

Difficulties in Mathematical Modelling of Control Processes in One-type Neuron Populations

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Abstract. *Geometry of a neuron is similar to a tree with branches of different diameters. There is a thin isolating cellular membrane instead of a bark of the tree. The intracellular plasma and extracellular liquid have different electric potentials. There are several types of ionic channels put in cellular membrane: channels controlled by electric field and chemically controlled channels (controlled by mediators). A rise and propagation of neuronal spikes are defined by electrically controlled channels. Chemically controlled channels are means of interactions between neurons. Equations of Hodgkin-Huxley type on geometrical graph-"tree" are used as a mathematical model of electrical state of a neuron. Such (or simplified) models are used in modelling of neural networks up to-date.*

However, morphology bibliography and experimental data of professor Sotnikov show that some processes of neighbouring neurons have connections like pores or electrical junctions (gap- and tight-junctions) in some structures of nerve system. It means that information is operated on some random neuronal clusters but not on a single neurons. This case of mathematical modelling gives rise to several new problems: 1) modelling of distribution of a number of neurons in a cluster, a model of "average" cluster; 2) generation of blocks of pulses in clusters; 3) modelling of retrograde spreading of pulses by dendrites; 4) functions of off-synaptic receptors and secondary messengers in controlling of dendrites electrical state.

There is a fundamental problem to discuss: why pores between dendrites (and, therefore clusters) in some structures are numerous but in neighbouring structures of the same brain they are seldom or never exist (Example: fascia dentata and CA3 field in hippocampus)? What does it mean in the concept of informational mechanisms?

Keywords

Mathematical modelling, control signals, pores, membrane perforation, clusters of neurons, neuron syncytium.

1 Introduction

Geometry of a neuron is similar to a tree with branches of different diameters. There is a thin isolating cellular membrane instead of a bark of the tree. The intracellular plasma and extracellular liquid have different electric potentials. There are several types of ionic channels in the cellular membrane: channels controlled by electric field and chemically controlled channels (controlled by extracellular mediators). Rise and propagation of neuronal spikes are defined by electrically controlled channels. Chemically controlled channels are means of interactions between neurons. Equations of Hodgkin-Huxley type on geometrical graph-"tree" are used as a mathematical model of electrical state of a neuron. Such (or simplified) models are used in modelling of neural networks up to-date.

However, morphological bibliography and experimental data of professor Sotnikov O.S. [1] show (Fig. 1) that some processes of neighbouring neurons have connections like pores or electrical junctions (gap- and tight-junctions) in some structures of nerve system. It means that information is operated on some random neuronal clusters but not on single neurons. There are three types of pores: 1) pores between dendrites; 2) pores between axons; 3) axon-dendritic pores.

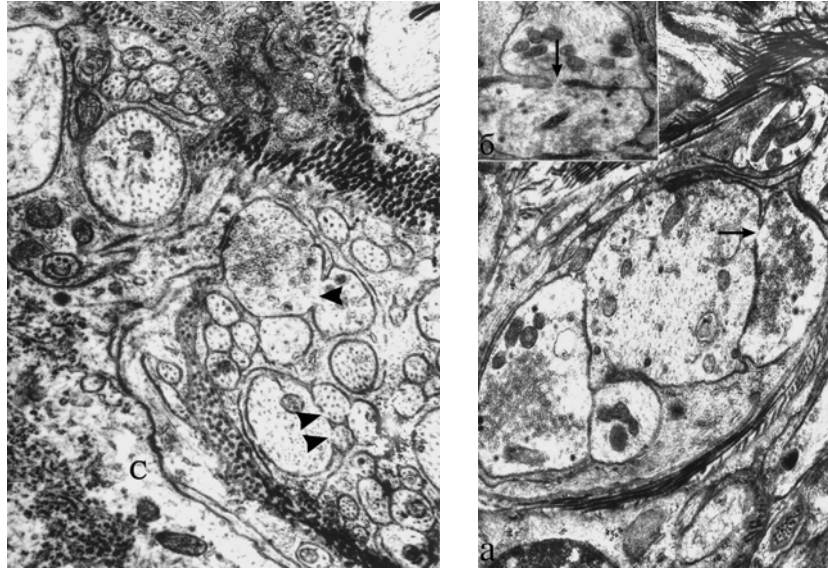


Fig. 1 LEFT: Syncytial junction of two axons and of three dendrites. Tips of arrows indicate interneuronal pores. **C** – soma of a neuron. Electronic microscopy. Magnification 30000.
 RIGHT: Syncytial pores (arrows) in the domain of axo-dendritic synapses.
a, b – alternate versions of the structure. Magnification 40000.

There are two types of chemical controllers for neurons: mediators control of chemically controlled ionic channels and control by intracellular secondary messengers of channels controlled by electric field. Molecules of secondary messengers are generated by metabolic extra-synaptic receptors during activation by the same mediators [2]; they are spread in neuron by diffusion [3].

There are three aspects of mathematical modelling of neuron populations: geometrical, electrical and diffusion. Modelling in each aspect is not only "translation" from experimental "language" to the "language" of equations, but also simplifications of problems. Simplifications cause errors; we propose that errors are small, but usually we must solve more complex problem to verify it.

2 Geometrical aspects

Neurons. Geometry of a neuron is similar to a tree with different oriented branches of different diameters. Branches are not ideal cylinders (see Fig. 1) and can be curved. The very thick part of a neuron is called "soma". Branches are called "dendrites", only one branch (usually the very long and thin) is called "axon". Points of branching are named "nodes". Soma and dendrites are usually overlapped by post-synaptic (receptors of chemically controlled ionic channels) parts of synapses. An axon is a mean of transmitting information in the form of nerve pulses to other neurons. Branches of an axon are overlapped by pre-synaptic parts of synapses; they extract mediators to extracellular liquid during pulses.

Let us draw smooth central line in each branch of the tree; we denote the length of the central line by L , coordinate of length by x , $0 < x < L$. Let us see a plane orthogonal to the central line for every x . Intersection of the plain with surface of the branch is a closed loop. Let us denote length of this closed loop as $l(x)$ and area of cross-section of the brunch as $s(x)$. For every x differential of the surface of the branch is equal to $l(x)dx$ and differential of the volume of the branch is equal to $s(x)dx$. Mathematical model of the tree is geometrical graph-tree Γ with edges of a graph γ_k , $k=1, \dots, K$ and nodes a_j , $j \in J$ [4]. Number of edges adjacent to the node is called index of the node. Every node with index 1 is the end of the edge. Nodes with index 2 are called degenerate nodes. Nodes with index 3 and more are called regular interior nodes. Regular point of branching in neuron is domain of branching with finite volume and surface; its surface is sum of cellular surface of the domain S_j and surfaces of cross-sections of the brunches. In the graph model a regular node is a point, its volume and surfaces of cross-sections are neglected, but surface S_j may be used as a parameter in equations.

Geometry of neighbouring neurons connected by pores is more complex. If pores are very large it may be modelled as a new node. If partial fusion of processes exists then it may be modelled as a new edge of the new complex graph which include both graphs of connected neurons. If a pore is small enough then it may be modelled as a new very short edge with two new nodes on processes of neurons. The last model can be used as well for electrical equations in the case of gap- and tight-junctions; for diffusion in this case there is no connection. It means that electrical and diffusion equations must be defined on different geometrical graphs.

In this text we use word "cluster" for several neurons linked by pores or junctions. A graph of a cluster contains graphs of included neurons. Connections between neurons are random ones; so the task of clusters' size distribution calculation as a function of probability of pores or junctions arises.

Geometry of interneuron liquid. There are thin isolating cellular membranes in nerve tissue. Conductive extracellular liquid is media for diffusion of mediators and conductive media for electrical currents and potentials. It is located in thin extracellular clefts of width about 20 -- 30 nanometers, all clefts are connected with each other. Mediator extracted to the cleft from presynaptic axonal part of a synapse diffuses across the cleft to receptors of chemically controlled channels in postsynaptic membrane. A small number of mediator molecules diffuse along the cleft to metabolic extra-synaptic receptors. Currents through neuronal membrane flow along the cleft and change electrical potentials in clefts, which can be measured by extracellular electrodes.

Mathematical model of extracellular media geometry is a smooth branching surface (it is a subclass of stratified sets [4],[5]). Let us see a two-dimensional smooth media surface in the cleft as a model instead of three-dimensional cleft. There are lines where three or more clefts are merged (see in Fig.1 lines of cross-sections of clefts). These smooth lines in three-dimensional space are merged in some points; these lines and points compose a full-connected net (wich is a type of geometrical graph). This net is a part of branching surface.

3 Electrical and diffusion aspects

There are two different sorts of potentials in nerve tissue: intracellular $V(x,t)$ and extracellular $\varphi(z,t)$. Intracellular potentials of different neurons are various. The same is true for intracellular potentials of different clusters. Extracellular potentials are potentials of extracellular liquid in clefts between cells. Mathematical model of extracellular potentials is potential of conducting branching surface. If branches of different neurons ore clusters are located at a short distance then their extracellular potentials are similar ore coincide. Partial derivatives of $V(x,t)$ we denote as $V_x(x,t)$ and $V_t(x,t)$.

Electrical currents. There are three sorts of currents in nerve tissue: intracellular currents $i(x,t)$ along edges of the graph (for neurons or clusters); extracellular currents $j(z,t)$ along branching surface of extracellular liquid; and density of transversal currents through neuronal surface $I(x,t)$ between neuron and cleft. Let us denote extracellular potential on the surface of the branch as $\varphi(x,t)$. We find (using Ohm's low):

$$i(x,t) = \sigma s(x)V_x(x,t); \quad x \in \gamma_k, \quad k = 1, \dots, K, \quad (1)$$

where σ is specific conductance of neuronal cytoplasm. For extracellular currents $j(z,t)$ Ohm's low in differential form can be used. Equation for $I(x,t) = I(x,t,V - \varphi(x,t))$ is

$$I(x,t) = l^{-1}(x)i_x(x,t) = \sigma l^{-1}(x)(s(x)V_x(x,t))_x = I_C + I_{Na} + I_K + I_L + I_S. \quad (2)$$

We use in this model the simple classic form of Hodgkin-Huxley equations [6] only adding synaptic currents I_S and changing several notations. Let as denote additional functions as $p_i(x,t)$, $q_i(x,t)$, $p_i \in [0,1]$, $q_i \in [0,1]$, $i = 1,2,3$. Currents in equation (2) are:

$$I_C = C(V_t(x,t) - \varphi_t(x,t)); I_{Na} = g_{Na} q_1^3 q_2 (V - \varphi - V_{Na}); I_K = g_K p_3 q_3^4 (V - \varphi - V_K); I_L = g_L (V - \varphi - V_L); \quad (3)$$

$$I_S = \sum_t \delta(x - x_t) \sum_{t_{i,n}} g_s(x_t, t - t_{i,n}) (V(x_t, t - t_{i,n}) - \varphi(x_t, t - t_{i,n}) - V_S). \quad (4)$$

Equations for additional functions $q_i(x,t)$, $i = 1,2,3$ are:

$$(q_i(x,t))_t = \alpha_i(V(x,t) - \varphi(x,t)) - [\alpha_i(V(x,t) - \varphi(x,t)) + \beta_i(V(x,t) - \varphi(x,t))]q_i(x,t). \quad (5)$$

Functions $\alpha_i(V)$ and $\beta_i(V)$ are defined in [6].

To this equations (2) - (5) on branches (on edges of the graph) two conditions in the nodes of the graph must be added: 1) continuity of $V(x,t)$ in nodes; 2) Kirchhoff condition: sum of the currents to the node must be equal zero.

Diffusion aspect. The most part of mediator extracted to the cleft from presynaptic axonal part of a synapse diffuses across the cleft to postsynaptic receptors. A small part of mediator diffuse along the cleft to metabolic extra-synaptic receptors. Correct description of mediator' diffusion is differential equations on branching surface. Rough description is differential equations in R^3 [3]. Value of error of the rough description is not estimated up to-day.

Diffusion of secondary messengers in branches. Diffusion flow Q of secondary messengers 1 and 2 are $Q_1(x,t) = -D_1 s(x)(p_1(x,t))_x$ and $Q_2(x,t) = -D_2 s(x)(p_2(x,t))_x$. Equation for diffusion of secondary messenger 1 is

$$(p_1)_t - D_1(s(x)(p_1)_x)_x + \varepsilon_1 p_1 = \mu \sum_v \delta(x - x_v) c(x_v, t). \quad (6)$$

Equation for concentrations p_2 and p_3 are:

$$(p_2)_t - D_2(s(x)(p_2)_x)_x + \varepsilon_2 p_2 = p_1; \quad p_3 = f(p_2(x,t)), \quad (7)$$

where $f(p)$ is monotone non-increasing function, $f(0) = 1$, $f(\infty) = 0$.

Conditions for concentrations in the nodes are: 1) continuity of concentrations in nodes; 2) sum of the diffusion flows to the node must be equal zero.

Conclusion

Mathematical model of a cluster contains equations (1) - (7) defined on the graph of the cluster. If the cluster contain gap- and tight-junctions then equations (2) - (5) and equations (6), (7) are defined on different graphs but they are one system. It is the first difficulty of neurons cluster's modelling. The second problem is difficulty of statistical description of neuronal clusters if pores and junctions are random distributed. And next, last but not least problem is difference between output spike sequences of cluster and of neurons without connections.

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