Research Results of the BCCN Freiburg presented at:

Eighth Göttingen Meeting of the German Neuroscience Society

March 25–29, 2009

32nd GÖTTINGEN NEUROBIOLOGY CONFERENCE
Symposium

S8: The fine-scale structure of the cortical network: implications for its dynamics and function

S8-1  Behavioral report of single-neuron stimulation in the somatosensory thalamocortical system
       Arthur Houweling

S8-2  Cortical feed-forward networks for binding different streams of sensory information
       Bjoern Kampa

S8-3  Mapping the Matrix: From Synapses to Circuits in Neocortex.
       Kevan AC Martin

S8-4  Computational power of recurrent neural networks: The role of spikes, network structure, and dynamics
       Robert Legenstein

S8-5  The effect of degree distribution on the dynamics of sparsely connected neuronal networks
       Alexander Roxin

S8-6  Propagation of synchronous activity in circuits without specific feed-forward anatomy
       Marc Timme, Raoul-Martin Memmesheimer
Symposium

S20: Networks on chips - spatial and temporal activity dynamics of functional networks

S20-1 Representation in large-scale random networks of cortical neurons
Shimon Marom

S20-2 State dependent I/O gain and interaction with ongoing activity in cortical networks in vitro
Oliver Weihberger, Samora Okujeni, Tayfun Gürel, Ulrich Egert

S20-3 Delay Lines and the Neurophonic Potential in the Sound-Localization Circuit of Birds
Nico Lautemann, Paula T. Kuokkanen, Richard Kempter, Hermann Wagner

S20-4 CMOS-Based High-Density Microelectrode Arrays for Subcellular Resolution Recordings
Andreas Hierlemann, Urs Frey, Flavio Heer, Sadik Hafizovic

S20-5 Artificial vision by multi-site electrical retina stimulation
Alfred Stett, M. Gerhardt, T. Herrmann, A. Mai, D. Schwenger
as a putative vulnerability factor in schizophrenia. Proc Natl Acad Sci USA 95:15718-15723.
State dependent I/O gain and interaction with ongoing activity in cortical networks in vitro

Oliver Weihberger\textsuperscript{1,2}, Samora Okujeni\textsuperscript{1,2}, Tayfun Gürel\textsuperscript{1,2}, Ulrich Egert\textsuperscript{1,3}

\textsuperscript{1}Berntein Center for Computational Neuroscience Freiburg, University of Freiburg, Hansastrasse 9a, 79104 Freiburg, Germany
\textsuperscript{2}Inst. of Biology III, Neurobiology and Biophysics, University of Freiburg, Germany
\textsuperscript{3}Biomicrotechnology, Dept. of Microsystems Engineering - IMTEK, University of Freiburg, Germany

The human brain, specifically the neocortex, receives massive sensory input, processes this information and generates output commands of astonishing precision and reliability. Although individual neurons fire reproducibly to natural stimuli, the responses of cortical networks to repeated sensory stimuli, however, vary considerably with respect to the number and distribution of the neurons involved as well as to timing and number of spikes, likely because incoming spike input interacts with ongoing activity. For example, visual responses in cat visual cortex depend on the activity at stimulus onset [1].

Our goal is to understand how neuronal networks respond to incoming stimuli, which interactions arise and how these influence their responses. We aim for predictable input/output relationships in user-defined, closed-loop interaction with neuronal networks.

As generic network models, we recorded spike activity in cortical cell cultures grown on microelectrode arrays. This enabled multi-site electrical stimulation to study the spatio-temporal processing of input patterns. Defined pharmacological modifications allow the identification of key mechanisms underlying spontaneous and induced activity. We show that stimulus/response dynamics are network-state dependent. Ongoing activity, consisting of network-wide bursting, modulates reliability, length and delay of polysynaptic responses. High bursting activity prior to stimulation resulted in short responses and large delays. Low bursting activity before stimulation led to long responses and short delays. Stimulus efficacy was modulated by 20-60 sec long periods of increased firing 3-4-fold above baseline, so called superbursts. Efficacy was maximal and responses were longest during superbursts. Responses were shortest or stimulation even failed to elicit spikes directly after superbursts.

State dependent stimulus efficacy hampers the identification of input/output relations and defined interaction with networks. Phase-coupled input, that is, stimulation during a pre-defined network-state increased response reliability and reproducibility. Gap–junction blockage with mefloquine or 2-APB, or blockage of NMDA-receptors by AP-5 suppressed superbursts and resulted in more homogeneously distributed burst lengths and intervals. Pharmacologically modified network states combined with electrical stimulation allowed us to reliably predict response types by means of Echo State Networks (ESN).

Modulation of input/output gain by ongoing activity thus gives rise to state-dependent processing of external inputs. Controlled interaction with and defined modulation of ongoing activity can significantly contribute to predictable responses and an understanding of the processing and storage capabilities in neuronal networks in vitro.


Supported by the German BMBF (FKZ 01GQ0420) and the EC (NEURO, No. 12788)
*left: post-burst stimulation and responses. right: smaller coefficient of variation values for post-burst stimulation.*
Relation between granule cell dispersion, neurogenesis and the spread of epileptiform activity in the hippocampus

Ute Häussler1, Lena Bielefeld1, Martin C. Müller1, Christian Garbers2, Carola A. Haas1,2

1 Experimental Epilepsy research group, Dept. of Neurosurgery, University of Freiburg, Breisacherstrasse 64, 79106 Freiburg, Germany
2 Bernstein Center for Computational Neuroscience, University of Freiburg, Hansastrasse 9a, 79104 Freiburg, Germany

In mesial temporal lobe epilepsy (MTLE) epileptic seizures are accompanied by hippocampal sclerosis, characterized by loss of neurons in the CA-region and the hilus, gliosis and pronounced granule cell dispersion (GCD). We have previously shown that GCD is most likely caused by a displacement of adult neurons in TLE patients and in the intrahippocampal kainate model for MTLE in mice, since neurogenesis is lost in these areas (Heinrich et al., 2006, JNS; Fahrner et al., 2007, Exp. Neurol.). In contrast, an increase in neurogenesis has been proposed to underlie the network changes in MTLE in other epilepsy models (Scharfman et al., 2000, JNS). Here, we want to investigate whether there is a spatial relationship between the spread of epileptiform activity (EA) during status epilepticus and recurrent seizures, the extent of GCD and changes in neurogenesis in the intrahippocampal kainate (KA) model for MTLE in mice.

Therefore, we recorded EA with electrodes implanted into the dentate gyrus at several positions along the septo-temporal axis in the ipsilateral and contralateral hippocampus of KA-injected mice. We recorded the initial status epilepticus and recurrent EA for several weeks after the injection. In parallel, we investigated the extent of GCD and neurogenesis in both hippocampi along this axis by combined bromodeoxyuridin (BrdU) injections and doublecortin (DCX) staining.

We show that during status epilepticus EA could be recorded at all positions in the ipsilateral and contralateral hippocampus. Additionally, at later time points recurrent EA was not limited to the area of strongest hippocampal sclerosis surrounding the injection site, but it spread along the whole length of the hippocampus. In contrast, GCD was limited to an area surrounding the injection site. Notably, the loss of DCX-staining for newly formed granule cells was spatially correlated with GCD and recovered at distance. In the distal and contralateral hippocampus DCX-staining was even increased compared to saline-treated controls, indicating increased neurogenesis. Therefore, we assume that status epilepticus and/or recurrent EA stimulate neurogenesis in the KA mouse model, as described in other animal models for MTLE. In contrast, GCD as well as the disturbance of the neurogenic niche close to the injection site seem to have additional underlying mechanisms despite EA.

(Supported by the DFG SFB TR3 and BMBF 01GQ0420).
Glia-neuron interaction during hippocampal epileptiform activity

Claudia Böhm¹, Ulrich Paul Froriep¹,⁴, Ute Häussler³, Ulrich Egert²,⁴

¹ Faculty of Biology, Albert-Ludwigs-University, Freiburg
² Faculty of Applied Sciences, Albert-Ludwigs-University, Freiburg
³ Experimental Epilepsy Group, Neurocenter, Albert-Ludwigs-University, Freiburg
⁴ Bernstein Center for Computational Neuroscience Freiburg

The intrahippocampal kainate model for Mesial Temporal Lobe Epilepsy (MTLE) in mice reproduces histological and functional changes of human MTLE, including cell loss in CA3 and CA1, granule cell dispersion and mossy fiber sprouting. In both human MTLE and the mouse model changes of the glia network were reported. Extent and structural reorganization of the glia network, as well as details of glia-neuron interaction in seizure initiation, however, are currently not known.

We recorded disinhibited hippocampal slices (bicuculline) from untreated (control-slices) and kainate injected mice (KA-slices) using microelectrode arrays (MEA). In KA-slices taken close to the injection site, EA could not be induced, whereas in distal KA-slices EA was readily elicited but the coherence of EA within hippocampal areas was lower than in control-slices (Häussler et al., SfN, 2007). To estimate contributions of the network size to EA induction we compared slices of 400 µm and 600 µm thickness with respect to inter-event-intervals (IEI), spatio-temporal structure, coherence and frequency spectrum of EA within hippocampal subregions. In thin KA-slices IEI were shorter than in thick slices, indicating a more stable balance of excitation and inhibition within the larger network. IEI distributions were, however, comparable in thin and thick control-slices.

In control-slices and KA-slices, EA could typically first be seen in CA1 or CA3, consisting of a low frequency LFP with spike activity superimposed. Activity in granule cell layer and hilus followed with approx. 5 – 10 ms delay. In most cases, EA was accompanied by large-amplitude oscillations >200 Hz, which were most prominent in the dentate gyrus.

To identify glia-neuron interaction during the initiation of epileptiform activity (EA) we pharmacologically attenuated the effect of glia-derived glutamate by blocking NR2B receptors (Ifenprodil). Preliminary results indicate that attenuation of glia-neuron interaction in KA-slices did not affect the IEIs, amplitude or shape of EAs, but decreased coherence within the dentate gyrus. In contrast, in control-slices coherence increased or did not change. This suggests a synchronizing, pro-epileptic effect of glia-neuron interaction in the epileptic tissue, possibly required for the initiation and/or maintenance of spontaneous seizures in the epileptic brain. In contrast, in the healthy tissue, glia-neuron interaction might have a less pronounced role in synchronizing neuronal activity or might even help to prevent EA by desynchronizing neuronal activity.

Supported by the German Federal Ministry of Education and Research (BMBF, 01GQ0420).
On the integration of parahippocampal networks in epileptiform activity

Ulrich Paul Froriep¹, Ute Häussler⁴, Claudia Böhm²,³, Carola Anneliese Haas¹,⁴, Ulrich Egert¹,²

(¹) Bernstein Center for Computational Neuroscience Freiburg, Germany
(²) Dept. of Microsystems Engineering - IMTEK, Faculty of Applied Sciences, Albert-Ludwigs-University, Freiburg, Germany
(³) Neurobiology and Biophysics, Faculty of Biology, Albert-Ludwigs-University, Freiburg, Germany
(⁴) Experimental Epilepsy Group, Neurocenter, Albert-Ludwigs-University, Freiburg, Germany

Mesial temporal lobe epilepsy (MTLE) is the most common classifiable form of focal epilepsies in humans. In most cases, MTLE is accompanied by histological changes within the hippocampal formation, generally summarized as hippocampal sclerosis. Removing the affected parts does not result in a seizure-free outcome in all cases. This suggests that regions beyond the hippocampus proper and dentate gyrus may contribute to initiation and propagation of epileptiform activity (EA).

We use the kainate mouse model, in which EA is observed after focal injections of kainic acid into the hippocampus. This is accompanied by cell loss in CA1 and CA3, granule cell dispersion and mossy fiber sprouting as well as recurrent epileptic seizures, manifest within two weeks after injection. Although the hippocampal network of the injected side is likely responsible for EA generation [1], hippocampal slices taken close to the injection site are unable to generate or sustain EA [2].

As a major source of direct input to the dentate gyrus, CA1 and CA3, the superficial layers of the entorhinal cortex (EC) could play a key role in EA generation. In addition, with its reciprocal connections to the EC and output structure of the CA region, the subiculum is part of a critical excitatory feedback loop.

Hence, we performed multi-site in vivo recordings along the hippocampal septo-temporal axis, the EC and the subiculum to identify the origin and propagation of EA in this animal model. Neuronal degeneration was detectable within the ipsilateral subiculum within one day after injection. Additionally, slight cell loss in the deep layers of the ipsilateral EC was detected after three weeks.

Preliminary results indicate that EA in the hippocampus distal to the injection site precedes proximal EA, whereas the neurons in EC and subiculum fire simultaneously with the septal hippocampus. EA appears to be generated in temporal or adjacent parahippocampal areas instead of parts close to the injection site that showed the most prominent histological changes.

Supported by the German Federal Ministry of Education and Research (BMBF grant 01GQ0420).


**Spike Sorting Errors: Statistical Differences of Cortical 'Single Unit' and 'Single Neuron' Activity.**

Martin Paul Nawrot¹

¹ Neuroinformatics and Theoretical Neuroscience, Freie Universität Berlin, Germany
² Bernstein Center for Computational Neuroscience Berlin
³ Neurobiologie und Biophysik, Institut für Biologie III, Albert-Ludwigs-Universität Freiburg, Germany
⁴ Bernstein Center for Computational Neuroscience Freiburg

Extracellular recording techniques are the preferred experimental means to monitor neuronal spiking activity in the nervous system of animals. Extracting the so-called 'single-unit' activity (SUA) from the extracellular signal involves two steps. First, 'spikes' that are assumed to reflect action potentials (APs) of nearby neurons are detected, e.g. by thresholding. Second, the spike sorting procedure assigns each individual spike to a particular 'unit'. All spikes of one unit are supposed to correspond to the APs generated by one single neuron. However, detection and sorting are error-prone. Spikes may be falsely assigned to a particular unit (false positives, FPs), and some spikes are missed and not assigned to the respective unit (false negatives, FNs). Indeed, several publications have estimated the amount of errors obtained in the process of spike sorting and FP/FN rates on the order of 10-15% (e.g. Pouzat et al., 2004; Joshua et al., 2007) seem plausible.

We investigated the effect of spike sorting errors on statistical properties of cortical spike trains. In particular we focused on 3 statistical features of cortical spike trains, namely (1) the negative serial correlation of neighboring intervals (Lebedev & Nelson, 1996, Nawrot et al., 2007, Engel et al., 2008), (2) the interval variability as measured by the coefficient of variation (CV), and (3) the spike count variability quantified by the Fano factor. To test the effect of FPs and FNs on these statistical measures, we used two methods of generating surrogate data sets with FPs and FNs. Firstly, we used a point process model with a realistic interval distribution and serial interval correlations (Farkhooi et al., 2008) and randomly inserted or deleted spikes from numeric realizations. Secondly, we used in vivo intracellularly recorded spike trains from cortical neurons (Nawrot et al., 2007) and mixed spikes of different independent recordings.

Our results demonstrate that (1) serial correlation is lost and becomes insignificant for a FP rate of about 10-15%, (2) the coefficient of variation monotonically increases with increasing FP or FN rate, and (3) the Fano factor increases even more strongly than the CV as negative serial correlation is lost which reduces the spike count variance in single neurons (Nawrot et al., 2007; Farkhooi et al., 2008). Thus, we conclude that a realistic rate of spike sorting errors can severely alter the statistics of the true single neuron spike train. Our results suggest that spike sorting may lead to a general over-estimation of single neuron variability, and that it conceals serial spike train statistics that are observed in true single neuron spike trains.

This research receives funding from the BMBF to BCCNs Berlin and Freiburg


Visual evoked activity in V1 of anesthetized rats: from gratings to natural images

Sébastien Roux¹, Dymphie Suchanek¹, Ad Aertsen¹, Clemens Boucsein¹

¹Institute of Biology III, BCCN, Albert-Ludwig-University, Neurobiology and Biophysics, Schänzlestrasse 1, 79104 Freiburg, Germany

In the primary visual cortex, preliminary studies showed that spiking activity dynamic is strongly influenced by the level of complexity of visual stimuli. In particular, it has been shown that spiking activity becomes sparser and more reliable under natural like condition, compared to the classical use of simplified artificial stimuli (such as moving gratings). Since in-vivo-experiments often rely on anesthetized animals, stimuli that were used to mimic natural conditions have been movies or static images animated according to a realistic eye-scan. Note, however, that this differs from real natural conditions, in which the oculomotor feedback is present.

In the present study, we want to investigate the dynamics of visual evoked activity in the primary visual cortex of anesthetized rats. For that purpose, we used extracellular recording techniques to monitor both spiking activity and local field potential (LFP) of a cortical volume using different types of visual stimulations. We have chosen to study V1 of rat because recent studies showed that the response properties of these neurons are surprisingly well tuned, with cells responding to a highly specific set of stimulus parameters and having receptive field organization characterized by complex interactions between center and surround components. Such findings indicate that the responses of these rodent V1 neurons are as specialized, in many ways, as those of highly visual animals (cat, primate). Technically, we recorded network activity with a 3 x 4 array of extracellular electrodes arranged in a plane perpendicular to the cortical surface. The visual stimulation paradigms we used are characterized by different levels of complexity, ranging from simple full-field bright flashes and drifting gratings to moving natural scenes. For the natural like condition, we animated a static picture by a saccadic eye movement model. The model was built according to the features of the saccadic behaviour of the rat described in the literature and includes fixations, saccades, micro-saccades and drifts. It is a major aim of this study to reveal how stimulus complexity is reflected in the spatio-temporal patterns of sensory input-evoked activity, and how dynamic properties of the network change according to it.

Consistent with previous studies, preliminary results showed that V1 neurons are indeed tuned to the features of artificial stimuli, such as orientation, spatial and temporal frequency of moving gratings. Under natural like conditions, we observed that activity dynamics changed and became sparser and more reliable as previously described in cats and monkeys. In particular, we observed that the major increase in reliability occurs within transient epochs of strong firing rate increase. In contrast to previous studies, however, these transient episodes of high activity seem not to be related to fixation onsets but rather to the saccades themselves.
Self-organized criticality (SOC) (Bak et al., 1987) was first described in neuronal cell cultures by Beggs & Plenz (2003). Neuronal networks being in a critical state produce avalanche-like discharges that are power-law distributed. The assessment of avalanches in neuronal networks is a new way of looking at neuronal activities apart from bursts, synchronization etc. The main novelty of our approach is to assess the avalanche distribution at different developmental stages of neuronal networks. For this, we used dissociated post-natal cell culture taken from the rat cortex (Experimental data was provided by the Ulrich Egert group, BCCN Freiburg, Germany). We found that different network states as subcritical, critical or supracritical specify a time and spatial activity profile that is linked but not equivalent to low, moderate or high levels in neuronal activity, respectively. We are the first who show that the activity profile in cell cultures develop from supracritical states over subcritical into critical states. To shed light to the dependency of SOC on network development, we used a self-organizing artificial neuronal network model based on a previous model by Van Ooyen and Abbott (Van Ooyen & van Pelt, 1994; Van Ooyen et al., 1995; Abbott & Rohrkemper, 2007). An important novelty of our model is that it is more detailed with respect to representing separate axonal and dendritic fields (Butz et al., 2008; Butz & Wörgötter, 2009). The model network aims to develop towards a homeostatic equilibrium in neuronal activity which is achieved by growth and retraction of axonal and dendritic fields. This abstract model already reproduces the transient behaviour as seen in cell cultures from supracritical over subcritical to critical states. However, we found that some cell cultures remain in a subcritical regime. The model offers a simple explanation as depending on the strength of inhibition, equivalent to the friction in self-organizing systems (Lauritsen et al., 1996), neuronal networks may or may not reach criticality even though they are homeostatically equilibrated.

References:


Layering of the dentate gyrus is crucial for homogeneous hilar mossy cell input

Janina Kowalski\textsuperscript{1}, Markus Geuting\textsuperscript{1}, Alexander Drakew\textsuperscript{1}, Carola A. Haas\textsuperscript{2,3}, Shanting Zhao\textsuperscript{1}, Michael Frotscher\textsuperscript{1,3,5}, Imre Vida\textsuperscript{3,4}

\textsuperscript{1}Inst. Anat. Cell Biol, Univ. Freiburg, Hansastr. 9A, 79104 Freiburg, Germany  
\textsuperscript{2}Neurozentrum Freiburg, Univ. Freiburg, D-79106 Freiburg, Germany  
\textsuperscript{3}BCCN, Univ. Freiburg, D-79104 Freiburg, Germany  
\textsuperscript{4}Div. of Neurosci. and Biomed. Systems IBLS, Univ. of Glasgow, G12 8QQ, United Kingdom  
\textsuperscript{5}SGBM, Univ. Freiburg, D-79104 Freiburg, Germany

Layered arrangement of neurons is a common feature of cortical regions. Although disrupted layering has been found to be associated with pathological conditions such as epilepsy, the functional relevance of cortical layering is still poorly understood. To investigate how changed neuronal layering influences synaptic properties in a small neuronal network we used reeler mutant mice as a model. In these animals the lack of reelin results in altered layering due to defects in neuronal migration. We focused our investigations on the dentate gyrus, the input region of the hippocampus. Dentate gyrus granule cells and most its interneurons receive entorhinal input via the perforant path in the outer molecular layer. Hilar mossy cells in turn receive their main input primarily from neurons of the dentate gyrus. We simultaneously recorded the extracellular activity of the dentate granule cell population and the intracellular activity of single mossy cells in response to stimulation of the perforant path, thus monitoring a well-defined disynaptic pathway.

In wild-type mossy cells, synaptic responses elicited by perforant path stimulation were uniform and dominated by a short-latency, long-lasting inhibition and a longer-latency, brief excitatory component corresponding to a disynaptic EPSC. In reeler, the synaptic responses were heterogeneous. In the majority of the cells, inhibition was markedly enhanced and the disynaptic EPSC was reduced. Additionally, in many cells a short-latency monosynaptic EPSC could be observed. As a consequence, action potentials (APs) were generated over a broader temporal window. While in some reeler mossy cells APs could be evoked monosynaptically with high temporal precision, in others, APs were generated with long latency and low temporal precision. The probability for disynaptic APs, but not for monosynaptic APs, was overall reduced.

Consistent with the electrophysiological findings, visualization of the intracellularly labeled reeler mossy cells revealed marked changes in the morphology and a high degree of heterogeneity in the localization and the distribution of dendrites. While in the wild-type hippocampus mossy cells and their dendrites were confined to the hilus, in reeler the cell bodies and their dendrites were often found in the molecular layer.

In summary, changes in localization and morphology of reeler mossy cells enable them to receive direct synaptic inputs from the perforant path. However, the disynaptic excitatory input via dentate granule cells is reduced and feed-forward inhibition is increased. Thus, changes in the connectivity associated with the altered lamination in reeler mice result in a reduced efficiency and higher temporo-spatial variability of synaptic activation in the dentate-hilar network.
Protein kinase C dependent connectivity and activity dynamics in developing cortical networks

Samora Okujeni¹, Steffen Kandler¹,², Oliver Weihberger¹,², Ulrich Egert¹,³

¹Bernstein Center for Computational Neuroscience, University Freiburg, Germany
²Institute of Biology III, Neurobiology and Biophysics, University Freiburg, Germany
³Biomicrotechnology, Department of Microsystems Engineering, University Freiburg, Germany

In early brain development, cortical circuitry and activity dynamics evolve on the basis of activity-regulated structural differentiation processes in neurons. In this scenario, a central regulator of neuronal morphology is the protein kinase C (PKC), which is activated via metabotropic glutamate receptor downstream signalling pathways. In a simplified model, activation of the PKC phosphorylates and mobilizes cytoskeletal proteins, thereby promoting structural plasticity. Antagonistic pathways involving the NMDA receptor mediated activation of protein phosphatases in turn promote cytoskeletal assembly and stabilization (Quinlan ‘96). The differential regulation of this structural homeostasis in the course of development is crucial for the establishment of proper connectivity statistics and the adaptive modulation of synaptic plasticity in neuronal networks.

We study this fundamental feature of neuronal systems in dissociated cortical cell cultures grown on micro-electrode arrays. These generic random networks display a self-regulated maturation process with similar phases as in the developing cortex. Within this period of network formation we interfered with the structural homeostasis by inhibiting PKC activity. Previous studies showed that inhibition of PKC activity in cerebellar slice cultures promotes dendritic outgrowth and arborization (Metzger ‘00) and that climbing fiber pruning is impaired in PCK deficient mice (Kano ‘95). Further in vitro data demonstrate the importance of PKC activity for experience-dependent modulation of synaptic weights on the basis of AMPA receptor trafficking (Zheng ‘08), suggesting reduced synaptic plasticity with PKC inhibition.

To assess the functional consequences of these dependencies, we chronically inhibited PKC activity in cortical cell cultures and compared network activity and connectivity characteristics. Applying new morphometrics, we found significantly increased arborization and extent of dendrites as well as increased synapse density, indicating increased connectivity in these networks. Spike activity remained organized in network-wide bursts that characteristically emerge in cortical cell cultures. Bursts were, however, more synchronized across the recording area and contained more spikes, suggesting faster propagation of activity through the network and longer reverberations due to increased connectivity. By further analyzing the temporal stability and the diversity of spatio-temporal activity patterns, we assess possible consequences of reduced PKC activity on the formation of functional pathways during early network development.

Supported by the German Federal Ministry of Education and Research (FKZ 01GQ0420).
Modulation of Stimulus Efficacy by Ongoing Activity and Reproducibility by Online-interaction with Neuronal Networks in vitro

Oliver Weihberger\textsuperscript{1}, Samora Okujeni\textsuperscript{1,2}, Ulrich Egert\textsuperscript{1,3}

\textsuperscript{1}Berntein Center for Computational Neuroscience Freiburg, Hansastrasse 9a, 79104 Freiburg, Germany
\textsuperscript{2}Institute of Biology III, Neurobiology and Biophysics, University of Freiburg, Germany
\textsuperscript{3}Biomicrotechnology, Dept. of Microsystems Engineering - IMTEK, University of Freiburg, Germany

The neocortex receives massive sensory input, processes this information and generates output commands of astonishing precision and reliability. In-vivo responses to the same stimuli are, however, highly variable with respect to number of spikes and phase-locking to the stimulus. In some cases, response prediction is possible only when the cortical activity state at stimulus onset is taken into account \cite{arieli1996}. Neuronal interactions during natural inputs are thus arising as dynamical processes and very little is known about the mechanisms that govern them. We want to understand how neuronal networks respond to incoming stimuli, which interactions arise and how these influence their responses. We aim for a user-defined interaction with ongoing activity that controls for the activity state during stimulation and thereby increases response reliability and reproducibility.

We use in vitro cortical cell cultures grown on microelectrode arrays as generic neuronal networks to address these issues. Neuronal activity can be recorded from 60 sites simultaneously over months under controlled conditions. Multi-site electrical stimulation enables to study the spatio-temporal processing of input patterns.

We show that stimulus efficacies are network-state dependent. Ongoing activity, consisting of synchronized, network-wide bursting, modulates response length and delay. High bursting activity prior to stimulation results in short responses and large delays. Low bursting activity before stimulation results in long responses and small delays. Stimulus efficacy was modulated by 20-60 seconds long periods of 3-4 folds increased firing above baseline, so called superbursts. Responses were longest and efficacy was maximal during superbursts. Responses were shortest or stimulation even failed to elicit spikes directly after superbursts.

Network-state dependent stimulus efficacies confine the examination of input/output dynamics and demand for a user-defined interaction with ongoing activity. Phase-coupled input, that is, stimulation during a pre-defined network state minimized the interference between spontaneous and induced activity. Response reliability and reproducibility was increased for phase-coupled compared to random, un-coupled stimulation.

Modulation of stimulus/response dynamics by ongoing activity gives thus rise to state-dependent processing of external inputs. Interaction with ongoing activity can improve response reliability and reproducibility and thereby contribute to an understanding of the processing capabilities in neuronal networks in vitro, and other, physiological more realistic systems in general.

The work presented in this manuscript was supported by the German BMBF (FKZ 01GQ0420) and by the EC (NEURO, No. 12788)

Structural and functional embedding of individual neurons into cultured neuronal networks

Steffen Kandler\textsuperscript{1,2}, Samora Okujeni\textsuperscript{1,2}, Sebastian Reinartz\textsuperscript{2}, Ulrich Egert\textsuperscript{1,3}

\textsuperscript{1}Bernstein Center for Computational Neuroscience, Univ. Freiburg, Germany
\textsuperscript{2}Neurobiology & Biophysics, Inst. of Biology III, Univ. Freiburg, Germany
\textsuperscript{3}Biomicrotechnology, Dept. of Microsystems Engineering - IMTEK, Univ. Freiburg, Germany

We investigated the local connectivity and individual activity of neurons as key features of their embedding into larger generic networks. In culture, dissociated cortical cells obtained from neonatal rats form such simple networks. When maturing, the neurons make synaptic connections in apparently random fashion and the networks display a characteristic bursting behavior (Maeda \textit{et al.}, 1995; Wagenaar \textit{et al.}, 2006) with simultaneous onset timing in a range of 10-100 ms. We recorded activity from networks with a local density (\textit{i.e.} in a 100 \textmu m radius) of 1,000-2,000 cells per mm\textsuperscript{2} with 60-site microelectrode arrays (MEA; 200 or 500 \textmu m electrode distance, 1.4x1.4 or 2.5x4.5 mm array size) and dual patch-clamp electrodes.

Based on the intracellular patch-clamp recordings, we determined the pairwise connection probability at up to 250 \textmu m distance. We identified excitatory (exc) and inhibitory (inh) postsynaptic potentials in response to presynaptically evoked action potentials (AP) as well as unidirectional (UD) or bidirectional (BD) connections. Of all neuron pairs (n=94), 38\% were connected and 62\% were unconnected, in agreement with reports in Nakanishi & Kukita (1998). We further found that 18\% of all pairs had UD exc and 4\% UD inh connections. 12\% of the pairs had BD exc-exc, and 2\% both BD inh-nh or BD exc-inh connections. The connection probability decreased with distance. The observed connection probability for UD and BD connections lies above the expectation values described by Song \textit{et al.} (2005) for the connectivity in native cortex.

We further characterized the functional embedding of individual neurons into the global bursting activity. Individual neurons followed bursts in the local network recorded extracellularly at nearby MEA electrodes with sharp onsets and narrow temporal jitter (\pm 10 ms). Local population activity onsets are thus predictive for the timing of activity onsets in individual neurons. Activity onsets of individual neurons with respect to distant network regions ranged from near-simultaneous to preceding or delayed timing, but likewise with only a small temporal jitter between pairs. In contrast, MEA electrodes that repeatedly fired before burst onsets in many network bursts, and thus reliably predicted burst onset in the network, only weakly predicted the spiking of individual cells, largely irrespective of their absolute distance. Individual delays to these predictors were broadly distributed, with a peak at approx. 50 ms. The overall activity within bursts was typically higher than average at these sites and their peak rate coincided with intracellular activity onsets.

The low probability for direct connections at distances of several hundred \textmu m suggests that this narrow timing of burst onsets at most sites in the network can be maintained via polysynaptic connections, which could be supported or mediated by bottlenecks or hubs in the propagation pathways within the network, such as described recently (Shahaf \textit{et al.}, 2008).

Supported by the German BMBF (FKZ 01GQ0420) and by the EC (NEURO, No. 12788).
Dopamine modulated plasticity enables TD learning in a spiking actor-critic neural network model

Wiebke Potjans¹, Abigail Morrison¹, Markus Diesmann¹,²,³

¹Theoretical Neuroscience Group, RIKEN Brain Science Institute, Wako City, Japan
²Brain and Neural Systems Team, Computational Science Research Program, RIKEN, Wako City, Japan
³Bernstein Center for Computational Neuroscience, Albert-Ludwigs-University, Freiburg, Germany

Synaptic plasticity is thought to underlie learning, but the exact relation between changes in synaptic efficacy and system-level learning remains unclear. One theory often considered in this context is reinforcement learning, in particular the variant known as temporal-difference (TD) learning. In a previous study [1] we showed that a spiking neural network model with biologically plausible plasticity rules is able to implement TD learning. However, the model does not assign a role to the dopaminergic neurons of the basal ganglia, although much of the neurophysiological evidence supporting the theory of TD learning in the brain is based on the dopamine system. Most notable in this context is the resemblance of dopaminergic activity to the TD error signal [2] and the finding that plasticity in the striatum is modulated by dopamine [3].

Here, we present a spiking neural network implementing actor-critic TD learning (see figure inset) that for the first time simultaneously describes the generation of a dopamine mediated TD error signal and the synaptic plasticity required to exploit the error information. The critic module is based on a simplified model of the basal ganglia [4]; the dopaminergic neurons respond to movements of the agent between states of different values with rate excursions of similar amplitudes to those observed in conditioning experiments [1]. The dopamine signal is in turn interpreted as the third factor in the plasticity of the synapses encoding the value function and the policy. Although the synaptic plasticity rules were postulated using a top-down approach, there is excellent agreement between the predictions of our synapse model and experimental findings on corticostriatal synapses [5].

We show that the network is capable of solving a non-trivial grid-world task with sparse rewards. It learns to evaluate the states with respect to reward proximity and adapts its policy accordingly. The learning performance is similar to that of a discrete-time TD learning algorithm (see figure; red: spiking network model, black: discrete time algorithm). Furthermore we analyse the learning behavior with respect to changes in the dopamine level and compare it to the learning behavior in Parkinson patients.

Partially funded by EU Grant 15879 (FACETS), BMBF Grant 01GQ0420 to BCCN Freiburg, Next-Generation Supercomputer Project of MEXT, Japan, and the Helmholtz Alliance on Systems Biology.

The impact of target type selection on the stability of layered cortical network dynamics

Tobias C Potjans¹, Markus Diesmann¹,²,³

¹Brain and Neural Systems Team, Computational Science Research Program, RIKEN, Wako City, Japan
²Theoretical Neuroscience Group, RIKEN Brain Science Institute, Wako City, Japan
³Bernstein Center for Computational Neuroscience (BCCN), Albert-Ludwigs-University, Freiburg, Germany

The local cortical network consists of distinctively interconnected layers. A feed-forward pattern of connections (layer 4 (L4) to L2/3 to L5 to L6) has been hypothesized on the basis of axonal branching properties as well as the tuning properties of cells in primary visual cortex (see [1] for review). Recently, evidence has been accumulated that this pattern is accompanied by “feedback” connections inverse to the feed-forward connections; strikingly these connections specifically select interneuronal targets (see e.g. [2]). This lead to the hypothesis that the resulting lack of excitatory feedback increases the sensitivity for time-dependent signaling and decreases the susceptibility to “over-excitation and epileptiform activity” [2]. However, the impact of target type selection on the activity dynamics of the local network remains unstudied - largely due to the incompleteness and shortcomings of even the most comprehensive data sets on cortical connectivity.

We overcome this problem with the compilation of an integrated data set on layer-specific connectivity based on anatomical and physiological data [3]. In addition, we incorporate information on target type selection from laser-scanning photostimulation [4] and electron microscopy studies [5]. On this basis, we present an algorithmic procedure to construct self-consistent data sets strictly fulfilling target type selection constraints.

We investigate the dynamical implications of target type selection in large-scale simulations. Our model consists of 80,000 I&F neurons and explains around 90% of the synapses that constitute the local cortical microcircuit. We find that networks exhibiting specific target type selection (target specificity) show superior stability compared to control networks lacking this feature. The figure shows the population rates (left, separate for excitatory, mean of inhibitory populations) and Fano Factor (right, mean of excitatory, inhibitory populations) for different values of target specificity (+/-1 for only selecting excitatory/inhibitory neurons; 0 for non-specific targeting). Note, that we solely alter the specific selection of targets of the feedback connections shown in the inset (arrow thickness represents connection probabilities, target specificity fixed to -0.4). With otherwise identical parameters, these minor changes in the connectivity drive the network non-linearly from a low-rate asynchronous irregular state to global over-excitation and epileptiform activity. Thus, we identify specific target type selection as a potential structural tipping element for network stability, establishing a link between microcircuitry and activity dynamics.


Acknowledgements
Partially supported by EU Grant 15879 (FACETS), Next-Generation Supercomputer Project of MEXT, Japan, and the Helmholtz Alliance on Systems Biology.
Dual measures for assembly activation based on the LFP and spike coincidences

Michael Denker¹, Sébastien Roux², Alexa Riehle³, Markus Diesmann¹, Sonja Grün¹

¹Theoretical Neuroscience Group, RIKEN Brain Science Institute, Wako City, Japan
² Bernstein Center for Computational Neuroscience (BCCN), Albert-Ludwigs University, Freiburg, Germany
³ Mediterranean Institute of Cognitive Neuroscience (INCM), CNRS - Univ. Aix-Marseille 2, Marseille, France

A common hypothesis concerning the strategies of information coding employed by cortical networks involves the propagation of activity through synchronously firing groups of neurons, termed assemblies. Despite recent advances in increasing the number of recorded neurons from cortical networks, the inherent undersampling of the system still prevents us to directly verify the existence of assembly activity in the living brain. However, a growing body of experimental studies indirectly substantiates the assembly idea with findings of significant synchronous spiking activity that relates to behavior (e.g., [1]). Independently thereof, a signal measuring directly on the population level, like the local field potential (LFP), typically exhibits temporally structured oscillations commonly interpreted as correlated network activity. Recently, we demonstrated a direct link between coincident spike events and their phase relationship to LFP beta oscillations in motor cortex of the awake behaving monkey [2]. In particular, we showed that Unitary Events (UEs, significant coincidences, cf. [3]) exhibit an exceptionally strong locking to the LFP that cannot be explained by the locking of the individual neurons.

In order to understand how the observed levels of synchrony and phase locking quantitatively translate to the assembly hypothesis we formulate a simplified model. It assumes that part of the spiking activity is involved in assembly activations, whereas the other part is not. In the model, UEs express observed assembly activity. Combined with the results in [2], we conclude that assembly spikes are more strongly entrained by the LFP than non-assembly spikes. In this framework, we demonstrate how to compute the minimal relative contribution of assembly spikes following two conceptually different approaches. First, we show how to estimate the fraction of spikes involved in assembly activations by comparing the phase distributions between time periods that exhibit UEs and those that do not. Second, we estimate this fraction as a function of the UE significance level given a model of injected spike synchrony into otherwise independent firing (cf. [4]), exploiting estimates of the expected and empirical coincidence distributions. Both methods are calibrated using simulated data before they are applied to the biological data. Finally, extending the former approach enables us to infer an estimate of the percentage of spikes a neuron contributes to assemblies. The consistency of the results of both approaches provides encouraging support for the assembly hypothesis.

Partially funded by the Helmholtz Alliance on Systems Biology, the French National Research Agency (ANR-05-NEUR-045-01), and EU grant 15879 (FACETS).

Self-sustained cell assemblies in structurally plastic networks

Moritz Helias\textsuperscript{1}, Stefan Rotter\textsuperscript{1,2}, Marc-Oliver Gewaltig\textsuperscript{1,3}, Markus Diesmann\textsuperscript{1,4}

\textsuperscript{1}Bernstein Center for Computational Neuroscience (BCCN), Freiburg, Germany  
\textsuperscript{2}Computational Neuroscience, Faculty of Biology, Albert-Ludwigs University Freiburg, Germany  
\textsuperscript{3}Honda Research Institute Europe, Offenbach, Germany  
\textsuperscript{4}Theoretical Neuroscience Group, RIKEN Brain Science Institute, Wako City, Japan

The connectivity structure of cortical networks was recently found to exhibit plastic changes even in adult animals [1]: there is a considerable continuous turnover of synapses. It is still unclear, how networks maintain their functionality despite this plasticity and what are the mechanisms ensuring network stability.

Here we investigate random and structured networks subject to structural reorganization. We exploit the idea of correlation based sorting, where new synapses are constantly created at a fixed rate between randomly chosen neurons and synaptic pruning is controlled by a correlation based selective elimination rule [2].

We show that this plasticity induces a homeostasis of firing rates in random recurrent networks. At realistically low firing rates as observed in neocortex, this structural plasticity effectively regulates the number of incoming connections per neuron.

To address the question how functionally important connections are maintained despite the synaptic turnover, we embed cell assemblies of $G_e$ neurons into the network (see Figure A) and investigate the stability of their characteristic connectivity. Earlier theoretical work [3] showed that cell assemblies are a viable substrate of associative memory and that structural plasticity improves the memory capacity. Our own prior work [2] demonstrated cooperation among synapses that are activated in a correlated way, resulting in a stabilization of these connections. The neurons of an assembly in our model exhibit such correlation which, by cooperation, effectively stabilizes its connectivity. Furthermore, a critical minimal connectivity $f>f_c$ is required for this self-sustained maintenance.

However, the embedded cell assemblies continuously recruit more cells and hence expand over time. Therefore this work prompts for further constraints of structural plasticity that prevent cell assemblies from unbounded growth.

In parallel to direct numerical simulations, we derive analytical results that enable us to predict the point of homeostasis, which corresponds to a stable fixed point (see Figure B) as well as the critical connectivity needed for self-sustained cell assemblies which is an unstable fixed point.

Partially funded by DIP F1.2, BMBF Grant 01GQ0420 to BCCN Freiburg, EU Grant 15879 (FACETS), and the Helmholtz Association on Systems Biology.

Functional consequences of correlated excitation and inhibition on single neuron integration and signal propagation through synfire chains.

Jens Kremkow$^1$, Laurent Perrinet$^1$, Guillaume S. Masson$^1$, Ad Aertsen$^{2,3}$

$^1$INCM, CNRS - Aix-Marseille University, Marseille, France
$^2$Neurobiology and Biophysics, University of Freiburg, Freiburg, Germany
$^3$Bernstein Center for Computational Neuroscience, Freiburg, Germany

Neurons receive a large number of excitatory and inhibitory synaptic inputs whose temporal interplay determines their spiking behavior. On average, excitation (Gexc) and inhibition (Ginh) balance each other, such that spikes are elicited by fluctuations [1]. In addition, it has been shown in vivo that Gexc and Ginh are correlated, with Ginh lagging Gexc only by few milliseconds (6ms), creating a small temporal integration window [2,3]. This correlation structure could be induced by feed-forward inhibition (FFI), which has been shown to be present at many sites in the central nervous system.

To characterize the functional consequences of the FFI, we first modeled a simple circuit using spiking neurons with conductance based synapses and studied the effect on the single neuron integration. We then coupled many of such circuits to construct a feed-forward network (synfire chain [4,5]) and investigated the effect of FFI on signal propagation along such feed-forward network.

We found that the small temporal integration window, induced by the FFI, changes the integrative properties of the neuron. Only transient stimuli could produce a response when the FFI was active whereas without FFI the neuron responded to both steady and transient stimuli. Due to the increase in selectivity to transient inputs, the conditions of signal propagation through the feed-forward network changed as well. Whereas synchronous inputs could reliable propagate, high asynchronous input rates, which are known to induce synfire activity [6], failed to do so. In summary, the FFI increased the stability of the synfire chain.

Supported by DFG SFB 780, EU-15879-FACETS, BMBF 01GQ0420 to BCCN Freiburg

Time-driven simulation as an efficient approach to detecting threshold crossings in precisely spiking neuronal network models

Susanne Kunkel¹, Alexander Hanuschkin¹, Moritz Helias¹, Abigail Morrison², Markus Diesmann¹,²

¹Bernstein Center for Computational Neuroscience, Albert Ludwigs University, Freiburg i. Br., Germany
²Theoretical Neuroscience Group, RIKEN Brain Science Institute, Wako City, Japan

In order to avoid artificial synchronization in neuronal network simulations, there is considerable interest in being able to compute spike times precisely. Recently, research has developed along two lines, which both enable the calculation of spikes with arbitrary precision: extending the set of neuron models that can be simulated in an event-driven scheme by developing appropriate spike-prediction algorithms [1,2], and detecting spikes between the sampling points of a time-driven scheme [3].

One potential advantage of the time-driven scheme is that a threshold crossing needs only be detected retrospectively, which is a simpler problem than the prediction required for the event-driven approach. We compare the simulation times of networks of neurons implementing spike-prediction algorithms as suggested by Brette [1] (Polynomial) and D'Haene et al. [2] (Envelope) and spike-detection algorithms as suggested by Morrison et al. [3] (Interpolation) and the extension of this framework to use iterative root-finding methods (Newton/Raphson), see figure. For orientation, the figure also shows the simulation times of a traditional grid-constrained neuron implementation as a function of the error in spike times of a single neuron simulation. All simulations were performed in NEST [4]. These results demonstrate that given a sufficiently high computational resolution (1 ms), sampling the membrane potential at every incoming spike provides an effectively fail-safe method of detecting recent threshold crossings that is more efficient than the elegant methods used for predicting a future spike proposed by Brette [1] and D'Haene et al. [2]. Moreover, the time-driven scheme can be applied to all linear and non-linear neuron models.

> By analyzing the dependence of simulation time on the computational resolution and the input and output rates of a medium size neuronal network (12,000 neurons), we conclude that the only regimes in which an event-driven scheme could be more efficient than a time-driven scheme are small networks at very low rates, and applications where the research domain forces a high resolution for the time-driven scheme, e.g. due to very short synaptic delays.

Partially funded by DIP F1.2, BMBF Grant 01GQ0420 to the BCCN Freiburg, and EU Grant 15879 (FACETS).

References:
The nonlinear response of a spiking neuron to a transient stimulus

Tilo Schwalger\textsuperscript{1}, Sven Goedeke\textsuperscript{2}, Markus Diesmann\textsuperscript{2,3}

\textsuperscript{1}Max-Planck-Institut für Physik komplexer Systeme, Stochastische Prozesse in der Biophysik, 01187 Dresden, Germany
\textsuperscript{2}Bernstein Center for Computational Neuroscience, Albert-Ludwig-University, 791004 Freiburg, Germany
\textsuperscript{3}RIKEN Brain Science Institute, Computational Neuroscience Group, Wako-shi, Saitama 351-0106, Japan

The propagation of synchronous firing activity in feed-forward neural networks has been proposed as a model (“synfire chain”) to explain precise spatio-temporal spike patterns in the cortex \cite{Abeles1991}. Numerical studies have revealed that such propagation is possible in physiologically realistic parameter ranges and that two variables are sufficient to describe the dynamics of the travelling activity pulse \cite{Diesmann1999}. To gain a general understanding we aim at a full analytical description of the activity dynamics. This inevitably requires the knowledge of the response of a single neuron to transient stimuli in the presence of background noise. An analytical solution of even this single neuron problem, which takes basic membrane properties into account, is still lacking, although progress has been made recently \cite{Goedeke2008}. The most likely reason for this, are general technical difficulties to treat time-inhomogeneous random processes.

Here, we present an explicit formula for the time-dependent firing rate of a leaky integrate-and-fire neuron in response to an arbitrarily strong, transient stimulus. With this formula, we are finally equipped with a theory that accurately predicts the expected response of a population of neurons to an incoming activity pulse. In other words, we are able to construct a transmission operator that iteratively maps the firing response of one neuron group to the firing response of the next group. This allows us to study the pulse propagation along the feedforward network analytically. The key idea to solve the time-dependent problem is based on an exact series representation for the first-passage-time density of differentiable random processes and its approximations \cite{Verechtachaguina2006, Ricciardi1983}. Already the first term of the series excellently accounts for the transient firing rate (see figure). For strong or fast stimuli, this approximation recovers previous results \cite{Goedeke2008}. Furthermore, the mean membrane potential excursion and its temporal derivative naturally appear in the formula, which justifies assumptions of previously used phenomenological models.

Clustered network topology and noise directly influence quasi-stable bursting behaviour

Sarah Jane Jarvis\(^1\), Stefan Rotter\(^1\), Ulrich Egert\(^{1,2}\)

\(^1\)Berstein Center for Computational Neuroscience Freiburg, Ulrich Egert, Hansastrasse 9A, 79104 Freiburg im Breisgau, Germany
\(^2\)Biomicrotechnology, Institute for Microsystems Engineering (IMTEK), Albert-Ludwigs-University Freiburg, Germany

Disassociated cortical cultures grown on multi-electrode 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 purpose is not understood but may saturate network dynamics. It has been demonstrated that bursts have different motifs and contain structure, refuting the possibility that they are merely chaotic activity. 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. Descriptive models have been promoted in order to understand their bimodal activity; however, a functional description might be of more use in investigating characteristics of bursting networks.

A type of recurrent neural network model termed Echo State Networks was proposed as a functional model of the disassociated cultures. We have previously demonstrated the effect of altering parameters such as connectivity and temporal resolution of individual units and reported that of all possible parameter changes, altering the structure of the reservoir most drastically changed network dynamics. Of specific interest were subreservoir configurations that resulted in a marked tendency for quasi-stable activity dynamics, which appears analogous to bursting. Furthermore, we established that temporal recall is related to the ratio between cluster size and number of clusters. Here, we further analyze this finding and examine network topology against dynamics by considering an extended collection of network configurations.

The robustness of the bursting-like model to noise was previously established by perturbing the system using small uniformly distributed noise and found to be lower for non-homogeneous reservoir architectures, supporting the hypothesis that these networks operate in a quasi-stable or 'critical' range as proposed elsewhere for reservoir networks. In addition, noise was also found to be responsible for determining the amount of variability observed in artificial bursts. Where previously only small amounts of noise were considered, we now examine the effect of larger noise values in order to identify an acceptable range of noise values and distributions that result in dynamics that are both quasi-stable and biologically plausible.

Supported by the German Federal Ministry of Education and Research (BMBF, 01GQ0420) and EU-NEURO (12788)
Structural plasticity in recurrent cortical networks

Moritz Deger\textsuperscript{1}, Moritz Helias\textsuperscript{1}, Markus Diesmann\textsuperscript{1,3}, Stefan Rotter\textsuperscript{1,2}

\textsuperscript{1}Bernstein Center for Computational Neuroscience (BCCN), Freiburg, Germany  
\textsuperscript{2}Computational Neuroscience, Faculty of Biology, Albert-Ludwig University Freiburg, Germany  
\textsuperscript{3}Theoretical Neuroscience Group, RIKEN Brain Science Institute, Wako City, Japan

We study recurrent neural networks exhibiting structural plasticity by formation and elimination of synapses: synaptic death is controlled by a biologically realistic correlation dependent learning rule \cite{helias2008} and synapse formation with a fixed rate takes place in a random manner.

The interplay between network dynamics and correlation dependent evolution of network structure exhibits an interesting feature: We observe the emergence of cell assemblies in initially random cortical networks upon correlated stimulation of a subgroup of neurons.

To gain a quantitative understanding, we reduce the detailed spike based learning dynamics to effective rate equations where the network dynamics follows the structure adiabatically. We show that this description captures the essential features of the interplay between structural plasticity and network dynamics. Comparison to direct numerical simulations proves the approximate procedures applied on many levels adequate.

With the theoretical treatment of network evolution ready, we can inquire into modes of stimulation that facilitate the induction of cell assemblies, and into the conditions that must be fulfilled to stabilize them for longer periods.

Extensions of our setup to include correlation dependent rather than random formation of synapses and sequential stimulation of several network subgroups will be treated as this project progresses.

\cite{helias2008} Moritz Helias, Stefan Rotter, Marc-Oliver Gewaltig, and Markus Diesmann. Structural plasticity controlled by calcium based correlation detection. 2008. submitted.

Partially funded by DIP F1.2, BMBF Grant 01GQ0420 to BCCN Freiburg, EU Grant 15879 (FACETS), and the Helmholtz Association on Systems Biology.
NeuralEnsemble: Towards a meta-environment for network modeling and data analysis

Pierre Yger\textsuperscript{1}, Daniel Brüderle\textsuperscript{2}, Jochen Eppler\textsuperscript{3,4}, Jens Kremkow\textsuperscript{4,5}, Dejan Pecevski\textsuperscript{6}, Laurent Perrinet\textsuperscript{5}, Michael Schmuker\textsuperscript{7}, Eilif Muller\textsuperscript{8}, Andrew Davison\textsuperscript{1}

\textsuperscript{1}CNRS, UNIC, France  
\textsuperscript{2}University of Heidelberg, Germany  
\textsuperscript{3}Honda Research Institute Europe GmbH, Germany  
\textsuperscript{4}BCCN, University of Freiburg, Germany  
\textsuperscript{5}INCM, CNRS, France  
\textsuperscript{6}Technical University of Graz, Austria  
\textsuperscript{7}Freie Universität Berlin, Germany  
\textsuperscript{8}EPFL, Switzerland

NeuralEnsemble (http://neuralensemble.org) is a multilateral effort to coordinate and organise neuroscience software development efforts based around the Python programming language into a larger, meta-simulator software system. To this end, NeuralEnsemble hosts services for source code management and bug tracking (Subversion/Trac) for a number of open-source neuroscience tools, organizes an annual workshop devoted to collaborative software development in neuroscience, and manages a google-group discussion forum. Here, we present two NeuralEnsemble hosted projects:

PyNN (http://neuralensemble.org/PyNN) is a package for simulator-independent specification of neuronal network models. You can write the code for a model once, using the PyNN API, and then run it without modification on any simulator that PyNN supports. Currently NEURON, NEST, PCSIM and a VLSI hardware implementation are fully supported.

NeuroTools (http://neuralensemble.org/NeuroTools) is a set of tools to manage, store and analyse computational neuroscience simulations. It has been designed around PyNN, but can also be used for data from other simulation environments or even electrophysiological measurements.

We will illustrate how the use of PyNN and NeuroTools ease the developmental process of models in computational neuroscience, enhancing collaboration between different groups and increasing the confidence in correctness of results. NeuralEnsemble efforts are supported by the European FACETS project (EU-IST-2005-15879)
Interacting point processes and neuronal modeling

Stefano Cardanobile¹, Stefan Rotter¹,²

¹Albert Ludwigs Universität Freiburg, BCCN Freiburg, Hansastrasse 9/a, D-79104 Freiburg, Germany ²Albert Ludwigs Universität Freiburg, Faculty of Biology, Department of Computational Neuroscience, Hauptstrasse 1, D-79104 Freiburg

Inhomogeneous Poisson processes are much employed for modeling and analyzing neuronal spike data: an inhomogeneous Poisson process is a Poisson process the rate of which changes over time. If the change of the rate depends on the realization of some other processes, then we speak of interacting point processes.

We investigate networks of interacting point processes that use the instantaneous firing rates of their neurons as state variables.

Generalizing Hawkes' [2],[3] linear model, our nonlinear description also admits inhibitory interactions. In particular, we present

1. a mathematical model of interacting point processes where spikes trigger changes in the instantaneous firing rates of the postsynaptic neurons;
2. an ordinary differential equation for the mean of the firing rates;
3. a point process equivalent of the leaky integrate-and-fire neuron;
4. a Fokker-Plank type equation for the distribution of the firing rates of the perfect integrator.

We analyze the dynamic behaviour of the firing rates in response to nonconstant inputs; this could shed some light on the observed precise response to input transients as found e.g. in [4] and exemplified in the plot of a simulation of our system in the attached figure.

Support by the German Federal Ministry of Education and Research (BMBF grant 01GQ0420) is gratefully acknowledged.

References:

Modeling Free Monkey Scribbling by the Propagation of Synchronous Activity

Alexander Hanuschkin\textsuperscript{1}, J. Michael Herrmann\textsuperscript{2}, Abigail Morrison\textsuperscript{3}, Markus Diesmann\textsuperscript{1,3}

\textsuperscript{1} Bernstein Center for Computational Neuroscience, Albert-Ludwigs-Universität, Freiburg, Germany  \textsuperscript{2} Institute for Perception, Action and Behaviour, University of Edinburgh, U.K.  \textsuperscript{3} Theoretical Neuroscience Group, RIKEN Brain Science Institute, Wako City, Japan

We present a model of free monkey scribbling where the propagation of synchronous activity represents unaccelerated movements in velocity space. Our architecture can be represented by a graph in velocity space: the edges of the graph represent synfire chains (SFCs) \cite{1} which transform the velocity of the trajectory linearly between the start and end vertex. Thus, each neuron group has a velocity coding depending on its position along the edge. A trajectory is generated by integrating the population vector of all neurons. Activity in the final group of a SFC can stimulate the first group of any SFC whose start vertex corresponds with the end vertex of the previously active chain. Reliable switching to select one of several candidate SFCs with the same start vertex is feasible by a switching method based on cross inhibition of the SFCs. The network activity is sustained by a background network of highly recurrent backward and forward connected chains (BFoCs). Self-ignition within this background ignites synfire activity in the model. The BFoCs activities are suppressed while the model is active. This network architecture guarantees random ongoing parabola trajectories with smooth transitions and a drawing dynamics that obeys the 1/3 power law as observed in experiments \cite{2,3}. An example of a 5 second trajectory generated by a graph of 10 SFCs simulated in NEST \cite{4} is shown in the figure, where each color corresponds to propagating activity in a particular SFC.

Partially funded by DIP F1.2, BMBF Grant 01GQ0420 to BCCN Freiburg, and EU Grant 15879 (FACETS).

\cite{1} M. Abeles, Corticonics: Neural Circuits of the Cerebral Cortex (1st ed.), Cambridge University Press, 1991
Count variability in doubly stochastic point processes

Oliver Muthmann¹, Stefano Cardanobile¹, Stefan Rotter¹,²

¹Bernstein Center for Computational Neuroscience (BCCN), Albert-Ludwig University Freiburg, Germany ²Computational Neuroscience, Faculty of Biology, Albert-Ludwig University Freiburg, Germany

Analysis of neuronal spike trains often assumes stationarity. Slow rate transients can be accounted for by estimating the rate profile. However, it is not possible to separate fast changes in rate from the interspike interval fluctuations of the underlying point process. Here, we approach this problem by modeling the process as a doubly stochastic point process and analyzing the behaviour of the Fano factor. The Fano factor FF[N_T] is a measure of the variability of the number of events N_T (e.g. spike counts) in a fixed interval of time.

\[
FF(T) = \frac{\text{Var}[N_T]}{E[N_T]}
\]

It is normalized to one for a Poisson process and will be smaller if the process is more regular and larger if the process is more irregular.

In general, the Fano factor depends on the length of the observation interval and on the firing rate. We study this phenomenon in the case of doubly stochastic processes with a stationary rate process. For the simulation, this can be accomplished by generating a renewal process with a constant rate in operational time and then applying a nonlinear transformation on the time axis to adjust the rate (see Figure).

In doubly stochastic point processes, the spike count variability is increased by the rate variability and related to the autocovariance of the underlying rate.

We simulate such doubly stochastic point processes with different autocovariance functions. For the rate process, we exponentiate a gaussian process to ensure that the rate is always positive. We investigate how nonstationary firing rates affect the dependence of the Fano factor on the length of the observation. The insight gained from these experiments will supply us with information valuable for the analysis of neuronal variability.
Detecting assembly-activity in massively parallel spike trains

Imke Christel Gudrun Reimer¹, Benjamin Staude¹, Stefan Rotter¹

¹Bernstein Center for Computational Neuroscience Freiburg, Albert-Ludwigs-Universität, Hansastrasse 9a, 79104 Freiburg, Germany

The cell assembly hypothesis [1] postulates dynamically interacting groups of neurons as building blocks of cortical information processing. Synchronized spiking across large neuronal groups was later suggested as a potential signature for active assemblies [2], resulting in specific higher-order correlations among assembly members. Recent advances in electrophysiological and optical imaging techniques allow to observe the spiking activity of large populations of neurons simultaneously, thereby increasing the chance to observe active cell assemblies in the working brain. The resulting multi-variate data sets, however, pose a major challenge to available analysis tools [3]. This holds in particular for approaches that transcend pure rate estimates or pairwise analysis, and aim for the analysis of higher-order correlations, as here the number of parameters grows exponentially with the number of recorded neurons [4]. The resulting requirements with respect to the size of the empirical sample limits the applicability of these approaches even for small populations of ~10 neurons.

We have recently presented novel procedures to detect higher-order interactions in massively parallel spike trains that are applicable to reasonable spike train samples of 10-100 seconds duration [5,6]. As a key ingredient, the procedures assume the compound Poisson process (CPP) as a parametric model to underly the superimposed and discretely sampled spiking activity of the neuronal population. This leads to a parsimoniously parametrized univariate estimation problem, circumventing the 'curse of dimensionality' and greatly reducing the necessary sample size. The parametric nature of the approach yields unprecedented sensitivity, such that existing higher-order correlations are detected even in very weakly correlated populations (average correlation coefficient ~0.01) of >100 spike trains, as was revealed by numerical simulations. In this study, we systematically investigate the sensitivity of the novel procedures with respect to violations of the stationary compound Poisson assumption. Specifically, we analyze populations of correlated Gamma-processes with prescribed correlation structure, and populations with time varying rate profiles.

Support by BMBF (grant 01GQ0420 to BCCN Freiburg), DFG (SFB 780) and EU (FACETS, grant 15879) is gratefully acknowledged.

References:

Photo-activation of neuronal tissue using a spatial light modulator (DMD)

Clemens Boucsein\textsuperscript{1}, Florian Rau\textsuperscript{1}, Martin Paul Nawrot\textsuperscript{3,4}, Ad Aertsen\textsuperscript{1,2}

\textsuperscript{1}University of Freiburg, Institute of Biology, Schaeenzlestrasse 1, 79104 Freiburg, Germany  \textsuperscript{2}Bernstein Center for Computational Neuroscience, Albert-Ludwigs-University, Freiburg, Germany  \textsuperscript{3}Neuroinformatics, Institute of Biology - Neurobiology, Freie Universität, Berlin  \textsuperscript{4}Bernstein Center for Computational Neuroscience Berlin, Germany

Photo-activation of excitable cells has proved to be a powerful tool to study connectivity patterns in neuronal slice tissue. Current experimental setups for the release of caged neurotransmitters or activation of transgenic cells with light sensitive ion channels employ a single light beam. In a conventional mapping experiment, an intracellular recording from a single cell in the slice is established, and the light beam is consecutively focused onto different locations within the surrounding tissue, eliciting spikes in the local cells. These spikes can be detected as postsynaptic events in the intracellular recording if a functional connection is present within the tissue, and a connectivity map can be generated from the location of light irradiation and the postsynaptic response measurement.

Single-beam based experimental systems impose certain limitations on spatial mapping experiments: the strictly sequential activation of cells limits the mapping speed, the spatial range of the maps depends on the optical properties of the microscope and objective. Moreover, the UV lasers usually used for photo-activation are expensive.

Here, we present a novel experimental setup for uncaging experiments that overcomes these limitations by employing a digital mirror device (DMD). It is used to project a spatial light pattern into the slice tissue, employing an ordinary arc lamp as light source. Our device can operate independently from the microscope optics and allows for an extremely flexible choice of stimulation parameters for each presynaptic location. In addition, the setup could also be used in dynamic stimulation paradigms and for parallel stimulation of multiple sites. Here, we explain the technical realization of the setup and demonstrate its use for the generation of connectivity maps in acute slices of neocortical tissue. Using spatial light modulators for photo-activation of neuronal tissue will open new possibilities for the investigation of connectivity and dynamic signal integration in neuronal tissue.

Work supported by BMBF grant 01GQ0420 to BCCN Freiburg and EU grant15879 FACETS.