**Workshop:**

**Multi-Scale Brain Function India-Italy Network of Excellence (MSBFIINE)**

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# Book of abstracts


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Multi-Scale Brain Function India-Italy Network of Excellence (MSBFIINE)

**Computational Reconstruction of BOLD Responses in the Cerebellar Granular Layer**

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Abstract

Building computational models with the goal of replicating and explaining observed or measured data to gain a better understanding of brain function dynamics is an important goal in the field of computational neuroscience. In the central nervous system, the cerebellum is a motor substructure known for regulations of sensory attainment, controlling timing, and the prediction of sensory consequences of action. Sensorimotor signals from the cerebral cortex influence the cerebellum's pattern-generating metaheuristic capabilities. In this talk, the functional integration of multisensory information by single granule neuron (Grc) from crus I, crus II and paraflocculus regions of cerebellum and corresponding hemodynamic changes will be showcased. The reconstructed firing behaviour showed a lower ISI during visual stimuli when compared with auditory stimuli, while the firing rate for auditory stimuli was higher than for visual stimuli. The spatiotemporal reconstructions of single granule neurons were also analysed during multimodal inputs. The model was used to explore the implications of induced spike-time dependent plasticity conditions. Our modelling indicated that the BOLD (blood oxygen level dependent) and CBV (cerebral blood volume) changes varied with respect to the frequency and change in inter spike interval of Grc responses during multimodal inputs. Mean BOLD and CBV amplitude changes during visual stimuli was more compared to the auditory stimuli, since the firing activity of Grc. The modelling could imply that the cerebellar cortex responds more strongly to visual stimulation than auditory stimulation.

**Computing with Rhythms: The search for Deep Oscillatory Neural Networks**

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Abstract

Oscillatory phenomena are ubiquitous in the brain. Although there are oscillator-based models of brain dynamics, they do not seem to enjoy the universal computational properties of rate-coded and spiking neuron network models. Use of oscillator-based models is often limited to special phenomena like locomotor rhythms and oscillatory attractor-based memories. If neuronal ensembles are taken to be the basic functional units of brain dynamics, it is desirable to develop oscillator-based models that can explain a wide variety of neural phenomena. To this end, we aim to develop a general theory of oscillatory neural networks. Specifically we propose a novel neural network architecture consisting of Hopf oscillators described in the complex domain. The oscillators can adapt their intrinsic frequencies by tracking the frequency components of the input signals. The oscillators are also laterally connected with each other through a special form of coupling we labeled as “power coupling”. Power coupling allows two oscillators with arbitrarily different intrinsic frequencies to interact at a constant normalized phase difference. The network can be operated in two phases. In the *encoding* phase the oscillators comprising the network perform a

Fourier-like decomposition of the input signal(s). In the *reconstruction* phase, outputs the trained oscillators are combined to reconstruct the training signals. We show that the network can be trained to reconstruct high-dimensional Electroencephalogram (EEG) signals, and fMRI signals paving the way to an exciting class of large-scale brain models of brain dynamics.

**Emergent movement from multiscale spino-musculoskeletal simulation and applications**

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Abstract

A variety of experimental results and models are available in the area of spinal cord and its

interaction with the musculoskeletal system. These include motor neuron and interneuron models, characterization of their ion channel physiologies, distributions of motor neurons and interneurons along the spinal cord or within the Rexed laminae, descending stimulation patterns from the motor cortex, effect of neuromodulation, patterns of afferent and efferent connections to muscles, proprioceptive feedback, spinal reflex circuitries, muscle fibre models, myotomes and musculoskeletal models. While we understand the workings of each these elements, how they come together to produce movement is unclear. Understanding the emergence of movement from the interaction of these diverse components at multiple scales is not trivial. We hope to understand the same by recreating known experimental results in a multiscale spino-musculoskeletal model. Building spino-musculoskeletal models require coupled simulation of neural and musculoskeletal system. Thus we started by building a platform called NEUROiD that performs a neuro-musculoskeletal cosimulation using NEURON and OpenSim simulators for the neuro and musculoskeletal simulations respectively. We next use the NEUROiD platform to build a spino-musculoskeletal model of upper and lower limbs. We also demonstrate that simulated micro-stimulation of the spinal cord at various spinal levels elicits a variety of movement types as expected from experimental results. We further demonstrate Reinforcement Learning(RL) based methods for design of descending cortical drives that result in a target upper limb posture. We finally propose methods for using these models to create a digital spino-musculoskeletal twin and its potential usages in clinical scenarios.

**A data-driven connection strategy for modelling large-scale point-neuron microcircuits**

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Abstract

The modeling of extended microcircuits is becoming an effective tool to simulate the neurophysiological correlates of brain activity and to investigate brain dysfunctions. The increasing availability of quantitative data on the human brain is opening new avenues to study neural function and dysfunction, thus bringing us closer and closer to the implementation of digital twin applications for personalized medicine. However, one of the main problems in the generation of realistic networks lies in the strategy adopted to build network connectivity. We have developed a method to implement neuronal networks at single cell resolution by using the geometrical probability density function associated with pre- and postsynaptic neurites. The probability density functions are inspired in their geometrical characteristics by the volumes approximately occupied by neuronal axons and dendrites. Neurons are then connected by intersecting probability density functions through an intersection algorithm allowing to calculate the connections pairs. This approach allows to build networks with plausible connectivity properties without the explicit use of computationally intensive algorithms that require 3D neuron reconstructions. The method has been benchmarked for the mouse and human hippocampus CA1 regions allowing to explore the computational efficiency of method at different spatial scales.

**Advanced modeling of cardiac myocytes**

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Abstract

Sudden cardiac death (SCD) remains a leading cause of death globally and regionally. At least, 250.000 SCD and, more broadly, 350.00 out-of-hospital cardiac arrest (OHCA) cases are expected each year in the European Union. In the United States, 370,494 SCDs were reported in 2019 yielding an estimated incidence of EMS-assessed cardiac arrests of 111 per 100.000. Despite more than seven decades of progress developing increasingly complex models of cardiac conduction efforts to translate this knowledge into broadly effective anti-arrhythmic therapy has been disappointing. To pave the way toward new therapies, building upon our studies of a novel family of remarkably potent modulators of cardiac conduction and rhythmicity known as fibroblast growth factor homologous factors (FHFs), we developed a combination of novel “FHF-aware” computational models of single-cell cardiac myocytes and gap junction-coupled strands of myocytes. We present here the latest development of our models, a two dimensional sheet of myocytes mimicking the spreading of cardiac action potentials along a small portion of the ventricular tissue. Finally, we show how lesions of specific shape lead to reentry of cardiac action potentials and arrhythmia in our simulations.

**Experimental investigation of microcircuit properties: the example of cerebellar network activity**

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Abstract

The study of neuronal microcircuits is one of the aspects that is growing in interest in current neuroscience research. Ensembles of interconnected neurons, each with its own electrophysiological characteristics, interact dynamically with each other by means of chemical or electrical synapses, determining the functioning of the microcircuit. Short- or long-term changes can modulate this activity, the investigation of which is an intermediate scale of study between single-cell experiments and large scale connectomic investigations. Experimental recordings of intact microcircuits are challenging. Techniques are needed to acquire data from several individual neurons, which must be uniquely identified and whose activity must be monitored over time. The cerebellar cortex microcircuit, with its highly ordered neuronal architecture and relatively simple and stereotyped connectivity pattern, is well suited for microcircuits studies. We investigated its functioning by performing two-photon calcium imaging experiments in acute cerebellar slices with a scanless spatial-light modulator two-photon microscope that allows to monitor the activity of hundreds of neurons simultaneously over time, while maintaining single-cell resolution. We acquired stimulus-induced calcium signals from neurons located in different areas of the circuit (granular layer, Purkinje cells layer and molecular interneurons layer), before and after the induction of long-term synaptic plasticity at the mossy fibers-granule cells synapses. The expression of long-term plasticity at the input stage of the circuit reverberated throughout the entire network, resulting in the expression of both short-term and long-term plasticity in Purkinje cells and molecular layer interneurons. These experiments provide insight into the role of different neuronal types in shaping the cerebellar cortex activity and how the latter is modulated by different forms of plasticity, deepening the knowledge of the dynamics of this microcircuit.

**Investigating brain reactivity with a perturb-and-measure approach**

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Abstract

Excitability and effective connectivity are key parameters of cortical circuits' functioning. Moreover, alterations of these parameters have been suggested to underlie neurologic and psychiatric conditions. Navigated Transcranial Magnetic Stimulation (TMS) combined with electroencephalography (EEG) allows non-invasively measuring brain responses to direct cortical stimulation, while bypassing sensory-motor pathways. The simultaneous application of TMS and EEG has several technical challenges, which can be solved by employing dedicated hardware solutions and by applying specific data analysis procedures. Artifact-free TMS-evoked potentials represent the genuine neuronal responses recorded over the whole brain to the stimulation of a specific cortical site, which can be selected almost arbitrarily using the navigation system: therefore, they can be used to estimate i) cortical excitability, as the amplitude of the early components elicited nearby the TMS target, ii) effective connectivity, as the spread of a focal

stimulation across distant cortical areas; iii) complexity, as the spatiotemporal distribution of the deterministic cortical activations following TMS pulses. Measuring these parameters may help identifying specific pathological alterations (e.g. cognitive impairment, psychiatric conditions,…) and can be reliably performed over time to quantitatively monitor the effects of treatment and spontaneous recovery. Finally, TMS/EEG provides, at the same time, a direct stimulation of virtually any cortical area and a quantitative neurophysiological output, regardless of any sensory or motor impairment: therefore, this tool is particularly useful for studying brain-injured patients, in whom the integrity of sensory-motor pathways might prevent the recording of standard event-related potentials.

**Information optimized multilayer network representation of high density electroencephalogram recordings**

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Abstract

High-density electroencephalography (hd-EEG) provides an accessible indirect method to record spatio-temporal brain activity with potential for disease diagnosis and monitoring. Due to their highly multidimensional nature, extracting useful information from hd-EEG recordings is a complex task. Network representations have been shown to provide an intuitive picture of the spatial connectivity underlying an electroencephalogram recording, although some information is lost in the projection. Here, we propose a method to construct multilayer network representations of hd-EEG recordings that maximize their information content and test it on sleep data recorded in individuals with mental health issues. We perform a series of statistical measurements on the multilayer networks obtained from patients and control subjects and detect significant differences between the groups in clustering coefficient, betwenness centrality, average shortest path length and parieto occipital edge presence. In particular, patients with a mood disorder display a increased edge presence in the parieto-occipital region with respect to healthy control subjects, indicating a highly correlated electrical activity in that region of the brain. We also show that multilayer networks at constant edge density perform better, since most network properties are correlated with the edge density itself which can act as a confounding factor. Our results show that it is possible to stratify patients through statistical measurements on a multilayer network representation of hd-EEG recordings. The analysis reveals that individuals with mental health issues display strongly correlated signals in the parieto-occipital region. Our methodology could be useful as a visualization and analysis tool for hd-EEG recordings in a variety of pathological conditions.

**Recalling what was there: looking at an absent offer location modulates neural responses in OFC**

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Abstract

When making choices among multiple options, we allocate our fixations to each contemplated option, and tend to look longer at more valued ones. The purpose of fixation during choice deliberation remains unknown. Here we examined behavioral and neural activity of rhesus macaques monkeys performing a two-options risky choice task in which offers occurred in sequence, each followed by a long (600 ms) blank screen delay period. As expected, we found that subjects allocated their gaze towards offer presentation locations and spent more time looking at most valuable offers. After factoring out the impact of offer value, we found that more looking time was devoted to the chosen offer since first offer onset and during the whole task execution. Surprisingly, we found this pattern since before choice execution and even when the screen was blank: subjects spent more time fixating the locations where valuable offers had occurred. Moreover, we found that neural encoding of the offers' expected values in orbitofrontal cortex (OFC) is modulated by eye position even when the screen is blank. Specifically, when gaze is directed to the location when a given offer was formerly presented, its encoding is more sustained in OFC, while the encoding of the alternative offer value is suppressed. The same modulatory effects by gaze on value encoding are observed later in the trial when monkeys were supposed to report their choice while both offers were presented simultaneously. Our results provide evidence that eye position reflect and internal deliberation process that modulates the encoding of imagined content, providing a new window to study the hidden dynamics of decision making.

**A novel multi-class logistic regression algorithm to reliably infer network connectivity from cell membrane potentials.**

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Abstract

In neuroscience, the structural connectivity matrix of synaptic weights between neurons is one of the critical factors determining the overall function of a network of neurons. The mechanisms of signal transduction have been intensively studied at different time and spatial scales and at both the cellular and molecular level. While a better understanding and knowledge of some basic processes of information handling by neurons has been achieved, little is known about the organization and function of complex neuronal networks. Experimental methods are now available to simultaneously monitor neural activities from a large number of sites in real time. Here, we present a methodology to infer the connectivity of a population of neurons from their voltage traces. At first, spikes and putative synaptic events are detected. Then, a multi-class logistic regression is used to fit the putative events to spiking activities. The fit is further constrained, by including a penalization term that regulates the sparseness of the inferred network. The proposed weighted Multi-Class Logistic

Regression with L1 penalization (MCLRL) was benchmarked against data obtained from in silico network simulations. MCLRL properly inferred the connectivity of all tested networks (up to 500 neurons), as indicated by the Matthew correlation coefficient (MCC), already with small samples of network activity (5 to 10 seconds). Then, we tested MCLRL against different conditions, that are of interest in concrete applications. First, MCLRL accomplished to reconstruct the connectivity among subgroups of neurons randomly sampled from the network. Second, the robustness of MCLRL to noise was assessed and the performances remained high (MCC>0.95) even in extremely high noise conditions (>95% noisy synaptic events). Third, we devised a data driven procedure to gather a proxy of the optimal penalization term, thus envisioning the application of MCLRL to experimental data. The proposed approach is ideally suited for populations recordings, where spikes and post-synaptic recordings can simultaneously be recorded (e.g. genetic encoded voltage indicators). Yet, the main message here is that a small fraction (<5%) of genuine synaptic events is sufficient to properly infer the underlying connectivity of a network.