BCAM Workshop
Quantitative Biomedicine for Health and Disease
Bilbao, February 24-25, 2016

BOOK OF ABSTRACTS

Organizers:

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- Jesus Cortes
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Speakers:

1. Paolo Bonifazi (Ikerbasque, Spain)

2. Cesar Caballero (BCBL, Spain)

3. Daniela Calvetti (Case Western Reserve University, Cleveland, USA)

4. Dante Chialvo (Conicet, Buenos Aires, Argentina)

5. Mauro D'Amato (Ikerbasque, Spain, and Karolinska Institute, Sweden)

6. Lulu Ritchie (Imperial College, UK)

7. Iñigo Gabilondo (BioCruces Health Research Institute, Spain)

8. Eugenio Iglesias (BCBL, Spain)

9. Banafshe Larijani (Ikerbasque, Spain)

10. Jose Ignacio Lopez (Cruces University Hospital, Spain)

11. Rafael Molina Soriano (University of Granada, Spain)

12. Maria Perez Zabalza (IDIBAPS Barcelona, Spain).

13. Alessandro Veneziani (Emory University, Atlanta, USA)

Program

Wednesday, February 24, 2016

9:00: Registration

9:15-9:30. Opening.

9:30-13:00   Session 1

   Chairman: *Luca Gerardo-Giorda*

     09:30-10:15 **Jose Ignacio Lopez**
     Intratumor heterogeneity: a simple approach to complexity

     10:15-11:00 **Mauro D'Amato**
     The genetics of irritable bowel syndrome; whatever that means...

     11:00-11:30. *Coffee Break*

     11:30-12:15 **Banafshe Larijani**
     Oncoprotein activation and dynamics in Cancer - a quantitative imaging approach

     12:15-13:00 **Alessandro Veneziani**
     Patient-Specific Numerical Modeling in the Clinical Practice: Mathematical Challenges of Computer Aided Clinical Trials

13:00-14:30 *Lunch*

14:30-18:00   Session 2

   Chairman: *Sebastiano Stramaglia*

     14:30-15:15 **Dante Chialvo**
     Physiological healthy dynamics is critical, a novel view

     15:15-16:00 **Lulu Ritchie**
     Airway modeling from the clinical perspective

     16:00-16:30 *Coffee Break*

     16:30-17:15 **Paolo Bonifazi**
     Structural-functional brain resting-state subnetworks: identification, description and application as biomarkers

     17:15-18:00 **Maria Perez Zabalza**
     Slow oscillations: laminar dynamics and role of thalamus

20:45 *Social dinner*

Thursday, February 25, 2016

9:30-13:45   Session 3

Chairman: *Jesus M. Cortes*

09:30-10:15 **Rafael Molina Soriano**
Probabilistic Modeling of Crowdsourcing Problems and applications to large biomed datasets

10:15-11:00 **Cesar Caballero**
The power of haemodynamic deconvolution for mapping brain dynamics with BOLD functional MRI

11:00-11:30. *Coffee Break*

11:30-12:15 **Daniela Calvetti**
A window on the functioning brain: iterative solvers meet Bayesian inference to solve the inverse problem of magnetoencephalography (MEG).

12:15-13:00 **Eugenio Iglesias**
Atlas construction and adaptive segmentation of the hippocampal substructures in brain MRI using ex vivo imaging and Bayesian inference

13:00-13:45 **Iñigo Gabilondo**
Quantitative imaging of the retina as a biomarker of neurodegenerative diseases

13:45-14:45 *Lunch*

14:45-15:00. Closing.

Abstracts

Intratumor heterogeneity: a simple approach to complexity

Jose Ignacio Lopez

Cruces University Hospital, Bilbao, Spain

Intratumor heterogeneity is an inherent process in the development of cancer. This heterogeneity follows in most cases a branched pattern of evolution, with different cell clones evolving independently along the time within different areas of the same tumor. The identification of this spatial and temporal diversity is crucial nowadays in terms of prognosis and treatment of patients. Clear cell renal cell carcinoma is a good example of a highly heterogeneous neoplasm, and this peculiarity makes difficult the implementation of successful treatment strategies. In the event the tumor cannot be totally studied due to its big size, pathologists decide which parts must be sampled for analysis. For such a purpose, pathologists follow internationally accepted protocols. On the light of the last findings, however, current sampling protocols seem to be insufficient for detecting intratumor heterogeneity with the expected reliability. This fact is especially concerning now that targeted therapies appear as a promising alternative to improve patient survival. We have developed an alternative method that enhances the detection of intratumor heterogeneity without increasing costs. This method is supported by a modelling approach in process of clinical validation.

The genetics of irritable bowel syndrome; whatever that means...

Mauro D'Amato

Ikerbasque, Spain, and Karolinska Institute, Sweden

Irritable bowel syndrome (IBS) and other functional gastrointestinal disorders (FGID) are common conditions of unknown etiology, and symptom-based criteria are currently the sole nosological tools for their clinical classification. Major insight into FGID pathophysiology is needed and, in recent years, increasing hope has been put on genetic research for the identification of causative pathways. A heritable component has emerged from epidemiological studies, but unequivocal risk genes have not yet been identified, possibly due to the relatively small sizes of existing patient cohorts and the difficulty in defining a common reliable study phenotype. Thousands of genetic variants have been undoubtedly linked to human disease through genome-wide association studies (GWAS), and we must adopt these powerful hypothesis-free approaches also in IBS/FGID, to begin to define their genetic architecture. Recently, we hypothesized that powerful approaches may include the study of large general population samples, where existing genotypic and phenotypic information may be exploited for gene-hunting efforts in IBS, with considerable gain in sample homogeneity and size. Results from our GWAS and meta-analysis efforts in large multi-national population-based cohorts will be presented and discussed in relation to the hardles of studying the genetic architecture of complex and heterogenous conditions like IBS.

Oncoprotein activation and dynamics in Cancer - a quantitative imaging approach

Banafshe Larijani

Cell Biophysics Laboratory, Ikerbasque Basque Foundation for Science, Unidad de Biofsica (CSIC, UPV/EHU) and Research Centre for Experimental Marine Biology and Biotechnology (PiE), University of the Basque Country (UPV/EHU), Leioa, Spain

Currently there is a transition point in cancer research, towards a need for a more profound understanding of molecular heterogeneity in various types of tumours as well as a sensitive and specific quantitative methodology for analysis of the activation status of biomarkers. Therefore, we developed of an innovative, portable approach to assess proteomic heterogeneity as well as activation status of biomarkers, which is a crucial contribution to the field of cancer research. To date studies of endogenous proteins using various imaging tools have been limited due to the lack of sensitivity. Our methodology is able to identify molecular heterogeneity of an established oncoproteins, between different regions of interest within the same tumour core and between various cores within the same patient. We have sought to explore the clinical relevance and molecular mechanisms underlying the activation of oncoproteins in different carcinomas. Our findings have the potential of determining a quantification parameter for molecular heterogeneity with a high degree of specificity, a major advance in cancer proteomics and diagnosis.

Patient-Specific Numerical Modeling in the Clinical Practice: Mathematical Challenges of Computer Aided Clinical Trials

Alessandro Veneziani

Emory University, Atlanta, USA

Numerical simulations have been proven to be a terrific tool for enhancing knowledge and performing predictions when studying cardiovascular diseases since 20 years at least. However, the step of bringing numerical modeling into clinical practice needs to be completed yet. In fact, beyond the numerous proofs of concept and the extraordinary advancements in image processing and numerical techniques, there are aspects that still prevent a massive use of mathematics as a decision-making support for clinicians. Nevertheless, Computer Aided Clinical Trials (CACT), i.e. clinical studies featuring a significant contribution coming from numerical simulations, are nowadays an emerging reality bringing the role of Cardiovascular Mathematics beyond the proof-of- concept stage. In this seminar, we will present some examples with significant challenges in (semi-automated) image processing and computational cost reduction. In particular, we will consider the reconstruction and the numerical simulation of patient-specific coronaries treated with bioresorbable stents and numerical techniques recently introduced based on the so-called "Hierarchical Model Reduction" (HiMOD). The latter is a smart combination of different numerical approximation methods (Finite Elements, Spectral Methods, Isogeometric Analysis) specifically customized for flows in pipe-like domains. A particular formulation of this approach, called ?Transverse Enriched Pipe Elements Method? has been recently proved to outperform classical finite element methods in simulating blood flow in coronary arteries.

Physiological healthy dynamics is critical, a novel view

Dante Chialvo

CONICET, Buenos Aires, Argentina

Human physiology is plenty of examples in which healthy performance is associated with the notion of flexibility and, conversely, pathology with rigidity. In the same direction, healthy dynamics in organs and systems, exhibits a peculiar mix of order and disorder, while the excess of either one, usually, implies a disease. These intuitive ideas have been recently formalized in the context of statistical physics, more specifically with the notion of criticality and phase transitions. In this talk we will offer an overview of our recent literature from brain science to molecular biology which support the value of this novel view. Papers and background information: www.chialvo.net

Airway modeling from the clinical perspective

Lulu Ritchie[1], Denis J. Doorly[1]

[1] Imperial College, London, UK

The talk describes recent progress in applying computational modeling to the upper airways. The work is discussed from the perspective of the clinician who seeks the best means to treat a large range of conditions. Three examples of problems of importance for airway surgeons are first outlined to illustrate the general area of interest and to indicate where computer-based methods could provide useful input to basic pathophysiological understanding, to clinical decision making and to the assessment of clinical outcomes

Taking as a specific example that of the nasal airways, the techniques used to transform image data into a computational model are reviewed. The nose affords a severe challenge for the definition of the airspace using current imaging techniques and serves to highlight generic problems in computer-based modeling applied to organs: the accuracy and uncertainty in the derived model and model-based predictions. The results of preliminary explorations of this topic are described. The overall purpose of the presentation is to stimulate further discussion of appropriate techniques to be applied to this area.

Structural-functional brain resting-state subnetworks: identification, description and application as biomarkers

Paolo Bonifazi[1], Ibai Diez[1], Iaki Escudero[1,2], Beatriz Mateos[1,2], Miguel A. Muoz[3], Sebastiano Stramaglia[1,4,5], and Jesus M Cortes[1,5,6]

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Elucidating the intricate relationship between brain structure and function, both in healthy and pathological conditions, is a key challenge for modern neuroscience. Recent progress in neuroimaging has helped advance our understanding of this important issue, with diffusion images providing information about structural connectivity (SC) and functional magnetic resonance imaging shedding light on resting state functional connectivity (rsFC). In this work, we adopted a complex networks approach, relying on modular hierarchical clustering, to study together SC and rsFC datasets gathered independently from healthy human subjects. By employing the template of hierarchical modular organization derived from structural data to represent the resting state functional one and vice versa, we searched for the optimal common partition shared by structure and function by maximizing a novel quantity, that we dub ?cross-modularity?. This procedure allows the extraction of an optimal partition that we uncovered divides the brain into distinct subnetworks that we refer to as common ?structure-function modules? (SFMs), representing a coarse-grained skeleton of the brain, which is largely shared by structure and function. First, we describe the emerging common structure - function modules (SFMs) and compare them with commonly employed anatomical or functional parcellations. Secondly, we use SFMs to characterize aging impact on brain networks. Specifically, by looking at the variation of the inter- and intra- module connectivity as a function of age, we show how a multiple linear regression model can describe global brain networks aging. In conclusion, our results show how the resting-state brain activity is shaped by the existence of structural-functional subnetworks whose interplay and connectivity varies as a function of age.

Reference

Diez I., Bonifazi P.,Escudero I., Mateos B., Muoz M., Stramaglia S., Cortes J. A novel brain partition highlights the modular skeleton shared by structure and function. Sci Rep. 2015 Jun 3;5:10532. doi: 10.1038/srep10532.

Slow oscillations: laminar dynamics and role of thalamus

Maria Perez-Zabalza[1], M. Mattia[2], N. Tort-Colet[1], MV. Sanchez-Vives[1,3]

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The spontaneous neuronal activity in anesthetized or during slow wave sleep (SWS) is organized in a slow (1 Hz) corticothalamic rhythmic pattern consisting of alternating high-firing rate Up and almost quiescent Down states ([11]). This activity propagates preferentially from frontal areas in an anteroposterior direction ([5, 7, 12]). There is still some debate about whether Up state onsets during slow oscillations (SO) are driven by cortico-cortical synaptic interactions ([11, 9, 8, 2, 12, 1]), or if they are due to the interplay between thalamic nuclei and cerebral cortex ([4, 6, 3, 10]). Here, we studied the laminar functional dynamics of SO in the visual cortex of ketamine/medetomidine anesthetized rats and found that columnar activation during SO initiates in layer 6 and spreads upward towards layer 5 and the cortical surface. Threshold-like activation of layer 5 persisted for short Up states after layer 6, giving rise to a hysteresis loop. The inactivation of LGN (Lateral Geniculate Nucleus) by means of TTX injection, only mildly reduced infragranular excitability without affecting the columnar activation pattern observed under control condition, and thus reserving for the first-order thalamus only a vicarious role in the generation of SO in visual cortex.

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Probabilistic Modeling of Crowdsourcing Problems and applications to large biomed datasets

Rafael Molina Soriano[1], A.K. Katsaggelos[2], E. Bessler[2], P. Ruiz[1]

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Supervised learning traditionally relies on a domain expert capable of providing the necessary supervision. The most common case is that of an expert providing annotations that serve as labels in classification problems. With the recent advent of social web services, data can now be shared and processed by a large number of users, as it happens for large public bio-banks. The use of labels from multiple annotators for the classification of data has become a very popular approach especially after the proliferation of crowdsourcing services in the last decade. The term ?crowdsourcing? was coined in 2006 by J. Howe to describe ?the act of taking a job traditionally performed by a designated agent (usually an employee) and outsourcing it to an undefined, generally large group of people in the form of an open call?. Amazon Mechanical Turk is an online system that allows the requesters to hire users from all over the world to perform crowdsourcing tasks. Galaxy Zoo is a website where visitors label astronomical images. Computer Aided Diagnosis (CAD) systems are built from labels assigned by multiple experts who come from a diverse pool. Very often, there is a lot of disagreement among the annotations. In this presentation we will review different approaches to solve the crowdsourcing-based classification problem. We will provide a probabilistic modeling of the problem, use Bayesian inference to find its solution and provide answer to the following interesting related questions: which sample should be labelled next?, which annotator should label it?, and how shall we detect bad (spammer) annotators?

The power of haemodynamic deconvolution for mapping brain dynamics with BOLD functional MRI

Cesar Caballero Gaudes

BCBL - Basque Center on Cognition, Brain and Language, San Sebastian, Spain

Functional magnetic resonance imaging (fMRI) enables to noninvasively map in space and time the hmodynamic response following neuronal activations through the blood-oxygenation level dependent (BOLD) effect. Typical fMRI data analysis is performed with confirmatory approaches to reveal voxels whose time series exhibit statistical evidence for a hypothetical task-related BOLD response, which thus require accurate timing descriptors of the neuronal events. In this talk I will present several recent methods that aim at mapping the brain's response in space and time without prior timing knowledge. Based on the numerical deconvolution of the haemodynamic response, these methods benefit from modern sparsity promoting regularization estimators, from standard L1-norm based estimators such as LASSO and Dantzig Selector to hierarchical structured sparsit and spatio-temporal methods based on generalized total variation. Beyond mathematical caprices, I will argue that these methods can serve as useful tools to explore the dynamics of brain function while executing a task or at rest, even at temporal resolution of single events and in individual subjects. Our results demonstrate that the proposed methodologies would enable a finer evaluation of between-subject differences in functional connectivity patterns measured with BOLD fMRI and allow the characterization of brain states reflecting cognitive processes, intrinsic neuronal fluctuations, and potentially the identification of signatures of disorder.

A window on the functioning brain: iterative solvers meet Bayesian inference to solve the inverse problem of magnetoencephalography (MEG).

Daniela Calvetti

Case Western Reserve University, Cleveland, Ohio, USA

The estimate of electromagnetic cerebral activity from measurements of the magnetic fields outside the head is notoriously challenging inverse problems. In this talk we formulate the problem within the Bayesian framework, introduce a hierarchical conditionally Gaussian prior model with a physiologically inspired component to take into account preferred directions of source currents. The hyper-parameter vector consists of prior variances of the dipole moments, assumed to follow a non-conjugate gamma distribution with variable scaling and shape parameters. A point estimate of both dipole moments and their variances are computed using a globally convergent iterative alternating sequential (IAS) updating algorithm. The numerical implementation uses a Krylov subspace iterative linear solver equipped with statistically inspired preconditioning and a suitable termination rule. The shape parameters of the model are shown to control the focality, and furthermore, using an empirical Bayes argument, it is shown that the scaling parameters can be naturally adjusted to provide a statistically well justified depth sensitivity scaling. The validity of this interpretation is verified through computed numerical examples. Preliminary results of a systematic sensitivity and specificity testing suggest the superiority of this approach to that of existing software, in particular in deeper brain regions.

Atlas construction and adaptive segmentation of the hippocampal substructures in brain MRI using ex vivo imaging and Bayesian inference

Eugenio Iglesias

BCBL - Basque Center on Cognition, Brain and Language, San Sebastian, Spain

Thanks to the absence of motion artifacts, ex vivo MRI enables us to use very long scanning times that yield ultra high resolution images. These images enable us in turn to create very detailed manual delineations of the brain at the substructure label. However, due to death and fixation, contrast properties of ex vivo MRI are very different from those of in vivo scans, which makes registration (and thus direct registration-based segmentation) unfeasible. In order to overcome this limitation, we decouple the modeling of the anatomy from the image formation process. The prior knowledge on the anatomy, which is learned from the manual segmentations using Bayesian inference, is encoded in a probabilistic atlas, which is described as a tetrahedral mesh endowed with a deformation model. The image formation process is assumed to be a Gaussian mixture model conditioned on the hidden, underlying segmentation. Given the generative model, automated segmentation of a MRI scan can be cast as a Bayesian inference problem. Since the Gaussian parameters are learned directly from the scan to analyze, the method is adaptive to MRI contrast, and generalizes immediately to multimodal data. Results on the construction of an atlas of the hippocampal substructures will be presented, along with a volumetric analysis of the hippocampi of a population with Alzheimer?s disease.

Quantitative imaging of the retina as a biomarker of neurodegenerative diseases

Iñigo Gabilondo

BioCruces Health Research Institute, Bilbao, Spain

Visual symptoms and higher order visual-spatial abnormalities are frequent in several common neurodegenerative diseases such as multiple sclerosis, Parkinson?s disease and Alzheimer?s disease. In fact, visual dysfunction and visual pathway damage have a demonstrated impact in their activities of daily living and cognitive disability. However, visual problems are commonly underdetected or underconsidered in the clinical routine of neurological care, not only those related to the damage of visual pathway but also those related to potentially treatable opthtalmological conditions. In the last decade, modern ophthalmological imaging techniques such as optical coherence tomography (OCT), OCT angiography, funds autofluorescence and adaptive optics scanning laser ophthalmoscopy (ASLO) have provided high and ultra-high resolution images of the retina in several neurological conditions, unveiling new and exciting insights about the involvement of visual system in neurodegenerative diseases. These techniques are now demonstrating their potential to identify biomarkers of neurodegeneration that may improve the precision in diagnosis and prognosis and promote the development of neuroprotective therapies in most disabling neurological disorders. Thanks to the development of these non-invasive imaging techniques, the retina, a highly specialized component of the central nervous system, is now considered a true window to brain diseases.

<u>NOTES:</u>

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