



Bernstein Centers for Computational Neuroscience

BCCN Newsletter



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Jan Benda



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Watching neuronal cells at work

Scientists improve a method for observing neuronal activity in the brain

Every impression and every piece of information that we pick up is processed in the brain through the electrical activity of neurons. To get a better understanding of these processes, it is the long standing dream of many scientists to be able to observe single neurons at work. In the recent years, calcium imaging has proven to be a powerful tool in this respect. By means of a fluorescent signal, this method allows to detect the activity of a large number of neurons in the brain simultaneously with high resolution. Every method though can only be used effectively when its potentials and pitfalls are well known. With a detailed analysis of the neuronal activity in the olfactory bulb of tadpoles, scientists around Bei-Jung Lin and Detlev Schild at the Bernstein Center for Computational Neuroscience and University of Göttingen have shed some light on the applicability of this promising technology. They show that the method is suitable for some cell types more than for others.

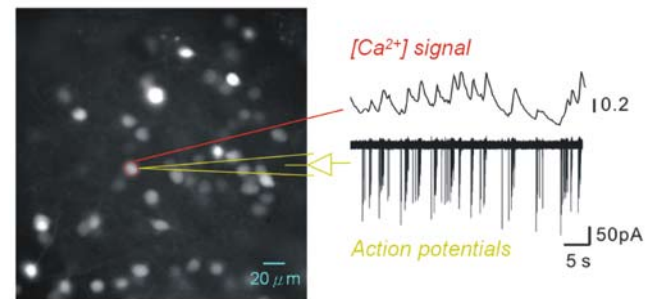
Most methods for analyzing the neuronal activity in the brain either have an insufficient temporal and spatial resolution or they are so intricate and time-consuming that only a small number of cells can be analyzed. Calcium-imaging covers exactly this gap between too gross and too fine an analysis. The calcium concentration of a neuronal cell rises when it sends out an electrical impulse. This rise in calcium can be easily detected using a fluorescent calcium indicator.

Calcium though has multiple functions in a cell. As Schild and his colleagues demonstrated, not every rise in calcium in a neuronal cell must necessarily reflect a neuronal impulse. Whether or not the calcium level is a reliable indicator for the

electrical activity of a cell very much depends on cell type. By recording the electrical activity of single cells in the olfactory bulb, the scientists could compare the cells' neuronal activity with the fluorescent calcium signal. For so-called mitral cells, a specialized cell type of the olfactory bulb, they found a clear correlation between the calcium concentration and the neuronal activity. For granula cells in contrast, such a correlation could not be established.

With this study, Schild and his colleagues have paved the way for a detailed analysis of the olfactory bulb and its response to odors. In addition, their work is a seminal step in the methodology of calcium imaging. Whereas most scientists as yet have generally assumed a close correlation between the calcium concentration and the cells neuronal activity, Schild and his co-workers have shown that this is not necessarily the case. For every cell type under investigation, this correlation first needs to be established.

Source: Lin, B.-J., Chen, T.-W. & Schild, D. (2007). Cell type-specific relationships between spiking and $[Ca^{2+}]_i$ in neurons of the *Xenopus* tadpole olfactory bulb. *J Physiol.* 582:163-75.



The calcium signal tightly matches the neuronal activity (action potentials) in certain cell types of the olfactory bulb.



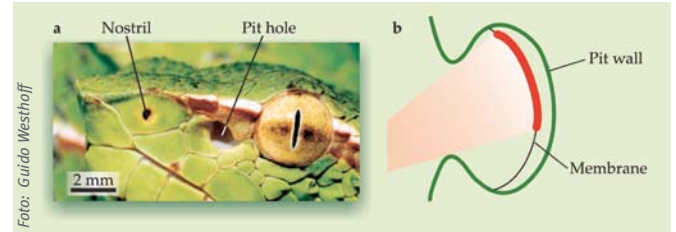
RECENT PUBLICATIONS

Catching prey in darkness, the sixth sense of snakes

Scientists find out how the infrared eyes of snakes function.

In complete darkness they can hunt and detect their warm-blooded prey very precisely – some types of snakes have a so-called pit organ with which they can perceive infrared radiation. It consists of a freely suspending pit membrane containing heat sensitive cells in a pit located beside each eye. The opening of the pit organ is big enough that sufficient infrared radiation can reach the membrane, allowing the snake to quickly recognise even fast moving prey. However, this also has disadvantages. In the same way that a pinhole camera can only take a very blurred picture when the aperture is set wide open, the image of the heat distribution on the membrane is also very unclear. That snakes can nevertheless clearly recognise their prey with the help of the pit organ is the paradox of the infrared detection system—the organ seems to work better than is physically possible. The scientists Andreas Sichert, Paul Friedel and Leo van Hemmen from the BCCN and the Technical University Munich have now found an explanation to this paradox.

Every point that radiates warmth on the surface of the prey is mapped onto the pit membrane through the opening of the pit organ as a large blob, every edge becomes blurred. The information about the original object of prey, however, is completely contained in the blurred picture on the pit membrane. Every point of the reconstructed image appears as a linear combination of all the measuring points of the heat distribution on the membrane. The scientists have now developed an algorithm, which allows them to infer the original image from the overlap of many spots and blurred edges. They call their reconstruction method a ‘virtual lens’. This reconstruction of the

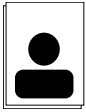


The pit hole is located between eye and nostril. As the schematic drawing shows, a point of the input is projected onto the pit membrane as a disc-shaped image because of the wide aperture of the pit organ.

original image is the exact equivalent of the calculation operation that a neural feedforward network can perform. Thus it has been shown that the brain of the snake can at least theoretically perform such a calculation.

By varying different parameters, the scientists found that the virtual lens reacts very sensitively to errors in measurements by the membrane. The prerequisite for the reconstruction of the image is therefore that the membrane can discern, very reliably, extremely small differences in the heat distribution. The membrane is only 15 micrometers thick and hangs freely suspended in the pit organ so that it is insulated by the air. Heat sensitive cells from the membrane react to differences in temperature of only a few millikelvins. How this sensitivity comes about is now the next question that the scientists in the group of Sichert and van Hemmen want to address. Up to now the pit organ is at room temperature 10 times superior to any un-cooled technical system. If it were possible to construct a highly sensitive infrared detection system, possibilities for application would be considerable. For example, if cars could use a similar system to sense pedestrians at night when they are crossing a street, this would be a great step forward to road safety.

Source : Sichert, A.B., Friedel, P., van Hemmen, J.L (2006). Snake's perspective on heat: reconstruction of input using an imperfect detection system. *Phys Rev Lett.* 97(6):068105



MEET THE SCIENTIST

Jan Benda

The role of background noise in sensory signal processing

The Bernstein Award of the BMBF, valued at 1.25 million Euros, is part of the 'National Network for Computational Neuroscience' and enables excellent young scientists to establish their own research group. The award is offered annually, the laureate for 2007 is Jan Benda.

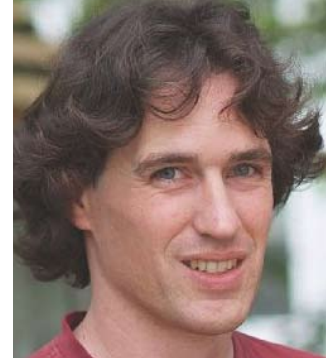
Any information an animal receives about the outside world is transformed to neuronal signals by the sensory organs – neurons 'fire' short electrical impulses. How is this information coded and processed in the spatial and temporal pattern of neuronal activity? What influence does background noise have on this process – stochastic fluctuations of the electrical signals of the brain? These questions are addressed by Jan Benda using weakly-electric fish as a model. 'The system is simply perfect for investigating the active role of noise,' he says. Benda did his PhD in the group of Andreas Herz at the Humboldt University (Berlin). During his subsequent post-doctoral studies at the University of Ottawa (Canada) in the group of Leonard Maler and Andre Longtin, Benda came into contact with weakly-electric fish for the first time. Since 2004 he has been back in Berlin, where the ideas for the research project took form, which he can now realize with help of the Bernstein Award. Benda will move to the Ludwig-Maximilians-University in Munich to carry out the project.

Weakly-electric fish use specialized organs to emit sequences of fast electric discharge resulting in an electric field, and they have electroreceptors to sense their own field. In this way they can detect prey or the presence of other fish whose electric field interferes with their own. The frequency of the electric organ discharge varies between individual fish and is generally higher in

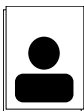
females than in males. Just like the interference of two sound waves of a similar frequency, the interference of the electric fields of two fish also results in a so called 'beat': the amplitude of the interference wave varies periodically. When two fish of the same gender meet, the beat frequency is below 30 Hertz; for two fish of opposite sex it is above 100 Hertz. In this way, the fish distinguishes whether it encounters a female or male individual and sends the according communication signals.

How information is coded and processed in the nervous system has been a major topic in the field of neuroscience for decades. In some cases, only the firing rate of a neuron matters; in other cases the exact timing of neuronal impulses plays a role. Benda showed that the coding of communication signals in weakly-electric fish follows yet another principle. Here, the crucial factor is how synchronous the roughly 10,000 electroreceptors fire.

When a male fish encounters a male conspecific, it sends aggression signals: short accelerations of the electric organ discharge frequency by about 100 Hz, called 'small chirps'. As a consequence, the amplitude of the beat rises abruptly (see fig. page 9). Receptor neurons fire in the rhythm of the electric organ discharge, though leaving out different cycles. Since different receptors skip different cycles, they fire asynchronously. However, receptor activity correlates with the amplitude of the beat signal – the greater the amplitude, the more impulses they send and the more synchronous their signal will thus become. Because of the sudden rise of the beat amplitude in a chirp, the activity of the receptors is exceptionally strong and thus they fire particularly synchronously.



Jan Benda

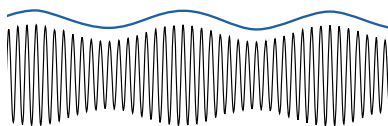


MEET THE SCIENTIST

When a male fish meets a female, the beat amplitude varies at a much higher frequency than when two males encounter. The receptor neurons correspondingly fire synchronously. The male fish sends courtship signals, accelerations of its electric organ discharge by about 600 Hz, termed ‘large chirps’. Large disrupt the fast beat considerably, and receptor neurons reacting to the amplitude of the beat are thrown out of their rhythm. Receptor neurons thus desynchronize in response to large chirps. ‘In both cases the level of synchronization carries the information – in one case neurons synchronize in response to a chirp, in the other case they desynchronize,’ says Benda.

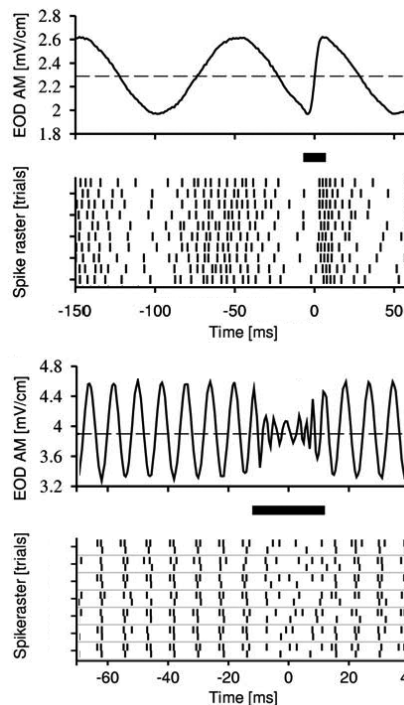
Such a synchronization code sheds a completely different light on the role of background noise in the nervous system. The amount of noise strongly influences the synchrony of the neurons and thereby has a direct impact on the information they transmit. ‘So far, background noise has generally been regarded as an unavoidable disturbance inherent to the system. However, it is also possible that the processing characteristics of a neuron are tuned by adjusting the noise level,’ says Benda. According to this idea, neurons have adapted their noise level in the course of evolution so that the fish can preferentially react to signals that are relevant to it; irrelevant signals would perish due to noise.

Until now, there have been very few experimental studies investigating the role of noise in neurons – and for good reason. ‘It is impossible to experimentally manipulate the noise level



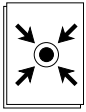
The superposition of two electrical fields leads a periodic variation of the amplitude, a so-called ‘beat’.

in many neurons simultaneously,’ says Benda. Electrosensory systems of weakly electric fish, however, offer a unique possibility to circumvent this



Synchronisation and desynchronisation of receptor neurons in response to small (top panel) and large (bottom panel) chirps.

experimental problem. Weakly-electric fish have two kinds of electroreceptors: those reacting to distortions of their own electrical field as described above and those perceiving the electric field of a prey, which forms through the fish’s muscle contractions. ‘Interestingly, the two receptor types differ considerably in their level of noise. Nonetheless, the neuronal processing circuits are very similar. Therefore, the two electrosensory systems are an ideal system for comparative experimental studies investigating the role of noise in sensory information processing,’ says Benda. His experimental work will be supported by theoretical studies, investigating how noise can shape neural population codes. Benda’s studies may contribute to a possible revision in our thinking about the function of neuronal background noise in sensory systems.



Learning from monkeys

Primate research contributes significantly to the understanding of the human brain

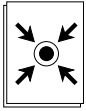
Understanding the complex functions of the brain is an extremely challenging task which can only be accomplished with the combined efforts of both theoretical and experimental research approaches. To reach this goal, theoreticians and experimenters in the Bernstein Centers for Computational Neuroscience work hand in hand. On the basis of experimental data, brain functions are simulated in computer models and quantitative hypotheses are generated, which are then in turn tested experimentally. Thus, experiments on animals are indispensable. A number of different animals are used – from flies to mice and on to primates – depending on the purpose



of the experiments carried out. The closer the question at hand gets to human biology, the more experiments with non-human primates become necessary. Although intellectually, humans are distinctly different from their primate cousins, on the level of basic brain functions such as visual processing and movement coordination, humans and monkeys are very similar. Therefore, results from primate research can be translated to humans; they can lead to clinical applications and open the doors to technological developments.

An example: A person looks for his coffee mug, finds it and reaches for it – this is something a machine cannot yet do, and the neuronal principles behind this amazing performance of the brain are currently barely understood. The person must be able to see, whereby attention plays an important role in shaping his perception. His eyes focus on the coffee mug; he decides to reach out for it and is capable of coordinating the movement of his arm. In a number of studies, researchers at the BCCN are investigating the principles that underlie these accomplishments of the brain. Here we present six research projects that cover different aspects of this example of neuronal processing, in which valuable knowledge has been achieved through primate experiments.

Seeing the coffee mug. Only a fraction of the visual information that falls onto the retina is consciously perceived by the brain. Higher cognitive functions, such as attention, interfere with the processing of visual information. ‘When we look for a coffee mug, we blind out other visual information,’ Stefan Treue (BCCN Göttingen) explains. Together with his colleagues, Treue is interested in finding out which neuronal connections underlie this process. For a long time, it was assumed that attention only plays a role at higher levels of visual processing – as a filter in a sense, which only lets relevant information through to the level of conscious perception. In experiments on primates, Treue and



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his team were able to show that attention already has an effect on the lowest level of image processing, where it modifies the activity of neurons. Attention thus literally sharpens the senses.

‘It is a general principle that feedback signals from higher brain areas modulate properties of cells in the primary areas of the brain,’ says Klaus Obermayer (BCCN Berlin), who deals with data analysis and modelling. His research covers various aspects of such feedback mechanisms and their contribution to visual perception – from attention to learning processes to so-called ‘context effects’. ‘Information processing in one part of the visual field is also influenced by occurrences in other parts of the visual field,’ says Obermayer, ‘and such context effects are astonishingly far-reaching’. With theoretical models and in collaboration with primate researchers, Obermayer examined which neuronal circuits underlie such context effects.

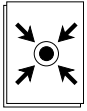
Understanding the neuronal fundamentals of attention has both medical and technological applications. In order to develop effective treatments for attention deficit disorders, a good understanding of the unimpaired abilities of the brain is essential. In addition, research on the principles of attention can contribute to the development of machine vision. A machine must – like a human – select which visual information to take in. Vision is a dynamic system that can perfectly adapt its limited processing resources to the respective situation. ‘I believe it is possible to build more efficient systems once these mechanisms of adaption are understood,’ says Obermayer.

Focussing on the coffee mug. In order to obtain a focussed image of the object of interest – the coffee mug – we direct our view to it. Ulrich Büttner (BCCN München) examines how the brain controls such eye movements. Even when following a moving object, we are able to keep it focused. Our eye movements ensure

that the object’s image is captured on the part of the retina that produces the sharpest possible image, the fovea. To achieve this task, the brain must take the object’s movement into account to be able to calculate its position. Such a ‘prediction’ is based on complex neuronal mechanisms. It would be impossible to control the motor performance simply by feedback mechanisms settling the differences between object position and the eye position. Due to the reaction time of the brain, this would result in a considerable delay and hence the eye would constantly lag behind the target. Based on data from primate research and already existing knowledge on brain circuits, Büttner and Ulrich Nuding (BCCN München) are developing a neuronal model for the calculation of such eye movements.

Several areas of the brain participate in the control of eye movements. ‘Only once these processes are understood more clearly, will it be possible to conclude which brain areas are affected in certain diseases, so that specific medical treatments become possible,’ Büttner explains. Eye movement is a special case of motor activity. Compared to arm movement, eye movement is far more constrained and simple. Hence, it is a good system to study the fundamental principles of motor activity. Implementing general mechanisms like ‘prediction’ in a machine, thereby enabling it to adapt its movement control to specific circumstances, is all but trivial. ‘One can only appreciate the accomplishments of the control circuit after attempting its reconstruction,’ Nuding says.

Realizing and deciding. Every action involves the short-term memory and the ability to make a decision. ‘What did I just look for? – oh yes, my coffee mug. Do I want to reach for it now?’ – we may think unconsciously. Christian Machens (BCCN München) investigates these processes. In experiments that were carried in collaboration with primate researchers, rhesus monkeys received



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two impulses – in this case vibration frequencies – and then had to decide which of the two was the faster. By computer-aided data analysis, Machens was able to show that the same neurons were involved in both short-term memory and decision making – two processes which up to now were thought to be based on separate neuronal entities. Machen's work represents an area of basic research; possible applications are still a distant prospect. 'Basic research is necessary to identify the right questions – without it, applied science would not be thinkable,' says Machens.

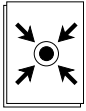
Reaching for the coffee mug. When we see a target, we can specifically reach for it. The brain uses visual information when planning motor activity. But also our decisions and acquired rules have an impact – we know what a coffee mug is and we only reach for it if we want to drink from it. Premotor cortex and parietal cortex are the brain regions in which decisions and visual information are converted into a motor plan. Using rhesus monkeys, Alexander Gail (BCCN Göttingen) examines how exactly this computation takes place. Certain neurons, he could show, 'know' the learned rules and code the movement goal accordingly.

This knowledge about how the brain plans and steers movements represents a prime requirement for neuroprosthetics, a large and new area of application that arose in the last decade thanks to the progress made in neurosciences. So-called 'Brain-Machine Interfaces' (BMI) will enable plegic and partially paralyzed patients to control prostheses or move a computer cursor only by means of their brain activity. While current approaches in neuroprosthetics usually focus on reconstructing movements directly from recordings of the brains motor control area, the work of Gail concentrates on decoding abstract movement goals from the brain activity. When controlling complex movements, as for example the coordination of arm and

hand in grasping, such signals can provide important additional information.

In electrophysiological experiments on primates, the electrodes not only record the activity of single cells, but also the activity of larger groups of neurons. These different types of signals can be separated electronically from one another. 'We are interested to see how these signals are related to each other and what information can be extracted from the different types of signals,' Ad Aertsen explains the research aim of the BMI group at the BCCN Freiburg. Their results have an immediate impact on the development of neuroprosthetics. Together with Carsten





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Mehring and colleagues (BCCN Freiburg) Aertsen was able to demonstrate for the first time that the movement of an arm can be effectively predicted from so-called ‘local field potentials’ – population signals of cells from an area of approximately 100 μm in diameter. While an electrode can lose the signal of a single cell, local field potentials can be reliably measured for months – a key advantage in clinical application. ‘A routine application of BMI will most probably take another ten years. But the “proof of the principle”, that BMI works, has been provided,’ says Aertsen.

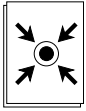
Basic research is a prerequisite of any kind of application. ‘When movement coordination first became a subject of study, neuroprosthetics was not thought of at all,’ Treue says. The same applies to brain pacemakers. Over many years, the fundamentals had to be established through comprehensive experiments, clinical examinations and data analyses – today, brain pacemakers help many patients suffering from motor disorders like Parkinson’s disease.

Primate research – how and why? Neuroscientists carry a responsibility both for future patients who may profit from scientific progress and for laboratory animals. Hence, prior to every animal experiment, the question whether the expected knowledge gain justifies the experiment needs to be carefully addressed. The responsible treatment of animals requires that not a single superfluous experiment be carried out and all tests be conducted with as much consideration as possible. This is not only the attempt of the researchers; the authorities too scrutinize the purpose of every animal experiment. In addition, researchers of the Bernstein Centers are working on the improvement of data analysis technologies in order to guarantee a maximum gain of information from every conducted experiment. ‘Computational neuroscience is required to make the most of the data,’ Machens says.

With imaging techniques like nuclear magnetic resonance, or methods such as electroencephalography it is possible to directly measure brain activity. Such ‘non-invasive’ methods are implemented wherever possible. However, for many questions that need to be addressed, these methods will not provide enough temporal and spatial resolution in the foreseeable future and therefore cannot fully replace experiments of invasive character. Only with the help of electrical recordings is it possible to measure the behaviour of single brain cells. Through the advancements of mathematical analysis tools, among others at the BCCNs, the resolution of non-invasive methods will be improved.

Keeping the number of primate experiments as small as possible also means planning them perfectly, right down to the last detail. Every experiment involving neuronal recordings from a monkey’s brain begins with psychophysical experiments on human subjects, from which a clearly defined hypothesis can be derived. Subsequently, the monkeys are trained to accomplish the corresponding tasks before the actual experiment is carried out. A researcher thus normally deals with one or two monkeys for a period of several years, so that the number of test monkeys is very small.

Before the recording of neuronal activity can begin, a small resealable opening is inserted into the skull of each laboratory animal while it is under general anaesthesia. Fine electrodes with a tip measuring 2-5 μm in diameter can be inserted just a few millimetres into the brain in order to measure the activity of neurons. When monkeys are not being tested, the skull is resealed and the animals are returned to their enclosure where they can move about freely with their fellow monkeys. The brain of a monkey – like the human brain – does not possess any pain receptors, which means the monkey cannot feel the



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electrodes during an experiment, and the method used is so inoffensive that it can be repeated many times on the same animal without causing damage to the brain tissue. This method allows for the precise recording of the activity of single cells or small groups of cells in the cerebral cortex while the animal performs complex and precisely defined behavioural tasks. Similar techniques are also applied to humans. In epilepsy patients, for example, the epileptic focus can be localized with the help of electrophysiological measurements.

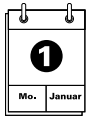
With their know-how of data analysis, computer simulation and mathematical modelling, scientists of the Bernstein Centers significantly contribute to setting up clearly defined hypotheses, to optimally conduct and evaluate animal experiments, and to thus make scientific results available for biomedical applications as soon as possible. The tight link between theoretical, experimental and medical research promotes scientific progress and helps scientists to fulfil their social responsibility also with respect to animal protection.

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Advanced Course as from 2008 in Freiburg

The internationally renowned summer school ‘Advanced Course in Computational Neuroscience’ (ACCN) will take place at the Bernstein Center for Computational Neuroscience in Freiburg from 2008 to 2010. This decision was announced by the ACCN’s Board of Directors at the end of this year’s summer school edition in Arcachon (France).

The ACCN, which has been offered since 1996, is a distinguished international four-week summer school in neuroscience designed for carefully selected outstanding students at the advanced PhD and post-doctoral level from throughout the world. The course consists of a mixture of lectures, tutorials and a research project. Its explicit goal is to train experimental neurobiologists and medical doctors together with researchers from mathematics, physics, engineering and computer science in the interdisciplinary area of computational neuroscience.

Informal and formal collaborations between students and faculty are frequent byproducts of the school. The course thus has a significant impact on the development of the field. Previous venues of the ACCN were Crete, Trieste, Obidos (Portugal) and Arcachon. The decision to hold the next school in Freiburg documents the international visibility of Computational Neuroscience in Germany.

Further information

<http://www.neuroinf.org/courses/courses.shtml>

‘CNS’-Course in Göttingen

For the fifth time, young scientists from Germany and other European countries gathered in Göttingen to be introduced to current developments in the field of theoretical neuroscience at the Max Planck Institute for Dynamics and Self-Organization from September 18 to 23, 2007. The ‘CNS’ course in computational neuroscience, which was supported by the medical engineering company Otto Bock Health Care, is part of the activities of the Bernstein Center Göttingen.

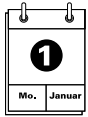
Further information:

<http://www.bccn-goettingen.de/events-1/cns-course>

Prize for exhibit on brain function

Making complex topics from the natural sciences accessible to young people in hands-on exhibits – this was the aim of the ‘ExpoNaTe’ competition of the Landesstiftung Baden-Württemberg. An exhibit explaining brain function, conceptualized by scientists of the BCCN Freiburg and implemented by the science museum Science House, received an honorary prize of 3.000 Euro. The exhibit describes the functional structure of the cerebral cortex. Defined areas of the cortex carry out specific functions. The exhibit allows the user to explore where areas specialized for given functions are located. When touching these areas, the respective function is indicated on a screen.

Further information: <http://www.bccn.uni-freiburg.de/news/news-events/hirnexponatpreis>



Bernstein Symposium 2007

The annual 'Bernstein Symposium for Computational Neuroscience' has become a tradition. This year was the third return of the conference; scientists from the four Bernstein Centers met to present lectures and posters and discuss their results. For the first time, the new members of the National Network for Computational Neuroscience participated in the meeting. With five 'Bernstein Groups' and eleven Bernstein Partner Projects, the network has increased considerably in the last year. This year's meeting, which was organized by the Bernstein Center in Göttingen, counted around 200 participants. In addition, renowned experts from abroad were invited to attend and present their work in special 'Bernstein Lectures'. Like

last year, the symposium was flanked by a satellite workshop on communication with the public and a seminar where PhD students and young post-doctoral students could exchange ideas.

A highlight of the symposium was the presentation of the Bernstein Award 2007 by Ministerial Director Dr. Peter Lange of the BMBF. The prize is equipped with 1.25 Million Euro and offered in an international competition. This year, the prize was awarded for the second time and received by Jan Benda (see page 9).

Further information:

<http://bccn.neuroinf.de/meetings/symposium-2007>



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Title image: The population code of receptor neurons in weakly-electric fish. The activity of the neurons varies with the so-called “beat” of the electrical field (view article about Jan Benda, page 7).

GEFÖRDERT VOM



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