



MARIE CURIE

ACTIONS



SEVENTH FRAMEWORK
PROGRAMME



NETT INTERNATIONAL CONFERENCE

ON SYSTEM LEVEL APPROACHES TO NEURAL ENGINEERING
BARCELONA 2015



NETT

NEURAL
ENGINEERING
TRANSFORMATIVE
TECHNOLOGIES



**Universitat
Pompeu Fabra**
Barcelona



**UNIVERSITAT POLITÈCNICA
DE CATALUNYA**
BARCELONATECH

VIABILITY AND ACTIVITY OF IN VITRO NEURONAL NETWORKS UNDER PERFUSION

Nitzan Herzog, University of Nottingham

Microfluidic-based cell-culture platforms are increasingly being applied in the field of neuroscience to construct constrained network topologies in which both the placement and directionality of neurites are controlled, and to expose networks to controlled chemical gradients. To date, however, applications involving rapid perfusion and fast gradient switching on cultured neurons have not been explored, due to the perceived vulnerability of cultured neurons to shear stress induced by high flow rates. We used a precise pressure-regulated flow control system to subject cultured neurons to a range of dynamic flow regimes, while monitoring both their viability (indicated by uptake of the DNA binding dye Propidium Iodide) and their action potential activity (measured using Micro-Electrode-Arrays). Viability was found to be compromised within several hours of initiating perfusion, but the rate of degeneration was dependent upon several variables. These included the culture size and plating density, the geometry of the microfluidic culture device, and on the provenance of the perfused media. Surprisingly, the culture viability was unaffected by flow rate across two orders of magnitude. In contrast, the electrical activity of the cells was highly correlated with flow rate: at relatively low flow rates, the spontaneous and evoked activity patterns resembled the baseline activity without flow, while at higher flow rates the spontaneous activity was either silenced, or became intense while reducing in synchrony. At the higher flow rates no stimulated responses could be evoked from the culture. Flow experiments were repeated with a commercial semi-permeable membrane separating the culture from direct perfusion, and thus reducing the imposed shear stress. Viability and electrical activity responses were not significantly altered by the inclusion of the membrane, indicating that the behaviour is not due to shear stress effects. Modelling in COMSOL, assuming a local cell environment exclusively dominated by diffusion, predicts that concentrations of small molecules in close proximity to the cells may be rapidly depleted when media is perfused at high flow rates through the microfluidic device. The assumption of a diffusion-dominated microenvironment is supported by observing the timescales for onset and removal of fluorescent dye in an identical device.

AXON GROWTH INVESTIGATION IN ASYMMETRIC MICROFLUIDIC CHANNELS

Eugene Malishev, Saint Petersburg Academic University

Microfluidic chips combined with microelectrode arrays provide a method to control morphology of the grown neural culture and study long term functional connectivity. Specific design of microfluidic channels, which connect separated chambers with neural sub-populations, may be used for setting axon outgrowth direction and providing one-way spike propagation in the neural culture. Such in vitro system with unidirectional connections between chambers provides an unique approach to study neural development, functional connectivity and synaptic plasticity. To increase the selectivity of such a 'directional filter' we investigated axon growth dynamics varying microchannels' designs based on a sequence of widening segments with narrow 'bottlenecks', concentrating 'forward-growing' and cutting off 'backward-growing' axons. The microchannels were done in PDMS by two-layer soft lithography and placed on glass slides or microelectrode arrays. Using visual inspection, immunocytochemistry and spike propagation analysis we defined optimal design of microchannel segments to improve unidirectional axon growth between different neural sub-populations. The results provide basic neuroengineering methods for neural circuit studies on cellular and network level.

DIRECT LASER WRITING OF MICROSTRUCTURES FOR PATTERNING IN VITRO NEURAL CELL CULTURES

Benjamin Paul, University of Nottingham

Co-ordinating the growth of neurons in vitro has been identified as a key challenge for in vitro neural interfaces since the late eighties (Kleinfeld et al 1988). The majority of these approaches have exploited surface modification and traditional lithographic techniques. However these 2D modifications get buried under extracellular matrix (ECM) secreted by the culture and traditional lithographic techniques tend to have multi-step processing making them inflexible when faced with the dynamic demands of coordinating the complex architecture of living systems. Direct laser writing (DLW) exploits the two photon absorption phenomenon offering the ability to build microstructures with feature size an over an order of magnitude smaller than a cell body (XY: 200 um, Z: 800 nm), and are therefore able to separate neural processes from cell bodies. As these microstructures can be built to heights over 100 um they are not vulnerable to being buried by secreted ECM. As ever more complex and dynamic patterning techniques move into the 3rd (Z-axis) and 4th (time) direct laser writing with full free form 3D fabrication and mild environmental conditions is well suited to the challenge. Using a state of the art Photonics Professional GmbH Nanoscribe microstructures of OrmoComp (Microchem), a commercially available hybrid photopolymer, were fabricated and used to influence the direction of neurite projections whilst confining cell bodies. 1 um gaps were left between 30 um compartments allowed for free passage along a path predefined and illustrated in red in the graphical abstract. Additionally cultures patterned with novel custom made pH-sensitive fluorescent hydrogels for providing additional sensory functionality have been developed. An approach for integrating these with microfluidics to provide artificial homeostatic feedback is also proposed.

DESIGN OF SYNAPTIC CONNECTIVITY AND CELL PATTERNS IN DISSOCIATED NEURONAL CULTURES USING MICROFLUIDICS AND MICROELECTRODE ARRAYS

Alexey Pimashkin, N.I.Lobachevsky State University of Nizhny Novgorod

Microfluidics and microelectrode technology recently have been advanced neuroengineering in fundamental research of the brain and medical applications. Dissociated neuronal cultures grown on microelectrode arrays allows continuous long term registration and electrical stimulation of the neuronal network. Microfluidic technology allows to grow neural branches (axons and dendrites) inside microchannels which separates cell clusters. We designed specific microchannels structure where only axons can grow between the cells. In this study we designed a microfluidic device combined with microelectrode array which allows to grow two separate neuronal cells cultured networks with directed synaptic pathways between. We investigated signal propagation through axonal pathways during culture development. Also one separate chamber can be used to grow the cells dissociated from embryonic mice (E18) and other chamber for neurospheres (hippocampal progenitor cells E14). Such methods can be used to investigate stem cells and progenitor cell differentiation and functional integration in the network. The results can be used in the study of neuroprosthetics, neurorehabilitation and synaptic plasticity.

CLUSTERED NEURONAL CULTURES: PROBING NEURONAL CIRCUITS IN A DISH

Sara Teller, Departament d'ECM, Universitat de Barcelona

Major dynamical traits of a neuronal network are shaped by its underlying circuitry. In several neurological disorders the deterioration of brain's functionality and cognition has been ascribed to the loss of specific connectivity pathways or a change in the topological properties of the brain's circuits. To deepen in the understanding of the activity-connectivity relationship, neuronal cultures have emerged as remarkable systems given their accessibility and easy manipulation. A particularly attractive configuration of these in vitro systems consists in an ensemble of interconnected clusters of neurons. These clustered neuronal networks exhibit a complex dynamics in which clusters fire in small groups, shaping communities with rich spatiotemporal properties. In our experiments we monitor spontaneous activity using calcium fluorescence imaging, which allows the detection of neuronal firing events with both high temporal and spatial resolution. The detailed analysis of the recorded activity in the context of network theory, information theory and community analysis allows the quantification of important properties such as the functional connectivity of the network, its relation to the structural one, and the structure and stability of the observed modules. Additionally, the networks can be also perturbed in a physical way using a two-photon microscope adapted for ablation, offering a unique scenario to study the resilience of the network to damage and the role of 'hub' nodes. The combination of all these approaches is helping to develop models to quantify damage upon network degradation, with promising applications for the study of neurological disorders in vitro.

AN AUTOMATED APPROACH FOR TWO-PHOTON TARGETED RECORDINGS IN VIVO

Luca Anecchino, Imperial College London

Understanding the functional principles of the mammalian cortical circuit is one of the major projects of modern neuroscience. To make progress on this problem, we need to be able to observe the behavior of the individual neuronal elements of this circuit. The whole cell patch clamp technique has been the 'gold standard' method for this, as it allows both sub-threshold and suprathreshold electrical signals to be recorded. Recently, Kodandaramaiah et al (Nature Methods 9:585-7, 2012) developed an automated approach for performing blind, in vivo patch clamping. Now, by targeting this technique to specifically labeled individual cells or cell classes (Margrie et al, Neuron 39:911-8, 2003), it may be possible to test a wide range of hypotheses concerning information processing operations performed by the cortical circuit. To make this possible, we have developed a strategy for two-photon targeting of an automated whole cell patch clamping algorithm. Our Robotic Integrated Targeted Autopatcher (RITA) is responsible for the control of a micromanipulator, a custom made electromechanical regulator for glass electrode internal pressure control, a microelectrode signal amplifier and a two-photon microscope. Images of fluorescently labelled neuronal tissue are acquired through the two-photon microscope, targets for patch clamp are selected via a point-and-click graphical user interface. Optical coordinates converted into the micromanipulator coordinate system, and then a suitable path calculated to guide the patch pipette towards the target. Our system allows us to compensate for brain tissue deformation and subsequent neuronal target movement caused by pipette insertion. RITA is currently being tested and calibrated for targeting specific cell classes in the cortex of the intact mouse brain labelled via either fluorescent dye loading (e.g. Oregon Green BAPTA-1) or genetically-encoded indicators (e.g. GCaMP6). The strategy at the core of RITA naturally scales to the selection of multiple identified neurons, and may thus permit simultaneous targeted patch clamp recordings from neuronal ensembles.

IMAGE ANALYSIS TOOLS FOR STUDYING AXONAL AND PRESYNAPTIC BOUTON DYNAMICS IN THE LIVING BRAIN

Cher Bachar, Imperial College London

Live brain imaging at cellular and synaptic resolution has dramatically improved our understanding of its organization and plasticity. A major issue in this field is the lack of automated tools to reliably analyse synaptic structures. Current methods to identify and track axonal boutons are still largely manual (e.g. imageJ-based), thus prone to be user-dependent and non-rigorous, a recognized problem in the synaptic structural plasticity field. To address these issues, we have developed a semi-automated reconstruction software named EPBscore that can automatically trace axons and measure synaptic bouton size (i.e. strength) and dynamics from time-lapse in vivo imaging experiments. Given a set of thresholds, EPBscore automatically and reproducibly tracks boutons and their sizes from time-lapse image stacks. EPBscore has been recently used in experiments that led to the discovery of altered synaptic dynamics in the aged brain (Grillo et al., 2013), and upon partial loss of connectivity (Canty et al., 2013a; Canty et al., 2013b). However, the automated tracing algorithm does not perform well on complex images with several (> 20 per region of interest) axons. To address this problem, we are developing software to automatically trace and detect boutons in such densely labelled areas. The tracing algorithm traces the axonal processes by detecting the direction of highest changes in gradient along the axon, and uses this information to select a direction vector. The bouton detection implements Support Vector Machine (SVM) classification using training data consisting of examples of boutons and non boutons, such as axon segments. To first automatically select points of interest, i.e. areas where there are potential boutons, we use a local feature detector, Speeded Up Robust Feature (SURF) detection, and then use the classification to select the boutons among these points of interest. The development of automatic image analysis tools to extract relevant information from axonal and presynaptic optical recordings allows us to analyse more axons per image, and to analyse the data without the bias that occurs in manual analysis. Here we have compared this tool with EPBscore

and applied it to the study of axon and synaptic regeneration in the somatosensory cortex of aged mice using two-photon microscopy and a minimal injury approach.

CHARACTERIZATION OF THE ELECTROPHYSIOLOGICAL ACTIVITY OF EHMT1-DEFICIENT NEURONAL NETWORKS DURING DEVELOPMENT

Monica Frega, Radboud University Nijmegen

Intellectual disability (ID) is present in a large and heterogeneous group of neurodevelopmental disorders. Recent studies have identified Euchromatic histone-lysine N-methyltransferase 1 (EHMT1) as a key epigenetic regulator during neurodevelopment. Heterozygous loss of this gene causes Kleeftstra syndrome, which is characterized by moderate-to-severe ID, autistic behaviour, microcephaly and dysmorphic features. Here, we studied the effect of EHMT1 deficiency on neuronal functional activity during development in vitro. The electrophysiological activity of neuronal cultures was investigated at the single cell and network levels. Using whole-cell patch clamp techniques, we investigated synapse formation and spontaneous action potential induced events. To analyse activity at the network level, we cultured neurons onto Micro Electrode Arrays (i.e., 60 micro-electrodes embedded in a glass substrate) in order to monitor the development of network organization. We investigated the physiological consequences of EHMT1 deficiency using three models: (1) rat dissociated cortical neurons where the loss of function was mimicked through lentivirus-delivered shRNA knock-down; (2) dissociated neuronal cultures from a heterozygous knock-down mouse; and (3) neurons derived from the Induced Pluripotent Stem Cells (iPSC) of Kleeftstra syndrome patients. In all cases, we compared the electrophysiological activity of EHMT1-deficient neurons to wild type controls. We found that EHMT1-deficient neuronal cultures showed severely impaired action potential behaviour early in development. The synchronization of action-potentials was affected by EHMT1 deficiency and impairments in the regularity of synchronous events were evident later in development. In conclusion, we showed that deficiency of EHMT1 affects spiking activity during development, and therefore epigenetic regulation by EHMT1 is important for the normal development of neuronal circuits.

THEORETICAL GROUNDWORK FOR VISUAL STIMULUS RECONSTRUCTION FROM TWO PHOTON CALCIUM IMAGING IN MOUSE V1

Stefania Garasto, Imperial College London

Processing of sensory information is a fundamental task in the brain and one of the challenges of neuroscience is the understanding of how neurons encode and decode this information. Unravelling the mechanism of translation between the visual experience in the physical world and the neural code is a key part of this and remains an open question, as well as the identification of the essential features to encode and decode information. Three approaches are usually employed to investigate these questions. A common one is to analyse encoding strategies, i.e. efficient image representation techniques using recorded or simulated neural activity. A second approach is to perform an identification task, in which the aim is to identify which of a predefined set of stimuli elicited a specific neural response pattern. A few studies have employed a more challenging approach, namely their aim is to reconstruct the visual stimuli given the neural response activity pattern, measured with fMRI recordings in humans. However, fMRI data currently lack the spatial and temporal resolution provided by in vivo techniques, such as two-photon calcium imaging. Algorithmically, the final result of the fMRI approach relies heavily on a previously defined set of images, thus making it more like an identification task, while we are interested in improving the results obtained with a pixel wise reconstruction. Another study used electrophysiological data, although recorded from the LGN, whose encoding strategies might differ from those of V1. Finally, none of the existent method consider the effect of using divisive normalization when modelling neural responses. In this work, we present a technique for visual stimuli

reconstruction which is based on the application of a forward receptive field based model to estimate the predicted neural response given a specific input. An inverse model is then used to recover which stimulus gave rise to a certain response pattern. We search for the optimal reconstruction in the pixel space and we aim to maximise a posterior probability using different types of prior probabilities. A training and a test dataset are used to determine the parameters of the forward model and to evaluate the quality of the reconstruction, respectively. We apply the algorithm to surrogate data and we quantify its performances using a similarity measure between the true and the reconstructed image. The use of an explicit forward model allows us to test which properties of the system are the most important in terms of the quality of the reconstruction and therefore for information transmission. To do this, we compare how the performance of the algorithm changes with the inclusion of a divisive normalisation step, at different levels of signal to noise ratio and with respect to the number of neural units used. The algorithm will then be applied to decode two-photon calcium imaging data from mouse V1.

THE STUDY OF AGE-RELATED CHANGES IN BRAIN CIRCUITS

Diana Lucaci, Imperial College London

Due to increasing longevity, the social and economic impact of our expanding older population is expected to become a major global challenge. With ageing, brain functions involved in attention, memory, motor control, and emotional control tend to be compromised. As such, cognitive decline is commonly observed in advanced ageing, even in the absence of disease. The prefrontal cortex (PFC) is one of the brain areas most often affected by age-related changes, but the functional consequences of normal ageing on PFC circuitry are poorly understood. Therefore, it is necessary to examine the mechanistic basis of ageing at the neuronal and synaptic level. For such resolution, optical neurotechnologies are needed in order to directly relate functional and anatomical changes in the PFC. Whilst anatomical changes in the density of synapses and dendritic spines have been associated with ageing, we understand very little about how and whether ageing preferentially affects neurons in different layers of the prefrontal cortex. Hence, we will explore the functional and anatomical consequences of ageing by combining electrophysiological recording with confocal imaging from single cells. Whole cell recording from cortical neurons will be used to compare the intrinsic and synaptic properties of prefrontal cortical neurons in adult and aged mice. The morphology of these functionally characterised neurons will be established using biocytin-conjugated fluorescent labelling followed by three-dimensional reconstruction with confocal imaging. In this way, we aim to determine the principal sites of functional and anatomical age-related changes within the PFC.

FLUORESCENCE IMAGING OF PERIPHERAL NERVES USING GENETICALLY ENCODED VOLTAGE INDICATORS

Peter Quicke, Imperial College London

Monitoring individual neuronal activity in peripheral nerve fibres could allow indirect readout of physiological parameters as well as information on coding in the peripheral nervous system. In conjunction with nerve stimulation, 'closed loop' peripheral nerve control could also lead to a novel 'electroceutical' therapeutic strategy. Optical monitoring techniques could represent an improvement over current electrode methods due to their high spatial resolution and neuronal specificity when combined with genetically encoded reporters. We aim to evaluate the feasibility of using genetically encoded voltage indicators to monitor nerve activity by characterising the peripheral nerve optical properties and the functional voltage imaging signal to noise ratio (SNR). We selectively expressed Voltage Sensitive Fluorescent Protein 2.3 (VSFP 2.3) in mouse cholinergic neurons using the cre-lox system with a ChAT promoter. We extracted lengths of the Vagus and Sciatic nerves and imaged the protein's fluorescence. We imaged intact nerve lengths using both 2 photon and widefield microscopy and also used a confocal microscope to image transverse sections of the nerve. We present fluorescence images of peripheral nerves demonstrating the voltage reporter localisation to the axonal membrane. We measured the nerve tissue extinction coefficient, which dictates the maximum imaging depth and hence the accessible fraction of axons. We will also describe

our latest results on functional voltage imaging in nerves.

LOWER BOUNDS ON THE TEMPORAL PRECISION OF SPIKE DETECTION FROM CALCIUM IMAGING DATA

Stephanie Reynolds, Imperial College London

Fast and accurate detection of action potentials (spikes) from neurophysiological data is crucial to understanding information processing in the brain. As the concentration of intracellular free calcium is a reliable indicator of spiking activity, optical imaging methods use calcium-sensitive fluorescent indicators. These calcium indicators report calcium concentration changes via changes in their fluorescence intensity. The characteristic pulse shape produced in a calcium transient time series in response to an action potential varies for each calcium indicator. This difference in pulse shape affects the ability of spike detection algorithms to estimate the position of spikes. We have calculated a result that provides a theoretical lower bound (the Cramér-Rao lower bound) on the uncertainty of the position of a detected spike in calcium imaging data. This bound is dependent upon the characteristic pulse shape of the calcium indicator used. We compared our lower-bound to the temporal precision achieved on surrogate data by a spike detection algorithm based on finite rate of innovation (FRI) theory (Oñativia et al 2014 J. Neural Eng. 50 046017). In particular, we made performance comparisons for the calcium-sensitive dye Oregon Green BAPTA (OGB) and two new protein calcium sensors GCaMP6f and GCaMP6s. We found that the FRI algorithm achieves near optimal performance compared to the lower bound for all indicators past a certain signal-to-noise ratio breakpoint. Under the same imaging conditions, the least uncertainty in spike position estimation is achieved with the calcium indicator GCaMP6s. This can be attributed to the relatively high operating signal-to-noise ratio of this calcium indicator. When comparisons are made linearly across signal-to-noise ratios it is the indicator with the fastest decay (GCaMP6f) that offers the lowest uncertainty. We are currently working on the calculation of performance bounds relating to the minimum resolvable distance between two spikes, we will compare how these bounds vary per pulse shape. Knowledge of the pulse shapes which are beneficial or detrimental to spike detection performance can inform the development of calcium sensors. Furthermore, lower bounds on spike detection performance act as a benchmark against which to compare algorithms – we have seen that the FRI algorithm achieves near optimal performance.

CHEMICAL FUNCTIONALISATION FOR SURFACE PLASMON RESONANCE IMAGING OF NEURAL NETWORKS ACTIVITY

Houda Sahaf, University of Nottingham

Surface plasmon resonance (SPR) is one of the most advanced technologies used for chemical and biological materials sensing. This technique is an optical detection phenomenon occurring when a polarized light excites metal (usually Gold) thin layer (nanoparticles, nanorods, nanofilm...) deposited on a glass coverslip. Depending on SPR conditions including the wavelength, polarization and incidence angle, free electrons at the surface absorb incident photons and convert them into surface plasmon intrinsic waves inducing a change in reflectivity of the light. Perturbations at the metal surface, such as an interaction between (probe/guest) molecules attached on the surface that capture target ions or molecules (host), produce a modification of surface plasmon resonance conditions and thus a change in reflectivity. These modifications can be measured and used as chemical or biochemical sensors. The SPR imaging (SPRI) takes SPR sensing a step further: In a SPRI experiment, these local changes in the reflectivity (due to chemical or bio-chemical changes) are recorded with a high-resolution CCD camera providing detailed data on molecular binding, biomolecular reactions and kinetic processes. This method is very attractive technique for the real-time detection of chemical interactions at solid surfaces because it is label-free, non-invasive and highly sensitive/selective. In this project, we are interested in using SPRI to record optically the response of the neural networks in the form of spatio-temporal patterns of action potentials. This is usually achieved using

electrodes that showed a poor spatial resolution and that are invasive. We are using a multi-modal optical imaging system that has been designed and implemented including a total internal reflection imaging system; surface plasmon resonance imaging; epi-fluorescence and transmission and reflection microscope. Currently, we are investigating the modification of the substrates surface chemistry in order to be able to perform a successful detection of the neural activity of network using potassium ions as a target. The surface chemistry has to be compatible with the stringent requirements of long-term neural network growth, stimulation and microfluidic systems.

RAPID THREE DIMENSIONAL TWO PHOTON NEURAL POPULATION SCANNING

Renaud Schuck, Imperial College London

Recording the activity of neural populations at high sampling rates is a fundamental requirement for understanding computation in neural circuits. Two photon microscopy provides one promising approach towards this. However, neural circuits are three dimensional, and functional imaging in two dimensions fails to capture the 3D nature of neural dynamics. Electrically tunable lenses (ETLs) provide a simple and cheap method to extend laser scanning microscopy into the relatively unexploited third dimension. We have therefore incorporated them into our Adaptive Spiral Scanning (SSA) algorithm, which calculates kinematically efficient scanning strategies using radially modulated spiral paths. We characterised the response of the ETL, incorporated its dynamics using MATLAB models of the SSA algorithm and tested the models on populations of Izhikevich neurons of varying size and density. From this, we show that our algorithms can theoretically at least achieve sampling rates of 36.2 Hz compared to 21.6 Hz previously reported for 3D scanning techniques.

ANTICIPATORY CONTROL BASED IN COUNTERFACTUAL SENSORY ERROR PREDICTIONS

Ivan Herreros Alonso, Universitat Pompeu Fabra / DTIC / SPECS, Barcelona

Predictive coding (PC) is a probabilistic framework that describes the goal of the brain as to predict the incoming stimuli. More precisely, the normative view of PC states that the goal of processing and learning is to reduce prediction errors, which measure the difference between the predicted stimuli and the actual ones. How this view applies to sensory processing is relatively clear, but its extension to motor control is still uncertain. The current theory assumes that while in perception sensory errors are suppressed by predicting the actual stimuli, in action, sensory errors have to be suppressed by actions. However, how the latter process is achieved is still uncertain. Moreover, whereas, in perception predictions are clearly constrained by the factual stimuli they anticipate, predictions in motor control, if they are sensory are counterfactual, as they should match, or better, anticipate, errors that do not occur. For this reason, we refer to the predictions of the second kind as counterfactual sensory errors (CSE). In this work, we address two types of questions: how do CSE predictions and the sensory errors from which they were learned relate, and what is the temporal order between them. Namely, when should a CSE prediction be issued in relation to sensory errors experienced in the past? We address these questions with a control theoretic approach, showing that in the noiseless case, for linear systems there is an analytic solution to these questions. Our results pave the way to a better understanding of the requirements posed by the extension of PC to motor control.

HUMAN-LIKE BIMANUAL SYNCHRONOUS MOVEMENTS IN ANTHROPOMORPHIC ROBOTS

Gianpaolo Gulletta, University of Minho

Autonomous manipulation skills in humanoid robots are required in many domestic and industrial applications and the generation of human-like movements facilitates human-robot interaction and cooperation because it satisfies people's expectations in robots. We present an algorithm that endow an anthropomorphic robot with the ability of generating bimanual synchronous trajectories for both arms and hands. Our approach takes inspiration from evidences widely observed on human upper-limbs movements during the execution of bimanual tasks. The movements of the arms and hands of an anthropomorphic robot have been formulated as a nonlinear optimization problem and the solver IPOPT has been used to find local optimal solutions. The obtained trajectories showed the kinematic features observed in human upper-limbs motion and the small computational cost makes real-time human-robot interaction feasible.

A SELF REGULATED AND ADAPTIVE HUMANOID ROBOT

Jordi-Ysard Puigbò Llobet, SPECS - Universitat Pompeu Fabra, Barcelona

We present a model of homeostatic regulation applied on an iCub humanoid robot. Homeostasis can globally be understood as the set of needs and drives that govern primitive animal behaviours, as is the case of maintaining body temperature or satiating hunger. Maintaining homeostasis allows animals to adapt to ever changing environment and body conditions. Our model generally defines needs or drives as a homeostatic level in any sensory dimension which has delimited a comfort zone (CZ). Whenever a boundary of the CZ is crossed, a value signal is generated, which triggers a purely reactive action, in the form of a reflex that tries to bring the robot internal state back to the CZ. On top of this purely reactive system, an adaptive controller tries to make sense of these value signals to optimize behaviour. We have constructed a two phase model of learning grounded on the classical conditioning paradigm. In a first phase, the value signal of the homeostatic controller goes to a model of the cerebellum, which anticipates the aversive signal of going out of the CZ using contextual data. The cerebellum is then producing a more appropriate, smoother action to avoid it. On a second phase, the value signal coming from the homeostatic controller increases plasticity in the cortex, thus allowing to learn relevant representations of

contextual data for the successful anticipation of going out of the CZ. We apply this model to social learning in a human-robot interaction setup. A need for human attention increases with time as long as the robot doesn't perceive any speech or skin tactile data from the human. Out of the CZ, the reactive behavior triggers speech and body movements to attract attention. The corticocerebellar structure will then anticipate the lack of attention from contextual data (distance, gaze, facial expressions), adapting to different interactions.

ADAPTIVE PATH INTEGRAL IMPORTANCE SAMPLING

Hans-Christian Ruiz, Radboud University Nijmegen

The path integral control theory is a class of control problems that have as formal solution a Feynman-Kac path integral and can be estimated using Monte-Carlo sampling. This can be viewed as an inference computation which is optimal whenever we have the optimal control solution. This equivalence is the basis of an adaptive importance sampling procedure used to recursively compute feedback controllers and, at the same time, improve the importance sampler corresponding to the inference computation. In this poster, a specific example of path integral importance sampling is shown in the context of the estimation of the posterior distribution in continuous time state-space models

ROBUST EEG BASED BCIS FOR THE DETECTION OF GAIT INTENTION

Andreea Sburlea, BitBrain Technologies, Zaragoza

Brain-computer interface (BCI) as a rehabilitation tool has been used to restore functions in patients with motor impairments by actively involving the central nervous system and triggering prosthetic devices according to the detected pre-movement state. This work addresses two issues in EEG-based BCI research for the detection of gait intention. First, most BCI studies in lower limbs rehabilitation are carried out with healthy subjects, even though insights gained from healthy populations may not generalize to patients in need of a BCI. Second, a BCI is usually calibrated at the beginning of each session due to the variability of EEG signals between subjects and recording sessions. Since (re)calibration is an inconvenient and tiring process, usability of BCIs could be improved by reducing or even removing (re)calibration time. We present a continuous EEG detector of self-initiated walking intention based on temporal and spectral features. We show the applicability of this detector in healthy and chronic stroke subjects for session-to-session transfer without recalibration and with short recalibration periods. The results show decay in performance of less than 4% for session-to-session transfer without recalibration, in healthy subjects relative to the cross-validated performance within a session. However, in stroke patients using a 10 minutes recalibration lead to comparable results to the ones obtained in healthy subjects.

LEARNING UNIVERSAL COMPUTATIONS WITH SPIKES

Dominik Thalmeier, Radboud University Nijmegen

The understanding of neural network dynamics on the mesoscopic level of hundreds and thousands of neurons and their ability to learn highly complicated computations is a fundamental open challenge in neuroscience. For biological systems, such an understanding will allow to connect the microscopic level of single neurons and the macroscopic level of cognition and behaviour. In artificial computing, it will allow to propose new, possibly more efficient computing schemes. Randomly connected mesoscopic networks can be a suitable substrate for computations, as they can reflect the input in a complicated, nonlinear way and thereby maintain fading memory of past inputs as well as of transformations and combinations of them. This includes the results of computations. Simple readout neurons may then learn to extract the desired result, the computations are executed in real time, i.e. without the need to wait for convergence to an attractor. Networks with higher computational power need to learn their recurrent connections or require an output feedback. In particular, this increases their

memory to arbitrary length and enables them to generate patterns of activity in self-sustained manner. However, network modelling approaches achieving universal (i.e. general purpose) computational capabilities so far, assumed networks of continuous rate units, they did not take into account the characteristics that neurons in biological neural networks communicate via spikes. Indeed, the dynamics of spiking neural networks are discontinuous, usually highly chaotic, variable, and noisy. This hinders computations following the described principle in particular in presence of plastic recurrent connections and feedback, and has questioned it as model for computations in biological neural systems. We derive for the first time a class of recurrent spiking neural networks that are suited for universal computations (continuous signal coding spiking neural networks, CSNs). They consist of standard, established neuron models, take into account synaptic or dendritic nonlinearities and are required to respect some structural constraints regarding the connectivity of the network. We endow them with learning rules for either the output or the recurrent connection weights and find that the so-derived plastic continuous signal coding spiking neural networks (PCSNs) are able to learn equally complicated, memory dependent computations as non-spiking continuous rate networks of similar size. We demonstrate the capabilities of our PCSNs by applying them to challenging learning problems which are of importance in biological contexts. In particular, we show for the first time how spiking neural networks can learn the self-sustained generation of complicated dynamical patterns, and how they can build world models, which allow to compute optimal actions to appropriately influence an environment.

FIRST STEPS IN ENCODING THE LINK BETWEEN SENSORY NEURAL FIRING AND BEHAVIOUR IN DROSOPHILA LARVAE

Nicole Voges, CRG - Systems Biology, Barcelona

Drosophila larvae orient in odour gradients through a sequence of stereotypical movements, i.e., runs, stops, head casts, and turns. During chemotaxis, the perceived odour is translated into neuronal firing which finally determines behaviour. By means of computational modelling, we investigate the relationship between sensory firing and movement switches. Combining an agent based model (Davies, Webb & Louis, PLOS Comput Biol, under revision), a set of differential equations describing the activity of olfactory sensory neurons, and a generalized linear model (Schulze et al. 2015, eLife 4:e06694), we compare our simulations to experimental data. Search trajectories were generated using genetically modified larvae that smell upon light stimulation (optogenetics) in a closed loop tracking system (Gomez et al. 2011). We here focus on the increased probability of terminating runs in response to negative gradients in neuronal firing. A critical question is if the transfer functions obtained from single isolated input curves yield realistic behavioural trajectories when simulating real world conditions.

NETWORK DYNAMICS OF THE HUMAN BRAIN CONNECTOME WITH BRAINX3

Xerxes D. Arsiwalla, Universitat Pompeu Fabra, Barcelona

BrainX3 is a large-scale simulation of human brain activity with real-time interaction, rendered in 3D in a virtual reality environment, which combines computational power with human intuition for the exploration and analysis of complex dynamical networks. We ground this simulation on structural connectivity obtained from diffusion spectrum imaging data and model it on neuronal population dynamics. Users can interact with BrainX3 in real-time by perturbing brain regions with transient stimulations to observe reverberating network activity, simulate lesion dynamics or implement network analysis functions from a library of graph theoretic measures. BrainX3 can thus be used as a novel immersive platform for exploration and analysis of dynamical activity patterns in brain networks, both at rest or in a task-related state, for discovery of signalling pathways associated to brain function and/or dysfunction and as a tool for virtual neurosurgery. Our results demonstrate these functionalities and shed insight on the dynamics of the resting-state attractor. Specifically, we found that a noisy network seems to favour a low firing attractor state. We also found that the dynamics of a noisy network is less resilient to lesions. Our simulations on MS perturbations show that even though TMS inhibits most of the network, it also sparsely excites a few regions. This is presumably due to anti-correlations in the dynamics and suggests that even a lesioned network can show sparsely distributed increased activity compared to healthy resting-state, over specific brain areas.

Work supported by the CEEDS project (258749 FP7-ICT-2009-5).

PHASE-COHERENCE TRANSITIONS AND COMMUNICATION IN THE GAMMA RANGE BETWEEN DELAY-COUPLED NEURONAL POPULATIONS

Alessandro Barardi, UPC, UPF, Barcelona

Synchronization of collective neuronal oscillations has been suggested to mediate communication between brain areas, with the global oscillations acting as 'information carriers' on which signals encoding specific stimuli or brain states are superimposed. This synchrony of neuronal activity can take place within a cortical patch or between different cortical regions. While short-range interactions between neurons involve just a few milliseconds, communication through long-range projections between different regions could take up to tens of milliseconds. How these transmission delays affect communication between neuronal populations is not well known. To address this question, we have used a biophysically realistic computational model of two synaptically coupled neuronal populations working in a collective gamma regime. Firstly we have examined how different synaptic delays give rise to in-phase/anti-phase transitions at particular frequencies in the gamma range and how this behaviour is related to the phase coherence between the two populations at different frequencies. Secondly we have quantified the information exchanged between the two networks based on Shannon Information theory. The results confirm that zero-lag synchronization maximizes information transmission, although out-of-phase synchronization allows for efficient communication provided the coupling delay, the phaselag between the two populations and the frequency of the oscillations are properly matched.

A BIOPHYSICAL NEURAL NETWORK MODEL FOR VISUAL WORKING MEMORY THAT ACCOUNTS FOR MEMORY BINDING ERRORS

Joao Barbosa, Intitut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona

Binding errors, also called swap errors, occur in working memory tasks when the participant fails to report the feature of a previously presented target but the response is accurate relative to a nontarget stimulus. These errors reflect the failure of the system to maintain bundled through memory the conjunction of features that define one object. The brain mechanisms that maintain integrated several features of an item in one single memory remain unknown. Conjunctive selectivity, where single units are selective to combination of stimuli, has been suggested as a possible solution. Here, we explore the hypothesis that synchrony of different neural assemblies coding each for a single feature of an item plays the main role. Because under this hypothesis there is no hardwired selectivity for each group of features, it allows conjunctive representations to emerge ex novo. To test the synchrony hypothesis, we built a biophysical neural network model for the storage of multiple items defined by one colour and one location in working memory. The model is composed of two one dimensional networks for working memory (ring models), one representing colours and the other one locations of equal eccentricity. These two networks are then connected via weak corticocortical excitation. With this model we are able to maintain persistent activity through recurrent synaptic interactions in memory bumps that encode colours and locations in each respective network. Fast recurrent excitation within each network induced gamma oscillations during bump activity through the interplay of fast excitation and slower feedback inhibition. We found that when multiple bumps were maintained within one ring model, the corresponding bump attractors oscillated out of phase with each other. Binding between colour and location was effectively accomplished through the synchronization of gamma oscillations between pairs of bumps across the two networks as a result of weak corticocortical excitation. As a result, different memorized items were held at different phases of a low frequency oscillation. In some simulations swap errors arose: 'colour bumps' abruptly changed their phase relationship with 'location bumps'. This led to a wrong association between colour and location that may underlie memory binding errors reported in working memory tasks.

SPATIO-TEMPORAL LINEAR RESPONSE OF SPIKING NEURAL NETWORK MODELS

Rodrigo Alejandro Cofre Torres, UNIGE

We study the impact of a weak amplitude time-dependent external stimulus, on the collective spatio-temporal spike train statistics produced by a stochastic conductance based integrate-and-fire (CIF) neural network model. On phenomenological grounds, this input-output mapping is often represented with models such as the linear-nonlinear (LN) Poisson or the so called generalized linear model. Although this approach produces interesting results in terms of prediction, the complete mechanistic description of how the structure of synaptic connectivity and the dynamical properties of the neuronal population influence the spiking response to a stimulus is missing. On theoretical grounds, this problem can be studied using spiking neural network models. Previous works have addressed this problem characterizing the change in firing rates and pairwise correlations in terms of network architecture and dynamics, using linear response techniques. Here, we propose an alternative formulation based on time dependent Gibbs distributions and linear response theory. Our approach allows to handle spatio-temporal correlations induced by the stimulus. We obtain a formal closed formula, written in terms of correlation functions of the spontaneous dynamics, which can be numerically approximated for the CIF. Especially, we obtained an explicit dependence in the network parameters (synaptic weights). Our main result is an extension of the Fluctuation-Dissipation theorem, which consider the non-stationary dynamics and infinite memory of the system. This work opens up new possibilities to explore and quantify the impact of network connectivity on any spatio-temporal pattern of spiking correlations in the presence of time dependent stimulus, which can be particularly relevant in the study of population

receptive fields.

TRAVELLING WAVE AND BUMP DYNAMICS IN A SPIKING NEURONAL NETWORK

Joshua Davis, University of Nottingham

As a result of modern imaging technologies, waves and bumps of neuronal activity have been experimentally verified at a variety of spatial scales in the cortex. Spatially localised bumps of activity are known to be involved in mechanisms of orientation tuning in the visual cortex, the rat head direction system, and working memory. In the turtle visual cortex, the presentation of stimuli has been shown to evoke propagating waves of activity. Also, numerous mental processes including sleep and binocular rivalry are characterised through waves, as well as neurological disorders such as epilepsy and migraines. In this poster we study existence and stability of coarse bumps and travelling waves in a bi-stable spiking neuronal network originally proposed by Laing and Chow. The network consists of a set of N leaky Integrate-and-Fire neurons with a non-local lateral inhibition connectivity function,

$$\frac{dv_i(t)}{dt} = v_i(t) + I + \sum_{j,m} W_{ij} \alpha(t - t_j^m) - \sum_{j,m} \delta(t - t_j^m) \quad i = 1, 2, \dots, N$$

Simulations of a discrete spiking network of integrate-and-fire network are shown to exhibit a rich variety of bump and wave states. In particular we find a family of coherent pulsating wave states composed of multiple synchronously firing neurons spread across the spatial domain. A continuum assumption is then taken to construct analytical solutions of such waves solely in terms the mean wave speed and firing times. The stability of the multiple spike waves is analysed by perturbing around firing times and an eigenvalue problem is solved and tested in the discrete regime. Numerical continuation is used to gain insight into the bifurcation structure of such waves investigated in terms of the parameters governing synaptic efficacy and connectivity. It is shown that multiple spike waves destabilise via a sequence of Hopf bifurcations. In addition, composite wave solutions are also found that match up in simulation to multiple spike pulses that have combined and coalesced.

SUPERBURSTS AND COMPLEX ACTIVITY PATTERNS IN MATHEMATICAL MODELS OF CULTURED NEURAL NETWORKS

Pavel Esir, N. I. Lobachevsky State University of Nizhny Novgorod

Bursting is a common activity pattern observed in neural networks under various experimental conditions. Its typical properties and mechanisms have been studied in numerous in vitro experiments on neural cultures and in mathematical modelling. Besides simple population bursts, neural cultures exhibit a variety of much more complex activity patterns called superbursts. Some of them are considered as an in vitro model of seizure-like activity. Existing mathematical models can not explain dynamical mechanisms and reproduce experimentally observed repertoire of superbursts. Here we propose a spiking neural network model and a rate-based model to explain complex activity patterns generated by neuronal cultures. The rate-based model is used to perform phase plane and bifurcation analysis to investigate network dynamics, describe possible dynamical modes and assess their parameter ranges. The spiking network model, capable to generate signalling patterns observed experimentally under normal and pathological conditions, can serve as an in silico 'mirror' platform for developing experimental protocols for novel class of substrate-integrated probes combining multichannel electrophysiological recordings and stimulation with microfluidic technology. Using these models we investigate interplays between biophysical processes with different time scales (e.g. NMDA currents, short-term synaptic plasticity, slow spike-frequency adaptation, bicarbonate-dependent depolarizing potentials) and their contribution to formation of complex activity patterns.

NETWORK SYNAPTIC PLASTICITY IN DISSOCIATED NEURONAL CULTURE WITH DIRECTED CONNECTIVITY

Arseniy Gladkov, N. I. Lobachevsky State University of Nizhny Novgorod

Dissociated neuronal cultures are widely used model for long term investigations of network plasticity, learning and memory. The plasticity research in the cultures appeared to be difficult due to a random morphological structure in the network. Recently developed microfluidic methods allowed to guide neurite outgrowth. We used microfluidic polydimethylsiloxane (PDMS) chips containing an array of microchannels between two separate chambers with neuronal cells. Specific shape of the microchannels defined axon outgrowth and a direction of the synaptic connection architecture. Electrical activity registration and stimulation were performed with microelectrode arrays (MEA). There were 3 electrode groups: located in two different sub-networks and under microfluidic channels with axons. Stimulation of the different electrode groups was used to induce network plasticity. This approach with a combination of the microfluidic and microelectrode methods allowed to investigate the network connection plasticity with STDP protocols on a long time scale.

SYNAPTIC MECHANISM OF REVERBERATION ACTIVITIES OF A SYNCHRONIZED BURSTING EVENT IN NEURONAL CULTURES

Yu-Ting Huang, Institute of Physics, Academia Sinica, Taipei

Synchronized bursting (SB) is a general spontaneous activity of neuronal cultures. Although their origin is still unclear, it is believed to be the result of the self-organized dynamics of a random network. We investigate properties of the SB in a growing neuronal network by high-resolution multi electrode arrays, which contain 64x64 electrodes, and find that there are fine structures as reverberation activities within the SB. SBs and its reverberations start from one of preferred points rather than completely random generation and propagate to entire network. These trajectories can be divided into several groups in term of propagate direction and the trajectories of each group show high degree of similarity. These reverberation patterns change with network maturation and the pattern can be modified by chemical treatments. These reverberations are enhanced by addition of bicuculline, which is GABAA receptor blocker, or decreasing the concentration of magnesium; these reverberations can be suppressed with the addition of glutamate. It suggests that these reverberations can be considered as a function of the network connectivity. A model base on short-term synaptic plasticity (STSP) can account for most of properties of these reverberations.

STIMULUS INDUCED RESONANCE IN A NEURAL MASS MODEL DRIVEN WITH A TEMPORALLY CORRELATED NOISE

Maciej Jedynak, UPF/UPC, Barcelona

Power spectra of experimental recordings such as EEG and LFP exhibit a broadband nature characterized by a stable $1/f^{\beta}$ background with embedded peaks. These peaks are associated with specific brain states and stimuli, and depending on conditions appear at different frequencies. Interactions between brain rhythms from different frequency bands are assumed to play an important role in brain functioning. Here we study theoretically a particular cross-frequency interaction that has been observed experimentally. That experiment examined the effect of slow rocking on sleep in human subjects, and showed that slow oscillatory stimulus related to rocking enhanced power in EEG measurements in low (0.6 - 4 Hz) and alpha frequency bands, thus revealing a cross-frequency transfer of power. We studied this effect by means of a neural mass de-

scription based on a model developed by Jansen and Rit. This model typically yields a power spectrum with a narrow peak that corresponds to its intrinsic frequency. In our case, however, a realistic $1/f^\beta$ spectrum with an embedded alpha peak is observed. This results from a combination of two factors. The first factor is a coexistence (or proximity) of different dynamical regimes near the working point of the model. The second factor is the presence of temporally correlated noise acting upon the model, which enforces flips between different dynamical regimes. Here, we examine systematically the effect of this stochastic driving on the single compartment and on collective effects occurring in the network of interconnected compartments. We show that the correlation time of the noise is one of the crucial factors that modulate the preference of dynamical regimes for a single compartment, and thus determine the model's activity. Furthermore, we show that this dependence has a non-trivial, non-monotonous characteristics. We find that experimental results obtained in the absence of a stimulus are best reproduced when the model operates close to a bifurcation. In the presence of the stimulus, computational results recapitulate the experimental observations when the alpha resonance is not fully developed. The emergence of resonance depends on the driving signal amplitude, properties of the noise, and it relies on collective synchronization, which in turn depends on the coupling between the network elements. The model allows us to make predictions for driving with frequencies greater than the one used in the experiment. Our results indicate that the cross-frequency transfer observed experimentally may occur only for slow driving: for faster input the alpha peak does not increase and might even be suppressed. In summary, our results show that a $1/f^\beta$ realistic power spectrum with an embedded alpha peak can be obtained realistic power spectrum with an embedded alpha peak can be obtained from a neural mass model driven by a temporally correlated noise. The model's dynamics depend in a non-monotonous way on the correlation time of the noise. Slow oscillatory driving of this model operating close to a bifurcation facilitates development of a resonance in the alpha band, giving rise to a cross-frequency power transfer, which reproduces experimental observations.

SYNCHRONIZED POPULATION ACTIVITY IN A SPIKING NEURAL NETWORK MODEL OF THE MIDBRAIN SUPERIOR COLLICULUS

Bahadir Kasap, Radboud University Nijmegen

Saccades are rapid and ballistic gaze shifts between points of interest in the visual field that are crucial for gathering sharp visual information. Single-unit electrophysiological recordings elucidate the neural coding of the gaze-orienting behaviour. The midbrain superior colliculus (SC) is the last common terminal in the saccadic neural pathway where a saccade command signal is identified. The saccade-related SC activity exhibit highly systematic properties SC activity exhibit highly systematic properties during saccades: (i) each motor map neuron elicits a fixed number of spikes for its optimal saccade; (ii) a neuron's spike counts vectors vary systematically with the saccade vector into its movement field; (iii) all recruited neurons have similarly-shaped (scaled) bursts during a saccade; (iv) peak firing rate, burst duration, and burst-profile skewness of the central neuron in a population vary systematically across the motor map. The temporal profiles of single SC neurons support the dynamic linear ensemble-coding model to decode the resulting saccade. According to this scheme, each SC neuron contributes to a planned saccade vector with a site-specific fixed mini-vector per its spike. The direction of mini-vectors are characterized by the spatial positions of the neurons, and the spike-timings of the recruited population produces the temporal evolution of the movement. Thus, the pathway downstream to SC decodes the dynamic SC output by linear vector summation to generate a saccade. However, it is still elusive how the observed SC population activity arise and how the SC motor map is formed. Here, we present a simple spiking neural network model, which accounts for the SC motor map functionality (as summarized in (i)-(iv)). Simulations with distinct SC neurons and lateral intra-SC interactions can describe the observed bursting profiles.

EEG-BASED DECODING OF ATTENTIONAL STATES DURING MOVEMENT

Filip Melinščak, BitBrain Technologies, Zaragoza

Importance of attention has been demonstrated in a variety of motor activities such as motor learning, execution, and adaptation. Attention has also been shown to affect the plasticity of the motor cortex, making it an important factor in physical rehabilitation, for example, after stroke. However, rehabilitation often includes repetitive exercises which can lead to inattentiveness, or mind wandering. Rehabilitation interventions could be improved if the attentional state of the patient could be monitored, but this presents a challenge due to the covert nature of kinaesthetic attention. In this study we propose an EEG-based brain-computer interface (BCI) to monitor the attentional state during a continuous motor task. The designed BCI was validated in an experimental protocol which emulated rehabilitation of lower limbs. During the experiment participants reported their attentional state, either as attending to the movement or mind wandering. EEG analysis has shown a decrease of power in the theta, alpha, and beta bands during attentive periods, relative to periods of mind wandering. Using these spectral features, the designed BCI achieved asynchronous classification accuracy from 60.8% to 68.4%, depending on the allowed classification delay.

MACROSCOPIC DESCRIPTION FOR NETWORKS OF SPIKING NEURONS

Ernest Montbrio, Universitat Pompeu Fabra, Barcelona

A major challenge of neuroscience, statistical physics and nonlinear dynamics over the last half century has been to understand the self-organizing principles governing the dynamics of large networks of spiking neurons. To this aim, researchers have proposed macroscopic descriptions of neural networks in terms of a relevant observable: the firing rate. Firing rate descriptions are broadly used in theoretical neuroscience, and have been proven to be extremely useful in understanding general computational principles underlying functions such as memory, or visual processing. However, to date, all of these theoretical approaches have been either heuristic or approximate. Moreover, firing rate descriptions have a key limitation since they cannot describe neuronal states where large fractions of neurons fire in concert, i.e. synchronous states. Here, for the first time, we formulate an exact firing rate description for a network of spiking neurons. Our results show that the firing rate alone is not sufficient to describe the network dynamics. Rather, we find that the single-cell spike generation mechanism dynamically couples the firing rate to another macroscopic variable: the mean membrane potential. The resulting firing rate equations fully describe the collective states of the network, including synchronization. Finally we show that the firing rate description is related, via a conformal map, with a low-dimensional description in terms of the Kuramoto order parameter, called Ott-Antonsen theory. We anticipate our results will be an important tool in investigating how large networks of spiking neurons self-organize in time to process and encode information in the brain.

THE EFFECTS OF HYPERPOLARIZATION-RESET ON ENTORHINAL GRID CELLS SCALE AND INTRINSIC FREQUENCIES ALONG THE DORSAL-VENTRAL AXIS

Diogo Santos Pata, SPECS, UPF, Barcelona

Grid-cells found in layer II of the medial entorhinal cortex (MEC) present a distinctive firing pattern that progressively increases in scale along the dorsal-ventral axis. This scale-up property has been modelled either through variations in net-

work connectivity strength (attractor models), or through injection of different frequencies (interference models). However, knockout of HCN genetic family encoding for hyperpolarization-activated cation currents (I_h) has been shown to disrupt both scale and frequency organization along the dorsal-ventral axis. To test the hypothesis that the observed scale gradient and that the different oscillatory frequencies observed along the dorsal-ventral axis are the result of cellular I_h properties, we have modelled and analysed data from a simulated grid-cell population of spiking Izhikevich neurons through low-dimensional attractor mechanism. We show that although theta oscillations do affect individual cell behaviour, cell after spike properties are sufficient to explain both the changes in grid scale and oscillatory frequency observed along the dorsal-ventral axis. Conclusions We tested the hypothesis of whether I_h current properties of stellate neurons could affect both scale and oscillatory frequency of grid-cells. Our results show that increasing after-spike reset-values (d) of simulated grid cells leads to the decrease of spatial scale and increase of the dominant frequency, which reflects the properties observed along the dorsal-ventral axis. Therefore, we propose a novel type of computational model for grid cell formation in which the intrinsic cellular features in combination with attractor network dynamics would define the spatial and oscillatory properties of this type of neurons.

CONTROL OF PATHOLOGICAL BEHAVIOURS USING FEEDBACK INTRACEREBRAL STIMULATION: USING THE BRAIN'S OWN DYNAMICS TO CONTROL ITS ACTIVITY

Jose Luis Perez Velazquez, University of Toronto

Diverse coordinated patterns of brain activity are associated with behavioural dispositions. The possibility of changing those collective activity patterns in order to alter behaviour is a current field of great interest in neuroscience, particularly to stop pathological manifestations of the brain activity in incidences like epileptic seizures or Parkinsonian tremor. However, most of the perturbations of brain dynamics done presently use a sort of brute-force approach, as the current deep brain stimulation (DBS) techniques are mostly blind to the intrinsic brain dynamics that are trying to control or perturb. In previous studies, we scrutinised the dynamics of the nervous system in epileptiform activity in vitro and in vivo, that revealed certain dynamical features which were then used in order to arrest seizure generation. Building on those results and on some theoretical considerations, we have developed a closed-loop stimulation device that detects a seizure precursor and then implements a short (5 seconds) intracerebral stimulation that arrests seizure generation in rats. The algorithm for the detection of paroxysms relies on the monitoring of fluctuations in the phase synchrony between brain signals, and detects/anticipates electrographic seizures as early as a few seconds to a few minutes before the behavioural and electrographic seizure onset, with a very low false positive rate of detection. Upon detection of the precursor, a short pulse (5 seconds at 5 Hz) is sent to the intracerebral electrodes that results in the suppression of the paroxysm onset. Based on the great efficacy of the method in the rodent seizure models we used, we are presently embarking on a proof-of-principle study in epileptic patients. We propose that the notion of detecting abnormal patterns of brain cellular collective activity, such as synchrony, and implementing feedback (on-demand, or closed-loop) stimuli to alter/perturb them, can be extended to other neuropsychiatric disorders, as some of these syndromes are known to be associated with specific synchrony patterns. The perturbation of the abnormal brain activity patterns using 'minimal' stimulation based on the intrinsic brain dynamics may result in the normalization of behaviours with almost no harmful side-effects, and hence represents an alternative to pharmacological treatments.

GPU ACCELERATED EVALUATION OF DELAYS NEURAL FIELDS

Sid Visser, Centre for Biomedical Modelling and Analysis, University of Exeter

Neural field equations allow one to study the spatio-temporal properties of the brain's electrical activity at a coarser level

than detailed neural network. Traditionally, these models are primarily studied mathematically in idealized settings that may not reflect the underlying physiology or anatomy at all. Whilst numerical studies are capable of handling features such as heterogeneity and morphology, these simulations can be very demanding from a numerical point of view. Particularly neural fields that include time delays have been ignored in the past for their numerical complexity; one needs to keep track and interpolate the systems history at every time step. Although several solutions or approximations exist, these all demand assumptions regarding homogeneity with respect to both connectivity and time delays. Here, I present novel computational scheme for the numerical evaluation of delayed neural fields with arbitrary connectivity and delays. The scheme exploits the computational power and hardware accelerated qualities of graphics cards to obtain an unprecedented computational speed for these models. The final scheme enables simulations of delayed neural fields on the neocortical surface at a spatial resolution comparable to MRI (± 2 mm).

CEREBELLAR CALIBRATION OF TOPOGRAPHIC MAPS IN THE SUPERIOR COLLICULUS USING THE ADAPTIVE FILTER MODEL

Emma Wilson, University of Sheffield

The intermediate and deep layers of the superior colliculus receive a massive cerebellar input which can directly influence collicular output cells. There has been little speculation about the function of this projection. Here we suggest that these cerebellar inputs play a role in calibrating the accuracy of collicular topographic maps. We investigate whether the adaptive-filter model of the cerebellar microcircuit, which has been applied successfully to a wide range of sensorimotor skills, can also be applied without change to the very different computational problem of calibrating a topographic map driving an orienting response. We propose a model in which the topographic map constitutes a probabilistic representation of target position obtained from sensory inputs, and the position of peak activity in the topographic map drives the orienting response. The input to the relevant cerebellar microzone is assumed to be a coarse coded representation of the topographic map, while the microzone output shifts the position of peak map activity over a local area of the map (by a process such as attentional gain modulation). Climbing fibre inputs to the microzone carry information about orienting errors, which serves as a teaching signal for cerebellar learning. We show in simulation that the proposed mechanism can successfully recalibrate topographic maps containing multiple targets which are subject to curvilinear miscalibrations. The case of a moving target in which sensory information is delayed relative to target acquisition (as in prey pursuit) is also investigated. Here the model learns to place targets at their predicted rather than actual positions, producing an accurate and properly timed orienting response.

LEARNING JOINT REPRESENTATIONS FOR ORDER AND TIMING OF PERCEPTUAL-MOTOR SEQUENCES: A ROBOTICS IMPLEMENTATION OF A DYNAMIC NEURAL FIELD MODEL

Weronika Wojtak, University of Minho

Fluent execution of many of our everyday tasks requires the control of the serial order and the timing of component actions. Using the dynamic neural field (DNF) framework, we address the learning of representations that support the performance of precisely timed action sequences. In continuation of previous modelling work and robotics implementations, we ask specifically the question how feedback about executed actions might be used by the learning system to fine tune a joint memory representation of the ordinal and the temporal structure which has been initially acquired by observation. We propose and test in robotics experiments a simple learning rule that detects a mismatch between the expected and realized timing of events and adapts the activation strengths in order to compensate for the movement time needed to achieve the

desired effect. The experimental results show that the effector-specific memory representation can be robustly recalled.

FLUCTUATIONS OF POPULATION ACTIVITY MODULATE NEURONAL TUNING AND IMPACT ENCODED INFORMATION

Iñigo R. Arandia, Foundation Sant Joan de Deu, Barcelona

Many studies have shown that stimuli modulate neuronal responses, but responses are also affected by the state of the local network. Attention or arousal changes are able to modify the tuning of sensory neurons, and fluctuations of the ongoing population activity have been shown to play many roles. However, little is known about how intrinsic fluctuations of stimulus evoked population activity modulate the sensory tuning of cells and whether they affect their encoded information. We found that fluctuations of population activity in monkey V1 modulate the tuning of individual neurons in a multiplicative and additive manner, with minor effects on the broadening or displacement of the tuning curves. Neurons with strong multiplicative effects tended to have little additive modulation, and the reversed was observed for neurons with strong additive effects. We also found that the fluctuations of ongoing activity before stimulus onset are able to modulate the tuning of individual neurons both multiplicatively and additively, but with a weaker effect on the tuning curves than the stimulus evoked activity. Then, we studied whether these fluctuations of the state of the network had any relationship to the amount of encoded information using state-of-art decoding techniques from simultaneously recorded neuronal populations. As predicted by a model based on a multi-gain model of population activity we found that the information encoded by multiplicatively-modulated neurons increased with greater population activity, while that of additively-modulated neurons decreased. These effects cancel each other in such a way that fluctuations of population activity had little effect on total information. Therefore, our results suggest that the global state of the network acts as a 'traffic light' that controls which subset of neurons are most informative without affecting total information.

IMPLEMENTATION OF SPARSE CODING FOR PITCH ESTIMATION

Oded Barzely, Tel Aviv University

Our acoustical environment is abound with sounds that repeat to some extent over time, a repetition that is related to the perception of pitch. It is still unknown how the auditory system relates a physical stimulus and its percept. In mammals, all auditory stimuli are conveyed into the nervous system through the auditory nerve fibers (ANFs), and a model should explain the perception of pitch as a function of this particular input. Pitch perception is invariant to certain features of the physical stimulus. For example, a missing fundamental stimulus with resolved or unresolved partials, or a low and high level amplitude stimulus with the same spectral content – these all give rise to the same percept of pitch. In contrast, the ANFs' representations for these different stimuli are not invariant to these effects. In fact, due to saturation and non-linearity of both cochlear and inner hair cells responses, these effects are enhanced by the ANFs. Thus there is a difficulty to explain how the pitch percept arises from the activity of the ANF. We introduce a novel approach to extract pitch cues out of the ANFs' activities for a given arbitrary stimulus. The method is based on a technique known as sparse coding (SC). It is the representation of pitch cues by a few atoms (templates) out of a large set of possible ones (a dictionary). The amount of activity of each atom is represented by an active coefficient, analogous to an active neuron. Such a technique was successfully applied to other modalities, especially vision. The model is composed of a cochlear model, an SC processing unit, and a simple implementation of a harmonic sieve. We show that the model can cope with different pitch phenomena. In particular, it enables the extraction of resolved and non-resolved harmonics, missing fundamental pitches, pitch of iterative ripple noise, and stimuli with both high and low amplitudes.

SPIKE-SYNCHRONIZATION: A PARAMETER-FREE AND TIME-RESOLVED COINCIDENCE DETECTOR WITH AN INTUITIVE MULTIVARIATE EXTENSION

Nebojša Božanić, ISC, CNR, Sesto Fiorentino

Techniques for recording large-scale neuronal spiking activity are developing very fast. This leads to an increasing demand for algorithms capable of analysing large amounts of experimental spike train data. One of the most crucial and demanding tasks is the identification of similarity patterns with high temporal resolution and across different spatial scales. To address this task, in recent years three time-resolved measures of spike train synchrony have been proposed, event synchronization, the ISI-distance, and the SPIKE-distance. Here we present SPIKE-synchronization, an improved and simplified extension of event synchronization with a more intuitive interpretation which holds for both the bivariate and the multivariate case. SPIKE-synchronization quantifies the degree of synchrony from the relative number of quasi-simultaneous appearances of spikes. Since it builds on the same bivariate and adaptive coincidence detection that was used for event synchronization, SPIKE-synchronization is parameter- and scale-free as well. This makes it easy to handle and allows for an objective estimation of neuronal synchronization. In contrast to the ISI- and the SPIKE-distance, SPIKE-synchronization is a measure of similarity. It is zero if and only if the spike trains do not contain any coincidences, and reaches one if and only if each spike in every spike train has one matching spike in all the other spike trains. We investigate the properties of SPIKE-synchronization and compare it against other time-resolved measures such as the Peri-Stimulus Time Histogram (PSTH) and the ISI- and the SPIKE-distance. We use simulated data to verify its usefulness and explore its performance on real data. Together with the ISI-distance and the SPIKE-distance, SPIKE-Synchronization is implemented in both the Matlab-based graphical user interface SPIKY and the Python library PySpike. Both packages provide ample documentation as well as platforms for user feedback. SPIKY even comes with an interactive Facebook-page and a Youtube-channel which includes movies demonstrating both the measures and the GUI.

ENVELOP CODING IN THE COCHLEAR NUCLEUS: A DATA MINING APPROACH

Alban Levy, University of Nottingham

Machine Learning and Data Mining are must-have skills in an era of big and complex data. In this work, we present the numerical comparison of many classification algorithms applied on spike train data. In a supervised learning framework, we compare their ability to discriminate the envelop of amplitude-modulated tones from single neuron responses, on different neuron types from the Cochlear Nucleus, the first stage of auditory processing after transduction in the cochlea. Whilst the results are useful for engineers by comparing algorithms (classifiers), preprocessing (feature vector on Interspike Intervals, time-binning, power spectrum or using a spike metric) and parameters (time-scales, features), it follows a long lineage of auditory research about the functional role of CN units and the neural code they use.

BENCHMARKING SPIKE-BASED VISUAL RECOGNITION

Qian Liu, University of Manchester

To gain a better understanding of the brain and build biologically-inspired computers, increasing attention is being paid to research into spike-based neural computation. Within the field, the visual pathway and its hierarchical organisation have been extensively studied within the primate brain. Spiking Neural Networks (SNNs) inspired by our understanding of observed biological structure and functions have been successfully applied to visual recognition/classification tasks. A new series of vision benchmarks for spike-based neural processing are now needed to quantitatively measure progress within this rapidly advancing field. We propose that a large dataset of spike-based visual stimuli is needed to provide a baseline for

comparisons. Furthermore a complementary evaluation methodology is also crucial to assess the accuracy and efficiency of an algorithm. First of all, an initial dataset of input stimuli based on standard computer vision benchmarks consisting of digits (MNIST database) is presented according to the current research on spike-based image recognition. Within this dataset, all images are centre aligned and with similar scale. We describe how we intend to expand this dataset to fulfil the needs of upcoming research problems. For instance, the data should provide cases to measure position-, scale-, and viewing-angle invariance. The data will be in Address-Event Representation (AER) format which is well-applied in neuromorphic engineering field unlike conventional images. These spike trains are produced by various techniques: rate-based Poisson spike generation, rank order encoding and recorded output from a silicon retina with both flashing and oscillating input stimuli. An evaluation methodology is also presented which describes how to consistently assess the accuracy, speed, efficiency and cost of an algorithm working with the dataset. Finally, we provide a baseline for comparison based on a proposed SNN's performance on the dataset. The network is trained on-line using the Spike Timing Dependent Plasticity (STDP learning rule on a massive-parallel neuromorphic simulator, e.g. SpiNNaker. With this benchmark we hope to (1) promote meaningful comparison among algorithms in the field of neural computation, (2) allow comparison with conventional image recognition methods, (3) provide an assessment of the state of the art in spike-based visual recognition, and (4) help researchers identify future directions and advance the field.

OSCILLATORY DYNAMICS OF FIELD POTENTIALS IN THE FRONTAL CORTEX DURING DECISION MAKING

Gorana Mijatović, Faculty of Technical Sciences, Novi Sad

Introduction: Most of our decisions are taken without a full knowledge of the constantly changing environment. Reducing uncertainty by deciding to seek or check for additional information is therefore often necessary to adapt and optimize behaviour. However, the underlying neurobiological processes and neural dynamics necessary to produce such decisions are yet poorly understood. We recorded intracortical activity (spikes and LFP) from two frontal regions (dorsal anterior cingulate cortex, dACC, and lateral prefrontal cortex, LPFC) in monkeys performing a dual-task in which they could decide to work on a categorization task (CT) or check whether a bonus reward was available (VT). We tested whether beta oscillations and spike-LFP relationships reflected particular dynamics in the two frontal areas specifically during decisions to check. Experiment: To induce checking behaviour 2 monkeys were trained in dual task protocol in which monkeys are free to select either: categorization task (CT) - a simple visual categorization based on the orientation of a stimulus- or a verification task (VT), i.e. to check the size of visual gauge indicating the proximity of a large bonus, and possibly get the bonus if the gauge is full. The bonus reward is offered only if the monkey perform the randomly selected number of correct CT trials. Methods: LFP recordings were analysed in the task selection period 2.5s before lever touch (CT and VT segments) and between stimulus presentation and choice selection (SS) during CT. Time-frequency analysis of LFP in β band was done using wavelet transformation (WT). Power spectral density (PSD) in β band over short stationary segments and dynamic changes in power over time $P(t)$ were estimated based on WT. We analysed changes in power-time profiles related to proximity of decision, preferred β frequencies, power amplitude modulation and eventual frequency shifts in different segments. Sample entropy was used to assess the changes in LFP regularity. Single unit analysis was complemented with distribution and magnitude of preferred beta phases. Results: Single-unit (spike) analyses revealed a functional dissociation depending on the kind of decision, in particular with specific MCC activity when monkeys decide to check and stronger contribution of LPFC for decisions in categorization trials. The time-frequency analysis of LFP's from MCC and LPFC during a decision making task, point to specific activation patterns of oscillations in β band, with preferred frequency subbands and amplitude modulation of β power. The PSD characteristics were task-dependent suggesting relationships between particular LFP oscillations and the functions engaged at specific time in the task. Sample entropy analysis revealed the increased LFP regularity in trial selection segments (VT, CT) as compared to SS segments.

This research was supported by bilateral cooperation grant 'Decoding hidden causes of decisions from brain signals,' Serbia-France and by the grant TR32040, Ministry of Science, Serbia.

TIME-RESOLVED AND PARAMETER-FREE MEASURES OF SPIKE TRAIN SYNCHRONY: PROPERTIES AND APPLICATIONS

Mario Mulansky, ISC, CNR, Sesto Fiorentino

The relevance of exact spike timings in neural coding was presumed since a long time and has now been experimentally established. A popular approach to the analysis of spike timings is to measure the synchrony of spike trains. With the recent advancements of the experimental techniques, it is now possible to simultaneously record the activity of hundreds of neurons. The analysis of such collective responses requires new mathematical tools that are able to detect synchrony in groups of spike trains. Here, we present three methods to quantify spike train synchrony that are applicable in such multivariate situations. All of these methods are parameter-free and time-resolved which makes them easy to handle and able to detect temporal changes of synchrony. Specifically, we discuss the ISI-distance, the SPIKE-distance and the very recently proposed SPIKE-Synchronization. The ISI-distance is based on the relative differences of interspike intervals, while the SPIKE-distance uses exact spike timings. SPIKE-Synchronization can be understood as a time-resolved, spike-wise coincidence detector. We analyse the mathematical properties of all three measures and discuss their advantages and disadvantages. Specific focus lies on the statistical relevance of the obtained values compared to random spike trains. By calculating the expectation values for Poisson spike trains we are able to provide an important point of reference for interpreting numerical and experimental results. Finally, we show exemplary applications of the methods to spike trains obtained from numerical simulations as well as experimental recordings. The methods are implemented in both the Matlab-based graphical user interface SPIKY and the Python library PySpike.

NEURONAL ACTIVITY IN OFC IS PREDICTIVE FOR RATS' UPCOMING CHOICE

Ramon Nogueira, Fundacio Sant Joan de Deu, Barcelona

Prefrontal Cortex (PFC) in mammals is well-known for playing a key role in executive function. Orbitofrontal Cortex (OFC), as a part of the PFC, is thought to be mainly involved in reward processing, a fundamental function in goal-directed behaviour. In particular it has been proposed that OFC is encoding the expected value of an outcome. Previous studies in rats have shown that neurons in OFC have information about expected reward or punishment, and guide the relationship between stimulus and reward in a reversal associative learning task. It has also been proposed to be involved in spatial representation as well as a proxy for confidence in perceptual decision making tasks. In our experiment three rats performed an auditory categorization task while populations of neurons were recorded in OFC. The task was designed such that rats could use both sensory information and task history information in order to maximize reward income. We found that neurons in rats' OFC conveyed a wide variety of task related variables each one with a different time dynamics. Surprisingly, before stimulus onset neuronal activity was predictive of rats' upcoming choice, a neuronal evidence of task-history related behaviour. Also before stimulus onset OFC neurons showed significant encoding of previous choice, previous reward and previous stimulus. After stimulus presentation neuronal activity correlated with stimulus difficulty, a proxy for the trial's expected value, as well as with stimulus and reaction time, the latter a well known proxy for metacognitive processes as confidence. Our results point in the direction that OFC in rats might not only be involved in reward processing but it also conveys a wide variety of task relevant variables. Our hypothesis is that OFC acts as a hub for decision-making, where information is processed and conveyed to other brain regions.

REINFORCING INPUTS OF SINGLE NEURON IN A SIMPLE MODEL OF SPIKING NEURAL NETWORK

Alexander Simonov, N.I.Lobachevsky State University of Nizhny Novgorod

Principles of reinforcement learning represent a remarkable example of self-organizing remodelling of network structure aimed to solve specifically addressed problems or improve existing algorithms for information processing. Inspired from computational principles of brain systems this concept has been successfully adopted for building mathematical theory and computer science approaches based on experimental findings in the cutting-edge neuroscience of recent decades. Nowadays new data uncovering neural correlates of reward-based learning and developing new functions are continuing to appear. Novel protocols to study learning in vitro cultured networks (Pimashkin, Gladkov, Mukhina, & Kazantsev, 2013; Shahaf & Marom, 2001) and especially recent in vivo results on operant conditioning of activity patterns (Ishikawa, Matsumoto, Sakaguchi, Matsuki, & Ikegaya, 2014) sparked new interest in computational neuroscience field. Here we propose a simple model of spiking neural network capable to reinforce a single synapse and inputs of a single neuron when their activity patterns meet pre-defined criteria. The network model is based on modified dopamine-based spike-timing dependent plasticity model (Izhikevich, 2007). Using computer simulations and analytical studies we show how activity of single neurons and synapses can be modified in an unsupervised manner under the impact of a non-specific reward signal introduced in response to generation of certain activity pattern. Stability, dynamical properties and interference of the newly learned activity patterns are investigated. Possible implications of our findings for developing close-loop experimental paradigm are also considered.

This study was supported by the Russian Ministry of Education, the Federal Program (unique identification number - RFME-FI58114X0011).

