International Journal of Bifurcation and Chaos, Vol. 14, No. 7 (2004) 2457–2466

MODEL OF CARDIAC TISSUE AS A CONDUCTIVE SYSTEM WITH INTERACTING PACEMAKERS AND REFRACTORY TIME

ALEXANDER LOSKUTOV*, SERGEI RYBALKO and EKATERINA ZHUCHKOVA
Physics Faculty, Moscow State University, Leninskie Gory, 119992 Moscow, Russia
**loskutov@moldyn.phys.msu.ru*

Received December 9, 2002; Revised September 12, 2003

The model of the cardiac 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. The obtained results make possible to predict the behavior 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 given.

Keywords: Arrhythmia; phase diagrams; interacting pacemakers; maps.

1. Introduction

One of the remarkable examples of excitable media is the cardiac tissue. Because the stability of its behavior is vitally important, investigations of processes occurring in the cardiac muscle attract a considerable scientific interest. Owing to extraordinary complexity of the system, many alternative models have been tested. One of them treats the cardiac tissue as an active conductive system. Then, the cardiac rhythms are described on the basis of the dynamical system theory (see e.g. [Courtemanche *et al.*, 1989; Goldberger, 1990; Bub & Glass, 1994; Glass *et al.*, 2002] and refs. therein).

Excitation waves in the cardiac tissue originate in the sinoatrial node (SA) and spread successively over the right atrium and the left atrium. Then they pass through 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 can reveal 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.

Often arrhythmia is the disturbance of the normal heartbeat caused by several propagation failures [Keener, 2000; Lewis & Keener, 2000]. In particular, arrhythmias can be evoked by the violation of the restitution of the cardiac tissue (so-called the reentry phenomenon) (see e.g. [Panfilov & Keener, 1995; Biktashev & Holden, 1998; Cytrynbaum & Keener, 2002; Glass *et al.*, 2002] and refs. therein).

In addition to such pathologies, the disturbances of the cardiac rhythms are induced by the appearance of ectopic excitation sources [Schamorth, 1980; Marriot & Conover, 1983; Zipes & Jalife, 1995; Winfree, 1987; Glass & Mackey, 1988]. Furthermore, a few abnormal sources and spiral waves result in a fibrillation phenomenon (in fact, a spatio-temporal cardiac chaos [Qu *et al.*, 1997; Qu *et al.*, 2000]). In this case it is necessary to involve the application of a high energy electric shock. A number of recent clinical studies aim at the improvement of defibrillation protocols in order

to minimize failure rates and reduce the amount of energy used and thus damage risk [Zipes & Jalife, 1995]. Recent studies provide a theoretical understanding of the underlying mechanisms of defibrillation [Krinsky & Pumir, 1998; Pumir *et al.*, 1998; Panfilov *et al.*, 2000].

When arrhythmias are presented via interaction of the pacemaker and the ectopic source (i.e. the reciprocal action of nonlinear sources), investigation of such cardiac pathologies can be subdivided into two large groups: First is based on the continuous time representations (i.e. using systems of ordinary differential equations) [van der Pol & van der Mark, 1928; Keener, 1981; Guevara & Glass, 1982; Hoppensteadt & Keener, 1982; Keener & Glass, 1984; Keith & Rand, 1984; West *et al.*, 1985; Signorini *et al.*, 1998] (and refs. therein), second — on the maps representation [Moe *et al.*, 1977; Jalife *et al.*, 1982; Honerkamp, 1983; Ikeda *et al.*, 1983; Glass & Mackey, 1988; Courtemanche *et al.*, 1989; He *et al.*, 1992; Bub & Glass, 1994; Kremmydas *et al.*, 1996; Ostborn *et al.*, 2001].

Since arrhythmias are dangerous heart diseases, investigation of such pathologies is of great importance. Moreover, analysis of the complex cardiac rhythms, treated as chaotic phenomena, can give a clue to the problem of controllability of the complex cardiac dynamics [Goldberger & Rigney, 1988; Goldberger, 1990; Garfinkel *et al.*, 1992].

In the present investigation, a general model of two nonlinear coupled oscillators describing certain types of cardiac arrhythmias (AV-blocks and parasistoles) is elaborated. The model occurs to be a universal in the sense that its predictions are not sensitive to 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 a plateau. This plateau models the refractory stage when the system does not respond to an external action. Note that the refractory stage plays an important role in the normal cardiac functioning. For example, the refractoriness extends almost over the period of the cardiac contraction, protecting the myocardium from premature heartbeats caused by the external perturbation. The refractoriness provides also the normal sequence of an excitation propagation in the cardiac tissue and the electrical stability of the myocardium [Marriot & Conover, 1983; Zipes & Jalife, 1995; Winfree, 1987; Glass & Mackey, 1988]. In the proposed model, possible areas of phase lockings, caused by the refractoriness, are investigated. We observe the splitting of the resonance tongues and the superposition of the synchronization areas. Using the obtained results we can classify the 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 our approach a theory of excitable media with interacting pacemakers under external actions may be elaborated. This fact can be of a great practical importance due to possible application in controlling the cardiac rhythms by external stimuli.

2. Heart Tissue as a Dynamical System

The cardiac arrhythmias may be described sometimes as an interaction of two spontaneously oscillating nonlinear sources. Such interaction can be analyzed in terms of influence of an external periodic perturbation (with a constant amplitude and frequency) on a nonlinear oscillator. In this case it is possible to use the well-known circle map [Guevara & Glass, 1982; Glass *et al.*, 1983; Glass & Mackey, 1988; Bub & Glass, 1994; Kremmydas *et al.*, 1996]:

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

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

One of the most important characteristics of the circle map is a rotation number ρ. It is defined as follows:

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

For stable phase locking the rotation number is rational. If ρ is irrational then the system behavior is quasiperiodic or chaotic.

It should be noted that such a one-dimensional approach imposes restrictions: We neglect the propagation of the excitation waves on the heart surface. Thus, the violation of the cardiac rhythm due to the absence of pulse coordinations in the whole myocardium cannot be described within this model.

Analyzing dynamics of the model based on the circle map, it is necessary to find a proper analytical approximation for the experimentally obtained PRC. This allows investigation of the most salient features of the system of interest.

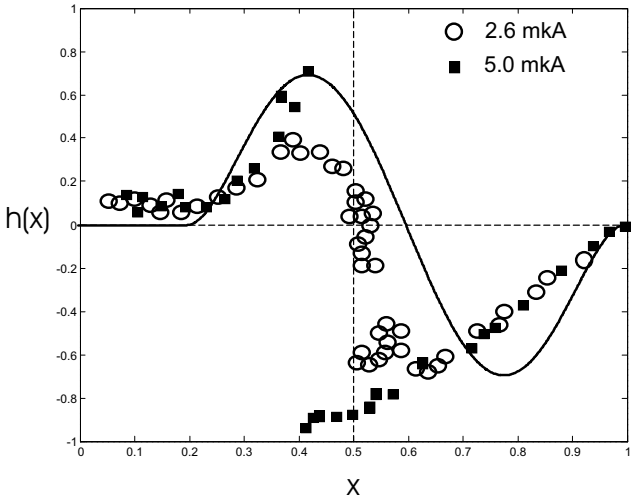


Fig. 1. Phase response curves: the experimental curves (dotted line) and their analytical approximation (solid line). The experimentally obtained phase response curves show the duration of perturbed cycle (in %) as a function of the input phase.

Experiments on the recording of phase shifts have been carried out for quite a large number of variety of systems, but we are interested in the PRC extracted from the real cardiac tissues. In [Weidmann, 1951; Jalife & Moe, 1976] measurements of the cycle durations of the spontaneously beating Purkinje fibers after stimulation by short electric current pulses have been performed. The obtained 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, 1951; Jalife & Moe, 1976; Glass *et al.*, 1986; Glass & Mackey, 1988]:

(1) Depending on the 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 with shifted phase.
(3) At some amplitudes of the stimulus the obvious breaks appear.

Also, it is necessary to take into account that: (i) The assumption of the immediate resetting of the pacemaker rhythm after the action of the external stimulus is a certain kind of idealization; (ii) for an adequate description of the third PRC feature it is necessary to choose a parametrical function $f(x) = f_a(x)$ which occurs to be discontinuous as the amplitude parameter a continuously changes. 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 commonly used. In the present paper we also accept this restriction.

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.

Applying the polynomial function as an approximation of the PRC, we construct a model of two *bidirectionally* interacting active oscillators.

3. A Model with 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 time t_n, and the pulse of the second oscillator (with the period T_2) beats at time τ_n. Then, the subsequent 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 under the influence of the second impulse the period of the first oscillator changes by the value of $\Delta_1((\tau_n - t_n)/T_1)$ (where the relation in brackets means that this value depends only on the phase of the second impulse), we get the expression for t_{n+1}: $t_{n+1} = t_n + T_1 + \Delta_1((\tau_n - t_n)/T_1)$. For further analysis, let us consider the case when the pulses of two oscillators strictly alternate

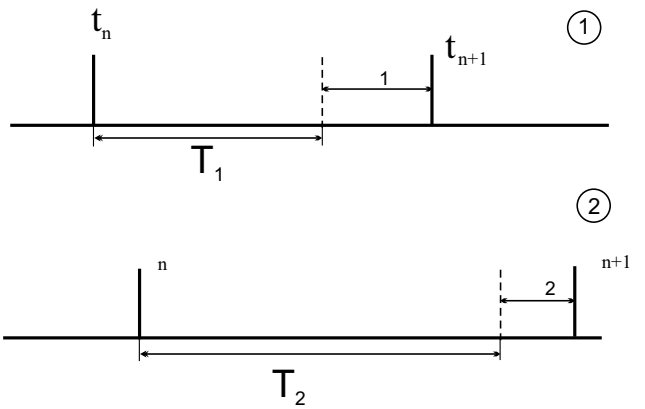


Fig. 2. Construction of the model of two nonlinearly interacting oscillators.

each other.[1] Then for the second oscillator we obtain: $\tau_{n+1} = \tau_n + T_2 + \Delta_2((t_{n+1} - \tau_n)/T_2)$. Dividing these relations by T_1, we arrive at the corresponding values for the phases:

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

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

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

which after some algebra yields the final expression for the phase difference of the oscillators:

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

where $x_n = \delta_n - \varphi_n$.

Obviously, the PRC changes its form depending on the amplitude of the external stimulus. In the simplest case this dependence can be approximated by the multiplicative relation. Then the phase response curves can be written as follows:

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

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

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

In the present paper the map (3) with the *polynomial* function $h(x)$ will be addressed. The obtained results are generalization of our previous studies [Loskutov, 1994; Loskutov *et al.*, 2002].

4. Phase Diagrams for Unidirectional Coupling of Oscillators

Let us analyze the situation when 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:

$$h(x) = Cx^2\left(\frac{1}{2} - x\right)(1 - x)^2. \tag{4}$$

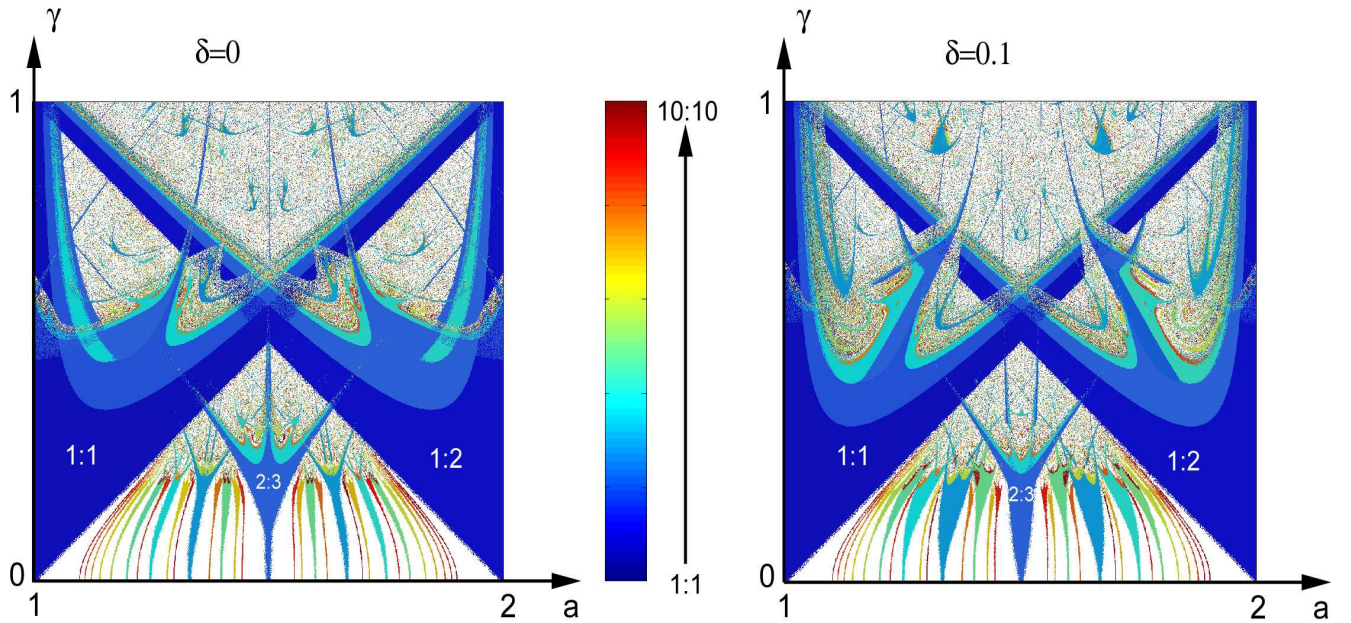
The normalizing factor C is chosen in such a way that the amplitude of $h(x)$ is equal to 1, i.e. $C = 20\sqrt{5}$ (see Fig. 1, solid line). Then taking into account the refractory time δ we can write the map (3) as

$$x_{n+1} = \begin{cases} x_n + a, & 0 \le x_n \le \delta, \pmod 1, \\ x_n + a - \gamma h\left(\dfrac{x_n - \delta}{1 - \delta}\right), & \delta < x_n \le 1, \pmod 1, \end{cases} \tag{5}$$

where $h(\cdot)$ is determined by (4). Now let us analyze the dependence of the system dynamics on the refractory time.

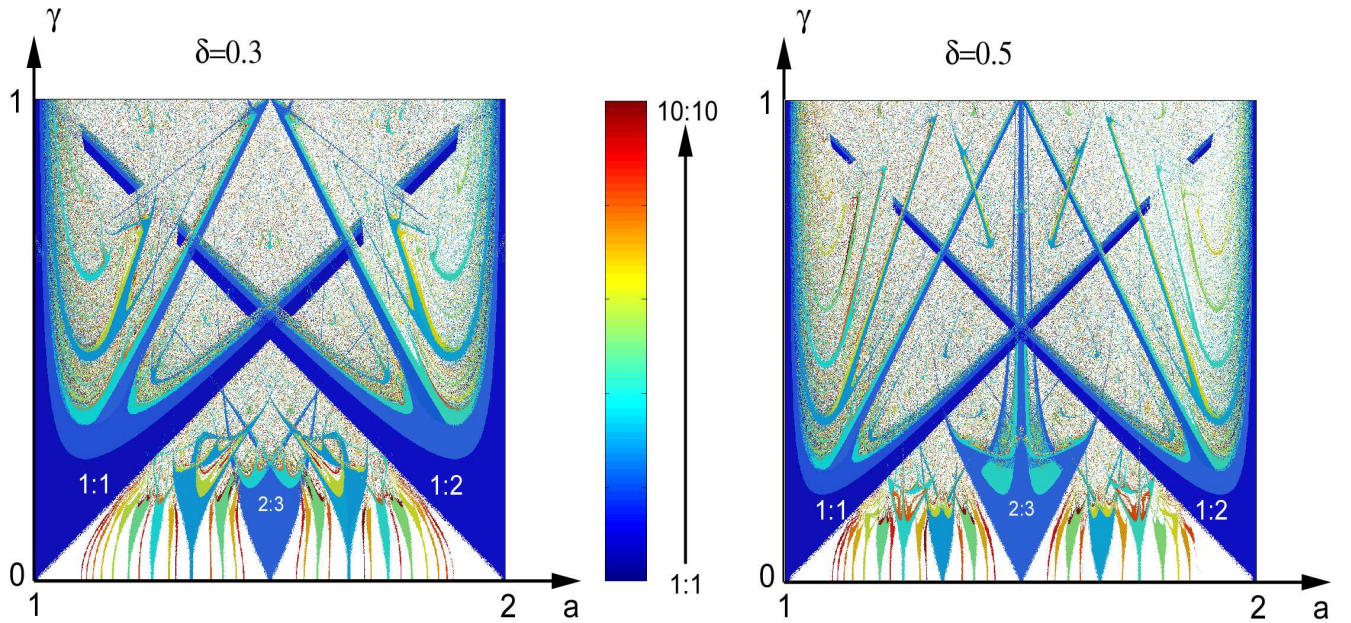
We start with the case when the refractory period is trivial, i.e. $\delta = 0$. The phase locking regions in the parametric space (a, γ) obtained by numerical analysis are shown in Fig. 3(a), where $a \in [1, 2]$ is chosen. Different colors define the phase locking areas with multiplicity $N : M$, where N cycles of external stimulus correspond to M cycles of the nonlinear oscillator. One can see that "tales" of the

[1]The case when the pulses of two oscillators are not intermittent is addressed in [Loskutov *et al.*, 2003].



(a) (b)

Fig. 3. Phase diagrams of the map (5): (a) $\delta = 0$; (b) $\delta = 0.1$.

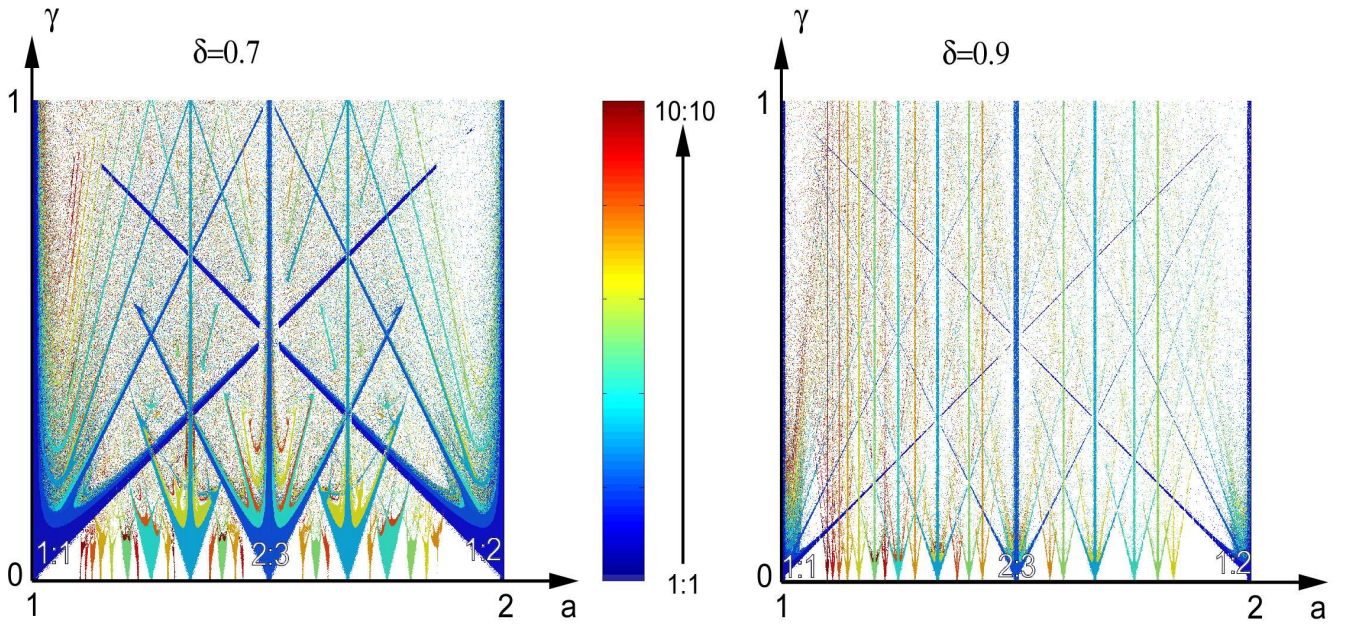


(a) (b)

Fig. 4. Phase locking areas of the map (5): (a) $\delta = 0.3$; (b) $\delta = 0.5$.

main locking regions are slightly split and overlap at large γ. As it follows from the analysis of the system (5) with $\delta = 0.1$ [Fig. 3(b)], nonvanishing refractory time leads to the extension of the phase locking areas and enhances splitting and overlap of their tales.

In Fig. 4(a) the numerically obtained phase diagram for $\delta = 0.3$ is shown. In this figure the same



(a) (b)

Fig. 5. Phase diagrams of the map (5): (a) $\delta = 0.7$; (b) $\delta = 0.9$.

$N : M$ stable phase lockings as in Fig. 3 are given for comparison. As it follows from the figure, the $2 : 3$ phase locking area increases with increasing refractory time; simultaneously the $1 : 1$ and $1 : 2$ areas decrease.

The phase locking regions for $\delta = 0.5$ are shown in Fig. 4(b). This phase diagram is *qualitatively* different from those shown 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 for $\delta = 0.7$ [Fig. 5(a)]. At $\delta = 0.9$ all phase lockings are degenerated into vertical lines. This situation is illustrated in Fig. 5(b). Note that for $\delta = 1$ (i.e. the system does not respond to the external action) there is no dependence on the stimulus amplitude γ.

5. Phase Diagrams for Systems with Bidirectional Interaction

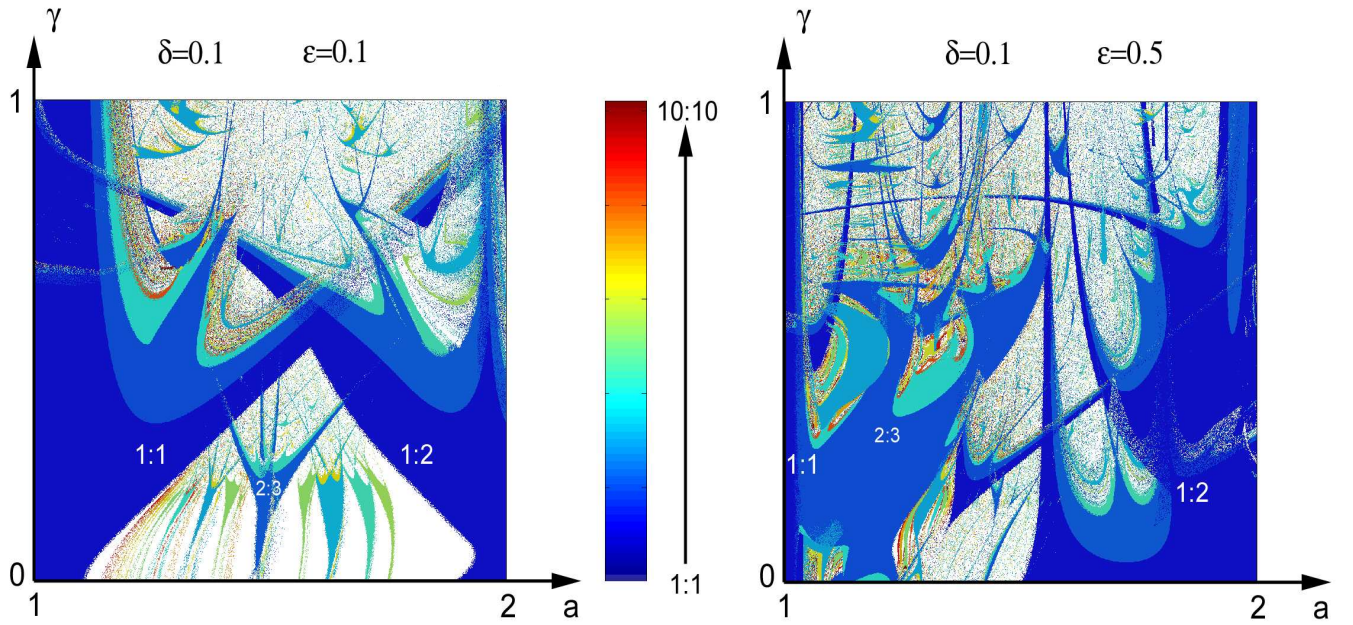
In this section the system (3) at $\delta = 0.1$ is considered. The analysis is performed in (γ, a)- and (γ, ε)-parametric spaces.

5.1. *Phase locking areas in the (γ, a)-space*

Assume that the influence of the first oscillator on the second is small enough, for example, $\varepsilon = 0.1$. The corresponding phase diagram for $\delta = 0.1$ is shown in Fig. 6(a). One can see that the mutual action leads to deformation and splitting in the phase locking areas. Note that even for small values of the amplitude of the second stimulus γ, the main phase locking areas overlap. This means that the system dynamics becomes multistable: Its limiting stage depends on an initial phase difference x_0. The growth of the refractory time in the model with $\varepsilon = 0.1$ leads to a more deep distortion of the forms of main tongues and disappearance of the splitting areas.

If, however, we increase the influence of the first oscillator up to, e.g. $\varepsilon = 0.5$, a very complicated structure with *much more deep* deformation of the main phase locking areas [see Fig. 6(b)] will appear. For example, the $1 : 1$ area will degenerate into a narrow strip, whereas the $1 : 2$ phase locking area will expand due to appearance of long narrow tongues.

Numerical analysis shows that the increase of ε up to approximately 0.5 is accompanied by the expansion of resonance zones. At the same time, the shape of the phase locking zones becomes more complex, and their location changes. This leads to the complete mixture of zones: Zones of various multiplicity may be found in a small neighborhood of almost any point (γ, a). Nevertheless



(a) (b)

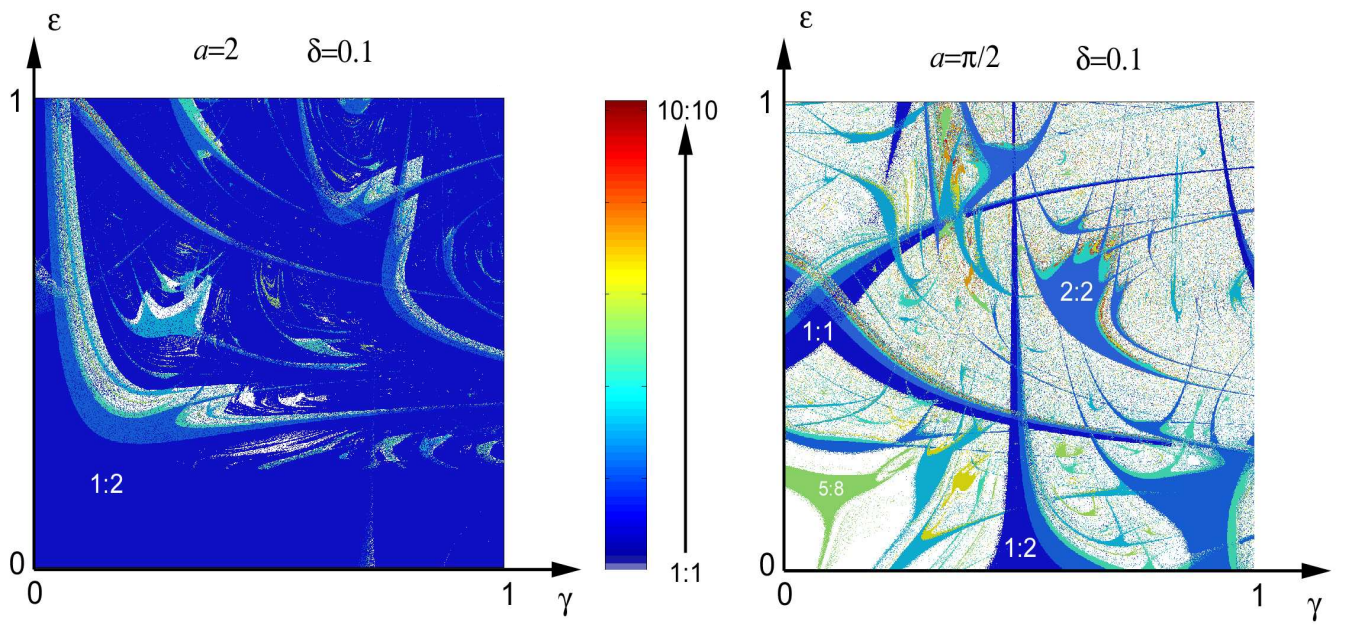
Fig. 6. Phase locking regions of the system of two bidirectionally interacting oscillators with $\delta = 0.1$: (a) $\varepsilon = 0.1$; (b) $\varepsilon = 0.5$.

at any given value of ε self-similarly structures are clearly observed.

Additionally, we have found as the nonlinearity parameter ε further grows, the resonance zones shrink and occupy a smaller area. In this case, the mixing of the resonance tongues also takes place. Thus, the increase of the interaction of the oscillators causes the mixing of the initially regular structures in the (γ, a)-space.

5.2. *Phase locking regions in the (γ, ε)-space*

Now we construct the phase diagrams of the interacting oscillators in the space of influence



(a) (b)

Fig. 7. Phase lockings in the space of stimulus amplitudes ($\delta = 0.1$): (a) $a = \pi/2$; (b) $a = 2$.

amplitude, i.e. (γ, ε). First we consider $a = 2$ [Fig. 7(a)]. This value of the period ratio implies that for $\gamma = \varepsilon = 0$ the rotation number (see Sec. 2) is rational, so that the dynamics of the system is periodic with the $1 : 2$ phase locking. Although for a large nonlinearity there exist phase lockings with another multiplicity, the behavior of the system is periodic, with $1 : 2$ phase locking, even at large γ and ε.

Qualitatively different behavior is observed at $a = \pi/2$. In this case the rotation number is irrational at zero stimulus amplitudes, and the system exhibits quasiperiodicity or chaoticity. However, as the nonlinearity increases the periodic behavior becomes possible [Fig. 7(b)]: For a sufficiently large ε, the decrease of the area occupied by the resonance zones may be observed. Therefore, at irrational values of a there exists a significant probability of the complex behavior of system (3).

6. Applications to Heart Rhythm Pathologies

Let us consider the analogy between the obtained results and 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 (sinoatrial) and AV (atrioventricular) nodes and impact of an external perturbation on the sinus pacemaker.

Consider the types of arrhythmias which 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 one can conclude that certain stable phase lockings correspond to cardiac pathologies which are detected in a clinical practice. In this case among various lockings one can observe 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 inverted Wenckebach rhythms (that are similar to the direct rhythms but the roles of ventricles and atria change places) which were recorded for some patients.

The existence of wide areas of phase lockings (see Figs. 3–7) confirms it is possible to observe synchronization of two oscillators qualitatively corresponding to some types of cardiac arrhythmias. The phase diagram makes possible to determine the type of synchronization corresponding to interaction parameters a, γ, ε and δ. Moreover, the phase pictures indicate that as the nonlinearity increases (i.e. at growing γ) the areas with various phase lockings start to overlap. The knowledge of such regions, predicted by the present model, is necessary to operate the system dynamics. In particular, removing the system from an undesirable mode of synchronization to an appropriate state by the external action may be of crucial importance for applications.

7. Conclusion

In the present study a quite general model of two nonlinear interacting impulse oscillatory systems is elaborated. On the basis of this model it is possible to predict certain types of cardiac arrhythmias. The constructed model is a universal one, in the sense that its properties do not depend on the chosen interaction type, i.e. on the form of phase response curve. Taking into account the refractory time the phase locking regions of the polynomial maps (which describe a nonlinear oscillator under the permanent inputs), are investigated. It is found that the nonvanishing refractory time causes the extension of the phase locking areas, significant splitting and overlap of their tails. Moreover, the phase locking areas shrink and tend to the vertical lines as the refractory time tends to one.

The detailed analysis of the phase diagram of the system with two bidirectionally interacting oscillators in the (γ, a)-space shows that besides the splitting of the central tongues there is an overlap of the main regions of synchronization, which corresponds to various types of cardiac arrhythmias. This bistability is observed even for *small enough* stimulus amplitude. The increase of refractory time leads to the distortion in the forms of main tongues and disappearance of the splitting areas. For sufficiently large values of the first stimulus ε a very complicated picture is observed, where the phase locking areas are interwoven with each other.

Another important property of the suggested model is that 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 quite small). If the coupling lacks (ε, $\gamma \to 0$), however, this would correspond only to the complex dynamics (quasiperiodic or chaotic).

The obtained results make possible to predict the dynamics of oscillatory systems, depending on the initial phase difference, on the type of interaction and its strength. Moreover, using the above approach one can develop a quite general theory of interacting oscillators under a certain periodic perturbation. In this case the knowledge of multistability areas would be helpful to stabilize the system dynamics and return the cardiac tissue to the required type of behavior.

References

Biktashev, V. N. & Holden, A. V. [1998] "Reentrant waves and their elimination in a model of mammalian ventricular tissue," *Chaos* **8**, 48–56.

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

Courtemanche, M., Glass, L., Belair, J., Scagliotti, D. & Gordon, D. [1989] "A circle map in a human heart," *Physica* **D49**, 299–310.

Cytrynbaum, E. & Keener, J. P. [2002] "Stability conditions for the traveling pulse: Modifying the restitution hypothesis," *Chaos* **12**, 788–799.

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* **D7**, 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, Yo., Hall, K., Talajie, M. & Nattel, S. [2002] "Predicting the entrainment of re-entrant cardiac waves using phase resetting curves," *Phys. Rev.* **E65**, 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 Scientific, Singapore), pp. 248–264.

Goldberger, A. L. [1990] "Nonlinear dynamics, fractals and chaos: Applications to cardiac electrophysiology," *Ann. Biomed. Eng.* **18**, 195–198.

Guevara, M. R. & Glass, L. [1982] "Phase locking, period doubling bifurcations and chaos in a mathematical model of a periodically driven oscillator: A theory for the entrainment of biological oscillators and the generation of cardiac dysrhythmias," *J. Math. Biol.* **14**, 1–23.

He, Y., Chi, R. & He, N. [1992] "Lyapunov exponents of the circle map in human hearts," *Phys. Lett.* **A170**, 29–32.

Honerkamp, J. [1983] "The heart as a system of coupled nonlinear oscillators," *J. Math. Biol.* **18**, 69–88.

Hoppensteadt, F. C. & Keener, J. [1982] "Phase locking of biological clocks," *J. Math. Biol.* **15**, 339–349.

Ikeda, N., Yoshizawa, S. & Sato, T. [1983] "Difference equation model of ventricular parasystole as an interaction between cardiac pacemakers based on the phase response curve," *J. Theor. Biol.* **103**, 439–465.

Jalife, J. & Moe, G. K. [1976] "Effects of electronic potencials on pacemaker activity of canine Purkinje fibers in relation to parasistole," *Circ. Res.* **39**, 801–808.

Jalife, J., Antzelevitch, C. & Moe, G. [1982] "The case for modulated parasistole," *Pace* **5**, 911–926.

Keener, J. P. [1981] "On cardiac arrhythmias: AV conduction block," *J. Math. Biol.* **12**, 215–225.

Keener, J. P. & Glass, L. [1984] "Global bifurcations of a periodically forced oscillator," *J. Math. Biol.* **21**, 175–190.

Keener, J. P. [2000] "Propagation of waves in an excitable medium with discrete release sites," *SIAM J. Appl. Math.* **61**, 317–334.

Keith, W. L. & Rand, R. H. [1984] "1:1 and 2:1 phase entrainment in a system of two coupled limit cycle oscillators," *J. Math. Biol.* **20**, 133–152.

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

Krinsky, V. & Pumir, A. [1998] "Models of defibrillation of cardiac tissue," *Chaos* **8**, 188–203.

Lewis, T. J. & Keener, J. P. [2000] "Wave-block in excitable media due to regions of depressed excitability," *SIAM J. Appl. Math.* **61**, 293–316.

Loskutov, A. [1994] "Nonlinear dynamics and cardiac arrhythmia," *Appl. Nonlin. Dyn.* **2**, 14–25 (Russian).

Loskutov, A., Rybalko, S. D. & Zhuchkova, E. A. [2002] "Dynamics of excitable media with two interacting pacemakers," *Biophys.* **47**, 892–901.

Loskutov, A., Rybalko, S. D. & Zhuchkova, E. A. [2004] in preparation.

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

Moe, G. M., Jalife, J., Mueller, W. J. & Moe, B. [1977] "A mathematical model for parasistole and its application to clinical arrhythmias," *Circulation* **56**, 968–979.

Ostborn, P., Ohlen, G. & Wohlfart, B. [2001] "Simulated sinoatrial exit blocks explained by circle map analysis," *J. Theor. Biol.* **211**, 219–227.

Panfilov, A. V. & Keener, J. P. [1995] "Re-entry in three-dimensional FitzHugh–Nagumo medium with rotational anisotropy," *Physica* **D84**, 545–552.

Panfilov, A. V., Muller, S. C., Zykov, V. S. & Keener, J. P. [2000] "Elimination of spiral waves in cardiac tissue by multiple electrical shocks," *Phys. Rev.* **E61**, 4644–4647.

Pumir, A., Romey, G. & Krinsky, V. [1998] "Deexcitation of cardiac cells," *Biophys. J.* **74**, 2850–2861.

Qu, Z., Weiss, J. N. & Garfinkel, A. [1997] "Spatiotemporal chaos in a simulated ring of cardiac cells," *Phys. Rev. Lett.* (*USA*) **78**, 1387–1390.

Qu, Z., Weiss, J. N. & Garfinkel, A. [2000] "From local to global spatiotemporal chaos in a cardiac tissue model," *Phys. Rev.* **E61**, 727–732.

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

Signorini, M. G., Cerutti, S. & di Bernardo, D. D. [1998] "Simulation of heartbeat dynamics: A nonlinear model," *Int. J. Bifurcation and Chaos* **8**, 1725–1731.

van der Pol, B. & van der Mark, J. [1928] "The heartbeat considered as a relaxation oscillation and an electrical model of the heart," *Phil. Mag.* **6**, 763–775.

Weidmann, S. [1951] "Effects of current flow on the membrane potential of cardiac muscle," *J. Physiol.* (*London*) **115**, 227–236.

West, B. J., Goldberger, A. L., Rovner, J. & Bhargava, V. [1985] "Nonlinear dynamics of the heartbeat. I. The AV junction: Passive conduit or active oscillator?" *Physica* **D17**, 198–206.

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. [1995] *Cardiac Electrophysiology — From Cell to Bed-Side*, 2nd edition (W. B. Saunders, Philadelphia).