\gamma\left(\dfrac{x_n - \delta}{1-\delta}\right)^2\left(\dfrac{1}{2} - \dfrac{x_n - \delta}{1-\delta}\right)\left(1 - \dfrac{x_n - \delta}{1-\delta}\right)^2, & \delta < x_n \le 1, \end{cases}$$

In contrast to the sinusoidal approximation, at $x = \delta$ the given curve is tangent to the abscissa axis (see Fig. 3, the dotted line). In other words, this means that the polynomial PRC in the system with the refractory time is a smooth function in the segment $[0, 1]$.

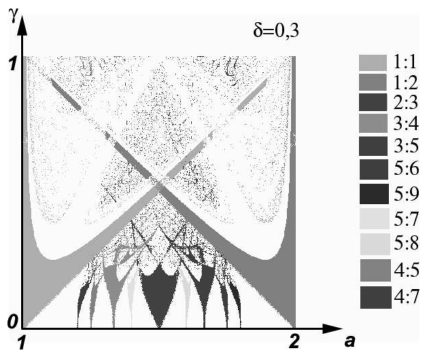

Fig. 5. The phase diagram of the map (5) with polynomial approximation of the PRC

In Fig. 5 the numerically constructed phase diagram is presented. For the comparison, in the given figure the same N:M stable phase lockings as in Fig. 4 are shown. One can see that owing to smoothness of the polynomial function the fuzzieness in the boundaries of the resonance tongues is much less than in Fig. 4. In addition, as follows from the analysis of the system (5) with $\delta = 0$, introduction of the refractory time leads to the widening of the phase locking areas, significant splitting and overlapping their "tails".

5. The phase diagrams for systems with the bidirectional interaction of active oscillators. Now we investigate the case of a mutual action of two impulse systems. Let us assume that the influence of the first oscillator on the second one is small enough, i.e. $\varepsilon = 0.1$. As an approximation of the PRC we take $h(x) = 20\sqrt{5}\gamma x^2(1/2 - x)(1 - x)^2$, where the normalizing factor has been chosen in such a way that all diagrams have the same scale. The phase diagram displaying the possible regimes of the system of two interacting oscillators (without the refractory time) is given in Fig. 6. One can see that the mutual action leads to a deformation and splitting of phase locking areas. Note that even for small values of the amplitude of the first stimulus γ the overlapping of the main phase lockings takes place. This means that the dynamics of the system becomes multistable. This corresponds to the situation when the limit state of the map depends on an initial phase difference x_0.

If, however, we take into account the refractory time in the model considered above, then we will see more deep deformation of the main phase locking areas (see Fig. 7).

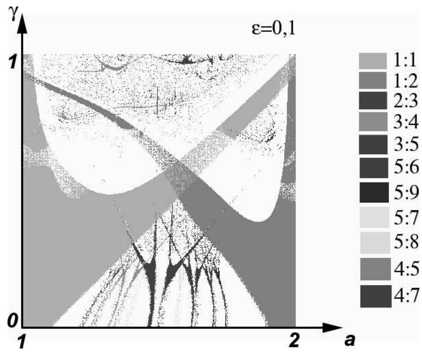

Fig. 6. The areas of phase lockings for the system of two bidirectionally interacting impulse oscillators

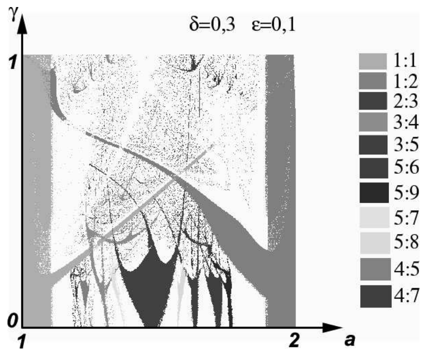

Fig. 7. The phase diagram of the system of two bidirectionally interacting oscillators with refractory time

Moreover, when the value of the refractory time is growing, the 2:3 phase locking area is increasing with simultaneous decreasing of the 3:4 and 3:5 areas.

As follows from the bifurcation diagrams obtained, including the refractoriness and mutual influence of the oscillators results in very complicated dynamics. Thus, modeling the cardiac tissue by a chain of pulse coupled elements (as in [33]) on the basis of our PRC-functions may lead to much more complex behaviour than described in [33]. Analysis of such a model requires a close scrutiny and deep computer simulations.

Summarising, we shall try to make an analogy between the results obtained and the pathological states of the cardiac tissue. Using the developed models it is possible, for example, to describe an interaction of the sine and ectopic pacemakers, the sinoatrial (SA) and the atrioventricular (AV) nodes and impact of an external perturbation on the sine pacemaker.

In the present paper we consider the model of the interaction of two impulse oscillators. Therefore, we restrict ourselves to some arrhythmias which can be predicted on the basis of the constructed system. If the first pulse oscillator is presented as the SA node, and the second one is considered as the AV node, then certain stable phase lockings turn out to correspond to the cardiac pathologies which are detected in clinical practice. In this case among various constructed lockings one can observe the normal sine rhythm (1:1 phase locking). In addition, in the diagrams we can see the classical rhythms of Wenckebach (N:(N-1) phase lockings) and N:1 AV-blocks.

When the first pulse system is considered as the AV node and the second one is regarded as the SA node, one can obtain the inverted Wenckebach rhythms (that are similar to the direct rhythms but the roles of ventricles and atria are interchanged) which are recorded in some patients.

Presence of wide areas of phase lockings (see Fig. 4-7) confirms that in such systems it is possible to observe various kinds of synchronization of two oscillators qualitatively corresponding to some types of cardiac arrhythmias. The phase diagram allows us to reveal under what interaction conditions (i.e. at what values of the parameters a and γ) one or another type of synchronization exists. Moreover, all phase pictures indicate that at the increasing the nonlinearity (i.e. at the growth of the parameter γ) areas with various phase lockings are overlapped. The knowledge of such regions and dynamics allows us to remove the system from an undesirable mode of synchronization to an appropriate state.

6. Concluding remarks. In the present paper a quite general model of two nonlinear interacting impulse oscillatory systems is developed. On the basis of this model it is possible to predict some types of cardiac arrhythmias. The constructed model is a universal one in the sense that it does not depend on the chosen interaction type, i.e. on the form of the phase response curve. Taking into account the refractory time the possible phase locking regions of the various maps (which describe a nonlinear oscillator under the permanent inputs) are investigated. The existence of the refractory time in the system with large enough values of the interaction of two oscillators leads to the widening and the essential diffusion of the phase locking areas, their splitting and self-crossing.

Detailed analysis of the phase diagram of the system with two bidirectionally interacting oscillators shows that besides splitting of the central tongues there is an overlapping of the main regions of synchronization which corresponds to various types of cardiac arrhythmias. This bistability is observed even for *small enough* values of the interaction. Including the refractory time leads to the distortion in forms of the main tongues and disappearance of the splitting areas.

The results obtained allow us to predict the dynamics of oscillatory systems depending on the initial phase difference, on the type and the intensity of the interaction. Moreover, using the principle of the construction of our model one can develop a quite general theory of interacting oscillators under a certain periodic perturbation. In this case the knowledge of multistability areas can serve to find a possibility to stabilize the system dynamics and remove the cardiac tissue to the required type of the behaviour.

A generalization of the results of this paper is given in [34].

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