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Invariance of network dynamics to biophysical properties

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Information processing in the brain involves interactions at multiple levels of organization ranging from molecular to cellular to networks. Thereby, biophysical properties at low levels may affect higher-level properties. For instance, the frequency of oscillations in coupled excitatory and inhibitory networks depends on the synaptic time constants [1]. On the other hand, it has been shown that network activity may not be affected by variations in the precise values of low-level properties [2]. Moreover, under certain conditions, when a system is faced with global constraints, the properties of the entire system may determine the properties of a part, without the properties of a part determining the properties of the whole system [3].

Here, we seek to understand how low-level properties influence network activity dynamics and stimulus-response properties that also depend on the particular network topology. To this end, we perform systematic investigations of the dynamics in spiking neural networks altering the firing profiles of the neurons in the network. Specifically, we study networks with different classes of neurons spanning all major experimentally observed spiking behaviors such as fast-spiking, bursting and adaptation, and measure their influence on network dynamics.

Our results indicate that global activity states are not qualitatively affected by low-level properties. The effects of low-level properties, however, become more salient in response of the network activity to temporally structured stimuli. These effects are, in addition, determined by the connectivity properties of participating neurons.

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Cooperation of synapses in structural plasticity

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Structural plasticity has been observed even in the adult mammalian neocortex -- in seemingly static neuronal circuits structural remodeling is continuously at work. Still, it has been shown that the connection patterns between pairs of neurons are not random. In contrast, there is evidence that synapses between a single pair of neurons cooperate [1]. Several experimental studies report either zero or about 3-6 synapses between neuron pairs (see [1] for references). The mechanism by which the synapses cooperate, however, has not yet been identified. Here we propose a model for structural plasticity that relies on local processes at the dendritic spine. We combine and extend the previous models of [1], [2] and [3] and determine the equilibrium distribution of synapse numbers of the model. By optimizing the parameters numerically for each of three reference datasets, we obtain equilibrium synapse number distributions that fit the references very well. We conclude that the local dendritic mechanisms that we assume suffice to explain the cooperative synapse formation in neocortex.

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Effect of correlated excitation/inhibition and network structure on spiking activity propagation in neuronal networks *in vitro*

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To exploit modularity of the brain, it is crucial that spiking activity can be propagated in a controlled manner from one module to the next.

The feedforward network (FFN) is a commonly used model to study signal propagation. Computational studies have shown that the structure of the FFN (shared connectivity, synaptic strength) determines whether rate signals (tonic activity) and/or temporal signals (transient activity) can propagate through a FFN [1].

Recently, we have shown that tonic and transient activity can be gated by feedforward inhibition (FFI) [2]. Here, the balance of excitation and inhibition allows to control the propagation of slowly varying rate signals (amplitude gating), whereas transient signals can be controlled by varying the temporal correlation of the excitation / inhibition (temporal gating) [2]. Thus, FFNs with appropriate FFI can serve as powerful building blocks for circuits in which to embed possibilities for propagating and gating a wide variety of spiking activities.

Up to now, only few experiments have been conducted to test these concepts in biological neural networks, primarily because it is not possible to selectively record from neurons belonging to a FFN. However, the FFN can be 'simulated' in vitro by an iterative stimulation approach, constructing a FFN from consecutive recordings from a single neuron. Using this approach, it was found that rate signals became increasingly correlated among neurons across multiple layers of a FFN [3].

In the present work, we test if predictions from theoretical studies [1] also apply to more realistic FFNs in vitro, specifically if rate signals may survive in a FFN by adjusting the connectivity parameters, and if FFI can implement amplitude and temporal gating in a biological FFN. We used dynamic current clamp [4] to stimulate single neurons in vitro with excitatory and inhibitory synaptic conductances, mimicking the input of the FFN.

We found that asynchronous rate signals can indeed propagate across multiple layers for low inter-group connectivity (<=5%) and strong individual synapses. By contrast, in high inter-group connectivity FFNs rate signals become increasingly correlated across multiple layers, consistent with theoretical predictions [1] and previous experimental work [3]. Finally, we show that both amplitude and temporal gating can be achieved in vitro by appropriately tuned FFI.

In conclusion, our in vitro experiments provide strong support for the model predictions about signal propagation and gating in FFNs..

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Directed coherence between high-gamma activities in pre- and primary human motor cortex during movement tasks

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In this study, we investigated interaction between pre- and primary motor areas by using partial directed coherence (PDC) of broadband high-gamma (60-200Hz) electrical potentials measured from fronto-parietal electrocorticographic (ECoG) recordings in humans during visually cued and self-paced motor tasks.

Five motor tasks were performed (each by 2-6 subjects): (1) cued finger flexion; (2) cued 8-directional center-out joystick movement; (3) cued brain-controlled 1D cursor movement based on motor imagery; (4) cued brain-controlled 1D cursor movement based on motor movements; (5) self-paced left/right joystick movements.

We computed PDC to analyze the possible interactions of the high-gamma activities between different parts of pre-motor cortex (PM) and primary motor cortex (M1). We found movement related modulations of the PDC in the high-gamma frequency range. Consistently across all five motor tasks, the PDC from pre-motor sites to primary motor sites increased briefly before and during the movements. Interestingly, the involvement of different parts of ventral and dorsal PM depended on whether the task was cued or self-paced: For self-paced movements (5), the most prominent observation was an increase in the PDC from ventral pre-motor cortex to primary motor cortex, while for cued movements (1-4), we observed an increase in the PDC from dorsal pre-motor to primary motor cortex, without an associated change in the PDC between ventral pre-motor and primary motor cortex.

Our results suggest that the observed directed coherence patterns reflect information transmission from pre- to primary motor cortex during preparation for, and execution of, movements. Moreover, our findings indicate differential involvement of different parts of pre-motor cortex depending on whether movements are externally cued or self-paced.

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AMPA, NMDA and GABA-A receptor mediated network dynamics in cortical cultures

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Synchronous patterns of activity, accompanied with intracellular Ca^{2+}-transients, are considered to play an essential role in the development of neuronal networks in a wide range of brain structures, including networks of dissociated cortical neurons in vitro. Synchronous activity in forms of network-wide bursts (NB) is thought to be generated by recurrent excitatory pathways. The inhibitory pathways suppressing excitation are also considered important in oscillatory network dynamics. As in native cortical tissue, glutamatergic AMPA receptors (AMPA-R) (expressing fast ion channel kinetics) and NMDA receptors (NMDA-R) (expressing slow ion channel kinetics, and both voltage and Mg^{2+}-dependency) are the main mediators of excitatory synaptic transmission among neurons in vitro. Fast inhibition is mediated through GABAergic transmission via $GABA_A$ receptors ($GABA_A$-R). Despite the solid biophysical characterization of AMPA-Rs, NMDA-Rs, and $GABA_A$-R at the monosynaptic level, their complex interplay on the network level is still not fully understood. In this work, we studied for first time the coordinated interplay between excitation and inhibition in network dynamics in dissociated neurons of rat neonatal cortex. Extracellular network-wide activity was recorded with 59 planar electrodes simultaneously under different pharmacological conditions. Firstly, we obtained spontaneous baseline activity. Secondly, we silenced each of the excitatory pathways by blocking either AMPA-Rs or NMDA-Rs with NBQX or D-AP5, respectively. Finally, we disinhibited the networks with $GABA_A$-R blocker PTX. This protocol allows us to investigate the temporal and spatial patterns of network dynamics, produced by fast and slow excitatory and fast inhibitory transmission. We analyzed the changes of overall network activity and NB frequency between baseline and AMPA-R or NMDA-R driven activity, as well as between the former ones and the disinhibited activity. Additionally, spatiotemporal structures of pharmacologically modified bursts and recruitment of electrodes during the NBs were studied. Our results show that AMPA-Rs and NMDA-Rs have clearly distinct roles in network dynamics. AMPA-Rs are in greater charge to initiate NBs, whereas NMDA-Rs maintain the already initiated NBs. $GABA_A$-Rs inhibit AMPA-R driven network excitation more strongly than NMDA-R driven during the bursts. However, $GABA_A$-R mediated inhibition slows down the propagation of NMDA-R mediated network activity more than AMPA-R mediated. These results indicate that dynamics of cortical networks in vitro incorporate a complex interplay between excitatory and inhibitory transmission.

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Implications of network structure on neural activity: Beyond statistical significance

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It is a common practice in experimental neuroscience to assess the statistical significance of spiking activity variations, measured from single or multiple neurons. For instance, in behavioral experiments, the probability of an increase in firing rate or correlation strength among a group of neurons is estimated under the assumption that an appropriately chosen null-hypothesis were true. If the probability for observing the experimental results under the null-hyppothesis is small, the results are deemed statistically significant and the neural activity is assumed to be functionally related to the task. Thus, it is also implicitly assumed that the statistically significant neural activity must have some effect on the network dynamics. However, this tacit inference is not warranted a priori. That is, the fact that the recorded neuronal activity is not a chance event does not necessarily imply that it will have an impact on local or downstream network activity, particularly when the network is not homogeneously random. Therefore, any strong, or even causal association to the behavior is not justified either.

We illustrate this largely ignored point by systematically analyzing the responses of 100 simulated spiking neuron networks, each composed of 10,000 neurons, to external stimulation. All networks had different topologies, however, the average connectivity parameters were kept constant. We measured the population activity and related it to network properties that characterize the way in which the stimulated neurons are embedded in their local environment. To estimate the embededness of neurons, we used known metrics from graph theory such as closeness centrality and k-shell decomposition. Our results indicate that the impact neuronal events have on local or downstream network dynamics strongly depends on the structural embeddedness of participating neurons. We discuss potential implications of our findings for the analysis of neuronal activity. We also point out additional hurdles that need to be overcome in extracting network function, which go beyond knowledge of the structure and dynamics.

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