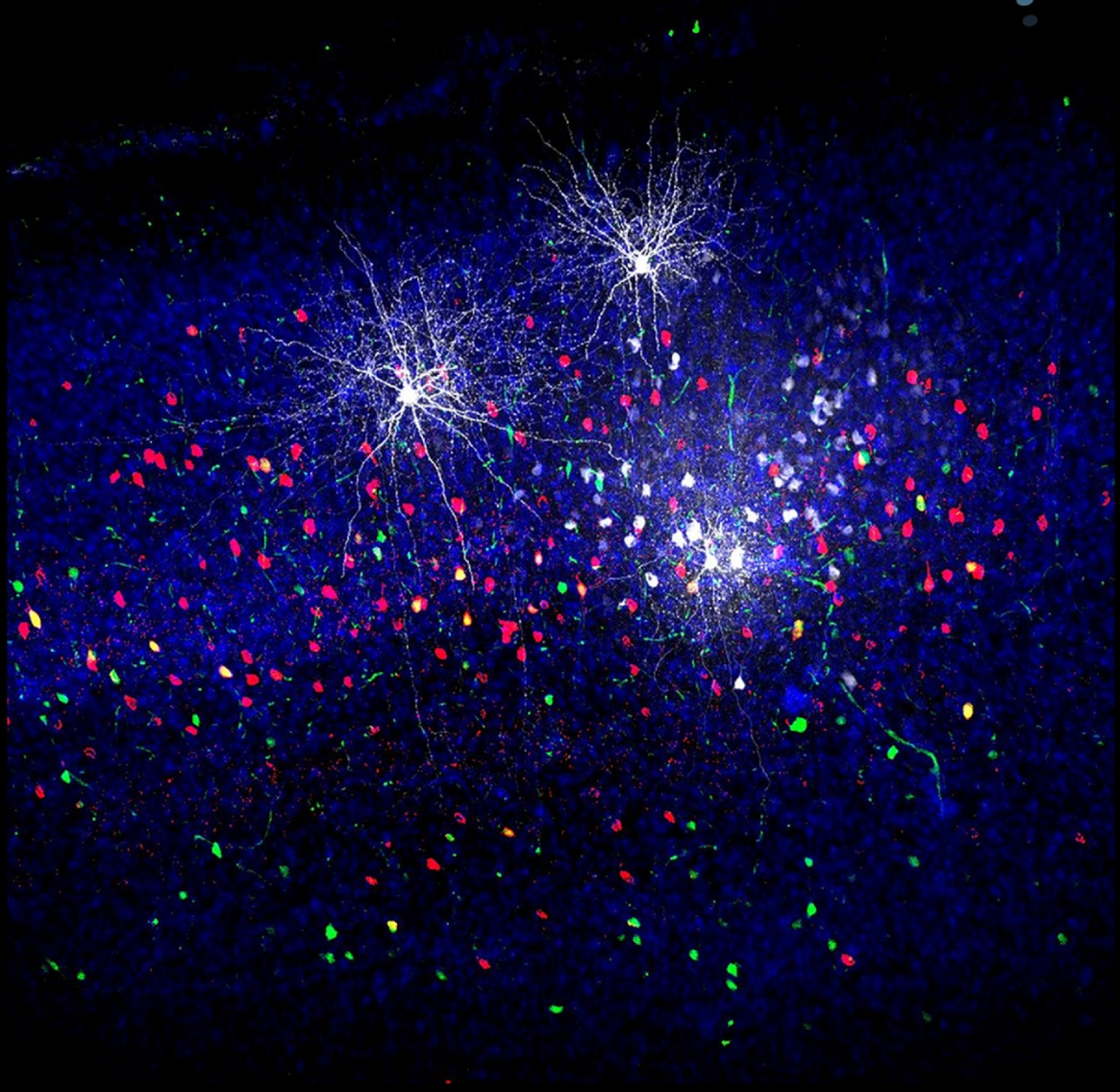
PhD CONFERENCE

iCoNeT



Experimental and Theoretical Perspectives on Neural Networks

October 1-2, 2013
Bernstein Center Freiburg

http://www.bcf.uni-freiburg.de/events/conferences-workshops/20131001-phd-conference

Program at a glance

	Tuesday, 1.10.	Wednesday, 2.10.
10:15 – 10:30	*Welcome by the organizers*	
	Basal Ganglia session	**Pathology session**
10:30 – 11:15	Kevin GURNEY	Valérie CREPEL
11:15 – 12:00	Arthur LEBLOIS	Christian MOLL
12:00 – 14:00	*Lunch*	*Lunch*
	Vision session	**Learning & memory session**
14:00 – 14:45	Sonja HOFER	Christoph SCHMIDT-HIEBER
14:45 – 15:30	Philipp BERENS	Henning SPREKELER
15:30 – 16:00	*Coffee break*	*Coffee break*
	Cortical dynamics session	
16:00 – 16:45	Johannes LETZKUS	Tiago BRANCO
16:45 – 17:30	Jonathan TOUBOUL	Jianfeng FENG
17:30 – 18:00	*Coffee break*	*End of the conference*
18:00 – 20:00	**Poster session**	
20:00	*Conference dinner*	

Organizing committee:

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Program

Tuesday, 1st of October 2013.

10:15 Welcome word from the organizers

Basal Ganglia session (chair: Marko Filipović)

10:30 **Kevin Gurney, Sheffield, UK**
"Dopamine-modulated dynamics of the GABAergic striatal microcircuit"

11:15 **Arthur Leblois, Paris, France**
"Function and dysfunction of the Basal Ganglia: from model to patient"

12:00 Lunch

Vision session (chair: Marko Filipović)

14:00 **Sonja Hofer, Basel, Switzerland**
"The emergence of functional microcircuits in visual cortex"

14:45 **Philipp Berens, Tübingen, Germany**
"Recording the entire visual representation along the vertical pathway in the retina"

15:30 Coffee break

Cortical dynamics session (chair: Tiago R. Félix)

16:00 **Johannes Letzkus, Frankfurt, Germany**
"Circuit mechanisms of associative fear learning in auditory cortex"

16:45 **Jonathan Touboul, Paris, France**
"From microscopic to macroscopic dynamics in large-scale networks: Mathematical explorations"

17:30 Coffee break

18:00 **Poster session**

20:00 Conference dinner

Wednesday, 2nd of October 2013.

Pathology session (chair: Antje Killias)

10:30 **Valérie Crepel, Marseille, France**
"Abnormal coding properties of dentate granule cells in temporal lobe epilepsy: role of kainate receptors"

11:15 **Christian Moll, Hamburg, Germany**
"Of mice and men. Clinical and physiological insights derived from invasive recordings in the basal ganglia"

12:00 Lunch

Learning & memory session (chair: Antje Killias)

14:00 **Christoph Schmidt-Hieber, London, UK**
"Probing mechanisms of grid cell formation"

14:45 **Henning Sprekeler, Berlin, Germany**
"A cellular mechanism for systems memory consolidation"

15:30 Coffee break

Cortical dynamics session (chair: Tiago R. Félix)

16:00 **Tiago Branco, Cambridge, UK**
"Dendritic computations in cortical pyramidal cells"

16:45 **Jianfeng Feng, Coventry, UK**
"Exploring mental disorders with imaging genetics approaches"

17:30 End of conference

Abstracts

Philipp Berens

"Recording the entire visual representation along the vertical pathway in the retina"

In the retina, the stream of incoming visual information is split into multiple parallel information channels, represented by different kinds of photoreceptors (PRs), bipolar (BCs) and retinal ganglion cells (RGCs). Here, we record from the majority of these cells in the vertical cone pathway using two-photon (2P) Ca^{2+} imaging in the mouse retina. This dataset allows us to study the computations performed along the retina's vertical pathway and to obtain a complete sample of the information the mouse eye sends to the mouse brain. We recorded light-evoked Ca^{2+} activity from BC synaptic terminals and RGCs loaded with synthetic Ca^{2+} indicator dyes in intact whole-mounted mouse retina using 2P microscopy. Light evoked activity of cone PRs was recorded in slices using transgenic animals expressing a genetically encoded Ca^{2+} indicator (Wei et al., 2012). Simple full-field light stimuli were used. Single cell activity patterns could be clustered into at least 8 functional BC types and at least 15 functionally distinct RGC types. In addition, we presented spatially modulated to identify different previously described functional types such as direction selective GCs. We found 8 functional BC types, which match anatomical types and project to the inner retina in an organized manner according to their response kinetics. The fastest BC types generate clear all-or-nothing spikes. In addition, we found >15 functional RGC types, including classic ON and OFF as well as transient and sustained types. We verified the functional clustering using anatomical data.

Conclusions: Our data suggest that neurons of the retina's vertical pathway can be clustered into functionally defined classes based on their Ca^{2+}-responses to simple light stimuli. This local retinal "information fingerprint" should be very informative for our understanding of neuronal computations in the healthy retina and as a research tool for evaluating specific functional deficiencies in diseased or degenerating retinae.

Tiago Branco

"Dendritic computations in cortical pyramidal cells"

Information is delivered to cortical pyramidal neurons via thousands of synaptic inputs, activated at different dendritic locations with varying degrees of temporal synchrony and in different sequences. Using electrophysiological recordings combined with two-photon glutamate uncaging and calcium imaging, we tested how different regions along single cortical dendrites integrate excitatory inputs, and whether they are sensitive to the sequence of synaptic activation. We found that dendrites of cortical neurons have gradients of non-linear synaptic integration, whereby proximal inputs sum linearly and require precise temporal coincidence for effective summation, whereas distal inputs are amplified with high gain and integrated over broader time windows. The mechanism involves dendritic impedance gradients and non-linear synaptic NMDA receptor activation, and also confers high sensitivity to the temporal input sequence, allowing dendrites to efficiently discriminate different sequences of synaptic activation. Compartmental modeling shows that these properties can be implemented at the level of single branches and of arbitrary regions of the dendritic tree, and contribute to the computation of orientation selectivity in the mouse visual cortex.

Valérie Crepel

"Abnormal coding properties of dentate granule cells in temporal lobe epilepsy: role of kainate receptors"

The dentate gyrus plays a major role at the gate of the hippocampus, filtering incoming information from the entorhinal cortex (Henze et al., 2002; Acsady and Kali, 2007). A fundamental coding property of dentate granule cells (DGCs) is their sparse firing mode (Jung and McNaughton, 1993). They behave as a coincidence detector due to the fast kinetics of excitatory synaptic events restricting integration of afferent inputs to a narrow time window (Schmidt-Hieber et al., 2007). In Temporal Lobe Epilepsies (TLEs), hippocampal neurons display alterations of the temporal organization of neuronal firing that favor the emergence of pathological fast oscillations (Foffani et al. 2007). Beside epileptiform activities, change of neuronal coding properties may also be involved in cognitive impairments in TLE (Hermann et al., 1997; Lenck-Santini and Holmes, 2008; Chauviere et al., 2009). In animal models of TLE and human patients, neuronal tissue undergoes major reorganization; some neurons die whereas others, which are severed in their inputs or outputs, sprout and form novel aberrant connections (Tauck and Nadler, 1985; Represa et al., 1987; Sutula and Dudek, 2007). In both human patients and animal models of temporal lobe epilepsy, it is well established that mossy fibers sprout to form an aberrant glutamatergic network between dentate granule cells. We have previously shown that these new synapses operate via long-lasting kainate receptor (KAR)-mediated events, which are not present in the naive condition (Epsztein et al., 2005). Our recent data reveal that aberrant KAR-operated synapses drastically impact the computational properties of DGCs in TLE. Indeed, KARs, in interplay with I_{NaP}, impose an abnormal temporal dispersion of spike discharge for low synaptic input rate in epileptic DGCs (Epsztein, Sola et al., 2010); in striking contrast, synaptic KARs, together with I_{NaP}, tune DGCs to fire with a robust sustained and rhythmic regime when the input dynamic reach theta-gamma frequencies (Artinian et al., 2011). Therefore, following the modality of synaptic inputs, the coding properties and the firing pattern of DGCs will be modulated in a different way by KAR-operated synapses in chronic epileptic conditions. We propose that these aberrant phenotypes may dramatically alter the coding properties of dentate gyrus in TLE.

Jianfeng Feng

"Exploring mental disorders with imaging genetics approaches"

To understand the complex diseases such as schizophrenia, depression, ADHD, AD and autism, we have collected large and complex data sets with whole genome, whole brain image, behaviour and environment data. To identify the key changed brain areas and key genes in these brain disorders both at the gene and brain image level becomes a challenging and pressing issue for us. In my talk, I will give a brief review of the current status of the imaging genetics. A few successful examples from our group are included to illustrate the theoretical approaches.

At the brain image level, traditionally, brain regions are used to single out the altered regions in the disease. We developed and applied a whole brain association method to tackle the issue and found, for example, in schizophrenia the most changed functional link is between thalamus and postcentral gyrus. Other quantities such as global entropy, local entropy and time-domain entropy are also introduced to facilitate the analysis.

At the brain image and gene level, we have developed and introduced random field theory in our analysis. The method is successfully applied to ADNI dataset, one of the largest data sets in AD, and for the first time in the literature to identify the key changed genes and corresponding brain regions.

If time is permitted, I will then introduce our large scale modeling exercises to help us confirm and test some conclusions above.

Kevin Gurney

"Dopamine-modulated dynamics of the GABAergic striatal microcircuit"

Within the striatum is a GABAergic microcircuit formed by the dominant medium-spiny projection neurons (MSNs) and fast-spiking interneurons (FSIs). While the patterns of interconnectivity in this circuit have been identified, there has been little progress in understanding the computations it performs. In order to address this problem, we have constructed a large-scale model of the striatal GABAergic microcircuit which is constrained by much of the available anatomical and physiological data. The connectivity statistics of the model were based on dendrogram data for MSNs and FSIs, together with cell density estimates. The model neurons were based on a novel variant of the Izhikevich scheme which incorporated dopamine-modulation. A new model of gap junctions between the FSIs was introduced and tuned to experimental data. Finally, we developed a novel spike-train clustering method which allowed us to find groups of synchronised neurons at multiple time-scales.

We found that, with realistic in vivo background input, small assemblies of synchronised MSNs spontaneously appeared, consistent with experimental observations. The number of assemblies and the time-scale of synchronisation were strongly dependent on the simulated concentration of dopamine, with low levels of dopamine promoting synchrony and distinct neural assemblies. This phenomenon may contribute to motor control problems following loss of dopamine cells.

We dissected the contributions of the circuit elements to the formation of the cell assemblies, and found that an MSN-only net showed increased synchrony at higher levels of dopamine than an intact model, indicating a role for FSIs in desynchronising the network. Preliminary experiments with selection properties of the network indicate competitive interaction between densely populated MSN 'channels'.

Sonja Hofer

“The emergence of functional microcircuits in visual cortex”

The ability of the brain to process sensory information depends on interactions of different cell types in precisely connected neural networks in the cerebral cortex. These complex interactions give rise to the selectivity of individual neurons for different sensory features and to a dynamic population code that can distinguish a myriad of sensory stimuli. One way to make sense of this complexity is to discover the rules by which neurons with different roles in the brain interact with each other. We have developed a new method for measuring synaptic connections between neurons with known functional roles in the network. We are using this method to study the organization of local connectivity in the visual cortex and the development of cortical microcircuits. Recently, we have discovered that in mature mice neurons in local cortical circuits are not randomly connected but form specific functional subnetworks, such that pyramidal neurons connect preferentially if they respond similarly to visual stimuli. Now we are focusing on how such fine-scale functional circuits emerge during postnatal development from an immature neuronal network. We find that local connectivity is immature at the time in development when animals first open their eyes and only matures after the experience of normal visual input. Our data indicate that neurons acquire visual feature preference by selecting feedforward inputs before the onset of sensory experience, after which patterned input drives the formation of cortical subnetworks through a redistribution of local synaptic connections.

Arthur Leblois

"Function and dysfunction of the Basal Ganglia: from model to patient"

Experiments performed in normal animals suggest that the basal ganglia (BG) are crucial in motor program selection. BG are also involved in movement disorders. In particular, BG neuronal activity in parkinsonian animals and patients is more oscillatory and more synchronous than in normal individuals.

I will present our new model for the function and dysfunction of the motor part of BG. We hypothesize that the direct (cortex–striatum–GPi) and the hyperdirect pathways (cortex–subthalamic nucleus–GPi) are involved in closed feedback loops of opposite polarity with the thalamus and the cortex. We show that the competition between these two loops provides the BG–cortex system with the ability to perform motor program selection. A two-level decision making is then incorporated, with a cognitive level selecting based on cue shape and a motor level selecting based on cue position, with information flowing from cognitive to motor loops. While decision is initially driven by a biasing signal from the striatum, we show that dopamine modulated learning at corticostriatal synapses is sufficient to drive the action selection based on learned visual cue values as learning progresses.

In our model, moderate dopamine depletion leads to a complete loss of action selection ability, while only high depletion can lead to synchronous oscillations, suggesting that Parkinson's disease motor impairments are not directly related to abnormal oscillatory activity. To investigate the dynamics of these pathological changes experimentally, I recorded spontaneous and movement-related neuronal activity in the internal pallidum of non-human primates during a progressive dopamine depletion process. Early in the protocol, voluntary movements were significantly slowed down and the neuronal response to movement execution was modified. In contrast, synchronous oscillatory activity appeared only after major motor symptoms developed, indeed ruling out causality between the pathological synchronous oscillations and main parkinsonian motor symptoms.

Johannes Letzkus

"Circuit mechanisms of associative fear learning in auditory cortex"

Memory formation is one of the most fundamental and fascinating functions of the brain. While synaptic plasticity as the putative cellular mechanism of learning has been studied in great detail, we know much less about the interactions of different types of neurons in the local network leading to memory formation. In particular, all aspects of circuit function are tightly regulated by different types of local inhibitory interneurons, but their role in learning is poorly understood. To address this question, we record activity in identified neurons in auditory cortex during formation of an associative auditory fear memory. Our results indicate that a mild foot-shock, which drives learning in this paradigm, elicits strong and differential responses in different types of auditory cortex interneurons, leading to disinhibition of pyramidal neurons. Importantly, optogenetic manipulations counteracting the observed disinhibition of pyramidal cells exclusively during the foot-shock strongly reduce fear memory acquisition, directly demonstrating causality between circuit events in auditory cortex and learning at the behavioral level. In addition, recent experiments suggest that disinhibition during the foot-shock is also a crucial mechanism for fear learning in the amygdala. Taken together, our results highlight the importance of interneuron-interneuron interactions for memory formation and suggest that disinhibition as a permissive mechanism for induction of learning-related plasticity is a general mechanism of aversive learning.

Christian Moll

"Of mice and men. Clinical and physiological insights derived from invasive recordings in the basal ganglia"

Beyond their practical relevance, intraoperative microelectrode recordings during stereotactic neurosurgery for medically refractory movement disorders (such as Parkinson´s disease and dystonia) provide unique close-up views on cellular processes in otherwise inaccessible depth structures. However, in the absence of data from healthy controls these results are notoriously difficult to interpret. In my talk, I will give a brief overview on our work during human surgery for movement disorders and complementary recordings carried out in the rodent laboratory.

The first part of my talk will focus on the striatum, which is the main input structure of the basal ganglia and central to all downstream flow of information through its components. Therefore, understanding of the striatal microcircuitry is key to advancing our knowledge of basal ganglia function in both health and disease. The physiological dissection of main cellular components of the human striatum will be compared to similar attempts in the striatum of healthy rats and mice, as well as to results from a genetic knock-out model of parkinsonism.

The second part of my talk will address the question how neuronal activity within surgically relevant basal ganglia compartments (i.e., globus pallidus and subthalamic nucleus) relates to the clinical phenotype of patients suffering from different movement disorders and how these signals may be used to improve therapy.

Finally, I will provide examples for distinct cognitive responses recorded in several structures along the human cortico-basal ganglionic-thalamic axis. These results may add to our current understanding of the physiological contributions of the basal ganglia to higher order brain processes.

Christoph Schmidt-Hieber

"Probing mechanisms of grid cell formation"

Neurons in the medial entorhinal cortex (MEC) exhibit a remarkable grid-like spatial pattern of spike rates that has been proposed to represent a neural code for path integration. How grid cell firing in MEC stellate cells arises from the combination of intrinsic conductances and synaptic input is not well understood. To address this question, we combine in vitro and in vivo experiments. Using two-photon glutamate uncaging in MEC stellate cells in slices from medial entorhinal cortex, we are examining how their dendritic excitability may contribute to shaping the input-output function during grid cell firing. In parallel, we are making whole-cell patch-clamp recordings in mice navigating in a virtual reality environment, in order to determine the membrane potential signature of stellate cells during firing field crossings. Together, these experiments are providing crucial information for a quantitative understanding of the cellular basis of spatial navigation, as well as essential constraints for grid cell models.

Henning Sprekeler

“A cellular mechanism for systems memory consolidation”

Ever since patient H.M. - arguably the most famous case study in neuroscience - we know that damages of a specific region of the brain, the hippocampus, causes a loss of memories for recent events while preserving memories of events in the distant past. Declarative memories are therefore only transiently dependent on the hippocampus, and appear to be gradually transferred into cortical networks. This process - termed "systems memory consolidation" - apparently takes place during sleep and is thought to be essential for long-term memory retention. Its cellular or systems level implementation, however, is still far from clear.

In my talk, I will suggest a mechanism for the consolidation of memories from hippocampus to neocortex. I will posit that the full consolidation process consists of a cascade of small consolidations steps, which gradually increase memory lifetime. In each step, memories are copied from one set of synapses to another by a combination of spike timing-dependent plasticity - a form of synaptic plasticity that is widely found in the brain - and a generic anatomical network motif that is also prominent throughout the nervous system. I will use theoretical arguments and simulations to first illustrate the mechanism in one of these consolidation steps, and then show that a hierarchical iteration of the same principle 1) can lead to power-law forgetting, i.e. to long memory retention times and is 2) consistent with lesion studies. I will close by discussing that the same mechanism could also serve for the consolidation of other forms of memory (such as perceptual or motor learning) and as a generic mechanism that simplifies information flow in cortical networks.

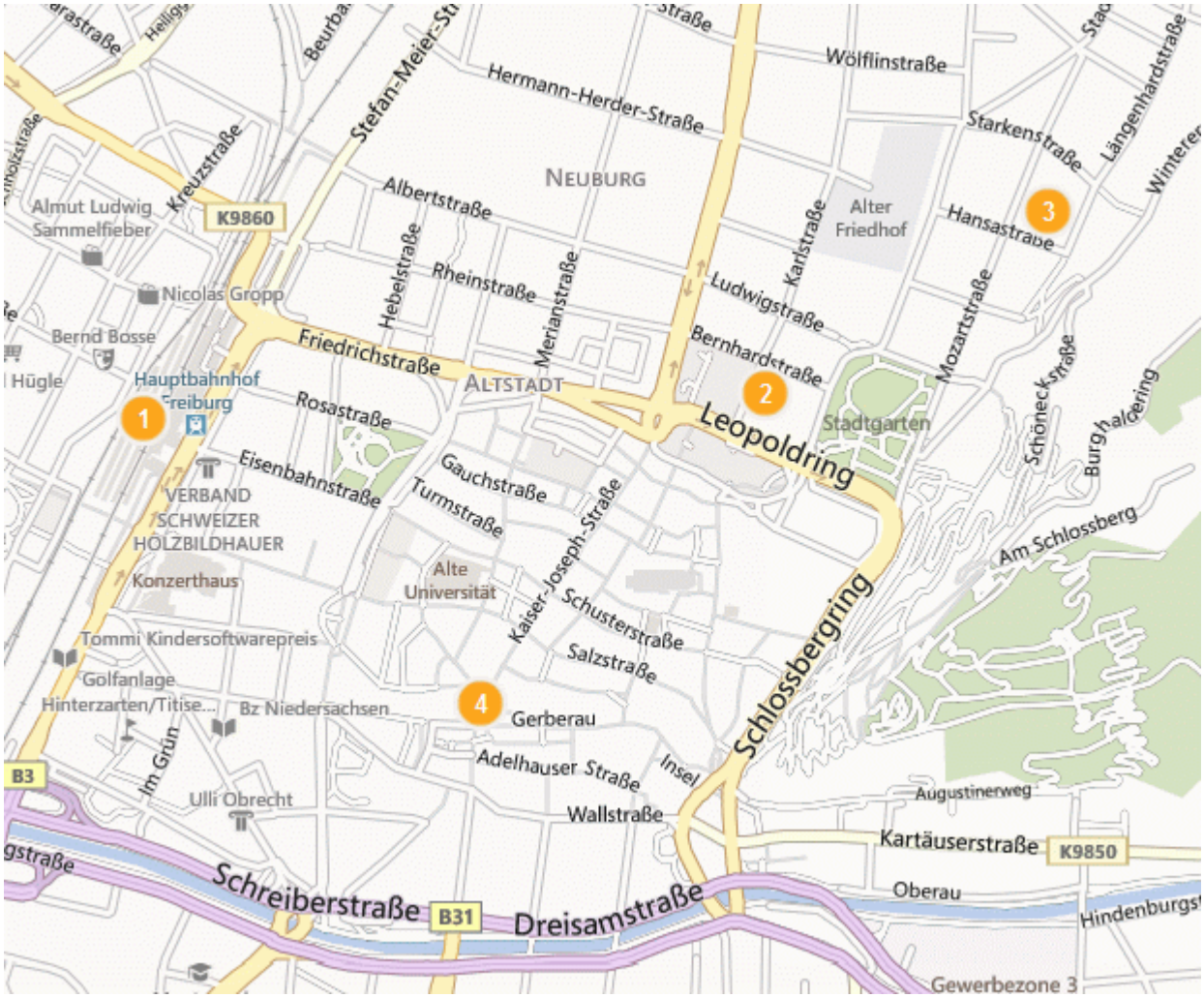
Jonathan Touboul

“From microscopic to macroscopic dynamics in large-scale networks: Mathematical explorations”

The brain is composed of a very large number of cells interconnected in an intricate fashion and subject to an intense noise. The cells composing these networks, as well as the interconnections, show a high degree of heterogeneity. These structures raise a number of mathematical issues that I will present in this talk. In particular, I will explain how the theory of statistical physics and stochastic calculus allows characterizing the state of large-scale neuronal assemblies in the presence of noise and heterogeneities. This provides a useful framework to rigorously address the role of noise and heterogeneities in the large-scale dynamics, and a few noise-induced transitions will be presented.

Speakers in alphabetical order

Find your way



1: Freiburg‘s main train station
2: Hotel – Stadthotel Freiburg, Karlstrasse 7
3: Venue – Bernstein Center Freiburg, Hansastrasse 9a
4: Conference dinner – Martinsbräu, Kaiser-Joseph-Strasse 237

Notes

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