A model of cardiac tissue as a conductive system with interacting pacemakers and refractory time

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Abstract

A model of the heart tissue as a conductive system with two interacting pacemakers and a refractory time, is proposed. In the parametric space of the model the phase locking areas are investigated in detail. Obtained results allow us to predict the behaviour of excitable systems with two pacemakers depending on the type and intensity of their interaction and the initial phase. Comparison of the described phenomena with intrinsic pathologies of cardiac rhythms is presented.

Short title: A model of cardiac tissue with interacting pacemakers

1 Introduction

One of the remarkable examples of excitable media is the cardiac tissue. Because the stability of its behaviour is essential for living creatures, investigations of processes occurring in the cardiac muscle attract a considerable interest of various scientists. Owing to a great complexity and a wide variety of the processes taking place in the heart, it can be considered with several points of view. One of them relies upon the interpretation of the cardiac tissue as an active conductive system. Then, the cardiac rhythms are described on the basis of the dynamical systems theory (see, for example [Glass et al., 2002]).

The excitation wave in the cardiac tissue originates in the sinoatrial node (SA) and spreads rapidly in succession over the right atrium, the left atrium, then the
atrioventricular node (AV), bundle of His and Purkinje fibers, and finally to the walls of the right and left ventricles. The normal rhythm of the heart is determined by the activity of the SA node which is called the leading pacemaker (a source of concentric excitation waves) or the first order driver of the rhythm. In addition to the SA node cells, the other parts of the cardiac conductive system reveal an automaticity. So, the second order driver of the rhythm is located in the AV conjunction. The Purkinje fibers are the rhythm driver of the third order. Moreover, for some pathological states of the heart arising of ectopic pacemakers is typical.

Appearance of several excitation sources leads to various disorders in the cardiac rhythm, i.e. arrhythmias [Schamorth, 1980; Marriot & Conover, 1983; Zipes & Jalife, 1985; Winfree, 1987; Glass & Mackey, 1988]. Because arrhythmias are dangerous diseases of the heart, their investigations have a great importance. Analysis of the complex cardiac rhythms on the basis of their interpretation as chaotic phenomena can give a clue to the problem of controllability of the complex cardiac dynamics and removing the cardiac tissue to the required regime [Goldberger & Rigney, 1988; Goldberger, 1990; Garfinkel et al., 1992].

As known, some arrhythmias can be presented by the interaction of spontaneous nonlinear sources [Glass et al., 1983; Glass & Mackey, 1988; Kremmydas et al., 1996]. In some cases, a model of impulse systems describing certain types of such arrhythmias is constructed in the framework of the theory of dynamical systems. This model is represented by coupled low-dimensional maps (circle maps) which can exhibit a complex dynamics. Such an approach is based on the fact that experiments on periodically stimulated cardiac cells are in a close agreement with the dynamics predicted by one-dimensional circle maps [Courtemanche et al., 1989].

In our investigations, a quite general model of two nonlinear coupled oscillators describing certain types of cardiac arrhythmias is constructed. 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 (PRC). The experimentally obtained PRC is
approximated by a certain polynomial function with plateau. This plateau describes a refractory time when the system does not respond to an external action. Note that the refractory time plays an important role for the normal cardiac functioning. For example, the refractoriness extends over almost the whole period of the cardiac contraction protecting the myocardium from premature heartbeats caused by an external perturbation. The refractoriness provides also the normal sequence of an excitation propagation in the heart tissue and the electrical stability of the myocardium [Marriot & Conover, 1983; Zipes & Jalife, 1985; Winfree, 1987; Glass & Mackey, 1988]. In the proposed model, taking into consideration the refractory time possible areas of the phase lockings are investigated. Phenomena of the splitting of resonance tongues and superposition of the synchronization areas are found. Using the obtained results we can define dynamics of the excitable media with two active pacemakers depending on the type and intensity of their interaction and the initial phase difference. Moreover, generalizing the principles of our construction one can develop a quite general theory of excitable media with interacting pacemakers under external actions. This fact has a great practical importance because admits to realize the control of the cardiac rhythms by external stimuli.

2 Heart Tissue as a Dynamical System

In certain cases cardiac arrhythmias can be described as an interaction of two spontaneously oscillating nonlinear sources. This interaction can be considered as an influence of some external periodic perturbation on a nonlinear oscillator (with the constant amplitude and frequency). So, for the description of such a situation it is possible to use the well-known circle map [Glass et al., 1983; Bub & Glass, 1994; Kremmydas et al., 1996]:

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

where $x_n$ is a phase difference in oscillators and the function $f(x)$ determines a change in the phase after action of stimulus. This function is called a phase response curve
One of the most important characteristics of the circle map is a rotation number $\rho$. It is defined as follows:

$$\rho = \lim_{n \to \infty} \frac{x_n - x_0}{n}.$$ 

For stable phase locking $N : M$ the rotation number is rational, $\rho = N/M$. If it is irrational the system behaviour is quasiperiodic or chaotic.

Analysing dynamics of the constructed model based on the circle map, 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.

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 obtained from the research of some cardiac tissues. In [Weidmann, 1961; Jalife & Moe, 1976] measurements of the cycle durations of the spontaneous beating Purkinje fibres after stimulation by short electric current pulses have been performed. The found phase response curve is shown in Fig.1 (dotted lines). Taking into account this experimental material, it is possible to make the following general conclusions [Weidmann, 1961; Jalife & Moe, 1976; Glass et al., 1986; Glass & Mackey, 1988]:

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

- depending on a phase the single input can lead to either increasing or decreasing of the period of a perturbed cycle;

- at some amplitudes of stimulus the obvious breaks appear.

The basic feature of any approximation of the PRC is the dependence on two physical parameters: on 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 polynomial function for the approximation of the PRC, we construct a model of two *mutually* interacting impulse active oscillators.

### 3 Analytical Model with a Mutual Influence of Impulses

Let us consider the system of two nonlinear interacting oscillators (Fig. 2). Suppose that the pulse of the first oscillator with period $T_1$ beats at $t_n$, and the pulse of the second oscillator (with period $T_2$) beats at $\tau_n$. Then the moments of time of the next appearance of the impulses are defined as follows:

\[
\begin{align*}
t_{n+1} &= t_n + T_1, \\
\tau_{n+1} &= \tau_n + T_2.
\end{align*}
\]

Now, taking into account the change in the period of the first oscillator under the influence of the second impulse by the value of $\Delta_1\left(\frac{(\tau_n - t_n)}{T_1}\right)$, one can get that

\[
t_{n+1} = t_n + T_1 + \Delta_1\left(\frac{(\tau_n - t_n)}{T_1}\right).
\]

By the same manner, for the second oscillator

\[
\tau_{n+1} = \tau_n + T_2 + \Delta_2\left(\frac{(t_{n+1} - \tau_n)}{T_2}\right).
\]

Dividing these expressions by $T_1$ we arrive at the corresponding values for the phases:

\[
\begin{align*}
\varphi_{n+1} &= \varphi_n + \frac{1}{T_1}\Delta_1 (\delta_n - \varphi_n), \\
\delta_{n+1} &= \delta_n + \frac{T_2}{T_1} + \frac{1}{T_1}\Delta_2 \left(\frac{t_n}{T_2} + \frac{T_1}{T_2} + \frac{1}{T_2}\Delta_1 (\delta_n - \varphi_n) - \frac{\tau_n}{T_2}\right).
\end{align*}
\]

Here $\varphi_n = t_n/T_1$ is a 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 parameters $a = T_2/T_1$ and $\Delta_1/T_1 = f_1$, $\Delta_2/T_1 = f_2$ one can write:

\[
\begin{align*}
\varphi_{n+1} &= \varphi_n + f_1 (\delta_n - \varphi_n), \\
\delta_{n+1} &= \delta_n + a + f_2 \left(\frac{1}{a} (\varphi_n + f_1 (\delta_n - \varphi_n) - \delta_n)\right).
\end{align*}
\]

Now, omitting intermediate calculations, for the final expression of the phase difference in the oscillators we get

\[
x_{n+1} = x_n + a + f_2 \left(\frac{1}{a} (1 + f_1 (x_n) - x_n)\right) - f_1 (x_n) \mod 1, \tag{1}
\]
where $x_n = \delta_n - \varphi_n$.

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

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

where $h(x)$ is a periodic function and $h(x + 1) = h(x)$. In such an assumption, the expression (1) takes the form:

$$x_{n+1} = x_n + a + \varepsilon h\left(\frac{1}{a} (1 + \gamma h(x_n) - x_n)\right) - \gamma h(x_n) \pmod{1}.$$

In the present paper we dwell on the investigations of the map (2) with a polynomial function $h(x)$. The obtained results are the continuation of our previous works concerning modeling certain cardiac arrhythmias [Loskutov, 1994; Loskutov et al., 2002].

### 4 Phase Diagrams for Unidirectional Coupling of Oscillators

First of all let us analyze the situation when the permanent inputs act on the nonlinear oscillator, i.e. $f_2(x) \equiv 0$ or $\varepsilon = 0$. As an analytical approximation of the experimental curve in Fig.1, let us consider the following polynomial function:

$$h(x) = Cx^2 \left(\frac{1}{2} - x\right) (1 - x)^2.$$

The normalizing factor $C$ we choose in such a way that the amplitude of $h(x)$ is equal to 1, so that $C = 20\sqrt{5}$ (see Fig.1, solid line). Then taking into account the refractory time $\delta$ the map (2) we can write as follows:

$$x_{n+1} = \begin{cases} x_n + a, & 0 \leq x_n \leq \delta, \pmod{1}, \\ x_n + a + C\gamma h\left(\frac{x_n - \delta}{1 - \delta}\right), & \delta < x_n \leq 1, \pmod{1}, \end{cases}$$

where $h(\cdot)$ is determined by (3). Now let us compare several cases with different values of the refractory time. First of all consider the case without the refractory period, i.e. $\delta = 0$. The phase locking regions in the parametric space $(a, \gamma)$ obtained by numerical
analysis are shown in Fig.3a. Without loss of generality, in this Figure we choose 
\(a \in [1, 2]\). Different colours define the phase locking areas with the multiplicity \(N : M\),
where \(N\) cycles of external stimulus correspond to \(M\) cycles of nonlinear oscillator.
One can see that ”tales” of the main locking regions are slightly splitted and overlap each other at large \(\gamma\). Note that as follows from the analysis of the system (4) with \(\delta = 0.1\) (Fig.3b), introduction of the refractory time leads to the extension of the phase locking areas and significant splitting and overlapping their ”tales”.

In Fig.4a the numerically constructed phase diagram in the case of \(\delta = 0.3\) 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 when the value of the refractory time is growing, the 2 : 3 phase locking area is increasing with simultaneous decreasing of the 1 : 1 and 1 : 2 areas.

The phase locking regions in the case of \(\delta = 0.5\) are shown in Fig.4b. This phase diagram is qualitatively different from pictures considered above. The form of 2 : 3 phase locking area is stretched and looks like an arrow. The forms of 3 : 4 and 3 : 5 regions also resemble arrows in the case of \(\delta = 0.7\) (Fig.4a). At \(\delta = 0.9\) all phase lockings are degenerated into vertical lines. This situation is presented in Fig.4b. Note that in the case of \(\delta = 1\) (i.e. the system does not respond to the external action) there is no any dependence on the stimulus amplitude \(\gamma\).

5 Phase Diagrams for Systems with Mutual Interaction

In this section the system (2) at \(\delta = 0.1\) is considered. The analysis is performed in the \((\gamma, a)\) and \((\gamma, \varepsilon)\)-parametric spaces.

5.1 Phase locking areas in the \((\gamma, a)\)-space

Let us consider the case of a mutual interaction of two impulse systems. Assume that the influence of the first oscillator on the second one is small enough, for example, \(\varepsilon = 0.1\). The corresponding phase diagram displaying the possible behaviour regimes
of the system for $\delta = 0.1$ is shown in Fig.6a. One can see that the mutual interaction leads to the deformation and the splitting of the phase locking areas. Note that even for small values of the amplitude of the second stimulus $\gamma$, the overlapping of the main phase lockings takes place. Thus, the system dynamics becomes multistable. This corresponds to the situation when the limit state of the map depends on an initial phase difference $x_n$. The growth of the refractory time in the model with $\varepsilon = 0.1$ leads to more deep distortion in the forms of the main tongues and disappearance of the splitting areas. If, however, we increase the influence of the first oscillator up to, for instance $\varepsilon = 0.5$, then one can see a very complicated structure with much more deep deformation of the main phase locking areas (see Fig.6b). For example, the $1:1$ area is degenerated into a narrow strip, whereas the $1:2$ phase locking area increases due to appearance of long narrow tongues.

The numerical analysis shows that at the growth of $\varepsilon$ up to approximately 0.5 the occupied by the resonance zones area becomes larger. At the same time, the shape of the phase lockings is complexified, and their location is changed. This leads to the almost full mixed picture, such that we can find zones of various multiplicity in a small neighborhood of almost any point $(\gamma, a)$. However, at the given values of $\varepsilon$ the self-similarly structures are clearly observed.

Additionally, we have found that at the further growth of the nonlinearity parameter $\varepsilon$ the resonance zones decrease, occupying the less space. In this case the mixing of resonance tongues also takes place. Thus, increasing the effect of the influence of oscillators leads to the mixing of initially quite regular structure in $(\gamma, a)$–space.

### 5.2 Phase locking regions in the $(\gamma, \varepsilon)$–space

Now we construct the phase diagrams of the interacting oscillators in the space of influence amplitudes, i.e. $(\gamma, \varepsilon)$. In the first instance, let us consider $a = 2$ (Fig.7a). This value of the ratio of periods means that for $\gamma = \varepsilon = 0$ the rotation number is rational, and the dynamics of the system is periodic with the $1:2$ phase locking. Although at the growth of nonlinearity it is possible to obtain the phase locking areas
with another multiplicity, even at the large values of $\gamma$ and $\varepsilon$ the system behaviour is periodic with the 1 : 2 phase locking.

Another situation is observed at $a = \pi/2$. Here the rotation number is irrational at zero stimulus amplitudes, and the system exhibits the property of quasiperiodicity or chaoticity. However, at increasing the nonlinearity the possibility of the appearance of the periodic behaviour exists (Fig. 7b). Here, as for a sufficiently large $\varepsilon$, one can observe decreasing of the area occupying the resonance zones. Therefore, at irrational values of $a$ the probability of the complex behaviour of the system (2) is a large enough.

6 Analogy with Pathological Heart Rhythms

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

Similar case of mutual interaction of the SA and AV nodes was investigated in [di Bernardo et al., 1998; Signorini et al., 1998]. The authors modeled the AV node as a van-der-Pol oscillator and the SA node was considered as a certain modified van-der-Pol oscillator. The obtained waveforms satisfactory replicated the action potentials of the SA and AV node cells. A bifurcation analysis performed in these works showed a possibility to reproduce and classify various types of cardiac pathologies.

Now let us consider some types of arrhythmias one can predict on the basis of our model. If the first pulse oscillator is presented as the SA node and the second one is considered as the AV node, then we come to conclusion that some stable phase lockings correspond to the cardiac pathologies which are observed in a clinical practice. In this case among various obtained lockings one can reveal the normal sinus 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
presented as the SA node, we obtain the known inverted Wenckebach rhythms found in some patients.

Presence of the wide areas of phase lockings (see Fig.3, 7) confirms that in such systems it is possible to observe the various kinds of synchronization of two oscillators qualitatively corresponding to some types of cardiac arrhythmias. The phase diagram allows us to reveal under what conditions of the interaction (i.e. at what values of the parameters $a, \gamma, \varepsilon$ and $\delta$) one or another type of synchronization exists. Moreover, the phase pictures indicate that at the increasing the nonlinearity (i.e. at the growth of the parameter $\gamma$) areas with various phase lockings are overlapped. The knowledge of such regions and the dynamics permits us to remove the system from an undesirable mode of synchronization to a more appropriated state by the external action.

7 Concluding Remarks

In the presented 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 polynomial maps which describe a nonlinear oscillator under the permanent inputs, are investigated. It is found that involving the refractory time leads to the extension of the phase locking areas, significant splitting and overlapping their ”tales”. Moreover, the forms of the phase locking areas are stretched and degenerated into vertical lines as the refractory time tends to one.

Detailed analysis of the phase diagram of the system with two mutually interacting oscillators in the $(\gamma, a)$-space 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. Increasing the refractory time leads to the distortion in the form of
the main tongues and disappearance of the splitting areas. For sufficiently large values of the interaction we obtain a very complicated picture, where the phase locking areas are interwoven with each other.

In addition, in the constructed model the phase lockings in the space of the stimulus amplitudes are observed. It is found that the interacting oscillators can be synchronized even if the ratio of their periods is irrational (note, that the probability of this phenomenon is a quite small). However, in the case without coupling this would correspond only to the complex dynamics (quasiperiodic or chaotic).

The obtained results 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 the model one can develop a quite general theory of the interacting oscillators under periodic perturbation. In this case the knowledge of the multistability areas can help to stabilize the system dynamics and remove the cardiac tissue to the required type of the behaviour.
References

Bub, G. & Glass, L. [1994] “Bifurcations in a continous circle map: A theory for chaotic cardiac arrhythmia,” *Int. J. Bifurcation and Chaos* 5(2), 359–371.

Courtemanche, M., Glass, L., Belair, J., Scagliotti, D. & Gordon, D. [1989] “A circle map in a human heart,” *Physica D* 49, 299–310.

di Bernardo, D. D., Signorini, M. G. & Cerutti, S. [1998] “A model of two nonlinear coupled oscillators for the study of heartbeat dynamics,” *Int. J. Bifurcation and Chaos* 8(10), 1975–1985.

Garfinkel, A., Spano, M. L. & Ditto, W. L. [1992] “Controlling cardiac chaos,” *Science* 257, 1230–1235.

Glass, L., Guevara, M. R., Shrier, A. & Perez, R. [1983] “Bifurcation and chaos in a periodic stimulated oscillator,” *Physica D* 7(1–3), 89–101.

Glass, L., Guevara, M. R. & Shrier, A. [1986] “Phase resetting of spontaneously beating embryonic ventricular heart cell aggregates,” *Am. J. Physiol.* 251, H1298–H1305.

Glass, L. & Mackey, M. [1988] *From clocks to chaos: the rhythms of life* (Princeton Univ. Press, Princeton).

Glass, L., Nagai, Y., Hall, K., Talajie, M. & Nattel, S. [2002] “Predicting the entrainment of reentrant cardiac waves using phase resetting curves,” *Phys. Rev. E* 65, 021908-1–021908-10.

Goldberger, A. L. & Rigney, D. R. [1988] “Sudden death is not chaos,” *Dynamic patterns in complex systems*, eds. Kelso, J. A. S., Mandell, A. J. & Schlesinger, M. F. (World Sci. Pub., Teaneck, NJ), 248–264.

Goldberger, A. L. [1990] “Nonlinear Dynamics, Fractals and Chaos: Applications to Cardiac Electrophysiology,” *Ann. Biomed. Eng.* 18(2), 195–198.

Jalife, J. & Moe, G. K. [1976] “Effects of electronic potentials on pacemaker activity of canine Purkinje fibers in relation to parasistole,” *Circ. Res.* 39(6), 801–808.

Kremmydas, G. P., Holden, A. V., Bezerianos, A. & Bountis, T. [1996] “Reprezentation of sino-atrial node dynamics by circle maps,” *Int. J. Bifurcation and Chaos* 6(10),
1799–1805.

Loskutov, A. [1994] “Nonlinear dynamics and cardiac arrhythmia,” Applied Nonlinear Dynamics 2(3–4), 14–25 (Russian).

Loskutov, A., Rybalko, S. D. & Zhuchkova, E. A. [2002] “Dynamics of excitable media with two interacting pacemakers,” Biophysics 47(5), 892–901.

Marriot, H. J. L. & Conover, M. M. [1983] Advanced Concepts in Cardiac Arrhythmias (C.V. Mosby, St. Louis).

Schamorth, L. [1980] The Disoders of the Cardiac Rhythm (Blackwell, Oxford).

Signorini, M. G., Cerutti, S. & di Bernardo, D. D. [1998] “Simulation of hertbeat dynamics: a nonlinear model,” Int. J. Bifurcation and Chaos 8(8), 1725–1731.

Weidmann, S. [1961] “Effects of current flow on the membrane potential of cardiac muscle,” Journal of Physiology 115, 227.

Winfree, A. T. [1987] When Time Breaks Down: The Three-Dimensional Dynamics of Electrochemical Waves and Cardiac Arrhythmias (Princeton Univ. Press, Princeton).

Zipes, D. P. & Jalife, J. [1985] Cardiac Electrophysiology and Arrhythmias, (Grune and Stratton, Orlando).
Figure captions

Fig.1. The phase response curves: the experimental curve (dotted line) and its analytical approximation (solid line). The experimentally obtained phase response curve shows a dependence of the duration of perturbed cycle (in %) on the phase of input.

Fig.2. A construction of the model of two nonlinear interacting oscillators.

Fig.3. The phase diagram of the map (1): a) $\delta = 0$; b) $\delta = 0.1$.

Fig.4. The phase locking areas of the map (1): a) $\delta = 0.3$; b) $\delta = 0.5$.

Fig.5. The phase diagram of the map (1): a) $\delta = 0.7$; b) $\delta = 0.9$.

Fig.6. The phase locking regions of the system of two mutual interacting oscillators with $\delta = 0.1$: a) $\varepsilon = 0.1$; b) $\varepsilon = 0.5$.

Fig.7. The phase lockings in the space of stimulus amplitudes ($\delta = 0.1$): a) $a = \pi/2$; b) $a = 2$. 
Figure 1: A. Loskutov, S. Rybalko & E. Zhuchkova
Figure 2: A. Loskutov, S. Rybalko & E. Zhuchkova
Figure 3: A. Loskutov, S. Rybalko & E. Zhuchkova
Figure 4: A. Loskutov, S. Rybalko & E. Zhuchkova
Figure 5: A. Loskutov, S. Rybalko & E. Zhuchkova
Figure 6: A. Loskutov, S. Rybalko & E. Zhuchkova
Figure 7: A. Loskutov, S. Rybalko & E. Zhuchkova