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COMPUTATIONAL NEUROSCIENCE

Intelligence in Intracellular Gene-Regulatory Networks

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I discuss results of theoretical modeling in very multi-disciplinary area between Systems Medicine, Synthetic Biology, Artificial Intelligence and Applied Mathematics. Multicellular systems, e.g. neural networks of a living brain, can learn and be intelligent. Some of the principles of this intelligence have been mathematically formulated in the study of Artificial Intelligence (AI), starting from the basic Rosenblatt's and associative Hebbian perceptrons and resulting in modern artificial neural networks with multilayer structure and recurrence. In some sense AI has mimicked the function of natural neural networks. However, relatively simple systems as cells are also able to perform tasks such as decision making and learning by utilizing their genetic regulatory frameworks. Intracellular genetic networks can be more intelligent than it could be assumed due to their ability to learn. Hence, one can speculate that each neuron probably has an intracellular network on a genetic level, based and functioning on the principle of artificial intelligence [1]. Such learning includes classification of several inputs or intracellular intelligence can manifest itself in the ability to learn association between two stimuli within gene regulating circuitry. However, gene expression is an intrinsically noisy process, hence, we investigate the effect of intrinsic and extrinsic noise on this kind of intracellular intelligence. We show that counter-intuitively genetic noise can improve learning inside the cell [2-4]. We discuss several designs of genetic networks illustrating the fact that intelligence, as it is understood in the science of artificial intelligence, can be built inside the cell, on the gene-regulating scale. Without any doubt, neurons or astrocytes, being a very sophisticated cells, use this possible functionality in one or another form. It is an intriguing question, how learning and changes of weighting is executed in the real genome of the neuron. We put forward the hypothesis that weights are implemented in the form of DNA methylation pattern, as a kind of long time memory. During the talk I will also include brief introductions/tutorials about Synthetic Biology, modelling of genetic networks and noise-induced ordering.

Acknowledgements

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Coherence Enhancement in Coupled Chaotic Neurons

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The emergence of order from chaos is one of the greatest mysteries of the universe. In his famous book "Order Out of Chaos" Ilya Prigogine argued that systems being far from equilibrium, with a high flow-through of energy could pro-

duce a higher degree of order (Prigogine, 1984). However, since all of his Nobel-Prize winning discussions have been philosophical and mathematical, some scientists criticized his view on evolution from chaos to order, saying that such phenomena may be manipulated on paper or on a computer screen, but not in real life. The manifestation of the emergence of regularity in interacting chaotic systems may shed light on understanding of essential mechanisms leading to self-organization of nature. Indeed, synchronization of chaotic systems is an example of self-organization in nature, and it is usually assumed that interaction between coupled oscillators enhances their synchronization. However, this is not always true. An increase in coupling between chaotic systems may result in unexpected behaviors, such as, e.g., oscillation death or deterministic coherence resonance. The latter has been theoretically predicted in two coupled chaotic Rössler oscillators (Pisarchik, 2015). The natural question arises: Can this phenomenon occur in a biological system? Our research gives a positive answer to this question. Here, we report on the first observation of resonant coherence enhancement in a deterministic neuron model. Through numerical simulations and electronic experiments we demonstrate the improved regularity in inter-spike intervals (ISI) of a chaotic Hindmarsh-Rose neuron affected by another chaotic neuron. Resonant chaos suppression is detected when the neurons are in a phase synchronization state. This surprising phenomenon resembles "stabilization of chaos by chaos", i.e., the chaotic signal from the presynaptic neuron makes the dynamics of the postsynaptic neuron more regular if there is a small mismatch between their parameters.

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Modeling Stochastic Processes in Neurons

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Many aspects of neuronal function, for instance spiking and synaptic transmission, are very noisy. To achieve a better understanding of how this noisiness can contribute to neural coding it is important to understand the causal processes. Detailed modeling using accurate stochastic methods is an essential tool because stochasticity can be manipulated in models, something that is often difficult to achieve in experiments.

To facilitate such modeling we have been developing the STEPS software, which is an efficient implementation of the Inhomogeneous Stochastic Simulation Algorithm (ISSA, also known as spatial Gillespie) applied on tetrahedral meshes to allow for accurate representation of neural morphology. Using STEPS we have investigated the role of stochasticity in the induction of synaptic plasticity and in the generation of dendritic calcium spikes in cerebellar Purkinje cells.

Dendritic calcium spikes vary a lot in shape but the underlying mechanisms were unclear. We showed that a system including calcium-activated channels behaves quite differently from one containing only voltage-gated channels. In the latter case stochastic effects disappear rapidly when the number of channels increases, but this is not true for calcium-activated channels. This leads to large variability in the number of spikes fired during a calcium burst when simulated in an unbranched cable and additional large spatial variability in membrane potential and calcium concentrations when simulated in a branched dendrite.

Unfortunately simulating stochastic processes in neuronal dendrites is very time consuming and we were limited to only simulating a small part of a dendrite because of runtime considerations. The ISSA method used in STEPS is inherently serial and cannot be parallelized. Recently we have described an effective and accurate approximate method on tetrahedral meshes that overcomes this limitation by using an operator splitting approach. The implementation in the STEPS software is the first truly accurate parallelization of an ISSA-like method and allows for good scaling of the parallel computation provided the meshes are partitioned properly. Using this approach we can now apply stochastic simulation to models of the complete Purkinje cell and study the mechanisms of variability of dendritic calcium spikes and other forms of spiking at the cellular level.

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Competitive Learning Mechanisms for Distributed Synthetic Gene Classifiers

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Motivation and Aims

Creating learnable classifiers based on synthetic gene circuits is one of the challenging tasks of modern synthetic biology (see references in [1,2]). A promising field where such classifiers can be applied is creation of intellectual biosensors which, in addition to sensing certain parameters of environment, produce some kind of decision based on these parameter values (e.g. whether the environment is safe or not).

Designing complicated classifier circuits within a single cell is limited by capabilities of present synthetic biology techniques (e.g. limited number of synthetic genes in a cell). A promising way of overcoming this limitation is a distributed classifier [1,2] which is essentially an ensemble of cells, where each cell is an elementary classifier, and the final decision is obtained from the overall ensemble output. Distributed classifiers are capable of solving problems which can not be solved by a single classifier cell [1,2].

If the full ensemble of cells ("master population") consists of a large number of elementary classifiers where some internal parameters are varied from cell to cell, then such distributed classifier can be trained by modifying the composition of the ensemble (by eliminating certain cells and duplicating others) without adjusting any internal parameters of each single cell. In our previous works [1,2] we considered two statements of the classification problem along with corresponding learning strategies.

The "hard" classification problem [2] assumes that the classes are separable, implying that the correct classification answer can be uniquely attributed to any classifier input (the corresponding regions in the input space do not intersect). In this case the training can consist of simply removing the incorrectly answering cells from the ensemble, which we refer to as "hard" learning strategy [2].

Conversely, the "soft" classification problem [1,2] admits inseparability of classes, which implies that the probability density functions corresponding to different classes (or to alternative a priori hypotheses) may overlap in the space of inputs. If the input falls within such overlap, then it cannot be uniquely classified, and classification error probability is necessarily non-zero. One can seek to optimize the classification rule in a certain sense. If the probability density functions of classes are known a priori, then the error probability is minimized by the Bayesian classification rule.

In [1,2] a "soft" learning strategy to address the soft classification problem was suggested and studied. It is assumed that the cell ensemble consists of "species" (or cell lines), so that the cells within each species are identical, but elementary classifier parameters are varied between different species. The "parameters" of the ensemble which are tuned in the course of learning are the sizes (the numbers of cells) of the species. The learning strategy is based on competition between the species with viabilities specifically designed in a way that the competitive dynamics produces a cell ensemble constituting a learned distributed classifier. A special mechanism to implement this competition using e.g. fluorescent-activated cell sorting was also suggested [1].

This strategy suffers from a major shortcoming which is essentially a special case of the Gause's competitive exclusion principle: only one species (having the strongest viability) remains in the limit, so the limiting state is trivial and generally can not be used as the learning outcome. States which approximate the optimum classification rule appear transiently in the course of the competitive dynamics, so a separate problem arises to stop the learning procedure at the right moment [1].

The aim of the present study is to design a competitive learning mechanism for a distributed classifier which would converge to a good approximation of the optimal classifier in the limit without the necessity of catching the correct transient state.

Methods and Results

We introduce a competition model which incorporates intra-species competition in addition to inter-species one. This produces the co-existence regime, where (generically) all species are present in the limiting equilibrium state of the ensemble. The sizes of the species in this limiting state are determined by the species viabilities.

Using the mathematical model of this competition we formulate the conditions ensuring that the limit state of the distributed classifier approximates the optimal Bayesian classification rule. We also suggest a mechanism to implement this learning strategy using standard tools like fluorescent-activated cell sorting technique.

The learning strategy based on competition with co-existence is more complicated to implement than one without coexistence, since an additional selective intra-species competition mechanism has to be organized. At the same time,

it has the following advantages: (i) classification accuracy monotonously increases in the limit, as the ensemble approaches the stable equilibrium state; (ii) the mathematical model of the competitive dynamics admits an analytical expression for species sizes in the equilibrium state, which theoretically allows to achieve the exactly optimal Bayesian classification rule as a result of learning in the limit of infinite training sequence.

Acknowledgements

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Computations with Intracellular Circuits

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Information processing, or computation, can be performed by natural and man-made «devices». Man-made computers are made from silicon chips, whereas natural «computers», such as the brain, use cells and molecules. At the same time there is a growing understanding that complex information processing in living systems goes beyond neurons, for example, in adaptive immune system, or in synthetically engineered bacterial cells. Even further, computation occurs on a subcellular level, that is regulatory and signaling pathways in individual cells. In fact, what we perceive as living processes originates from the remarkable ability of integrated biological «elementary» circuits to perform sophisticated computations. For neuronal systems it follows that their information processing abilities may substantially involve similar mechanisms. In our talk we will introduce the key concepts and discuss recent progress that has been made in biomolecular computing. As a proop of principle we present our recent results on a scheme of a synthetically engineered distributed genetic circuit capable of solving classification tasks for quite generic input vectors of chemical signals.

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Synaptic Origins of Working Memory Capacity

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Working memory plays a fundamental role in many cognitive tasks. It is thus puzzling that its capacity is extremely limited, averaging just 4 items for most of the people. The origins of this limit are not clear. I will consider this issue in the framework of synaptic theory of working memory. I will derive an analytical estimate for capacity in terms of basic parameters of short-term synaptic plasticity and neuronal spike-generation dynamics. The obtained expression indicates that capacity can be tuned to the desired level by modulating the average excitation in the network. If time permits, I will show how this process could account for spontaneous chunking of word lists in free recall experiments.

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Model of Neuronal Activity in Cultural Network with Energy Feedback

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Living networks in dissociated neuronal cultures are widely known for their ability to generate spatiotemporal activity patterns that satisfy the power scaling law and thereby exemplify self-organized criticality in living systems. Here we propose a simple network model with energy feedback regulating of the strength of local neural connectivity. Such regulatory mechanism results in the overall model behavior that can be characterized as balancing on the edge of the network percolation transition. Network activity in this state shows population bursts satisfying the scaling avalanche conditions. This network state is self-sustainable and represents a kind of energetic balance between global structural network-wide processes and spontaneous activity of individual elements.

Methods

In this work we further contribute to the idea that several features of SOC-like behavior (e.g. the neuonal avalanches, periodic and chaotic spiking) observed in live neuronal cultures and networks can be explained by local connectivity patterns, expressed by probabilities of connections between cells, neuronal activation dynamics, and by an additional regulatory variable that can be viewed as a generalized an energy supply. In our approach the network topology formation is assessed within the framework of percolation thresholds. Using this framework we establish critical connectivity parameters and employ them in dynamical models of neural activity. At first a simple percolation-based geometric model describing the evolution of cells' connectivity is presented. The model allows to accommodate biologically relevant features such as axons and dendrites; it also enables to replicate directional connectivity that is inherent to living systems including neuronal cultures. The model analysis reveals that sharp changes in the overall clustering and connectivity of the evolving network in both directed and undirected settings is determined by a single parameter describing average connection density in the network. After that we present a mean-field approximation to neuronal activity in cultures and show that if the model is supplied with energy-dependent activation then the connectivity parameter may be used to describe periodic spiking, irregular dynamics, and population bursts. And at last, we provide results of large-scale simulation of evolving network of neuron-like agents of which the activation probability depends on their current energy level.

Results

Our geometric model reveals that networks with coordination numbers exceeding these critical values are likely to form spanning clusters that are capable of connecting nearly all elements in the system. The mean-field dynamic model contains two additional variables: one is the maximal probability of neuronal activation in response to incoming spike, and the other is an exogenous "resource" variable determining if a neuron has enough energy to elicit a spike. The mean-field bursting dynamics resembles that of the population bursts observed in live neuronal evolving cultures. An important factor in successful replication of this behavior was the energy variable coupled with the energy-dependent activation probability. The mean-field model, however, lacks spatial variability and as such is only a rough approximation of activity propagation in neuronal cultures. In our multi-agent model emerging population bursts appear to be synchronized with the peaks of the energy function, because in network models the connections change according to rate dependent synaptic plasticity. Moreover, the same behavior can be observed in the dynamics of mean-field approximation. Hence, the exogenous energy variable introduced here from mere phenomenological considerations might constitute a macroscopical model of how the neuron's ability to transmit spikes influence the network's dynamics. Finally, since in our simulations network connectivity was always kept above the corresponding percolation thresholds neuronal avalanches where observed. The avalanches, however, appeared only when the energy level was sufficiently high.

Conclusion

In summary, we have proposed a network model explaining burst generation in living networks. A distinct feature of our model is presence of a dynamic exogenous energy variable and neuronal activation probability that is made dependent on the energy. We showed that introduction of these modifications already enables to explain evolution

of cultures from resting state to population bursts, at least in the mean-field approximation. Large-scale multi-agent simulations enabled to demonstrate that these additional variables representing very basic physical mechanisms, including energy feedback are capable of stirring the network's dynamical state to the edge of percolation transition.

With respect to dynamics of signals in the network, we have shown that population bursts naturally arise in the network's state corresponding to the energy homeostasis. Statistical properties of the bursts, as was observed in many experimental and theoretical studies, inherit essential features of SOC-statistics: e.g. presence of multiscale excitations. Given that systems operating in the percolation state are exhibit increased sensitivity to external perturbations, we can conclude that networks operating in this regime may offer increased responsiveness to incoming stimulation.

Finally, we showed that a network in which the evolution of connectivity is balanced by the generalized energy consumption eventually arrives at the dynamical state characterized by extremely robust and persistent bursting.

Acknowledgements

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Multistability and Coherent Dynamics in Directed Networks of Heterogeneous Neural Oscillators with Modular Network Topologies

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Understanding the dynamics of interconnected systems of nonlinear ordinary differential equations is arguably amongst the oldest and inspiring problems. Objects of this type occur in a broad range of fields of engineering and science [1]. Significant progress has been made in this area with regards to general laws governing the emergence of various synchronous states, see e.g. [2] and references therein; and the presence of intricate dependencies between network topologies, properties of individual nodes and dynamics in networks have now been elucidated by many authors [3], [4], [5], [6], [7], [8], [9]. Despite this progress, however, a few fundamental questions remain, including the question, how a specific configuration of network topology and weights may affect the overall behavior of the network.

It has been shown recently in [10], [11] that "closing" a chain of identical nonlinear oscillators with directed coupling by adding a directed feedback from the last element in the chain to the first dramatically affects the dynamics of the system. In the chain one only finds a single coherent state, the full synchronization. Closing the chain results in the creation of a new system, in which multiple coherent states may coexist: rotating wave solutions of various modes and a fully synchronous state. The observed abrupt change in dynamics has been attributed to the behavior of the spectrum of the network Laplacian matrix. Furthermore, it has also been shown in [10], [11] that rotating wave solutions prevail in long directed cycles.

In this work we develop and generalize these results in the following two directions. First, instead of directed chains we consider networks with modular structure. Such networks comprise of diffusively and undirectly coupled groups of nodes (modules). These groups are linked by directed connections forming a directed cycle. We show that, remarkably, the spectrum of the network Laplacian for such modular structures is closely related to that of individual isolated modules and the corresponding ring or cycle. Similar to our previous work [11] we hypothesise that rotating wave solutions are likely in such networks. In addition, rotating wave solutions are expected to occur more frequently in the directed cycle of modules than

in the directed cycle of simple oscillators. Numerical simulations confirm this hypothesis. Second, in addition to nodes with identical dynamics, we numerically investigate the case in which individual oscillators differ; their parameters are randomly sampled from a distribution centered at fixed nominal values. We observe that, provided that coupling within individual modules is strong enough, solutions resembling rotating waves emerge in this system, too. The latter regime co-exist with nearly synchronous state giving rise to coupling strength-modulated multi-stability and coherence in such systems.

Acknowledgements

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Cocaine Addiction as a Homeostatic Reinforcement Learning Disorder

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Background

Current addiction theories diverge and depict cocaine addiction as a disorder of either reinforcement learning or hedonic homeostatic regulation. The learning-based theories, in particular, suggests that addiction results from transition from a voluntary and goal-directed, to a habitual decision process. Underlying all of these computational theories is the central role of the dopaminergic system signaling reward information. Under cocaine, as under other addictive drugs, this signaling is pathologically influenced by the pharmacological action of the drug.

Methods

Here we propose a new theory of addiction that integrates the brain reinforcement learning and hedonic homeostatic regulation systems. As opposed to habit-based theories, we postulate that in addicts, a goal-directed planning system remains in charge of fulfilling drug-related homeostatic needs of the organism, while drugs gradually modify the need structure, as well as associative learning mechanisms. Formal mathematical modeling and simulation, as well as cocaine self-administration paradigm in rats are combined to test key predictions of our theory.

Results

Simulations show that our new theory accounts for key behavioral and neurobiological features of addiction, most notably, escalation of cocaine use, drug-primed craving and relapse, individual differences underlying susceptibility to addiction, and dopamine D2-receptor down-regulation in addicts. The theory also generates unique predictions about cocaine self-administration behavior in rats that are confirmed by new experimental results.

Conclusion

We show that our integrative theory explains many behavioral and neurobiological aspects of cocaine addiction that

were previously explained by different theories. We also discuss the limitations of previous theories, particularly that viewing addiction as a habit-based disorder can be fundamentally inconsistent with certain aspect of addiction.

Electro-Diffusion in Dendritic Spines and the I-V Relation

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Electrical activity of dendritic spines in cellular microdomains in general remains unclear unresolved. The electrical current is carried by moving ions and induces a local change in the voltage, which can modulate the opening of channels and contribute to the initiation of an action potential. The ionic flow in dendritic spines is driven by the coupled electric field to the charge densities that interact through the non-cylindrical spine geometry.

Due to small nanometric scale and the charge-voltage interaction, the voltage-current (I-V) relation and its regulation by geometry remains difficult to investigate. I will present here our recent effort to deconvolve the response of the slow genetically encoded voltage sensor in hippocampal neurons and to compute from the electro-diffusion theory, the electric field and the ionic flows in the spine head. We resolve here the I-V relation and extract the spine resistance, which is certainly insufficient to characterize the nonlinear I-V interaction. Coll. R. Yuste (Columbia).

Delayed and Asynchronous Neurotransmitter Release

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Asynchronous release of neurotransmitter is an important phenomenon known to occur in certain neurons. It is linked to short term synaptic plasticity, memory formation, modulation of inhibition, etc.

We have designed a model system describing the exocytotic cycle of vesicles at excitatory and inhibitory synapses that accounts for asynchronous release. Our system models the interaction of the SNARE and SM proteins and predicts a delayed inertial protein unbinding associated with the SNARE complex assembly immediately after vesicle priming. The underlying mathematical mechanism is bifurcation delay, which is a phenomenon known to occur in systems with multiple time-scales.

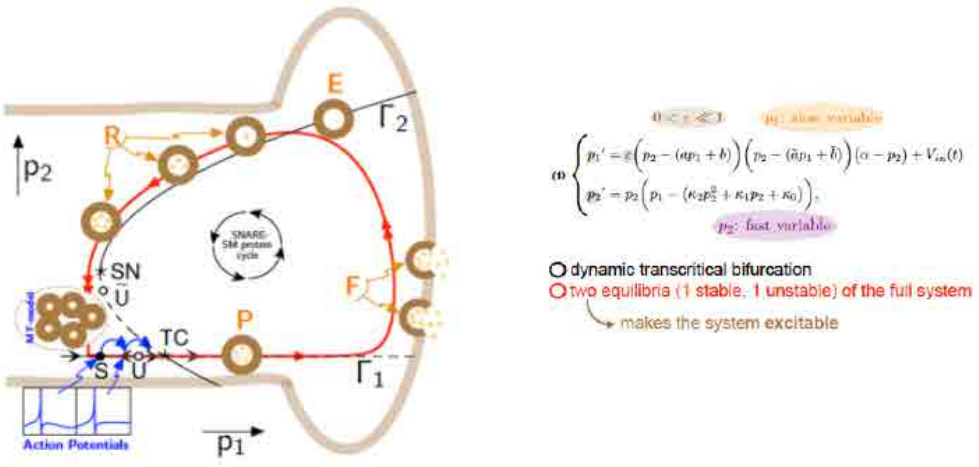

Fig.1. *Time-coded neurotransmitter release at excitatory and inhibitory synapses, S. Rodrigues, M. Desroches, M. Krupa, J. Cortes, T. J. Sejnowski, A. B. Ali, PNAS 2016*

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Hearing: the Next Level of Understanding

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Despite a long history of research involving some of the greater physicists the world has known (Ohm, von Helmholtz, von Bekesy), the understanding of the mammalian, in particular human, hearing is still in its infancy. The present state of teaching of how we hear and listen is still centered around the Fourier analyzer partitioning incoming sounds into its frequency components, and that is it pretty much.

We will, however see that the strong nonlinearities at work in the cochlea (providing a dynamical range of the signal up to 130 DB), demand this simple view to be dramatically changed. To show this, we follow a complex sound that enters the cochlea and consider what parts of the cochlea are elicited, and what turns out in the end to be responsible for human pitch perception. We do this on the basis of our biophysically detailed model of the cochlea [1-4] (based on Andronov-Hopf small signal amplifying outer hair cells [5]) that has been shown to reproduce all - even the most intricate - measured features of mammalian hearing (e.g. loudness dependence of pitch, pitch-shift effects, phase properties along the cochlea and much more [4, 6-7]), the measurements originating from laser-interferometry as well as results psychoacoustic roasts (for the latter, it is essential that the signal remains essential unaltered during the signal transduction from the continuous biophysics motions of the basilar membrane to the spike patterns at the upper end of the auditory nerve (to achieve this, biology exploits the potential of stochastic resonance [8]).

We look at this neuronal system (outer hair cells can be regarded as an archetype of such cells) from the angle of criticality, a viewpoint that is presently widely taken by neuroscientists with a physics background. A critical state of a (neuronal) network is characterized by power-law statistics, as the fingerprint of existing long-range correlation within the system at this state. We find, indeed, power-law distributions of links leading from already activated sites to consecutively activated sites within the cochlea, following the nonlinear interaction paradigm of combination tone generation.

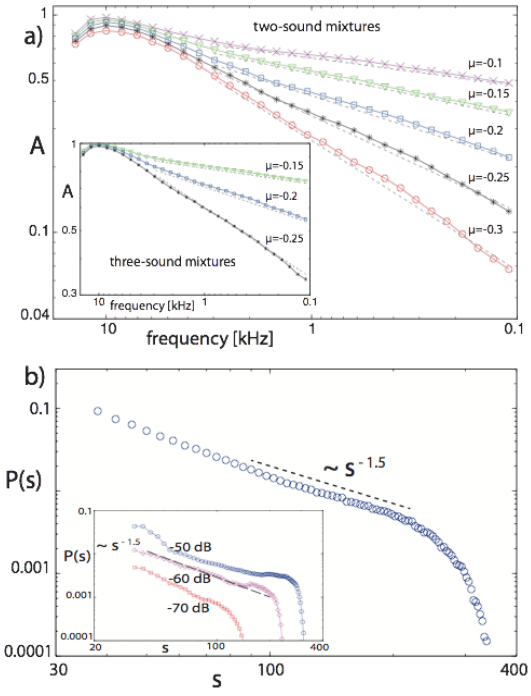

Fig. 1. *a) A: number of activations i.e. above hearing threshold. Random sound levels (-80,-40) dB (rms) complex мtones.b) s: size of activation network by number of links. Two complex tones of random amplitude and frequency. Insets: Results for fixed amplitudes, indicating subcritical, critical and supercritical network states*

These results suggest a critical network of the branching percolation universality class, paving more generally the way towards a novel understanding of the meaning of learning in neuronal networks. In our paradigm, learning is implemented by tuning away amplifier units that are unrelated to the desired signal. Indeed, in this way, substantial auditory scene analysis can be achieved [7].

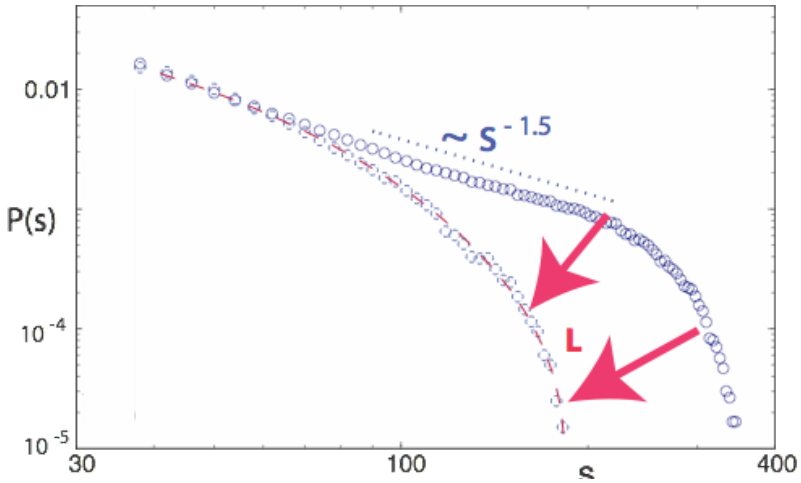

Fig. 2. *Detuning of two frequency bands (nodes 15,16 and nodes 19,20,21) from μ = −0.25 to μ = −2.0: The initial s−1.5 power-law distribution changes into a strictly convex distribution shape (line L)*

In the context of the theory of the thermodynamical formalism of dynamical systems, this change can be interpreted as the specification of a ground state of the network able to accommodate all potential stimulations, towards a more specific sound-targeting network.

In this way, the analysis of the hearing system contributes fundamental insight also for the brain.We hope that our approach will also lead us to a deeper understanding of the nature of otoacoustic emissions, the phenomenon of the sounds generated in many constructs of the mammalian ear.

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Analysis of the Brain Activity in Rodents Being Under Influence of General Anesthesia

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This time a great attention of researchers is devoted to the study of the brain activity [1; 2]. Such interest is connected, first of all, with the desire of the researchers to understand the fundamental principles of the brain activity as well as

with the possibility to apply the obtained knowledge for creation of the brain-computer interfaces. It should be noted that a number of research teams and private companies (for example, Google and Honda) are currently working on solution of this complex interdisciplinary problem. However, for realization of such ambitious problem it is necessary to understand the main fundamental processes occurring in the brain during the solution of different tasks. One of such tasks is the problem of cognitive behavior of living subject in the real world. Such function is known to be controlled by the neural activity in the hypothalamus in the brain of mammals. Thus, there is an interesting question related to the study of oscillatory activity of neural ensembles in the hypothalamus by means of the fundamental approaches of nonlinear dynamics.

In present Report we have studied the behavior of rodents being in the state of rest (under the influence of general anesthesia). We have considered the electrical activity observed in the left and right hippocampus of rats using the continuous wavelet transform with the complex basis [3 – 5]. Using continuous wavelet transform spectral analysis was carried activity of local field potentials generators in the left and right hippocampus of rats. The electrical activity observed in the left and right hippocampus of rats, we can distinguish two characteristic modes of behavior primarily is a mode with a slowly varying amplitude oscillations (4 - 12 Hz), the so-called hippocampal the theta rhythm. In addition, you can select the second mode for typical generators field potentials in the left and right hippocampus of rats, this behavior is rapidly changing the amplitude of the oscillations (30 - 60 Hz). Thus, these results confirm that the bond between the generator field potentials in right and left hippocampus of rats is performed in the frequency range (0 - 60 Hz). It should be noted that the degree of coherence (or, in turn, the relationship between the potentials of the field generators in the right and left side of the rat hippocampus) vary depending on the experiments.

We have found the characteristic features of the brain activity in the case when the animal does not solve any problem of cognitive navigation. The study intermitentnoy synchronization fluctuations in the ways Schaffer, in which has been developed and used a new technique based on a previously proposed methods of analysis on different time scales synchronization [6]. Thus it was obtained the dependence of duration synchronous behavior between field potentials generators right and left parts of the rodent hippocampus, which is close to exponential.

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Learning in Coupled Neural Networks with Heteroclinic Circuits

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Relatively recently it has been shown that regular but complex enough oscillatory activity in dynamical systems can emerge from the so-called stable heteroclinic channels [1,2]. In a neural network consisting of several coupled cells, one may observe a situation when all neurons are excited sequentially, i.e. each neuron becomes a winner for a limited time. Such a dynamic regime, called winner-less competition (WLC), can be implemented in a vicinity of heteroclinic trajectories connecting saddle equilibria in a loop [3,4]. From the one side, earlier it has been shown that a heteroclinic circuit may exist if certain relationships among synaptic coupling strength in the neural network are fulfilled [5,6]. From the other side, in neuronal systems synaptic plasticity may potentially change dynamic regimes. The latter may enable the emergence of WLC under special network training.

In this work we propose a model of learning, i.e., a learning rule, which allows one neural network, call a teacher, to impose its own dynamic to another neural network, call a learner. As a result, in the learner there appear WLC oscillations synchronized in phase with the oscillations of the teacher.

The model of a neural network that we used is:

$$\frac{dA_i(t)}{dt} = A_i(t)\left[1 - \sum_{j \neq i} \rho_{ij} A_j(t)\right] + \xi_i(t) \quad (1)$$

were $A_i(t)$ describes the activity of the i-neuron at time instant t, $\xi_i(t)$ is the Gaussian white noise, and ρ_{ij} is the matrix of couplings that determines the system dynamic. Figure 1 (left column) shows an example of oscillations in two neural networks (teacher and learner) with different directions of excitation and the period of dominant activities.

For network training we apply the follow learning rule [7]:

$$\dot{\alpha}_i^l = \frac{\Delta\phi_2}{|\Delta\phi_2|} c\left(\left(A_i^t\right)^2 - \left(A_i^l\right)^2\right) \cdot \alpha_i^l\left(1-\alpha_i^l\right), \Delta\phi_2 = \left(A_2^t + A_3^l - A_3^t - A_2^l\right) \quad (2)$$

were c is the learning rate, α_i^l is the element in the coupling matrix of the learner (see [5], all $\beta_i = 2.8$ in both system). The elements in the coupling matrix of the teacher are fixed: $\alpha_1^t = 0.7$, $\alpha_2^t = 0.4$ $\alpha_3^t = 0.2$. At t = 0 we set the elements in coupling matrix of the learner to: $\alpha_1^l = 0.35$ $\alpha_2^l = 0.15$ $\alpha_3^l = 0.2$

At the beginning both networks exhibit significantly different WLC dynamics (Fig. 1, left column). The teacher implements red->blue->green->red cycle, while the learner follows red->green->blue->red sequence. Then the purpose of learning is to synchronize oscillations in the learner with the teacher by tuning the coupling strengths in the learner. After a transient time the learner drastically changes its dynamics and starts reproducing the teacher cycle (Fig. 1, right column). Thus, we obtained the structural synchronization of two neuronal circuits by learning.

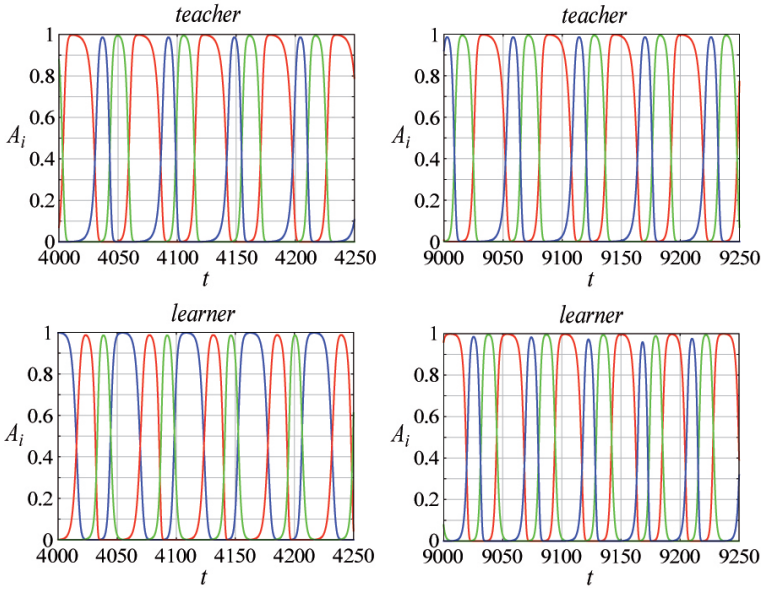

Fig.1. *The dynamic of the teacher and learner networks before learning (left column) and after learning (right column)*

We note that the learning was implemented through a rule that changes local couplings in the learner according to the own and the teacher dynamics. Thus, no direct influence of the teacher to the state variables of the learner exists. Such a mechanism of synchronization differs significantly from much more common models of synchronization based on couplings among state variables describing the system dynamics and better describes learning among spatially segregated neural networks.

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Simulations of Chloride Pathology as a Mechanism for Generation of Abnormal Neural Activity

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Pharmacoresistant epilepsy is a chronic neurological condition in which a basal brain hyper excitability results in paroxysmal hyper synchronous neuronal discharges. Human temporal lobe epilepsy has been associated with dysfunction or loss of the potassium-chloride co-transporter KCC2 in a subset of pyramidal cells in the subiculum, a key structure generating epileptic activities. KCC2 regulates intra-neuronal chloride and extracellular potassium levels by extruding both ions. Absence of effective KCC2 may alter dynamics of chloride and potassium levels during repeated activation of GABAergic synapses due to interneuron activity. In turn such GABAergic stress may itself affect Cl- regulation. Such changes in ionic homeostasis may switch GABAergic signaling from inhibitory to excitatory in affected pyramidal cells and also increase neuronal excitability. Possibly they contribute to periodic bursting in pyramidal cells, an essential component in the onset of ictal epileptic events. We tested this hypothesis with a computational model of a subicular network with realistic connectivity. The pyramidal cell model explicitly incorporated the cotransporter KCC2 and its effects on the internal/external chloride and potassium levels Our network model suggested the loss of KCC2 in a critical number of pyramidal cells increased external potassium and intracellular chloride concentrations leading to seizure-like field potential oscillations. These oscillations included transient discharges leading to ictal-like field events with frequency spectra as in vitro. Restoration of KCC2 function suppressed seizure activity and thus may present a useful therapeutic option. These simulations therefore suggest that a reduced KCC2 cotransporter activity alone may underlie the generation of ictal discharges.

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