Special Session 77: Theoretical, Technical, and Experimental Challenges in Closed-Loop Approaches in Biology

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Characterization and control of nonlinear and non-stationary processes is an active topic in the general field of the applied theory of dynamical systems, and in the specific scope of complex biological systems. In this context classical control techniques cannot be applied straight away, and thus observation and actuation should be properly incorporated into a real-time feedback (or closed-loop) methodology. This being the case, modern activity-dependent stimulation protocols should be used to reveal dynamics (otherwise hidden under traditional stimulation techniques), achieve control of natural and pathological states, induce learning, bridge between disparate levels of analysis and for a further automation of experiments. Furthermore, closed-loop interaction calls for novel real time analysis, prediction and control tools and a new perspective for designing stimulus-response experiments, which can have a large impact in biological research. In this special session the closed-loop methodology is discussed through recent contributions in both the theoretical and experimental study of biological systems.

Automatic event detection and characterization in the context of real-time control of complex time-varying dynamical systems

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The general framework of control theory is very dependent on the outcomes of previous and/or simultaneous system identification. Given a set of standard inputs, we can proceed by deriving a describing function for the input-output functional correlation. However, in an experimental setup this need is very difficult to be satisfied. First, from a general point of view we do not have total access to the inner state of the system to be controlled. Certainly, our data is mainly constructed by partial observations of the underlying system dynamics. Second, partial observations should be modeled in a fast and accurate way to achieve controlability and observability. In fact, if the considered systems are nonlinear and time-varying then the describing function must be adapted as the system evolves. Furthermore, the input-output relationship could be history dependent, which results in an adequate system identification in case we apply classical identification techniques. As a possible alternative we can construct data-driven control procedures guided by efficient and precise tools for detecting and characterizing events automatically. In this communication we discuss this possibility by means of our recent results on the application of symbolic dynamics and time-frequency signal processing to such a goal.

A biophysical observation model for neural field effects

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Neural field effects, such as ephaptic interactions, can be described by a closed-loop between neural activity and the surrounding electromagnetic field: active neurons generate their characteristic electric dipole fields which superimpose to the local field potential (LFP) of a coherent neural population. This endogenous electric activity could feed back on the activation threshold of the individual neurons. Sofar, this mechanism has been described by phenomenological mean field models, disregarding the biophysical details of electric dipole field generation. We suggest to close this gap by a spatially extended model of a simple leaky integrate-and-fire (LIF) neuron. Introducing three compartments for the apical dendritic tree, for the perisomatic dendritic tree and for the axon hillock, we derive the standard LIF evolution equation augmented by an observation model of the dendritic field potential that allows estimation of the LFP of a neural population. We present simulation results of the forward model and indicate possible ways for the closed-loop approach toward ephaptic field effects.

References
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The role of sensorimotor feedback in cognition

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Recently there has been a significant movement in the cognitive sciences that emphasises the centrality of sensorimotor feedback for accounts of cognition. Despite this success the migration of this focus to mainstream systems neuroscience has been slow. Recent experimental innovations mean that this state of affairs is beginning to radically change. Closed-loop experimental paradigms that utilise virtual reality in mice and fish and well circumscribed sensory-motor systems are becoming more widespread. Consequently, in vivo electrophysiology and optogenetics of behaving animals is quickly becoming an achievable gold standard. This work places the sensorimotor loop at the heart of neural processing and promises to give sensorimotor accounts renewed relevance for mainstream neuroscience. Here we utilise these technologies to examine the role of sensorimotor feedback for accounts of neural dynamics and brain function.

Ready to close the loop: modulation of cortical oscillations through DC electric fields

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Brain stimulation techniques such as tDCS or TMS play a growing role in the treatment of neurological disorders. However the thorough understanding of the cellular and network mechanisms recruited by these strategies is missing. We use the slow oscillatory activity from the cortical network (Steriade et al (1993) J Neurosci 13, 3252 and Sanchez-Vives, M. V. & McCormick, D. A. (2000) Nat Neurosci 3, 1027) as a model of a relatively regular activity amenable to be modulated by electric fields (Frohlich, F. & McCormick, D. A. (2010) Neuron 67, 129). To investigate the underlying mechanisms that lead to changes in network activity we applied DC electric fields in vitro to active brain slices. We find that the DC fields effects are limited to specific aspects that characterize slow oscillations and they are highly dependent on the initial activity. Considering the high complexity and non-linear dynamics of the involved networks, the linearity of the changes that we observe in some specific parameters provide an operational window that could lead to an online control through a closed-loop system, a solution with wide clinical implications. Supported by Ministerio de Economia y Competitividad (BFU2011-27094) EU PF7 FET CORTICONIC contract 600806.

Experience-guided combination of principal and independent component analyses to rescue pathway-specific electrical fields in the brain

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The unpredictable discontinuous activation of electrical sources in the brain plus their mixing in the volume constitute major handicaps for analysis based on averaging or frequency-decomposition. Indeed, none captures the natural temporal dynamics of current sources contained in local field potentials (LFPs). Since sources are static, they are amenable to disentanglement through blind-source separation techniques. We earlier combined spatial independent component analysis (sICA) and hierarchical clustering to segregate intracerebral sources into spatially coherent groups that represent pathway-specific activations of target populations. The spatial and temporal mixings influence the efficiency of the separation, which can be strongly optimized by a priori knowledge of the sources features. Thus, we used known mixtures of sources from real experiments to reproduce spatiotemporal fluctuations of LFPs in silico through a realistic multineuronal multicompartmental model. Virtual LFPs were essayed to check the advantages of using PCA prior to ICA. The flexibility of this approach allows the repeated modification of the initial conditions for data choice and pretreatment in an experience-guided cyclic process. We also present hints to increase the relative variance of weak sources and to reduce cross-contamination.

Weakly electric fish information processing analyzed through close-loop code-driven stimulation

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Activity-dependent stimulation techniques in Neuroscience have been implemented through the concept of dynamic clamp in electro-physiological experiments. The same generic principles underlying the dynamic-clamp technique can be used to develop novel protocols to study information processing in the context of electrocommunication of weakly electric fish. Specifically, here we address the use of these protocols in the elephant fish, Gnathonemus petersii, an animal that uses a weak electric field to locate obstacles or food while navigating, as well as for electro-communication with other fishes. To investigate the electrical coding in this fish, we use an adaptive electrical stimulation as a function of the animal's electrical activity. To map this electrical activity to a time series of events, we represent the recorded electrical signal as a binary string. Then we take data words of predetermined length to define information events by considering the correlation between consecutive pulses. From the information analysis, we chose a representative word to trigger the stimulation delivered in the close-loop. We compare the electrical activity generated by Gnathonemus petersii during the closed-loop stimulation protocol versus a random stimulation. Finally, we discuss how this comparison can serve to understand the underlying information processing.

Close-loop stimulation in real-time functional magnetic resonance imaging

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Real time analysis of Functional Magnetic Resonance Imaging allows quality control and analysis of the data while the subject is in the scanner. In experimental settings, very fast processing times have been achieved, and recent studies have shown that RT fMRI feedback is feasible (Weiskopf et al. 2012). RT fMRI, in comparison to all other human brain mapping techniques, represents the only non-invasive method allowing feedback regulation of deep subcortical brain regions. In current fMRI experiments, activity is regulated by the user as a result of the feedback. Closing the loop in real-time fMRI setups will allow the implementation of online activity-dependent stimulation protocols. The close-loop will take a major role in the control of brain activity, facilitating and improving subject self-regulation. The combination of different sources of stimuli (olfactory, visual and auditory) with a certain temporal structure will expose brain pathways and connectivity. By controlling all these stimuli, and modulating them online as a function of activation, we will unveil sequential activations associated to the encoding of sensorial input including cognitive responses.

Weiskopf et al. Real-time fMRI and its application to neurofeedback. Neuroimage 62(2): 682-92, 2012.

Long range dependence and the dynamics of exploited fish populations

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Long range dependence or long memory is an important notion in many processes in the natural world. Sometimes considered a nuisance in the study of these processes, the existence of long memory is in fact a bonus, in the sense that it provides a window on the underlying mechanisms that generate the observed data. Long range dependence may only be found in the higher order characteristics of the process. A process that looks short range when looked at through second-order properties, may in fact have an underlying long range dependence of higher order properties. This mechanism is illustrated by analyzing some data related to the abundance of exploited fish populations in the North Atlantic.

Inhibitory synapses control anticipation in neuronal circuits

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When the connectivity between two brain regions is such that one them (the sender) strongly influences the other (the receiver), a positive phase lag is often expected. The assumption is that the time difference implicit in the relative phase reflects the transmission time of neuronal activity. However, experiments performed in monkeys engaged in processing a cognitive task, a dominant directional influence from one area of sensorimotor cortex to another may be accompanied by either a negative or a positive time delay. Here we present a model of two brain regions, coupled with a well-defined directional influence, that displays similar features to those observed in the experimental data. By reproducing experimental delay times and coherence spectra, our results provide a theoretical basis for the underlying mechanisms of the observed dynamics, and suggest that inhibitory neurons might play a crucial role in the response time of neuronal populations.

Neuro-DYVERSE: building hybrid systems neuroscience

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Tools from control engineering, formal methods of computer science and network science hold the promise of transforming the course of computational neuroscience. In this talk, we will explore how these tools can be combined in a framework called Neuro-DYVERSE. Neuro-DYVERSE is a work in progress and aims towards a further understanding of the adaptive dynamical processes involved in the formation and consolidation of memory in the human brain. In neuroscience, this is known as neuroplasticity: the brainś ability to change due to experience or damage. The dynamical behaviour of networks of billions of neurons is still poorly understood, as is its relationship to the emergence of learning and memory. Pre-existing models are still fairly limited. The multi-scale complexity of the problem requires the combination of paradigms from different fields, mainly: hybrid systems, control engineering, automated verification, dynamical systems and network science. Neuro-DYVERSE is built upon the computational-mathematical framework DYVERSE. DYVERSE stands for the DYnamically-driven VERification of Systems with Energy considerations, and focuses on hybrid systems models and tools capturing the mixture of continuous dynamics with discontinuities - that is, abrupt changes or transitions. This work leads towards a new branch of computational neuroscience: hybrid systems neuroscience, to coin a term.

Dynamic Observer: Can we use closed loop observation to characterize individual neurons?

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The standard method for characterising ion channels in neurons is voltage clamp in patch clamp recordings [1]. However, in the classical procedure measurements are performed with constant voltage steps and chemical channel blockers are used to isolate individual ion channel types. Because chemical blockers can be irreversible, different ion channels of the same neuron type have to be measured in different individual cells, potentially even in separate preparations from different individual animals. This can be highly problematic and it has been observed that so combining measurements from many different cells does not allow to build accurate whole cell models [2]. Here we introduce a proposal to go beyond the classical constant steps and try to design optimised stimulation patterns to isolate the effect of different ion channels without blockers. Furthermore, we propose to use closed-loop online parameter estimation methods with simulated “dynamic clamp” coupling to then build a model of all ionic currents in an individual neuron simultaneously. If successful this new closed-loop experimentation technology could have deep impacts on our understanding of how individual neurons vary in their ion channel content.

References

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Towards Model-Based Closed-Loop Control of Neuronal Networks

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Since the 1950s, there have been a steadily maturing theory for model-based control of systems, as well as a steadily improving computational neuroscience demonstrating models with increasing fidelity to the biophysics and dynamics of neuronal systems. We have recently demonstrated that there is an emergent unification between seizures and spreading depression (the physiology of migraine auras), derived by improving the biophysical modeling and introducing conservation principles into an extension of the Hodgkin-Huxley equations. Such models represent nodes within neuronal graph directed networks. The topology of how such nodes are connected determines the structural observability and controllability of neuronal systems, which is highly dependent upon the presence of symmetries in such connectivity. We discuss the implications of nodal dynamics and topology on strategies for closed-loop control of neuronal systems.

Closed-loop aproaches to characterize transient neural dynamics

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During the last 30 years there has been a large development in experimental and theoretical approaches in neuroscience research. However, the assessment of neural dynamics, both in experimental and in modeling efforts, continues to be based to a large extent on a classical, but at the same time very limited, stimulus-response paradigm. In this paradigm a stimulus is deliver to a neural system, and the characteristics of the response are then studied offline in relationship to the given stimulus. In addition, the study of information processing in the nervous system is also often based on the assumption that neural mechanisms are well approximated by steady-state measurements of neural activity. However, transient states may, in many cases, better describe neural network activity. In this talk we will emphasize the need of closed-loop approaches to deal with transient neural dynamics. Our goal is to link new theoretical descriptions of transient neural dynamics with experiments that implement goal-driven closed-loop activity-dependent stimulation. Real-time stimulation feedback enables a wide range of innovative studies to characterize information processing with transient dynamics in neural networks, and to exploit the robustness, flexibility and capacity of this type of dynamics.