



Official English translation

The impact of electrical couplings on the dynamics of the ensemble of inhibitory coupled neuron-like elements

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Topic. The phenomenological model of ensemble of three neurons coupled by chemical (synaptic) and electrical couplings is studied. Single neuron is modeled by van der Pol oscillator. **The aim** of the work is to study the influence of coupling strength and frequency detuning between elements in the case of regime of sequential activity that is observed in ensemble of neuron-like elements with chemical inhibitory couplings. **Method.** The research is made with usage of analytical methods of nonlinear dynamics and computer modeling. **Results.** It was shown that adding of arbitrarily small electrical coupling to ensemble of van der Pol oscillators with chemical synaptic inhibitory couplings leads to the destruction of a stable heteroclinic contour between saddle limit cycles. It was also shown that nonidentity of elements (while electrical couplings are absent) do not lead to destruction of heteroclinic contour. This situation, in general, is not typical for such systems. **Discussion.** We suggest to consider the ensemble of elements as phenomenological model of neuronal network. Such approach has the following advantage: it is possible to study low-dimensional neuronal models and reproduce the main effects that are observed in more complex models, for example, in biologically realistic model of Hodgkin–Huxley and also in real experiments.

Key words: neuron, chemical coupling, electrical coupling, van der Pol oscillator, heteroclinic contour.

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Introduction

In the last years the new area of medicine – bioelectrical medicine – is actively developing [1]. It is based on electromagnetic influence upon human organism instead of chemical (pharmacological) one. The target of electrical effects are mainly nerve fibers, while the signals are delivered to them using implants or wearable devices. The reasons

for such interest to this area are associated with the rapid improvement of technology (among the factors we can note the emergence of biocompatible soft electronics, rapid growth of computer performance, small size of modern devices [2]) and with limited pharmacology success in the treatment of neurological disorders. In this regard, it is also worth noting that in the nearest decades the problem of treatment of diseases of the nervous system will become more and more actual which is associated with the aging of the population and the growing stress in the modern world. This is why some scientists and companies prefer to bet on bioelectric medicine. As some last works show [1,3], this approach can be successful not for treatment of diseases of the nervous system, but also for cardiovascular, inflammatory, metabolic and endocrine diseases, which is confirmed by animal testing and clinical practice. The nervous system is the main regulator of internal processes in human organism, namely: thinking, digestion, motor activity, etc. [4] In this regard, interest is growing in the study of electrical couplings in the nervous system and their role in generation of different regimes of neuron activity and mechanisms of their occurrence and suppression. To develop new medical technologies and introduce them in real treatment we need more deep understanding how peripheral nervous system is involved in the regulation of various processes in human organism.

The aim of this work is investigation of the influence of electrical couplings and of elements nonidentity upon the regime of sequential burst activity in the model of neural ensemble with chemical (synaptic) couplings. For this, we consider a phenomenological model of minimal ensemble containing three neurons with the named type of connections. Every neuron is modelled by van der Pol oscillator with different natural frequencies. Earlier in the work [5] an ensemble of identical van der Pol oscillators with only chemical inhibitory couplings have been studied in detail. In particular, the various dynamic modes that are observed in such ensemble with the change of the parameters of the forces of chemical couplings, as well as the scenarios of their appearance and extinction, have been studied. In the following works [6–8] we have shown that the studied types of activity, the mathematical images, on which they are based, and the scenarios of transition from one activity type to another are universal for a whole class of systems. Taking into account the influence of electrical couplings and the effect of nonidentity of the elements of the neuron ensemble, allows to obtain results, which by their characteristics are qualitatively similar to what is observed in real biological experiments [9]. This work is focused on the investigation of evolution of the regime of sequential activity, because it is one of most important from point of view of neurodynamics.

1. Model

Ensemble of three nonidentical neuron-like elements, coupled by mutual chemical (synaptic) inhibitory and electrical couplings, is modelled by a system of three van der Pol oscillators:

$$\begin{cases} \ddot{x}_j - \mu[\lambda(x_j, \dot{x}_j) - x_j^2]\dot{x}_j + \omega_j^2 x_j + d(x_{j+1} - 2x_j + x_{j-1}) = 0, \\ j = 1, 2, 3, \end{cases} \quad (1)$$

Here x_j phenomenologically describe the change of membrane potential of j -th neuron-like element. The electrical couplings between elements are described by the expressions

$d(x_{j+1} - 2x_j + x_{j-1})$, where parameter d is the coefficients of electrical coupling. Chemical (synaptical) inhibitory interaction between neuron-like elements is phenomenologically described in the same way as it was done for the other elements of an ensemble in the work [5] with the use of the parameter λ , depending on the values of the membrane potential and the rate of its change, as follows:

$$\lambda(x_j, \dot{x}_j) = 1 - g_1 F\left(\sqrt{x_{j+1}^2 + \dot{x}_{j+1}^2}\right) - g_2 F\left(\sqrt{x_{j-1}^2 + \dot{x}_{j-1}^2}\right). \quad (2)$$

Here g_1 and g_2 and the inhibitory couplings strengths directed clockwise and counter-clockwise, respectively (Fig. 1); $F(z)$ is the activation function with threshold value z_0 , phenomenologically describing the principle of synaptic coupling

$$F(z) = \frac{1}{1 + \exp(-k(z - z_0))}. \quad (3)$$

With the values of the parameters $k = 100$ and z_0 chosen for the simulation, the nonlinear function $F(z)$ is close to stepwise, but wherein smooth. When the argument achieves the threshold value, which corresponds to the case when the presynaptical element generates oscillations with amplitude above some threshold, function $F(z)$ grows spasmodically from 0 to 1 and with further increasing of argument value remains equal to 1. This, in turn, leads to that, in the presence of enough strong coupling, the presynaptic neuron-like element with the help of generating of high-amplitude oscillations, suppresses the activity of the postsynaptic neuron-like element. It is known that in real experiments the registered frequencies differ for different neurons and clusters of neurons. This allows to add parameter Δ to the system (1) (where $\omega_2 = \omega_1 - \Delta$, $\omega_3 = \omega_1 + \Delta$). Parameter $\mu \ll 1$ defines the dynamics of single element, in which, in the absence of coupling, quasi-harmonic fluctuations are observed [10].

In the work [5] we have shown that the regime of sequential bursting activity is observed in the system with $d = 0$ and $\Delta = 0$ in the case of strong asymmetry of chemical coupling. For investigation of influence of electrical coupling and elements frequency detuning upon the evolution of sequential activity regime, we have built (Fig. 2) the charts of the two maximal Lyapunov exponents on the parameter plane (d, Δ) . For calculation of Lyapunov exponents we have used the well-known Benettin algorithm [11, 12], described, for example, in [13]. Wherein for calculation of the two maximal exponents, besides the basic trajectory we also have used two auxiliary trajectories of the same dynamical system, with the initial conditions close of the basic trajectory, and the time evolution of the distance between these trajectories has been tracked. In the chart (see Fig. 2) there are the marked areas I , corresponding to positive maximal Lyapunov exponent $\Lambda_1 > 0$,

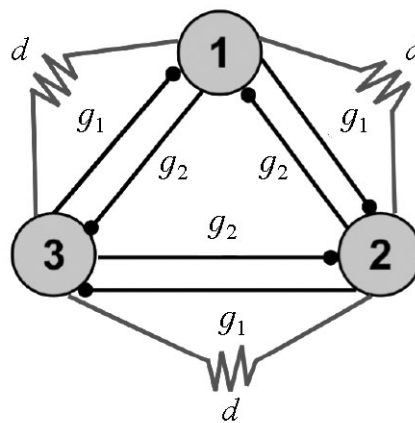


Fig. 1. The topology of chemical (synaptic) couplings g_1 and g_2 and electrical couplings d in the ensemble of neuron-like elements described by system (1)

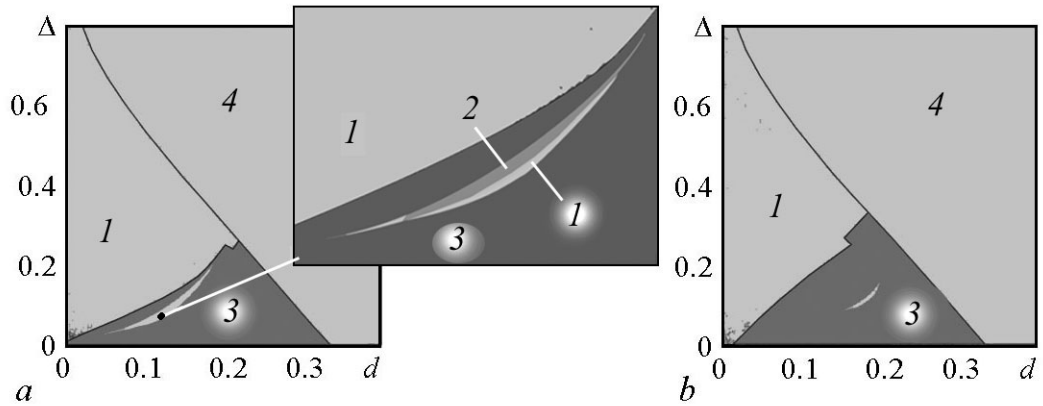


Fig. 2. Charts of the largest Lyapunov exponent of the system. $a - (g_1, g_2) = (0, 5)$; $b - (g_1, g_2) = (5, 0)$. 1 corresponds to the regions, where $\Lambda_1 > 0$; 2 - $\Lambda_1 = \Lambda_2 = 0$; 3 - $\Lambda_1 = 0$; regions 4 corresponds to the case, when trajectories of the system go to the infinity

which shows the presence of chaos which occurs at destruction of stable heteroclinic contour (observed in the system with $d = 0$). The absolute value of Λ_1 in this case, as a rule, is not very large. The area 2 (see fragment of Fig. 2, a) corresponds to $\Lambda_1 = \Lambda_2 = 0$. In the phase space of the system in this case one can observe a torus. The areas 3 refers to periodical dynamics. As one can see from the figure, in both cases the threshold relation between d and Δ , above which the trajectories of the system begin to go to infinity (areas 4). This fact is in good agreement with the data of biological experiments, which show that in real biological systems it is impossible to increase the coupling strength infinitely. In the framework of this limitation for various ratios between d and Δ the system demonstrates periodical, quasi-periodical and chaotic regimes which were not observed in the absence of electrical communication and frequency detuning.

2. Evolution of the sequential activity regime

Let us recall that the regime of sequential burst activity is observed in the system with a strong asymmetry of couplings [5]. For example, when the value of coupling parameter g_1 is essentially larger than g_2 , which is small or equal to zero. The main peculiarity of this regime is exponential growth of the bursting. The mathematical image of the sequential activity in the phase space of the system (1) is the stable heteroclinic contour arising between saddle limit cycles. A phase point, asymptotically approaching to the heteroclinic contour, stays for a longer time in the neighborhood of saddle limit cycles. This means increasing of the period of activity of the ensemble elements.

Let us make an analytical study how this contour evolves with adding of electrical coupling $d \neq 0$ and nonidentity of elements, i.e. with $\Delta \neq 0$. Let's take $\omega_1 = 1$, $d = \mu d_1$, $\Delta = \mu \Delta_1$. Rewrite the system of equations (1) as follows:

$$\begin{cases} \ddot{x}_1 + x_1 = \mu[\lambda(x_1, \dot{x}_1) - x_1^2]\dot{x}_1 - \mu d_1(x_2 - 2x_1 + x_3), \\ \ddot{x}_2 + (1 + \mu \Delta_1)x_2 = \mu[\lambda(x_2, \dot{x}_2) - x_2^2]\dot{x}_2 - \mu d_1(x_1 - 2x_2 + x_3), \\ \ddot{x}_3 + (1 - \mu \Delta_1)x_3 = \mu[\lambda(x_3, \dot{x}_3) - x_3^2]\dot{x}_3 - \mu d_1(x_1 - 2x_3 + x_2). \end{cases} \quad (4)$$

Applying the method of van der Pol [14] and averaging over period $T = 2\pi$, we obtain an equation for complex amplitudes z_1, z_2 и z_3

$$\begin{cases} \dot{z}_1 = [\lambda(z_1, \dot{z}_1) - z_1 \bar{z}_1]z_1 + id_1(z_2 - 2z_1 + z_3), \\ \dot{z}_2 = [\lambda(z_2, \dot{z}_2) - z_2 \bar{z}_2]z_2 + id_1(z_1 - 2z_2 + z_3) + i\Delta_1 z_2, \\ \dot{z}_3 = [\lambda(z_3, \dot{z}_3) - z_3 \bar{z}_3]z_3 + id_1(z_1 - 2z_3 + z_2) - i\Delta_1 z_3. \end{cases} \quad (5)$$

Let us transit to real amplitude and phases using the following equations:

$$\begin{cases} z_1 = \frac{R_1}{2} e^{-i\phi_1}, \\ z_2 = \frac{R_2}{2} e^{-i\phi_2}, \\ z_3 = \frac{R_3}{2} e^{-i\phi_3}, \end{cases} \quad (6)$$

as the result we obtain the following system:

$$\begin{cases} \dot{R}_1 = \left[\lambda(R_1, \dot{R}_1) - \frac{R_1^2}{4} \right] R_1 - R_2 d_1 \sin(\phi_1 - \phi_2) - R_3 d_1 \sin(\phi_1 - \phi_3), \\ \dot{R}_2 = \left[\lambda(R_2, \dot{R}_2) - \frac{R_2^2}{4} \right] R_2 - R_1 d_1 \sin(\phi_2 - \phi_1) - R_3 d_1 \sin(\phi_2 - \phi_3), \\ \dot{R}_3 = \left[\lambda(R_3, \dot{R}_3) - \frac{R_3^2}{4} \right] R_3 - R_1 d_1 \sin(\phi_3 - \phi_1) - R_2 d_1 \sin(\phi_3 - \phi_2), \\ R_1 \dot{\phi}_1 = 2d_1 R_1 - R_2 d_1 \cos(\phi_1 - \phi_2) - R_3 d_1 \cos(\phi_1 - \phi_3), \\ R_2 \dot{\phi}_2 = 2d_1 R_2 - \Delta_1 R_2 - R_1 d_1 \cos(\phi_2 - \phi_1) - R_3 d_1 \cos(\phi_2 - \phi_3), \\ R_3 \dot{\phi}_3 = 2d_1 R_3 + \Delta_1 R_3 - R_2 d_1 \cos(\phi_3 - \phi_2) - R_1 d_1 \cos(\phi_3 - \phi_1). \end{cases} \quad (7)$$

In the absence of electrical coupling, i.e. when $d = 0$, the system (7) divides into two subsystems. The first subsystem contains equations for averaged amplitudes

$$\begin{cases} \dot{R}_1 = \left[\lambda(R_1, \dot{R}_1) - \frac{R_1^2}{4} \right] R_1, \\ \dot{R}_2 = \left[\lambda(R_2, \dot{R}_2) - \frac{R_2^2}{4} \right] R_2, \\ \dot{R}_3 = \left[\lambda(R_3, \dot{R}_3) - \frac{R_3^2}{4} \right] R_3. \end{cases} \quad (8)$$

The second subsystem contains phase equations

$$\begin{cases} \dot{\phi}_1 = 0, \\ \dot{\phi}_2 = -\Delta_1, \\ \dot{\phi}_3 = +\Delta_1. \end{cases} \quad (9)$$

Analytical study of the subsystem (8) has been made earlier in the work [5]. The system (8) has been reviewed consistently on invariant planes $R_1 = 0$, $R_2 = 0$ и $R_3 = 0$. In particular, for the case of asymmetric coupling it has been shown that there are three equilibrium states on every invariant planes [unstable node (0,0), saddle (2,0) and stable node (0,2)]. Wherein the equilibrium states (2,0) and (0,2) are connected with stable heteroclinic trajectory. These three heteroclinic trajectories, found on every of the phase planes (R_1, R_2) , (R_1, R_3) и (R_2, R_3) , make a stable heteroclinic cycle of the system (8). From the equations (8)–(9) it is easy to see that this result remains true also for nonidentical elements (with non-zero frequency detuning $\Delta_1 \neq 0$), nonetheless the frequencies of the elements differ in this case. We must mark that heteroclinic contours usually appear in symmetrical systems and are destroyed when symmetry disappears. In this case the non-identity of the elements breaks the symmetry, but the heteroclinic contour exists because the amplitude dynamics defined by the subsystem (8), doesn't depend on the phases given by the equations (9).

Let's study how the appearance of electrical coupling acts on the stable heteroclinic cycle. For this we consider the system (7) on the plane $R_2 = 0$, where it is converted to the following form, including a system of ordinary differential equations of the fourth order

$$\begin{cases} \dot{R}_1 = \left[\lambda(R_1, \dot{R}_1) - \frac{R_1^2}{4} \right] R_1 - R_3 d_1 \sin(\phi_1 - \phi_3), \\ \dot{R}_3 = \left[\lambda(R_3, \dot{R}_3) - \frac{R_3^2}{4} \right] R_3 + R_1 d_1 \sin(\phi_1 - \phi_3), \\ R_1 \dot{\phi}_1 = 2d_1 R_1 - R_3 d_1 \cos(\phi_1 - \phi_3), \\ R_3 \dot{\phi}_3 = 2d_1 R_3 - \Delta_1 R_3 - R_1 d_1 \cos(\phi_1 - \phi_3) \end{cases} \quad (10)$$

and two equalities

$$\begin{cases} R_1 \sin(\phi_1 - \phi_2) = R_3 \sin(\phi_2 - \phi_3), \\ R_1 \cos(\phi_1 - \phi_2) = -R_3 \cos(\phi_2 - \phi_3). \end{cases} \quad (11)$$

From the last two equations (11) we obtain that $\phi_1 = \phi_3$. Thus the system (10) converts to the following form, including a system of ordinary differential equations of the second order

$$\begin{cases} \dot{R}_1 = \left[\lambda(R_1, \dot{R}_1) - \frac{R_1^2}{4} \right] R_1, \\ \dot{R}_3 = \left[\lambda(R_3, \dot{R}_3) - \frac{R_3^2}{4} \right] R_3 \end{cases} \quad (12)$$

And an equality

$$R_3^2 d_1 = \Delta_1 R_1 R_3 + R_1^2 d_1. \quad (13)$$

It's easy to see that from three equilibrium states (0,0), (2,0), (0,2) of the system (12) only the state (0,0) satisfies the equation (13). In the other cases the system is incompatible for $d \neq 0$. Thus, bringing in a weak electrical coupling between elements leads to the fact that only the unstable state (0,0) is left in the system and heteroclinic contour between the saddle equilibrium states in the system (7) is destroyed. Therefore, the addition of

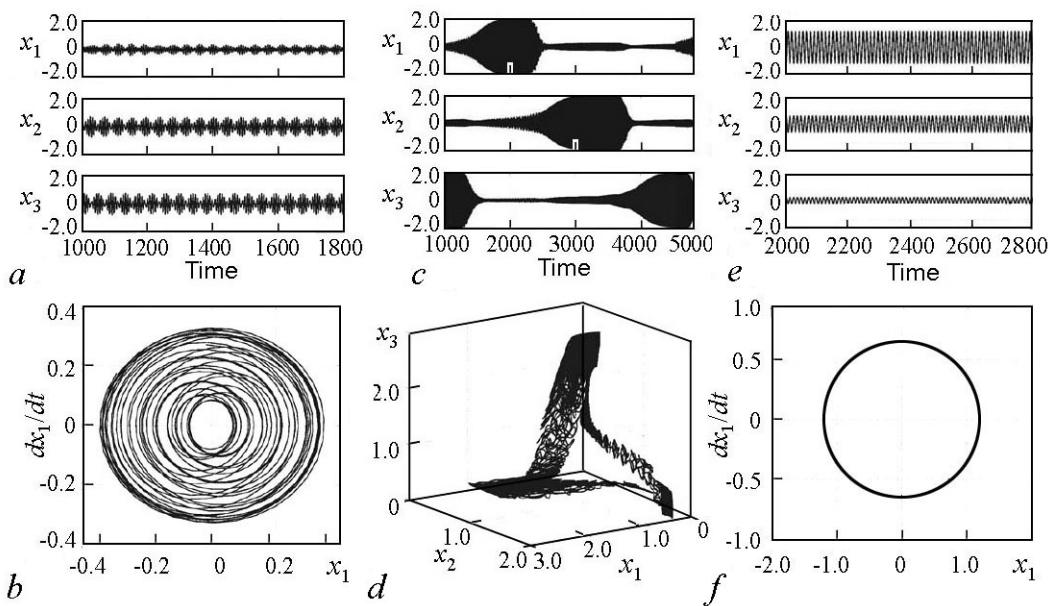


Fig. 3. Time series x_1, x_2, x_3 and projections of the phase trajectories of the system (1) on the 2-dimensional subspace (x_1, x_2) in the case of strong asymmetry in the coupling strengths. Parameter values for chemical couplings: $(g_1, g_2) = (0, 5)$. Parameter value for electrical couplings and frequency mismatch: $(a, b) - d = 0.1, \Delta = 0.02$; $(c, d) - d = 0.1, \Delta = 0.4$; $(e, f) - d = 0.2, \Delta = 0.1$

a weak non-zero electrical coupling between elements leads to destruction of the stable heteroclinic cycle which existed in the source system (1). However, from the numerical experiments it can be seen that with relatively small d , corresponding to the areas I in the charts of the maximal Lyapunov exponent (see Fig. 2), in the vicinity of the heteroclinic contour there remain many trajectories, which consistently visit areas near saddle limit cycles for an unlimited time (Fig. 3, *b*). Since the phase trajectories in this case are not attracted to the destroyed saddle cycles but only get to some of their neighborhood, the activity time of the elements is constant and is determined by the strength of the electrical coupling and the frequency detuning between the elements (see Fig. 3, *a*). The maximal Lyapunov exponent is wherein positive, $\Lambda_1 > 0$. This scenario is similar to the scenario of destruction of the heteroclinic circuit in the presence of noise, described in the work [5].

In the case when the frequency detuning is relatively small ($0 \leq \Delta \leq 0.235$), with further increase of the strength of the electric coupling d , the system dynamics become regular, namely, in computer experiment one observe the regimes of periodical (Fig. 3, *c*) and quasiperiodical (Fig. 3, *b*) oscillations. When passing to the region of quasiperiodical oscillations, in the phase space of the system a torus arises (Fig. 3, *d*). With further increase of the electric coupling d the torus destroys, in its place a stable limit cycle appears (Fig. 3, *f*) as the result of rigid bifurcation of Neymark–Sacker.

Conclusion

The ensemble of neuron-like elements investigated in the present work we propose to consider as a phenomenological model of a neural network. This approach has the following advantages: one can study low-dimensional neuron models and reproduce the

main effects observed in more complex models, for example, in the biologically realistic Hodgkin–Huxley model [15], and also in real experiments. Our research has shown that introduction of arbitrarily small electrical couplings into an ensemble of van der Pol oscillators with chemical synaptic inhibitory couplings leads to destruction of stable heteroclinic contour between saddle cycles. It has been also shown that the nonidentity of elements (without electric coupling) doesn't lead to destruction of the named heteroclinic contour, which, in general, is not typical for such systems. A heteroclinic contour, as a rule, exists in systems with symmetry and disappears when symmetry is destroyed. In our case the heteroclinic contour doesn't destroy because the amplitude dynamics of the system doesn't depend from the phase one. It has been also shown that with the destruction of the contour wear chaotic activity appears, but further increasing of electrical coupling leads to regularization of the system dynamics.

The obtained results give an opportunity of more deep understanding of the work of electrical couplings in nervous system. Studying their influence on evolution neural activity is not interesting only for nonlinear dynamics, but also contributes to the development of the theoretical base of bioelectric medicine and to the creation of new methods and approaches for the treatment of nervous diseases that are difficult to treat with pharmacological agents.

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