Fourth BCAM Workshop
Quantitative Biomedicine for Health and Disease
Bilbao, February 28 - March 1, 2018

BOOK OF ABSTRACTS

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2. Juan Manuel Encinas (Achucarro, Bilbao)
3. Asier Erramuzpe (BioCruces HRI, Bilbao)
4. Jean-Frédéric Gerbeau (INRIA Reo, Paris)
5. Alessio Gizzi (Universitá Campus Biomedico, Rome)
6. Alessandro Gozzi (IIT, Trento)
7. Mazahir T. Hasan (Achucarro, Bilbao)
8. Guillaume Houzeaux (Barcelona Supercomputing Center)
9. Gemma Huguet (Universitat Politècnica de Catalunya, Barcelona)
10. Denny Milakara (Charité - Universitätsmedizin Berlin)
11. Reza Mohammadi (University of Amsterdam)
12. Argyrios Petras (BCAM, Bilbao)
13. Esther Pueyo (Universidad de Zaragoza)
14. Serafim Rodrigues (BCAM, Bilbao)
15. Alessandro Treves (SISSA, Trieste)

Program

Wednesday, February 28, 2018

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

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

10:00-13:30 **Session 1 - Chairman:** *Luca Gerardo-Giorda*

10:00-10:45 **Mazahir T. Hasan**
Fear memory engram is sequentially printed across brain regions

10:45-11:30 **Alessandro Gozzi**
Voxel-wise mapping of spontaneous network dynamics in the mouse brain

11:30-12:00 *Coffee Break*

12:00-12:45 **Juan Manuel Encinas**
Activation and decay of neural stem cells in the adult mouse hippocampus

12:45-13:30 **Asier Erramuzpe**
Hierarchical structure-function connectomics to unveil brain ageing: the importance of fronto-striatal-thalamic circuit

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

14:30-18:15 **Session 2 - Chairman:** *Sebastiano Stramaglia*

14:30-15:15 **Denny Milakara**
Trajectory reconstruction and speed estimation of spreading depolarization waves on the brain surface in stroke patients

15:15-16:00 **Gemma Huguet**
Neuroprotective role of gap junctions in a neuron-astrocyte network model

16:00-16:30 *Coffee Break*

16:30-17:15 **Guillaume Houzeaux**
Particle transport in the respiratory system - Computational challenges

17:15-18:15 **Short communications**

Caroline Garcia Forlim
Disrupted Cerebrum-cerebellum network in Schizophrenia revealed by network-based statist and graph theory

Roma Siugzdaite
Congruency investigation of language lateralization between task and resting state fMRI in humans with situs inversus totalis

Maite Termenon
'Hub Disruption Index' (κ), an index that measures brain networks reorganization

20:45 Social dinner

Thursday, March 1, 2018

9:30-13:45 Session 3 - Chairman: *Nicole Cusimano*

09:30-10:15 **Jean-Frédéric Gerbeau**
Numerical methods for variability modeling and biomarkers design

10:15-11:00 **Alessio Gizzi**
Theoretical and computational modeling of cardiac electromechanics: stress-assisted diffusion and multiphysics couplings

11:00-11:30 *Coffee Break*

11:30-12:15 **Yves Coudière**
Modeling the propagation of cardiac action potential in hearts with structural heterogeneities

12:15-13:00 **Esther Pueyo**
Characterization of abnormal cardiac dynamics in aged and failing hearts: insights from experimental and computational research

13:00-13:45 **Argyrios Petras**
Mathematical and computational modeling of the radiofrequency ablation for cardiac arrhythmias via open-irrigated catheter

13:45-14:45 Lunch

14:45-17:30 Session 4 - Chairman: *Jesús Cortés*

14:45-15:30 **Serafim Rodrigues**
Time-coded neurotransmitter release at excitatory and inhibitory synapses: a slow-fast modeling approach

15:30-16:15 **Alessandro Treves**
Approaching language processes with cortical computation

16:15-16:45 *Coffee Break*

16:45-17:30 **Reza Mohammadi**
Statistical inference for brain connectivity in prodromal Alzheimer's disease

17:30-17:40 Closing remarks

Abstracts

Fear memory engram is sequentially printed across brain regions

Mazahir T. Hasan[1]

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Whether memory engram is localized or distributed is 'hotly' debated. We have settled this debate using a simple classical fear conditioning experimental paradigm. It is known that the lateral and basolateral amygdala (LA/BLA) and the medial prefrontal cortex (mPFC) are synaptically interconnected. Importantly, both LA/BLA and mPFC provide direct input to the central nucleus of the amygdala, the main output center for fear expression. We have discovered that the fear memory engram is sequentially printed from LA to mPFC brain region to the next and can be retrieved from either LA/BLA or mPFC. Blocking synaptic output from LA/BLA to other brain regions, before, but not after fear-conditioning, interfered with fear expression, suggesting that the fear memory engram becomes distributed to other brain region(s) after learning. Interesting, blocking mPFC synaptic output before and after fear conditioning did not interfere with fear memory expression. Remarkably, when mPFC output was constitutively blocked, and the BLA output was blocked after fear conditioning, fear expression was impaired. However, when both BLA and mPFC outputs were blocked after fear conditioning, fear expression was unaffected. These results suggest that fear memory engram is distributed and it is transferred from LA/BLA to mPFC and, subsequently, to other brain regions. Importantly, optogenetic stimulation of genetically-tagged engram neurons in the LA/BLA and mPFC enabled fear memory retrieval, without the cue, that typically elicit freezing behavior after cued-fear conditioning. Our results thus reveal for the first time that fear memory is sequentially routed from one brain region to the next and it is distributed between the different brain regions, where they are likely performing different functions along the emotional-cognitive networks continuum.

Voxel-wise mapping of spontaneous network dynamics in the mouse brain

Alessandro Gozzi[1]

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Intrinsic brain activity as measured with resting-state fMRI exhibits rich spatio-temporal structure. Recent theoretical and experimental work has linked slow oscillatory activity to fMRI signal dynamics. Building on this framework, we employed frame-wise clustering of whole-brain fMRI signal to map the dynamics of spontaneous fMRI activity with voxel resolution in the living mouse brain. We show that brain-wide patterns of fMRI co-activation and deactivation can be reliably mapped at the group and subject level, exhibit rich network structure, and can be classified into opposing "state" and "anti-state" pairs characterized by contrasting patterns of spontaneous fMRI activity involving the opposing engagement of default-mode and latero-cortical networks. Importantly, using a novel common temporal reference determined by global fMRI signal fluctuations, we further show that the observed brain states exhibit oscillatory dynamics, with transitions occurring at specific phases of global fMRI signal. Our results document previously undescribed oscillatory network transitions as a defining characteristic of resting brain activity, and provide a novel interpretative framework for the emergence and brain-wide modelling of spontaneous functional coupling.

Activation and decay of neural stem cells in the adult mouse hippocampus

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Radial neural stem cells (NSCs) persist in the hippocampus of most mammals and are able to generate neurons through adulthood, a process known as adult neurogenesis. Adult neurogenesis is important for spatial memory and learning, pattern separation and responses to stress and anxiety. Radial NSCs are more multipotent than previously thought and can generate not only neurons, but also more copies of themselves, astrocytes and reactive astrocytes. Their potential as stem cells is however limited, as NSCs divide only 2.5 on average. The population of NSCs decays overtime in an activation dependent manner and the initial population is established in a postnatally critical period. Different levels of neuronal activity control their rate of activation, but also their differentiation and final fate. Thus, the total amount of neurons that they can generate is constrained by the size of the initial population, the dynamics of their activation and their biological intrinsic properties. These constrains define the behavior of the NSCs and their neurogenic output in normal conditions, during aging and in pathophysiological contexts such as epilepsy.

Hierarchical structure-function connectomics to unveil brain aging: the importance of fronto-striatal-thalamic circuit

Asier Erramuzpe[1]

[1] BioCruces Health Research Institute, Bilbao, Spain

Chronological age, defined as the time running since birth, differs from the maturity level that the brain has at the operational level. To proof this, we show here that the chronological age can be estimated by only looking to brain connectivity patterns, and that, this estimation can be modulated by the level of physical activity that participants perform in everyday life, by which physical activity enhances brain resilience by slowing age-related disconnection. In proving this statement, and in agreement with previous work, we have learned that ageing widely affects brain connectivity of multiple structures, such as the anterior cingulate, basal ganglia, thalamus, insula, cingulum, hippocampus, occipital cortex, precuneus and temporal pole. But, in contrast to the common belief that the hippocampus is the most important brain area for the study of brain age-related degeneration, here we show that is the fronto-striato-thalamic complex the circuit that makes the major contribution towards the prediction of brain ageing. Therefore, we infer from this result that future research on brain ageing should make an increasing effort to study this circuit in much more detail, thus clearly differentiating two classes of age-deterioration, the two driven by alteration of different circuits, healthy ageing mediated by the fronto-striato-thalamic circuit and neurodegenerative hippocampus-mediated ageing.

Trajectory reconstruction and speed estimation of spreading depolarization waves on the brain surface in stroke patients

Denny Milakara[1]

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Objectives: We hypothesized that the trajectory of a spreading depolarization (SD) wave could be determined by the time-difference-of-arrival (TDOA) combined with the cortical curvature providing the unique solution. Otherwise inapt co-linear electrodes allow this method to become viable due to intrinsic aspects of brain's surface curvature. Estimated origin of the wave would indicate the likely source of ongoing ischemic injury or metabolic vulnerability. As a corollary, we hypothesized that the onset of new propagation patterns would indicate new areas of secondary injury, and this may serve as a warning sign to clinicians and indication for additional imaging studies.

Methods: Subdural collinear electrode strip with six platinum electrodes was placed on brain surface during surgical brain decompression. Electro-corticography (ECoG) was continuously recorded during 15 days. MPRAGE MRI and CT scans were used for creating a discrete mesh which represents the brain surface and for electrodes localization. The SD's TDOAs on electrodes from ECoG combined with the brain geometry were used to reconstruct the SD trajectories on the brain surface. The model assumes a semi-circular wave-front which propagates across the mesh surface. The curvature radius and the speed of the wave-front were variable parameters combined with the constant TDOAs and the constant geometry. Allowed curvature radius ranged between 0mm and 5mm and speed between 0mm/min and 15mm/min.

Results: The rate of 'could fit' solution was at 76.8% and at 62.2% for the hit-sequences cleared of wave branching and for those in full form, both at the highest tolerance values, respectively. The speed of calculated trajectories ranged between 2-8mm/min with the outliers up to 12mm/min in form of standard distribution. Estimated speeds from reduced hit-sequences showed somewhat higher aberration from the neurosurgical data than the full ones (95% CI).

Conclusion: Change in speed did not seem to be useful predictive factor in contrast to number of successful reconstructions. It seems that energetically more compromised tissue shows more complex depolarization patterns, thus failed the reconstruction significantly more often. A more complex electrode strip with two or more rows could provide less ambiguous information about the angle of incidence of an incoming SD. Thus it could differentiate between the chaotic mass depolarization and real surface propagation. Once the problem of geometric surface reconstruction is solved, a statistical relationship could be established between the heatmaps from the aggregated events and the tissue riskmaps. Given that current cortical geometry is always available, it would be possible to localize nascent SD sources and display them in 3D in near real-time at the patients bedside.

Neuroprotective role of gap junctions in a neuron-astrocyte network model

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I will present a detailed biophysical model for a neuron/astrocyte network in order to explore mechanisms responsible for the initiation and propagation of cortical spreading depolarizations (slowly propagating waves of rapid, near-complete depolarization of brain cells that may last for about a minute) and the role of astrocytes in preventing these pathological waves. Simulations of the model illustrate how properties of spreading depolarizations, such as wave-speed and duration of depolarization, depend on several factors, including the neuron and astrocyte pump strengths. In particular, we consider the neuroprotective role of astrocyte gap junction coupling. The model demonstrates that a syncytium of electrically coupled astrocytes can maintain a physiological membrane potential in the presence of an elevated extracellular potassium concentration and efficiently distribute the excess potassium across the syncytium. This provides an effective neuroprotective mechanism for delaying or preventing the initiation of spreading depolarizations.

Particle transport in the respiratory system - Computational challenges

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Drug delivery through the respiratory system is an attractive technique which is receiving an increasing interest. At the computational level, basic simulations involve the solution of the airflow through the region of interest and the simulation of the particles, usually addressed by individual Lagrangian transport equations.

Simulating the airflow accurately requires very fine meshes to capture the right behaviour of the air, where three states co-exist: laminar, transitional and turbulent. Such simulations are therefore intensive so that computational efficiency is required. When considering in addition particle transport, additional difficulties arise as the computational requirements of this transport are very different from that of the airflow.

We will address some of the computational challenges involved in the transport of particles in the large and small airways.

Disrupted Cerebrum-cerebellum network in Schizophrenia revealed by network-based statist and graph theory

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Schizophrenia is a mental illness that is characterized by heterogeneous symptoms ranging from positive symptoms such as delusions and hallucination to negative symptoms such as lack of motivation and reduced emotional expression among others. It has been suggested that schizophrenia is related to disrupted brain connectivity. Graph theoretical studies have found abnormal structural and functional in multiple brain networks supporting the theory of disconnectivity syndrome (Hadley et al., 2016) and suggesting wide-range of connectivity disturbances (van den Heuvel and Fornito, 2014). Nevertheless, there is no consensus regarding localized mechanisms and their associated symptoms. The cerebellum, an often overlooked region, might play a key role in schizophrenia. It has been suggested that a misconnection between cerebellum and cortex can lead to a misinterpretation of the information arriving from the cortex, resulting in, for example, experiences of delusion and auditory hallucinations (Andreasen and Pierson, 2008).

Here, we first extract a functional subnetwork from resting state fMRI using network-statistic approach and then applied graph measures. Network-based statistic method is a nonparametric cluster statistic, to look for differences in the subnetwork brain wiring. In order to relate functional connectivity and graph measures to psychopathology, we correlated these measures with clinical symptoms scales. Furthermore, we sought to relate these measures to state aspects of clinical symptoms and presented participants eleven questions concerning their subjective experience during the resting state immediately after the measurement.

We found a single disrupted subnetwork in cerebrum-cerebellum mainly comprising brain regions related to visual processing and the cerebellum. More precisely: inferior and superior occipital, lingual, cuneus, fusiform, thalamus and Vermis. Schizophrenia patients presented higher functional connectivity, strength, global efficiency and betweenness than the healthy control participants, showing increased information processing.

Regarding the relationship of these measures with psychopathology, we did not find an association with any of the symptom scales but observed that all graph measures of this subnetwork were anti-correlated with reports of being externally influenced during the resting state measurement. These findings reinforce the role of the occipital lobe and cerebellum in schizophrenia and it is consistent with structural imaging studies that showed alteration in the cerebellum (Okugawa et al., 2005, Chuang et al., 2014) and in the occipital lobe (Chuang et al., 2014, Tohid et al., 2015)

Congruency investigation of language lateralization between task and resting state fMRI in humans with situs inversus totalis

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The total reversal of internal organs is a congenital condition called situs inversus totalis (SIT). Though with the exception of the reversed frontal and occipital petalia observed using anatomical MRI techniques, the left hemisphere dominance for language in SIT was still found similar to controls (Sun et al., 2006, Ihara et al., 2010). The objective of this study was to investigate functional brain asymmetries of language network in SIT subjects in a bigger sample.

15 SIT (4 left handed) and 15 matched controls underwent the scanning session performed on 3T Siemens scanner. Structural T1-weighted image was acquired for each participant using MPRAGE sequence (176 slices, $TR = 2250$ms, $TE = 4.17$ma, $FA = 9$ deg, $1 \times 1 \times 1$ m^3 voxel size, $FOV = 256$mm). For resting state fMRI images were acquired using echo planar imaging (EPI) gradient-echo sequence 484s long (220 volumes, $TR = 2$s, $TE = 24$, flip angle 90 degrees, 42 interleaved slices per volume and cubic 3mm voxel size, $FOV = 192$mm, 64×64 acquisition matrix).

FMRI images were preprocessed in SPM12 using standard preprocessing pipeline. To individuate resting state networks of interest we performed independent component analysis using GIFT toolbox. From 25 independent components only Language network was selected for further analysis. Group comparison was performed and laterality index was calculated to find language dominant hemisphere.

We observed that language network was not reversed in SIT group, though asymmetries were more consistent with left-handedness of subjects. We found that for the speech production left language lateralization was observed in 13 from 15 controls and 11 from 15 SITs, clearly showing left hemisphere dominance for language. On group level the Language network measured during resting state was not reversed in the SIT group.

We then investigated the language component on a single subject level. Lateralization of the connectivity patterns in Broca's area in the LN showed 47 percent corresponding to the task data (correspondence between task and rest fMRI, for lateralization indexes in the task above 0.7 was 67 percent congruent in SITs and 54 percent in SS).

In this study we investigated congruency between word generation task and Language network in rs-fMRI and their hemispheric preferences. Both groups showed similar activation patterns, but only during the task we found small significant differences. Though as a group SIT did not show functional asymmetry in the Language network. On a single subject level group the higher congruency between the task and the rest was observed only if the task showed high lateralization index. Even though there is no consistency between subjects inside the group, further research and more participants needed to understand sources of variability in the group of SIT.

'Hub Disruption Index' (κ), an index that measures brain networks reorganization

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Background: In the last few years, brain functional connectivity has been widely used to investigate the neuronal networks in several clinical conditions such as Alzheimer, Parkinson, autism, epilepsy, schizophrenia, and also in studies that involve normal human brain (development, aging, gender differences). There are several approaches to study functional connectivity, among them, **graph based analysis** is a technique where the brain can be regarded as a network with nodes that represent different brain areas and edges representing communication pathways. The communication is coded by temporal dependencies between the activity of different brain regions, allowing to describe whole brain patterns and inter-regional interactions. As a drawback, it requires long scan length acquisitions and it is dependent on the parcellation of the brain in different areas.

The majority of networks are too complex to analyze them visually, this is why it is necessary to extract metrics from the graphs that allow us to study the importance or roles of certain nodes and edges. Global graph metrics are sometimes too general to find particular characteristics of a brain, and nodal graph metrics are limited by multiple comparisons. This is why the 'Hub Disruption Index' (κ) was introduced by Achard et al. (2012) as a meta-metric sensitive to the changes in overall nodal metrics.

What is κ? It is a metric that evaluates the nodal network topology of a subject in relation to a referential network topology. Given a nodal graph metric, a subject S, and a reference group R, the differences between the nodal metric of S and the mean of nodal metric in R are computed at all nodes of the brain graph. The slope of the linear fit of these differences vs. the mean nodal metric in the R group corresponds to κ. It is thus sensitive to the nodal network topology of S in comparison to the network topology of R. If no reorganization is present in a network, then κ is about 0 and if reorganization in the network occurs, a negative kappa value is obtained. This index can be used to compare the behavior of the network of a single subject (healthy or patient) or to compare the mean differences between a group of patients and R. A prerequisite before translating this index to clinic is to assess its reliability. The **aim** of this abstract is to compare, using the test-retest data from the Human Connectome Project (HCP), the reliability of κ against the reliability of global graph metrics such as global efficiency (E_{glob}), betweenness centrality (B), local efficiency (E_{loc}) and clustering (C).

Methods: Graph analysis was performed following the method described in (Achard et al., 2006) in a cohort of 100 subjects from the Human Connectome Project at different costs. The Anatomic-Automatic Labelling (AAL) parcellation scheme was used to extract the nodes of the graphs. The reliability of κ was measured by computing the intraclass

correlation coefficient (ICC), applying bootstrapping and permutation techniques and varying the number of subjects and the cost of the graph. We also measured the reliability of global metrics for comparison purpose.

Results: We found that κ was more reliable than global graph metrics at all costs and whatever the number of subjects. We also showed through examples from the published literature that κ index presents a higher discriminability between groups of patients and of healthy subjects in comatose (Achard, 2012), epilepsy (Ridley, 2015) and stroke (Termenon, 2016).

Conclusion: These results support the view that κ may be a better candidate than global graph metrics to study large-scale brain networks reorganization in clinical studies.

Numerical methods for variability modeling and biomarkers design

Jean-Frédéric Gerbeau[1]

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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 sets in cardiac electrophysiology will be presented.

In biophysics and medicine, the system of interest is often studied by monitoring quantities, called biomarkers, extracted from measurements. These biomarkers convey some information about relevant hidden quantities, which can be seen as parameters of an underlying model. We propose a strategy to automatically design biomarkers to estimate a given parameter. Such biomarkers are chosen as the solution of a sparse optimization problem. We will show applications in electrophysiology where our algorithm provides composite biomarkers which improve the parameter estimation and the classification problems.

Theoretical and computational modeling of cardiac electromechanics: Stress-assisted diffusion and multiphysics couplings

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Cardiac tissue is a complex multiscale medium constituted by highly interconnected units, cardiomyocytes, that form a so-called syncytium with unique structural and functional properties. Cardiomyocytes, excitable and deformable muscular cells, present an additional multiscale architecture in which plasma membrane proteins and intracellular organelles all depend on the current mechanical state of the tissue. Ion channels and gap junctions, ruling the passage of charged particles throughout the cell as well as between different cells, are usually described mathematically through multiple reaction-diffusion (RD) systems. These different multiscale interactions have been referred in the literature as the mechano-electric feedback (MEF) already for over a century. Though, still preserve several open questions: what is the effective contribution of stretch-activated ion channels? which is the most appropriate way to mathematically describe them? what is the clinical relevance of MEF in patients with heart disease? how MEF mechanisms translate into ECGs?

On this ground, we introduce a new model to describe diffusion processes within active deformable media, namely stress-assisted diffusion (SAD). Our general theoretical framework is based on physical and mathematical considerations, and it suggests to employ diffusion tensors directly influenced by the coupling with mechanical stresses. The proposed generalized approach reveals that initially isotropic and homogeneous diffusion tensors turn into inhomogeneous and anisotropic quantities due to the intrinsic structure of the nonlinear coupling.

We investigate the physical properties leading to these effects and characterize mathematical conditions for its occurrence. We numerically investigate the role of mechanical stress in modifying the conductivity properties of the cardiac tissue and its impact in computational models for cardiac electromechanics. In particular, we compare and contrast SAC and SAD effects, underlying the most reliable mathematical description against experimental evidence. We show that i) only specific combinations of the two MEF effects allow proper conduction velocity measurement; ii) expected heterogeneities and anisotropies are obtained via the novel stress-assisted diffusion mechanisms; iii) spiral wave meandering and drifting are highly mediated by the applied mechanical loading.

Together, the mathematical model and the numerical results support important consequences of stress-driven diffusion into anisotropy patterns, drifting, and conduction velocity.

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Modeling the propagation of cardiac action potential in hearts with structural heterogeneities

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The bidomain or monodomain equations model the propagation of the cardiac action potential (AP) at the tissue scale. They rely on the tissue being described as a regular, homogeneous, network of cardiomyocytes. Though, several pathologies can affect the organisation of cells at various scales, e.g. in fibrosis (remodeling), fatty infiltrations, border zone of an infarct scar, myostructural diseases in general. Such regions with structural defects are hypothesized to play a role in arrhythmias. I will present an adaptation of the bidomain model to these situations. It is obtained by multiscale analysis, assuming a periodic alterations in the tissue, and it allows to explore the role of heterogeneities in the mechanisms of arrhythmias. I'll show how the propagation velocity is modified by these structural defects, and how we used the model to build a computational heart model accounting for structural heterogeneities from high-resolution MR images of a rat heart.

Characterization of abnormal cardiac dynamics in aged and failing hearts: insights from experimental and computational research

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Cardiovascular diseases (CVDs) are responsible for more than 4 million deaths per year in Europe, representing 45% of all deaths. Age is the single major risk factor for CVD. Europe, as well as other industrialized regions, is facing a striking change in their demographics with an increasingly larger proportion of citizens aged 65 years and over. Aging leads to a progressive decline in the physiological functions of the body, with very notable effects on the heart. These effects are associated with enhanced predisposition to cardiac arrhythmias. CVDs like heart failure, with high prevalence in the elderly population, are also linked to increased risk for arrhythmia development, in some cases leading to sudden cardiac death.

In this presentation, alterations in heart function as well as in its modulation by the Autonomic Nervous System (ANS) will be investigated in both aged and diseased hearts. An integrative methodological framework in which in silico modeling is combined with in vitro cell and tissue analysis and in vivo electrocardiographic evaluation will be introduced. This will serve to elucidate how aging and other cardiovascular diseases manifest at a range of scales, covering from ion channels in the cell membrane to whole-body surface potentials. The role of electrical, structural and autonomic alterations in contributing to such manifestations will be explored. By using feedback control approaches within the proposed integrative framework, indices describing spatio-temporal dynamics of cardiac electrophysiology will be evaluated. Inter-individual variations in those indices will be assessed in populations of elderly and diseased individuals and links to arrhythmia susceptibility will be set. Advances towards the proposal of a set of non-invasive markers able to identify aged and diseased individuals at high arrhythmic risk will be presented.

Mathematical and computational modeling of the radiofrequency ablation for cardiac arrhythmias via open-irrigated catheter

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Radiofrequency ablation is an effective treatment process for cardiac arrythmias. Using an open-irrigated catheter, the arrythmogenic tissue is burnt via electrocautery, forming lesions on the tissue at the temperature of 50°C. The radiofrequency ablation is generally considered a safe treatment for cardiac arrhithmias, however complications can occur, including the possibility of thrombus formation, in case the blood temperature reaches 80°C, and steam pops, in the occurence of overheating of the tissue (around 100°C).

We present a mathematical model for the radiofrequency ablation process that uses an open-irrigated catheter. Our model includes the blood-saline interaction through the incompressible Navier- Stokes equation. The temperature change is modelled by Pennes bioheat equation, using a source term for the heat generation due to the thermoelectric effect. The electrical potential generated by the electrodes at the tip of the catheter is considered space and temperature dependent. The Hertzian theory in contact mechanics is used to model the deformation of the tissue due to the pressure from the catheter tip at the tissue-catheter contact point.

The system is discretized and solved numerically using the finite element method. Our implementation uses FEniCS-HPC for the approximation of the solution of the system of equations. A post-processing step, implemented Matlab, calculates the size of the lesion by tracking the 50°C contour of the temperature. The geometric characteristics of the computational lesion, i.e. depth, maximum width etc., are approximated and compared with in vitro experimental results. In addition, estimations of possible thrombus occurence and steam pops are presented by tracking the 80°C contour on the blood-tissue interface and the 100°C contour in the tissue respectively.

Reference

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Time-coded neurotransmitter release at excitatory and inhibitory synapses: a slow-fast modelling approach

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Communication between neutrons at chemical synapses is regulated by hundreds of different proteins that control the release of neurotransmitter that is packaged in vesicles, transported to an active zone, and released when an input spike occurs. Neurotransmitter can also be released asynchronously, that is, after a delay following the spike, or spontaneously in the absence of a stimulus. The mechanisms underlying asynchronous and spontaneous neurotransmitter release remain elusive. In this talk we will describe a model we have developed of the exocytotic cycle of vesicles at excitatory and inhibitory synapses that accounts for all modes of vesicle release as well as short-term synaptic plasticity (STSP). The model inspires from the work of 2013 Nobel Prize winner Thomas Sudhoff, where we bridge the gap between the dynamics of the SNARE-SM Protein bio-molecular machinery for excocytosis, neuro-transmitter release and neuronal electrical activity. As a consequence techniques from multi-scale model (slow-fast dynamical system) is employed to model and characterise all three modes of excocytosis. For asynchronous release, the model predicts a delayed inertial protein unbinding associated with the SNARE complex assembly immediately after vesicle priming. Experiments are proposed to test the models molecular predictions for differential exocytosis. The simplicity of the model will also facilitate large-scale simulations of neural circuits.

Approaching language processes with cortical computation

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The traditional box-and-arrow model of the process of reading aloud posits the crucial involvement of a specialized box, the Phonemic Output Buffer, which takes a string of discrete phonemes in input and produces a sequence of articulatory commands in output. Yet, the evidence suggests that the POB does not operate as a digital computer, is not strictly specialized for language and is not even a box, in any way different from adjacent cortical circuitry. We are exploring to what extent one can analyze how the POB works by capitalizing on insight obtained analyzing spatial computation in rodents.

Statistical inference for brain connectivity in prodromal Alzheimer's disease

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Alzheimer's Disease (AD) is the most common neurodegenerative disease, characterized by a range of pathological brain alterations that can be assessed using various neuroimaging methods, including MRI and PET. The current application of multimodal imaging requires adequate analysis methods. Most existing brain connectivity research for AD is based on mass-univariate analysis. Instead of investigating only a single region-of-interest that leads to Alzheimer's, network analysis considers whole-brain regions. Modern statistical tools can infer the brain connectivity network, but most approaches only estimate network structure, which introduces a new abstraction level but does not derive meaningful results about the pathophysiology of AD. In this talk, I discuss the problems related to statistical computation of brain connectivity estimation with a motivating example of prodromal AD using multimodal MRI/PET data. I offer several solutions to cope these problems. In addition, I introduce the user-friendly R package BDgraph which can be applied for brain connectivity estimation.

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