5th BCAM Workshop
Quantitative Biomedicine for Health and Disease
Bilbao, February 13 - 14, 2019

BOOK OF ABSTRACTS

Organizers:

- Luca Gerardo-Giorda
  BCAM - Basque Center for Applied Mathematics, Bilbao, Spain
- Jesús M. Cortés
  Biocruces Bizkaia, Bilbao, Spain
- Sebastiano Stramaglia
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Local organizing committee:

- Martina Conte
- Nicole Cusimano
- Julia M. Kroos
- Isabella Marinelli

Speakers

1. Paolo Bonifazi (Biocruces Bizkaia, Bilbao, Spain)
2. Eva Crosas-Molist (Queen Mary University of London, UK)
3. Maurizio De Pittà (BCAM, Bilbao, Spain)
4. Marina de Tommaso (Policlinico di Bari, Italy)
5. Bruce J. Gluckman (Penn State University, USA)
6. Daniele Marinazzo (Ghent University, Belgium)
7. Daniela Pietrobon (University of Padova, Italy)
8. Luigi Preziosi (Politecnico di Torino, Italy)
9. Juan Soler (Universidad de Granada, Spain)
10. Christina Surulescu (Technische Universität Kaiserslautern, Germany)

Program

Wednesday, February 13, 2019

9:30 - 9:50 **Registration**

9:50 - 10:00 **Opening and Welcome**

10:00 - 13:15 **Session 1 - Chair:** *Jesús M. Cortés*

10:00 - 10:45 **Daniele Marinazzo**
Modeling brain dynamics in brain tumor patients using The Virtual Brain

10:45 - 11:30 **Maurizio De Pittà**
Multistable neuron-glial networks in health and disease

11:30 - 12:00 *Coffee Break*

12:00 - 12:45 **Paolo Bonifazi**
The brain is always active: what spontaneous activity can tell us about the structure and (dys)function of brain circuitries

12:45 - 13:15 **Short talk: Antonio Jimenez-Marin**
New method for assessing functional connectivity of differentiated cognitive networks: application to multiorgan failure

13:15 - 14:30 **Lunch**

14:30 - 17:00 **Session 2 - Chair:** *Nicole Cusimano*

14:30 - 15:15 **Luigi Preziosi**
How can mathematical modelling support cancer research?

15:15 - 16:00 **Eva Crosas-Molist**
Targeting cytoskeletal dynamics as a therapeutic approach in cancer

16:00 - 16:30 *Coffee Break*

16:30 - 17:00 **Short talk: Andrea Trucchia**
Seeding and dispersal of planar microbial biofilms: a chance for modelling

20:45 / 21:00 **Social dinner**

Thursday, February 14, 2019

10:00 - 13:15 Session 3 - Chair: *Sebastiano Stramaglia*

10:00 - 10:45 **Bruce J. Gluckman**
Spreading depolarization happens spontaneously in models of epilepsy

10:45 - 11:30 **Marina de Tommaso**
Mapping pain-related EEG perturbation in high frequency range in migraine and non migraine subjects

11:30 - 12:00 *Coffee Break*

12:00 - 12:45 **Daniela Pietrobon**
Mechanisms of cortical spreading depression: insights from genetic mouse models of migraine

12:45 - 13:15 **Short talk: Gabriela Capo Rangel**
Multiscale coupling of electrophysiology, metabolism and hemodynamics in the neuron-astrocyte complex

13:15 - 14:30 Lunch

14:30 - 17:15 Session 4 - Chair: *Luca Gerardo-Giorda*

14:30 - 15:15 **Christina Surulescu**
Multiscale modeling of glioblastoma: the influence of the tumor microenvironment

15:15 - 16:00 **Juan Soler**
Glioblastomas and cell communication mediated by cytonemes

16:00 - 16:30 *Coffee Break*

16:30 - 17:00 **Short talk: Sebastiano Stramaglia**
Synergy as a warning sign of transitions

17:00 - 17:15 Closing remarks

Abstracts

Modeling brain dynamics in brain tumor patients using The Virtual Brain

Daniele Marinazzo[1], Hannelore Aerts[2], Michael Schirner[3], Ben Jeurissen[4], Dirk van Roost[2], Eric Achten[2] and Petra Ritter[5]

[1] Dept. of Data Analysis, Ghent Univ., Belgium
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Presurgical planning for brain tumor resection aims at delineating eloquent tissue in the vicinity of the lesion to spare during surgery. To this end, non-invasive neuroimaging techniques such as functional MRI and diffusion weighted imaging fiber tracking are currently employed. However, taking into account this information is often still insufficient, as the complex non-linear dynamics of the brain impede straightforward prediction of functional outcome after surgical intervention. Large-scale brain network modeling carries the potential to bridge this gap by integrating neuroimaging data with biophysically based models to predict collective brain dynamics. As a first step in this direction, an appropriate computational model has to be selected, after which suitable model parameter values have to be determined. To this end, we simulated large-scale brain dynamics in 25 human brain tumor patients and 11 human control participants using The Virtual Brain, an open-source neuroinformatics platform. Local and global model parameters of the Reduced Wong-Wang model were individually optimized and compared between brain tumor patients and control subjects. In addition, the relationship between model parameters and structural network topology and cognitive performance was assessed. Results showed (1) significantly improved prediction accuracy of individual functional connectivity when using individually optimized model parameters; (2) local model parameters can differentiate between regions directly affected by a tumor, regions distant from a tumor, and regions in a healthy brain; and (3) interesting associations between individually optimized model parameters and structural network topology and cognitive performance.

Multistable neuron-glial networks in health and disease

Maurizio De Pittà[1]

[1] Group of Mathematical, Computational and Experimental Neuroscience, BCAM, Bilbao, Spain

Astrocytes – a predominant cortical glial cell type – have been implicated in the active regulation of synaptic transmission, through modulation of either pre- or post-synaptic receptors by activity-depedent release of neurotransmitters also known as gliotransmitters. The need for gliotransmission and its possible implications in pathophysiology of the brain however remain elusive. Starting from a classical model of cortical neural networks, I will introduce some mathematical arguments to model gliotransmission, leveraging on the implications of these arguments on stability of neural dynamics. In particular, I will show how gliotransmitter-mediated increases of synaptic release could promote multistability, underpin emergence of oscillations, or exacerbate existing rhythmic activity promoting epileptiform neural dynamics. Biophysical conditions for existence of functional (or dysfunctional) gliotransmission will accordingly be discussed in connection with morphology of the neuron-glial tissue.

The brain is always active: what spontaneous activity can tell us about the structure and (dys)function of brain circuitries

Paolo Bonifazi[1,2]

[1] Biocruces-Bizkaia Health Resarch Institute, Bilbao, Spain

[2] Ikerbasque: The Basque Foundation for Science, Bilbao, Spain

Starting from evidence of how spontaneous activity is a shared property of multi-scaled neuronal circuitries, I will introduce the framework of complex networks to study the structure-function relationship of brain circuits, distinguishing among structural, functional and effective connectivity. In this framework, I will present multi-scale evidence of how neuronal spontaneous dynamics allows highlighting key features of structural-functional connectivity both in physiological conditions, where the fingerprint of functional modules and neuronal hubs ultimately emerges, and in pathological conditions, such as the ATM-KO cerebellar circuits, where impaired synchronizations emerge. Finally, I will show how astrocytic replacement can impact ATM-KO cerebellar circuits topology and restore neuronal synchronizations.

New method for assessing functional connectivity of differentiated cognitive networks: application to multiorgan failure

Antonio Jimenez-Marin[1]

[1] Computational Neuroimaging Lab, Biocruces Bizkaia Health Resarch Institute, Spain

Multiple Organ Dysfunction Syndrome (MODS) is a life-threating and potentially reversible condition that can affect patients admitted to Intensive Care Units (ICUs). It has been noted that patients who survive MODS with no apparent brain damage (NABD) frequently present long-term neurological, cognitive and neuropsychiatric defects. However, the changes to the brain that explain such disabilities are unclear. Here, we made use of state of the art methods in brain functional connectivity to compare between patients with NABD and healthy controls (HCs). We found that MODS patients presented significant hyperconnectivity (a node degree of the FC matrix increase) in the default mode network (DMN) towards three classes of networks: primary sensory (auditory, sensory-motor and visual); multimodal integration (dorsal and ventral attention); and higher order cognitive networks (fronto-parietal, executive control and language). Therefore, although these patients do not have an apparent structural damage after MODS, at the functional level, we found brain network alterations coexisting with hyperconnectivity of the DMN, that similar to what happens at the onset of other pathologies, might indicate a possible mechanism for brain compensation occurring after MODS.

How can mathematical modelling support cancer research?

Luigi Preziosi[1]

[1] Dipartimento di Scienze Matematiche, Politecnico di Torino, Italy

After a brief overview of the type of problems that can be encountered in medicine ad can profit from the expertise of mathematicians, the talk will focus on several examples deriving from the collaboration with cancer research centers and hospitals. They will deal with the vascular and invasive phase of tumour growth, including the formation of vascular networks and the interaction of invading cells with the surrounding environment. A glance on how this research can be applied to the construction of artificial tissues or in wound healing will also be given.

Targeting cytoskeletal dynamics as a therapeutic approach in cancer

Eva Crosas-Molist[1] and Victoria Sanz-Moreno[1]

[1] Barts Cancer Institute - Queen Mary University of London, UK

Metastasis and drug resistance are key problems in cancer management. To metastasise, tumor cells must move through tissues which requires cell motility, remodelling of cell-cell contacts, interactions with the extracellular matrix and survival at distant sites. Our lab is interested in how Rho GTPase signalling and cytoskeletal remodelling can control cell invasion, cell survival, metastatic success and therapy response. We are particularly interested in how cancer cells sense extracellular signals via their cytoskeleton and integrate the responses altering gene transcription to either invade, survive or respond to therapy. Our group is working on identifying physical and chemical cues that will aid in cancer progression via the crosstalk between the cytoskeleton and the nucleus. Furthermore, how cancer cells interact with the tumour microenvironment is key for tumour progression and dissemination. Therefore, another goal in the lab is to understand how the cytoskeleton in cancer cells affects cancer-stromal communication. The lab is highly multidisciplinary, as we use a combination of OMICs, state of the art microscopy, molecular and cellular biology, animal models and patient material. We have developed co-cultures and 3-Dimensional matrix imaging systems to analyse communication of cancer cells, epithelial/endothelial cells and immune cells, as well as interaction with the matrix. Our ultimate goal is to define if manipulations of the cytoskeleton of cancer cells will lead to improved efficacy of current therapeutic approaches in patients.

Seeding and dispersal of planar microbial biofilms: a chance for modelling

Andrea Trucchia[1]

[1] Group of Statistical Physics, BCAM, Bilbao, Spain

In this talk is proposed a novel modeling approach to study how mature biofilms spread and colonize newareas by predicting the formation and growth of satellite colonies generated by dispersing biofilms. This model provides the basis for better understanding the spatial and temporal evolution of dispersal cells, phenomenon that cannot, as yet, be predicted from knowledge of the genome. The model results were promising as supported by the experimental results. The proposed approach is modular, in the sense that it allows for further improvements through more detailed sub-models for front propagation, seeding, availability and depletion of resources. The present study constitutes then a successful proof-of-concept in answering the following questions: Can we predict the colonization of new sites following biofilm dispersal? Can we generate patterns related to seeding dispersal? These are fundamental issues for developing novel approaches to manipulate biofilm formation in medical, industrial and environmental applications.

Spreading depolarization happens spontaneously in models of epilepsy

Bruce J. Gluckman[1]

[1] Center for Neural Engineering, Dept. Engineering Science and Mechanics, Dept. Neurosurgery, and Biomedical Engineering, Penn State University, USA

Although spreading depression of brain activity was discovered by Leao in induced seizure experiments, it has rarely been directly observed with spontaneous seizures in the epileptic brain. Recently, spreading depression is shown to underlie sudden unexplained death in epilepsy (SUDEP) in murine models, and assumed without proof to underlie post-ictal generalized suppression. The physiological underpinning of spreading depression is an electrical spreading depolarization (SD) of brain cells. We developed a recording system for chronic, long-term measurements capable of observing the prolonged (>10s) large (>15mV) and slowly propagating negative deflections in tissue potential that are the hallmark of SD. With it we performed thousands of days of continuous recording, from two very different animal models of epilepsy. We find that SDs are observed with approximately a third of all spontaneous convulsive seizures, and that there are complex interactions between seizures and SDs that may mediate between seizures in clusters. I'll describe these findings, our planned efforts to connect these findings with epilepsy-SD unification modeling, and potential relations to neurological co-morbidities.

Mapping pain-related EEG perturbation in high frequency range in migraine and non migraine subjects

Marina de Tommaso[1], Iege Bassez[2], Katia Ricci[1], Marianna Delussi[1] and Daniele Marinazzo[2]

[1] Applied Neurophysiology and Pain Unit, SMBNOS Department, Polyclinic General Hospital, University of Bari, Italy

[2] Department of Data Analysis, Ghent University, Belgium

Migraine is a disabling disorder of neuro-vascular origin, affecting more than the 20% of general population in adult and childhood age. In migraine patients, processing of sensory stimuli is different from healthy subjects, even during the inter-critical phase. Reduced habituation to repetitive multimodal stimuli is a well known feature of the migraine brain, together with abnormal synchronization of EEG rhythms in resting state and during visual stimulation. Migraine is thus considered an oscillopathy, caused by disturbed thalamo-cortical connections. The changes in the modality of nociceptive stimuli processing, e.g. reduced habituation or different synchronization pattern- may facilitate the evolution into chronic migraine. Selective modalities of nociceptive fibers stimulation evoke cortical potentials, which could reflect the modality of cortical processing of painful inputs. However, the specificity of these Event Related Potentials (Laser Evoked Potentials-LEPs) and their cortical sources for painful vs multimodal salient stimuli was debated. The response to nociceptive stimuli may be dissected into EEG rhythms, which change in synchronization could explain some aspects of cortical elaboration of pain. The high frequency oscillation in gamma band-GBO, have been considered a correlate of subjective perception of pain in normal subjects, more specific for pain phenomena than LEPs. However, their detection is flawed for the contamination with muscles artifacts. The time frequency analysis with the Multitaper method, allowed to detect some differences between the time preceding and following the laser stimuli, with a slight prevalence in migraine. However, a weak correlation with the subjective pain was present in healthy controls, and absent in migraine patients, who showed a relationship between GBO and symptoms of central sensitization. The GBO could not be considered a correlate of subjective pain, but they could contribute to discover relevant aspects of cortical pain processing in migraine patients.

Mechanisms of cortical spreading depression: insights from genetic mouse models of migraine

Daniela Pietrobon[1]

[1] Dept. of Biomedical Sciences and Padova Neuroscience Center, University of Padova, Italy

Cortical spreading depression (CSD) is thought to play a key role in migraine in that it is the neurophysiological mechanism underlying migraine aura and, in animal studies, it activates the trigeminovascular pain network and hence migraine pain. CSD induction and propagation are facilitated in knock-in (KI) mouse models carrying mutations that in humans cause a rare form of migraine with aura (familial hemiplegic migraine: FHM). The molecular, cellular and network mechanisms that make the brain of migraineurs susceptible to CSD ignition are largely unknown. To tackle this question, we studied the mechanisms underlying CSD facilitation in KI mice carrying either a FHM type 1 (FHM1) or a FHM type 2 (FHM2) mutation. FHM1 is caused by gain-of-function mutations in the neuronal $Ca_V2.1$ channel, a voltage-gated calcium channel that plays a dominant role in controlling neurotransmitter release at brain excitatory and inhibitory synapses. FHM2 is caused by loss-of-function mutations in the α_2 Na/K ATPase, an isoform that in the adult brain is expressed almost exclusively in astrocytes. We measured synaptic transmission at different cortical excitatory and inhibitory synapses in FHM1 KI mice and rates of glutamate and K+ clearance during neuronal activity in FHM2 KI mice. Our findings support the conclusion that excessive cortical excitatory synaptic transmission and excessive activation of glutamate NMDA receptors, due either to enhanced glutamate release in FHM1 or impaired rate of glutamate clearance in FHM2, are the main mechanisms underlying facilitation of CSD in the genetic migraine models. Together with pharmacological data in wild-type mice, the findings in FHM mutants support a model for CSD initiation in which $Ca_V2.1$-dependent glutamate release from cortical synapses and activation of NMDARs play a key role in the positive feedback cycle that ignites CSD, while α_2 Na/K ATPase-dependent glutamate clearance by astrocytes has a dampening role.

Multiscale coupling of electrophysiology, metabolism and hemodynamics in the neuron-astrocyte complex

Gabriela Capo Rangel[1], Jamie Prezioso[2], Luca Gerardo-Giorda[1], Erkki Somersalo[2], Daniela Calvetti[2]

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[2] Dept. of Mathematics, Applied Mathematics and Statistics, Case Western Reserve University, Cleveland, USA

Several mathematical models have been developed in the recent years to describe the brain activity. The latter is a complex interaction between several dynamics that coexist in a working brain. In particular, we highlight the electrophysiological activity of the neurons, the metabolic cycle of the neuron-astrocyte complex that provides the neurons with the energy needed to produce action potentials, the nutrient supply through the Brain Blood Barrier from the capillaries that irrigate the cerebral tissue, and the blood flow in the circulatory system. Building on the electro-metabolic double feedback model introduced in [1], we include hemodynamic processes in the brain by considering a neurovascular unit comprising of arteries, veins and capillaries. The hemodynamic model employed estimates the blood vessel compliance and the corresponding blood flow changes during neuronal activation. Aiming at providing a deeper understanding of the mechanisms through which the brain regulates cerebral blood flow and metabolism in order to produce the required amount of energy for the neuronal activation, we analyze the changes in membrane potential and ionic concentrations, the metabolite concentrations and the blood flow in response to a vasodilatory stimulus. The proposed integrated model presents nontrivial computational challenges stemming from the dramatically different time scales of the dynamics at play: milliseconds for the electrophysiology, minutes for the metabolism and seconds for the blood.

Reference

[1] Calvetti, D., Capo Rangel, G., Gerardo-Giorda, L., Somersalo, E. *A computational model integrating brain electrophysiology and metabolism highlights the key role of extracellular potassium and oxygen*, J. Theor. Biol. 446 (2018), 238-258.

Multiscale modeling of glioblastoma: the influence of the tumor microenvironment

Christina Surulescu[1]

[1] Technische Universität Kaiserslautern, Germany

We present several model classes for cancer (in particular glioma) invasion, thereby including the influence of soluble and unsoluble components of the microenvironment on the tumor spread. Various modeling scales are accounted for, and the settings couple different types of PDEs. Modeling as well as mathematical challengings are addressed.

Glioblastomas and cell communication mediated by cytonemes

Juan Soler[1]

[1] Universidad de Granada, Spain

New results in the fundamentals of cell communication raise the need to question a new way of modeling these processes and their influence on the evolution of tumors, specifically in glioblastomas. These new experiments show that the basis of cellular communication is cell-to-cell contact mediated by cytonemes. From this approach, we propose to explore new ways to model and understand tumor dynamics.

Synergy as a warning sign of transitions

Sebastiano Stramaglia[1]

[1] INFN, University of Bari, Italy

We consider the formalism of information decomposition of target effects from multi-source interactions, i.e. the problem of defining unique, redundant (or shared), and synergistic (or complementary) components of the information that a set of source variables provides about a target, and apply it to the two-dimensional Ising model as a paradigm of a critically transitioning system. We show that the physical quantity that reveals an upcoming transition is the synergy, which peaks in the disordered phase, while the redundancy reaches its maximum at the critical temperature. With respect to previous literature, we show that such reliable marker of an impending dynamical change, the synergy, can be identified considering as few as three variables, and that lagged correlations are not necessary to this scope. Our results provide a conceptual background for the investigation of a variety of systems prone to crisis, like financial markets, social media, or epileptic seizures.

NOTES:

Participants

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