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Role of neurogenesis in temporal lobe epilepsy

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The subgranular zone (SGZ) of the dentate gyrus is one of the few brain regions where the formation of new neurons takes place even in the adult. In particular, status epilepticus has a stimulating effect on neurogenesis in the SGZ. The role of newly born neurons in the epileptic hippocampus is, however, a matter of ongoing controversy.
To address this issue, we used the intrahippocampal kainate mouse epilepsy model, which recapitulates the main features of mesial temporal lobe epilepsy in humans: recurrent focal seizures, granule cell dispersion and selective cell death in the hippocampus. Following the focal injection of kainate into the hippocampus, we performed multi-site in vivo local field potential recordings along the septotemporal axis of the kainate-injected and in the contralateral hippocampus and quantified the strength of status epilepticus (SE) and recurrent epileptiform activity (EA). In addition, we used bromodeoxyuridine injections to monitor proliferative activity, immunohistochemical analysis to determine cell fate and patch-clamp recordings to investigate the functional integration of newly born granule cells after SE.
We show that following kainate injection into the septal hippocampus, SE spread along the septotemporal axis of both hippocampi, with stronger intensity at temporal and contralateral sites. Similarly, cell proliferation was strongly increased in the temporal ipsilateral and entire contralateral SGZ, giving rise to immature granule cells, which functionally integrated into the hippocampal network, as shown by perforant path stimulation. In contrast, in the septal portion of the KA-injected hippocampus, proliferation was increased in the hilus, but gave rise to glial cells instead of new neurons. Notably, intrahippocampal recordings at three weeks after injection revealed that the septotemporal position where strongest EA was measured coincided with the area of transition from lost to increased neurogenesis. This suggests a pro-epileptogenic effect of neurogenesis and the integration of newborn neurons, e.g. by alteration of network connectivity.

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Input-Resistance Dependent Switch in Spiking Precision of Neocortical Pyramidal Cells

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The temporal precision with which action potentials are generated strongly influences network activity dynamics and has far-reaching implications for coding schemes utilized in the brain. From their spiking dynamics, the majority of neurons can be assigned to one of two classes: fast spiking cells that precisely follow synaptic input and show properties of a resonator, and regular spiking cells which respond with much less temporal precision to incoming signals, but faithfully translate the integrated amount of input into a wide range of firing rates.

Here, we tested principal cells of the neocortex for their ability to respond precisely to slightly supra-threshold, transient inputs. In contrast to their counterparts in the hippocampus, neocortical pyramidal cells locked precisely to short current pulses, even though they are generally classified as regular spiking cells or integrators. Surprisingly, however, most neocorical pyramidal cells switched to temporally imprecise spiking dynamics when depolarized towards the spike threshold. Pharmacological blocking experiments and artificial changes of leak conductance via dynamic clamp revealed that this switch in spiking dynamics can be explained by a change in input resistance, rather than by properties of specific voltage gated channels. Simulations and phase-plane analysis of neuron models revealed that neocortical pyramidal cells are readily switched from resonators to integrators by membrane resistance changes well within the physiologically plausible range.

Taken together, our findings implicate that neocortical cells can operate in any one of two distinctworking regimes, with qualitatively different spiking dynamics. A switch between these two regimes may occur through any slow modulatory mechanism that causes moderate changes in input resistance.

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Differential dendritic and somatic input mapping in layer V pyramidal neurons

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Layer V pyramidal neurons of the rat neocortex play an important role in signal processing, constituting the major output of the cortical volume. They show a very specific morphology including a prominent apical dendrite spanning all layers and terminating in an extended tuft. EPSPs arising from contacts at distal dendrites are strongly attenuated while they propagate to the soma, where they are often hardly detectable. However, recent studies showed that the dendrites of pyramidal neurons are capable of regenerative potential generation like calcium and NMDA spikes, even though the physiological conditions under which they occur and the neuronal populations driving them remain speculative. In contrast to the connectivity of the somata examined with paired recordings, photo stimulation and anatomy, very little is known about the projection patterns onto the different dendrites of the neurons and the contribution of the presynaptic neurons from different layers to the signal integration within these structures.

In the present study, simultaneous dendritic and somatic whole-cell patch-clamp recordings in combination with presynaptic photo stimulation via glutamate un-caging were used to assess the properties and layer dependency of synaptic inputs onto different compartments of layer V pyramidal neurons in acute slices of the rat somatosensory cortex.

With recordings from the apical dendrite it was possible to detect connected presynaptic neurons with horizontal distances of up to 1mm eliciting only small EPSPs which were not detectable at the soma. The obtained functional input maps from the distal dendrite and those obtained from the soma show differences concerning the layer dependency of the connected presynaptic neurons. In addition to the reported input populations onto the somata of layer V pyramidal neurons from other studies located in layer II/III, V and VI, we found the supragranular layers constituting the most prominent input to the distal apical dendrites of layer V neurons. The specific projection pattern of presynaptic neuron populations onto different postsynaptic compartments of layer V pyramidal cells points to a distributed integration of inputs from different layers, which may also have an impact on the generation of regenerative potentials in dendrites. Our findings could help to further understand the effect of dendritic integration, in particular nonlinear mechanisms and the involved neuron populations, on signal integration in layer V neurons.

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Differentiated dentate granule cells start to migrate under epileptic conditions

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Characteristic features of temporal lobe epilepsy (TLE) are recurrent, focal seizures and Ammonshorn sclerosis including a widening of the granule cell layer, called granule cell dispersion (GCD). The electrophysiological and neuropathological characteristics of TLE, including GCD, can be mimicked by unilateral, intrahippocampal injection of the glutamate receptor agonist kainate (KA) in adult mice. Using this animal model we have previously shown that GCD develops within two weeks after KA injection due to displacement of differentiated granule cells (Heinrich et al., 2006, JNS 26(17). In order to unravel the mechanism of this intriguing finding, we used Thy-1-eGFP transgenic mice, in which eGFP is primarily expressed in a subset of differentiated dentate granule cells. With the aim to monitor GCD formation in real time, we established organotypic hippocampal slice cultures (OHC) from Thy-1-eGFP transgenic mice and developed a protocol to induce GCD in vitro. OHC were prepared from P8 mouse pups, kept in culture for seven days and were treated with 15 µM KA for 8 hours on three consecutive days. This treatment caused a significant displacement of eGFP-positive granule cells leading to a strong widening of the granule cell layer (123.6 ± 5.0 µm) when compared to untreated controls (78.8 ± 2.4 µm). As a next step, life cell imaging of control and KA-treated OHC was performed. To this end, eGFP-positive granule cells were observed by confocal time-lapse videomicroscopy in an aerated chamber for different periods of time (6h, 12h and 24h). During the whole observation period, images were acquired every 20 min to monitor the position of eGFP-positive granule cells. Preliminary results indicate that in KA-treated OHC differentiated granule cells move actively towards the hilar region. Further studies will clarify the exact mechanism of this migration process.

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Mismatch in network dynamics in a model of temporal lobe epilepsy

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Mesial temporal lobe epilepsy (MTLE), the most common form of focal epilepsies in adults, is often accompanied by histological changes within the hippocampal formation, summarized as hippocampal sclerosis (HS). In many cases, surgical removal of the sclerotic parts does not result in a seizure-free outcome. In the intrahippocampal kainate mouse model of MTLE, recurrent epileptiform activity (EA) and HS are observed after focal injection of kainic acid (KA) into the dentate gyrus (DG) [1]. In this animal model, the sclerotic parts close to the injection site have been found to be unable to generate or sustain EA [2]. It has therefore been suggested that parahippocampal structures could also be involved in EA generation.
As a major source of direct input to the DG, the superficial layers of the entorhinal cortex (EC) could be a key candidate. However, so far, most studies on the role of the EC in animal models of MTLE have been performed after a systemic, not focal, application of pharmacological agents and therefore, a specific role of the EC in the generation of EA could not be isolated.
Thus, we performed simultaneous in vivo local field potential (LFP) recordings at the injected DG and the EC to investigate the relation between these two structures in the focal kainate model. We found a phase shift in EA-free baseline activity between the DG and the EC in kainate mice which was never observed in controls. This suggests that the mutual coupling between the EC and the DG in ongoing activity between EA periods is impaired. To investigate the neural mechanisms underlying this observed delayed synchrony we used a computational model of the entorhinal-hippocampal network. Consistent with cell loss throughout the septal hippocampus, our simulation results suggest that asymmetric coupling between the DG and the EC may underlie the observed temporal shift in the entorhinal-hippocampal loop.

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Role of inhibition in unleashing and quenching oscillations in the basal ganglia

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Neural mechanisms underlying slow oscillations and increased synchrony in the basal ganglia associated with various motor dysfunctions of Parkinson's disease[1,2] are poorly understood. Using a minimal model of basal ganglia, validated by biologically realistic simulations, we show that the strength of the inhibitory inputs from the striatum to the globus-pallidus-external is the key parameter that controls the oscillatory behavior of the basal ganglia.

In fact, experimentally observed increase in the striatal activity[3,4] is sufficient to unleash the oscillations in the basal ganglia. This theoretical framework provides a possibility to understand and optimize the deep-brain-stimulation protocols. We show that broadband stimulation of the subthalamaic nucleus could be more efficient than the conventional periodic stimulation in quenching oscillations. Finally, this unified explanation of both emergence and quenching of oscillations naturally leads to novel therapeutic suggestions for electrical and chemical intervention of oscillations in the dopamine-depleted basal ganglia.

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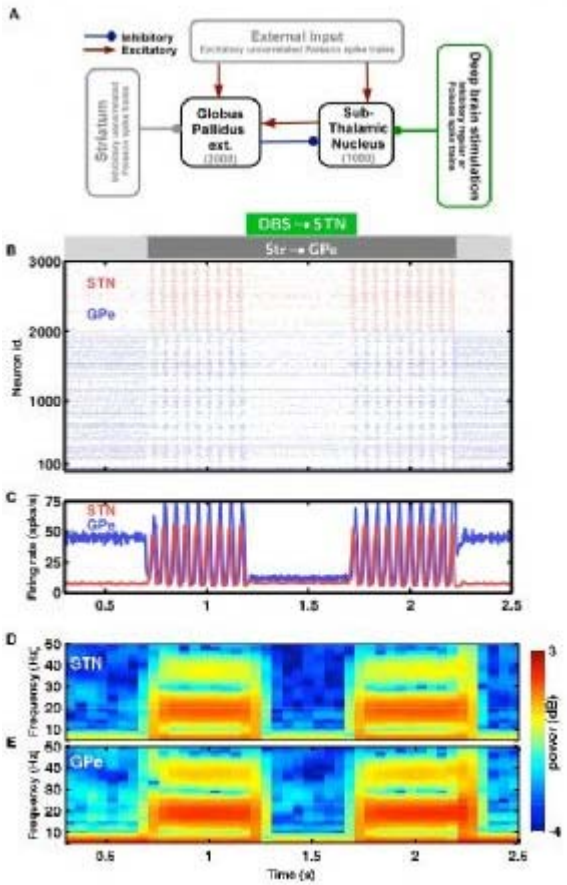
A
Inhibitory
Excitatory
External Input
Striatum
Globus Pallidus ext.
(2000)
Sub-Thalamic Nucleus
(1000)
Deep brain stimulation
B
DBS → STN
Str → GPe
STN
GPe
Neuron id.
3000
2000
1000
100
C
STN
GPe
Firing rate (spk/s)
75
50
25
0
0.5
1
1.5
2
2.5
D
STN
E
GPe
Frequency (Hz)
60
40
30
20
10
3
-4
power (dB)
Time (s)

Plasticity in the HVC of the Bengalese finches is crucial for song syntax stability

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The high vocal center (HVC) of the Bengalese finch relies on reafferent signals from the auditory system to generate variable squences of syllables (song syntax) [1]. This leads to the hypothesis that song syntax memory is stored in the efferent connections from the auditory areas to the HVC nuclei. Deafening experiements in the Bengalese finch reveal a gradual loss of the song syntax over the course of a week [2,3]. This finding cannot be explained by a loss of song syntax memory, because the bird is able to reproduce the original syntax once auditory feedback is restored [4].
In a computational study we investigate the change of song syntax in the presence and absence of auditory feedback and with altered auditory feedback. Changes in song syntax are quantified by the sequencing stereotype S* and the average transition entropy [3]. The gradual loss of syntax can only be reproduced if plasticity in the HVC is assumed. We discover the gradual loss of syntax is accounted for by the hypothesis that the song syntax is imprinted on the network structure through repetition. Similarly, an alternative hypothesis that an efference copy of the HVC motor pattern is learnt can also account for the data. The figure illustrates our simulation results. Before 4000s the song syntax is stably produced in the presence of auditory feedback (S*=0.75+/0.02 with S*=0.75 for perfect syntax). Between 4000s and 8000s the auditory feedback is suppressed. The resulting gradual decrease in sequencing stereotype can be fitted by a power law. After 8000s auditory feedback is restored and the original song syntax is immediately reestablished (S* =0.73+/0.02). The plasticity in HVC is behaviorally relevant for the Bengalese finch in order to keep the song syntax stable in the presence of natural auditory feedback perturbations.

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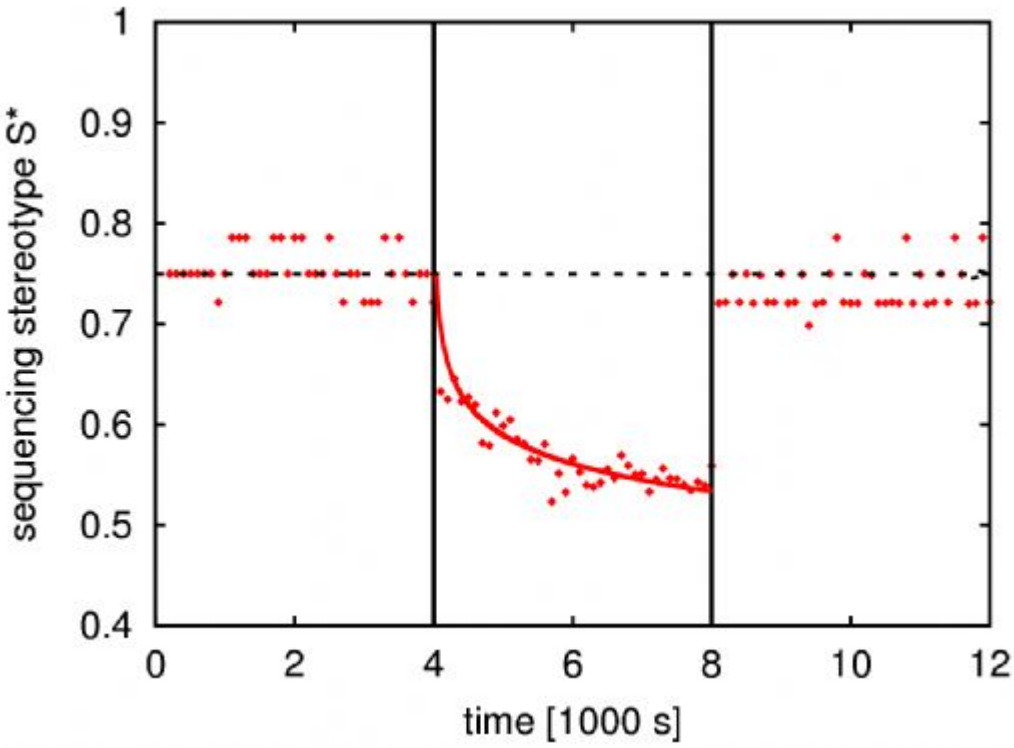
sequencing stereotype S*
1
0.9
0.8
0.7
0.6
0.5
0.4
0
2
4
6
8
10
12
time [1000 s]

Physiological properties of non-local, horizontal projections onto layer 5 pyramidal neurons

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Local cortical networks and their role in information processing in the brain have been studied on many different levels and scales, both experimentally and theoretically. Although the properties of local and inter-laminar synaptic connections have been investigated in great detail, the question remains if this is sufficient to describe more generic properties of cortical networks in terms of information processing and propagation. In recent years, the impact of long-range horizontal connections on neocortical networks has therefore drawn increasing attention, since several neuroanatomical studies (Hellwig 2000; Binzegger et al., 2004; Stepanyants et al., 2009; Voges et al. 2010) have consistently suggested that an estimated 50-75% of the connections a neuron receives originate outside the local volume (radius: ~250µm). Due to the strong drop in connection probability of laterally displaced pairs of neurons and the resulting methodological constraints for classical investigation with paired recordings, the properties of these connections have not been elucidated yet, although their impact on local information processing could be substantial.
Here, we used photostimulation to map long-range horizontal projections to layer 5B pyramidal neurons in acute cortical slices. For lateral distances of 200-1500µm, we found intact projections which were preserved in the slice and characterized their physiological properties as well as their layer of origin. The average amplitude of EPSCs slightly dropped with distance, while strong connections were still present over long distances. Short and long range connections showed an equally high synaptic reliability of 100% in most tested synapses, the same level of amplitude variability, and an equally high temporal precision of <1ms. In summary, our data provide an initial parameterization of long-range connections, which could be used to refine structured models of cortical networks. We conclude that long-distance horizontal connections could represent a substantial fraction of inputs to the local, cortical network. Secondly, although they showed a slight drop in amplitude with increasing distance, they contribute with reliable and precise inputs to the single neurons in layer 5, thus impacting the local computation considerably.

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Learning from positive and negative rewards

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Animal learning is highly driven by reward and punishment. However, it is still an open problem in the field of computational neuroscience how reward learning is carried out on the neuronal level. One influential hypothesis in this context is that the brain implements temporal-difference (TD) learning, an algorithm capable of solving complex tasks with sparse reward. This hypothesis is mainly based on experimental findings involving the dopaminergic system. In particular, it has been found that the phasic dopaminergic activity resembles the TD error during reward learning [1] and that cortico-striatal synaptic plasticity is modulated by dopamine [2]. However, the phasic dopaminergic signal can only realize an imperfect TD error due to the low baseline firing rate. In addition, synaptic weights are limited in their ability only to represent estimates of future rewards, due to their inherent lower bound.

To analyze the consequences of a dopaminergic system on TD learning, we develop a spiking neuronal network model that integrates multiple experimental results. Our model generates a phasic dopaminergic signal with realistic firing rates which is in turn exploited by dopamine-dependent plasticity that is consistent with experimental data with respect to pre- and postsynaptic activity and dopamine concentration. Our analysis shows that the deviation of the neuronal error signal from the theoretical TD error results in a slightly modified TD learning method with self-adapting learning parameters.

We demonstrate that the spiking neuronal network is able to learn a grid-world task with sparse reward with similar speed and equilibrium performance to a traditional TD learning implementation. However, differences in the learning behavior between the neuronal and the traditional algorithm become apparent in cliff-walk tasks, where the agent is punished when stepping into a certain region. If an external reward is present in addition to punishment, we find that the neuronal agent is still able to learn the cliff-walk task, albeit with a slightly different learning strategy than the traditional TD learning agent. However, if learning is driven exclusively by punishment, we find that the task can no longer be learned by the neuronal agent, as in this case all synaptic weights reach their minimal allowed values.

Our results show that dopamine-dependent plasticity modulated by a phasic dopaminergic error signal enables TD learning when learning is predominantly driven by reward, but not by punishment. In the literature, two main hypotheses have been proposed to account for how negative errors are represented in the mammalian brain. Whereas it has been suggested that negative error could be encoded in the duration of the phasic activity of the dopamine neurons [3], our results support the second hypothesis, namely that negative errors are represented by a different neuromodulator such as serotonin [4].

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Why feed-forward structure fails to propagate in plastic recurrent networks

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Spike-timing dependent plasticity (STDP) has traditionally been of great interest to theoreticians, as it seems to provide an answer to the question of how the brain can develop functional structure in response to repeated stimuli. However, despite this high level of interest, convincing demonstrations of this capacity in large, initially random networks have not been forthcoming. Such demonstrations as there are typically rely on constraining the problem artificially. Techniques include employing additional pruning mechanisms or STDP rules that enhance symmetry breaking, simulating networks with low connectivity that magnify competition between synapses, or combinations of the above (see, e.g. [1,2,3]).
Here, we describe a simple model for the propagation of feed-forward structure in plastic recurrent networks. The key prediction of the model is that the number of neurons recruited by a repeated synchronous stimulus protocol is subject to an unstable fixed point. A synchronously firing group of neurons of a size below that of the fixed point recruits a smaller group, leading to a failure of the structure to propagate, whereas a synchronously firing group of a size above that of the fixed point recruits a larger group, causing the whole network to be recruited. In other words, a synchronous stimulus is always either not enough or too much. We demonstrate by simulation that a large-scale network behaves as predicted by the theory. Finally, we investigate biologically motivated adaptations to the balanced random network model that have been proposed to facilitate structure formation in large-scale simulations.

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Beyond local cortical network modeling: linking microscopic and macroscopic connectivity in brain-scale simulations

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What does a single cortical neuron "see"? A single neuron receives on the order of 10,000 synaptic inputs. These inputs originate in various parts of the brain and can be categorized into local, long-range intrinsic and extrinsic inputs. The extrinsic inputs originate in several subcortical structures and also in on the order of 10 other cortical areas [1]. Therefore, a single cortical neuron processes inputs from potentially every other part of the brain. It has been found that the detailed connectivity structure on the microscopic and the macroscopic level depends on the cell type of a neuron, i.e. on its area, its layer etc. [1,2]. The exact ratio of long-range and local inputs a neuron receives is not known [3].

Cortical network modeling typically involves a single scale: either the scope is the local microcircuit on the level of single neurons [2] or exclusively the macroscopic network missing the link to single-neuron activity [4]. Local cortical network models comprising on the order of 100,000 neurons represent the majority of the local synapses (around 1 billion) and treat the extrinsic inputs as external. These models can adequately explain the local interactions based on the microcircuitry and consistently replicate prominent features of the cell-type specific activity observed in awake animals [2]. However, their explanatory power is limited because the origin of a major fraction of the excitatory inputs is left unexplained.

Here, we present our approach to combine local microcircuit modeling with the macroscopic brain network: the figure shows a cartoon of the local cortical microcircuit on the left and the macroscopic connectivity pattern on the right. In the center, our brain-scale model is depicted that combines both network levels. The link between the microscopic and the macroscopic network is the cell-type specificity of the long-range connections. This specificity has been used by others to construct a theory on hierarchical information processing in the brain [1].

Brain-scale simulations require progress in simulation technology as these models comprise millions of neurons with around 10,000 synapses each. Therefore, we review the technical challenges to scale up the simulations software [5] to tens of thousands of processors for the routine investigation of brain-scale models at synaptic resolution.

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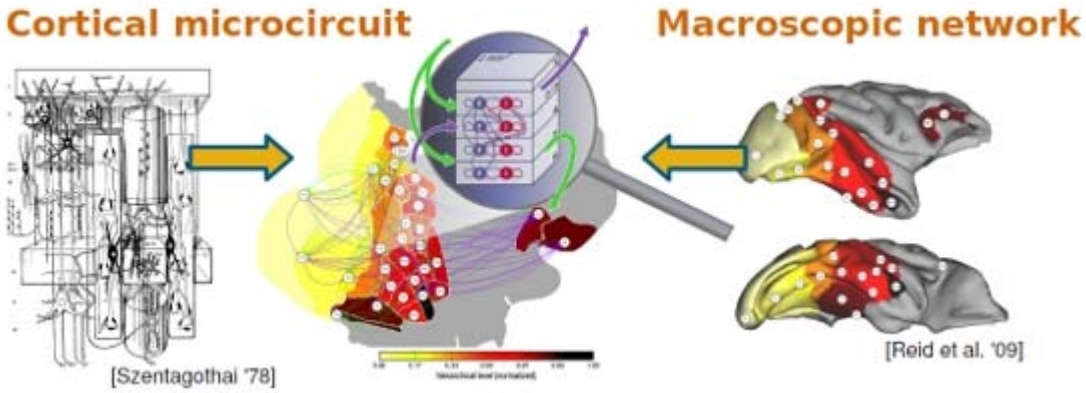

Decorrelation of neural-network activity by inhibitory feedback

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Spatial correlations in spike-train ensembles can seriously impair the en- and decoding of information in the spatio-temporal structure of these spike trains [1,2]. A potential source of correlation in finite neural networks is shared presynaptic input [3]. Recent theoretical and experimental studies have demonstrated that spike correlations in neural networks can be considerably smaller than expected based on the amount of shared presynaptic input in such systems [4,5,6].

Here, we provide an explanation of this observation by means of a simple linear model and simulations of networks of integrate-and-fire neurons. We show that pairwise correlations and hence population-rate fluctuations are actively suppressed by inhibitory feedback. To investigate the role of feedback we compute the response for the intact recurrent system and for the case where the 2nd-order statistics of the feeback channel is perturbed while the shared-input structure and the 1st-order statistics are preserved.

In general, any modification of the feedback statistics causes a shift in the power and coherence of the population response. In particular, the neglect of correlations within the ensemble of feedback channels or between the external stimulus and the feedback can amplify population-rate fluctuations by orders of magnitude. This effect can be observed both in networks with purely inhibitory and in those with mixed excitatory-inhibitory coupling. We show that the observed suppression of response fluctuations by inhibitory feedback in high-dimensional systems can be intuitively understood already by a simple one-dimensional linear model. For the n-dimensional case, we provide analytical solutions of the population-averaged correlations. In purely inhibitory networks, shared-input correlations are canceled by negative correlations between the feedback signals. In excitatory-inhibitory networks, the responses are typically positively correlated. Here, the suppression of input correlations is not a result of the mere existence of correlations between the responses of excitatory (E) and inhibitory (I) neurons, but is instead a consequence of the heterogeneity of response correlations across different types of neuron pairs (EE, EI, II).

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Finite brains see single spikes

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Mean-field arguments suggest that the effect of a single spike on the correlation of neurons can be neglected compared to the feed forward component of correlation. However, the recent experimental finding that single spikes have a substantial effect on the rest of the network [1] and the observation that the mean-field component is suppressed in balanced networks [2, 3] require a thorough theoretical assessment of these two contributions.

Here we augment the theory of correlations in purely excitatory recurrent networks presented in [4] by inhibition and delayed spiking interaction. We analytically determine the self-consistent correlation structure of recurrent finite-size random networks of spiking excitatory and inhibitory Poisson neurons with delayed pulse coupling to extend earlier feed-forward approximations [5] and the theory of zero-lag correlation in the asynchronous irregular state [6, 3].

We find that correlation functions generically contain two components: the feed-forward contribution of correlation expected from mean field arguments (Fig. A) and the echo of single spikes in the network (B). For realistic network parameters, both are of similar magnitude (C,D). The additive contribution of spike feedback explains why inhibition seems to lag excitation in recurrent networks, leading to asymmetric cross correlation functions (E). Moreover, our model explains generic features of correlations: the origin of side troughs, the emergence of damped oscillatory correlation functions, and the transition to fast global delay oscillations [7].

The availability of analytical expressions for correlations in finite excitatory-inhibitory networks will facilitate the investigation of their functional implications, in particular in the light of their critical interaction with spike timing dependent plasticity [8].

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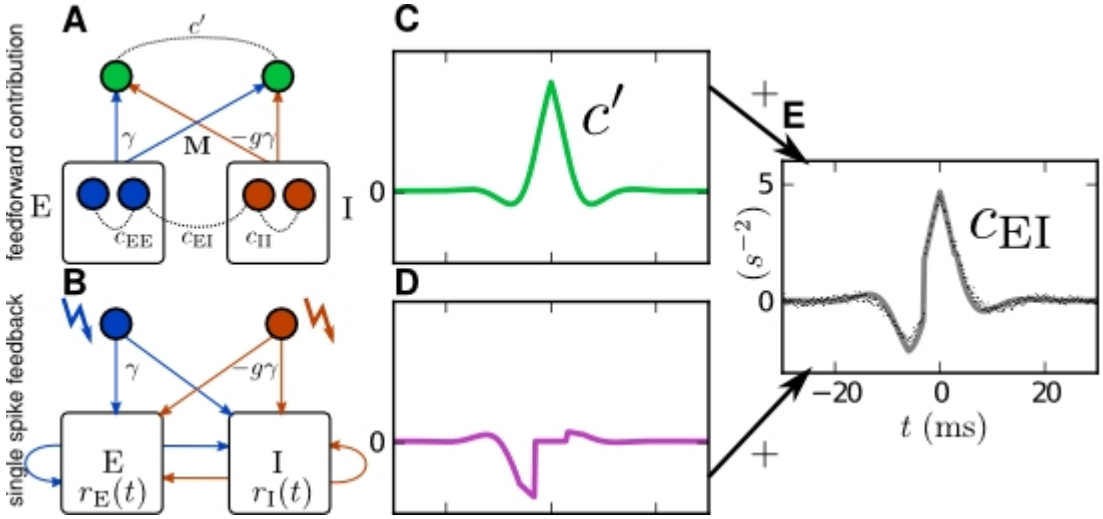

How much synchrony would there be if there was no synchrony?

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Ever since the discovery of precisely timed events of cortical neurons [1], their role for information processing has been highly debated. The widespread belief that synchrony is an epiphenomenon caused by shared afferents among neurons [2] has constantly been challenged by reports observing task related modulation of synchrony, lately in primary visual cortex [3] and motor cortex [4]. More so, the recently found decorrelation in cortical networks [5] suggests that the ground state of recurrent balanced networks provides a suitable substrate on top of which synchronized events can represent information. Theoretical insights [6] indicate that even weakly synchronous afferent activity is highly effective to cause synchronized spikes in integrate-and-fire neurons due to non-linear amplification.

In this work we theoretically investigate to what extent common synaptic afferents, fast rate changes, and synchronized inputs each contribute to closely time-locked spiking activity of pairs of neurons [7]. We employ direct simulation and extend earlier analytical methods based on the diffusion approximation [8] to pulse-coupling, in order to answer the question how much synchrony is caused by afferent synchronized events and how much is intrinsic to cortex.

We find that the firing rate dependence of correlation transmission [8] effectively modulates how much synchrony is transferred from the input to the output of pairs of neurons. Rate transitions per se, however, do not contribute significantly, whereas already weakly synchronous inputs are sufficient to cause detectable synchrony in the outgiong spiking activity.

Our quantitative assessment of the different contributions and understanding the underlying mechanisms will support the
interpretation of experimentally observed precisely time-locked events [3,4].

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On the contribution of structural inhomogeneities to network burst initiation and propagation in dissociated cortical cultures

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Dissociated cortical cultures grown on multielectrode arrays (MEA) have been established as a useful biological model in the analysis of network dynamics. Present in their dynamics are periods of strongly synchronized spiking by the network, termed `bursting', whose role is not understood but dominates network dynamics. It has been demonstrated that bursts have different motifs and contain structure, refuting the possibility that they are merely chaotic activity. Of particular interest are the conditions required for bursting to be initiated and propagated throughout the entire network. Within cultures, initiation sites can be well characterized in their location, even while varying different parameters such as cell density, while propagation waves display fairly regular patterns of neuron recruitment within the network burst. However, in order to minimize bursting and promote closed-loop communication with the disassociated culture, it is of interest to understand what conditions are necessary for bursting to arise.

Interestingly, the propagation of bursts has been observed to be faster than can be accounted for by only local connectivity. While paired intracellular recordings have revealed some clues as to the local structure and short range connectivity, they are unable to clarify the contribution of long-range connectivity of neurons to burst propagation. Additionally, pharmacological studies which result in freezing of synaptic plasticity and impaired cell migration have demonstrated that modifications to connectivity can greatly disrupt the pattern of burst propagation.

As network structure has been established to strongly affect dynamics, we identify network topologies that can account for observed burst initiation and propagation patterns by considering network models implementing several likely models of long-range connectivity. Specifically, we investigate the contribution of long-range connections within a 2D model network of spiking neurons representing a mature dissociated cortical culture. We previously demonstrated with networks of rate-based units that within clustered topologies, the relative number of long-range connection to cluster size greatly affects the robustness of the network to noise and ability to sustain activity. Here, we extend these networks to a population of spiking units and chart the effect of introducing inhomogeneities and a non-uniform distribution of connections, while also considering parameters such as the numbers and location of post-synaptic connections of each unit. By driving the network with low levels of background activity, we observe how different configurations change the burst initiation site and alter the propagation wave throughout the network. We establish the burst profiles for different network configurations and comment on their comparability to their biological equivalents.

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Refractoriness of individual neurons exposed in population spike trains

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Poisson processes are often used to model neuronal population spike trains. It is known, though, that superpositions of realistic, non-Poissonian spike trains do not necessarily inherit the Poisson propery [1,2]. We indeed confirm that the population activity constructed from in vivo recordings in rat somatosensory cortex strongly deviates from the Poisson assumption. An improved minimal model of single neuron spike trains, the Poisson process with dead time (PPD; [3]), overcomes the associated difficulties by taking the effective refractoriness of neurons into account. In fact, many aspects of the statistics of superpositions constructed from in vivo spike trains agree with our analytical results for superpositions of the PPD matched to individual spike trains. In simulations, we observed that model neurons receiving superimposed spike trains as input are highly sensitive for the statistical differences induced by refractoriness of the component spike trains. We further present an efficient generator of superpositions of PPDs. It can be applied to produce more realistic background input for simulations of networks of spiking neurons.

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Single drops decide about rise and fall of the diffusion approximation - Neuronal consequences of pulsed communication

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A generic property of the communication between neurons are synaptic pulses exchanged at discrete points in time defined by the action potentials. However, the current theory of spiking neuronal networks of integrate-and-fire neurons invokes the diffusion limit [1,2] to approximate synaptic impulses by Gaussian noise. Associating each impulse with a rain drop, performing the diffusion limit corresponds to the change from torrent rain to dense fog. The shishi odoshi (A), a device found in traditional Japanese gardens, is in some respects a suitable analog of a neuron. As a single drop of rain ultimately causes the shishi odoshi to tilt (B), a single additional synaptic impulse will finally cause an action potential in a neuron. This explains why the membrane voltage density close to firing threshold sensitively depends on the size of the synaptic amplitude [5,6]. Here we combine pulsed synaptic interaction with the analytical ease of the diffusion limit by means of a novel boundary condition at threshold [5,6]. Our theory explains why neural transfer is instantaneous rather than exhibiting lowpass characteristics, depends nonlinearly on the amplitude of synaptic impulses, is asymmetric for excitation and inhibition and is promoted by a characteristic level of synaptic background noise. These findings finally resolve contradictions between the earlier theory [1,2] and experimental observations [3,4].

We thank Johanna Derix for the idea of the shishi odoshi as an analogy for neural dynamics and are especially grateful to Susanne Kunkel for creating the artwork. We thank our colleagues in the NEST Initiative. Partially funded by BMBF Grant 01GQ0420 to BCCN Freiburg, EU Grant 15879 (FACETS), EU Grant 269921 (BrainScaleS), DIP F1.2, Helmholtz Alliance on Systems Biology (Germany), and Next-Generation Supercomputer Project of MEXT (Japan).

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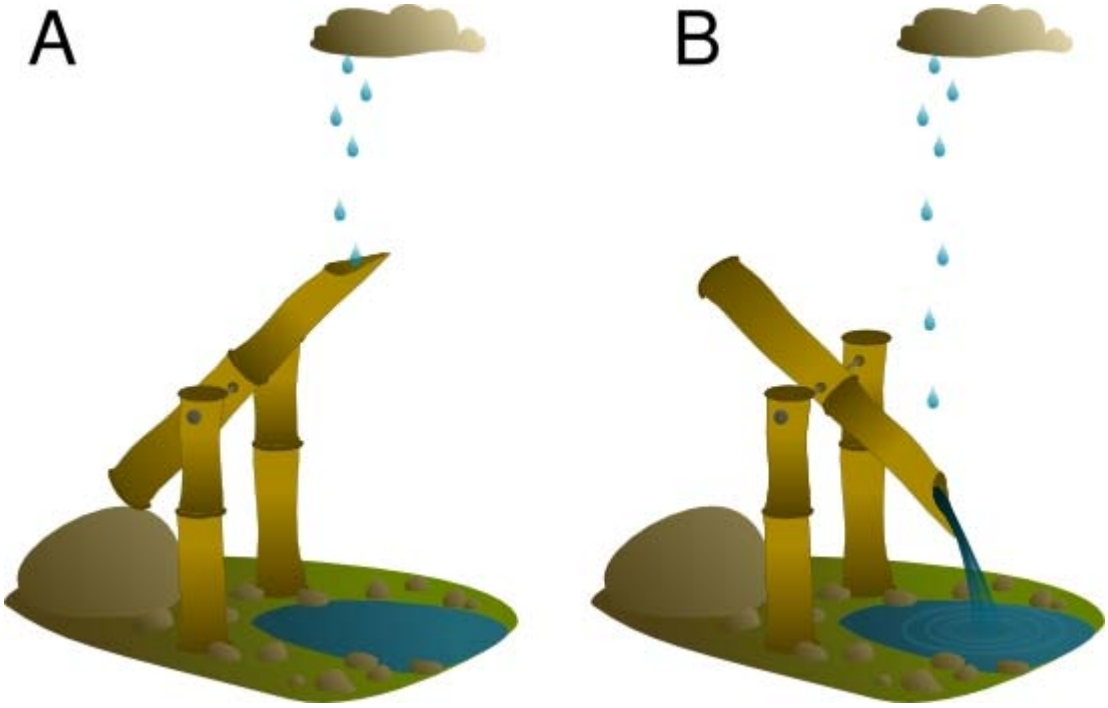

NEST: An efficient simulator for spiking neural network models

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NEST is a simulator for networks of point neurons or neurons with a few electrical compartments [1]. It is suited for a broad range of spiking neural network models and runs on standard desktop computers, computer clusters, or HPC facilities such as the IBM BlueGene. Distributed simulations show excellent scaling up to the order of one thousand processors, and current research extends the scalability into the range of ten thousand processors and beyond [2,3]. Recent additions to NEST include the incorporation of new neuron models such as the MAT(2) model [4] and spike-timing and neuromodulation dependent plasticity [5,6]. To increase its usability and follow software trends in the neuroscience community, NEST provides a convenient user interface based on the Python programming language [7]. NEST also supports the MUSIC interface to communicate with other simulators [8] and provides visualization tools [9] and a topology module that allows the specification of spatially structured networks [10]. The developers continually improve the algorithms in NEST, e.g. for the calculation of 'off-grid' spike times and the integration of non-linear neuron models such as the AdEx model [11,12,13]. Release stability is guaranteed by an automated test suite [14].

NEST can be extended by the user through dynamically linked modules that contain new neuron and synapse models, stimulus and recording devices, or functionality for the analysis of the resulting data.

NEST is developed by the NEST Initiative, an international collaboration between academic and industrial research institutes. The NEST Initiative provides regular public releases of NEST to give users access to the newest technology. The releases together with documentation on the usage of NEST, and a list of neuroscientific publications that use NEST are available on the homepage of the NEST Initiative at www.nest-initative.org.

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New possibilities for advanced analysis methods in neuroscience through modern approaches to trivial parallel data processing

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In addition to the increasing amounts of data gushing out from neuroscientific experiments, the complexity of modern data analysis techniques places new demands on the computing infrastructure required for data processing. In particular, the observation that neuronal data typically exhibit non-stationary statistics complicates the task of finding the correct null-hypothesis to assess the significance of a variety of test parameters. Modern computer resources enable a data-based approach to tackle significance estimation: surrogate techniques. In this framework the original data is modified in a specific way so as to keep some aspects of the data (e.g., the non-stationary nature of the data), while deliberately destroying others (i.e., those described by the test parameter). Repeating this procedure many times estimates the distribution of the test parameter under the null hypothesis.

However, the required resources exceed the speed and memory constraints of a classical serial program design and require scientists to parallelize their analysis processes on distributed computer systems. Here, we explore step-by-step how to transform on-the-fly a typical data analysis program into a parallelized application. This approach is facilitated by the observation that a typical task in neuronal data analysis constitutes an embarrassingly parallel problem: the analysis can be divided up into independent parts that can be computed in parallel without communication. In particular for surrogate-based analysis programs, finding the decomposition of the analysis program into independent components is often trivial due to the inherent repetition of analysis steps. On the conceptual level, we demonstrate how in general to identify those parts of a serial program best suited for parallel execution. On the level of the practical implementation, we introduce four methods that assist in managing and distributing the parallelized code. By combining readily available high-level scientific programming languages and techniques for job control with metaprogramming no knowledge of system-level parallelization and the hardware architecture is required. We describe the solutions in a general fashion to facilitate the transfer of insights to the specific software and operating system environment of a particular laboratory.

The details of our technique accompanied by concrete examples form a chapter of the new book “Analysis of parallel spike trains” edited by Sonja Grün and Stefan Rotter and published at Springer 2010.