ACTIVITY 2016
REPORT 2018

POLITÉCNICA
"Ingeniamos el futuro"

CAMPUS
DE EXCELENCIA
INTERNACIONAL

CTB centro de tecnología biomédica

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Universidad Politécnica de Madrid
Campus Montegancedo
Autovía M40 Km.38
28223 Pozuelo de Alarcón - Madrid

Depósito Legal.: M- 13750-2020
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■ Gustavo Guinea.CTB Director - January 2019

FOREWORD

The end of the 2016-2018 triennium saw the tenth anniversary of the CTB (founded in February 2008 by the approval of the Consejo Social de la Universidad Politécnica de Madrid), and its beginning was almost coincident with my appointment as director on 1 February 2016, a post in which I succeeded Professor Francisco del Pozo –Paco– promoter and founder of the Centre and its first director.

Sadly, this triennium will always be marked by his death at the end of January 2018 due to an unexpected setback in the illness from which he had been suffering since the end of 2017. Up to the very moment of his death Paco gave the best of himself to the CTB, with intensive work and kind attention to everyone around him. A plaque on the outside of the building, his name in the main hall and the annual prize established for the best Doctoral Thesis remind us of his figure and of all that he gave to us through the CTB.

Since its foundation, the CTB has always sought to attain the maximum excellence in biomedical technology by means of interdisciplinary collaboration among researchers of different institutions within a dynamic and creative environment to stimulate personal development and innovation.

This activity report highlights a great part of the scientific-technological achievements obtained during the triennium along with the most relevant formative and diffusion activities carried out, all of which have made it possible for the CTB to occupy a permanent place among the three best R&D centres within the UPM.

In addition, during the 2016-2018 triennium different actions have been performed in order to provide the centre with a more balanced and stable structure, consolidating and strengthening the work of researchers and laboratories. The constitution of the Scientific Advisory Board and the first external evaluation of the centre performed in March 2016 –which demonstrated the great capacity and potential of the CTB in the field of neurosciences– can be highlighted among the most relevant actions. The assessment also exhibited the permanent need for greater integration and joint work among all the groups. Furthermore, the approval in April 2017 of the new internal regulations allowed for simplification, and greater agility, within administrative procedures and led to the setting up of the Committee for Quality, which performed its first quality assessment within the centre (laboratories and researchers) in September 2017.

The data contained in this report allow for optimism as regards the centre's future and project. Nevertheless, we should not relax our efforts in our work or in our level of self-demand, but continue along the path marked out since the centre's foundation a decade ago.

■ Francisco del Pozo. 1948 - 2018

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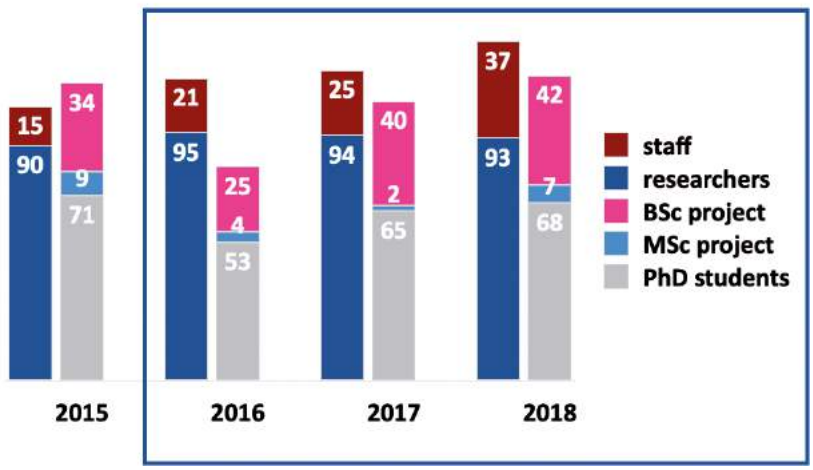

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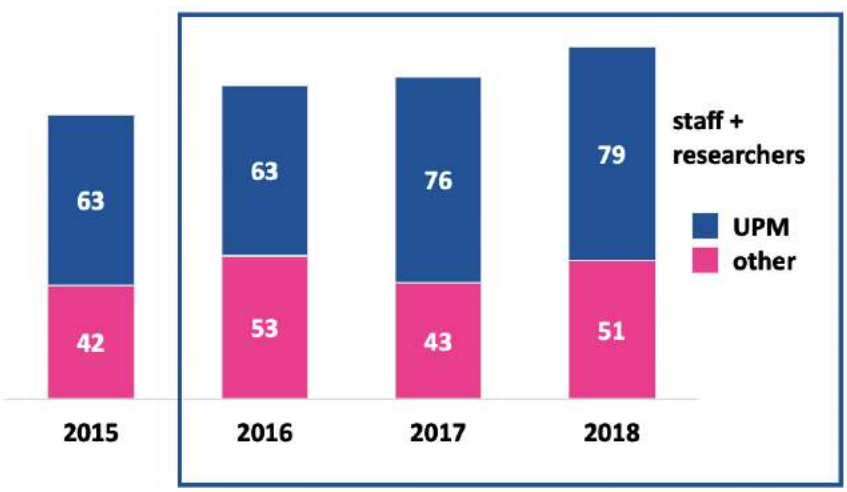

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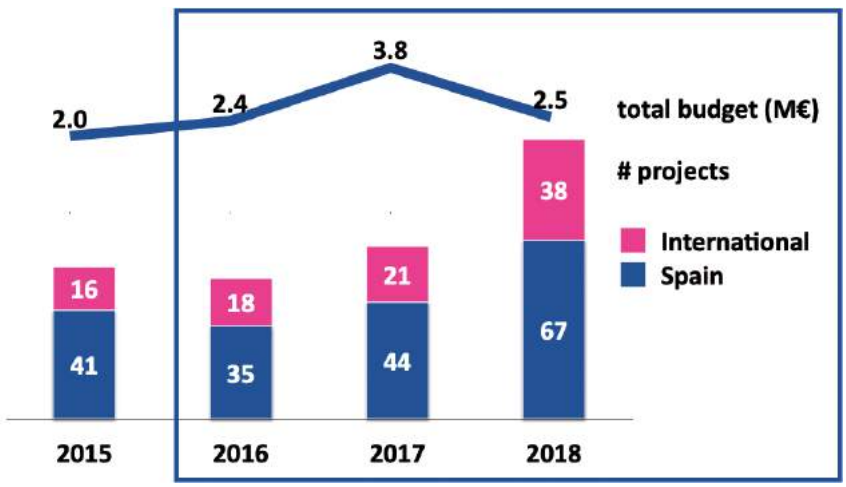

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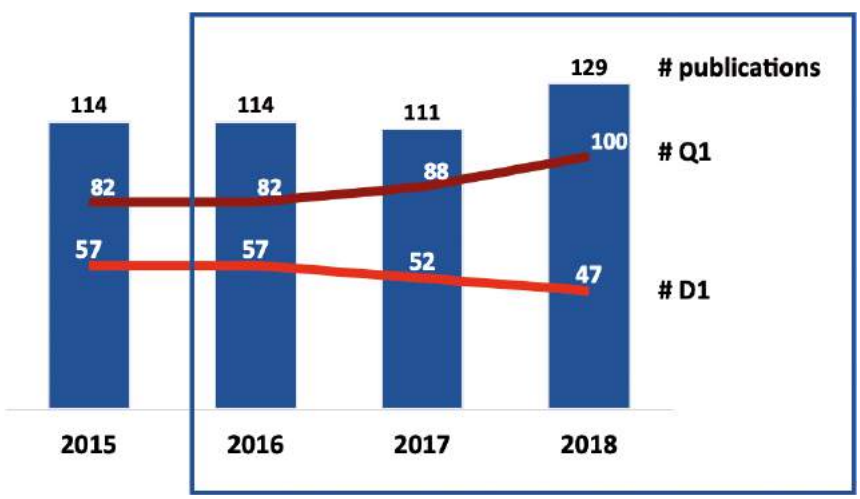

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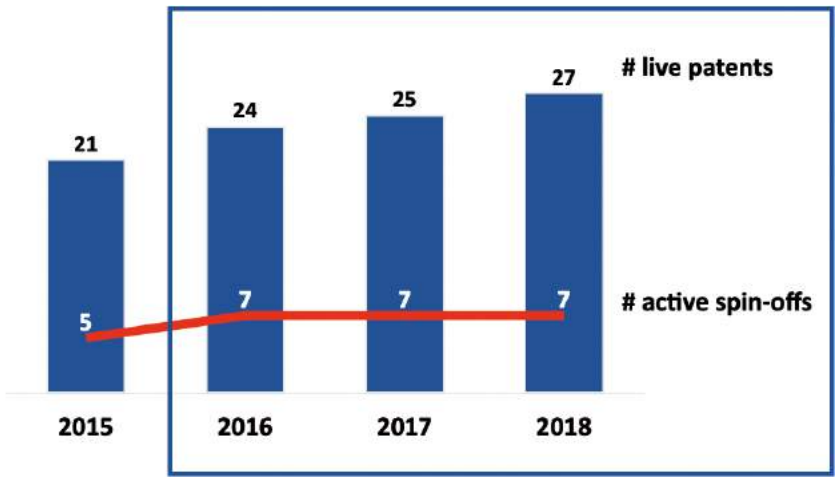

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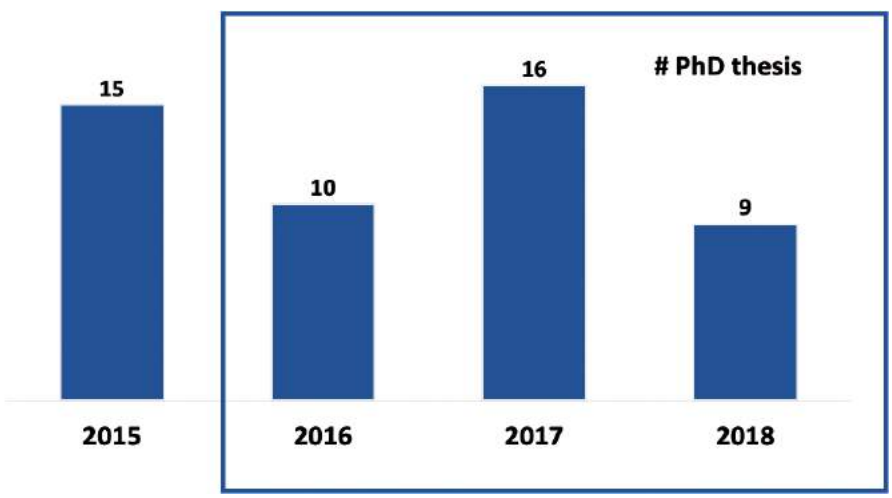

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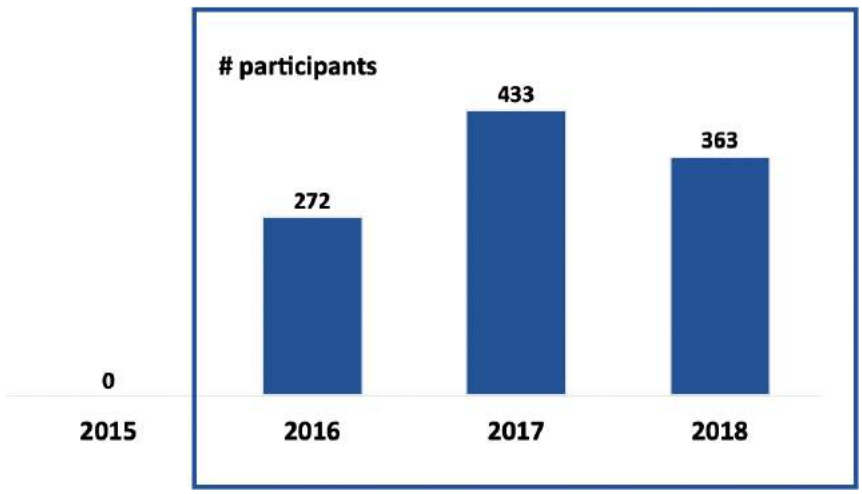
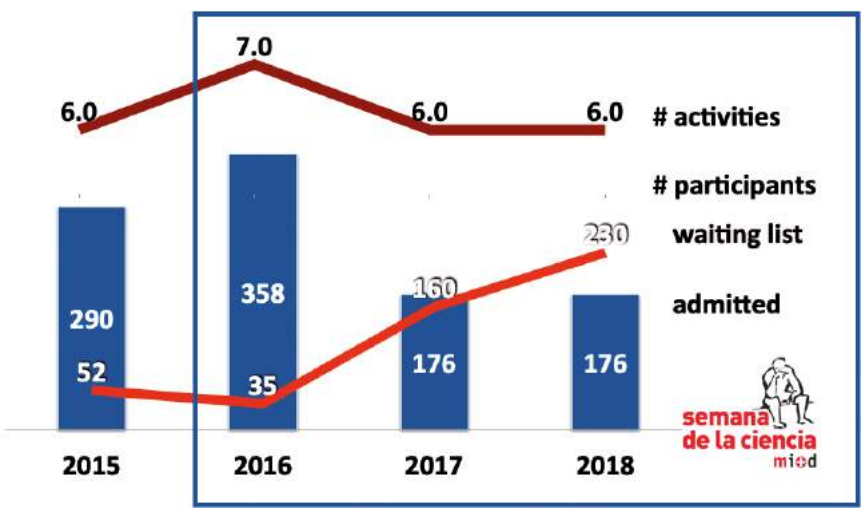
■ Workshops for schools



■ Science Week in Madrid



2 ORGANIZATION

DIRECTORATE

Director: Prof. Gustavo Víctor Guinea Tortuero
Deputy Director: Prof. Francisco Javier Rojo Pérez
Academic Secretary: Prof. Consuelo Gonzalo Martín

QUALITY COMMITTEE

Prof. Gustavo Víctor Guinea Tortuero
Prof. Francisco Javier Rojo Pérez
Prof. Javier Martín Buldú
Prof. José Javier Serrano Olmedo
Prof. Ceferino Maestú Unturbe
Prof: Stephan Moratti
Prof. Francisco del Pozo Guerrrero

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CEO, Nielseninnovation AB

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Director, IBEC (Institute for Bioengineering of Catalonia)

Prof. Rafael Yuste, M.D., Ph.D.
Director, NeuroTechnology Center, Columbia University

SUPPORT SERVICES (ADMINISTRATION)

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Ana Cristina Heath Cabellos
Soledad Martínez Montero
María Jesús Pioz Soriano
Mayte Sánchez Muñoz

3 RESEARCH ACTIVITY

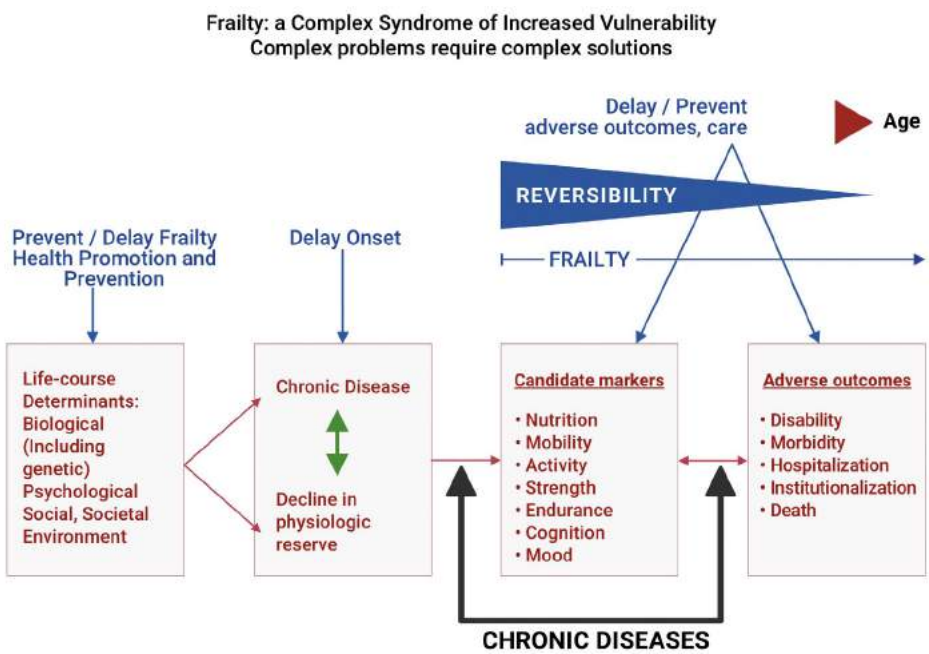
Ageing Lab - Alberto Salgado Alba Joint Lab (UPM - FIBHUG)

PRESENTATION/INTRODUCTION

This joint laboratory of the Hospital Universitario de Getafe and the CTB-UPM was created on July 2014 to take advantage of the synergies derived from the collaboration of clinical experts in ageing from the Hospital Universitario de Getafe, together with their worldwide community of collaborators, and technologists from the CTB-UPM into a multi-disciplinary research team. These synergies allow the validation of research activities in patients treated at their usual health care setting; thus, fostering translational research.

The consequences of ageing are a major challenge for modern societies. The WHO "World Report on Ageing and Health" (October 2015) states that assistance and care for the elderly must aim to maintaining functional autonomy rather than treating or curing a disease. The Ageing Lab focuses on one of the main healthrelated problems in the older people: disability; and its main risk factor: frailty. Disability has a strong impact on both people's quality of life (individual impact) and healthcare and social systems sustainability (socio-economic impact).

■ Route leading to disability in elderly people.



Upon such a theoretical framework, the general objectives of this joint laboratory are:

1. **"Understanding fundamentals of ageing".** Clinical and biological mechanisms of ageing, frailty, functional impairment, and related syndromes and pathologies; with an emphasis on interactions between them.
2. **"Developing tools to better care older adults".** ICT-based systems and computational models for the integrated care of the elderly, including diagnosis and objective assessment via continuous, ubiquitous, and unobtrusive care.
3. **"Promoting autonomy".** Including prevention of decline and fostering selfmanagement for both the elderly and caregivers.
4. **"Ageing and society".** Economic, societal, legal, and other issues related to ageing. Studying the proper ecosystems for older people to develop an active and healthy ageing.

A. MEMBERS

PI: Elena Villalba

Senior researchers: Leocadio Rodríguez, Alexander Pisarchik, Pilar Herrero, Xavier Ferré

Post-doctoral Fellows: Cristian Moral, Antonio Cobo, Pedro Antonio Moreno, Rodrigo Pérez, Cristina Alonso

PhD students: Sofía Ahufinger, Parth Cholak, Francisco Javier Martín, Alberto Sánchez, Myriam Valdés, Ali Abavisani, Roberto Petidier Torregosa, Mariano Alberto García Vellisca, Guiomar Niso Galán

Others: Sergio Barrero, Ismael González, Walter Escalante

B. RESEARCH LINES

Human cognitive abilities and brain-to-brain interfaces

Short description:

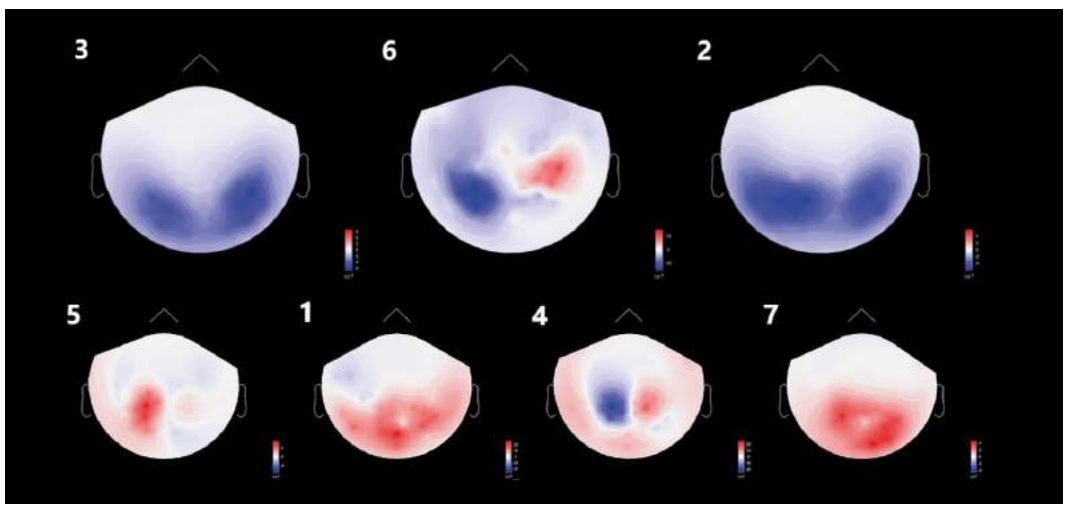
The brain is likely the most convoluted and enigmatic object for comprehensive studies attracting the burning interest of the broad scientific community. The understanding of brain functionality requires a multidisciplinary approach involving different areas of science, engineering and technology.

Traditional brain-computer interfaces (BCIs) imply the interaction between brains and machines with the aim to repair or increase human performance in solving different tasks or to help paralyzed people to interact with an environment. Unlike a BCI, a brain-to-brain interface (BBI) allows a direct information exchange between brains. The BBI development is one of the most progressing research directions at the intersection of physics, mathematics,

informatics, psychology and neuroscience. The main trend in the BBI research is aimed at providing people with a new way for communication directly from one brain to another, to monitor and control mental states and increase working performance by using cognitive recourses of multiple brains. This particularly important for a group of people working together on a common task which requires sustained attention and alertness.

In addition, understanding the neurophysiological mechanisms responsible for motor imagery (MI) is essential for the development of brain-computer interfaces (BCI) and bioprostheses. MEG experiments with volunteers confirm the existence of two types of motor imagery, kinesthetic (KI) and visual (VI), which can be distinguished by activation or inhibition of different brain areas in α and β frequency bands.

■ Illustration of typical ERS / ERD results averaged for KI and VI

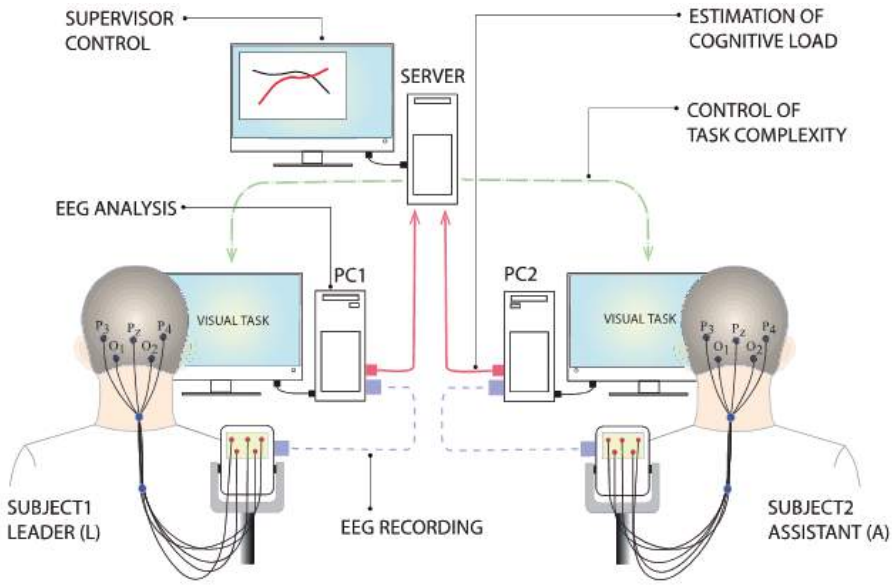


Main results:

The first successful attempt to implement our solution for Brain to Brain Interfaces has been made in our laboratory. We developed novel methods of nonlinear and stochastic analyses of neurophysiological data, as well as artificial intelligence for pattern recognition and classification in electro-and magneto-encephalograms.

Although KI brain activity is usually observed in specially trained subjects or athletes, we show that it is also possible to identify characteristics of MI in untrained subjects. Similar to the actual movement, KI implies muscular sensation when performing MI that leads to event related desynchronization (ERD) of cerebral rhythms associated with MI. On the contrary, VI refers to the visualization of the corresponding action that results in even related synchronization (ERS) of the brain activity at α and β waves. A notable difference between the KI and VI groups occurs in the frontal area of the brain. In particular, the analysis of the evoked responses associated with MI shows that in all KI subjects the frontal cortex activity is suppressed during MI, while in VI subjects the frontal cortex is always active. The accuracy in the classification of the left arm and

■ Illustration of brain-to-brain interaction



the MI of the right arm using artificial intelligence is similar for KI and VI. Since untrained subjects generally demonstrate the VI mode, the possibility of increasing accuracy for VI is in demand for BCI. The application of artificial neural networks allows us to classify the MI by raising the right and left arms with an average accuracy of 70% for both KI and VI using adequate filtration of the input signals. The same average accuracy is achieved by optimizing the MEG channels and reducing their number to only 13.

Brain Connectivity analysis and visualization tools

Short description:

Nowadays brain connectivity plays a key role within the development of different neural diseases, but also in the normal working brain. Understanding brain connectivity is highly useful for understanding the normal processes of the brain and how changes in these processes may lead to a certain disease.

However, most of the tools for EEG/MEG processing which are available nowadays do not provide functionalities for obtaining connectivity measures and those that provide these functionalities are not intuitive. Furthermore, only few of them allow visualizing this kind of information, but only by using matrix and graph representations. This is such an important problem not only for the research community but also for the clinicians, because it makes the interpretation of the results such a complex task. For this reason, this research line develops a new useful and efficient tool for the visualization of brain connectivity data, in a way that the

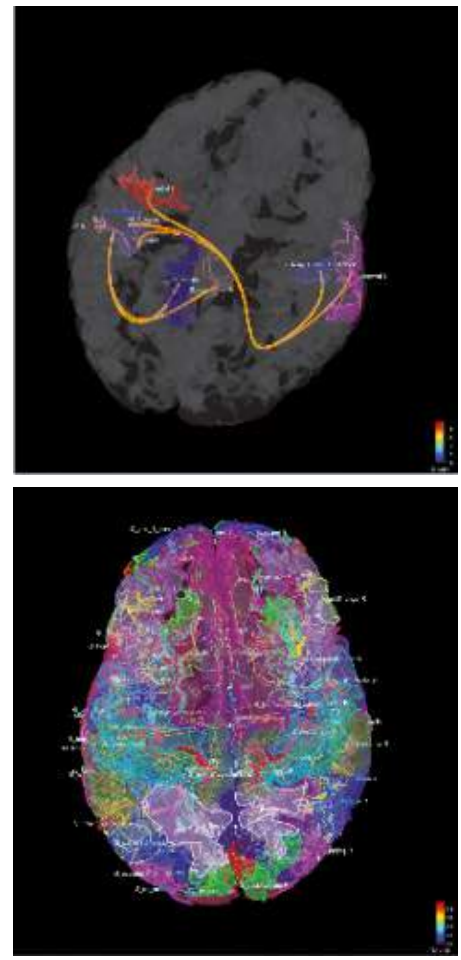
end-user can visualize the important information in an interactive way. For this aim, we are following a user-centered design which involves the endusers during the whole process, considering their opinion and needs.

Electroencephalography is well-known for its importance in the diagnosis and treatment of different mental and neural disorders. This is due to its high temporal precision but also for being an inexpensive technology. However, the technology available nowadays is limited by several facts such as the limitation of the patient's mobility due to the high amount of wires that keep the patient attached to the bed. This is an important issue since it makes the patient feel uncomfortable and hence, the EEG session might not represent the normal activity of the patient. On the other hand, this makes the work of the whole medical or research staff even more difficult, especially in patients which are not able to move easily or even worse, in young-age patients or those who are suffering a seizure. For this reason, with this research line, we decided to develop an application for using a wireless EEG in the monitorization of patients, in order to make the patient experience better and the staff work easier. For this purpose, we are following a user-centered design which involves the end-users during the whole process, considering their opinion and needs.

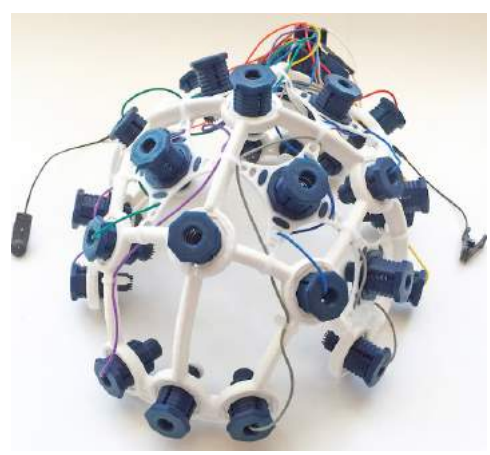
Main results:

We have performed several interviews and observation sessions in order to understand the environment in which our tool will be used, the different profiles of users and the task that they need to perform. This allowed us to define our Context of Use and based on this context of use we created a low-fidelity prototype and a high-fidelity prototype. We also evaluated both prototypes with different participants which belong to the different defined profiles.

■ Illustration of brain-to-brain interaction



■ Illustration of brain-to-brain interaction



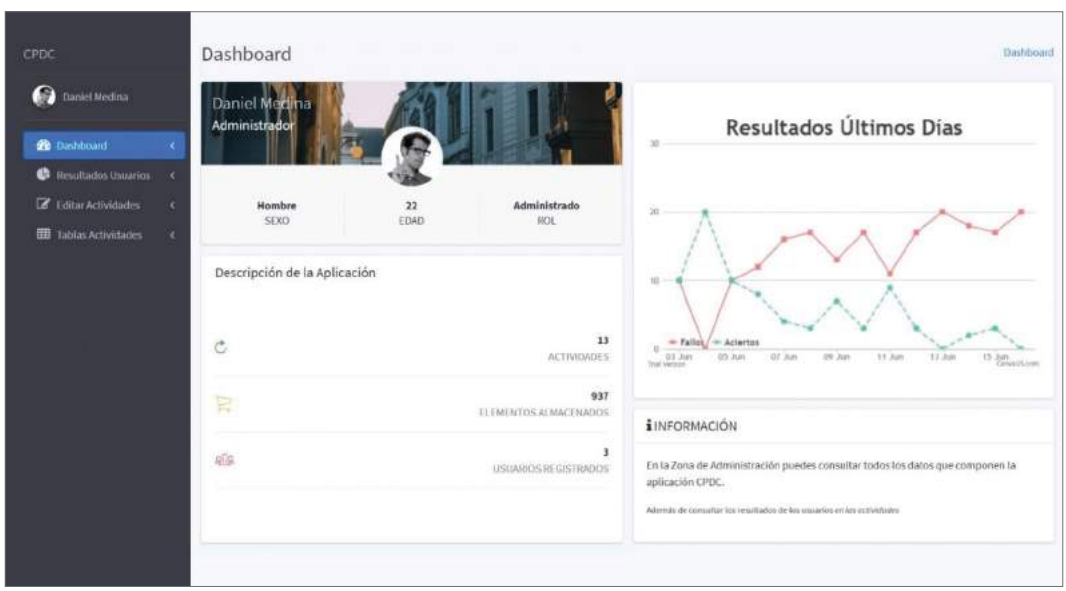
Monitoring and stimulation to assess cognitive decline and prevent its onset and worsening

Short description:

This research line focuses, on the one hand, on unobtrusive monitoring of cognitive decline; and on the other hand, on game-based stimulation for preventing the progression of cognitive diseases.

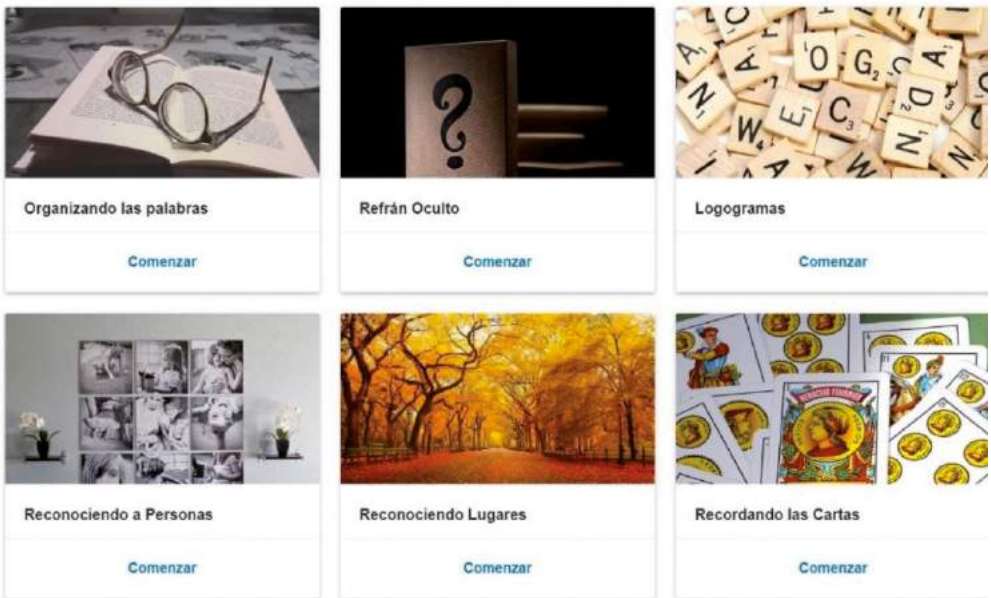
This research line explores gamified test for cognitive evaluation and stimulation. One of the objectives is to find which strategies contribute to increase patient adherence to stimulation activities. Computerized games offer many advantages, such as simultaneously conducting both evaluation and stimulation activities and automatic data capture. Besides, this research line explores a new organizational model based on enhancing the role of the case manager. Case managers lead the care process in an integrated fashion acting like a hub between patients and relevant caregivers and stakeholders. This new organizational model is supported using digital environments where information between different stakeholders is shared for data visualization, decision support, and therapy adjustment.

■ Illustration of monitoring of cognitive decline

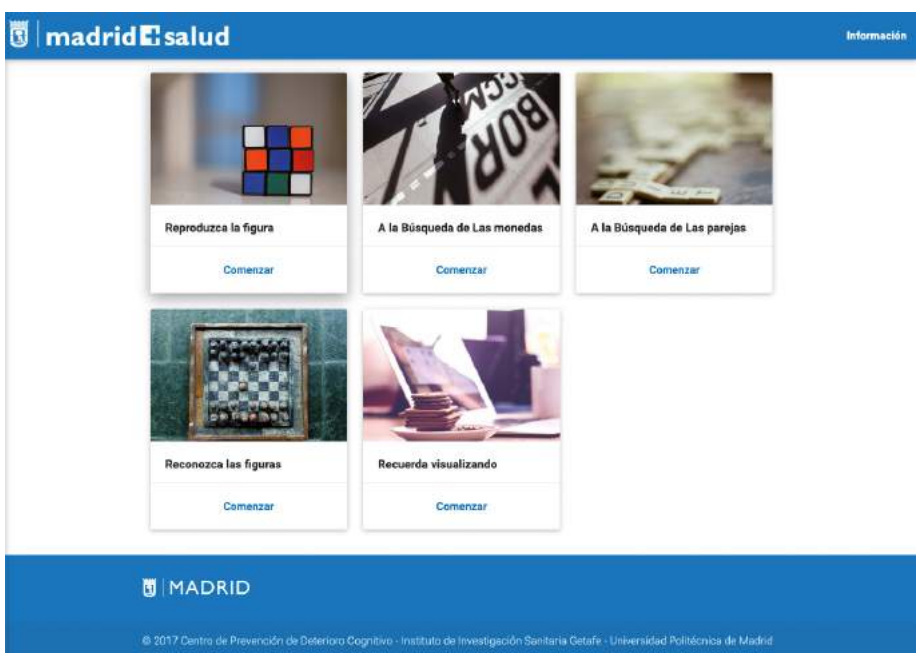


Main results:

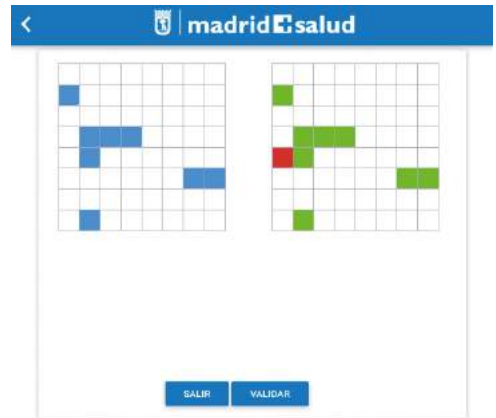
Cognitive exercises for Madrid+ Salud:



Main screen displays the activities available:



Some of the cognitive exercises in execution:



Once finished, results are record and stored on patient profile.

Internet of Things (IoT) for intrinsic capacity monitoring and assessment to prevent frailty and disability

Short description:

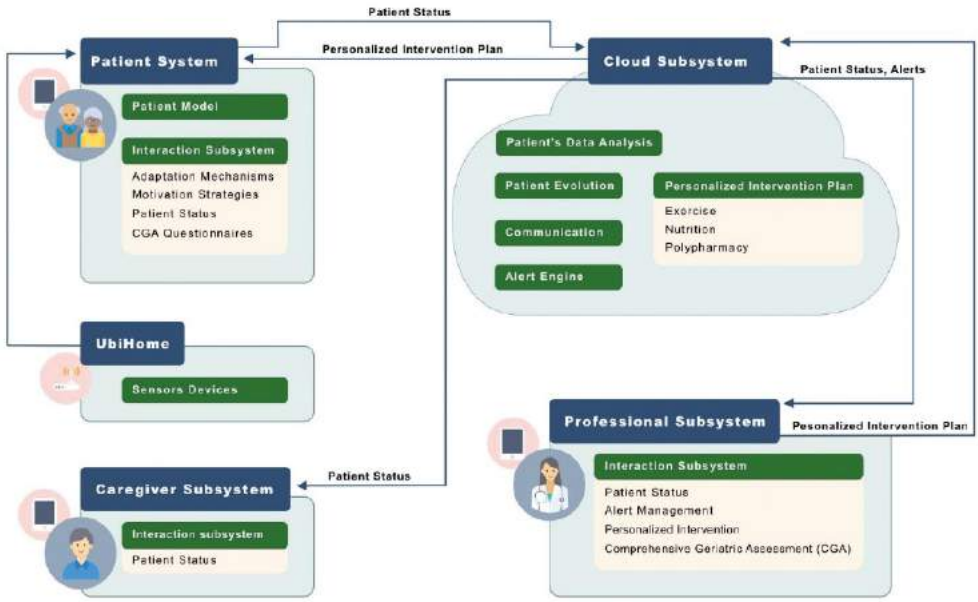
This line of research focuses, on the one hand, on unobtrusive monitoring and follow-up of the intrinsic capacity of the elderly; and on the other hand, on personalized interventions to prevent the onset of frailty, recurring falls, and disability for elderly.

Geriatric assessment is a time-consuming activity. Hospitals count with a limited workforce that is unable to manage all patients so they should focus on treating patients at higher risk. The older population must be monitored in unobtrusive and comfortable environment.

The current research line aims to create a technology able to collect relevant information at community dwelling with the following features: (i) frailty onset or worsening identification, (ii) personalized intervention according to patient health function and psychological dimensions (iii) data extraction and knowledge generation from frailty monitoring, and (iv) professional interventions and assessments.

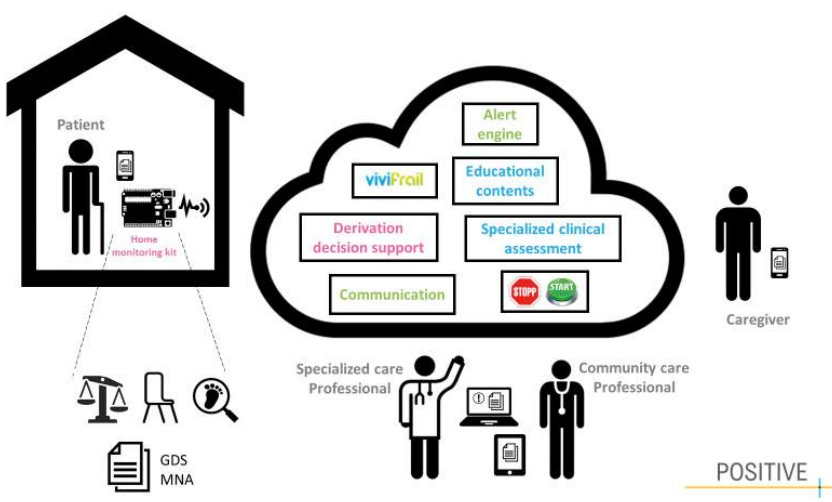
Interventions must consider patient motivation traits and contextual information tied to patient dwelling. Such interventions involve different patient activities, including VIVIFRAIL exercise program for frailty prevention, nutrition behavior, polypharmacy reduction, and promote independence and empowerment through educational content as media, tips, and feedback from healthcare professionals, inter alia.

Accordingly, activities that include devices and/or apps have been designed considering user-centered design and gamification strategies to minimize current generational gap between elderly and technology.



Main results:

Our main contribution in this research line is the design and deployment of an ecosystem that provides unsupervised monitoring of pre-frailty and frailty status in a community setting. To detect the onset of frailty and assess its evolution, a Comprehensive Geriatric Assessment (CGA) has been designed, compose by a holistic evaluation where physical status, mental, social, functional status are assessed. CGA includes the most relevant assessment tools: *Barthel index, Lawton Index, Weight Scale, Gait Speed, Chair Stand Test, Short Physical Performance Battery, Frail Index and Fried Frailty* Criteria for physical assessment; and Mini Nutritional Assessment (MNA) for nutritional status.



These tools have been deployed in order to be implemented at home. To do so, a set of hardware devices connected with mobile apps have been designed to support patient healthcare by health professionals remotely, including setup and data collection from the sensor-based devices.

The *Gait Speed* is a measuring device to monitor patient gait speed, an extensively test used in clinical practices. In a nutshell, the device is a pair of ultrasonic sensors deployed over a folding bar, placed at one side of a corridor, to prevent deterioration and patient injury. Ultrasonic sensors are capable to characterize the patient gait speed without supervision and able to be easily portable and installable at home. Further, the *Chair Stand* device monitors patient lower limb strength using motion sensors.

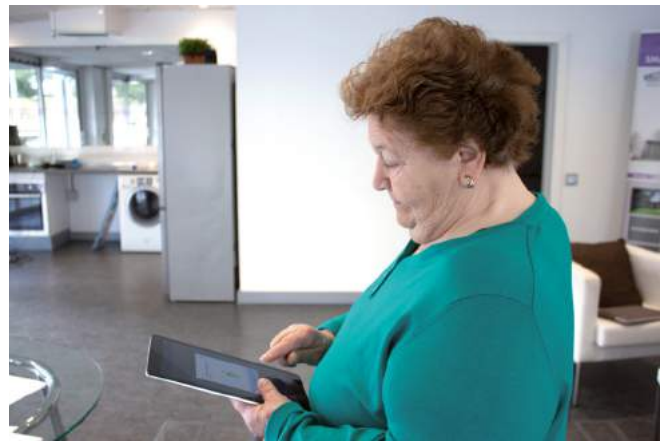
UX and usability for older users

Short description:

This is a transversal research line offering support to every project in the laboratory. It involves the use of the User-Centered Design paradigm to provide all the technological outcomes in the laboratory designed for our target population: elders and their whole ecosystem of integrated care, with an adequate level of usability, user experience (UX), and accessibility.

Elders form a very special segment of users. They are affected by age-related limitations such as:

- Reduced eyesight.
- Hearing loss.
- Memory problems.
- Changes in proprioception and coordination.
- Difficulties for using touchscreens due to skin dryness.



In addition, some of them face literacy and technological skills challenges. They can sometimes limit themselves in the usage of technology because they think they will not be able to learn to use new technology or have been restricted to do so by their loved ones so they don't get into any technological risk (fraud, loss of data, etc.).

Our thesis is that elderly can take advantage of the technology if the design takes them into account, with their special characteristics and limitations. Interaction demands must remain very simple while not losing any informative capabilities.

Motivation is a key aspect for technology adoption. E-health monitoring systems can provide this motivation for the elderly, because they feel that technology can provide them a more regular contact with their physician, and that they are better cared for as a result.

Main results:

The analysis of the results of extensive usability testing with older users of the e-health mobile applications developed in the Ageing Lab has shown that there are some generic usability heuristics that need some adaptation for this kind of users, and there are some specific guidelines to be considered.

Jakob Nielsen proposed 25 years ago a list of teen usability heuristics for user interface design, which have been widely adopted as the generic usability heuristics for application across different domains. Nevertheless, three of this ten heuristics need to be contextualized for this user population, as follows:

- User control and freedom: Older users need a more focused interaction, so there are less options to get the wrong path. A majority of these users have a low IT literacy, being a more directed interaction the most effective interaction design approach.
- Flexibility and efficiency of use: Efficiency of use is typically less important than the error rate for these users. Any strategy to make the expert user more efficient has the risk to increase the error rate, so designers need to be very cautious with this kind of interaction solutions, avoiding providing added flexibility if it can make the interaction more complex.
- Help and documentation: Extensive user manuals or online documentation are a burden for most older users. Alternative approaches like brief and focused tutorials or videos are preferred.

All the rest of Nielsen's heuristics apply for older users, but we have found that consistency and standards is the top priority heuristic to consider when designing a user interface for this user population.

Guidelines obtained for the design of user interfaces for older adults include:

- Use large fonts and enough contrast foreground/background.
- Avoid complex and long pieces of text.
- Provide focus.
- Don't include multiple actions in one screen.
- Use both text and audio for every piece of instruction for the user.
- Use simple backgrounds and don't use text overlaid in images.
- Avoid assumptions about knowledge of common user interface widgets or icons.

C. FACILITIES AND TECHNIQUES

Facilities/Infrastructures

Ageing lab comprises facilities both at the Hospital Universitario de Getafe and the CTB. One lab is devoted to these tasks at the Research Unit of the Hospital Universitario de Getafe, where two full-time researchers work on the previously described research programs and lines.

Techniques

- Mobile computing (mHealth, software engineering)
- User Experience, Human-Computer interaction (User-Centred Design)
- Behavioural biometrics
- Data analytics (machine learning, (stream) data mining, natural language processing)
- Signal processing (data fusion)
- Biomechanics

D. RESEARCH PROJECTS

BRAIN NOISE: Development of novel methods for experimental study and control of stochastic processes in the human brain during visual perception

PI: Alexander Pisarchik

Funding Agency: Ministerio de Economía y Competitividad

Budget: 84.700€

Period: 30/12/2016-29/12/2019

Other institutions participating: Universidad Rey Juan Carlos

BRAIN EXTREME: Characterization and prediction of extreme events in neurophysiological brain activity

PI: Alexander Pisarchik

Funding Agency: UPM

Budget: 4.000€

Period: 01/07/2018-31/12/2018

CATRACLIM: Predictability of catastrophic transitions in climate

PI: Alexander Pisarchik

Funding Agency: UPM

Budget: 4.000€

Period: 01/07/2017-31/12/2017

SMART NEURON: Training neural networks to enhance memory and leaning capacity

PI: Alexander Pisarchik

Funding Agency: Fundación para el Conocimiento Madri+d

Budget: 1.000€

Period: 01/06/2015-31/05/2016

STATIP16: Organization of Seminar and Workshop "Multistability and Tipping: From Mathematics and Physics to Climate and Brain"

PI: Alexander Pisarchik, Ulrike Feudel, Ken Showalter

Funding Agency: Max Planck Institute for Physics and Complex Systems

Budget: 15.000€

Period: 01/11/2014-31/10/2016

Other institutions participating: University of Oldenburg, Germany and West Virginia University, EUA

ACANTO: A CyberphysicAl social NeTwOrk using robot friends-No 643644

PI: Elena Villalba Mora / Leocadio Rodríguez Mañas

Funding Agency: EU - H2020

Budget: 360.000€

Period: 01/02/2015-31/03/2018

Other institutions participating: University of Trento, FORTH, University of Northumbira, University of Siena, INRIA, SERMAS, SIEMENS, Telecom Italia, ATOS, Envitel

■ Web link http://www.ict-acanto.eu/

DECI: Digital Environment for Cognitive Inclusion. Grant No.643588

PI: Elena Villalba / Rodrigo Pérez

Funding Agency: EU - H2020

Budget: 300.000€

Period: 01/07/2015-30/06/2018

Other institutions participating: Foundation of the Polytechnic University of Milan, Fondazione Con Carlo Gnocchi Onlus, Chalmers University Of Technology, Consoft Sistemi, Västra Götalandsregionen, SERMAS, Roessingh Research and Development

■ Web link http://deci-europe.eu/deciproject/

FACET16: Integrated supportive services/products to promote FrAilty Care and wEll funcTion

PI: Francisco del Pozo

Funding Agency: EIT HEALTH

Budget: 96.910€

Period: 01/01/2016-31/12/2016

Other institutions participating: Abbott, SERMAS, ATOS, GMV, Aberystwyth University

- Web link: https://eithealth.eu/project/facet/

FACET17: Integrated supportive services/products to promote FrAilty Care and wEll funcTion

PI: Francisco del Pozo

Funding Agency: EIT HEALTH

Budget: 128.000€

Period: 01/01/2017-31/12/2017

Other institutions participating: Abbott, SERMAS, ATOS, GMV, Aberystwyth University

- Web link: https://eithealth.eu/project/facet/

FACET18: Integrated supportive services/products to promote FrAilty Care and wEll funcTion

PI: Francisco del Pozo / Consuelo Gonzalo

Funding Agency: EIT HEALTH

Budget: 125.000€

Period: 01/01/2018-31/12/2018

Other institutions participating: Abbott, SERMAS, ATOS, GMV, Aberystwyth University

- Web link: https://eithealth.eu/project/facet/

Centro tecnológico para el estudio y tratamiento integrado de los desórdenes neurológicos neurocentro-CM-B2017/BMD-3760

PI: Pilar Herrero

Funding Agency: Comunidad de Madrid

Budget: 26.000€

Period: 01/01/2018- 31/12/2021

Other institutions participating: Hospital Clínico San Carlos, Hospital La Paz, CSIC, Universidad Complutense, Universidad Politécnica de Madrid

- Web link: http://unidaddeinnovacion.shealth.eu/madrid-neurocenter

Contrato privado CUIDAME

PI: Elena Villalba

Funding Agency: Julián Villacastín S.L.

Budget: 20.090€

Period: 01/07/2018-31/06/2019

PAPHOS 2017

PI: Francisco del Pozo

Funding Agency: EIT HEALTH

Budget: 100.000€

Period: 01/01/2017-31/12/2017

Other institutions participating: ATOS Spain S.A, BULL SAS, CEA, GMV, KTH, Université Grenoble Alpes

- Web link: https://www.eithealth.eu/paphos

Ayudas a proyectos de i+d de investigadores posdoctorales

PI: Elena Villalba

Funding Agency: UPM, Programa Propio 2018

Budget: 10.000€

Period: 01/01/2018-31/12/2018

Frailty, falls and functional loss education (3FIGHTS@EDU)

PI: Xavier Ferré

Funding Agency: EIT HEALTH

Budget: 6.000€

Period: 01/01/2018-31/12/2018

Other institutions participating: University of Lisbon, University of Copenhagen

- Web link: https://connections.eithealth.eu/web/internet-eithealth/frailty-falls-and-functional-loss-education-3fights-edu-

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5. Feudel, U., Pisarchik, A.N., Showalter, K., (2018) Multistability and tipping: Fron mathematics and physics to climate and brain, Chaos, 28.
6. Garcia-Vellisca, M. A., Pisarchik, A. N., & Jaimes-Reategui, R. (2016). Experimental evidence of deterministic coherence resonance in coupled chaotic systems with frequency mismatch. Physical Review.E, 94(1-1), 012218.
7. Hramov, A.E., Frolov, N.S., Maksimenko, V.A., Makarov, V.V., Koronovskii, A.A., Garcia-Prieto, J., Antón-Toro, L.F., Maestu, F., Pisarchik, A.N., (2018) Artificial network detect human uncertainty, Chaos, 28.
8. Hramov, A. E., Koronovskii, A. A., Moskalenko, O. I., Zhuravlev, M. O., Jaimes-Reategui, R., & Pisarchik, A. N. (2016). Separation of coexisting dynamical regimes in multistate intermittency based on wavelet spectrum energies in an erbium-doped fiber laser. Physical Review E, 93(5), 052218.
9. Hramov, A. E., Maksimenko, V. A., Pchelintseva, S. V., Runnova, A. E., Grubov, V. V., Musatov, V. Y., et al. (2017). Classifying the perceptual interpretations of a bistable image using EEG and artificial neural networks. Frontiers in Neuroscience, 11, 674.
10. Kumarasamy, S., & Pisarchik, A. N. (2018). Extreme events in systems with discontinuous boundaries. Physical Review E, 98 (3).
11. Makarov, V. V., Zhuravlev, M. O., Runnova, A. E., Protasov, P., Maksimenko, V. A., Frolov, N. S., et al. (2018). Betweenness centrality in multiplex brain network during mental task evaluation. Physical Review E, 98(6).
12. Maksimenko, V. A., Hramov, A. E., Frolov, N. S., Lattjohann, A., Nedaivozov, V. O., Grubov, V. V., et al. (2018). Increasing human performance by sharing cognitive load using brain-to-brain interface. Frontiers in Neuroscience, 12, 949.
13. Maksimenko, V. A., Kurkin, S. A., Pitsik, E. N., Musatov, V. Y., Runnova, A. E., Efremova, T. Y., et al. (2018). Artificial neural network classification of motor-related EEG: An increase in classification accuracy by reducing signal complexity. Complexity.
14. Maksimenko, V. A., Pavlov, A., Runnova, A. E., Nedaivozov, V., Grubov, V., Koronovslii, A., et al. (2018). Nonlinear analysis of brain activity, associated with motor action and motor imaginary in untrained subjects. Nonlinear Dynamics, 91(4), 2803-2817.
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16. Maksimenko, V. A., Runnova, A. E., Zhuravlev, M. O., Makarov, V. V., Nedayvozov, V., Grubov, V. V., et al. (2017). Visual perception affected by motivation and alertness controlled by a noninvasive brain-computer interface. Plos One, 12(12), e0188700.
17. Maksimenko, V. A., Runnova, A. E., Zhuravlev, M. O., Protasov, P., Kulanin, R., Khramova, M. V., et al. (2018). Human personality reflects spatio-temporal and time-frequency EEG structure. Plos One, 13(9).
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19. Pisarchik, A.N., Jaimes-Reategui, R., Gracia-Vellisca, M.A., (2018) Asymmetry un electrical coupling between neurons alters multistable firing behavior, Chaos, 28.
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Bioinstrumentation and Nanomedicine (UPM)

PRESENTATION/INTRODUCTION

The main aim of this laboratory is the development of new devices for medical or social use in order to help practitioners and other related workers to improve people's health and wellbeing. We co-create new solutions from sharing with final users and other stakeholders the process by which the problem is first identified and afterwards its solution is designed, implemented and finally is validated to measure the real added value. We specially contribute to that process in the prototype design and implementation stages where we can apply our expertise in electronics (new developments and/or integration of commercial sensors) and software development (instrumentation control, virtual and augmented reality tools and AI techniques). Our target as final outcome is the deployment of technology ready to be transferred to the health sector and to the society.

A. MEMBERS

PI: José Javier Serrano Olmedo

PhD students: Michael Zeinoun, Andrés Martínez Miranda, Rodolfo Maestre, Luis Armando Carvajal Ahumada, Carlos David Amaya Jaramillo, Oscar Casanova Carvajal, Nancy Enriqueta Guerrón Paredes

Others: A number of pre-graduated students usually contributes to the research as they perform several academic tasks (practices, final degree thesis, etc.). We also have permanent collaborations with other laboratories from CTB and from outside.

B. RESEARCH LINES

Design of medical devices: new sensors and instruments

Short description:

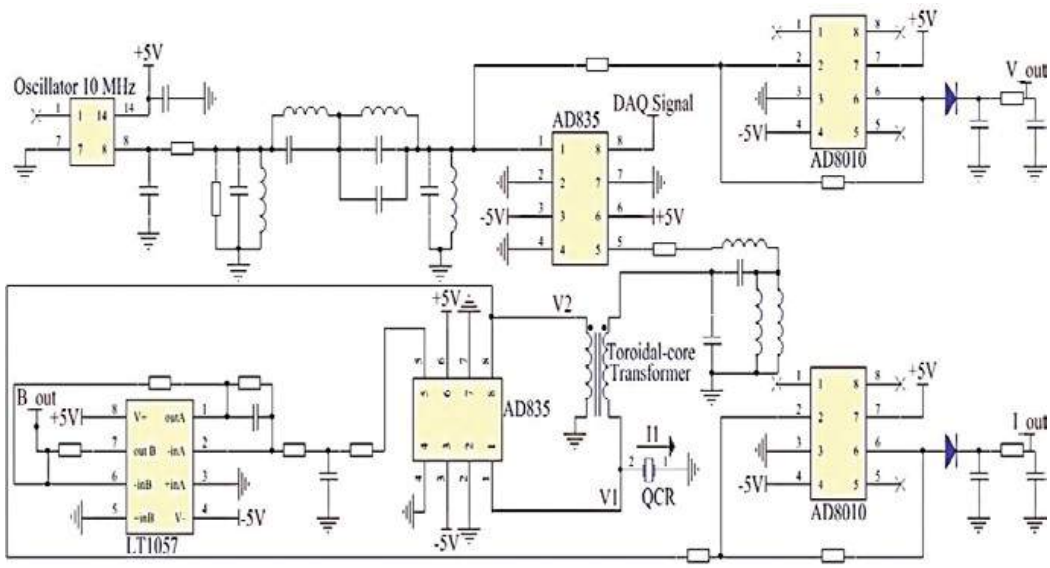
We are exploring solutions for new and old problems by taking advantage of the rising of new technologies from a variety of fields: microelectromechanical systems (MEMS), high throughput digital converters, high frequency electronics and piezoelectric materials, artificial intelligence and machine learning, etc.

Each new improvement of these enabling technologies offers possibilities to overcome still unsolved problems, which demand reliable measurement of physiologic variables or the enhancement of the efficiency of existing medical devices.

Particularly we are currently working two main branches:

- Electromedical instruments with more refined and even other novel characteristics like the new objective audiometric system which has generated the spin-off *LBN Innovative Solutions S.L*. Contrary to what is conventional, the patient does not need to actively participate in the auditory test because no verbal answer is expected while performing the task. The system determines the loss of hearing automatically and autonomously.
- Devices based on the use of inertial measurements units (IMUs). Many passive world wide spread devices for the daily life, sports and physical rehabilitation are waiting to be made smart from integrating movement and position tracking sensors, low power communications and some algorithmic for the new Internet of Things (IoT) era.

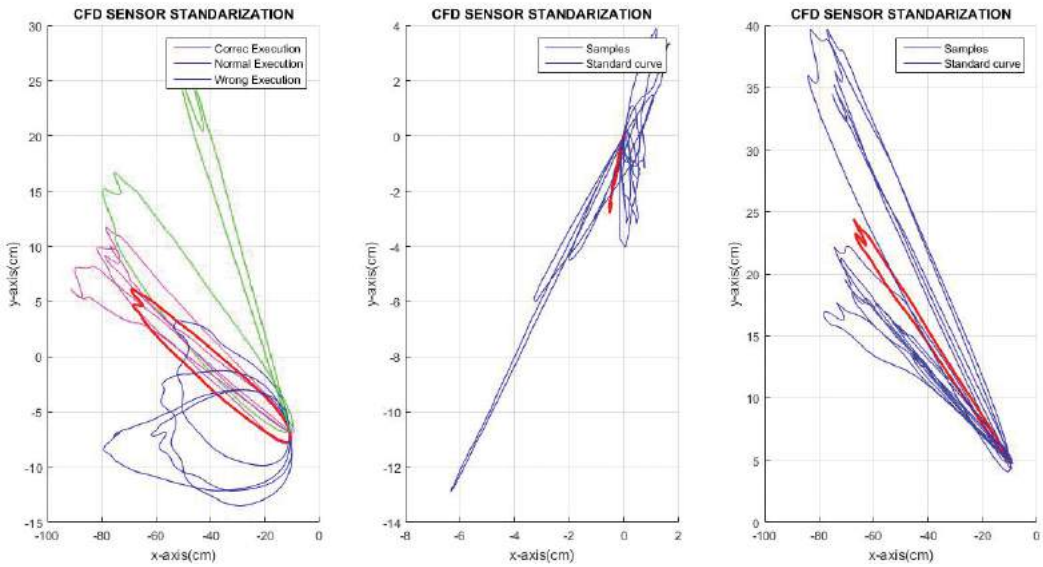
■ Circuit developed for signal conditioning of quartz scale microbalance sensors developed in the LBN



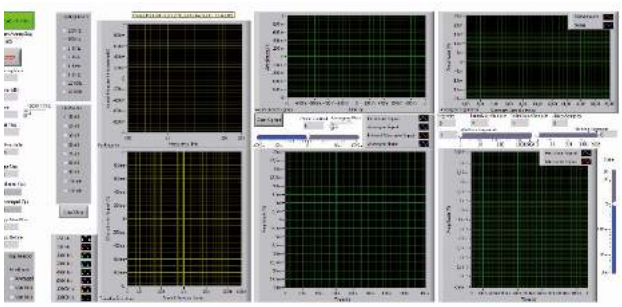
Main results:

1. Smart Kneepad. We are developing a smart knee pad to measure knee performance when doing sports, daily life activities or knee rehabilitation.
2. An objective audiometer which does not need the active collaboration of the patient. Especially useful for babies and for elderly with cognitive impairment.
3. A new family of biosensors based on the use of low-cost quartz microbalance (QCM). Measurement of viscosity in very tiny amounts for biological fluid is possible in the first step. Detection of cells and, up to some extreme, identification of them is in the path ahead.

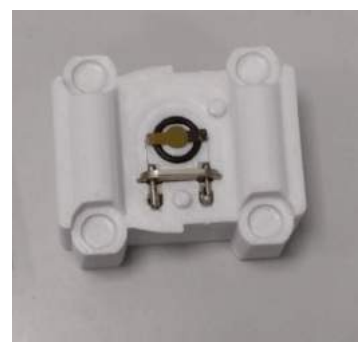
■ Traces followed by several points of a knee when doing a squat



■ First prototype of the objective audiometer: hardware and user interface



■ First prototype of the biosensor based on QCM



Development of hyperthermia induction in living tissues with optical, magnetic and radiofrequency related energies, as new tools for anticancer therapies

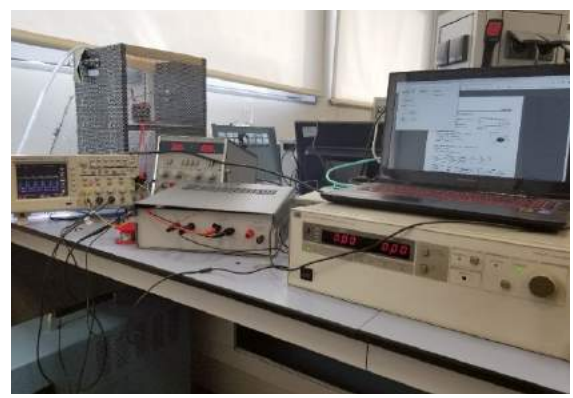
Short description:

Hyperthermia as a mean to facilitate therapies against cancer and other diseases has a long history. The use of nanoparticles as vectors to deliver heat or mechanical energy to the cancerous cells or tissues is showing many side effects, mostly related to the need of huge amounts of energy to be applied or very high nanoparticles concentrations that, afterwards, are toxic and of a general concern even is toxicity is not very explicit. Therefore new techniques are needed to make hyperthermia more effective, either changing the energy delivery mechanism or making better respondent particles.

We have chosen the first way, and we are developing various instruments where the core idea is to change some aspects of the current conventional techniques in order to dramatically reduce the amount of energy needed to provide hyperthermia at the lethal level. We are working on several techniques:

1. Two different ways of applying optical hyperthermia, which uses gold nanoparticles as heat vectors. We assay with the biofunctionalization to make the particles to arrive to the cells and to be internalized by them, and also we try new ways to deliver the energy using other particles as auxiliary ones to increase the optical density in the volume of therapy, so that the gold nanoparticles could be more effective in transforming the energy of the light in heat.

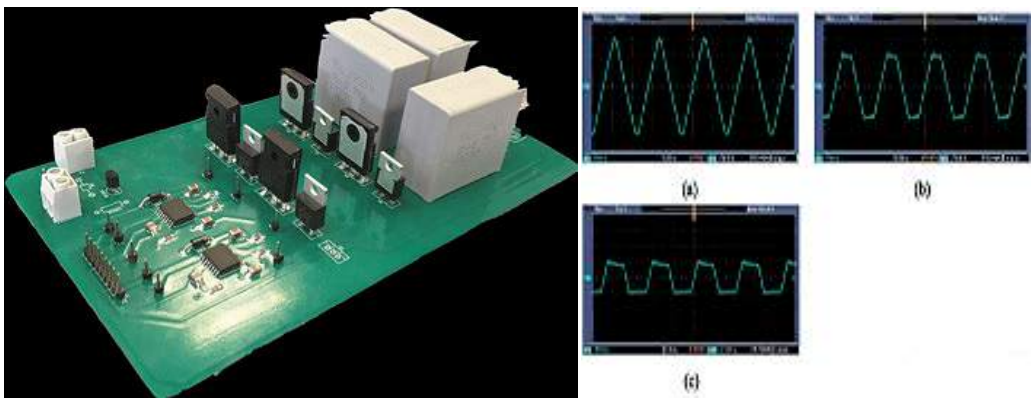
■ Development of new instruments for magnetic hyperthermia at LBN



2. Two different magnetic/radiofrequency designs, which use magnetic nanoparticles and microparticles to heat the samples. We explore other waveforms and mechanisms of activating the energy delivery (heat and mechanical energy) to produce lethal effects. This leads to the developing of new instrumental designs.

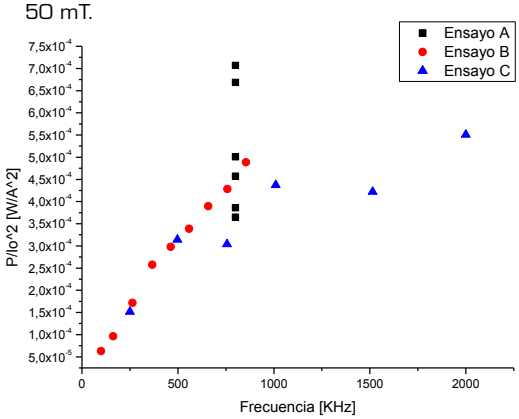
Main results:

■ Prototype of non-conventional RF hyperthermia system

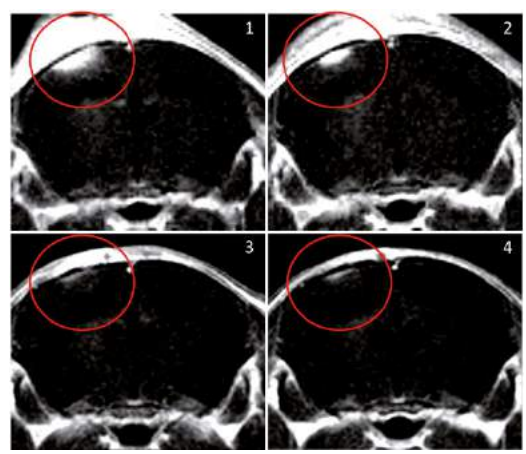


The experiments in magnetic hyperthermia with new signals different from the conventional sinusoidal one demonstrate (square dots) that not only frequency is ruling the power delivery as classical theory says but that up to 40% increase is achievable just adjusting the active cycle with square waveform a fixed frequency.

■ The system is unique and can produce alternating magnetic fields from DC to 1 MHz with different waveforms (square, triangular, trapezoidal) up to 50 mT.



■ Although it is not statistically significant, and new experiments and now been carried on, when assaying a new technique to remove brain tumors (glioblastoma multiforme) in mice using optical hyperthermia, while we could demonstrate the slowdown of the tumor growing, we also could observe in a couple of cases an almost complete removal of the treated tumors. Steps 1 to 4, one per week, observing the reduction of the tumor.



Design of medical devices: new sensors and instruments

Short description:

Development of systems to ease the social integration of people with different sensorial capabilities, especially in the labor market. Starting on the new paradigm of the Internet of Things (IoT), we work on the design of applications and devices that can offer new tools for the disable people for their daily life activities or as new aids in order to improve the rehabilitation procedures by which they can acquire the skills they need to become fully integrated. Disable people have to overcome the many barriers they find when accessing common situation in the regular life (labor place, transportation, free time, home, etc.). In the case of sensory handicapped people, especially blind people, they don't receive the feedback from the surrounding that is used almost unconsciously by sighted people, to regulate their physical actions and their living together in society.

■ Example of virtual space for training of blind people

Therefore, the new aids must be design to overcome this disadvantageous situation by providing them with the missing data and information. We use virtual and augmented reality technologies (UNITY, 3D video capturing and processing) and integration of several kinds of sensors (IMUs, pressure sensors, electromyography, diadem for EEG capturing, etc.) and other devices (beacons, bone headphones), altogether with processing of data using AI technologies as the basis for the aids we are developing.

Main results:

eGLANCE (http://eglance.ctb.upm.es/es/eglance/). We have developed a methodology to help the autonomous mobility in-doors of blind people that we call eGLANCE. We can help blind people in two complementary ways.

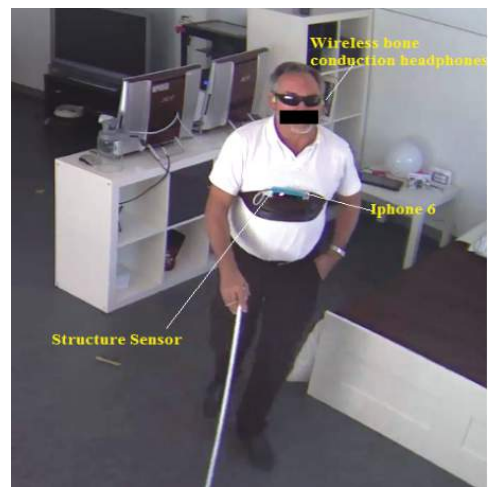
Virtual Visit. Places that want to be friendly for blind people are virtualized and the obtained virtual space is enriched with related information. From this, we generate an application as a kind of virtual game to be played by blind people. The user gathers the

■ Figurative representation of a virtualized space being virtually visited by a blind

capability to remotely explore those places when using the corresponding games. The goal here is that the blind acquires the knowledge about those spaces as if they had physically visited them. Then, in case they visit them physically, they can manage in a more autonomously way as compare with the common situation when they need a lot of help or they need to spend much time to explore the place have get an idea about the infrastructure, the furniture, etc. In case of visiting public spaces like hotels, mall, offices, etc. blind people are not going to be so dependent on other people help if the had previously "visit" the space.

Real visit. When visiting a real space we can also help because we have developed a methodology to track the blind position and orientation as they move around. Therefore, if the space has been previously virtualized, the blind can be informed proactively or on demand by the system on what furniture, infrastructure, objects are near or far of their position. The name of the project "eGLANCE" is given from comparison between what a sighted people, take a look, or have a glance, to know about what is around. eGLANCE operates under the same idea, the blind can "have a glance" aided by the system. Therefore the blind can be informed about facts and objects in a similar way as a sighted is, then, hopefully, reducing the barrier that in-doors spaces oppose to the mobility of the blind people.

■ Volunteer testing the real visit concept in the LST living lab at ETSIT



C. FACILITIES AND TECHNIQUES

Facilities/Infrastructures

Fast prototyping infrastructure

The laboratory contains a quite complete set of instruments for fast prototyping including electronic and chemistry instrumentation. It is possible to design and develop electronic circuits (analog and digital) for applications in a very wide range of frequencies from DC to the microwave limit (20 GHz). The instrumentation includes, together with conventional bench instrumentation, non-conventional like picoamperometry, lock-in amplifier up to 104 kHz, several spectrum analyzer raging from ultra-low frequency up to the microwave limit and a set of tools to build microwave experimental sets. The laboratory can solve electronic problems by producing the prototypes from scratch to the minimum valid device. It includes a solder station for surface mounting of integrated circuits, 3D printers (3D PRINTING, Anycubic i3 Mega uses FDM technology) for print pieces with PLA or ABS materials with maximum dimensions of 210 x 210 x 205 mm) and other workshop tools for fast prototyping.

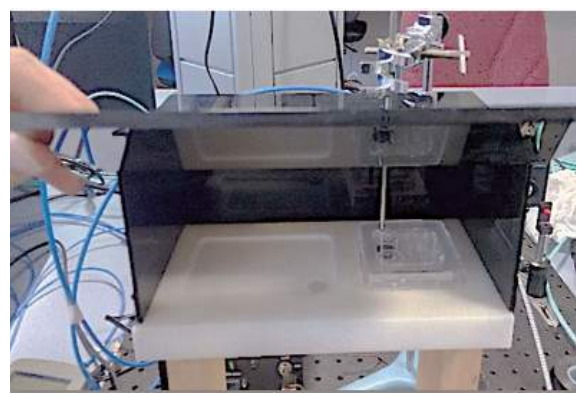
To be able to manage the application side of the problem, the laboratory has a ventilated chamber to allow for working with some toxic chemicals, and other means like selective electrodes for electrochemical measurements, a centrifuge, a rotational viscometer, a couple of ovens for material curing with controlled temperature patterns, a microgram balance, and other devices for managing chemical reactions, etc.

■ Some pictures of the lab facilities

Optical hyperthermia

Commutable wave (CW) laser from DC up to 25 kHz, working at 808 nm, with a maximum output power of 5 W, beam height from base of 29 nm, beam diameter at aperture of 5-8 mm. Some auxiliary instruments like powermeter, spectrometer, monochromator, and optical fibers to set the perfectly controlled experiments. A dark box to prevent laser light to run out of the system, containing a sample holder for cell cultures grown in standard holders and calibrated temperature meter are the main elements of the experimental area. To measure temperature there capability to do it by means of optical fibers with a resolution of 0.02°C in the range from 4°C to 80°C, in eight independent points of measurements.

■ Details of the laser (left) and dark box for experimentation



Magnetometer of high resolution

Magnetometry on nanoparticles in solid form, ultra thin films, powders, liquids and even slurries: magnetization curves, coercitivity (normal and remanent), magnetization vs. time curves, first order reversal curves (FORC) diagrams, diamagnetic and paramagnetic susceptibilities (measurement of the gradient in the second quadrant), remanent and saturation magnetization, initial permeability.

■ Alternating gradient force magnetometer (CIBER-BBN facility for the characterization of magnetic nanoparticles)

Equipment description: Alternating Gradient Magnetometer: MicroMag M2900-4 AGM (Princeton Measurements Corporation, USA) for the magnetic and mechanical characterization of nanoparticles in various different media: Magnetic Moment Range: 1nA.m' to 5mA.m' full scale (1μemu to 5emu). Resolution: 0,005% of full scale with 60% overrange capability. Speed of measurement: 100 ms/point. High sensitivity: 10 pA.m² (10 nemu) of standard deviation at room temperature and with 1 second of averaging time. High performance with samples of very small magnetization and dimensions (few nanometers). The AGM can accommodate a large range of samples with widely different properties.

Fast Magnetic Field Cycling Relaxometer.

Measurement of the relaxation times in aqueous solutions and biological samples containing superparamagnetic nanoparticles as contrast agents for MR images. For T1 in the continuous range 10kHz to 80MHz; for T2 in the range 10 M Hz to 80MHz, Characterization of contrast agents for MR imaging, ascertaining their relaxivity and the dominant effect, Measurement of the Nuclear Magnetic Relaxation Dispersion (NMRD) profile of samples in aqueous solutions and biolog1cal media.

Equipment description: T1 and T2 Nuclear Magnetic Resonance Relaxometry: Stelar SmarTRACER (Italy) + Bruker (Germany) 2 T electromagnet. Fast Field Cycling designed to measure longitudinal nuclear magnetic relaxation as a function of the magnetic field intensity. Measurements of the longitudinal (T1) and transverse (T2) time constants as a function of the Larmor frequency. Measurement range: continuous measurement from 10kHz (almost null field) to 10 MHz (0.25T) to obtain T1. Measurement range: measurement from 10 MHz (0.25T) to 80 MHz (1.9T) at desired intervals to obtain T1 and T2. Inhomogeneity lower than 150 PPM. Main pulse sequences 1mplemented with the possibility of modifying

parameters to the design and programming of new sequences. Temperature control from -120˚(to +140˚(with accuracy and stability of 0.1˚C).

■ Relaxometry equipments (CIBER-BBN facility for the characterization of magnetic nanoparticles)

Techniques

VR/AR applications development: Development of virtual games based on UNIT for Virtual/ Augmented reality applications and IoT system developments.

D. RESEARCH PROJECTS

Development of an automatic objective audiometric system based on microphonic cochlear signals detection

PI: José Javier Serrano Olmedo

Funding Agency: Ciber BBN & LBN innovative solutions S.L.

Period: 2014-2019

Desarrollo de un modelo de biosensensor con fines de detección de tuberculosis

PI: José Javier Serrano

Funding Agency: Centro de Investigación y Desarrollo de Electrónica Industrial de Colombia

Period: 2014-2017

eGLANCE: sistema tiflotécnico para la integración laboral de discapacitados visuales

PI: José Javier Serrano

Funding Agency: Consejo de Cátedras Indra-Fundación Adecco

Period: 2014-2019

Development of new nanoparticles and protocols for enhanced hyperthermia. Nanohyperthermia

PI: José Javier Serrano

Funding Agency: CIBER-BBN

Period: 2014-2020

Biological Fluid Viscosity Measurement by Gravimetric Transducers (ViscoGrav)

PI: José Javier Serrano

Funding Agency: CIBER-BBN

Period: 2018-2020

Asistente virtual para apoyo al entrenamiento para la movilidad de invidentes

PI: José Javier Serrano

Funding Agency: SENACYT

Period: 2014-2018

Estudio de nuevas aplicaciones del resonador de cristal de cuarzo (QCR) para la caracterización de propiedades viscoelásticas de fluidos biológicos de interés para diagnosis médica

PI: José Javier Serrano

Funding Agency: CONACYT

Period: 2018-2021

E. PUBLICATIONS

1. Ahumada, L. A., Gonzalez, M. X., Sandoval, O. L., & Olmedo, J. J. (2016). Evaluation of hyaluronic acid dilutions at different concentrations using a quartz crystal resonator (QCR) for the potential diagnosis of arthritic diseases. *Sensors (Basel, Switzerland), 16*(11), E1959.
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3. Fernández-Cabada, T., Pablo, C. S. d., Pisarchyk, L., Serrano-Olmedo, J. J., & Ramos-Gómez, M. (2016). Optical hyperthermia using anti-epidermal growth factor receptor-conjugated gold nanorods to induce cell death in glioblastoma cell lines. *Journal of Nanoscience and Nanotechnology, 16*(7), 7689-7695.
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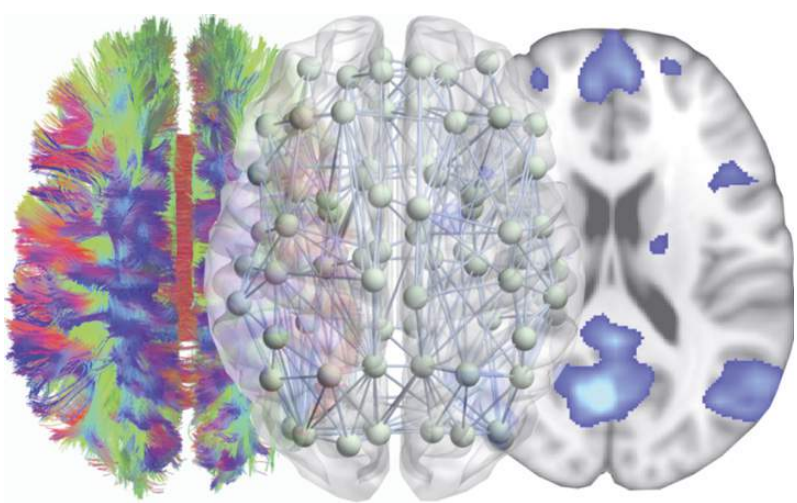
Biological Networks (UPM-URJC)

PRESENTATION/INTRODUCTION

The Laboratory of Biological Networks aims at increasing the understanding of the structural and functional organization of biological systems using methods from statistical physics, nonlinear dynamics and network science. Our research combines a comprehensive approach mixing analytical treatment with large scale numerical modeling, and a corroboration of the entire body of predictions by means of real data analysis and experiments conducted at our laboratories of Nonlinear Dynamics & Networks and of Neuronal Cultures.

The way an ensemble of units of a system arranges its interactions into a complex topological wiring of connections, or accommodates its dynamics into a collective state, is at the basis of the functioning, performance, robustness and adaptability of a wealth of biological networked systems. Examples include from genes, proteins and metabolites interacting in the cell, to neurons operating collectively in a culture or in the brain. Therefore, it is of the paramount importance to properly frame such systems into unifying concepts and representations, as well as to fully understand the way they organize their topological and dynamical states. Our work is organized into two interrelated areas, focusing on neuronal dynamics at both the micro-(cellular) and macro-scale (whole brain).

■ Network Neuroscience takes advantage of nonlinear dynamics, statistical physics, graph theory and Big Data to analyze hoe the structure and functioning of the complex interactions of the brain are related to the process occurring in it



A. MEMBERS

PI: Javier Martín Buldú
Senior researchers: Juan A. Almendral, Inmaculada Leyva, Irene Sendiña-Nadal
PhD students: Ignacio Echegoyen Blanco, Alejandro Tlaie Boria

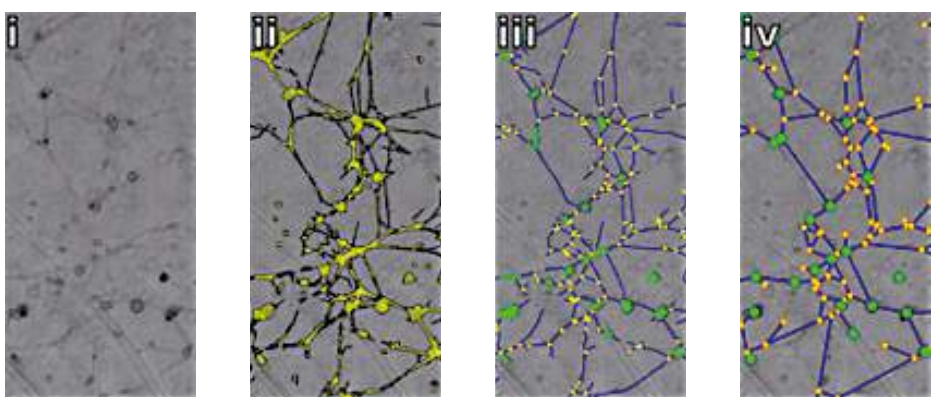
B. RESEARCH LINES

Structure and function of cultured neuronal networks

Short description:

At the cellular level, we use in vitro two-dimensional cultures of neurons as a paradigmatic model of the mechanisms governing the dynamics of neuronal growth and network organization in their in vivo counterparts. We investigate self-organization phenomena in networks of in-vitro neuronal cultures during the course of development. In parallel with the morphological development, we have started working on data from extracellular recordings to elucidate the relationship between the complexity associated with the registered electrical signals and the topological properties of functional networks.

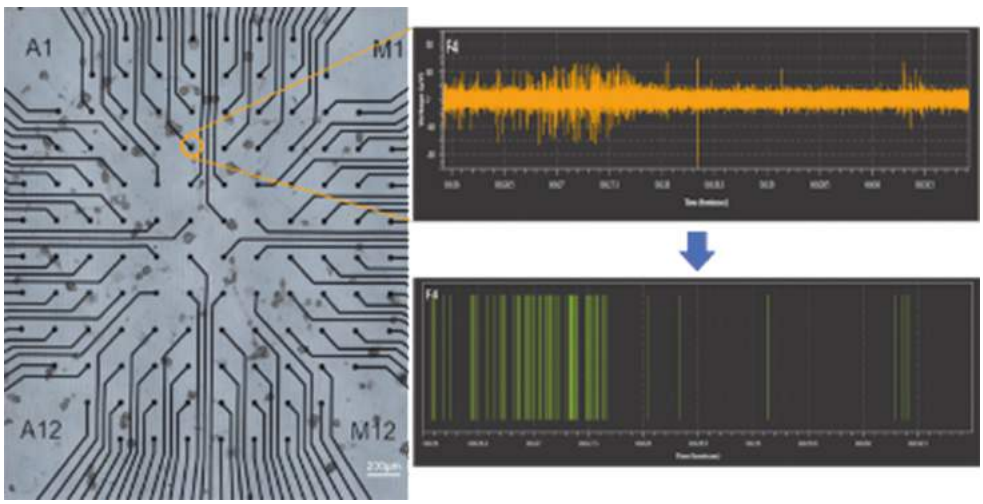
■ Graph-based unsupervised image segmentation algorithm for the longitudinal tracking and modeling of the underlying network structure of neuronal cultures.



Our ultimate aim is to be able to simultaneously study the anatomical and functional neuronal networks, to understand the structure-function relationship and to help devising new methods for brain functional network reconstruction.

We also model and simulate the emergent dynamics of coupled neuron-like units, with both chemical and electrical synapses using the connectome observed in the neuronal cultures and characterized by the setting of a small-world connectivity, a property that has direct implications for the integration-segregation balance of the neuronal activity.

■ A cultured neuronal network grown on top of a 120 microelectrode array (MEA) which allows monitoring the activity of the whole network of neurons. The highlighted electrode (F4) is recording the spiking activity of a neuron (top-right panel), extracellular signals produced by the action potential of a neuron. Through a voltage threshold process, the voltage time series is transformed into a sequence of spiking time stamps (bottom-left), which can be used to construct a functional network.

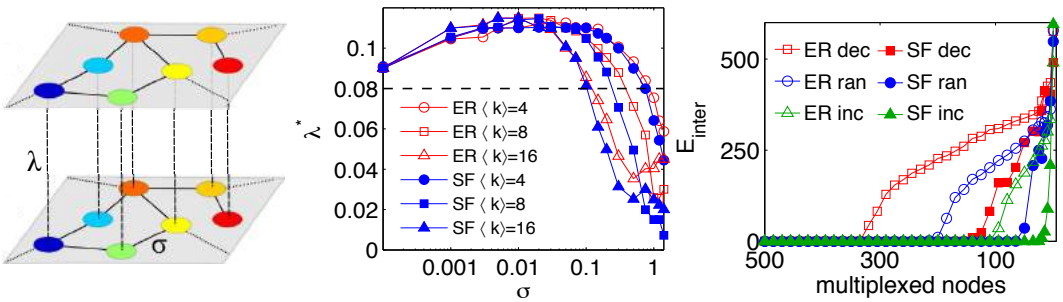


Main results:

Our main results uncover the emergence of collective dynamical effects in multiplex networks, specifically on the as yet unnoticed phenomenon of inter-layer synchronization, whereby each constituent in a given layer of a system undergoes a synchronous evolution with all its replicas in other layers, regardless of whether or not it is synchronized with the other units of the same layer. Our findings provide novel hints that may be useful in elucidating fundamental questions in regard to emerging phenomena in complex systems, such as how biological systems can collectively organize in a redundant way so that their effective functioning occurs through distinct (yet synchronized) layers of interactions (Sevilla-Escoboza et al., 2016, Leyva et al., 2017).

We have also investigated relay synchronization, an important phenomenon allowing distant coordination between two not directly connected oscillators as it occurs in neuronal populations through thalamo-cortical pathways. Using as a framework multiplex networks of several layers of oscillators, inter-layer synchronization occurs between distant layers mediated by a relay layer that acts as a transmitter. We found that, as long as symmetry conditions are preserved, lower degree nodes in the synchronized outer layers are responsible for the resilience of the synchronous state, while hubs can be safely disconnected. Our results provide a new path for starting the study of the role of symmetries in setting long distance coherence in real systems (Leyva et al., 2018).

■ (Left) Schematic representation of a multiplex of two layers of identical oscillators which evolve synchronously (same color top and bottom) while oscillators within each layer are not synchronized (different colors). (Middle) The onset for the inter-layer synchronization as a function of the intra-layer coupling strength σ for different network topologies. (Right) The inter-layer synchronization state persists even if a large fraction of nodes is disconnected.



We also further extended our research in explosive synchronization, an abrupt transition between incoherent and synchronized states in networks of coupled oscillators (with two review works, Boccaletti et al., 2016; Leyva et al, 2018) to an adaptive network model based on the competition between attractive coupling at the node level and anti-Hebbian repulsive dynamics at the link level. The dynamical organization of the emerging systems leads spontaneously to degree-frequency correlation at the node level, a structure typically associated to networks able to sustain explosive synchronization. Our results can widen our understanding of the shaping mechanisms behind the structural organization of some real-world systems such as brain networks where the emergence of explosive synchronization has been observed (Avalos-Gaytán et al., 2018).

Functional brain networks

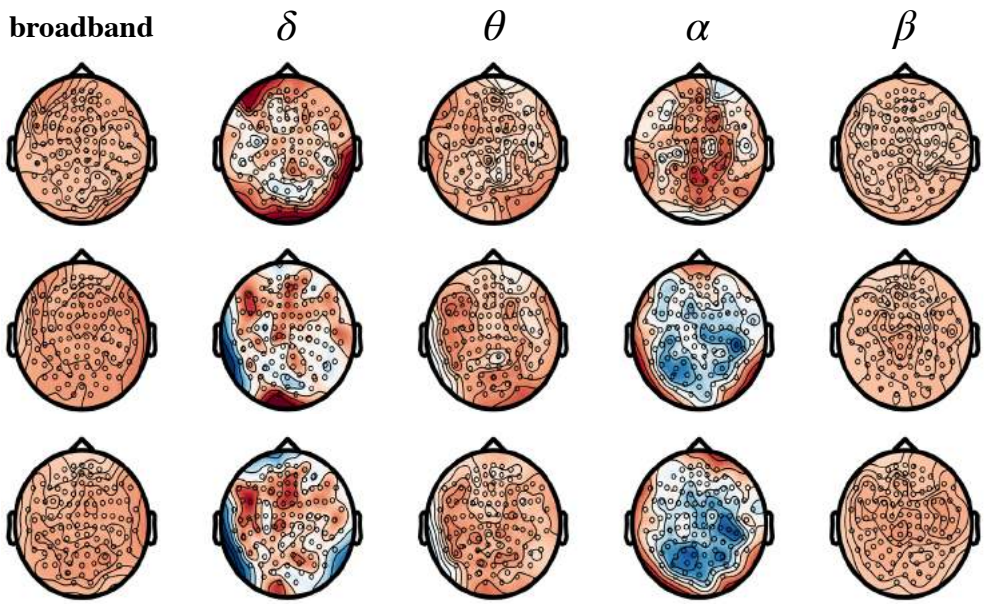
Short description:

At the macro-scale, our unique access to MEG recordings from both healthy subjects and patients suffering from different diseases, allows us monitoring the time-varying reorganization of functional networks.

A key issue in neuroscience is the coexistence of local specialization and long distance integration in brain functioning. Graph theory approaches lead to a characterization of structural and functional brain networks, typically endowed with high clustering and short topological distance between nodes (Papo et al., 2014a, 2014b, 2014c). In addition, functional networks analysis helps identifying signatures of impairment in pathological conditions, such as Mild Cognitive Impairment or Alzheimer's disease (AD).

The identification of pre-symptomatic indicators of disease could significantly enhance the benefit of new drugs and vaccines in AD and other diseases. In this sense, we have experience in modeling both traumatic (Castellanos et al., 2010) and neurodegenerative brain diseases (Buldú et al, 2011) with evolutionary network models.

■ Characterization of brain activity at difference frequency bands. In the panel, different brain regions are identified to be the hubs of the functional networks of three different groups of individuals: (i) mild cognitive impairment vs. controls (upper row), (ii) Alzheimer's disease vs. controls (middle row) and (iii) Alzheimer's disease vs. mild cognitive impairment (bottom row).



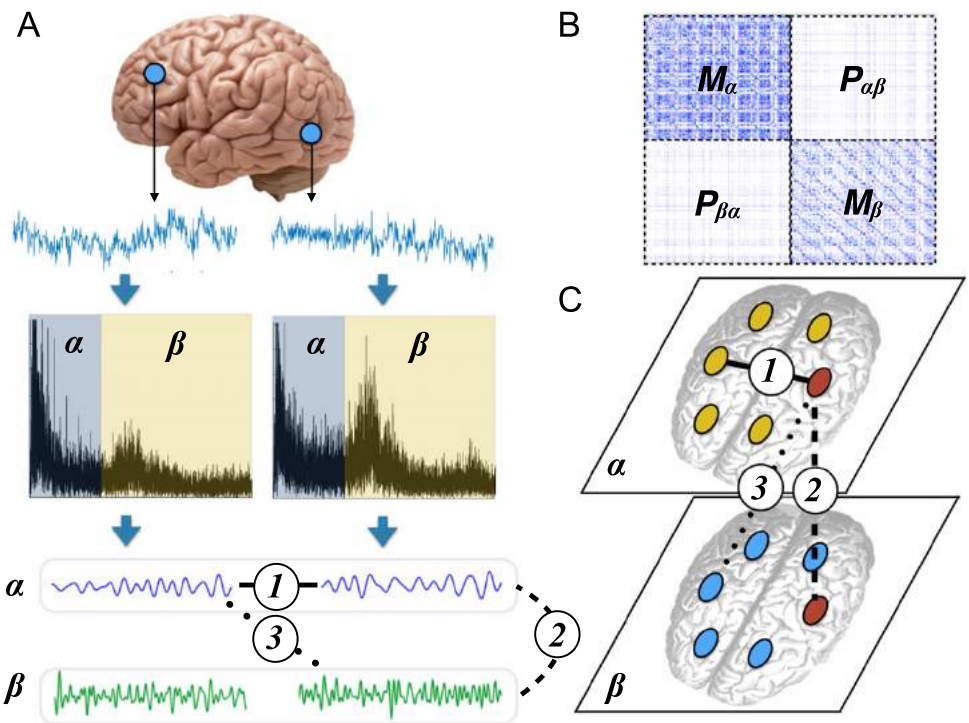
Parallel to these main lines the Laboratory of Biological Networks is also concerned about the development of new theoretical and methodological tools aiming to describe and understand how complex networks organize and function, with applications not only in biology but also in technological and social systems.

Summarizing, the goal of the Group of Biological Networks is to foster new insights about the functioning and organization of real-world biological networks, which we expect will generate applications of relevance and value for basic science, industry, and the society in general.

Main results:

The identification of presymptomatic indicators of a given disease could significantly enhance the benefit of new drugs and vaccines in AD and other diseases. In this sense, we have experience in modeling both traumatic (Castellanos et al., 2010) and neurodegenerative brain diseases (Buldú et al., 2011, *PLOS ONE*) with evolutionary network models. Furthermore, we are experts on the application of Network Neuroscience to describe healthy aging, evaluate cognitive reserve (Martínez et al., 2018) or the ability of the brain to overcome active interferences (Ariza et al., 2015). We have also contributed to the development of new methodologies to obtain hidden information from functional brain networks (Buldú et al., 2018; Martínez et al., 2018b).

■ Encoding brain dynamics as a multilayer functional network. (A) We band-pass filter the MEG signals at two frequency bands: alpha [8-12] Hz and beta [12-30] Hz. We use mutual information to quantify coordination between brain regions. This yields three different type of functional edges: Edge type "1" quantifies coordination between different regions at the same frequency band; edge type "2" corresponds to interlayer edges, which couple the activity of the same region at different frequency bands; and edge type "3" quantifies cross-frequency coupling (CFC) between two brain regions. Multiplex networks include only edges of types 1 and 2, whereas more general multi- layer networks include all three types of edges. (B) Schematic of the supra-adjacency matrix of a two-layer network. (C) Schematic of the intralayer and interlayer edges in the multilayer functional network.



C. FACILITIES AND TECHNIQUES

To carry out the described research activities, the group manages the *Laboratory of Neuronal Cultures* and the *Laboratory of Nonlinear Dynamics & Networks*; both infrastructures are designed to conduct experiments for the understanding of the behaviour of biological systems from the network science perspective.

Facilities/Infrastructures

Laboratory of Neuronal Cultures

The Laboratory of Neuronal Cultures is fully equipped to produce primary cultures of neurons extracted from the frontal ganglia of the Schistocerca gregaria specimens and to perform

automatic neuronal morphology detection using phase contrast microscopy and extracellular electrophysiology with microelectrode arrays of any type of neuron or brain tissue culture.

Equipment:

- Nikon Eclipse Ti-S with a XYZ motorized stage
- In vitro microelectrode array system (MEA 2100 from Multichannel Systems) with temperature control
- Zeiss Stemi 2000-C stereo microscope
- Horizontal laminar airflow workstation
- Incubator
- Eppendorf Minispin plus microcentrifuge
- Vacuum pump, ph-meter, autoclave
- Cages for locust cultures

■ Laboratory of neuronal cultures. Microscope and multi-electrode array image.

Laboratory of Nonlinear Dynamics & Networks

The main objective of the Laboratory of Nonlinear Electronics is to construct small to intermediate networks of electronic oscillators to analyze the interplay between the structure and dynamics of networks. The activity of the Laboratory is fundamental to relate the results obtained in electronic networks with those reported in functional and anatomical brain networks. The Laboratory of Nonlinear Electronics is fully equipped to generate, acquire and process analog and digital signals allowing to carry out the implementation of networked electronic circuits. The Laboratory has 3 analog-to-digital acquisition cards, several delay lines, 2 electronic oscilloscopes and the software for controlling and recording the dynamics of networks of up to 96 electronic oscillators.

Equipment:

- 1 Oscilloscope Agilent Technologies DSO 3202A 1GSa/s, 2 channels
- 2 Data acquisition card: NI USB-6259 32 inputs, 4 outputs. 1MSa/s
- 1 Data acquisition card: NI USB-6363 32 inputs, 4 outputs. 8 MSa/s
- Different electronic implementation of nonlinear oscillators: (i) Rössler system, (ii) Lorenz system, (iii) Chua circuits, (iv) electronic neuron models
- 4 personal computers

■ Example of 32 Rössler oscillators connected through ha small-world topology. Coupling and acquisition is controlled and recorded by an analog-to-digital card. The signal is sent to a personal computer and can be controlled in real time.

Techniques:

- **Analysis of neuron cultures:** Longitudinal analysis of anatomical neuronal networks from optical observations and extraction of the adjacency matrix using image segmentation software.
- **Multielectrode array recordings and analysis:** Longitudinal analysis and stimulation of functional neuronal networks from recordings of extracellular potentials of neuronal cultures grown on top of microelectrode arrays.
- **Analysis of EEG/MEG datasets:** Construction of functional brain networks based on EEG/MEG recordings and analysis/interpretation of their structure.
- **Analysis of social networks:** Acquisition of Twitter activity (subjects, companies, etc…) and projection of the datasets into networks. Detection of spreaders and most influencer users together with their basin of influence.

D. RESEARCH PROJECTS

Interaccion entre Estrucura y Función en Redes Complejas: Teoria, Experimentos y Aplicaciones (Fis2017-84151-P)

PI: Irene Sendiña-Nadal & Javier M. Buldú

Funding Agency: Ministerio de Economía y Competitividad (MINECO)

Period: 2018-2020

Other institutions participating: Universidad Politécnica de Madrid

Red Sobre Dinámica y Sincronización en Redes (Fis2017-90782-Redt)

PI: Alejandro Arenas (URV, Coordinador Nacional), Inmaculada Leyva (Coordinador nodo URJC-CTB)

Funding Agency: Ministerio de Economía y Competitividad (MINECO)

Period: 2018-2019

Other institutions participating: Universidad de Zaragoza, Universidad de Barcelona, Universidad Politécnica de Catalunya, Universidad Rovira I Virgili, Universidad de La Laguna, Universidad Complutense, IDIBAPS, Universidad de las Islas Baleares.

Análisis Multiescala de Redes Complejas: Teoría, Experimentos y Aplicaciones. (Ref. Fis2013-41057-P)

PI: Irene Sendiña-Nadal & Javier M. Buldú

Funding Agency: Ministerio de Economía y Competitividad (MINECO)

Period: 2014-2017

Other institutions participating: Universidad Politécnica de Madrid

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Biomaterials and Regenerative Engineering (UPM)

PRESENTATION/INTRODUCTION

The main target of our lab is to conduct research to develop new biomaterials for applications in tissue engineering, mainly based on silk fibroin in different formats and on the biofunctionalization of conventional biomaterials. Related to this aim, our research also intends to contribute to the understanding of basic questions in the field of biomechanics.

We are working in four main research areas regarding biomaterials, tissue engineering and biomechanics: (1) Development of new bioinspired silk-based biomaterials. (2) Characterization and modeling of natural collagen-based materials (pericardium, tendons, blood vessels) and development of collagen-based prostheses. (3) Application of cell mechanics as diagnostic tool, and (4) functionalization of biomaterials to enhance biocompatibility.

A. MEMBERS

PI: Gustavo V. Guinea

Emeritus Professor: Manuel Elices Calafat

Senior researchers: José Pérez Rigueiro, José Miguel Atienza Riera, Francisco J. Rojo Pérez, Gustavo R. Plaza Baonza, Rafael Daza García

PhD students: Blanca González Bermúdez, Paloma Lozano Picazo, Adriana Torres

Research assistants: Luis Colchero Paetz

B. RESEARCH LINES

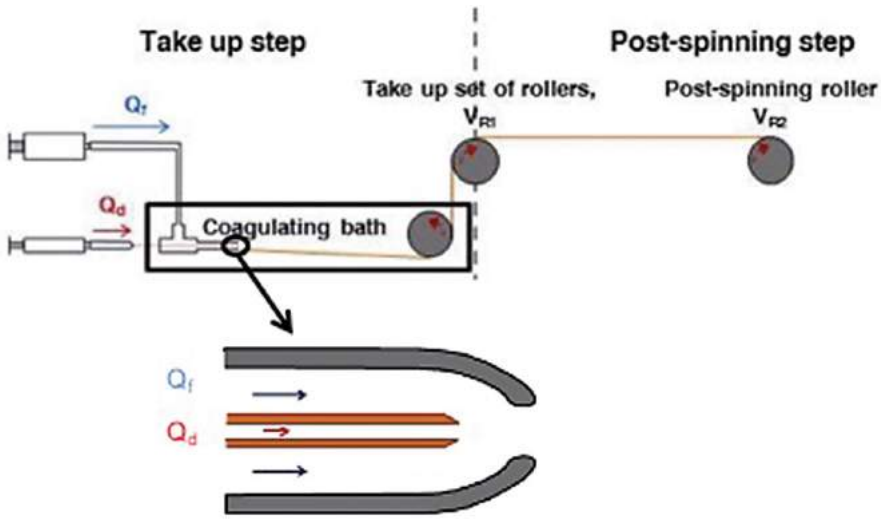
Study of silk fibers and silk-based biomaterials

Short description:

Following our long experience in the field of natural silk fibers, we are working in the development of new bioinspired fibers for biomedical applications. In collaboration with various groups, we pursue to obtain high performance artificial fibers from either the natural proteins (regenerated fibers) or from proteins obtained by genetic engineering (bioinspired fibers).

Our in-house-built spinning devices include techniques such as wet spinning and electrospinning, but is mostly focused in the Straining Flow Spinning process, developed in our laboratory.

■ Study of silk fibers and development of silk-based biomaterials. Scheme of a straining flow spinning process with its main elements. The inset shows a detail of the capillary-nozzle system in which the flow of the dope (Qd) and of the focusing fluid (Qf) are indicated.



Silk proteins are also used for the production of other formats such as hydrogels, mats or nanoparticles in order to produce scaffolds for tissue engineering applications. Thus, we have developed silk fibroin mats by electrospinning for peripheral nerve regeneration, implantable hydrogels intended to enhance the healing process after a possible brain damage, and silk nanoparticles to serve as drug delivery systems. Our current work also includes the production of silk fibroin scaffolds for applications in skin regeneration and some of the previous formats have been used on animal models.

Mechanics of soft tissues and development of soft biomaterials

Short description:

We study the mechanical behavior of collagen-rich tissues like blood vessels, tendons and pericardium. The goal is to improve the analysis and treatment of cardiovascular diseases and trauma.

During these three years we worked on an improved technique to characterize the mechanical properties and the calcium absorption for pericardium films, simulating the physiological conditions for artificial heart valves.

■ Study of the mechanical properties of soft tissues and development of soft biomaterials. (A) electron microscope of the group; (B) Precision mechanical-testing machine for biological samples.

Cell mechanics and mechanobiology

Short description:

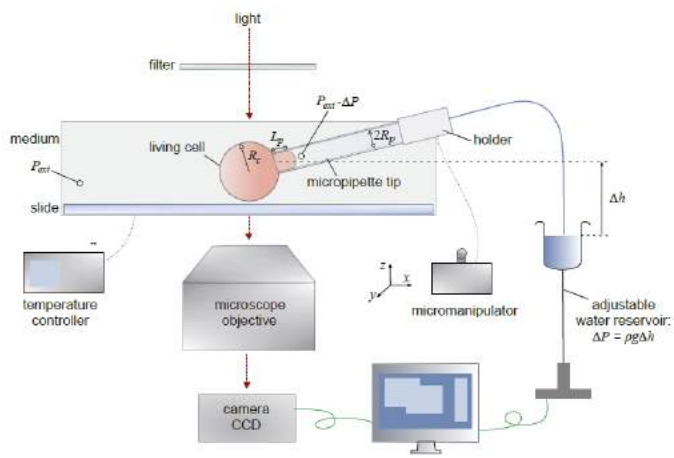
We are interested in studying the mechanical properties of cells, the relationship to their constituents, and the importance in diagnosis and in the functionality of biomaterials. Within this frame, we are developing and establishing experimental techniques in the laboratory.

During these three years we have particularly worked on new applications of the micropipette aspiration technique and on improving the use of atomic force microscopy in this field.

From 2017 we have worked on a project aiming to analyze the relationships between deformability, internal components and functionality of immune cells. We have obtained significant results to be published in 2019.

■ Nanotec nanolife© atomic force microscope.

■ Scheme of the micropipette-aspiration device developed in the laboratory to measure mechanical properties of cells.



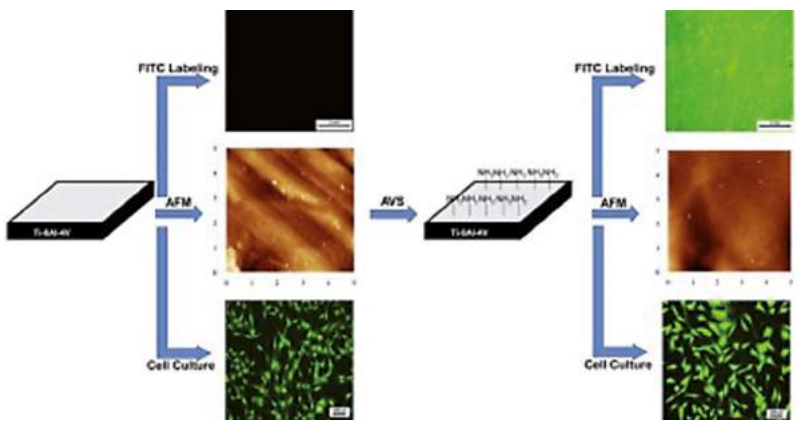
Functionalized materials of enhanced biocompatibility

Short description:

We produce new functional coatings on conventional biomaterials such as titanium alloys in order to enhance biocompatibility. Functionalization is mostly performed through activated vapour silanization (AVS), a variant of the usual chemical vapour deposition technique, developed in our laboratory.

AVS-functionalized substrates show a large surface density of amine groups to which molecules of biological significance, such as adhesion proteins, can be covalently attached.

■ Functionalization of biomaterials. Scheme of the procedure used to functionalize Ti-6Al-4V samples.



C. FACILITIES AND TECHNIQUES

Infrastructure:

Three atomic forces microscopes, three universal mechanical testing machines, environmental chamber, two scanning electron microscopes (in the Department of Materials Science site), activated vapour silanization device, differential scanning calorimeter, dynamic thermomechanical analysis, infrared spectroscopy, digital laser cutting machine, electrospinning devices, straining flow spinning system, basic biochemical equipment, home-made small angle light scattering device, home-made micropipette-aspiration device, microtome.

Techniques:

Mechanical testing of materials, atomic force microscopy, electron microcopy, micropipette-aspiration technique, infrared spectroscopy, optical microscopy, spinning of fibers, activated vapour silanization, small angle light scattering, differential scanning calorimetry, microtomy; other techniques using devices in other centers: X-ray diffraction, Raman spectroscopy.

D. RESEARCH PROJECTS

Desarrollo de nuevos biomateriales de fibroína de seda para regeneración cerebral. MAT2016-79832-R

Period: 2017-2019

Funding Agency: Ministerio de Economía y Competitividad

PI: Gustavo V. Guinea

Deformabilidad de linfocitos T como biomarcador mecánico de inmunosenescencia y desarrollo de tecnología para su aplicación clínica Period: 2017-2019

Funding Agency: Ministerio de Economía y Competitividad

PI: Gustavo R. Plaza Baonza

Producción y evaluación de la respuesta biológica de fibras de seda de altas prestaciones para aplicaciones en terapias de tendones y ligamentos. MAT2016-75544-C2-1-R

Period: 2017-2019

Funding Agency: Ministerio de Economía y Competitividad.

PI: José Pérez Rigueiro

Centro Tecnológico para el Estudio y Tratamiento Integrado de los Desórdenes Neurológicos NEUROCENTRO-CM B2017/BMD-3760

Funding Agency: Dirección General de Investigación e Innovación, Consejería de Educación e Investigación, Comunidad de Madrid

Period: 2018-2021

PI: Gustavo V. Guinea

Contract for a Research Assistant, Blanca González-Bermúdez

Period: 2016-2018

Funding Agency: Comunidad Autónoma de Madrid

PI tutor: Gustavo R. Plaza Baonza

E. PUBLICATIONS

1. L Fernández-García, J Pérez-Rigueiro, R Martínez-Murillo, F Panetsos, M Ramos, GV Guinea, D González-Nieto (2018). Cortical reshaping and functional recovery induced by silk fibroin hydrogels-encapsulated stem cells implanted in stroke animals. Frontiers in Cellular Neuroscience 12:296.
2. D González-Nieto, L Fernández-García, J Pérez-Rigueiro, GV Guinea, F Panetsos (2018). Hydrogels-assisted cell engraftment for repairing the stroke-damaged brain: chimera or reality. Polymers 10: 184.
3. P Rezvanian, R Daza, PA López, M Ramos, D González-Nieto, M Elices, GV Guinea, J Pérez-Rigueiro (2018). Enhanced biological response of AVS-functionalized Ti6Al4V alloy through covalent immobilization of collagen. Scientific Reports 8: 3337.
4. R. Madurga, A. M Gañán-Calvo, G. R Plaza, J.M. Atienza, G. V Guinea, M. Elices, P. A López, R. Daza, D. González-Nieto, J. Pérez-Rigueiro (2018). Comparison of the effects of post-spinning drawing and wet stretching on regenerated silk fibers produced through straining flow spinning. Polymer 150: 311-317.
5. R. Madurga, A. M Gañán-Calvo, T. Mariscal, G. R Plaza, G. V Guinea, M. Elices, J. Pérez-Rigueiro (2018). Production of regenerated silkworm silk fibers from aqueous dopes through straining flow spinning. Textile Research Journal 2018: 0040517519838050.
6. J. Pérez-Rigueiro, R. Madurga, A. Gañán-Calvo, G. Plaza, M. Elices, P. López, R. Daza, D. González-Nieto, G. V. Guinea (2018). Straining Flow Spinning of Artificial Silk Fibers: A Review. Biomimetics 3: 29.
7. Shen, YJ; Cheng, Y; Uyeda, TQP; Plaza, GR (2017). Cell Mechanosensors and the Possibilities of Using Magnetic Nanoparticles to Study Them and to Modify Cell Fate. Ann. Biomed Eng. 45: 2475-2486.

8. Gonzalez-Bermudez, B; Li, QX; Guinea, GV; Penalva, MA; Plaza, GR (2017). Probing the effect of tip pressure on fungal growth: Application to Aspergillus nidulans. Phys Rev. E 96: 022402.

9. J Nieto-Márquez Calvo, M Elices, GV Guinea, J Pérez-Rigueiro, M Arroyo-Hernández (2017). Stability and activity of lactate dehydrogenase on biofunctional layers deposited by activated vapor deposition (AVS) and immersion silanization (IS). Applied Surface Science 416: 965-970.

10. R Madurga, GV Guinea, M Elices, J Pérez-Rigueiro, AM Gañán-Calvo (2017). Straining flow spinning: simplified model of a bioinspired process to mass produce regenerated silk fibes controllably. European Polymer Journal 97: 26-39.

11. Madurga, R; Ganan-Calvo, AM; Plaza, GR; Guinea, GV; Elices, M; Perez-Rigueiro, J (2017) Straining flow spinning: production of regenerated silk fibers under a wide range of mild coagulating chemistries. Green Chemistry 19: 3380-3389.

12. Esteban-Manzanares, G, Gonzalez-Bermudez, B, Cruces, J, De la Fuente, M, Li, QX, Guinea, GV, Perez-Rigueiro, J, Elices, M, Plaza, GR (2017). Improved Measurement of Elastic Properties of Cells by Micropipette Aspiration and Its Application to Lymphocytes. Annals of Biomedical Engineering 45: 1375-1385.

13. Madurga, R, Ganan-Calvo, AM, Plaza, GR, Guinea, GV, Elices, M, Perez-Rigueiro, J. (2017). Production of High Performance Bioinspired Silk Fibers by Straining Flow Spinning. Biomacromolecules 1: 1127-1133.

14. Andersson, M, Jia, QP, Abella, A, Lee, XY, Landreh, M, Purhonen, P, Hebert, H, Tenje, M, Robinson, CV, Meng, Q, Plaza, GR, Johansson, J, Rising, A (2017). Biomimetic spinning of artificial spider silk from a chimeric minispidroin. Nature Chemical Biology 13: 262.

15. Shen, YJ, Wu, CY, Uyeda, TQP, Plaza, GR, Liu, B, Han, Y, Lesniak, MS, Cheng, Y (2017). Elongated Nanoparticle Aggregates in Cancer Cells for Mechanical Destruction with Low Frequency Rotating Magnetic Field. Theranostics 7: 1735-1748.

16. P Rezvanian, M Arroyo-Hernández, M Ramos, R Daza, M Elices, GV Guinea, J Pérez-Rigueiro (2016). Development of a versatile procedure for the biofunctionalization of Ti-6Al-4v implants. Applied Surface Science 387: 652-660.

17. L Fernández-García, N Marí-Buyé, JA Barios, R Madurga, M Elices, J Pérez-Rigueiro, M Ramos, GV Guinea, D González-Nieto (2016). Safety and tolerability of silk fibroin hydrogels implanted into the mouse brain. Acta Biomaterialia 45: 262-275.

18. GB Perea, C Solanas, N Marí-Buyé, R Madurga, F Agulló-Rueda, A Muinelo, C Riekel, M Burghammer, I Jorge, J Vázquez, GR Plaza, AL Torres, F del Pozo, GV Guinea, M Elices, JL Cenis, J Pérez-Rigueiro (2016). The apparent variability of silkworm (Bombyx mori) silk and its relationship with degumming. European Polymer Journal 78: 129-140.

19. R Madurga, GR Plaza, TA Blackledge, GV Guinea, M Elices, J Pérez-Rigueiro (2016). Material properties of evolutionary diverse spider silks described by variation in a single structural parameter. Scientific Reports 6: 189-91.

20. A Tobaruela, M Elices, JY Bourges, FJ Rojo, JM Atienza, G Guinea 2016. Tear and decohesion of bovine pericardial tissue. J of the mechanical behavior of biomedical materials 63: 1-9.

21. A Tobaruela, FJ Rojo, JM García Paez, JY Bourges, EJ Herrero, I Millán, L Alvarez, A Cordon, GV Guinea (2016). Indentation hardness: A simple test that correlates with the dissipated-energy predictor for fatigue-life in bovine pericardium membranes for bioprosthetic heart valves. J of the mechanical behavior of biomedical materials 61: 55-61.

22. F Montini-Ballarin, D Calvo, PC Caracciolo, FJ Rojo, PM Frontini, GA Abraham, GV Guinea (2016). Mechanical behavior of bilayered small-diameter nanofibrous structures as biomimetic vascular grafts. J of the mechanical behavior of biomedical materials 60: 220-233.

Cajal Cortical Circuits (UPM-CSIC)

PRESENTATION/INTRODUCTION

The Cajal Cortical Circuits Laboratory (CCCL) was created in 2008 as a joint research laboratory between UPM and Instituto Cajal (IC-CSIC). CCCL represents a UPM experimental neuroscience unit made up of expert researchers in neuroscience (neuroanatomy) from the IC-CSIC and computer scientists from the UPM. The CCCL was created with the aim of combining experimental studies of the brain with computer science technologies, in particular with several neuroinformatic groups with expertise in statistics, informatics tools and analysis of images. The main experimental research line conducted at the CCCL focuses on the analysis of the microanatomy and neurochemical organization of the cerebral cortex, by means of a variety of techniques such as intracellular injection in fixed tissue, histochemical and inmunocytochemical techniques for optical and electron microscopy, and new 3D reconstruction methods (confocal and FIB/SEM microscopy). Data generated in the CCCL is analysed with the help of the computer science groups. The most relevant methodology carried out at CCCL include intracellular injection in fixed tissue; histochemical and inmunocytochemical techniques for optical and electron microscopy and image processing; 3D reconstruction methods (confocal and FIB/SEM microscopy); tract-tracing anatomical methods; stereology.

A. MEMBERS

PI: Javier de Felipe

Senior researchers: Angel Merchán, José Rodrigo-Rodríguez, Ruth Benavides-Piccione, Lidia Alonso-Nanclares, Alberto Muñoz

Post-doctoral Fellows: Lidia Blázquez, Gonzalo León, Isabel Fernaud, Asta Kastanauskaite, Silvia Tapia, Andrea Santuy, Laura Fernández, Laura Tomás

PhD students: Diana Furcila, Alejandro Antón, Guillermo Aparicio, Marta Turégano, Mª del Carmen Regalado, Sandra Ostos, Marta Domínguez

Others:

Laboratory Technicians: Lorena Valdés, Mari Carmen Álvarez, Miriam Marín, Débora Cano, Ana Isabel García, Diana Sánchez

Project Manager: Pilar Flores Romero

Admin. Manager: Marta Barbado

Financial Manager: Yago Rodríguez

PI's Assistant: Montserrat Fernández

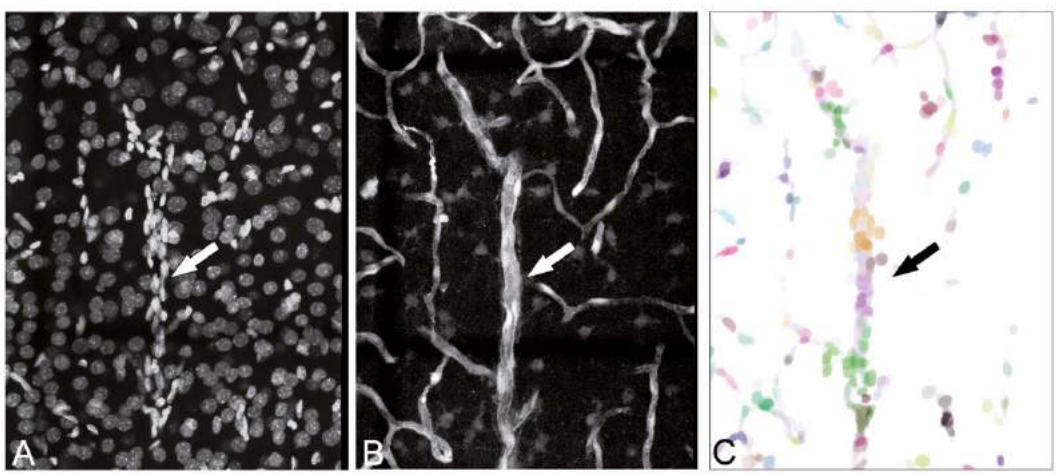
B. RESEARCH LINES

Microorganization of the normal cerebral cortex and alterations of cortical circuits in brain pathologies

Short description:

The CCCL mainly focuses on the microorganization of the normal cerebral cortex (including hippocampus) in various species (particularly humans) and on the alterations of cortical circuits in epilepsy and Alzheimer disease. These studies are performed through the use of anatomical tracers, high-resolution immunocytochemistry and 3D light and electron microscopy. Another major aim is to develop informatics technologies to examine the brain. In particular, the research lines carried out at the CCCL are as follows:

- A and B: confocal images from the same field and plane of a brain section double-labeled for DAPI (cells) and Sulforhodamine (blood vessels), respectively. A: DAPI channel image showing nuclei from all cell types. B: Sulforhodamine channel image showing the blood vessels. Arrows (A,B) indicate the same blood vessel in both channels. C: Segmentation of the DAPI positive cells located inside or in close apposition to the blood vessel, which will be removed from neuron segmentation.

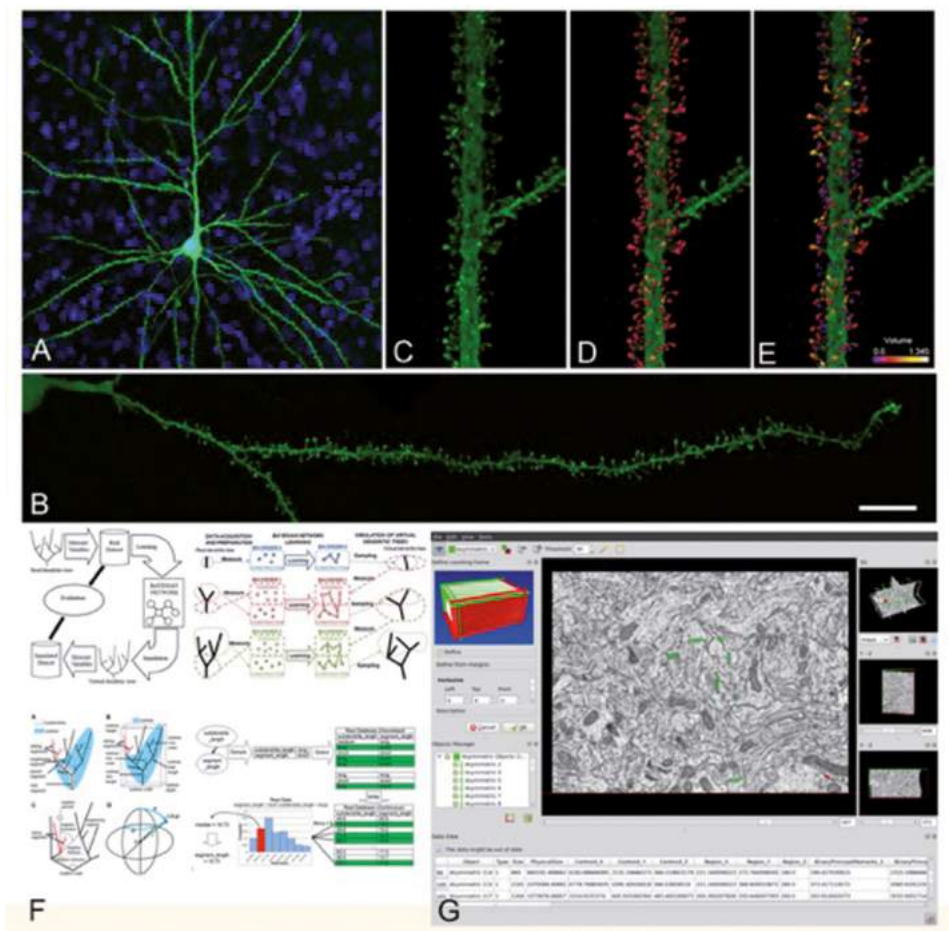


Study of the components of the column

1. Development and validation of software tools for 3D segmentation of cells of the complete cortical column in stacks obtained by confocal microscopy in samples from the somatosensory neocortex.
2. Spatial analysis distribution of the segmented cell to determine the distribution patterns of different cell types.
3. Analysis of the spatial distribution of synapses in the six cortical layers by means of spatial statistical tools. Calculation of the volume fraction occupied by mitochondria in the six cortical layers.

4. Fine-tuning of the algorithm for automatic segmentation of neuronal and non-neuronal cells: filter vascular cells and non-neuronal cells to improve neuronal segmentation by removing the non-neurons.

■ A-E: Confocal microscopy images showing pyramidal cells in different layers of the human temporal cortex. Pyramidal cells were injected intracellularly with Lucifer Yellow (a fluorescent marker) in paraformaldehyde-fixed tissue. F: Bayesian network model to generate virtual dendrites. G: Visualization and analysis of a series of images of the cerebral cortex using ESPINA software.



Pyramidal cells:

1. Intracellular injections and 3D-reconstruction of pyramidal cells and to analyse the microanatomy of these cells in different cortical areas, layers and species.

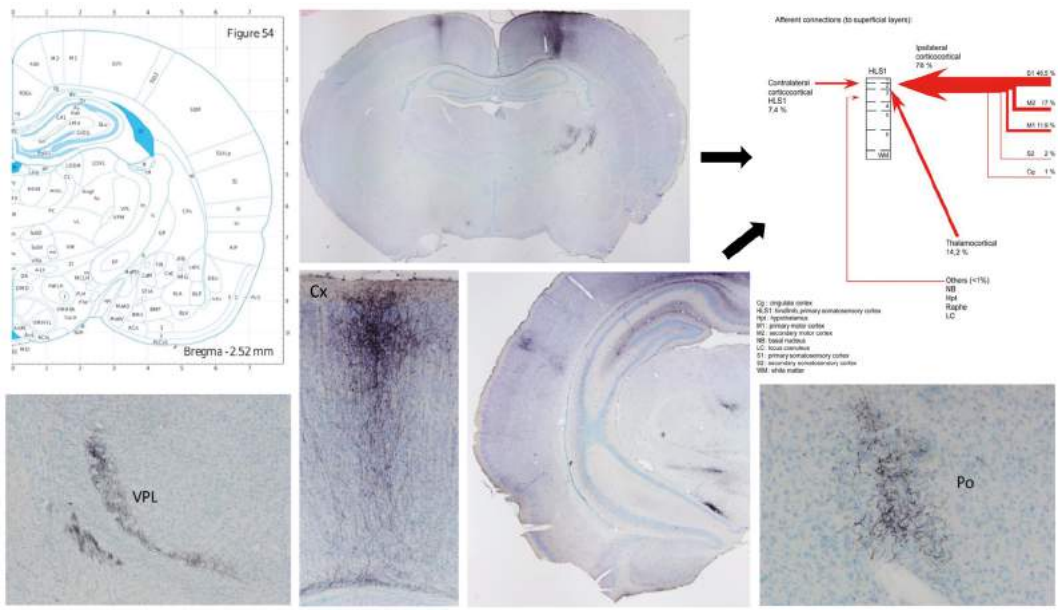
2. Generation of high resolution confocal microscopy stacks of images of pyramidal cells to analyze the distribution and morphology of dendritic spines in different cortical areas, layers and species.

Intrinsic and extrinsic connectivity of the cortical column

Short description:

1. Target identification of cortical synapses (FIB/SEM) to determine the proportion of synapses on dendritic spines and dendritic shafts.
2. Analysis of synaptic sizes (FIB/SEM) and development of computer models to explore the possible relationship between synaptic morphology and physiology.
3. Characterization of the afferent and efferent connections of the hindlimb representation area of the primary somatosensory cortex in P14 rats in tract-tracing experiments.

■ Characterization of afferent projections to HLS1 at P14



Quantification of cellular and subcellular alterations in Alzheimer's disease (AD) and the possible influence of these alterations on cognition

Short description:

1. Quantification of specific synaptic alterations in the neuropil and in identified 3D reconstructed cortical neurons from areas showing early histopathological changes in AD.
2. Application of systematic methods to human tissue from AD patients.

3. Correlation of quantitative results with cognitive impairment.
4. The most relevant projects that are currently being carried out at the CCCL in which the research lines outlined above are being implemented are *Cajal Blue Brain Project* (MINECO), *Human Brain Project* (EC), *The Pyramidal Neuron in Cognition and Alzheimer's Disease* (The Alzheimer's Association, US). See the Section 'Research Projects' for further information.

Main results:

The main achievements from the above main lines of research are as following:

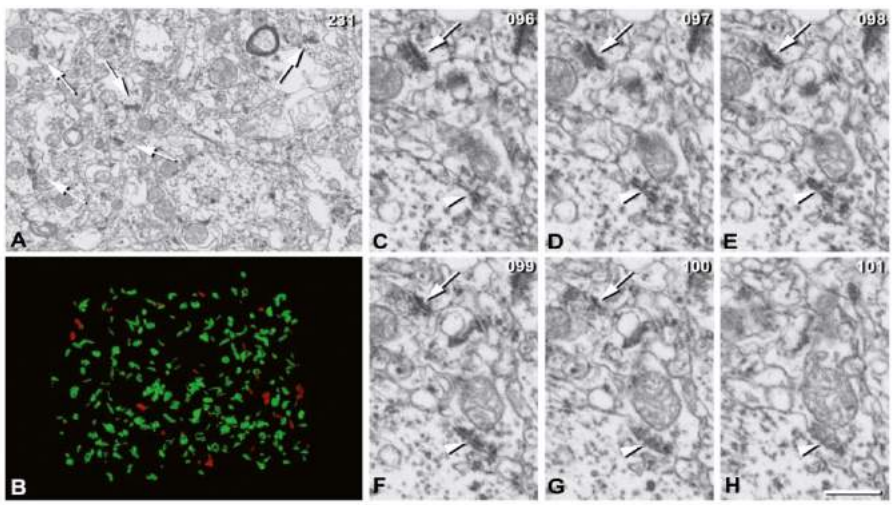
1. Detailed models of pyramidal cells from human neocortex, including models on their excitatory synapses, dendritic spines, dendritic NMDA- and somatic/axonal Na+ spikes that provided new insights into signal processing and computational capabilities of these principal cells. This study provides the most comprehensive model of any human neuron to-date demonstrating the biophysical and computational distinctiveness of human cortical neurons.
2. Generation of new large quantitative dataset to advance in the brain study: new datasets from reconstructions of the dendritic trees and from morphological characteristics of the axon initial segments to build models of the Cerebellum and the Basal Ganglia; new data on quantitative ultrastructural data from the rodent hippocampus and neocortex for the modeling of hippocampal and neocortical neurons; new human data of the neuropil at the ultrastructural level for circuit building and for comparatives studies on the microanatomy and physiology of mice and humans; and 3D reconstructions of pyramidal cells from different species and from different cortical areas to implement comparative studies.
3. Development of a computer method based on synaptic sizes to analysis the relationship between synaptic morphology and physiology.
4. Development and validation of software tools for 3D segmentation of cells of the complete cortical column in samples from the somatosensory neocortex.
5. Development of MultiMap, a new tool that allows the visualization, 3D segmentation and quantification of fluorescent structures selectively in the neuropil from large stacks of confocal microscopy images. The major contribution of this tool is the possibility to easily navigate and create regions of interest of any shape and size within a large brain area that will be automatically 3D segmented and quantified to determine the density of puncta in the neuropil.

6. Development of a method that makes it possible to obtain high-resolution scanning EM images of large areas of the brain in the millimeter to nanometer range. Since this method is compatible with light microscopy, it is also feasible to generate hybrid light and electron microscopic maps.

7. Development of a novel graphical tool designed to help neuroanatomists to better understand and detect morphological characteristics of neuronal cells.

These achievements have led to 46 scientific articles listed below.

■ FIB/SEM images obtained from the plaque-free region from the frontal cortex (Brodmann area 10) of patient P2. A stack of 351 serial images separated by 20 nm was obtained. A, Image 231 of the series showing several synaptic contacts (arrows). B, Three-dimensional reconstruction of all the synaptic junctions present in the same stack of serial sections. Green and red objects represent asymmetric (glutamatergic) and symmetric (GABAergic) synaptic profiles, respectively. C-H, Consecutive serial sections (096-101 of the stack of images) illustrating an asymmetric (arrows) and a symmetric synapse (arrowheads). Note the difference in the thickness of the post-synaptic densities between asymmetric (thick) and symmetric (thin) synapses. Scale bar (in F): A, 2 µm; B, 3.2 µm; C-H, 0.8 µm. Taken from Blazquez-Llorca L et al. (2013). J Alzheimers Dis 34:995-1013.



C. FACILITIES AND TECHNIQUES

Facilities/Infrastructures

The CCL laboratory has dedicated bench space for 15 to 20 investigators. The lab includes an Image Analysis room with 7 computers for image analysis (Imaris software), two microscopes connected to computers with software for image acquisition and analysis (Neurolucida and Stereo Investigator) and a Confocal Microscopy Facility. A large amount of laboratory space is dedicated to histology. This includes reagents and devices for various histological and immunohistochemical techniques, two Ted-Pella vibratomes and a cryostate (Thermo) for sectioning tissue, as well as a separate room housing 4 microscope

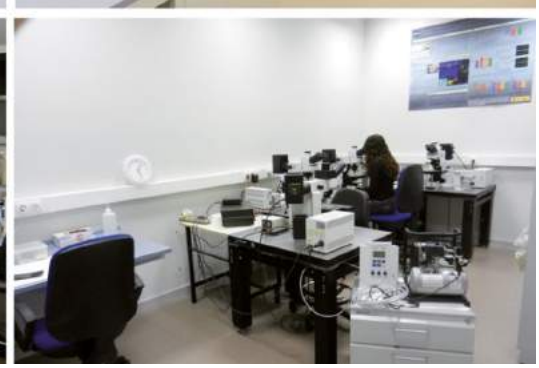
set-ups for intracellular injections in fixed tissue. In addition, the laboratory has an area dedicated to small animal perfusion, and a fully equipped electron microscopy laboratory with a rotary microtome (Microm), laboratory microwave oven (Ted Pella), a pyramidotome (Leica EM Trim) for tissue preparation and an Ultracut (Leica EM UC6) to obtain semithin and ultrathin sections.

Confocal and electron microscopy facilities:

The Confocal Microscopy Facility, directed by Prof. de Felipe includes two laser scanning confocal microscopes: a Zeiss LSM 710 with 5 laser-heads (405, 488, 543, 594 and 633nm) and a Leica SP8 AOBS, WLL Laser + Argon (458, 476, 488, 496, 514,) and 405 lasers and 2PMT+2HyD. This facility also has two direct microscopes with motorized stages connected to two computer workstations and two additional workstations capable of image processing and deconvolution, 3-D reconstruction, etc.

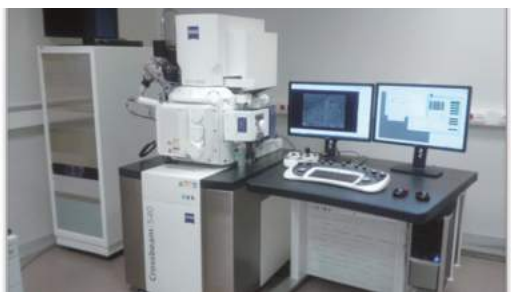
■ Confocal microscope facility

■ Histology laboratory and set-ups for intracellular injections in fixed tissue



Prof. de Felipe also has a separate room housing a dual-beam electron microscope (Zeiss NEON 40EsB) and its auxiliary equipment, which is capable of acquiring serial high-resolution images of neural tissue. Additionally, Prof. de Felipe has a transmission electron microscope (Jeol 1011, 100 Kv; equipped with an 11 Mpx Gatan-Orius camera), and four computer workstations for electron microscope image processing, 3-D reconstruction and analysis — using software (e.g., ESPINA) developed for the Cajal Blue Brain Project (Spanish partner of the Blue Brain Project initiative from EPFL, Switzerland), which is led by Prof. de Felipe. Other equipment includes an icemaker, a Millipore water purification system, a glassware washer, 3 chemical fume hoods, water baths, microscope slide warmers, refrigerators, and other small pieces of laboratory equipment.

■ Dual-beam electron microscope (Zeiss, CrossBeam 540) facility and laboratory



■ Transmission electron microscope facility and laboratory

■ Image analysis facility

D. RESEARCH PROJECTS

Estudio de la microorganización de la corteza cerebral en pacientes de Alzheimer y de hámster como modelo para estudiar la fosforilación de TAU

PI: Javier de Felipe

Funding Agency: Ministerio de Economía y Competitividad

Budget: 237.160€

Period: 2016-2018

Estudio multi-escala de la disfunción sináptica posterior al ictus

PI: Javier de Felipe

Funding Agency: Ministerio de Ciencia, Innovación y Universidades: Programa internacional "NEURON ERANET", EC

Budget: 919.000€

Period: 2018-2021

Cajal Blue Brain

PI: Javier de Felipe

Funding Agency: Ministerio de Economía y Competitividad

Budget: 25.000.000€

Period: 2009-2018

Human Brain Project, Ramp-Up Phase

PI: Javier de Felipe (HBP-SP1)

Funding Agency: FP7

Budget: 934.500€

Period: 2013-2016

Human Brain Project, SGA1

PI: Javier de Felipe (HBP-SP1)

Funding Agency: HORIZON 2020

Budget: 1.322.944€

Period: 2016-2018

Human Brain Project, SGA2

PI: Javier de Felipe (HBP-SP1)

Funding Agency: HORIZON 2020

Budget: 1.013.255€

Period: 2018-2020

Alteración de los circuitos corticales en la Enfermedad de Alzheimer

PI: Javier de Felipe

Funding Agency: Instituto de Salud Carlos III. CIBERNED

Budget: 146.762€

Period: 2016-2018

Convocatoria de financiación interna para proyectos colaborativos centrales y de investigación traslacional

PI: Javier de Felipe

Funding Agency: Instituto de Salud Carlos III. CIBERNED

Budget: 70.000€

Period: 2016

The pyramidal neuron in cognition and Alzheimer's disease

PI: Javier de Felipe

Funding Agency: Alzheimer's Association: 2015 Zenith Fellows Award

Budget: 450.000 US$

E. PUBLICATIONS

1. Anton-Sanchez, L., Bielza, C., Larrañaga, P., & de Felipe, J. (2016). Wiring economy of pyramidal cells in the juvenile rat somatosensory cortex. *Plos One, 11*(11), e0165915.
2. Anton-Sanchez, L., Bielza, C., Benavides-Piccione, R., de Felipe, J., & Larrañaga, P. (2016). Dendritic and axonal wiring optimization of cortical GABAergic interneurons. *Neuroinformatics, 14*(4), 453-464.
3. Barth, A., Burkhalter, A., Callaway, E. M., Connors, B. W., Cauli, B., de Felipe, J., et al. (2016). Comment on "principles of connectivity among morphologically defined cell types in adult neocortex". *Science (New York, N.Y.), 353*(6304), 1108.
4. Bosch, C., Masachs, N., Exposito-Alonso, D., Martinez, A., Teixeira, C. M., Fernaud, I., et al. (2016). Reelin regulates the maturation of dendritic spines, synaptogenesis and glial ensheathment of newborn granule cells. *Cerebral Cortex (New York, N.Y.: 1991).*
5. Broadhead, M. J., Horrocks, M. H., Zhu, F., Muresan, L., Benavides-Piccione, R., de Felipe, J., et al. (2016). PSD95 nanoclusters are postsynaptic building blocks in hippocampus circuits. *Scientific Reports, 6*, 24626.
6. de Felipe, J. (2016). Phospho-tau and cognitive decline in alzheimer's disease. commentary: Tau in physiology and pathology. *Frontiers in Neuroanatomy, 10*, 44.
7. de Felipe, J., Douglas, R. J., Hill, S. L., Lein, E. S., Martin, K. A., Rockland, K. S., et al. (2016). Comments and general discussion on "the anatomical problem posed by brain complexity and size: A potential solution". *Frontiers in Neuroanatomy, 10*, 60.
8. Eyal, G., Verhoog, M. B., Testa-Silva, G., Deitcher, Y., Lodder, J. C., Benavides-Piccione, R., et al. (2016). Unique membrane properties and enhanced signal processing in human neocortical neurons. *Elife, 5*, 10.7554/eLife.16553.
9. Fernandez-Gonzalez, P., Benavides-Piccione, R., Leguey, I., Bielza, C., Larrañaga, P., & DeFelipe, J. (2016). Dendritic-branching angles of pyramidal neurons of the human cerebral cortex. *Brain Structure & Function*, 222(4),1847-1859, doi: 10.1007/s00429-016-1311-0.
10. Leguey, I., Bielza, C., Larranaga, P., Kastanauskaite, A., Rojo, C., Benavides-Piccione, R., et al. (2016). Dendritic branching angles of pyramidal cells across layers of the juvenile rat somatosensory cortex. *The Journal of Comparative Neurology, 524*(13), 2567-2576.
11. Leon-Espinosa, G., Garcia, E., Gomez-Pinedo, U., Hernandez, F., de Felipe, J., & Avila, J. (2016). Decreased adult neurogenesis in hibernating syrian hamster. *Neuroscience, 333*, 181-192.
12. Marquez Neila, P., Baumela, L., Gonzalez-Soriano, J., Rodriguez, J. R., de Felipe, J., & Merchan-Perez, A. (2016). A fast method for the segmentation of synaptic junctions and mitochondria in serial electron microscopic images of the brain. *Neuroinformatics, 14*(2), 235-250.
13. Mellstrom, B., Kastanauskaite, A., Knafo, S., Gonzalez, P., Dopazo, X. M., Ruiz-Nuno, A., et al. (2016). Specific cytoarchitectureal changes in hippocampal subareas in daDREAM mice. *Molecular Brain, 9*(1), 22-016-0204-8.
14. Rabano, A., Cuadros, R., Merino-Serrais, P., Rodal, I., Benavides-Piccione, R., Gomez, E., et al. (2016). Protocols for monitoring the development of tau pathology in alzheimer's disease. *Methods in Molecular Biology (Clifton, N.J.), 1303*, 143-160.
15. Rojo, C., Leguey, I., Kastanauskaite, A., Bielza, C., Larrañaga, P., de Felipe, J., et al. (2016). Laminar differences in dendritic structure of pyramidal neurons in the juvenile rat somatosensory cortex. *Cerebral Cortex (New York, N.Y.: 1991), 26*(6), 2811-2822.
16. Toharia, P., Robles, O. D., Fernaud-Espinosa, I., Makarova, J., Galindo, S. E., Rodriguez, A., et al. (2016). PyramidalExplorer: A new interactive tool to explore morpho-functional relations of human pyramidal neurons. *Frontiers in Neuroanatomy, 9*, 159.
17. Antón-Fernández, A., Merchán-Rubira, J., Avila, J., Hernández, F., de Felipe, J., & Munoz, A. (2017). Phospho-tau accumulation and structural alterations of the golgi apparatus of cortical pyramidal neurons in the P301S tauopathy mouse model. *Journal of Alzheimer's Disease, 60*, 1-11.
18. Anton-Sanchez, L., Larrañaga, P., Benavides-Piccione, R., Fernaud-Espinosa, I., de Felipe, J., & Bielza, C. (2017). Three-dimensional spatial modeling of spines along dendritic networks in human cortical pyramidal neurons. *PloS One, 12*(6), e0180400.
19. Blazquez-Llorca, L., Valero-Freitag, S., Rodrigues, E. F., Merchán-Pérez, A., Rodríguez, J. R., Dorostkar, M. M., et al. (2017). High plasticity of axonal

pathology in Alzheimer's disease mouse models. *Acta Neuropathologica Communications, 5*(1), 14.

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Clinical Neuroscience (UPM)

PRESENTATION/INTRODUCTION

The Laboratory for Clinical Neuroscience (LCN) was created in 2011 with the aim to explore the cerebral basis of cognitive function in healthy people and in patients with neurological and psychiatric diseases. A particular focus is the study of human memory function and emotional processing. We are affiliated to a number of clinical institutions in Madrid-Hospital Clinico San Carlos, Hospital Ruber Internacional and Centre for Alzheimer's Disease of the Fundación Reina Sofia-which together with the facilities at the CTB provide an interdisciplinary platform for clinical and cognitive neuroscience. We have set up a number of highly exciting research lines, some of which are unique within Spain and indeed Europe. In 2019, a 5-year Consolidator Grant awarded to the PI of the lab by the European Research Council (ERC) will push forward understanding on the human subcortical-cortical circuit dynamics for remembering salient events.

A. MEMBERS

PI: Bryan Strange
Senior researchers: Stephan Moratti
Post-doctoral Fellows: Alejandra Korovaichuk, Linda Zhang, Manuela Costa
PhD students: Svenja Treu, Marta Garo

B. RESEARCH LINES

The cerebral basis of cognitive function in healthy people and in patients with neurological and psychiatric diseases

Short description:

Location: a. Ruber Hospital Internacional
b. Hospital Clínico San Carlos

Intracranial recordings provide a unique insight into human brain function, as they provide millisecond resolution in the temporal domain with anatomical specificity that cannot be achieved with electro- or magneto-encephalography (EEG/MEG).

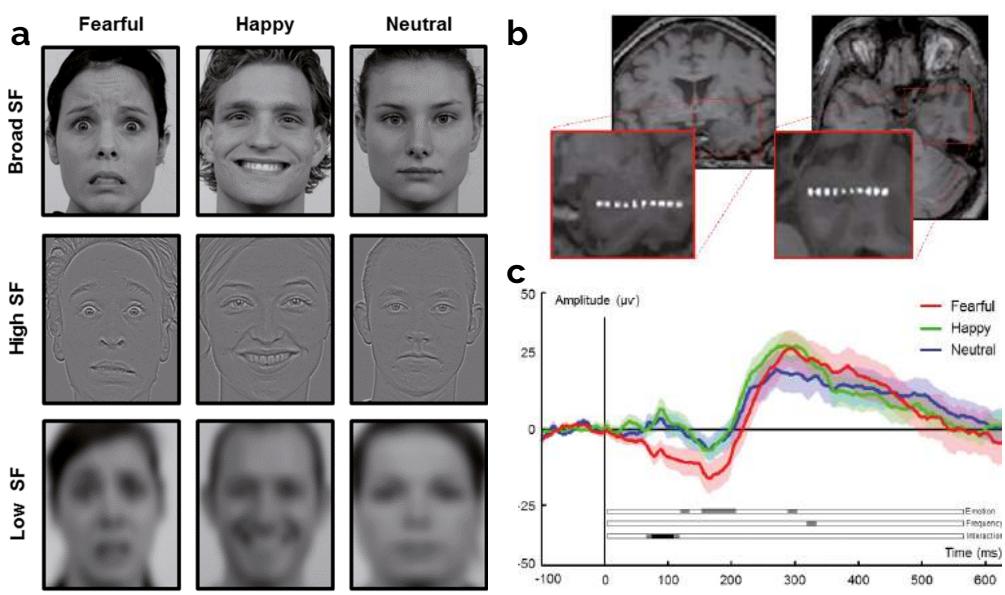
There are relatively few labs in the world with access to these highly interesting patients.

a) At the Ruber Hospital the LCN collaborates with Antonio Gil-Nagel, head of epileptology, to record from intracranial electrodes implanted in patients

with medication-resistant epilepsy. These patients are candidates for surgical management of their epilepsy and spend 5 days with the video-telemetry unit of the Ruber Hospital to determine their epileptic focus via intracranial electrophysiological recordings. During this period, these patients also consent to participate in cognitive tests, enabling us to acquire data at high temporal and spatial resolution. At present, patients participate in a battery of tasks exploring medial temporal lobe function. Local field potential data from the amygdala are proving extremely interesting. In one study in particular, we provide the first evidence for fast-latency amygdala responses to threat-related stimuli (fearful faces). As predicted by animal models, this fast response only occurs to low-frequency information that is relayed to the amygdala via a magnocellular pathway.

b) At the Clínico San Carlos, the LCN is collaborating with Juan Barcia (Head of Neurosurgery service) and Blanca Reneses (Head of Psychiatry service) in studies of deep-brain stimulation in patients with treatment resistant psychiatric disease. We have studied a cohort of 10 patients with obsessive-compulsive disorder (OCD), one patient with depression, all of whom have had electrodes implanted to stimulate the nucleus accumbens. We are also studying one patient with schizophrenia, in whom electrodes have been implanted in the ventral tegmental area. In all patients, we perform single-unit recordings in the target structure during the operative

■ Fast latency amygdala responses to fear. a. Examples of face stimuli presented to patients-some are normal broadband photos while others have been filtered to leave only low and high spatial frequencies (SF). b. Electrode contacts are localised to the amygdala by coregistering the post-operative CT to the pre-operative structural MRI. c. Intracranial event-related potentials to facial expression. An average of the activity evoked in the amygdala of 8 patients is plotted, specific for each emotional expression. There is a fast latency response to fearful faces that is only observed to the broadband and low spatial frequency fearful faces.



procedure. As the patient is awake during the operation, we can record from single-units while the patient performs a simple cognitive task in the operation theatre.

In the post-operative phase, the electrode leads are externalized for 1 week, during which local field potentials are recorded from the target structures while the patients perform cognitive tasks. For some tasks, we also record simultaneous scalp electroencephalogram (EEG) recordings.

Cognitive effects of deep-brain stimulation (DBS)

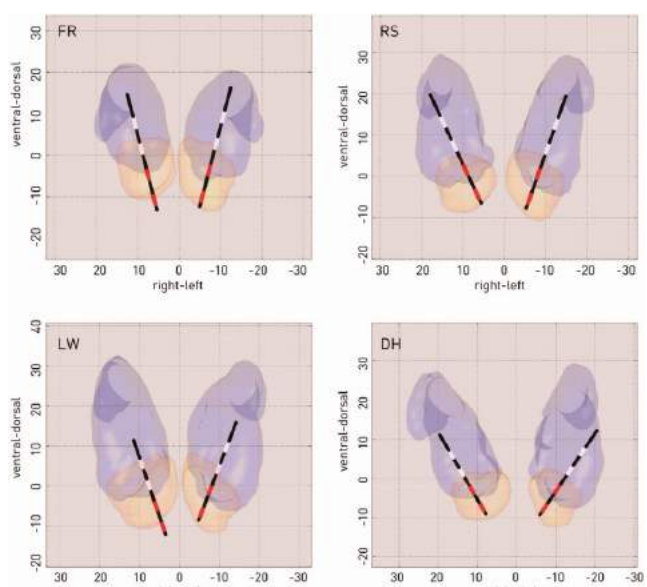
Short description:

Location: Hospital Clínico San Carlos

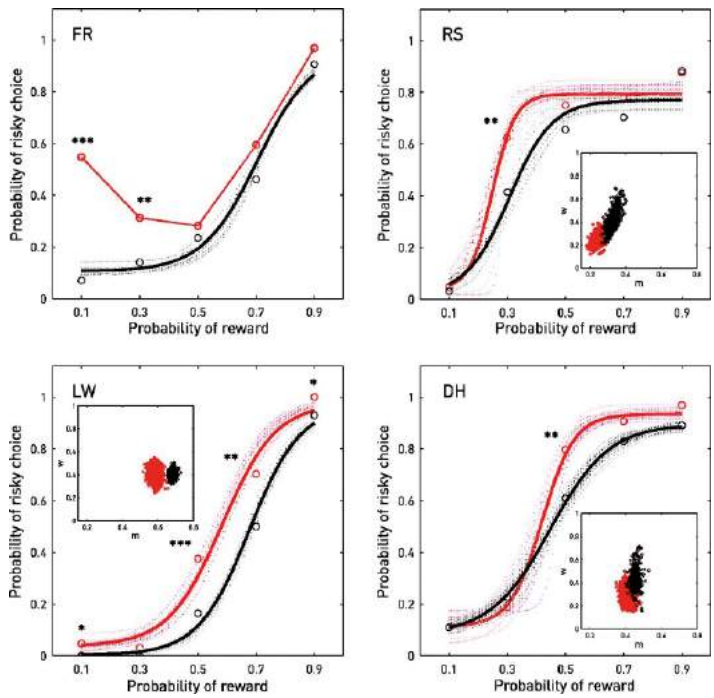
DBS is being increasingly applied in the management of treatment-resistant neurological and psychiatric diseases. The stimulated sites are often subcortical structures-such as subthalamic nucleus for Parkinson's disease and NAc for OCD-that play important roles in a number of cognitive processes. However, the cognitive of DBS remain largely unexplored. In addition to recording from target structures in patients with DBS electrodes, we also measure patients' performance on cognitive tasks as a function of whether the stimulator is 'on' or 'off' (with the 'on' stimulation parameters identical to that used chronically for the management of the patients' psychiatric disease).

We have discovered that phasic stimulation of the NAc in patients with OCD or depression leads to an increase in risky decision-making in a gambling task in which patients play for real money (Figures 2-3). In patients with OCD, NAc stimulation has been found to enhance episodic memory encoding in a simple laboratory test of visual memory. This enhancement in laboratory testing predicts memory improvement at neuropsychological testing after 2 months of chronic NAc stimulation.

■ Coronal view showing the critical electrode contacts (in red) in relation to the nucleus accumbens (translucent yellow), and the caudate (translucent blue), with dimensions relative to the anterior commissure. Taken from Nachev et al., Brain (2015).



■ The relation between the probability of reward on risky trials and the propensity to choose them was modelled individually for each participant and for each condition (on and off stimulation) as a psychometric function of logistic form, estimated within a Bayesian framework with the aid of MCMC sampling. These estimates are line-plotted—in black for off and red for on—together with illustrative samples from the posterior distribution of functions. The 'on' condition in Patient FR produced non-monotonic behaviour that could not be modelled. The circles, analogously colour-coded, show the actual choice performance at each probability, with the threshold of significance indicated by asterisks (*P < 0.05, **P < 0.01, ***P < 0.001). Taken from Nachev et al., *Brain* (2015).



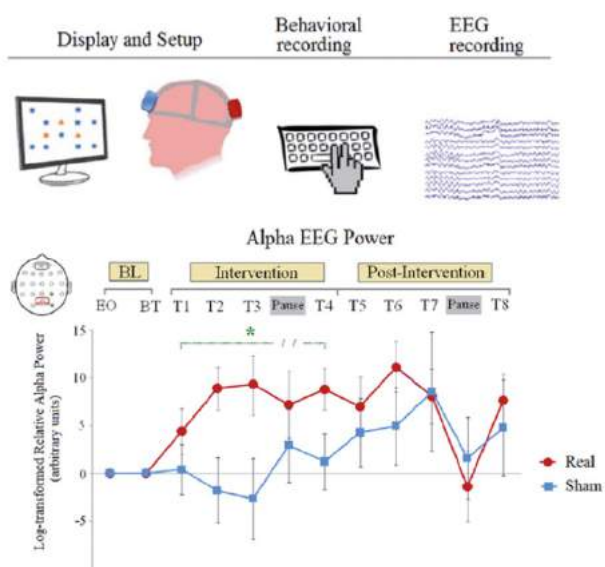
Non-invasive brain stimulation

Short description:

Location: CTB, Hospital Nacional de Parapléjicos, Toledo

In addition to well-established techniques to non-invasively stimulate the brain, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), a close collaborator (Antonio Oliviero at the Hospital Nacional de Paraplégicos, Toledo) has recently invented transcranial *static* magnetic stimulation (tSMS). This technique involves placing a powerful magnet on the scalp to modulate brain activity.

The LCN has been involved in characterising the effects of tSMS on the resting EEG-we have discovered that magnets increase alpha oscillation power (Figure 4)-and we have also found that placing the magnet over the visual cortex worsens performance on a visual task. Given that this novel safe technique, which is both portable and inexpensive, can influence human brain activity and behaviour, the LCN is now involved in a series of studies further characterising the effects of tSMS in healthy controls and patient populations.



■ Transcranial static magnetic stimulation (tSMS). Top: Experimental protocols and setup. The magnet is held in place over the occiput, with a frontal metallic cylinder as a counter-weight. Bottom: Real-tSMS (red) over visual cortex during the 12 min intervention session induced a relative increase in alpha EEG power compared with sham tSMS (blue) during visual search. Plot illustrates the enhancement in the relative alpha power for electrodes (highlighted in green on electrode scalp maps, as well as their position relative to the magnet) showing statically significant differences between groups (real vs sham: *p<0.01).

Neuropsychopharmacology

Short description:

Location: Hospital Clínico San Carlos

In collaboration with Dr Victoria Acedo (Department of Anaesthesia, Hospital Clínico San Carlos) we are currently examining whether the general anaesthetic propofol can be used to weaken the strength of previously acquired aversive memories. This is the first step in a longer term goal of using propofol as a treatment for patients with post-traumatic stress disorder (PTSD). The results of our first study were published in Science Advances, and were featured in the popular press (including *Scientific American* and *New Scientist* magazine.

Magnetoencephalography recordings

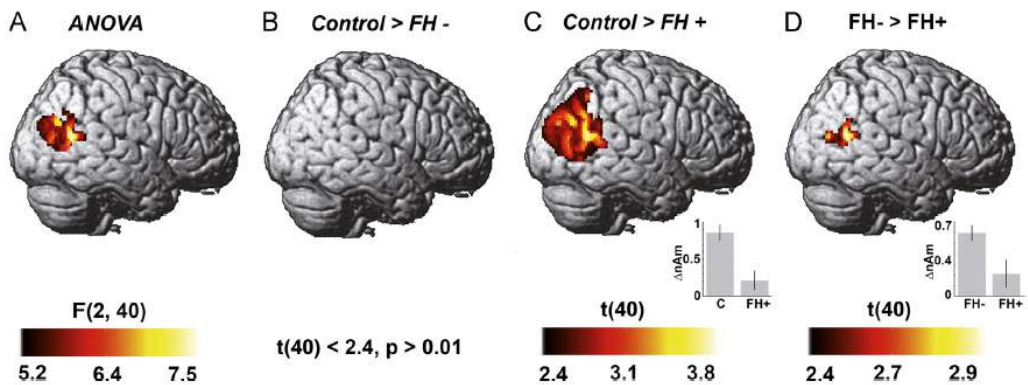
Short description:

Location: CTB

With Stephan Moratti as lead investigator, the LCN is engaged in measuring human brain responses to emotional stimuli using MEG, both in healthy controls and psychiatric patients such as those with depression or PTSD. Specifically, we are interested in how cortical responses to emotional stimuli are modulated as a function of family history of depression,

and how fear learning malfunctions in patients with PTSD. Analyses incorporate novel techniques in source localization and measures of directed connectivity (Granger causality) and effective connectivity (Dynamic Causal Modelling).

■ Reduced activity modulation in right temporoparietal cortex in depression with family status. *From Moratti et al., Journal of Affective Disorder, 2015.*



The ageing brain and predicting mild cognitive impairment

Short description:

Location: Centre for Alzheimer's Disease of the Fundación Reina Sofia

The Reina Sofia Centre for Alzheimer's Disease operates under the auspices of the Research Center for Neurological Diseases (CIEN, for its acronym in Spanish). CIEN is part of the Joint Programme for Neurodegenerative Diseases (JPND) research that is being developed in the European Union. Its excellent infrastructure, modern methodologies and cutting edge technologies as well as the available critical mass of researchers were the criteria most valued by the representatives of this organization when they were proposed by the Carlos III Institute of Health. In addition, CIEN is integrated into the international network of Centers of Excellence in Research on Neurodegeneration (COEN).

The flagship neurodegeneration research activity funded by the Reina Sofia Foundation and Carlos III Institute of Health is the "Vallecas project". Vallecas is a suburb in south Madrid where the Reina Sofia centre is based and from where a pool of over 1200 healthy elderly volunteers (70-85 yrs; male and female) has been recruited for this 5-year longitudinal study (currently in year 4). At each yearly visit, volunteers undergo detailed neuropsychological and clinical evaluation, serum biochemistry, as well as a multi-sequence magnetic resonance imaging (MRI) protocol, with genetic data acquired on visit 1.

The goals of the LCN members working on the Vallecas Project are:

Goal 1) To characterize differences in brain structure, perfusion and resting functional activity present prior to development of MCI.

Goal 2) To combine demographic, neuropsychological, genetic, serum biochemistry and MRI data to develop a statistical algorithm for predicting whether a healthy individual will develop MCI.

C. FACILITIES AND TECHNIQUES

Facilities/Infrastructures

In addition to behavioral testing rooms, lab facilities include portable EEG platforms and a MEG system available at CTB (described in the previous lab). The LCN offers a unique opportunity to record intracranial depth EEG during surgical and post-surgical interventions in neurological and psychiatric patients, as well as simultaneous intracranial and scalp EEG recordings.

The PI of the Laboratory for Clinical Neuroscience is also director of the Neuroimaging Department of the Reina Sofia Centre for Alzheimer's Disease, which houses a 3 Tesla MRI (Signa HDxt, General Electric, Waukesha, USA), with a phased array 8 channel head coil.

Techniques

- Human intracranial and scalp EEG
- Human intracranial spike recordings
- MEG: 306-channel system (Elekta©, VectorView)
- Structural, functional and diffusion MRI
- Deep-brain stimulation
- Transcranial magnetic stimulation
- Human behavioural and neuropsychopharmacology studies

D. RESEARCH PROJECTS

EMOTIONCOG. Exploring the effects of emotion on human cognition No. 04248

PI: Bryan Strange

Funding Agency: EU-FP7 Marie Curie Career Integration Grant

Budget: 100.000€

Period: 01/03/2012-29/02/2016

■ **Web link**: https://cordis.europa.eu/project/id/304248

Eliminando recuerdos no deseados en humanos mediante anestesia general SAF2014-62116-EXP

PI: Bryan Strange

Funding Agency: Ministerio de Economía y Competitividad

Budget: 30.000€

Period: 01/09/15-31/08/17

Aumento de memoria en seres humanos mediante estimulacion cerebral profunda del nucleo accumbens SAF2015-65982-R

PI: Bryan Strange

Funding Agency: Ministerio de Economía y Competitividad

Budget: 149.000€

Period: 01/01/16-31/12/18

OCD-DBS-icEEG. Characterizing the neural bases of deep brain stimulation to alter the symptoms of obsessive-compulsive disorder using EEG and icEEG

PI: Javier González Rosa & Bryan Strange

Funding Agency: Ministerio de Economía y Competitividad

Budget: 203.401€

Period: 01/01/16-31/12/18

Amyloid PET Imaging for the Vallecas Project

PI: Miguel Medina & Bryan Strange

Funding Agency: Instituto de Salud Carlos III

Budget: 90.000€

Period: 01/04/2016-31/03/2018

The healthy elderly brain: MRI predictors for developing MCI. 2016-NIRG-397128

PI: Bryan Strange

Funding Agency: Alzheimer's Association New Investigator Research Grant

Budget: 100.000€

Period: 01/06/16-30/05/18

Intracranial Recordings and Deep-Brain Stimulation of the Ventral-Tegmental Area in Patients with Schizophrenia. NARSAD-25960

PI: Bryan Strange

Funding Agency: Brain and Behaviour Research Foundation NARSAD Independent Investigator Award

Budget: 100.000€

Period: 15/09/17-14/09/18

E. PUBLICATIONS

1. Mendez-Bertolo, C., Moratti, S., Toledano, R., Lopez-Sosa, F., Martinez-Alvarez, R., Mah, Y. H., et al. (2016). A fast pathway for fear in human amygdala. *Nature Neuroscience, 19*(8), 1041-1049.

2. Strange, B. A., & Galarza-Vallejo, A. (2016). Bidirectional synaptic plasticity can explain bidirectional retrograde effects of emotion on memory. *Behavioral and Brain Sciences, 39*, e224. doi:10.1017/S0140525X15001958

3. Carrasco-López, C., Soto-León, V., Céspedes, V., Profice, P., Strange, B. A., Foffani, G., et al. (2017). Static magnetic field stimulation over parietal cortex enhances somatosensory detection in humans. *The Journal of Neuroscience, 37*(14), 3840-3847. doi:10.1523/JNEUROSCI.2123-16.2017

4. Lozano-Soto, E., Soto-León, V., Sabbarese, S., Ruiz-Alvarez, L., Sanchez-del-Rio, M., Aguilar, J., et al. (2018). Transcranial static magnetic field stimulation (tSMS) of the visual cortex decreases experimental photophobia. *Cephalalgia, 38*(8), 1493-1497.

Cognitive and Computational Neuroscience (UPM-UCM)

PRESENTATION/INTRODUCTION

The mission of the Cognitive and Computational Neuroscience Lab is to study the relations between cognitive functions and neurophysiological phenomena both in normal subjects and in patients with different neurological or psychiatric disorders. The principal idea is trying to understand brain functioning as a network, therefore as a constant interchange of information in a three dimensional space (space-time-frequency) to support cognitive and affective process. Our framework is using "connectivity analysis" and "network theory" as the basis of our understanding of the neurophysiological phenomena supporting cognitive functions, and neuropsychiatric dysfunction. Thus, the study of functional connectivity in neurological disorders such as Alzheimer´s Disease, epilepsy or stroke as well as in psychiatric disorders such as depression, autism or alcoholism is providing a new perspective on these neuropsychiatric disorders.

This Laboratory is a joint lab created by the Universidad Politécnica de Madrid and Universidad Complutense to bring together neuropsychologists, physicists, engineers, and medical doctors from UCM and UPM in an interdisciplinary environment to promote knowledge interchange and new questions about the functioning of the human brain.

A. MEMBERS

PI: Fernando Maestú Unturbe

Senior researchers: Ricardo Bajo, Leónides Canuet, Alberto Fernández, Stephan Moratti, Angel Nevado, Ernesto Pereda, David del Río, Pablo Cuesta, Gianluca Susi, Pablo Cuesta, María Eugenia López, Angeles Correas, Javier García Pacios and Ricardo Bruña

Post-doctoral Fellows: Guiomar Niso Galán

PhD students: David López, Inmaculada Rodriguez, Mari Carmen Martín-Buro, Teodoro Pascual, Carmen Cámara, Jaisalmer de Frutos, Ignacio de Ramón, Noelia Serrano.

B. RESEARCH LINES

Analysis of the oscillatory activity of the brain. Towards the understanding of brain functional networks

Short description:

The final objective of this investigation is the study of the brain connectivity and synchronization phenomena in a cognitive neuroscience framework and in neuropsychiatric diseases. This is mainly based on MEG technology but as well using a multimodality

neuroimaging approach, with an integration of functional and anatomical connectivity information.

Several applications of these techniques include:

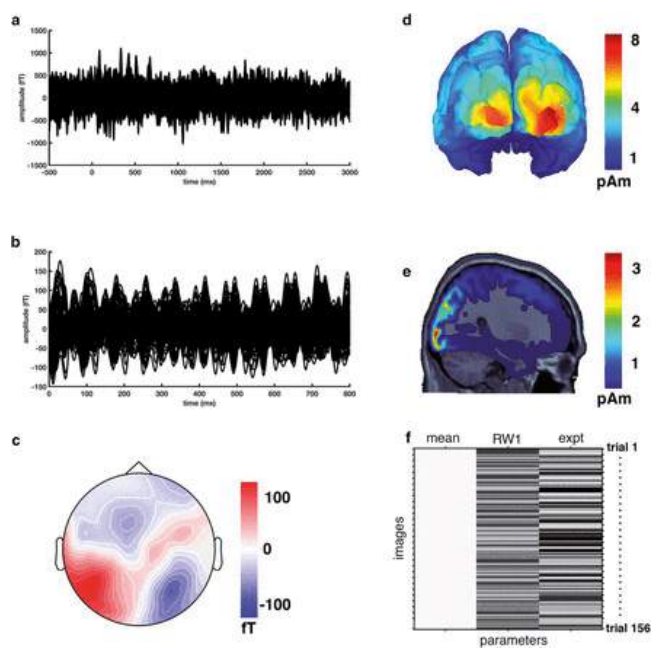
- Reliable biomarkers for early detection of neurodegeneraive diseases. Notably: early detection of dementia.
- Assessment of the therapeutic effectiveness of interventions: pharmacological, lifestyle, diets, exercise, gaming, etc.
- The study of ageing with a healthy brain.
- Assessment of the plasticity phenomena and network reorganization in patients with Traumatic Brain Injury and Stroke.
- Study of the brain oscillatory activity associated with emotions and its implication in psychiatric disorders such as depression or Post-Traumatic Stress Disorder.
- Presurgery mapping of epileptic lesions: motor, visual, speech and hearing cortex.
- Neurophysiological mechanisms of memory control or the intimate relations between memory and executive functions.
- Working memory and attentional process.

Main results:

Brain is a complex system where the communication between his brain regions or nodes are essential for supporting high order cognitive process as well as emotions.

Under this perspective no cognitive function would be localized in one particular brain region, as the traditional view establish, the cognitive system would rely in a particular network architecture. Under this view, we have developed a series of studies to demonstrate how phenomena such as brain plasticity or neurodegeneration modifies the functional organization of the brain in resting state and during cognitive tasks. Additionally, we have been studying how emotional processing can show particular profiles of brain activity in healthy controls but as well in patients with depression.

■ (Yuan et al, 2018)

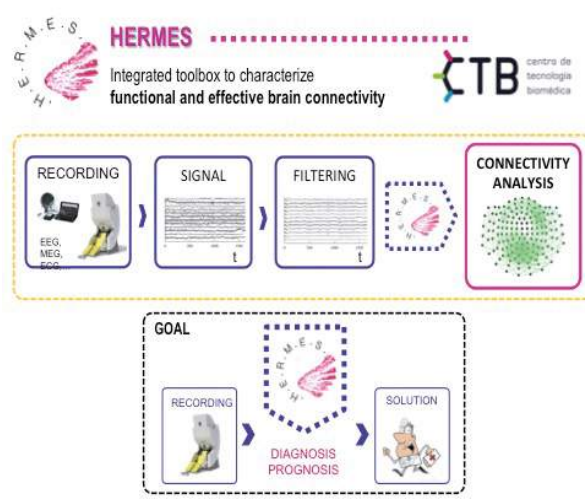


Brain Connectivity Methods

Short description:

The integrated use of: 1) Neuroimaging; 2) Multivariate time series analysis; 3) Connectivity Analysis and Network Theory; and 4) Complex system synchronization modelling, configure one of the principal hallmarks of the research of this laboratory, to contribute to understand the neurophysiological phenomena supporting cognitive functions, and their associated neurological and neuropsychiatric dysfunctions.

The mission of this Brain Connectivity Methods activity is to provide innovative tools to study the relations between cognitive functions and neurophysiological phenomena, both in normal subjects and in patients with different neurological or psychiatric disorders. Innovation that is based on the study of the brain functional connectivity networks, and how they express their dependency with neurological disorders, to provide a new perspective of these disorders. The efficiency and robustness of these methods will be applied and evaluated for those pathologies central of this laboratory, as depicted below.



This research line includes the following activities:

1. Continuing the development of HERMES Toolkit (open software free available at http://hermes.ctb.upm.es), an advanced Platform for the analysis of encephalographic time series, which provides a variety of multivariate and non-linear analysis methods to characterize functional connectivity networks, both in the sensors and in the sources spaces. This toolbox includes, apart from classical correlation procedures, other non-linear procedures such as: phase synchronization, generalysed synchronization, Granger causality, etc. It is including now statistical analysis and soon more advanced versions of the visualization
2. Brain network modelling and visualisation. Innovative tools are applied to developed the connectivity matrices derived from the multivatiate time series (MEG/EEG) to identify biomarkers for cognitive neuroscience and neuropsychiatric disorders (see research lines of Biological Networks Laboratory)

3. Classification tools for clinical diagnosis and neurosciences. Including among other: Random Forest [RF] (Breiman, 2001); Naïve Bayes Network [NB] (Buntine, 1991); C4.5 induction tree [C4.5] (Quinlan, 1993); K-Nearest Neighbour [KNN] (Cover and Hart, 1967); Logistic Regression [Logistic](Ng and Jordan, 2002); Support vector machine [SVM] (Platt, 1999)
4. Application of communication coding knowledge to brain synchronisation models. In collaboration with the researches in Computational System Biology and specialist in Communication from UPM (i.e.: special case of spread spectrum coding)
5. Research on revised algorithms to calculate functional connectivity at the source spaces
6. Code speedup to derive optimized version of the biomarkers: CPU and GPU Parallelization. In both cases, we initially use the functions incluided in Matlab's Parallel Computing Toolbox, which are already implemented to work with NVIDIA GPUs using Matlab code. Then, we will use ad hoc code compiled with CUDA / OpenMP for those processes such as partical mutual information or partial transfer entropy, which are very computationally demanding

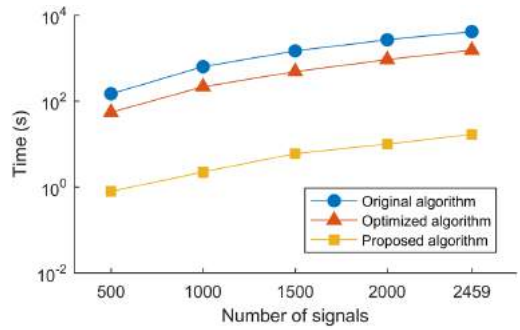
Main results:

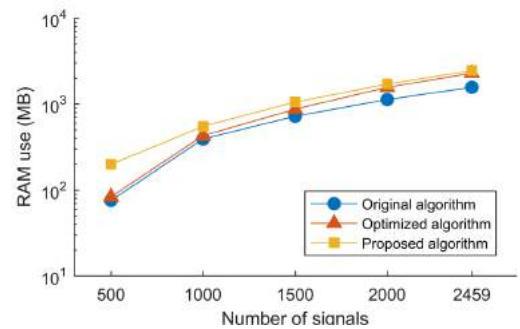
This toolbox (HERMES) is being used now all over the world with downloads the five continents and with a high number of references in scientific papers. Publications are mainly using our toolbox for characterizing functional connectivity parameter in MEG and EEG, with applications in topics such as cognitive neuroscience and medicine.

The analysis of the interdependence between time series has become an important field of research in the last years, mainly as a result of advances in the characterization of dynamical systems from the signals they produce, the introduction of concepts such as generalized and phase synchronization and the application of information theory to time series analysis. In neurophysiology, different analytical tools stemming from these concepts have added to the 'traditional' set of linear methods, which includes the cross-correlation and the coherency function in the time and frequency domain, respectively, or more elaborated tools such as Granger Causality. This increase in the number of approaches to tackle the existence of functional (FC) or effective connectivity (EC) between two (or among many) neural networks, along with the mathematical complexity of the corresponding time series analysis tools, makes it desirable to arrange them into a unified-easy-to-use software package.

The goal is to allow neuroscientists, neurophysiologists and researchers from related fields to easily access and make use of these analysis methods from a single integrated toolbox. Here we present HERMES (http://hermes.ctb.upm.es), a toolbox for the Matlab® environment (The Mathworks, Inc), which is designed to study functional and effective brain

connectivity from neurophysiological data such as multivariate EEG and/or MEG records. It includes also visualization tools and statistical methods to address the problem of multiple comparisons. We believe that this toolbox will be very helpful to all the researchers working in the emerging field of brain connectivity analysis.





Recently our lab was able to develop a new method for functional connectivity ciPLV (Bruña et al, 2018) which is trying to eliminate the cross talk, which could create spurious synchronization. This method is being used by several groups, even in a very short period of time since it was published. We start from the original implementation of phase locking value (PLV) and re-formulated it in a computationally very efficient way. What is more, this formulation stresses its strong similarity with coherence, which we used to introduce two new metrics insensitive to zero lag synchronization: the imaginary part of PLV (iPLV) and its corrected counterpart (ciPLV).

The new implementation of PLV avoids some highly CPU-expensive operations and achieves a 100-fold speedup over the original algorithm. The new derived metrics were highly robust in the presence of volume conduction. Moreover, ciPLV proved capable of ignoring zero-lag connectivity, while correctly estimating nonzero-lag connectivity. Our implementation of PLV makes it possible to calculate whole-brain connectivity in much shorter times. The results of the simulations using ciPLV suggest that this metric is ideal to measure synchronization in the presence of volume conduction or source leakage effects.

Biomarkers for the early detection of dementia

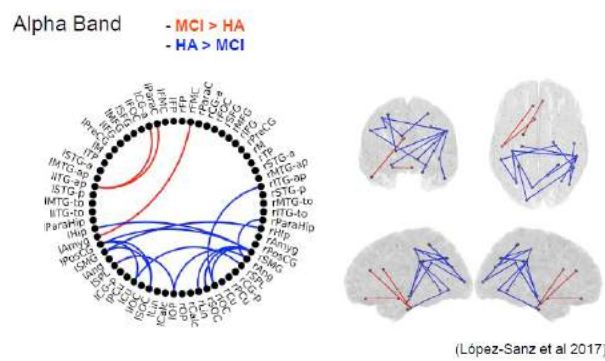
Short description:

Our group has been investigating the biomagnetic profiles of healthy and pathological aging. In the first and seminal project we were describing how elderly subjects showed differential biomagnetic activity in comparison to young subjects at the encoding, maintenance, interference and recognition stages of a retroactive interference forgetting task with interruption and distraction conditions (Solesio et al, 2009; Solesio-Jofre et al, 2011; Solesio-Jofre et al, 2012; García-Pacios et al, 2013; Ariza et al, 2015). Subsequently, in a multimodal and multilevel approach in which genetics, neuropsychology and anatomo-functional networks were evaluated we were

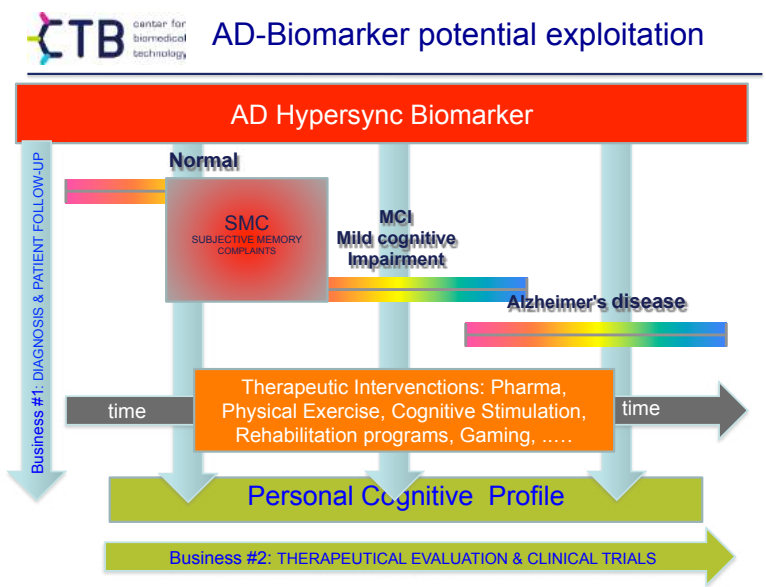
able to characterize network disruption in patients with MCI (Bajo et al, 2010; Bajo et al, 2012; Garcés et al, 2014; Pineda-Pardo et al, 2014; Cuesta et a, 2015a). Thanks to this coordinate project we were able to publish more than 20 papers. In a subsequent project about SCD in the elderly, we investigated again from a multimodal and multilevel point of view the anatomo-functional networks of these elderly subjects at higher risk of dementia (López-Sanz et al, 2017).

Finally, we have investigated the long-term effect of cognitive intervention in subjects with SCD. The international collaboration that resulted from this last project made possible to publish how the amyloid deposition (PET-PIB) in healthy elderly subject disrupts the functional networks when the morphology of the brain and the cognitive system is still preserved (Nakamura et al, 2017; Nakamura et al, 2018). The study found an increased alpha band synchronization between anterior and posterior brain regions (mainly anterior cingulate cortex and orbitofrontal cortex / parieto-occipital cortex), in converters from MCI to AD, in SCD subjects, in carriers of the APOE-ε4, in healthy subjects with high amyloid in their brains as well as in MCI with high p-tau in their cerebrospinal fluid.

Technology transfer and clinical translation. Since this lab is primarily concerned with the translation of neuroscience research to the clinical setting and the transfer of innovation to the industrial world, it is shown in the figure two business cases that are now in progress in the specific case of the biomarkers for the early detection of Azheimer's Disease.

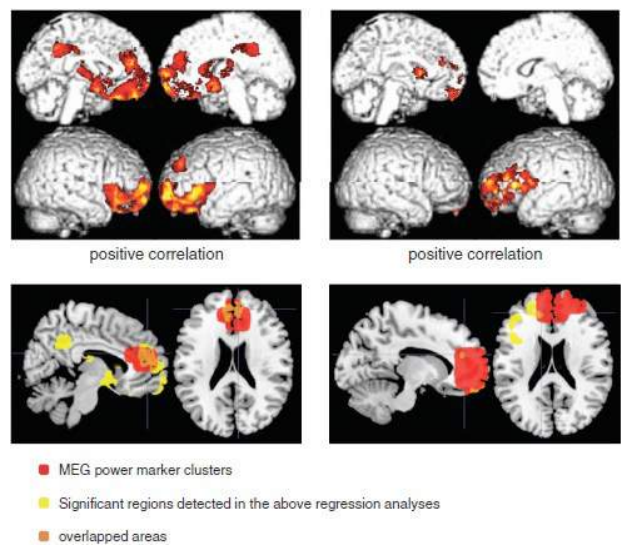


(López-Sanz et al 2017)



Main results:

In the last five years our lab has been very active in the comparison between current biomarkers such as amyloid PET and levels of Tau protein at the cerebrum spinal fluid (CSF). In Nakamura et al (2018) we were testing the relations between amyloid PET and MEG profiles. The physiological relevance of EEG/MEG signal changes and their role in pathophysiological processes such as amyloid-b deposition and neurodegeneration need to be elucidated. We evaluated 28 individuals with mild cognitive impairment and 38 cognitively normal individuals, all of whom were further classified into amyloid-b-positive mild cognitive impairment (n = 17, mean age 75±5 years, nine males), amyloid-b-negative mild cognitive impairment (n = 11, mean age 74±9 years, eight males), amyloid-b-positive cognitively normal (n = 13, mean age 72±4 years, seven males), and amyloid-b-negative cognitively normal (n = 25, mean age 73±3 years, 11 males) individuals using Pittsburgh compound B-PET. We measured resting state MEG for 5 min with the eyes closed, and investigated regional spectral patterns of MEG signals using atlas-based region of interest analysis.



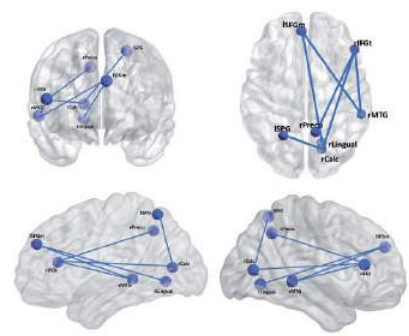
Then, the relevance of the regional spectral patterns and their associations with pathophysiological backgrounds were analyzed by integrating information from Pittsburgh compound B-PET, fluorodeoxyglucose-PET, structural MRI, and cognitive tests. The results demonstrated that regional spectral patterns of resting state activity could be separated into several types of MEG signatures as follows: (i) the effects of amyloid-b deposition were expressed as the alpha band power augmentation in medial frontal areas; (ii) the delta band power increase in the same region was associated with disease progression within the Alzheimer's disease continuum and was correlated with entorhinal atrophy and an Alzheimer's disease-like regional decrease in glucose metabolism; and (iii) the global theta power augmentation, which was previously considered to be an Alzheimer's disease-related EEG/MEG signature, was associated with general cognitive decline and hippocampal atrophy, but was not specific to Alzheimer's disease because these changes could be observed in the absence of amyloid-b deposition. The results suggest that these MEG signatures may be useful as unique biomarkers for the predementia stages of Alzheimer's disease.

Recently we were able to describe, for the first time, a neurophysiological model for the prediction of what MCI patients would develop dementia. Hypersynchronization has been proposed as a synaptic dysfunction biomarker in the Alzheimer's disease continuum, reflecting the alteration of the excitation/inhibition balance. While animal models have verified this idea extensively, there is still no clear evidence in humans. Here we test this hypothesis, evaluating the risk of conversion from mild cognitive impairment (MCI) to Alzheimer's disease in a longitudinal study.

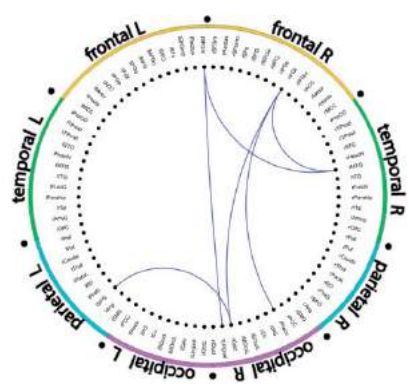
We compared the functional resting state eyes-closed magnetoencephalographic networks of 54 patients with MCI who were followed-up every 6 months. According to their clinical outcome, they were split into: (i) the 'progressive' MCI (n = 27) group; and (ii) the 'stable' MCI group (n = 27).

They did not differ in gender or educational level. For all participants, two magnetoencephalographic recordings were acquired. Functional connectivity was evaluated using the phase locking value. To extract the functional connectivity network with significant changes between both magnetoencephalographic recordings, we evaluated the functional connectivity ratio, defined as functional connectivity post-/pre-condition, in a network-based statistical model with an ANCOVA test with age as covariate. Two significant networks were found in the theta and beta bands, involving fronto-temporal and fronto-occipital connections, and showing a diminished functional connectivity ratio in the progressive MCI group.

These topologies were then evaluated at each condition showing that at baseline, patients with progressive MCI showed higher synchronization than patients with stable MCI, while in the post-condition this pattern was reversed. These results may be influenced by two main factors in the post-condition: the increased synchrony in the stable MCI patients and the network failure in the progressive MCI patients.



These findings may be explained as an 'X' form model where the hypersynchrony predicts conversion, leading subsequently to a network breakdown in progressive MCI. Patients with stable MCI showed an opposite phenomenon, which could indicate that they were a step beyond in the Alzheimer's disease continuum. This model would be able to predict the risk for the conversion to dementia in MCI patients.

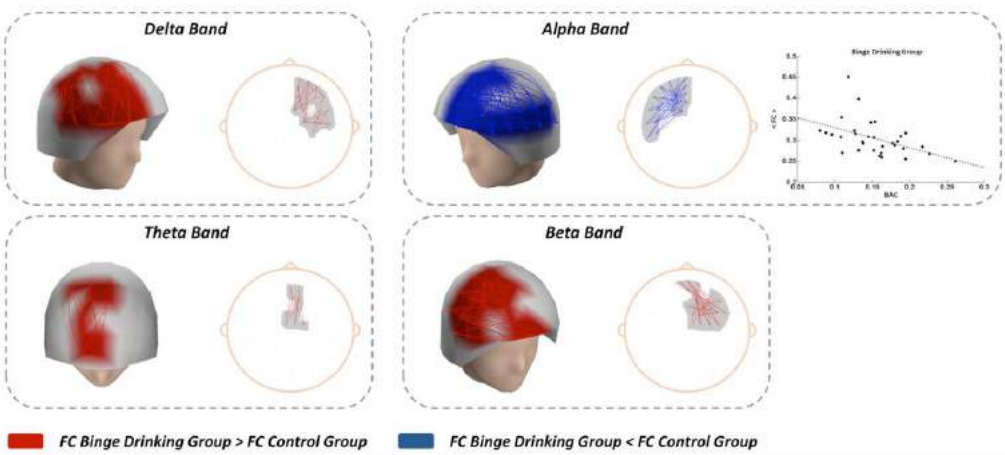


Study based on network theory in Binge Drinking

Short description:

There is a social demand for studying the consequences of Binge Drinking pattern of alcohol consumption in our European societies. In this regards our lab started an important collaboration with the university of Santiago de Compostela (faculty of Psychology), where the group lead by Fernando Cadaveira were studying the effects of this pattern of alcohol consumption for any years. As well and along with the faculty of education of the Complutense University of Madrid and specifically with the group headed by Luis Miguel García Moreno, we have studied binge drinking in teenagers.

■ This figure shows how young subjects binge drinkers present a differential profile in comparison with a control group. In red those connections with higher values in binge drinkers. (Correas et al, 2015)



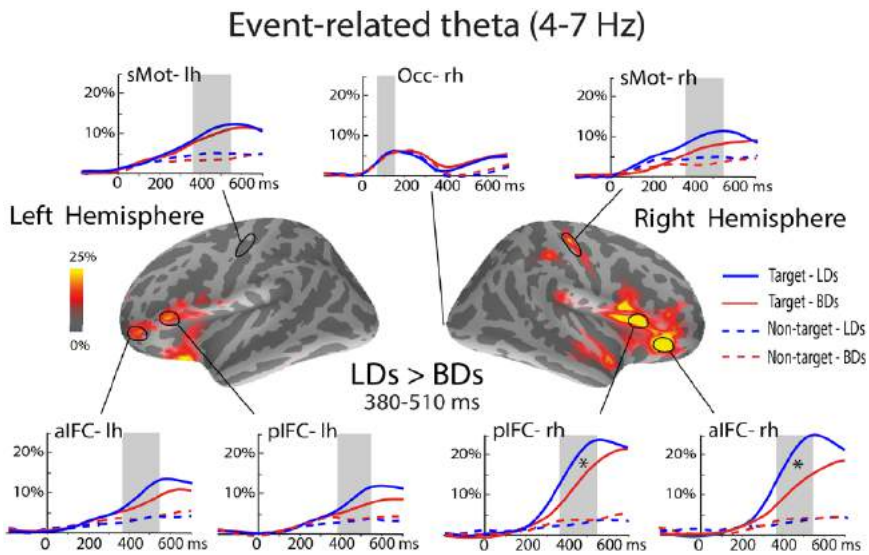
Main results:

In the last five years we have received funding in two consecutive projects from the National Plan of Drugs to study the effects of binge drinking in young subjects. Initially our efforts were concentrated on the description of the effects of alcohol on university students with or without binge drinking. The prevalence of binge drinking has risen in recent years. It is associated with a range of neurocognitive deficits among adolescents and young emerging adults who are especially vulnerable to alcohol use.

Attention is an essential dimension of executive functioning and attentional disturbances may be associated with hazardous drinking. The aim of the study was to examine the oscillatory neural dynamics of attentional control during visual target detection in emerging young adults as a function of binge drinking. In total, 51 first-year university students (18 ± 0.6 years) were assigned to light drinking (n = 26), and binge drinking (n = 25) groups based on their alcohol consumption patterns. A high-density magnetoencephalography signal

was combined with structural magnetic resonance imaging in an anatomically constrained magnetoencephalography model to estimate event-related source power in a theta (4-7 Hz) frequency band.

■ (Correas et al, 2018)



Phase-locked co-oscillations were further estimated between the principally activated regions during task performance. Overall, the greatest event-related theta power was elicited by targets in the right inferior frontal cortex and it correlated with performance accuracy and selective attention scores.

Binge drinkers exhibited lower theta power and dysregulated oscillatory synchrony to targets in the right inferior frontal cortex, which correlated with higher levels of alcohol consumption. These results confirm that a highly interactive network in the right inferior frontal cortex subserves attentional control, revealing the importance of theta oscillations and neural synchrony for attentional capture and contextual maintenance. Attenuation of theta power and synchronous interactions in binge drinkers may indicate early stages of suboptimal integrative processing in young, highly functioning binge drinkers.

Computational Neuroscience

Short description:

In this research line we employ mathematical models and theoretical analysis to understand the principles that govern the physiology, structure and development of the nervous system, and related functional aspects.

The main activities of our laboratory in this field are:

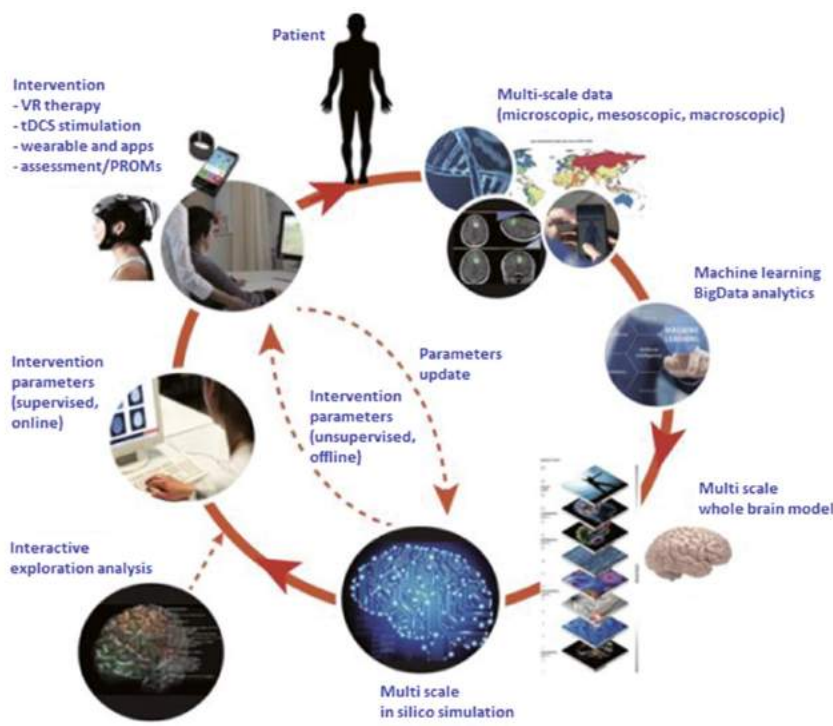
1. Brain network simulation based on real structural and functional brain data, with the aim of reproducing network dynamics in health and disease, and improving early patient-specific diagnosis and treatment;
2. Development of novel bio-inspired classification techniques.

With regards to the point 1), the laboratory is one of the co-beneficiary of *Virtual Brain Cloud* (VBC), a 4-year European project partner of the *Human Brain Project*, aimed at developing a cloud-based simulation platform for personalized medicine in neurodegenerative diseases (https://virtualbraincloud-2020.eu/tvb-cloud-main.html). The laboratory plays an important role in the project both for being the provider of brain data, and for being involved in the brain network simulation process and characterization of dementia.

In addition, in collaboration with the University of Rome, the Laboratory has developed the software FNS (https://www.fnsneuralsimulator.org/), a Spiking Neural Network (SNN) simulator characterized by high temporal precision and a good biological plausibility, based on *parallelization* and *event-driven computation* techniques, and supporting neural plasticity.

With regards to the point 2), the laboratory has been developing neuro-inspired decoding structures for learning and recognition of multi-neuronal spike trains arising from neuronal ensembles.

■ The figure describes the workflow of VirtualBrainCloud: integrating 'big data' of multiple multimodal data platforms by linking systems biology with brain network modelling



Main results:

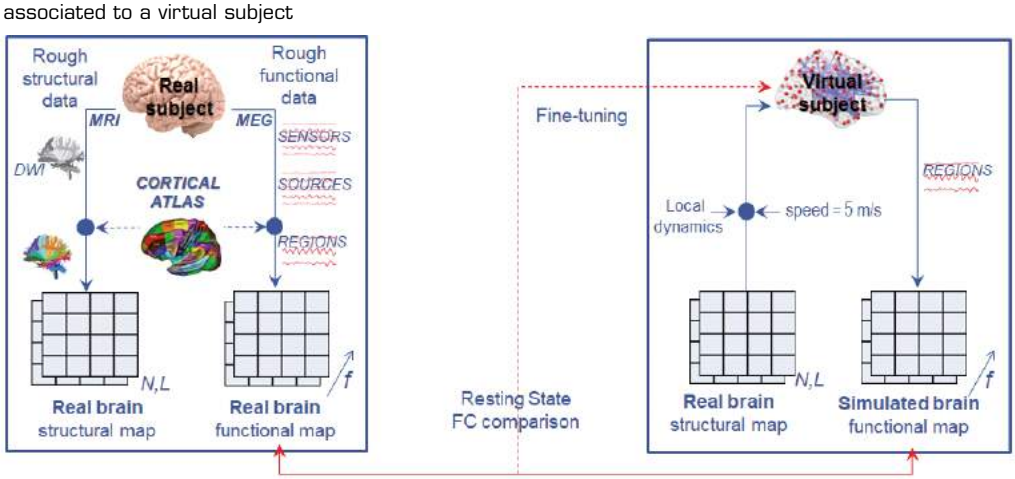
Using our software FNS we have been carrying out simulations aimed at unveiling the FC transitions in the Default Mode Network during the early stage of Alzheimer's disease (AD). We showed that the deterioration of the hippocampus could be playing a pivotal role on the disruption of the FC during the initial stage of disease, predicting up to 78% of the transitions found in the real case (results to be published).

Regarding the neuro-inspired classification method, in Susi et al., 2018 we presented the multi-neuronal spike sequence detector (MNSD), a neuronal microcircuit able to map spatio-temporal neuronal stimuli into a multi-dimensional, temporal, feature space. The structure is able to self-regulate its weights, allowing the learning and recognition of multi-neuronal spike trains arising from neuronal ensembles. We applied our method to experimental MEG data obtained from a motor-inhibitory cognitive task (Go-NoGo), with performances that are comparable to the most used classifiers, such as SVM. Its simplicity and low computational cost suggest a large scale implementation for real time recognition applications in several areas, such as brain computer interface, personal biometrics authentication, or early detection of diseases.

With regard to VBC, we are in the first phase of the project, concerning data sharing within the consortium. The need of data harmonization among the partners has led us to organize a large part of MEG and MRI lab data following the BIDS format, facilitating future sharing and automatized analysis.

Concerning brain simulation, we are focusing on strategies to implement structural network modifications typical of Alzheimer's disease (as the β-amyloid-related degeneration and demyelination in the structures affected by neurofibrillary pathology). We have been invited on a dedicated seminar on the topic, proposing TVB simulations informed by SNN ones and we are currently working on it.

■ The figure describes the processes of FC and SC extraction, model synthesis and tuning of the SNN associated to a virtual subject



C. FACILITIES AND TECHNIQUES

Facilities/Infrastructures

Magnetoencephalography (MEG) equipment. Elekta-Neuromag, with 306 sensors (204 planar gradiometers and 102 magnetometers). Three workstations, one for acquisition and two for analysis that contains the software Cogent Stim, eprime, presentation and Stim.

Simultaneous recordings EEG/MEG of 32 EEG channels. Additional equipment for the EEG 64 channels, Neuroscan.

Techniques

- Magnetoencephalography recordings.
- Single and simultaneous recording of EEG and MEG to identify EEG dementia biomarkers.
- Design and implementation of cognitive paradigms in stimulation programs.
- Localization of epileptiform activity in patients with epilepsy.
- Pre-surgery functional mapping of motor cortex, auditory, visual and linguistic.
- Behavior.
- Genetic analysis in collaboration with Hospital Universitario San Carlos.
- Neurophysiological time series analysis and modeling techniques. HERMES Platform for functional connectivity analysis.
- EMG-imaging. Source reconstruction.
- Neuroimaging methods Platform: volumetry, spectroscopy, VBM, diffusion imaging, iron content, tensor based morfometry, etc.
- Computational analysis and graph theory, in collaboration with MEDAL and Biological Networks laboratories of CTB.
- Data mining procedures: in collaboration with MEDAL group of CTB.

D. RESEARCH PROJECTS

Human Connectome Project: Connectomics of Brain Aging and

PI: James Becker.

PI Spain: Fernando Maestú

Funding Agency: National Institute of Health

Budget: 6.000.000$

Period: 01/01/2018-31/06/2021

BIOFIND: Biomagnetic Framework for identifying network dysfunction in dementia

PI: Laura Hughes

PI Spain: Fernando Maestú

Funding Agency: Joint programing for the neurodegenerative diseases (JPND) H2020

Period: 01/05/2016-31/04/2018

Virtual Brain Cloud

PI: Petra Ritter

PI Spain: Fernando Maestú

Funding Agency: European Commission. H2020-SC1-DTH-2018-2020/H2020-SC1-DTH-2018-1

Budget: 15ME (Spain 396,250)

Period: 01/12/2018-31/12/2022

Other institutions participating: Charité Universitätsmedizin Berlin, Germany. Aix-Marseilles Univ., France. Fraunhofer Institute for Algorithms and Scientific Computing SCAI, Germany. Univ.of Oxford, United Kingdom. Institut de Cerveau et de la Moelle Epinière, France. Forschungszentrum Jülich, Germany. Institut National de Recherche en Informatique et Automatique, France. Institut de Bioenginyeria de Catalunya, Spain. Univ. of Helsinki, Finland. Univ. of Genoa, Italy. Univ. Complutense de Madrid, Spain. Codebox Computerdienste GmbH, Germany. Codemart SRL, Cluj Napoca, Romania. Eodyne Systems SL, Spain. Univ. of Vienna, Austria. tp21 GmbH, Berlin, Germany. Alzheimer Europe, Luxembourg, Luxembourg.

■ **Web link:** https://virtualbraincloud-2020.eu/tvb-cloud-main.html

NEUROCENTRO. Comprehensive program of biomedical engineering for the development of diagnostic and therapeutic techniques in neurological diseases. B2017/BMD-3760

PI: Gustavo Guinea

Funding Agency: Comunidad de Madrid

Budget: 702.000€

Period: 01/01/2018-31/12/2021

Other institutions participating: Univ. Complutense de Madrid, Hospital Clínico San Carlos, Hospital Universitario de la La Paz, Consejo Superior de Inv. Científicas

E. PUBLICATIONS

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Experimental Neurology Unit (UPM)

PRESENTATION/INTRODUCTION

The Experimental Neurology Unit is focused on understanding the pathophysiological mechanisms of a variety of neurological disorders, searching for therapeutic and early diagnostic opportunities. Our research lines have a double aspect, basic and applied. Main research areas are the following:

- Drug/cell based therapies to neuroprotect and repair the neurovascular microenvironment of the injured brain in cerebrovascular diseases and neurodegenerative disorders (i.e. Stroke, TBI, Alzheimer's and Parkinson´s).
- Biomarkers based on cell/molecular, imaging and electrophysiological cues with valuable early diagnosis and prognosis in cerebrovascular and neurodegenerative disorders.
- Development of selective contrast agents based on magnetic nanoparticles for early diagnosis of Alzheimer´s disease by RMI.
- Gold nanorods and magnetic nanoparticles for cell death induction in glioblastoma cell lines based on hyperthermic therapy.
- Intercellular communication through functional and dysfunctional Connexins in cerebral ischemia, Alzheimer´s disease, hypomyelinating leukodystrophy, epilepsy and sudden infant death syndrome.
- Interaction between electromagnetic fields and biological systems at different frequencies and amplitudes interaction models.
- Therapeutic applications of electromagnetic fields of low intensity and frequency in fibromyalgia, chronic fatigue, muscle injury, depression, arthritis and arthrosis.
- Electromagnetic field personnel dosimetry and environmental dosimetry in urban environments.
- Biomarkers for tumoral growth in response to low-intensity electromagnetic fields in cells and animal models.

A. MEMBERS

PI: Daniel González-Nieto

Senior researchers: Ceferino Maestú Unturbe, Milagros Ramos Gómez, Luis Carlos Barrio, Carlos Paino

Post-doctoral Fellows: Nazario Felix

PhD students: Rocío Fernández, Rebeca Gallego, Atocha Guedán, Olga García-Minguillán, Marco Rivera, J.M. Gómez-Arguelles, Laura Fernández García

Others: Soledad Martínez Montero, Francisco Mikuski, María Puyuelo

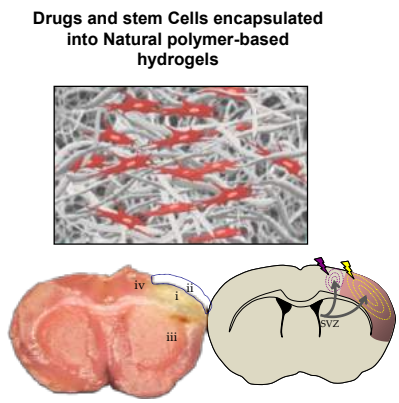
B. RESEARCH LINES

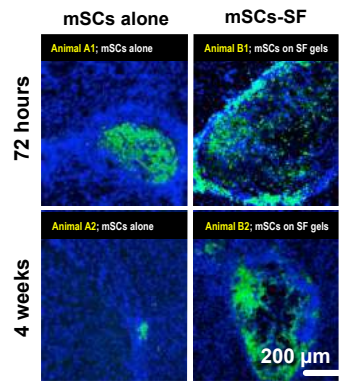
New approaches for therapeutic intervention after cerebral damage

Short description:

Diseases: stroke, traumatic brain injury, Parkinson´s and Alzheimer´s diseases.

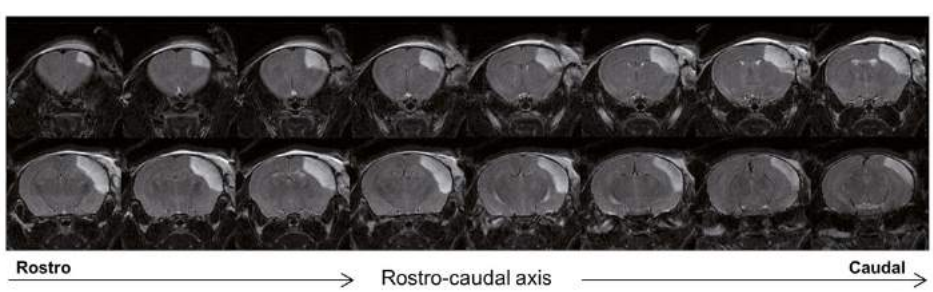
■ Mesenchymal stem cells encapsulated into silk fibroin (SF) matrices survive for longer periods of time after transplantation and neuroprotect and repair the stroke damaged brain. (Front Cell Neurosci (2018), Polymers (2018))





- We aim to rationally identify and investigate new neuroprotective compounds with significant effects over secondary injury; inflammation, excito-toxicity, oxidative stress and spreading depolarization waves, all of them, well known mechanisms that contribute to exacerbate neurological damage.
- We are exploring cell-based therapies using native and reprogrammed stem cells to neuroprotect the damaged brain and/or to enhance brain plasticity and functional recovery. We aim to develop and construct advanced and sophisticated polymers for drug and stem cell encapsulation and delivery towards the injured brain with precise control of release in spatial and dynamic terms.

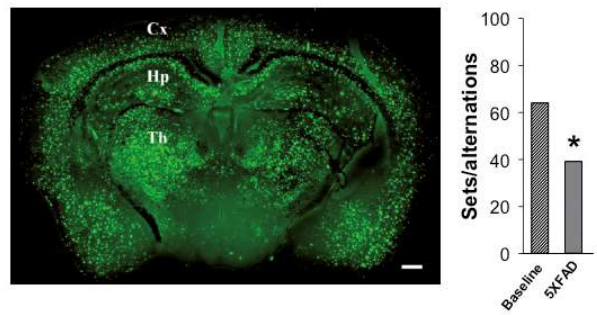
■ Our animal model: Representative MRI images of mouse brain sections with cortical stroke. (Front Cell Neurosci (2018))



- Our strategies in this area are aligned with H2020 personalized medicine and innovative health and care industry priorities, development of new biohybrid materials, medical devices and biomedical procedures for better understanding, control and treatment of major diseases and conditions.

For many neurological diseases cell transplantation is very promising but important concerns need first to be overcome. We aim also to develop radical strategies to avoid conventional cell transplantation procedures and all the inherent problems associated with exogenous cell transplantation. Specifically we are developing advances approaches to stimulate host stem cell and progenitors neuroprotective and regenerative capacity.

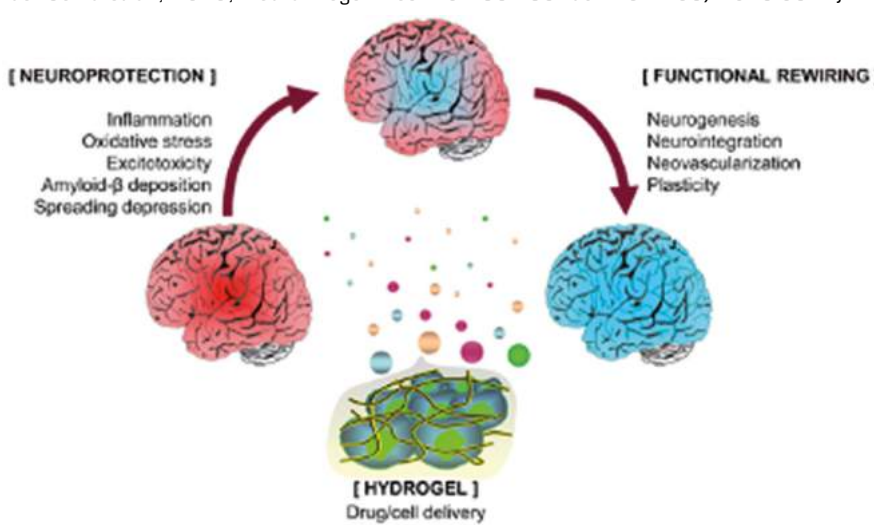
■ Our animal model: 5XFAD mouse, a model of Alzheimer's disease shows amyloid deposits and impaired spatial memory examined by the Y-Maze test. (Acta Biomater (2016))



Main results:

We are currently exploiting novel strategies to neuroprotect and repair the injured brain. In stroke for example we are grafting stem cells and different biomolecules against secondary damage to attenuate inflammation, oxidative stress, excitotoxicity and spreading depression.

■ Hydrogel scaffolds for brain engineering. Biomaterial-based Hydrogels and nanoparticles (micelles, liposomes, polymeric and inorganic nanoparticles) may overcome actual limitations of classical drug/cell delivery approaches. In our group we essentially exploit the advantages that this technology and biomaterial formats may offer for the resolution of conflicting classical cell/drug delivery strategies. (From Fernandez-Serra et al., 2020, Neural Regen Res. 15:783-789. doi: 10.4103/1673-5374)



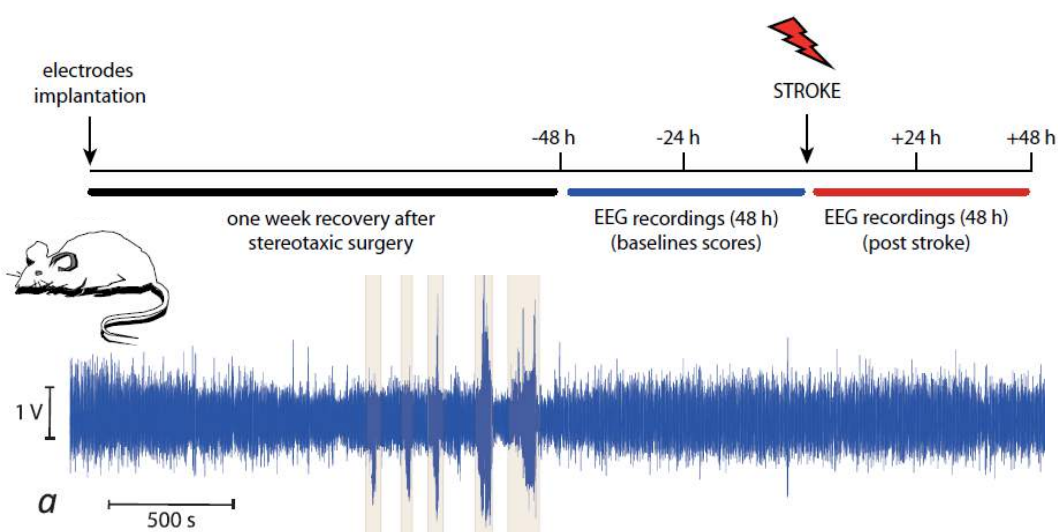
We recently developed a brain ischemia mouse model correlating the sensorimotor function with the activity of somatosensory cortex examined by evoked potentials (Barios et al., 2016; JCBFM). In our hands this approach is crucial to explore the efficacy of different biomolecules against secondary damage and to examine the mechanisms of spontaneous plasticity in the damaged and intact hemisphere in the chronic phase of stroke, as well the plasticity changes induced by transplantation of stem cells delivered from silk-based biomaterials; in collaboration with the group of Tissue Engineering and Biomaterials at CTB. We also have demonstrated the compatibility of silk fibroin hydrogels with brain function using electrophysiological techniques (Fernández-García et al., 2016; Acta Biomaterialia) and found that stem cells encapsulated into silk fibroin hydogeles enhance recovery after stroke (Fernández-García et al., 2018; Frontier in Cellular Neuroscience) through a massive release of the anti-inflammatory molecule TGF-Beta-1 (to be published). Non-published precise results remain confidential.

Electrophysiology-based biomarkers for early diagnosis and prognosis in cerebrovascular and neurodegenerative diseases

Short description:

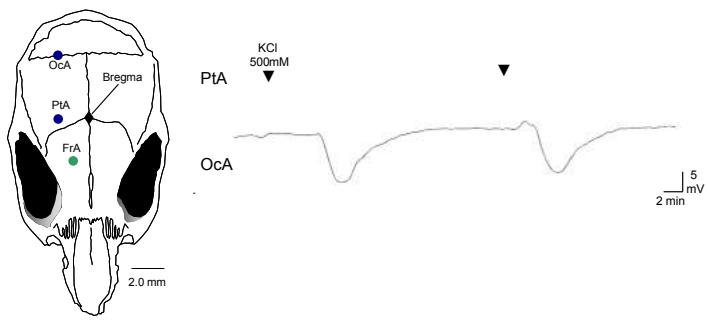
Diseases: Stroke, traumatic brain injury, Parkinson and Alzheimer

■ Typical post-stroke seizures in the EEG of stroke mice (seizures appears 2 h after the induction of stroke). (Eur. Phys. J. Special Topics (2018))



- We study 1) brain spreading depression/depolarization waves; 2) EEG and sleep/wake cycle regulation; and 3) cortical field potentials as biomarkers for early diagnosis/prognosis in stroke, TBI and Alzheimer´s disease. We aim to identify brain electrical activity patterns in cerebrovascular and neurodegenerative preclinical models. For example, In the context of Alzheimer´s disease, we aim to better understand the relationship between Alzheimer progression and structural/functional changes in different brain areas to develop algorithms with value for early diagnosis and prognosis in patients.

■ Our animal model: Spreading depolarization waves can be induced in mice by different strategies (stroke, TBI, KCl, Pinprick)



Main results:

We have characterized the patterns of brain electrical activity and focal seizures during the acute phase of stroke in a model of permanent ischemia (Pisarchik et al., 2018, Eur. Phys. J. Special Topics). Aberrant sleep-wake cycle, delta and theta bands were also impaired (under preparation). We are characterizing the sleep-wake cycle and cortical spontaneous/induced cortical activity of 5xFAD Alzheimer´s mouse models to find specific biomarkers with prognostic and diagnostic value. Non-published precise results remain confidential.

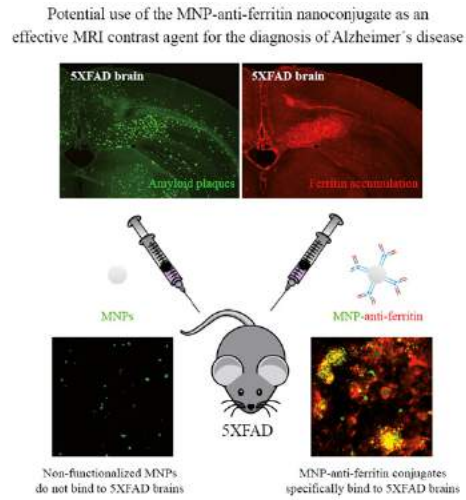
Development of selective contrast agents based on magnetic nanoparticles for early diagnosis of Alzheimer´s disease by RMI

Short description:

This research line is focused on the study of the interaction of new micro and nanomaterials with cell biology, working in the development of functionalized nanoparticles useful in diagnosis and therapy of neurodegenerative diseases (Alzheimer, Parkinson).

Alzheimer's disease (AD) is the leading cause of dementia in the elderly and the most prevalent neurological disease affecting developed countries. The major pathologic hallmarks of AD are extracellular deposits of amyloid peptides in the brain parenchyma that form amyloid plaques (AP) and intracellular accumulation of abnormally phosphorylated

tau protein that forms neurofibrillary tangles (NFTs). Currently, the post-mortem histological observation of amyloid plaques and neurofibrillary tangles is the only definitive diagnosis available for AD. Therefore, there is a strong need to develop new techniques to detect these pathologic hallmarks in vivo. This could add a great deal of confidence to the diagnosis of AD and potentially might allow therapeutic intervention much earlier to prevent the rapid progression of the disease.



Main results:

At the present, several contrast agents based on MNPs have been synthesized to detect some hallmarks of Alzheimer´s disease. A nanoconjugate composed of magnetic nanoparticles bound to an antiferritin antibody has been developed based on the existence of iron deposits and high levels of the ferritin protein present in areas with a high accumulation of amyloid plaques (particularly the subiculum, in the hippocampal area) in the brain of a transgenic mouse model with five familial AD mutations.

Another contrast agent has been proposed to be synthesized composed of magnetic nanoparticles bound to an anti-cholesterol antibody, to detect the abnormal deposits of cholesterol observed in senile plaques in Alzheimer's disease by magnetic resonance imaging. The results have been published in ACS Chem Neurosci (2018).

Nanoparticles for cell death induction in glioblastoma cell lines based on hyperthermic therapy

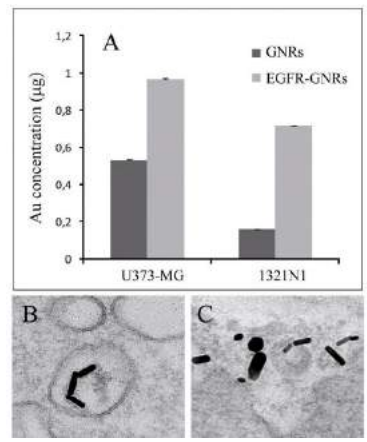
Short description:

Metallic nanorods and magnetic nanoparticles are promising agents for a wide range of biomedical applications. In this research line we have developed an optical hyperthermia method capable of inducing *in vitro* and *in vivo* glioblastoma cell death. The procedure is based on the irradiation of gold nanorods with a continuous wave laser. The effectiveness of the method has been determined by measuring changes in cell viability after laser irradiation of glioblastoma cells in the presence of gold nanorods. Additionally, the use of magnetic nanoparticles to eliminate cancer cells has also been evaluated. A new technique based on a magnetic force produced by an alternating magnetic field gradient inside a constant field magnet, has been used to design new equipment used to produce cell death.

Main results:

Our results suggest that the functionalization of gold nanorods (GNRs) with an EGFR modification improves GNR uptake and increases GNR-mediated cell death after laser irradiation. This technique may have the potential to be used clinically as a tool to help complete resection of brain tumors during surgery. These data have been published in the Journal of Nanoscience and Nanotechnology (2016). Regarding the magnetic nanoparticles, we have determined the interaction of these particles with cells under different conditions such as incubation time with particles, particle size, magnetic field exposition time, and different current waveforms at different frequencies to produce a magnetic field gradient. The results confirmed that cancer cells can be eliminated in response to the forces caused by the movement of magnetic nanoparticles of the appropriate size under the application of a specific magnetic field. This method could be of great interest to remove cancer cells. These results have been published in the Journal of Nanoparticle Research (2017).

■ Cellular uptake of GNRs and EGFR-GNRs by U373-MG and 1321N1 cells, Au ion concentration was measured by TXRF after preincubating cells (2×105 cells) with gold nanorods at 0.06 mg/ml for 75 min (A). TEM images of U373-MG cells treated with GNRs (B) and EGFR-GNRs (C). Scale bar: 80 nm.

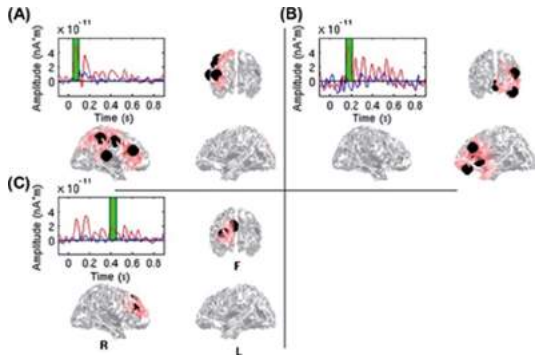


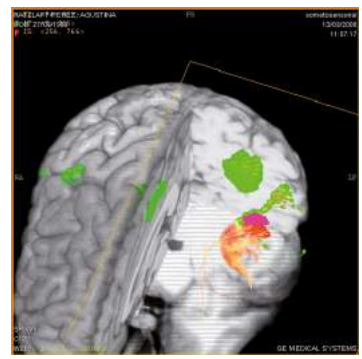
Modification of brain functions with electromagnetic fields. Research on brain communication mechanisms with very low frequency and intensity pulsed magnetic fields. Clinical applications

Short description:

We are involved in the development of new treatments for the pathologies associated with central sensitivity syndrome (Yunus 2005). Through the application of actuators with electromagnetic fields of low intensity and low frequency that modify the responses of altered neuromodulators characteristic of these pathologies, such as fibromyalgia, chronic fatigue, electromagnetic hypersensitivity, etc. especially some of its symptoms such as pain manifestations Clin Neurophysiol. 2013 Apr; 124 (4): 752-60). Tests were achieved by applying mechanical stimulation systems painful, with a patented device developed in the CTB that allows mechanical stimulation compatible with MRI systems and MEG. Currently we have achieved the CE marking for clinical application In these tests we checked different processing of pain signals compared to control subjects, in this case using a tensor diffusion.

- By applying low-intensity magnetic fields devices, we can reverse those painful symptoms, by modifying the processing of the pain signals to the brain. The application device has been authorized by the Agency of Medicine and Health Product (No.2019 07 0893 CP) and it is now being used in clinical practice. More than 3500 patients have been treated with this technique, showing results in the reduction of symptomatic (pain, headache, sleep disorders, etc.) in over 80 % of the cases.



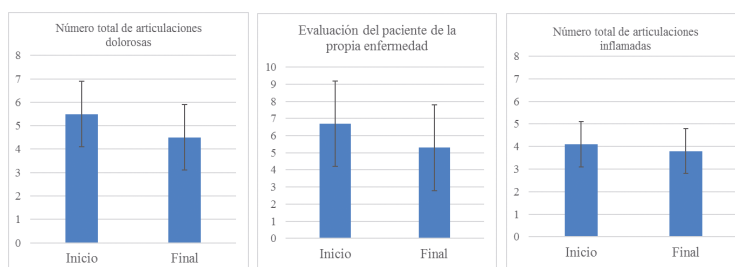


Applicator gloves for arthritis and osteoarthritis

Short description:

Pre-clinical intervention models have been developed for application in degenerative joint processes such as arthritis or osteoarthritis. Continuing with the models of interaction of the pulsed magnetic field and the effects on living systems, we have studied the behavior of certain cell lines such as chondrocytes, since our experimental developments have allowed us to see how they align in their growth in the direction of the fields applied electromagnetic,

- When comparing the measurements obtained in the control hand and the hand that received magnetic therapy, improvements in the treated hand differ with respect to the control in terms of pain and inflammation. While the control hand remained practically the same regarding the number of painful joints (0.5% increase), the treated hand suffered a reduction of 11.1%, about 2 painful joints less than at the beginning of the treatment. Likewise, the control hand remained constant (increase of 1.6%) in the number of inflamed joints, unlike the hand with therapy, which reduced this amount by 5.5%.



also improving the growth of these cells. These cells play a fundamental role in the development of some pathologies such as arthritis or osteoarthritis.

For this we have developed actuator devices on a glove to apply these fields in the joints of the fingers.

Main results:

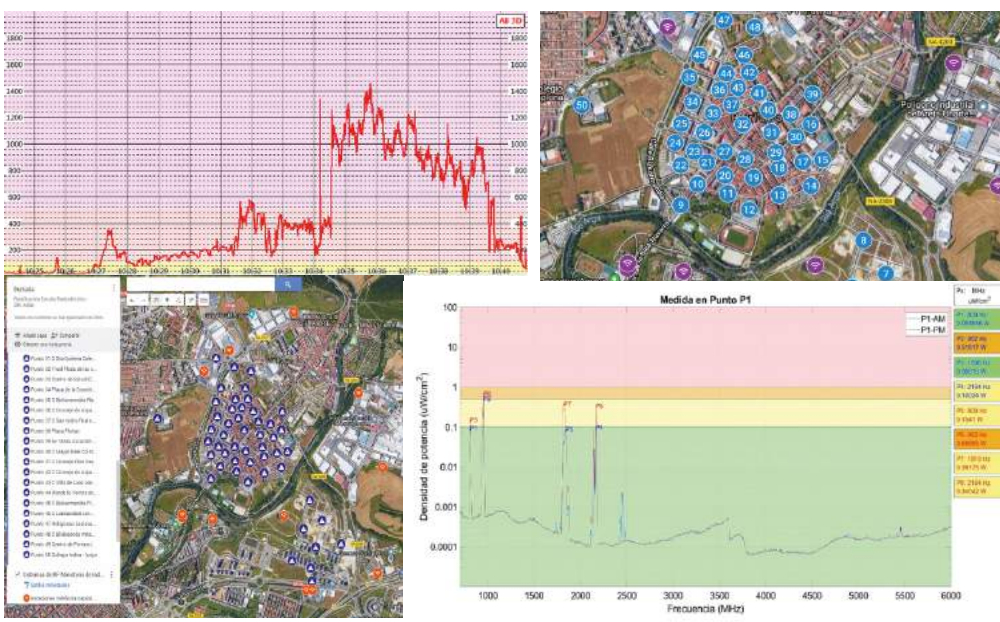
Application tests will be developed once the invention patent is established.

Environmental EMF dosimetry

Short description:

The control of the levels of exposure to artificial electromagnetic fields is among the more sensible concerns of the citizens, which justify the need to develop systems and procedures for the effective control of the dosimetry levels of the population's exposure. The analysis of the effects of electromagnetic fields on the population, including all the different electromagnetic radiation sources we live within is important for us, from the low frequency of the electric energy networks and appliances to the high frequencies (500 MH to 6 GHz) of the radio communication networks.

■ Radio map of the municipality of Burlada(Navarra) for example. Indicated by colors as follows: green: measurements below 0.1µW / cm2, yellow: measurements between 0.1 and 0.5µW / cm2, orange: measures between 0.5 and 1 µW / cm2; and red: measurements greater than 1 µW / cm2.



Personal EMF dosimeter

Short description:

In our laboratory we are developing a portable personal dosimetric system to capture the environmental electromagnetic field and configure the received electromagnetic radiation footprint and configure the personal dosimetric history.

Main results:

The portable electronic circuit of a spectrum analyzer system tested in anechoic chamber has been designed and developed. Application tests will be developed once the invention patent is established. In order to establish personal dosimetric history through interpretation and accumulation of results software.

Cell Exposition to high frequency electromagnetic fields

Short description:

The use of wireless technologies has rapidly expanded and increased over the past decade. Within its frequent use, human beings are thus exposed to a wide range of EFs and MFs, including low frequency magnetic fields (ELFs). Numerous in vivo and in vitro studies have been performed with the aim of evaluating the effects of low-frequency EMFs at various frequencies and amplitudes on cell cycle, apoptosis, and viability of the Glioblastoma Multiforme (GBM) cell line (U87). Glioblastoma multiforme (GBM) is the most malignant brain cancer that causes high mortality in humans. It responds poorly to the most common cancer treatments, such as surgery, chemo-and radiation therapy. In the present study we assess the impact of ELFs on GBM cells and rodents knockout p53, evaluating the eventual negative or positive effects of different low frequency EMFs, at various frequencies (800, 1800, 2450 MHz), both sinusoidal and square type of wave and an intensity of 450 *μW/cm2,* following the low criteria established in the law approved for wireless technologies in Spain IET/787/2013, 25th April, which approves the national table of frequency allocation.

The cells was exposed to those ELF-PEMFs for 1 and 24h studying their morphology properties, cell viability and gene expression of proteins involved in cell cycle regulation (Heat Shock Protein and p53) and proliferation. By the same time, rodents with three experimental groups (I-III) will be exposed to the same ELFPEMFs for 3 and 30 days, as follows: (I) General control wild type; (II) General control rodent's knockout p53; (III) Experimental control rodent's knockout p53. Rodent's brain will be investigated after exposure evaluating GBMs proliferation at different stages assessing EMFs as an ambient cofactor of GBM.

C. FACILITIES AND TECHNIQUES

Our multidisciplinary team manages classical techniques such as genetic engineering, protein engineering, viral transduction, biofunctionalization of nanoparticles and different polymers, histology, cell and molecular biology techniques, confocal and fluorescence microscopy, cell culture and animal experimentation (wild type and transgenic mouse models). We manage a set of in vivo techniques to examine functional outcome in different cerebrovascular and neurodegenerative mouse models, i.e. dMCAO model (transient and permanent), TBI model (controlled cortical imact), 5xFAD Alzheimer´s Disease model, stereotaxic surgery for electrode and cells/polymers implantation. We have expertise in different electrophysiological techniques (SSEPs, EEG/EMG in awake animals, local field potentials and DC components for spreading depolarization events)

All these specific electrophysiological tools allow us to explore, in addition to commonly used cognitive/sensorimotor behavioral tests, the efficacy of different compounds and cell-therapy approaches to promote recovery after cerebral injury as well as to identify possible biomarkers with predictive character in neurodegenerative disorders. The unit is well equipped with various instruments and equipments: stoves, centrifuges and ultra-centrifuges, spectrophotometers, freezers (- 20 &-80C), refrigerators, shaking water baths, a luminometer, UV transilluminators (one equipped with a digital camera), and refrigerated rooms. Likewise, our center has centralized services with responsible personnel such are Animal Facility at the CTB (registration number: ES280790002070), Animal Behavior laboratory, Protein tools, Molecular and Cellular Biology Service and Histology facility. The Unit has access to additional equipment and bench space, a tissue cell culture laboratory containing two 4-ft flow cabinets, two CO2 incubators, chemical hood, bench and desk space, inverted microscopes, refrigerated centrifuge, a microscopy room containing fluorescence microscope, confocal microscope, a microtome, thermocycler for RT-PCR, Microplate Reader & a electrophysiology laboratory with complete setups for SSEP and EEG/EMG recordings (portable EMG-EP device amplifiers, cyberamp 380 & 320 devices, A/D cards and several PCs with signal acquisition and analysis. Our system has electromagnetic field dosimetry unit with high and low frequency electromagnetic field meters. In addition to our dosimetry equipment developed in the CTB.

Facilities/Infrastructures

Electrophysiology Lab: The electrophysiology laboratory allows the registration of cellular electrical activity as well as the registration of laboratory animals to obtain electrical responses to certain stimuli or dysfunctions.

In vivo electrophysiology: EEG/EMG recordings in awake mice, motor potentials, somasensory evoked potentials (SSEPs) and cortical spreading depolarization recordings.

MCAO: Transient and permanent ischemia in mice.

Cell cultures: Bone marrow mesenchymal stem cell isolation and expansion. Adhesion, proliferation, migration, survival and ELISA assays.

GTEM Lab.: Exposure camera for radiofrequency. In addition, for the recording of intracellular electrical activity we have signal amplifiers and signal collectors, as well as several faraday and mumetall cages to screen the environmental electromagnetic field, as well as non-magnetizable micromanipulators.

DOSIMETRIC Lab.: Low and high frequency recording system for application in environmental dosimetric studies as well as in laboratory tests. It consists of high precision spectrum analyzer units. as well as magnetic field sensors

D. RESEARCH PROJECTS

MARKET FIT

PI: María Teresa Arredondo Waldmeyer

Funding Agency: EIT HEALTH-Call 2016-ACCELERATOR/17372

Period: 01/01/2017-31/12/2018

MINIQ: Optimising drug treatment among older people through a patient centered web based decision support-the miniQ innovation

PI: María Teresa Arredondo Waldmeyer

Funding Agency: EIT HEALTH-Call 2015-2016-INNOVATION by DESIGN and by IDEAS/17523

Period: 2017-2018

Centro Tecnológico para el Estudio y Tratamiento Integrado de los Desórdenes Neurológicos (NEUROCENTRO) B2017/BMD-3760

PI: Gustavo Guinea Tortuero

PI of team: Daniel González-Nieto

Funding Agency: Comunidad de Madrid

Period: 2018-2021

Health Sciences Technologies

PI: Daniel González-Nieto

Funding Agency: UPM-Groups of excellence

Period: 2017-2019

Development of new silk-fibroin-based biomaterials for brain regeneration (MAT2016-79832-R)

PI: Gustavo Guinea Tortuero

Funding Agency: Ministerio de Economía y Competitividad

Period: 2017-2019

Development of low-field magnetic stimulation devices

PI: Ceferino Maestu Unturbe

Funding: Pneuma technomedical research

Period: 2015-2019

OCARIOT Project. Development a platform to control child obesity

PI: Ceferino Maestu Unturbe / M.T Arredondo Waldmeyer

Funding Agency: EIT Health EU

Period: 2018-2020

Other institutions participating: CVE

E. PUBLICATIONS

1. Barios, J. A., Pisarchyk, L., Fernandez-Garcia, L., Barrio, L. C., Ramos, M., Martinez-Murillo, R., et al. (2016). Long-term dynamics of somatosensory activity in a stroke model of distal middle cerebral artery oclussion. *Journal of Cerebral Blood Flow and Metabolism : Official Journal of the International Society of Cerebral Blood Flow and Metabolism, 36*(3), 606-620.
2. Fernández-Cabada, T., Pablo, C. S. d., Pisarchyk, L., Serrano-Olmedo, J. J., & Ramos-Gómez, M. (2016). Optical hyperthermia using anti-epidermal growth factor receptor-conjugated gold nanorods to induce cell death in glioblastoma cell lines. *Journal of Nanoscience and Nanotechnology, 16*(7), 7689-7695.
3. Fernandez-Garcia, L., Mari-Buye, N., Barios, J. A., Madurga, R., Elices, M., Perez-Rigueiro, J., et al. (2016). Safety and tolerability of silk fibroin hydrogels implanted into the mouse brain. *Acta Biomaterialia, 45*, 262-275.
4. Ramos-Gómez, M., & Martínez-Serrano, A. (2016). Tracking of iron-labeled human neural stem cells by magnetic resonance imaging in cell replacement therapy for parkinson's disease. *Neural Regeneration Research, 11*(1), 49-52.
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ICT for Personalized Medicine Lab (UPM)

PRESENTATION/INTRODUCTION

The *ICT for Personalized Medicine Lab* mainly works in the field of patient care technologies, providing technological solutions for professionals and patients. Research activities include information systems for home monitoring; the integration of medical devices in telemedicine systems; the artificial pancreas; automatic data processing with artificial intelligence approaches; and decision support systems.

A. MEMBERS

PI: M. Elena Hernando

Senior researchers: Gema García, Agustín Rodríguez, María del Carmen Pérez, José Manuel Iniesta

Post-doctoral Fellows: Fernando García García

PhD students: Leonel Vasquez Ceballos, José Antonio García Corbalán, José Tapia-Galisteo, Estefanía Caballero Ruiz, Iñaki Martínez Sarriegui

B. RESEARCH LINES

Personalized decision support tools for patients and health care professionals

Short description:

The aim of this research line is to use artificial intelligence methodologies to build decision support tools and predictive models of patients' response to treatment. Machine learning techniques, such as linear regression models, support vector machines, neuronal networks, decision trees, or random forests, are exploited to build the tools and to discover the characteristics with higher impact in the prediction.

In the field of home monitoring for patients with chronic diseases, the goals are to optimize clinicians' time for clinical assessment and to enhance patient's adherence to recommended treatments, contributing to improve quality of care. The personalization to each specific patient considers information from several heterogeneous sources, such as patient's characteristics (demographics, diet, physical activity habits, etc.), real-time patient monitoring, current therapy, health state, impact of previous clinical decisions, and the prognosis of patient evolution through simulations with computational models.

■ Personal assistants for patients with chronic diseases

Main results:

Some examples of personalized decision support tools:

- Intelligent algorithms for the detection of deficient metabolic states in patients with diabetes gestational combined with decision support tools for prescription of diet changes and insulin therapy adjustments. The intelligent modules were integrated in a telemedicine decision support tool that has been evaluated in a randomized clinical study.
- Models for glucose prediction based on artificial neural networks to predict future glucose concentration levels combining data from continuous glucose monitoring (CGM) sensors, insulin doses and diet intake. Predictors detect in advance anomalous situations (e.g. hyperglycemia or hypoglycaemia), useful to trigger alarms or to help patients to anticipate correction decisions in terms of insulin and diet adjustments. Both population-based and individualized predictive models are available.
- Intelligent algorithms for the real-time automatic classification of physical activity in terms of intensity and metabolic pathway (aerobic/anaerobic) through the combination of accelerometry data and heart rate measurements.
- Decision support tool for the prediction of the risk of dropping out from a residential cocaine-addiction treatment that can assist professionals who approve or deny hospital admission for drug addiction rehabilitation upon patient referral.

Telemedicine platforms and personal health devices

Short description:

This research activity is focused on the design and development of innovative technological platforms to promote healthy lifestyles; to prevent the appearance of diabetes or the progression of diabetes-related complications; and to provide personalized nutrition in cancer.

The aim is to create platforms able to reach efficacy in behavioral modification by means of the intensive utilization of ICT technologies and personal health devices (e.g. wearable physical activity devices) for monitoring and assessing metabolic risks, as well as increasing patient adherence and optimizing the communication between subjects and health care providers on demand.

■ Communication with medical devices for patient monitoring

■ PREDIRCAM platform

Main results:

Some examples of telemedicine platforms and medical devices:

- PREDIRCAM: Telemedicine platform designed to monitor, prevent and provide follow up of patients with cardiometabolic risk, overweight or obesity. It has been evaluated in three Spanish Hospitals (Hospital de Sant Pau in Barcelona, Hospital La Fe in Valencia and Hospital Virgen de la Victoria in Málaga).
- SINEDIE: Telemedicine platform for monitoring patients with gestational diabetes developed in collaboration with Hospital de Sabadell in Barcelona. The aim of Sinedie is to reduce face-to-face encounters making care processes more efficient and to achieve a good metabolic control. Monitoring data are sent remotely and are automatically analyzed by an intelligent module that detects deficient health states and proposes automatic therapy recommendations and notification messages for both patients and clinicians.

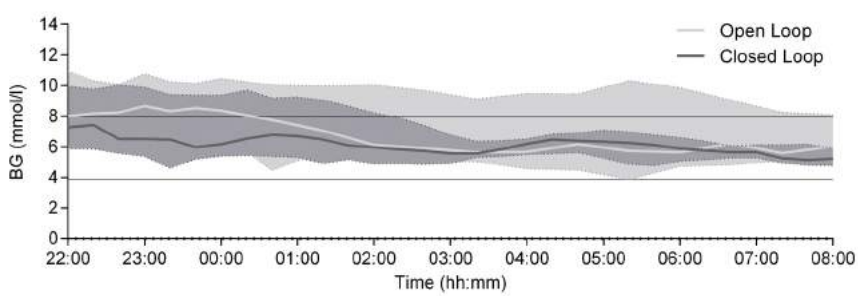
- Mobile applications that integrates medical devices (glucose meters, oximeters, blood pressure meters, insulin pumps, ECG bands etc) and wearables to monitor physiological parameters, patient lifestyle and sleep quality. Some applications have been home monitoring of chronic patients and physical activity monitoring in different pathologies (i.e. gestational diabetes, atrial fibrillation, lifestyle interventions for weight loss, children with Type 1 diabetes).
- NUTRIPRECISION platform: to support the prescription of a personalized diet to patients with cancer.

Artificial pancreas

Short description:

The aim of this research activity is to develop a control algorithm able to keep blood glucose levels in normal ranges for type 1 diabetes patients. An artificial pancreas is a system based on a Continuous Glucose Monitoring (CGM) sensor that provides real-time measurements and informs to an algorithm for "closed-loop" control that automatically adjusts the correct insulin dose administered by a Continuous Subcutaneous Insulin Infusion (CSII) system. Ideally, the system would not require the patient's intervention.

Our predictive personalized control algorithm (called pRBA) integrates a glucose predictor and a rule-based fuzzy logic module to control the insulin pump. The pRBA has been tested in an intra-hospital setup for overnight glucose control with 10 T1DM patients at the Hospital de Sabadell. Time spent in normoglycemia (3.9-8.0 mmol/L) during the nocturnal period (12 a.m.-8 a.m.), expressed as median (interquartile range), increased from 66.6% (8.3-75%) in open-loop to 95.8% (73-100%) using the closed-loop algorithm ($p<0.05$).



We are working on incorporating physical activity monitoring data processed by algorithms developed in the research group into the pRBA so that the closed-loop algorithm is able to control exercise-induced changes in glycemia.

Main results:

CLoop platform: a telemedical artificial pancreas system; it is based on the Bluetooth™ communication between medical devices and a Smarphone application which integrates the pRBA algorithm. The system is connected to a telemedicine system which provides real-time supervision of the artificial pancreas algorithm by endocrinologists.

■ CLoop platform for artificial pancreas

C. FACILITIES AND TECHNIQUES

Facilities/Infrastructures

Equipment for patient monitoring: Medical sensors such as glucose meters, blood pressure meters, accelerometers, heart rate monitors, ECG, Continuous Glucose Monitoring sensors and insulin pumps; Smartphones and tablets with Android and iOS operating systems; RedCap service.

Research and teaching laboratories: Two research laboratories and one teaching laboratory for master and undergraduate students. Room with 3 servers for telemedicine platform deployment and data analysis. Artificial intelligence tools.

Techniques

- Mobile applications for patient monitoring and interactive feedback
- Machine learning tools
- Physiological modelling tools

D. RESEARCH PROJECTS

PERSSILAA: PERsonalised ICT Supported Service for Independent Living and Active Ageing (FP7-ICT-610359)

PI: María Elena Hernando / Enrique J. Gómez Aguilera

Funding Agency: European Commission

Budget: 557.745€

Period: 01/11/2013- 31/10/2017

Other institutions participating: University of Twente (The Netherlands). Roessingh Research and Development (The Netherlands). Federico II Hospital (Italy). Fundação da Faculdade de Ciências da Universidade de Lisboa (Portugal). University of Cork (Ireland). The Fundació Privada Institut de Neurorehabilitació Guttmann (Spain). Nexera (Italy)

■ **Web link:** https://cordis.europa.eu/project/id/610359/es

FitCloop: Incorporación de la medida continúa de ejercicio al control en lazo cerrado en la diabetes tipo 1 (FIS PI14/00109)

PI: María Elena Hernando / Gema García Sáez

Funding Agency: Fondo de Investigaciones Sanitarias

Budget: 11.410€

Period: 01/01/2015-30/06/2019

Other institutions participating: Hospital de Sabadell

EMERGE: Evaluating mHealth technology in HIV to improve Empowerment and healthcare utilisation: Research and innovation to Generate Evidence for personalized care (Grant agreement no: 643736)

PI: Mª Elena Hernando / Enrique J. Gómez

Funding Agency: European Commission

Budget: 230.300€

Period: 2015-2020

Other institutions participating:

■ **Web link:** https://www.emergeproject.eu/

NUTRIPRECISIÓN: Estrategias para La Mejora de La Calidad de Vida de Colectivos Pre-Senior y Senior Basadas en la Nutrición de Precisión -

PI: Enrique J. Gómez

Funding Agency: Programa Estratégico de Consorcios de Investigación Empresarial Nacional (CIEN-CDTI)

Budget: 100.000€

Period: 01/11/2016-31/10/2020

Cognitive Computing Aplicado a Psiquiatria

PI: María Elena Hernando

Funding Agency: Private funding (IBM)

Budget: 12.000€

Period: 2016-2020

Other institutions participating: Clínica Nª Sª dela Paz (San Juan de Dios) e IBM

Estudio sobre el Estado del Arte en el Desarrollo de Aplicaciones Móviles para Atención Socio Sanitaria a Mayores

PI: Enrique J. Gómez

Funding Agency: Private funding (Acciona)

Period: 2016

Sistemas Inteligentes y de Educación para el Control de la Diabetes Diagnosticada en el Embarazo

PI: María Elena Hernando

Funding Agency: Private funding (Corporacion Parc Tauli)

Period: 2016

Evaluación Sistema Telecuidado

PI: María Elena Hernando

Funding Agency: Financiación privada (Corporacion Parc Tauli)

Period: 2015-2016

SINEDIE-Móvil- Sistemas inteligentes y de educación para el control de la diabetes diagnosticada en el embarazo.

PI: Gema García Sáez

Funding Agency: Fundació Parc Taulí

Entidades participantes: UPM, Hospital Sabadell-Parc Taulí

Budget: 12.000€

Period: 2017-2018

E. PUBLICATIONS

1. Caballero-Ruiz, E., García-Sáez, G., Rigla, M., Villaplana, M., Pons, B., & Hernando, M. E. (2016). Automatic classification of glycaemia measurements to enhance data interpretation in an expert system for gestational diabetes. *Expert Systems with Applications, 63*, 386-396.
2. Garcia-Garcia, F., Benito, P. J., & Hernando, M. E. (2016). Automatic identification of physical activity intensity and modality from the fusion of accelerometry and heart rate data. *Methods of Information in Medicine, 55*(6), 533-544.
3. Caballero-Ruiz, E., García-Sáez, G., Rigla, M., Villaplana, M., Pons, B., & Hernando, M. E. (2017). A web-based clinical decision support system for gestational diabetes: Automatic diet prescription and detection of insulin needs. *International Journal of Medical Informatics, 102*, 35-49.
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5. Rodriguez-Vila, B., Sánchez-González, P., Oropesa, I., Gomez, E. J., & Pierce, D. M. (2017). Automated hexahedral meshing of knee cartilage structures-application to data from the osteoarthritis initiative. *Computer Methods in Biomechanics and Biomedical Engineering, 20*(14), 1543-1553.
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7. Orozco-Lopez, J. O., Castaneda, C. E., Rodriguez-Herrero, A., Garcia-Saez, G., & Hernando, E. (2018). Linear time-varying luenberger observer applied to diabetes. *IEEE Access, 6*, 23612-23625.
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9. Rigla, M., Martínez-Sarriegui, I., García-Sáez, G., Pons, B., & Hernando, M. E. (2018). Gestational diabetes management using smart mobile telemedicine. *Journal of Diabetes Science and Technology, 12*(2), 260-264.
10. Vasquez-Cevallos, L., Bobokova, J., Bautista-Valarezo, E., Davalos-Batallas, V., & Hernando, M. E. (2018). Telemedicine in medical training in ecuador. *2017 IEEE 2nd Ecuador Technical Chapters Meeting, ETCM 2017, January*. pp. 1-5.
11. Vasquez-Cevallos, L. A., Bobokova, J., González-Granda, P. V., Iniesta, J. M., Gómez, E. J., & Hernando, M. E. (2018). Design and technical validation of a telemedicine service for rural healthcare in ecuador. *Telemedicine and e-Health, 24*(7), 544-551.

Medical Data Analytics Laboratory (UPM)

PRESENTATION/INTRODUCTION

Medical Data Analytics Laboratory (MEDAL) is composed by a team of professors, researchers and students with deep experience in the field of data management, data processing and artificial intelligence techniques. The main goal of MEDAL is the acquisition, integration and analysis of medical-based information to extract knowledge that can be used as the basis for the design and implementation of smart products and tool to support decision making process and the creation of health intelligent applications for physicians and health managers to support their daily-practice. In the last years the laboratory has focused their efforts in projects dealing with the complexity of retrieving, managing and analyzing data from different sources and with a large variety of formats. The team has a deep experience in the concept of Big Data, mainly in the health sector, where several projects within this scope have been running in the past and are being executed nowadays. The main goals of the projects under execution in the lab include electronic health records (EHR) knowledge extraction, image analysis and understanding, AI, data mining and machine learning analysis to discover pattern in specific diseases (lung cancer and dementia), NLP to analyze clinical narratives, as well as broader areas such as disease understanding by using complex networks creation and analysis or health-related social media analysis.

A. MEMBERS

PI: Alejandro Rodríguez González

Senior researchers: Ernestina Menasalvas Ruiz, Consuelo Gonzalo Martin, Víctor Robles Forcada

Post-doctoral Fellows: Massimiliano Zanin, Antonio Jesús Díaz Honrubia, Angel García Pedrero

PhD students: Gerardo Lagunes Garcia, Marjan Najafabadipour, Oswaldo Solarte, Nisreen Abdelrahim, Cesar Ortiz Toro, Rubén Galeano González, Roberto Costumero Moreno, Edurne Ibarrola Ulzurrún

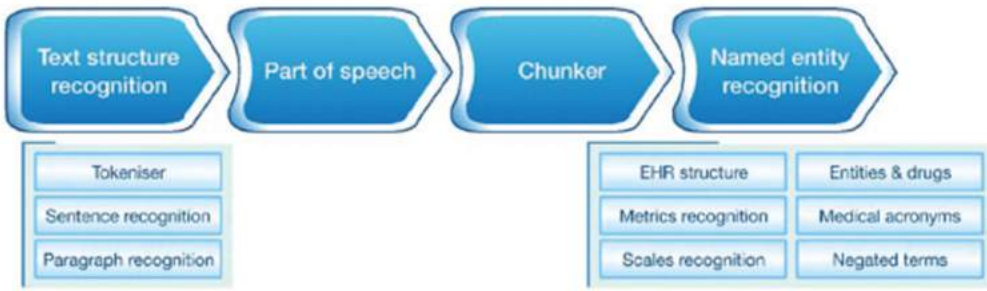
Others: Juan Manuel Tuñas, Roberto Garrido García, Diego Fernández Peces-Barba, Pablo García Encinas, Jorge Sánchez, Lucia Prieto Santamaría, Guzmán Bermejo, Hector Ambit Hernández, Luis Pulido, Isaac Sánchez Ruiz

B. RESEARCH LINES

Knowledge extraction from clinical narratives

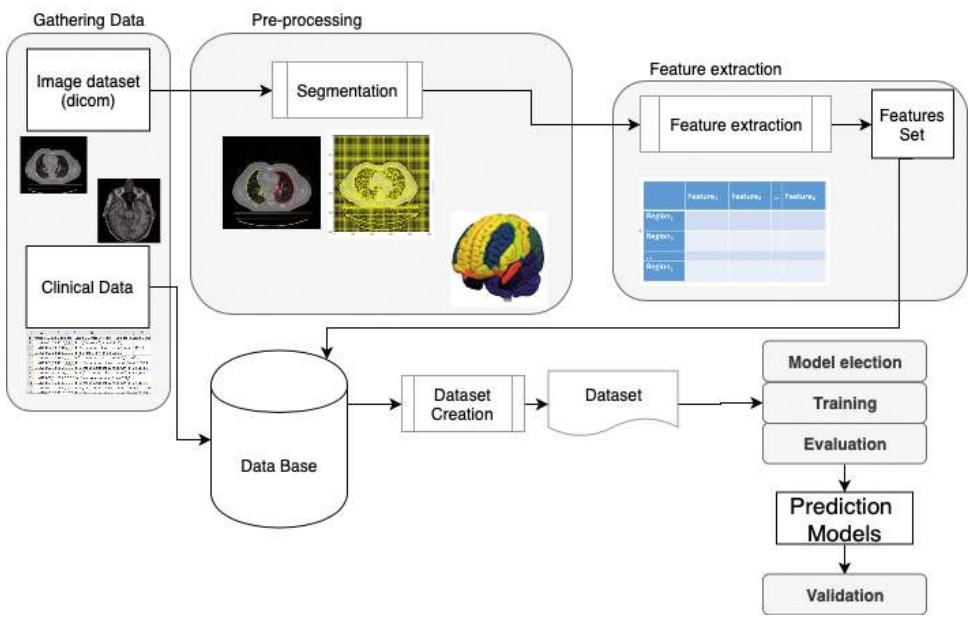
This research line involves Natural Language Processing (NLP), indexing and knowledge discovery process to extract from clinical narratives first of all the natural history of the patient and once data is structure application of AI techniques to extract patterns. The

integration of the knowledge obtained from the analysis together with other information contained in the EHR can help identifying subjects for clinical trials, finding common patterns of behavior of drugs and treatment, for example. The methodology used in the laboratory for clinical narratives was successfully applied for social networks analysis, in law sentences analysis and for analysis of public sources of medical information.



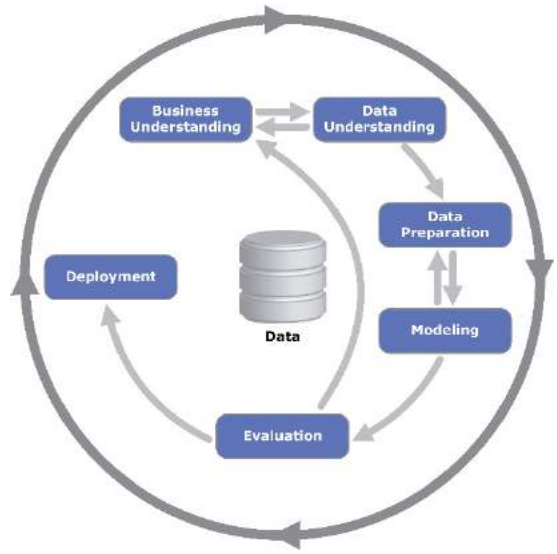
Medical image processing, analysis and understanding

The extraction of a large number of features (Radiomics) from different medical images modalities, has allowed to develop different algorithms, methodologies and tools to help diagnosis and prognosis, as well as monitoring illnesses progress. Moreover, specific algorithms for medical image annotation provide useful information for integrating with other health records. The algorithms developed for medical imagery have been applied to other areas as remote sensing for agricultural and environmental applications.



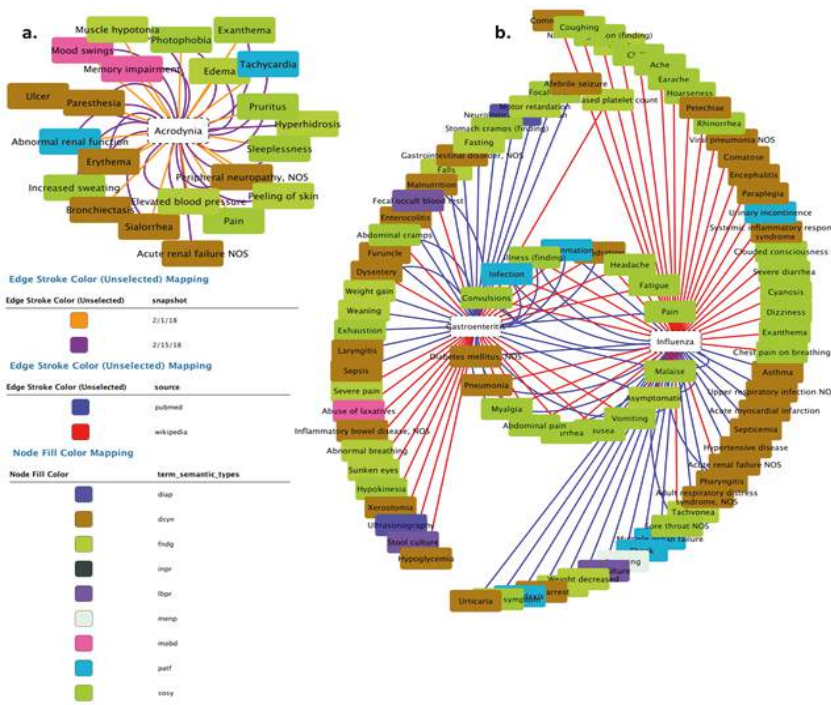
Data Science project development

The laboratory has a deep expertise in applying data mining (mainly CRISP-DM methodology) to several domains with special emphasis in the biomedical domain. We have a deep expertise in the application of very different algorithms to perform both descriptive and predictive analytics that can be used in real environments in the health sector.



Disease understanding

MEDAL laboratory has expertise in the extraction of information about diseases from public sources and its use and analysis to improve the current knowledge that we have about the diseases. Disease similarities is one of the main fields where the laboratory is focusing, in order to discover what are the main elements that the diseases share and how these elements can affect their internal behavior or how this knowledge can be used within several fields, such as drug repositioning.



C. FACILITIES AND TECHNIQUES

Techniques

- Development of a methodology and architecture for the extraction of information and knowledge from unstructured textual sources in the clinical context. The MEDAL laboratory has a pipeline developed on the Apache UIMA architecture that allows the extraction, structuring and exploitation of clinical information.
- Development of techniques and methods for the exploitation of clinical data, especially in the field of lung cancer, with the aim of calculating toxicities, identifying comorbidities, survival curves and descriptive and predictive models.
- Development of specific methodologies for the extraction and analysis of health information from social networks, with special emphasis on the detection of the feelings expressed on these social networks through the application of commercial models and ad-hoc metamodels.
- Development of specialized data analysis techniques focused on the concept of data science and its exploitation throughout its value chain through the application of the CRISP-DM methodology.
- Development of techniques and methods for the extraction of health information from public sources and its exploitation with the aim of generating greater knowledge of the similarities of diseases and the application of this knowledge to specific tasks such as the repositioning of drugs.
- Development of techniques and methods for the generation of high spatial and spectral quality images. These results have been included in an open access framework that incorporates a battery of image fusion algorithms, developed in-house, as well as the metrics to evaluate the quality of the fused images (http://ijfusion.es).
- Development of new artificial neural network algorithms for their application to image analysis in different domains.
- Development of object-based image processing and analysis methodologies for application in precision agriculture and disease detection.

Knowledge transfer to the public-private productive sector, through platforms in operation and with socio-economic impact.

Aquasat: Dynamic support system for irrigation decision making at farm level in agriculture.

NDMONITOR: Platform for monitoring and helping patients with neurodegenerative diseases.

D. RESEARCH PROJECTS

RETHINK big: Roadmap for European Technologies in Hardware & Networking for Big Data. CORDIS 619788

PI: Ernestina Menasalvas

Funding Agency: H2020

Budget: 215.873€

Period: 01/03/2014-29/02/2016

Other institutions participating: Universidad Politécnica de Madrid, Barcelona Supercomputing Center, Techniche University Berlin, Ecole Polytechnique, Thales, ARM, Alcatel Lucent, ParStream, CWI, Norack, Universidad de Manchester, Internet Memory Research

■ **Web link**: http://www.rethinkbig-project.eu/

FACET 2018: Integrated supportive services/products to promote FrAilty Care and wEll function

PI: Consuelo Gonzalo Martin

Funding Agency: EIT Health

Budget: 122.000€

Period: 01/01/2018-31/12/2018

PAPHOS 2017: Platform for advanced prescriptive health operational system

PI: Consuelo Gonzalo Martin

Funding Agency: EIT Health

Budget: 82.000€

Period: 01/01/2018-31/12/2018

Plataforma Integral de bajo coste para la monitorización y ayuda de pacientes de enfermedades neurodegenerativas graves en capacidades mentales. NDMonitor

PI: Alejandro Rodríguez González

Funding Agency: Ministerio de Economía y Hacienda

Budget: 76.592€ (Total: 354.072€)

Period: 01/01/2016-31/03/2018

Other institutions participating: Universidad Politécnica de Madrid, Universidad de Murcia, Proassistech

IASIS: Integration and analysis of heterogeneous big data for precision medicine and suggested treatments for different type of patients. CORDIS ref.: 727658

PI: Ernestina Menasalvas

Funding Agency: H2020 (RIA)

Budget: 456.250€ (Total: 4.337.475€)

Period: 01/01/2017-31/12/2019

Other institutions participating: National Center for Scientific Research DEMOKRITOS, Athens Technology Center S.A, Rheinische Friedrich-Wilhems Universitat Bonn, Universidad Politécnica de Madrid, Servicio Madrileño de Salud, St George's Hospital Medical School, Alzheimer's Research UK, Funcacio Centre de Regulacio Genomica, Grupo español de investigación en cancer de pulmón, University System of Maryland Foundation INC

■ **Web link**: http://project-iasis.eu/

BigMedilytics: Big Data Medical Analytics. CORDIS ref.: 780495

PI: Alejandro Rodríguez González

Funding Agency: H2020 (IA)

Budget: 230.000€ (Total: 14.997.306€)

Period: 01/01/2018- 28/02/2021

Other institutions participating: Phillips, INCLIVA, ITI, Univ. Rotterdam, Achmea, GIE AXA, Optimedis, ATOS Spain, TNO, Univ. Eindhoven, ContextFlow, Huawei, Royal College of Surgeons in Ireland, Stockolms Lans Landsting, HPI, NCSR, ATC, Univ. Bonn, UPM, SERMAS, Univ. Med. Viena, IBM Israel, Institut Curie, Teknologian Tutkimuskeskus VTT Oy, Deutsches Forschungszentrum fur

Kunstliche Intelligenz, Charite-Universtaetmedizin Berlin, AOK Nordost, Universitaetsklinikum Essen, University of Southampton, My Health, Astrazeneka UK, Onze Lieve Vrouwe Gasthuis, ETZ, Univ. Rotterdam

■ **Web link**: https://www.bigmedilytics.eu/

CROSS CPP: Ecosystem for Services based on integrated Cross-sectorial Data Streams from multiple Cyber Physical Products and Open Data Sources. CORDIS ref.: 780167

PI: Ernestina Menasalvas

Funding Agency: H2020 (IA)

Budget: 322.781€ (Total: 3.505.978€)

Period: 01/12/2017-30/11/2020

Other institutions participating: Volkswagen, Siemens, Meteologix, ATOS, X/OPEN Company, UPM, Vysoke Uceni Technike V Brne, Institut Fur Angewandte Systemtechnik Bremen

■ **Web link**: https://cross-cpp.eu/

BDVe: Big Data Value ecosystem. CORDIS ref: 732630

PI: Ernestina Menasalvas

Funding Agency: H2020 (CSA)

Budget: 337.125€ (Total: 4.940.286€)

Period: 01/01/2017-31/12/2020

Other institutions participating: Universidad Politécnica de Madrid, SAP, ATOS, Siemens, Insight, EIT Digital, University of Duisburg-Essen, TILDE, Big Data Value Association, OgilvyOne Worldwide (OG1), TNO

■ **Web link:** https://www.big-data-value.eu/

CUREX: seCUre and pRivate hEalth data eXchange. CORDIS ref: 732630

PI: Alejandro Rodríguez González

Funding Agency: H2020 (RIA)

Budget: 204.375€ (Total: 4.987.825€)

Period: 01/12/2018-30/11/2021

Other institutions participating: University Of Piraeus Research Center, Atos Spain Sa, Almerys, Cyberlens Bv, Intrasoft International Sa, Suite5 Data Intelligence Solutions Limited, Time.Lex, Eight Bells Ltd, Gioumpitek Meleti Schediasmos Ylopoiisi Kai Polisi Ergon Pliroforikis Etaireia Periorismenis Efthynis, University Of Surrey, Universidad Politecnica De Madrid, University Of Cyprus, Aristotelio Panepistimio Thessalonikis, Servicio Madrileno De Salud, Fundacion Privada Hospital Asil Degranollers, Karolinska Institutet, University Of Greenwich.

■ **Web link:** https://cordis.europa.eu/project/id/826404

E. PUBLICATIONS

1. Benítez-Andrades, J.A., Rodríguez-González, A., Benavides, C., Sánchez-Valdeón, L., García, I. (2018). A semantic social network analysis tool for sensitivity analysis and what-if scenario testing in alcohol consumption studies. International Journal of Environmental Research and Public Health.

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Neuromorphic Voice Processing Laboratory (UPM)

PRESENTATION/INTRODUCTION

The aims of the Neuromorphic Voice Processing Laboratory (NeuVox) are the understanding of the neural processes behind speech production and perception at a functional level. The relationships among cortical areas responsible for speech understanding and planning, as well as the neuromotor areas related with speech production and the activation of the complex phonation and articulation systems involved in voice and speech production are to be modeled at functional and biomechanical levels using advanced speech processing analysis and statistical pattern matching. The specific targets of the study are the following, among others related:

- Description of functional circuits in the brain for speech perception and production.
- Study of biomechanical systems involved in phonation and articulation.
- Definition of voice and speech specific biomarkers to detect and monitor neuromotor and cognitive dysphonic markers.
- Application of dysphonic markers to emotion state detection and monitoring.
- Development of voice processing tools for the detection and monitoring organic and neurodegenerative disease involving dysphonic markers.

A. MEMBERS

PI: Pedro Gómez Vilda
Senior researchers: Agustín Álvarez, Rafael Martínez, Víctor Nieto, Victoria Rodellar
Post-doctoral Fellows: Daniel Palacios Alonso
PhD students: Andrés Gómez
Others: Eustaquio Alfonso Castillo

B. RESEARCH LINES

Description of functional circuits in the brain for speech perception and production

Short description:

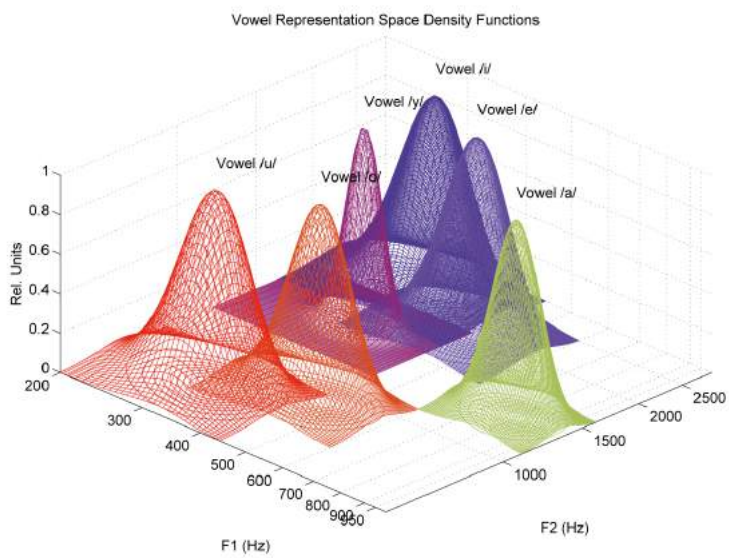
The objectives of this line are the description of speech processing structures from the cochlear nucleus to the cortical areas involved in semantic liaisons to cover the semantic

gap from spectral representations to the symbolic translation into phonemes and words and the construction of morphosyntactic structures. Speech coding and compression in the auditory lower and upper pathways are being described as application toolboxes using low level receptive fields and a systemic architecture. At the production level syntactic planner and neuromotor cortical areas, and peripheral bulbar, cerebellar and extrapiramidal structures are also being modeled.

Main results:

Vowel representation spaces at the cortical level depend on the detection of pairs of auditory nerve firing prominences projected from the hypothalamus to the primary auditory cortex associated to spectral formants. Computer simulations allow fixing the assignment density functions associated to each Vowel Receptive Field in the phonetic-phonologic mapping known as the "magnet effect" as seen in the picture.

■ Probability density functions associated to the Receptive Fields in Wernicke's Area detecting the cardinal vowels of Spanish including an 'alien' vowel [y:]



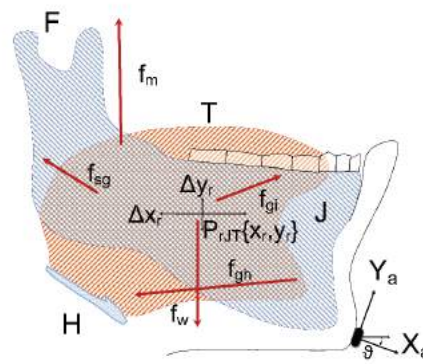
Study of biomechanical systems involved in phonation and articulation

Short description:

This line is devoted to the study of the biomechanical behavior and response of the glottal, respiratory, mandibular, lingual and nasopharyngeal systems responsible of phonation

conditioning and modification to describe articulated speech. A general direct model is proposed, amenable of system inversion to deconstruct speech into phonation and articulation markers directly related with neuromotor activity.

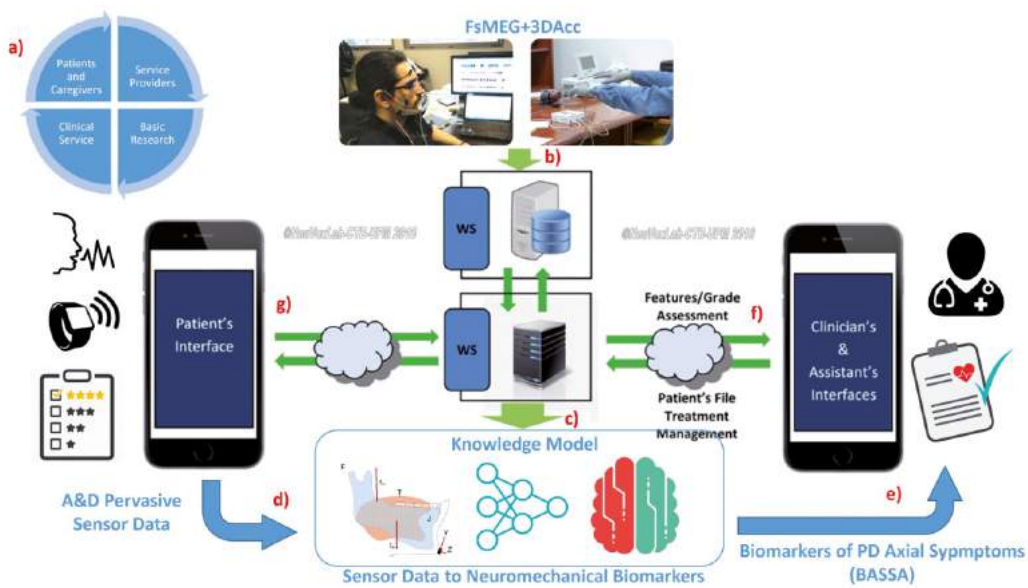
■ Jaw-Tongue neuromechanical model of the biomechanical activity in the sagittal plane



Main results:

A joint jaw-tongue neuromechanical model has been established to correlate neuromotor activity in the masseter estimated from Surface Electromyography, biomechanical mandibular activity given by 3D accelerometer and Speech, as represented in the figure. This model has helped in validating Speech as a vehicular biomarker for neurodegenerative disease detection and monitoring.

■ Conceptual description of remote monitoring tasks by smart devices collecting sEMG, 3DAcc and speech, modeling and report generation for clinicians and caregivers using Big Data and Deep Learning methodologies within project Teca Park

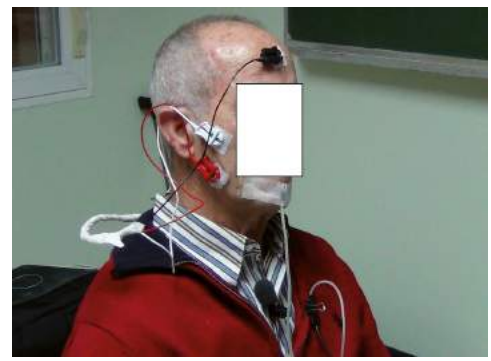


Definition of voice and speech specific biomarkers to detect and monitor neuromotor and cognitive dysphonic markers

Short description:

This line is oriented to recruit specific databases from normative and dysphonic speakers affected by organic and neurodegenerative diseases, and to the estimation and statistical characterization of specific features amenable of being used as markers with capability in pathology detection, grading and monitoring. Main targets are Parkinson's Disease and Amyotrophic Lateral Sclerosis, and Alzheimer Disease.

■ Recording session of surface electromyography, 3D accelerometry and speech from a volunteering PD patient



Main results:

A database of neuromotor activity in the jaw from Parkinson's Disease patients have been acquired including signals of surface electromyography, 3D accelerometer and high quality of speech. This database is being used to better understand and monitor facial mask rigidity effects in Parkinson's Disease, articulation instability and tremor.

■ App for tele-monitoring PD patients at home or at Patients' Association facilities (see Project TecaPark)

Application of dysphonic markers to emotion state detection and monitoring

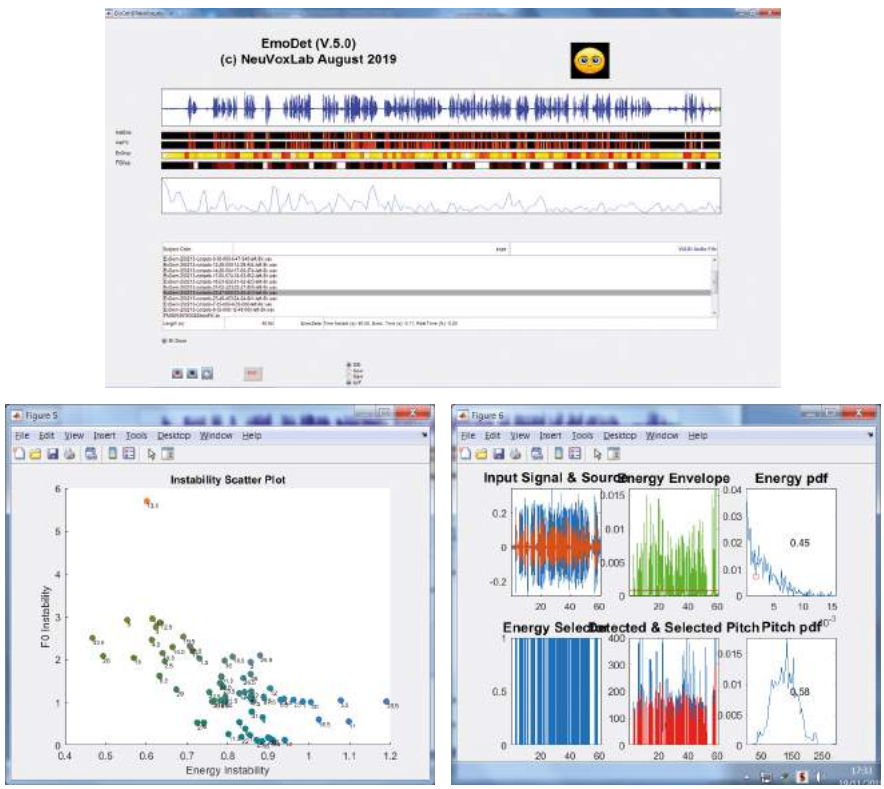
Short description:

This line is concentrated on the study on how emotional altered states produce changes in the statistical description of speech features at the phonation, articulation and fluency levels, and how these markers can be used in on-line detection and 1grading of activation and valence of emotion states. The application level is aimed to neuromarketing and customer resource management, among others.

Main results:

An app and a batch application for the detection and monitoring of stressed speech have been developed (see the associated figure below).

■ Emotional Speech User Interface showing altered speech features (top). Instability scores on a speech frame basis (bottom left), and statistical distributions associated (bottom right)

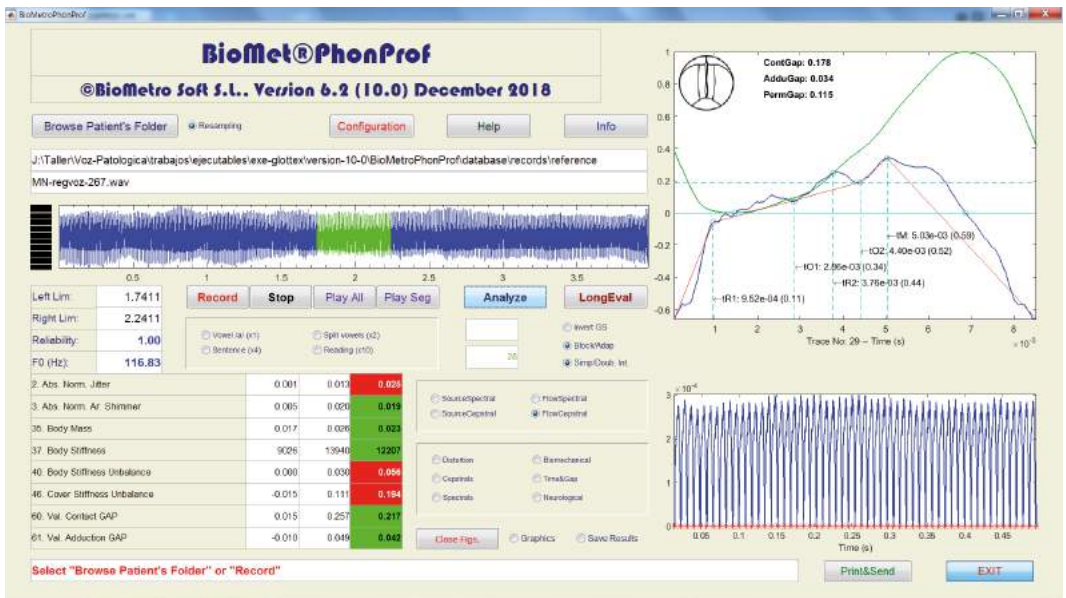


Development of voice processing tools for the detection and monitoring organic and neurodegenerative disease monitoring involving dysphonic markers

Short description:

This activity is very much aimed to the design of Voice Processing Tools for the detection and monitoring the organic and neurologic pathology in speech. It is well known that many neurological diseases leave a fingerprint in voice and speech production. The detection and monitoring procedure is based on a simple voice test. The availability of advanced tools and methodologies to monitor the organic pathology of voice facilitates the implantation of these tests.

■ Graphical user interface for advanced voice quality analysis used in organic and neurologic pathology detection and monitoring from phonation



Main results:

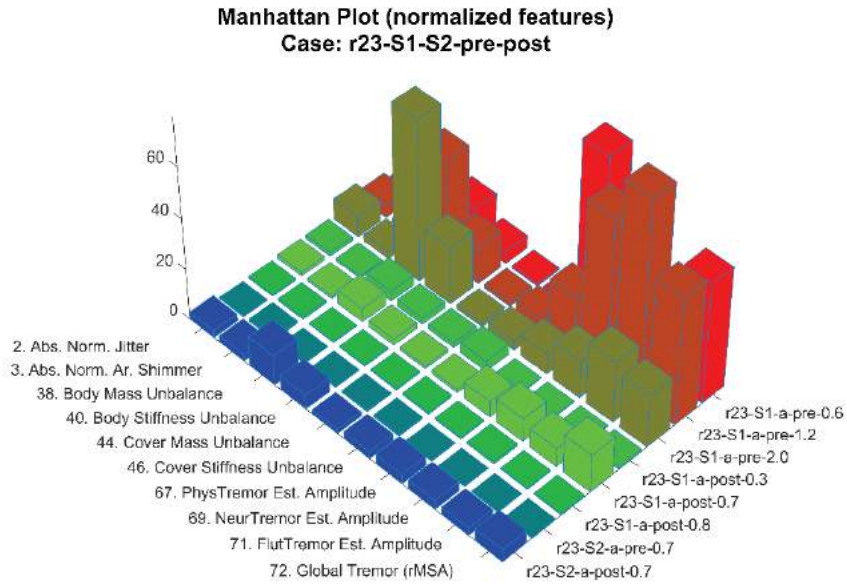
Based on these premises the Laboratory NEUVOX has developed several voice analysis tools devoted to the organic and neurologic disease monitoring (BioMet®Phon) and speech discourse (BioMet®Neur) which are being currently used in the following fields:

- Organic and neurologic disease monitoring from voice tests.
- Biometrical description of the speaker with forensic capability.
- Acoustic quality analysis of the singing voice.
- Phonation and speech rehabilitation.

Several applications have been developed to monitor voice quality in medical, forensic, singing and emotional studies involving phonation. The application allows browsing a patient's database or produce on-the-fly voice recordings and analysis. The application estimates up to 72 features of interest, including distortion (jitter, shimmer, noise-to-harmonic, mucosal wave ratio), cepstral, spectral, biomechanical (dynamic mass and stiffness of the vocal fold body and cover), open, return and close quotients, contact and permanent gap defects, and tremor in voice. These features are contrasted against a normative database and allow the production of longitudinal reports as the one shown in the figure below.

Other fields of application are the monitoring of neurological disease from phonation and speech, as in the following template where measurements on the vowel triangle are used to assess Alzheimer's Disease and Amyotrophic Lateral Sclerosis Progression.

■ Example of neuromotor tracking on a Parkinson's Disease patient before (pre-stimulus) and after (post-stimulus) neuroacoustical stimulation using BioMet®Phon. The features covered are the most relevant ones in detecting phonation instability



C. FACILITIES AND TECHNIQUES

Facilities/Infrastructures

- Speech Communication Lab "Robert W. Newcomb".
- High quality voice, speech and singing recording (in situ and in studio).
- Signal processing and pattern recognition methodologies to extract and represent the following correlates from voice and speech:
  - Distortion parameters (jitter, shimmer, hnr, nhr, gne, etc.).
  - Spectral and cepstral profiles of the glottal source.
  - Biomechanical parameters of the vocal folds (dynamic mass and stiffness).
  - Open, close and return quotients.
  - Glottal gap defects.
  - Tremor and vibrato in voice.
  - Vocal effort.
- Audio recording equipment: Audio instrumentation (analog and digital), sound proof chamber.
- Audio and video processing: signal processing workstations and associate software (proprietary and second sources).
- Portable recording and voice quality analysis equipment.

D. RESEARCH PROJECTS

Descripcion biométrica del locutor basada en correlatos de accion motora y estado cognitivo con aplicaciones en seguridad y rehabilitación TEC2016-77791-C4-4-R

PI: Agustín Álvarez

Funding Agency: Ministerio de Economía y Competitividad

Period: 30/12/2016-29/12/2019

Other institutions participating: Universidad de Las Palmas de Gran Canaria, Instituto Politécnico de Mataró

Monitorización y Seguimiento del Paciente de Parkinson mediante la evaluación de su Locución. MonParLoc, TECA-PARK 55 02 CENIE POCTEP

PI: Pedro Gómez-Vilda

Funding Agency: Fundación General del Consejo Superior de Investigaciones Científicas (CENIE)

Period: 30/04/2018-31/12/2019

Other institutions participating: Universidade do Minho (Portugal), Universidad de Oviedo, Massachusetts Institute of Technology

E. PUBLICATIONS

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3. Gómez-Vilda, P. (2017). Biomedical applications of voice and speech processing. *Loquens, 4*(1).
4. Gómez, P., Mekyska, J., Gómez, A., Palacios, D., Rodellar, V., Álvarez, A. (2017). Monitoring Parkinson disease from speech articulation kinematics. *Loquens, 4*(1).
5. Gómez-Vilda, P., Mekyska, J., Ferrández, J. M., Palacios-Alonso, D., Gómez-Rodellar, A., Rodellar, V., et al. (2017). Parkinson disease detection from speech articulation neuromechanics. *Frontiers in Neuroinformatics, 11*.
6. Gómez-Vilda, P., Palacios-Alonso, D., Rodellar, V., Álvarez-Marquina, A., Nieto-Lluis, V., & Martínez-Olalla, R. (2017). Parkinson's disease monitoring by biomechanical instability of phonation. *Neurocomputing, 255*, 3-16.
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8. J. Mekyska, Z. Galaz, T. Kiska, V. Zvoncak, J. Mucha, Z. Smekal, I. Eliasova, M. Kostalova, M. Mrackova, D. Fiedorova, M. Faúndez, J. Solé, P. Gómez, I. Rektorova. (2017). Quantitative analysis of relationship between hypokinetic dysarthria and the freezing of gait in Parkinson's disease. *Cognitive Computation, 10*(6), 1006-1018.
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10. Martinez, U., Calvo, P., Gómez-Vilda, P., Ecay, M., López, K. (2017). *ALZUMERIC*: A decision support system for diagnosis and monitoring of cognitive impairment. *Loquens, 4*(1).
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12. Gómez, P., Londral, A. R. M, Gómez, A., Palacios, D., Rodellar. V. (2018). Monitoring ALS from speech articulation kinematics. *Neural Computing and Applications*, 1-12.
13. San Segundo, E., Tsanas, A., & Gómez-Vilda, P. (2017). Euclidean distances as measures of speaker similarity including identical twin pairs: A forensic investigation using source and filter voice characteristics. *Forensic Science International, 270*, 25-38.

Neurorehabilitation Engineering (UPM)

PRESENTATION/INTRODUCTION

The CTB works jointly with the Neurorrehabilitation Hospital "Institut Guttmann" (http://www.guttmann.com), and the Berenson-Allen Center for Noninvasive Brain Stimulation (CNBS, http://tmslab.org) at Beth Israel Deaconess Medical Center and Harvard Medical School, a world leader in research and development, clinical application, and teaching of noninvasive brain stimulation.

A. MEMBERS

PI: Enrique J. Gómez

Post-doctoral Fellows: Ruth Caballero, Javier Solana Sánchez, María Guadalupe Cortina Januchs, Alexis Marcano Cedeño, José María Martínez Moreno

PhD students: Marta Luna, Mailin Adriana Villán Villán, Jorge Ramón García Novoa, Fernando Molina Najera, Paloma Chausa, Borja Rodríguez, Julio Ontiveros, Francisco José Gárate, Diego Moreno

Others: Julio Ignacio Piquero

B. RESEARCH LINES

Neurorehabilitation modeling; dysfunctional and hybrid bionic models

Short description:

Objectives:

- To define a conceptual framework of neurorehabilitation procedures.
- To model cognitive and physical neurorehabilitation processes.
- To model dysfunctional disability profiles in Acquired Brain Injury.
- To integrate dysfunctional models, and technologies and systems involved in the neurorehabilitation process in a hybrid bionic model.

Cognitive rehabilitation aims to reduce the impact of the impairments after an ABI in order to increase patient's autonomy and reduce functional limitations. GBT has defined an ABI cognitive dysfunctional profile that includes not only neuropsychological assessment data but also neuroanatomical information from medical imaging theoretical models and previous empirical knowledge about cognitive processes. In order to generate the cognitive dysfunctional profile, a system has been implemented to formalize the body of knowledge

associated with the assessment of ABI patients. It permits to test hypothesis about the relationship between anatomical structures and function.

Main results:

The cognitive conceptual framework and the system implemented aims to provide powerful tools to personalize patient's treatments as well as to improve the body of ABI neurorehabilitation knowledge.

Intelligent monitoring of cognitive and physical rehabilitation

Short description:

Objectives:

- To investigate on motion capture techniques for measuring patient´s movements in real time, mainly in physical rehabilitation (optical, ultrasound, video, intertial and range cameras).
- To research on a new patient interaction paradigm based on eye movement tracking system so that patient´s attention level can be measured.
- To monitor activities of daily living (ADL) integrated into AAL paradigms.

Main results:

The group has defined and developed a system to acquire visual attention data while a patient is carrying out an ADL using a virtual environment based on interactive video technology. Therapists extract useful information about how patients have performed their rehabilitation tasks, being able to reproduce where patients focused their gaze. Additionally, objective data on stimuli most visualized by them can be obtained, which could provide the basis for a reliable assessment of their performance. Moreover, the ability to detect attention deficits could serve as a trigger to modify the task flow in order to hold patient's attention on the important stimuli.

Interactive virtual environments and neurorehabilitation content development and management technologies

Short description:

Objectives:

- To generate and edit personalized multimedia therapeutic contents based on interactive video technologies, including a "therapeutic procedures

editor" in order to speed up the composition process of basic information units (video, 3D objects and scenes, image, audio and text).

- To analyze and process video information: segmentation, object tracking, multimedia content incorporation, etc.
- To generate interactive virtual environments based on interactive video and augmented reality.
- To develop multi-platform systems to display neurorehabilitation therapeutic contents (PC, gesture-based entertainment systems, mobile devices, RFID, IPTV and TDT systems).
- Interactive virtual environments and neurorehabilitation content development and management technologies.

Main results:

New technologies such as virtual reality or interactive video allow developing rehabilitation therapies based on reproducible Activities of Daily Living (ADLs), increasing the ecological validity of the therapy. However, the lack of frameworks to formalize and represent the definition of this kind of therapies can be a barrier for widespread use of interactive virtual environments in clinical routine. In order to provide neuropsychologists with an instrument to design and evaluate ADL-based therapeutic intervention strategies, the group has defined a new methodology that solves actual limitation of virtual scenarios.

Moreover, it can be used for ecological rehabilitation of cognitive deficit in daily clinical practice. The proposed methodology is used to model therapeutic interventions during virtual ADLs considering cognitive deficit, expected abnormal interactions and therapeutic hypotheses. It allows identifying abnormal behavioural patterns and designing interventions strategies in order to achieve errorless-based rehabilitation. As a result, an ADL case study ('buying bread') has been defined according to the guidelines established by the ADL intervention model. This case study has been developed, as a proof of principle, using interactive video technology and is used to assess the feasibility.

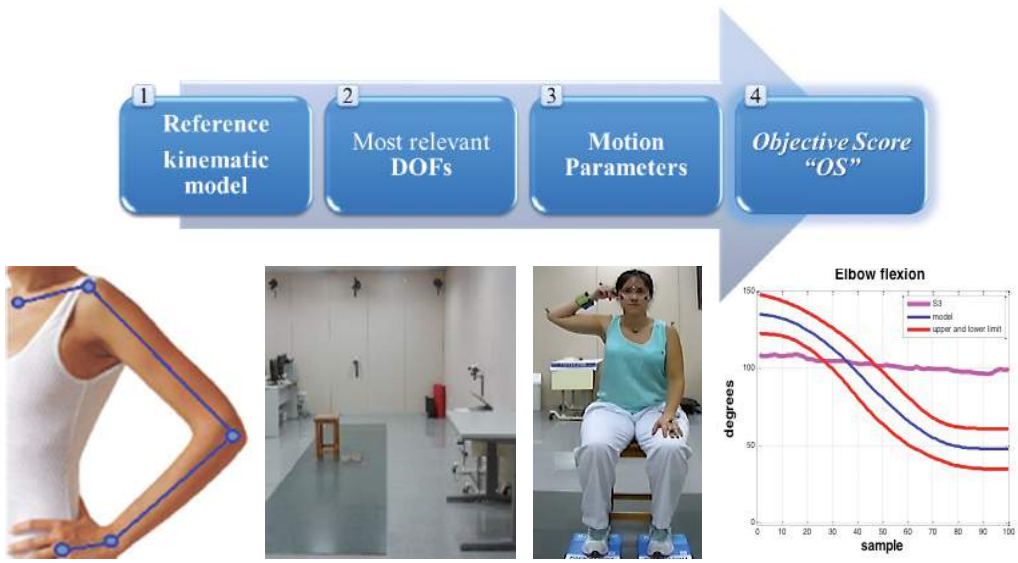
Modeling and intelligent adaptation of upper-limb neurorehabilitation therapies

Short description:

Objectives:

- To define an upper extremity biomechanical model with 6 degrees of freedom (3 shoulder, 2 elbow and 1 wrist).
- To define a new methodology for modelling upper limb Activities of Daily Living to apply new technological solutions that provide independence to patients.

- To define an upper extremity dysfuntional model for Acquire Brain Injury patients.
- To define and develop new algorithms for adapting the sequence of actions to be carried out during the therapy as a function of partial and final results.
- To define and develop intelligent procedures to measure the extent to which the therapeutic objective is achieved.
- Modeling and intelligent adaptation of upper-limb neurorehabilitation therapies.



Quantitative measurements of human movement quality are important for discriminating healthy and pathological conditions and for expressing the outcomes and clinically important changes in the subjects' functional state. Nevertheless, upper limb motor assessment is focused on clinical tests highly dependent on the criteria and experience of the examiner.

Main results:

The group has proposed a first approach for the automation of the Fugl-Meyer assessment scale used in physical neurorehabilitation. The main goal is to automatically estimate an objective measurement for five Fugl-Meyer scale items related to the assessment of the upper limb motion.

Knowledge management and data mining applied to neurorehabilitation data to generate clinical evidence

Short description:

Objectives:

- To define and develop new intelligent adaptive and incremental algorithms for optimizing cognitive rehabilitation (therapeutic objectives) and functional rehabilitation (assisted-as-needed).
- To investigate different machine learning and data mining techniques in order to generate medical knowledge that will be applied to adapt automatically and improve the neurorehabilitation process.
- To design and develop new decision support systems for the definition and personalization of the therapy plan using several clustering, neural networks, temporal data mining and pattern recognition techniques.
- To define new knowledge management system architectures.

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Main results:

The group has participated in the design and development of an algorithm, named Intelligent Therapy Assistant (ITA), which automatically selects, configures and schedules rehabilitation tasks for patients with cognitive impairments after an episode of Acquired Brain Injury. The ITA is integrated in "Guttmann, Neuro Personal Trainer" (GNPT), a cognitive tele-rehabilitation platform that provides neuropsychological services. The ITA selects those tasks that are more suitable for the specific needs of each patient, considering previous experiences, and improving the personalization of the treatment. The system applies data mining techniques to cluster the patients according their cognitive impairment profile. Then, the algorithm rates every rehabilitation task, based on its cognitive structure and the clinical impact of executions done by similar patients. Finally, it configures the most suitable degree of difficulty, depending on the impairment of the patient and his/her evolution during the treatment.

The group has also explored different algorithms and methods, such as decision trees, multilayer perceptron and general regression neural networks, to predict the effectiveness of rehabilitation programs. Several predictive models have been developed to obtain new knowledge to evaluate and improve the effectiveness of the cognitive rehabilitation process.

Analysis and classification of structural alterations resulting from an acquired brain injury based on medical imaging

Short description:

Objectives:

- To define and develop tissue and structure segmentation algorithms.
- To define and develop algorithms for identifying acquired brain injury affected regions.
- To define and develop systems for displaying and storing the affected regions and the clinical reports related.
- To create a knowledge database containing image studies and clinical reports available.
- Analysis and classification of structural alterations resulting from an acquired brain injury based on medical imaging.

Main results:

The group has worked in the definition of a methodology to extract information relative to patient brain structures altered after an ABI event based on medical imaging. The approach proposed in this method obtains imaging information based on intensity and location values by applying a featured-based detection algorithm named Neuroanatomic-Based Detection Algorithm (NBDA). This algorithm is based on SURF (Speeded Up Robust Feature). The main goal is to register injured neuroanatomic structures to generate a database containing patient's structural impairment profile.

This kind of information permits to establish a relation with functional disorders and the prognostic evolution during neurorehabilitation procedures. As a result of this research, an image analysis module has been implemented containing four main sub-modules: the content based image retrieval system (CBIR), the preprocessing and the analysis subsystems and finally, the ABI report sub-module, as can be shown in next figure. The first sub-module permits to retrieve slices or image studies similar to a determined slice or study. The preprocessing and analysis subsystems implement the algorithms to remove the background information of the image study, to spatial and intensity normalize each study and to obtain the anatomical features to detect the injured anatomical structures. The report sub-module generates an inform containing the identification and the localization of injured neuroanatomical structures.

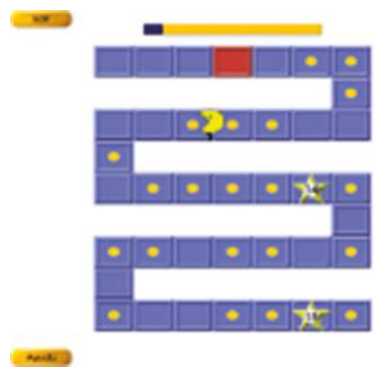
The group has also proposed a new methodology to model three types of brain injury: stroke, tumour and traumatic brain injury; and implements a system to navigate among simulated MRI studies. These studies can be used on research studies, to validate new processing methods and as an educational tool, to show different types of brain injury and how they affect to neuroanatomic structures.

Tele-Neurorehabilitation technologies and systems

Short description:

Objectives:

- To define tele-neurorehabilitation platforms (cognitive and physical rehabilitation).
- To design high usability user interfaces for patients and therapists.
- To define evaluation methodologies (usability and clinical).
- To design and develop clinical information systems focus in neurorehabilitation.



Main results:

The group has participated in the design and development of a telerehabilitation platform called Guttmann Neuropersonal Trainer (GNPT, https://www.gnpt.es/es) which provides new strategies for cognitive rehabilitation, improving efficiency and access to treatments, and to increase knowledge generation from the process.

A cognitive rehabilitation process has been modeled to design and develop the system, which allows neuropsychologists to configure and schedule rehabilitation sessions, consisting of set of personalized computerized cognitive exercises grounded on neuroscience and plasticity principles. It provides remote continuous monitoring of patient's performance, by an asynchronous communication strategy. An automatic knowledge extraction method has been used to implement a decision support system, improving treatment customization. GNPT has been implemented in 27 rehabilitation centers and in 83 patients' homes, facilitating the access to the treatment. In total, 1660 patients have been treated.

Usability and cost analysis methodologies have been applied to measure the efficiency in real clinical environments. The usability evaluation reveals a system usability score higher than 70 for all target users. The cost efficiency study results show a relation of 1-20 compared to face-to-face rehabilitation. GNPT enables brain-damaged patients to continue and further extend rehabilitation beyond the hospital, improving the efficiency of the rehabilitation process. It allows customized therapeutic plans, providing information to further development of clinical practice guidelines.

Biomedical Technologies for Brain Health

Short description:

Brain health has a direct impact on people's well-being and quality of life, delaying the onset of disease and optimizing the brain's ability to promote overall health.

The research activity line focused on "Intelligent Brain Coaching" (iBC) coordinates an interdisciplinary strategic alliance in Biomedical Engineering to face a problem of Health, Demographic Change and Welfare of great magnitude: the maintenance of brain health in an increasingly aging population.

Research goals:

- Investigate on technological solutions to create new coaching services promoting brain health. A suite of apps (encompassed in the Intelligent Brain Toolkit) and a common service technological platform (iBC) is being developed.
- Define and develop monitoring methodologies and multimodal interaction methods.

- Define and implement a platform that allows clinical professionals to optimize and personalize coaching proposals, as well as generate a knowledge base in brain health.
- Design a data analysis tool that, based on the conceptual models of brain health and the information collected in the BBHI for each individual, allows the identification of brain health patterns and disagreements between the subjective perception of an individual and their clinical evaluations.
- Design a decision support tool that, based on an individual's brain health patterns, uses predictive models to identify the specific needs of each individual and recommendation and personalization systems to generate personalized proposals for activities and strategies coaching for the maintenance and improvement of your brain health.
- The results will be validated technologically and clinically in a study with 500 volunteers.

The project benefits from the Barcelona Brain Health Initiative (BBHI) initiative, which began in 2016, which investigates brain health mechanisms to detect indicators of transition to disease situations and promotes healthy living habits. BBHI is performed with a cohort of 5,000 healthy subjects with a follow-up of at least 6 years. Our clinical study will be conducted in coordination with the BBHI, which will provide the 500 volunteers, their clinical data and information regarding their lifestyle.

The ambition of the project and the essential complementarity of its research areas are dealt with by a technological and clinical interdisciplinary team made up of the Biomedical Technology Centre-Universidad Politécnica de Madrid, the Artificial Intelligence Research Institute-CSIC and the Guttmann Institute hospital. The research team maintains close scientific collaboration with international entities such as Harvard Medical School and European institutions to internationalize the results of the project and contribute to the leadership and international projection of the research team.

Main results:

Under this project, two PhD have been developed:

Title: "New monitoring, personalizing and coaching techniques to achieve healthy habits for brain health promotion". **Objectives:** The main objective of this PhD thesis is to design, implement and validate an intelligent system for personalized monitoring and intervention of healthy lifestyles based on AI algorithms that provides user adapted intervention proposals to the professional.

The specific objectives of this thesis are:

1. Design of a user model based on the parameters extracted from questionnaires and monitoring data.

2. Design of an intelligent classifier that allows a personalization of the intervention for each user based on new User Experience (EU), gamification and intelligent systems methods and techniques to improve healthy habits for brain health promotion.
3. Design and implement a mobile application that integrates the methods and techniques resulting from the previous design.
4. Design a validation study to validate the hypotheses.

Title: "Data Analysis, Recommendation and Artificial Inteligence Models for Brain Health Promotion". **Objectives:** Propose new methodologies of analysis, prediction and recommendation that will allow coaches to monitor the activity of participants, assess their needs and propose the activities that best fit their needs.

C. FACILITIES AND TECHNIQUES

Facilities/Infrastructures

- Software licenses/Open Source: Matlab, SPSS
- Intellectual properties: Guttmann NeuroPersonalTrainer
- Commercial systems: Microsoft Kinect (x3), Eye Tracking devices (x2), Leap Motion
- Image data bank: Magnetic resonance image (MRI) studies
- Clinical data bank: ABI patient database

Techniques

- Motion capture techniques
- Eye-tracking, dysfunctional and hybrid bionic models
- Augmented reality and interactive video technologies
- Medical image segmentation
- Automatic landmark detection
- Upper limb dysfunctional models
- Machine learning and data mining techniques

D. RESEARCH PROJECTS

BIOMed: New Horizons Biomedical Informatics Observatories in Mediterranean Region. 318905.

PI: Enrique J. Gómez

Funding Agency: European Commission

Budget: 58.900,00€

Period: 01/10/2020-30/09/2016

Other institutions participating: National And Kapodistrian University Of Athens, Universidad Politécnica De Madrid, Akdeniz University, Yarmouk University, Academy Of Scientific Research And Technology Asrt

EMERGE: Evaluating mHealth technology in HIV to improve Empowerment and healthcare utilization: Research and innovation to Generate Evidence for personalized care. 643736.

PI: Enrique J. Gómez

Funding Agency: European Commission

Budget: 396.018,80€

Period: 01-05-2015 / 30-04-2020

Other institutions participating: Brighton And Sussex University Hospitals Nhs Trust, Prins Leopold Instituut Voor Tropische Geneeskunde, Fundacio Privada Clinic Per A La Recerca Biomedica, Centro Hospitalar De Lisboa Central, Epe, Klinika Za Infektivne Bolesti, Universidad Politecnica De Madrid, University Of Sussex, European Aids Treatment Group Ev, University Of Brighton, Modus Research And Innovation, Npms-Hcc-Cic, Mhealth Futures Ltd.

Nutriprecisión: Estrategias Para La Mejora De La Calidad De Vida De Colectivos Pre-Senior Y Senior Basadas En La Nutrición De Precisión. Pcd1709560129

PI: Enrique J. Gómez

Funding Agency: Programa Estratégico de Consorcios de Investigación Empresarial Nacional (CIEN)

Budget: 100.000,00€

Period: 01/11/2016-31/10/2020

Other institutions participating: Ica, Informática Y Comunicaciones Avanzadas

NEUROCHILD: NeuroChild EyeTracking: Nehabilitación Cognitiva de Niños con Daño Cerebral Adquirido basada en Serious Games para Dispositivos Móviles y con Control Visual de Atención. RTC-2014-2228-1

PI: Enrique J. Gómez

Funding Agency: Ministerio de Economía, Industria y Competitividad

Budget: 124.591,00€

Period: 01/07/2014-31/12/2016

Other institutions participating: Centro De Vision Por Computador, Fundacio Privada Institut De Neurorehabilitacio Guttmann, Ica Informatica Y Comunicaciones Avanzadas Sl.

Estudio sobre el Estado del arte en el desarrollo de aplicaciones móviles para atención socio sanitaria a mayores

PI: Enrique J. Gómez

Funding Agency: Acciona

Budget: 3.000,00€

Period: 01/10/2016-31/10/2016

IBC: Intelligent Brain Coaching: Modelos y Tecnologías de Monitorización, Interacción e Inteligencia Artificial para la Promoción de la Salud Cerebral. DPI2017-86088-C3-1-R

PI: Enrique J. Gómez

Funding Agency: Ministerio de Economía, Industria y Competitividad

Budget: 127.050,00€

Period: 01/01/2018-31/12/2020

NeuroIBC: Intrabody Communication for the Optimization of Neuromodulation Techniques

PI: Patricia Sánchez, Enrique J. Gómez

Funding Agency: Centro de Investigación Biomédica en Red en el área temática de Bioingeniería, Biomateriales y Nanomedicina

Period: 01/07/2016-30/06/2018

Other institutions participating: GBT-UPM (PI: Enrique Gómez); Grupo de Trastornos del Movimiento, IBiS Sevilla, CIBERNED, Hospital Universitario Virgen del Rocío (GTM-IBiS, PI: Pablo Mir)

E. PUBLICATIONS

1. Villán-Villán, M. A, Pérez-Rodríguez, R., Martín, C., Sánchez-González, P., Soriano, I., Opisso E., Hernando, ME, Tormos. J. M,, Medina, J., Gómez, E. J. (2018). Objective motor assessment for personalized rehabilitation of upper extremity in brain injury patients. NeuroRehabilitation.;42(4):429-439. doi: 10.3233/NRE-172315.

2. Vasquez-Cevallos, L. A., Bobokova, J., González-Granda, P. V., Iniesta,J. M., Gómez, E.J. and Hernando, M. E. (2018). Design and Technical Validation of a Telemedicine Service for Rural Healthcare in Ecuador. Telemedicine and ehealth, Telemedicine and e-HealthVol. 24, No. 7, 1 Jul, https://doi.org/10.1089/tmj.2017.0130.

3. Sanchez-Margallo, J.A., Sanchez-Margallo, F.M., Oropesa, I., Enciso, S., Gomez, E.J.. (2017). Objective assessment based on motion-related metrics and technical performance in laparoscopic suturing. Int J Comput Assist Radiol Surg. Feb;12(2):307-314. doi: 10.1007/s11548-016-1459-3. Epub 2016 Jul 16.

4. Rodriguez-Vila, B., Sanchez-Gonzalez, P., Oropesa, I., Gomez, E.J., Pierce, D.M. (2017). Automated hexahedral meshing of knee cartilage structures-application to data from the osteoarthritis initiative. Computer Methods in Biomechanics and Biomedical Engineering.; 20(14):1543-1553.

5. Ortega-Morán, J F., Pagador, J.B., Sánchez-Peralta, L.F., Noguera, J., Burgos, D., Sánchez-Margallo, F. M., Sánchez-González, P., Gómez, E.J. (2017). Validation of the three web quality dimensions of a minimally invasive surgery e-learning platform, International Journal of Medical Informatics; 80:115-124.

6. Martínez-Moreno, J.M., Sánchez-González, P., Luna, M., Roig, T., Tormos, J.M., Gómez, E.J. (2016). Modelling Ecological Cognitive Rehabilitation Therapies for Building Virtual Environments in Brain Injury. Methods of Information in Medicine. Jan 8; 55(1):50-9. doi: 10.3414/ME15-01-0050.

Optics, Photonics and Biophotonics (UPM)

PRESENTATION/INTRODUCTION

The Optics, Photonics and Biohotonics Group (GOFB) is specialized in Research, Technological Development and Innovation of advanced chemical, biochemical and in-vitro diagnostic systems, as well as in the implementation of photonic transducers and bio transducers on a chip, biokits, readout platforms, bioreactors, tissue-on-a-chip and organ-on-chips.

Thus, the GOFB is covering the whole value chain from the basic and technological research to the demonstration and final prototyping, being the main activities conducted from the analytical and numeric simulation and design to the final implementation of the biokits, bioreactors and readout platforms. The GOFB is focus either on disruptive and singular applications or in those more market oriented. In this term, is worthy to mention here that the exploitation of the research and technological development is conducted through industrial partners and the start-up company Bio Optical Detection (www.biod.es) that was set-up in 2010 from researchers of the GOFB group.

A. MEMBERS

PI: Miguel Holgado

Senior researchers: María Fe Laguna, Rafael Casquel, Álvaro Lavín

Post-doctoral Fellows: Ana L. Hernández

PhD students: Beatriz Santamaría, Sergio Quintero, Rocío López, Yolanda Ramírez, Pedro Herreros, Luca Tramarín, María Jesús Píoz, Ana M. Martín Murillo

Others: Francisco Javier Sanza

B. RESEARCH LINES

In the GOFB the main motivation is the development of In-Vitro diagnostic systems and platform to face the following challenges: relating with the increasing incident diseases (Neurodegenerative, Cancer, Infectious, Cardiovascular, etc.) in an ageing society with chronic diseases and with the increasing cost of drugs discovery and development and therefore: cost effectiveness, diagnostic must be accessible, time to results must be faster, time to therapy must be reduced, need to discover and develop new and efficient drugs, need to go towards a personalized medicine , need to acute control of contamination in environment, need to acute control of food.

Lately, the GOFB has gained experience in the development of novel microfluidic chips where to culture different types Cells and mimic different organs. In this term the GODF is currently working in three dimensional skin models on a chip, different models for brain on a chip and cancer cells models on a chip. This novel project is being developed with the Regional (Biopiletec-CM), National (HERON) and International (BITFORM) in collaboration with the UCLA in California projects.

The main research technologies of the Group GOFB are:

- Design and simulation of Photonic structures
- Simulation of fluidic behavior of molecules and nanoparticles
- Micro-nano fabrication of photonic transducers
- Micro-fabrication and packaging of multiplexed KITs
- Surface chemistry and biofuntionalization with bioreceptors
- Development of biochips and biokits
- Development of bioreactors
- Implementation of optical readout platforms (optical fiber based and free space)

The main Research lines applications of the Group GOFB are:

- Biosensing
- Chemical Sensing
- Organ and tissue on a chip
- Point-of-Care and Point-of-Need devices
- In-vitro platforms for cellular screening
- Innovation perspective and scouting

Development of In-Vitro diagnostic systems

THE CHALLENGES OF THE ACTUAL DIAGNOSIS

- Increasing incident of diseases: Cancer, cardiovascular, diabetes, Infectious, neurodegenerative diseases
- Society Ageing: Higher incidence of chronic diseases
- Increasing cost of the diagnostic technique but less contribution to the National Health System
- Increasing cost of drugs development
- Need of a personalised medicine and diagnostic
- Need of acute control of the contamination in the food and the environment
- World´s most burdensome diseases: Tuberculosis, malaria, HIV, Dengue,... mainly in resource-constrained settings

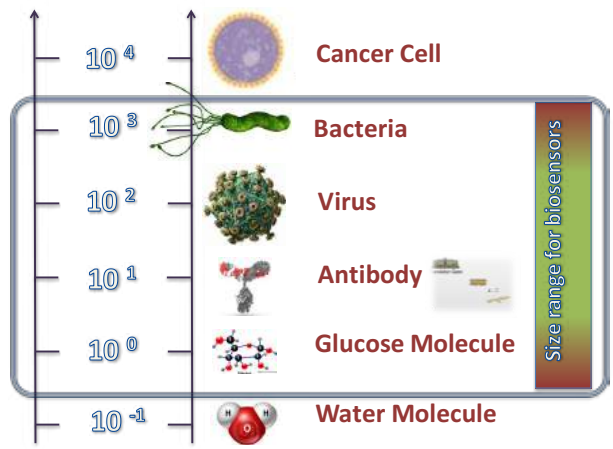
- Diagnostic: must be accessible for all
- Time to results: must be faster
- Time to therapy: must be reduced
- Price: must be low-cost

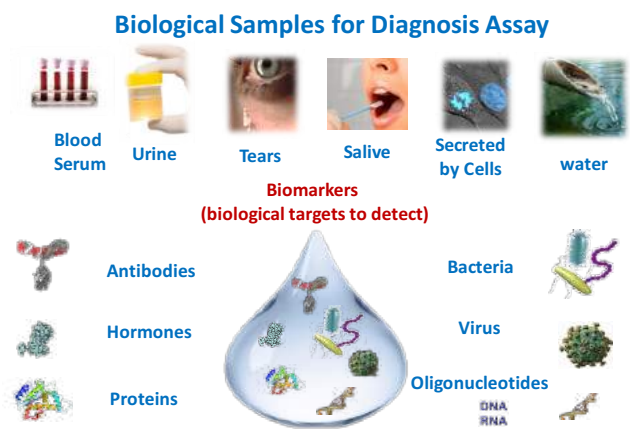
Thus, in the classification of the *In vitro* diagnostic (IVD) system, the GOFB is mainly focused on near patient testing (Point of care) or other Point of need applications. However, the trend and future developments are also oriented to the final user testing. Thus, the IVD can be classified as: Clinical Laboratory testing, Near Patient Testing and Self-testing.

Sensing and biosensing

The researchers belonging to the GOFB have a lot of experience developing sensing system to detect different types of biological targets and agents. Thus, in the GOFB we design and adapt, not only the transducers and biotransducers, but also the readout system to optimize the sensing system platform as a whole.

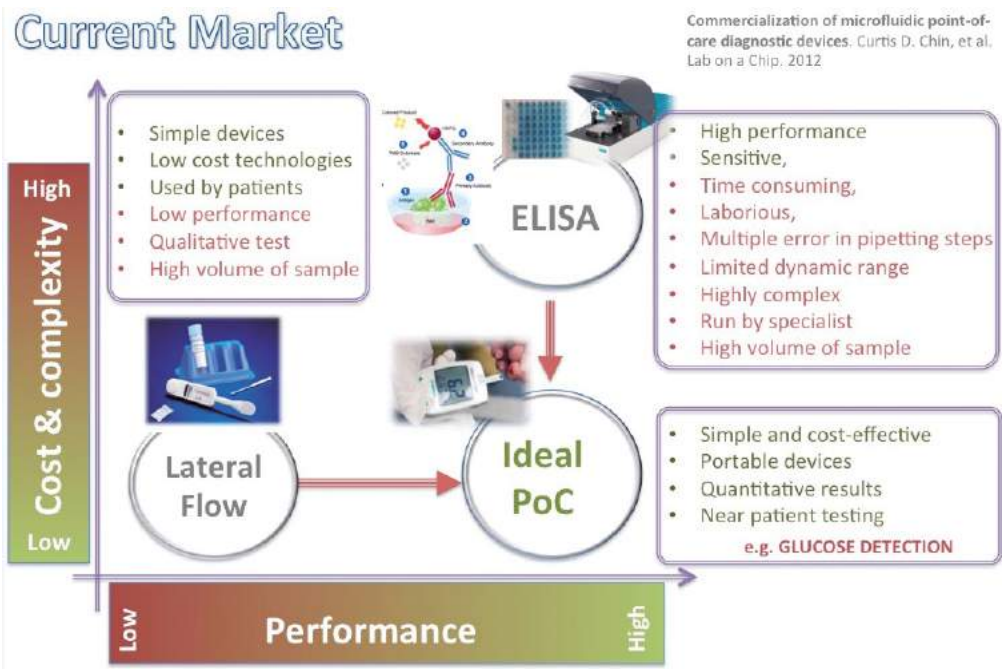
Another remarkable point to bear in mind is the biological sample: blood, serum, urine, tears, cells, water, among others, where the biological targets are together with other multiple components. Those components produce an unspecific adsorption. As a result, the background signal is increased jeopardizing the specific signal in the sensing systems. Multiple strategies at GOFB has been developed in order to avoid this unspecific adsorption problem.





Point-of-Care and Point-of-Need devices

The main objective is to develop the ideal Point of Care (PoC) devices; in fact, this ideal PoC should be capable of measuring with the same performance of modern ELISA tests but in a cost-effective manner as the current lateral flow systems which are closer to the final user and can be handle easily with non-expert persons.

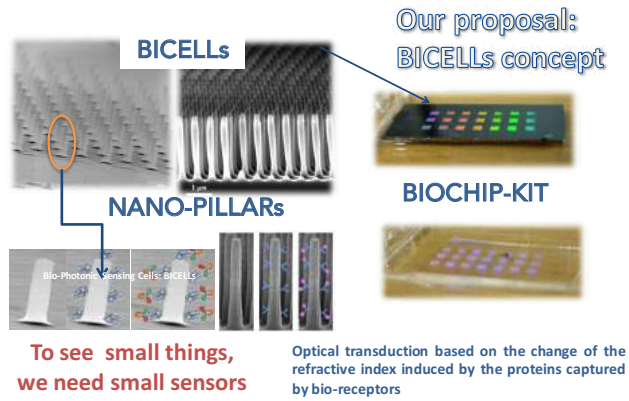


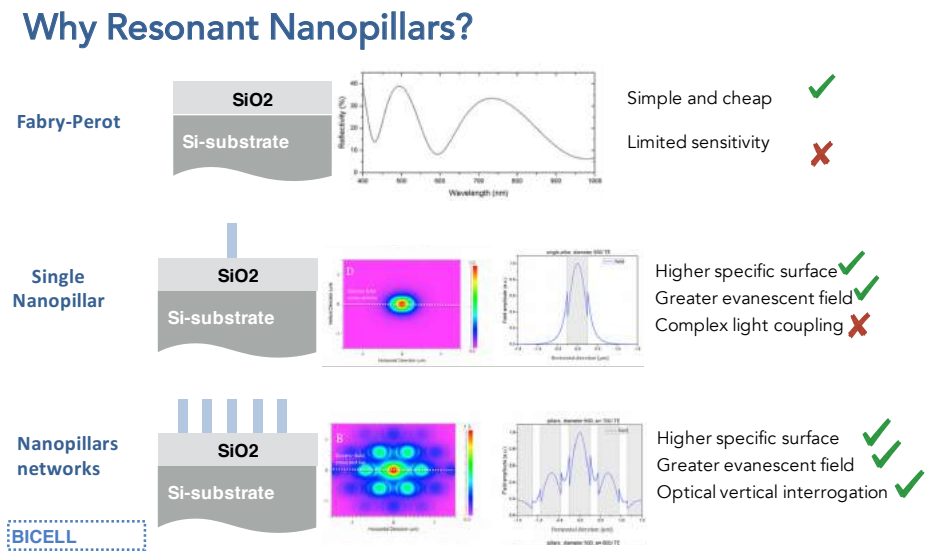
Development of photonic and biophotonic transducers

GOFB has developed multiple photonic and biophotonic transducers and those based on the arrays of Resonant Nano Pillars (RNPs) were patented some years ago to produce high sensitivity effective photonic transducers. Those arrays of RNPs can be integrated on a chip, and they have the advantage to be interrogated vertically avoiding complex coupling system when the readout signal is coming from an optical waveguide. This advantage allows us to implement effective readout optical plataforms.

Intuitively it can be imagined that to detect small molecules we need small sensors (the Nano Pillars (NP). However, the optical interrogation of a single NP (in the order of 150 nm in diameter) seems to be quite challenging and complex to be implemented for the development of PoCs. For that reason, it is much simpler to interrogate multiple NPs in a single array. We call this array of NPs a sensing cell, and if these arrays are biofunctionalized we call these Bio Photonic Sensing Cells (BICELLs).

Thus, in the case that the NPs can be nano-resonators, then we have an array of RNPs as photonic transducer that are suitable for detecting, not only biological agents, but also the liquid proprieties. Moreover, an important effect of the arrays of NPs or RNPs is the light enhancement when travelling through these structures because it is increased the interaction with the biomolecules attached onto the sensing surface. We call this effect enhancement of the evanescent field detection.



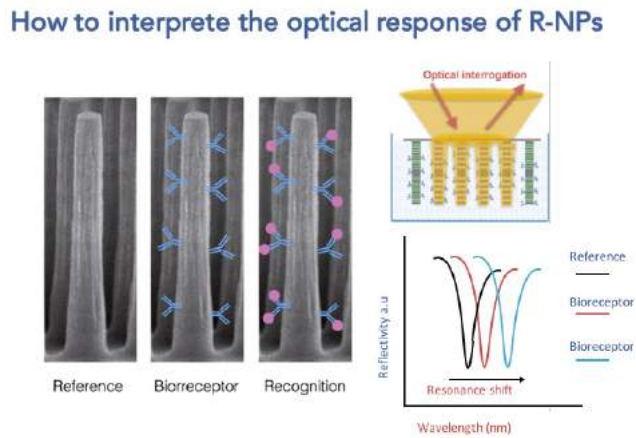


As abovementioned, the optical interrogation of these sensing arrays or cells are done vertically and the response can be collected in both: reflection of transmission of the light. Moreover, another important remark is that these structures can be implemented in transparent substrates and the signal can be obtained from the back-side of the substrate.

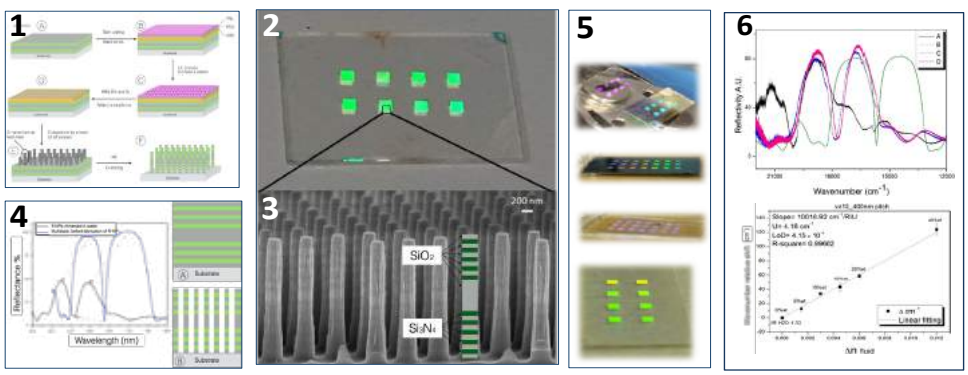
This important aspect permits the use of RNPs arrays, not only from static mode working with simple drops of sample or biological samples, but also working in continuous flow, were the liquid is covering the sensing surface of the RNPs and optical the interrogation is done through the substrate. This basic layout gives us a lot of possibilities for implementing

advanced readout sensing systems in a large variety of layout depending of the final application.

There are a number of possibilities to interpret the signal, for example the wavelength shifts of the resonance mode when the accumulation of recognition of biomolecules event take place during the interrogation process. This wavelength shift is a proportional measure of the biomolecules captured onto the sensing surface.

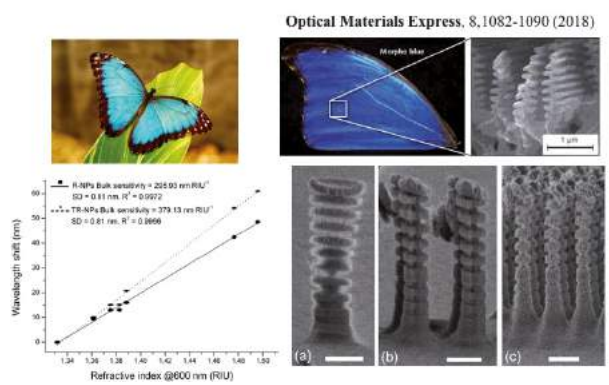


Another important advantage of this BICELLs on a chip is the multiplexing capability. In this term chips with a number of arrays can be easily implemented to detect multiple arrays simultaneously, just to increase the reliability of the biochemical sensing or just to motorize different biological agents simultaneously.

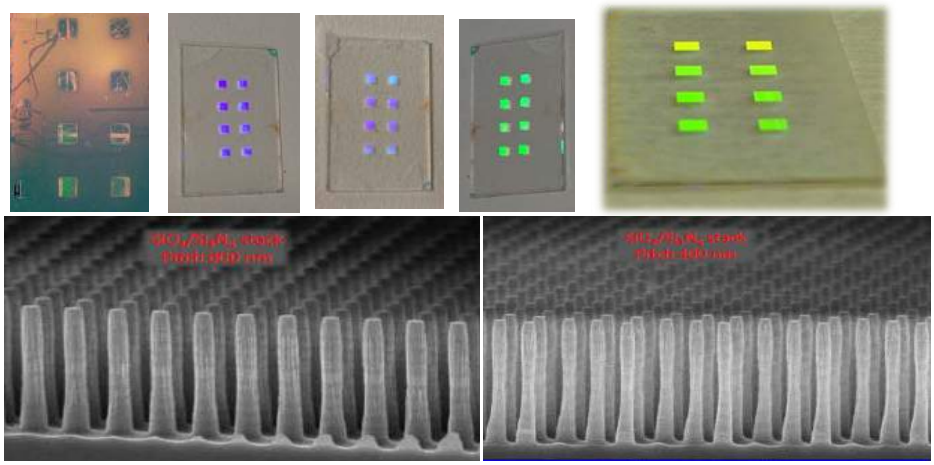


Although the fabrication of the RNPs are well developed by the group, other singular structures can be implemented that mimic nature. This is the case of tiered RNPs emulating the natural structures of the butterfly wings.

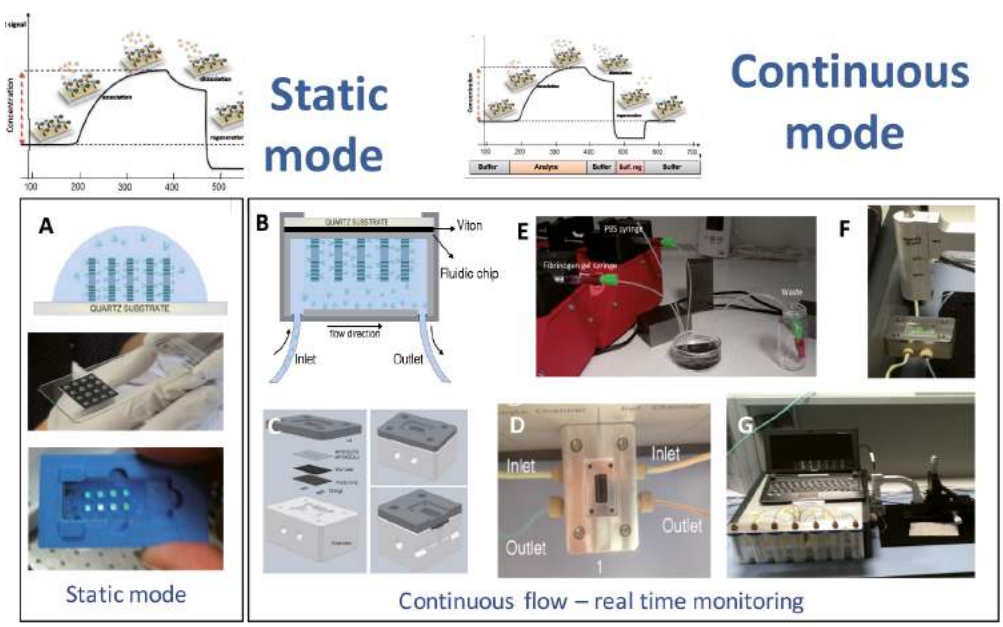
Another important advantage of the RNPs arrays is robustness. As a single RNPs behaves as a single



nano sensor, and in an array of RNPs there are multiple nanosensors, if some of them are destroyed (e.g. some scratchers) the information remains unchanged given that the other RNPs are giving the same information. This particular feature is quite relevant to implement these structures on real scenarios.

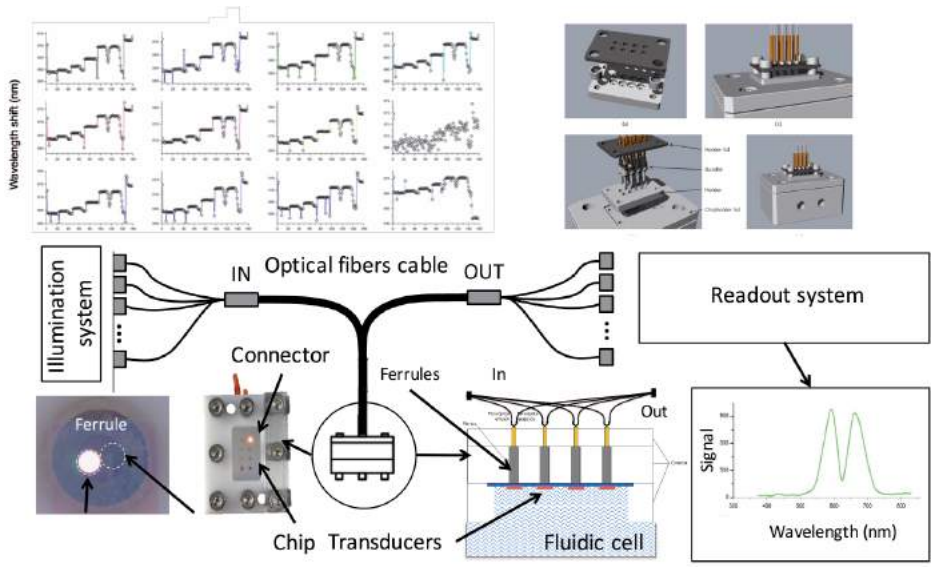


These real scenarios depend on the application, in which the application can be in real time and continuous flow or can be in static mode by using single drops of biological sample in a limited volume of liquid. In the example below, it can be observed both possibilities.

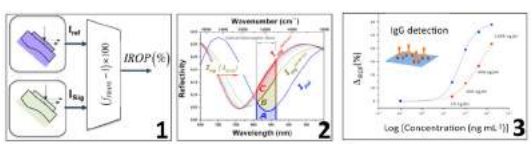


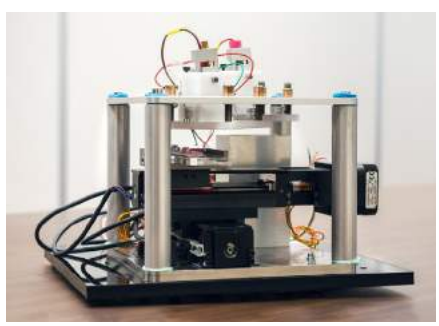
Technology for readout platforms

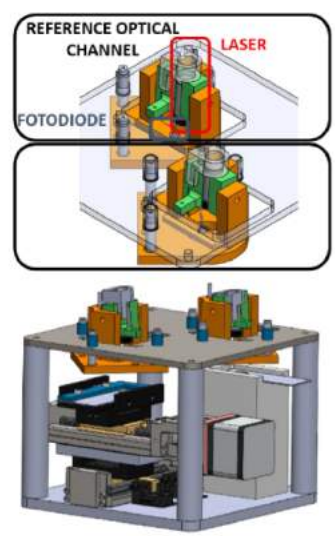
When continuous flow and multiplexing is needed, the RNPs on a chip interrogated by means of optical fibers is an ideal approach. This feature permit us to monitor of the resonance responses of multiples BICELLs in real time.



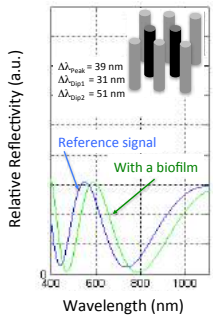
When the interrogation is carried out for single drops of biological samples other advanced interrogation techniques can be used. Some of them are also patented by the GOFB to enhance the sensing system as a whole. In this particular case also transferred to the BIOD company (www.biod.es).

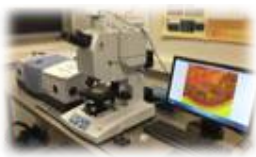




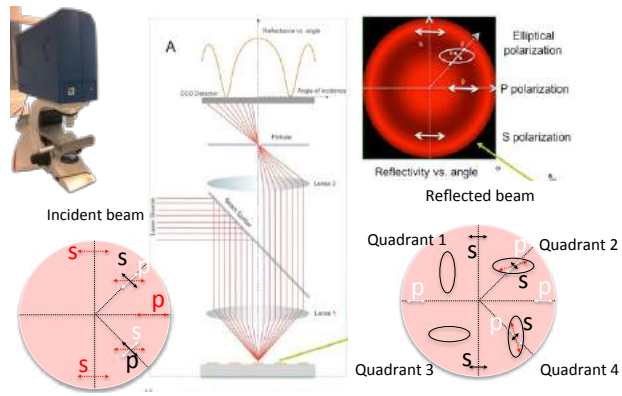


■ Broadband-based optical techniques





■ Laser-based optical techniques

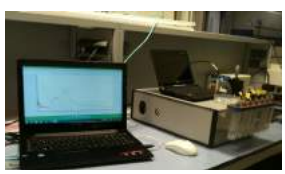


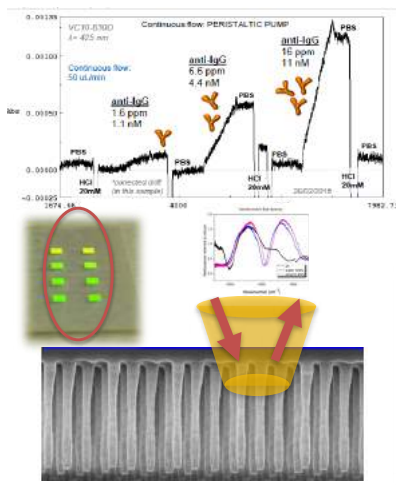
Main results of the research lines mentioned above. In order to demonstrate some of the developments carried out, below some examples implemented for different applications:

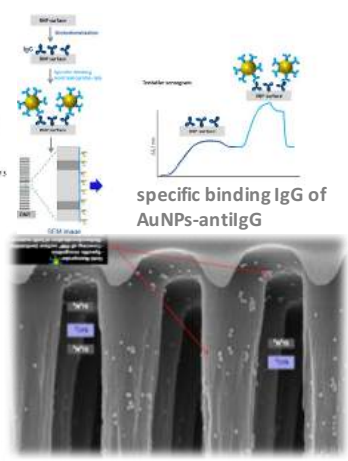
Biological agents detection for aquiculture

Aquiculture IVD in real time

Results

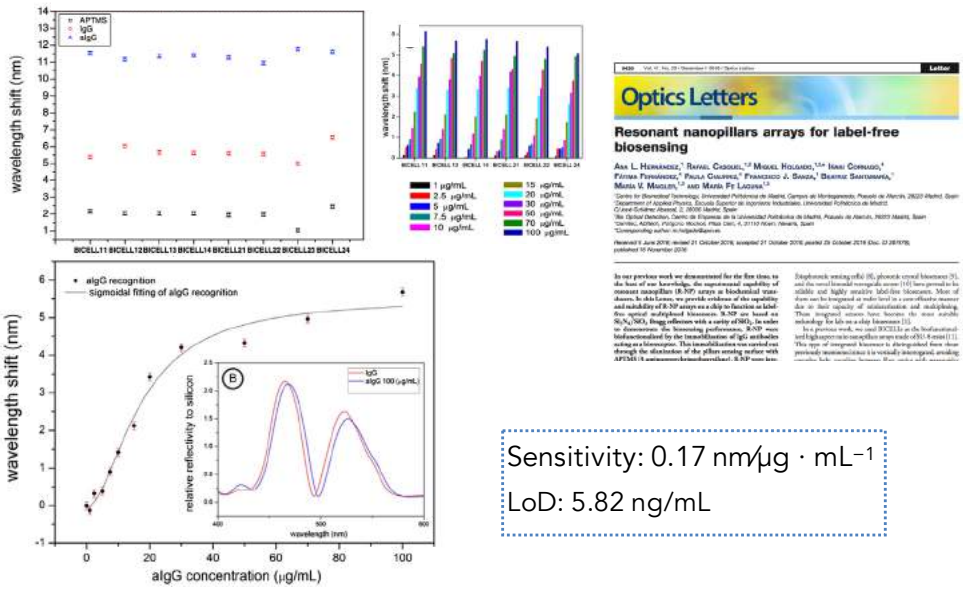






Multiplex capability detecting multiple biological targets

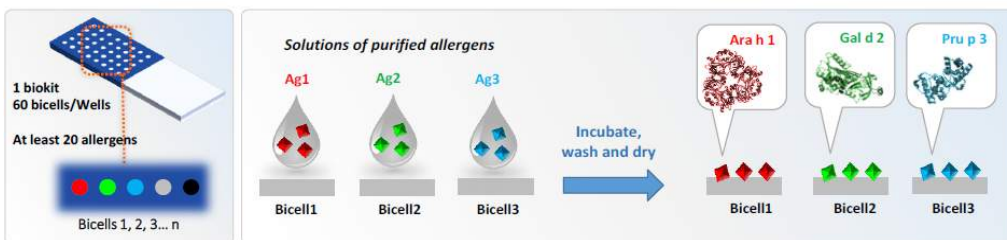
R-NPs in static mode Immunoassay

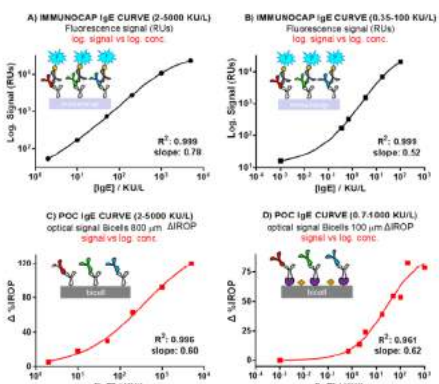


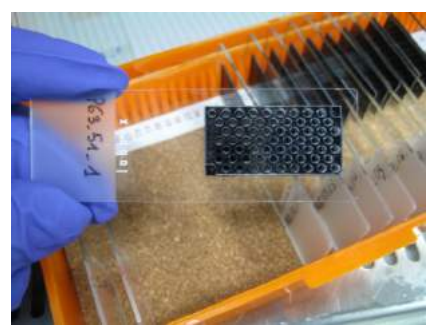
Sensitivity: 0.17 nm/μg · mL^{-1}

LoD: 5.82 ng/mL

Multiplex KIT for in-vitro detection of Food allergy

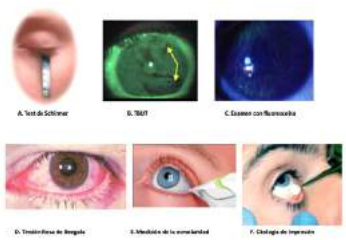






Detection of biomarkers in a single drop of tear

Ophthalmological applications



Novel biomarkers are proposed for optimal accuracy in correct diagnosis of dry eye: S100A6, ANXA1, ANXA11, CST1, PLAA, PRDX5.

Table 4 – Results of individual biomarker power for dry eye discrimination in different tear collection methods.

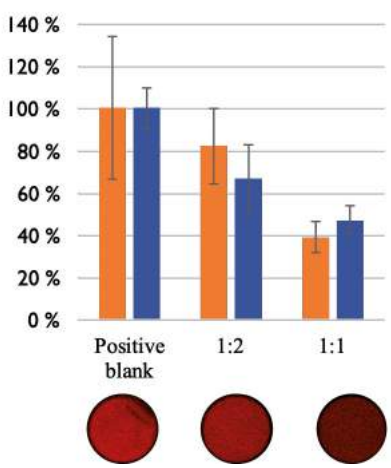
Collection method	Protein	OA (%)	Sens. (%)	Spec. (%)
Sponge validation 1	S100A6	90.6	93.8	84.8
	ANXA1	89.7	90.0	89.4
	CST1	67.7	90.2	27.2
	ANXA11	78.0	84.0	61.8
	PLAA	92.5	94.2	88.0
	PRDX5	75.1	91.8	49.8
Capillary validation 1	S100A6	83.8	90.2	60.8
	ANXA1	73.8	85.0	76.5
	CST1	76.2	70.0	82.4
	ANXA11	78.3	80.0	76.5
	PLAA	81.6	75.0	88.2
	PRDX5	[illegible]	[illegible]	[illegible]

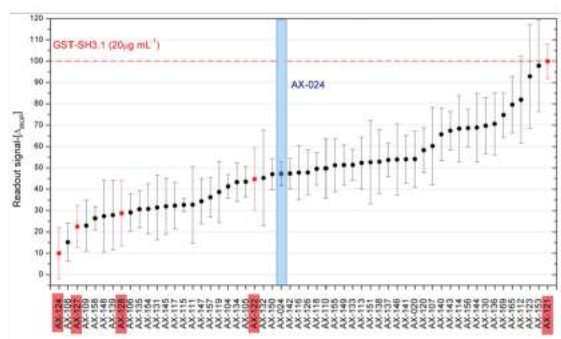
OA = correct assignment, Sens. = sensitivity, Spec. = specificity, Mann-Whitney test analysed.

Measuring for drops of 4 µL of Tears

High throughput screening applications for discovering drugs

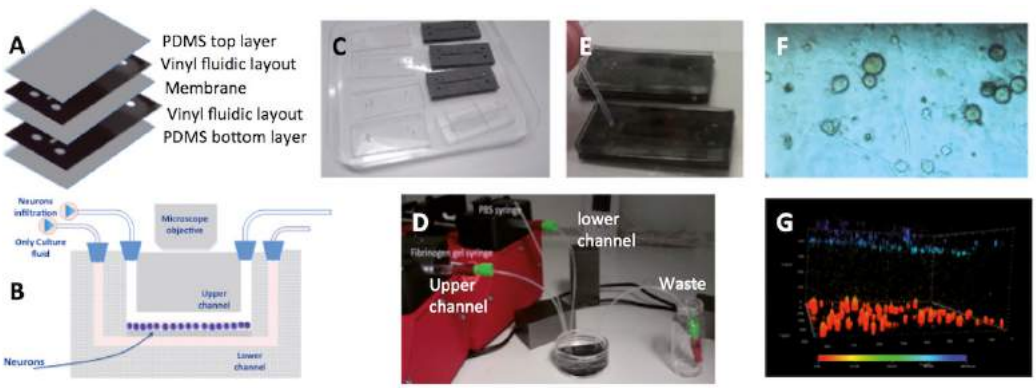
Screening applications





Development of bioreactors

Another important field in which the GOFB is working intensively is in the development of bioreactors for tissue on a chip and organ on chips architectures. These chips are used for multiple applications covering the development of in-vitro cellular screening platforms and monitoring of biological networks, such as the case of neurons on a chip. In this case, the research work is carried out in collaboration with the Biological Networks group (Prof. Dr. Irene Sendiña and Prof. Dr. Inmaculada Leyva) also belonging to the Center for Biomedical Technology.



C. FACILITIES AND TECHNIQUES

Simulation

Simulation workstation, CONSOLE simulation design software, RSOFT photonic Design software, MATLAB, Own codes for 1 and 1,5 D simulation.

Micro Nano fabrication

Micro Nano fabrication tool (Mask projection and NIL), Resist deposition, Oxygen etcher, Hot plate, Hot plates, Laminar flow chamber class 10, Mechanical plotter, 3D printing, Furnace.

Optical Characterization

Optical Microscopes, FTIR, High spatial Resolution Beam profile reflectometer, Thin film thickness, Infra-Red Spectrometer, Optical light sources, Visible Spectrometer, UV Spectrometer Optizen Alpha, Optical power meter.

Biochemical

Low volume dispensing of biological samples, ELISA Plate Reader, Ultra, High resolution laboratory scale, Incubator, Biological cabin, Portable station for dried and particle less air, Extraction chamber, pH meter, Ultrasonic cleaner, Refrigerator, Freezer.

Biochemical readout platforms

Pont of Care Device of BIOD, Optical Fiber readout platform static mode, Optical Fiber readout platform continuous mode, Multi parametric readout platform, Organ on chip platform.

D. RESEARCH PROJECTS

PLATON: Biochip kits basados en celdas biofotónicas y plataformas avanzadas de interrogación óptica. TEC2012-31145

PI: Miguel Holgado

Funding Agency: Ministerio de Economía y Competitividad

Budget: 154.440€

Period: 01/02/2013-31/12/2016

Diseñar un sistema grabador de etiquetas con códigos inteligente e invisibles basadas en capas delgadas orgánicas e híbridas que integren moléculas de colorante con la funcionalidad química o física deseada

PI: Miguel Holgado

Funding Agency: ARQUIMIAS INGENIERIA S.L.U

Period: 06/07/2015-06/07/2018

Photonic integrated circuits for telecommunication and bio sciences. TEC2015-69787-REDT

PI: Miguel Holgado

Funding Agency: Ministerio de Economía y Competitividad

Budget: 30.000€

Period: 01/12/2015-01/12/2017

ATAPOC: Desarrollo y validación clínica de un dispositivo para el diagnóstico y seguimiento de las alergias y tolerancias alimentarias. RTC-2015-3273

PI: Maria Fe Laguna

Funding Agency: Ministerio de Economía y Competitividad

Budget: 49.500€

Period: 02/12/2015-02/12/2017

- **Web link**: http://biod.es/es/Project/atapoc-es/

Diseño de un dipositivo POC para medidas de marcadores oftalmológicos

PI: Miguel Holgado

Funding Agency: Comunidad de Madrid-Innovation check

Period: 01/12/2016-01/12/2018

- **Web link**: http://biod.es/Project/inhibidores_sistema-2-2/

INSPIRE: Monitorización en tiempo real de múltiples propiedades de fluidos mediante transductores fotónicos y electromagnéticos (REMO)

PI: Miguel Holgado

Funding Agency: REPSOL & INDRA

Period: 28/07/2015-28/07/2018

Descubriendo la ciencia desde cinco laboratorios del Centro de Tecnología Biomédica de la Universidad Politécnica de Madrid. FCT-16-10672

PI: Francisco del Pozo & Miguel Holgado

Funding Agency: FECYT

Period: 31/12/2015-31/12/2016

AENOR-1997/0740/PIV/02 FUNDACION TEKNIKER

PI: Maria Fe Laguna

Funding Agency: AENOR

Period: 01/04/2017 -

ALLERSCREENING: Point-of-care device based on KETs for diagnosis of food allergies. H2020-2017-768641

PI: Miguel Holgado

Funding Agency: EUROPEAN COMMISSION

Budget: 1.182.250€

Period: 01/10/2017-30/09/2021

Other institutions participating: Bio Optical Detection SL. Consulting Quimico Sanitario S.L. Microfluidic Chipshop Gmbh. Servicio Andaluz De Salud. Clinica San Carlo Casa Di Cura Privata Polispecialistica Spa. Universiteit Antwerpen. Medizinische Universitaet Wien. Klinikum Rechts Der Isar Der Technischen Universitat Munchen. Consejeria De Salud Y Familias De La Junta De Andalucia

- **Web Link**: http://www.aller-screening.upm.es/index.php/en/homee

Validación experimental de un dispositivo POINT-OF-CARE para la evaluación de inhibidores del sistema inmunológico mediante técnicas alternativas estándar

PI: Miguel Holgado

Funding Agency: Comunidad de Madrid-Innovation check

Period: 16/11/2017-16/05/2018

- **Web link**: http://biod.es/Project/inhibidores_sistema-2-2/

AENOR-2014/0993/PIV/03 IBEC

PI: Maria Fe Laguna

Funding Agency: AENOR

Ciencia para todos desde el Centro de Tecnología Biomédica de la Universidad Politécnica de Madrid

PI: Maria Fe Laguna

Funding Agency: FECYT

Period: 01/01/2018-31/12/2018

HERON: Transductores avanzados, biochips y plataformas de lectura para biosensores de alto rendimiento, detección de líquidos y monitorización de células. TEC2017-84846-R

PI: Miguel Holgado

Funding Agency: Ministerio de Economía y Competitividad

Budget: 212.960€

Period: 01/01/2018-31/12/2020

E. PUBLICATIONS

1. Aparicio, F. J., Alcaire, M., González-Elipe, A. R., Barranco, A., Holgado, M., Casquel, R., et al. (2016). Dye-based photonic sensing systems. *Sensors and Actuators B: Chemical, 228*, 649-657.
2. Canalejas-Tejero, V., Hernández, A. L., Casquel, R., Quintero, S. A., Laguna, M. F., & Holgado, M. (2018). Fabrication of Si3N4/SiO2 tiered resonant nanopillars with nickel caps arrays: Application for optochemical sensing. *Optical Materials Express, 8*(4), 1082-1090.
3. Canalejas-Tejero, V., López, A., Casquel, R., Holgado, M., & Barrios, C. A. (2016). Sensitive metal layer-assisted guided-mode resonance SU8 nanopillar array for label-free optical biosensing. *Sensors and Actuators B: Chemical, 226*, 204-210.
4. Cornago, I., Hernández, A. L., Casquel, R., Holgado, M., Laguna, M. F., Sanza, F. J., et al. (2016). Bulk sensing performance comparison between silicon dioxide and resonant high aspect ratio nanopillars arrays fabricated by means of interference lithography. *Optical Materials Express, 6*(7), 2264-2272.
5. Espinosa, R. L., Laguna, M. F., Fernández, F., Santamaria, B., Sanza, F. J., Maigler, M. V., et al. (2018). A proof-of-concept of label-free biosensing system for food allergy diagnostics in biophotonic sensing cells: Performance comparison with immunoCAP. *Sensors (Switzerland), 18*(8)
6. Fernández, F., Ciaurriz, P., Cornago, I., Casquel, R., Hernandez, A. L., Sanza, F. J., et al. (2017). Optical sensor based on periodic array of resonant nanopillars for real time monitoring. *Sensors and Actuators B: Chemical, 244*, 323-326. doi:https://doi.org/10.1016/j.snb.2016.12.140
7. Hernández, A. L., Casquel, R., Holgado, M., Cornago, I., Fernández, F., Ciaurriz, P., et al. (2016). Resonant nanopillars arrays for label-free biosensing. *Optics Letters, 41*(23), 5430-5433.
8. Hernández, A. L., Casquel, R., Holgado, M., Cornago, I., Fernández, F., Ciaurriz, P., et al. (2018). How the surrounding environment affects the biosensing performance of resonant nanopillars arrays: Under dry conditions or immersed in fluid. *Sensors and Actuators, B: Chemical, 259*, 956-962.
9. Holgado, M., Maigler, M. V., Santamaría, B., Hernandez, A. L., Lavín, A., Laguna, M. F., et al. (2016). Towards reliable optical label-free point-of-care (PoC) biosensing devices. *Sensors and Actuators B: Chemical, 236*, 765-772.
10. Lavin, A., de Vicente, J., Holgado, M., Laguna, M. F., Casquel, R., Santamaria, B., et al. (2018). On the determination of uncertainty and limit of detection in label-free biosensors. *Sensors, 18*(7), 2038.
11. López-Santos, M., Alvarez, R., Palmero, A., Borrás, A., Casquel, D. C., Holgado, M., et al. (2017). Micron-scale wedge thin films prepared by plasma enhanced chemical vapor deposition. *Plasma Processes and Polymers, 14*(12), 1700043.
12. Santamaría, B., Laguna, M. F., López-Romero, D., Hernandez, A. L., Sanza, F. J., Lavin, A., et al. (2017). Development towards compact nitrocellulose-based interferometric biochips for dry eye MMP9 label-free in-situ diagnosis. *Sensors (Basel, Switzerland), 17*(5), 1158.

Personal Health Systems (UPM)

PRESENTATION/INTRODUCTION

Personal Health Systems (PHS) is a research and innovation group devoted to the design, development and evaluation of services and applications based on Information and Communication Technologies in order to create and promote new ideas, methods and technological solutions in every aspect of the value chain organization. The group develops methods and technological solutions in the areas of:

- Personalised health services
- Active and Healthy Aging
- Accessibility
- Smart cities
- Internet of Things

Within these areas of work, the collaboration with the CTB is established through the Gamification Lab that aims at integrating game mechanism, dynamics and data measurement, and modelling transferred from traditional digital games to support different sectors of the society such as health, culture and education.

Through these developments, this area attempts to take advantage of the opportunities and the potential of digital games to approach social innovation in the above-mentioned sectors. The final objective will be to stimulate the escalation cross-transference of digital gaming technology to ensure affordability and financial sustainability of new or enhanced services as well as future educational, health and culture approaches.

A. MEMBERS

PI: Mª Teresa Arredondo Waldmeyer

Senior researchers: Mª Fernanda Cabrera Umpiérrez

Post-doctoral Fellows: Giuseppe Fico, Alessio Fioravantti, Juan Bautista Montalvá Colomer, Manuel Ottaviano, Cecilia Vera Muñoz

B. RESEARCH LINES

Gamification in education

Short description:

In the context of education, the research currently under development is in the area of inclusive education.

The group is working in the use of non-leisure gaming toolkits by children to develop and play digital games on mobile devices-with the aim of enhancing their abilities across all academic subjects, as well as their logical reasoning, creativity and social skills.

By using the Pocket Code programming environment the technique used for the learning empowerment is based on the idea of a "playful learning". To learn with play and fun it's much more easy and spontaneous. This fact is especially true for children where the findings are about the stimulation of their intrinsic motivation. This idea is the pillar of the concept of "Playful learning".

Gamification in health

Short description:

In the context of this research line, the group is currently working in the recognition and treatment of Parkinson's Disease (PD).

Different devices and wearable sensors are being tested to carry out the continuous monitoring, as well as to enable the performance of phone-based test and delivery of education and training using games.

Several algorithms are being designed and developed for the automatic detection and assessment of some of the PD motor symptoms, particularly gait degradation and bradykinesia, as well as the development of a mobile tool for the assessment of the cognitive capabilities of PD patients through serious gaming techniques.

C. FACILITIES AND TECHNIQUES

Facilities/Infrastructures

As part of its infrastructure, PHS owns the "Experimental Centre of Ambient Intelligence Services and Applications -Smart House Living Lab Madrid", located at the School of Telecommunication Engineering of UPM, that is part of the European Network of Living labs (ENOLL) and member of the Lab Research Network of Madrid Community. This is an accessible and age-friendly infrastructure that is being used to train users and test, evaluate and assess applications and services, and to test the performance of new technological developments (laboratory perspective) in an environment that can recreate different scenarios, a smart home, a classroom, a workplace, etc.

With an area of over 150 m^2, it features modern control technology, monitoring and regulation of the environment, and a 3D immersive room that includes the virtual reality infrastructure. (See https://www.lst.tfo.upm.es/).

D. RESEARCH PROJECTS

No One Left Behind (645215)

PI: Mª Teresa Arredondo Waldmeyer

Funding Agency: EC-H200

Budget: 440.687€

Period: 01/01/2015-30/06/2017

Other institutions participating: Gamecity Ltd., Hochschule Der Medien, Technische Universitaet Graz, The Nottingham Trent University, Zed Worldwide S.A.

■ **Web link:** http://no1leftbehind.eu/

Mhealth platform for Parkinson's disease management (PD MANAGER-643706)

PI: Mª Teresa Arredondo Waldmeyer

Funding Agency: EC-H200

Budget: 440.687€

Period: 01/01/2015-31/03/2018

Other institutions participating: Institut Jozef Stefan, Biotronics 3d Limited, Fondazione Ospedale San Camillo, Fondazione Santa Lucia, Globo Software-Mobile Telephony Services Anonymous Company, Moticon, Panepistimio Ioanninon, Synthema S.R.L, University Of Surrey, Univerzitetni Rehabilitacijski Institut Republike Slovenije-Soca

■ **Web link:** http://www.parkinson-manager.eu/

Independent living support functions for the elderly (IN LIFE-643442)

PI: Mª Fernanda Cabrera Umpiérrez

Funding Agency: EC-H200

Budget: 200.687€

Period: 01/02/2015-31/01/2018

Other institutions participating: Ethniko Kentro Erevnas Kai Technologikis Anaptyxis, Vastra Gotalands Lans Landsting, Linkopings Universitet, Fundacion Instituto Gerontologico Matia-Ingema, Consorcio Regional De Transportes De Madrid, The University Of Sheffield, Roessingh Research And Development Bv, Dublin City University, Internationales Informationszentrum Fur Terminologie, Institut Jozef Stefan, Mls Pliroforiki Ae, Open Evidence, Stichting Trivium Meulenbelt Groep, Virtualware 2007 Sa, Geniko Nosokomeio Thessalonikis G.Papanikolaou, Verein Zur Foerderung Assistierender Technologie In Europa, Byte Computer Anonymi Viomichanikiemporiki Etaireia, Sheffcare Limited, Doktor 24 Zdravstvene In Telemedicinske Storitve Doo

■ **Web link:** http://inlife-project.eu/

ACTIVE HANDS

PI: Mª Teresa Arredondo Waldmeyer

Funding Agency: EIT HEALTH

Budget: 746.499€

Period: 01/01/2016-31/12/2016

Other institutions participating: Commissariat A L Energie Atomique Et Aux Energies Alternatives

LIVING LABS & TEST BEDS 2016

PI: Mª Teresa Arredondo Waldmeyer

Funding Agency: EIT HEALTH

Period: 01/01/2016-31/12/2016

Other institutions participating: Delf University of Technology-TU Delft, IMEC-Interuniversity Microelectronics Centre, LEITAT, MADoPA, RISE Research Institutes of Sweden

■ **Web link:** https://eithealth.eu/project/living-labs-and-test-beds/

Neurobehavioural predictive and personalised modelling of depressive symptoms during primary somatic diseases with ICT-enabled self-management procedures (NEVER MIND-689691)

PI: Mª Teresa Arredondo Waldmeyer

Funding Agency: EC-H2020

Budget: 501.878€

Period: 01/01/2016-30/06/2020

Other institutions participating: Universita Di Pisa, Associação Para Investigação E Desenvolvimento Da Faculdade De Medicina, Gaia Ag, Inventya Ltd, Karolinska Institutet, Smartex S.R.L., Universita Degli Studi Di Torino, University Of Essex

■ **Web link:** http://www.nevermindproject.eu/

MINI Q

PI: Mª Teresa Arredondo Waldmeyer

Funding Agency: EIT HEALTH

Period: 01/01/2016-31/12/2016

Other institutions participating: Karolinska Institutet, Servicio Madrileño De Salud, Keele University West Midlands Academic Health Science Network, Genesis Biomed

■ **Web link:** https://eithealth.eu/project/miniq/

Big data and models for personalized head and neck cancer decision support (BD2Decide-689715)

PI: Mª Teresa Arredondo Waldmeyer

Funding Agency: EC-H200

Budget: 415.000€

Period: 01/01/2106-30/09/2019

Other institutions participating: Azienda Ospedaliero-Universitaria Di Parma, All-In-Image Ltd, Athens Technology Center Anonymi Biomichaniki Emporiki Kai Techniki Etaireia Efarmogon Ypsilis Technologias, Fondazione Irccs Istituto Nazionale Dei Tumori, Fraunhofer Gesellschaft Zur Foerderung Der Angewandten Forschung E.V., Heinrich-Heine-Universitaet Duesseldorf, Multimed Engineers Srl, Politecnico Di Milano, Stichting Maastricht Radiation Oncology Maastro Clinic, Stichting Vu , Stichting Vumc, Universita Degli Studi Di Parma

■ **Web link:** http://www.bd2decide.eu/

Participatory urban living for sustainable environments (PULSE-727816)

PI: Mª Teresa Arredondo Waldmeyer

Funding Agency: EC-H200

Budget: 609.506€

Period: 01/11/2106-30/04/2020

Other institutions participating: Asus Cloud Corporation, Agencia De Salut Publica De Barcelona, Birmingham City Council, Centre National De La Recherche Scientifique Cnrs, Connected Health Alliance Cic, Future Cities Lab Ltd, Genegis Gi Srl, Institut Mines-Telecom, Preduzece Za Informacione Tehnologije I Elektronsko Trgovanje Belit Doo, The New York Academy Of Medicine, Universita Degli Studi Di Padova, Universita Degli Studi Di Pavia

■ **Web link:** http://www.project-pulse.eu/

Predictive neural information for proactive actions: From monkey brain to smart house control (Plan4Act-732266)

PI: Mª Teresa Arredondo Waldmeyer

Funding Agency: EC-H2020

Budget: 749.687€

Period: 01/01/2017-31/12/2020

Other institutions participating: Georg-August-Universitat Gottingenstiftung Offentlichen Rechts, Deutsches Primatenzentrum Gmbh, Mysphera Sl, Syddansk Universitet

■ **Web link:** http://plan4act-project.eu/

Activating innovative IOT smart living environments for ageing well (ACTIVAGE-732679)

PI: Mª Teresa Arredondo Waldmeyer

Funding Agency: EC-H200

Budget: 1.450.468€

Period: 01/01/2107-30/06/2020

Other institutions participating: Medtronic Iberica Sa, Stmicroelectronics Grenoble Sas, Televes Sa, Mysphera Sl, Fraunhofer Gesellschaft Zur Foerderung

Der Angewandten Forschung E.V., Commissariat A L Energie Atomique Et Aux Energies Alternatives, Ethniko Kentro Erevnas Kai Technologikis Anaptyxis, Ibm Research Gmbh, Lepida Scpa, Cup 2000 Scpa, Universitat Politecnica De Valencia, Hop Ubiquitous Sl, National University Of Ireland Galway, Medea Srl, Fundacion Tecnalia Research & Innovation, Centre Expert En Technologies Et Services Pour Le Maintien En Autonomie A Domicile Des Personnes Agees, Fundacion Vodafone Espana, Cruz Roja Espanola, Csem Centre Suisse D'electronique Et De Microtechnique Sa-Recherche Et Developpement, Samsung Electronics (Uk) Limited, Tercera Edad Activa Sl, Fundacion De La Comunitat Valenciana Para La Promocion Estrategica El Desarrollo Y La Innovacion Urbana, Onsiglio Nazionale Delle Ricerche, Azienda Usl Di Parma, Universita Degli Studi Di Parma, Aurora Domus Cooperativa Sociale- Onlus, Wind Tre Spa, Technosens Evolution, Technosens, Departement De L'isere, Inter Mutuelles Assistance, L'institut Du Bien Vieillir Korian, Ajt Wohn- Und Quartierzentrum Weiterstadt Gmbh & Co. Kg, Sageliving Gmbh , Servizo Galego De Saude, Gestio Sociosanitaria Al Mediterrani Sl, Anaptyxiaki Diadimotiki Eteria Psifiakes Polis Kentrikis Elladas Ae Ota (Intermunicipal Development Company Digital Cities Of Central Greece Sa), Gnomon Informatics Sa, Dimos Metamorfoseos, Exypnou Logismikou Kykloforias & Metaforon Ae, Swarco Hellas Systimata Kykloforias Anonymi Etaireia, Dimos Pylaias Chortiati, Institute Of Communication And Computer Systems, Se Innovations Oy, Goodlife Technology Oy, Eseteli Palveluverkko Oy, Turun Ammattikorkeakoulu Oy, Leeds City Council, University Of Surrey, Iniciativa Social Integral Per Al Benestar Slu

■ **Web link:** http://activageproject.eu/

LIVING LABS & TEST BEDS 2017

PI: Mª Teresa Arredondo Waldmeyer

Funding Agency: EIT HEALTH

Period: 01/01/2017-31/12/2017

Other institutions participating: Delf University Of Technology-Tu Delft, Imec-Interuniversity Microelectronics Centre, Leitat, Madopa, Rise Research Institutes Of Sweden

■ **Web link:** https://eithealth.eu/project/living-labs-and-test-beds/

LIVING LABS & TEST BEDS 2018

PI: Mª Teresa Arredondo Waldmeyer

Funding Agency: EIT HEALTH

Period: 01/01/2018-31/12/2018

Other institutions participating: Delf University Of Technology-Tu Delft, Imec-Interuniversity Microelectronics Centre, Leitat, Madopa, Rise Research Institutes Of Sweden

■ **Web link:** https://eithealth.eu/project/living-labs-and-test-beds/

Smart childhood obesity caring solution using IOT potential (OCARIOT-777082)

PI: Mª Teresa Arredondo Waldmeyer

Funding Agency: EC-H2020

Budget: 285.625€

Period: 01/11/2017-31/10/2020

Other institutions participating: Fundacion Tecnalia Research & Innovation, Ethniko Kentro Erevnas Kai Technologikis Anaptyxis, Unparallel Innovation Lda., Colegio Virgen De Europa, Servicio Madrileno De Salud, Ellinogermaniki Agogi Scholi Panagea Savva Ae

■ **Web link:** https://www.ocariot.eu/

Home-use health tool for Parkinson's disease patients (HOOP 2.0)

PI: Mª Teresa Arredondo Waldmeyer

Funding Agency: EIT HEALTH

Period: 01/01/2018-31/12/2018

Other institutions participating: Friedrich-Alexander-Universität Erlangen-Nürnberg, Genesis Biomed, Madopa, Rise Research Institutes Of Sweden.

■ **Web link:** https://eithealth.eu/project/hoop-2-0/

E. PUBLICATIONS

1. Bousquet, J., Bewick, M., Cano, A., Eklund, P., Fico, G., Goswami, N., de Oliveira-Alves, B. (2017). Building bridges for innovation in ageing: Synergies between action groups of the EIP on AHA. Journal of Nutrition, Health and Aging, 21(1), 92-104. doi:10.1007/s12603-016-0803-1

2. Dagliati, A., Sacchi, L., Tibollo, V., Cogni, G., Teliti, M., Martinez-Millana, A., Bellazzi, R. (2018). A dashboard-based system for supporting diabetes care. Journal of the American Medical Informatics Association, 25(5), 538-547. doi:10.1093/jamia/ocx159

3. Fabris, C., Facchinetti, A., Fico, G., Sambo, F., Arredondo, M. T., & Cobelli, C. (2016). Parsimonious description of glucose variability in type 2 diabetes by sparse principal component analysis. Journal of Diabetes Science and Technology, 10(1), 119-124. doi:10.1177/1932296815596173

4. Fico, G., Fioravanti, A., Arredondo, M. T., Gorman, J., Diazzi, C., Arcuri, G., Pirini, G. (2016). Integration of personalized healthcare pathways in an ICT platform for diabetes managements: A small-scale exploratory study. IEEE Journal of Biomedical and Health Informatics, 20(1), 29-38. doi:10.1109/JBHI.2014.2367863

5. García-Betances, R. I., Cabrera-Umpiérrez, M. F., & Arredondo, M. T. (2017). Computerized neurocognitive interventions in the context of the brain training controversy. Reviews in the Neurosciences, 29(1), 55-69. doi:10.1515/revneuro-2017-0031

6. García-Betances, R. I., Cabrera-Umpiérrez, M. F., Ottaviano, M., Pastorino, M., & Arredondo, M. T. (2016). Parametric cognitive modeling of information and computer technology usage by people with aging-and disability-derived functional impairments. Sensors (Switzerland), 16(2) doi:10.3390/s16020266

7. Gemou, M., Montalva Colomer, J. B., Cabrera-Umpierrez, M. F., de los Rios, S., Arredondo, M. T., & Bekiaris, E. (2016). Validation of toolkits for developing third-generation android accessible mobile applications. Universal Access in the Information Society, 15(1), 101-127. doi:10.1007/s10209-014-0377-9

8. Tsiouris, K. M., Gatsios, D., Rigas, G., Miljkovic, D., Seljak, B. K., Bohanec, M., Fotiadis, D. I. (2017). PD-manager: An mHealth platform for parkinson's disease patient management. Healthcare Technology Letters, 4(3), 102-108. doi:10.1049/htl.2017.0007

Surgical Training and Image Guided Surgery (UPM)

PRESENTATION/INTRODUCTION

The goal of the Surgical Training and Image Guided Surgery Lab is the development of new techniques, methods and algorithms for the acquisition, processing and analysis of medical images and laparoscopic videos for MIS training, assessment and image guided surgical applications.

This work is carried out in an interdisciplinary fashion with strategic partners across Europe, such as the Jesús Usón Minimally Invasive Surgery Centre (Cáceres, Spain), SINTEF (Trondheim, Norway), the Delft University of Technology (Delft, The Netherlands), Leiden University Medical Center (Leiden, The Netherlands) or the Spanish National Center for Cardiovascular Research (Madrid, Spain).

A. MEMBERS

PI: Patricia Sánchez

Senior researchers: Enrique J. Gómez, Ignacio Oropesa, Borja Rodríguez, Manuel Rodríguez, Daniel Camba

PhD students: Alexander Peter Seiffert, Carmen Guzmán

B. RESEARCH LINES

Medical image processing

Short description:

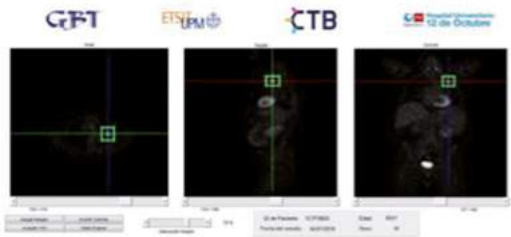
Medical image-based developments for neurorehabilitation, vascular interventions or intraoperative imaging, amongst other applications:

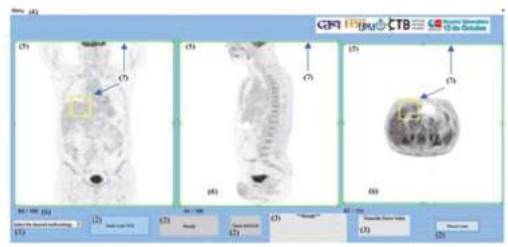
1. Neuroimaging in neurorehabilitation solutions offers an algorithm for the automatic detection of injured brain structures based on T1w MRI studies. The algorithm segments the brain structures of the patient by means of a novel parametric landmark-based non-rigid registration applied to a chosen brain atlas. The proposed registration method uses not only intensity-based information but also spatial information in order to increase the robustness of the method.

2. Vascular interventions, such as aortic catheterization. Finite element analysis (FEA) can be used to create patient-specific simulations that will offer extra information about the patient specific conditions, including wall stresses and stretches, blood flow or even rupture risk. The proposed solution covers from automatic segmentation of the vessel wall and the intraluminal thrombus from MRI studies, to methods for developing patient-specific hexahedral meshes.
3. Evaluation of pancreatic neoplasia. Laparoscopic ultrasound (LUS) has shown to improve the results from the preoperative CT, but requires an extra specialization. Current research is oriented to image analysis of LUS pancreatic images to develop a clinical decision support system for pancreatic cancer staging.
4. Neuroimaging in neurodegenerative diseases. Extracellular amyloid plaques in the brain are closely linked to cognitive decline and Alzheimer's disease. The dual-phase acquisition of amyloid PET images (early-phase and late "standard" images) can yield information regarding the neurodegeneration as seen on metabolism images (FDG-PET), as well as information about the presence and/or extension of amyloid plaques. A quantitative analysis of early-phase amyloid PET images is performed based on SUVR parameters. Moreover, texture-based analysis of late amyloid PET images compared to the extraction of SUVR parameters is evaluated as an alternative method of quantitative analysis.
5. Treatment response in Hodgkin's and non-Hodgkin's lymphoma. The evaluation of the response to chemotherapy is based mainly on the visual examination of baseline and interim FDG-PET (after 2 cycles of chemotherapy) images using the Deauville criteria. Quantitative analysis can standardize the assessment between different readers and can play an important role in the classification of borderline cases.
6. Evaluation of lung nodules. Current classification algorithms that differentiate malignant from benign pulmonary nodules are based on the patient's clinical data and CT features. The addition of features extracted from FDG-PET images could increase the predictive accuracy. Thus, SUV-based and texture-based features are proposed to be evaluated for their discriminative abilities.
7. Cardiotoxicity. Chemotherapy can have negative effects on the cardiovascular system. A retrospective, texture-based analysis of FDG-PET images of patients affected by cardiotoxicity could yield risk factors of alterations in the cardiovascular system due to chemotherapy. Consequently, chemotherapists would be able to, based on the image analysis, change the proposed type of chemotherapy at an early stage.

Main results:

Image processing algorithms and workstations. Some results are shown in the following figures:





Medical video analysis

Short description:

Laparoscopic video-based developments: Image processing of the laparoscopic videos is performed for detection and tracking of surgical instruments, laparoscopic optic, trocars and/or organs present in the surgical scene. Based on that, a 3D reconstruction of the surgical scene is performed using techniques like shape-from-motion and shape-from-shading.

Image and Video Guided Surgery: The main goal of this research area is to develop new surgical navigation systems in order to guide surgeons during the intervention, providing them with extra information enhancing orientation, accuracy and patient safety. Three main fields of applications are being addressing in this lab, according to three main clinical domains:

1. Image-guided catheterization. The main goal is to develop an augmented reality navigation platform that closes the existing gap between the reality of the catheter inside the cardiovascular system and the manner in which this reality is presented and made accessible to the interventionist. This can be further segmented into the following objectives:

- Robust segmentation independent of the anatomical source image quality.
- Model construction and parameterisation of the vascular anatomy. Automatic detection of risk zones within the aortic wall.
- Design and development of an advanced graphical interface for interventional guidance.

2. Image and video guided liver interventions. Research is focused on the improvement of the surgical eligibility and prognosis for liver resection by the creation of innovative surgical navigation systems. The motivation is the efficient introduction and use in the operating room of the rich anatomical information available preoperatively from medical imaging studies for the interventional guidance. We call this new navigation paradigm image and video guided surgery (IVGS). Specific goals of this research line are:
   - To exploit the endoscopic video´s information and biomechanical organ modelling.
   - To track all elements within the surgical scenario (organs-deformable biomechanical models), tools (3D tracking) and endoscope (determined by the trocars' relative position).
   - To develop and evaluate an IGS navigation prototype.
3. Pancreatic cancer surgical navigator. The main objective of this research is to make a break-through in pancreatic cancer surgical interventions and patient safety through the development of an intelligent surgical navigator incorporating a Clinical Decision Support System (CDSS), mainly based on the use of information from the endoscopic video and laparoscopic ultrasound images. The research thus draws from the IVGS paradigm proposed in the previous case study and expands it with the inclusion of a CDSS.

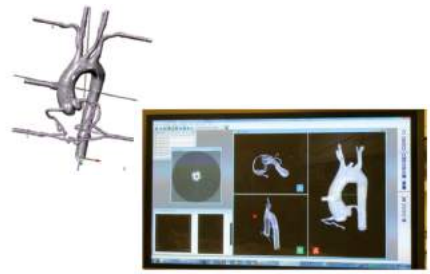
Robotic assisted surgeries: The main objective is to develop new robotic systems to help surgeons during surgical procedures. Ergonomics, control and interaction are three of the main focus of this area.

Main results:

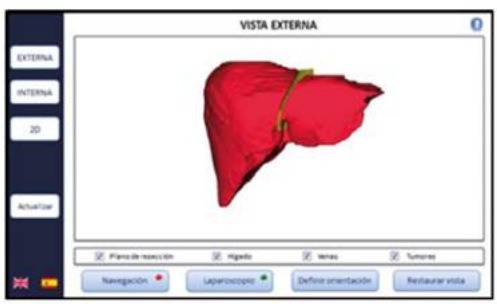
EVA tracking system: EVA is a video-based solution to track laparoscopic instruments inside box trainers. Motion analysis on the trajectories recorded during task performance allows calculating metrics that can be used to assess the competencies of surgeons. In this sense, validation studies have shown that the measurements obtained using the system can be used to differentiate between expert and novel surgeons. Currently, the EVA Tracking System is also adapted to be used in virtual learning scenarios, such as simulators and serious games.

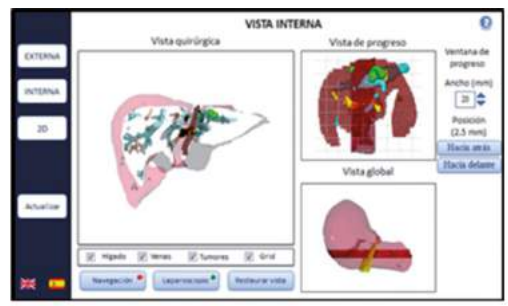
Surgical navigation systems: These navigation systems include:

1. Cardiovascular catheterization procedures. To this end, it is important (1) to develop an advanced geometrical, mechanical and physiological model of the patient's circulatory system; (2) to develop a virtual reality environment that helps the interventionist, by showing him relevant information at any given time during the procedure.



2. Image and video-guided liver resections. Research is focused on the improvement of the surgical eligibility and prognosis for liver resection by the creation of innovative surgical navigation systems. The motivation is the efficient introduction and use in the operating room of the rich anatomical information available preoperatively from medical imaging studies for the interventional guidance.





Technology enhanced learning for minimally invasive surgery

Short description:

Training of minimally invasive surgical (MIS) skills is a serious endeavour comprising technical (psychomotor) and nontechnical (including cognitive, judgement and communication) abilities. A common trend in recent decades has been the introduction of Technology Enhanced Learning (TEL) to support MIS learning. The challenge here is how to integrate TEL into these novel structured learning processes, aligning them to the learning objectives required for new surgeons in order to supplement and enhance the training processes. This is the goal that we pursue within this line of work. More specifically, research areas can be broken down into:

- TEL for non-technical skills learning. Our goal is to develop new pedagogically-supported online solutions for ubiquitous learning of MIS non-technical skills. Previously existing solutions had focused on acting as

video repositories whose pedagogical foundations are not sufficiently detailed or non-existent, making comparison between and assessment of them complicated, if not impossible. Starting with national project TELMA and consolidating at a European level with project MISTELA and EASIER, our research has led to the development of a pedagogically-supported TEL solution centred on the didactic exploitation of existing laparoscopic video repositories.

- TEL for technical skills training and assessment. Our goal is to develop and integrate innovative simulation technologies for MIS technical skills training. In the past, we have designed and developed virtual reality simulators for laparoscopic training and objective skills assessment, as well as multimedia didactic tools for surgical cognitive skills transfer.

This research line also explores new ways to enhance and improve surgical accreditation curricula, with the search of new objective metrics for evaluation and new tools for their acquisition. The main goal is to design solutions for psychomotor skills assessment both in laboratory settings (box trainer, VR simulators, serious games) and in the OR.

Main results:

AMELIE tool: The authoring tool, AMELIE, provides the means to edit and augment laparoscopic videos in order to enhance their didactic value. It allows creating dynamic didactic layers that can be turned on/off during playback depending on the training needs of the learner. Layers include text, audio, segmentation and tracking of anatomical structures and interactive assessment exercises. Additionally, the tool supports clipping and documentation of the video.

Innovative environments for medical professional: The main achievement in this area is the development of a VR simulator (MIS-SIM) that allows users to create and share with the community virtual tasks personalized to the training needs of medical learners. This research area includes training activities to (1) teach mentors how to harness the potential of our environment MIS-SIM to create effective learning scenarios; (2) teach residents medical skills in MIS-SIM-based courses; and (3) empower medical professionals on designing learning technologies in the hospital.

New interaction devices: Current research focuses on the validation of new interaction devices for surgical training in simulation settings (HTC VR glasses, Leap Motion, Eye Tracking), as well as on the development of augmented reality applications.

Analytic applications for assessment support: Using machine learning approaches, we train models based on motion data obtained from the performance of training tasks that are able to predict the skill of a surgeon based on how he/she fares on the simulator. Among other things, our experiments have led us to conclude that motion analysis is a good predictor of surgical expertise.

C. FACILITIES AND TECHNIQUES

Facilities/Infrastructures

Intellectual properties

Intellectual properties regarding virtual reality simulator, endoscopic video analysis workstation, virtual reality platform for aortic catheterization, 3D registration and medical image fusion workstation, AMELIE Authoring Tool, EVA Tracking System, MIS assessment tasks (x3), surgical navigator.

Commercial systems

Commercial systems available in our lab are the following: Microsoft Kinect (x3), Eye Tracking devices (x2), Leap Motion, 3D position electromagnetic sensors, Immersion haptics system, SIMULAP IC-05 box trainer.

Image data bank

Image data bank including laparoscopic videos (simulator, porcine models), liver CT studies (porcine models), pancreas CT, MR, LUS studies (porcine model) among others.

Techniques

- Medical image segmentation
- Automatic landmark detection
- Non-rigid image registration
- Classification of anatomical structures
- Quantification of volume variations
- Video-based tracking
- Video-based 3D reconstruction
- Visualization technologies
- System integration
- Motion analysis
- Supervised classification of surgical performance

D. RESEARCH PROJECTS

ITHOS: Cirugía Robótica para el Tratamiento de Cálculos Renales RTC-2016-5338-1

PI: Patricia Sánchez, Enrique J. Gómez

Funding Agency: Ministerio de Economía y Competitividad

Budget: 143.359,00€

Period: 01/04/2016-31/12/2018

Other institutions participating: Fundacion Centro de Tecnologias De Interaccion Visual y Comunicaciones, Vicomtech, Robotics Special Applications S.L.

EASIER: European Knowledge Alliance for innovative education of Surgical and Interventional skills. 588404-EPP-1-2017-1-ES-EPPKA2-KA

PI: Enrique J. Gómez

Funding Agency: Cooperation for innovation and the exchange of good practices. Erasmus +

Budget: 185.194,00€.

Period: 01/11/2017-31/10/2020

Other institutions participating: Fundación Centro de Cirugía de Mínima Invasión Jesús Usón (CCMIJU), Delft University of Technology (TUDELFT), MediShield BV (MEDISHIELD), SIMENDO (SIMENDO), Fundatia MEDIS (MEDIS), Department of Surgical Research and Techniques, Semmelweiss University (DSRT-SU), Cyprus Research and Innovation Centre (CYRIC), University of Cyprus (UCY)

- **Web link:** http://www.easier-project.eu/

MIS SIM: A new virtual reality learning paradigm for medical education (2018). 18638

PI: Patricia Sánchez

Funding Agency: EIT Health

Budget: 80.542,00€

Period: 01/05/2018-31/12/2018

Other institutions participating: LUMC, TU Delft, Semmelweis

- **Web link:** https://connections.eithealth.eu/en_US/web/internet-eithealth/innovative-education-mis-sim

STAG: Multiparametric Clinical Decision Support System for STAGing in Pancreatic Carcinoma

PI: Patricia Sánchez González, Enrique J. Gómez

Funding Agency: Centro de Investigación Biomédica en Red en el área temática de Bioingeniería, Biomateriales y Nanomedicina

Period: 2014-2016

Other institutions participating: Hospital Clínico San Carlos

E. PUBLICATIONS

1. Oropesa I., Pérez Escamirosa F, Sánchez-Margallo J. A., Enciso S., Rodríguez-Vila B., Minor Martínez A., Sánchez-Margallo F. M., Gómez E.J., Sánchez-González P. (2018). Interpretation of motion analysis of laparoscopic instruments based on principal component analysis in box trainer settings. Surgical Endoscopy(1-12)

2. Pérez-Escamirosa F., Oropesa I., Sánchez-González P., Tapia-Jurado J., Ruiz-Lizarraga J., Minor-Martínez A. (2018). Orthogonal cameras system for tracking of laparoscopic instruments in training environments. Cirugía y cirujanos:86(548-555)

3. Villán-Villán M. A., Pérez-Rodríguez R., Sánchez-González P., Opisso E, Tormos J. M., Medina J, Gómez E.J. (2018). Objective motor assessment for personalized rehabilitation of upper extremity in brain injury patients. NeuroRehabilitation, 42(4):429-439

4. Rodríguez-Vila B., Sánchez-González P., Oropesa I., Gómez E.J., Pierce D. M. (2017). Automated hexahedral meshing of knee cartilage structures-application to data from the osteoarthritis initiative. Computer Methods in Biomechanics and Biomedical Engineering(1-11)

5. Órtega-Morán J. F., Pagador J. B., Sánchez-Peralta L. F., Sánchez-González P., Noguera J., Burgos D., Gómez E.J., Sánchez-Margallo F.M. (2017). Validation of the three web quality dimensions of a minimally invasive surgery e-learning platform. International Journal of Medical Informatics, 107(1-10)

6. Oropesa I., de Jong T. L., Sánchez-González P., Dankelman J., Gómez E.J. (2016). Feasibility of tracking laparoscopic instruments in a box trainer using a leap motion controller. Measurement, 80(115-124)

7. Sánchez-González P., Oropesa I., Rodríguez-Vila B., Viana M., Fernández-Pena A., Arroyo T., Sánchez-Margallo J. A, Moyano J. L., Sánchez-Margallo F. M., Gómez E.J. (2016). Laparoscopic Video and Ultrasounds Image Processing in Minimally Invasive Pancreatic Surgeries. Innovation in Medicine and Healthcare 2016-Smart Innovation, Systems and Technologies, pages 333-343.

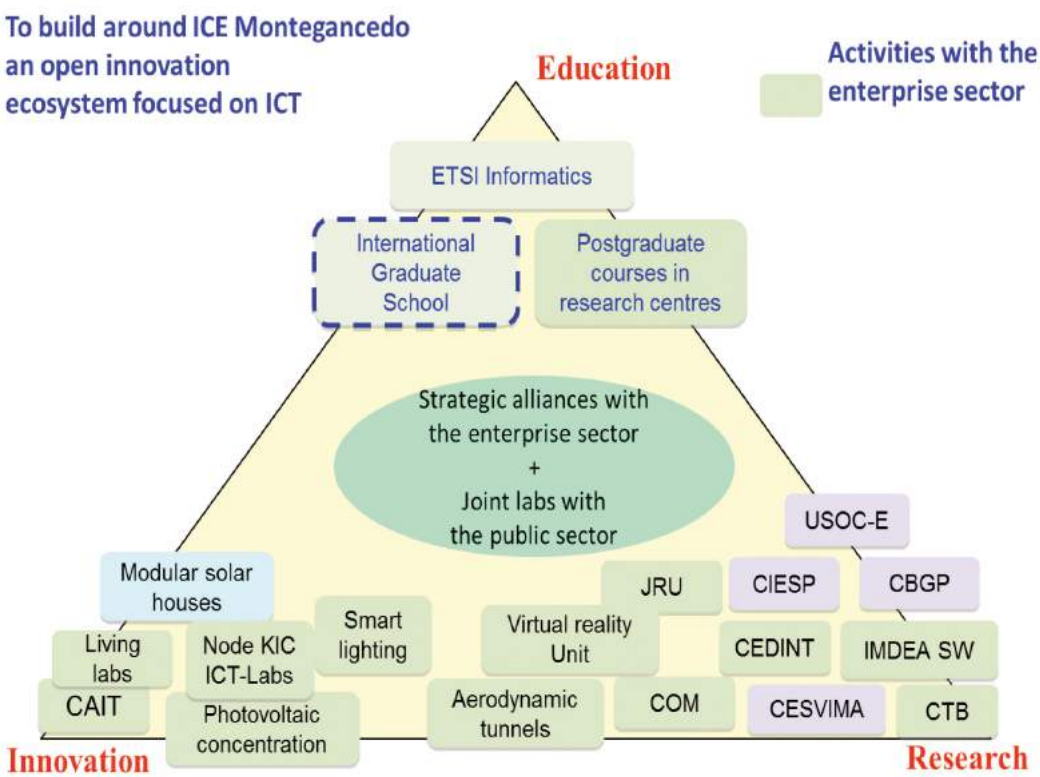
8. Martínez-Moreno J. M., Sánchez-González P., Luna M., Roig T., Tormos J. M., Gómez E.J. (2016). Modelling ecological cognitive rehabilitation therapies for building virtual environments in brain injury Methods of information in medicine, 55(1) (50-59)

4 TECHNOLOGY TRANSFER

Innovation can only happen if research discoveries leave the lab and reach the market and users. Translating discoveries into market-ready products requires effective liaison with industry, as well as an adequate training on business creation and entrepreneurship of the researchers.

CTB Innovation Transfer takes place in the Open Innovation Ecosystem of the Science and Technology Park at Montegancedo Campus of UPM, following the knowledge triangle model of the figure, where CTB integrates with the enterprise sector and the education campus there located.

The technologies that reach appropriate KPI (key performance indicator) are supported to evolve toward products: sensors, devices, diagnostic or therapeutic intervention protocols and guidelines. Most of the tech-transfer and translation processes from the CTB have been done in cooperation with the Centre of Support for Technological Innovation (*CAIT*)-Innovatech at the Montegancedo UPM Campus.



PATENTS

Priority Date: 04/02/09
App. No: 200900310-PCT/ES2010/070054
Title: Procedimiento de marcaje, encriptación, etiquetado y codificación óptica
Licensing Status: Under negotiation

Priority Date: 02/07/09
App. No: 200901528
Title: Procedimiento de detección de nanopartículas magnéticas mediante magnetoencefalografía
Licensing Status: Under negotiation

Priority Date: 29/07/09
App. No: P200802565
Title: Sistema de detección óptica para bio-ensayos de alta sensibilidad sin marcado
Licensing Status: Under negotiation

Priority Date: 01/10/09
App. No: 200930776
Title: Fantoma de sangre humana
Licensing Status: Under negotiation

Priority Date: 10/02/10
App. No: 201030183-PCT/ES2011/000025
Title: Portable digital transducer device that is programmable, has high discrimination at low frequency and low intensity
Licensing Status: Licensed to PNEUMA RESEARCH SL

Priority Date: 18/03/10
App. No: P201030183
Title: Transductor portátil digital programable de campos EMF pulsantes APCM-01 para aplicaciones biomédicas
Licensing Status: Under negotiation

Priority Date: 05/08/10
App. No: 201031221
Title: Dispositivo y metodo para monitorizacion de la ingesta
Licensing Status: Under negotiation

Priority Date: 29/12/10
App. No: 201001641
Title: Antena para monitorización del campo electromagnético ambiental en tiempo real
Licensing Status: Under negotiation

Priority Date: 27/06/11
App. No: 201131069-PCT/ES2012/000137
Title: Método y sistema para la estimación de parámetros fisiológicos de la fonación
Licensing Status: Licensed to GLOTTEX VAS, BIOMETROSOFT

Priority Date: 19/07/11
App. No: 201131226
Title: Dispositivo ocular
Licensing Status: Under negotiation

Priority Date: 28/02/12
App. No: P201230297
Title: Dispositivo portable para registrar niveles de radiación electomagnética
Licensing Status: Under negotiation

Priority Date: 27/07/12
App. No: 12126586
Title: Dispositivo transductor digital portátil programable con alta discriminación en baja frecuencia y de baja intensidad
Licensing Status: Under negotiation

Priority Date: 31/08/12
App. No: P8362EP00
Title: Interferometric detection method
Licensing Status: Under negotiation

Priority Date: 01/02/13
App. No: 201330114
Title: Procedimiento de obtención de una enzima inmovilizada en un soporte renovable derivado de un residuo agroalimentario
Licensing Status: Under negotiation

Priority Date: 10/05/13
App. No: 2013059719-PCT/EP2013/059719
Title: System and method for locating objects using radio frequency identifiers
Licensing Status: Licensed to TARANTO ESTUDIOS E INVERSIONES, S.L.

Priority Date: 24/06/13
App. No: 201330947
Title: Método de obtención de una estructura de polímero de impronta molecular (MIP)
Licensing Status: Under negotiation

Priority Date: 25/04/14
App. No: 201400342
Title: Procedimiento para adquisición, procesado y visualización de datos adquiridos simultáneamente de imágenes de resonancia magnética y señales electrofisiológicas
Licensing Status: Under negotiation

Priority Date: 19/08/14
App. No: 201431232
Title: Método de reconstrucción con un dispositivo háptico de espinas dendríticas
Licensing Status: Under negotiation

Priority Date: 08/10/15
App. No: 201730337
Title: Dispositivo modular para aislamiento electromagnético
Licensing Status: Under negotiation

Priority Date: 27/10/15
App. No: 201531540
Title: Sensor, aparato y procedimiento para la determinación de la concentración de solutos en disoluciones
Licensing Status: Under negotiation

Priority Date: 18/12/15
App. No: EP15382646.6-PCT/EP2016/081267
Title: Method for producing elongated structures such as fibers from polymer solutions by straining flow spinning
Licensing Status: Licenses to INGENIATRICS S.L.

Priority Date: 22/01/16
App. No: 201630077
Title: Dispositivo terapéutico portátil para el tratamiento de la artritis mediante estimulación magneto-térmica
Licensing Status: Under negotiation

Priority Date: 04/05/16
App. No: 201630575
Title: Procedimiento de estimación del ruido cerebral a través de imágenes ambiguas
Licensing Status: Under negotiation

Priority Date: 13/12/16
App. No: 201631583
Title: Método y sistema electrónico para la asistencia cognitiva integral
Licensing Status: Under negotiation

Priority Date: 24/11/17
App. No: 201731360
Title: Dispositivo para la medida de la velocidad de la marcha
Licensing Status: Under negotiation

Priority Date: 13/03/18
App. No: 201830247
Title: Dispositivo y método de infusión continúa de dosis de insulina con control PID híbrido correctivo y predictivo
Licensing Status: Under negotiation

Priority Date: 27/07/18
App. No: 201830777
Title: Método para obtener puntas sensoras de microscopía de fuerza atómica funcionalizadas mediante silanización por vapor activado, y las puntas obtenidas por dicho método
Licensing Status: Licensed to SILKBIOMED S.L.

SPIN-OFFS AND START-UPS

SILKBIOMED S.L.

Spin-off created to bring novel technological solutions from the field of the research to clinical applications and to medical therapies.

BRAINVESTIGATIONS S.L.

Spin off created to offer scientific-based strategy consultancy

BIOD S.L.

Technology Based Start-up initiative for optical IVD: Micro-nano photonics and bio-photonics, Label-free Biosensing, Point-of-care devices, Lab-on-a-chip, Optical-readers, photonic transducers, advanced optical characterization

BIOMETROSOFT S.L.

Provides software and services for the implantation of solutions using the human voice for medical applications, biometrical and linguistic applications, as well as consulting in forensics and security voice systems.

LBN INNOVATIVE SOLUTIONS S.L.

To translate the intellectual property generated by the Laboratory of Bioinstrumentation and Nanotechnology (LBN). The first product is an objective audiometric system, developed at LBN in collaboration with CIBER-BBN

PNEUMA RESEARCH. S.L.

Developed by the Bioelectromagnetics unit with the goal of placing in the market the biomedical devices developed: low-field magnetic stimulation, personal dosimeters, and measures of environmental electromagnetic field.

NAUTA TECNOMEDICAL RESEARCH.S.L.

Distributes devices low-field magnetic stimulation, personal dosimeters, and measures of environmental electromagnetic field.

OTHER INNOVATION ACTIVITIES

2016

Pedro Gomez Vilda, et al

ICPRS 2016. Best paper award

Pattern Matching of Voice Quality Features from Vocal-Fold Paralysis Patients Treated with Stem-Cell Grafting

Antonio Cobo Sánchez De Rojas

UPM. Biomedical Technology Entrepreneurship and Innovation Lab' 2016

Accelerator and training tool

Cristian Moral Martos, et al

FRONTIERS-UPM. I Edition of the Competition Actúaloop

Journal Advisor

Jorge Cancela

ACTUAUPM. Entrepreneurship Competition

mPark

Giuseppe Fico, Maria Teresa Arredondo Waldmeyer

ISAHP 2016. Most innovative idea

AHP In Ehealth: The Missing Puzzle Between (Users?) Needs Eliciation, Requirements Design and Specification Writing

2017

Jose Manuel Iniesta Chamorro

MINISTERIO DE EDUCACIÓN. XV Certamen Arquímedes de Introducción a la Investigación Científica

Diseño e implementación de arquitectura y módulos de la Plataforma PREDIRCAM 2 y desarrollo de aplicación móvil con conexión a Wearables

Mariano Alberto Garcia Vellisca

ACTUAUPM. Entrepreneurship Competition

Software design for academic and scientific support

Jose Javier Serrano Olmedo, Antonio Cobo Sánchez De Rojas, Nancy Enriqueta Guerrón Paredes

LA RAZÓN. 1st Innovation and Technology Award for Social Innovation

E-Sight

Giuseppe Fico

UPM. Outstanding Doctorate Award 2015/2016

A multidisciplinary reference framework to support innovative design, implementation and assessment of chronic care models

2018

Miguel Holgado Bolaños

UPM. Association of Former Students ETSI Industriales

Ingeniero emprendedor

Beatriz Santamaria Fernandez

UPM. II Edition of the Symposium: "Tell us your PhD thesis in 4 minutes", sesión BIOMEDICINE & MATERIALS

Optical Label-Free diagnosis for Dry Eye Disease

Nancy Enriqueta Guerrón Paredes, Antonio Cobo Sánchez De Rojas, Jose Javier Serrano Olmedo

14th International Conference on Mobile Learning. Outstanding Paper Award

Methodology for building virtual reality mobile applications for blind people on advanced visits to unkown interior spaces

Fernando Maestú Unturbe

FENIN, Fundación Tecnología y Salud. Technology and Health Awards2018

Recognition for the work carried out in the field of cognitive, anatomical and genetic bases of Alzheimer's disease

5 COMMUNICATION & OUTREACH

SCIENTIFIC EVENTS AND SEMINARS

CTB has organized and hosted several scientific events and seminars related to its strategic research objectives:

I Jornadas de Neurocientíficas (12/02/2018)

On the occasion of the Women's and Girl's Day in Science, and with the support and coordination of the Spanish Society of Neuroscience (SENC), the event took place on February 12th at the Center for Biomedical Technology of the Universidad Politécnica de Madrid.

During the event, several women researchers with a consolidated career shared their professional trajectory, as well as the experiences and obstacles encountered during it. In addition, it offered the opportunity to young researchers of our Center to share their current research work. A round table was established in which a moderate debate brought up some topics related to the role of women in science.

The aim of these conferences was to promote the participation of women in science, highlight the difficulties they encounter during their professional career, as well as encourage young researchers to continue with their scientific careers.

Scientific Seminars

2016

B. Luque-UPM

Voz crítica autoorganizada y patrones universales en el habla humana

2017

C. García Herrera- UPM

Comportamiento biomecánico de arterias afectadas por condiciones de falta de oxígeno

S. P. Pujari-Univ. Wageningen

Romantic Surface (funcionalization of biomolecules on surfaces

J. Yang-Univ Tecnológica de Texas

Digital Human Modeling and Simulation for Engineering and Biomechanics

D. Morera- Brainvestigations

Neurociencia aplicada al mundo de la empresa

M. Marín-Padilla-The Geisel School of Medicine at Dartmouth

La morfología de la neurona piramidal durante el desarrollo del cerebro humano. Estudio con el método de Golgi

N. Martín-UCM

Síntesis de nanoestructuras de carbono glicosiladas: inhibidores multivalentes de la infección del virus del Ébola

F. J. Ayala -UCI

Copérnico y Darwin: Dos Grandes Revoluciones del Pensamiento

A. E. Hramov-Saratov State University

Recent research in Russia: Nonlinear dynamics of complex systems, human perception of ambiguous images, epilepsy in WAG\Rij rats, synchronization of cardio-system and brain activity

2018

J.C. del Álamo-UCSD

The mechanics of leukocyte extravasation and subsequent migration through the three-dimensional extracellular matrix

D. Hayn- Austrian Institute of Technology

Predictive Analytics Toolset for Healthcare (PATH)

A. Rising & J. Johansson-Instituto Karolinska

Production of recombinant silk protein and some applications

I. Belinchón-Brainvestigations

Neurociencia aplicada a los recursos humanos de las empresas, lo último del siglo XXI

Lab.Cajal de Circuitos Corticales - CTB & CSIC

Introduction to the study of Cortical Microanatomy

C. Letellier-Normandy University

Assessing the observability of complex networks: a nonlinear theory

OUTREACH

SCIENCE WEEK

2016

Charlas en torno a la memoria humana y las emociones

Dª. Mar Yebra Dr. Stephan Moratti

El microscopio de fuerza atómica: una poderosa herramienta para la biología

Dr. Rafael Daza, Dr. Rodrigo Madurga, Dª. Blanca González

Cómo crear neuronas artificiales

Dr. Alexander Pisarchik, D. Mariano Alberto García-Vellisca

Conoce tu voz, descubre tu mente

Dr. Pedro Gómez Vilda

Conoce el laboratorio de magnetoencefalografía de la UPM

Dª. Noelia Serrano, D. Luis Fernando Antón, Dª. Su Miao Ye Chen, Dª. Ángeles Correas

Visita al Laboratorio Cajal de Circuitos Corticales: Charla sobre las principales líneas y actividades de investigación del Laboratorio y visita a los laboratorios de microscopía óptica y electrónica

Dª. Andrea Santuy, Dra. Isabel Fernaud, Dª. Iulia Diana Furcila, D. Guillermo Aparicio, Dª. Marta Montero, Dª. Marta Turégano

El cerebro y Facebook son primos hermanos

Dr. Javier Martín Buldú

2017

Visita al Laboratorio Cajal de Circuitos Corticales

Andrea Santuy, Guillermo Aparicio, Marta Turégano, Marta Domínguez

Conoce el laboratorio de magnetoencefalografía del CTB-UPM

Noelia Serrano, David López, Federico Ramírez, Isabel Suárez

El microscopio de fuerza atómica: una poderosa herramienta para la biología

Dr. Rafael Daza

Conoce tu voz, descubre tu mente

Dr. Pedro Gómez-Vilda, D. Andrés Gómez

Redes Complejas y Epidemias: ¿por qué Brad Pitt está siempre enfermo?

Dr. Javier Martín Buldú

Ruido del cerebro y detector de mentiras

Dr. Alexander Pisarchik

2018

Visita al Laboratorio Cajal de Circuitos Corticales

Andrea Santuy, Guillermo Aparicio, Marta Turégano, Marta Domínguez

Huella cerebral: Como identificar la personalidad usando datos neurofisiológicos

Dr. Alexander Pisarchik, D. Parth Chholak

El microscopio de fuerza atómica: una poderosa herramienta para la biología

Dr. Rafael Daza

¡Gánale la carrera al Alzheimer!

D. Luis Antón Toro, Dª Jaisalmer de Frutos

Binge learning: consumo de alcohol y cerebro Dª Jaisalmer de Frutos, D. Luis Antón Toro

SpiderMouse: los superpoderes de la seda Paloma Lozano, Rocío Fernández

MEDIA COVERAGE

16/02/2016. Answers to the enigma of spider silk.
Diario La Razón
- http://www.larazon.es/sociedad/medio-ambiente/la-extraordinaria-resistencia-de-la-tela-de-arana-BB11981505#.Ttt1vovOTE3LSri

04/05/2016. To how much electromagnetic radiation do I expose daily?
Diario ABC
- http://www.abc.es/sociedad/abci-cuanta-radiacion-electromagnetica-expongo-cada-201605031350_noticia.html

Agencia de noticias SINC
- http://www.agenciasinc.es/Noticias/Un-dispositivo-de-bolsillo-para-registrar-niveles-de-radiacion-electomagnetica

03/11/2016. Science week in the CTB-2016
RTVE news (from minutes 4:52 and 12:57)
- https://www.rtve.es/alacarta/videos/informativo-de-madrid/informativo-madrid-18-11-16/3806269/

15/11/2016. Cooperation between weak communities, more beneficial than submission to a strong community.
Diario La Vanguardia
- https://www.lavanguardia.com/vida/20161114/411846614435/la-cooperacion-entre-comunidades-debiles-mas-beneficiosa-que-la-sumision-a-una-comunidad-fuerte-segun-un-estudio.html

16/01/2017. An international group of researchers produces artificially a natural fabric stronger than steel.
Diario El País
- https://elpais.com/elpais/2017/01/12/ciencia/1484246686_023038.html

09/03/2017. Prize in the XV University Contest "Archimedes"
- https://www.ciber-bbn.es/noticias/jose-tapia-accesit-en-el-certamen-arquimedes-de-introduccion-a-la-investigacion-cientifica

12/06/2017. Aggregates of nanoparticles to destroy cancer cells.
Ecodiario.es
- https://ecodiario.eleconomista.es/salud/noticias/8423698/06/17/consiguen-destruir-celulas-tumorales-con-agregados-de-nanoparticulas-magneticas.html

Radio 5 (RNE) (29/09/2017)
- https://mediavod-lvlt.rtve.es/resources/TE_SLABJAL/mp3/0/0/1506686083700.mp3

17/07/2017. Anticipating Alzheimer's: What happens in the brain when you start to feel that memory fails?

BioTech-Spain.com

- http://biotech-spain.com/es/articles/adelantndonos-al-alzheimer-qu-pasa-en-el-cerebro-cuando-empiezas-a-sentir-que-falla-la-memoria-/

18/09/2017. Interview with Javier de Felipe in the *journal Quo*

- https://www.quo.es/ciencia/a68153/seleccion-espanola-de-la-ciencia-2017-javier-de-felipe/

https://www.youtube.com/watch?v=dWFrJdt0oh4

19/09/2017. New collaboration agreement of the CTB with the Centro Universitario Los Lagos (Mexico)

Centro Universitario Los Lagos

- http://www.lagos.udg.mx/noticia/firma-de-acuerdo-de-colaboracion-entre-el-culagos-y-el-ctb-de-la-universidad-politecnica-de

20/09/2017. Alzheimer's Disease: genetics and lifestyle. Fundación La Caixa interviews Jaisalmer de Frutos, from the Cognitive Neuroscience Laboratory of the CTB.

Fundación La Caixa

- https://www.becarioslacaixa.net/es/web/guest/noticias/alzheimer-genetica-y-estilo-de-vida-entrevista-a-jaisalmer-de-frutos

26/09/2017. María del Carmen Martín-Buró, finalist of the JotDown Scientific Outreach Contest with the work "Delete only this memory, please".

Jot Down

- https://www.jotdown.es/2017/09/borre-solo-este-recuerdo-por-favor/

27/09/2017. Javier de Felipe, PI of the Laboratory Cajal of Cortical Circuits in

RNE

- https://mediavod-lvlt.rtve.es/resources/TE_OJUPAPA/mp3/0/9/1506155570290.mp3

6/10/2017. Report on Santiago Ramón y Cajal. Interview with Javier de Felipe.

Diario La Vanguardia

- https://www.lavanguardia.com/ciencia/ciencia-cultura/20171006/431828043534/ramon-y-cajal-nobel-alma-artista-ilustraciones.html

30/10/2017. The Laboratory of Optics, Photonics and Biophotonics has developed a cheap and simple technology for the diagnosis of dry eye.

Agencia de noticias SINC

- https://www.agenciasinc.es/Noticias/Una-tecnologia-barata-y-sencilla-para-el-diagnostico-de-ojo-seco

14/02/2018. Interview in *Diario El País* with the CTB Academic Secretariat and researcher Prof. Consuelo Gonzalo and Guiomar Niso on "The Day of women and girls in science"

- https://elpais.com/elpais/2018/02/08/ciencia/1518108051_555486.html

05/03/2018. e-Glance: An electronic look within the reach of blind people.

Revista Autonomía Personal

- https://www.burgosconecta.es/tecnologia/investigacion/eglance-realidad-aumentada-20180308173606-ntrc.html

16/04/2018. Technique allows detecting Alzheimer's Disease years before the first symptoms.

Cadena Ser

- https://cadenaser.com/ser/2018/04/10/ciencia/1523375739_040612.html

(From muinute 46)

- https://play.cadenaser.com/audio/cadenaser_hoyporhoy_20180411_080000_090000/

16/04/2018. Spanish scientists develop a technique to detect Alzheimer's Disease 25 years before the first symptoms.

La Sexta

- https://www.lasexta.com/noticias/ciencia-tecnologia/cientificos-espanoles-desarrollan-una-tecnica-para-detectar-el-alzheimer-25-anos-antes-de-los-primero-sintomas_201804125acf61fc0cf2e6c5e738307d.html

16/04/2018. Biomarker that predicts Alzheimer's.

Radio 5 (RTVE)

- https://www.rtve.es/alacarta/audios/inquietamente/inquietamente-biomarcador-predice-alzheimer-10-04-18/4558644/

23/04/2018. Researchers from the UPM improve the response of the human body to implants.

Madri+d.org

- http://www.madrimasd.org/notiweb/noticias/consiguen-mejorar-respuesta-cuerpo-humano-los-implantes

09/05/2018. IX Scientific weekend-2018. Laboratory of Optics, Photonics and Biophotonics.

Fundación Española para la Ciencia y la Tecnología

- https://www.fecyt.es/es/noticia/mas-de-8000-personas-participaron-en-el-finde-cientifico

23/05/2018. Elena Hernando, Senior Group Researcher at the

CIBER-BBN (Center for Biomedical Research in the Bioengineering, Biomaterials and Nanomedicine Network of the Instituto de Salud Carlos III)

- https://www.ciber-bbn.es/noticias/rosa-corcoy-y-elena-hernando-nuevas-jefas-de-grupo-del-ciber-bbn

11/06/2018. Enrique Gómez named "IFMBE Honorary Life Member"

International Federation for Medical and Biological Engineering

- https://ifmbe.org/announcements/awards/

23/06/2018. Interview with Fernando Maestú, Cognitive Neuroscience Laboratory, in the program "Cruce de caminos".

Radio Intereconomía

09/07/2018. Nanoparticles to detect Alzheimer's disease with magnetic resonance.

Madri+d

- http://www.madrimasd.org/notiweb/noticias/nanoparticulas-detectar-enfermedad-alzheimer-resonancia-magnetica

20/09/2018. Award of the Technology and Health Foundation 2018 for the Cognitive and Computational Neuroscience Lab. *Infosalus.com*

- https://www.infosalus.com/asistencia/noticia-carmen-ayuso-fundacion-luzon-reconocidos-fenin-premios-tecnologia-salud-2018-20180920203433.html

08/10/2018. The use of Complex Networks to study the behavior of football teams.

Diario La Vanguardia

- https://www.lavanguardia.com/deportes/20181003/452161917636/la-ciencia-de-las-redes-llega-al-futbol.html

Diario El Mundo Deportivo

- https://www.mundodeportivo.com/futbol/20181003/452161928782/la-ciencia-de-las-redes-llega-al-futbol.html

29/10/2018. Interview with our colleague Fernando Maestú in

iSanidad.com

- http://isanidad.com/125817/fernando-maestu-investigador-hemos-conseguido-medir-las-redes-neuronales-con-una-prueba-no-invasiva-la-magnetoencefalografia/

06/11/2018. New advanced biomaterial to repair damaged nerve tissue

Diario La Vanguardia

- https://www.lavanguardia.com/local/madrid/20181106/452780990587/desarrollan-un-biomaterial-avanzado-para-reparar-el-tejido-cerebral-danado.html

La Sexta

- https://www.lasexta.com/tecnologia-tecnoxplora/sinc/nuevo-biomaterial-reparar-tejido-nervioso-danado-ictus_201811075be2a1f80cf22a784ac365e9.html

Telecinco

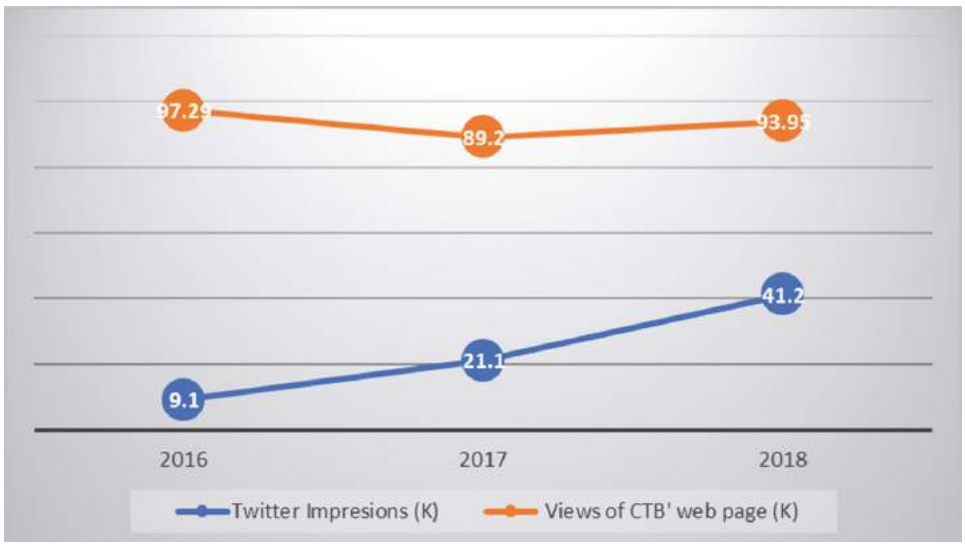
- https://www.telecinco.es/informativos/ciencia/Nuevo-biomaterial-reparar-tejido-nervioso_0_2655975042.html

Infosalus.com

- https://www.infosalus.com/salud-investigacion/noticia-investigadores-espanoles-desarrollan-nuevo-biomaterial-celulas-madre-reparar-tejido-nervioso-danado-20181112171113.html

ACTIVITY IN THE SOCIAL NETWORKS AND WEB PAGE

During this period the CTB has intensified its activity in Twitter to communicate our research to society obtaining four times more impressions in 2018 than in 2016. The number of visits to the web page has remained stable in the period, as the plot below shows.



Linkedin: https://www.linkedin.com/in/ctb-upm-centro-de-tecnolog%C3%ADa-biom%C3%A9dica-0365b2179/

Instagram: ctb.upm

Facebook: @ctb.upm

Twitter: @CTBUPM

News blog: https://ctbupm.blogspot.com/

Web page: www.ctb.upm.es

6 NETWORKING

During the 2016-18 period, we have consolidated several partnerships that were developed before and established new ones. The following lines summarize the most important ones:

CIBER-BBN

CIBER-BBN is one of nine CIBER consortia in Spain, created under the leadership of the Instituto de Salud Carlos III (ISCIII) to promote research excellence and build a critical mass of researchers in the field of Biomedicine and Health Sciences.

The research programs of the CIBER-BBN are: Bioengineering and Medical Imaging, Biomaterials and Advanced Therapies and Nanomedicine. The CTB is part of CIBER-BBN, being Prof. Francisco del Pozo, Director of the CTB, the group leader.

CIBER-BBN is composed of 44 research groups, selected by scientific merit across Spain, and organized to develop an intramural research program, aimed to promote and emphasize the clinical and industrial translation of biomedical research. The center has the ambition to become a global player in the field, by maintaining the highest degree of excellence and combining technical oriented researchers with clinical ones and industrial players at the same setup.

HBP

The Human Brain Project is a ten-year project that began in 2013, funded under FP7, with support from a special flagship ERANET and Horizon 2020. The goal of the project is to build a completely new ICT infrastructure for neuroscience, and for brain-related research in medicine and computing, catalysing a global collaborative effort to understand the human brain and its diseases and ultimately to emulate its computational capabilities.

The infrastructure consists of six ICT-based research platforms, providing neuroscientists, medical researchers and technology developers with access to highly innovative tools and services that can radically accelerate the pace of their research.

These include a Neuroinformatics Platform, that links to other international initiatives, bringing together data and knowledge from neuroscientists around the world and making it available to the scientific community; a Brain Simulation Platform, that integrates this information in unifying computer models, allowing in-silico experiments; a High Performance Computing Platform that provides the interactive supercomputing technology neuroscientists need for data-intensive modelling and simulations; a Medical Informatics Platform that federates clinical data from around the world, providing researchers with new

mathematical tools to search for biological signatures of disease; a Neuromorphic Computing Platform that makes possible to translate brain models into a new class of hardware devices and to test their applications; a Neurorobotics Platform, allowing neuroscience and industry researchers to experiment with virtual robots controlled by brain model developed in the project

EIT-HEALTH

PM is core partner of the EIT-Health program, coordinated by the Centre for Biomedical Technology (CTB). A consortium of more than 50 core partners and 90 associate partners from leading businesses, research centres and universities from across 14 EU countries. The goal of EIT-Health is to contribute to increase the competitiveness of European industry, improve the quality of life of Europe's citizens and the sustainability of healthcare system.

The partnership will promote entrepreneurship and develop innovations in healthy living and active ageing, providing Europe with new opportunities and resources. This will be achieved through delivering products, concepts and services, including educational programmes that will nurture talents and train the workforce of tomorrow. Adopting an investor approach, EIT-Health will drive the integration of business, research and higher education, boost innovation, and be a catalyst for new solutions for Europe.

EIT-Health will overcome the fragmentation of different healthcare systems in Europe and give companies easier access to markets across the EU. The critical mass of partners from business and industry, education, research, healthcare providers and insurance companies within EIT-Health, opens the path to reduce time-to-market for added-value products and services.

NEUROCENTRO

NEUROCENTRO, a biomedical engineering program for the development of diagnostic and therapeutic technology of neurological pathologies, is a 4-year project which began in 2018, funded by the Consejería de Educación e Investigación of the Comunidad de Madrid, and coordinated by the Center for Biomedical Technology. The main goal of NEUROCENTRO is to create a reference center in the region of Madrid for the integrated study of neurological disorders. NEUROCENTRO integrates clinical and scientific groups and technology companies, with the goal of improving the care, diagnosis and treatment of patients suffering from these diseases.

The participating institutions in Madrid Neurocenter are:

- Univ. Politécnica de Madrid
- Fund. Investigación Biomédica del Hospital Clínico San Carlos
- Univ. Complutense de Madrid
- Consejo Superior de Inv.Científicas
- Fund Investig. Biomédica del Hospital Universitario de La Paz

ISCIII

The collaboration with the *Instituto de Salud Carlos III* has two purposes. The first one is with the Foundation CIEN of ISCiii in the development of tools for the early diagnosis of neurodegenerative diseases based on MRI; the study of brain connectivity for the same purpose with MEG technology; and the research on neuropsychological profiles of people with memory decline and subjective memory complaints.

The second one is to collaborate to create a technology observatory to support technology assessment and technology funding within the ISCiii.

7 CORE FACILITIES

MAGNETOENCEPHALOGRAPHY

The CTB has the only equipment of magnetoencephalography with clinical and health research applications in Spain. The equipment, Elekta-Neuromag, has 306 sensors (204 planar gradiometers and 102 magnetometers) refrigerated with liquid helium.

The Elekta-Neuromag Magnetoencephalography (MEG) Equipment located in the Cognitive and Computational Neuroscience Laboratory has 306 sensors (combination of 204 planar gradiometers and 102 magnetometers) and one of the most modern designs of this type of technology. It also has blinking control in patients with epilepsy (improvement performed by the LNCyC).

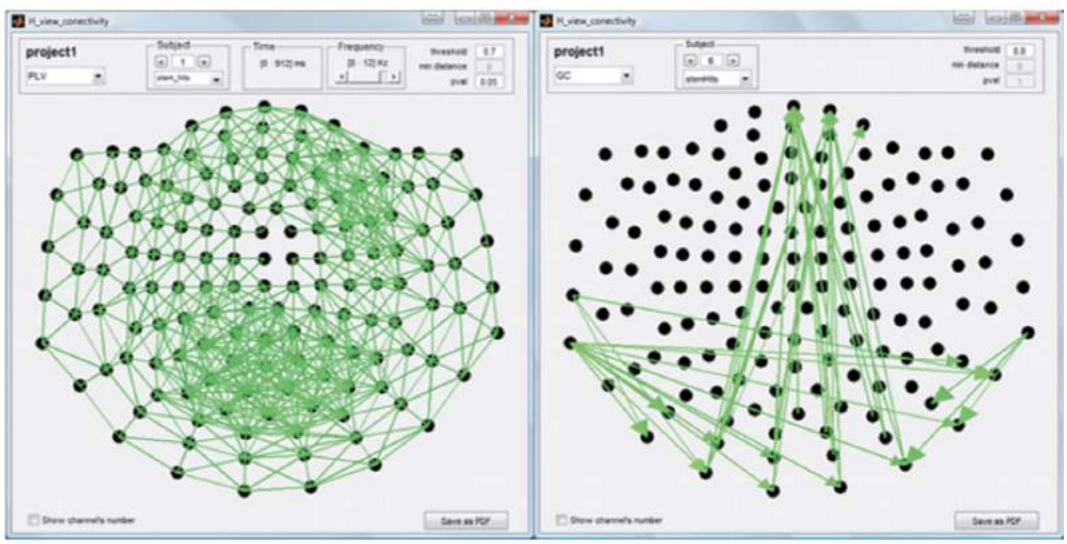
Associated with this system there are three work stations, one for acquisition and two for analysis, which contains the software provided by the company, in addition to the Cogent, Eprime, Presentation and Stim programs. It also has the HERMES software (HERMES GPL GNU Public License), open access, created by the laboratory itself for the analysis of the signals captured by the equipment.

In addition, using a 32-channel electroencephalograph coupled to the MEG equipment, simultaneous electroencephalography (EEG) / MEG records can be made. There is also an autonomous auxiliary equipment of EEG of 64 channels of the Neuroscan brand.

A helium recycler allows you to minimize the consumption of this refrigerant, use to obtain maximum sensitivity and precision in the magnetic field sensors.

The CTB is an accredited health center by the local authorities from the Community of Madrid. The authorization recognizes the facilities in the Laboratory of Cognitive and Computational Neuroscience as (**C.3)** a health service integrated in a non-health organization with the following units:

- U.1 General Medicine
- U.17 Neurology
- U.900 Other assisting units (sanitary psychology)



ANIMAL HOUSE

The animal facility is an important core of the Center for Biomedical Technology (CTB), for breeding and maintenance of different species of rodents giving support to the research activity of groups working with preclinical models.

The unit is a conventional module separated into several areas: quarantine room, surgery room, two rooms for rodents housing and a warehouse for feed store. The animal facility provides a controlled environment for the animals, with periodic control of diet, water, temperature, air, natural light-dark cycle, housing and husbandry conditions. Control of microbiological and genetic quality of the animals used in experimentation is routinely performed.

In our University, CTB and Animal Core, a main priority is to ensure that all research involving animal subjects is conducted in the safest, most humane and ethical manner, with a focus on respecting the vital contribution that the animal research subjects are making to the scientific mission of CTB and the Universidad Politécnica de Madrid.

After obtaining the required authorization from the former Ministerio de Agricultura, Alimentación y Medio Ambiente, (Ministry of Agriculture, Food and Environment), at present, several CTB research groups are able to use genetically modified mice to study different pathologies, being:

1. Genetically modified mice to emulate Alzheimer's disease.
2. Genetically modified mice expressing the green fluorescent protein (EGFP)
3. Genetically modified mice of X-fragile syndrome

CULTURE ROOM

The center has a molecular and cellular biology service with a tissue cell culture laboratory containing two 4-ft flow, Class II Biological safety cabinets Nuaire NU-437-400E, two CO2 incubators Thermo scientific, chemical hood, bench and desk space, inverted microscopes, refrigerated centrifuge Rotina 380R, one -80ºC Ultralow temperature freezer Nuaire NU-9668E and a microscopy room containing a fluorescence microscope and a microtome. The lab has approved the biosafety level 1 by the local authorities, that corresponds to non-human cells, and we are working on a new lab which will get the biosafety level 2 and will be adequate to work with non-risky human cells.

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