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New Approach to the Defibrillation Problem: Suppression of the Spiral Wave Activity of Cardiac Tissue

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A model of an excitable medium is considered for describing the development of fibrillation (i.e., spatiotemporal chaos) in cardiac tissue through the generation of a set of coexisting spiral waves. It is shown that a weak external point action on such a medium leads to the suppression of all spiral waves and, correspondingly, to the stabilization of the system dynamics. After reaching the regular regime, only the external source exists in the medium. The frequencies and amplitudes at which such stabilization occurs are determined. The case of the action of several point sources is considered. Analysis is performed using the Bray method to identify the number of spiral waves.

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The suppression of the turbulent dynamics of excitable media, which appears through a set of coexisting spiral waves, by means of a small periodical (almost) point action is a very important area of current investigations in view of application in cardiology. The dominating hypothesis in the current theory of excitable systems is that fatal cardiac arrhythmias, fibrillations, occur due to the creation of numerous autowave sources, spiral waves or vortex structures (i.e., spatiotemporal chaos, see, e.g., [1, 2] and references therein), in cardiac tissue.

The current methods for stabilizing such regimes by means of single electrical pulses (including those from implanted defibrillators) are very inflexible and are not necessarily successful. However, recent investigations open new possibilities. A large-amplitude pulsed action is not directly necessary and can be weakened in a number of cases [3]. Moreover, the turbulent regime in many excitable media can be stabilized by a weak periodic parametric [4, 5] or force action applied to certain medium regions [6–9].

In this work, for the simple FitzHugh–Nagumo model [10] of the excitable medium in the modification proposed for describing cardiac tissue [11], it is shown that the turbulent dynamics appearing owing to the decay of spiral waves can be suppressed using a small-amplitude point action. In addition, the problem of determining the frequencies and amplitudes that ensure the effective suppression of all spiral waves is solved. After such stabilization, the medium remains in the spatially uniform state.

The FitzHugh–Nagumo model describes the two-component activator–inhibitor system:

$$\begin{aligned} \partial U/\partial t &= \Delta U - U(U-\alpha)(U-1) - V, \\ \partial V/\partial t &= \beta U - \gamma V. \end{aligned} \tag{1}$$

In application to the dynamics of cardiac muscle, the variable U corresponds to the action potential of cardiac cells. This model is widely used as the basic model and satisfactorily describes the propagation of an excitation in cardiac tissue at the qualitative level, because it demonstrates the basic types of structures appearing in excitable activator–inhibitor media. Nevertheless, it is inapplicable for quantitative analysis, because it does not involve certain important properties of cardiac tissue such as the dependence of the refractory period on the amplitude and duration of the excitation phase.

In order to develop a more adequate description, system (1) is usually represented in the generalized form

$$\begin{aligned} \partial U/\partial t &= \Delta U - f(U) - V, \\ \partial V/\partial t &= g(U, V)(kU - V), \end{aligned} \tag{2}$$

where the functions f and g are chosen so as to ensure the correspondence of the resulting profiles of the action potential to experimental data.

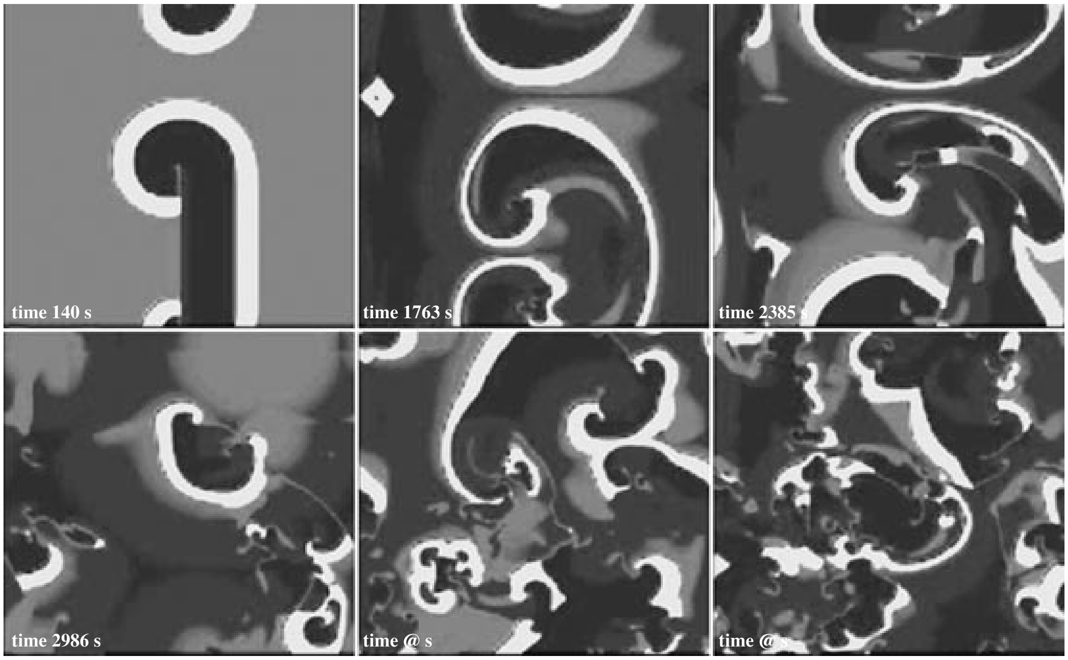

Fig. 1. Destruction of a spiral wave and creation of chaos for the parameters $G_1 = 0.01$ and $G_3 = 0.5$.

At present, the model proposed in [11] is widely used, where f and g are piecewise-linear functions:

$$f(U) = \begin{cases} C_1 U, & U < U_1, \\ -C_2 U + a, & U \in (U_1, U_2), \\ C_3(U-1), & U > U_2, \end{cases}$$
$$g(U, V) = \begin{cases} G_1, & U < U_1, \\ G_2, & U > U_2, \\ G_3, & U < U_1, \quad V < V_1. \end{cases} \tag{3}$$

One of its advantages is the presence of two independent relaxation parameters. One of them (G_3) determines the relative relaxation period for small U and V values. The other parameter (G_1) specifies the absolute relaxation period for large V values and intermediate U values, which correspond to the forward and backward fronts of waves. For greater correspondence to cardiac tissue, the system parameters are taken as follows: $C_1 = 20$, $C_2 = 3$, $C_3 = 15$, $U_1 = 0.0026$, $U_2 = 0.837$, $V_1 = 1.8$, $a = 0.06$, and $k = 3$. In this case, $1/100 \le G_1 \le 1/33$, $G_2 = 1$, and $0.1 \le G_3 \le 2.0$.

In spite of its simplicity, the model given by Eqs. (2) and (3) describes real experimental data sufficiently well even with the myocardium tissues of mammals [12]. For example, it correctly reproduces the shape of the action potential when varying the parameters and initial conditions in wide intervals and can demonstrate all types of structures inherent in excitable tissue.

The dynamics of the system given by Eqs. (2) and (3) is considered in the square region 350×350 node in size. To exclude edge effects, the periodic conditions are specified at the boundaries; i.e., the domain under investigation has torus topology. Autowave solutions of the spiral wave type are unstable in the parameter intervals indicated above. With time, they decay into smaller waves, so that the spatiotemporal-chaos regime thereby develops in the system (see Fig. 1). Excited sections of the medium are shown in Fig. 1 in white, the dark color corresponds to the refractory state, and light gray domains correspond to the rest state.

Spiral waves constitute the basic type of autowave solutions in this system, which allows one to use their number as a criterion of complexity of the regime existing in the system. However, it is impossible to separate each spiral in the situation of production–walk–annihilation. Nevertheless, the problem is simplified, because the core of each spiral wave is its indispensable attribute.

There are several approaches to solving the problem of identifying the number of spiral waves in the medium [13–16]. In this work, we use the method proposed in [13] that is based on the fact that the core of the spiral wave (as well as any point of discontinuity of the wave front) is a singularity for the phase field $\varphi(x, y, t) = \arctan2(U(x, y, t) - U^*, V(x, y, t) - V^*)$. In this case, the quantity

$$n = \frac{1}{2\pi}\oint \nabla \varphi dl,$$

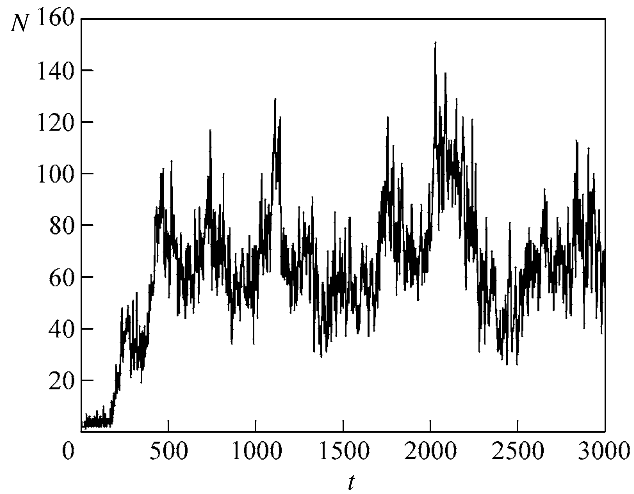

Fig. 2. Time dependence of the number of the cores of spiral waves when a single spiral wave is destroyed and chaos appears for the parameters $G_1 = 0.01$ and $G_3 = 0.5$.

which is called the topological charge, is not equal to zero only for the case where such a singularity is located within the integration contour. In this case, n is an integer, whose sign determines the chirality of the spiral wave.

Figure 2 shows the time dependence of the thus calculated number of the cores of spiral waves when chaos appears from a destroyed single spiral wave in the system specified by Eq. (3). This figure corresponds to the spatial pattern shown in Fig. 1. This regime was used for further analysis as the initial state of the system when studying the possibility of the suppression of turbulent dynamics.

At present, there are two qualitatively different approaches to this problem. The first of them ensures the transformation of the system from the chaotic regime to the regular one by means of external perturbations without feedback; i.e., it does not take into account the current state of the system. This method was proposed and justified in [17, 18]. A qualitatively different method is implemented by means of a correcting action and thereby involves feedback as a necessary component of the dynamical system [19]. In the last 15 years, it has become popular owing to its successful use. However, it is inapplicable to solve the problem formulated above, because it is applicable only for concentrated systems. In turn, each of these methods can be implemented by the parametric or force method. The introduction of feedback is a certain advantage, because such a method of the external action leads to a required result in most cases. At the same time, methods without feedback are more stable under noise actions, and this property significantly simplifies their use in applications.

For certain reasons, the parametric method has certain advantages over the force method. One of them is that, owing to the additive external action, phase trajectories can leave the physically allowable region. At the same time, the parametric action means change in the resources of the system and, thus, is finer than the force action.

For the system given by Eqs. (2) and (3) considered in this work, the situation is opposite: its dynamics is determined by the electrochemical potentials of muscle cells and forced change in their properties (such as cell-membrane capacitance, the intensity of the operation of ion pumps, the conductivity of ion channels, etc.) requires the periodic removal injection of certain substances. This is very laborious (if even possible), the more so as immediate intervention is required when fibrillation is developed. The implementation of additive perturbation is much simpler: it is sufficient to introduce electrodes into tissue and to supply pulses through these electrodes. Implanted defibrillators operate in such a way. In this case, the shape of the pulse, as well as its frequency and amplitude, can be varied in a wide interval.

For these reasons, we use point action. In this case, the initial system given by Eq. (3) acquires the form

$$\frac{\partial U}{\partial t} = \Delta U - f(U) - V + \sum_{i=1}^{N} I_i(x, y, t),$$

$$\frac{\partial V}{\partial t} = g(U, V)(kU - V),$$

$$0 \le x \le L_x, \quad 0 \le y \le L_y, \tag{4}$$

$$U(x, y) = U(x + L_x, y) = U(x, y + L_x),$$

$$V(x, y) = V(x + L_x, y) = U(x, y + L_y).$$

Here, the external potential is specified by the function $I_i(x, y, t) = AS^{\Omega_i}(x, y)\varphi_i(t)$, where A is the voltage amplitude on the electrodes, Ω_i is the region of contact with the ith electrode, $S^{\Omega}(x, y)$ is the marker function of the region Ω, which is equal to one and zero inside and outside the region Ω, respectively, and $\varphi_i(t)$ is a periodic time function. The region Ω is taken in the form of a small square (point electrode approximation).

Thus, a combinatorial optimization problem with three unknowns—amplitude, frequency, and pulse shape—appears.

In this work, we used several various pulse shapes of the external action. However, suppression was observed only for biphase rectangular and biphase sawtooth pulses. A biphase pulse is necessary in this case, because the action potential of cells simulated by Eq. (4) has both a positive and negative part. For this reason, the action shape must also have a negative action, which promotes the repolarization phase of cells.

Since a random search for suppression frequencies is very inefficient, we used a method that makes it pos-

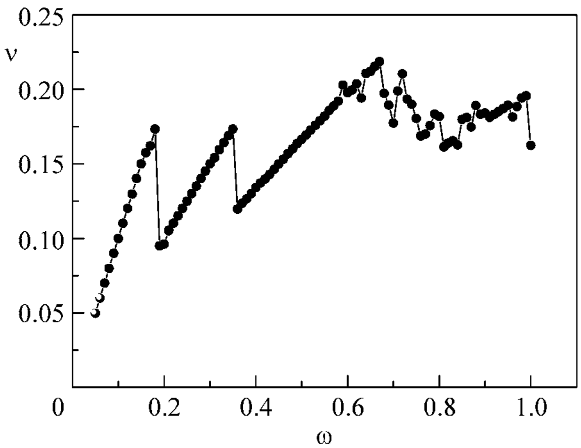

Fig. 3. Dependence $\nu(\omega)$ for the parameters $G_1 = 0.01$ and $G_3 = 0.5$.

sible to preliminarily localize frequency intervals ensuring suppression. This method is based on a known property of excitable media: among competitive wave sources, the source with the highest frequency of generated waves survives. Thus, the most favorable frequencies for suppression are external-action frequencies at which the frequency of circular waves excited by them is close to the maximum possible value for given medium parameters. In this case, it is necessary to take into account that the spiral waves cannot excite the medium in the relative refractory period, because additional energy is required. This is possible only with an external excitation source whose action amplitude exceeds the excitation threshold. Owing to this feature, the pacemaker can generate circular waves with a frequency higher than the frequency of spiral waves. It is clear that the efficiency of suppression depends directly on the difference between these frequencies. In our problem, this difference is small and the efficiency of suppression is significantly affected by other factors such as initial conditions, the drift of spiral waves, etc. We do not consider these factors and use only the first approximation. However, even the first approximation provides an important conclusion: the suppression of the turbulent dynamics of the medium in a finite time is possible.

In order to achieve suppression, it is necessary to determine the interval of the maximum natural frequencies of circular waves. This interval appears to be very narrow (~0.05) for the system under investigation. This means that it is necessary to scan a sufficiently wide frequency range with a small step (~0.01) in order to determine the efficient frequencies. In combination with the computational inconvenience of the problem, this strongly hinders solving the problem. For this reason, we use a method described in, e.g., [6]. In a small region of the medium, circular waves are generated and the frequency ν of generated waves is determined as a function of the natural frequency ω of the point source (see Fig. 3). The frequency intervals near the maxima of this dependence are considered as candidates for deeper analysis.

When seeking the efficient-suppression amplitudes, it is necessary to take into account that the action magnitude must be on the order of the amplitude of excitations inherent in this system. Moreover, it must correspond to the previously determined frequency.

It is worth noting that, to construct the dependence $\nu(\omega)$, it is sufficient to simulate a small medium region with a size of several tens of periods. However, to verify the existence or absence of the suppression effect at a given frequency, it is necessary to consider large medium regions with a size of several hundred periods,

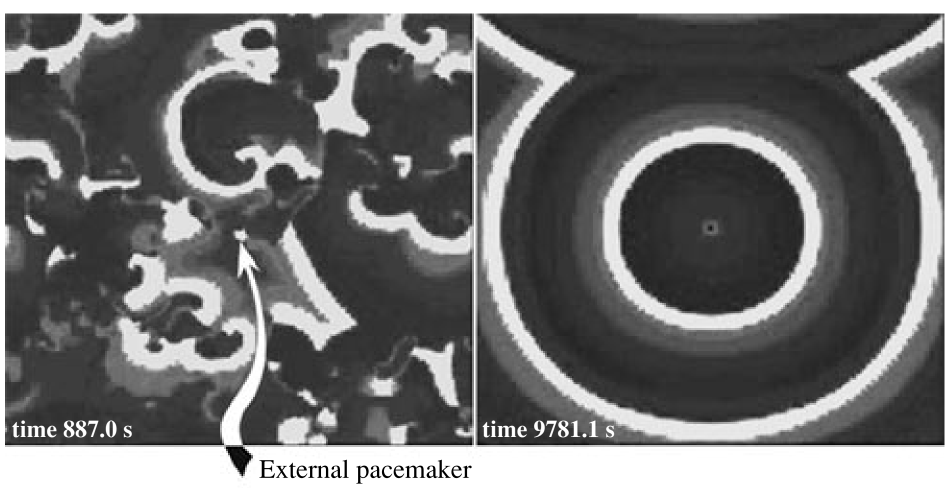

Fig. 4. Result of the point action on the system with developed spatiotemporal chaos for the parameters $G_1 = 0.02$, $G_3 = 0.3$, and $A = 6$.

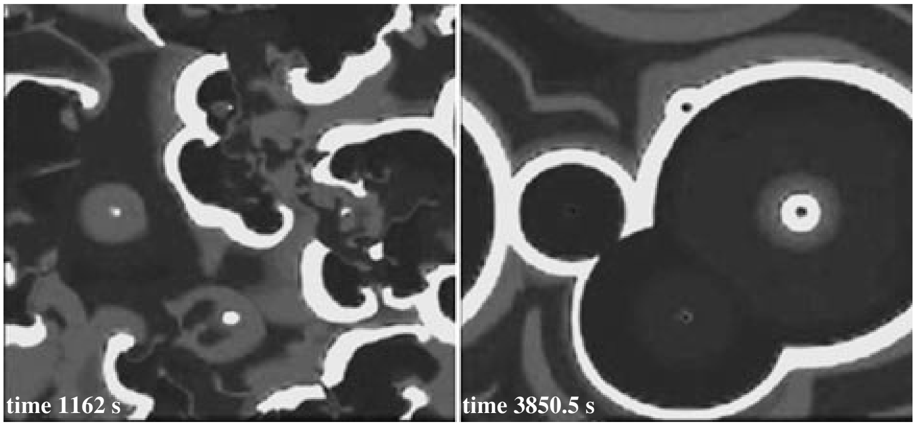

Fig. 5. Result of the simultaneous action of four pacemakers on the system with developed spatiotemporal chaos for the parameters $G_1 = 0.01$, $G_3 = 0.5$, and $A = 6$.

because otherwise the turbulent regime is not sufficiently developed.

System (3) is investigated for various values of the parameters $G_1$and G_3, which are responsible for the refractory period. We analyzed values corresponding to long refractory periods and unstable wave fronts. Although we also considered the case of stable wave fronts, some interesting processes such as the recovery of chaos in the system after suppression are not observed in this case. We succeeded in the suppression of chaos in the system for almost all parameter values considered to date. Figure 4 shows the result of the suppression of the turbulent dynamics at frequencies near the maximum of the dependence $\nu(\omega)$.

The numerical analysis shows that the stabilization of dynamics by one source is not necessarily possible. This is associated with the complex behavior of the system when wave fronts are unstable and boundary conditions are periodic. For example, a case where the external source at the initial time is surrounded by wave fronts of nearest spirals is possible. In this case, this source is suppressed by arms of spiral waves for a long time. Owing to periodic boundary conditions, the collision of two wave fronts from the external source is also possible. In this case, an unstable “island” of the refractory region is formed in the collision region, and the wave fronts of the next pulses can decay in contact with this island, which leads to the renewal of spiral waves and even to the suppression of the external source.

For this reason, we also analyze the behavior of the system with several (from two to eight) external excitation sources. Figure 5 shows the case of the stabilization by four sources. In this case, the efficiency of suppression strongly depends on the distance between them. In contrast to expectation, this dependence is far from linear.

It is worth noting that the amplitudes used in the model that are recalculated to volts are approximately one thousand times lower than pulses used in implanted defibrillators. This can be very important in applications, because patients have strong pain shock from implanted defibrillators and, as a result, feel stress in the expectation of repeated pulses. In addition, such a pulse leads to the destruction of cardiac cells.

Thus, the theory of dynamical systems [20] can be a key to a more fundamental understanding of fibrillation and its therapy. The general conclusion of this work is as follows. To solve the defibrillation in the parametric medium space, it is necessary to find the regions corresponding to the developed spiral wave turbulence. Then, the introduction of a weak point excitation with a certain frequency and shape leads to the complete displacement of all spiral waves, i.e., to defibrillation. There are all backgrounds for experimental verification of this result in high-technology clinical laboratories [3].

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