“Imaging neural activity in sensory systems: experimental and modeling approach”

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From perception to action: the role of ongoing and evoked activity

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We have studied the spatio-temporal organization of ongoing and evoked coherent activity in neuronal assemblies and the way it affects the actual behavior. In my talk I will bridge the gap between the recordings of single neurons and the recordings of large populations of neurons: from intracellular recording to LFP, VSD, EEG & fMRI; from sensory to motor processing; from anesthetized cat to alert human.

We found that ongoing activity encompasses a set of dynamically switching cortical states, including the orientation pinwheel structure. The neuron is most likely to fire when this pattern (cortical state) emerges in the area surrounding the neuron. Following visual stimulation, there is a strong decrease in the correlation between the evoked cell and the surrounding neuronal population. So while in the absence of a stimulus the cortical population works together as a highly coordinated group, in the presence of a stimulus each cell tends to go its own way and follow the dictates of its receptive field properties. Furthermore, the ongoing activity affects the behavioral response of the monkeys, indicating that the brain does not 'average out' the variability found in cortical evoked activity. Rather, this variability has a direct impact on the manifest behavior.

What does multi electrode array data reveal about cortical microcircuits?

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The primary somatosensory (barrel) cortex of rodents is an ideal model system to study how synaptic connections bind together functional modules and how intra- and transcolumnar microcircuits are laid out to segregate and also integrate information. Apart from these fundamental aspects the well described organization of the barrel cortex allows for investigating the consequences of distorted brain development or neuronal modulators on structure and function of cortical networks. Extracellular multi-electrode-array (MEA) recordings of stimulus induced local field potentials (LFPs) in combination with whole cell patch clamp in acute brain slice preparations offer the opportunity to investigate the dynamics of cortical network function of the barrel cortex both on population and on single cell level.

Stimulus induced LFPs are a reflection of firing and synaptic activity of neural populations. The complexity of cortical networks makes their correct interpretation very demanding. As a result, the observed spatiotemporal LFP profiles have been used primarily as signatures of the underlying circuitry, to pinpoint changes due to genetic or pharmacological modulation. To arrive at a deeper understanding about the mechanisms underlying the LFPs, it is essential to link the data with simultaneously observed single neuron activity, and to add in profound prior knowledge of the underlying structural connectivity. The final validation step is to build a generative model which reproduces the measurements within all the known biophysical constraints.

In this talk we present experimental data from in vitro brain slice preparations of juvenile rat barrel cortex and highlight the potential problems and opportunities of MEA recordings in such model systems. We will hypothesize what the data reveals about the spatial and temporal properties of intracortical signal propagation and plasticity, based on combined MEA and patch-clamp recordings and detailed knowledge on layer specific afferent and efferent structural connectivity. We demonstrate how we perform high-throughput, automated data analysis, and how indispensable this has become in electrophysiology research. We show what the signatures of the stimulus-evoked LFPs are, both in the original and reconstructed Current Source Density (CSD) domain.

Extractin information from multielectrode data by means of biophysical modeling

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While extracellular electrical recordings have been the work horse in electrophysiology, the interpretation of such recordings is not trivial. The recorded extracellular potentials in general stem from a complicated sum of contributions from all transmembrane currents of the neurons in the vicinity of the electrode contact. The duration of spikes, the extracellular signatures of neuronal action potentials, is so short that the high-frequency part of the recorded signal, the *multi-unit activity (MUA),* often can be sorted into spiking contributions from the individual neurons surrounding the electrode. However, no such simplifying feature aids us in the interpretation of the low-frequency part, the *local field potential (LFP)*. To take a full advantage of the new generation of silicon-based multielectrodes recording from tens or hundreds of positions simultaneously, we thus need to develop new data analysis methods.

From volume conduction theory it follows that the extracellular potentials can be calculated by adding contributions from the transmembrane currents around the electrode contact [1], and with morphologically reconstructed neurons a straightforward computational scheme can be used to calculate the extracellular potential from a single neuron at any point in space [2-4]. Due to the linearity of the electrostatic equations, the scheme directly generalizes to extracellular potentials generated by populations of neurons [5]. In this two-step computational scheme, morphologically reconstructed neurons are first simulated with compartmental modeling using a simulation program such as NEURON to provide transmembrane currents, and next the extracellular potentials are calculated based on these [2-5].

In the talk I will briefly discuss some results from our group where this scheme has been used to illuminate (A) frequency filtering and size variation of extracellular signatures of action potentials [3], (B) the frequency spectra and spatial range of the local field potential (LFP) [4], and (C) the relationship between the LFP and multi-unit activity (MUA) with the underlying neural activity in an activated columnar population of pyramidal neurons [5]. Next, examples of developments aided by this scheme of new analysis methods for data from multielectrode recordings such as iCSD [6], laminar population analysis (LPA) [7], and population firing-rate model extraction [8], will be briefly presented. Finally, example results from a project involving generation of test data to stimulate and aid the development and testing of automated spike-sorting algorithms for tetrode data, will be shown and discussed.

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The eye as a window to the brain

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For non-invasive analysis of physiological and pathophysiological processes in the brain sophisticated methods are required as the skull is an obvious obstacle for imaging. Methods like MRI or PET are limited in their spatial resolution and/or require extensive preparations, financial efforts and skills. On the other hand, invasive standard procedures like histology/immunohistochemistry have several drawbacks: large numbers of animals are needed, only inter-group comparisons are possible and no data about function are available.

With In vivo COnfocal Neuroimaging (ICON) it is possible to overcome some of these limitations. It enables researcher to analyse neuronal structure and function with a cellular resolution and in a non-invasive way. This allows repetitive measurements and therefore intra-group comparisons.

To perform ICON, Retinal Ganglion Cells (RGCs) are labelled by retrograde transport of a fluorescent dye injected into the superior colliculus of rodents. After approximately 1 week maximum labelling is achieved and with a fluorescent microscope it is possible to focus onto the retina of a live rat placed beneath the objective. Such experiments can provide data about the number and the size of RGCs. In addition, after a lesion (e.g. optic nerve trauma) swelling and cell death can be monitored over days and weeks. Moreover, using a calcium sensitive dye as a marker, changes in intracellular free calcium concentrations can be analysed. The retrograde transport of the markers also allows investigating axonal transport: injection of fluorescent dyes after induction of optic nerve trauma can reveal whether or not axonal function is (partially) preserved and whether or not it can recover. Moreover, the function of the blood-brain barrier can be visualised with ICON by i.v. injection of fluorescent tracers, drugs or nanoscale carrier systems and imaging the kinetic of the fluorescent signal in the retinal vessels and tissue.

The limitations of ICON are the slightly blurry microphotographs caused by the movement of the living animal (breathing and heartbeat) and the difficulties to focus due to the spherical shape of the retina.

However, also other groups have discovered the advantages of non-invasive brain imaging via the eye – partially with a bit different technical approaches – and provide ideas for even more applications, such as measurement of apoptosis and beta-amyloid plaques. Even clinical applications are of the horizon, which will hopefully contribute to an increasing usage and proliferation of this method in the neuroscience community.

High-resolution imaging of neural activity with multielectrode arrays

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Neural interfaces based on microelectrode arrays (MEAs) allow imaging of activity of a large number of neurons simultaneously, both in-vitro and in-vivo, as well as stimulation of this activity by injecting electrical current into the extracellular medium. The current state-of-the-art MEA-based systems can record activity of hundreds of closely spaced neurons simultaneously, with temporal resolution of individual action potentials. This open up new possibilities for the investigation of information processing in local neural networks. In this talk I will present principles of MEA recordings techniques and current status of the MEA technology. I will also discuss results of recent MEA-based recordings from the retina and brain circuits, as well as experiments employing combined multielectrode recording and multichannel electrical stimulation.

Three-tiered architecture of lateral connections in primary visual cortex

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In the superficial layers of the visual cortex long-range lateral connections have been assumed to provide the structural basis of interactions through which low level perceptually relevant feature integration and/or saliency events take place. According to the current concept, such horizontal interactions are primarily carried out between cells (columns) representing similar functional features such as orientation preference. While this concept is indeed supported by data obtained in superficial layers little if any is known about the functional topography of lateral connections of deeper layers.

Here we investigated the functional topography of upper (layer2/3 or tier 1), middle (layer 4 or tier 2) and deep layers (layer 6 or tier 3) connections using a combination of intrinsic signal optical imaging and single cell tracing in the cat primary visual cortex (areas 17 and 18). Orientation maps were generated to stimuli consisting full-field square wave gratings followed by microinjections of biotinylated dextran-amine at several locations within the mapped region. After histology, labelled neurons were screened for completeness and reconstructed in 3D using the Neurolucida reconstruction system. Then the axonal (bouton) distribution pattern of each reconstructed neuron type was compared to functional orientation maps and evaluated quantitatively.

(i) Layer 2/3 pyramidal cells (n=4) cells were subjected to a model-based analysis according to which the bouton distribution patter of single cells can be reasonably predicted by the convolution of Gaussian and von Mises distributions as a function of cortical location and orientation, respectively. We observed that the model describes well the clustered pattern of layer 2/3 pyramidal cell axons (boutons) and the iso-orientation biased connectivity.

(ii) Our data for layer 4 excitatory cells (n=23), including spiny stellate and star pyramidal neurons revealed connectivity to a broad range of orientation in particular in the case of distal connections. Boutons of each layer 4 cell were partitioned into 1-15 distinct clusters (mean-shift algorithm) of which about half of them preferred iso-orientation whereas the other half preferred cross-orientation. Importantly, the very same layer 4 cells could emit iso- and cross-orientation preferring bouton clusters resulting in broad orientation tuning of the axons.

(iii) Local boutons of layer 6 cells (n=19) occupied similar orientation preferences to that of the parent soma. However, their tuning width was broader than that of layer 2/3 spiny cells. Distal boutons of layer 6 cells showed only a weak iso-orientation preference and in this regard differed from those of layer 2/3 counterparts.

In conclusion, the functional selectivity of layer 4 and layer 6 spiny neurons differed from that of layer 2/3 cells. The overall pattern was least patchy for layer 6 cells while the largest proportion of non-iso orientation connections found for layer 4 cells. Hence, lateral connections of middle- and deep layers are organised differently from that of iso-orientation dominant layer 2/3 connections and probably each tier processes visual signals in different manner from the other.

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Thalamo-cortical interactions in different behavioral states

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Multichannel local field potential recordings allow for long-term of neuronal activity in non-anesthetized animals. In our experiment, we used this technique to register responses evoked by tactile stimulation in somatosensory pathways of awake rats at different levels of arousal. Electrodes were implanted in the ventral postero-medial nucleus, VPM (first-order thalamic relay), medial posterior nucleus, PoM (higher-order relay) and in the barrel cortex. Cross-trial correlation analysis (CTC; Sobolewski et al., 2010) - a recently developed method of imaging functional strengths of neuronal connections - allowed to asses the activation flow in first- and higher-order thalamo-cortical loops.

At low arousal level (no aversive stimuli) the sensory signal was primarily relayed from first-order VPM to the barrel cortex and from there to higher-order PoM. However, at high arousal level this network scheme was altered and the barrel cortex also received input directly from PoM. We show that sensory pathways form a dynamic system, which is capable of reconfiguring the sensory signal's route to cortical areas in step with the animal's behavioral context.

A. Sobolewski et al. J. Comp. Neurosci., 2010, 29(3):485-493. See also poster by A.Sobolewski, @ session P7 (Sensory and Motor Systems) on Friday 23rd of September.

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Mechanisms underlying the orientation tuning of surround suppression in V1

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Three major pathways provide "long-range" inputs to primary areas of the neocortex: afferents from the thalamus, feedback from higher cortical areas, and long-range projections within the area itself. In the cortex of mammals with highly developed visual systems such as cat and monkey there are differing views as to the relevance of each circuit in mediating the well-studied phenomenon of surround suppression of neurons in primary visual cortex (V1). We combined the use of intrinsic signal optical imaging and single-unit recording in cat V1 to show that 1) the orientation selectivity of the suppressive-surround of a cell depends on the intrinsic organization of V1 (i.e., the location of the cell within the orientation preference map); 2) that the 'near' component of the surround is primarily responsible for the orientation selectivity; and 3) that selectivity peaks relatively late in time. Together, his neurophysiological evidence points to a more predominant role of ong-range intrinsic connections in shaping the surround characteristics in V1.

Current source density - analysis of multielectrode recordings

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Local field potentials (LFP), the low-frequency part of the extracellular electric potentials, reflect dynamics of the brain at the population level. The interpretation of these signals is complicated by the fact that the electric signals propagate in the tissue, and the signal recorded at each position may have contributions from neurons located more than a millimeter away. Therefore it is useful to estimate and analyze the current source density (CSD), the volume density of transmembrane currents which generate the observed LFP. In the past few years new methods for CSD estimation has been developed, such as the inverse CSD, based on the inversion of the forward-modeling scheme, or the kernel CSD, which employs kernel techniques used in machine learning. I will present a review of these methods, and show a recent example when CSD estimation was combined with independent component analysis to decompose evoked activity in the rat somatosensory tract.

Patterns of spiking activity in large populations of extracellularly recorded neurons

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Large scale electrophysiological recordings from neuronal ensembles offer the opportunity to investigate how the brain orchestrates the wide variety of behaviors from the spiking activity of its neurons. To investigate the structure of spiking activity patterns, we recorded from populations of 40 - 100 neurons in auditory and somatosensory cortices of anesthetized and awake rats using silicon microelectrodes. Population spike time patterns were broadly conserved across multiple sensory stimuli and spontaneous events. Although individual neurons showed timing variations between stimuli, these were not sufficient to disturb a generally conserved sequential organization observed at the population level, lasting for approximately 100 ms. Preserved constraints were also seen in population firing rate vectors, with vectors evoked by individual stimuli occupying subspaces of a larger but still constrained space outlined by the set of spontaneous events. These results suggest that population spike patterns are drawn from a limited "vocabulary", sampled widely by spontaneous events but more narrowly by sensory responses.

Stochastic properties of superior colliculus neuronal responses to moving stimuli

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Single neuron can generate different spike trains in response to repeatedly presented stimulus. Such a trail-to-trail variability is a broadly observed phenomena in the nervous system and as a stochastic property can be described in the language of point processes. Spikes are then assigned to their time of occurrence and probability of spike generation in a given moment of time can be described by conditional intensity function. In principle conditional intensity function can depend on history of spike generation. Choice of particular form of conditional intensity function define point process model.

In our study we considered four models: inhomogeneous Poisson process (IP), parametric and nonparametric versions of inhomogeneous Markov interval process (IMI) and inhomogeneous Gamma process (IG). All models were fitted to data from from cat's superior colliculus (SC). The variability of experimental data was then compared to variability of surrogate data sets.

The extracellular single unit activity was recorded from superficial, retinorecipient layers of the SC of anesthetized and paralyzed cats. As a visual stimulus a light spot moving with different velocities was used. On the basis of the velocity response profiles the recorded cells were classified into group presumably receiving input from Y ganglion cells and group presumably receiving input from W ganglion cells.

The time-dependent variability of responses of these neurons was quantified by Fano factor (FF) calculated in discrete time windows. The FF for cells responding to low-velocity stimuli (W input) increased with the increase in the firing rate. The dynamics of activity of the cells responding to fast moving stimuli (Y input) correlated negatively with changes of FF.

The nonparametric IMI models could account well for the properties of responses to fast stimuli and revealed drop of variability during increase of firing rate. Similarly, but to lower extent, did parametric gamma IMI model. For most of the neurons the best fit of the IG model resulted in low values of shape parameter which, in principle, made it possible to attain variability higher than one (IP level) observed in experimental data for low velocity responses. However, the study of IG surrogate data did not reveal changes of variability consistent with the experimental data at any velocity. The variability of IP surrogate data fluctuated around theoretical value equal one and was not correlated with changes of response level at any velocity.

No model of the data could fully recover dependencies between firing rate of SC cells and their response variability even though all models mimicked well the average evoked level of neuronal activity.

Modelling Cortical Representations

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In my talk I will first present results from a map model of primary visual cortex, where we analysed how much evidence recent single unit recordings from cat area 17 provide for a particular cortical "operating point". Using a Bayesian analysis we find, that the experimental data most strongly support a regime where the local cortical network provides dominant excitatory and inhibitory recurrent inputs (compared to the feedforward drive). Most interestingly, the data supports an operating regime which is close to the border to instability, where cortical responses are sensitive to small changes in neuronal properties.

Secondly, I will talk about new ways to quantify spike count correlations among populations of neurons. I will use copulas to construct discrete multivariate distributions that are appropriate to model dependent spike counts of several neurons. With copulas it is possible to use arbitrary marginal distributions such as Poisson or negative binomial that are better suited for modeling single neuron noise distributions than the most often applied normal approximation. Copulas place a wide range of dependence structures at the disposal and can thus be used to quantify higher order interactions. I will apply this framework to multi-tetrode data recorded from macaque prefrontal cortex, where standard noise models fail to accurately describe the measured spike-count distribution.

Finally, I will show results of a study where we investigated visual attention in humans in a probabilistic reward-based visual discrimination task. We find that behavioural performance is not optimal but consistent with a heuristic based on a moving average estimate of stimulus predictability and reward. We also found that the amplitudes of early visual, attention-related EEG signals quantitatively reflect these estimates. Thus, information about stimulus statistics and reward are already integrated by low-level attentional mechanisms.

Practical

Structural and functional imaging of the human brain - neuroimaging workshop for beginners

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This half day workshop is directed mainly to students and young researchers who would like to enter the field of magnetic resonance imaging studies (design and data analysis). Participants will acquire the ability to design experiments using structural and functional MRI and to conduct basic data analyses. An important focus of the program will involve new clinical application of neuroimaging techniques in diagnosis of developmental disorders and neurodegenerative diseases. A wide range of software for qualitative assessment of MRI data as well as quantitative analysis of MRI and fMRI data will be introduced.

Workshop program

Session I

- Brief introduction to MRI physics
- What can we measure using an MRI scanner?
- Different approaches to study structure and function of the human brain
- Clinical application in developmental and neurodegenerative diseases
- Introduction to software (MriCro, MriCron) for qualitative assessment of MRI data
- Voxel Based Morphometry method

Session II

- Introduction to fMRI method
- Experimental designs in fMRI experiments
- Introduction to software (SPM8) for analysis of fMRI data
- Pre-processing of fMRI data (realigment, coregistration, normalization, smoothing)
- Introduction to statistical analysis of fMRI data
- Results visualisation and interpretation