Discrete Mathematical Model of Simulation of Autowave Processes in Biomembranes

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Abstract: *In this work we introduce mathematical (logical) model of biological membrane, which simulates generation and progression of some non-linear processes. Using discrete approach seems to be more effective in comparison to classical continuous methods. Medium was fragmented to a finite amount of regions with specific characteristics, and relations among them were investigated. It turned out that macrophenomena in medium rises on the basis of microphenomena, i.e. they are contingent on relations among components of medium. By the help of discrete models we can very effective simulate properties of medium and processes proceeding in it. Result is a mathematical model, which consist of abstract cellular mosaic) automaton - homogeneous structure. We have derived basic properties of automaton, i.e. state of the element and transition functions, and using them we have made simulations of generation and propagation of special non-linear (autowave) processes.*

Keywords: *nonlienear model, cellular automaton, autowaves*

1. Introduction

Mathematical models represent a language for formalising the knowledge on live systems obtained in theoretical biophysics. Basic models represented by one or two equations allowing a qualitative examination, make it possible to describe principal regularities of biological processes: growth restrictions, presence of several stable stationary states, oscillations, quasistochastic regimes, travelling pulses and waves, and the structures inhomogeneous in space. The nonlinearity of these models is their most important property: it reflects mathematically the openness of biological systems and their state beyond thermodynamic equilibrium [1].

Autowaves are non-linear waves observed in spatially distributed media of physical, chemical, and biological nature, when wave propagation is supported by a source of energy stored in the medium. In a two-dimensional autowave medium there may exist autowave vortices appearing as rotating spiral waves and thus acting as a sources of periodic waves. Their existence is not due to singularities in the medium but is determined only by development from initial conditions. In a slightly perturbed medium, e.g. spatially inhomogeneous, or subject to time-dependent external forcing, a spiral wave drifts, i.e. its core location and frequency change with time.

The first direct experimental observation of spiral waves in a chemical oscillatory medium, the Belousov-Zhabotinsky reaction [2], triggered a huge amount of interest and activity in the area. Soon after that spiral waves were observed in cardiac muscle [3], a rabbit ventricular tissue [4], and later in a variety of other spatially distributed active systems: in chick retina [5], colonies of social amoebae, cytoplasm of single oocytes, in the reaction of catalytic oxidation of carbon oxide and in laser systems [6].

Property	linear waves	autowaves
Conservation of energy	+	-
Conservation of amplitude and shape	-	+
Interference	+	-
Annihilation	-	+
Reflection	+	-
Diffraction	+	+

Table 1: Comparison of autowaves and classical wave processes [7]

All biological systems - biomacromolecules, cells, tissues, organisms - are active distributed media. Transition of matter and energy in such media is proceeding in every single elementary volume, those are influenced each other by transfer of matter, energy or information, owing to outside forces or with a special adaptable mechanism. Every of these elementary volumes presents open system far from thermodynamic equilibrium. The matter carrying energy or other sources of energy are interspersed in space and interconnected by flow of matter and energy. In those media we can find so called autowave processes: pulses and excitable waves propagation, organisation of stationary spatial non-homogeneous distribution of matter and other self-organising phenomena. Most often investigated are processes in excitable membranes of nerve fibres, waves in nerve network of the brain and excitable waves in muscle tissue.

Autowaves are wave processes, maintained in media and by equally small changes of initial and boundary conditions are preserved. Autowaves rise in active non-linear media only. The basic characteristic of autowaves is maintaining of their properties (period, wave length, amplitude and shape of the wave [8]. These characteristics are maintained thanks to fact, that autowaves while propagating are taking energy from medium. As a source of energy we can consider also non-homogeneity, these are a potential source of autowaves as well. Autowaves are radically different in some basic properties from linear wave processes, which are describing by hyperbolic equations, (Tab.1).

Autowaves do not conserve energy, they take it directly from medium. The main property of active non-linear medium is refractoriness. Refractoriness (or time of refractoriness) is a minimal time in that can autowave follow another by assumption that both propagate. Consequently, it is a relaxation time needed for element of medium to get back to its origin state. During relaxation time element is deaf towards excitation. Simulation of generation and propagation of autowaves in often realised by continuous methods [8]. This method lies in solving of differential equations, however these are often not solvable exactly, so results do not reflect properties of medium in acceptable degree. So there are very often used discrete models investigating relation among elements of medium. Networks of integrate-and-fire neurons with rare connections were investigated in [9] using a Fokker - Planck - Kolmogorov equation that describes dynamics of a probabilistic neuron membrane potential distribution function. Different network states are conceivable depending on parameter values, e.g. a synchronous state in which neurons exhibit regular firing patterns and an asynchronous state with stationary global activity and very irregular discharges by individual neurons.

In this paper we introduce model of biomembrane based on cellular automaton. Model is realised through rotary movement of phospholipid and consists of cellular mosaic automaton, homogeneous structure. Every molecule of phospholipid has assigned to abstract finite automaton. Interaction among

particular automata is executed by neighbourhood scheme and swapping of information about states of automaton.

2. Method

Prefigurement for models of real systems are formal systems, those are relatively far from real systems. Coupling of formal and real systems represent abstract systems. System, which is most often used for modelling of real life systems in the presence is relative closed system. Characteristic property of relative closed system are its exactly defined inputs and outputs, that execute communication of system and surroundings. We assume, that input **x**, respectively output **y**, consist of particular inputs x_1, x_2, ..., x_m, respectively particular outputs y_1, y_2, ..., y_m. Particular inputs, respectively outputs we can understand as components of input vector **x**, respectively output vector **y**, which is component of set of inputs X, respectively set of outputs Y of a system, whereas set X, respectively Y is subset of m-dimensional space R_m, respectively n-dimensional space R_n, **x** = (x_1, x_2, ..., x_m) $\in$ X $\subseteq$ R_m, **y** = (y_1, y_2, ..., y_m) $\in$ Y $\subseteq$ R_n.
We define input as transformation T of input vector **x** $\in$ X to output vector

$$\mathbf{y} = T(\mathbf{x}) \tag{1}$$

to every input **x** $\in$ X is by transformation assigned single output. Thus values of outputs are functions of input values,

$$y_1 = f_1(x_1, x_2, ..., x_m), y_2 = f_2(x_1, x_2, ..., x_m), \cdots y_n = f_n(x_1, x_2, ..., x_m), \tag{2}$$

We write function f = (f_1, f_2, ..., f_n) as a vector function independent vector x = (x_1, x_2, ..., x_m), then we can rewrite system (1) to a vector state **y** = f(**x**). Systems like this are called deterministic. In case, that there are more inputs, by ambiguous T, exists at least one input **x** $\in$ X, to which belongs more than one output **y** $\in$ Y. In general, to given input **x** $\in$ X exists non-empty subset Y'$\in$ Y of outputs **y** $\in$ Y', which are possible reactions of system to input x. And if exists stochastic distribution p(y) of set Y which define probability of assignment certain output y $\in$ Y', for given input x $\in$ X, so we talk about stochastic systems.

System mentioned above do not consider factor of time. We assumed, that answer of a system appear on output at the same time as impulse **x** on a input. Actually, between acceptation of input **x** and delivering of output **y** exists some time delay $\triangle$t. So for input and output we can write:

$$\mathbf{y}(t + \triangle t) = f(\mathbf{x}(t)). \tag{3}$$

By the investigation of systems we consider input, output and state values dependence on time, systems are called dynamic systems. Time dependence can be realised as a continuous or discrete quantities. So we can distinguish continuous and discrete systems, for which are changes realised by steps in certain beats (analogous respectively digital computers).

3. Results

Mathematical model of biomembrane introduced in this work is an abstract cellular (mosaic) automaton - homogeneous structure. It is a discrete model, which base is to study relations among single elements of homogeneous structure - cells, that presents individual finite automata.

Biological membrane is possible to imagine as finite set of bounded units. Viewing membrane from above (we define view from above as view parallel with phospholipid axis) we can see typical distribution of phospholipids and proteins (periphery and integrated). Under layer of phospholipids is not visible, neither trans-membrane proteins, that do not pass to outer side of membrane.

Basic element of model is limited planar element - cell, which contain one phospholipid. Single cells are ordered to discrete cellular network. Often used for modelling biomembranes are square-shaped types of cellular networks, but more useful appear to use hexagonal types, that more clearly and homogeneously capture real-life positions of phospholipids.

Neighbourhood O_1(x, y) of cell (x, y) consists of cells directly adjacent to cell (x, y) and cell (x, y), i.e. O_1(x, y) = (x, y), (x+1, y), (x, y+1), (x-1, y), (x, y-1), (x+1, y+1), (x-1, y-1). Neighbourhood k^{th} degree O^k(x, y), for k = 0,1,... is defined by recurrent formula:

$$O_{k+1}(x, y) = O(O_k(x, y)), \tag{4}$$

where O_0(x, y) = $\{$(x, y)$\}$.

As it was presented, base of the model is abstract finite automaton. Abstract automaton A is a single cell of homogeneous structure HS_6 on a base of constantly hexagonal network given by ordered pair:

$$A = (S, f), \tag{5}$$

where S is (finite) set of states of automaton A and f is transition function:

$$f_k(x, y) : S^7 \rightarrow S, \tag{6}$$

defined on neighbourhood of k^{th} degree of cell (x,y) homogeneous structure HS_6, whereas S^7 is Cartesian product of (S^7 = SxSxSxSxSxSxS).

Lipids in biomembranes can perform several types of movement. In our model of cellular membrane we consider only rotary movement of molecules with its qualitative properties (direction, velocity, orientation). With help of them we define state of the element.

State of the element (x,y) is given by following:

$$S(x, y) = \{O_t, D_t, R_t\}, \tag{7}$$

where single symbols have this meanings:

O_t - is a property of phospholipid, which determines its current orientation. O_t = 1,2,3,4,5,6, single component of the set respond to following angles: 1 - 0°, 2 - 60°, 3 - 120°, 4 - 180°, 5 - 240°, 6 - 300°.

D_t - is direction of rotation of phospholipid. D_t = 0,1,2, where 1 - clockwise rotation, 2 - counter clockwise rotation, 0 - no rotation.
R_t - is velocity of phospholipid rotation. R_t = 0,1,2,3. 0 - no rotation, 1 - slow rotation, 2 - quick rotation, 3 - very quick rotation.

Spiral autowave is most common of all types of autowave processes. It originate in certain place of non-homogeneous active medium, and then it rotates around it by a constant angular velocity. The wave spreads to the environment as a signal, i.e. does not happen transference of energy nor matter, only information is transmitted. This information is represented by state of the lipid in time t. We choose one state of all, S, which has most significant influence in cellular network, i.e. it is able to affect its neighbours most of all. This state presents information, which is the base of simulated spiral autowave.

Generator of autowave process

The place in the net, in that autowave process starts is called generator of autowave process. Generator of autowave process (GAP) is defined as following group of elements:

$$GAP = \{(x, y), (x, y + 1), (x - 1, y + 1)\}, \tag{8}$$

whereas:
S(x,y) = S(x,y+1) = S(x-1,y+1) = $\{O_i, 1, 3\}$, where O_i is set of defined orientations of lipid, $O_i \in$ {1,2,3,4,5,6}.
State S(x,y) is called signal state.
Autowave process starts, when in homogeneous structure HS_6 appear suitable oriented, directionally and velocity synchronized cells, moreover suitable adjacent.

The amount of output variable is 3, so they are expressed by $\lceil log_2 3 \rceil$ = 2 binary variables, z = z1 z2, where $z_i \in$ 0,1, whereas z = 01 is counter clockwise generators, z = 10 clockwise generator and z = 00 means the case, when given triplet of cells does not present generator of autowaves processes. Variables x_{ij} are absolute positions of elements of generator in network.
z = z_1 z_2 = f_g (b_1, b_2, b_3) =
= f (x_{11}, x_{12}, x_{13}, x_{14}, x_{15}, x_{21}, x_{22}, x_{23}, x_{24}, x_{25}, x_{31}, x_{32}, x_{33}, x_{34}, x_{35}).

Propagation of autowave process

Autowave process starts in the case, that somewhere in medium appears generator of autowave processes. Generator provides information about direction of autowave propagating. For exactly formulation of boundary conditions of autowave process is necessary to know some parameters: the power of curvature, the power of signal attenuation and direction of propagation. While first two parameters depend on HS_6 properties (definition of transition function), direction of propagation is given by generator itself. Autowave can propagate into two different directions: clockwise and counter clockwise.

Direction of signal propagation

Last property of model now defined is direction of signal propagation. In continuous space is spiral curve expressed in polar coordinate system by following formula:

$$R = K.\alpha, \tag{9}$$

where R is distance from the middle, α is an angle, $\alpha \in$ [2kΠ, 2(k+1)Π], k ∈ Z, and K is a constant determining power of spiral curvature.
To discretise spiral curve we take angle α. We fragment interval [2kΠ, 2(k+1)Π] to finite amount of intervals [2kΠ + P_i, 2(k+1)Π + P_i], where P_i is a number of steps, during that angle changed from value 2kΠ to 2(k+1)Π. Spiral is then divided to P_i curves. When we join points R_1 = K.(2kΠ + P_i) and R_2 = K.(2(k+1)Π + P_i) we obtain lines, that are expression of discrete spiral.
In our case is spiral curve divided into 12 parts, i.e. P_i = 12. Every part is represented by a line given by its slope of straight line. To express them exactly is not necessary, because in hexagonal network HS_6 we can express only twelve direction (when we consider 18-neighbourhood. Direction in HS_6 is given with help of three adjacent elements of automaton.

Model consists of abstract finite automaton with defined properties (state of the automaton, transition function) and defined functions of autowave process originate, the way and direction of signal propagation. All properties were expressed as Boolean function types, or by concatenations of them.

Model was graphically visualised in programming environment Microsoft Visual Basic 6.0.

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5. Conclusion

Mathematical model introduced in this paper consists of abstract cellular (mosaic) automaton - homogeneous structure. It come from real consternation of phospholipids in biomembrane, thus the basic element of the net is hexagonal cell. Model studies relations among cells through 1^{st} degree neighbourhood of cell - O_1(x,y) and 2^{nd} degree neighbourhood of cell - O_2(x,y). Consternation of elements in hexagonal network is the best representation of spatial conditions in biomembrane and allows to define local transition functions describing non-linear processes appearing in biomembranes. Computer execution of hexagonal network is relatively uncomprendious and graphically difficult, thus was used transformation of hexagonal network to squared, whereas all transition functions and rules from original network were maintained. Model describes environment working in autowave mode. It simulates conditions of autowave originate, conditions of autowave propagate, i.e. transition function, function of signal curvature, quasi-memory of environment. Through these base conditions were simulating autowave processes in biomembranes with the maximal accession of behaviour of such processes in real membranes. All functions are expressed binary (Boolean type of functions). This makes this model very versatile, because it works on level of logical circuits and so it allows easy data handling and possibility to expand it with more properties. However, model works with some restrictions. The most significant restriction is assuming of high degree of homogeneity of environment, so we can consider symmetric consternation of membrane phospholipids. Actually, other components in biomembrane (glycolipids, periphery and integrally proteins) cause asymmetric consternation of phospholipids. This has admittedly an influence on processes appearing in biomembrane.

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