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Neural electrical activity and neural network growth

F.M. Gafarov *

Institute of Computational Mathematics and Information Technologies, Kazan Federal University, Kremlevskaya 35, Kazan, 420008, Russia
Laboratory of Neurobiology, Kazan Federal University, Kremlevskaya, 35, Kazan, 420008, Russia

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ABSTRACT

The development of central and peripheral neural system depends in part on the emergence of the correct functional connectivity in its input and output pathways. Now it is generally accepted that molecular factors guide neurons to establish a primary scaffold that undergoes activity-dependent refinement for building a fully functional circuit. However, a number of experimental results obtained recently shows that the neuronal electrical activity plays an important role in the establishing of initial interneuronal connections. Nevertheless, these processes are rather difficult to study experimentally, due to the absence of theoretical description and quantitative parameters for estimation of the neuronal activity influence on growth in neural networks. In this work we propose a general framework for a theoretical description of the activity-dependent neural network growth. The theoretical description incorporates a closed-loop growth model in which the neural activity can affect neurite outgrowth, which in turn can affect neural activity. We carried out the detailed quantitative analysis of spatiotemporal activity patterns and studied the relationship between individual cells and the network as a whole to explore the relationship between developing connectivity and activity patterns. The model, developed in this work will allow us to develop new experimental techniques for studying and quantifying the influence of the neuronal activity on growth processes in neural networks and may lead to a novel techniques for constructing large-scale neural networks by self-organization.

1. Introduction

During ontogeny, neural subnetworks in the developing brain evolve from the initial disconnected state to the connected matured state (Ko, Cossell, Baragli, Antolik, Clopath, Hofer, & Mrsic-Flogel, 2013; Quartz, 1999; White & Fitzpatrick, 2007). The formation of correct neural connectivity during the nervous system development is important for high-level cognitive and motor behaviors. It is widely accepted that topographic organization in the nervous system is generated by the patterns of gene expression (Ackley & Jin, 2004) and the patterns of electrical activity (Krubitzer & Kahn, 2003). According to the early ideas by Hebb (1949) new synaptic connections preferentially grow between active neurons. The connectivity is fixed not only during development but also in the adulthood and massive processes of synapse deletion and reorganization of the connectivity during ontogeny (Butz, Wrgtter, & van Ooyen, 2009; Chklovskii, Mel, & Svoboda, 2004). The electrical activity of neurons triggers secondary processes in the form of molecular signaling cascades which leads to the corresponding changes in the shapes of neurons, dendritic spines and axonal boutons configuration, receptor configuration, neurite branching, growth and guidance (Borodinsky & Belgacem, 2016; Lim, Stafford, Nguyen, Lien, Wang, Zukor, He, & Huberman, 2016; Neely & Nicholls, 1995). However, the fundamental mechanisms controlling the developmental process of realistic connectivity generation in neural networks remain unknown. A deeper understanding of the connections growth process in neural networks will give us information about early developmental stages of the brain.

Neuroscientists believe that information is stored in the connection weights of neural networks (Chklovskii et al., 2004; Quartz & Sejnowski, 1997). Despite considerable progress in neuroanatomy, electrophysiology and imaging (Stetter, Battaglia, Soriano, & Geisel, 2012) of the detailed mapping of neural connectivity is a difficult task. The relationship between the connectome (Sporns, Tononi, & Ktter, 2005) and cortical function remains unclear, so we need to discover the nature and purpose of the principles underlying cortical connectivity (Budd & Kisvrday, 2012). Each sensory stimulus causes a complex pattern of activity in the neural populations of multiple cortical areas. The relationship between sensory stimuli, and firing patterns they evoke defines the 'neural code' of the corresponding populations of neurons (Harris & Mrsic-Flogel, 2013). A precise understanding of local networks dynamics requires relating circuit activity with the underlying network structure.

* Correspondence to: Institute of Computational Mathematics and Information Technologies, Kazan Federal University, Kremlevskaya 35, Kazan, 420008, Russia.
E-mail address: fgafarov@yandex.ru.

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Biological neural networks are spatially embedded and each neuron of the network occupies a specific position in 3D space, therefore the distances between neurons and spatial geometry must play an important role in the network topology generation. Therefore, developing neural networks must be considered as a dynamically growing networks which evolve gaining links and nodes as they develop over time, by using the spatio-temporal network frameworks (Holme & Saramki, 2012; Yuan, Zhou, Li, Chen, & Wang, 2013), and achievements of the modern complex networks theory methods (Boccaletti, Latora, Moreno, Chavez, & Hwang, 2006). Many complex systems are very often organized in the form of networks where nodes and edges are embedded in physical space with a strong relationship between geometry and network connections (Barthélemy, 2011; Roberts, Perry, Lord, Roberts, Mitchell, Smith, et al., 2016). Complex networks with dynamic links are presented in different fields and several network generative mechanisms have been proposed: random, scale-free, small-world network, etc. (Albert & Barabási, 2002; Erdős & Rényi, 1960; Small, Li, Stemler, & Judd, 2015; Watts & Strogatz, 1998). By using the methods of complex networks theory many studies considered neural networks as random, small-world and scale-free networks (Bassett & Bullmore, 2017; Kim & Lim, 2016; Muller, Destexhe, & Rudolph-Lilith, 2014; Rubinov, Sporns, van Leeuwen, & Breakspear, 2009; Yu, Xu, Zhou, & Li, 2017).

In our previous theoretical works (Gafarov, Khusnutdinov, & Galimyanov, 2009; Suleymanov, Gafarov, & Khusnutdinov, 2013) we developed a spatially based growing network model for studying the statistical properties of the developing neural networks. By using numerical simulations we have shown that the activity-dependent growth in neural networks results in the formation of a well-known "small-world" network (Gafarov, 2016; Gafarov & Gafarova, 2016). In this work we developed a general model for theoretical description of activity-dependent growth in neural networks and conducted numerical simulations for three types of network connectivity generation mechanisms: activity-dependent growth, activity independent(random) growth and random (Erdős–Rényi) network. The influence of synapse type generation rules (homeostatic, "Hebb"-like and genetically predefined) to network generated activity dynamics is analyzed as well. The dynamics of the activity patterns, generated by growing networks is carefully investigated by using different statistical methods. The theory and statistical methods, developed in this paper can be used to understand and explore how the neuronal activity affects the growth processes in the developing neural networks. The quantitative parameters will allow us to develop new methods for experimental setups and perform quantitative estimates of the role of neuronal activity in the formation of initial interneuronal connections.

2. Experimental background

Neurons at a specific position within the nervous system are directed to innervate other neurons at another specific position. Neural electrical activity, molecular cues and genetic mechanisms cooperate to form precise neuronal circuits (Wen & Zheng, 2006). Concrete genes work at specific time moments, orchestrating the development of distinct neural networks and of the whole brain Bae, Jayaraman, and Walsh (2015). Molecular biological, anatomical, and electrophysiological techniques show that the choice of pathway and selection of targets by axons is regulated by molecular guidance mechanisms. It is a highly specific neural mechanism by which neurons may extend their axons and find potential synaptic targets (Plachez & Richards, 2005). The chemoaffinity hypothesis, formalized by Sperry (1963), suggests that growing neurons must carry static individual identification tags that allow the recognition between synaptic partners. Modern studies show that electrical activity in developing neocortical networks plays important roles during the early and subsequent development (Luhmann, Sinning, Yang, Reyes-Puerta, Stttgen, Kirischuk, & Kilb, 2016) and the precise pattern of neural firing is believed to be important for instructing connections refinement (Munz, Gobert, Schohl, Poquérusse, Podgorski, Spratt, & Ruthazer, 2014).

2.1. Axon guidance

The diffusion of a target-derived chemoattractants is an effective mechanism by which axons can be guided to their targets (Dickson, 2002; Tessier-Lavigne & Goodman, 1996). Neurons synthesize and secrete specific signal proteins called guidance factors (Keynes & Cook, 1995). Many families of guidance factors, which have different effects on neurites guidance are found experimentally (Chao, 2003; Huang & Reichardt, 2001; Skaliora, Singer, Betz, & Pschel, 1998). These factors influence growth processes by transducing the extracellular signal to intracellular events, by regulation the transcription of genes, by binding to membrane receptors, etc. (Dent & Gertler, 2003; Yuan, Jin, Xu, Song, Wu, Poo, & Duan, 2003). This type of communication is a slow process compared to the electrical communication between neurons, but it regulates the morphological properties of neurons and the connectivity structure between them. Neurite growth occurs in a time scale of hours or days (Catig, Figueroa, & Moore, 2015; Hjorth, van Pelt, Mansvelder, & van Ooyen, 2014), whereas the electrical activity of neurons (generation of the action potential) occurs within in a millisecond scale. Different parts of the neuron respond differently to extracellular guidance factors, but axons and dendrites are mostly influenced by these factors (Franze & Guck, 2010). A specialized structure at the tip of the extending axon (growth cone), is a highly motile structure that explores the extracellular environment, determines the direction of growth, and then guides the extension of the axon in that direction (Goodhill, Faville, Sutherland, Bicknell, Thompson, Pujic, et al., 2015). The growth cones may sense the concentration difference of a guidance factor across their spatial extent, and convert it into a signal to move up or down along the concentration gradient (Kater, Mattson, Cohan, & Connor, 1988). The axon guidance factors form the basis of the genetically encoded developmental scheme (Borisyuk, Cooke, & Roberts, 2008). The target neurons may secret signaling molecules that can attract or repel axons. Therefore, axon guidance by the guidance factor's gradients plays an important role in wiring up the developing of the nervous system (Catig et al., 2015).

2.2. Synaptogenesis

Synapses assembly process begins when axons approach their targets and establish contact with dendritic arbors or soma of their target neurons. For a long time it was believed that the neurotransmitter type was predetermined with the specification of the neuron (Strata & Harvey, 1999). However, many studies spanning through the last decades discovered both activity-independent and activity-dependent processes in regulating early synaptogenic events in the developing brain (Borodinsky & Belgacem, 2016; Chih, Engelman, & Scheiffele, 2005; Cohen-Cory, 2002). According to Dale's Principle, each type of neurons releases only a single type of transmitter (Strata & Harvey, 1999). But in the past few decades scientists have found clear evidence of multiple transmitters released by the same neuron (Demarque & Spitzer, 2012; Seal & Edwards, 2006; Vaaga, Borisovska, & Westbrook, 2014). Some forms of plasticity in developing networks do not follow Hebbian- or anti-Hebbian paradigms of plasticity but rather appear to contribute to the homeostasis of the network activity (Keck, Toyoizumi, Chen, Doiron, Feldman, Fox, et al., 2017).

2.3. External signal and spontaneous activity of neural networks

Recent studies have indicated that spontaneous activity (Price, Kennedy, Dehay, Zhou, Mercier, Jossin, et al., 2006) and external sensory input (Eguchi & Stringer, 2016) are required at early stages of axon targeting. At embryonic stages, when immature neurons start to develop voltage-dependent channels and synaptic connections, brain networks reveal distinct spontaneous neuronal activity patterns (Ben-Ari, Gaiarsa, Tyzio, & Khazipov, 2007; Luhmann et al., 2016). There is a considerable evidence that the spontaneous patterns of activity drive the refinement and formation of specific features of adult circuits and sensory maps (Kirkby, Sack, Firl, & Feller, 2013). For example, spontaneous oscillations were observed in the newborn rat cortices as soon as neurons began to form local connections (Savarraj & Chiu, 2014), embryonic mouse spinal cord (Yvert, Branchereau, & Meyrand, 2004), and avian cranial motor nerves at early developmental stages (Fortin, Kato, Lumsden, & Champagnat, 1995). Spontaneous electrical activity generated by different mechanisms in the developing neural networks (Trapani & Nicolson, 2011) is monitored by using calcium fluorescence imaging (Eckmann, Feinerman, Gruendlinger, Moses, Soriano, & Tlusty, 2007), multi-electrode arrays (MEAs) and multi-patch-clamp (Obien, Deligkaris, Bullmann, Bakkum, & Frey, 2015; Vardi, Goldental, Sardi, Sheinin, & Kanter, 2016) techniques.

2.4. The role of electrical activity in neural circuits formation

The development of neuronal systems requires interplay between sensory experiences, spontaneous neural activity, and genetically encoded programs (Ganguly & ming Poo, 2013). Neural network development mechanisms can be divided generally into two classes: activity-independent mechanisms and activity-dependent mechanisms. Activity-independent mechanisms are determined by genetic programs and include differentiation, migration and axon guidance to their initial target areas (Ackley & Jin, 2004). These processes are thought of as being independent of neural activity and sensory experience (Shen & Scheiffele, 2010; Sur & Rubenstein, 2005). However, recent research has shown that neuronal activity modulates brain networks development by promoting the formation and stabilization of appropriate synaptic connections based on functional activity patterns (Hua & Smith, 2004), activity is required for initial targeting decisions made by thalamic axons as they traverse the subplate and for initial steps of cortical target selection by thalamic axons (Catalano & Shatz, 1998). Activity dependent axon–target interactions play a key role in helping partner cells find one another and connect. Different mechanisms of activity-dependent regulation of axon pathfinding, target selection and connectivity refinement are widely presented in neurobiological literature (Cao, Rickenbacher, Rodriguez, Moulia, & Albers, 2012; Li, Yang, Zhang, Gao, Wang, Liu, et al., 2016; Lim et al., 2016; Login, Butowt, & Bohm, 2015; Pratt, Hiramoto, & Cline, 2016). Activity is the main driving force for adaptive changes in the nervous system, selectively enhancing existing neural circuits or promoting the formation of new functional circuits. Early spontaneous activity patterns control the formation of developing neural networks, and disturbances of these activity patterns may lead to long-lasting neural deficit (Luhmann et al., 2016). Recent results suggest that dissociated neurons can self-organize into complex neural networks that allow reliable flow and processing of information even during early phases of development (Dranias, Ju, Rajaram, & VanDongen, 2013; Sun, Kilb, & Luhmann, 2010). Under special conditions in vitro dissociated neurons self-organize into neural clusters, which are linked by bundles of axons (Segev, Benveniste, Shapira, & Ben-Jacob, 2003) and multi-electrode array measurement reveals that they are electrically active and exhibit synchronized bursting events (Kawasaki & Stiber, 2014).

Different models have been presented for the description of the neural connectivity evolution as activity-dependent adaptive processes, which include generation of synapses, growth and retraction of spines, remodeling of dendritic and axonal branches, and synaptic plasticity (Bamford, Murray, & Willshaw, 2010; Bornholdt & Röhl, 2003; Volman, Baruchi, Persi, & Ben-Jacob, 2004). The detailed analysis and theoretical models to account the recent experimental data on the growth of cortical neural networks in vitro is presented by Lai, Jia, and Chan (2006). Novel computational modeling approaches are proposed for activity-dependent structural plasticity that implement regulations for structural modifications at the cell level and then compute the network dynamics over time. A more general theory of how sensory information is encoded in the connectivity map and activity patterns of neural populations is proposed based on the agent-based model (Schweitzer & Tilch, 2002). Numerical experiments of the activity-dependent model of self-wiring, inspired by communicating walkers presented in Segev and Ben-Jacob (2000) demonstrates its ability to form fine structures in simple networks of few neurons.

3. Theoretical description of neural networks growth

Recent studies have shown that alongside with the modifications of the existing synapses weights (synaptic plasticity) (Baram, 2017; Beck et al., 2000; Saleewong, Srikiatkhachorn, Maneepark, Chonwerayuth, & Bongsebandhu-Phubhakdi, 2012) biological neural networks reveal ongoing activity dependent structural plasticity, i.e. creation and formation of new synaptic connections in activity-dependent manner (Butz et al., 2009), therefore synaptic connectivity patterns may also change as a result of the structural plasticity. For example, synaptic rewiring can be the result of retraction and reformation of dendritic spines and of re-routing of axonal branches within brain neuronal networks. Changes in the anatomical and functional connections are crucially dependent on morphological changes in individual neurons. The electrical activity of neurons is found as a crucial factor governing structural plasticity as far as neurons tend to maintain their homeostasis (Butz, Steenbuck, & van Ooyen, 2014; Butz et al., 2009).

3.1. General theoretical framework

In general, the time dynamics neural network can be described by the following dynamical variables: $\mathbf{S}(t)$-activity (in neurobiological context it is the variable describing the average spiking rate of neurons), $\mathbf{W}(t)$-connectivity matrix, $\mathbf{D}(t)$-positions of neurites in 3D space, and $\mathbf{E}(t)$-external signal. The synaptic plasticity controls how effectively two neurons communicate with each other (Abarbanel, Talathi, Gibb, & Rabinovich, 2005; Chen & Jasnow, 2011). The time dynamics of neural network's state, which contains only this kind of plasticity, can be described using the system of ordinary differential equations for neuronal activity and synaptic weights:

$$\frac{d\mathbf{S}(\mathbf{t})}{dt} = U(\mathbf{S}(\mathbf{t}), \mathbf{W}(\mathbf{t}), \mathbf{E}(\mathbf{t}), t) \tag{1a}$$

$$\frac{d\mathbf{W}(\mathbf{t})}{dt} = V(\mathbf{S}(\mathbf{t}), t) \tag{1b}$$

In these equations the functions U and V are generally nonlinear functions. The first equation describes the dynamics of the network's electrical activity $\mathbf{S}(t)$, the second equation describes the plasticity of synaptic weights $\mathbf{W}(t)$. Naturally, in these equations no dynamics of spatial characteristics of neurons is present.

For the description of structural plasticity we must add an equation describing the dynamics of neurites positions:

$$\frac{d\mathbf{S}(\mathbf{t})}{dt} = U(\mathbf{S}(\mathbf{t}), \mathbf{W}(\mathbf{t}), \mathbf{E}(\mathbf{t}), t) \tag{2a}$$

$$\frac{d\mathbf{D}(\mathbf{t})}{dt} = G(\mathbf{S}(\mathbf{t}), \mathbf{D}(\mathbf{t}), t) \tag{2b}$$

$$\frac{d\mathbf{W}(\mathbf{t})}{dt} = V(\mathbf{S}(\mathbf{t}), \mathbf{D}(\mathbf{t}), t) \tag{2c}$$

Here, the function G describes the activity-dependent time dynamics of neurites in 3D space and function V describes the process of new synapses creation and the process of existing synapses modification. In comparison with the system of equations for synaptic plasticity Eq. (1), there already exists an equation describing the dynamics of neurites, i.e. here, the spatial (geometric) features of neurons are already taken into account (structural plasticity). Therefore, the inclusion of activity-dependent structural plasticity mechanisms for the description of plasticity in neuronal networks gives us more general framework than the description containing only synaptic plasticity, and opens up many new opportunities in neuronal networks research.

Synaptic plasticity mechanisms are widely accepted as essential mechanisms in developing and learning neuronal systems and have been studied experimentally in the cultured networks (Massobrio, Tessadori, Chiappalone, & Ghirardi, 2015; Tsukada, 2016). These mechanisms may also largely determine the development of activity patterns, in particular at the later developmental stages (Beck, Goussakov, Lie, Helmstaedter, & Elger, 2000), whereas structural plasticity plays an important role at the early stages of development.

3.2. The detailed neural network growth description

Here we describe a specific mathematical modeling framework based on the neurobiological experimental data given in Section 2. The dynamics of the system will be described on the basis of discrete equations.

Neurons are placed on a three-dimensional lattice $M * M * M$ with a spatial distance between two grid points of $D + \xi$, where ξ is a uniform random variable ($\xi \in [-0.2D, 0.2D]$) labeled as i ($i = 1, 2, \ldots, N$). Spatial positions of neurons in biological neural networks can be quite complex, this depends on many factors, naturally, they are not located in a regular lattice. For modeling specific areas of the brain, it is possible to specify the positions of neurons basing on specific experimental data. Here we consider a general case and therefore we have decided to arrange neurons in a regular lattice but with some randomization.

The dynamics of neuron's electrical activity may be modeled on the bases of different models: Hodgkin–Huxley, FitzHugh–Nagumo, coupled oscillators (Kuramoto oscillators, Rossler oscillators, and the Hindmarsh–Rose neuron), Integrate and Fire (Siettos & Starke, 2016). As neurite growth process is a slow process (time scale of hours or days), whereas the electrical activity of neurons is very fast (milliseconds), there is no particular need to use such complex models to describe the neuronal activity, therefore we used the discrete time binary neuron activity model. At each discrete time step ($t = 0, 1, 2, \ldots$) every neuron in the network has a state $S_i(t)$, which comes from the set {0,1}. The evolution of the whole network state $\mathbf{S}(\mathbf{t}) = (S_1(t), \ldots, S_N(t))$ is determined for all discrete time moments by using a two-state activity model with discrete time. The state of each neuron $S_i(t)$ at the moment of time t is determined by the following equation:

$$S_i(t) = H\Big(\sum_{j=1}^{N} W_{j,i}(t-1)S_j(t-1) + E_i^{ext}(t-1)\Big). \tag{3}$$

Here $S_j(t-1)$—the state of other cells, $W_{i,j}$—synaptic connections weights, and $E_i^{ext}(t-1)$—external signal at a previous time moment and H(x)—discrete Heaviside step function.

According to Section 2.3 the origin of the external signal $E_i^{ext}(t)$ can be of two types: external sensory input and spontaneous random activity. The external signal $E_i^{ext}(t)$ is characterized by two parameters I_{ext} and L_{ext} and is modeled as a binary numbers sequence, where 1 and 0 values are taken with probabilities I_{ext} and $1 - I_{ext}$, L_{ext} is the average length of 1 valued words.

Connections between neurons are formed when each neuron sends neurites that migrate through the interneuronal environment. At the beginning of the growth process the neurite begins to migrate from its own cell's soma. According to Section 2.1 and 2.4 we consider here three types of network growth rules:

(1) **Activity-dependent growth network (ADGN).** In this model type the axon's tips grow toward active neurons according to the rule

$$d_{i,j}(t+1) = d_{i,j}(t) - rS_j(1 - S_i), \tag{4}$$

where $d_{i,j}$ is the distance from ith neurons axon tip to jth distant neuron and r is the growth rate. Here the term $(1-S_i)$ shows that the growth of axon tips is inhibited when the neuron is active. It was derived by a number of studies that demonstrated that high levels of electric activity (high rate) inhibitors neurite outgrowth, and low levels of activity led to intensive growth. It has been widely accepted that intracellular Ca^{2+} concentration is the underlying mechanism regulating this activity-dependent outgrowth (Kater et al., 1988; Neely & Nicholls, 1995).

(2) **Activity-independent growth network (AIGN).** The activity independent growth model is more simple and does not contain directional growth of axon tips toward active neurons and no growth inhibition if the neuron is active, i.e.

$$d_{i,j}(t+1) = d_{i,j}(t) - r\eta, \tag{5}$$

where η is a random variable which takes values 0 or 1. The variable η values to satisfy the condition: during simulation the average connectivity $\langle k\rangle$ of activity-independent and activity-dependent networks should be equal for correct comparison statistical properties of the generated networks with activity-independent and activity-dependent growth rules. The average connectivity $\langle k\rangle$ is defined as a sum of all weights divided by the number of nodes, i.e. $\langle k\rangle = \frac{\sum_{i,j=1}^{N} W_{j,i}}{N}$.

(3) **Random network (RN).** The random network model is presented by Erdős and Rényi (1960). This network model has been used extensively as null-hypothesis model of the real-world networks in various fields, particularly in neurobiology. During numerical simulations, random networks were generated with the same average connectivity $\langle k\rangle$ as in the simulated activity-dependent growth network.

When the neurite approaches one of the possible target cells, with which it will finally form a synaptic connection, it has to be connected to that cell's soma. Numerous mechanisms coordinate synapses formation and maturation in the developing brain. We did not include such complex mechanisms in our model. We simply assumed that the growth cone makes a synaptic connection when it first reaches a cell's soma. According to Section 2, we consider here three kinds of rules of synapse type selection:

1. **Hebb-like rule.** Here the type of newborn connection is based on Hebb's rule (Hebb, 1949): if the presynaptical and postsynaptical neurons have the same activity at the moment of synapse formation, the connection weight is set to 1, otherwise it is set to -1, i.e. $W_{ij}(t) = +1$, if $S_i(t) = S_j(t)$ and $W_{ij}(t) = -1$, if $S_i(t) \neq S_j(t)$.
2. **Homeostatic rule.** This rule suggests that neuronal morphogenesis is driven by the need of neurons to establish and maintain a homeostatic equilibrium of their average

electrical activity. The type of synaptic connection is determined only by the state of postsynaptic neuron at the time moment of synapse formation: $W_{ij}(t) = +1$, if $S_i(t) = 0$ and $W_{ij}(t) = -1$, if $S_i(t) = 1$.

3. **Dale's principle.** Here the type of each neuron is defined at the simulation starting by parameter P_{in}, which describes the fraction of inhibitory neurons.

These models describe activity-dependent or activity-independent initiation of synaptic contacts and formation of the new synapses between neurons. The structural plasticity in the developing and mature neural systems is also associated with elimination of synapses (Butz et al., 2009) because functional neural circuit formation during postnatal development involves also the elimination of the early-formed redundant synapses (Kano & Hashimoto, 2009). This process occurs between early childhood and at the onset of puberty in many mammals (Tau & Peterson, 2010). In this work, we simulate earlier stages of the nervous system development, namely, the processes of the initial growth of interneural connections, therefore we did not include in the model the elimination of synapses. Activity-dependent synapses elimination is an important part of structural plasticity and therefore in the future it is planned that this model will be developed taking into account this process.

In biological neural networks there is a process of synaptic plasticity, which leads to an increase or decrease of the synaptic weight (Beck et al., 2000). In our model, we do not consider synaptic plasticity. At the time of birth synapses receive weights (-1 or $+1$) and then these weights do not change during simulation. There are different types and models of synaptic plasticity (Dayan & Abbott, 2005; Hennig, 2013; Morrison, Diesmann, & Gerstner, 2008), but adding this kind of plasticity to our model will greatly complicate it. In the work we consider the plasticity of the network caused by activity dependent neurite growth, therefore we decided not to include the synaptic plasticity in our model, in the future it will be included to fully model the developing neural networks in all stages.

4. The results of numerical simulations

In all numerical experiments we simulated networks with $N = 4096$, spatial distance between two lattice points of $D = 150$ μm, growth rate $r = 10$ μm per time step. The fraction of inhibitory neurons is P_{in}=0.5 for Dale's principle ADGN, but for AIGN and RN this value slightly changed ($\pm\sim0.1$) for holding the total quantity of excitatory and inhibitory connection equal for all types of networks. This equality is very important for correct comparison of simulation results for different networks and therefore it was maintained very strictly in all simulations. We started each network simulation with zero connectivity and zero synaptic elements. At each subsequent discrete time step, the simulated networks grow according to the models presented in Section 3.2. Throughout the paper, we have used synchronous update of all three types of networks (ADGN, AIGN and RN).

The firing dynamics of neural networks depends on the overall balance between excitation and inhibition, therefore maintaining the excitatory/inhibition balance of neurons inputs is crucial for the normal functioning of the nervous system (Barral & D'Reyes, 2016). The balanced state of neural network is characterized by neuronal activities that are neither completely silent nor saturated. We analyzed the networks connectivity structure in terms of the balance of excitation and inhibition of individual neurons input connections. The degree k_i of a node is defined as the number of connections of the ith node (Albert & Barabási, 2002). It can be divided into the in-degree k_i^{in} (number of incoming connections) $k_i^{in} = \sum_j W_{ji}$ and out-degree $k_j^{out} = \sum_i W_{ji}$ (number of outgoing connections). The node degrees probability distribution $P(k)$ is the probability that a randomly selected node has a degree k (Albert & Barabási, 2002). The degree distribution strongly controls the behavior of the network. We calculated input node degree asymmetry as the difference between input excitatory and input inhibitory node degrees $m_i^{in} = k_i^{in+} - k_i^{in-}$ for each neuron, and then plotted the distribution function $D_{diff}(m^{in})$. The dependence of a node degree asymmetry on the network growth type and the rule synapse type selection (Fig. 1) was analyzed. For AIGN (Fig. 1b) and RN (Fig. 1c) we see wider distribution of m^{in} than for ADGN (Fig. 1a), and the peak of distribution function for ADGN is higher than for AIGN and RN. This means a stronger asymmetry of neuron's input synaptic connections for the activity-independent and random growth compared to the activity-dependent growth. This distribution shape differs depending on the rule of synapse type selection too. The homeostatic rule gives a more symmetric picture, "Hebb"-like rule leads to a strong bias towards negative values, and Dale's principle on the contrary leads to a predominance of neurons with excitatory input connections. This predominance is caused by the fact that the excitatory neurons formed more output connections than the inhibitory ones. The most symmetrical picture is observed for activity-dependent growth network with homeostatic synapse type selection rule.

The excitatory/inhibitory balance of the input connections can be clearly identified by carrying out statistical analysis of the neural network's activity dynamics. To detect quantitative differences in excitatory/inhibitory balance for different network growth rules we calculated the average value of each neuron's activity $\langle S_i \rangle$ during simulation (see, Fig. 2). This parameter shows how often each neuron is active or inactive, i.e. if $\langle S_i \rangle = 0$ means that neuron is always inactive, and if $\langle S_i \rangle = 1$ means that the neuron is always active. Distribution function of $\langle S_i \rangle$ is presented in Fig. 2 for different growth rules and different synapse type selection rules. Comparing to AIGN and RN in ADGN network, there are pronounced peaks (at $\sim$05 for homeostatic and at $\sim$0.3 for Hebb-like growth rule). The absence of a pronounced peak for AIGN in RN, and also for Dale's principle ADGN, suggests that in these cases the average activity of individual neurons is either too low or too high.

Next, the average value of network activity for each time step $\langle S(t) \rangle = \frac{\sum_i^N S_i(t)}{N}$ was calculated for the description of the time dynamics of the network's activity level. The influence of growth type and the rule of synapse type selection on the dynamics of the average network activity $\langle S(t) \rangle$ was analyzed Fig. 3. The average network activity grows extremely fast for AIGN (Fig. 3b) and RN (Fig. 3c) networks with Dale's principles of the rule of the synapse type selection, and the value of this parameter significantly exceeds the value of 0.5, which means significant over-excitation in the neural network. For the network with homeostatic synapse type selection rule the average activity value grows above 0.5, for Hebb-like synapse type selection rule at the beginning of the simulation we observe increase of the average activity to the values of $\sim$0.4, then this value decreases to 0.3 for all types of network growth. In the case of ADGN network with Dale's synapse type selection rule we observe fast oscillations of network activity in the wide ranges, the average activity $\langle S(t) \rangle$ greatly fluctuates and its values vary widely from 0.2 to 0.6.

The irregularity of activity patterns was estimated by counting the number of constant words i.e., blocks of constant states confined by the respective binary state. The probability p_i^l is that the number of constant words of the l length is divided by the number of all words found in the time series of ith neuron. The maximal possible word length given by the length T of the time series is analyzed. We built the average probability distribution of p_i^l for the entire network $P(l) = \frac{\sum_1^N p_i^l}{N}$ in double logarithmic scale Fig. 4. The distribution of $P(l)$ for AIGN (Fig. 3b) and RN (Fig. 3b) looks like a

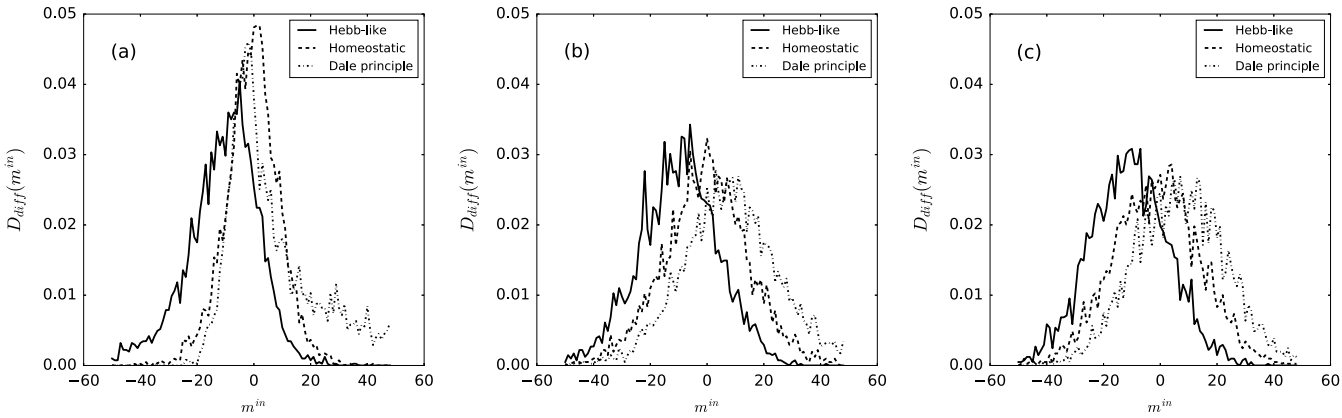

Fig. 1. The distribution of difference between excitatory inhibitory input node degrees for different growth types (a—ADGN, b—AIGN, c—RN). For activity-independent and random growth networks a number of neurons in which inhibitory or excitatory input connections prevails is greater than for activity-dependent growth network.

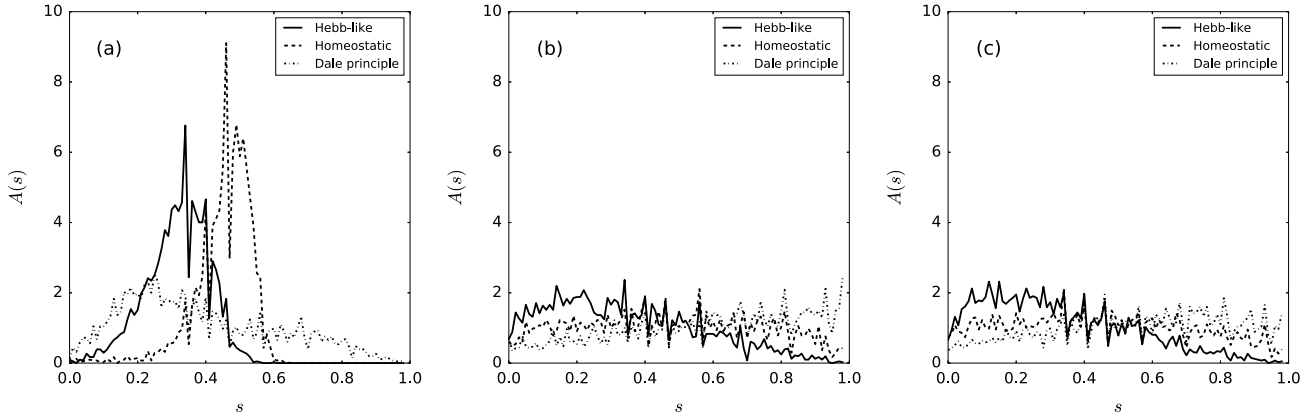

Fig. 2. The distribution function of neuron's average activity for different network growth types (a—ADGN, b—AIGN, c—RN). Due to high imbalance between excitatory and inhibitory inputs the majority of neurons will stay in an active or inactive state for a long time in AIGN and RN. Activity dependent growth gives a more balanced total neuron input, due to which the activity of neurons is more variable.

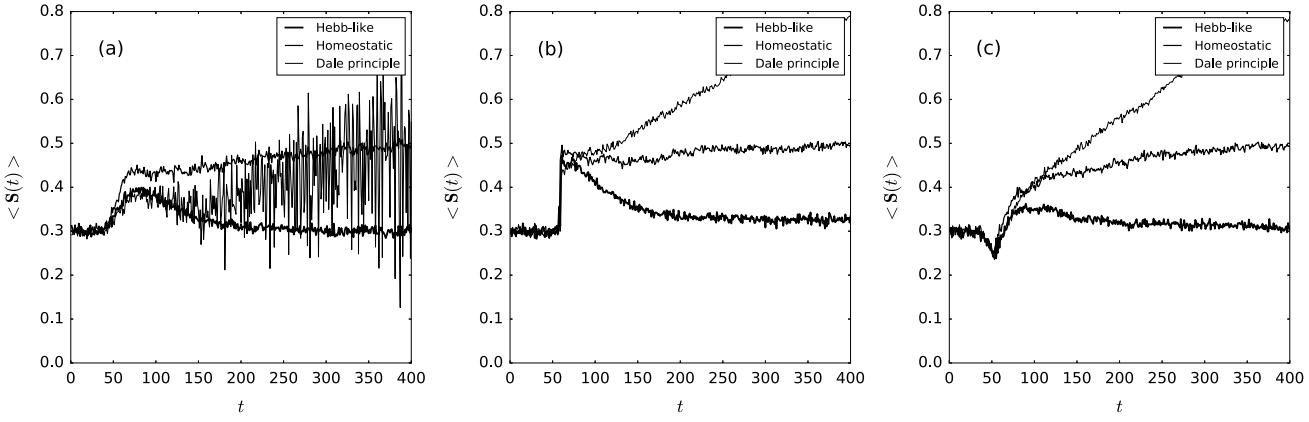

Fig. 3. The dynamics of the average network activity level $\langle S(t)\rangle$ for different growth types (a—ADGN, b—AIGN, c—RN). The parameter value grows very fast ($\langle S(t)\rangle > 0.5$) for AIGN and RN networks with Dale's principles synapse type selection rule, which means significant overexcitation in the neural network.

straight line in the double logarithmic scale, what means that $P(l)$ follows the power law. But for ADGN (Fig. 4a) the distribution of p_i^l follows the power law only for Dale's principle network, and for Hebb-like and homeostatic synapse type selection rule no power law is observed. This shows a fundamental difference of activity patterns between activity-dependent and activity-independent mechanisms in neural networks development.

Finally, we investigated the influence of the external signal $\mathbf{E^{ext}}$ properties on the characteristics of growing networks activity patterns. The simulations were conducted with the constant level of the external signal intensity $I_{ext} = 0.5$ but for different values of external signal irregularity L_{ext}. These simulations were performed only for ADGN with homeostatic and Hebb-like synapse type set rule because the changes in these parameters cannot affect the growth in AIGN and in the networks with Dale's principle synapse set type. Fig. 5a shows the distributions of the average activity levels for Hebb synapse type selection rule network Fig. (5b) and homeostatic synapse type selection rule (Fig. 5b). Increasing the

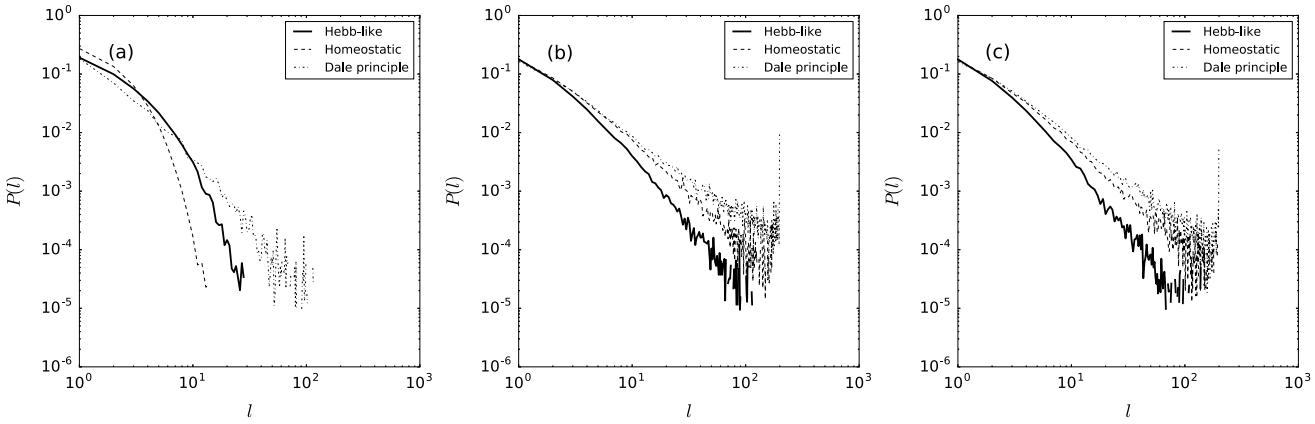

Fig. 4. The average probability distribution of $P(l)$ for the entire network in double logarithmic scale different growth types (a—ADGN, b—AIGN, c—RN). For AIGN and RN the distribution of $P(l)$ follows the power law, whereas for Hebb-like and homeostatic synapse type selection rule no power law is observed.

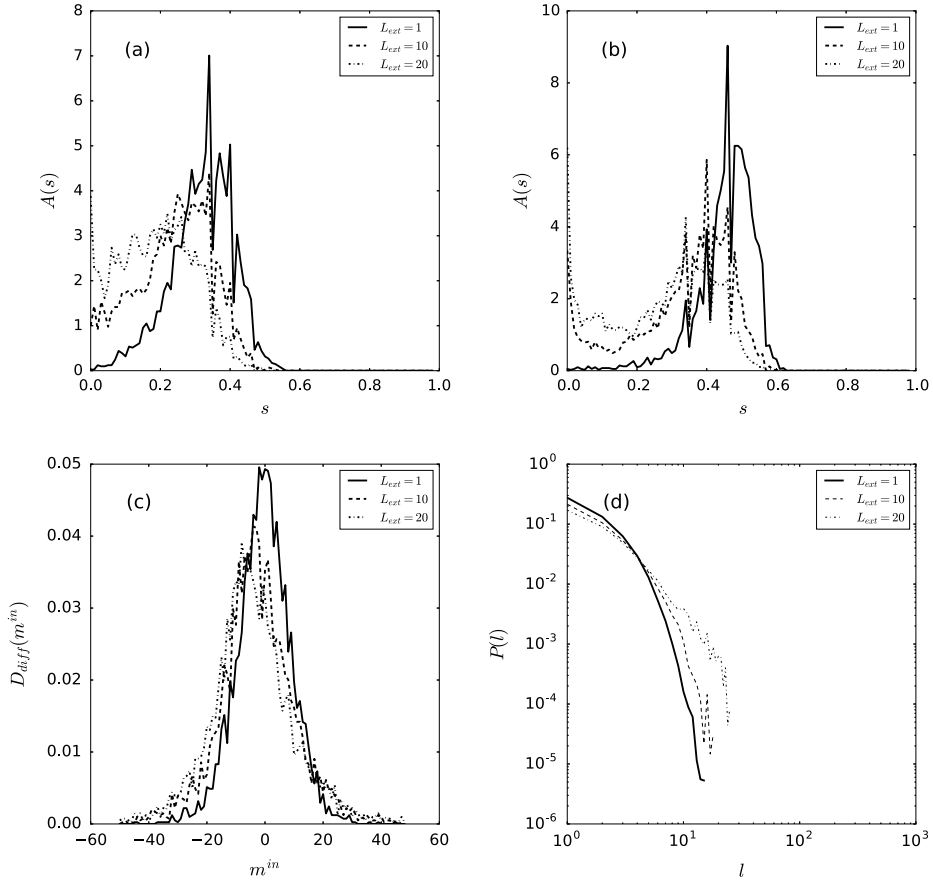

Fig. 5. The influence of L_{ext} to the distribution function of the average value of each neuron activity for Hebb-type (a) homeostatic (b) networks. The influence of L_{ext} on the distribution of difference between excitatory inhibitory input node degrees (c) and the average probability distribution of p_i^l (d). Increasing the L_{ext} parameter of external stimulation leads to increasing inhibition by shifting excitatory/inhibitory balance to more negative values.

value of L_{ext} parameter of external stimulation leads to long periods of stimulation alternating with long periods without stimulation of the same neurons. This results in a shift the peak of the distribution to the smaller value of the average activity, what indicates an increase in the proportion of less-active neurons and inhibition of network's activity. As seen from Fig. 5c, this increase of inhibition is caused by shifting excitatory/inhibitory balance to more negative values by increasing the L_{ext} parameter value. But the distribution of the lengths of the words $P(l)$ is highly sensitive to the values of L_{ext} (Fig. 5d), and its increase leads to a decrease in the graph slope in the double logarithmic scale, like for AIGN and RN cases.

5. Conclusions

A fundamental issue in neurobiology defines the mechanisms by which neurons recognize and innervate their targets, because the presence of synapses between neurons and the position of each synapse cannot be predetermined genetically (Ackley & Jin, 2004; Krubitzer & Kahn, 2003; Sur & Rubenstein, 2005). The ability to construct neuronal networks that grow in activity-dependent manner opens up many opportunities in neurobiological studies. These range from developing better methods for analyzing spiking activity of neural networks to studying how large neuronal

circuits operate and how different brain regions communicate and cooperate.

In this paper, we developed a general theoretical framework with a detailed set of cellular rules that govern the activity-dependent neural circuit generation. By computational modeling of growth processes in activity-dependent and activity-independent neural networks we have shown the influence of neural activity on neural network growth and development. We have analyzed the connectivity structures in the generated networks in terms of excitation/inhibition balance. Activity-dependent growth model gives a more better excitatory/inhibitory balance than activity-independent and random growth network models. For activity-independent models, a large number of neurons is constantly in an active state for a long time, and the other part is in inactive state for a long time whereas for activity-dependent growth model active or inactive states of neurons are balanced. We have found that the connectivity structure and activity pattern of activity-dependent growth network strongly depend on the structure of external signal.

The model proposed in this work gives us a general theoretical concept and approach for estimation the of neural activity influence on growth processes in neural networks. It is rather abstract and it is not tied to the specific part of the nervous system, therefore the results obtained here may be dependent on the choice of parameters, rules and models of the neurons. The models developed in this work can be an initial framework to a large-scale neural network generation framework and are the first step toward the development of more complex and detailed models. For modeling growth processes in the specific parts of the nervous system when parameters of the system can be taken from experimental data, and more suitable in a particular case complex and biologically-realistic models can be used. This work is perhaps one of the first and fundamental steps toward understanding the relationship between brain functional dynamics and its connectivity structures. Our results can be used to generate empirically testable hypotheses of the relationship between network activity dynamics and emergent functional connectivity, and explicitly compare the structure and dynamics of dissociated neuronal cultures, throughout the period of self-organization (Schweitzer & Tilch, 2002; Segev et al., 2003). The theoretical models, developed in this work can give us new understanding of the mechanisms by which a topographic pattern of connectivity is achieved and modified as a consequence of gene expression and sensory experience and might provide important steps toward understanding of self-organization in central nervous system (Bornholdt & Röhl, 2003).

Coordinated spontaneous activity is present in different brain systems during the early stages of development. During the visual system development spontaneous retinal waves are the major neural activity (Chandrasekaran, Plas, Gonzalez, & Crair, 2005; Lee & Chiao, 2016; Nicol, Voyatzis, Muzerelle, Narboux-Nme, Sdhof, Miles, & Gaspar, 2007; Owens, Feldheim, Stryker, & Triplett, 2015). Retinal ganglion cells (RGCs) axons grow in response to trophic factors and this growth is greatly potentiated by physiological levels of electrical activity (Goldberg, Espinosa, Xu, Davidson, Kovacs, & Barres, 2002). Short-term alteration of neural activity with a specific temporal pattern in retinas of later developmental stages is sufficient to enhance neurite outgrowth of retinal explants (Lee & Chiao, 2016). Activity-dependent mechanisms play a preferential role in the mapping of the nasal–temporal axis of the retina onto the colliculus (Chandrasekaran et al., 2005). In the posterior superior colliculus molecular and activity-dependent cues drive topographic mapping stochastically. Disruption of spontaneous waves of retinal activity resulted in uniform map organization in mutant mice, demonstrating that correlated spontaneous activity is required for map heterogeneity (Owens et al., 2015). The responses of axons to guidance factors depend on oscillations in intracellular cyclic nucleotide (cAMP) levels, which result from the activity of RGCs and activity-dependent oscillations of cAMP in the growth cones act in synergy with local guidance cues. A direct molecular link exists between spontaneous neural activity and axon guidance mechanisms during the refinement of neural maps (Nicol et al., 2007).

Experimental results provide in vivo evidence that pre-synaptic and post-synaptic neuronal activities play critical, and presumably differential, roles in axon growth, branching, arbor formation and elaboration during cortical axon development. Silencing both pre-synaptic and post-synaptic neurons suggests that certain levels of firing activity in pre-synaptic and post-synaptic neurons are required for proper development of neural connectivity (Mizuno, Hirano, & Tagawa, 2010). The loss of neural activity during development also leads to a regional mistargeting and disruptions to patterned layering in the cortex (Catalano & Shatz, 1998). Global activity contributes to the initial guidance to the target but is not necessary for overall pathfinding and silencing neural activity globally by tetrodotoxin decreased the area covered by axon branches during pathfinding (Kita, Scott, & Goodhill, 2015). The emergence of mature topography among motor nuclei involves an interplay between spontaneous activity, cadherin expression and gap junction communication. Inhibition of activity disrupts nucleogenesis, suggesting that activity feeds back to maintain integrity among motor neurons within a nucleus (Montague, Lowe, Uzquiano, Knüfer, Astick, Price, & Guthrie, 2017). Spatially balanced activity between regions is required to establish their appropriate connectivity and alterations in the patterns of sensory and cortically driven activity may have profound effects on commissural axon targeting (Surez, Fenlon, Marek, Avitan, Sah, Goodhill, & Richards, 2014).

We hope that the theoretical approaches and models developed in this work will serve as a basis for theoretical study, understanding and computer simulations of the above mentioned processes in developing neural networks. The theoretical study of interrelations between morphology and activity of evolving neural networks will allow us to develop experimental techniques for studying and quantifying the influence of neuronal activity on the growth processes in neural networks and may lead to novel techniques for constructing large-scale neural networks by self-organization.

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