Joint
EuroSPIN / NeuroTime
Meeting
2013

January 14-16, 2013 / Schloss Beuggen, Germany / Organized by the Bernstein Center Freiburg

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Program at a glance

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Detailed Program

Monday, January 14, 2013

9:00	Welcome by the Organizers
9:15	Welcome by the EuroSPIN-Coordinator
9:30	Welcome by the NeuroTime-Coordinator
9:45	Keynote lecture: Matthias HENNIG: **"Homeostatic feedback control in neural circuits: Is there a neural set-point?"**
10:45	*Coffee break*
11:15	Jan PIECZKOWSKI: **"Dynamics of information transfer"**
11:45	Miha PELKO: **"Determining synaptic input properties from intra-celular recordings *in vivo*"**
12:15	Tiago M. ROCHA FELIX: **" Dissecting the auditory cortical circuitry: Influence of dendritic versus perisomatic inhibition on network oscillations"**
12:30	Anu NAIR: **"System dynamics of long-term synapic plasticity"**
12:45	*Lunch*
14:00	Ekaterina BROCKE: **"Tool development for multiscale simulations"**
14:30	Sayyed Auwn MUHAMMAD: **"Protein domain evolution"**
14:45	Maria SHIPPI: **" Schemas and memory consolidation: From experiments to theory"**
15:15	*Coffee break*
15:30	Philip TULLY: **"A Bayesian-Hebbian Learning Rule for Spiking Neurons"**
16:00	Yann SWEENY: **"Modeling homeostatic control of function and metabolic efficiency in single neurons"**
16:30	Sander KEEMINK: **" The functional role of center surround interactions in V1"**
16:45	Dinesh NATESAN: **"Characterization and modeling of neural circuits that integrate visual and mechanosensory stimuli in antennal mechanosensor of hawk moths"**
17:00	*Coffee break*
17:30	Keynote Lecture: Sanjay SANE: **"Fast, Small, yet still in Control: a long view of insect flight"**
18:30	*Dinner*
19:30	Parallel sessions: • Meeting of the EuroSPIN Steering Committee (Chair: Jeanette Hellgren-Kotaleski) • Meeting of the NeuroTime Steering Committee (Chair: Domitille Boudard) • Meeting of the PhD-Students of both programs (Chair: Miha Pelko, Carlos D. Toledo Suárez, Jan Pieczkowski)

Tuesday, January 15, 2013

9:00	Keynote Lecture: Israel NELKEN: **"The representation of surprise in auditory cortex"**
10:00	Jens-Oliver MUTHMANN: **"Spike detection in high density microelectrode array recordings"**
10:30	Stojan JOVANOVIC: **"Higher-order correlations among spiking neurons induced by network structure"**
10:45	*Coffee break*
11:15	Simachew MENGISTE: **"Controllability of neural networks"**
11:45	Tanzil M. AREFIN: **"Patterns of neurocircuitary modifications in alcoholism: in vivo assessment in mouse models of alcohol addiction"**
12:00	Jelena SCEKIC-ZAHIROVIC: **"Modelling amyotrophic lateral sclerosis in mice using gene targetting in ALS8/VAPB and ALS6/FUS"**
12:15	Wisse VAN DER MEIJDEN: **"The effect of red and blue light exposure on pupil diameter and vigilance"**
12:30	Matthias HENNIG & Marc VAN ROSSUM: **IRSES-Proposal**
12:45	*Lunch*
14:00	Free time for discussion
18:30	*Dinner*
19:30	Special Evening Lecture by Amos ARIELI: **"Ongoing Dynamics and Brain Connectivity: From Intracellular Recordings to Human Neurophysiology"**

Wednesday, January 16, 2013

9:00	Keynote Lecture: Andreas LÜTHI: **"Anatomical and temporal specificity in neuronal circuits of fear"**
10:00	Martin ANGELHUBER: **"The neural circuitry of fear"**
10:15	Carlos D. TOLEDO SUÁREZ: **"Liquid state partitioning in a network of striatum"**
10:45	*Coffee break*
11:15	Jovana BELIC: **"The role of intra-striatal synaptic interactions for shaping cortico-striatal network dynamics"**
11:45	Jyotika BAHUGUNA: **"Firing rate dynamics of striatal circuit in Go NoGo task"**
12:15	Marko FILIPOVIC: **"The role of domapine in neuronal assemblies within the striatum"**
12:30	Pawan Kumar JHA: **"Indequate sleep, glucose homeostasis and circadian rhythmicity"**
12:45	*Lunch*
14:00	Renato C. FARINHA DUARTE: **"Processing structured symbolic sequences with recurrent neural networks"**
14:30	Meeting of the EU-representative with the Steering Boards of both programs
15:15	*Coffee break*
15:30	Meeting of the EU-representative with the PhD-Students of both programs
16:15	Meeting of the PhD-students with the Advisory Board
17:00	Meeting of the Steering Boards with the Advisory Board
17:45	Farewell

Abstracts

The neural circuitry of fear conditioning

Martin ANGELHUBER
Bernstein Center Freiburg / FMI Basel / Université de Strasbourg
Supervisors: Arvind Kumar, Andreas Lüthi, Pierre Veinante

Classical fear conditioning is one of the most powerful models to study the neuronal substrates of associative learning in the mammalian brain. The amygdala is generally acknowledged to be the key structure in classical fear conditioning. In my project I will focus on the role of the Central Amygdala (CEA) and address the question how input from basolateral Amygdala and cortex is integrated in the CEA, how it is processed in the two stage inhibitory network of the CEA, and how output to downstream structures, such as PAG and other brainstem targets, is generated. Previous experimental studies in the Luethi lab have identified distinct cell types in CEl which can be defined on a functional or genetic basis. The aim of the first part of the project is to devise a computational model of the CEA based on these findings and more recent recordings.

Patterns of Neurocircuitries modification in alcoholism: *In vivo* assessment in mouse models of alcohol addiction

Tanzil M. AREFIN
Bernstein Center Freiburg / Université de Strasbourg
Supervisors: Laura Harsan, Brigitte Kieffer

Alcoholism is a chronic relapsing disorder characterized by compulsive drinking, loss of control over intake, and impaired social and occupational function. The aim of this project is to combine brain magnetic resonance imaging (MRI), genetic and molecular approaches for examining the brain adaptations to alcohol exposure, in validated animal models of alcoholism. It has been suspected that the endogenous opioid system, as well as Nr4a1 and Gpr88 genes contribute to the modification of brain connectivity during alcohol addiction. To justify this hypothesis, cutting edge mouse brain imaging approaches will be applied to knockout mice. DTMRI and fiber tracking will be used to map the structural connectivity and to check the brain fibers integrity over time at different stages of the addiction cycle. Moreover, fcMRI, rsfMRI will be implemented to assess the functional relevance of any identified alterations.

Firing rate dynamics of striatal circuit in Go and No-Go tasks

Jyotika BAHUGUNA
Bernstein Center Freiburg / KTH Stockholm
Supervisors: Arvind Kumar, Jeanette Hellgren-Kotaleski

To correctly govern the action-selection it is important that D1 and D2 neurons have differential firing rates such that either direct or indirect pathway can win. To understand how dopamine depletion in the striatum could affect the balance of firing rate in the D1 and D2 Medium Spiny Neurons (MSNs) it is important to consider dichotomous integration properties and connectivity. Our preliminary results based on reduced firing rate model and numerical stimulations revealed several important insights: 1.) D1 MSNs are massively inhibited by the D2 MSNs and require stronger cortical drive to overcome the recurrent inhibition from D2 MSNs. 2.) Firing rates of D1 and D2 change in a non-monotonic fashion as a function of the strength of cortical inputs. For low input rates D1 MSNs have higher firing rate than D2 MSNs and vice versa. This is due to the preferential connection by FSI to D1, which at higher cortical input inhibits D1 more than D2. 3.) The cortical input rate at which D2 MSNs surpasses D1 MSNs, depends on the strength of cortico-striatal synapses and firing rates of fast-spiking interneurons (FSI). 4.) The STN can control the activity of FSIs via the GPe neurons and thus can adjust the decision threshold.

The model suggest that under dopamine depletion conditions even for weak cortical inputs D2 MSNs activity is higher than D1 MSNs consistent with the fact that PD patients have difficulty in making voluntary decision. We also observed that dopamine depletion reduced the parameter regime supporting D1 MSNs activation, suggesting that under dopamine depleted state striatum would require arbitration by STN-GPe network even for low conflict task, providing a plausible explanation of increased reaction times in PD patients. Finally, reduced activity in STN and GPe during DBS could also reduce the activity of FSIs in the striatum such that D1 MSNs fire at higher rates than D2 MSNs creating a situation similar to impulsivity.

The role of intra-striatal synaptic interactions for shaping cortico-striatal network dynamics

Jovana BELIĆ
KTH Stockholm / Bernstein Center Freiburg
Supervisors: Jeanette Hellgren-Kotaleski, Abigail Morrison

The basal ganglia consist of several interconnected subcortical nuclei that are supposedly involved in many motor and cognitive functions. The striatum, the input stage of the basal ganglia, is a major recipient of massive glutamatergic inputs from the cerebral cortex and thalamus. Medium spiny neurons (MSNs) dominate in the striatum (up to 95% in rodents). They are inhibitory (GABAergic) and have membrane properties that give them a high threshold for activation. MSNs interact with each other through weak recurrent inhibitory synapses and with low connection probability. Fast-spiking GABAergic interneurons (FSNs) can delay or prevent the emission of an action potential in MSNs. FSNs receive convergent inputs from a wider range of distinct cortical regions compared to nearby MSNs, and despite the fact that they are relatively sparse elements (1-2%) it seems that they have very prominent role in shaping the output of the striatum.

Neuronal avalanches are a type of spontaneous activity first observed in vitro by recording local field potentials in cortical neural networks using slices of rat cortex as well as cultured networks. Propagation of spontaneous activity is balanced and shows a branching parameter close to 1. In addition, the number of electrodes driven over threshold during activity is distributed approximately like a power law with an exponent of -3/2 for event sizes suggesting a critical dynamics. Neural avalanches have been shown to provide: optimal information transmission, maximal information capacity and maximal dynamic range.

We are studying simultaneously striatal and cortical activity in vitro. Preliminary results show that neuronal avalanches in cortex induce activity clusters in striatum whose size distribution can be approximated by a steeper power law than observed in cortex. Based on this we have developed network models in order to determine the impact of different striatal neurons on the more negative exponent.

Tool development for multiscale simulations

Ekaterina BROCKE
KTH Stockholm / NCBS Bangalore
Supervisors: Jeanette Hellgren Kotaleski, Mikael Djurfeldt, Upinder Singh Bhalla

To understand the brain, there is a need to study multiscale phenomena and to detail out how phenomena at one level of organization are affected by the ongoing brain activity at other levels. Computational modeling and simulations provide an important approach in these attempts. Simulation studies of integrated levels could help to validate the consistency of the anatomical data, identify crucial missing parameters and constrain ranges for yet unknown parameters. While there exists simulators/frameworks, such as GENESIS (GEneral NEural SImulation System) and MOOSE (Multiscale Object-Oriented Simulation Environment), which span multiple scales (kinetikit/HH-models), most software applications are specialized for a given domain. The initial important step could be to develop a general framework that supports the integration of subcellular receptor induced signaling models with models of the electrical activity in neurons and network of neurons.
The goal of this project is to study multiscale phenomena, to take the first steps towards multiscale framework development and to use obtained knowledge for addressing particular scientific question in Neuroscience looking at different spatial and temporal scales integrated in a single model.

Processing Structured Symbolic Sequences with Recurrent Neural Networks

Renato C. FARINHA DUARTE
Bernstein Center Freiburg / University of Edinburgh
Supervisors: Abigail Morrison, Peggy Seriès

The ability to encode, process and represent structured sequences of perceptual information as well as the ability to finely sequence motor actions are ubiquitous features of human cognition, fundamental to a variety of common, everyday tasks. Sequential learning provides a domain-general mechanism for acquiring predictive relations between sequence elements abiding to a set of structural regularities, upon which the brain can anticipate upcoming elements.
To account for the ability of neuronal circuits to process data with embedded temporal dependencies (expressed as symbolic time series), recurrent neural network (RNN) models are naturally suitable by virtue of their inherent recurrent connectivity (that allows context information to be kept in units' activities), but also due to their biological plausibility.
In this work, we explore the properties and characteristics of different recurrent network models, built according to the reservoir computing framework, involved in a series of different sequence processing tasks, designed to assess their ability to acquire and learn temporal dependencies and statistics of the input data. We assess their properties and performance as 'predictive machines' (relating it to the capacity to learn the set of generative rules underlying different grammars), and explore their ability to adequately capture and represent variable length temporal dependencies embedded in the input sequences. We also compare models with varying degrees of biological realism, while exploring the trade-off between abstraction and biological realism in this specific domain.

The role of dopamine in neuronal assemblies within striatum

Marko FILIPOVIĆ
Bernstein Center Freiburg / KTH Stockholm
Supervisors: Arvind Kumar, Gilad Silberberg

Striatum is the main input stage of the basal ganglia and plays crucial role in various cognitive and motor functions. Recently, both in vitro experimental data and numerical simulation of striatal network have suggested that neural activity in the striatum is organized in distinct short-lived neural assemblies. We argue that a rich repertoire of behaviors requires an equally rich repertoire of neuronal assemblies within the striatum and mechanisms to rapidly switch between them.
Recently experiments have revealed a number of heterogeneities within the striatal network e.g. D1 and D2 MSNs differ in morphology, integrative properties, synaptic dynamics and recurrent connectivity. Considering these recent experimental data we are interested in understanding the mechanisms that maximize the number of neural assemblies and create those composed of only one type of MSNs. In addition, we will characterize how phasic and tonic levels of dopamine can restrict the number and switching between different neural assemblies.

Inadequate sleep, glucose homeostasis and Circadian Rhythmicity

Pawan Kumar JHA
NIN Amsterdam, Université de Strasbourg
Supervisors: Andries Kalsbeek, Etienne Challet

Sleep is an essential component of everyday life to maintain the metabolic and physiological health. Increasing evidence suggests that sleep also plays an important role in the control of daily glucose metabolism. Plasma glucose concentrations and glucose utilization is highest in morning and lowest in evening in humans, but it is oppositely phased in nocturnal rodents like mice and rats. Based on experimental studies these similar but oppositely phased rhythms in rodents have been ascribed to different neural mechanisms employed by the suprachiasmatic nucleus (SCN) to regulate glucose tolerance and insulin sensitivity. Human studies on sleep deprivation indicate that a reduction in sleep duration and/or sleep quality results in obesity and impaired glucose tolerance, on the other hand sleep deprivation studies in rodents usually result in weight loss. One possible explanation for these contrasting results could be the opposite activity patterns of diurnal humans and nocturnal rodents with regard to the light/dark-cycle and the activity pattern of the central clock in the SCN. To test this hypothesis we will investigate the effects of sleep deprivation on glucose homeostasis and study the SCN mechanisms that control the daily rhythms of glucose tolerance and insulin sensitivity and in a diurnal rodent, i.e., the *Arvicanthis ansorgei*. In addition, we will study the feedback effects of sleep deprivation on the master circadian clock and its impact on synchronization to light in *Arvicanthis ansorgei*.

Higher-order correlations among spiking neurons induced by network structure

Stojan JOVANOVIC
Bernstein Center Freiburg / KTH Stockholm
Supervisors: Stefan Rotter, John Hertz

Nerve cells are highly sensitive to synchronous input from larger groups of neurons. Which synchronous patterns are favored by a recurrent network, therefore, depends to a large degree on network structure. Recently, we were able to dissect the contribution of specific structural motifs in networks of arbitrary topology to pairwise correlations. The case of higher order correlations, however, is complicated by the fact that several different concepts to describe multi-neuron interactions are in use. Models based on stochastic point processes have frequently been employed as generative models in neuroscience. They also represent a suitable starting point to develop efficient methods for neuronal data analysis as they admit a natural link to multivariate cumulants. In this project, we strive to generalize our dynamical systems approach to build a concrete physical interpretation of higher-order correlations and find out which network motifs are responsible for their generation.

The functional role of center-surround interactions in V1

Sander KEEMINK
University of Edinburgh / Bernstein Center Freiburg
Supervisors: Mark van Rossum, Clemens Boucsein

Receptive fields (RF) in V1 have been well classified and studied, and have been used for many successful models of V1. A well-known feature of the RFs is the center-surround interaction. Although presenting stimuli in the RF surround alone does not produce a response, it can influence the response to stimuli inside the RF. These interactions have been well classified experimentally, and several models have been developed explaining them qualitatively. Far less studied, however, is their functional role; there has mostly been speculation on the interactions aiding in saliency detection. In our work we aim to study the functional role of center-surround interactions by studying the following questions: How do the different qualitative models perform at saliency detection? What would be the optimal center-surround interaction given image statistics? What are the dynamics of the interaction? We hope to combine these studies with extra-cellular recordings from the rat visual system.

Controllability of Neural Networks

Simachew MENGISTE
Bernstein Center Freiburg / KTH Stockholm
Supervisors: Arvind Kumar, Jeanette Hellgren-Kotaleski

Biological neural network (BNN) in the brain can be thought of as a dynamical system whose activity constantly changes in time and the different network states correspond to different behaviors and cognitive states of the animal. Thus, animal behavior and sensory-motor transforms can be considered as a control problem. I am interested in identifying the essential components of neural hardware (neuron and synapse properties, connectivity) that define the controllability of a BNN. To this end we are exploiting the concept of 'structural controllability' where full knowledge of synaptic strengths can be neglected, yet the complete controllability is implied. In my talk I will make a case that disease of brain dynamics such as epilepsy, Alzheimer's disease, can be understood in terms of loss of the controllability of the BNN. Specifically I will discuss which changes in the network structure affect the controllability. In addition I will discuss how rewiring of recurrent and input projections can restore the controllability of a BNN.

Protein Domain Evolution

Sayyed Auwn MUHAMMAD
NCBS Bangalore / KTH Stockholm
Supervisors: Ramanathan Sowdhamini, Jens Lagergren

Protein domains are fundamental evolutionary elements and most of them are of interest for many areas of research in proteins. Some proteins have more than one domain. Advances in domain modeling and collection are making it possible to build the model of evolution for studying the evolutionary changes in protein domains across the species. Protein domain evolution link evolutionarily related proteins and highlight their shared functions. In our case, we are interested in better understanding this association by identifying the specific domain and its evolutionary pathways by which extant domains may have evolved through species. We are trying to propose a model of evolution based on protein domains. For this purpose, we are planning to update a software package Prime: Probabilistic Integrated Models of Evolution for protein domain evolution. In this way we can investigate how proteins evolve through speciation and duplication and how different species conserved some of the domains.

Spike detection in high density microelectrode array recordings

Jens-Oliver MUTHMANN
NCBS Bangalore / University of Edinburgh
Supervisors: Upinder S. Bhalla, Matthias Hennig

High density microelectrode arrays enable studies of neuronal activity in cultures with a high spatial and temporal resolution. However, the thermal noise of the preamplifiers causes problems for spike detection in recordings of hippocampal cultures and a large fraction of spikes will be subthreshold when a conservative threshold is applied. I estimate the fraction of falsely detected spikes based on correlations with the activity in other recording channels, and show that this procedure works as well in recordings of the immature retina in mice.

System dynamics of long term synaptic plasticity

Anu G. NAIR
KTH Stockholm / NCBS Bangalore
Supervisors: Jeanette Hellgren-Kotaleski, Omar Gutierrez Arenas, Upinder Singh Bhalla

Long-term plasticity is an activity dependent change of the synaptic weight. This is considered as the basis of learning and memory. The quantitative details of the signaling pathways underlying long-term plasticity are not very well understood. This is partly due to the sheer size and complexity of the network and its counter intuitive behavior. We are modeling the dynamics of these biochemical reaction networks from a system-biology perspective. We are interested in modeling the signaling cascade triggered by different inputs. A particularly interesting system in this regard is the medium spiny neurons in the striatum of basal ganglia. These neurons receive a variety of inputs such as glutamate from cortico-striatal projections, dopamine from the nigro-striatal projections and ACh from cholinergic interneurons. Our aim is to understand the phenotypic effects of these neuromodulators and how they are coordinated with each other.

Characterization and modeling of neural circuits that integrate visual and mechanosensory stimuli in antennal mechanosensors of hawk moths

Dinesh NATESAN
NCBS Bangalore / KTH Stockholm
Supervisors: Sanjay P. Sane, Örjan Ekeberg

Insect antennae provide a wide variety of sensory inputs to the insect nervous system. Antennal sensors send olfactory, mechanosensory and sometimes, thermosensory and hygrosensory information that influence the overall behavior of the insect. For optimal acquisition of these inputs, the precise positioning of the antennae positioning may be crucial. In the Oleander hawk moth, Daphnis nerii, it has been recently shown that a set of antennal mechanosensory hair at the base of the antennae, called the Böhm's bristles, help in maintaining a constant antennal angle during flight via a classic reflex arc Moreover, vision also influences antennal positioning response in insects. Because visual latencies typically exceed mechanosensory latencies, it is useful to study this circuit to understand how inputs of disparate latencies combine to generate a precise response of the antenna to external perturbation. We will combine techniques from neurobiology and computational biology to understand this multisensory integration. On the neurobiological front, we will investigate the neural circuitry using behavior and electrophysiological techniques. This data will then be then used to create a model of the circuit using computational techniques. Such computational models are often predictive in nature, so we hope that these models would suggest experiments and vice-versa.

Determining synaptic input properties from intra-cellular recordings *in vivo*

Miha PELKO
University of Edinburgh / Bernstein Center Freiburg
Supervisors: Mark van Rossum, Clemens Boucsein

A cortical neuron in vivo is bombarded with excitatory and inhibitory inputs that underlie the neuron's activity. The transformation between input and output, which is determined by the synaptic integration and the action potential generation, is core to neural information processing and neural coding. However, the precise transformation between input and output is unclear. Although it is currently impossible to exactly measure all the presynaptic spike trains to a specific neuron, much can be learned from recordings of the post-synaptic membrane potential. In this study we outline a procedure to estimate the presynaptic activity based on the statistics of the membrane voltage obtained in in-vivo patch-clamping experiments. We apply the procedure to measurements of the membrane voltage fluctuations in motor cortex of awake mice during the resting state and a spontaneous movement state. The results allow us to suggest an explanation for the observed changes between the two states.

Dynamics of Information Transfer

Jan PIECZKOWSKI
KTH Stockholm / University of Edinburgh
Supervisors: Jeanette Hellgren-Kotaleski, Mark van Rossum

The transmission of information is a fundamental part of information processing in the brain. This processing can be considered on many levels, from subcellular biochemical signalling pathways, over single-neuron computation, to the dynamics of large-scale neural networks and the interplay of different brain regions. Information theory provides a strong framework that lends itself to analyzing the dynamics of these systems in a common way. On this basis, I have recently tackled the question of information representation by investigating optimal coding of multiple stimuli, some results of which I will present here. On the network level, the transmission of information is closely intertwined with topology and neural dynamics. Further studies will concern measures of information to estimate similarity between different stages of processing.

Dissecting the Auditory Cortical Circuitry: Influence of Dendritic versus Perisomatic Inhibition on Network Oscillations

Tiago M. ROCHA FÉLIX
Bernstein Center Freiburg / FMI Basel / University of Strasbourg
Supervisors: Marlene Bartos, Andreas Lüthi, Didier Pinault

In the auditory cortex, gamma rhythms are critical for acoustic information processing impacting greatly on frequency, intensity and spectral modulation preferences. GABAergic inhibitory interneurons are highly diverse and can be divided in various subtypes, most notably perisoma inhibiting interneurons (PIIs) and dendrite inhibiting interneurons (DIIs). PIIs play a key role in the emergence of fast brain rhythms by synchronizing the activity of large principal-cell populations. DIIs seem to control the activity state of their target cells by local electrogenesis; however, it remains unclear how the different DII subtypes contribute to fast gamma oscillations and sensory information processing. We aim to address this open question and identify the role of perisomatic vs dendritic inhibition in network synchronization in the auditory cortex using a multidisciplinary strategy comprising neuroanatomical, in vitro and in vivo electrophysiological, 2P imaging and computational approaches.

Schemas and memory consolidation: From experiments to theory

Maria SHIPPI
University of Edinburgh / KTH Stockholm
Supervisors: Mark van Rossum, Anders Lansner

Systems memory consolidation is usually defined as a long reorganization process, taking weeks or longer, whereby hippocampus dependent memory traces become stabilized in the neocortex, and some of them become hippocampus independent. Theoretical studies suggest that a long gradual consolidation process is important in order to avoid catastrophic interference (McLelland et al, Psych. Rev., 1995). However, based on experimental studies, it was shown that memory consolidation can occur rapidly without interference, if an associative framework of knowledge has been previously created, called an associative "schema", into which new memory traces can be incorporated (Tse, Langston et al, Science, 2007). This rapid consolidation is accompanied by an upregulation of plasticity-related immediate early genes in the prelimbic region of medial prefrontal cortex at the time of memory encoding (Tse, Takeuchi et al, Science, 2011). Pharmacological interventions targeted at the prelimbic region prevented both, new learning and the recall of remotely, and recently consolidated information, complementing other studies (Lesburgueres et al, Science, 2011).
Using Restricted Boltzman Machines, we present a theoretical model of systems memory consolidation including the concept of schema which explicitly considers the role of prior knowledge in guiding the consolidation process. We investigate the role of the hippocampus, the prelimbic cortex and their dynamic interaction during schema learning, and memory encoding and assimilation of additional related memory traces. Our results are in agreement with both human (van Kesteren et al, PNAS, 2010) and animal (Tse, Takeuchi et al, Science, 2011, Tse, Langston et al, Science, 2007) studies of schemas and memory consolidation.

Modelling amyotrophic lateral sclerosis in mice using gene targeting in ALS8/VAPB and ALS6/FUS

Jelena SCEKIC-ZAHIROVIC
Université de Strasburg / FMI Basel / Bernstein Center Freiburg
Supervisors: Luc Dupuis, Pico Caroni, Marlene Bartos

Amyotrophic lateral sclerosis (ALS) is a progressive and fatal neurodegenerative disease involving degeneration of motor neurons in the brainstem and spinal cord. No curative treatment is currently available for ALS. A subset of ALS cases is of familial origin and most research has focused on the mechanisms underlying ALS due to mutations in ALS1/SOD1. However, animal models derived from ALS1/SOD1 were found irrelevant for preclinical research. In the last few years, mutations in various genes have been linked to ALS. Our laboratory created two transgenic mouse models based on targeted mutations on ALS8/VAPB and ALS6/FUS and this project aims at elucidating the mechanisms underlying these two familial forms of ALS.

ALS6/FUS is a DNA/RNA binding protein which appears to be associated with multiple nuclear and cytoplasmic steps of RNA processing. It seems that FUS/TLS generally regulate transcription and pre-mRNA splicing. ALS6 mutations in FUS are clustered in the C-terminal nuclear localization signal and impair nuclear localization of the protein. Indeed, some ALS6 mutations generate truncated FUS proteins retained in the cytoplasm. Whether the loss of correct subcellular localization of FUS is causing the disease is postulated but still unclear. To address this question, we generated knock-in mice expressing a chimeric mRNA encoding a truncated R506X FUS protein. Heterozygous (R506X/+) mice (+/-) are viable, fertile and grossly healthy up to 8 month of age. Homozygous (R506X/R506X) mutant mice are currently being generated. Using this novel ALS animal model we will study whether FUS truncation leads to a motor and/or behavioral phenotype. In order to achieve this set of behavioral protocols will be used (SHIRPA screening of behavioral abnormalities, Rotarod and Grip strength test). Further, we will be studying downstream effects of FUS truncation using standard techniques (RT-PCR) as well as motor neuron laser micro-dissection associated with next-generation sequencing.

ALS8/VAPB (vesicle-associated membrane protein/synaptobrevin-associated membrane protein B), is a resident protein of the endoplasmic reticulum (ER) that modulates cellular trafficking of endosomes and VAPB is implicated in unfolded protein response (UPR) signaling pathway.

Results of recent research conducted in our laboratory showed that VAPB deletion (VAPB null -/- mice) leads to a mild motor-sensory deficit without abnormal neuromuscular junction morphology at late stages. Based on these results in basal condition we want to investigate whether VAPB deletion sensitizes motor neuron to axonal or metabolic injury.

Our results will help to define the role of ALS6/FUS and ALS8/VAPB, and allow the understanding of the molecular function of these new ALS genes. Understanding the molecular and cellular basis of fALS might provide major insights into the pathogenesis of sALS, eventually leading to effective therapies.

Modelling homeostatic control of function and metabolic efficiency in single neurons

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Intrinsic electrical properties of neurons are controlled by a number of homeostatic mechanisms, among which are the modulation of conductances of voltage-dependent ion channels. One such example is mediated by Nitric Oxide (NO) in the Medial Nucleus of the Trapezoid Body (MNTB), relay neurons located in the auditory brainstem and involved in sound localisation. NO is released here in an activity-dependent manner and switches the basis of action potential (AP) repolarisation from Kv3 to Kv2. We have investigated this homeostatic regulation in a multi-compartment neuron model and have measured the transmission fidelity and metabolic efficiency of AP generation for different NO states. Preliminary results suggest that the role of NO is to minimise the metabolic cost of APs against the constraint of maintaining sufficient EPSC transmission fidelity.

Liquid state partitioning in a network model of striatum

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I present a purely inhibitory micro-circuit model of the striatum that reproduces experimentally observed activity statistics and allows an efficient state partitioning of a 2D environment, based on its transient high-dimensional, i. e. liquid state dynamics generated when stimulated with the spike coded position of an agent, and use it for the supervised learning of trajectories on a flat surface employing only four simple linear readouts. I show performance and generalization scans over scales of cortico-striatal versus intra-striatal synaptic weights for multiple instantiations of the circuit, and their comparison against a measure of circuit's sensitivity to small input perturbations i.e. chaotic behavior. I finish presenting a preliminary implementation of a reinforcement learning task using the same proposed model.

A Bayesian-Hebbian Learning Rule for Spiking Neurons

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The Bayesian statistical inference paradigm has provided an intuitive framework of how the nervous system could theoretically represent uncertainty by combining prior knowledge with the information it accumulates during sensory input events. These ideas have received increasing attention in light of recent experimental findings describing evidence in which populations of spiking neurons could code for probability distributions of stimuli during perceptual, motor control, and decision making tasks. However, there are competing views that dispute at which level of complexity in the neural substrate these probabilistic computations should be performed.

An artificial neural network (ANN) model of unsupervised Hebbian learning based on graded unit activations, the incremental Bayesian Confidence Propagation Neural Network (BCPNN), is converted to a frequency-based biophysical learning rule implemented at the synaptic level of neural circuitry. In this interpretation, a BCPNN synapse low-pass filters binary spiking events, estimating the confidence of presynaptic spikes (prior distribution) along with spiking activity of the postsynaptic neuron in the context of the input (posterior distribution), to determine its degree of belief in the events. Estimation of the terms used for the Bayesian weight update is performed using a set of differential equations implementing exponentially weighted moving averages. The time constants of the decaying exponentials are phenomenologically mapped to plasticity-relevant synaptic changes that take place during learning.

We show how terms associated with the ANN version of the model can represent the behavior of neuron populations under more realistic conditions. For example, the bias term in the artificial context, which previously indicated the level of unit activity, is shown to mimic a neurons' electrical properties that are modified as they are exposed to prolonged synaptic input, i.e. its intrinsic excitability. Also, the description of a Kappa term which functionally served as a global 'print now' signal to increase sensitivity during learning epochs is refined to express effects of a neuromodulator (e.g. dopamine) on synaptic plasticity. We show that for the classic experimental pre-post pairing scheme, BCPNN synaptic dynamics exhibit temporally symmetric weight dependent Hebbian spike timing-dependence. Despite this seemingly destabilizing learning property, the spiking rule exhibits a unimodal equilibrium weight distribution that is well-fitted by a Gaussian, owing to the fixed-point dynamics of BCPNN in its artificial description. We conclude with preliminary results describing how these probabilistic computations could be applied to functional network models that implement decision making and word list learning.

The effect of red and blue light exposure on pupil diameter and vigilance

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The human retina contains, next to rods and cones, melanopsin containing intrinsically-photoreceptive Retinal Ganglion Cells (ipRGCs). The optimal stimulation wavelength of the melanopsin cells is shorter, compared to rods and cones, and is located around 480 nm (blue light). Previous research suggested that ipRGCs might play a key role in circadian processes such as vigilance regulation, since they project onto the suprachiasmatic nucleus (i.e. the internal clock). An easily measurable output variable associated with ipRGC function could be of great value for vigilance studies. Pupil diameter might be the appropriate output variable, because it is also influenced by ipRGCs. When a blue light is presented to the eye, pupil size diminishes. This effect is sustained, even after the light goes off. This sustained decrease in pupil diameter is attributed to the properties of ipRGCs. When a red light stimulus is used, this sustained pupil effect is hardly perceptible and the pupil diameter quickly returns to baseline. Red light can be used as a control condition for the assessment of the contribution of ipRGCs to the pupillary light response.
The aim of this project is to relate vigilance alterations with pupil size. Therefore, participants are exposed to 2 light conditions (blue and red), while performing a psychomotor vigilance task. In the future, it might be interesting to implement pupillometry to examine the functioning of ipRGCs in subjects suffering from sleeping disorders. It might be a fast and straightforward diagnostic tool to implement in case of sleeping disorders and it might lead to new insights in the understanding of the ipRGCs and their relation with sleep and the biological clock.

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