Synchronization properties of oscillatory ensembles under the passive elements impact

Valentin S. Petrov[1], Grigiry V. Osipov[1], Johan A.K. Suykens[2]
[1]: Department of Control Theory, Nizhny Novgorod University,
Gagarin Avenue, 23, 603950 Nizhny Novgorod, Russia
[2]: K.U. Leuven, ESAT-SCD/SISTA,
Kasteelpark Arenberg 10, B-3001 Leuven (Heverlee), Belgium
Valentin.S.Petrov@gmail.com

Abstract

In this paper we focus on the influence of passive elements the synchronization properties of ensembles of coupled nonidentical oscillators. It is demonstrated that the introduction of passive elements may lead to both an increase or decrease of the global synchronization threshold. Apart from it we show that the steady state of the passive element is a key parameter which defines how this passive element affects the synchronization properties of the oscillatory ensemble.

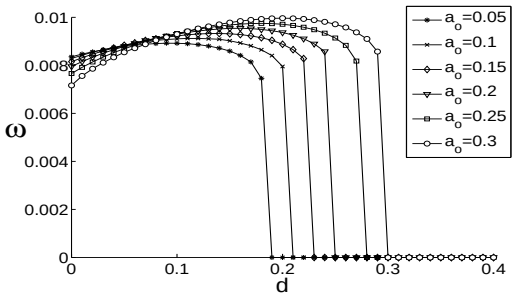

Figure 1: Dependency of the oscillation frequency ω of the oscillatory Bonhoeffer-Van der Pol element on the parameter of the unidirectional coupling with a passive element d for different values of the parameter a_o.

1 Introduction

The study of collective dynamical effects in systems of coupled elements is one of the modern problems of many branches of physics [1, 2]. Lately various kinds of collective behavior have been considered in systems with a non-homogeneous distribution of parameters [3]. However, the presence of another type of inhomogeneity is characteristic for many real systems. In [4], for example, the role of heterogeneity in the emergence of global oscillations in the initially excitable medium was discussed. Such systems consist of elements having essentially different dynamics, namely, oscillatory and/or excitable and/or passive elements. In this way, for example, the heart may be considered as a dynamical system which is an ensemble consisting of such elements [5]. The heart tissue is composed of cells of three major types: pacemaker cells (pacemakers), cardiomyocytes and fibroblasts, that from the point of view of nonlinear dynamics are oscillatory, excitable and passive elements respectively. The main difference between these certain cell types is that pacemakers are able to generate periodic oscillations of electrical action potentials while cardiomyocytes can only produce an action potential in response to the incoming stimulus. Fibroblasts, in turn, do not generate action potentials even in response to external excitation, but just relax to the steady state.

In this paper the emphasis is put on the interaction between oscillatory and passive elements. In the heart such kind of interaction is observed in the sino-atrial node that consists of pacemakers and fibroblasts. The amount of the latter cells in this region of the heart may come to 60-70% according to the physiological experiments [6]. Apart from it, the total number of fibroblasts can vary in time due to the heart tissue aging processes or various kinds of diseases. The influence of these cells on the dynamics of the sino-atrial node and the heart in general is the subject of many studies based on biological experiments as well as numerical simulations [7]. In these papers many evidences are presented indicating that the presence of fibroblasts may affect the synchronization properties of cells in the sino-atrial node, as well as deeply influence the characteristics of wave processes in the system, e.g. action potential conduction velocity. From the point of view of the heart functioning this may lead to the development of different arrhythmias. That is why the study of dynamics of mixed ensembles of oscillatory and pas-

sive elements is an important and acute task.

Firstly, the results of simulations with Bonhoeffer-Van der Pol oscillator are presented. Very often [4, 8] cells of different types are described by phenomenological Bonhoeffer-Van der Pol model with different parameters. This is the simple but usually good enough approximation because it reproduces oscillatory, excitable or passive dynamics depending on the value of parameters. And secondly, we present the results of modeling with biophysically relevant Luo-Rudy model of cardiac cell.

2 The Influence of passive elements on the synchronization properties of oscillatory ensembles

2.1 Dynamical regimes in pair: oscillatory element and passive element

In this section interaction between oscillatory and passive Bonhoeffer-Van der Pol elements is studied. Isolated oscillator is described by a system of two ordinary differential equations:

$$\begin{aligned} \dot{x} &= x - x^3/3 - y \\ \dot{y} &= \varepsilon(x + a - y). \end{aligned} \qquad (1)$$

In application to biological systems, x in (1) denotes the action potential and y plays the role of the variables describing the ionic currents flowing through the membrane of a cell. The parameter a is the control parameter. By varying this parameter one can observe different dynamical regimes of isolated elements: oscillatory, excitable and passive [8]. This feature allows us to use this system as a simplified version of biological cell model applicable to study the main dynamical properties. For parameter range $(a < -8/3) \cup (a > 8/3)$ the system is passive. When $-1/3 < a < 1/3$ the system is in oscillatory regime. For all other values of parameter a the system (1) exhibits excitable behavior.

Let us now consider a system consisting of two unidirectionally coupled oscillatory and passive elements:

$$\begin{aligned} \dot{x}_o &= x_o - x_o^3/3 - y_o + d(x_o - x_p) \\ \dot{y}_o &= \varepsilon(x_o + a_o - y_o) \\ \dot{x}_p &= x_p - x_p^3/3 - y_p \\ \dot{y}_p &= \varepsilon(x_p + a_p - y_p). \end{aligned} \qquad (2)$$

The parameters a_o and a_p in (2) were chosen in such a way that the first and the second element were in oscillatory and passive regime, respectively. The individual frequency of the oscillatory element depends on value of a_o. The term $d(x_o - x_p)$ describes the unidirectional influence of the passive element on the oscillatory one.

Fig. 1 illustrates the dependency of the oscillation frequency ω of the first Bonhoeffer-Van der Pol element on the parameter of unidirectional coupling with the passive element d for different values of parameter a_o corresponding to different individual frequencies of the oscillator.

It is clearly seen that every two curves in Fig. 1 have an intersection point. That means that for two oscillatory Bonhoeffer-Van der Pol elements with initially different individual frequencies there exists such a coupling value d with the passive element, when the effective frequency mismatch will equal zero. With the further growth of d this effective frequency mismatch increases. Thus, the influence of a passive element changes the frequency of an oscillatory element and therefore affects the synchronization properties in such systems. Besides, it is worth saying that for some critical coupling value d in this system, the effect of oscillatory death is observed, i.e. vanishing of oscillations in the initially oscillatory element.

2.2 Synchronization of two oscillatory Bonhoeffer-Van der Pol elements under the influence of a passive element

Let us now proceed to the study of the influence of a passive element on the threshold and frequency of synchronization. Consider the system of three coupled Bonhoeffer-Van der Pol elements:

$$\begin{aligned} \dot{x}_{o1} &= x_{o1} - x_{o1}^3/3 - y_{o1} + d_1(x_{o2} - x_{o1}) + d_2(x_p - x_{o1}) \\ \dot{y}_{o1} &= \varepsilon(x_{o1} + a_{o1} - y_{o1}) \\ \dot{x}_{o2} &= x_{o2} - x_{o2}^3/3 - y_{o2} + d_1(x_{o1} - x_{o2}) + d_2(x_p - x_{o2}) \\ \dot{y}_{o2} &= \varepsilon(x_{o2} + a_{o2} - y_{o2}) \\ \dot{x}_p &= x_p - x_p^3/3 - y_p \\ \dot{y}_p &= \varepsilon(x_p + a_p - y_p). \end{aligned}$$

Let the first two elements be oscillatory with different individual frequencies. To be more concrete let us consider $a_{o1} = 0.31$, $a_{o2} = 0.25$. Coefficients d_1 and d_2 describe the interaction between the oscillatory elements and the unidirectional impact from the passive element on them, respectively. As far as in this situation the limit case of unidirectional coupling is observed, the passive element is in its steady state $x_p = x_p^*$. Parameter a_p was chosen in simulations such that $x_p^* = 2.5$.

Fig. 2(a) demonstrates the synchronization threshold d_1^s tuning coupling with passive element d_2. It is seen that with an increasing influence of the passive element on the oscillatory ones, a significant lowering of the synchronization threshold d_1^s takes place. At $d_1^s \approx 0.11$ it almost reaches zero. Then the value of the synchronization threshold starts to increase back again and, starting from a certain value of $d_2 \approx 0.25$,

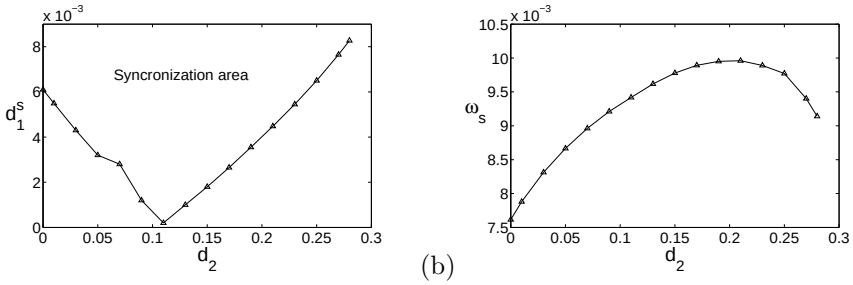

Figure 2: Influence of a passive element on the synchronization properties of two coupled Bonhoeffer-Van der Pol oscillators: (a) dependency of the synchronization threshold d_1^s on coupling with a passive element d_2; (b) dependency of the synchronization frequency on the coupling parameter d_2.

even exceeds the initial value that was observed in the case of no coupling with passive element ($d_2 = 0$). Hence the introduction of a passive element may lead to both a decrease and increase of the synchronization threshold due to a decrease or increase of the effective frequency mismatch between the oscillatory elements, respectively. Notice that when the influence of the passive element is too large ($d_2 \gtrsim 0.28$) then the effect of oscillation death takes place.

Fig. 2(b) illustrates the dependency of the synchronization frequency ω_s on the parameter d_2. Comparing this curve with the ones in Fig. 1 one can state that the synchronization frequency increases with growth of d_2 for almost the same values of d_2 when the frequency of the single element increases with enlarging the coupling to the passive element and vice versa. In other words the character of the curve in Fig. 2(b) is defined mainly by the kind of dependency of the frequency of the single oscillatory element on the coupling with the passive element (Fig. 1). The analytical description of these effects is given in the following section.

3 Synchronization of cardiomyocytes under the fibroblasts impact

In the current and all following sections, we present results obtained using the model of cardiac cell dynamics. In the introduction it has already been noticed that the heart consists of cells of different types. Among them one can single out oscillatory cardiac cells (pacemakers) and passive cardiac cells (fibroblasts). Further, for convenience in description, the biological terms pacemaker (fibroblast) and nonlinear dynamics oscillatory (passive) cell are considered as synonyms.

3.1 Cardiac cells models

In the numerical experiments, biologically relevant models describing electrical activity of cardiac cells were used. As a model of oscillatory cardiac cell (pacemaker) we use the Luo-Rudy phase 1 model [9]. This is the Hodgkin-Huxley type model consisting of eight nonlinear differential equations. The first equation describes the action potential V rate of change:

$$C_m \frac{dV}{dt} = -(I_{ion} + I^{ext}),$$

where V denotes the cell membrane voltage measured in millivolts, $C_m = 1\ \mu\text{F/cm}^2$ is the membrane capacity. The time unit of the model is 1 millisecond. I^{ext} is a constant external electrical stimulus and I_{ion} is a sum of six ionic currents flowing through the membrane:

$$I_{ion} = I_{Na} + I_{si} + I_K + I_{K1} + I_{Kp} + I_b,$$

where I_{Na} is a sodium current, I_{si} slow inward calcium current, I_K potassium current, I_{K1} stationary potassium current, I_{Kp} plateau potassium current and I_b a background current. These currents are measured in $\mu\text{A/cm}^2$ and defined by:

$$\begin{array}{rcllll} I_{Na} & = & G_{Na} & \cdot & m^3hj & \cdot & (V - E_{Na}) \\ I_{si} & = & G_{si} & \cdot & df & \cdot & (V - E_{si}(V,c)) \\ I_K & = & G_K & \cdot & xx_i(V) & \cdot & (V - E_K) \\ I_{K_1} & = & G_{K1} & \cdot & k_{1i}(V) & \cdot & (V - E_{K1}) \\ I_{K_p} & = & G_{Kp} & \cdot & k_p(V) & \cdot & (V - E_{K1}) \\ I_B & = & G_b & \cdot & (V - E_b) & & \end{array}$$

Here G_q and E_q for $q \in \{Na, si, K, K1, Kp, b\}$ denote respectively the maximal conductance and the reversal potential of the corresponding ionic current. Each of the gating variables $g_i \in \{m, h, j, d, f, x\}$, $i = 1, \ldots, 6$ is described by the ordinary differential equation as follows:

$$\dot{g}_i = \alpha_{g_i}(V)(1 - g_i) - \beta_{g_i}(V) g_i.$$

Nonlinear functions $\alpha_{g_i}(V)$ and $\beta_{g_i}(V)$ as well as $E_{si}(V, c)$, $x_i(V)$, $K_{1i}(V)$, $K_p(V)$ are fitted to the experimental data [9]. The dynamics of the external concentration of calcium ions is given by the first order differential equation:

$$\dot{c} = 10^{-4} I_{si}(V, d, f, c) + 0.07(10^{-4} - c).$$

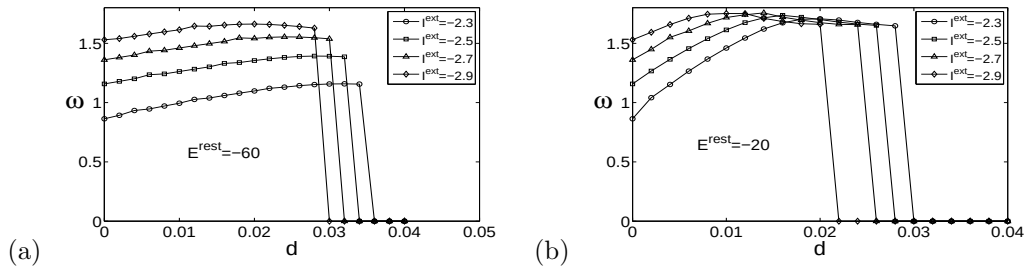

Figure 3: The curves of dependency of the single pacemaker frequency on the coupling with fibroblast for the value of resting potential of fibroblast $E^{rest} = -60mV$ (a) and $E^{rest} = -20mV$ (b).

In this system we emphasize a control parameter I^{ext}. The variation of this parameter allows to change the dynamics of the isolated Luo-Rudy element from the excitable regime to the oscillatory and vice versa. If $-3.8 \lesssim I_{ext} \lesssim -2.21$ the system is oscillatory otherwise it is excitable. Moreover different values of I_{ext} correspond to different individual frequencies of the oscillatory cell.

As a model of fibroblast we use the Kohl model of a passive cardiac cell [10]. This system is described by the simple first order linear differential equation:

$$\dot{V}_F = -\frac{1}{C_F} G_F (V_F - E^{rest}).$$

The key parameter here is E^{rest} which is the resting potential of fibroblast that may vary in the range from -60 to -10mV.

3.2 Fibroblast impact on the oscillatory cardiac cell dynamics

As demonstrated in section 2.1 and 2.2 using the Bonhoeffer-Van der Pol model, it is possible to judge qualitatively the influence of a passive element on the synchronization properties in oscillatory ensembles from the character of the dependency of the single oscillatory element frequency on the coupling with a passive element (Fig. 1). So, in order to understand if it is possible to obtain effects like those that were observed in sections 2.1 and 2.2, but in case of coupled cardiac cells, the dependencies of frequency of single pacemaker on the coupling with fibroblast d were obtained. Fig. 3(a,b) shows the curves for the oscillatory Luo-Rudy element under unidirectional fibroblast influence with $E^{rest} = -60mV$ (a) and $E^{rest} = -20mV$ (b) for different values of parameter I^{ext}, i.e. for different individual frequencies of pacemaker. It is clearly seen that introduction of fibroblast with any resting potential within the range $E^{rest} \in [-60, -20]mV$ leads to a decrease of the effective frequency mismatch and increase of pacemaker frequency. The value of E^{rest} in this case affects just the degree of the effects development.

Thus, analyzing the dependencies in Fig. 3 one can suppose that it is possible to obtain synchronization of two different oscillatory cardiac cells due to the fibroblast impact. The numerical simulations results confirming this fact are presented in the next section.

3.3 Synchronization of two pacemakers due to the fibroblast

In this section the results of numerical simulations of the system of three coupled elements are presented. Consider two coupled pacemakers under the fibroblast influence. Let us also introduce three new parameters d_{pp}, d_{fp}, d_{pf} denoting respectively (i) symmetrical diffusive coupling between oscillatory elements, (ii) the coupling directed from fibroblast to pacemakers, (iii) the coupling directed from pacemaker to fibroblast.

Fig. 4(a) shows the dependency of frequencies of two pacemakers on coupling with fibroblast d_{fp} for resting potential of fibroblast $E^{rest} = -30mV$ and coupling parameters $d_{pp} = 0.0005$, $d_{pf} = 0$. Hence, we deal with the limit case of unidirectional coupling. The control parameters defining individual frequencies are: $I_1^{ext} = -2.3$, $I_2^{ext} = -2.4$. It is seen from the Fig. 4 that increase of coupling from fibroblasts leads to convergence of individual pacemakers frequencies and for the chosen parameters the regime of synchronization of two pacemakers sets in starting from some critical value d_{fp}. With further increase of d_{fp} the effect of oscillation death also takes place. Apart from it, Fig. 4(c) shows the same dependency as one in Fig. 4(a) but for the value of fibroblast resting potential $E^{rest} = -60mV$. In these case the regime of synchronization between pacemakers can not be achieved because influence of fibroblast with $E^{rest} = -60mV$ does not provide convergence of individual frequencies of pacemakers. This fact confirms that steady state of passive element (resting potential of fibroblast) is an important parameter defining whether it is possible to obtain synchronization or not. Thus, the results of numerical simulations support the preliminary qualitative analysis given in section 3.2.

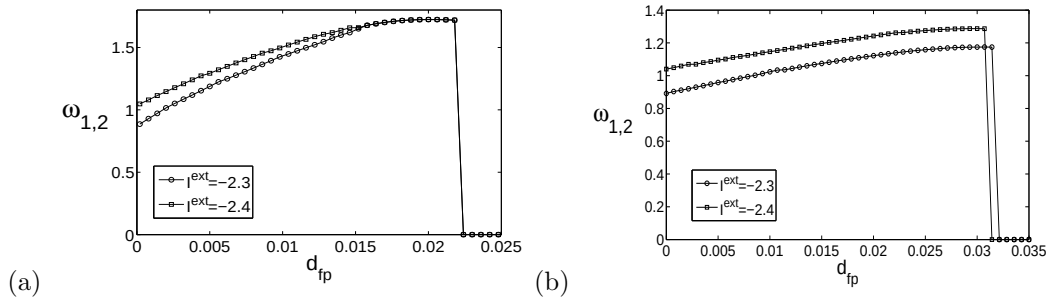

Figure 4: The dependency of frequencies of two pacemakers on the coupling with fibroblast for the fibroblast resting potential is $E^{rest} = -30mV$ (a) and $E^{rest} = -60mV$ (b).

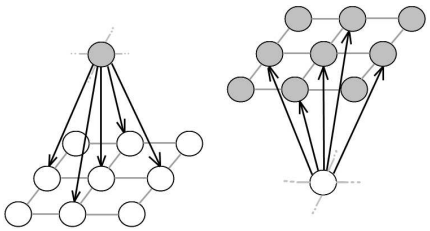

Figure 5: The topology of the studied system: two two-dimensional lattices of 200x200 elements located one above the other. White colored circles denote pacemakers, gray colored circles denote fibroblasts.

3.4 Synchronization in large oscillatory ensembles

As far as many real systems are distributed ensembles of a large number of coupled elements, in order to demonstrate the generality of the effects obtained earlier, we performed a set of numerical experiments with the systems composed of a large number of oscillators. The concrete topology of the studied system is shown in Fig. 5.

This topology is two two-dimensional lattices of 200x200 elements located one above the other. The lower lattice consists of oscillatory Luo-Rudy elements with a random distribution for the control parameter $I_i^{ext} \in [-2.4, -2.3]$ defining individual frequencies of pacemakers. The upper lattice is composed of identical fibroblasts with resting potential $E^{rest} = -40mV$. The coupling between the elements of each lattice is the diffusive coupling with four nearest neighbors. The coupling between lattices is organized in such a way that each element of one lattice is coupled with five nearest elements of the other lattice (Fig. 5). The boundary conditions in each lattice are zero-flux. This topology is an approximation to the real sino-atrial node consisting of mixed oscillatory and passive cells. Like it was done earlier in section 3.3 let us introduce coupling coefficients $d_{pp} = 0.0001$, $d_{pf} = 0$. The coefficient d_{fp} is varied. Let us also introduce a new coefficient $d_{ff} = 0.3$ describing the coupling strength between fibroblasts in the upper lattice. In the numerical experiments, for each value of parameter d_{fp}, average oscillation frequencies of all oscillatory elements of the lower lattice were calculated.

The results of these calculations are presented in Fig. 6. Here the ordinate axis shows the frequencies of each oscillatory element in the lower lattice and absciss axis shows the coupling of these elements with fibroblasts d_{fp}. The three insets in Fig. 6 illustrate the frequency distribution of the number of oscillatory elements $N_\omega(\omega)$ for three fixed values $d_{fp} \in \{0; 0.0006; 0.005\}$. In other words $N_\omega(\omega^*)$ is the number of pacemakers oscillating with the frequency ω^*. It is seen from the figure that initially for $d_{fp} = 0$ the oscillation frequencies in the lower lattice are distributed randomly and uniformly in the range from 0.85 up to 1.03 Hz (see corresponding inset in Fig. 6). This indicates that there is no synchronization in the system. With increase of fibroblast impact d_{fp} the range of the observed frequencies significantly narrows and for $d_{fp} = 0.0006$ is about $[0.99, 1.11]Hz$. At the same time the significant peak appears in the distribution N_ω (inset $d_{fp} = 0.0006$ in Fig. 6). Thus more elements become to oscillate with the same frequency indicating that synchronization starts to set in. Finally, for high enough values of d_{fp} the regime of complete synchronization takes place in the system. So, for example, for $d_{fp} = 0.005$ one can see that the distribution N_ω is nothing but narrow and highly peaked, corresponding to a synchronization regime. Notice that with increase of the impact from fibroblasts on pacemakers the average frequency of oscillations also increases as it was in the experiments in section 3.3. Apart from it, like in the previous sections the effect of oscillatory death can also be observed here starting from the value $d \approx 0.005$. Thus, in this section we demonstrated the possibility of the synchronization regime onset in the large oscillatory ensemble due to the coupling of oscillatory elements with passive ones.

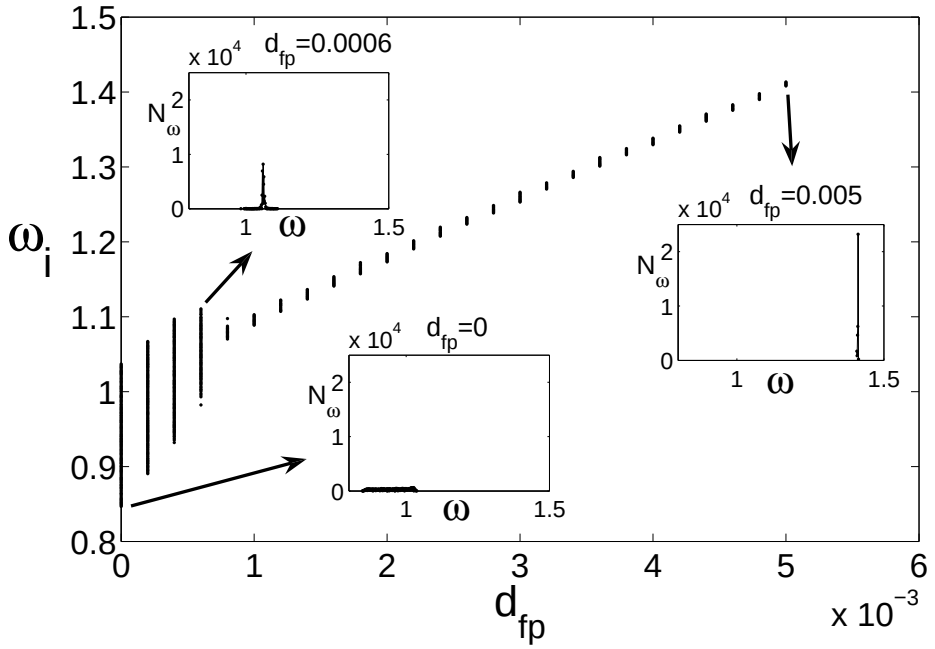

Figure 6: Dependency of the frequency of every oscillatory element in the lower lattice on coupling with fibroblasts d_{fp}. Three insets present distributions of the number of oscillatory elements on frequencies $N_\omega(\omega)$ for three fixed values $d_{fp} \in \{0, 0.0006, 0.005\}$. One can observe that synchronization sets in with increase of d_{fp}.

In order to compare the obtained results with real biological experiments one may turn, for example, to the paper [8]. There the results of real biological experiments with cardiac cells cultures composed of pacemakers and fibroblasts are presented. It is shown in [8] that with increase of coupling of pacemakers with fibroblasts in the culture of oscillatory cardiac cells the regime of synchronization sets in, moreover it is accompanied with the growth of the average oscillation frequency in the system. Thus, the results obtained in numerical and analytical studies find their confirmation in nature.

4 Conlusions

The influence of passive elements on the synchronization properties of oscillatory ensembles was studied. The results were discussed in the context of cardiac cell dynamics and compared with physiological data. It was demonstrated that depending on the value of steady state of the passive element (the resting potential of fibroblast) one can observe decrease or increase of synchronization threshold in the oscillatory ensemble with growth of passive elements impact.

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