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&

10TH NEUROBIOLOGY CONFERENCES LADISLAV TAUC

GIF-SUR-YVETTE, FEBRUARY 15-16, 2010

MULTISCALE ANALYSIS OF NEURAL SYSTEMS: TAKING THE CHALLENGE SERIOUSLY

L'ANALYSE MULTIECHELLES DES SYSTEMES NEURAUX: MOYENS, ENJEUX, PROSPECTIVE

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Joint meeting

ITMO Neurosciences, Cognitives Sciences, Neurology, Psychiatry
&
10th NEUROBIOLOGY CONFERENCES LADISLAV TAUC

Multiscale Analysis of Neural Systems:
Taking the challenge seriously

L'analyse Multiéchelles des Systèmes Neuraux :
moyens, enjeux, prospective

Gif-sur-Yvette, February 15-16, 2010

The conference will address the questions arising from multiscale analysis in Neurosciences. From cell to behaviour, the nervous system can be described as networks of components interacting at different temporal and spatial scales, exchanging flux of information. Emergent and immergent properties of neural systems affect the robustness of functions, their plasticity, adaptability and evolvability. Very large sets of phenomenological data can now be obtained from multiple scales of investigations by increasingly sophisticated techniques of imaging and quantitative recordings of all kinds. They need to be brought together and analysed by methods borrowed from various mathematical approaches and statistical physics. It remains that many problems come up from data gathering, data handling and storage and from the theoretical treatment and modelling of the studied objects. Multiscale analysis of complex systems can be applied to many different fields of neurosciences, including cellular neurosciences, development and evolution of the nervous system and cognitive sciences. Both plenary lectures and workshops have been selected and designed for this purpose. New research directions, necessary structures and instruments, sources of funding, education, will be discussed. The format of this meeting aims to attract all neuroscientists or biologist interested in these challenging but very promising approaches.

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Scientific program

Lundi 15 février 2010
Monday 15th February

9:00 Welcome and Registration

10h Introductory remarks - *Remarques introductives*.
Bernard BIOULAC and Alexis BRICE

Session 1 : Systèmes neuraux: réseaux – *Neural systems: networks* .

10h10 Blue Brain Project – Simulation-based Research and Multiscale.
Felix SCHÜRMANN (Brain Mind Institute, Ecole Polytechnique, Lausanne, Suisse)

10h50 Multiscale analysis and stochastic processes in neurons.
Alain DESTEXHE (CNRS UNIC, Gif-sur-Yvette, France)

11h30 Break - *Pause* : Posters

Session 2: Neural systems : coding

11H50 Frontiers in neuromorphic computing: the hardware viewpoint.
Karlheinz MEIER (Kirchhoff-Institut für Physik, Heidelberg University, Germany)

12H30 From individual neurons to models of cortical areas: mean-field, neural masses and neural fields.
Olivier FAUGERAS (INRIA, Sophia-Antipolis, France)

13h10 Lunch - *Déjeuner*

14H30 **Panel Discussion 1: Complex systems and multiscale analysis: Phenomenological reconstruction – *Systèmes complexes et analyse multiéchelle: Reconstruction phénoménologique.***

Chairman: Nadine Peyriéras (ISC – CNRS NeD, Gif-sur-Yvette)

Discussants: Emmanuel Beaurepaire (Polytechnique), Pascal Calvat (IN2P3), Laurent Groc (CNRS - Univ Bordeaux II), Stavros Katsanevas (IN2P3), Jean Livet (INSERM), Christoph von der Malsburg (FIAS), Karlheinz Meier (Heidelberg), Francois Molino (IGF), Antoine Triller(ENS).

16H00 Break - *Pause* : Posters

16H30 **Panel Discussion 2: Complex systems and multiscale analysis: Theorical reconstruction and modelling – *Systèmes complexes et analyse multiéchelle: Reconstruction théorique et modélisation.***

Chairman: Franck Varenne (Université de Rouen – GEMAS, Paris)

Discussants: Paul Bourgine (Polytechnique), Yves Burnod (INSERM), Peter Dayan (Gatsby), Ralph Dum (CE), Yves Frégnac (CNRS), Annick Lesne (IHES), Michel Morvan (Dir. Scientifique VEOLIA).

Mardi 16 février 2010
Tuesday 16th February

Session 3 :

9h40 Time-resolved large-scale brain activity.
Virginie van Wassenhove (CEA, Saclay, France)

10h30 Multiscale imaging and morphogenetic modelling.
Jacques DEMONGEOT (TIMC – IMAG, Grenoble, France)

11h10 Break - *Pause* : Posters

Session 4 : .

11h40 Pattern-based decoding from fine-grained fMRI signals.
John-Dylan HAYNES (Bernstein Center for Computational Neuroscience, Germany)

12H20 Reconstructing multiscale dynamics in early embryogenesis.
Nadine PEYRIÉRAS (ISC – CNRS NeD, Gif-sur-Yvette, France)

13H10 Lunch - *Déjeuner*

14H30 **Panel Discussion 3: Complex systems and multiscale analysis: Training, Education – *Systèmes complexes et analyse multiéchelle: Formation, Enseignement*,**

Chairman: René Doursat (ISC – CREA, Paris)

Discussants: Simone Cardoso de Oliveira (Freiburg, BCOS), Peter Dayan (Gatsby), Elisabeth Giacobino (CNRS, Univ. Paris 11), Pierre Kornprobst (INRIA,Sophia-Antipolis), Jean-Louis Martin (Polytechnique), Manuel de Tunon de Lara (Président Université Bordeaux 2).

16H00 Break - *Pause* : Posters

16H30 **Panel Discussion 4: Complex systems and multiscale analysis: Structures, Support – *Systèmes complexes et analyse multiéchelle: Structures, Moyens*.**

Chairman: Paul Bourgine (CREA – RNSC, Paris)

Discussants: Bernard Bioulac (CNRS/ITMO Neuro), Alexis Brice (INSERM/ITMO Neuro), Frédéric Dardel (INSB, CNRS), Peter Dayan (Gatsby), Ralph Dum (CE), Raymond Fournier (ANR), Pierre Legrain (CEA), Karlheinz Meier (Heidelberg), Antoine Triller (ENS).

18H00 End - Fin

Poster abstracts

Control of persistent spiking activity by background correlations.

M. Dipoppa, B. S. Gutkin

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A telltale feature of working memory (WM) is the sustained neural activity associated with holding necessary information on-line (e.g., Romo et al. 1999 Nature: 399, 470-473). A key unresolved question is how the cortical machinery manipulates this sustained activity in order to perform WM tasks. Here we show that it is possible to control multiple aspects of the persistent activity at once via variable correlations in the background noise.

As a model of sustained activity we consider a network of QIF neurons coupled with all-to-all recurrent synaptic excitation and background noise in which we can modify the correlations among neurons. Synaptic strength and time-scale are tuned such that the network exhibits bistable behavior with sustained activity state and quiescence. We find that in the absence of noise, the sustained activity state shows a specific spike-time structure referred to as "splay-state". This spike-time structure is characterized by maximum anti-synchrony among the active neurons (the spikes of N-1 neurons constituent in a network sized N are equally splayed out within an interspike interval of the Nth neuron). We show this splay-state spike arrangement to be robust to variations in PSP shape.

Furthermore the network responses and the robustness of the sustained splay-state are examined under noisy conditions. For a given noise strength, we find that noise correlations robustly promote transitions from the splay-state to the quiescent state while suppressing spurious reactivation of the sustained activity. We find that these transitions are due to noise induced increases in spike-time coherence among the active neurons. This effect becomes dominant as the network size grows. We thus find a stochastic analogue of synchrony-induced turn-off of sustained activity as proposed by Gutkin et al., (2001 J Comp Neurosci: 11, 121-134). We further find that for strongly correlated noise no splay-state activation is possible.

Hence by tuning correlations in the background activity we can control 1. the ability of an incoming stimulus to initiate sustained activity, 2. spurious activations of sustained activity, 3. the mean life-time of the persistent state, 4. the ability of excitatory transients to read-out and turn-off the activity rapidly. In conclusion, correlated stochastic input can gate persistent activity during a working memory task and slow variations of the background correlations may embed task-timing information directly into the working-memory trace.

Linking Social and Vocal Brains: Social Withdrawal Prevents a Proper Development of the Central Primary Auditory Area in a Female Songbird.

H. Cousillas, I. George, L. Henry, J.-P. Richard, M. Hausberger

UMR 6552 - Ethologie animale et humaine, Université Rennes 1 - CNRS, Rennes, France

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Direct social contact and social interaction affect both speech development in human infants and song learning in songbirds, and are required in order to maintain perceptual abilities. However, the processes involved are still poorly known. In the present study, we tested the hypothesis that social withdrawal would prevent the proper development of a central auditory area, using an established animal model of vocal development, a songbird. Based on our knowledge of European starlings' vocal behaviour and development, we raised young female starlings with peers and adult male tutors only. This ensured that these females would show neither social bond with nor vocal copying from males. Electrophysiological recordings performed when these females were adult revealed perceptual abnormalities: they presented a larger auditory area, a lower proportion of specialized neurons and a larger proportion of generalist sites than wild-caught females, whereas these characteristics were similar to those observed in socially deprived (physically isolated) females. These results confirmed, and added to, earlier results for males, suggesting that the degree of perceptual deficiency reflects the degree of social withdrawal. To our knowledge, this report constitutes the first evidence that the lack of social interactions can, as much as physical separation, alter the development of a central auditory area.

The neural bases of vocal behaviour in relation to its communicative/social aspects: Differential representation of sounds with distinct biological significance in an avian associative auditory area.

I. George, H. Cousillas, M. Hausberger

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Categorization is essential to all cognitive processes, but identifying the neural substrates underlying categorization processes is a real challenge. Among animals that have been shown to be able of categorization, songbirds are particularly interesting because they provide researchers with clear examples of categories of acoustic signals allowing different levels of recognition, and they possess a system of specialized brain structures found only in birds that learn to sing: the song system.

In this study, we demonstrate that the activity of a songbird's non-primary, associative auditory area can indicate or represent classes of sounds corresponding to behaviourally-defined recognition processes. This auditory area has been compared to the superficial layers of auditory cortex or to secondary mammalian auditory regions such as the lateral belt in primates or Wernicke's area in humans. By showing differential representation of sounds with distinct biological significance (as observed in the field), as seen in higher-order fields of the auditory cortex of mammals, including humans, our study actually reinforce the parallel between these structures, and contribute to widen the impact of studies on songbirds. Moreover, given the many parallels that exist between birdsong and speech, we believe our results may contribute to a better understanding of the neural bases of speech.

Toward reconstructing a central circuit using light microscopy.

Katie Matho, May Zhang, David Mou,
Stéphane Fouquet, Shu-Hsien Sheu, Karine Loulier and Jean Livet

As we advance from the reconstruction of single neurons to the 'connectomic' tracing of entire circuits, new challenges appear. In particular, verifying the origins of neuronal processes is difficult in the absence of markers that would identify each neuron in a reconstruction. Brainbow transgenes drive combinatorial expression of multiple colors of fluorescent proteins in a neuronal population, thereby providing a way to label those neurons with a multitude of colors. We are developing methods using this labeling technique to reconstruct circuitry and visualize neuronal interactions in the central nervous system.

As a first model, we decided to focus on the 'binaural' circuit of the auditory brain stem. This particular circuit presents several key advantages. It contains a relatively low number of neurons (<3000), large and easily identifiable synapses called calices of Held, axons with few branches and planar orientation. Despite its simple organization, this circuit exhibits properties characteristic of complex central circuits including topographic organization.

We present the steps undertaken to reconstruct this circuit in adult mice: data collection using confocal microscopy, and attempts to trace the circuitry. We anticipate that the tools and techniques developed here will be widely applicable to the analysis of circuitry and cellular architecture in a variety of models.

Ascending pathways from the nucleus prepositus hypoglossi to the posterior parietal areas LIPv and MIP: Neural bases for transmission of eye position and velocity signals, revealed by retrograde transneuronal transfer of rabies virus.

V. Prevosto[1], *G. Ugolini*[1], *W. Graf*[2]

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Gain field modulation of neuronal activity by eye position and gaze signals participates in updating spatial representations in the posterior parietal cortex (PPC) and has a major influence on the spatial accuracy of goal-directed movements. Using retrograde transneuronal transfer of rabies virus, we studied polysynaptic inputs to the PPC ventral lateral intraparietal area (LIPv) and medial intraparietal area (MIP) in non-human primates, to identify possible sources of eye position and gaze signals to these areas. A mixture of rabies virus and a conventional tracer (Cholera toxin B fragment, CTB) was injected into LIPv or MIP. The tracers were detected immunohistochemically 2.5 and 3 days later. This tracer combination enables simultaneous identification of 1) the injection site and first-order neurons (e.g., thalamo-cortical) (CTB) and 2) higher-order neurons (rabies virus: second-order at 2.5 days, third-order at 3 days) (Prevosto et al. 2010, Cereb Cortex 20:214-28). We found that LIPv and MIP receive ascending disynaptic inputs from the horizontal eye position integrator network (nucleus prepositus hypoglossi, PH) via the thalamus (central lateral, CL and caudal ventral lateral, VLc, nuclei). PH populations targeting MIP and LIPv show major topographical differences that likely reflect transmission of different eye movement signals. LIPv receives projections from the ipsilateral rostral PH, which may carry ipsilateral eye position and fixation signals. In addition to the rostral PH, MIP receives projections especially from the contralateral caudal PH, which can transmit eye position and velocity signals.

Our study provides the first demonstration that PH inputs reach cortical areas. These pathways constitute suitable neural bases for online gain field modulation, rapid updating of spatial representations and spatial accuracy of movements. Modulation of spatial representations by eye position signals has major clinical relevance, as gaze orientation significantly influences the amplitude of visuospatial deficits in neglect patients (Vuilleumier & Schwartz 2001, Neuroreport 12:2101-04). The results may also help explain why patients with thalamic (VLc/CL) lesions are impaired in using corollary discharge information (Bellebaum et al 2005, Brain 128:1139-54).

Online readout of somatosensory frequency information.

Adrien Wohrer[1], *Ranulfo Romo*[2], *Christian Machens*[1]

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How many neurons in a given area contribute to an animal's percept and behavior? Traditional experiments have suggested that a single sensory neuron can convey more information about a stimulus than an animal will use in a given task, raising questions about the usefulness of population-based codes. However, recent experiments suggest that the predictive power of single neurons had been overestimated because their firing rates were computed over periods of time (~ 1-2 sec) much longer than what a monkey actually uses to make a decision (~ 200-300 msec). In fact, the number of neurons contributing to a code and the time scale of integration used by that code are in a natural trade-off relation (for example, the spike trains of N identical homogeneous Poisson neurons over a period of time T carry the same information as a single neuron's spikes over a period NT).

Here, we study quantitatively this trade-off, in macaque somatosensory areas SI(3b), SI(1) and SII, during a two-frequency discrimination task. Instead of the traditional spike count code, we investigate an "online readout" code, in which a sliding-window count of the population's spikes linearly provides an online estimate of stimulus value (a vibratory frequency), which must be as temporally stable as possible. We compute the efficiency of such a code depending on the area considered, the sliding window size, and the number of neurons involved. Analytical formulas also allow to predict the impact of noise correlations.

We find that: (1) The monkey's behavioral level of performance is compatible with neural populations (> 50 neurons) being read out with short counting windows (< 100 msec). (2) Admissible readout windows are markedly longer in area SI(3b) than in the higher-level areas SI(1) and SII. (3) These results still hold in presence of various noise correlation structures consistent with our data.

These results suggest the existence of a non-trivial integration of information from area SI(3b) to areas SI(1) and SII, efficient enough for these areas to convey a reliable prediction of stimulus value in their ▪ ginstantaneous ▪ h population activity (i.e., computed over a few tens of milliseconds), which could therefore be in direct correlation with the monkey's ▪ ginstantaneous percept ▪ h of stimulus value.

Multiple measures of peripheral nerve excitability *in vivo* in a mouse model of demyelinating neuropathy.

Boërio-Guéguen D.[1,2], Lefaucheur J.-P.[2,3], Créange A.[2,4], Benoit E.[1]

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Objective : To characterize excitability changes in a mouse model of demyelinating neuropathy.

Methods : Acquired demyelination was induced in 6 Swiss female mice at the age of 13 weeks, by injecting 100µl of physiological solution containing 124 units of a protease of bovine pancreas in the perineural space of the caudal nerve, at the base of the tail. Excitability properties were assessed by stimulating the caudal motor nerve at the base of the tail and recording the compound muscle action potential (CMAP) using needle electrodes inserted into the tail muscle. A first evaluation was performed before the induction of demyelination and then repeated recordings were achieved over 40 days. A control group (age- and gender-matched) was injected with placebo and recorded according to the same schedule, to appraise the effects of substance injection and repeated recordings. Excitability measurements included stimulus-response, strength-duration and current-threshold relationships, threshold electrotonus and recovery cycle.

Results : Two days after protease injection, mice displayed a reduced CMAP amplitude associated with an increased threshold, a reduced strength-duration time constant, smaller superexcitability and late subnormal period ($p<0.05$). Furthermore, they also exhibited a fanning in of the electrotonus, *i.e.* smaller threshold changes in response to polarizing currents ($p<0.05$). Gradual recovery was observed throughout 21 days until complete recovery after 29 days. Conversely, excitability properties of the control group remained fairly stable along the evaluation period.

Conclusion : Acquired demyelination induced within 2 days transient axonal excitability changes in mice, *in vivo*, suggesting an impairment of membrane potential and/or ion channels functioning associated with myelin sheath alteration. Taking into account the results of clinical evaluation of patients showing demyelinating neuropathy, this mouse model is potentially of great interest to appraise the ability of therapeutics to counteract the observed changes and exacerbate their recovery.

Model of bistability and inverse stochastic resonance of Purkinje cell.

Anatoly Buchin

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Purkinje neurons play an important role in Cerebellar computation. Their axons are the only projection from the cerebellar cortex to deeper cerebellar structures. These neurons appear to have a type II excitability, which can be revealed by a discontinuity in their F-I curves. This intrinsic membrane property of the Purkinje cells implies bistable behavior that can underly bimodality observed in vivo. This feature is tested experimentally by measuring the frequency hysteresis in response to slow ramp of current. Another effect recently found for the continuous neuronal models is the inhibition of firing by external noisy input, so called inverse stochastic resonance. We found similar phenomena measured in Purkinje cells. An adaptive Exponential Integrate-and-Fire model with adaptation is proposed to explain such properties. This model reproduces the bistability and inverse stochastic resonance observed experimentally. In this work we present experimental results and bifurcation analysis of the model explaining these two effects. We found numerically the optimal amplitude and optimal correlation of the noise stimuli for inhibition. We propose that such tuning is directly linked to the switching between quiescent and spiking state of Purkinje neurons revealing definitively their bistability.

Single neuron features versus network connectivity: a robust neural circuit model of the oculomotor integrator.

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The oculomotor neural integrator controls the position of the eyes during fixations and saccades. A prime candidate for horizontal, fixational control are the "position" neurons (PN), which fire persistently with a frequency that is proportional to the horizontal eye position (Major, Tank *Curr Opin Neurobiol* 2004,14:675–84). Past research has focused on three properties of this system:

(1) Recruitment order: The slope of the PN tuning curves increases as their firing threshold moves towards more eccentric eye positions (Aksay et al *J Neurophysiol* 2000,84:1035–49).

(2) Hysteresis and fine-tuning: most models of the oculomotor system rely on fine-tuning of synaptic parameters (<1%), yet how a biological system can fine-tune its synapses remains an open issue (Seung *PNAS* 1996,93:13339-44). Some models solved this by making neurons or dendrites bistable (Koulakov et al *Nat Neurosci* 2002,5:775-82; Goldman et al *Cereb Cortex* 2003,13:1185–95), in agreement with the hysteresis found in the tuning curves of PN.

(3) Bilateral dependency: Silencing of PN from one side impairs the functioning of the contralateral neurons in half of the oculomotor range (Aksay et al *Nat Neurosci* 2007,10:494-504). This led to suggest that the two sides of the system work as independent networks. Modeling work showed that proper coordination of the two networks is possible if individual neurons have high synaptic thresholds.

Here we investigate the construction of models that observe all these features, yet rely on standard single neurons – without the need for bistability or high synaptic thresholds.

Using rate models, we show that the inactivation result does not prove the independence of the two sides, but could be a simple consequence of the recruitment order of PN.

We solve the fine-tuning problem by introducing a feedback adaptation into the network, based on (Moreau, Sontag *Phys Rev E* 2003,68:020901). The adaptation leads to a network that is more robust than fine-tuned network models. With this adaptation rule, hysteresis emerges as observed in the data, suggesting that hysteresis is a signature of an active robustness mechanism, but not necessarily of a hidden bistability.

We conclude by suggesting further experiments to test existing models.

Elucidation of Pituitary Gland Functional Wiring Patterns.

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The pituitary gland, located just ventral to the brain, is the master endocrine organ responsible for regulating a wide range of important homeostatic processes. To achieve this, thousands of individual endocrine cells must co-ordinately respond to positive and negative inputs to temporally release hormone into the blood. The extent and duration of hormone release are decoded by peripheral tissues/organs to generate an appropriate physiological response. We have previously shown that rather than being a collection of dispersed endocrine cells, the pituitary gland is actually composed of topologically organised cell networks. Despite this, little is known about the structure-function relationships which allow individual endocrine cells to act as a population to drive hormone release.

Using 2-photon multicellular Ca2+-imaging of fluorescently-tagged pituitary slices, we have recently been able to probe the large-scale structure-function relationships of endocrine cell networks. In particular, we have focused on the lactotroph network which must spontaneously release high levels of prolactin (PRL) to support lactation. By applying a range of statistics, typically used for the analysis of neural network dynamics, we have been able to elucidate the functional wiring patterns which enhance cell-cell communication and drive PRL output in response to physiological demand. Briefly, in virgin animals, the connection distribution of the lactotroph-network obeys a power-law distribution with a high exponent value, a feature of scale-free networks where a small number of cells host the majority of connections. These activity hubs drive basal PRL release by allowing the network to display organised activity, as demonstrated by moderate levels of cell co-activity due to the firing of spontaneous Ca2+ spikes. In comparison, during lactation, an increase in the cluster co-efficient value is associated with the appearance of multiple well-connected hubs which are able to pace the rhythm of coordinated cell activity in an autonomous manner. Following weaning, multiple hubs still persist, albeit less well-connected than during lactation, suggesting that as well as an inherent capacity for autonomous function, the PRL-network possesses a long-term memory which may shape future hormone release. In marked contrast, growth-hormone secreting cells also form a functional network but only display co-ordinated activity in the presence of a central (GHRH) input. In summary, these results demonstrate the application of large-scale network analyses of cell-cell coordination to non-neuronal systems which drive basic body functions such as lactation.

STDP as a Mechanism for Invariant LFP –Spike Phase Coupling.

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How does a neuron learn to phase-lock to its inputs? In many brain areas – including the hippocampus and auditory cortex – the coupling between local field potential (LFP) oscillations and spiking (i.e. spike phase) can be highly precise. This phase-locking behavior has been observed to carry information reliably and is extremely robust across both pyramidal and interneuron cell types and across variation of membrane parameters. However the mechanism by which such invariant phase-locking is learned remains unexplained. We have investigated a simple mechanism for this process – the reliable change of firing rates during oscillations.

We consider an integrate-and-fire (IF) model neuron receiving Poisson distributed synaptic inputs, whose mean rates are modulated sinusoidally in time. The IF neuron is investigated within the 1:1 phase-locking regime. When oscillations are within the biological range (2 –150 Hz), firing rates of the inputs change on a timescale relevant to spike timing-dependent plasticity (STDP). Through analytic and computational methods, we find a point of stable phase-locking for a neuron with plastic input synapses. The location of this stable point 1) is independent of oscillation frequency within the biological range (2 –150 Hz) and 2) depends on the ratio of depotentiation to potentiation in the STDP rule.

With this mechanism, a heterogeneous population of neurons can learn to phase-lock to a specific point in the oscillation cycle, regardless of differences in initial excitation. Thus, this mechanism provides a simple and robust explanation for the precise coupling between LFP and spiking found throughout the brain.

Bioemergences Platform.

Louise Duloquin, Thierry Savy,
Emmanuel Faure, Camilo Melani, Paul Bourgine, Nadine Peyrieras

CNRS Gif-sur-Yvette, ISC PIF, CREA Polytechnique

BioEmergences responds to the most advanced needs of integrative biology that aims at reconstructing multi scale dynamics from adequate measurements obtained from *in vivo* observation at the relevant spatial and temporal resolution.
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- Optimized protocols for 4D imaging with dedicated MLSM (multiphoton laser scanning microscopy) or DSLM (Digital scanned light sheet microscopy which a variant of the SPIM selective plane illumination microscopy concept);

- Imaging with MLSM and DSLM dedicated set up;

- Production of standard format 4D data sets and transfer to the BioEmergences database in ccIN2P3 (calculation centre of the CNRS in Lyon) with the SRB and soon iRODS procedure through the BioEmergences web interface (professional design by DENALI SA)

- Identification of the most suitable algorithmic pipeline to achieve the reconstruction of 4D image data sets: filtering and/or deconvolution, 3D multi view reconstruction for DSLM data, objects segmentation, object tracking

- Computation of algorithmic pipelines either on the EGEE computation grid or ccIN2P3 computer clusters

- Evaluation of the reconstruction precision and accuracy

- Interactive visualisation of reconstructed and raw data with the BioEmergences visualisation interface, data annotation

- Custom data analysis including statistical analysis of spatio temporal correlations.

Context-dependent information transfer in model thalamocortical circuits.

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The thalamus is the major gateway for the flow of sensory information to the cerebral cortex. At the cellular level, the relay of information depends on the transfer function of the thalamocortical (TC) cells, which has been proposed to be highly modulated by contextual synaptic bombardment (Wolfart et al., Nat Neurosci 2005, 8:1760). Many TC neurons converge synaptically to a recipient cortical neuron, and at the level of the thalamic population, the functional consequence of synaptic background remains unknown. We investigate this issue by modeling a biologically realistic retino-thalamo-cortical microcircuitry in which a cortically-induced synaptic bombardment is mimicked through the injection of stochastically fluctuating mixed excitatory and inhibitory conductances in TC cells. The models of conductance are either based on a Gaussian distribution to convey general statistics of synaptic bombardment or driven by fine temporal correlations to reflect the TC microcircuitry specificities. Using mutual information analysis we show in computo that information transfer in the TC system is strongly modulated by three parameters: 1) the number of TC cells; 2) the statistics of synaptic bombardment; 3) the degree of correlated synaptic bombardment across the TC cells. Interestingly, a reduced correlation enhances the transfer efficiency suggesting conversely that correlated synaptic bombardment could be a mechanism to selectively decrease the thalamocortical response to distinct pools of visual afferents. This hypothesis is supported by the parallel and orthogonal organization of the corticothalamic feedback projections originating from single cortical cells (Sillito et al., TINS 2006, 6:307). Finally, we will test the paradigm in biological cells in vitro using dynamic clamp to assess the contribution of the cell-to-cell variability in membrane properties with a focus on the T-type Ca++ current. Supported by ANR (T-state), DGA, European Commission-funded (Facets) grants.

On the utility of neural perturbation experiments for identifying the neural components of an integrated system.

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Living animals are sensorimotor systems endowed of properties that allow them to explore and interact with their environment. The orienting reaction is one of these systems by which animals can establish equilibrium between their endogen properties and the constraints imposed by the milieu. Indeed, variations in the environment (like the sudden appearance of an event) or fluctuations in the inner state (e.g., the hypovolemia) often break this equilibrium and lead to coordinated movements which are aimed at restoring it. As such, the orienting reaction can be viewed as a transition, whose detailed analysis can provide a picture of the dynamic properties of a neurobiological system, at different time scales (e.g., from the systematic orientation to its habituation) and spatial scales (e.g., from the saccade and its underlying neural network to the bistable properties of recruited neurons). Most often, this reaction consists in orienting the sensory organs toward the source of external events. Many neuronal groups are involved in generating a reaction that fits with the spatiotemporal properties of targeted events. These groups are distributed in several brain regions whose interactions generate streams which are more or less independent or cooperative. Among those regions, the medio-posterior cerebellum (MPC) is known to play a major role in the adaptability of the orienting reaction.

By a series of experiments which consisted in reversibly perturbing, in the feline and primate species, the output nucleus of MPC, the caudal fastigial nucleus (CFN), we have been able to identify different sub-systems involved in orienting the fovea toward a visual target, with or without the contribution of the head, and at different times from the target appearance to its foveal acquisition. Our studies suggest that the CFNs, through their connections toward the rostral Superior Colliculi, would adjust miniature saccades generated when foveating a target presented in the central visual field. Through their connections toward premotor centers in the reticular formation, the CFNs would adjust the balance between excitatory and inhibitory commands for generating the proper drive to quickly and accurately orient the eye and the head toward peripheral targets. Differences observed in the effects of functional perturbations between the feline and primate species reveal different strategies which depend upon the nature of the target and the neuro-morphological organization of the oculo-cephalic system.

Future comparative studies should reveal the evolutionary aspects of a complex system which progressively integrates the properties of the environment and the inner physiology.

Complexity of neural activity in multiple sclerosis.

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Experimental recordings of the temporal evolution of cortical activity can be encoded into symbolic sequences. Within this framework, the nervous system whether chaotic or not, generates messages and can thus be considered as an information source. The characteristics of this source can then be used to quantify the dynamics of cortical electrical activity.
We focus here on the study of the disturbance of cortical activity in multiple sclerosis. Numerous studies have underlined that demyelination involves degeneration of conductive capacities and reduced communication between separate cortical regions. EEG signals recorded during resting condition were used to estimate several indicators related to both, the intrinsic dynamic (i.e. the complexity) and the information transmission of neural activity in control subjects and patients suffering from relapsing-remitting multiple sclerosis.

First, the entropy rate (or Kolmogorov-Sinai entropy) was computed using an algorithmic estimator of this quantity which estimation is often hampered in practice by the finite length of the data. The estimation procedure is based on Lempel-Ziv complexity which takes into account the multi-scale correlation structure of the signals and allows one to obtain a meaningful index to quantify the dynamic features of experimental time series.

The averaged EEG entropy/complexity is signifiantly higher in patients with multiple sclerosis than in control subjects and thus quantitifes the disorganization induced by demyelination. In addition, we evaluate the interhemispheric information transmission, computing the averaged Shannon mutual information between different cerebral hemispheres. This quantity is significantly lower in patients group than in control group and decrease with illness duration. These findings support that complexity and information indices obtained in a resting state from EEG activity are potential markers for the neurological damage induced by relapsing-remitting multiple sclerosis.

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Pitmap Project : 3D Mapping of the Mouse Pituitary Structure and Development.

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Using high-throughput 3D imaging on transgenic animals, we will reconstruct at cellular resolution the structure of a whole mammalian organ, the mouse anterior pituitary gland, at different stages during development.This gland is composed of five endocrine cell types, secreting six different hormones.

The structure is relevant to the physiological response of the gland.

This has been demonstrated using both traditional qualitative histology to image portions of the gland at different stages of development, and functionally using electrophysiology and calcium imaging.Cells exhibit correlated behaviour dependent on their organisation in networks, which are plastic, depending on changing physiological needs.

The complexity of the structure is tractable.

Other organs in the body can exhibit simpler 3D structure (the thymus) but no evidence exists for functional role of any precise 3D organisation. On the other hand, brain systems are functionally crucially dependent on their network structure, but the details of this structure are beyond our imaging capacities. In the pituitary the structure is both relevant and accessible, the cells being of compact shapes and making mainly nearest-neighbour contacts. Moreover, only five cell families exist, which enable us to image the separated cell networks using a limited number of transgenic animals.

Methods

The Montpellier lab has the experimental facility to perform 3D histology on the whole gland, using an apotome microscope in combination with a microtome. Stacks of confocal-like images of 30 microns depth are obtained at a given level, and a 25 micron slice of the gland is then removed and the section below imaged.

As the gland is composed of roughly **1 million cells** identified on ~4000 image stacks, automatic identification of the cells will be necessary. We have the tools available to obtain 90% accurate identification, as tested on small-scale image stacks. To perform the segmentation of the whole gland will necessitate GRID distributed computation technology, to reduce the process to 2-3 days of computational time per gland. This is necessary to achieve high-throughput analysis, which is required since in the details every pituitary will be different: the relevant structural data which differentiate animals of different developmental stages/sexes can only be described statistically.

Functional connectivity: Gaussian graphical models on the brain.

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Functional brain connectivity, as revealed through distant correlations in the signals measured by functional Magnetic Resonance Imaging (fMRI) has been used to reveal functional segregated cognitive networks as well as small-world properties of brain functional architecture.

We are interested in the estimation and comparison of probabilistic models of functional connectivity from fMRI data using Gaussian graphical models.

We learn the correlation structure of the cognitive networks between 30 regions of interests on a population of healthy control at rest. Strongly-integrated sets of regions can be identified to resting-state networks well-known from the literature.

We compare this graphical model to models learned on stroke patients. We find that correlations within resting-state networks are impacted selectively, even between regions not damaged by the focal lesion. These connectivity perturbations seem correlated to behavioural symptoms.

To pave the road for similar analysis with many regions of interest, we propose to address the problem of multiple comparisons by introducing covariance selection. In the framework of Gaussian graphical models, we learn an independence structure that generalizes well between subjects. This amounts to a statistically-controlled pruning of our graphical model.

We compare several covariance selection procedures: L1-penalized, group-L1-penalized maximum likelihood, as well as greedy L0 procedures. We test for generalization to new subjects using the multivariate normal likelihood. We find that generalization scores are limited by inter-subject variability and that there is a trade-off between generalization and reducing the number of edges studied on the graph.

In the corresponding graphs, we find indications of hub nodes, characteristic of small-world topology, as well as large structures that we interpret as cognitive networks.

Marine dinoflagellates produce novel macrocyclic imine neurotoxins targeting nicotinic acetylcholine receptors with high affinity.

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Spirolides and gymnodimines constitute a novel family of phycotoxins of global distribution that target nicotinic acetylcholine receptors (nAChR). Spirolides contain an unusual 5,5,6-bis-spirocetal moiety together with a 6,7-spirocyclic imine structure that is also found in gymnodimines. First isolated from digestive glands of mussels and scallops, spirolides and gymnodimines are produced by the dinoflagellates Alexandrium ostenfeldii and Karenia selliformis, respectively. Marine molluscs that filter feed on dinoflagellates can accumulate a series of toxic molecules and may act as vectors for transferring these toxic chemical compounds to crabs, fish, birds, marine mammals, and ultimately to humans, menacing thus, public health. Analysis of 13-desmethyl spirolide C, 13,19-didesmethyl spirolide C and gymnodimine A by ligand binding assay and voltage-clamp recordings on muscle-type $\alpha 12\beta 1\gamma\delta$ and human neuronal $\alpha 4\beta 2$, $\alpha 3\beta 2$ and $\alpha 7$ nAChR reveal sub-nanomolar affinities and potent antagonism together with limited subtype selectivity.

However, as shown by electrophysiology on Xenopus laevis oocytes having incorporated Torpedo membranes or expressing human $\alpha 4\beta 2$ and $\alpha 7$ nAChR, the interaction between spirolides and nAChRs is irreversible under the used experimental conditions, while gymnodimine is readily washed-out from the cholinergic receptors. Our data show for the first time that spirolides and gymnodimines target nAChRs by the presence of their cyclic imine in their structure, and explain the basis of their fast neurotoxicity when tested by mouse bioassay.

The discovery of these new compounds and the elucidation of their molecular mechanisms of action may be extremely useful for developing front-line drugs for neurodegenerative diseases related to neuronal nAChRs: non-selective ligands may be of utility to control the general activation or desensitization of nAChRs, and selective ligands are of paramount importance to decipher the particular role of a nAChR sub-type over a neural function/ dysfunction. Our next aim is to use molecular components of these macrocyclic imines as leads for conceiving novel ligands with specific subtype nAChR selectivity.

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Revisiting the Regression/Classification Problem in Brain-Computer Interfaces: a Reservoir Computing Approach.

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Brain-Computer Interfaces (BCIs) aim at decoding neural signals in order to enable direct communication between subjects' intention and electronic devices such as computers, neuroprostheses... For this particular purpose, electrical brain signals are usually recorded from the scalp (non-invasive recording method) using electroencephalograms while the subject is performing a mental task chosen among a predefined set of tasks. In the standard setup, the tasks are chosen by the experimenter during a learning phase to train the parameters of the method and freely chosen by the subject while intentional control is aimed.

The mental tasks are usually characterized using different kind of a priori knowledge, gathering informations about the spatial locations of brain activations during task performance, frequencies of interest, and temporal succession of brain patterns (“features construction”). In this work, we first show that Echo State Networks (introduced by Jaeger in the machine learning community in 2001) can be used as a “dictionary” of dynamics for encoding the three preceding kinds of information (spatial, frequential and temporal). These dynamics are created using a sparsely and randomly connected reservoir, constituting a recurrent neural network (RNN). We then propose that a small number of “relevant” (in the sense that it helps decoding signals) dynamics has to be selected among the huge set of available signals. We show that this can be done by regularizing the reservoir-to-output linear transformation using a sparse norm.

Depending on the application, the features (reservoir signals) are mapped onto commands (output) in a discrete or continuous manner, this constitutes the “classification/regression” step. We explore different regularized linear models to perform this task and compare the regression approach against the classification one. The proposed method is evaluated using real signals recorded during a Brain-Computer Interface experiment based on two-task motor imagery (left hand against right hand motor imagery). The dataset was provided to the BCI community in 2008 during the BCI Competition IV.

Separation of Traveling Waves in Cortical Networks Using Optical Imaging.

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This poster introduces a mathematical model of the spatio-temporal patterns of visually evoked activity observed using Voltage-Sensitive Dye Imaging (VSDI) of the visual cortex. The cortical activity is described using a linear superposition of waves traveling with different speeds.

This model improves the quality of the wave detection and still respects the previous approaches, as it integrates several biologically plausible constraints:

1) separability of the sources in terms of cortical location;
2) separability of the waves in terms of propagation speed, and
3) additivity of the depolarizing effects of the waves.

Under these assumptions, a traveling component analysis algorithm performs a full separation of the set of waves and recovers the locations of the neural sources. Both features could help to better understand the dynamics of evoked activity in cortical sensory networks.

Intrinsic dendritic plasticity maximally increases the computational power of CA1 pyramidal neurons.

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What additional computing power do dendrites add to a neuron? Previous work using artificial neural networks has suggested that active dendrites improve the computing power of CA1 pyramidal neurons by increasing the number of possible input/output relationships (Poirazi et al 2001). However, several key questions remain open: what characterizes these new input/output behaviors? Is there a dendritic morphology which maximally increases the computational power of such « dendritic » neurons? And which physiological parameters of the neuron should change to reach this maximal computational power? In order to address these issues we start out with the approach of Poirazi et al (2003) and consider the CA1 pyramidal neuron as a two layer neural network with excitatory connections.

We begin by showing that we can exhaustively characterize the entire space of possible two-layer networks. Extending results on single layer networks by Minsky and Papert (1988) we prove that any two layer neural network, with real, positive synaptic weights and thresholds, has a discrete, weightless equivalent with the same input/output mapping. Using this discretization, we are able to enumerate all possible input/output functions of a two layer neural network (for up to 6 distinct inputs).
Analytically we identify an input/output combinations that could only occur in two-layer but not in one-layer networks. Such input/output combinations, should they be identified in a CA1 pyramidal neuron, would indicate that the cell functionally implements a two-layer neural network. For instance, given four independent Schaeffer collaterals (A, B, C and D) impinging on a CA1 pyramidal neuron, our analysis predicts that if both A+B and C+D elicit a response, but A+C, A+D, B+C or B+D do not, then the dendritic tree is equivalent to a two-layer network, and cannot be reduced to a single layer.
Our analysis also shows that a surprisingly low number of dendrites, in the order of the number of afferent, is required to maximize the computational power of CA1 neurons.

Finally, we find that modification of the somato-dendritic coupling strengths does not change the input/output mapping of the neuron. Conversely, we show that modifying dendritic branch excitability is necessary to access the full range of input/output functions. Thus, our model suggests that intrinsic dendritic plasticity is key to maximizing the computational power of a CA1 pyramidal neuron, consistent with recent experimental demonstrations of dendritic plasticity in CA1 pyramidal cells (Losonczy et al. 2008).