# BCAM Workshop
# Quantitative Biomedicine for Health and Disease
# Bilbao, February 21-22, 2017

# BOOK OF ABSTRACTS


**Organizers:**

- Luca Gerardo-Giorda
  BCAM - Basque Center for Applied Mathematics, Bilbao, Spain
- Jesús Cortés
  BioCruces Health Research Institute, Bilbao, Spain
- Sebastiano Stramaglia
  INFN, University of Bari, Italy
- Nicole Cusimano
  BCAM - Basque Center for Applied Mathematics, Bilbao, Spain

## Speakers:

1. Jean Bragard (U. Navarra)
2. Oscar Camara Rey (U. Pompeu Fabra)
3. Marina de Tommaso (U. Bari)
4. Adelaide de Vecchi (King's College)
5. Ibai Diez (BioCruces Health Research Institute)
6. Luca Faes (U. Trento)
7. Jean-Frédéric Gerbeau (INRIA)
8. Plamen Ch. Ivanov (Boston University and Harvard Medical School)
9. Julia Kroos (BCAM)
10. Daniele Marinazzo (U. Ghent)
11. Pandelis Perakakis (U. Granada)
12. José Luis Pons (Inst. Cajal, CSIC)
13. Mark Potse (U. Bordeaux)
14. Javier Rasero (U. Bari)
15. Javier Saiz Rodriguez (U. Politécnica Valencia)
16. Mariano Vázquez (Barcelona Supercomputing Center)

# Program

## Tuesday, February 21, 2017

**8:30 Registration**

**8:50-9:00 Opening**

**9:00-13:30 Session 1 - Heart modeling and methods**

**Chairman:** *Luca Gerardo-Giorda*

09:00-10:00 **Javier Saiz Rodriguez**
*Digital heart. Application to the study of cardiac arrhythmias*

10:00-11:00 **Mark Potse**
*Patient-specific modeling to understand cardiac disease*

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

11:30-12:30 **Jean-Frédéric Gerbeau**
*Modeling variability in cardiac electrophysiology*

12:30-13:30 **Adelaide de Vecchi**
*Image-based patient-specific modelling for prediction of ventricular haemodynamics after mitral valve replacement*

**13:30-14:30 Lunch**

**14:30-18:00 Session 2 - Brain modeling and methods**

**Chairman:** *Jesús Cortés*

14:30-15:30 **José Luis Pons**
*Hybrid Neuroprosthetics and Neurorobotics: assessment and associative therapies*

15:30-16:00 **Ibai Diez**
*Neuroimage connectivity methods and brain injury*

16:00-16:30 **Javier Rasero**
*Consensus clustering approach to group brain connectivity matrices*

**16:30-17:00** *Coffee Break*

17:00-18:00 **Daniele Marinazzo**
*Sensitivity of the resting-state haemodynamic response function estimation to autonomic nervous system fluctuations*

**20:45 Social dinner**

## Wednesday, February 22, 2017

**9:00-13:30 Session 3 - Heart modeling and methods**

**Chairman:** *Nicole Cusimano*

09:00-10:00 **Oscar Camara Rey**
*Mind the translational gap: from sophisticated computational tools to more quantitative clinical routine*

10:00-11:00 **Mariano Vázquez**
*Cardiovascular organ level simulations on supercomputers*

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

11:30-12:30 **Pandelis Perakakis**
*How exercising the heart makes a brighter brain: In search of new methodological tools to study brain-heart interactions in the context of physical activity*

12:30-13:00 **Julia Kroos**
*Patient-specific modeling of the cortical spreading depression*

13:00-13:30 **Jean Bragard**
*Comparison of defibrillation protocols through a simple cardiac dynamic model*

**13:30-14:30 Lunch**

**14:30-18:00 Session 4 - Brain modeling and methods**

**Chairman:** *Sebastiano Stramaglia*

14:30-15:30 **Plamen Ch. Ivanov**
*The new emerging field of Network Physiology: from complex dynamics of individual systems to networks of organ interactions and the Human Physiolome*

15:30-16:30 **Marina de Tommaso**
*Neurophysiological and clinical correlates of migraine aura*

**16:30-17:00** *Coffee Break*

17:00-18:00 **Luca Faes**
*Multiscale analysis of information dynamics and the brain-heart interactions in wake conditions and during sleep*

**18:00-18:10 Closing**

# Abstracts

# Digital heart. Application to the study of cardiac arrhythmias

Javier Saiz Rodriguez

Institute for Research and Innovation in Bioengineering, Universitat Politécnica de Valencia, Spain

Multi-scale heart models (Digital Heart) are powerful tools for studying the cardiac electrical activity at cellular, tissue and whole heart level, under normal and pathological situations. They allow for in-depth understanding the electrophysiology of the heart and contribute to improve strategies of therapy, like e.g. ablation procedures and to optimize the design of medical devices like e.g. ablation catheters and the development of drugs. In this talk, different advances of our group in the field of computational models of the heart will be presented and will focus on pathological situations as ischemia, heart failure and atrial fibrillation.

# Patient-specific modeling to understand cardiac disease

Mark Potse

Inria Bordeaux and IHU Liryc - Cardiac Arrhythmia and Modeling Institute, Bordeaux, France

It is more and more recognized that different patients react differently on the same treatment. As a result there is a rising interest in patient-tailored numerical modeling. It is hoped that models tailored to the patients characteristics will be able to predict how this specific patient will react on a treatment, so that he best treatment option can be chosen. I think that this is a very ambitious target and would like to point out a scientifically very interesting side-effect of patient-tailored modeling attempts: the possibility to validate, or rather invalidate, our models using the most relevant data available: those of the actual patients for whom we are doing our modeling work. In this presentation I would like to show some results of my attempts to reproduce ECG and intracardiac electrogram data in two groups of patients with very different diseases: heart failure and sudden-cardiac-death syndromes. While the results of these studies are inconclusive, they show how this approach can lead to interesting new insights about the models as well as about the measured data.

# Modeling variability in cardiac electrophysiology

Jean-Frédéric Gerbeau, Damiano Lombardi, and Eliott Tixier

Inria Paris and Laboratoire JL Lions, UPMC, France

Many phenomena are modeled by deterministic differential equations, whereas the observation of these phenomena, in particular in life science, exhibit an important inter-subject variability. We will address the following question: how the model can be adapted to reflect the variability observed in a population?

We will present a non-parametric and non-intrusive procedure based on offline computations of the deterministic model. The algorithm infers the probability density function of uncertain parameters from the matching of the observable statistical moments at different points in the physical domain. This inverse procedure is improved by incorporating a point selection algorithm that both reduces its computational cost and increases its robustness.

The method will be illustrated for different models, based on Ordinary or Partial Differential Equations. In particular, applications to experimental data set in cardiac electrophysiology will be presented.

# Image-based patient-specific modelling for prediction of ventricular haemodynamics after mitral valve replacement

Adelaide de Vecchi[1], David Nordsletten[1], Vinayak Bapat[2], Ronak Rajani[3], and Steven Niederer[1]

[1] Dept. of Biomedical Engineering, King's College London, St Thomas' Hospital, London, UK
[2] Dept. of Cardiothoracic Surgery, Guy's and St Thomas' NHS Foundation Trust, London, UK
[3] Dept. of Cardiology, Guy's and St Thomas' NHS Foundation Trust, London, UK

*Background.* The progress achieved by transcatheter mitral valve replacement (TMVR) has made bioprosthetic valve implantation available to patients too frail to withstand open-heart surgery. The volume of TMVR interventions has increased considerably over the years, exposing the necessity to identify guidelines for the device choice and positioning. The implantation of a bioprosthetic valve affects left ventricular haemodynamics and can lead to severe complications, such as left ventricular outflow obstruction, resulting, in turn, in the need for reoperation with associated risks [1]. Further, ventricular function, anatomy, and degree of subvalvular calcification can vary considerably between patients, meaning that a patient-specific approach is preferable to population-based guidelines when addressing this problem [2].

*Methodology.* This study proposed a novel way to assess and predict the ventricular haemodynamic response using image-based personalised computer models of computational fluid dynamics (CFD). The models are personalised based on the patient anatomy and wall motion, from multi-phase Computer tomography datasets (CT), and the transvalvular flow from Doppler echocradiography datasets, all acquired before intervention [3]. A baseline model pre-TMVR is created for each patient. Subsequently, three different sizes of bioprosthesis are added to the model to quantify changes in pressure gradients, outflow obstruction, and particle pathways.

*Results and conclusions.* CFD simulations of 8 patients showed some clear trends. The pressure gradient in the outflow tract decreases moderately with increasing obstruction, due to a pressure recovery area located near the narrowing due to the valve frame protruding in the aortic outflow tract. This is not sufficient to counteract the significant increase in the pressure gradient from the apex of the ventricle to the aortic valve, which increases significantly with the degree of obstruction. The pressure difference required to eject the flow is thus proportional to the degree of obstruction, suggesting a less energy efficient process. Similarly, the particle pathways are altered by the presence of the valve, with less particles able to enter and leave the ventricle within one cycle (direct flow) and a spatial displacement of the residual volume of blood in the cavity at the end of the cycle as the degree of obstruction increases. In patients with dilated cavities, where the valve frame does not obstruct the outflow, a decrease in the diastolic pressure gradients is reported with higher valve frames, implying that the cylindrical shape of the valve can facilitate the inflow of blood when not associated in partial blockage of the outflow. Overall the introduction of a bioprosthetic valve generates significant changes in pressure and flow behaviour when associated with a degree of obstruction in the outflow tract greater than 30%.

## References

[1] Bapat V, Pirone F, et al. Factors influencing left ventricular outflow tract obstruction following a mitral valve-in-valve or valve-in-ring procedure, part 1, *Catheterization and Cardiovascular Interventions*, 86(4):747-760, 2015.

[2] Blanke P, Naoum C, et al. Multimodality Imaging in the Context of Transcatheter Mitral Valve Replacement: Establishing Consensus Among Modalities and Disciplines, *JACC. Cardiovasc Imag*, 8(10):1191-208, 2015.

[3] De Vecchi A, Nordsletten D, et al. A novel methodology for personalized simulations of ventricular hemodynamics from noninvasive imaging data, *Comp Med Imag and Graph*, 51:20-31, 2016.

# Hybrid Neuroprosthetics and Neurorobotics: assessment and associative therapies

José Luis Pons

Grupo de Neuro-Rehabilitación, Instituto Cajal, Consejo Superior de Investigaciones Científicas, Madrid, Spain

Wearable exoskeletal robotics (Neurorobots) can play a role in assessment, rehabilitation and functional compensation in a number of neurological conditions, e.g. hemiplegia post stroke, paraplegia or quadriplegia post SCI, which lead to severe motor impairments. However, in general, the musculoskeletal system after the insult is preserved and Motor Neuroprostheses (MNPs) can also be considered as valid technologies for rehabilitation and functional compensation. In view of the pros and cons of both technologies, our current approach at the Neural Rehabilitation Group (Cajal Institute, CSIC) is to study the combination of neurorobots (NRs) and motor neuroprostheses for rehabilitation and functional compensation of motor disorders of neurological origin. In this concept, three players are to be combined for an optimal intervention, i.e. the patients with their latent motor capabilities, and the two technologies NRs and MNPs. Association of the intervention to the motor status of patients is paramount, and this implies a precise assessment based on these technologies.

# Neuroimage connectivity methods and brain injury

Ibai Diez

BioCruces Health Research Institute, Bilbao, Spain

Magnetic Resonance Imaging has emerged as a key tool to study the organization of brain functional and structural networks and their alterations in the pathological brain. In this talk, I will introduce basic neuroimage methods to build brain networks, describing the types of used images and the main processing steps. Finally, I will briefly talk on two projects where these methods were applied to understand brain network disconnection and reorganization after traumatic brain injury.

# Consensus clustering approach to group brain connectivity matrices

Javier Rasero

BioCruces Health Research Institute, Bilbao, Spain
Dept. of Physics and INFN, University of Bari, Bari, Italy

In the supervised analysis of human connectome data, subjects are usually grouped by high-level clinical categories (e.g., patients and controls). However, the population of healthy subjects (as well as those of patients) is typically highly heterogeneous: clustering algorithms find natural groupings in the data, and therefore constitute a suitable technique for disentangling the heterogeneity that is inherent to many diseases and to the cohort of controls. Such an unsupervised classification may also be seen as a preprocessing stage, so that the subsequent supervised analysis might exploit the knowledge of the structure of data.

We propose here a new method, rooted on the consensus clustering paradigm developed in Complex Networks theory, where the connectivity pattern of each brain region is analyzed by a standard clustering algorithm and a consensus matrix is built by merging the partitions obtained in correspondence of each brain region.

The unsupervised strategy we propose here to group subjects, without using phenotypic measures, consists of (i) definition, for each node, of a distance matrix for the set of subjects (ii) clustering the distance matrix for each node, by k-medoids method (iii) build the consensus network from the corresponding partitions and (iv) extract groups of subjects by finding the communities of the consensus network thus obtained.

By analyzing publicly available data-sets, as well as a simulated toy system, we demonstrate that the proposed approach allows to robustly identify groups of subjects with similar connectomes, thus providing a partition of subjects beyond the measured labels associated to them.

# Sensitivity of the resting-state haemodynamic response function estimation to autonomic nervous system fluctuations

Daniele Marinazzo

Dept. of Data Analysis, Faculty of Psychological and Pedagogical Sciences, Ghent University, Gent, Belgium

The haemodynamic response function (HRF) is a key component of the blood oxygen level-dependent (BOLD) signal, providing the mapping between neural activity and the signal measured with functional magnetic resonance imaging (fMRI). Most of the time the HRF is associated with task-based fMRI protocols, in which its onset is explicitly included in the design matrix. On the other hand, the HRF also mediates the relationship between spontaneous neural activity and the BOLD signal in resting-state protocols, in which no explicit stimulus is taken into account. It has been shown that resting-state brain dynamics can be characterized by looking at sparse BOLD events, which can be retrieved by point process analysis. These events can be then used to retrieve the HRF at rest. Crucially, cardiac activity can also induce changes in the BOLD signal, thus affecting both the number of these events and the estimation of the haemodynamic response. In this study, we compare the resting-state haemodynamic response retrieved by means of a point process analysis, taking the cardiac fluctuations into account. We find that the resting-state HRF estimation is significantly modulated in the brainstem and surrounding cortical areas. From the analysis of two high-quality datasets with different temporal and spatial resolution, and through the investigation of intersubject correlation, we suggest that spontaneous point process response durations are associated with the mean interbeat interval and low-frequency power of heart rate variability in the brainstem.

# Mind the translational gap: from sophisticated computational tools to more quantitative clinical routine

Oscar Camara Rey

Information and Communication Technologies Department, Universitat Pompeu Fabra, Barcelona, Spain

Even with the deluge of data, knowledge and advanced technologies available nowadays, there is only a few examples of computational tools translated into a clinical environment and having an impact in patient management. Some of the main reasons hampering the daily use of these tools in hospitals include their high complexity and associated computational times, lack of a clear clinical question/need to answer or the difficulty to obtain measurements. In consequence, clinicians only have access to a limited number of computational tools that met the requirements (robustness, user-friendly, fast) for being used in clinical routine, quite often ending up with qualitative and user-dependent assessment of patient condition. In this talk I would review research and development works achieved in the PhySense research group at Universitat Pompeu Fabra aiming providing clinicians with more quantitative tools to support their medical decisions, including data processing and management tools, machine learning techniques, electrophysiological and fluid models.

# Cardiovascular organ level simulations on supercomputers

Mariano Vázquez

Barcelona Supercomputing Center (BSC), Barcelona, Spain

As a physical system, the human heart is the most beautiful challenge. It is multi-scale, multi-physics, transient, highly non-linear, full of uncertainties and controversial models, fully coupled, with scarce, unreliable and indirect experimental data to validate the models. From the computational mechanics point of view, to write a code to simulate the pumping action of the heart is one of the most difficult tasks one can find, so complex, that the efficient use of large computational resources is mandatory. In this talk we describe our research programme using our parallel software, Alya.

# How exercising the heart makes a brighter brain: In search of new methodological tools to study brain-heart interactions in the context of physical activity

Pandelis Perakakis and Daniel Sanabria

Centro de Investigación Mente, Cerebro Y Comportamiento, Universidad de Granada, Spain

Physical inactivity is a leading risk factor and a global pandemic that imposes annual economic costs of 80.4 billion Euros and results in over 500,000 deaths per year in the European region only. On the contrary, regular physical activity improves cardiovascular fitness and has shown to dramatically reduce a number of physical disorders. More recently, cardiovascular fitness was also associated with improved cognitive performance in healthy individuals. However, the mechanisms responsible for the cognitive benefits demonstrated by physically fit individuals are not well understood. To date, research has focused on anatomical changes induced by aerobic exercise in the cardiovascular system and the brain, but has overlooked the physiological brain-heart coupling mediated by the afferent and efferent pathways of the autonomic nervous system. In this talk, I will briefly review the research on the acute and long-term effects of aerobic exercise on brain structures related to cognitive performance, and focus on recent findings from our group suggesting improved brain-heart communication at the physiological level as a possible mechanism to explain the cognitive benefits of regular physical activity. I will attempt to engage the audience in a discussion on new conceptual and methodological frameworks for studying brain-heart dynamical coupling in the context of acute and chronic physical exercise.

# Patient-specific modeling of the cortical spreading depression

Julia M. Kroos

Basque Center for Applied Mathematics (BCAM), Bilbao, Spain

Migraine is a common disease in present day population and a third of the migraine patients suffers from migraine aura, perceptual disturbances preceding the typical headache. Cortical Spreading Depression (CSD), a depolarisation wave that originates in the visual cortex and propagates across the cortex to the peripheral areas, has been suggested as a correlate of visual aura by several studies. Until now little is known about the origin of this phenomenon and possible curative treatments. However, the complex and highly individual characteristics of the brain cortex suggest that the geometry might have a significant impact in supporting or contrasting the propagation of CSD. Accurate patient-specific computational models are thus fundamental to cope with the high variability in cortical geometries among individuals, but also with the conduction anisotropy induced in a given cortex by the complex neuronal organisation in the grey matter.

In order to study the role the geometry has in shaping the CSD, we introduce a distributed model for extracellular potassium concentration on a personalized brain geometry obtained from MRI imaging. Patient-specific conductivity tensors are derived locally from Diffusion Tensor Imaging (DTI) data and provide detailed information about the anisotropy and the electrical conductivity properties of the cortical tissue. Additionally, we introduce a multiscale PDE-ODE model that couples the propagation of the depolarisation wave associated to CSD with a detailed electrophysiological model for the neuronal activity to capture both macroscopic and microscopic dynamics. We study the traveling patterns of the CSD wave that indicate the effect of the geometry shape on the propagation behavior of the CSD. Our study reveals dynamical aspects of CSD, which, if applied to subject-specific cortical geometry, might shed some light on how to differentiate between healthy subjects and those suffering from migraine.

# Comparison of defibrillation protocols through a simple cardiac dynamic model

Jean Bragard

Dept. of Physics and Applied Mathematics, University of Navarra, Pamplona, Spain

Defibrillation is the standard clinical treatment used to terminate ventricular fibrillation. An electrical device delivers via a pair of electrodes a controlled amount of electrical energy in order to reestablish the normal heart rate. However, in order for the shock to be successful it is necessary to apply high energies, typically around 150 Joules for the transthoracic defibrillation. These high energy shocks have several side effects. There have been numerous attempts to reduce the defibrillation thresholds by, e.g., reversing the polarity of the shock during the defibrillation and optimizing the reversal time, waveform and duration of the shock.

In this talk we propose to evaluate the efficiency of different standard and non-standard protocols for defibrillation. To do this, we have used a simple numerical model. The model consists of a one-dimensional ring of cardiac tissue. The electrical behavior of the cardiac tissue is modeled through the bidomain model and a modified Beeler-Reuter system of differential equations are used for modeling the active properties of the cell membrane. The mechanisms of successful defibrillation were also analyzed and they revealed that the biphasic shocks were more efficient than monophasic shocks due to the higher level of tissue activation at high energy level.

## References

Bragard J. et al., *Chaos*, 23 (4):043119, 2013.

Bragard J. et al., *Physical Review E*, 92 (6):062919, 2015.

# The new emerging field of Network Physiology: from complex dynamics of individual systems to networks of organ interactions and the Human Physiolome

Plamen Ch. Ivanov

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Harvard Medical School and Division of Sleep Medicine, Brigham and Women Hospital, Boston, MA, USA

The human organism is an integrated network where complex physiological systems, each with its own regulatory mechanisms, continuously interact to optimize and coordinate their function. Organ-to-organ interactions occur at multiple levels and spatiotemporal scales to produce distinct physiologic states: wake and sleep; light and deep sleep; consciousness and unconsciousness. Disrupting organ communications can lead to dysfunction of individual systems or to collapse of the entire organism (coma, multiple organ failure). Yet, we know almost nothing about the nature of the interactions between diverse organ systems and their collective role in maintaining health. Through the prism of concepts and approaches originating in statistical and computational physics and nonlinear dynamics, we will present basic characteristics of individual organ systems, distinct forms of pairwise coupling between systems, and a new framework to identify and quantify networks of interactions among diverse organ systems. We will demonstrate how physiologic network topology and systems connectivity lead to integrated global behaviors representative of physiologic states and functions. We will discuss implications for further theoretical developments and practical applications within the context of the emerging field of *Network Physiology*, where physicists have a key role in uncovering basic principles and mechanisms. The presented investigations are initial steps in building a first atlas of dynamic interactions among organ systems and the *Human Physiolome*.

# Neurophysiological and clinical correlates of migraine aura

Marina de Tommaso

Università degli Studi di Bari, Bari, Italy

Migraine is an invalidating disorder of neurovascular origin. The pathophysiology of migraine is still under debate, though a better knowledge of mechanisms subtending attack onset may improve the therapeutical approach. Typical migraine aura is characterized by visual and sensory disturbances, which seem to be subtended by an electrophysiological phenomenon known as cortical spreading depression (CSD). CSD is a wave of complete neuronal and glial depolarization that, once initiated by a sufficiently strong stimulus, propagates centrifugally in gray matter irrespective of functional divisions and arterial territories. The correlation between the electrophysiological characteristics of this phenomenon and the clinical features of migraine aura and headache, including their response to treatments, are still an open question. It is still unclear if cortical spreading depression may be present also in migraine without aura attacks. A different state of cortical excitability and connectivity, would cause a different progression of CSD through the cortex, determining or not the subjective perception of sensory symptoms preceding headache. Genetic predisposition and epigenetic factors may account for the clinical phenotype toward low frequency migraine with aura forms or chronic migraine.

# Multiscale analysis of information dynamics and the brain-heart interactions in wake conditions and during sleep

Luca Faes

IRCS-FBK and BIOtech, Dept. of Industrial Engineering, University of Trento, Italy

In the study of complex physical and physiological systems represented by multivariate time series, an issue of great interest is the description of the system dynamics over a range of different temporal scales. A framework, for the analytical computation of information dynamics at different time scales, will be described as well as its application to analyze brain-heart interactions in wake and sleep conditions.

NOTES: