Activity-dependent self-wiring is a basis of structural plasticity in neural networks

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Abstract

Dynamical rewiring in neural networks is carried out by activity-dependent growth and retraction of axons and dendrites, guided by gudance molecules, released by target cells. Experience-dependent structural changes in cortical microcurcuts lead to changes in activity, i.e. to changes in information encoded. Specific pattens of external stimulation can lead to creation of new synaptical connections between neurons. Calcium influxes controlled by neuronal activity regulates processes of neurotrophic factors release by neurons, growth cones movement and synapse differentiation in developing neural system, therefore activity-dependent self-wiring can serve as a basis of structural plasticity in cortical networks and can be considered as a form of learning.

I. INTRODUCTION

The neural system is a complex self-wiring system, which consists of a huge number of interconnected individual cells (neurons). Two main types of signaling exist in a neural system: short-range synaptic signaling between neurons, provided by neurotransmitters, which acts on postsynaptic neuron's state and long(short)-range signaling by chemicals that acts on neuron's geometrical properties (position of cell, dendrites, axons). Each function of the mature neural system depends on the actions of distinct neuronal circuits and therefore proper functioning of the neural net depends on correctness of axonal projections and interneuronal connections.

In *in vitro* experiments it is shown that neurons self-organize into homogeneous or clustered networks and correlations between neurons activity emerges (Segev at all 2003; Shefi at all 2002.; Sorkin at all 2006). A model for description of activity-dependent neural network development has been proposed by van Ooyen and collaborators. The model consists of initially disconnected neurons, modelled as neuritic field, which are organized into a network under influence of their internal activity (van Ooyen 1994; van Ooyen at all 1996). Outgrowth of neurites connected with Ca^{2+} concentration inside the cell. Therefore growth of neurons depends on their own level of activity, and the neurons become connected when their fields overlap. According this model high level of activity causes neurites to retract, whereas low level allows further outgrowth. Using mathematical model they showed, that spatial distribution of the cells can create connectivity patterns in which hysteresis appears and complex periodic behavior take place (van Ooyen A & van Pelt J. 1994; van Ooyen A & van Pelt J. 1996;). Segev & Ben-Jacob presented a model that incorporates stationary units representing the cells soma and communicating walkers representing the growth cones. The dynamics of the walker's internal energy is controlled by the soma, and they migrate in response to chemorepulsive and chemoattractive glues emitted by the soma and communicate with each other and with the soma by means of chemotactic feedback (Segev & Ben-Jacob 2000).

It is currently accepted that cortical maps are dynamic constructs that are remodelled in response to external input (Majewska & Sur 2006). Two types of plasticity in neural system is known: synaptical plasticity and structural plasticity. Synaptical plasticity involves activity-dependent weight changes between previously connected neurons (Kempter at all

1999). Structural plasticity includes remodelling of axons and dendrites, synapse formation and elimination (Chklovskii at all 2004). Dynamical rewiring could provide an important mechanism for information storage, although at a cost of more complex biological machinery and slower learning. Understanding structural plasticity requires identification of physical mechanisms that lead to formation new synaptical connections. Like as synaptical plasticity structural plasticity is controlled by neuronal activity. Neuronal activity controls metabolic process in neurons through calcium influx through voltage dependent calcium channels. Calcium transients plays a cental role in axon guidance, neuron differentiation and synaptical plasticity (LTP,LTD) (Jin at all 2005; Ming at all 2001; Henley & Poo 2004).

In this paper, using the framework presented in (Gafarov 2006) is demonstrated that activity-dependent self-wiring could provide sufficient basis for structural plasticity in the developing neural system. The model is based on the following experimental data (i)-(iii) and assumption (iv)-(v):

(i) Development of neuronal connectivity dependents on the neurons activity (Zhang & Poo 2001; Catalano & Shatz 1998.) ;

(ii) Direction of motion of the growth cones is controlled by diffusible chemicals - axon guidance molecules (AGM) (Goodhill & Hu 2005;Goldberg 2003; Henley & Poo 2004;Hentschel & van Ooyen 1999);

(iii) Axon's growth rate dependent on the neuron's activity (Ming at all 2001);

(iv) Depolarization causes neurons to release axon guidance molecules (Balkowiec & Katz 2000; Balkowiec & Katz 2002; Hartmann at all 2001.);

(v) Type of neuronal connectivity is determined postsynaptically during synaptogenesis (Zhang & Poo 2001; Spitzer at all 2000).

II. STRUCTURAL PLASTICITY IN SRM NEURONS NETWORK

The neurons extend axons because of a specialized structures at the end of axons called growth cones, which have a several important properties. The most important property is that the growth cones contain several finger-like projections called filopodia which can sense local environmental chemicals (Goldberg 2003). To reach their proper targets, axons rely upon the actions of attractive and repulsive axon guidance molecules (AGM's), including the netrins, Slits, semaphorins, ephrins and other chemicals (Keynes & Cook 1995; Dickson 2002; Tessier-Lavigne & Goodman 1996; Palmer & Klein 2003; Nieto 1996).Therefore, axons find their targets using chemicals released by a target and surrounding cells (Yu & Bargmann 2001). The growth cone is able to detect gradients of AGM as small as a difference of a single molecule across its structure (Betz at all 2006). Chemotropic molecules are released from a target cells and establish a gradient of increasing concentration toward the target. Concentration gradients of these extracellular chemicals and cellular interactions are translated by receptors at the cell surface into physical forces that control the dynamic architecture of the axon as it explores the surrounding terrain (Goldberg 2003). Growth cone feels concentration gradients of AGM's and turns in the direction of increasing (chemoattractant) or decreasing (chemoreppelent) chemical's concentration. These guidance systems are used to generate an astonishingly varied set of neuronal circuits. Axon elongation is a complex process, which includes construction of cytoskeleton and insertion of new membrane regulated by internal and external environment. Using mathematical framework of gradient detection by growth cone have been made estimations for axonal response to attractive and repulsive gradients of different concentrations and steepness and had been found, that for target-derived diffusible chemicals range of guidance is about 1 mm, and 1 cm for substrate -bound gradient (Goodhill 1998; Goodhill at all 2004).

Cell's electrical activity and electrical stimulation, via calcium dependent mechanisms, influences axonal pathfinding, and results on a marked alternation of turning responses of the growth cone induced by gradients of AGM's (Ming at all 2001). The action potentials induced by electrical stimulation causes depolarization of the neuronal membrane and cause calcium influx through voltage-dependent calcium channels, what alters turning responses of the growth cone. Turning of the growth cones in gradients of AGM's depends on the number, frequency and pattern of the stimuli (Ming at all 2001). Calcium signals trigger intracellular mechanisms leading to the cytoskeletal rearrangement required for growth cone elongation and turning. Environmentally regulated growth cone calcium transients also control axon growth, and the rate of axon outgrowth is inversely related to the frequency of spontaneous growth cone calcium transients (Gomez & Zheng 2006). Depending on the type of neuron and experimental situation, the different responses of growth cones have been observed, from increasing growth cone motility to inhibition of neurite growth. Different levels of intracellular calcium concentration regulate different cellular events and can lead to a diametrically opposite effects on growth cone motility (Henley & Poo 2004; Robles at all 2003).

In the model we supposed that the rate of axon's growth depends on AGM concentration gradient $\nabla C(\mathbf{g}_k^n, t)$ at the growth cone's position and axon's firing rate $\nu(t)$, and growth cone's equation of motion can be written in the form

$$\frac{d\mathbf{g}_k^n}{dt} = \lambda F(\nabla C(\mathbf{g}_k^n, t), \nu(t)), \tag{1}$$

where λ is a coefficient describing axon's sensitivity and motility, $\mathbf{g}_k^n$ is a vector describing n-th neuron's k-th growth cone's position. Here we used the most simple case of the function describing axon outgrowth

$$\frac{d\mathbf{g}_k^n}{dt} = \frac{\lambda}{1 + e^{-b\nu(t)}} \nabla C(\mathbf{g}_k^n, t) \tag{2}$$

For description of neuron's activity we used Spike-Response Model (SRM) (Gerstner & van Hemmen 1992; Gerstner 1995). Following (Gerstner & van Hemmen 1992; Gerstner & Kistler 2002) the membrane potential $u_j(t)$ of j-th neuron at time t is defined as

$$u_i(t) = \eta(t - \hat{t}_j) + \sum_j w_{ij} \sum_f \epsilon_0(t - t_j^{(f)}) + \int_0^\infty k(s) I_i^{ext}(t - s) ds. \tag{3}$$

The response kernels η, ϵ_0, k that describe the effects of spike generation, spike reception and external input on the membrane potential are described by the following functions (Gerstner & Kistler 2002):

$$\eta(t - \hat{t}) = -v - \eta_0 \exp\left(\frac{t - \hat{t}}{\tau_{refr}}\right) \Theta(t - \hat{t}) \tag{4}$$

$$\epsilon_0(t - t_i) = \frac{1}{1 - (\tau_s/\tau_m)} \left[\exp\left(-\frac{t - t_i}{\tau_m}\right) - \exp\left(-\frac{t - t_i}{\tau_s}\right)\right] \Theta(t - t_i) \tag{5}$$

$$k(s) = \exp\left(-\frac{s}{\tau_e}\right) \Theta(s) \tag{6}$$

If $u_j(t)$ crosses from below ($\frac{du}{dt} > 0$) a threshold θ at a moment $t_j^{(f)}$ then a spike is generated.

In (Gafarov 2006) was proposed a hypothesis that neurons release AGM at firing time. The activity dependent release of AGM is a key point in our model. As far as we know in neurobiological literature there is no complete proof of the activity dependent AGM release and we consider this point as an hypothesis. Release of some neurotrophic factors can be triggered by external stimulation and neuron's electrical activity (Balkoweic & Katz 2000; Balkoweic & Katz 2002; Hartmann at all 2001). We suppose that all neurons release the unit amount of the one type AGM which causes only attraction of growth cones. Therefore, the concentration of AGM, c_{ij}, released by the i-th cell at the moment t_j can be found as the solution of the diffusion equation

$$\frac{\partial c_{ij}}{\partial t} = D^2 \Delta c_{ij} - k c_{ij}, \tag{7}$$

with the initial conditions $c_{ij}(\mathbf{r}, \mathbf{r}_i, t_j) = \delta(\mathbf{r} - \mathbf{r}_i)\delta(t - t_i^j)$ (point-like sources). Here D and k are AGM's diffusion and degradation coefficients in the intracellular medium. For simplicity let's consider the case without boundary conditions. The solution of this equation, describing the concentration of AGM released by a single spike of $i - th$ neuron is

$$c_{ij}(\mathbf{r}, \mathbf{r}_i, t, t_i^{(f)}) = \frac{\Theta(t - t_i^{(f)})}{(2D\sqrt{\pi(t - t_i^{(f)})})^3} \exp\left(-k(t - t_i^{(f)}) - \frac{|\mathbf{r} - \mathbf{r}_i|^2}{4D^2(t - t_i^{(f)})}\right). \tag{8}$$

The total concentration and gradient of concentration of AGM at the point $\mathbf{r}$ can be found by summation of concentrations and and gradients of concentration of AGM which were released by each cell (Gafarov 2006)

$$C(\mathbf{r}, t) = \sum_{i=1}^{N} \sum_{f=1}^{\infty} c_{ij}(\mathbf{r}, \mathbf{r}_i, t, t_i^{(f)}), \tag{9}$$

$$\nabla C(\mathbf{r}, t) = \sum_{i=1}^{N} \sum_{f=1}^{\infty} \nabla c_{ij}(\mathbf{r}, \mathbf{r}_i, t, t_i^{(f)}), \tag{10}$$

where

$$\nabla c_{ij}(\mathbf{r}, \mathbf{r}_i, t, t_i^{(f)}) = \frac{\Theta(t - t_i^{(f)})(\mathbf{r} - \mathbf{r_i})}{16D^5\pi^{3/2}(t - t_i^{(f)})^{5/2}} \exp\left(-k(t - t_i^{(f)}) - \frac{|\mathbf{r} - \mathbf{r}_i|^2}{4D^2(t - t_i^{(f)})}\right). \tag{11}$$

If the position of some 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 synaptic connection between these neurons will be established. Synapse formation is controlled by dynamic interactions between various genes and their encoded proteins and occurs throughout development to generate synapse specificity (Munno & Syed 2003; Garner at all 2002). The modern version of Dale's principle suggests that all of a particular neuron's terminals release the same set of neurotransmitters (Eccles 1986). Nevertheless, it is well known that a neuron can store and presumably release the different sets of transmitters from individual axonal endings (Sossin at all 1990). For example, the release of glutamate and GABA from MF could also be segregated according to the type of target onto which they impinge. Their expression is regulated in an activity-dependent manner and coincides with the appearance of GABAergic transmission from the mossy fibers to pyramidal cells in area CA3 (Romo-Parra at all 2003). Golgi cell can perform pure GABAergic inhibition of granule cells and pure glycinergic inhibition of unipolar brush cells. This specialization depends from the differential expression of $GABA_A$ and glycine receptors by target cells and not from a segregation of GABA and glycine in presynaptic terminals (Dugué G at all 2005). Developing hippocampal granule cells express the markers of the glutamatergic and GABAergic phenotypes, but when development is ended, the GABAergic phenotype shuts off. The neurotransmitter choice of the granule cells depends on programmed and environmental factors, and this process is neither limited by a critical period nor restricted by their insertion in a network (Gómez-Lira 2005). Calcium transient patterns play a key role in the differentiation of neural precursor cells, and their frequency may specify neuronal morphology and acquisition of neurotransmitter phenotype (Ciccolini at all 2003). Electrical activity can regulate the choice of neurotransmitter in cultured neurons through calcium influx and can differentially affect the regulation of transmitter expression (Gutiérrez R. 2005). Certain neurons choose the neurotransmitter they use in an activity-dependent manner, and different trophic factors are involved in this phenotypic differentiation during development. Regulation of transmitter expression occurs in a homeostatic manner. Suppression of activity leads to an increased number of neurons expressing excitatory transmitters and a decrease number of neurons expressing inhibitory transmitters and vice versa (Borodinsky at all 2004).

Due to above discussion we supposed in framework of our approach that each neuron's different terminals (branches of the same axon) can release different neurotransmitters and can establish different types of synaptic connections (inhibitory or excitatory). The type of synapse can be determined by state of presynaptic or/and postsynaptic neuron. For simplification we assumed also that the type of a synaptic connection between cells depends on the state of postsynaptic cell at synaptogenesis process. This assumption can be changed for special neurons, according to experimental data. For simplicity the type of the neuronal connections between i-th and n-th neurons we described by using static synaptic weights $w_{n,i}$ ($w_{n,i} = 1$ means excitatory and $w_{n,i} = -1$ inhibitory connections) and the type of synaptic connection established between neurons depends on the state of postsynaptic cell at synaptogenesis moment (if $\nu_i(t) > \nu_{tr}$ then $w_{n,i} = -1$, else $w_{n,i} = -1$).

The model gives a closed set of equations describing AGM's release and diffusion, and axons growth and synaptical connections establishment as well as the net's electrical activity dynamics. The concentration of AGM in the extracellular space is controlled by neurons activity. Growth and movement of growth cones is managed by the concentration gradients of AGM and neuronal activity. Growth cones can make synaptic connections with other neurons and change the network's connections structure which change the network's activity.

Numerical simulation of the model were performed using the net which consist of N=8 neurons, placed at tops of a cube (Fig.1). Initially all neurons has no synaptic connections and all axons placed near the the soma. Different values of parameters gives different connectivity patterns between neurons, because these parameters characterize neuron's electrical properties,and growth cone's movement speed, and AGM's acting distance, and etc. The figures presented here have been obtained using the following values of parameters: $\eta_0 = 0.06$, $\tau_{refr} = 0.1$, $v = 0.03$, $\theta = -0.02$, $\tau_s = 0.01$, $\tau_m = 0.2$, $\tau_e = 0.1$ and $D = 0.8$, $a = 0.2$, $\lambda = 0.00005$. External current were taken in the form $I_i^{ext} = 0.5\sin(0.2(i-4)t+i)+1$, where i is the number of neuron. After simulation start, growth cones began moving in the direction of concentration gradients (Fig. 1). Several studies show that neural activity affects individual axonal branching in vivo. Increasing of neuronal activity leads to appearance of new branches (Uesaka 2005; Portera-Cailliau at all 2005). In the model, branching of growth cone is dependent on activity (new branch added only if $\nu_i > 10\ c^{-1}$).

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. 2). The synapse type (inhibitory or excitatory) is depicted by color of a curve (bright - excitatory, dark-inhibitory). When the branch of the same axon reaches the another cell, which has already connected with it, this branch will be deleted. Structural changes leads to changes in electrical activity of neurons, i.e to changes in the time dependence of membrane potentials $u_j(t)$ (Fig. 3).

III. CONCLUSIONS AND SUGGESTIONS FOR FUTURE MODELLING

Neural activity plays a central role in experience-dependent rewiring of cortical microcircuits. Activity-dependent structural plasticity can be considered as a special case of synaptical plasticity in fully connected network. Both of these types of plasticity are dependent on activity pattern of neurons. But in contrast to synaptical plasticity structural plasticity imply changes in connection map. Real neural net are sparsely connected and in

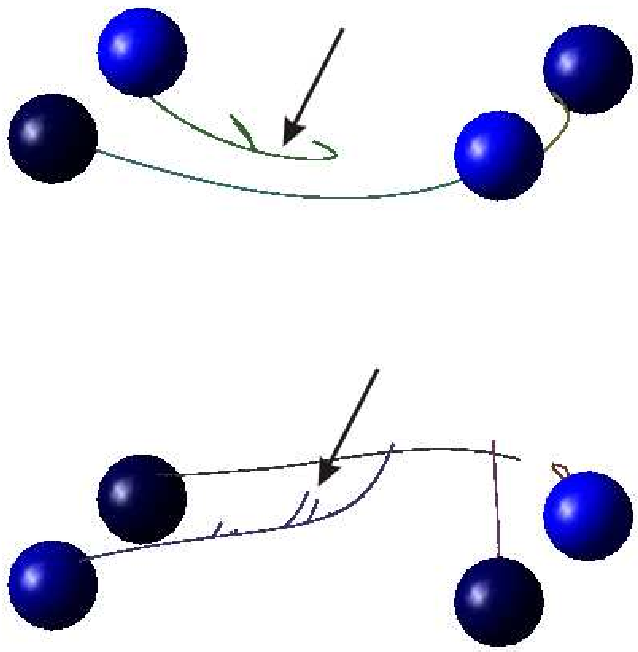

FIG. 1: Three dimensional picture of the state of the net at the simulation beginning. Individual neurons (whilst without neuronal connections) depicted as spheres, the firing rates depicted by brightness (bright - hight firing rate, dark- low). The growing axons are depicted as thin curves. One can see from this figure, how axons grow toward active cells and that some axons began branching (new branches pointed by arrows).

no circumstances we cannot consider them as fully connected network. Activity-dependent self-wiring involves establishment of new synaptic connections between previously unconnected cells, and this conception is important for investigation of learning in real networks. In the model developed here, finding of appropriate partnership between pre- and postsynaptic neuron is controlled by activity of neurons, therefore different patterns of external input I_i^{ext} through regulation of neuronal activity will lead to functionally distinct circuits, and changes in connections structure can lead to changes in activity (Fig. 3) of the wholly network. For the further theoretical and computational investigations of structural plasticity in neural networks the model presented here, can be sophisticated on the basis of new experimental findings, for example:

- Cells can release also repellant in activity-dependent or activity-independent manner, therefore a model where at inactive state cells release a repellant, at active state - an attractant, or vice versa, can be considered.

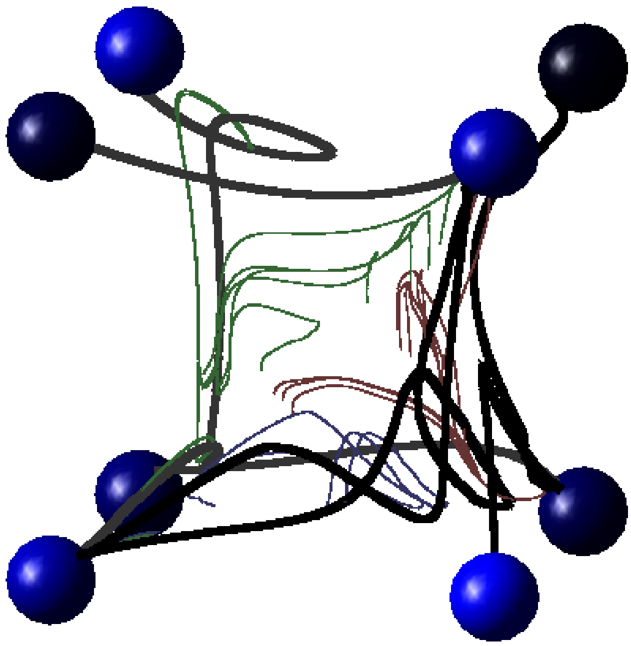

FIG. 2: Three dimensional picture of the final state of the net. The net has weighs $w_{5,7} = 1$, $w_{2,4} = 1$,$w_{8,4} = -1$, $w_{3,4} = -1$, $w_{1,6} = 1$, $w_{7,6} = -1$, $w_{6,7} = -1$.

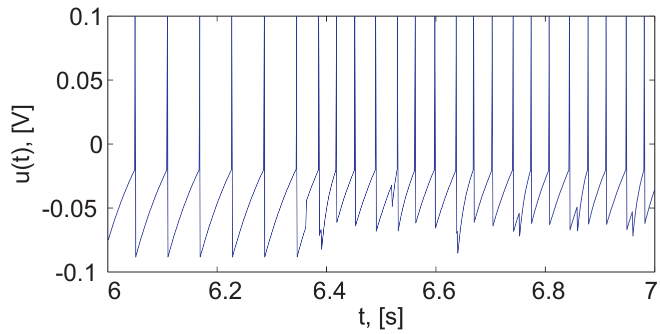

FIG. 3: The time dependence of membrane potential of 5-nd neuron. One can see postsynaptic potentials, and firing rate increasing after $t = 6.35$ c because of new synaptic connection between 7-nd and 5-nd neurons.

- A set of cells releasing different types of AGM, and different types of growth cones regulated by different AGM can be considered.
- Depending on the cell's level of activity, a growth cone can be repelled or attracted by the same AGM.
- Growth cones themselves can release chemicals and influence other growth cones move-

ment.

- A real neurons has also dendrites. For simplification of model we did not consider them, and supposed that axons connect directly to a soma. Incorporation into model also guidance of dendrites by different chemicals, can cause discovery of a new interesting properties of structural plasticity.
- Hebbian learning can be incorporated.

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