DYNAMICS OF BIOLOGICAL EXCITABLE MEDIUM

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Abstract. We present some methods to analyze a biological excitable medium. We provide local-global considerations to describe biological excitable media based on delay-differential equations. We find that there are the following modes: rest, steady state, regular oscillations, deterministic chaos and phenomena of oscillation failure.

In recent years the theory of excitable medium has rapidly developed and its results have been applied in various areas: chemistry, biology, ecology, electric engineering, populations dynamics, cardiology, neurology. Classical works by N. Wiener, V.I. Krinsky, B.P. Belousov have allowed to carry out the problem statement, to define the major features for functioning of excitable medium. A.N. Kolmogorov, V.I. Arnold, J. Moser, J.G. Sinay, A.T. Winfree, L. Glass, and others contributions in the field of mathematics and biophysics have allowed to understand more features in the dynamics of excitable medium.

At present, different approaches for the mathematical description of biological excitable medium dynamics by means of partial-differential equations, functional-differential, functional and discrete equations are applied. It is conditionally possible to emphasize two directions in quantitative researches on chaos dynamics in an excitable medium: the quantitative description of the propagation properties of nonlinear excitation waves (local statement of problem) and modelling mechanisms of regulation and self-control (global statement of problem).

The modern technique for the quantitative description of excitable medium begins from works by A.L. Hodgkin , A.F. Huxley [1]. Though A.L. Hodgkin and A.F. Huxley have developed a mathematical model describing excitation in nerve, their work was a basis for many mathematical works on biological excitable medium. Models on the quantitative description of excitation in cardiac tissue, carried out by FitzHugh-Nagumo (1961), Noble (1966), Beeler-Reuter (1977), Luo-Rudy (1991-1994) and others have been developed on the basis of Hodgkin-Huxley equations.

A very effective method for the quantitative researches of biological excitable medium is the local-global consideration of processes in excitable medium which takes into account the local features of excitation propagation between each element of active medium and global mechanisms in external regulation system with feedback and self-control. Let us consider this method in more detail.

Reactive capability and elements finiteness of the excitable medium imply the presence of "mixing" process and feedback existence. Let us assume existence of some time average (h) during feedback. It means that the influence of the signal has an effect on an element after an interval of time h. Then, the activity of the i-th element of the excitable medium can be described by following equation:

$$\frac{dX_i(t)}{dt} = a_i f_i(X_1(t-h), ..., X_n(t-h)) - b_i X_i(t) \tag{1}$$

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where $X_i(t)$ is the activity of the i-th element; a_i is the functional parameter of the i-th element; $f_i(\cdot)$ is the feedback function; b_i is the decay constant, $i = 1, 2, \ldots, n$.

The kind of function $f_i(\cdot)$ depends on concrete characteristics of the considered excitable medium (for example, neural networks, cellular systems etc.). An elementary way to define the kind of function $f_i(\cdot)$ is the method of limiting factors [2]. In this case we have

$$f(\xi) = A - \xi.$$

The A parameter limits the level of elements excitation.

In many cases [3, 4, 5]:

$$f(\xi) = \frac{a}{1 + d\xi} \tag{2}$$

or

$$f(\xi) = \frac{a\xi}{1 + d\xi}. \tag{3}$$

Using (2) we obtain represser systems of regulation and application (3) in the certain cases can reflect systems with the combined feedback.

In analysis of regulatory mechanisms in cellular systems the function $f_i(\cdot)$ is used as [6]:

$$f(\xi) = a\xi^k e^{-\xi}, \tag{4}$$

where k is a positive number. The concrete value of k is defined by character of mutual relations between elements. In the elementary case, taking into account research experience for complex systems, we can accept that $k = 2$ and the feedback function have the form:

$$f(\xi) = a\xi^2 e^{-\xi}. \tag{5}$$

Note, that in concrete mathematical modelling, the influence from external factors on feedback realization can be taken into account. For example, let us consider the equations for the mathematical model of regulatory mechanisms for cellular division (mitosis) [7]:

$$\begin{gathered}
\frac{dC_i(t)}{dt} = \epsilon\epsilon_i a_i D(t) \exp\left(-\sum_{j=1}^{N} \sigma_{ij} R_j(t - \tau_2)\right) - b_i C_i(t); \\
\frac{dX_i(t)}{dt} = \nu_i C_i(t - \tau_1) - d_i X_i(t); \\
\frac{dR_r(t)}{dt} = kP_r(t)C_r(t); \\
\frac{dP_1(t)}{dt} = g_1 X_1(t) - f_1 P_1(t); \\
\frac{dP_r(t)}{dt} = g_r X_r(t) - f_r P_r(t); \\
\frac{dP_m(t)}{dt} = g_m X_m(t) - f_m D(t) P_m(t); \\
\frac{R_1(t)}{dt} = g_1 X_1(t) - h_1(R_1(t) - NR_e(t - \tau_3)); \\
\frac{dR_m(t)}{dt} = g_m X_m(t) - f_m R_m(t);
\end{gathered} \tag{6}$$

$$\frac{dR_e(t)}{dt} = h_1(R_1(t) - NR_e(t)) - f_e R_e(t);$$

$$\frac{dD(t)}{dt} = k_D(1-\epsilon)(2D_0 - D(t))t_S;$$

$$\epsilon = \begin{cases} 0- & \text{in} \quad S, M \\ 1- & \text{in} \quad G_1, G_2; \end{cases} \qquad \epsilon_1 = \begin{cases} 0 & \text{at} \quad R_m(t) > A_1 \\ 1 & \text{at} \quad R_m(t) \le A_1; \end{cases}$$

$$\epsilon_r = \begin{cases} 0 & \text{at} \quad R_1(t) > A_r \\ 1 & \text{at} \quad R_1(t) \le A_r; \end{cases} \qquad \epsilon_m = \begin{cases} 0 & \text{at} \quad R_i(t) > A_m \\ 1 & \text{at} \quad R_i(t) \le A_m. \end{cases}$$

Here $i = 1, r, m$ designates conformity to functional, plastic and mitotic genes group; $C_i(t), X_i(t), P_i(t), R_i(t), (i = 1, r, m)$ are the m-RNA concentrations indices, initial groups of proteins, protein-ferments and repressers respectively; $R_e(t)$ is the repressers concentration in medium; $D(t)$ is DNA quantity; D_0 is DNA quantity before mitosis; t_s is the time counted from the beginning of S-period; N is the generated cells quantity at the time t; all coefficients of (6) are positive constants; S, M, G_1, G_2 are mitosis periods.

Using (1), (5) we have the equations for an element activity of excitable medium:

$$\frac{dX_i(t)}{dt} = a_i \left(\prod_{j=l_1^i}^{l_2^i} X_j(t-h) \right) \exp\left(-\sum_{j=1}^{n} d_{ij} X_j(t-h) \right) - b_i X_i(t), \tag{7}$$

where l_1^i, l_2^i- the elements indices which are carrying out influence on the considered element in the excitable medium; n is the number of elements; all parameters are positive.

Using (7) we can investigate the behavior of the excitable medium. For this it is necessary to specify the mechanism for a choice l_1^i, l_2^i for each element. In concrete cases the given mechanism follows from physical substance of considered problem. Often, it is accepted represser character for all elements, which have an influence on the given element. Sometimes, there are special represser elements in the considered excitable medium. As an example, let us consider the delay-differential equations for apoptosis regulation:

$$\frac{dC_i(t)}{dt} = S_C(t)\epsilon\epsilon_i e^{-\sum\limits_{j=1}^{3} d_{ij} R_j(t-\tau_2)} - b_i C_i(t);$$

$$\frac{dX_i(t)}{dt} = S_X(t) C_i(t-\tau_1) - d_i X_i(t);$$

$$\frac{dR_r(t)}{dt} = S_r(t) P_r(t) C_r(t);$$

$$\frac{dP_1(t)}{dt} = g_1 X_1(t) - f_i P_i(t);$$

$$\frac{dP_r(t)}{dt} = g_r X_r(t) - f_r P_r(t);$$

$$\frac{dP_m(t)}{dt} = g_m X_m(t) - f_m D(t) P_m(t);$$

$$\frac{dR_1(t)}{dt} = g_1 X_1(t) - h_1(R_1(t) - S_R(t) N R_e(t-\tau_3));$$

$$\frac{dR_m(t)}{dt} = g_m X_m(t) - f_m R_m(t);$$
$$\frac{dR_e(t)}{dt} = h_1(R_1(t) - R_e(t)) - f_e R_e(t);$$
$$\frac{dD(t)}{dt} = S_D(t)(1-\epsilon)(2D_0 - D(t))t_S,$$

where only $R_1(t), R_2(t), R_3(t)$ suppress the system activity; S_C, S_X, S_r, S_D are the functions which are taking into account the influence of thyroid hormones on intercellular regulation by means of sphingolipid metabolites; other parameters and variables are similar to the parameters and variables in (6).

As another example, we consider the delay-differential equations of cardiac excitation [8]:

$$\frac{dX(t)}{dt} = a_1\Theta(t-\tau_0)\eta(t-\tau_0)e^{-\delta_1\Theta(t-\tau_0)-\delta_2\eta(t-\tau_0)} - b_1X(t);$$
$$\frac{dY(t)}{dt} = a_2 f_1(X(t-\tau_1)) - b_2Y(t);$$
$$\frac{dZ(t)}{dt} = a_3 f_2(X(t-\tau_2)) - b_3Z(t);$$
$$\frac{d\Theta(t)}{dt} = a_4 f_3(Y(t-\tau_3)) - b_4\Theta(t);$$
$$\frac{d\eta(t)}{dt} = a_5 f_4(Z(t-\tau_4)) - b_5\eta(t),$$

where $X(t), Y(t), Z(t), \Theta(t), \eta(t)$ are the variables expressing the excitation level in pacemakers, auricles and ventricular respectively; $\{f(\cdot)\}$ are smooth functions; $\{a\}, \{b\}, \{\delta\}, \{\tau\}$ are positive constants.

Equation (7) can be used for working up equations for the concrete excitable medium and for the analysis of the most general regularities of chaos dynamics in the excitable medium.

It can be assumed that the minimal basic model of the excitable medium has the form:

$$\frac{dX_1(t)}{dt} = a_1X_2(t-h)X_3(t-h)e^{-d_1X_2(t-h)-d_2X_3(t-h)} - b_1X_1(t);$$
$$\frac{dX_2(t)}{dt} = a_2\Psi_1(X_1(t-h_1), X_2(t-h_1)) - b_2X_2(t); \tag{8}$$
$$\frac{dX_3(t)}{dt} = a_3\Psi_2(X_1(t-h_2), X_2(t-h_2)) - b_3X_3(t),$$

where $X_1(t)$ is the elements activity in active area (pacemakers); $X_2(t), X_3(t)$ are the elements activity outside of pacemaker area; Ψ_1, Ψ_2 are continuous functions; a, b are the functional parameters; d_1, d_2 are non-negative parameters expressing negative feedback; $\{a\}, \{b\}, \{h\}$ are positive.

In the qualitative analysis of the general mechanisms for excitable medium activity, we can consider the simplified equations:

$$\frac{dX_1(t)}{dt} = a_1X_2(t-h)X_3(t-h)e^{-d_1X_2(t-h)-d_2X_3(t-h)} - b_1X_1(t);$$
$$\frac{dX_2(t)}{dt} = a_2X_1(t-h) - b_2X_2(t); \tag{9}$$

$$\frac{dX_3(t)}{dt} = a_3X_1(t-h) - b_3X_3(t),$$

where all parameters are positive.

The equations (8), (9) are the functional-differential equations and have an infinite number of basic functions [9, 10]. Let us consider the following problem for (9):
Let $\varphi_1(t), \varphi_2(t), \varphi_3(t)$ be initial functions which are continuous on the interval $[-h, 0]$ and

$$X_i(t) = \varphi_i(t), t \in [-h, 0], i = 1, 2, 3. \tag{10}$$

It is required to define the continuous solution (9) at $t > 0$, satisfying (10). Using (10), we have

$$\frac{dX_1(t)}{dt} = a_1\varphi_2(t-h)\varphi_3(t-h)e^{-d_1\varphi_2(t-h)-d_2\varphi_3(t-h)} - b_1X_1(t);$$

$$\frac{dX_2(t)}{dt} = a_2\varphi_1(t-h) - b_2X_2(t); \tag{11}$$

$$\frac{dX_3(t)}{dt} = a_3\varphi_1(t-h) - b_3X_3(t).$$

If we replace $X_i(t)$ by $Y_i(t)e^{-b_it}, (i = 1, 2, 3)$ in (11) we get

$$\frac{dY_1(t)}{dt} = e^{b_1t}a_1\varphi_2(t-h)\varphi_3(t-h)e^{-d_1\varphi_2(t-h)-d_2\varphi_3(t-h)};$$

$$\frac{dY_2(t)}{dt} = e^{b_2t}a_2\varphi_1(t-h); \tag{12}$$

$$\frac{dY_3(t)}{dt} = e^{b_3t}a_3\varphi_1(t-h).$$

Integrating (12) in $t \in (0, h]$, we obtain

$$Y_1(t) = \varphi_1(0)+$$

$$\int_0^t e^{b_1s}a_1\varphi_2(s-h)\varphi_3(s-h)e^{-d_1\varphi_2(s-h)-d_2\varphi_3(s-h)}ds;$$

$$Y_2(t) = \varphi_2(0) + \int_0^t e^{b_2s}a_2\varphi_1(s-h)ds;$$

$$Y_3(t) = \varphi_3(0) + \int_0^t e^{b_3s}a_3\varphi_1(s-h)ds.$$

We have

$$X_1(t) = e^{-b_1t}[\varphi_1(0)+$$

$$\int_0^t e^{b_1s}a_1\varphi_2(s-h)\varphi_3(s-h)e^{-d_1\varphi_2(s-h)-d_2\varphi_3(s-h)}ds];$$

$$X_2(t) = e^{-b_2t}\left[\varphi_2(0) + \int_0^t e^{b_2s}a_2\varphi_1(s-h)ds\right]; \tag{13}$$

$$X_3(t) = e^{-b_3 t}\left[\varphi_3(0) + \int_0^t e^{b_3 s} a_3 \varphi_1(s-h)ds\right].$$

If we take (13) as initial functions, we get solutions for the interval $[h, 2h]$ etc. Such integration allows to obtain the continuous solution at $t > 0$.

For the analysis of the general regularities for chaos dynamics in excitable medium, we can simplify the considered equations using the method of simplification of the delay-differential equations [11]. In the elementary case the model system for (9) is one delay-differential equation:

$$\theta\frac{dX(t)}{dt} = aX^2(t-1)e^{-X(t-1)} - X(t), \tag{14}$$

where

$$\theta = (b_1 h)^{-1};$$

$$a = \frac{a_1 a_2 a_3 b_2 b_3}{b_1(d_1 a_2 b_3 + d_2 a_3 b_2)};$$

If θ is small then we obtain the functional equation:

$$X(t) = aX^2(t-1)e^{-X(t-1)}$$

and the discrete equation

$$X_{k+1} = aX_k^2 e^{-X_k} \tag{15}$$

where X_k is the pacemaker activity on k-th iteration step .

It can easily be checked that (14) has steady trivial state (trivial attractor). If $a = e$ then there is non-trivial equilibrium $X_0 = 1$, which splits into α, β as parameter a increases and

$$0 < \alpha < 1 < \beta. \tag{16}$$

Results of the qualitative research show, that β is attractor with (α, ∞) basin. Linearizing (14) neighbourhood of the non-trivial equilibrium we get

$$\theta\frac{dX(t)}{dt} = (2 - X_0)X(t-1) - X(t).$$

The characteristic equation has the form

$$\theta\lambda = (2 - X_0)e^{-\lambda} - 1$$

or

$$(\lambda + a)e^{\lambda} + b = 0, \tag{17}$$

where $a = 1/\theta, b = (X_0 - 2)/\theta$.

Using method of [10] we can see that the roots of equation (17) have the negative real parts if

$$a > -1;$$

$$a + b > 0;$$

$$b < \xi\sin\xi - \cos\xi,$$

where ξ is a root of the equation $\xi = a\tan\xi$ and $0 < \xi < \pi$, if $a \neq 0$; $\xi = \pi/2$, if $a = 0$.

Qualitative studies show that α is unstable. Second non-trivial equilibrium β is attractor that can be unstable under certain parameters with the appearance of Poincaré type limit cycles.

The most convenient for qualitative research of characteristic solutions is the discrete equation (15). Using Lamerey diagram we find that the attractor β can be transformed into strange attractor with the appearance of irregular oscillations, there is the deterministic chaos (Figure 1).

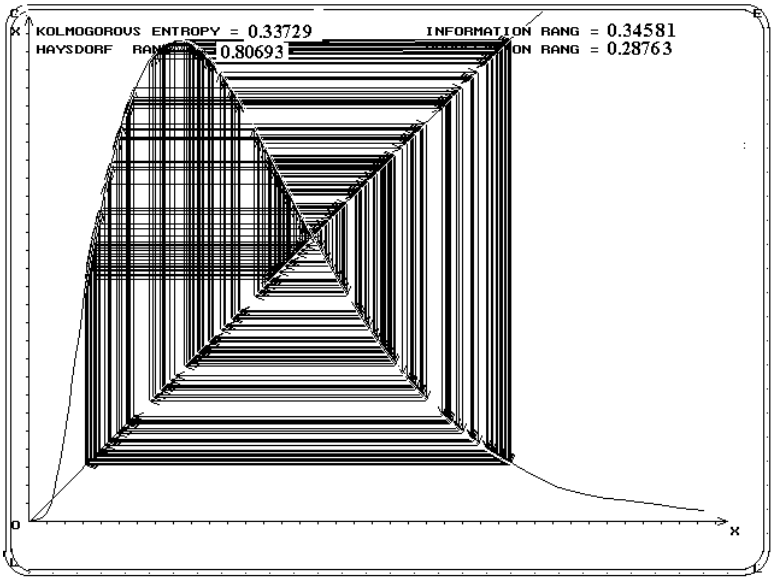

Figure 1: Computer analysis of the deterministic chaos

Results of the quantitative research of oscillation character based on Kolmogorov entropy show that in the deterministic chaos area there are small regions with regular oscillations. Also using the method of Lamerey diagrams we find that area of irregular oscillations can transform into the area of " black hole" (oscillation failure). The solutions are broken down into the trivial attractor (Figure 2):

As example we consider the following discrete equation for the cardiac activity

$$X_{k+1} = \frac{p}{q} X_k^2 e^{-X_k}, \tag{18}$$

where p is the parameter of potential activation of cardiac muscle cells; q is the velocity parameter of the electric signal decay. On the basis of the qualitative and quantitative analysis, the parametrical portrait for (18) (Figure 3) is obtained. In chaos area there are "r-windows"(areas with regular behavior).

Identification of the deterministic chaos with arrhythmia and "black hole" effect with sudden cardiac death allows using results for the quantitative analysis of mechanisms for origin, existence and development of abnormal modes in the cardiac activity.

Thus, using the elementary equations which are constructed based on the firmly established biological facts for the excitable medium we show that there are the following modes: rest, steady state, limit cycles, irregular oscillations and solutions failure into trivial attractor.

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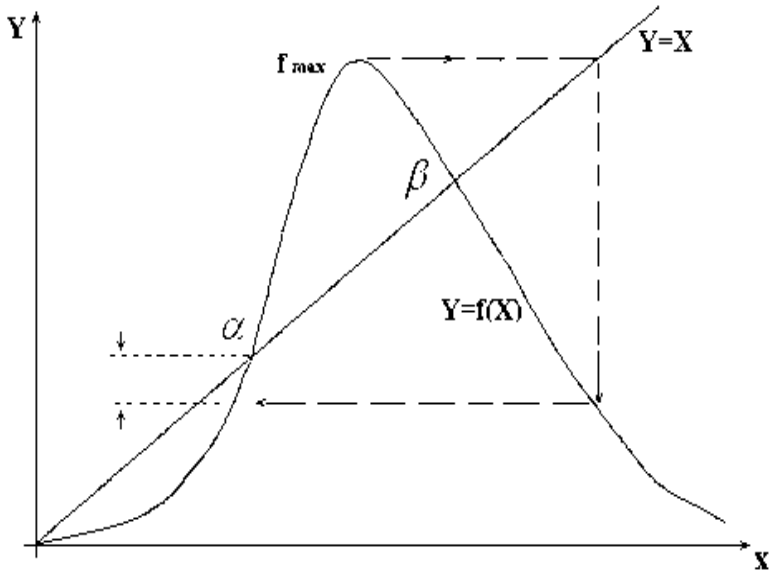

Figure 2: Conditions for oscillation failure ("black hole" effect)

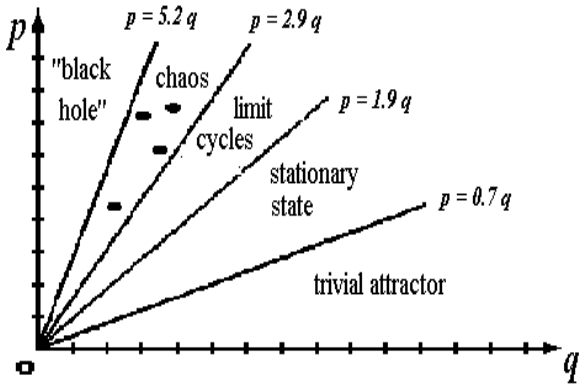

Figure 3: Parametrical portrait for the equation (18)

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