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Different density of the $GABA_{B1}$ subunit in subcellular compartments of CCK- and PV- containing hippocampal interneurons

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$GABA_B$ receptors mediate metabotropic effects of the inhibitory neurotransmitter GABA in the brain. Presynaptic receptors regulate neurotransmitter release, whereas the activation of postsynaptic ones activate a K+conductance resulting in slow IPSPs. In the hippocampus, high levels of the $GABA_{B1}$ subunit have been observed in somata of a subset of GABAergic interneurons. To investigate the cellular and subcellular distribution of the $GABA_{B1}$ subunit in interneurons, we preformed double immunofluorescent labelling and high-resolution pre-embedding electronmicroscopy.In the present study we focused on cholecystokinin (CCK)- and parvalbumin (PV)- containing interneurons. Light microscopic investigations revealed that CCK+ cells contain a large intracellular reserve pool of the $GABA_{B1}$ subunit, whereas PV+ cells contain less protein in their somata. Electron microscopic analysis showed, that the $GABA_{B1}$ protein was found along the extrasynaptic plasma membrane of dendritic shafts and to a lesser extent on axon terminals of both types of interneurons. Quantitive analysis revealed, that the density of immunogold particles is higher on dendrites and axons of CCK+ interneurons, than on those of PV+ interneurons.

These results suggest a differential regulation of $GABA_B$ receptor expression in the two types of interneurons and indicate stronger modulation of CCK interneurons by GABAergic system.

Generation of epileptiform activity requires sclerotic and intact networks

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The mesial Temporal Lobe Epilepsy (MTLE) syndrome is among the most prevalent forms of partial epilepsies, however, network structures and dynamics involved in the generation of seizures are still fairly unknown. MTLE is associated with severe changes in the hippocampal network histology, termed hippocampal sclerosis and recurrent epileptic seizures occurring in temporal brain areas. Since MTLE is usually pharmacoresistant, the only possibility to suppress seizures is the surgical resection of involved brain areas. To advance less invasive therapy options it is necessary to understand on which time scale processes initiating epileptic seizures act and if this initiation is confined to the histologically changed hippocampal areas or additionally involves other brain areas.
We addressed these questions using a model for MTLE in mice in which a single unilateral injection of kainate into the hippocampus induces histological changes comparable to human hippocampal sclerosis. We recorded recurrent epileptiform activity (EA) in the injected and in the contralateral, intact hippocampus and measured inter-hippocampal coherence to investigate generation processes of epileptiform events (EE) on a timescale that would allow direct intervention. Coherence decreases considerably in high frequency bands several seconds before the onset of EEs, indicating an early decoupling of the ipsilateral hippocampus from the contralateral, intact hippocampus during seizure initiation. To investigate if the histologically changed ipsilateral hippocampus could be the generator of EEs, we prepared slices from kainate injected hippocampi and recorded with multielectrode arrays. Surprisingly, the most sclerotic areas of the ipsilateral hippocampus could neither generate nor sustain EA, while hippocampal slices distant from the injection site with apparently intact histology could sustain EA. However, spontaneous EA could not be observed there either, so the network structure generating EA still unknown. Our results suggest in contrast to previous assumptions, that sclerotic areas of the hippocampus are not sufficient to generate EA, but that the interaction with presumably healthier areas is necessary. The initiation of EEs may involve a rather complex network, instead of the homogeneously damaged area central to the affected region. This challenges the classical definition of an epileptic focus and inspires further diagnostic investigation on the interaction of sclerotic tissue with healthy brain areas in humans.

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Learning Functional Connectivity in Neuronal Cultures

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Discovering the functional connectivity and modelling the dynamics of neuronal networks is essential to understand neural information processing. In the current work, we focus on neuronal cultures, which are small living networks in a closed system. We present a machine learning approach, which constructs the functional connectivity map of a neuronal culture based on multiple spike trains of its spontaneous activity recorded by Multi-Electrode-Arrays (MEA). The spike train of an electrode is modelled as a point process, where the rate depends on the finite spike history of all electrodes. For a similar model, Chornoboy et al. presented a maximum likelihood approach for learning the parameters offline. To capture the network plasticity, however, we follow a steepest descent approach, which naturally allows for online learning. A ROC curve analysis of our experiments shows that this online approach predicts the upcoming spiking activity well.

A model for correlation detection based on Ca2+ concentration in spines

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Understanding the mechanisms of correlation detection between pre- and postsynaptic activity at a synapse is crucial for the theory of Hebbian learning and development [3] of cortical networks. The calcium concentration in spines was experimentally shown to be a correlation sensitive signal constrained to the spine: A supralinear influx of calcium into spines occurred when presynaptic stimulation preceded a backpropagating action potential within a short time window. Its magnitude depended on the relative timing t_{post}-t_{pre} [1,5].

There is strong evidence that NMDA receptors are responsible for the supralinear effect [1]. Previous simulation studies related the occurrence of spike time dependent plasticity to the calcium signal [2,4]. However, these simulations mainly focused on pairs and triplets of pre- and postsynaptic spikes, rather than on irregular activity.

Here, we investigate the properties of a biologically motivated [1,5] model for correlation detection based on the calcium influx through NMDA receptors under realistic conditions of irregular spike trains containing a fraction ε of events correlated in time. We identify the regime (rate, correlation coefficient, detection time) in which this mechanism can assess the correlation between pre- and postsynaptic activity. A computationally effective implementation usable for large scale network simulations is devised. We find that a simple thresholding mechanism acts as a sensitive correlation detector, that can be adjusted to work robustly at physiological firing rates.

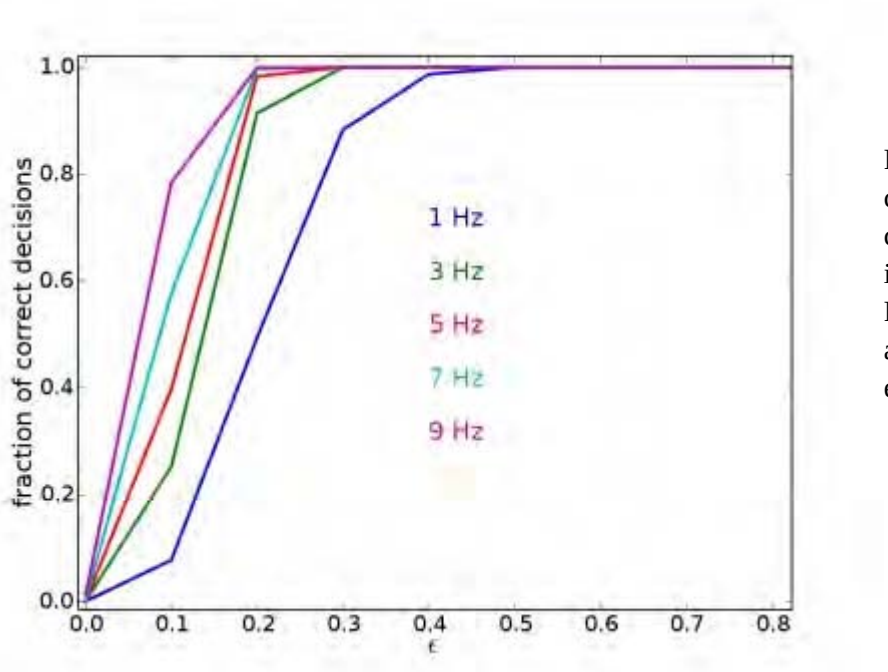

Figure: Fraction of trials where correlation is detected as a function of the correlation coefficient. Firing rates are identical for the pre- and postsynaptic Poisson spike trains. Simulation results are based on 1000 trials of 30s duration each.

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Adding structure to *in vitro* neuronal networks

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The relation between the computational properties and the connectivity in neuronal circuits is not well understood. While discussions on such structure-function relations mostly focus on cortical tissue with its prominent layered structure, its complexity limits theoretical and experimental analyses as well as control over structural and/or functional aspects of the underlying neuronal circuits. Simpler and generalized neuronal networks would allow manipulations and matching simulations, thus enabling the verification of theoretical assumptions and the test of predictions of neuronal computation. This would facilitate a bottom-up approach to understanding the functional architecture of natural neuronal networks.

Networks in dissociated cortical cultures are such generic networks. They do not develop predefined anatomical structure or predictable connectivity in first place. Moreover, microengineering techniques enable the design of patterned cell culture substrates with cell-adhesive and cell-repellent areas. On such substrates, the adhesion of neurons can be restricted and the outgrowth of neurites can be influenced. If cultured on planar microelectrode arrays (MEA), the activity dynamics in these networks can be monitored continuously.

In our work, we use this approach to modulate the connectivity statistics of networks in culture to identify general principles of structure-function relations. Tissue from the prefrontal cortex of neonatal rats was dissociated and cultured on 60-site MEAs and glass coverslips. The substrate surfaces were patterned with the covalently linked polymers polyethylene imine (PEI; adhesion-promoting) and the polydimethyl acrylamide (repellent). In contrast to other common patterning techniques, photolithographically designed structures are stable for weeks under serum-enriched medium conditions, enabling long-term studies of the network dynamics in MEA recordings.

On these patterns, cell somata and neurite outgrowth can be restricted to the nodes of the adhesive PEI patterns; the probability for cell connections between nodes is limited to the pathways linking them. We compare the electrophysiological properties of structured and random-like networks. This approach enables the investigation of the principles of structure-function dependencies in very basic but structured neuronal circuits.

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Eigensystems and dynamics of complex networks of excitatory and inhibitory neurons

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The coupling structure of local cortical networks and its impact on the ongoing dynamics are still to a large degree unknown. Still, modeling efforts can help to understand basic features of how underlying structure shapes network activity.
We analyzed the impact of different coupling schemes on the dynamics of networks of integrate-and-fire neurons with topologies that display random, lattice or 'small-world' characteristics. Special emphasis is laid on networks with distance dependendent coupling which may serve as models for a 2-dimensional layer of cortical tissue.
To describe those systems, we apply both graph theoretical methods as well as numerical network simulations with the goal to find critical structural parameters to describe the features of the systems on a statistical level.
In particular we found that the distribution of weights is much more important than the underlying mere topology (i.e. "who's connected to whom"). The assumption that all synapses of a neuron can only be either inhibitory or excitatory, but not both at the same time leads to synchronization phenomena and spatio-temporal pattern formation that is not captured by existing mean-field approaches. Moreover, we show that minimal models for networks of inhibitory and excitatory neurons must be 2-dimensional to describe the full spectrum of activity dynamics, which occur in the according numerical simulations.
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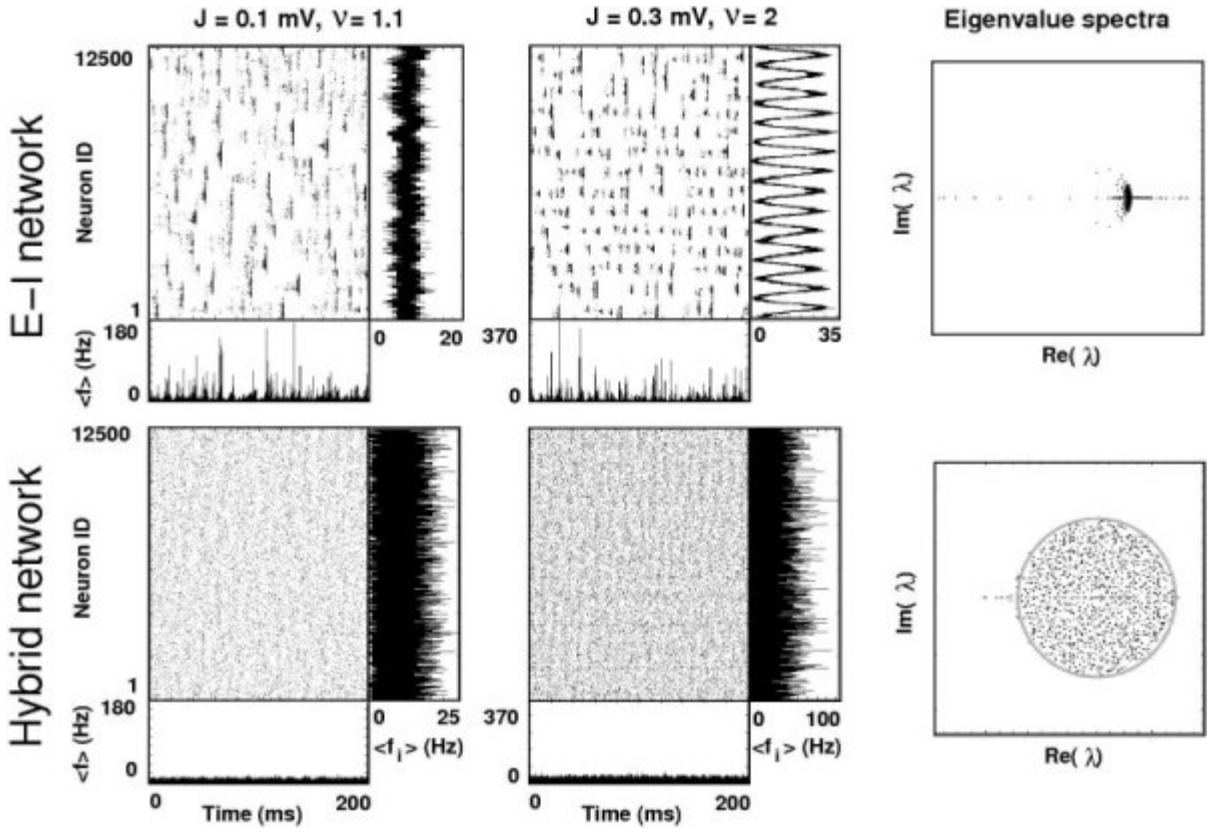
Caption: Numerical simulations of 12,500 integrate-and-fire neurons living on a ring topology, and qualitative eigenspectra of the respective network coupling matrices. The first two pictures in each row show raster plots, population rate <f> and rate per neuron <f_i> of networks where neurons are either purely hyper- or depolarizing, whereas in the hybrid case neurons can be both. This leads both to random dynamics and nearly random eigenvalue spectra.



Modeling the dynamics of higher-order correlations in feed-forward networks

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Correlated spiking activity has been observed in various brain areas. While it is an open issue whether correlated spiking is relevant for information processing, it has been shown that correlations in the input ensemble can significantly influence the response properties of individual neurons. In this context, Kuhn et al. (2003) emphasized that in particular the higher-order correlation structure is critical. To this end, they introduced the Multiple Interaction Process (MIP) as an example model of correlated spike train ensembles. Its higher-order statistics is fully determined by only two parameters: the average firing rate and the pairwise correlation.

In this study we examined if neural network dynamics can be reproduced when MIP is used as a phenomenological model of spike patterns with higher-order correlations. We focused onto simple feed-forward networks (synfire chains) where highly synchronous spike patterns gradually emerge from an asynchronous state. We demonstrate that this synchronization process can be qualitatively reproduced if the input spike train ensembles are replaced by MIP. However, as important features of the spike patterns emerging in the chain cannot be captured by MIP and extended versions, the emulation of the dynamics exhibits several artifacts. In particular, the correlation build-up is significantly overestimated (even for small correlations) -- a fact that might limit the applicability of MIP also in other contexts.

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Spotting higher-order spike patterns with low-order measures

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The cell assembly hypothesis (Hebb, 1949) postulates dynamically interacting groups of neurons as the building blocks of cortical information processing. Synchronized spiking across groups of neurons was later suggested as a potential signature for active assemblies. In this scenario, the assembly members would exhibit specific higher-order spike correlations. Although mathematical concepts for the detection of higher-order correlations have been suggested in the past (e.g. Nakahara & Amari, 2002), statistical estimation of the associated parameters from spike train recordings poses serious problems, mainly due to constraints induced by too small samples. As a consequence, most attempts to directly observe cell-assemblies resort to pairwise interactions. However, such approaches obviously cannot draw any conclusions about the joint operation of larger groups of neurons.

Here we present a novel procedure to spot higher-order patterns in massively parallel spike trains that circumvents the need to estimate a many higher-order parameters. Currently, our method works for correlated Poisson processes, where correlations of any order are induced by `inserting' appropriate patterns of near-synchronous spikes (see illustration below). Based on estimates of only a few low-order cumulants of certain compound signals we can devise a test for the presence of higher-order patterns in the original data, which is surprisingly sensitive. As a consequence, our method is less susceptible to limitations in sample size and can, in principle, be applied to data commonly recorded in behaving animals using multi-electrode technology. The sensitivity and reliability of the new method for data, where the Poisson assumptions are not strictly satisfied, will be critically discussed.

Acknowledgments
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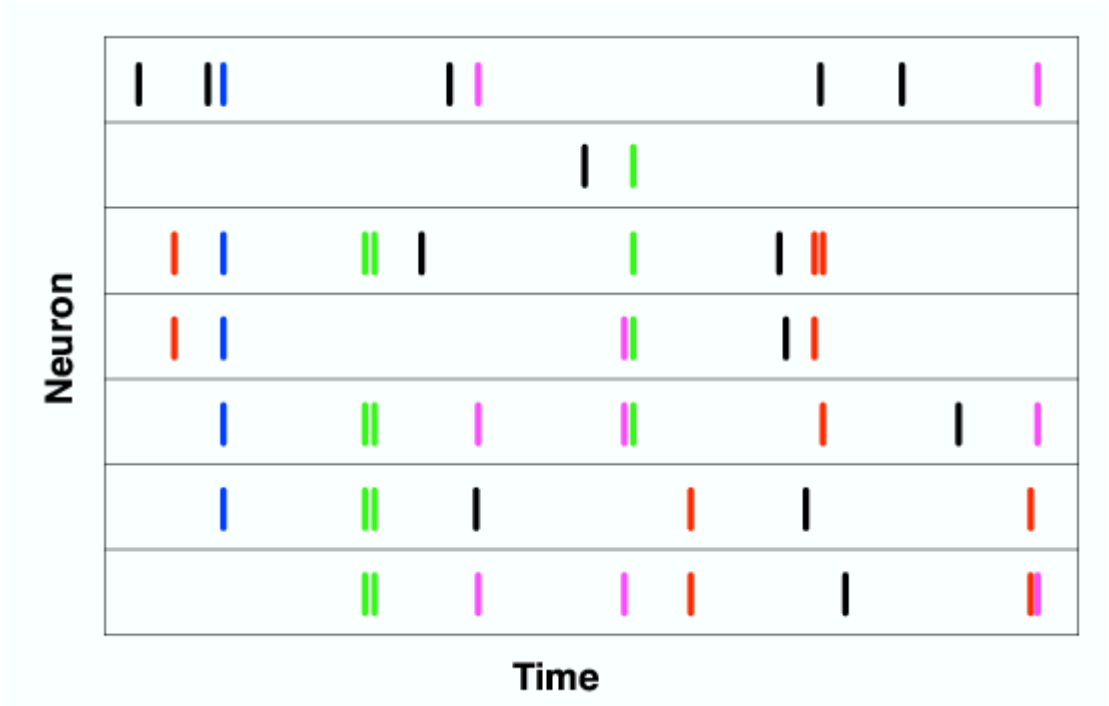

Time scale dependence of neuronal correlations

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Neural activity is processed and measured at various signal levels. Neural systems update their states by evaluating for example synaptic conductances, synaptic currents or membrane potentials. Experimenters additionally use spike counts, local field potentials, EEG or fMRI BOLD signals to quantify the state of the system. Correlated activity has been observed at all these signal levels in different areas of the brain and has been suggested to provide valuable information about the architecture of the underlying system and the nature of neural processing. Many of these signals can be considered as filtered (superpositions of) spike trains. It is largely unknown how this filtering alters the correlation structure of the underlying spike data and what the consequences for the dynamics of the system on the one hand and for the interpretation of measured correlations on the other hand are.

In this study we focus onto signals derived from general spike signals (point processes) by linear filtering (shot-noise). As a prominent example of spike correlations we consider those caused by overlapping presynaptic neuron populations (common input correlations) in different network models. We study the effect of the marginal statistics of the presynaptic sources and of the filter kernel on the (joint) statistics of the resulting shot-noise signals both analytically and numerically.

We demonstrate that the interaction between the original spike train auto/cross-correlation structure and the filter kernel generally results in a complex dependence of second-order measures like variances, covariances and correlation coefficients a) on the statistics of the presynaptic spike trains and b) on the filter properties. Spike count correlation coefficients, for example, generally depend on the length of the counting window if the spike trains have non-Poissonian statistics. Similarly, correlations between intracellular signals like synaptic currents or membrane potentials depend on the time constants of the synapses or the membranes. Further, we show that changes in the marginal statistics of the presynaptic sources (e.g. the frequency of network oscillations) can effectively modulate the strength of correlation between postsynaptic responses. We propose that both mechanisms may be used in the brain to modulate the interaction strength between neurons or neuron populations. Finally, we show that for a large class of spike processes the high frequency components of the coherence (which does not dependent on the linear filter properties) reflects the strength of common input, irrespectively of the marginal statistics of the sources. In our network models it therefore allows a reliable estimation of the network connectivity from intracellular recordings of pairs of neurons.

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Cortical networks with long-range patchy connections

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Most studies of cortical network dynamics assume completely random wiring, a practical but simplistic approach: The cortex has both a delicate columnar and laminar structure, e.g. featuring a combination of local and long-range connections. As the architecture of a complex network is presumably an essential determinant of its functions it is our aim to design and analyze more realistic network models of the cortex.

We embedded all neurons into a 2D space to enable distance dependent connectivity that reflects the geometry of dendrites and axons. We considered pyramidal cells with both neighborhood coupling and long-range connections, the latter arranged either in a random fashion or as clustered projections [1]. As shown the figure, three different spatial settings for the patchy projections (disks) of pyramidal cells (dots) were distinguished: Randomly and independently selected positions (left), overlapping patches for neighboring cells (middle), and a shared patches model (right).

An important difference between the various model scenarios for long-range connections is the amount of common input or output, respectively, asigned to any pair of neurons. This was quantified by a detailed input/output projection field analysis. Additionally, stochastic graph theory was used to characterize other global structural features of these networks, and to compare them to well-known types of abstract random graphs, like the small-world network.

Our approach of combining neuron geometry and network topology allows us to devise new models for cortical networks with horizontal structure, including the feature of patchy projections. We expect that our investigations will help to interpret neuroanatomical data, and thereby contribute to improve our understanding of cortical function.

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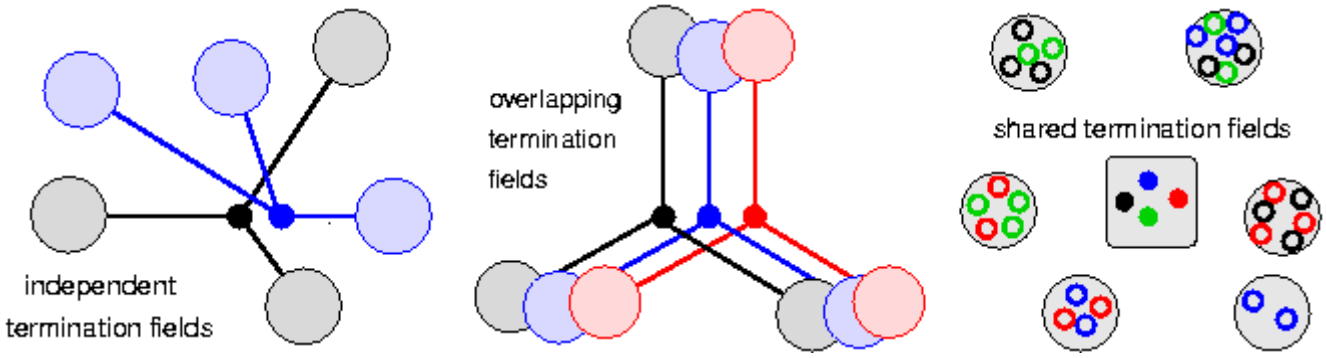

Stimulus induced activity propagation in a layered cortical network model

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The local network of sensory cortices is reported to be organized vertically in six layers which show a high degree of heterogeneity in neuron properties, synaptic connectivity and degree of recurrence. Thalamic input, arriving in layer 4, travels through layer 2/3 down to layer 5 and 6, and closed a loop by projections from layer 6 to the thalamus. Although, anatomically well described, it is not fully understood how activity entering the system in layer 4 interacts with the ongoing recurrent activity and is eventually transferred to other parts of the network. The weak synapses (~0.1 mV) in the neocortex in vivo, further complicate the flow of activity, as any individual synapse is not able to elicit a spike in its post-synaptic neuron on its own, and it has to depend on the recurrent activity.

To understand the evolution of stimulus driven activity in the cortical layers, we simulated a layered network comprising of 200,000 neurons, mimicking about 4 mm^3, volume of cat cortex. The network connectivity was taken from Binzegger et al. (2004). In a previous work we described the emergent dynamical states of the layered network (Kremkow et al. 2006). Here we focused on evolution of input activity in an asynchronous-irregular (AI) type background activity state.

We stimulated the layer 4 either with AI type activity at varying frequencies, or with a synchronous volley of spikes. We found that a synchronous volley of spikes was most effective in eliciting significant responses in all subsequent cortical processing stages (layer 2/3, 5 ,6). In contrast, uncorrelated asynchronous-irregular activity with same amount of spikes, was not able to drive the whole layered network. Our results are in good agreement with recently reported in vitro data (Bruno & Sakmann 2006). We conclude therefore, that a stimulus that is composed of synchronous activity is more effective in driving the cortex. Uncorrelated inputs require a rather high input firing rate which may render the network strongly precarious.

This was work supported in parts by the BMBF grant 01GQ0420 to the BCCN Freiburg, GIF and the 6th RFP of the EU (grant no. 15879-FACETS).

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FIND - Finding Information in Neuronal Data
An open-source analysis toolbox for multiple-neuron recordings and network simulations

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In parallel to the tremendous technical progress in data acquisition (e.g. large number of simultaneous electrode recordings), there is a growing need for new computational tools to analyze and interpret the resulting large data flow from experiments and simulations. While there is undeniable progress in novel analysis methods, implementations are difficult to reproduce based on literature or are hidden in (ill-documented, in-house) software collections.

We are developing *"FIND"* (www.find.bccn.uni-freiburg.de) to address the urgent need of an unified, well-documented interface, to various analysis tools.

FIND - stands for Finding Information in Neuronal Data and will be shared to the community as an open-source analysis toolbox for electrophysiological recordings and network simulation environments.
This platform-independent toolbox can be used to analyze neurophysiological data from single- and multiple-electrode recordings by providing a set of standard and more advanced analysis and visualization methods.
We are building on experience in design and application of such methods [1] (www.meatools.brainworks.uni-freiburg.de) and furthermore, we will also incorporate other open source toolboxes (e.g. neuroanalysis.org/toolkit, an information theory based toolbox).
Currently the *FIND-Toolbox* accommodates import of multiple proprietary data formats, based on the Neuroshare Project (www.neuroshare.org). Physiological data from different acquisition systems (up to now: Alpha Omega, Cambridge Electronic Design, Multi Channel Systems GmbH, NeuroExplorer, Plexon Inc., R.C. Electronics Inc., Tucker-Davis Technologies, Cyberkinetics Inc.) and data from Network simulations Environments (e.g. NEST, www.nest-initiative.org [2]) can now be compared using identical analysis methods. This allows verifying of both results across experiments and laboratories as well as direct comparison of simulation results and electrophysiological recordings.
To enable the incorporation of new algorithms - a weakness of most commercial toolboxes - FIND will be open source, providing the possibility to extend the collection of algorithms and data formats with new ones. We expect that this will facilitate the development and distribution of new techniques among the scientific community.

Please visit www.find.bccn.uni-freiburg.de to see announcements for new features, release versions, tutorials and training workshops.

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The morphology of excitatory central synapses: From structure to function

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Synapses are the key elements for signal transduction and plasticity in the brain. For a better understanding of the functional signal cascades underlying synaptic transmission a quantitative morphological analysis of the pre- and postsynaptic structures that represent morphological correlates for synaptic transmission is important. In particular, realistic values of the number, distribution and geometry of synaptic contacts and the organization of the pool of synaptic vesicles provide important constraints not only for realistic models but also numerical simulations of those parameters of synaptic transmission that, at present, are still not accessible to experiment. Although all synapses are composed of nearly the same structural elements it is, however, their actual composition within a given synapse and the microcircuit in which they are embedded that determines its function.

One possible way to analyse synapses in sufficient detail are computer-assisted three-dimensional reconstructions of these structures and their subsequent quantitative analysis based on ultrathin serial sections. Here, we summarize, compare and discuss the morphology of three central excitatory synapses: the so-called Calyx of Held, a giant synapse in the medial nucleus of the trapezoid body (MNTB) in the auditory brain stem, the Mossy Fiber Bouton (MFB) in the hippocampus predominantly terminating on proximal dendrites of CA3 pyramidal neurons and cortical input synapses found on basal dendrites of layer 5 pyramidal cells.

The detailed morphological description of synaptic structures beside describing their geometry may help to define morphological correlates of functional parameters of synaptic transmission such as the number, distribution and size of synaptic contacts at active zones, the readily releasable pool (RRP) of synaptic vesicles, for release and the variability of quantal size and might therefore explain existing differences in the function between individual synapses embedded in different microcircuits.

Opposite roles of Reelin in the lamination of dentate granule cells by binding to different receptors

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Control of neuronal migration is essential for the correct formation of neuronal layers during brain development. Previous studies have shown that Reelin, an extracellular matrix protein, is required for the proper positioning of neurons. Reelin binds to the ApoE receptor 2 (ApoER2) and the VLDL receptor (VLDLR) and induces the phosphorylation of the adaptor protein Dab1. In reeler mutant mice lacking Reelin, layer formation is severely altered in the hippocampus, neocortex and cerebellum. ApoER2/VLDLR double knock-out mice and Dab1 knock-out mice show a phenotype similar to that of reeler mutants. Recently, we have shown that Reelin secreted by different cell types in various brain regions of wild-type animals could induce layer formation of granule cells in the reeler dentate gyrus when the reeler hippocampus was cocultured with different wild-type tissue containing Reelin. In the present study, we performed an in vitro assay using PP2 that inhibits the phosphorylation of Dab1 and examined the layer formation of dentate granule cells in wild-type mice, VLDLR knock-out mice, and ApoER2 knock-out mice by immunostaining for prox-1, a marker of dentate granule cells. Our results indicate that Reelin plays opposite roles in the layer formation of dentate granule cells at different stages during neuronal migration by binding to two different receptors. We hypothesize that during early stages of neuronal migration Reelin binds to ApoER2 and acts as an attractive signal to promote granule cell migration towards the Reelin-rich marginal zone. As soon as the migrating granule cells reach this zone, Reelin binds to VLDLR and acts as a stop signal to arrest the migration of granule cells that form a densely packed cell layer.
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Reelin is secreted by the classical secretory pathway, but independent of neuronal activity

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The extracellular matrix protein reelin controls neuronal migration during brain maturation. In layered structures such as hippocampus and neocortex, it is synthesized and secreted by Cajal-Retzius cells during development and by GABAergic interneurons in the adult. Until now, very little is known, whether and how reelin secretion is regulated. To address this question, we used organotypic rat hippocampal slice cultures as a model to study reelin secretion. First, we investigated whether reelin release is influenced by neuronal activity. To this end we either blocked neuronal activity in hippocampal slice cultures by tetrodotoxin (TTX) or stimulated them with KCl or kainic acid. Subsequently, the reelin content of tissue and of supernatants was analyzed by quantitative Western blot analysis. Addition of 5 mM KCl and 5 µM kainic acid for 3, 24 and 48 h induced a transient c-fos expression peaking at 3 h, but did not elicit any changes in the reelin content of slices or supernatants at any time point studied. Similarly, TTX treatment did not have any effect. In order to investigate whether reelin is secreted in a Ca^{2+}-dependent manner, we blocked presynaptic, voltage-dependent Ca2+- channels of the P/Q-, N- and R-type with subtype-specific neurotoxins (ω-agatoxin IVA, ω-conotoxin GVIA and SNX-482). Treatment of hippocampal slice cultures with these three compounds for 3, 24, 48 h did not affect reelin secretion either. To exclude a secretion mechanism independent from the ER/Golgi-complex, hippocampal slice cultures were incubated for 12 h with Brefeldin A, which interferes with the ER/Golgi apparatus. Addition of Brefeldin A to the medium resulted in an accumulation of full length reelin (400kDa) in slices and in a significant reduction of the reelin content in supernatants. These data indicate that reelin is processed and secreted by the classical secretory pathway (Brefeldin A-sensitive), but it is released independent of neuronal activity and presynaptic, voltage-dependent Ca^{2+}- channels do not play a role.(Supported by the DFG: TR3).

Early experience alters hippocampal reelin gene expression in a gender-specific manner

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Early-life experience has long-term consequences on behavior and stress responsiveness of the adult. Environmental influences during sensitive time windows of early postnatal life interfere with the development of emotional and cognitive functions. Recent studies in rodents have shown that functional maturation of higher associative cortical regions, in particular those of the limbic system are strongly influenced by emotional experience. In rats chronic environmental impoverishment results in decreased brain size, cortical thickness, dendritic complexity and spine density. Since little is known how these processes are regulated at the molecular level, we used an early separation paradigm in mice followed by a hippocampal expression analysis of molecules important for cortical development (reelin and brain-derived neurotrophic factor, BDNF) and synapse formation (synaptopodin, synapsin I). We compared four experimental groups: NH (not handled), H (handled), MS (maternal separation, intact litter separated from the mother for three hours daily), ED (early deprivation, individual isolation of each pup for three hours daily). The separation paradigms were performed from postnatal day (PND) one until PND fifteen followed by immediate or delayed real time RT-PCR analysis at PND 70. At PND fifteen male mice responded to handling and early deprivation with a strong and significant increase in the expression of reelin, BDNF and synaptopodin mRNA as compared to non-handled ones. Female pups showed the same expression pattern for BDNF mRNA, but they did not respond to handling with a significant up-regulation of reelin and synaptopodin mRNA expression. In the adult mice (PND 70) none of the separation paradigms elicited any changes in gene expression. Taken together, our data show that the expression of molecules important for cortical development can be modified by environmental stimuli in a gender-specific fashion during early postnatal life.

Transport of HCN1 channels to presynaptic compartments: novel plasticity that may contribute to establishment of connectivity in developing hippocampus

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Developing neuronal networks evolve continuously, requiring that neurons modulate their intrinsic properties and responses to synaptic input. Increasing evidence supports roles for the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel-mediated current (Ih) in these functions. Here we describe a novel developmental plasticity involving transient HCN channel expression in axonal and presynaptic compartments. Using immunohistochemistry, electron microscopy and in vitro pathway ablation, we show that HCN1 channels are expressed within axon terminals of the medial perforant path (mPP) of immature rats, yet disappear with maturation. Using electrophysiology, we show that these presynaptic HCN channels modulate the efficacy of perforant path synapses in age- and frequency-dependent manner: Blockade of Ih using ZD7288 (10 µM) or zatebradine (20 µM) increased short-term depression (STD) when mPP was stimulated with 20 Hz, but not after stimulation with 1, 5, or 10 Hz. Consistent with the anatomical data, this effect was age-dependent, and observed in slices from immature but not adult rats. In addition, whereas STD was less pronounced in immature compared to adult mPP when HCN channels were functional, blockade of Ih increased STD of immature mPP to values indistinguishable from the adults. These data suggest that presynaptic HCN channels contribute to age-dependent regulation of short-term plasticity at medial perforant path-granule cell synapses that could be important for the maturation of medial perforant path-granule cell connectivity.

Divergent roles of ApoER2 and VLDLR in neuronal migration

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The mammalian neocortex consists of six layers of neurons with distinct functional and morphological identities. These layers are generated in an inside-out sequence, with early born cells in the deep layers and later born cells in the outer layers. To generate this pattern, cells migrating to the cortical plate must stop at their appropriate destinations. The molecular mechanisms that regulate the interaction of the migrating neurons with their environment, the signalling cues they receive during migration and subsequent differentiation, are complex and as yet poorly understood. One major signalling pathway which regulates the migration of neurons during formation of the cortex involves the extracellular matrix protein Reelin. The target cells of Reelin express the Reelin receptors very low-density lipoprotein receptor (VLDLR) and apolipoprotein E receptor 2 (ApoER2) and the cytoplasmic adaptor protein disabled 1 (Dab1), which binds to these receptors. The reeler mouse lacking Reelin, shows an inversion of cortical layers. Mice defective in both ApoER2 and VLDLR, and dab1 mutants show a phenotype reminiscent of reeler. Milder phenotypes are found if only one of the two lipoprotein receptors for Reelin is absent. However it is unclear whether both Reelin receptors have similar functions, during cortical development. To address this question, we combined bromodeoxyuridine (BrdU) labelling of newly generated neurons with staining using specific markers of individual cortical layers and co-culture experiments on VLDLR-/- and ApoER2-/- mutant mice. We present evidence for divergent roles of the two Reelin receptors with VLDLR mediating a stop signal for migrating neurons and ApoER2 being essential for radial glia-guided migration during late phases of cortical layer formation.

Detailed passive cable models of hippocampal granule cells obtained with two-photon microscopy

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The electrotonic structure of a neuron largely shapes the propagation of synaptic potentials along its dendrites. To obtain detailed passive cable models of adult dentate gyrus granule cells, we combined patch-clamp recordings with morphological 3-dimensional reconstructions. Simultaneous two-pipette somatic recordings were performed in acute slices from adult 2- to 4-months old mice at 22°C. Short current pulses (0.5 ms, 80-200 pA) were injected via one pipette while voltage responses were recorded with the other pipette. The voltage transient following the current pulse showed a pronounced initial rapid decay ($t < 2$ ms) that accounted for 79.9 ± 2.9 % of the total amplitude, as estimated by peeling the slow component ($t0 = 35.3 \pm 5.7$ ms, mean ± SEM, n=4). The morphology of the biocytin-filled FITC-avidin-labeled cells, including soma, dendrites and part of the axon, was reconstructed using two-photon microscopy (Zeiss LSM 510, Coherent Chameleon-XR tuned to 790 nm). After deconvolution of the 3-dimensional image stacks, an automated filament-tracing software was used to obtain unbiased detailed compartmental models. Specific membrane capacitance ($Cm = 0.98 \pm 0.03$ µF/cm2), specific membrane resistance ($Rm = 41.2 \pm 2.0$ kΩ cm2) and intracellular resistivity ($Ri = 180 \pm 30$ Ω cm) were obtained by direct least-squares fitting of the model's response to the experimental data assuming homogenous membrane properties. Spine density was counted on representative dendritic segments after deconvolution, and spines were implemented into the model by scaling Rm and Cm of spine-bearing compartments appropriately. Both the rise as well as the fast and slow components of the decay in the voltage response could be precisely reproduced by the model. However, when spines were omitted, an appropriate fit of the fast components could not be achieved.

In conclusion, two-photon microscopy was used to obtain a detailed 3-dimensional geometry and a corresponding cable model of hippocampal granule cells. The results suggest that the detailed morphology appears to be critically important for the shape of transient voltage responses as they occur during brief excitatory synaptic inputs.

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Role for the spine apparatus organelle in synaptic plasticity

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Current concepts of synaptic plasticity mainly involve mechanisms of transmitter release, transmitter receptor recruitment, and the formation of new synaptic sites, in particular the de novo formation of dendritic spines. Cytoplasmic organelles such as the spine apparatus present in many forebrain dendritic spines have not been studied in great detail, and their roles in synaptic transmission and synaptic plasticity remain to be determined. We have recently shown that mutant mice lacking synaptopodin fail to form a spine apparatus and show deficits in synaptic plasticity and learning and memory (Deller et al., 2003). However, these studies did not elucidate synaptopodin's role in the formation of the spine apparatus nor did they determine the mechanism(s) by which the spine apparatus contributes to synaptic transmission. Here, we will summarize our recent attempts aimed at characterizing the functional significance of the spine apparatus. Evidence will be provided that the spine apparatus is a calcium store involved in the regulation of hippocampal synaptic plasticity such as long-term potentiation.

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Reference:

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The morphology of excitatory central synapses: From structure to function

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Synapses are the key elements for signal transduction and plasticity in the brain. For a better understanding of the functional signal cascades underlying synaptic transmission a quantitative morphological analysis of the pre- and postsynaptic structures that represent morphological correlates for synaptic transmission is important. In particular, realistic values of the number, distribution and geometry of synaptic contacts and the organization of the pool of synaptic vesicles provide important constraints not only for realistic models but also numerical simulations of those parameters of synaptic transmission that, at present, are still not accessible to experiment. Although all synapses are composed of nearly the same structural elements it is, however, their actual composition within a given synapse and the microcircuit in which they are embedded that determines its function.

One possible way to analyse synapses in sufficient detail are computer-assisted three-dimensional reconstructions of these structures and their subsequent quantitative analysis based on ultrathin serial sections. Here, we summarize, compare and discuss the morphology of three central excitatory synapses: the so-called Calyx of Held, a giant synapse in the medial nucleus of the trapezoid body (MNTB) in the auditory brain stem, the Mossy Fiber Bouton (MFB) in the hippocampus predominantly terminating on proximal dendrites of CA3 pyramidal neurons and cortical input synapses found on basal dendrites of layer 5 pyramidal cells.

The detailed morphological description of synaptic structures beside describing their geometry may help to define morphological correlates of functional parameters of synaptic transmission such as the number, distribution and size of synaptic contacts at active zones, the readily releasable pool (RRP) of synaptic vesicles, for release and the variability of quantal size and might therefore explain existing differences in the function between individual synapses embedded in different microcircuits.

Application of Exogenous Reelin Attenuates the Development of Granule Cell Dispersion in a Mouse Model for Temporal Lobe Epilepsy

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A characteristic structural abnormality of the epileptic hippocampus is the widening of the granule cell layer termed granule cell dispersion (GCD). Recently we have shown that the development of GCD correlates with a decreased expression of the extracellular glycoprotein reelin. Moreover, neutralization of reelin by chronic infusion of a function-blocking antibody into the adult mouse hippocampus leads to a local GCD-like effect, suggesting that a loss of reelin causes GCD in the epileptic hippocampus (Heinrich et al., J. Neurosci. 26, 2006). Based on these findings we designed an experiment to prevent the development of the GCD in a mouse model of temporal lobe epilepsy. We performed unilateral intrahippocampal injection of kainic acid (KA) in adult mice known to induce GCD formation within fourteen days. One day after KA injection, when the initial status epilepticus had ceased, recombinant reelin was chronically infused into the hippocampus using osmotic minipumps over a period of fourteen days. A control group was treated with reelin-free medium. A third group of mice was injected with KA only. After a survival time of eighteen days, the animals were perfusion-fixed and the width of the granule cell layer (GCL) was measured in cresyl violet-stained hippocampal tissue sections. The average width of the GCL was 129 ± 4.3 µm in the reelin-treated group vs. 144 ± 7 µm in the control group. The third group of mice with KA injection alone displayed an average GCL width of 159 ± 2.5 µm. In order to check the stability of the reelin protein under our experimental conditions, we performed Western blot analysis of reelin which hat been incubated at 37°C for fourteen days. We detected the three reelin isoforms (400, 320 and 180kDa) only, but no degradation products. Taken together our data show that the continuous application of exogenous reelin into the epileptic hippocampus can partially compensate the reelin loss and thus confirm the crucial role of this protein for GCL maintenance. (Supported by the DFG: TR3).

Spike-timing dependent plasticity in balanced random networks

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The balanced random network model attracts considerable interest because it explains the irregular spiking activity at low rates and large membrane potential fluctuations exhibited by cortical neurons in vivo. Here, we investigate to what extent this model is also compatible with the experimentally observed phenomenon of spike-timing dependent plasticity (STDP). Confronted with the plethora of theoretical models for STDP available, we re-examine the experimental data. On this basis we propose a novel STDP update rule, with a multiplicative dependence on the synaptic weight for depression, and a power law dependence for potentiation. We show that this rule, when implemented in large (100,000 neurons) balanced networks of realistic connectivity and sparseness (10,000 synapses per neuron), is compatible with the asynchronous irregular activity regime. The resultant equilibrium weight distribution is unimodal with fluctuating individual weight trajectories, and does not exhibit development of structure. We investigate the robustness of our results with respect to the scaling of the depressing increments. We introduce synchronous stimulation to a group of neurons, and demonstrate that the decoupling of this group from the rest of the network is so severe that it cannot effectively control the spiking of other neurons, even those with the highest convergence from this group.

A composition machine for complex movements

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Synfire chains that are mutually and weakly interconnected with excitatory synapses are capable of synchronizing and thus aggregating their traveling waves [1,2]. This process is considered to be a candidate neural mechanism for binding and compositionality, potentially underlying higher brain functions such as pattern recognition, memory retrieval, movement preparation and movement execution [4,5]. It has been shown that a layered structure of synfire chains can indeed provide the required building blocks [2]. Based on these principles, we present a prototypical but complete composition machine that composes complex movements out of movement primitives to generate scribbling trajectories. The system is realized by a spiking neuronal network model using the simulation tool NEST [3].

The movement trajectory is obtained by integrating the population vector of the directionally tuned motor neurons constituting the output of the network model. Depending on the spatio-temporal patterns applied to the synfire chains of the input layer, a sequence of movement primitives is activated which generates a movement trajectory. The length of a top level chain determines the duration of activation of the respective primitive. Autonomous activity in the lower layer generates a random sequence of primitives resulting in scribbling-like behavior. Thus, we have formulated a model in which we can test algorithms for the detection and categorization of primitives and conservation laws on the level of movement trajectories (behavior) as well as on the level of spikes (electrophysiological). Furthermore we can now derive predictions for the relationship between properties of the spiking activity (e.g. rate, synchrony) and properties of the movement trajectory (e.g. direction, acceleration).

Figure. Movement generation with synfire chains.
A) Various reaching task trajectories generated by the same network of synfire chains. The precise shape is determined by the relative timing of the initial stimuli activating the movement primitives.
B) Scribbling-like trajectory generated by the same network as in A operating autonomously.

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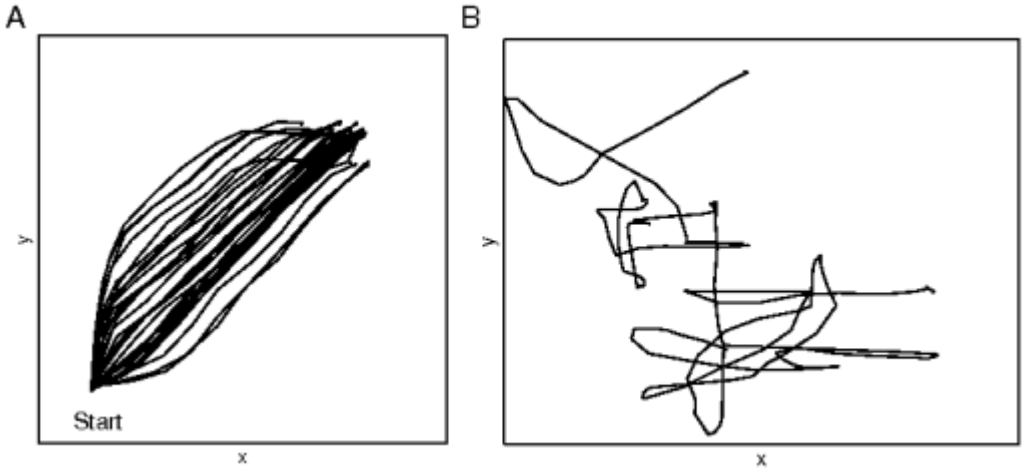

Online interaction with in vitro neuronal networks

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The whole brain as well as single neurons process information parallel at multiple spatial and temporal scales. Random ex-vivo neuronal networks provide means to study generic neuronal and network function. Cell cultures develop and adopt oscillations and spikes over a broad range of time scales. They are structurally rich and experimentally stable over several weeks. The goal of our work is to understand the principles underlying functional network differentiation, modification and stability. By applying electrical stimulation that interacts with the network connectivity, we want to identify the mechanisms that induce synchronized bursting and selective learning in neuronal cultures.

We use neocortical neurons cultured on microelectrode arrays (MEAs) that develop into random networks and are accessible for simultaneous recording and stimulation through multiple electrodes. After about one week in vitro, these networks change their activity from uncorrelated spiking to more and more complex synchronized bursts. The bursts may have physiological relevance in the culture, e.g. they may induce synaptic plasticity. However, they also resemble epileptiform activity and may result from the lack of physiological input to the culture. To attain control over the state of network activity, we first dissociate or reduce bursting by applying multi-site electrical stimulation to the networks.

Additionally, this leads to a second aspect which is to use a defined stimulation paradigm to embed functionality into the networks from outside. We show that the Stimulus Regulation Principle, a universal learning principle advocated by behaviorists over 60 years ago, is inherent to cultured neuronal networks. In particular, we 'teach' the network predefined activity patterns or 'spatial spiking tasks'. We apply low-frequency stimulation that interferes with the network and promotes changes in synaptic connectivity. By removing the stimulus whenever a predefined response is observed, we preclude the acquisition of any new stimulus-response association. This change in the drive underlying the exploration in the space of possible responses can be seen as the physiological counterpart of behavioral reward and realize selective learning in neuronal networks.

These experiments require fast and flexible interaction with the networks. The stimulation induces changes in network dynamics requiring adaptation of the stimulation patterns over timescales ranging from milliseconds to days. The efficacy of a stimulation pattern and the storage capacity also depends on the state of the network. For these reasons, we have established a LINUX-based activity-controlled feedback system for neuronal networks grown on MEAs. Selected features of the neuronal activity can be extracted online and used to control a stimulus generator connected to the MEA system. This closed-loop setup allows direct interaction with cultured neuronal networks to better understand their functional principles.

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Sensory responses in different layers of the neocortex in vivo

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Laminar processing of information in the neocortex is believed to contribute to the exceptional information processing capability of this part of the brain. Neuro-anatomical data suggest that information flow is directed from the input layer IV to layers II and III, where most of the intra-area processing takes place. The processed signals are then most likely transferred to layer V and VI, where cells with long-range connections to other brain areas are commonly found. Electrophysiological studies have revealed increasing levels of complexity of optimal stimulus features along this putative information processing path (Hirsch and Martinez 2006). Direct observations of activity spreading through the layers of the neocortex, however, have not yet been reported. To date, the information about differences in the activity in different layers is limited to single cell recordings or relatively course estimations of the in vivo firing rates in different layers (Gur et al. 2005; Haupt et al. 2005).

In the present study, we investigated the spatio-temporal structure of activity spreading in the rat visual cortex in vivo. We recorded from a 3 x 4 array of extracellular electrodes arranged in a plane perpendicular to the cortical surface and used optical stimulation to elicit sensory responses. To reveal the exact positions of the recording sites, silver was deposited from the electrode tips after the recording session and stained post mortem by means of a silver enhancement staining.

Analysis of multi-unit spike signals confirmed previous findings about layer-specific mean firing rates in the neocortex. More importantly, the response latencies to visual stimulation differed between layers, as well as the frequency of rate oscillations after stimuli suitable to elicit oscillatory activity. Our data suggest that differences of signal processing in different layers may be reflected in different firing rates and the spatio-temporal pattern of stimulus-evoked activity in primary sensory areas of the brain. Studying the activity dynamics with respect to cortical layering will help to better define the roles of different layers for information processing in the brain.

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Spatio-temporal structure of spontaneous state transitions in the neocortex

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Spontaneous state transitions of neocortical activity, as observed during slow-wave sleep or under certain anesthetics, are characterized by fast changes between epochs of intense network activity (up-states), and silent periods, where spiking activity is virtually absent (down-states). In single cells, up-states are characterized by massive synaptic input, leading to a strongly fluctuating, depolarized membrane potential, while in down-states, the membrane potential shows only few fluctuations at a hyperpolarized level. The strong synchronization between cells during this kind of activity is reflected in population signals, such as the local field potential and the EEG. Waves of synchronized activity have been demonstrated to travel from varying initiation points over the human cortex during slow-wave sleep (Massimini et al. 2004). In animal experiments it was shown that only a small, time-varying fraction of the cells in a given cortical volume takes part in the oscillatory activity (Kerr et al. 2005).

We investigated the spatio-temporal structure of slow-wave activity in vivo in the rat neocortex under ketamine/xylazine anesthesia, combining extracellular recordings with up to 12 electrodes with one simultaneous intracellular recording, which was used to detect state transitions. Triggered on these, we extracted episodes of spike activity from the extracellular electrodes and determined the distribution of times of the state transition for each of the electrodes from the individual episodes. The emerging spatio-temporal pattern was then tested for pattern consistency and variability across repeated activity waves employing single trial rate estimates (Nawrot et al. 2003).

In a plane parallel to the cortical surface, we found that in most recordings there was considerable variability with respect to the precise spatio-temporal structure of activity waves. However, in many cases a preferred direction of activity spread could be identified during limited recording periods. By contrast, recordings from different cortical layers revealed that state transitions occurred much more simultaneously throughout the depth of the cortex. These findings indicate that under ketamine/xylazine anesthesia, activity waves may travel in a stereotypic manner across the surface of the neocortical tissue, recruiting cells in all cortical layers synchronously. Such stereotypic patterns of activity might lead to selective strengthening of active synapses, linking slow-wave activity to learning-related phenomena like memory consolidation during slow-wave sleep.

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Reinforcement learning in an actor-critic spiking network model

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Computationally powerful reinforcement learning algorithms have been developed in the context of machine learning [1]. Experimental evidence [2] suggests that such algorithms are used by the mammalian brain [3]. However, it is still unclear how reinforcement algorithms capable of solving non-trivial tasks could be implemented in biological neuronal systems. A major obstacle to overcome is that neuronal systems operate in continuous time whereas common reinforcement learning algorithms are formulated in discrete time.

Here, we demonstrate how the arctor-critic architecture [4,5], an efficient and widely used realization of reinforcement learning, can be implemented by a suitably structured network of spiking integrate-and-fire neurons. The fundamental components of this architecture, the policy and value functions, are both represented by synaptic weights. The synaptic learning mechanisms are local plasticity rules motivated by biological findings.

We test the learning capability of the neuronal system on navigational tasks in one and two dimensional "grid-world" environments [1]. The network is able to accurately evaluate the quality of a state and adapt its policy accordingly, resulting in a learning curve similar in speed and stability to that of the corresponding discrete time computer algorithm (Fig. 1). This work shows that, in principle, reinforcement learning can be realized in a network of spiking neurons with plastic synapses.

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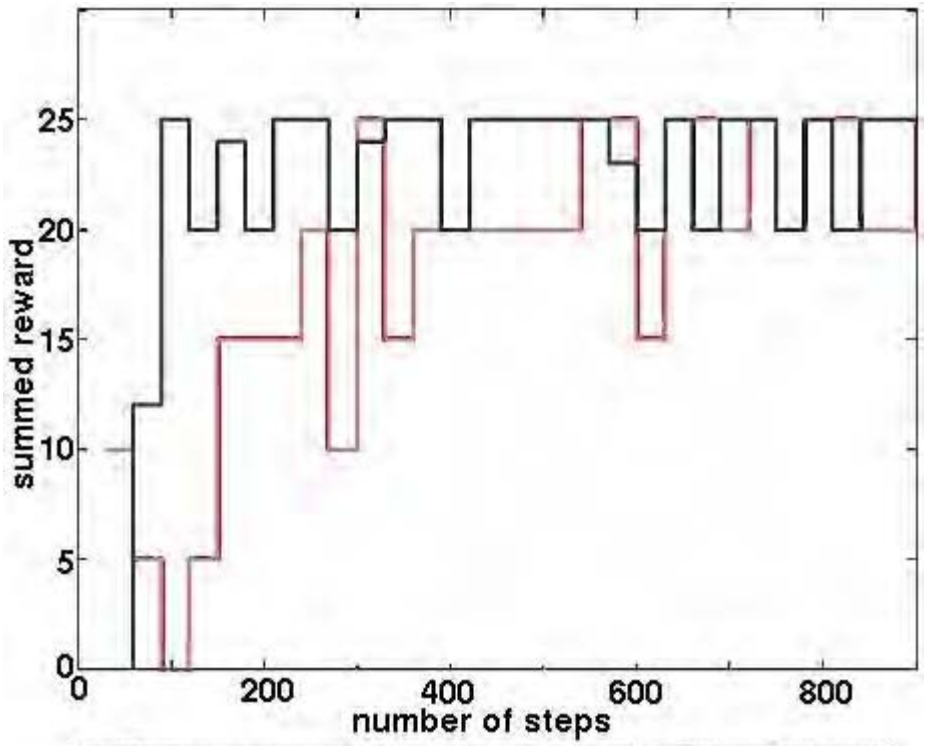

Performance on a one-dimensional grid-world task: continuous time neuronal network, red curve; discrete time computer algorithm, blue curve.