National Network
for Computational Neuroscience

4th Bernstein Symposium

October 8-10, 2008
München

08

Analysis of mechanisms in the initiation and perpetuation of epileptiform activity

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Abstract This project is characterized by joint experimental approaches which contribute to the development of new network models of one of the most common neurological diseases - epilepsy. Basic parameters of synaptic transmission and membrane properties in different neuronal cell types in animal models and in the human will be determined. These biophysical parameters will serve to establish realistic models of computational behavior of neurons and neuronal networks. This in turn will permit to establish models with increasing complexity and to predict both functional and dysfunctional synchronization patterns. These predictions will then be tested experimentally in order to validate the models. In this project, the role of inhibitory interneurons for generation of interictal and ictal epileptic activity will be assessed by three complementary approaches: (1) Electrophysiological measurements in slices from acute animal models of focal epilepsy (Physiology, University of Rostock), both in normal and chronically epileptic tissue, started to determine the role of different types of interneurons at initiation of epilepsy and interictal-ictal transitions. Further we investigate the role of the GABAergic system and of different chloride-cotransporters in functional changes, that observed in the hippocampus by chronic temporal lobe epilepsy. (2) In-vitro electrophysiological investigations of human slices of neocortical focal epilepsies (focal cortical dysplasia, Epilepsy Center, University Hospital Freiburg) aiming at a detailed biophysical description of the main properties of inhibitory synaptic transmission in the epileptogenic tissue. (3) Transfer of experimental data from (1) and (2) for modelling of the behaviour of individual interneuronal subtypes as well as global cortical networks at the Bernstein Center for Computational Neuroscience, Freiburg. Preliminary results suggest that in a model of chronic epilepsy, postsynaptic changes of GABAergic function occur as reversal potentials of GABA-induced currents are shifted to more positive values, which can contribute to hyperexcitability and abnormal synchronisation within the epileptogenic hippocampus. In the further course of the project, a detailed analysis of interneuron-principal neuron interactions will be undertaken.

Funded by the BMBF: 01GQ0751 / 01GQ0752.

Spatial and structural requirements for initiation of epileptiform activity in a model for Temporal Lobe Epilepsy

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Abstract 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 addition, in both human MTLE and the model, morphological alteration of the glia network occur. Changes induced by focal injection of kainic acid into the dorsal hippocampus are most prominent close to the injection site and are less pronounced in more distal areas. Extent and structural reorganization of the glia network, as well as a possible role of glia-neuron interaction in seizure initiation remain to be determined. In this study we recorded hippocampal slices from kainate treated mice on microelectrode arrays (MEA). To reveal possible effects of glia-neuron interaction in the initiation of epileptiform activity we pharmacologically attenuated the actions of glial-derived glutamate. Since epileptic activity could not be induced in disinhibited slices from the most affected regions (1) we used slices distal from the injection site with low histological changes. In these slices coherence of population activity within hippocampal areas was shown to differ from control slices (1). To allow a better understanding of the size of the network necessary to induce epileptiform activity we investigated slices of 400 µm and 600 µm thickness. Under these different experimental conditions we analysed the frequency of epileptiform events as well as coherence of epileptiform activity within hippocampal subregions to improve our understanding of the dynamic processes underlying generation of epileptiform activity. In disinhibited slices of 600 µm thickness from kainate treated mice, induction of epileptiform activity was not always possible. The frequency of epileptiform events was lower than in slices of 400 µm thickness, indicating a more stable balance of excitation and inhibition within the larger network. Preliminary results indicate that attenuation of glia-neuron interaction in disinhibited slices from kainate treated mice did not affect the frequency of epileptiform events but led to an increase in coherence within the hilus. In contrast, in control slices coherence decreased within the granule cell layer as well as within the hilus. This suggests a synchronizing effect of glia-neuron interaction in the healthy brain, whereas in the epileptic brain the functional alterations of the glia network lead to a desynchronization of epileptiform activity.

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

Dynamical response properties of neocortical neuron ensembles: multiplicative versus additive noise

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Abstract To understand the mechanisms of fast information processing in the brain, it is necessary to determine how rapidly populations of neurons can respond to incoming stimuli in a noisy environment. Recently it has been shown experimentally that an ensemble of neocortical neurons can track a time-varying input current in the presence of additive correlated noise very fast - up to frequencies of several hundred Hertz. Modulations in the firing rate of pre-synaptic neuron populations affect, however, not only the mean but also the variance of the synaptic input to postsynaptic cells. It has been argued that such modulations of the noise intensity (multiplicative modulation) can be tracked much faster than modulations of the mean input current (additive modulation). Here, we compare the response characteristics of an ensemble of neocortical neurons for both modulation schemes. We injected sinusoidally modulated noisy currents (additive and multiplicative modulation) into layer V pyramidal neurons of the rat somatosensory cortex and measured the trial- and ensemble-averaged spike responses for a wide range of stimulus frequencies. For both modulation paradigms we observed low-pass behavior. The cutoff frequencies were markedly high - considerably higher than the average firing rates. We demonstrate that modulations in the variance can be tracked significantly faster than modulations in the mean input. Extremely fast stimuli (up to 1kHz) can be reliably tracked, provided the stimulus amplitudes are sufficiently high.

Neural networks and interacting point processes

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Abstract Inhomogeneous Poisson processes are much employed for modelling and analyzing neuronal spike data; the basic parameter of such models is the instantaneous firing rate. Here, we investigate networks of coupled point processes that use the instantaneous firing rates of their neurons as state variables. Generalizing Hawkes (1971a, 1971b) 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) differential equations for mean and variance of the firing rates;
(3) a point process equivalent of the leaky integrate-and-fire neuron.

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Structural plasticity in recurrent cortical networks

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Abstract 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 [1] and synapse formation takes place in a random manner. The interplay between the network dynamics and the correlation dependent evolution of the network structure exhibits an interesting feature: We observe 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.

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Bernstein Focus: Neurotechnology Freiburg • Tübingen – Hybrid Brain

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Abstract Stroke, injuries to the brain, epilepsy, Parkinson's disease and similar neurological syndromes seriously impair the movement and communication capacity of the patients. They reduce the quality of life and limit participation in daily life. In a considerable fraction of cases pharmacological treatment is ineffective or insufficient to alleviate the symptoms. Neurotechnology is a rapidly growing field of research, which, according to our definition, thrives to treat, replace or support physical functions lost through diseases of the nervous system with technical means.

Towards this goal, electrical or chemical signals recorded in the brain are used to control external or implanted devices. Based on the analysis and interpretation of electrical signals, computers could be controlled without keyboard or mouse. Prostheses could be constructed to reinstate voluntary movement based on the activity recorded via brain-machine-interfaces (BMI). Similarly, electrical stimuli or drugs could be delivered not on a regular schedule, but depending on the need determined from brain activity, e.g. to intervene with upcoming epileptic seizures or migraine episodes. Such devices could significantly improve the quality of life of these patients, as do cochlea-implants for the deaf and deep brain stimulators for some patients with Parkinson's disease, devices already in use. Nonetheless, extensive research is needed to improve recording and interpretation of the neuronal signals, to stabilize them for long-term implants, maximize information retrieval and use this to control devices. The electrode-to-tissue interfaces need to be optimized to minimize short- and long-term tissue damage, in particular when used to apply electrical stimuli for defined effects and efficacy. While considerable progress has been reported in recent years, mostly with invasive electrode arrays inserted into the neocortex of monkeys in the US, devices for human usage are still in an early stage of development. Furthermore, ethical and technical aspects demand that less invasive approaches be evaluated and pursued. BMI research in Europe has mostly emphasized these techniques, such as recording with electrode grids placed on top of the cortex (electrocorticogram (ECoG) or on the skull (EEG). The former is less invasive than implanted electrodes, but more specific and yielding information EEG recordings. The approach is promising for its flexibility, not only to control motor control devices, but also to exploit brain activity in other regions, which subject can learn to control to some extent.

The "Bernstein Focus Neurotechnology" (BFNT-Freiburg/Tuebingen, briefly BFNTFT) with the title "Hybrid Brain" is an initiative of 32 scientists of the universities of Freiburg and Tuebingen, Germany, their neurological and neurosurgical university clinics, the Max-Planck Institute for Biological Cybernetics Tuebingen, the Natural and Medical Sciences Institute Reutlingen (NMI). In addition, several industrial partners contribute to the BFNT-FT, namely Multi Channel Systems, Inomed and the Honda Research Institute. The BFNT-FT thus ties together numerous new and established projects to form the biggest cluster for neurotechnological research in at least Germany. Their aim is fundamental neurotechnological research, the development of new techniques based on these and the clinical development of neurotechnological devices. These are intended primarily to establish movement and communication capabilities in patients. These new tools could one day assist the therapy of severely paralyzed patients, e.g. suffering from amyotrophic lateral sclerosis (ALS), but also those with intractable epilepsy or drug-resistant migraine.

Decomposition of neuronal assembly activity via empirical de-Poissonization

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Abstract 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], and recent advances in multi-electrode recording and optical imaging techniques provide promising data sets to rigorously test the assembly hypothesis [3]. However, currently available analysis techniques aimed to detect synchronously spiking groups in massively parallel spike train recordings face severe limitations. On the one hand, estimated pairwise interactions [4] alone do not allow to infer on large synchronized neuronal pools, and are insensitive for sparse synchronous events [5]. Approaches that transcend pairwise interactions by estimating higher-order correlations, on the other hand, require vast sample sizes, as the parameter space grows exponentially with the number of recorded neurons [6]. Here, we present a novel analysis technique for massively parallel spike train data that transcends the estimation of pairwise interactions, yet avoids the need for extensive sample sizes. Instead of estimating interactions among individual neuron-pairs, triplets, quadruplets, etc., we base our inference on the population spike counts, i.e. the spike counts extracted from the superimposed spiking activity of all recorded neurons. This leads to a parsimoniously parametrized univariate estimation problem, circumventing the curse of dimensionality and greatly reducing the demands with respect to the size of empirical samples. Specifically, we assume correlated Poisson processes as a simple descriptive parametrization of higher-order effects, where interaction in a group of neurons is modeled by inserting precisely synchronized spikes into the corresponding spike trains [7]. Our inference procedure is based on the observation that the characteristic function of the population spike counts of correlated Poisson processes is essentially a Fourier series whose coefficients are the interaction parameters of the model. Corresponding estimates are thus defined via Fourier-inversion of the empirical characteristic function. Expressions for their asymptotic (co)-variances are then used to construct combined hypothesis tests, e.g., whether or not a data sets exhibits interactions above a certain order. The method is illustrated by extensive Monte-Carlo simulations, showing its surprising sensitivity for higher-order interactions present in the data, even in situations where average pairwise correlation coefficients c are very small (in the range of $c \tilde{0} .01$, compare cf. [6]).

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Acknowledgments: Supported by the German Federal Ministry of Education and Research (BMBF grant 01GQ0420), and DFG SFB 780

Validation of seizure prediction performances in epilepsy

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Abstract In recent years, several methods for the prediction of epileptic seizures have been proposed, which are based on recordings of surface and invasive electroencephalograms (EEG). By application of linear or nonlinear measures, pre-seizure changes have been reported. Of crucial importance is the question whether observed prediction performances are statistically significant, i.e. better than random. In this study, we compare analytical and numerical approaches for statistical validation of prediction performances. We apply and evaluate the bivariate mean phase coherence (MPC) as a measure for the interdependence between two channels of the EEG. Data was recorded intracranially for four patients, lasting in total 31 days and including on average 18 seizures per patient. The predictive performance of the MPC was assessed by evaluating the observed sensitivity for a fixed maximum false prediction rate depending on the duration of the prediction horizons. These sensitivities were then compared to critical sensitivity values of both an analytical random predictor and so-called 'seizure times surrogates', which are based on Monte Carlo simulations of randomized seizure onset times. For all patients, the critical values of the numerical validation method exceed the critical values of the analytical random predictor. The observed sensitivities are higher than the critical value of the analytical random predictor for 3 patients, while only for one patient they are higher than the critical value of the analytical method. The distribution of the randomized 'surrogate' onset times reveals an explanation for this discrepancy: the limited number of seizures produces a biased estimate of the critical value. Therefore, statistical tests using the analytical random predictor have a higher power to correctly identify prediction performances as significant, while keeping to the correct coverage.

Acknowledgments This work was supported by the German Federal Ministry of Education and Research (BMBF grant 01GQ0420), the European Union (Grant 211713) and the German Science Foundation (Ti 315/4-2; Sonderforschungsbereich-TR3; He1949/1-1).

Spike Sorting and Detection with Optimal Multichannel Filters

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Abstract For purpose of studying information transmission within the nervous system, the extracellular recording of a neural signal is very useful, since it enables simultaneous monitoring of activities of several nearby neurons. Usually the recorded data includes action potentials from multiple cells which are physically near the electrode tip and, thus, the data should be classified into spike trains from each individual cell (spike sorting) for further analysis. Efficient spike-sorting methods should ideally allow the real time detection and classification of spikes, good sorting performance in the presence of overlaps and low signal-to-noise ratio and minimal human interaction or supervision. Linear filtering with optimal multi channel filters seems to be a promising approach [1,2]. For every recorded neuron - and its specific waveform - an optimal multichannel filter is constructed. This filter should optimally have a high output energy for the correct waveform and zero output energy for noise and waveforms of other neurons. The task of spike detection is reduced to a simple detection of high peaks in the filter output. Since every filter detects only one putative neuron, spike detection and spike clustering are done in the same step. Overlapping spikes can be disentangled, because both the filter operation and the superposition of spikes are linear. In contrast to [1,2] we use standard spike sorting techniques to estimate the templates autonomously from a 10 to 30 second piece of recorded data. A set of optimal discriminating multichannel filters is calculated from the templates. Thereafter the algorithm can run in real-time. We evaluate the method with simulated and experimental data. We compare the results to existing spike sorting methods including thresholding combined with principal component analysis. We conclude that our algorithm is indeed able to successfully resolve overlapping spikes and outperforms the other methods under realistic signal to noise ratios.

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Acknowledgments: We thank Sven Daehne for his help. This work was supported by BMBF grants 01GQ0743 and 01GQ0410.

FIND - Finding Information in Neuronal Data: An open source framework for the analysis of neuronal activity data

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Abstract The complexity of neurophysiology data has increased tremendously over the last years, especially due to the widespread application of multi-channel recording techniques. With increasing computing power, the current limitation for sophisticated data analysis is the effort and time it takes scientists to translate their ideas into working code. Advanced analysis methods are complex and often lack reproducibility on the basis of published descriptions. To overcome these limitations we developed FIND (http://find.bccn.uni-freiburg.de) as a platform-independent, open source framework for the analysis of neuronal activity data based on MATLAB (Mathworks). FIND provides unified data import from various proprietary formats, simplifying standardized interfacing with tools for analysis, simulation and visualization (Meier, R. et al. 2008a). The toolbox FIND covers a steadily increasing number of well documented tools. Analysis tools address various types of neural activity data, including time series of spike events, analog data (intra-cellular recordings and population activity data) and imaging data. Additionally, the toolbox provides solutions for the simulation of multi-variate stochastic point processes to model multi-channel spiking activity. Recently, support for the HDF5 Data Format, Clean Data (Musial et al. 2002), and the ability to calculate nonlinear interdependences in a massively parallel fashion (Meier et al. 2008b) using the Message Passing Interface (MPI) were added to the toolbox. We will outline design and functionality of the toolbox and show a usage example from a study in which FIND was used on multi electrode array data to analyse the network activity dynamics causing the transition from normal brain activity into hypersynchronous epileptiform spiking in mesial temporal lobe epilepsy (Meier et al. 2008b). Project funded by BMBF grant 01GQ0420 to BCCN Freiburg and EU grant 15879-FACETS.

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Burst Clustering and Prediction in Neuronal Cultures

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Abstract Recordings of spontaneous activity from neuronal cultures have shown that the activity is composed of irregular network-wide bursts of spikes. These networks display little or no spiking activity most of the time (that is, between bursts) and extremely high spiking activity during the bursts. Based on the similarity of their spatio-temporal activity patterns, bursts in a culture can be clustered into several clusters. In the current work, we show that burst types do not appear in random order but they rather occur in a predictable manner. We successfully trained Echo State Networks of leaky-integrator neurons to predict the type of a network burst, before it starts. We argue that high prediction accuracy indicates that the mode of activity in neuronal cultures is determined by stimulus and activity history.

Relation between granule cell neurogenesis and the spread of epileptiform activity in the epileptic hippocampus

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Abstract Hippocampal sclerosis in mesial Temporal Lobe Epilepsy (TLE) is associated with pronounced granule cell dispersion (GCD) which is not caused by increased neurogenesis but by a displacement of adult neurons in patients and in the intrahippocampal kainate model in mice (Heinrich et al., JNS 2006; Fahrner et al., Exp. Neurol. 2007). In contrast, increased neurogenesis has been proposed to underlie the network changes in TLE (Scharfman et al., JNS 2000). Here, we want to clarify whether excessive excitatory activity during seizures has a depressing or stimulating effect on neurogenesis, separated from the effects of kainate. We recorded epileptiform activity with implanted electrodes in the granule cell layer at several positions along the hippocampal septo-temporal axis of intrahippocampally kainate-injected mice. In parallel, we marked proliferating cells with bromodeoxyuridin (BrdU) and newly generated neurons with doublecortin (DCX) stainings to characterize neurogenesis along this axis. We show that epileptic spikes are not limited to the area of strongest sclerosis surrounding the injection site but spread along a large extent of the septo-temporal axis of the hippocampus from the first days after injection until at least four weeks later. Yet, the loss of neurogenesis, as well as GCD in the dentate gyrus remains limited to a focal area surrounding the kainate injection site. At distance and in the contralateral hippocampus, the number of DCX-positive neurons in the subgranular zone is increased compared to controls, indicating increased neurogenesis. Epileptiform activity does not disturb, but most likely stimulate neurogenesis which in turn may contribute to the development of epileptic seizures.

Time-driven simulation with fully asynchronous pulse coupling

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Abstract Artificial synchrony can be introduced by discrete time simulation of neuronal networks, since they typically constrain spike times to a grid determined by the computational step size [1]. Event-driven algorithms avoid this problem but are computationally demanding, both with respect to calculating future spike times and to event management, particularly for large network sizes. To address this problem, Morrison et al. [2] developed a general method of handling off-grid spiking in combination with exact subthreshold integration in globally time-driven simulations [3,4] using interpolation to approximate threshold crossings. In the framework of event-driven simulations, Brette [4] presented an elegant method of calculating spike times of integrate-and-fire neurons with exponentially decaying currents. The prediction of the next threshold crossing of the membrane potential is reformulated into a root finding problem of the equivalent polynomial. Here, we show that this scheme can also be implemented in the time-driven environment of NEST [4]. Additionally, we extended the model of Morrison et al. [2] by replacing the interpolation of threshold crossings with the computationally more expensive, but numerically more exact, Newton-Raphson technique. We compare the accuracy of the three approaches in single-neuron simulations and the efficiency in a balanced random network of 12,000 neurons [6]. For small input and output rates the polynomial method is more efficient than the interpolated one whereas for high input or output rates the interpolated method is more efficient than the polynomial one. The direct numerical method based on Newton-Raphson root finding outperforms both the interpolation and the polynomial approach at all input/output rates.

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

Effects of Levetiracetam on granule cells and fast spiking basket cells in the dentate gyrus

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Abstract Levetiracetam (LEV) is one of the most important antiepileptic drugs commonly used in clinical practice. Although binding studies have shown that LEV interacts with the synaptic vesicle proteine 2A (SV2A), it's mechanism of action has largely remained unknown. Furthermore, experimental data have also shown small effects on voltage-gated ion channels. Here we used mainly transverse hippocampal slices of juvenile rats (P17-P22) in order to study the electrophysiological effects of the active enantiomer of LEV (100 μM) on granule cells (GCs) and fast spiking basket cells (BCs) in the dentate gyrus (DG)at room temperature. Current clamp recordings in both cell types show no effect on resting membrane conductance, de- and re-polarization kinetics of action potential waveforms, afterde- or afterhyper-polarization potentials, input-output curves, constructed by 1 second lasting constant current injections (-0,1 to 1-1,2 nA) or bursting patterns induced by short, depolarizing current pulses in both GCs and BCs. These data argue against a significant physiological effect of LEV through voltage-gated channels. However, preliminary data show a reduction of spontaneous IPSC amplitudes recorded in GCs. Importantly, this effect was reversible, and its time course was compatible with the onset of the effect of LEV seen upon intravenously applied drug in epileptic patients. Thus, fine-tuning of GABAergic inhibitory transmission may be the main effect of LEV. In the next step, we will now repeat these experiments in human tissue and thereafter integrate the data in a simple neuronal network in order to perform a computational analysis of the effects of LEV on ictogenesis.

Systems Neurophysiology in the Age of Global Neuroinformatics

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Abstract The global scale of neuroinformatics offers unprecedented opportunities for scientific collaborations between and among experimental and theoretical neuroscientists. To fully harvest these possibilities, a set of coordinated activities is required that will improve three key ingredients of neuroscientific research: data access, data storage, and data analysis, together with supporting activities for teaching and training. Focusing on the development of tools aiming at neurophysiological data, the German Neuroinformatics Node (G-Node) aims at addressing these aspects as part of the International Neuroinformatics Coordination Facility (INCF). Based on its technical and scientific scope, the Node could play a substantial role for cellular and systems neurophysiology as well as for the neuroscience community at large.

Effects of network composition against network stability and temporal resolution in recurrent neural networks: identifying criteria for network bursting

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Abstract Disassociated cortical cultures grown on multi-electrode arrays have been established as a useful biological model in the analysis of network dynamics. Their activity has been demonstrated to be consistent regardless of species and origin of neuron while they have been shown to exhibit induced synaptic changes, suggesting that they are a valid experimental paradigm for studying generic neural dynamics and learning. An interesting feature displayed by cortical networks are instances when a significant number of neurons are synchronized in their firing, a behaviour termed 'bursting'. Prevalent in disassociated cultures, the purpose of bursting within networks has not been conclusively established; however, the presence of structure within bursts suggests that they may be related to network formation. Several approaches have been proposed to limit their impact on the behaviour of the network, with various degrees of success.

Though the effects of varying attributes such as neuronal density as well as artificially stimulating the network have been investigated biologically, understanding and prediction of network dynamics remains limited. Practically, this is due to the high dimensionality of the data in addition to substantial undersampling, making it impossible to reconstruct the network and hence also its functional connectivity. Here, a type of recurrent neural network model termed Echo State Networks was proposed as a mathematical model of the disassociated cultures. Different architectural configurations and parameters, such the degree of memory retention by individual units, were evaluated in order to identify potential realizations, most specifically with respect to temporal resolution and stability of the network in addition to correlation against their biological homologue. Of specific interest were configurations that displayed quasi-stability where the network responded to stimulations with alternating periods of sustained ongoing activity and quiescent behaviour, which could potentially be considered analogous to bursting as observed in disassociated cultures. This hypothesis was tested by using the models to formulate criteria for generating bursting responses before examining methods for modifying the network response to configurations of more stable behaviour. Finally, the validity of the interpretation was then evaluated by comparing these conclusions against the known properties of biological neuronal networks, such as burst duration and interburst intervals.

Local connectivity and embedding of individual neurons in cultured neuronal networks

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Abstract The integration of individual neurons into a larger network is a key feature for understanding principles of neuronal computation. In this work, we investigated these principles in generic networks of dissociated cortical cells of neonatal mice. In culture, such cells form simple neuronal networks with random-like connection probability that can be manipulated experimentally and maintained and studied over weeks in vitro. With network maturation, our cultures display characteristic bursting activity that is highly synchronized and comprises spatiotemporal subpatterns. We recorded activity from dense networks of 1,000-2,000 cells per square mm simultaneously with 60-site microelectrode arrays (MEA) and double patch-clamp electrodes. Based on the intracellular patch-clamp recordings, we determined the pairwise neuron-to-neuron connection probability in a range of up to 250 μm and identified excitatory and inhibitory connections as well as single or reciprocal connections. We found a high degree of neuron-to-neuron connections; of all recorded neuron pairs 74% were connected, 68% of these had excitatory and 6% inhibitory connections, 19% of all pairs had reciprocal connections. The connection probability thereby decreased with greater neuron-to-neuron distance. Currently, we investigate the functional embedding of individual neurons into the networks global bursting activity. Based on spike-triggered averaging relative to the intracellularly recorded spikes, we found timing differences in the peaks of MEA channel spike histograms. Firing rates of channels that displayed early network burst participation peaked before, whereas most of the other channels peaked after the intracellular reference spikes. These findings might indicate that certain spots in the network have a higher impact on network activity and burst initiation. Furthermore, channels that were neighboring the intracellular recording site were closely locked in time to the intracellularly recorded reference spikes, supporting our findings of a high degree of local connectivity. In summary, our work adds to the understanding of the horizon of individual neurons and how they structurally and functionally integrate within a larger network.

Supported by the BMBF (01GQ0420) and the EU (NEURO, 012788).

Performance and control error-related neuronal signals in human ECoG recordings during a continuous task

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Abstract From previous studies it is known that error-related neuronal signals can be found in human EEG and fMRI. These studies investigated error-related signals using trial-based paradigms with a binary outcome, correct or false. Therefore, the reported error signals provide the information whether the subject achieved the goal of trial correctly or not. While these signals can be discriminated very reliably, the information they provide is binary and trial-based, and therefore limited. Thus, it is not clear if during a continuous BMI control task, e.g. continuous cursor control, such error-related activity can also be detected. In addition it is not clear if such responses are similar to the trial based error responses and if one can differentiate the error-related signals when related to different contexts. In the task we designed two kinds of errors were present: one related to the subject's performance, and the second one related to the subject's control.

We recorded ECoG and EEG signals from two epilepsy patients playing a video game with two different kinds of sessions. (I) In movement sessions subjects played a simple game in which they controlled a spaceship with a joystick in the horizontal dimension (left-right). The task was to evade the blocks dropping from the top of the screen. The game was challenging enough so that the spaceship from time to time collided with a block (performance error). In addition the spaceship would occasionally move in the opposite direction to the joystick movement (control error). As a measure of performance, points were awarded for moving the spaceship. (II) In replay sessions subjects watched a replay of one of their earlier movement sessions. Control errors were noticeable only by both controlling the spaceship and simultaneously looking at the screen.

We found separate ECoG electrodes and ECoG signal components that coded for control errors only, for performance errors only and for both control and performance errors. These electrodes were located in different brain regions including the motor cortex. The majority of the signal components related to errors were in the high gamma frequency range (40Hz - 128Hz). The observed neuronal error-related signals could not be attributed to the movement of the subjects as channels with error-related signals exhibited no or only very weak tuning for movements. Watching the spaceship collisions during the visual control sessions produced similar neuronal performance error signals but no neuronal control error signals.

Results suggest that neuronal correlates of performance error and control error can be discriminated from the baseline activity and from one another during a continuous task. To fully verify this statement we will investigate in future work whether detection of these signals from the continuous ECoG recording is possible. When successful, such error detection from brain signals could be used to facilitate adaptation of the BMI decoder and improve the performance of BMI applications.

Acknowledgements: Work supported by BMBF 01GQ0420 to BCCN Freiburg and BMBF GoBio grant 0313891.

Serial correlation in neural spike trains: experimental evidence, point process modelling and single neuron variability

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Abstract The activity of spiking neurons is frequently described by renewal point process models that assume the statistical independence and identical distribution of the intervals between action potentials. However, the assumption of independent intervals must be questioned for many different types of neurons. We review experimental studies that reported the feature of a negative serial correlation of neighbouring intervals. This has been observed in peripheral sensory neurons, and more recently in central neurons, notably in the mammalian cortex [1], and in the insect mushroom body [2]. To model serial interval correlations of arbitrary lags we suggest a family of autoregressive point processes. Its marginal interval distribution is described by the generalized gamma model which includes as special cases the log-normal and the gamma distribution, both have been widely used to characterize regular spiking neurons. We argue that the feature of a negative serial correlation is common to the large class of spike frequency adapting neurons [3] and that it might have been largely overlooked in extracellular single unit recordings, possibly due to spike sorting errors. In numeric simulations of our model we show that a realistic number of between 5% and 15% errors (e.g. [4]) can readily extinguish the significance of the serial correlation. We investigated how serial correlation affects the variance of the neural spike count. The experimentally confirmed negative correlation strongly reduces single neuron variability in our point process model [2] as well as in computational models [3]. This effect is strongest for large observation intervals and, by theoretic argument [5], diminishes for short intervals. This prediction is confirmed in the spontaneous activity of cortical neurons where the Fano factor is decreased by up to 30% [1]. Finally, we examined the effect of serial interval correlation in individual neurons on the significance of coincident spikes in pairs of neurons under stationary rate conditions. We report that a negative serial correlation in the experimentally reported range always reduces the number of chance coincidences [6]. Taken together, we reach the following conclusion: The negative serial correlation - and more generally the SFA mechanism - facilitates the reliable transmission of a rate code as well as the detectability of spike coincidences in postsynaptic neurons. We will test this hypothesis in further experimental and model studies.

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Keywords: Renewal process, Fano factor, Markov process, neuronal variability, spike sorting, spike frequency adaptation

Connectivity statistics and their implications on activity dynamics in cortical cell cultures

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Abstract In the absence of complex architecture, central parameters of connectivity in neuronal networks are the size of dendrites and axons in conjunction with the spatial distribution of neurons. The homeostatic regulation of neurite fields is crucial for the maintenance of stability in the activity dynamics. We analyze these fundamental properties of neuronal networks in dissociated cortical cell cultures grown on micro-electrode arrays (MEAs). These generic random networks display a self-regulated maturation process that is characterized by neurite outgrowth, synapse over-expression and pruning similar to the critical period in the developing cortex. Within this period of network formation we manipulated neuronal connectivity by pharmacological intervention with structural differentiation processes. Previous studies showed that pharmacological inhibition of protein kinase C (PKC) activity enhances neurite outgrowth [1] and impairs cell migration [2] and network pruning [3] in early neural development. Following these findings, we chronically treated cortical cell cultures with PKC inhibitors and characterized them morphologically and functionally. To capture connectivity statistics we applied a modified Scholl analysis [4] to describe the radial dendritic field density of neurons embedded into the network. The method involves the grouping of neurons into classes of defined local neuron density to account for local differences in the overlap of dendritic fields of spatially non-uniformly distributed neurons. Dendrite profiles across conditions were subsequently compared based on these classes. Blocking PKC activity significantly enhanced radial arborization by +15% at intermediate (DIV14) and about +50% at later stages (DIV40) of development. The evolution of dendritic fields furthermore revealed an ongoing extension in cultures exposed to PKC inhibitors in contrast to an incipient reduction found under control conditions. This suggests an impaired downregulation of neurite outgrowth and pruning with the ending of the initial wiring phase. To further confirm these findings, dendrites of neurons in sparse cultures with negligible dendritic field overlap were traced manually and likewise showed significantly increased arborization and enhanced segment extension. By correlating local and global neuron density [5] we moreover found reduced clustering in the networks developing under inhibited PKC activity, indicating impaired cell migration. Electrophysiological recordings were performed during the development to assess functional consequences of the altered network differentiation. In cultures exposed to PKC inhibitors we had a higher yield of electrodes displaying neuronal activity, which accounts for a higher probability of finding neurons in the vicinity of an electrode in absence of neuronal clustering. The number of active electrodes furthermore remained stable in the course of development in contrast to a decrease found under control conditions, which provides electrophysiological evidence for the non-initiation of pruning processes. The activity stayed organised in network-wide bursting events that characteristically emerge in neuronal cell cultures. Bursts however tended to be more compact, occurred at a higher frequency and were stronger synchronized over the MEA. This suggests a faster propagation of activity through the networks with enhanced inter-neuronal connectivity. In summary we show that inhibition of PKC activity in developing cortical cell cultures increases connectivity and relate the structural changes to functional differences in the activity dynamics.

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

Movement-Related ECoG Signals in the Human Brain

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Abstract It is a well established fact that some properties of body movements can be decoded from neuronal signals. While most of these results have been obtained in animal experiments, using highly invasive recording techniques, the recent years have seen some studies in humans, often using non- or less-invasive techniques. Here we will present some recent findings from studies using electrocorticograms (ECoG) - intracranial potentials measured on the cortical surface - from epilepsy patients, undergoing presurgical evaluation. We show that we can reliably distinguish between two grasp-types in natural movements, and to some extent predict continuous hand-arm movement trajectories from the ECoG. This might lead to the development of brain-machine interfaces based on cortical surface potentials.

Neural mechanisms improving spike timing reliability under noisy and unreliable conditions.

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Abstract In this contribution we discuss a set of computational experiments which demonstrate that spiking neurons are able to learn and precisely reproduce sequences of spikes even for the highly noisy and unreliable input signals. As a result of this study we identify some cellular mechanisms which can be potentially exploited by the biological neurons to deal with noise and to produce accurate and reliable responses.

Method: A single Leaky-Integrate-and-Fire neuron with multiple synaptic inputs (n=100) was repeatedly stimulated with a set of Poissonian stimuli. The neuron was trained to respond with some predefined sequences of spikes to the particular sets of input signals. The training was performed according to ReSuMe - a supervised learning algorithm operating on the precise timing of spikes [1]. In the particular experiments different sources of noise were simulated by adding a background or synaptic noise to the neuron or by 'jittering' the particular spikes in the input and target signals. In each experiment the sequences of spikes generated by the neuron were recorded. The correlation of the recorded patterns with the target sequences, as well as the variability of the generated spikes over the particular trials were calculated.

Results and conclusions: Our results demonstrate accurate and reliable spike timing in response to the stimuli used during training. At the same time it is observed that the neuron spikes highly unreliably for other stimuli (not used during training). We note, however, that the necessary condition in our experiments for the neuron's reliability was that the training was performed already in the presence of noise. In the case of the noise-free training, the reliability of neuron in the noisy testing phase was reduced dramatically. Our findings are consistent with the recent experimental results, which indicate that the same neuron may have very accurate spike timing in response to one stimulus, and unreliable spike timing for another [2]. This observation suggests also that the results of at least some *in vivo* and *in vitro* experiments 'proving' the unreliability of spike timing of the biological neurons should be re-investigated, since they could be erroneously affected by using the inappropriate stimuli. As a result of our study we identified some intracellular mechanisms by which the neurons can deal with noise and unreliability. These are:

(1) significant increase of excitation shortly before the target firing times, and the reduction of excitation at all other times;

(2) reduced significance of the individual EPSPs on the spike generation in favour of the groups of EPSPs (it is observed that many more EPSPs contribute to the single spike generation in the noisy case, as compared to the noise-free, reliable case).

The identified mechanisms seem to be not necessary attributed to the particular properties of the learning method used in our experiment and the same effects are likely to arise while using the learning rules possibly utilized in the central nervous system. Hence, they are proposed as potential candidates for the mechanisms employed by the biological neurons to deal with noise.

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Improved response reproducibility in neuronal networks in vitro by means of phase-coupled electrical stimulation and stimulation at pre-selected sites

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Abstract Information processing and storage are main functions of neuronal systems. Dynamical, network-wide interactions are underlying those functions and it is unclear by which mechanisms they are governed. The goal of our research is to understand how neuronal networks respond to incoming stimuli, which interactions arise and how this enables the processing and storage of information. We aim for predictive input/output relationships to improve response reproducibility for a thorough examination of their information processing capabilities. Cortical cell cultures grown on microelectrode arrays (MEAs) provide a viable neuronal network model that is accessible for simultaneous recording and stimulation via 60 electrodes. The network's activity undergoes a transition from single spikes uncorrelated across recording sites to synchronous network-wide bursts and repeated, stereotypical burst patterns, called Superbursts, at later stages. Spontaneous bursting activity modulated neuronal responses in several ways: Response length increased with decreasing time since last burst before stimulation and vice versa. Stimulation during Superbursts yielded the longest responses with high reliability, whereas stimulation after Superbursts resulted in markedly decreased response reliability. The delay of the first spike in the long-term response component ($\geq$ 50-75 ms post stimulus) increased with increasing level of activity prior to stimulation. Interestingly, the pre-stimulus activity on a timescale of seconds determined over the response delay on a millisecond timescale. This suggests a strong dependency between state of the network at the moment of stimulation and induced response. We show that repeated stimulation during a defined network state ('phase-coupled') improves response reproducibility. We obtained decreased response length variability for phase-coupled stimulation compared to random stimulation during different network states. Furthermore, stimulation at network sites that initiated network bursts more often than others reversibly suppressed Superbursts and hence eliminated a big source of response variability.

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

MEG-BCI: Adaptive online-decoding of movement direction and application in rehabilitation

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Abstract Decoding brain states which can be reliably used for Brain-Computer-Interfaces (BCI's) is one of the most challenging topics in neuroscientific research. A recent study showed that movement direction in a centre-out task can be inferred by non-invasive recordings. It was also shown that magnetoencephalography (MEG) compared to electroencephalography led to a higher decoding accuracy for movement direction. These findings raise hope to overcome frequent limitations of BCI's which use predefined classification schemes. In our approach we seek to construct an online-adaptive MEG-BCI which decodes hand movement direction in a centre-out task. Low-pass filtered MEG signal of 52 channels over sensorimotor areas were used to predict the movement direction. The classification parameters were adapted on a single-trial basis in order to compensate for non-stationarities during recordings. Furthermore, we provided subjects with visual feedback of the current decoding result to include subject-specific learning effects. The preliminary results showed that we were able to reach a mean decoding accuracy of 72%. Moreover, the combination of machine- and feedback-learning increased decoding performance compared to earlier results based on a non-adaptive approach. These promising findings indicate that a non-invasive online-BCI for hand movements can be achieved without extensive subject training or demanding computational processes. Future applications therefore might include pre-surgery testing of ECoG-patients or rehabilitation after stroke. This is supported by recent results by our group where a MEG-based BCI has been applied to train motor functions in chronic stroke patients suffering from subcortical stroke in the pyramidal tract. We were able to show that all patients could increase motor-related brain activity in motor and pre-motor cortex of the lesioned hemisphere. Furthermore, discriminability of brain activities related to opening and closing the hand was increased over training sessions and led to clinically relevant increase of motor function in one subject.

Guided adhesion and outgrowth of a constrained network on tailormade surfaces

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Abstract Planar micro-electrode arrays have now been used for some time to investigate the activity dynamics and response of neural networks to electrical or chemical stimuli. Constructing defined connectivity statistics under cell culture conditions that allow the maturation of the neuronal networks for a long period has not been achieved so far. Such networks would be useful to understand the influence of the composition, connectivity statistics, and plasticity in a neuronal network on the dynamics of electrical activity. Successful reports of constrained neuronal networks have used serum free medium to minimize the masking of the pattern by proteins. Serum free medium, however, impairs glia develop-ment, which has shown to have significant effects on network maturation and long-term vitality of the neurons, whereas serum containing medium may mask the patterned molecular layers (e.g. stamped proteins), which leads to a loss of constrained neuronal networks after several hours. The key issue is the control of the spatial and long-term stability of neuronal cell adhesion and neurite outgrowth by physicochemical surface modifications under cell culture conditions that allow long-term maintenance of these networks on a micro-scale. This can be achieved by using thin polymer coatings, whose cell adhesion property is not affected by serum-proteins. We report a simple way to tailor the surface-chemistry using a photochemical approach, leading to the covalent attachment of polymer layers to glass and MEA surfaces. We examined the biocompatibility of polymer layers with different properties, such as hydrophilicity and charge, and their potential to promote or inhibit neuronal cell adhesion. Finally, patterns with cell attractive domains were obtained using pin printing or μ-contact printing (μ-CP) of polymer solutions. These patterns were able to guide neuronal cells in a constrained network and were stable over several weeks in a serum containing cell culture medium.

Published by:
Bernstein Center for Computational Neurosciene Munich
www.bccn-munich.de

Editor: Dr. Dagmar Bergmann-Erb
Dr. Miruna Szabo
Cover: Jana Erb

Funded by

Federal Ministry
of Education
and Research