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Short Communication

SELF-WIRING IN NEURAL NETS OF POINT-LIKE CORTICAL NEURONS FAILS TO REPRODUCE CYTOARCHITECTURAL DIFFERENCES

FAIL M. GAFAROV

Department of Theoretical Physics
Tatar State University of Humanity and Pedagogic
420021 Kazan, Mezhlauk Street, 1 Russia
fgafarov@yandex.ru

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We propose a model for description of activity-dependent evolution and self-wiring between binary neurons. Specifically, this model can be used for investigation of growth of neuronal connectivity in the developing neocortex. By using computational simulations with appropriate training pattern sequences, we show that long-term memory can be encoded in neuronal connectivity and that the external stimulations form part of the functioning neocortical circuit. It is proposed that such binary neuron representations of point-like cortical neurons fail to reproduce cytoarchitectural differences of the neocortical organization, which has implications for inadequacies of compartmental models.

Keywords: Brain development; axon pathfinding; growth cone; neural circuits integration; chemoattractants; chemoreppelents.

1. Introduction

The nature of processes underlying the brain's self-organization into functioning neocortical circuits remains unclear. Various methods have been proposed for the theoretical description of activity-independent and activity-dependent emergence of complex spatio-temporal patterns, and establishment of neuronal connections [1, 6, 7, 16, 23, 24]. These theoretical investigations give a fresh understanding of the observed phenomena and stimulate discovery of emergent features of neural circuits. In this paper, we propose a new theoretical approach for the description of activity-dependent evolution and self-wiring between binary neurons. We propose a model based on the following experimental data (i)–(iii) and hypotheses (iv)–(v):

(i) Development of neuronal connectivity dependents on the neurons activity [5, 18, 21, 22];

(ii) Direction of motion of the growth cones is controlled by diffusible chemicals-axon guidance molecules (AGM[a]) [9, 11, 20, 25];
(iii) Axon's growth rate dependence on the neuron's activity [12, 13, 15, 19];
(iv) Depolarization causes neurons to release axon guidance chemicals [3, 14];
(v) Type of neuronal connectivity is determined postsynaptically during synaptogenesis [4, 8, 10].

A state of all cells at some moment is known as the activity pattern and sequential alternation of activity patterns are known as activity dynamics. We suppose that each neuron receives an external signal from a sensory cell (optical, taste, smell, etc.) and patterns of external signals are known as training patterns. We demonstrate an example of training process by stimulation of the developing net by the sequence of training patterns. The sequence of training patterns can be considered as a training program. The goal of the training is the creation of complex connections structure between initially disconnected neurons. For mathematical description of net's electrical activity, we use the simplest model [2]. We take into account only properties which are most important to the description of the activity-dependent self-wiring.

2. Mathematical Framework

In this section, we consider a mathematical basis for description of the activity-dependent self-wiring in neural nets. For mathematical description of neurons states and activity patterns, we use simple representation from modern neurobiology and artificial neural nets theory. At state of rest, neuronal membrane is polarized. When the membrane is locally depolarized up to a certain value of transmembrane potential by opening the ligand activated synaptic ion channels, then the voltage gated ion channels are opened, causing the generation of the action potential. The action potential travels along the axon and causes local depolarization of other neurons through synapses. We suppose that each neuron at each moment of time can be in two states: active, $S_i(t_j) = 1$, or inactive, $S_i(t_j) = 0$. For real neurons, the active state can be regarded as the real neuron's single spike or a sequence of spikes with frequency above some value.

We consider the ith neuron's cell body as a spherical object with center at the point with the radius-vector $\mathbf{r}_i$ in extracellular environment. For implementation of activity-dependent release of AGM in our model, we suppose that neurons release AGM at a moment of depolarization. For simplification, we assume that all neurons fire and release AGM synchronously, depending on their state. AGM released by neurons diffuse through the extracellular space, then bind to the axon's growth cone receptors and control their growth. When we consider AGM release by neurons, we neglect geometrical properties and consider them as a point sources of AGM.

[a]Abbreviations: AGM-axon guidance molecules.

According to our model, if the neuron is in active state, $S_i(t_k) = 1$, it releases some amount of AGM. We suppose that all neurons release the unit amount of one type of AGM which attracts the growth cones.

For description of AGM diffusion process, we use a simple diffusion equation. The concentration of AGM, c_{ij}, released by the ith neuron at the moment t_j can be found as the solution of the equation

$$\frac{\partial c_{ij}}{\partial t} = D^2 \Delta c_{ij} - k c_{ij} \tag{2.1}$$

with the initial conditions $c_{ij}(\mathbf{r}, \mathbf{r}_i, t_j) = \delta(\mathbf{r} - \mathbf{r}_i) S_i(t_j)$. Here, D and k are AGM diffusion and degradation coefficients in the intracellular medium respectively. We consider the case without boundary conditions. The solution of this equation, describing the concentration of AGM at the point $\mathbf{r}$ and at time t is

$$c_{ij}(\mathbf{r}, \mathbf{r}_i, t, t_j) = \frac{S_i(t_j)}{(2D\sqrt{\pi(t - t_j)})^3} \exp\left(-k(t - t_j) - \frac{|\mathbf{r} - \mathbf{r}_i|^2}{4D^2(t - t_j)}\right). \tag{2.2}$$

Total concentration of AGM at point $\mathbf{r}$ can be found by summation of concentrations of AGM, which were released by each neuron

$$C(\mathbf{r}, t) = \sum_{i=1}^{N} \sum_{j=1}^{k} c_{ij}(\mathbf{r}, \mathbf{r}_i, t, t_j). \tag{2.3}$$

According to the experimental data, we suppose that a growth cone will move only if its soma is at inactive state, and the force acting on it is proportional to AGM concentration gradient ∇C at the growth cone's position. Therefore, the equation of motion of the nth neuron's kth growth cone, described by the radius-vector $\mathbf{g}_k^n$ in the chemical field, can be written in the following form

$$\frac{d\mathbf{g}_k^n}{dt} = \lambda \nabla C(\mathbf{g}_k^n, t)[S_n(t) - 1] \tag{2.4}$$

where λ is a coefficient describing axon's sensitivity and motility. Taking into account the expression for total concentration from Eq. (2.3) and substituting it into Eq. (2.5) we obtain

$$\frac{d\mathbf{g}_k^n}{dt} = \lambda[S_n(t) - 1] \sum_{i=1}^{N} \sum_{j=1}^{k} \nabla c_{ij}(\mathbf{g}_k^n, \mathbf{r}_i, t, t_j). \tag{2.5}$$

From Eq. (2.2), we find the expression for gradient of AGM concentration c_{ij} in the form below

$$\nabla c_{i,j}(\mathbf{r}, \mathbf{r}_i, t, t_i) = -\frac{S_i(t_j)(\mathbf{r} - \mathbf{r}_i)}{16D^5 \pi^{\frac{3}{2}} (t - t_j)^{\frac{5}{2}}} \exp\left(-k(t - t_j) - \frac{|\mathbf{r} - \mathbf{r}_i|^2}{4D^2(t - t_j)}\right). \tag{2.6}$$

If a growth cone is close to the another cell's soma, i.e., if $|\mathbf{g}_k^n - \mathbf{r}_i| < \varepsilon$ (ε can be considered as the soma's geometrical radius), then synaptogenesis process takes place and synaptic connection between these neurons will be established. We describe the type of neuronal connections between ith and nth neurons using synaptic weights

$w_{n,i}$ ($w_{n,i} = 1$ means excitatory and $w_{n,i} = -1$ inhibitory connections). In our model, the type of synaptic connection established between neurons depends on the state of postsynaptic cell at synaptogenesis moment (if $S_i(t_k) = 1$ then $w_{n,i} = 1$, else $w_{n,i} = -1$). For implementation of the network's electrical activity dynamics, several models can be used (firing rate models, integrate and fire neurons, etc.). For simplicity, we will exploit the simplest one. We assume that the state of each cell at next moment of time is determined by states of another neurons, neuronal connections weights, and the external signal. Each postsynaptic cell integrates inputs coming from all presynaptic neurons and an external signal S_i^{ext}

$$s = \sum_{n=1}^{N} w_{n,i} S_n(t_i) + S_i^{\text{ext}}, \tag{2.7}$$

and the state of each neuron at next moment is determined by following the rule: if $s > 0$ then $S_i(t_{i+1}) = 1$, else $S_i(t_{i+1}) = 0$.

This model gives a closed set of equations describing AGM's release and diffusion, and axons growth and neuronal connections establishment, as well as the net's dynamics. In the flowchart (Fig. 1), the back loop in the neural net's activity-dependent development and self-wiring are shown. The concentration of AGM in the extracellular space is controlled by neurons state. Growth and movement of growth cones is managed by the concentration gradients of AGM. Growth cones can make

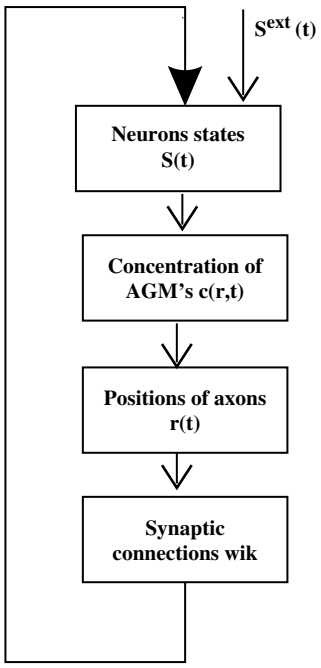

Fig. 1. A flowchart of self-wiring process.

neuronal connectivity with other neurons and change the network's connections which in turn change the network's activity.

3. Numerical Analysis

In this section, we present the result of the numerical simulation of the self-wiring net presented above. For testing possibilities and properties of self-wiring nets, we use the net with 27 neurons, $N = 27$, placed at the points with radius-vectors $\mathbf{r}_1 = (0, 0, 1)$, $\mathbf{r}_2 = (0, 0, 0)$, $\mathbf{r}_3 = (0, -1, 0), \ldots, \mathbf{r}_{27} = (1, 1, -1)$ (see Fig. 3). Each neuron has 27 growth cones, which can be considered as branches of its axon. Initially, all growth cones are located near the soma $\mathbf{g}_k^n = \mathbf{r}_k + \varepsilon, |\varepsilon| < 0.01$, and all synaptic weights are set equal to zero ($w_{ik} = 0$ $i, j = 1, \ldots, N$).

We can write Eq. (2.6) for AGM's gradient using a discrete time $t = n\Delta t$ (present time), $t_m = m\Delta t$ (release time) in the following form

$$\nabla c(\mathbf{r}, \mathbf{r}_i, m\Delta t, n\Delta t) = \frac{S_i(n\Delta t)(\mathbf{r} - \mathbf{r}_i)}{16D^5\pi^{\frac{3}{2}}((n-m)\Delta t)^{\frac{5}{2}}} \exp\left(-kt - \frac{|\mathbf{r} - \mathbf{r}_i|^2}{4D^2(n-m)\Delta t}\right), \tag{3.1}$$

where Δt is a time interval between the net's iterations. For simplication, we set $\Delta t = 1$ and rewrite Eq. (3.1) in terms of indices m, n

$$\nabla c_{m,n}(\mathbf{r}, \mathbf{r}_i) = \frac{S_i(n)(\mathbf{r} - \mathbf{r}_i)}{16D^5\pi^{\frac{3}{2}}(n-m)^{\frac{5}{2}}} \exp\left(-kt - \frac{|\mathbf{r} - \mathbf{r}_i|^2}{4D^2(n-m)}\right). \tag{3.2}$$

For numerical integration, we have to rewrite a growth cone equation of motion (2.5) in terms of the discrete time. Using the time interval $\Delta t = 1$, we obtain the recursion relation which allows us to calculate the spatial position of each growth cone at the moment $k + 1$, in terms of the kth moment

$$\mathbf{g}_{k+1} = \mathbf{g}_k + \lambda[S_n(t_k) - 1] \sum_{i=1}^{N} \sum_{m=1}^{k} \nabla c_{m,k}(\mathbf{g}_k, \mathbf{r}_i). \tag{3.3}$$

In the above equation, we have omitted indices, describing a cell's and the growth cone's number. The value $\Delta t = 1$ is not critical for numerical calculations of the model and it was only used for the sake of simplification. Different values of parameters D, k, λ gives different connectivity patterns between neurons, because these parameters characterize growth cone's movement speed, and AGM's acting distance. Basic properties of the net have remained unchanged. For all subsequent numerical calculations, we have used the following values: $D = 0.1$, $k = 0.1$, $\lambda = 10$.

In Fig. 2, we present the contour plot of the section by plane $z = 0.02$, the static AGM concentration when the 6th, 7th, 15th, 16th, 19th neurons are in active state. The arrows reproduce the concentration gradients which point to the axons movement directions at the particular place.

By using the appropriate training patterns sequence, the net is built with inhibitory and excitatory connections, which is evolved in an oscillatory manner

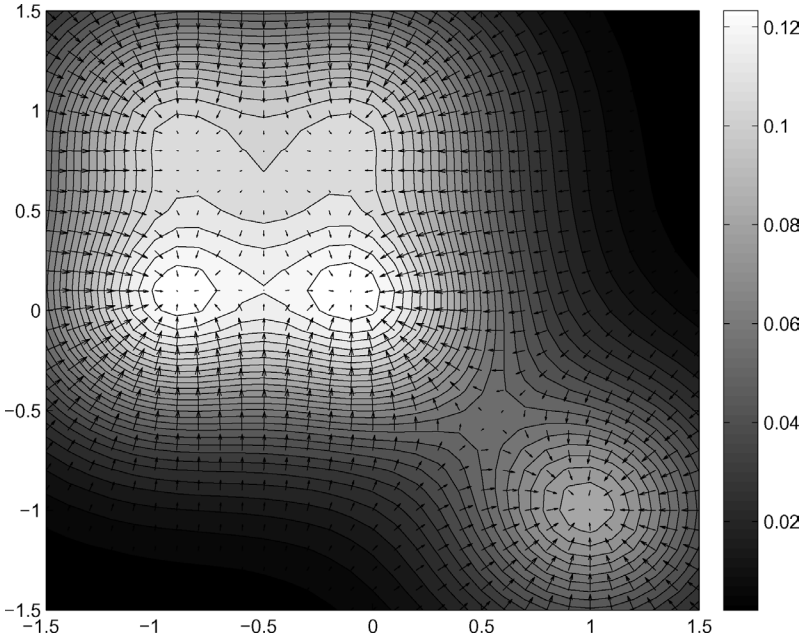

Fig. 2. The contour plot of target-derived AGM concentration. The concentration of AGM is higher in lighter regions of the figure. The arrows reproduce the concentration gradients which means the axons movement directions for the particular place.

without any external stimulation. As an example, we present the results of the network training process which was obtained by using the following training pattern sequence: $S_{11}^{\text{ext}} = 1$ for $10 < n < 192$; $S_{14}^{\text{ext}} = 1$ for $192 < n < 360$; $S_{5}^{\text{ext}} = 1$ for $360 < n < 515$; $S_{5}^{\text{ext}} = 1$ for $525 < n < 576$; $S_{2}^{\text{ext}} = 1$ for $580 < n < 875$; $S_{6}^{\text{ext}} = 1$ for $580 < n < 880$; $S_{8}^{\text{ext}} = 1$ for $580 < n < 880$; $S_{23}^{\text{ext}} = 1$ for $580 < n < 880$. In Fig. 3, we reproduce three-dimensional picture of the state of the net at the beginning of simulation. Individual neurons (whilst without neuronal connections) are depicted as spheres and its states depicted by shade (bright — active state, dark — inactive). The traveling axon's branches are depicted as thin curves. From this figure, one can see how axons grow toward the active cell. When the growth cone reaches the soma of another neuron, two neurons became connected and axon's connected branch is depicted by thick curve (Fig. 4). The synapse type (inhibitory or excitatory) is depicted by the shade of a curve (bright — excitatory, dark — inhibitory). When the branch of the same axon reaches another cell, which has already connected with it, this branch will be deleted. The neural net obtained by training is shown in Fig. 5.

Further training of this net is a hard problem because the internal oscillation will influence the training process. The oscillating patterns of neuronal activity will cause establishment of new connections, even after switching off the external stimulation, and can cause uncontrolled self-wiring. In the forthcoming papers, we plan to develop programming (training) methods in order to build the net with initially defined connections.

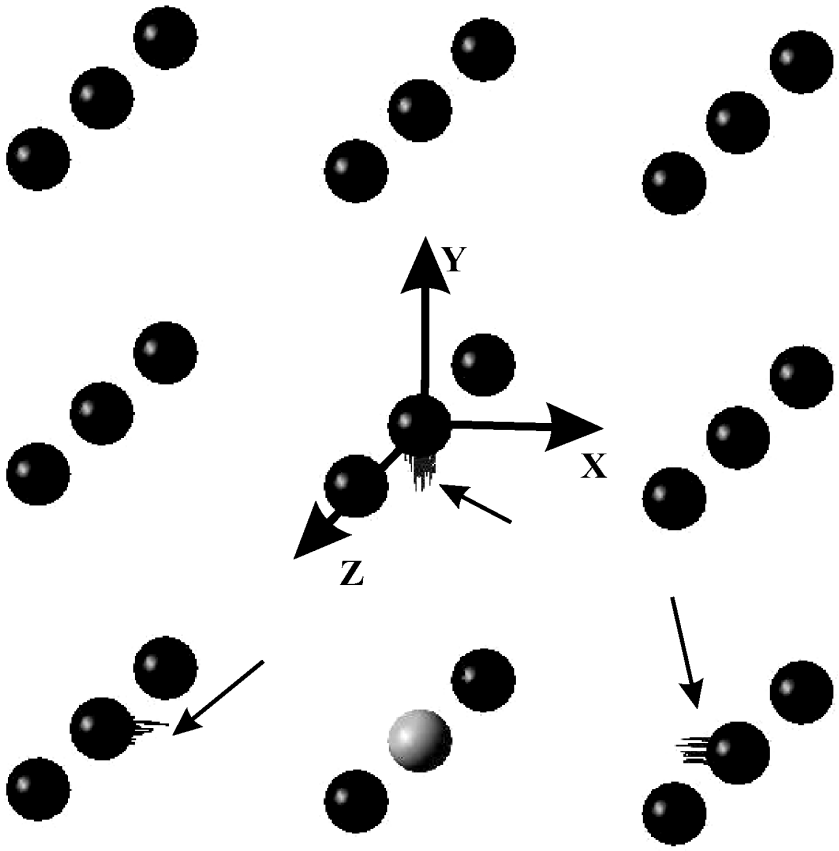

Fig. 3. Activity-dependent evolution at the beginning of simulation ($n = 110$), see Section III. One of the cell has stimulated by the external signal $S_{11}^{\text{ext}} = 1$ (bright sphere), and other neurons are at inactive state. The axon's branches of the nearest neurons have started to grow in the direction of the active cell because it releases AGM.

We can gain access to the patterns stored in the net by stimulating them by external patterns. As an external stimulation will cause activation of neurons and release of AGM, we conclude that access to the memory can change the connectivity pattern, i.e., patterns stored in the memory.

4. Conclusions

In this paper, we presented a mathematical model describing processes of self-wiring in neural nets. The model can give us a new understanding of real neural nets development and functioning. By using the computer simulations, we showed that the long-time memory can be encoded in neuronal connectivity and in what way the external stimulations builds a functioning neural network.

Hypotheses that are proposed here should be tested experimentally (*in vivo*, *in vitro*), to verify the possibilities of presented model application for qualitative

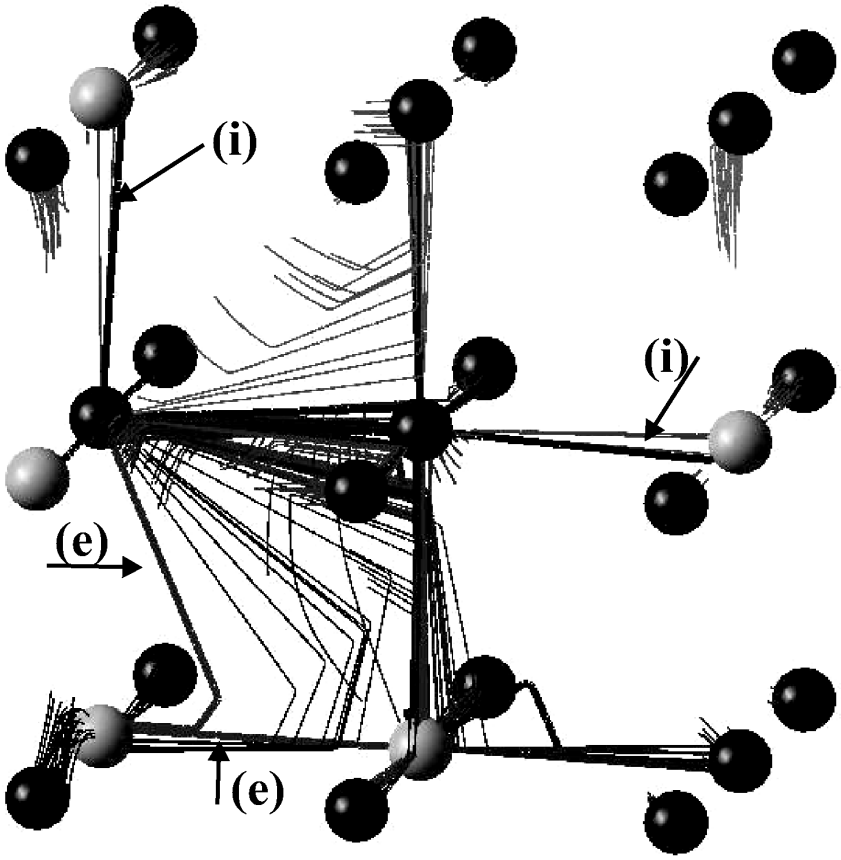

Fig. 4. Activity-dependent evolution at $n = 680$. Between some of the neurons inhibitory (i) and excitatory (e) connections have been established.

and quantitative description of a neuronal integration processes in a real nets. Our approach gives only general modeling scheme of activity-dependent network formation processes and in accordance with experimental data, the model can be complicated and a particular rule describing separate processes can be changed.

The theoretical framework developed here can be used for describing the development of a particular set of neurons constituting the neural system, which can be located in the media also containing other type of neurons and glial cells. In our model, axon's branches began to grow directly from the soma. In a real nets, growth cones can be guided at the beginning of growth by other mechanisms (e.g., genetically determine contact adhesion, etc.) and by the mechanism presented in this paper. Geometrical properties and activity of real neurons are more complicated and they have dendrites. Here, we used the most simple representations of hypothetical neurons (large spherical soma without dendrites) and its activity (binary neurons). Using the approach described here, it is possible to construct a model for describing real particular networks, using more realistic models of neurons (ingrate-and-fire,

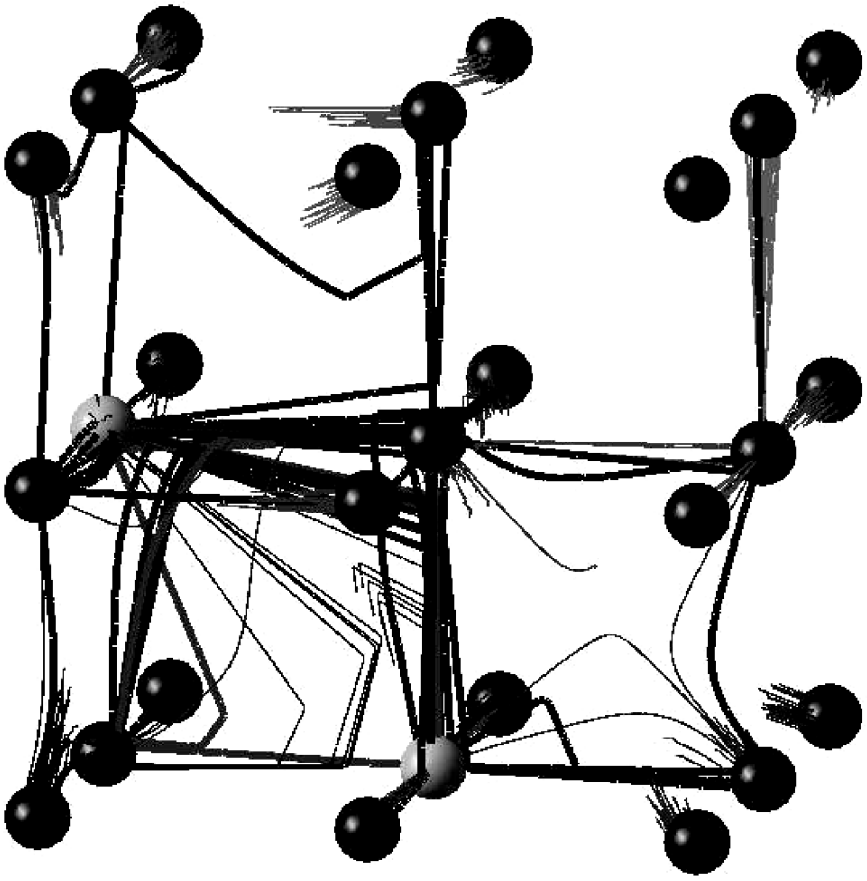

Fig. 5. Activity-dependent evolution at ($n = 910$). By using the training program the complicated connections pattern between neurons have been created. The network has following neuronal connections: $w_{10,11} = 1$, $w_{12,11} = 1$, $w_{2,11} = 1$, $w_{13,14} = -1$, $w_{15,14} = -1$, $w_{5,14} = -1$, $w_{23,14} = -1$, $w_{17,14} = -1$, $w_{11,14} = 1$, $w_{6,5} = -1$, $w_{4,5} = -1$, $w_{8,5} = -1$, $w_{2,5} = 1$, $w_{11,5} = -1$, $w_{17,5} = -1$, $w_{15,5} = -1$, $w_{13,5} = -1$, $w_{12,5} = 1$, $w_{14,5} = 1$, $w_{10,5} = 1$, $w_{14,11} = -1$, $w_{20,11} = -1$, $w_{1,2} = -1$, $w_{3,2} = -1$, $w_{7,8} = -1$, $w_{23,24} = -1$, $w_{22,23} = -1$, $w_{26,23} = -1$, $w_{9,6} = -1$, $w_{15,6} = -1$, $w_{9,8} = -1$, $w_{17,8} = -1$, $w_{3,6} = -1$, $w_{12,2} = -1$, $w_{14,2} = -1$, $w_{5,11} = -1$, $w_{5,6} = -1$, $w_{14,23} = -1$, $w_{17,6} = -1$, $w_{12,6} = -1$, $w_{14,6} = -1$, $w_{10,6} = -1$, $w_{20,6} = -1$, $w_{20,2} = -1$, $w_{13,16} = -1$, $w_{20,23} = -1$, $w_{10,2} = -1$, $w_{13,11} = -1$, $w_{5,2} = 1$.

Hodgkin–Huxley, etc.) and taking into account neurons geometrical properties and dendrites. We suppose that the model presented can be used for describing self-wiring processes in a developing (embryonal) as well as adult neuronal systems.

Cytoarchitectural differences between different cortical areas are the result of differences in the distributions of neuronal phenotypes and morphologies. Self-wiring between binary neurons fails to reproduce cytoarchitectural differences of the neocortical organization, which has implications for inadequacies of compartmental models. In order to reproduce cytoarchitectural differences, axonal and dendritic morphologies of single neurons [17] need to be integrated into the model.

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