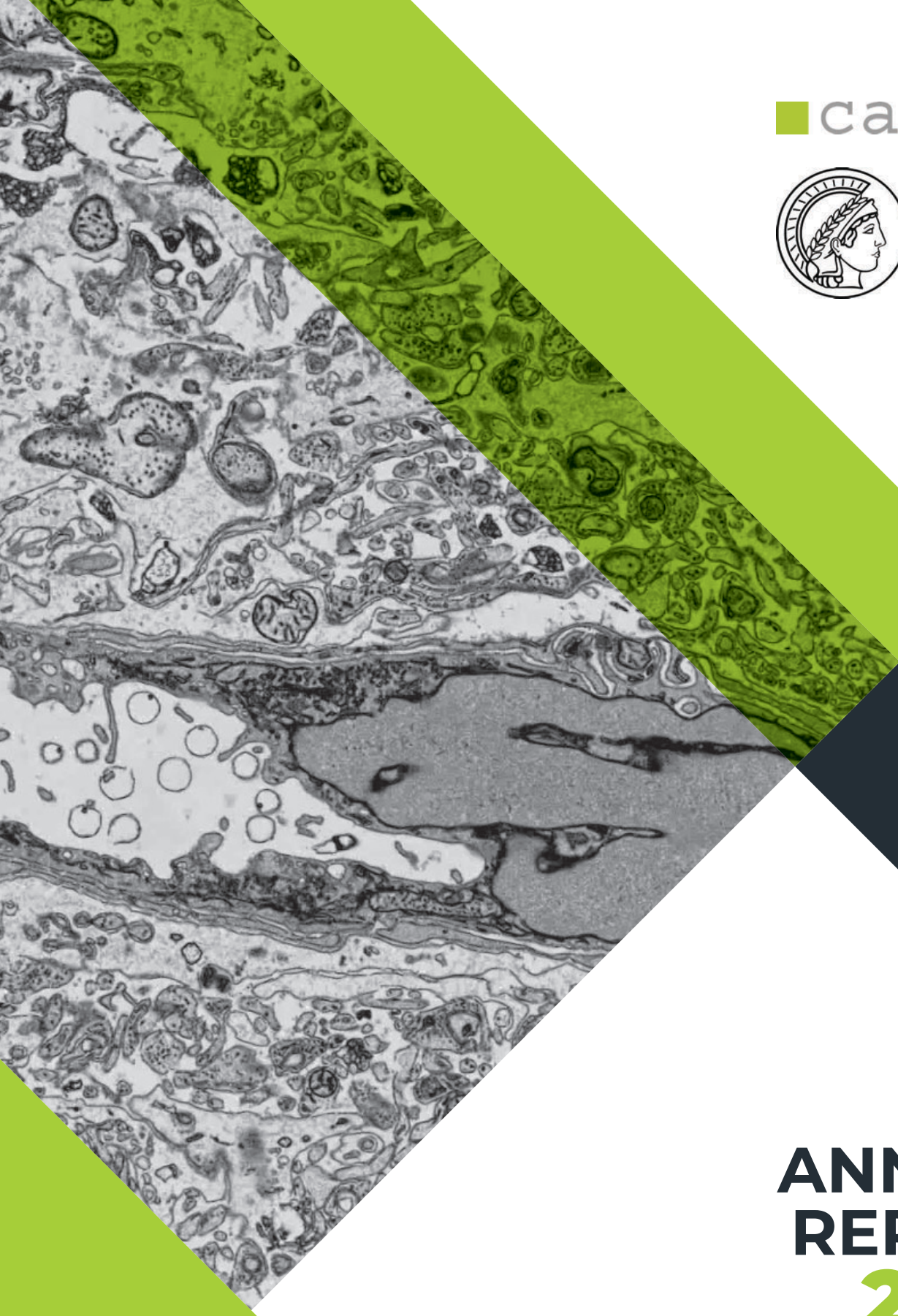
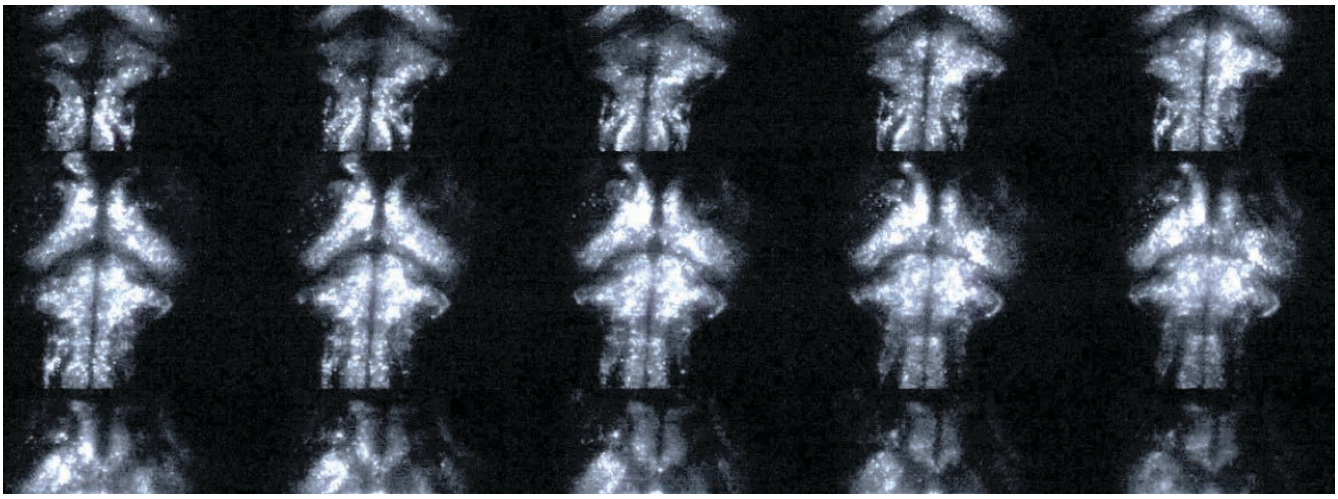


caesar

associated with the Max Planck Society

ANNUAL REPORT 2018

PREFACE



As a neuroethology institute, the research groups at caesar study how the collective activity of the vast numbers of interconnected neurons in the brain gives rise to the plethora of animal behaviors. To this end, our research groups and departments bring a collectively unique combination of experimental and computational approaches together. Our research spans a large range of temporal and spatial scales, from nano-scale imaging of brain circuitry to large-scale functional imaging of thousands of neurons in the brain, to the quantification of natural animal behavior across many species.

Over the past year we have continued to build caesar into a unique neuroethology institute. As a vibrant research environment requires a critical mass of young researchers, in 2018 we held a search symposium with the aim of attracting two new group leaders to fill vacancies created by outgoing group leaders who moved on to professorships.

This approach was successful in identifying two outstanding young scientists to join caesar in 2019. Dr. Monika Scholz comes from the Department of Physics, Princeton University, New Jersey, USA and uses the foraging behavior of the roundworm *C. elegans* to investigate general principles of signal compression, attention and context-dependency in neural systems.

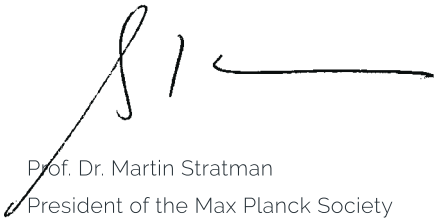
Dr. E. Pascal Malkemper, from the Institute of Molecular Pathology (IMP), Vienna, Austria works with the subterranean African mole rat (*Fukomys anselli*) to study the neurobiological basis of magnetic orientation in mammals. The arrival of the new groups will add to the number of species studied at caesar and the experimental approaches to study core questions of neuroscience. To ensure that caesar is in a position to fully implement its ambitious scientific concept, a plan was developed to modernize and expand our core scientific facilities, which was fully endorsed by the Foundation Board in December 2018.

Given that a major current challenge in neuroscience is how to integrate findings at disparate scales, we invited a range of internationally renowned scientists, from both experimental and theoretical neuroscience, to share their expertise on how to bridge between relevant scales of brain structure and function as well as between experimental data, numerical simulations and conceptual models. To this end, the 7th International caesar Conference was held on June 5th and 6th, 2018 under the topic of "Missing links in neuroscience: Bridging scales in theory and experiment". The conference also provided an excellent opportunity to gather the regional neuroscience community at caesar for scientific exchange.

Finally, like many others of the more than eighty Max Planck institutes, on September 14th 2018 we opened our doors to the public and gave the opportunity to hear about some of the research undertaken at caesar. This "Max Planck Day" marked two milestone anniversaries: the 70th anniversary of the foundation of the Max Planck

Society, and the 100th anniversary of Max Planck being awarded the Nobel Prize in physics for his discovery of energy quanta. This celebration provided an excellent opportunity to showcase some of the work from two of our Group leaders with a public lecture.

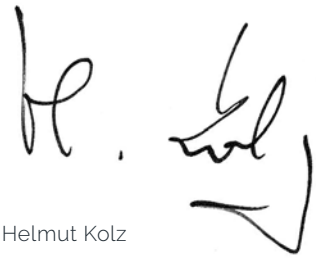
We anticipate that the up and coming year at caesar will be as productive as the past year, providing a fruitful and collaborative research environment for studying vexing problems at the interface of brain and behavior.



Prof. Dr. Martin Stratman
President of the Max Planck Society
Chairman of the Foundation Board

Dr. Kevin Briggman
Managing Scientific Director

Prof. Dr. Jason Kerr
Scientific Director



Helmut Kolz
Administrative Director

Prof. Dr. Martin Stratmann

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OUR RESEARCH

caesar is a neuroethology institute that studies how the collective activity of the vast numbers of interconnected neurons in the brain gives rise to the plethora of animal behaviors. Our research spans a large range of scales from the nano-scale imaging of brain circuitry, to large-scale functional imaging of brain circuitry during behavior, to the quantification of natural animal behaviors.

The function of the brain is to coordinate and control animal behaviors. Establishing the link between the brain and behavior is known as 'neuroethology' and requires the combination of research studies focusing on different levels of detail - ranging from the dense anatomical reconstruction of neural circuits to the quantitative behavioral analysis of freely moving animals. The central goal of neuroethology is to understand how the collective activity of the vast numbers of interconnected neurons in the brain gives rise to the plethora of animal behaviors. A major current challenge in neuroscience is how to integrate findings at these disparate levels of scale so that the behaviors of an animal can be understood in terms of activity on the scale of neural circuits; for it is how an animal makes use of computations in the brain that is ultimately important, not how brain computations are performed in isolation. What makes this an especially challenging problem is that the link between brain function and behavior can only be studied in a behaving animal, and studying the brain in action poses substantial technical challenges. By overcoming these technical hurdles, both experimental and computational, this approach allows us to address some of the big unanswered questions in neuroscience, such as how the brain maintains a dynamic model of the environment and makes decisions and how the brain enables complex social interactions.

caesar is a research institute dedicated to the neuroethological study of animals. The research groups and departments bring a collectively unique combination of experimental and computational approaches to bear on the question of how the brain controls behavior. Our research spans a large range of scales from the nano-scale imaging of the brain, to large-scale functional imaging of thousands of neurons in the brain, to the quantification of natural animal behavior. Our expertise drives the development of new technological contributions, both in experimental instrumentation as well as in computational modeling and data analysis methods. In addition to the technological breadth of the research groups and departments at caesar, our neuroethological questions are comparative in nature and incorporate a diverse set of species allowing us to study the wide repertoire of behaviors across the animal kingdom.

ABOUT THE FOUNDATION

The institute is operated by a non-profit foundation under private law. The president of the Max Planck Society chairs the foundation board. Trustors are the Federal Republic of Germany, the Federal State of North Rhine-Westphalia and the city of Bonn.

caesar is regularly evaluated by a scientific advisory board. The scientific evaluation, as well as all other scientific measures are being conducted according to the procedures and criteria of the Max Planck Society.

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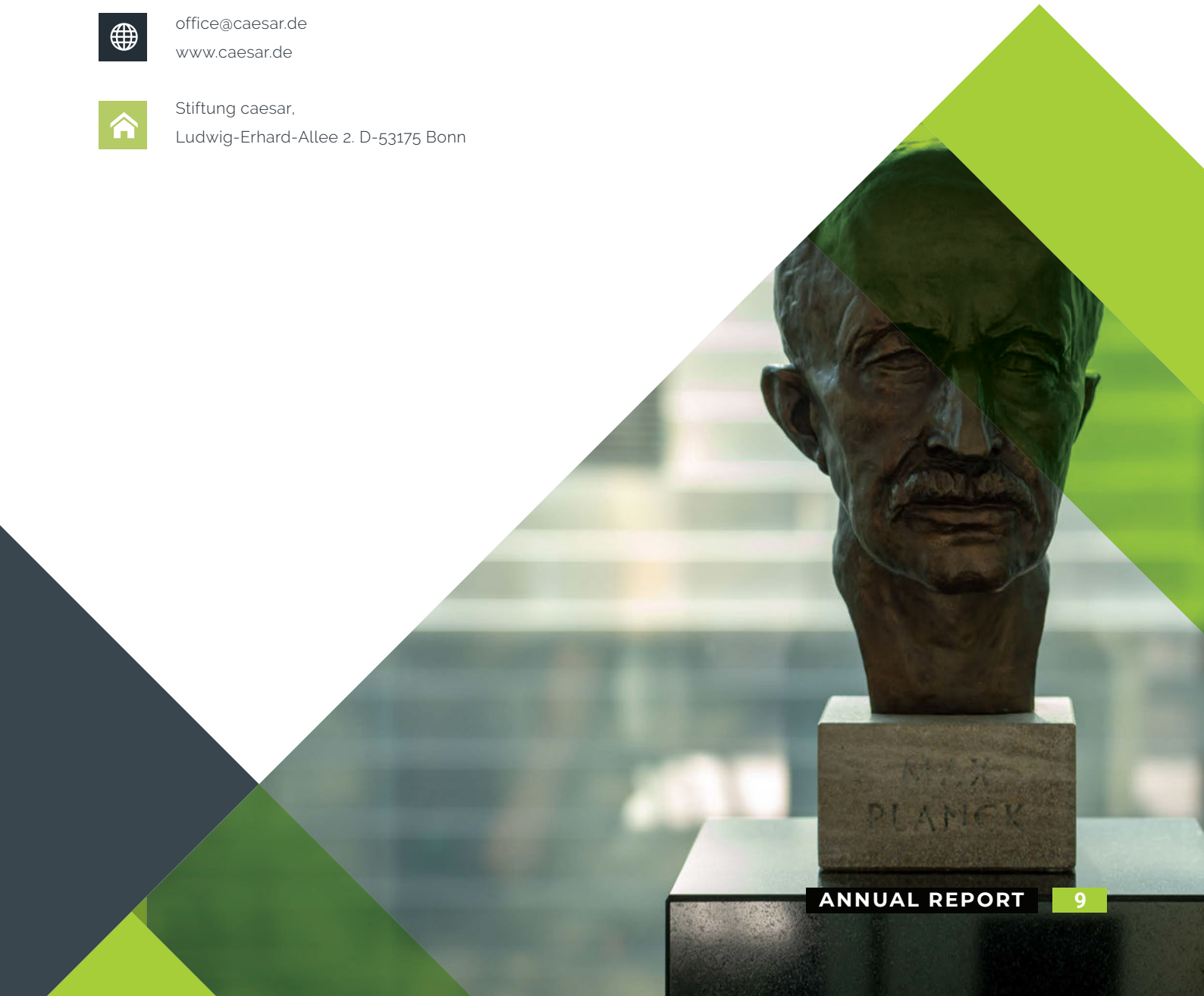


SCIENTIFIC REPORTS

Research groups in 2018

DEPARTMENT OF
COMPUTATIONAL NEUROETHOLOGY

DEPARTMENT OF
BEHAVIOR AND BRAIN ORGANIZATION

MAX PLANCK RESEARCH GROUP
IN SILICO BRAIN SCIENCES

MAX PLANCK RESEARCH GROUP
NEURAL CIRCUITS

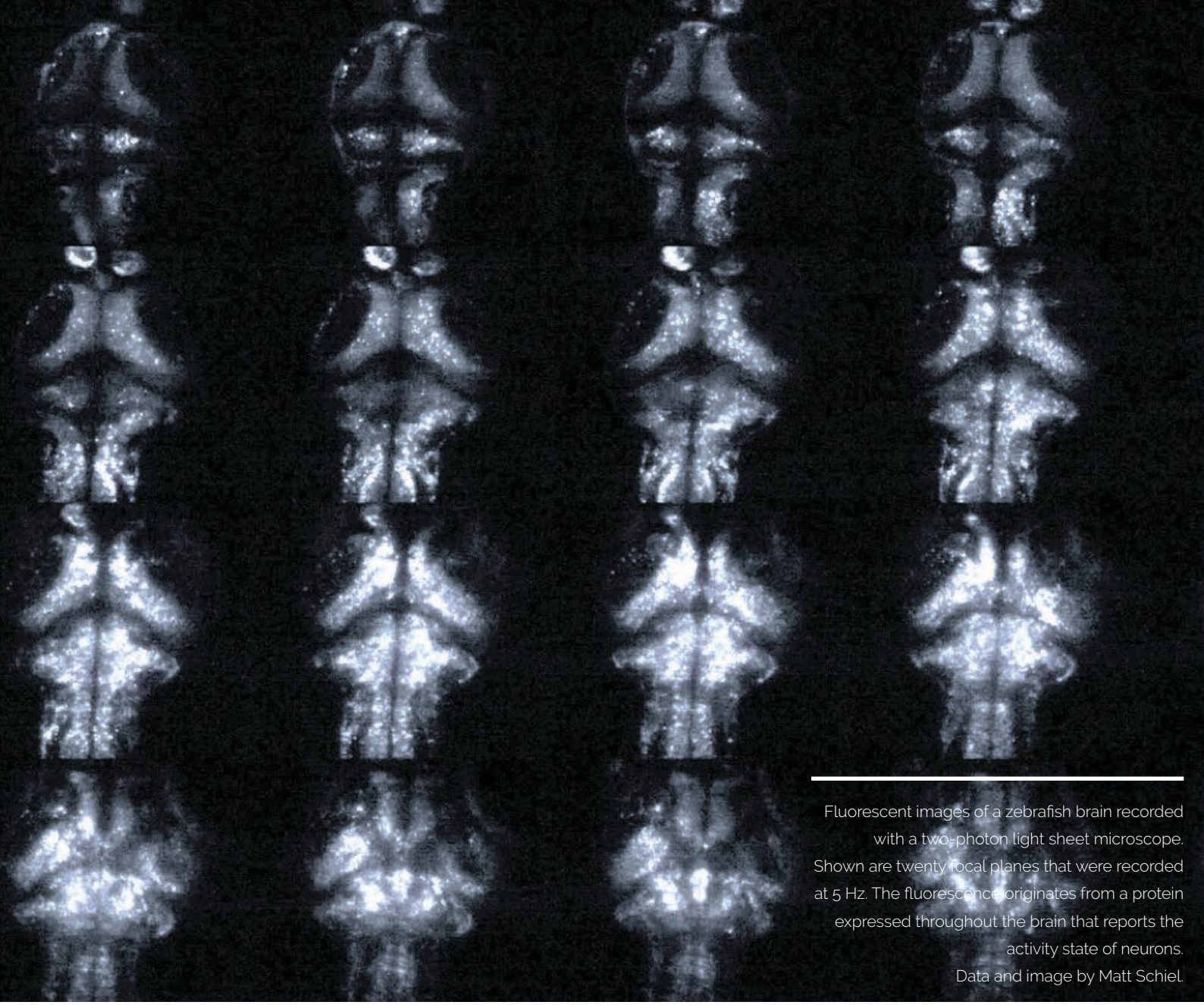
MAX PLANCK RESEARCH GROUP
NEURAL SYSTEMS ANALYSIS

MAX PLANCK RESEARCH GROUP
STRUCTURAL DYNAMICS OF PROTEINS

EMMY NOETHER GROUP
NEUROBIOLOGY OF FLIGHT CONTROL

EMERITUS GROUP
MOLECULAR SENSORY SYSTEMS

MAX PLANCK FELLOW
CHEMICAL BIOLOGY



Fluorescent images of a zebrafish brain recorded with a two-photon light sheet microscope. Shown are twenty focal planes that were recorded at 5 Hz. The fluorescence originates from a protein expressed throughout the brain that reports the activity state of neurons. Data and image by Matt Schiel.

Scaling up cellular resolution whole brain imaging

By Kevin Briggman, Computational Neuroethology

Our primary goal is to relate the synaptic connectivity of neural circuits in the central nervous system to the computations they perform. Identifying these circuit mechanisms would aid our understanding of how brain networks translate sensory information and respond with appropriate behaviors.

We are particularly interested in the initial stages of sensory processing in the visual and olfactory systems. Using a multidisciplinary approach including optical imaging, electron microscopy, electrophysiology and computational modeling, we seek to map the synaptic connectivity of each neuron in a circuit after having previously recorded their functional properties. We take a comparative approach, studying sensory pathways in both the mouse, fish, and frog nervous systems to take advantage of the experimental advantages in each model system. By understanding the wiring in typical wild-type animals, we ultimately aim to provide a baseline of comparison to eventually study wiring deficiencies under pathological conditions.

Retinal connectomics

In 2018, we continued our collaborative studies of the detailed connectivity of neurons in the mammalian retina. A collaboration with Dr. Sebastian Seung's group at Princeton University led to the most complete accounting to date of the diversity of morphological types of retinal ganglion cells in the mouse retina [1]. We also contributed to studies of the detailed synaptic wiring of intrinsically photosensitive retinal ganglion cells [2] as well as the amacrine cell circuit that mediates nighttime versus daytime vision [3]. One of our ongoing goals is to study the evolution of retinal circuits across mammalian species. In our recent research [4] we compared the retinal circuitry responsible for the computation of visual motion between rabbit and mice. We are in the process of extending this approach to study the detailed neuroanatomy of the primate retina and the fish retina. We have successfully collected large-scale anatomical datasets from the retina of a macaque monkey and are in the process of analyzing the connectivity of the thousands of neurons contained within the data (Fig. 1).

Correlative microscopy and whole brain imaging

An important component to understanding how synaptic wiring relates to circuit function is to explicitly link the function of neurons to their connectivity. We are approaching this both from a physiological perspective by recording neural activity from large populations of neurons as well as from a genetic perspective by mapping the proteins different neuron types express. We have chosen to focus on vertebrate species in which the brain volume is small enough for us to record from nearly every neuron in the brain prior to mapping neuronal connectivity. Using the zebrafish as a model organism, we constructed a microscope that

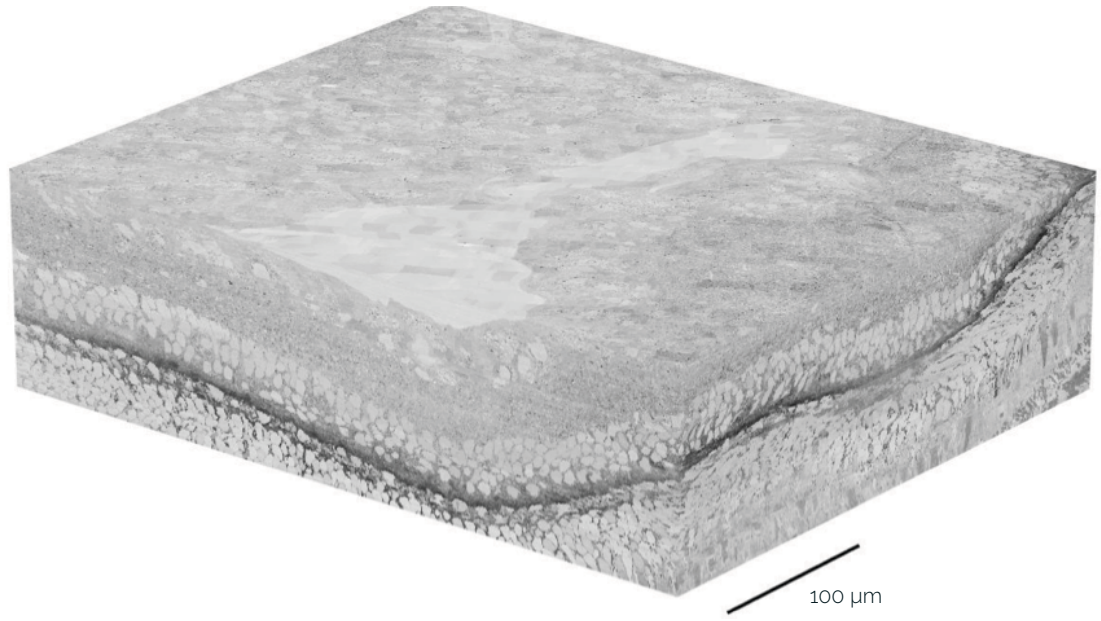


Figure 1. A 3D electron microscopy data volume of a macaque monkey retina. This dataset was acquired with a novel method to collect thousands of serial sections and then imaged with a multibeam scanning electron microscope. We are in the process of reconstructing neurons from this volume. Data and image by Kara Fulton, Silke Haverkamp and Paul Watkins.

allows us to record from tens of thousands of neurons throughout the brain as the fish responds to external stimuli. This two-photon light sheet microscope uses infrared light to avoid perturbing the visual system as we record. We typically sample 20 focal planes rapidly to sample neurons across the dorsal to ventral axis of the brain (image page 12). We are in the process of analyzing such large-scale neural recordings to identify neurons that are related to the animal perceiving external stimuli and neurons that convert that perception into a behavioral response. Following each functional recording experiment, we preserve the brain and use serial-section electron microscopy to collect nanometer resolution neuroanatomical data from the entire brain using a multibeam scanning electron microscope. We have recently developed a novel automated method to collect the tens of thousands of serial tissue sections from plastic embedded brain tissue that are required to map each and every neuron throughout the zebrafish brain. Finally, we have completed a computational pipeline to align the terabyte-scale datasets that we are now able to routinely collect.

In parallel efforts we have developed a method to label the proteins within neurons with fluorescent antibodies. The challenge has been to combine such an approach with subsequent electron microscopy of the tissue. Antibodies are relatively large proteins and previous protocols have required dissolving cellular membranes to allow them to penetrate deep into the brain. The step of dissolving membranes corrupts the ability to subsequently collect high-quality neuroanatomical data with electron microscopy. Our new optimized correlative microscopy protocol removes the need to dissolve membranes and therefore improves the ability to first label proteins within neurons and then reconstruct how the labeled neurons are connected to each other.

Aquatic transgenic facility

Finally, we established an aquatic facility in the department in 2018 to house multiple aquatic species for our studies going forward. The facility is designed to rear various fish species as well as frogs which allows us to compare neural circuits across evolutionary time scales. We are in the process of applying the latest gene editing technologies to generate transgenic animals expressing proteins that will allow us to monitor the activity of neurons across the brain as well as manipulate neuronal activity in behaving animals.

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DEPARTMENT OF COMPUTATIONAL NEUROETHOLOGY

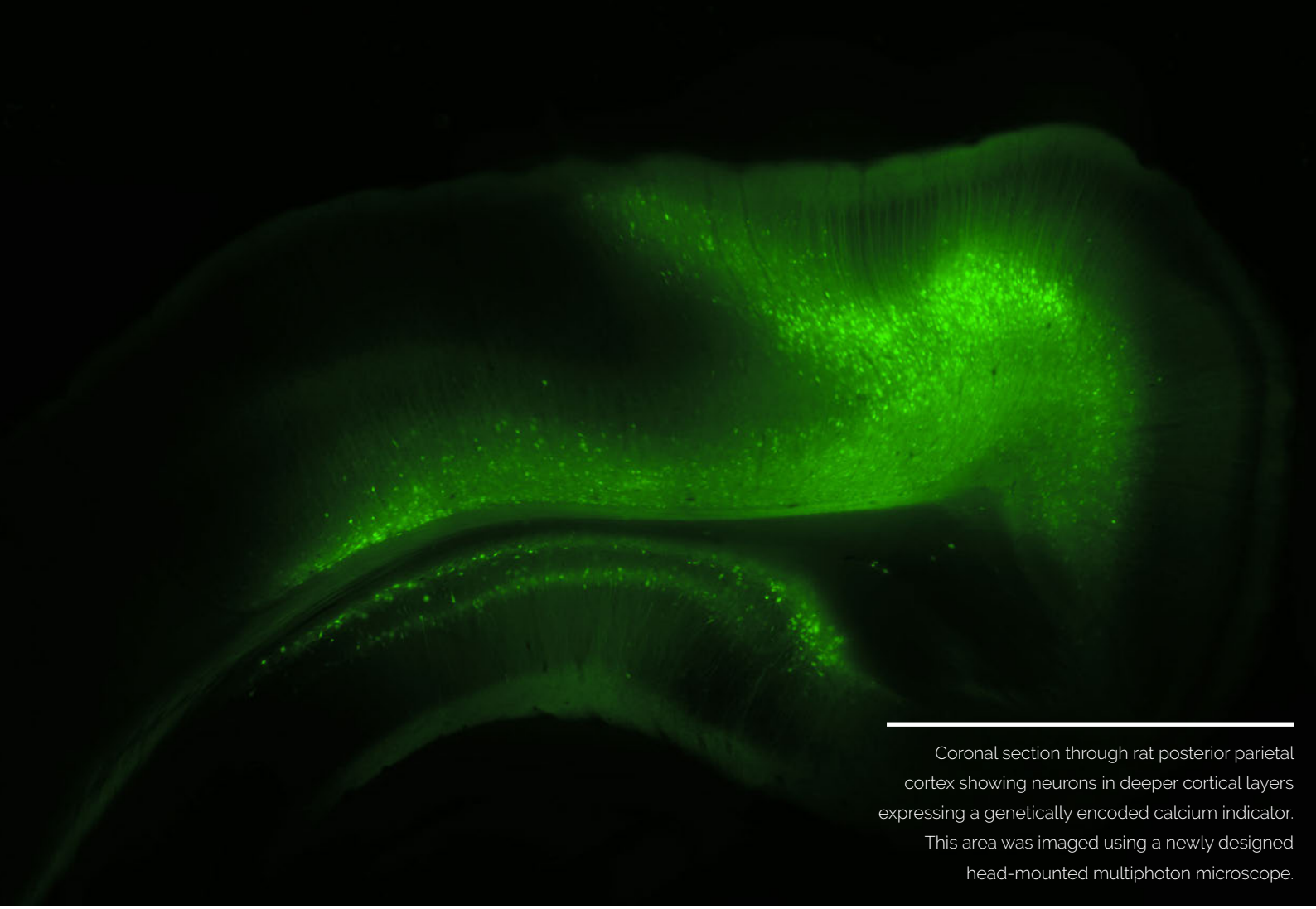
Kevin Briggman

Scientific Director

Computational Neuroethology

The goal of the Department of Computational Neuroethology (CNE) is to develop computational models which can predict goal-directed animal behaviors. To acquire the data needed to build biologically plausible models, we develop and utilize a muti-disciplinary range of experimental techniques. We record cellular resolution images of neuronal populations from behaving animals. In addition, we use fluorescence microscopy to identify the expression patterns of specific proteins. Finally, we reconstruct synaptic connectivity using 3D electron microscopy.

By combining these methods within individual brains, we aim to discover the relationships between the structure and function of neuronal networks driving behavior. Firstly, we want to understand how sensory stimuli are transformed in the brain to ultimately generate motor decisions. Building on this understanding, we aim to identify the sources of variability during goal-directed behaviors. To address these questions, we compare and analyze neural circuits across mammals, fish and amphibians to determine which aspects of a computation are species-specific and which generalize across species.



Coronal section through rat posterior parietal cortex showing neurons in deeper cortical layers expressing a genetically encoded calcium indicator. This area was imaged using a newly designed head-mounted multiphoton microscope.

Watching the brain in action: Circuit interrogation in freely moving animals

By Damian J. Wallace and Jason N. D. Kerr,
Behavior and Brain Organization

The function of the brain is to coordinate and control animal behaviors. The link between brain function and behavior can only be studied in a behaving animal, but studying the brain in action poses substantial technical challenges. In the department BBO we are developing new imaging tools to quantify brain activity as well as behavior in the freely moving animal. In this section of the annual report we outline some of the challenges as well as the future prospects for imaging neuronal activity in the freely moving animal.

Developments in imaging tools are making it possible to record activity from both large neuronal populations and sub-cellular components in freely moving animals. With the combination of both genetically expressed optical probes [1] and linear and non-linear imaging techniques [2], activity recordings from large neuronal populations and the manipulation of circuits in behaving animals have become mainstays of neuroscience. Conventional microscopes that use multiphoton excitation facilitate the optical interrogation of circuitry by allowing unambiguous measurement from single cells and subcellular structures or, when combined with activity-reporting fluorescence probes, by assigning the resulting fluorescence unambiguously to the emitting structure. This ability was a major breakthrough for studies of animals trained in complex behavioral tasks as the same circuitry could be interrogated over days with single-cell specificity [3]. Although the ability of optical methods to generate such detailed information about neuronal activity in the performing brain has been defining neuroscience for the past decade, transferring these abilities to freely moving animals, as was achieved for intracellular and extracellular electrical recordings [4,5], is still a major technical challenge. At the core of these challenges are both the interpretation of the resulting activity transients, which should be comparable with the vast reams of electrical recordings collected under equivalent behavioral conditions, and the quantification of behavior. More recently, with the ability to functionally establish the tuning of neurons

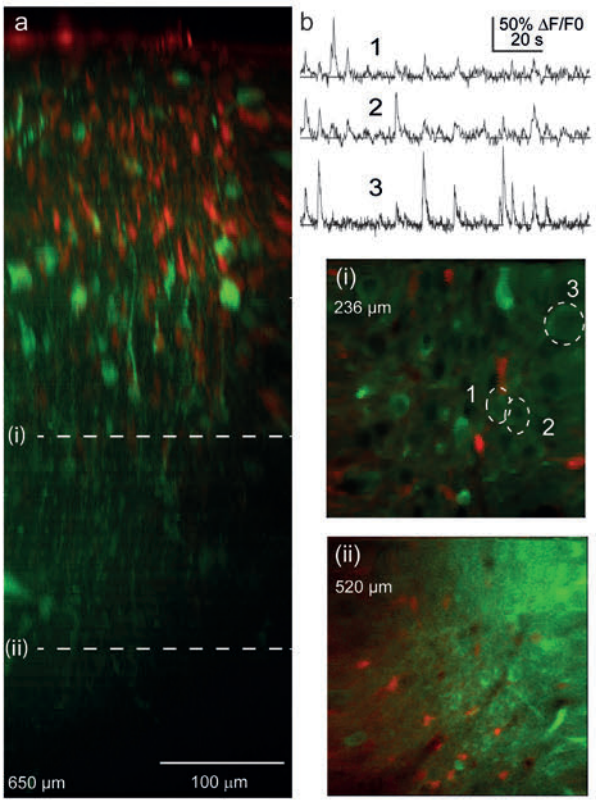


Figure 1. a. Side-projection of an image stack acquired with a head-mounted 2-photon microscope of rat cortex with bulk-expressed genetically encoded Ca^{2+} indicator (GCaMP6s, green) and sulforhodamine 101 (red) for astrocyte staining. b. Upper, simultaneous Ca^{2+} transients of spontaneous activity recorded from neurons shown in b. middle. Middle, xy image of stained neurons shown in a. taken from 236 µm below pia surface. Lower, xy image of stained neurons shown in a. taken from 520 µm below pia surface.

and then build a circuit-level model by reconstructing the neuronal circuitry at the nanometer scale [6], neuroscience has been making progress toward the goal of a mechanistic understanding of neuronal circuitry [7,8]. In the following, we introduce available techniques for imaging freely moving animals in the context how they relate to the goal of achieving a mechanistic description of the neuronal basis of animal behavior. Although these developments are enabling relationships between brain activity and complex behaviors to be explored, many challenges need to be overcome before the potential of the freely moving animal can be fully utilized.

Why freely moving?

Studying the freely moving animal, by definition, is about gaining access to animal behaviors that are self-determined and during which the animal is free to use all of its available resources, such as sensory and vestibular systems, to make informed behavioral choices. The discovery of place cells [5], head-direction cells [9] and grid cells [10] exemplifies the benefits of this approach. With further, carefully controlled experiments, the initial findings were shown to rely, at least partially, on the various self-generated motion cues and external landmark cues available to the animal. As another example, eye movements are large and constant in freely moving rodents but essentially absent under head restraint, where the vestibular system is unstimulated [11]. Although it is possible to further investigate some of these findings in head-restrained animals, it is difficult to imagine how they would have been discovered in the absence of free movement. Given the advantages provided by imaging technologies for the interrogation of neuronal circuitry and the insights provided by electrophysiology in unrestrained animals, the motivation for imaging in the freely moving animal is obvious.

What is in the imaging toolbox?

Techniques are about gaining access to new areas to explore. The range of imaging techniques for freely moving animals can be considered as tools to explore the brain during behavior. As with all toolboxes, it is important to know the limits and applicability of the available tools, as one tool cannot be applied to all situations and the data gleaned have their limitations. Current systems for imaging activity in the freely moving animal fall broadly into three categories: fiber-type systems, single-photon miniature microscopes and multiphoton miniature microscopes, all of which have advantages and disadvantages concerning the type and resolution of data that can be collected and how these data can be related back to the underlying neuronal circuitry that generated them.

In the fiber-type systems, the majority, if not all, of the microscope optics and acquisition system is based remotely from the animal, and the on-animal components are limited to an implanted optical fiber with or without a GRIN lens system. The simplest of these systems involves implanting an optical fiber, which serves for both excitation and detection, in close proximity to the labeled area of interest, thereby enabling recording of the bulk-averaged fluctuations in fluorescence through time. Although it is difficult to make circuit-level statements using this approach, when used in combination with selective neuronal labeling in small distinct nuclei, this technique has provided information about, for example, the activity of subpopulations of neurons with specific projection targets [12]. Another implementation of this class of fiber-optic systems combines holography-based patterned illumination, which restricts the lateral and axial excitation dimensions, and allows for targeted optogenetic activation and simultaneous Ca^{2+}-imaging [13]. This sophisticated system can approach near-cellular resolution imaging combined with simultaneous optogenetic manipulation. However, as this system also uses single-photon excitation, the benefits of this approach are realized mainly in sparsely labeled tissue.

Single-photon head-mounted miniature microscopes have the advantage of being lightweight, allow full-frame imaging over large areas, and require minimal tethering, as both the excitation-source LED and the detection sensor are head-mounted [14]. When the microscope is placed within close proximity of the imaging target, these systems provide wide-field cellular activity data. The caveat is that the use of single-photon illumination prevents single-cell resolution, especially in densely labeled tissue, and a complex post-imaging analysis of the resulting fluorescence data is required to make sense of resulting signals. This approach has been successfully applied to tease apart activity in both

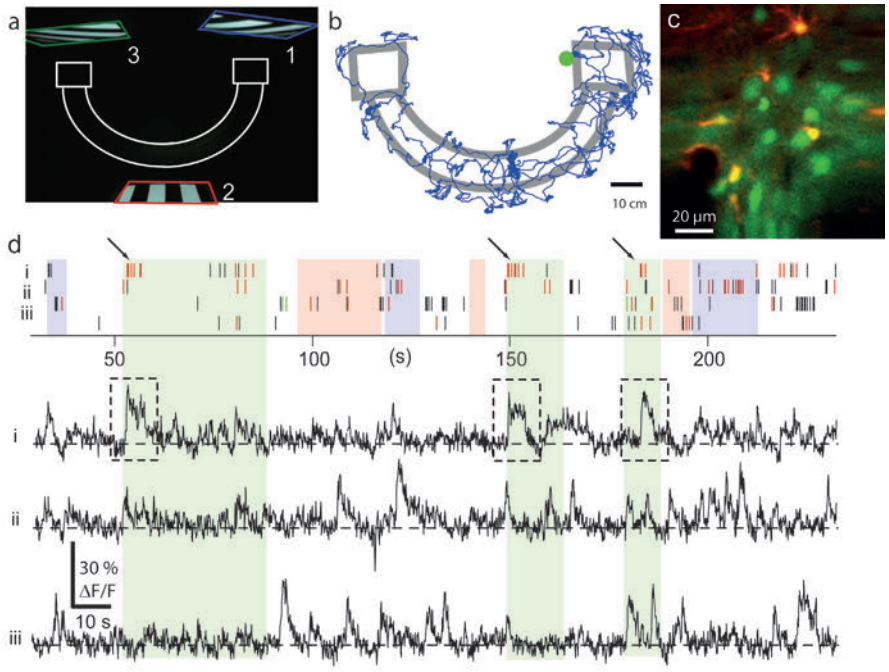


Figure 2. Overhead-camera view of elevated semicircular track and the monitors used for visual stimulation (numbered 1-3). b. Overlay of animal trajectory (blue) on track outline (start at the green circle). c. Overview image of neurons (green) and astrocytes (red sulforhodamine 101) expressing Ca^{2+} indicator (OGB1) taken in L2/3 of rat visual cortex using head-mounted 2-photon microscope. d. Upper, simultaneous Ca^{2+} transients of spontaneous activity recorded from three neurons and a raster plot of resulting inferred spiking (upper raster) recorded from freely moving animal exploring a novel environment. shown below. Coloured background blocks denote when the animal's gaze was towards the monitors displaying static images (a). Note neuronal (i) activity (arrows, and dashed boxes) coincides with periods when the animal's gaze moved across monitor 3 (green).

the hippocampus (15), where neuronal somata are present in a single layer, and the striatum [16], where two sparse populations of neurons were separately labeled. The recent extension of this approach, which incorporates a microlens system in front of the detection sensor, provides high.speed (16 Hz) volumetric imaging in freely moving animals as small as mice when combined with a customized demixing algorithm [17]. Although this approach can detect activity from an impressive number of presumptive neuronal somata in 3D, the technique has limited optical sectioning and therefore the fraction of neurons recorded from remains unclear, at least in the cortex. From a biological perspective, the central limitations of the techniques mentioned so far is the requirement for restricted labeling and the lack of unambiguous single-cell resolution.

Multiphoton miniature microscopes provide the benefit of optical sectioning, which in turn provides cellular resolution, within a depth of several hundred micrometers from the objective lens [18,19]. The advantage of this approach is single-cell and subcellular resolution, which enables unambiguous assignment of activity to neuronal structure, even in densely labeled cortical tissue (Fig. 1). However, the first of these described systems [18], which uses a piezo-based scanner unit, was too heavy to place on a mouse, and the second, using a microelectromechanical scanner [19], has a limited field of view but single-dendritic-spine resolution. Although multiphoton imaging is suited to extracting activity of single cells in densely labeled tissue (Fig. 2), such as the cortex, the downside is that complicated optical pathways are required, and the fiber-based tethering

system restricts the size of the behavioral arena that can be made available to the animal.

Thus, the imaging toolbox contains a variety of approaches with various scales of cellular resolution. But whether single-cell resolution is required depends on the experimental design and the circuit-based questions being addressed. Furthermore, although calcium indicators are designed to report spiking activity, the relationship between the recorded transients and the underlying spiking activity is complex [1]. In order to take full advantage of what parallel recordings have to offer [20], the relationship between calcium transients and the underlying spiking will need to be determined. The single-photon imaging approaches can give rise to useful details when genetically targeted populations of neurons or an isolated pathway are active during behavioral epochs. However, as not all neurons are represented in a recorded dataset it remains to be determined how to place these data into the context of dense circuit reconstructions, as has been achieved in the retina (6). Dense reconstruction of neural tissue with synapse-level precision [6,7,21] is now feasible for tissue volumes comparable in size to the imaging fields of view achievable with these imaging systems for freely moving animals. These dense reconstructions allow the development of circuit models, which in turn can be used to generate predictions of circuit function. Combining dense reconstruction with similarly dense functional recordings has the capacity to provide a mechanistic description of the neuronal basis of behavior.

Animal behavior

One of the central benefits of imaging in the freely moving animal is the lack of restrictions imposed on the animal's behavior. Although it is feasible to replicate some behaviors - for example navigation, exploration or object recognition - by using virtual reality in restrained animals [22-24], any uncertainty about the influence of head restraint or the completeness of the environmental reproduction is eliminated if the animal is free to move in a self-determined way. For example, any study of social behavior is limited under head fixation (25), as is any study of the neural basis of prey capture or predator evasion. However, one of the criticisms of the free-movement paradigm is the lack of similarity between trials, as even for a relatively predictable behavior such as gap-crossing, subtle trial-to-trial variability in the animal's behavior occurs. This criticism can be addressed, to a certain extent, by the application of sophisticated high-resolution behavioral tracking of the animal, combined with digital reconstruction of the local environment. With this type of approach, it was possible to reconstruct an individual animal's visual point of view during single trials of gap-crossing, which, in vision studies, allows a moment-by-moment quantification of the visual scene as seen by the animal (11). While the majority of free-movement imaging studies have tracked animal's behavior through simplistic descriptions of position and speed, we believe that the real power of studying neuronal activity in the freely moving animal is yet to come and will require the combination of cellular-resolution population-imaging techniques with high-resolution and detailed quantification of behavior.

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DEPARTMENT OF BEHAVIOR AND BRAIN ORGANIZATION

Jason Kerr

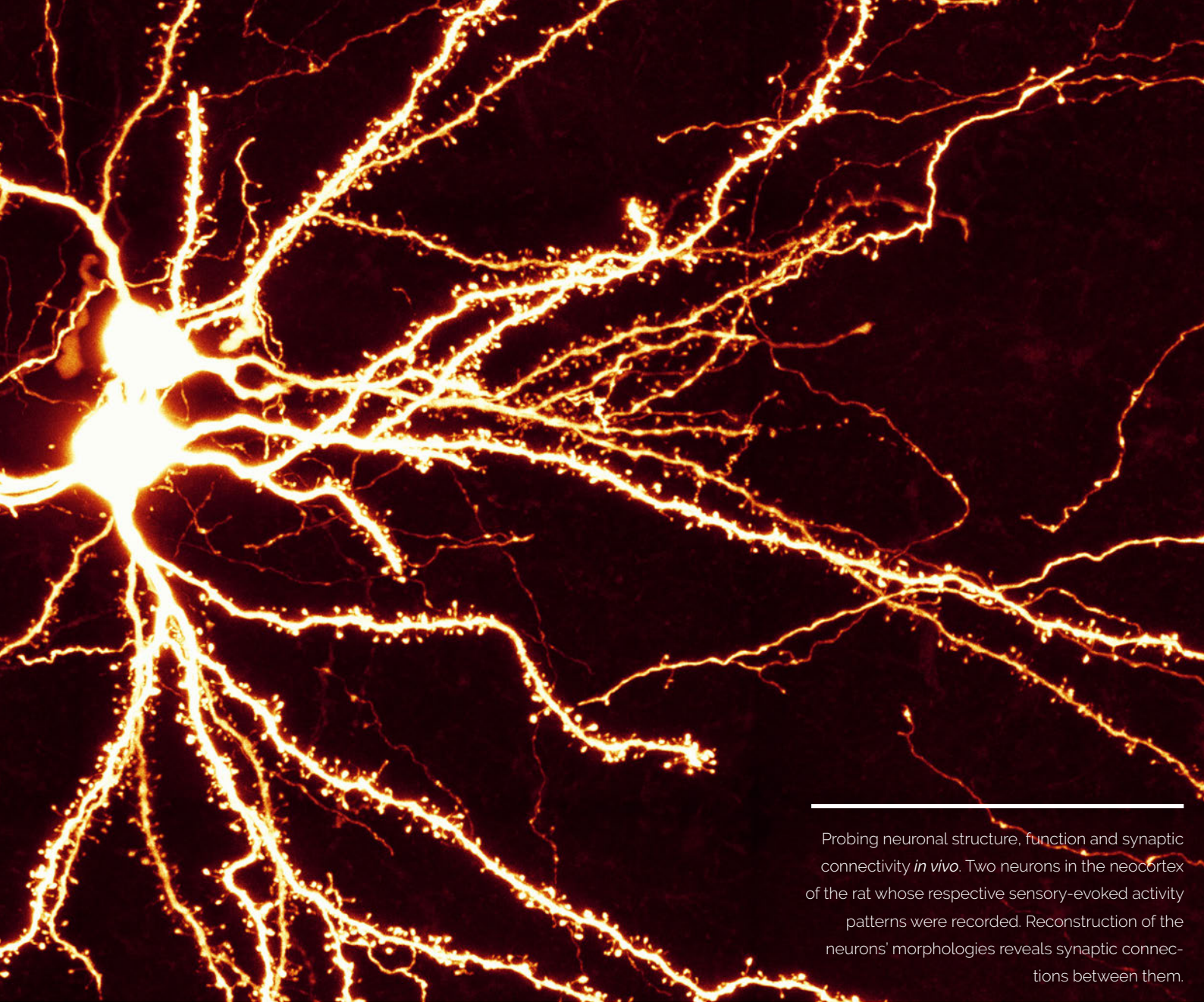
Scientific Director

Behavior and Brain Organization

The primary aim of the Department of Behavior and Brain Organization (BBO) is to understand how mammals use vision to make decisions and what the underlying neural processes are. BBO combines imaging, computation, behavioral analysis, electrophysiological recordings, and anatomical mapping to explore the connection between behavior and neuronal activity.

The research of BBO can be divided into two broad regions. The first develops tools and techniques, which have single cell and single action-potential resolution, for recording and analyzing neuronal activity from large populations of cortical neurons in the awake and freely moving mammal.

The second is focused on understanding the neuronal mechanisms underlying vision-based decision making in freely moving mammals. This involves the development of special multiphoton microscopes and of optics-based head and eye tracking techniques that can be used on freely behaving animals from a range of mammalian species. The use of different species allows, for example, the comparison of how the eye movements of different animals vary in coordination and nature. The overall aim of this approach is to generate a thorough understanding of mammalian vision and the organization of the underlying neuronal circuits.



Probing neuronal structure, function and synaptic connectivity *in vivo*. Two neurons in the neocortex of the rat whose respective sensory-evoked activity patterns were recorded. Reconstruction of the neurons' morphologies reveals synaptic connections between them.

Cortex in Silico – Digitizing the brain's networks

By Marcel Oberlaender, In Silico Brain Sciences

In 2018, we generated an anatomically detailed digital representation of the rat 'barrel cortex', a brain region concerned with processing sensory information that is acquired during rhythmic movements of whiskers on the animals' snout.

Background

Understanding how the brain is able to tranform sensory input into behavior is one of the major challenges in systems neuroscience. While recording/imaging during sensory-motor tasks identified neural substrates of sensation and action in various areas of the brain, the crucial questions of 1) how these correlates are implemented within the underlying neural networks and 2) how their output triggers behavior, may only be answered when the individual functional measurements are integrated into a coherent model of all task-related neuronal circuits.

Our group uses the whisker system of the rat for building such a model in the context of how a tactile-mediated percept (e.g. object shape via whisker touch) is encoded by the interplay between different cellular and network mechanisms. Rodents, such as rats and mice, actively move their facial whiskers to explore the environment. Our group has developed approaches for generating a digital (i.e., in silico) representation of the rodent whisker system. The resultant anatomically and functionally detailed neuronal network models allow performing computer simulations that mimic the *in vivo* stream of whisker-evoked excitation at subcellular resolution and millisecond precision. The simulations provide unique opportunities to investigate how the interplay between different cellular and network properties can give rise to neural substrates that underlie sensory information processing, and ultimately sensory-guided behaviors.

Barrel Cortex *In Silico*

In a series of previously reported studies, we had characterized the structure and whisker-evoked function for a representative sample of individual neurons that comprised all of the major cell types in the rat barrel cortex and thalamus (reviewed in [1]).

In 2018, we have succeeded to combine these data with precise measurements of the barrel cortex geometry and its cellular composition. We demonstrate that our computational approaches for integrating such systematically collected data into a common framework result in digital representations of the

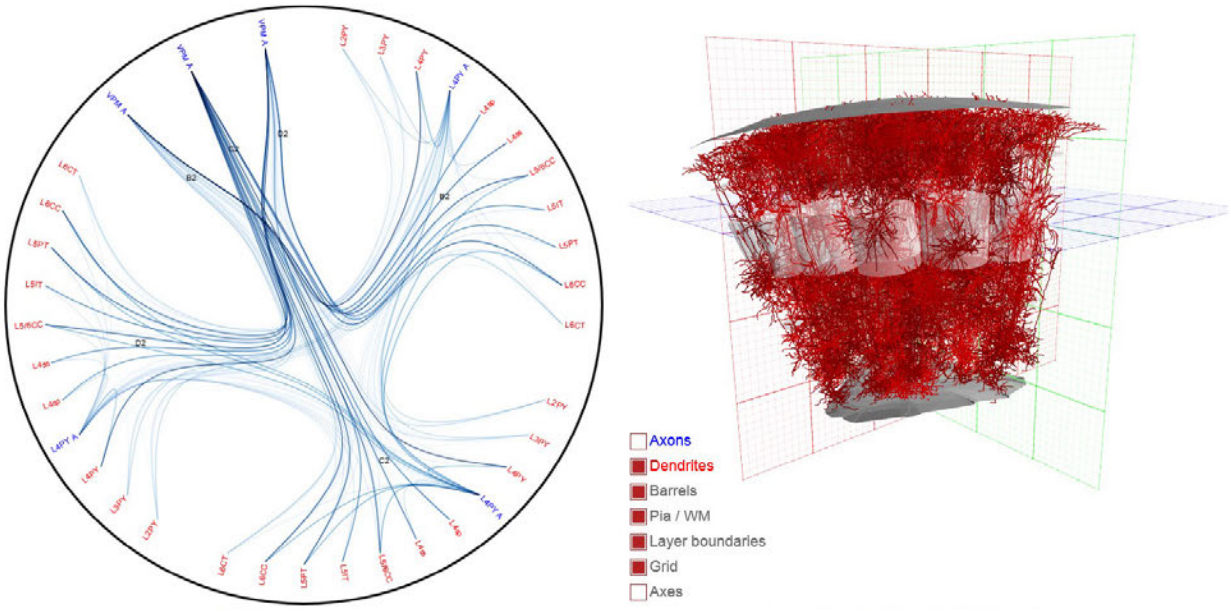


Figure 1. Digital model of the rat barrel cortex, which is based on systematically collected empirical anatomical data, such as precise reconstructions of the cortex geometry, cellular composition and synaptic connectivity. The model is accessible via a publically available web interface, which allows (1) exploring our data, (2) performing of virtual experiments, and (3) comparing the predictions of these *in silico* experiments with empirical measurements. Image was adopted and modified from (Udvary et al., in preparation).

neuropil – the Barrel Cortex *in Silico* – that mimic in anatomical detail and complexity the structural organization observed empirically for this area of the neocortex.

In contrast to previous studies that reported large-scale neuronal network models (e.g. the Blue Brain Project), synaptic wiring patterns in our models were not constrained by a particular set of empirical connectivity measurements. Instead, wiring patterns in the Barrel Cortex *in Silico* represent predictions from mathematical rules, which reflect assumptions about how synapses form. This difference is of utmost importance, because we show that any empirically determined statistics about neocortical wiring will be systematically affected by the ways in which neuronal populations are sampled. Extrapolation of sampling-dependent statistics to larger volumes, different cortex areas and/or cell types is hence in general not justified.

Our novel approach for generating neuronal network models is neither limited to a particular set of synapse formation rules, nor to the rat barrel cortex. We therefore designed a web-based version of our computational frameworks – Cortex *in Silico* – which provides a set of interfaces to explore, test and compare different synapse formation hypotheses. The functionalities of Cortex *in Silico* are depicted on the website as follows (Figure 1):

1. Explore the digital model of the rat barrel cortex. Learn more about the structure and function of this brain region, and explore the empirical data the model is based on. Registered users are eligible to download the complete model for their own scientific purposes.

2. Test hypotheses of synaptic wiring by performing *in silico* experiments to compare empirical connectivity measurements with those predicted by the digital model. The in silico predictions are compatible with data acquired by all of the currently available experimental strategies that measure connectivity at subcellular, cellular and network levels.

3. Discover which hypotheses of synapse formation are most consistent with your empirical data. Utilizing the advanced settings of *in silico* connectivity experiments, you can specify your own mathematical rules for

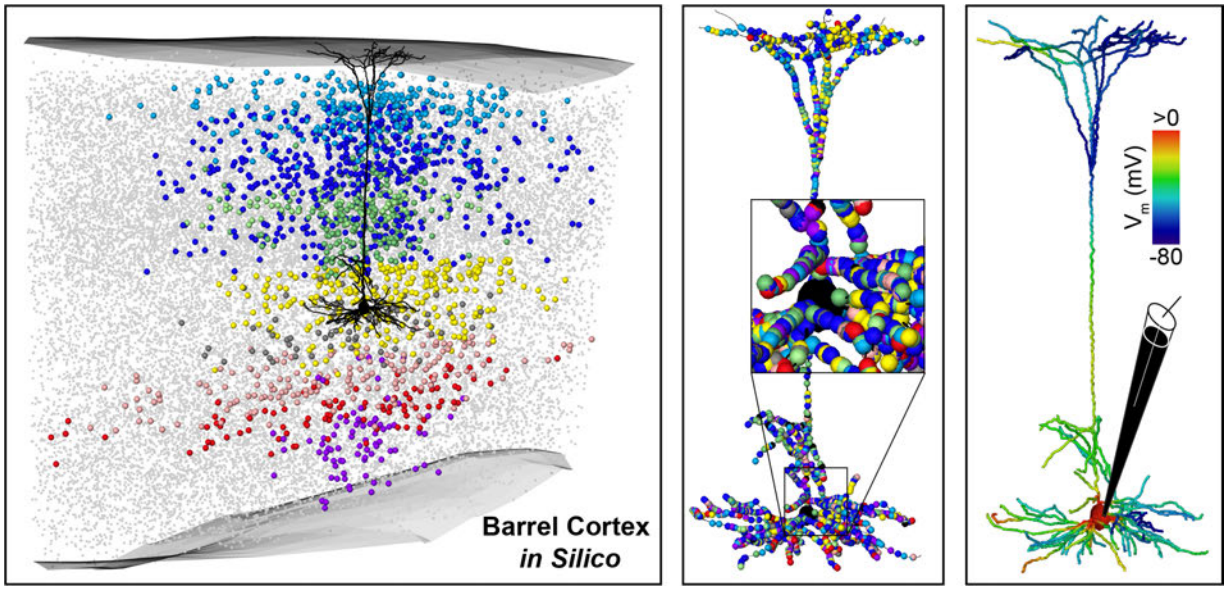


Figure 2. Left panel: Pyramidal tract neuron (PTN, black) embedded into anatomically realistic network model of rat barrel cortex. Spheres (colored by cell type) represent cell bodies of those neurons that can provide input to the PTN (all other neurons are shown in grey). Center panel: Location of putative synaptic inputs along the dendrites of the PTN from those neurons shown in the left panel. Right panel: Exemplary simulation of how *in vivo*-like synaptic inputs that mimic whisker touch are integrated by the dendrites and cell body of the PTN model.

synapse formation, and compare the different predictions.

Cortex in Silico is hence more than 'just' a web-based version of our digital barrel cortex model. It provides a general strategy, the necessary algorithms and analysis tools for exploring how synapse formation mechanisms shape the logic and organization of neocortical networks.

Outlook

The anatomically realistic network models of the barrel cortex can be combined with functional measurements, which allow performing simulations that mimic the *in vivo* stream of whisker-evoked excitation at single neuron and population levels (Figure 2). We reported first results from such simulations, and confirmed the simulations' predictions empirically by combining *in vivo* recordings with optogenetic input mappings and pharmacological manipulations. We discovered a previously unknown pathway in the deep layers of the neocortex, which amplifies and relays sensory-evoked inputs from the thalamus to pyramidal tract neurons – the major output cell type to subcortical brain regions. We show that activation of this pathway is necessary for pyramidal tract neurons to reliably broadcast the results of cortical processing to downstream target areas [2].

As a long-term goal, we aim to use the strategy introduced above to perform simulations that mimic the conditions during sensory-guided behaviors – for example a whisker-based gap-cross. This ambitious goal requires a quantitative empirical description of all task-related neural networks throughout the rodent brain – beyond the barrel cortex, and physiological access to the function of these networks during the behavior. To address these major challenges, we have started to develop an approach which is based on injections of a multi-trans-synaptic rabies virus into individual facial whisker muscles [3]. The rabies virus crosses synapses in retrograde directions, allowing to first reveal the motoneurons that innervate the whisker muscle, followed by subsequent labeling of neurons of all cell types and in all brain regions that are involved in whisker motor control and sensory-motor feedback.

Ultimately, the combination of rabies virus muscle injections with our computational approaches will set the stage to generate an anatomically realistic model of the brain-wide, whisker-related networks – the 'Whisker Connectome in Silico'.

In 2018, we have attracted third party funding to support our Cortex *in Silico* and simulation projects from the German Research Council (DFG priority program: SPP2041 Computational Connectomics) and the German Ministry for Science and Education (BMBF program on artificial intelligence: Automated, data-driven inference in mechanistic models). Moreover, we have continued our collaboration with Dr. Michael Long (NYU, New York) to transfer our empirical and computational approaches for neuron and network reconstructions to the sound vocalization system of the songbird [4,5].

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MAX PLANCK RESEARCH GROUP

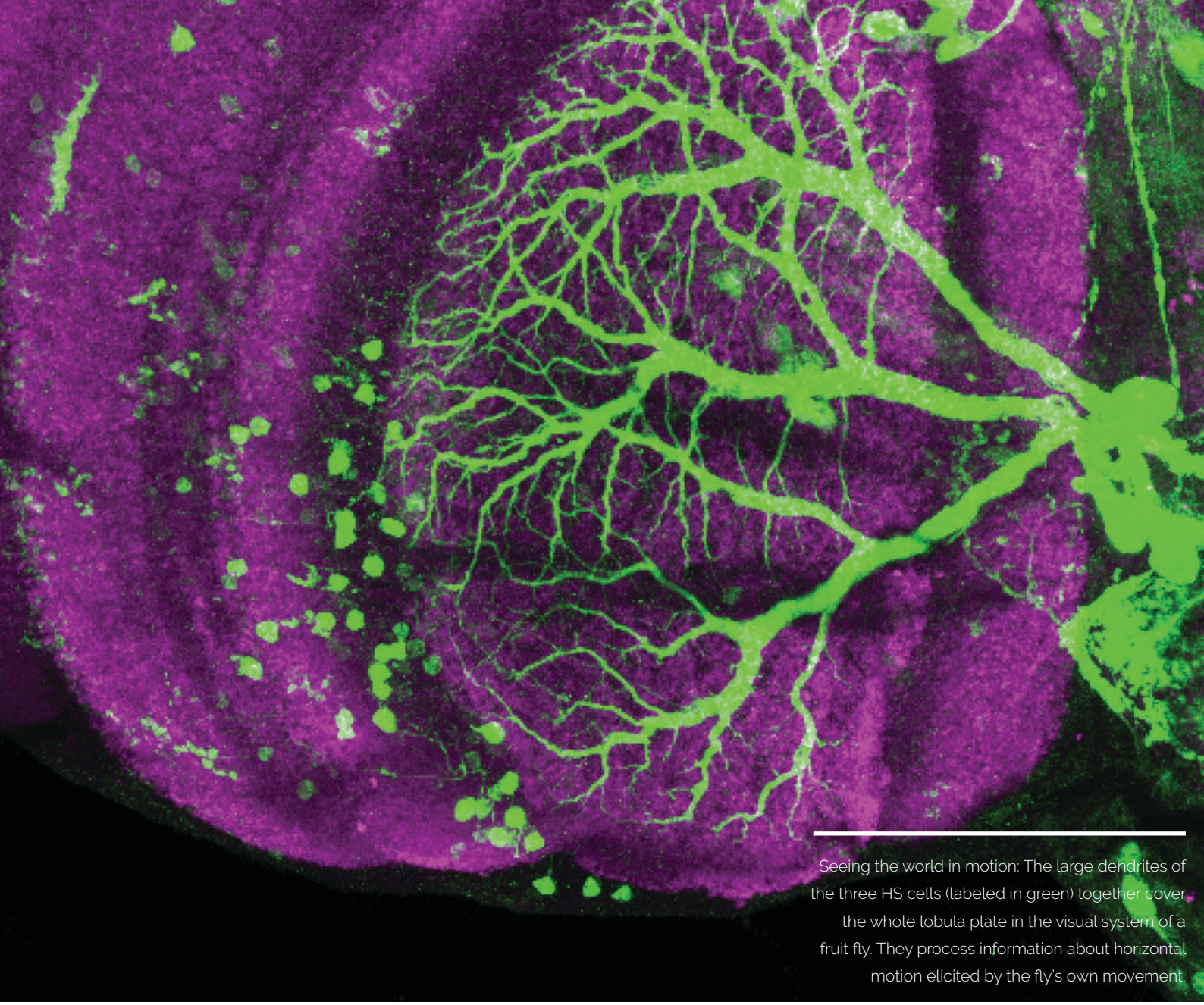
IN SILICO BRAIN SCIENCES

Marcel Oberlaender

Group leader

In Silico Brain Sciences

The overarching goal of our research is to understand how the interplay between biophysical, synaptic, cellular and network mechanisms in the mammalian brain can encode perception and trigger behavioral responses, such as decision making during a sensory-motor task. To pursue this goal our group employs a multidisciplinary approach, combining network anatomy with cellular physiology and computational modelling. The long-term goal of Dr. Oberlaender's research is to generate anatomically realistic neuronal network models, and to use these in silico representations of the mammalian brain for simulation experiments that mimic *in vivo* conditions, for example during sensory-guided behaviors.



Seeing the world in motion: The large dendrites of the three HS cells (labeled in green) together cover the whole lobula plate in the visual system of a fruit fly. They process information about horizontal motion elicited by the fly's own movement.

Neuronal control of a fly's flight path

By Bettina Schnell, Neurobiology of Flight Control

Using the flight maneuvers of the fruit fly *Drosophila melanogaster* as a model system, we study how behavioral actions are controlled by neural circuits and how the behavioral state of an animal in turn influences the processing of sensory information.

Optic flow is useful for guiding locomotion

Everybody has probably experienced this phenomenon: When you sit on a train and a train on the neighboring track starts moving, you often experience the strong sensation that it is yourself who is moving although your body remains stationary. Visual motion of the surrounding (optic flow) can serve as a strong cue for self-motion and is very important for controlling locomotion and image stabilization. Behavioral responses to optic flow have been well described in a variety of species. In flies, optic flow can serve animals to detect deviations from their intended trajectory. Therefore, if you present a fly with a rotating pattern, it will turn with the direction of pattern motion in the so-called optomotor response, which serves to stabilize a straight flight path. This response can even be measured in fixed animals that cannot actually turn by tracking the difference in amplitude of the left and right wing stroke (L-R WSA). The experimental accessibility makes flies perfect model organisms for studying the circuits underlying optomotor behavior.

Large field neurons in the fly process optic flow

Within the lobula plate of the fly (a part of the optic lobes) there is a set of large field visual neurons, the lobula plate tangential cells, that sum input of many local motion detectors. They have very large receptive fields and respond to visual motion in a directional-selective fashion. This makes them ideal candidates for detecting optic flow. Horizontal System cells (HS cells) for example respond strongest to horizontal motion as elicited when the fly rotates around the vertical body axis. HS cells are thus thought to mediate the optomotor response to horizontal motion. HS cells do not fire full-blown action potentials as most mammalian neurons do, but encode information as graded changes in membrane potential. Their membrane potential increases (depolarization) for front-to-back motion on the same side and decreases (hyperpolarization) to back-to-front motion [1]. How information about horizontal motion is further processed on the way to the motor system is not well known though.

Postsynaptic partners of HS cells might temporally integrate visual motion

One of our goals is to find and describe the descending pathways that transmit information from the HS cells in the brain to the flight motor system in the ventral nerve cord, the fly's equivalent of the spinal cord. To first identify neurons, which are postsynaptic to HS cells, we used a novel transgenic tool called transTANGO using a genetic driver line that specifically targets HS cells [2]. Using transTANGO we could identify several neurons that show strong overlap with the axon terminals of HS cells in the central brain (Fig. 1A). Some of them descend to the ventral nerve cord. In the next step we will perform whole-cell patch-clamp recordings from the cell bodies of these neurons to study their responses to horizontal motion during flight in detail. One hypothesis that we are going to test is, whether the responses of neurons postsynaptic to HS cells reflect the temporal integral of the presented visual motion stimulus. I have shown previously that the optomotor response of the fly strongly increases with increasing duration of visual motion, but the membrane potential of HS cells does not [3]. When we measured the increase in calcium concentration in the terminal of HS cells using a genetically encoded calcium indicator, however, we found that the increase in fluorescence upon presentation of horizontal motion strongly increases with increasing duration very similar to the behavioral response. Calcium accumulation in the terminals of HS cells could thus serve as a mechanism for computing the temporal integral, which according to our hypothesis would then be transmitted to downstream neurons via chemical synapses. We would therefore expect that postsynaptic neurons connected to HS cells via chemical synapses encode the temporal integral of the visual motion stimulus, whereas neurons that only make electrical synapses with HS cells do not. Temporal integration in the optomotor system likely functions to fully compensate for perceived error signals (detected in this case as visual rotation of the surround) as in proportional-integral feedback control systems that are very common in engineering.

Flight processing of visual motion in HS cells

The optomotor response is a reflex-like reaction that corrects for any deviations from a straight flight path. How then does a fly turn voluntarily without the optomotor response counteracting the turn? HS cell recordings during tethered flight have recently revealed that an efference copy influences the HS cell membrane potential during saccades [4]. This effect depends on the direction of the turn. During a rightward turn, which leads to motion to the left, the HS cells in the left optic lobe are hyperpolarized and the HS cells on the right are depolarized. The efference copy thus has the right sign to suppress responses of HS cells to the stimulus that would be caused by the fly's self-rotation. However, this has not been conclusively shown, yet. One of our goals it to study the influence of saccades onto the processing of visual motion in HS cells in more detail. To do so, we present rapidly expanding (looming) stimuli that mimic approaching objects, such as predators, on the left or the right side of a tethered fly. These stimuli elicit fast, evasive turns away from the stimulated side, which we can measure as changes in L-R WSA (Fig. 1B,C). Simultaneously we monitor the membrane potential of HS cells using whole-cell patch-clamp recordings [5]. Preliminary results suggest that the effect of looming-elicited turns is different from spontaneous saccades. During looming stimuli, HS cells get hyperpolarized independent of whether the stimulus was presented on the right or the left side, but only during flight not during rest (Fig. 1D,E). Further experiments will be necessary to determine, whether this effect is caused by the looming stimulus itself or whether it is dependent on the fly's behavioral reaction to the stimulus.

Conclusion

Altogether, our findings suggest that processing of sensory information is dependent on the behavioral state in a very specific manner. This is true already at early processing stages, such that information that is not needed might be discarded early on. This flexibility in information processing might explain, how the fly brain with its only ca 10.000 neurons can control sophisticated behaviors such as flight maneuvers.

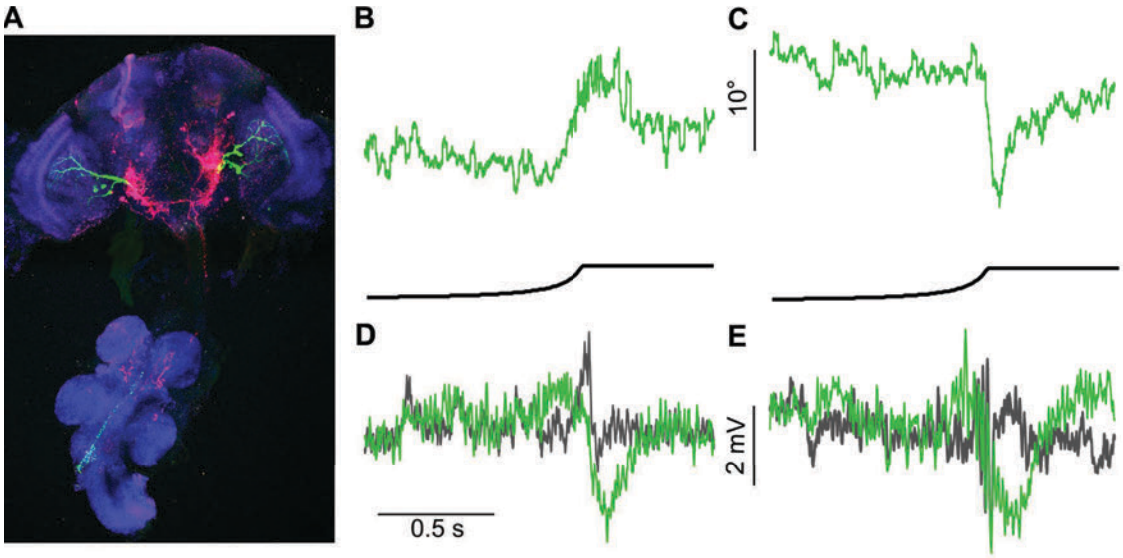


Figure 1. Z-Projection of a *Drosophila* brain and ventral nerve cord, in which transTANGO was expressed in HS cells (green). Potential postsynaptic partners of HS cells are labeled in red. B/C) Turning response (L-R WSA) of a fly to a looming stimulus presented on the left/right. An increase in L-R WSA corresponds to a rightward turn. The angular extent of the stimulus is shown in black. D/E).Membrane potential of HS cells in response to the same stimulus as in B/C, respectively, during rest (grey) and flight (green).

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EMMY NOETHER GROUP

NEUROBIOLOGY OF FLIGHT CONTROL

Bettina Schnell

Group leader

Neurobiology of Flight Control

The research group "Neurobiology of Flight Control" is interested in how the tiny brain of *Drosophila* controls complex behaviors guided by sensory information. To answer that question, we make use of recent technological advances, which allow us to measure the activity of single neurons in head-fixed, but flying flies. In addition, we use the elaborate genetic tool kit available in *Drosophila* to manipulate the function of specific neurons. Combining all these techniques we aim to identify and study individual neurons that control steering maneuvers during flight, the circuits they are embedded in, and the computations they perform. We hope that this work will provide insights into general mechanisms of how neural circuits control behavior and make decisions.

The key to fishing for proteins is not patience, but choosing the right hook. In order to work with and image proteins, we first need to get them onto our sample carriers. For dilute protein solutions this is not a trivial task - especially as proteins, similar to fish, do not like the air-water interface...

Fishing for proteins

By Elmar Behrmann, Structural Dynamics of Proteins

Recent advances in technology and methodology have allowed electron microscopy (EM) access to the near-atomic resolution realm [1]. Still, and not surprisingly, the challenge of first obtaining the protein one wants to study and then getting it onto a sample carrier remains [2].

Investigating smaller and smaller proteins

Cryo-electron microscopy (cryo-EM), primarily owing to the poor contrast of proteins embedded into a vitrified ice layer, was for a long time limited to solving structures of large assemblies such as virus capsids, ribosomes and chaperones. Technical and computational breakthroughs have recently pushed the boundary down from the mega-Dalton regime to several tens of kilo-Dalton. Thus now the majority of proteins has become a potential target to be studied by cryo-EM. Not surprisingly, many place a lot of expectations into cryo-EM, hoping it will solve long-standing questions for proteins ill amenable to protein crystallography – such as ion channels, the electric gatekeepers of our cells. Still, while many technical challenges have been overcome with respect to imaging and data processing, the trend towards smaller and smaller target proteins has unveiled unexpected issues.

If contrast is hardly an issue anymore, why were there still more than 10times more structures solved by X-ray protein crystallography (9901) compared to cryo-EM (849) in 2018? One challenge comes from the fact that smaller proteins are much more mobile compared to larger ones, as the diffusion coefficient is related to the mass of a protein. Consequently, smaller proteins more often come into contact with the air-water interface [3], in other words with the top layer of the sample drop deposited and thinned on the sample carrier. Results of these contacts can be detrimental for the protein – consider the effects of stirring egg white to bring air into this protein solution… Additionally, even partial denaturation of a limited surface area on a small protein has much more severe implications compared to the same area denatured on a huge protein complex – simply as this area represents a significantly larger relative part of the total structure. Membrane proteins, such as ion channels, are especially prone to partial, or complete, unfolding at the air-water interface. The reason for this is that they contain hydrophobic patches on their surface, required for their embedding into lipid cell membranes. A common approach is to use detergent molecules to cover these patches in order to make membrane proteins soluble in aqueous buffers. Detergents however are strongly attracted to the air-water interface, and tend to form monolayers at the interface – at the cost of the protein that now loses its detergent belt. The use of other means of solubilization, such as nanodiscs

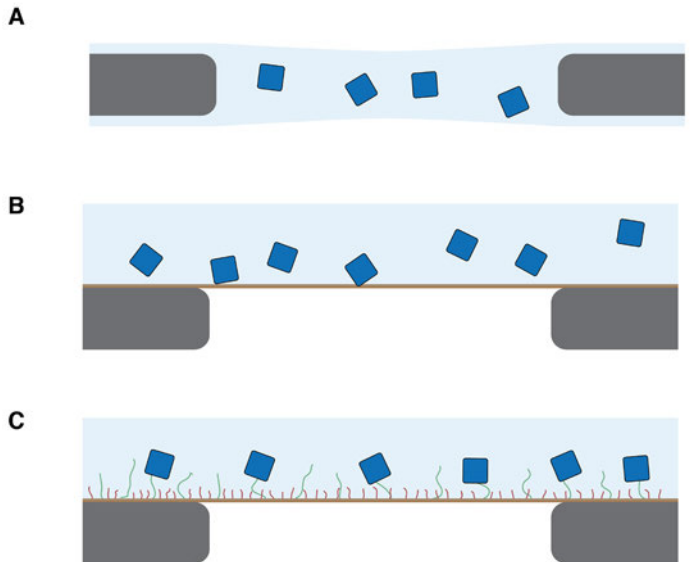

Figure 1. Conventional and functionalized grids. Cartoons depicting (a) holey-carbon grids (ice in light blue, carrier carbon in dark grey), (b) holey-carbon grids with an unmodified continuous carbon overlay (shown in brown), and (c) grids with a functionalized carbon film (capture groups in green, passivation groups in red). Protein is depicted in dark blue.

or amphiopols, can alleviate this issue, but ideally one would envision means to prevent or at least minimize air-water interface contacts of the protein.

How thin is thin? And how many is enough?

Routine sample carriers in cryo-EM comprise a carbon carrier film with defined, micrometer-sized holes that constitute the imaging areas. Proteins are embedded into these holes into an thin film of aqueous buffer, which is rapidly frozen solid before being transferred into the microscope to stop all molecular motion and make the sample better withstand the harsh conditions inside the optical system. But how thin is thin? A common notion is that the liquid film should not be much thicker than twice or at most trice the diameter of the protein studied – in order to maximize contrast. Thus, the liquid film can be up to 100 nm thick for imaging ribosomes, but smaller proteins require even thinner layers. So thin is indeed thin, and any protein in such a liquid film faces not one but two water-air interfaces in closest vicinity (Fig. 1a). Employing an additional, 2 to 5 nm thick, continuous carbon layer blocks access to one of the air-water interfaces (Fig. 1b) and furthermore increases the mechanical stability to the liquid film. Given that proteins must not overlap to extract true transmission images, and typical field of views are in the range of 200^2 to 400^2 nm^2, we can estimate that one can get somewhere between 25 and 250 individual particles onto a single micrograph. While this does not sound like much, one has keep in mind that protein is not only in a single imaging area, but distributed over the complete sample carrier surface. More critically, one cannot apply a liquid film thinner than 100 nm by routine techniques. Therefore, the predominant technique is to apply bulk solution onto the sample carrier grid and then wick away excess liquid. All in all, the target protein actually has to be enriched to a rather high concentration for cryo-EM experiments. Again, this can pose a formidable challenge for scarce membrane proteins such as ion channels.

Fishing for proteins with molecular tethers

The main benefit of using continuous carbon films as additional support on the sample carriers is that these films are (a) easy to prepare, (b) stick willingly to the holey carbon carrier film of the grid, and (c) do not introduce too much additional background signal. These films are however pretty much inert: they are neither able to enrich most proteins nor to immobilize them to prevent interaction with the air-water interface. Even if a protein sticks to amorphous carbon, for example due to hydrophobic patches on its surface, this interaction is ill defined and often leads to (partial) denaturation. Organic chemistry offers a wealth of functional groups that can be used to interact in a defined and controlled manner with specific functional groups on a protein's surface. A good, and widely used, example is the Ni-NTA system: nitrilotriacetic acid (NTA) and surface histidines have a high affinity for each other if bridged by a nickel ion. Already 10 years ago the benefits of this system had been recognized to functionalize carrier grids [4]. However, the preparation method was cumbersome and consequently these grids hardly found application in the field.

During our recent endeavors to design molecular scaffolds for lipid deforming proteins, we (re)discovered a straight-forward to apply chemistry allowing us to anchor modified Polyethylenglycol (PEG) to carbon surfaces. Application is a simple 'pipette-and-incubate' reaction that can be carried out directly on the grid; making this approach very user-friendly. However, by attaching PEG to the grid surface we do not yet create molecular tethers that would allow us to "fish" for proteins since PEG is known to be pretty much inert towards proteins – and indeed we use this type of molecular tether for blocking the carbon surface if required. Instead we rely on bi-functional PEGs: one side carrying the molecular interface responsible for attachment to the carbon surface, the other carrying a functional capture group – such as nitrilotriacetic acid – as hook and bait to capture proteins. By using mixtures of bi-functional PEGs with tether and capture group and PEGs with only the tether group we can even define the amount of capture groups present on the grid surface (Fig. 1c), and thus tune protein density on the surface.

While the Ni-NTA system is widely used it is neither applicable in all settings, nor always the best option. Therefore, we have also devised a versatile, generic PEG tether that has an azide group instead of NTA and

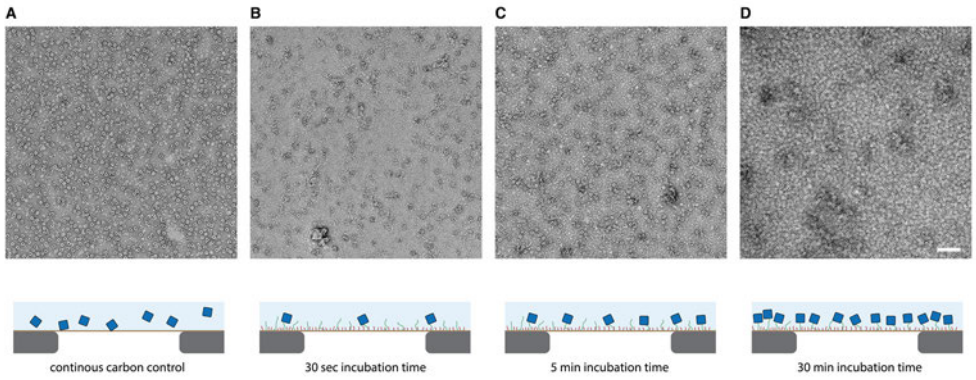

Figure 2. Capturing apoferritin on functionalized grid surfaces. Negative-stain substituted vitrified grids of a diluted apoferritin sample. (a) Control for the protein density on a non-functionalized, commercial sample carrier grid. (b-d) Samples taken after (b) 30 sec, (c) 5 min, and (d) 30 min of incubation on covalent linker functionalized sample carrier grids. The time course clearly shows a strong enrichment on the surface.

thus allows the introduction by click-chemistry of any capture group that can be modified with an alkine. We are for example using this to tether known ligands of ion channels to the sample carrier grid surface.

Additional benefits of the fishing trip

Non-covalent capture groups as described above have the drawback that, at least for commonly observed affinities, they do not really enrich the sample from the bulk solution onto the grid surface – they only increase the dwell time on the surface and thus reduce air-water interface encounters. Therefore, we also devised a molecular tether that covalently reacts with any primary amine group present on the surface of the proteins – permanently linking them to the carbon surface. Proof-of-principle experiments performed with diluted samples of apoferritin, a commonly used reference protein in cryo-EM, highlight the potential of our system (Fig. 2). Importantly, surface exposed lysines, which contain a primary amine, are common in most proteins thus making our molecular fishing rod a generic tool.

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MAX PLANCK RESEARCH GROUP

STRUCTURAL DYNAMICS OF PROTEINS

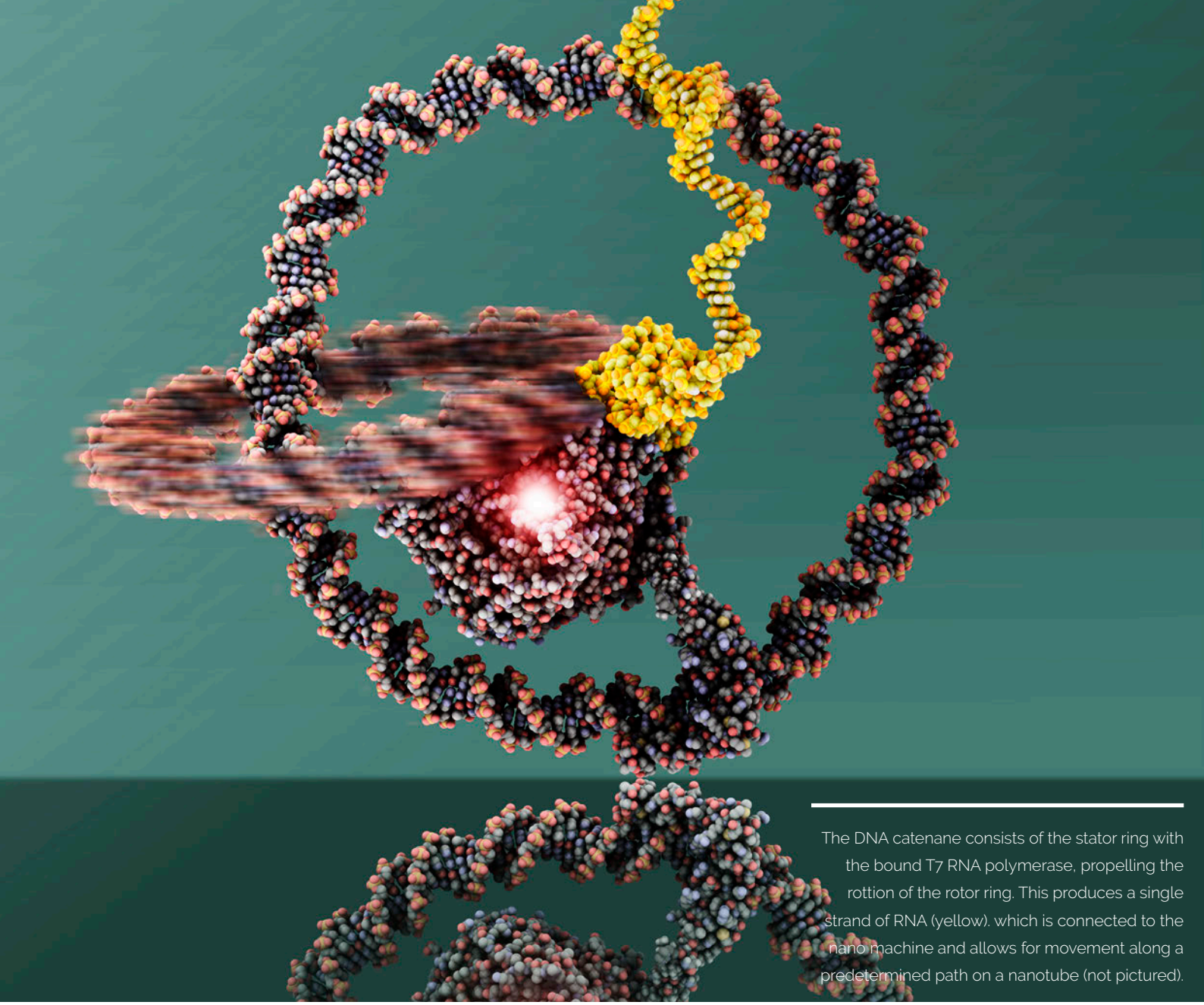
Elmar Behrmann

Group leader

Structural Dynamics of Proteins

Life is not static and neither are the majority of proteins crucial to the function of our cells. However, our structural understanding of these microscopic machines is often limited to one or at best few static snap-shots.

We focus on the application of electron microscopy to visualize such dynamic entities in a native-like environment in order to deduce the structural pathways at the heart of biological processes. Our main interest is in those proteins that are embedded into the lipid membranes of our cells. The structural basis for how proteins can give diverse functions to membranes is still largely lacking, especially with regard to the dynamic interplay between lipids and proteins. To allow us to visualize such dynamic entities in their native-like environment, we develop sample preparation strategies that will enable us to investigate membrane proteins in defined functional states.



The DNA catenane consists of the stator ring with the bound T7 RNA polymerase, propelling the rottion of the rotor ring. This produces a single strand of RNA (yellow). which is connected to the nano machine and allows for movement along a predetermined path on a nanotube (not pictured).

Small tools for large molecules

By Michael Famulok and Anton Schmitz, Chemical Biology

As chemical biologists we uses chemical tools to investigate, modulate or generate biological structures including naturally occuring proteins as well as synthetic nucleic acid-based nanoarchitectures.

Almost all biological processes are executed by macromolecules, primarily proteins and nucleic acids. In most cases, these macromolecules assemble into large complexes composed of two to hundreds of identical or different subunits. The strength of chemical biology lies in its ability to provide tools, typically small molecules which are accessible to chemical synthesis, to analyse or control these large assemblies or to equip them with new functions.

Small molecule to analyze the structure of a protein complex

The flow of information between and in cells, called cellular signaling, relies on the transient assembly of signaling complexes. We wanted to analyze a particular signaling complex assembled from two copies of the epidermal growth factor receptor (EGFR). For this purpose we synthesized a small molecule which bound to a defined site in the EGFR and thereby transferred a label specifically to one single cysteine residue out of more than 50 cysteine residues present in the EGFR (Fig. 1). Due to this precise labelling it became possible to use electron-paramagnetic resonance spectroscopy to measure the distance between two of these labels in the assembled signaling complex composed of two EGFR molecules. By these measurements, we could substantiate models predicting a particular geometry of the actively signalling EGFR [1].

Small molecule to analyze the structure of a nucleic acid

Riboswitches, found primarily in bacteria, are ribonucleic acids which regulate gene expression depending on whether a particular metabolite is present or not. This is achieved by a change of conformation in the riboswitch upon metabolite binding, e.g. upon binding of the nucleic acid precursor preQ1. To monitor this conformational change in a preQ1-sensing riboswitch we did not use a labelled binding partner as in the case described above but directly synthesized a modified version of the riboswitch containing two small molecule labels each covalently attached to a specific base of the riboswitch. As above, we used electron-paramagnetic resonance spectroscopy to determine the distance between the two labels and thus could show the switch upon binding of preQ1 [2].

Small molecules to regulate a DNAzyme by light

DNAzymes are deoxyribonucleic acids which catalyze chemical reactions analogous to protein enzymes. We used a DNAzyme which when completely folded catalyzes the oxidation of a colorless substrate to a colored product. This DNAzyme was made switchable by the substitution of particular bases by either of two different photoswitchable small molecules (azobenzene or azopyrazole derivatives). When incorporated into the DNAzyme these molecules support the folding of the DNAzyme when they are in the trans conformation but prevent it when they are in the cis conformation. Switching from trans to cis and vice versa is achieved by irradiation with light of distinct wavelenghts specific for each molecule. Thus, the combination results in four possible configurations of the DNAzyme which can be distinguished by the degree of catalytic activity. The great advantage of using light as a switch instead of a chemical switch (i.e. a molecule binding to the DNAzyme and thereby inducing a conformational change) is that light does not pollute the system and thus the switching can be performed theoretically indefinitely. Indeed, we could show that the DNAzyme can be turned on and off many times. As the DNAzyme reacts on different combinations of the different wavelengths with different and distinguishable catalytic activity the DNAzyme represents a logic device (a 4:2 multiplexer) which could be integrated into DNA computing devices [3].

Small molecules to control a DNA walker

In the last annual report we already introduced a project which we could complete during the current report period. We constructed a bio-hybrid nanoengine which could move unidirectionally along a given path. The nanoengine (see the title figure) was built by the combination of a DNA nanostructure and a force-generating protein, a RNA polymerase, and used the hydrolysis of energy-rich nucleotides for the movement (analogous to the energy source of muscle). It moved fast and autonomous [4]. Now, we report a DNA walker built from DNA only which is powered and simultaneously controlled by light. The walker consists of two legs held together by a short body.

Each leg contains two distinct stretches of bases which can bind to complementary stretches on the path (governed by the same principle of base pairing as the formation of the DNA double helix).

In the legs the stretches contain several bases which are replaced by two distinct photoswitchable small molecules (azobenzene derivatives) which behave similar to those described above. The difference is that in the DNAzyme base pairing within the DNAzyme was affected by the light-induced cis/trans isomerization of the small molecules whereas in the walker base pairing

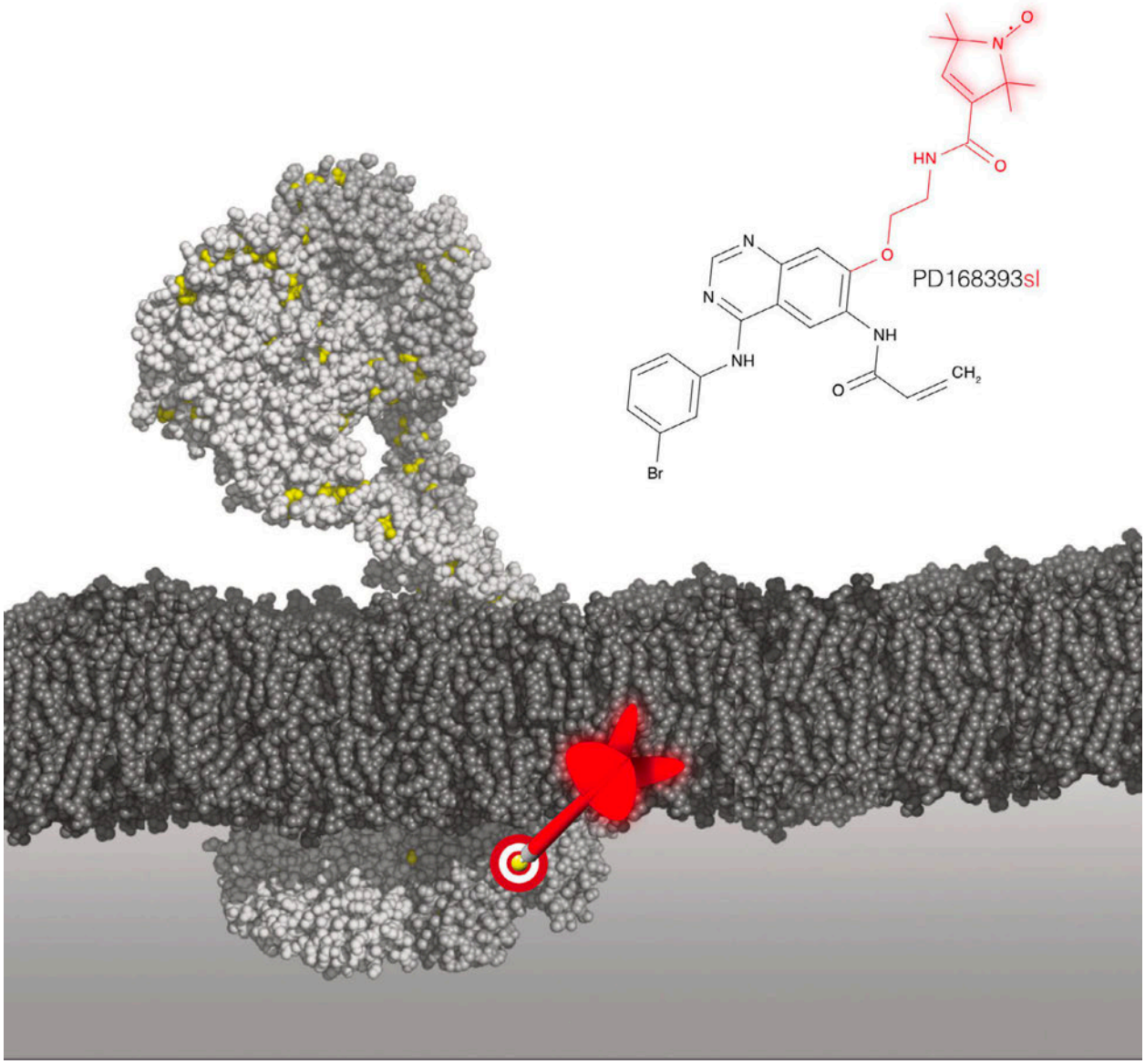


Figure 1. A small molecule is used to transfer a label (red) specifically to one single cysteine residue (indicated by the arrow) out of more than 50 cysteine residues (yellow) present in the EGFR molecule (light grey). With the help of two of these labels the geometry of two EGFR molecules representing the biologically active complex can be analysed. (Taken from Yin et al., 2018; Courtesy of Dr. G. Hagelueken)

between the walker and the path is targeted. Therefore, by choosing the wavelength of irradiation the operator can dictate where the walker has to move to. Thus, in contrast to the bio-hybrid nanoengine, the DNA walker is non-autonomous. Each step has to be triggered by the operator and can be controlled by the operator. Also in contrast to the bio-hybrid nanoengine, the DNA walker does not consume energy-rich nucleotides but uses the energy of the base pairing for the movement. As a consequence, energy input by light is required to brake the base pairings to allow the next step. Thus, the DNA walker represents an approach entirely different from the bio-hybrid nanoengine with distinct advantages and disadvantages over the latter. A disadvantage is that the walker is not well suited for long distances whereas the nanoengine is. However, when precisely controlled short-distance movements are required the DNA walker is superior. Accordingly, one could imagine as a future application a nanoscale assembly plattform where several distinctly controlled walkers bring together chemical building blocks, in a spatio-temporally ordered manner, which then react to a defined product [3].

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MAX PLANCK FELLOW

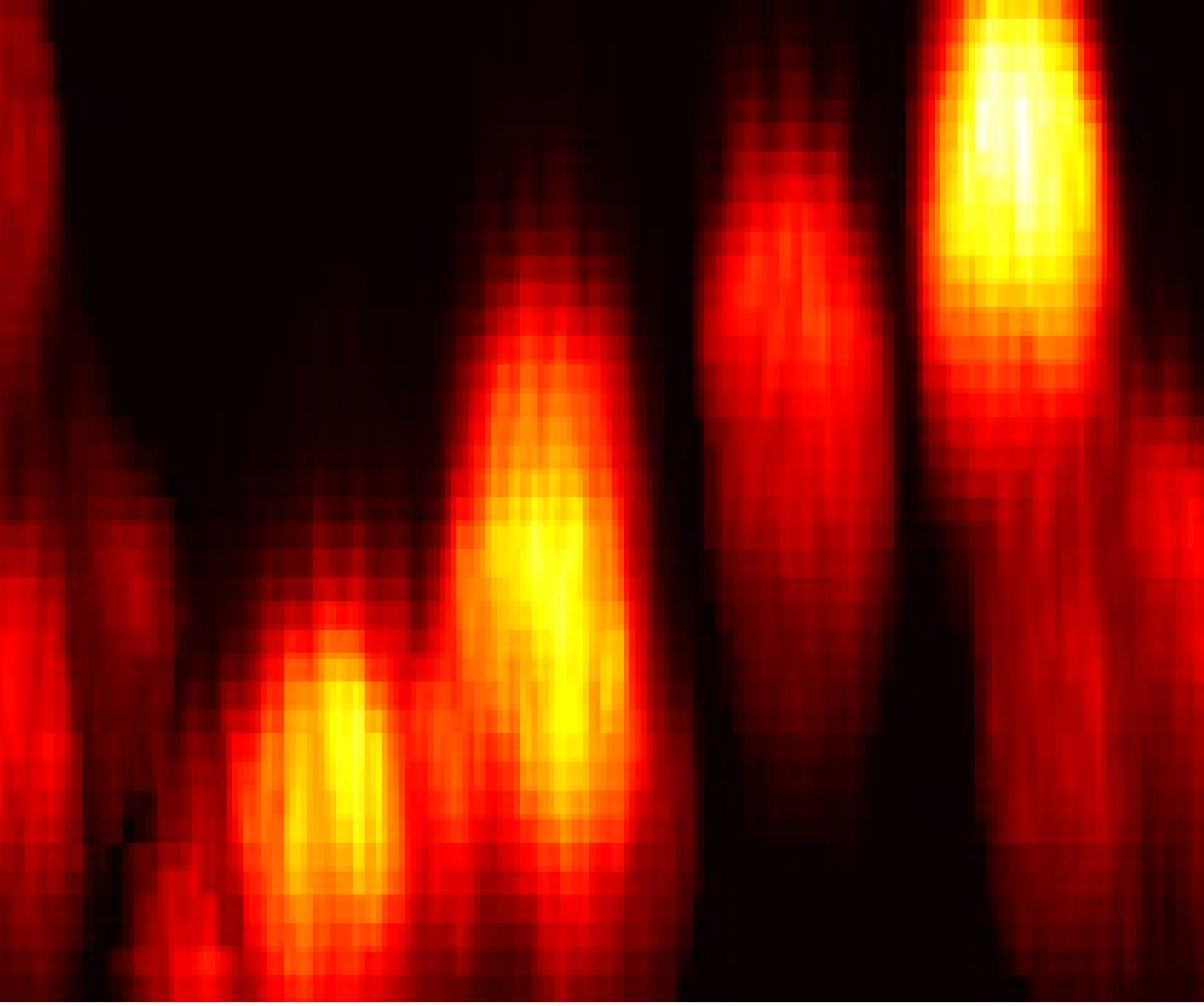
CHEMICAL BIOLOGY

Michael Famulok

Max Planck Fellow

Chemical Biology

The major activities of the Max Planck Fellow group Chemical Biology can be split into two fields of interest. On the one hand we use chemical tools to provide analytical reagents to study biological processes in a broad sense. These tools range from small organic molecules to nucleic acid-based aptamers and are obtained by chemical synthesis, by biochemical enzyme-catalyzed synthesis or by a combination of both. On the other hand we use chemical tools to construct nucleic acid-based nanoarchitectures and nanomachines as well as bio-hybrid nanoengines. A particular focus is to design these nanodevices in a way that their properties and functions can be controlled by light.



Tomography for fluorescence imaging

By Johannes Seelig, Neural Circuits

Many biological systems, such as neural circuits in the brain, show dynamics that are distributed and evolve over a volume. We developed a light microscopy method targeted towards fast imaging of sparse volumetric samples.

Neurons and neural circuits in the brain are distributed in three dimensions. But laser scanning microscopes, which are commonly used to study the dynamics of such circuits, typically image a single focal plane at a time. While this approach provides high-resolution, diffraction-limited images, it on the other hand limits the rate at which activity can be recorded from multiple neurons distributed in different focal planes. To record neural activity from volumes, the focal plane of the microscope needs to be moved sequentially to different positions, which limits the recording speed. And additional constraint on imaging speed is given by the requirement to detect sufficient signal in each pixel, that is, to integrate a sufficient number of fluorescence photons in each scanned pixel to form an image.

Imaging using extended focal spots

To overcome the limit imposed by the pixel integration time, different strategies have been conceived to record in parallel from multiple pixels. One way to achieve such parallelization uses extended focal lines, so called Bessel beams, instead of a single focal spot for fluorescence excitation. One can picture this as taking an image with many focal spots tightly stacked on top of each other; since light in this situation is also detected simultaneously from this entire focal line, the signal is summed along the direction of the Bessel beam and results in a projection of the entire illuminated volume without axial resolution. This approach therefore works best for samples that are sparse, that is, only fill a small fraction of the imaged volume to limit the overlap of objects in different planes in the projected image.

Tomographic imaging

To nevertheless also obtain axial information from Bessel beam imaging one can take advantage of tilted Bessel beams. Using two Bessel beams that point in slightly different directions, two views at different angles can be recorded and, similar to stereovision, volume information can be extracted from spare

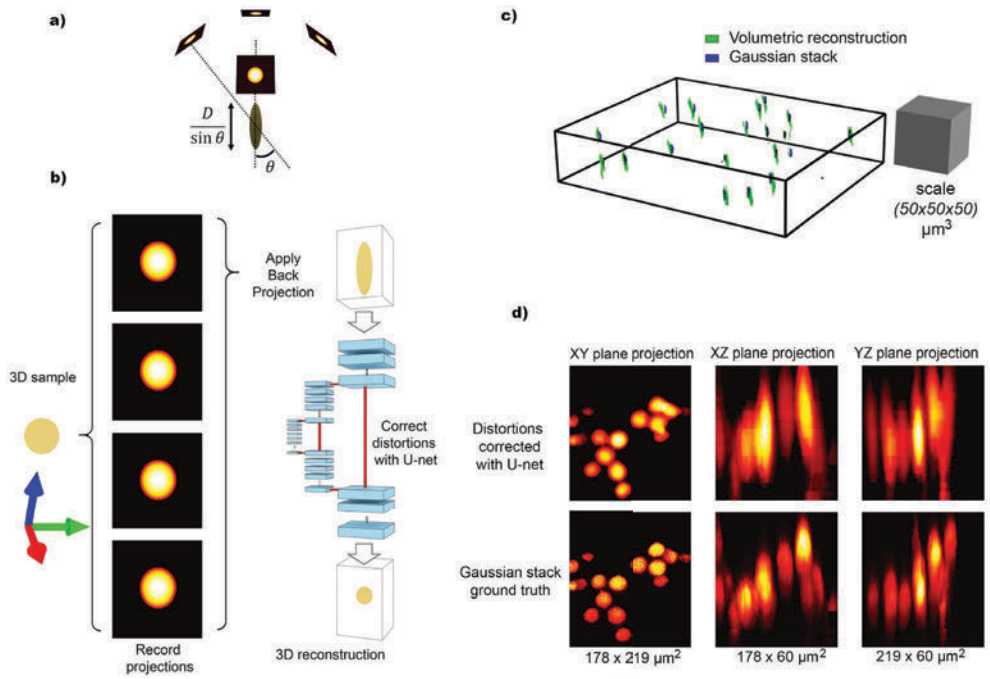


Figure 1. a) Four different projections are generated by scanning four tilted Bessel beams. The tilt angle of the Bessel beam leads to a distortion of a spherical object with diameter D.
b) Artificial neural networks are used to partially reverse this distortion.
c) For small objects, such as small fluorescent beads, axial resolution can be recovered using standard tomography approaches adapted for Bessel beam scanning.
d) For larger objects, such as pollen grains, a combination of standard tomographic reconstruction and artificial neural networks allows recovering axial information.

samples [1]. More generally, recording projections at different viewing angles forms the basis of tomography, such as for example X-ray computed tomography (CT). In that case, many projections from a wide range of angles are recorded and, taking advantage of the known imaging geometry, inverting these projections allows reconstructing volume information.

Transferring this tomography approach to fluorescence microscopy on samples that can only be accessed from one side, as is typically the case when imaging in the brain *in vivo*, is faced with several challenges: The angular range accessible with a Bessel beam through a microscope objective and therefore the number of different projections that one can record are very limited. Further, the projections need to be recorded nearly simultaneously, not sequentially, due to the fast dynamics of the samples.

To address the latter problem we took advantage of a method that can associate the detected fluorescence signal with the corresponding excitation laser pulse [2]. In this way, multiple beams, each with a specific temporal delay, can be used to record independent projections at the same time. Using this approach we simultaneously record four projections from four different sides, which, at least for an isolated object, is expected to be sufficient (see Fig. 1a) to extract much of the information available under illumination at the given small projection angles [3].

Volume reconstruction using machine learning

The first problem mentioned above, the constrained angular range accessible with Bessel beams, limits the axial resolution of our imaging approach for extended objects when reconstructed using conventional tomography techniques. To mitigate this effect we took advantage of machine learning which has been shown to be well suited for tomographic image reconstruction with shallow projection angles in other imaging modalities [4]. Machine learning for image reconstruction in microscopy typically takes advantage of large datasets of matched pairs of low-resolution and high-resolution images of the same sample. Training artificial neural network models on such a data set then makes it possible to infer high resolution images from previously unseen low resolution ones. For our application, we simulated a large number of sample volumes similar to the ones we recorded in experiments and also simulated the corresponding tomographically reconstructed volumes based on the measured imaging configuration. This way of image reconstruction indeed led to the the (Fig. 1b) recovery of axial resolution for extended objects, such as the pollen grains shown in figure 1d.

Imaging in behaving animals

We are planning to use this method for monitoring neural activity in the brain of fruit flies that navigate in a virtual reality environment. In this situation, the fly walks on a freely rotating air supported ball that serves as a treadmill. Treadmill motion is typically read out using optical mice; these optical mice need however to be carefully calibrated which is particularly difficult for small balls such as the one used for fly behavior experiments. We therefore developed a system for ball tracking based on a high-resolution camera which gives full control over the imaging as well as image processing parameters [5]. Ball tracking is integrated with an open source virtual reality system which allows us to display arbitrary virtual environments with a short latency of 30 ms from motion initiation to display update. We are now using these techniques to study neural circuits underling the navigational behavior of flies.

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MAX PLANCK RESEARCH GROUP

NEURAL CIRCUITS

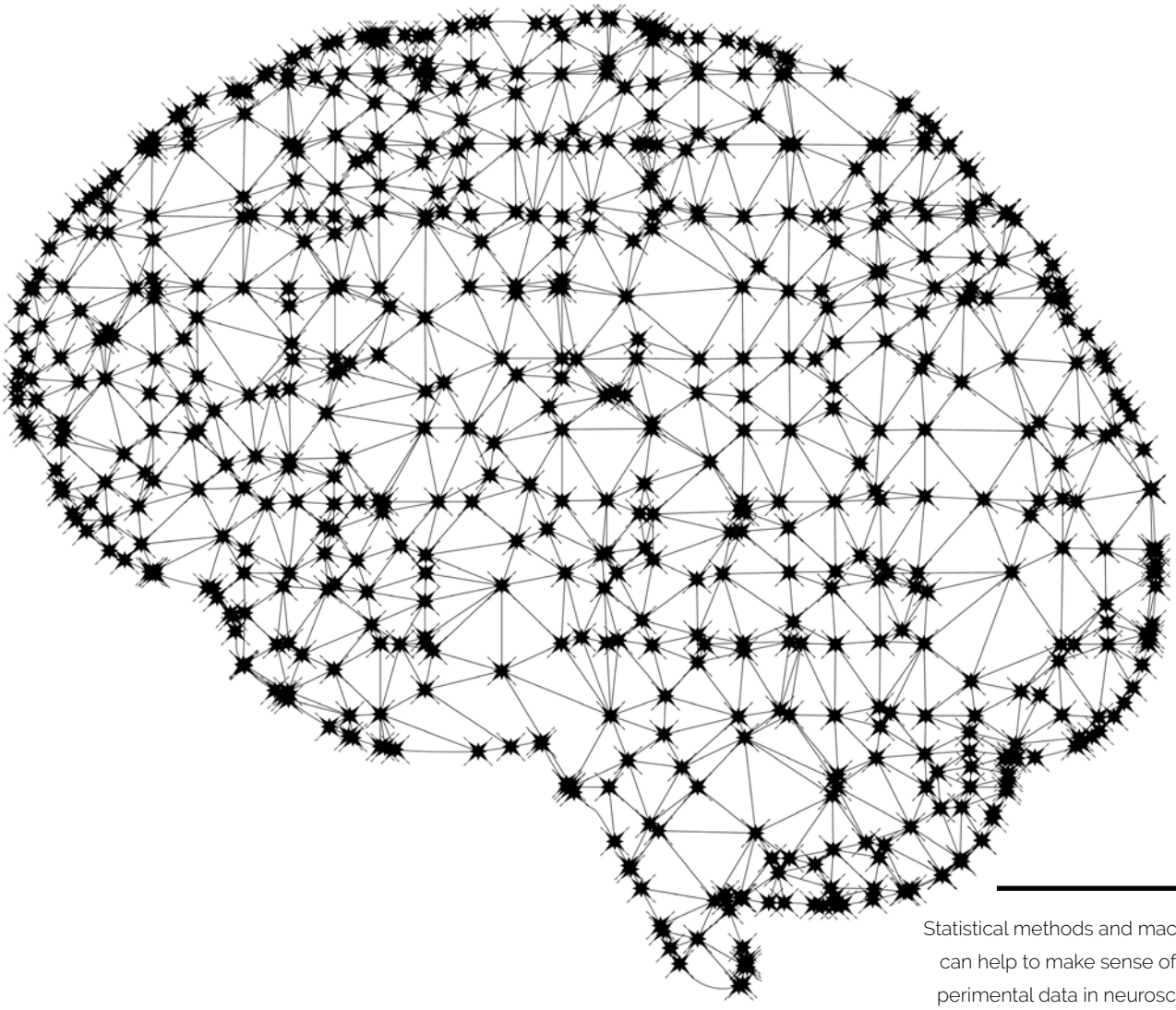
Johannes Seelig

Group leader

Neural Circuits

We use optical microscopy techniques, such as two-photon calcium imaging, to understand how neural networks in the brain change over time, from single synapses to entire circuits, and how these changes relate to behavior. Our research focuses on the model organism *Drosophila melanogaster* where genetically identified, comprehensive neural networks underlying adaptive behaviors can be studied. We interpret and guide our experiments using computational modeling of neural circuit dynamics. Molecular, structural, and functional similarities of neural circuits across species suggest that insights gained in the fly brain will also contribute to our understanding of the mammalian brain.

In a second line of research we apply and develop novel optical microscopy methods with the aim of optimizing the temporal as well as spatial resolution of functional imaging in animals engaged in virtual reality behavior.



Statistical methods and machine learning can help to make sense of complex experimental data in neuroscience, linking mechanistic models of neural dynamics with experimental observations.

Statistical inference of mechanistic models of neural dynamics

By Pedro Goncalves and Jakob Macke, Neural Systems Analysis

How can we make sense of complex experimental data in neuroscience? We build statistical methods and machine-learning algorithms for analyzing high-dimensional measurements of neural activity and behavior, and for linking them with theoretical models of neural dynamics and computation.

Introduction

Advances in experimental techniques make it possible to measure the activity of many neurons simultaneously, and to map the connectivity of neural circuits at unprecedented scale and resolution. However, interpreting the complex data generated by these approaches has proven to be a difficult challenge. At the same time, the field of machine learning is being revolutionised by 'deep learning' approaches: Powerful algorithms for extracting structure from data can be built using artificial neural networks. However, one shortcoming of such machine-learning approaches is the fact that they are typically built on generic, and very complex models which can be hard to interpret. How can one combine the strengths of classical, `mechanistic' modeling in neuroscience with these data-driven machine-learning approaches? We here report on two central questions which we are pursuing in collaboration with experimental laboratories: First, how can we link models of neural dynamics with electrophysiological recordings [1, 2, 3]? Second, how can we scale current approaches for statistical inference to large-scale applications [4]?

How can we link mechanistic models of neural dynamics with experimental observations?

Computational neuroscientists have developed a cornucopia of models that aim to capture neural dynamics, and give insights into the underlying mechanisms. However, a common challenge in working with these models is the fact that it is typically difficult to quantitatively link them to data: In particular, we developed a method for statistical inference on simulation-based models which can be applied in a 'black box' manner to a wide range of models in neuroscience [1]. The key idea is to first generate simulations from the model, and then to train a artificial neural network to identify parameters that are consistent with the data (Fig. 1). Having characterized these parameters, we can then refine models, or estimate which additional data will be most useful for constraining or comparing models. Our approach is applicable to a wide range of problems in neuroscience, from the operation of single channels, to the dynamics of populations of neurons, and the computations underlying behaviour, applications which we are currently pursuing in collaboration with a diversity of experimental laboratories. We are currently extending our toolbox of methods for statistical inference in mechanistic models with approaches for model emulation [2] and model comparison [5].

How can we scale statistical inference to large-scale applications?

In conventional statistical inference approaches, once inference is performed for particular measured data, new measured data require a full new inference procedure (Fig. 2A). This process is typically computationally expensive, and limits the use of statistical inference in time-critical and high-throughput settings, e.g. where large repositories of measured data are available and it would be desirable to fit the same model to a large number of data-sets.

Our approach can be naturally extended to such applications. Instead of training one network per measured data as in the classical setting, a large network is trained on a large dataset of simulations not tuned to particular measured data (Fig. 2B). Given the network size and large number of simulations, network training is slow. However, once the network is trained, inference can be rapidly performed on new measured data, consisting in directly inspecting the output distribution of the network given the input measured data. In such setting, inference is amortised— we use experience from past inference tasks to quickly solve new ones.

We demonstrate a large-scale, fully-automated application of amortised inference in the context of ion channel models, which are central to realistic biophysical modelling in neuroscience. We perform inference of a general formulation of a non-inactivating potassium channel model (the ``omnimodel'') (Fig. 2C), given the multitude of responses of a set of 370 non-inactivating potassium channel models from the IonChannelGenealogy (ICG) database [6].

To that goal, we simulate current responses of the omnimodel to voltage-clamp protocols, for a wide range of omnimodel parameters. These data are used to train a shared inference network. After training, our approach allows us to inspect and sample from posterior distributions given original ICG current responses (Fig. 2D-F).

To validate our approach, we inspect the omnimodel posterior distributions given the original current responses from the large and diverse set of ion channel models from ICG. The high similarity between the original model responses and the omnimodel responses at the respective posterior modes illustrates the success of the approach: the lowest correlation between both responses is 0.91 (Channel 86537_kdr in Fig. 2G), and for 94% of channels, correlation coefficients are greater than 0.98.

The approach will enable neuroscientists to perform scalable statistical inference on large-scale datasets and complex models without having to design model-specific algorithms, closing the gap between mechanistic and statistical approaches to neural dynamics.

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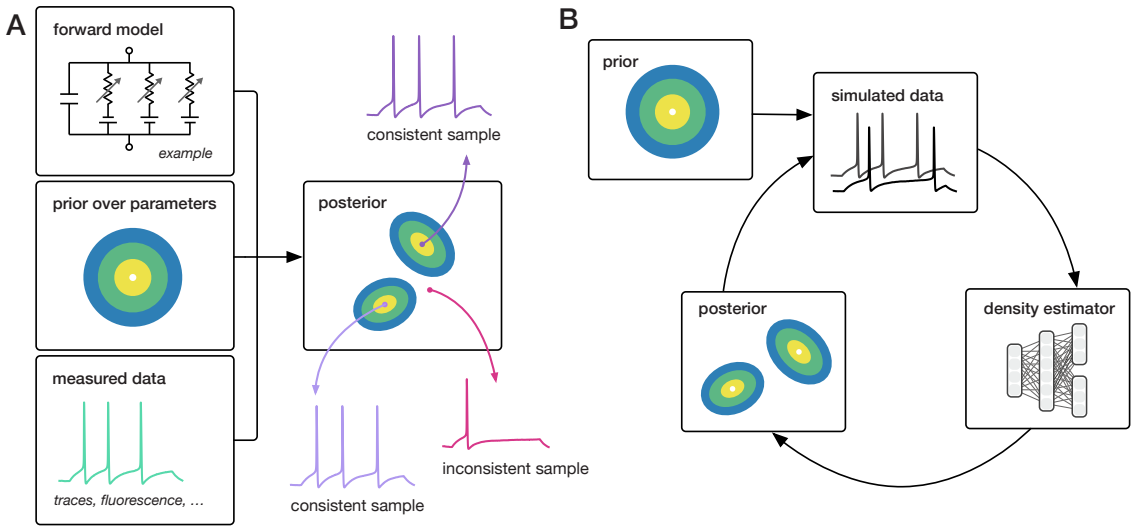

Figure 1. Linking mechanistic models with experimental data through simulation-based statistical inference.
(A) Given a candidate model to explain the data, prior knowledge over the model parameters, and the observed data, we want to recover the full space of parameters consistent with the data, i.e. the posterior distribution. The higher the probability of the parameters, the closer the output of the model is to the measured data.
(B) Our method consists in using a neural network to perform inference on simulated data. The approach is done sequential until convergence.

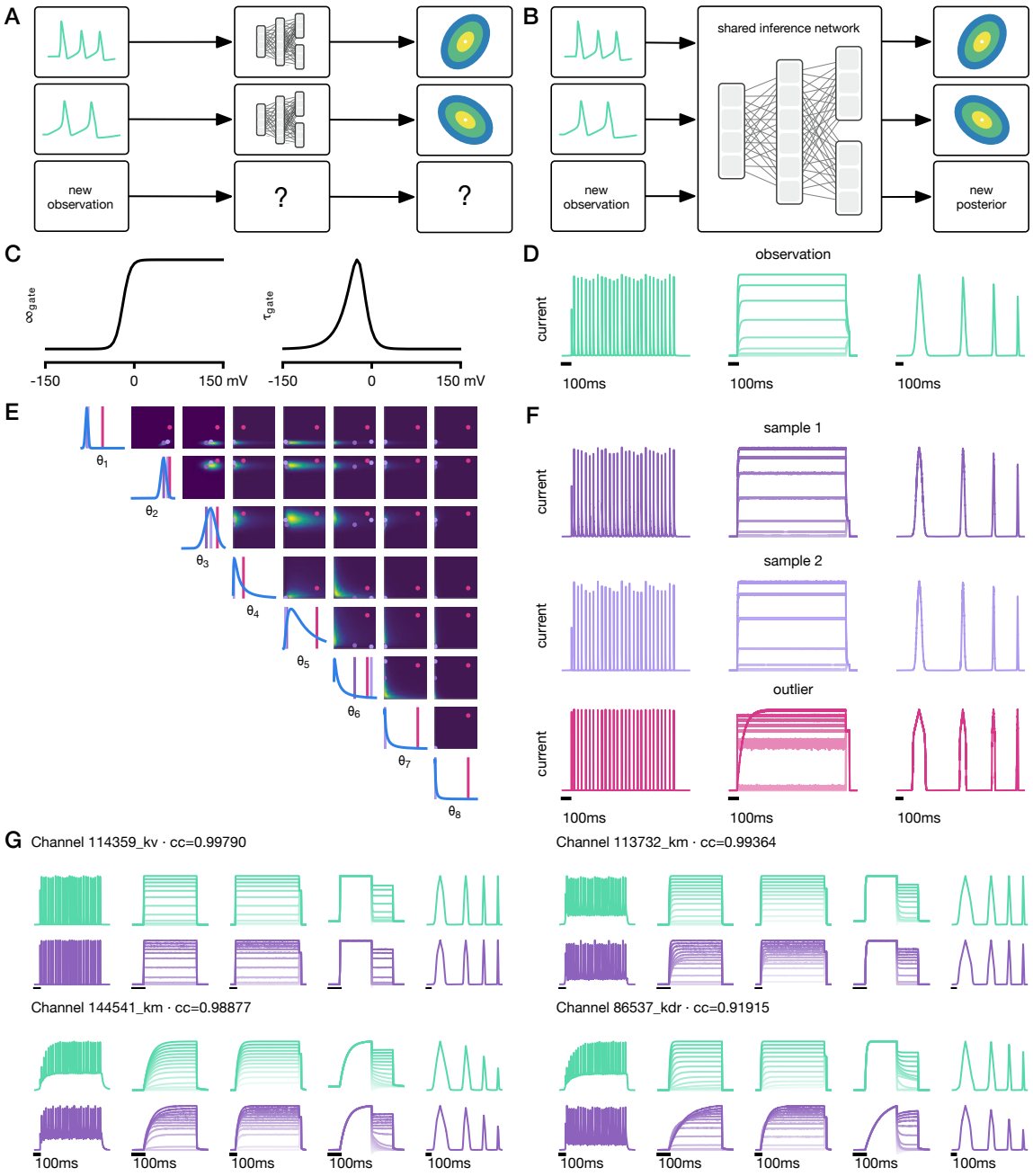

Figure 2. Inference of ion-channel models.

(A) Classical approach: inference network for each observation.

(B) Amortised inference: shared network.

(C) We perform inference over channel model parameters. Channel kinetics are described by steady-state activation curves, ∞_{gate}, and time-constant curves, τ_{gate}.

(D) Responses of a channel model to three voltage-clamp protocols.

(E) Posterior distribution over eight model parameters, 1 to 8.

(F) Traces obtained by drawing from the posterior distribution in E. Purple traces are samples from the posterior. The pink traces correspond to parameters of low probability.

(G) Observations (teal) and traces generated by posterior samples (purple) are shown for four models from the ICG database.

MAX PLANCK RESEARCH GROUP

NEURAL SYSTEMS ANALYSIS

Jakob Macke

Group leader

Neural Systems Analysis

The central goal of the Neural Systems Analysis group is to understand how populations of neurons collectively process sensory input, perform computations and control behaviour. To this end, we develop computational tools for interpreting neural and behavioral data. Our goal is to provide tools which make it possible to distill interpretable descriptions from high-dimensional, complex data, and to link these data to theoretical models of neural dynamics and computation. We build on recent advances in Bayesian inference and deep learning to design statistical models, and efficient algorithms for inferring their parameters. These methods allows us to characterize which models are consistent with existing measurements, and which additional measurements would be most informative in constraining them. We extensively collaborate with experimental groups at caesar Bonn as well as at other research institutes.

PUBLICATIONS

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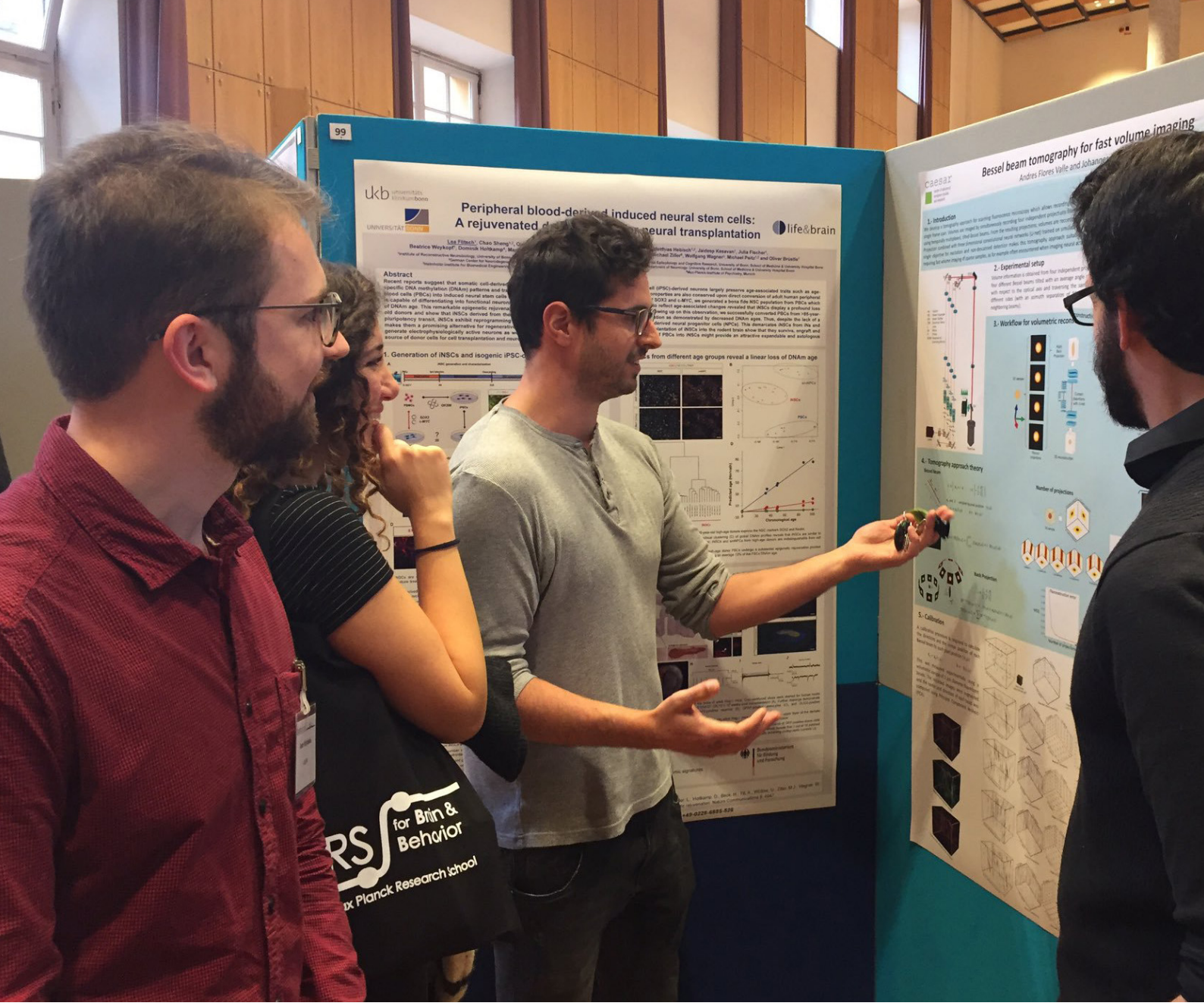
CAESAR INSIGHTS



News from the IMPRS for Brain and Behavior

By Ezgi Bulca, IMPRS coordinator

The IMPRS for Brain and Behavior completed its third full year of operation in 2018. The program's aim is to recruit outstanding doctoral students and immerse them in a stimulating environment that provides novel technologies to elucidate the function of the brain, from molecules to animal behavior.

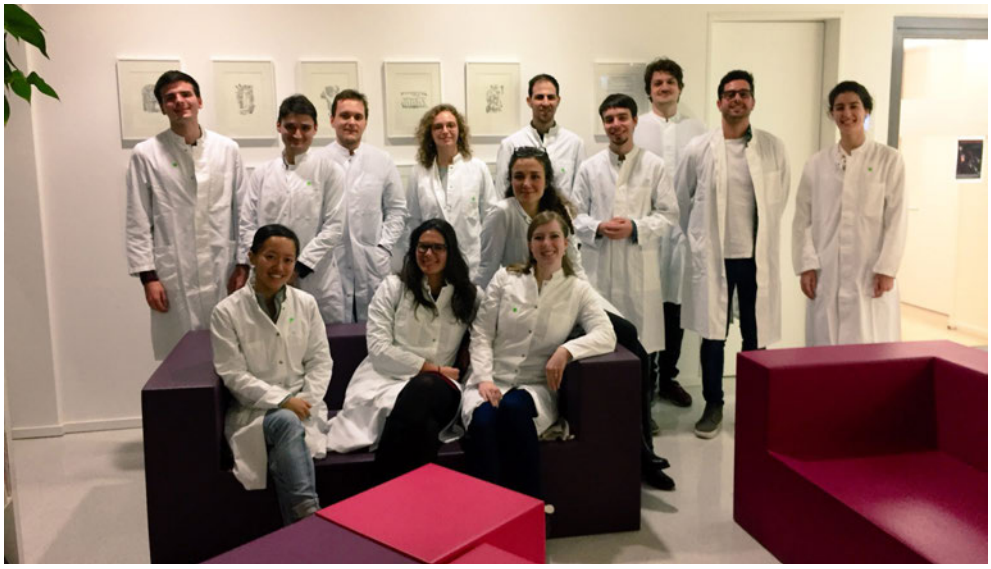
The graduate school is the first transatlantic cooperation in neuroscience between two neuroscience institutions connected with Max Planck (caesar – associated with the Max Planck Society – and the Max Planck Florida Institute of Neuroscience (MPFI)) and two universities (University of Bonn and Florida Atlantic University). The program is funded predominantly by a Max Planck Society IMPRS grant with additional support for student positions, research costs and overhead by the participating institutions, and grants to individual investigators. caesar and MPFI host the coordination offices for the school in Bonn and Florida respectively.

In 2018, new IMPRS Coordinators were hired at caesar and at MPFI to replace outgoing Coordinators. Ezgi Bulca is the new IMPRS Coordinator at caesar who brings experience from the IMPRS for Translational Psychiatry Coordination Office in Munich and Dr. Paul Evans is the new IMPRS Coordinator at MPFI who brings experience from completing postdoctoral training in Ryohei Yasuda's lab.

In 2018, 7 new PhD students were recruited, 3 of which are employed at caesar. Our new students are from 5 countries with 1 from Italy, 1 from China, 1 from Israel, 1 from Spain, and 3 from Germany. In total, there are 24 students in our IMPRS coming to us from 14 different countries: 13 males, 11 females. Students are accepted annually with a call for applications from September 1st to December 1st and a selection symposium in mid-March. The selection symposium was held at caesar on March 12-13, 2018.

The curriculum of the program comprises both theoretical and practical hands-on training elements. To maximize the benefits of international education, students take workshop courses and attend symposia at both caesar and MPFI, allowing students to interact with a broad group of international scientists.

IMPRS students in Bonn had their 2018 Student Retreat in Frankfurt at the Max Planck Institute for Brain Research from November 29th until December 1st. Each student had the opportunity to present their research project and receive feedback from their peers. We had three guest speakers giving chalk talks on a variety of neuroscientific topics and life in academia in general. MPI for Brain Research Director Gilles Laurent who talked about his group's research on olfactory and visual areas in the reptilian brain, combining



experiments, quantitative analysis and modeling techniques. Johannes Letzkus then introduced his group's research on neocortical circuits, and Julijana Gjorgjieva explained how her group utilizes computational models to study neural network dynamics. All guest speakers were happy to discuss the individual challenges they faced during their careers and how persevering helped them succeed. Students found these discussions very helpful in guiding their own careers. There was a scientific poster session where guest students from the MPI for Brain Research also joined. IMPRS students at the end of the second day visited some of the labs at the institute and had more time to socialize with other PhD students.

Learn more about IMPRS at:

www.imprs-brain-behavior.mpg.de/

Scientific, PR and Outreach events at caesar

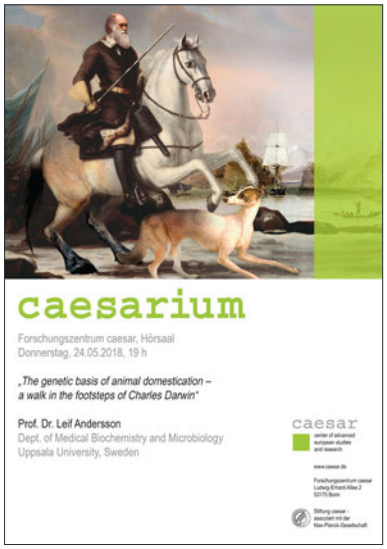
By Mia von Scheven and Sebastian Scherrer

caesarium

2018 was once again a great success for our popular public seminar series, the caesarium. Talks are designed for an interested lay audience, covering a wide range of current scientific topics. The seminars stimulate discussions and questions within the public and enjoy great popularity.

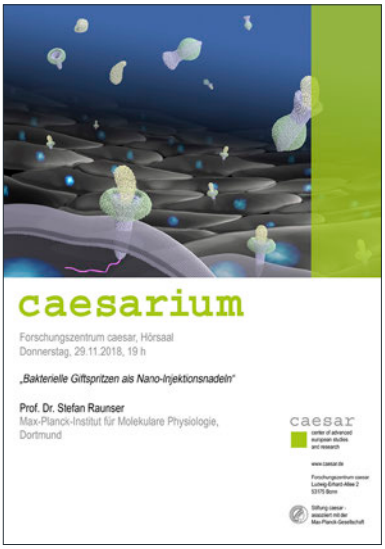
24.05.2018
"The genetic basis of animal domestication
– a walk in the footsteps of Charles Darwin"

Prof. Dr. Leif Andersson, Department of Medical Biochemistry and Microbiology,
Uppsala University, Sweden



28.06.2018
„Wer kontrolliert mein Gewicht? - Das Gehirn als Schaltzentrale des Stoffwechsels"
Prof. Dr. Jens Brüning, Max Planck Institute for Metabolism Research, Cologne

29.11.18
"Bacterial injections on a nano scale"
Prof. Dr. Stefan Raunser, Max Planck Institute for Molecular Physiology, Dortmund.



caesar Conference 2018 (05.06. - 06.06.2018)

On June 5th – 6th, 2018, caesar was hosting the 7th International Caesar Conference "Missing links in neuroscience: Bridging scales in theory and experiment". Outstanding scientists from both, experimental and theoretical neuroscience, got together with the aim to foster discussions on how to bridge between relevant scales of brain structure and function as well as between experimental data, numerical simulations and conceptual models.

Neuroscience Seminar Series

We launched our new 'Neuroscience Seminar Series' in November 2018. Both, postdocs and PhD students, are involved in the invitation process and the hosting of our guests, providing an excellent opportunity for career development and networking for our young scientists. The following talks took place in 2018:

19.11.18
"Experience-dependent synapse reorganization in the living brain"
Prof. Yi Zuo, Sinsheimer Laboratories, University of California, Santa Cruz

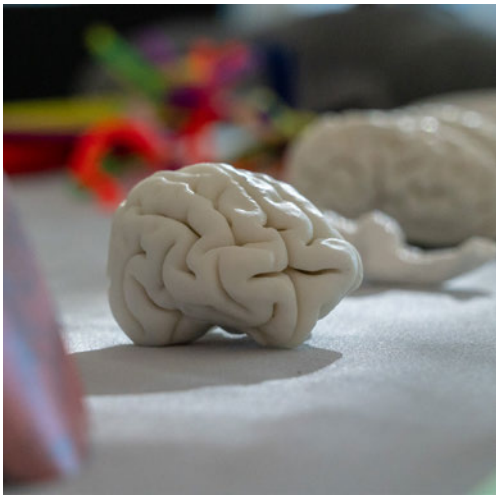
26.11.18
"Brain-computer interfaces for basic science"
Prof. Byron Yu, Carnegie Mellon University, Pittsburgh

Bonn Science Night (17.05. - 18.05.2018)

Every other year, Bonn presents its scientific side over two days at the "Bonn science night". With nearly 20.000 visitors the 11th science night under the topic 'circuits' was a great success. caesar joined in at the science tent at Münsterplatz, giving an insight into the field of neuroethology. In a hands-on approach caesar presented, besides various other activities, a virtual tour of a retina and the chance to see fluorescent labelled neurons under the microscope.

Max Planck Day (14.09.2018)

On 14th September we celebrated the May-Planck Day. The event took place in all Max-Planck Institutes throughout Germany, celebrating science with the public and giving them an insight into various research fields.



caesar researchers engaged with the public via various hands on activities for all ages and various talks throughout an in-house evening.

An introduction to the life and person of Max Planck himself made a great start into the lecture series. Scientific talks were held by our research group leaders in a full house lecture hall, allowing first hand insights into recent findings, debates and discoveries.

Games about testing the own senses as well as matching up a brain model to the corresponding animals inspired all ages likewise. Our younger audience had the chance to build their own brain hat and to craft a colorful neuron to take home with.

caesar Science Slam (20.09.2018)

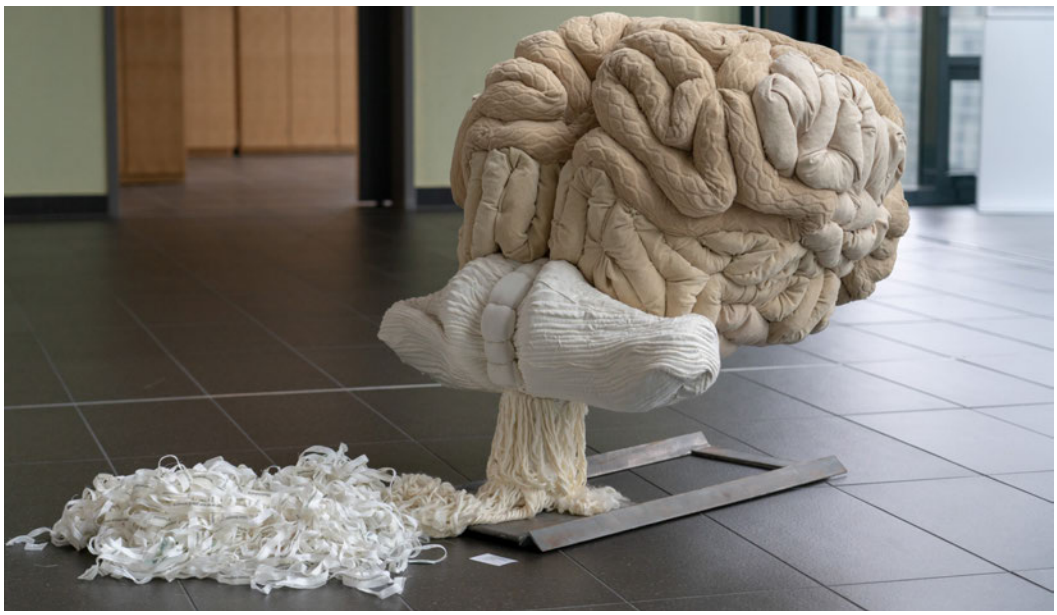
A great success again for our annual science slam on 20th September 2018, in collaboration with the IGEM team in Bonn. The slammers invited the audience to a fun science event with plenty of curiosity and humor.

Participating in the 2018 science slam were:

- Ulrike Neumann, bio economist from Hohenheim presented: "Inflammation - what do you do when the fire starts?"
- Lars Dittrich. The neuro scientist and sleep researcher spoke about: "Are you really tired or already sleeping?
- Ann-Charlott Schneider, unveiled the secrets of the cornea in her talk "Why blood vessels are bad for cornea transplantation"
- Stefan Schneider drew parallels between neuro-science and religion, in his talk "What would have happened if Jesus had suffered from dementia?"
- The winning talk: Stefan Mader's slam on "Seeing the invisible - detecting nano particles"

Art exhibition: “Exploring the senses in art and brain” (28.9. - 29.11. 2018)

Once again, caesar was a fantastic venue for this year’s art exhibition ‘Exploring the senses in art and brain’. 13 artists from Belgium, Germany and the Netherlands were presenting their paintings, sculptures and object arts in different styles, inviting the visitors to a visual tour of a diverse and inspiring world.



Company run (13.09. 2018)

Perfect weather conditions for the 12th company run in the Bonn Rheinaue. Thousands of participants, 5.7 km, a fantastic atmosphere and lots of team spirit. This is what the company run is about. Once again, a small caesar team took part and made it to the finish line in no time.

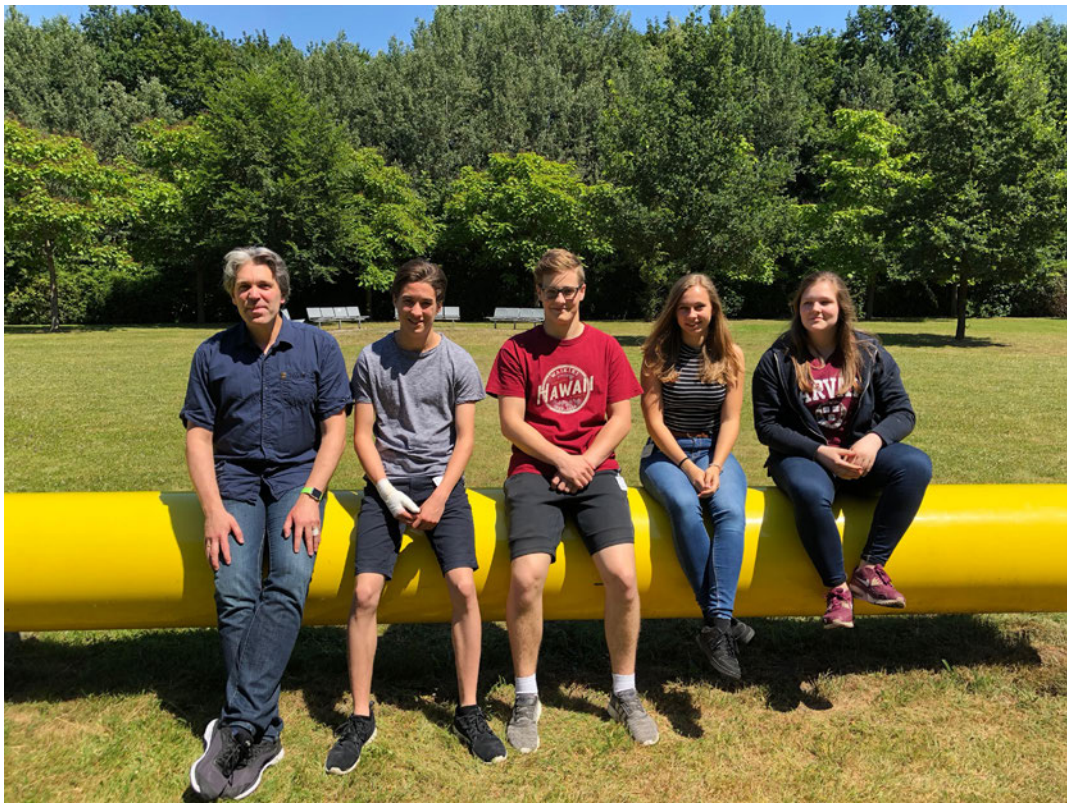
Workshop in collaboration with “Deutsches Museum” (7.11.2018)

From 7th – 9th November 2018, Bonn was hosting the annual communication conference “Forum Wissenschaftskommunikation”. As part of the satellite program and in collaboration with the ‘Deutsches Museum Bonn’, caesar was conducting a workshop, titled ‘Learning by doing – old philosophy, new approaches’. The interactive workshop was as fantastic opportunity for further networking and discussions with professional science communicators throughout Germany. .

Other activities in 2018

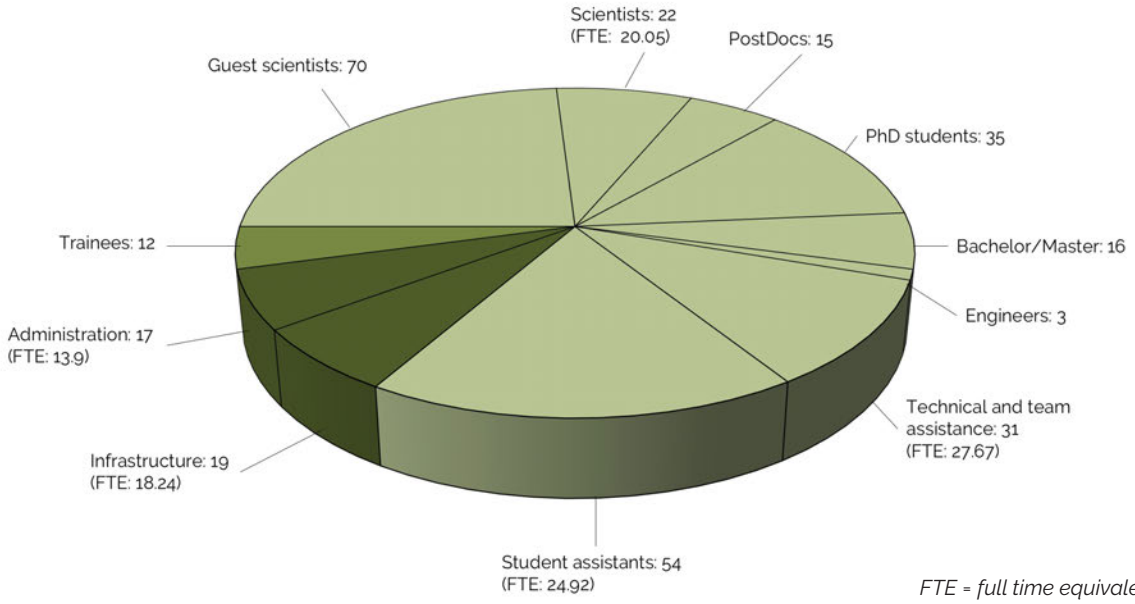
caesar was conducting various events and activities for school children and thereby fostering its relationships to local schools and supporting their MINT activities.

- Girls’ Day/Boys’ Day (26.04.2018)
- ‘support for the gifted’ – Intensive internship - electron microscopy (25.–29.06.2018)
- Visits of school classes
- Career and science talks in schools
- Internship for winners of the ‘Jugend forscht’ competition (02.-06.07.2018)
- Other scientific and administrative internships



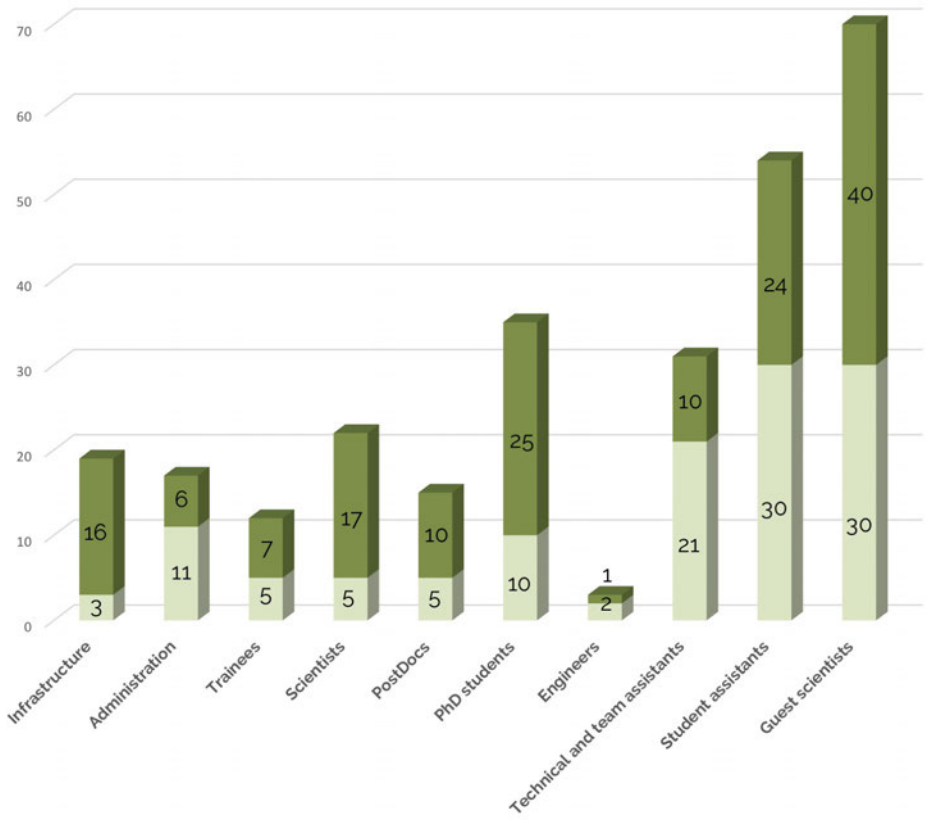

FRONTAL LAPPEN
TEMPORAL LAPPEN
OCCIPITAL LAPPEN
INTERPRETATION
MOTORISCHER KORTEX
SENSORISCHER KORTEX
BROCA AREAL
FRONTAL LOBE
PARIETAL LOBE
MOTOR CORTEX
PRE-MOTOR AREA
SENSORY CORTEX
creativity
Mapped
LEITZ

FACTS AND FIGURES



FTE = full time equivalent

As of December 31st, 2018 the research center caesar employed 224 personnel in total and hosted 70 guest scientists. The distribution of the employees within the departments and functions is deductible from the above graph. Converted into full-time positions there are 13.9 people working in the administration and 18.24 in the infrastructure. Furthermore, caesar instructed 12 trainees in 5 departments: tool mechanic, laboratory assistant in biology and chemistry, administration and animal care.



The ratio of female coworkers in the scientific departments amounts to 44 %. The distribution of female and male employees, regarding the individual functional areas, is represented by the above graph.

Finances

Basis of the caesar foundation

caesar was established as a non-profit foundation under private law by the Federal Republic of Germany and the state of North Rhine-Westphalia in accordance with the Bonn-Berlin compensation act.

The foundation's assets amount to 383,4 Mio. € with 6,6 Mio. € added property value, which was entrusted to caesar by the city of Bonn.

286.3 Mio. € of the foundation's capital were invested in the capital market on a long-term basis. The revenue funds the research of caesar.

ASSETS 2018	
Tangible assets	83.578.551 €
Financial assets	301.736.604 €
Miscellaneous	24.368.078 €
Total assets	409.683.233 €

INCOME 2018	
Income from sales revenues and promotions	4.753.365 €
Income from securities and interest	13.630.797 €
Total income	18.384.162 €

EXPENSES 2018	
Personnel expenses	8.959.344 €
Material expenses and others	5.427.030 €
Amortisations	3.652.498 €
Total expense	18.038.872 €

Balance sheet

Final balance as of December 31st, 2018

ASSETS	31.12.2018	31.12.2017
A. Capital assets		
I. Intangible assets	**105.008 €**	**139.286 €**
II. Tangible assets		
Property and construction	68.769.854 €	69.969.487 €
Various investments	13.868.729 €	13.829.248 €
Advance payment & investment in construction	939.968 €	712.387 €
Total of II.	**83.578.551 €**	**84.511.122 €**
III. Financial assets		
Assets	330.000 €	330.000 €
Securities of capital assets for investment of foundation capital	290.575.021 €	290.575.021 €
Securities of capital assets for reacquisition of property	10.831.583 €	10.831.583 €
Total of III.	**301.736.604 €**	**301.736.604 €**
Total of A.	**385.420.163 €**	**386.387.012 €**

Final balance as of December 31st, 2018

	31.12.2018	31.12.2017
B. CURRENT ASSETS		
I. Inventory stock	**382.325 €**	**316.950 €**
II. Accounts and other assets		
Trade accounts receivables	485.070 €	599.357 €
Receivables from affilliated companies	0 €	0 €
Miscellaneous assets	1.587.701 €	2.033.002 €
Total of II.	**2.072.770 €**	**2.632.359 €**
III. Securities	**0 €**	**0 €**
IV. Cash assets, Federal bank balances, credit balances and checks	**21.618.692 €**	**19.797.225 €**
Total of B.	**24.073.787 €**	**22.746.534 €**
C. Deferred income	**189.283 €**	**285.626 €**
Total capital	**409.683.233 €**	**409.419.172 €**

Final balance as of December 31st, 2018

LIABILITIES	31.12.2018	31.12.2017
A. Capital assets		
I. Foundation assets		
Financing capital	286.323.453 €	286.323.453 €
Investing capital	97.145.457 €	97.145.457 €
Support City of Bonn	6.681.051 €	6.681.051 €
Apropriation reserves	1.283.957 €	1.283.957 €
Total of I.	**391.433.918 €**	**391.433.918 €**
II. Reserves		
Free reserves in accordance with § 58 Nr. 7a AO	8.716.424 €	8.371.133 €
Maintenance reserves	4.943.789 €	4.943.789 €
Total of II.	**13.660.213 €**	**13.314.922 €**
III. Result		
Annual surplus / deficit	0 €	0 €
Total of III.	**0 €**	**0 €**
Total of A.	**405.094.131 €**	**404.748.840 €**
B. Exceptional items for investment subsidies	**2.770.722 €**	**3.207.721 €**
C. Provisions	**831.496 €**	**511.007 €**
D. Payables		
Received payables	175.000 €	0 €
Trade account payables	681.691 €	793.619 €
Other payables	129.806 €	157.985 €
Total of D.	**986.497 €**	**951.604 €**
E. Deferred income	**387 €**	**0 €**
Entire assets	**409.683.233 €**	**409.419.172 €**

FOUNDATION BODIES

Foundation bodies

Foundation board

As of Dec 31st, 2018, the foundation board consisted of:

Chairman

- Prof. Dr. Martin Stratmann
  President of the Max Planck Society for the Advancement of Science e.V.,
  Munich

Members

- Prof. Dr. Philippe Bastiaens
  Max Planck Institute for Molecular Physiology,
  Dortmund

- Prof. Dr. Jens Brüning
  Max Planck Institute for Metabolism Research,
  Cologne

- MinDir'in Prof. Dr. Veronika von Messling
  Head of department 6 in the Federal Ministry of Education and Research,
  Berlin

- Prof. Dr. Winfried Denk
  Max Planck Institute for Neurobiology,
  Martinsried

- Prof. Dr. Pascal Fries
  Director of the Ernst Strüngmann Institute gGmbH,
  Frankfurt a.M.

- Prof. Dr. Bill Hansson
  Vice-president of the Max Planck Society for the Advancement of Science e.V.,
  Max Planck Institute for Chemical Ecology,
  Jena

- Prof. Dr. Michael Hoch
  Rector of the Rheinische Friedrich Wilhelms Universität Bonn,
  Bonn

- Prof. Dr. Regine Kahmann
  Max Planck Institute for Terrestrial Microbiology,
  Marburg

- Tankred Schipanski
  Member of the German Bundestag,
  Berlin

- Ulrich Schüller
  Head of department 4 in the Federal Ministry of Education and Research,
  Bonn

- Karl Schultheis
  Member of the Landtag North Rhine-Westphalia,
  Düsseldorf

- Ashok-Alexander Sridharan
  Head major of the Federal city of Bonn,
  Bonn

- Annette Storsberg
  State secretary in the Ministry for Culture and Science of North Rhine-Westphalia,
  Düsseldorf

- Prof. Dr. Heinz Wässle
  Max Planck Institute for Brain Research,
  Frankfurt a.M.

- Dr. Norbert Windhab
  Evonik Nutrition & Care GmbH,
  Darmstadt

Executive board

As of Dec 31st, 2018, the caesar executive board consisted of:

- Dr. Kevin Briggman
  Managing Director
  Director of the Department "Computational Neuroethology"

- Prof. Dr. Jason Kerr
  Director of the Department "Behavior and Brain Organization"

- Helmut Kolz
  Administrative Director

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