BCAM Workshop
Quantitative Biomedicine for Health and Disease
Bilbao, February 17-18, 2015

BOOK OF ABSTRACTS

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1. Adam Barrett (University of Sussex, UK)
2. Pierrick Coupé (CNRS, FR)
3. Mathieu Desroches (INRIA, FR)
4. Aciel Eshky (Edimburgh University, UK)
5. Luca Faes (Trento University, IT)
6. Andrea Fuster (Eindhoven University of Technology, NL)
7. Estibaliz Garrote (Tecnalia, SP)
8. Albert Granados (INRIA, FR)
9. Bert Kappen (Radboud University, Nijmegen, NL)
10. Pablo Lamata (King's College, London, UK)
11. Alberto Llera (Donders Institute, Radboud University, Nijmegen, NL)
12. Daniele Marinazzo (Gent University, BE)
13. Paolo Paradisi (CNR, IT)
14. Ernesto Sanz-Arigita (VUmc, Amsterdam, NL)
15. Jordi Soriano (Universitat Barcelona, SP)
16. Ruedi Stoop (ETH Zurich, CH)
17. Joanna Tyrcha (Stockholm University, SE)
18. Edward J. Vigmond (Bordeaux University, FR)

Program

Tuesday, February 17, 2015

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Chairman: *Luca Gerardo-Giorda*

09:30-10:10 **Joanna Tyrcha**
Stochastic stability and dynamic behavior of a compound cell-cycle model

10:10-10:50 **Mathieu Desroches**
Mixed-Mode Bursting Oscillations (MMBOs): slow passage through spike-adding canard explosion

10:50-11:30 **Albert Granados**
The period adding phenomenon in periodically driven hybrid spiking models

11:30-12:10. *Coffee Break*

12:10-14:10 Session 2.

Chairman: *Ruedi Stoop*

12:10-12:50 **Edward J. Vigmond**
Cardiac Applications of Computational Electrophysiology

12:50-13:30 **Pablo Lamata**
Extraction of diastolic biomarkers through personalization of computational models

13:30-14:10 **Aciel Eshky**
Condition Monitoring of Athletes with a Wearable Heart Rate Variability Sensor

14:10-15:20 *Lunch*

15:20-17:20. Session 3.

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15:20-16:00 **Andrea Fuster**
Geometric framework for diffusion MR images of the brain: theory and applications

16:00-16:40 **Ernesto Sanz**
Multimodality MRI in different groups at risk for developing Alzheimer's disease: towards multidimensional brain imaging biomarkers.

16:40-17:20 **Pierrick Coupé**
New patch-based estimators for early detection of Alzheimer's disease

Wednesday, February 18, 2015

9:30-11:30. Session 4.

Chairman: *Sebastiano Stramaglia*

09:30-10:10 **Bert Kappen**
Explaining missing heritability with Gaussian Process regression

10:10-10:50 **Alberto Llera**
Efficient Gaussian/Inverse Gammas mixture-models: a new tool for thresholding ICA statistical maps from fMRI data

10:50-11:30 **Estibaliz Garrote**
Computer vision applied to digital pathology: image search engine based on clinical similarity

11:30-12:10 *Coffee Break*

12:10-14:10. Session 5.

Chairman: *Daniele Marinazzo*

12:10-12:50 **Ruedi Stoop**
Power-law size distribution of activated avalanches - what do they really mean?

12:50-13:30 **Luca Faes**
Dynamics of Information Storage, Transfer and Modification in the Cardiovascular System

13:30-14:10 **Adam Barrett**
Synergistic and redundant information sharing in Gaussian systems

14:10-15:20 Lunch

15:20-17:20. Session 6.

Chairman: *Jesus Cortes*

15:20-16:00 **Daniele Marinazzo**
Tracking slow modulations in synaptic gain using dynamic causal modelling: Validation in epilepsy

16:00-16:40 **Paolo Paradisi**
Intermittency-based complexity measures in brain EEG data

16:40-17:20 **Jordi Soriano**
Experiments in Neuronal Cultures: Exploring Open Questions in Physics and Medicine

Abstracts

Stochastic stability and dynamic behavior of a compound cell-cycle model

Joanna Tyrcha

Stockholm University, Sweden

The timing of key events in the eukaryotic cell cycle is remarkably stochastic. Special attention had been paid to the START transition, when the cell starts to synthesize DNA. Experiments have shown that START in budding yeast proceeds in two distinct steps, both of which are stochastic. We therefore generalized earlier work and studied a model in which the cycle has two parts, the durations of both of which are assumed to be random and independent. We find a stability condition on their distributions: For the distribution of cell sizes be stable in the limit of many generations, all moments of both distributions must be finite and the sum of the mean durations must be less than the cell-size doubling time. When these conditions are satisfied, the asymptotic size distribution has inverse-power-law form and we derive an equation for the exponent.

In our current work, we are taking a closer look at the cellular reactions responsible for the stochasticity in these and similar transitions. Their dynamics can be described by stochastic differential equations, allowing us to write a path-integral representation for the transition rate. When this rate is small, we can evaluate it for a model in which mRNA lifetimes are much shorter than protein ones and a key protein feeds back to promote transcription of its own DNA (as is known to happen at START).

Mixed-Mode Bursting Oscillations (MMBOs): slow passage through spike-adding canard explosion

Mathieu Desroches[1], Martin Krupa[1], and Tasso Kaper[1]

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In this talk, I will present the phenomenon of Mixed-Mode Bursting Oscillations (MMBOs). These are solutions of slow-fast systems of ordinary differential equations that exhibit both small amplitude oscillations (SAOs) and bursts consisting of one or multiple large-amplitude oscillations (LAOs). The name MMBO is given in analogy to Mixed-Mode Oscillations (MMOs), which consist of alternating SAOs and LAOs, without the LAOs being organized into burst events. I will show how MMBOs are created naturally in systems that have a spike-adding bifurcation, or spike-adding mechanism, and in which the dynamics of one (or more) of the slow variables causes the system to pass slowly through that bifurcation. Canards are central to the dynamics of MMBOs, and their role in shaping the MMBOs is two-fold : saddle-type canards are involved in the spike-adding mechanism of the underlying burster and permit one to understand the number of LAOs in each burst event, and folded-node canards arise due to the slow passage effect and control the number of SAOs. The analysis is carried out for a prototypical fourth order system of this type, which consists of the third-order Hindmarsh-Rose (H-R) system, known to have the spike-adding mechanism, and in which one of the key bifurcation parameters also varies slowly.

The period adding phenomenon in periodically driven hybrid spiking models

Albert Granados and Martin Krupa

INRIA Rocquencourt, France

In this work we consider a general non-autonomous spiking model based on the integrate-and-fire model, widely used in neuronal modeling. Our unique assumption is that the system is monotonic, possesses an attracting subthreshold equilibrium point and is forced by means of periodic pulsatile (square wave) function.
In contrast to classical methods, in our approach we use the stroboscopic map instead of the so-called firing-map, and becomes a discontinuous map. By applying theory for piecewise-smooth systems, we avoid relying on particular computations and we develop a novel approach that can be easily extended to systems with other topologies (expansive dynamics) and higher dimensions.
We rigorously study the bifurcation structure in the two-dimensional parameter space formed by the amplitude and the duty cycle of the pulse. We show that it is covered by regions of existence of periodic orbits given by period adding structures. They completely describe all the possible spiking asymptotic dynamics and the behavior of the firing rate, which is a devil's staircase. Our results allow us to show that the firing-rate also follows a devil's staircase with non-monotonic steps when the frequency of the input is varied, and that there is an optimal response in the whole frequency domain.

Cardiac Applications of Computational Electrophysiology

Edward J. Vigmond

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Use of computer models in the clinic is being driven by increasing computational performance, due to hardware and software advances, combined with greater physiological knowledge and better clinical data acquisition. Of particular note is the recent use of inverse mapping technology to guide ablation[1]. Starting with potentials recorded on the body surface, the potentials on the heart surface are recreated, and arrhythmias analyzed to determine the crucial regions driving the activity. Furthermore, the activity is usually described in terms of phase rather than voltage[2]. Imaging clinical data is rapidly improving in quality but functional data remains rather low resolution compared to model needs. This talk will discuss issues related to the modelling of arrhythmias, and how clinically acquired data can be used to personalize models. Topics include large scale computing, reduced atrial models to allow long simulation times, and methods for assigning ventricular properties. Lastly, we will look at incorporating scar data into models.

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Extraction of diastolic biomarkers through personalization of computational models

Pablo Lamata

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Heart failure (HF) is a clinical condition where the heart is not able to pump enough blood, and its management is a major social problem. Specifically, HF with a normal ejection fraction (HFNEF) is characterised by an impaired left ventricular filling caused by changes in relaxation and compliance, but these are difficult to assess in-vivo, and are currently characterised by indirect surrogates with limited success. In this talk I will present our recent advances to characterise the diastolic performance of the heart, its ability to relax and fill with blood. Cardiac biomarkers of ventricular diastolic function (relaxation, compliance, blood pressure gradients) can be extracted from the personalization of computational physiological models to available clinical data. Magnetic Resonance Images capture the deformation of the cardiac structures and the velocity of the blood flow. Computational models, based on physiological and physical laws, are personalised to each patient, revealing the hidden diagnostic parameters. The goal of this research is to propose new diagnostic indexes that will help cardiologists to detect heart failure at an earlier stage, to risk-stratify patients, and to tailor the treatment to each patient.

Condition Monitoring of Athletes with a Wearable Heart Rate Variability Sensor

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Introduction

Despite the rapid increase in the popularity of 'wearable' sensors, there is a scarcity of analytical tools that interpret the data coming from these devices in order to enable advice and intervention [1]. In this paper, we address an aspect of this, focussing on defining and estimating indicators that enable condition monitoring of an athlete. Our experiments are based on subjects who are users of the athlete app (HRV Fit Ltd.) Using a physiological model of response to training load [2], we perform a gradient-descent fit of the nonlinear model to daily recorded data, per athlete. When the quality of fit is deemed acceptable, the time constant parameter of this model informs us about the degree of recovery of the subject. Next, we study the relationship between heart-rate-variability and heart rate, both within subject and across a batch of subjects. We find that there is systematic variation, which can be observed by performing kernel density estimation of the bivariate data and separating the resulting multi-modal distribution into classes. Each of these classes corresponds to a type of athlete, based on cardiac condition.

Estimating Recovery from Training Impulses.

We base our estimation on the Banister model [2]

$$y_n = y_0 + k_1 \sum_{i=1}^{n-1} w_i e^{-(n-i)/\tau_1} - k_2 \sum_{i=1}^{n-1} w_i e^{-(n-i)/\tau_2} \tag{1}$$

where y_n is the HRV on day n, w_i is the training load on day i, and k_1, k_2, τ_1, τ_2 all > 0, are scaling parameters (during model fitting, these are estimated using non-linear least squares given the y_n and w_i). In the above, the first sum on the left is a *super-compensation* term, defining the improvement in performance due to training load, whereas the second term is a fatigue term defining the reduction in performance due to training load. The observed effect of a training load on performance is typically a dip, due to fatigue followed by a rise due to super-compensation – this is typically referred to as the 'double-exponential model' of HRV and training load. The two key parameters of interest for our study are recovery and fatigue characteristics, which are represented by k_1, τ_1 and k_2, τ_2 respectively. While this is a generally accepted description in sports science, the model is not universal, in that the parameters minimizing squared error depend on units of training load. So, we select a standard parameter setting $k_1 = 1$ and $k_2 = 0.5$, with the understanding that super-compensation term ought to be larger than the fatigue term, and then estimate τ_1 and τ_2 parameters using a gradient descent procedure. These estimates enable decisions about when exercise is likely to be fruitful as opposed to when it can cause injury.

Unsupervised Athlete Type Categorization.

Physiologists expect that distinct subgroups of subjects exist, possibly characterised in

terms of their HR/HRV profile. We study this in an exploratory analysis, where we fit a Kernel Density Estimate (KDE) to joint measurements of HR and HRV for all our data, across subjects. KDE is a non-parametric technique useful for identifying regions of high data concentration without making assumptions about the distribution. We identify two subgroups: (1) low HR, high HRV (2) high HR, low HRV. The pairing of low HR, high HRV is associated with fitter individuals, and thus we think of these as (1) elite and (2) beginner athletes. We then estimate a KDE for each subject's data separately, and find unimodal PDFs, i.e. the majority of a subject's HR/HRV measurements fall into one of the two categories. In order to provide actionable advice, we wish to estimate the class label for each subject and identify the point when they have moved from one class to another. For this, we use a Gaussian Mixture Model (GMM) with a diagonal covariance matrix, and two components to match the structure in the KDE. The GMM identifies the same two groups as our KDE. Because the GMM is a probabilistic model, we are then able to predict for each subject the probability of belonging to some group or "cluster".

Conclusion

This project is an attempt at performing condition monitoring of athletes, based on data obtained daily from a heart rate variability monitor. Our focus is on estimating physiological parameters that are indicative of recovery and cardiac condition, in order to enable actionable advice on the part of the sports scientist. Such advice includes, e.g., knowing when to engage in especially rigorous bouts of training.

Acknowledgment

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Geometric framework for diffusion MR images of the brain: theory and applications

Andrea Fuster[1], T.C.J. dela Haije[1], C.M.W. Tax[2], A. Tristan-Vega[3], C.-F. Westin[4], A. Leemans[2], L.M.J. Florack[1]

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Diffusion-weighted MRI (dMRI) is a magnetic resonance imaging technique that measures the diffusivities of water molecules in biological tissue in a non-invasive way. It is mostly used for the study of brain white matter. Different models to describe the rather complex dMRI signal have been proposed, for example, diffusion tensor imaging (DTI) and higher order diffusion tensors (HOT's). Information about the white matter architecture, for example, can then be extracted with the aid of such models. We consider diffusion MR images of the brain within a geometric framework, and present two different but complementary applications: geodesic tractography and sheet structure.

In our geometric approach white matter is described as a Riemannian manifold, with a metric related to the diffusion tensor. In this way, geodesic tractography can be performed to infer the architecture of white matter pathways in the brain. We propose a novel Riemannian metric and present promising tractography results. The second application concerns the brain's sheet structure, which has been recently postulated by Wedeen et al. and published in Science. The presence of sheet structure is assessed by employing Lie brackets, which can be constructed from multiple vector fields extracted from the brain dMRI data. We study the quantification of Lie brackets and show our latest results.

Multimodality MRI in different groups at risk for developing Alzheimer's disease: towards multidimensional brain imaging biomarkers.

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Alterations in brain structure and functional resting state networks can be can be detected in the early phases of Alzheimer's disease (1-3). However, the precise development of the changes preceding dementia remain unclear (4). Moreover, the relationship between structure and function remains elusive and their correlation with preclinical cognitive changes has not been fully explored (5,6). In this lecture we will present a comprehensive magnetic resonance imaging study of early structural and functional changes of the brain related to the most common risk factors for the development of late-in-life Alzheimer's disease. We will describe a set of analyses performed in the same population exploring (a) volumetric brain changes computed with voxel-based-morphometry, (b) coordinated patterns of cortical thickness analyzed with graph analysis, (c) resting state functional connectivity by independent component analysis, and (d) global functional connectivity centrality with graph analysis. We will also briefly describe the main cognitive correlates to the early structural and functional changes found. Finally, we will introduce a new project aimed to develop a multimodality imaging biomarker combining structural and functional MRI data sets by means of pattern classification methods like support vector machines (SVM). Thanks to the combined predictive power of the information derived from different imaging techniques, we aim to implement an automated method for early dementia diagnosis that will contribute to the understanding of the development of Alzheimer's disease and related neurodegenerative disorders.

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New patch-based estimators for early detection of Alzheimer's disease

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The diagnosis of Alzheimer's disease (AD) at pre-clinical stages or the prediction of conversion of patients with mild cognitive impairment (MCI) to AD is a very challenging problem receiving attention because of the immense associated social and economic costs. Several biomarker candidates have already been studied in depth with the goal of achieving this task. Nowadays, measures of neuronal injury and neurodegeneration are among the most important biomarkers of AD. Cerebral atrophy caused by the progressive neurodegeneration can be measured in detail by magnetic resonance imaging (MRI). Optimizing such MRI-based biomarkers for detection and prediction of AD may have a significant impact on early diagnosis of patients as well as being valuable tools when designing therapeutic studies of individuals at risk of AD to prevent or alter the progression of the disease. In this talk, new patch-based methods will be presented to accurately detect and predict Alzheimer's disease (AD).

First, a new patch-based label fusion (PBL) method for structure segmentation will be detailed. Inspired by recent work in image denoising, our patch-based label fusion involves patch comparison where the weight assigns to each label depends on the similarity between the current patch and the training patch. The search of similar training patches is based on nonlocal strategy to better handle the inter-subject variability and to capture registration inaccuracies. In a limited computational time this method achieves state-of-the-art segmentation accuracy. Consequently, since its introduction, our PBL has been intensively studied and many improvements have been proposed. Some of them will be presented during this talk with of focus of our recent near real PBL method: OPAL. Then, an innovative extension of this method to structure scoring will be discussed. This new method simultaneously performs segmentation and scoring of structures to efficiently capture the anatomical alterations caused by AD. Known as SNIPE (Scoring by Non-local Image Patch Estimator), this scoring measure is based on a nonlocal means framework to estimates the similarity of a new MRI compared to several populations of training MRI. With the nonlocal framework, SNIPE is able to handle inter-subject variability by enabling a one-to-many mapping between the subject's anatomy and those of the training templates. Moreover, by employing the patch-based comparison principle, SNIPE can detect subtle anatomical changes caused by the disease. Finally, a validation of the ADNI database (>800 subjects) will be presented. Detection and prediction aspects will be investigated using several methods. Finally, a comparison with recent studies on MRI-based biomarkers will be discussed.

Explaining missing heritability with Gaussian Process regression

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For many traits and common human diseases, causal loci uncovered by genetic association studies account for little of the known heritable variation. ?Missing heritability? might lie in the effect of non-additive interactions between multiple loci, but this has been difficult to test using existing parametric approaches. We employed a non-parametric, Bayesian method, based on Gaussian Process Regression, for identifying associated loci in the presence of interactions of arbitrary order. We analysed 46 quantitative yeast phenotypes and found that over 70% of the total known missing heritability could be explained using common genetic variants, many without significant marginal effects. Importantly, the availability of biological replicates significantly improved the power to identify such loci and, hence, to explain variance . These results represent a significant advance in approaches to understanding the missing heritability problem with potentially important implications for studies of complex, quantitative traits.

Efficient Gaussian/Inverse Gammas mixture-models: a new tool for thresholding ICA statistical maps from fMRI data

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Introduction

Gaussian/Gamma mixture models (GGM) [1,2.3] provide the means for thresholding statistical maps generated from a probabilistic ICA decomposition of functional imaging data [2]. Since there exists no closed form Maximum Likelihood (ML) estimation for all the parameter values of the Gamma distribution, the usual EM-algorithm for Maximum Likelihood learning a GGM becomes an expensive process. An interesting solution was proposed in [1] and uses the method of moments (MM) for the Gamma distribution [9] for translating the estimated means and variances into parameter values for the Gamma components. We show using synthetic data that the GGM has a practical limitation when the number of samples in an active component is small with respect to the number of samples in the Gaussian component (non-active samples) and propose a new Gaussian/Inverse Gamma mixture model (GIM) that it is faster and shows an improved level of robustness relative to sparse activations. The new method is validated using synthetic and resting state fMRI data.

Methods

Consider an Inverse Gamma distribution [5], parametrized using shape a and rate b, and approximate its first 2 moments [5] by its Gaussian equivalent. This results in a system of two equations: solving for a and b results in the method of moments for the Inverse Gamma distribution, namely $a = (m^2/v) + 2$, $b = m((m^2/v) + 1)$, where m and v are data mean and variance. Similar to what has been proposed for a GGM [1,3], the proposed GIM algorithm is learned from the standard EM for GMM [4], using the methods of moments (MM) for translating estimated means and variances into a and b parameters for the Inverse Gamma. Since the performance of both, the GGM [1,2] and the proposed GIM algorithms depends on the quality of the method of moments for estimation of the corresponding Gammas or Inverse-Gammas distributions respectively, we compare these MM estimations with pure ML estimations; for ML estimation of the Gamma distribution we used the algorithm proposed in [8] and we developed a new algorithm for ML estimation of the Inverse Gamma distribution that I) allows comparison with the MM and II) can be used to build a pure EM algorithm for learning a Gaussian/Inverse Gamma mixture (it is not further considered in this text).

Results

We first compare numerically the MM with the ML algorithms for learning Gamma or Inverse Gamma distributions: although there is a trade off between accuracy and speed, we conclude that MM provides a fast accurate solution better suited for iterative procedures as learning mixture-models. Then we compare the GGM vs the GIM model via simulated data: we compute ROC curves, and observe that at low active proportion of

voxels the GGM fits very well the right tail of the activation distribution independently of the nature of the underlying data, but, in fact, it might underestimate the noise resulting in an inflated false positive rates. The presented model for learning Gauss/Inverse Gamma mixture models is i) approximately 3 times faster than the previous state of the art GGM, and ii) results in robust and accurate model fits even at low activation levels. The validation on real fMRI data shows that both models provide similar thresholds in most cases. We also confirmed that in fact they can provide different noise estimations.

Conclusions

Although GIM might underestimate the signal if signal was Gauss or Gamma, it results in similar final thresholds when compared to the GGM model. However, it provides a better noise estimation at low activation number of voxels which can improve the quality of the final statistics. Ongoing work investigates the use of additional spatial information [7] as well as the use of mixture model model selection before the final statistical map computation.

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Computer vision applied to digital pathology: image search engine based on clinical similarity

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The advances in medical data digitalization are moving forward and new departments are converging into this trend. In standard medical procedures, medical images mainly from the Radiology Departments are acquired and stored in the Picture Archiving and Communication Systems - PACS. The Anatomical Pathology (AP) Departments are beginning to move along this path. A DICOM (Digital Imaging and Communications in Medicine) Standard is under construction but due to both the big size of the files (between 1GB and 6GB) as well as its multizooming nature, its progression is slow. In this scenario AP Departments and Biobanks are digitalizing their samples. In these huge databases, a search engine capable of locating a case not only by text on the clinical history but also on the real content of the physical sample is crucial. Computer vision techniques provide a sample characterization tool able of gathering the clinically relevant features present in each sample.

Power-law size distribution of activated avalanches - what do they really mean?

Ruedi Stoop

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Function and computational power of information-processing networks are determined by their topological network structure (connectivity), as well as by their node dynamics. An important class of real-world networks have nodes that are only occasionally activated and where the set of activated nodes depends predictably on the stimulation. For the cochlea, a prototypical example of this class, we demonstrate the natural emergence of avalanches with power-law size distributions. We show, moreover, that learning (or impairment of the hearing sensor) modify the power-law characteristics in the mildest conceivable manner and we exhibit how this affects the small-world property hosted by the unbiased networks. From our observations, we conclude that activation subnetworks of power-law size distributions characterize a fundamental ground-state of biological information processing. Our interpretation is corroborated and put into a wider context from making the connection from power-law distributions to the theory of dynamical systems formulated in the framework of the thermodynamic formalism of complex systems. Our approach also provides an unbiased, objective, measure of the loss of information resulting from an impairment of hearing sensor.

Dynamics of Information Storage, Transfer and Modification in the Cardiovascular System

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Cardiovascular regulation is accomplished through the combined activity of several physiological systems, including the cardiac, vascular and respiratory systems, which exhibit autonomous dynamics but also interact with each other in order to preserve the homeostatic function of the organism. This complex network of physiological interactions can be probed measuring physiological variables such as heart rate (HR), arterial pressure (AP) and respiratory flow (RF), and describing their joint beat-to-beat variability through suitable methods for multivariate time series analysis. In this study, the analysis of physiological networks is performed in the emerging framework of information dynamics, which provides entropy-based measures quantifying different aspects of how information is processed inside a network of interacting dynamic systems. Specifically, we consider two nested information decompositions which allow (i) to dissect the predictive information about an assigned "target" system into amounts of information stored in the system and information transferred to it from the "source" systems, and (ii) to evaluate how the information transferred to the target from multiple sources is modified according to mechanisms of redundancy and/or synergy. The decomposition (i) is performed quantifying information storage and transfer in terms of mutual information and conditional mutual information between the present of the target system and the past of the source systems; the decomposition (ii) is performed both making use of classical information concepts, whereby a single measure quantifying redundancy or synergy is obtained in terms of interaction information, and making use of partial information decomposition, whereby independent measures of redundancy and synergy are defined together with measures of the ?unique information? provided about the target separately by each source. Computing all the considered information measures under the linear Gaussian assumption, we first perform a simulation study in which realistic HR, AP and RF processes are generated and the properties of information storage, transfer and modification are studied as a function of the simulation parameters. Then, the framework is applied to the variability series of HR, systolic AP and RF measured from healthy subjects during standard experimental protocols (supine vs. upright position, spontaneous vs. paced breathing). Our results show that the different information decompositions lead to a thorough description of the physiological mechanisms of short-term cardiovascular regulation. In particular, we find that the measures of information storage, transfer and modification provide a new, integrated perspective for describing respectively the balance between sympathetic and parasympathetic activity, the cardiovascular and cardiorespiratory interactions, and the mechanisms of respiratory sinus arrhythmia.

Synergistic and redundant information sharing in Gaussian systems

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To fully characterize the information that two 'source' variables carry about a third 'target' variable, one must decompose the total information into redundant, unique and synergistic components. However Shannon's theory of information does not provide formulae to fully determine these quantities. I introduce some recently proposed approaches to addressing this, and apply them to systems of interacting Gaussian variables. Subject to reasonable axioms, I show that for a broad class of Gaussian systems: (i) redundancy reduces to the minimum information provided by either source variable, and is independent of correlation between sources; (ii) synergy is the extra information contributed by the weaker source when the stronger source is known, and can either increase or decrease with correlation between sources. I demonstrate that very simple Gaussian systems can exhibit net synergy, i.e. have the information carried jointly by both sources be greater than the sum of informations carried by each source individually. I discuss implications for measures of information transfer and information-based measures of complexity, both generally and within a neuroscience setting. Importantly, the formulae for separately quantifying synergy and redundancy on continuous time-series data pave the way for new, more detailed approaches to characterizing and quantifying information sharing amongst complex system variables.

Tracking slow modulations in synaptic gain using dynamic causal modelling: Validation in epilepsy

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In this work we propose a proof of principle that dynamic causal modelling can identify plausible mechanisms at the synaptic level underlying brain state changes over a timescale of seconds. As a benchmark example for validation we used intracranial electroencephalographic signals in a human subject. These data were used to infer the (effective connectivity) architecture of synaptic connections among neural populations assumed to generate seizure activity. Dynamic causal modelling allowed us to quantify empirical changes in spectral activity in terms of a trajectory in parameter space ? identifying key synaptic parameters or connections that cause observed signals. Using recordings from three seizures in one patient, we considered a network of two sources (within and just outside the putative ictal zone).Bayesian model selection was used to identify the intrinsic (within-source) and extrinsic (between-source) connectivity. Having established the underlying architecture, we were able to track the evolution of key connectivity parameters (e.g., inhibitory connections to superficial pyramidal cells) and test specific hypotheses about the synaptic mechanisms involved in ictogenesis. Our key finding was that intrinsic synaptic changes were sufficient to explain seizure onset, where these changes showed dissociable time courses over several seconds. Crucially, these changes spoke to an increase in the sensitivity of principal cells to intrinsic inhibitory afferents and a transient loss of excitatory?inhibitory balance.

Intermittency-based complexity measures in brain EEG data

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In recent years, many authors are finding interesting results regarding brain dynamics. In particular:

(i) Fingelkurts and Fingelkurts introduced the concept of Rapid Transition Processes (RTPs) that, in some conditions, can be identified in EEG records by means of event detection algorithms. These authors associate RTP occurrences with short-time transitions among different self-organized structures in the brain. Such structures were identified with neural assemblies formed in the brain neural network to carry out some specific function and/or to process some information.
(iii) On the other hand, Chialvo and co-workers found, from suitable fRMI data analyses, that the brain displays a behavior similar to that of critical phenomena. In fact, the network shows the same degree distribution of the Ising spin model at the critical temperature (second order phase transition). Other authors associate brain dynamics with Self-Organized Criticality (SOC).
(iii) In the field of complex systems it is recognized that complexity is not only associated with long-range correlations of emerging self-organized structures, but also with an intermittent behavior identified with a birth-death process of self-organization in which the inter-event times are distributed according to a inverse power-law (fractal intermittency). This condition is also denoted as Temporal Complexity.

In this talk we will show that:
(a) critical dynamics was found to be consistent with fractal intermittency [Contoyiannis and Diakonos];
(b) the intermittency features can be exploited to define a (temporal) complexity index that can be used to define a complexity measure of complex systems and, in particular, of brain dynamics;
(c) the intermittency-based complexity measure based is associated with the presence of absence of integrated dynamics in the brain and, then, it is proposed as a possible measure of consciousness.

Regarding point (b) we will discuss some applications on real EEG data in different conditions (wake, sleep). The last point (c) will be explained by means of a simple stochastic model that is able to explain the absence of consciousness as the decrease of integration and the emergence of a segregated brain dynamics.

Experiments in Neuronal Cultures: Exploring Open Questions in Physics and Medicine

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The major dynamical features of a neuronal network are shaped by the underpinned neuronal 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 dynamics-connectivity relation, neuronal cultures have emerged as remarkable systems given their accessibility and easy manipulation [1]. In our group we study spontaneous activity in diverse configurations of neuronal cultures as model systems for Physics, Neuroscience and Medicine. In the experiments, we monitor spontaneous activity using calcium ?uorescence imaging, which allows the detection of neuronal firing events with both high temporal and spatial resolution [2,3]. The detailed analysis of the recorded activity in the context of network theory, information theory and non-linear physics allows for the quantification of important phenomena, including the repertoire of activity patterns [2,3], functional connectivity [3], or the resilience of the network to damage [3]. The talk will illustrate the potential of using several interdisciplinary tools to investigate these phenomena, and how they can be further exploited to investigate in vitro specific diseases such as Sanfilippo or Alzheimer's.

References

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