CTB center for biomedical technology

CEI-Moncloa
13 de Junio de 2012

POLITÉCNICA "Ingeniamos el futuro" CAMPUS DE EXCELENCIA INTERNACIONAL

Centro de Tecnología Biomédica

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Defining our ecosystem

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The current healthcare models, regardless if it is public or private, or the level of healthcare considered are nowadays unsustainable, due to some unquestionable facts, a thousand times repeated:

•The aging of the population.

•Unwieldy and uncoordinated providers systems, that threaten the economies on which they are based, that demand urgently new business models.

•Runaway costs and commitments.

•Increased health care demands, both in terms of quality expectations and coverage, that include promotion actions and health prevention.

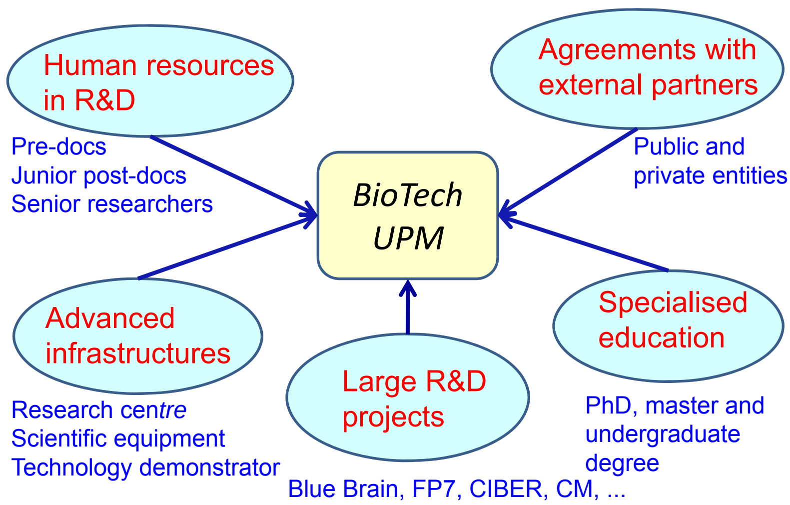
•Technology is worldwide acknowledged an essential component or an indispensable facilitator of the process towards new sustainable healthcare models.

Defining our ecosystem

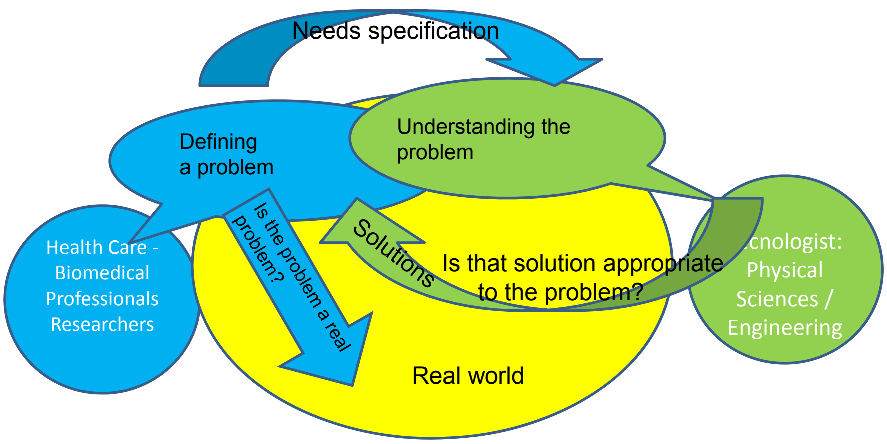
Some actions seem unavoidable to get:

- New systems, devices and sensors are required for cost-efficient specific niches of diagnosis and therapy.
- New competencies that increases the services´ value to meet the new ecosystem's needs and demands.
- Removal of barriers that hamper the coordination amongst the different and fragmented agents involved.
- The complexity of the health systems cannot be an excuse: there are powerful tools to serve that purpose.
- Programs to create talent that incorporate the new necessary skills.
- Personalization of care, and achieving the patient's active involvement in his/her own care.
- Business models must follow criteria based on results, rather than on payment for services, adapted to the global ecosystem.

BIOTech

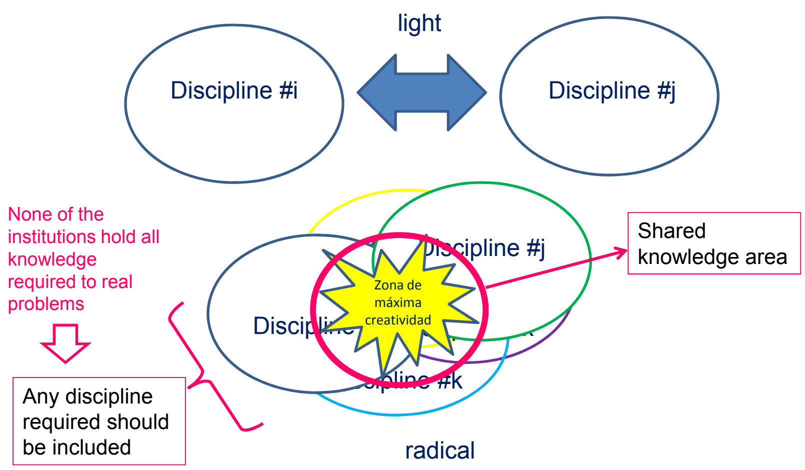


Vision: problem solver - problem definer



Vision: to cope with that -> Interdisciplinarity

Interdisciplinarity: ligth *vs* radical



Mission

Bring together outstanding groups of researchers and technologists, from a variety of biomedical and technological disciplines, in a stable environment of multidisciplinary research, with a size and infrastructure appropriate to approach successfully some of principal health and biomedical challenges nowadays.

And having in mind another fact: “the great innovation normally reside at the intersection of disciplines”

Design criteria I

1. Technology Transfer

The CTB adopts a clear strategy toward industrial technology transfer: the development of applicable technologies that translates basic research into clinical solutions

Design criteria II

2. Translational Research

The CTB recognizes that generating clinically and commercially useful technologies relay on clinical validation.

CTB will include a clinical trials unit to facilitate the design and practical implementation of clinical trials to minimize the high costs always involved in clinical trials and the difficulties to achieve the strict associated requirements recommend including as a principal functional part of CTB this single step office to support, design and manage clinical trials. dedicated to the pre-commercial evaluation of laboratory research reducing the risk of full clinical development.

Design criteria III

3. Education and Training

The training of CTB researchers and professionals is another important issue. Which will include:

1. A multidisciplinary multinstitutional and international Postgraduate Program on Health Sciences Technology:
2. Hopefully coordinated with the Graduate Degree on Biomedical Engineering
3. A variety of courses and seminars oriented to specific research and professional groups including postgraduate international degrees

CTB Laboratories

- Laboratory of Bioinstrumentation
- Laboratory of Nanobiotechnology (UPM(CTB-ISOM)-UCM)
- Laboratory of Biomedical Image. Neuroimaging (UPM-URJC)
- Laboratory of Cognitive and Computational Neurosciences (UPM-UCM)
    - Laboratory of Magnetoencephalography MEG
    - Biosignal analysis and modeling: synchronization and inverse engineering
- Laboratory of Clinical Neuroscience
- Laboratory of Computational Systems Biology (UPM-BBVA)
- Laboratory of Biological Networks (UPM-URJC)
- Laboratory on Applied Mathematics to Biomedicine (UPM-URJC)

CTB Laboratories (2)

- Laboratory of Experimental Neurology and Animal Models (UPM-HURyC)
- Laboratory of Cellular Growth
- Laboratory of Biochemistry. Biofunctionalization
- Laboratory of Bioelectromagnetism
    - Unit of celular studies
    - Unit of clinical application
    - Unit of dosimetry electromagnetic fields
- Laboratory Cajal of Cortical circuits (UPM-CSIC: Blue Brain)
- Laboratory of Internet of Things and Social Networks
- Laboratory of Personalised Care
- Laboratory of Internet of Things and Social Networks
- Laboratory of Biomedical Informatics: Data mining and visualization
- Laboratory of Biomaterials and Tissue Engineering
- Laboratory of Diabetic technology and metabolic modeling

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CTB services

- Clinical and experimental Magnetoencefalography
- Nano-structures and nano-conjugated fabrication for clinical and research applications (CTB-ISOM)
- Physical and functional characterization of nanostructures (CIBER_bbn)
- Remote post-processing of medical images
- Studies of electromagnetic radiations and dosimetry
- Brain electrophysiological activity characterization
- Technology transfer, including spin-off temporal nurturing
- Clinical Trials support
- Postgraduate education area management

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CTB Research Lines

Advanced biomedical imaging technologies

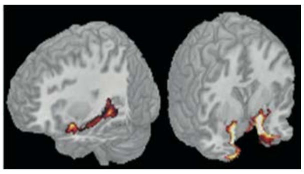
Target: Neuroimage post-processing to develop new objective biomarkers

•Neuroimaging. Advanced functional and quantitative biomedical imaging techniques for the early diagnosis of neurodegenerative diseases
•Multiscale studies for an early diagnosis of Alzheimer's disease
•Platforms development to include advanced processing, integration/fusion of different imaging modalities and decision making tools to support research and clinical practice
•Research on neurophysiological basis of pain. MRI compatible pneumatic somatosensorial stimulation
•Image banks and advanced teleradiology environments
•Multimodality cardiovascular imaging technology
•Simulation, virtual reality and image guiding technologies for training and the planning of minimally invasive surgery

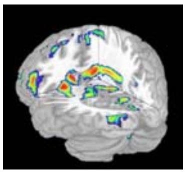
Laboratories:
Neuroimaging
Cognitive and Computational Neuroscience
Blue Brain
Bioelectromagnetism
Biomedical Imaging
Molecular Biology and Biochemistry
Advanced Mathematics applied to Biomedicine

Neuroimaging. Advanced imaging techniques for the early diagnosis of neurodegenerative diseases

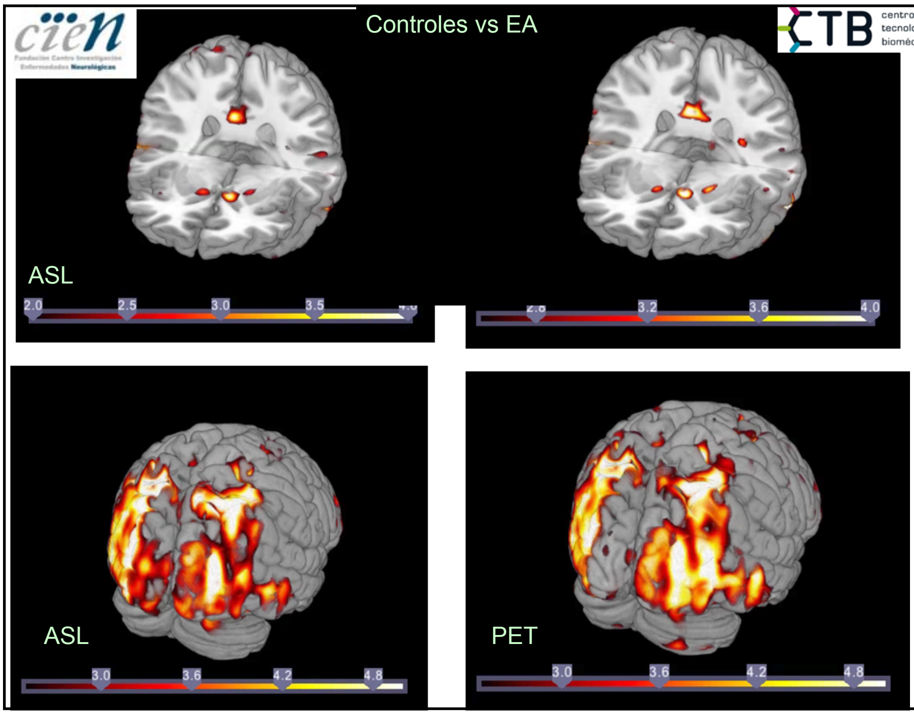
Determining the ties between cognitive assessments and their anatomical correlation, both in grey and white matter.

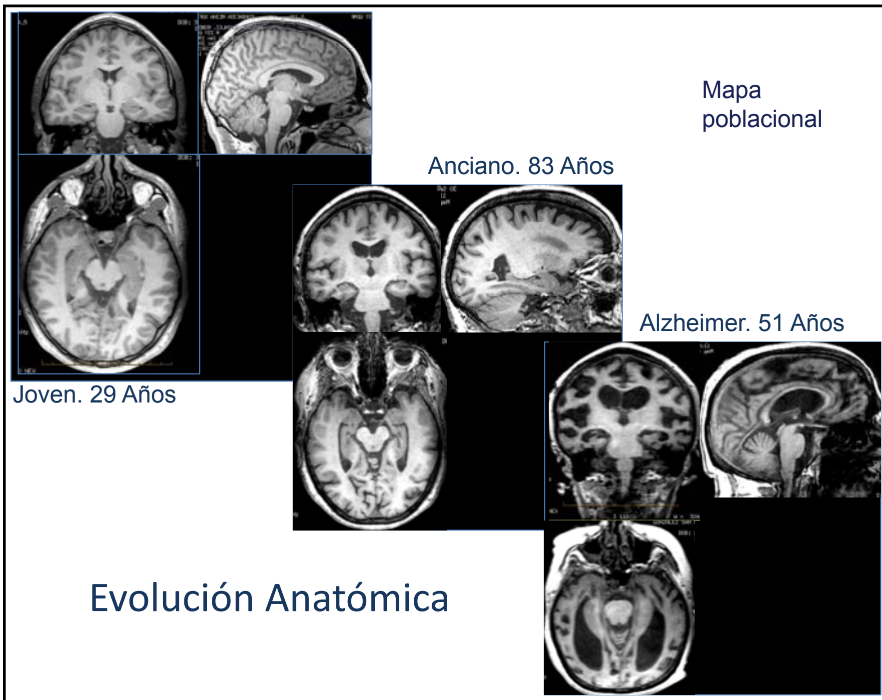


Temporal lobe atrophy in AD in the studied population sample.

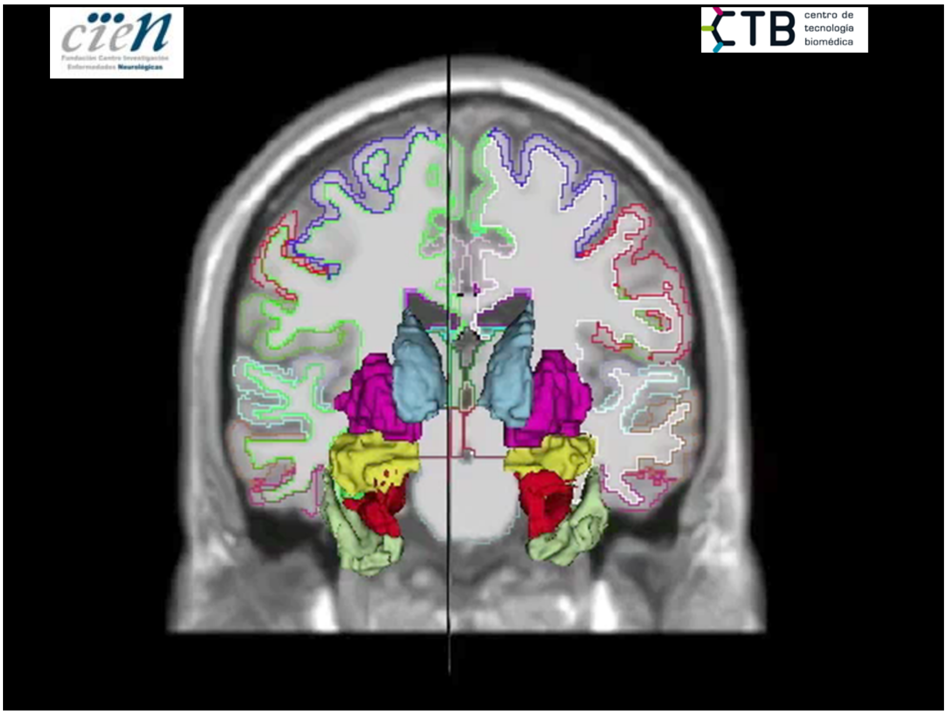


Anatomical localizations with volume alterations in psychotic population.

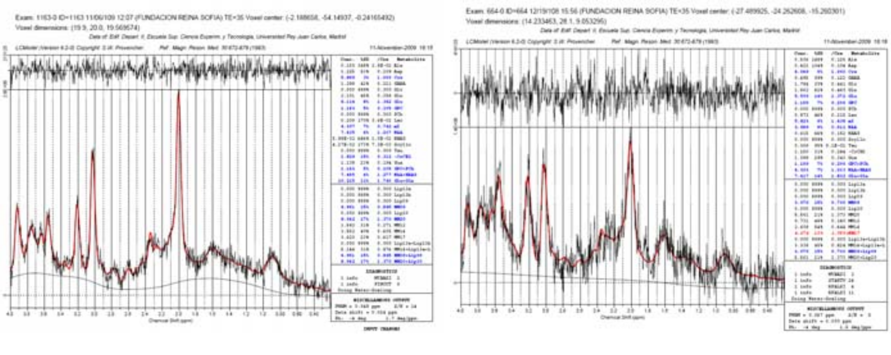


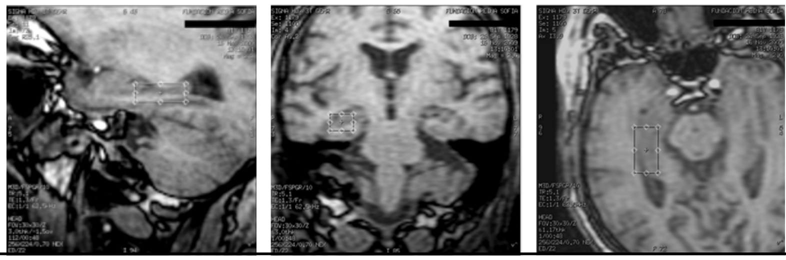


Evolución Anatómica

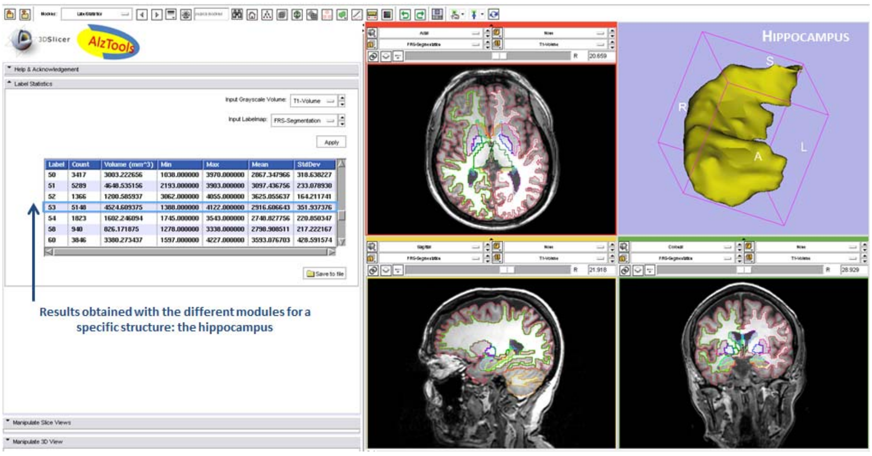


ESPECTROSCOPÍA





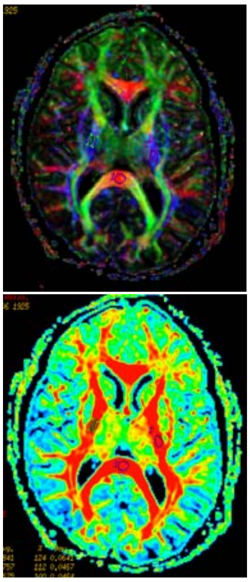
Hippocampus volumetry

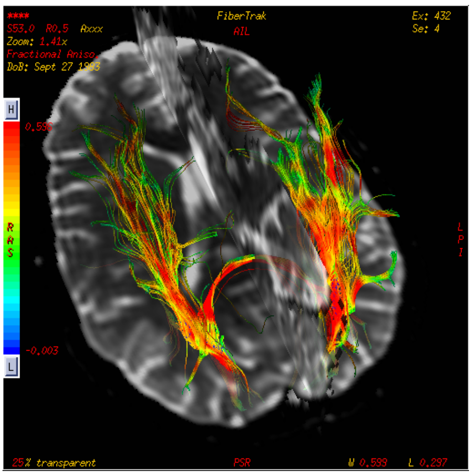


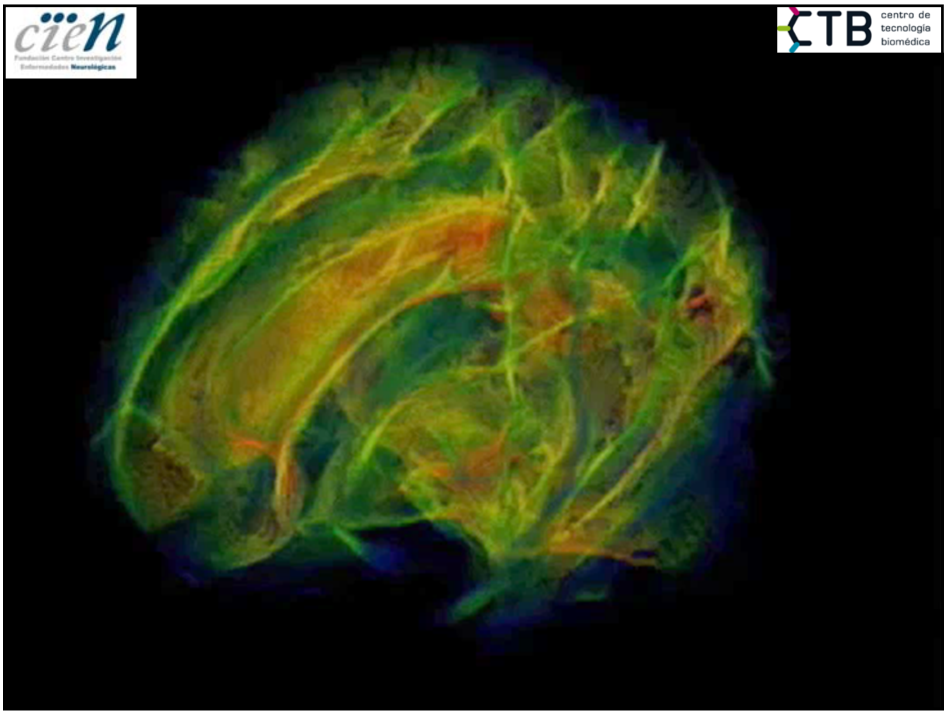
Label	Count	Volume (mm^3)	Min	Max	Mean	StdDev
50	3417	3003.222656	1038.000000	3970.000000	2867.347966	318.638227
51	5289	4648.535156	2193.000000	3903.000000	3097.436756	233.078930
52	1366	1200.585937	3062.000000	4055.000000	3625.055637	164.211741
53	5148	4524.609375	1388.000000	4122.000000	2916.606643	351.937376
54	1823	1602.246094	1745.000000	3543.000000	2748.827756	220.850347
58	940	826.171875	1278.000000	3338.000000	2798.908511	217.222167
60	3846	3380.273437	1597.000000	4227.000000	3593.076703	428.591574

Results obtained with the different modules for a specific structure: the hippocampus

TENSOR DE DIFUSIÓN



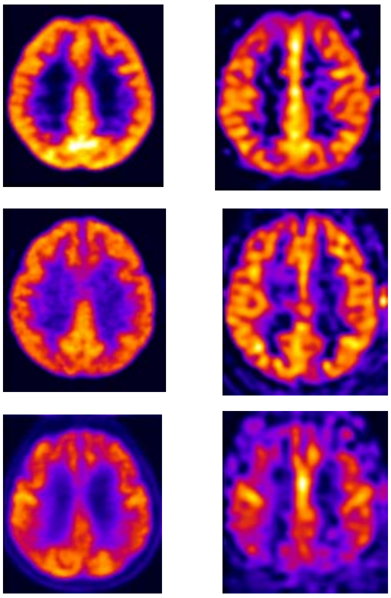




Metabolismo y Perfusión ASL

Validating new imaging methods

PET ASL



Joven. 29 años

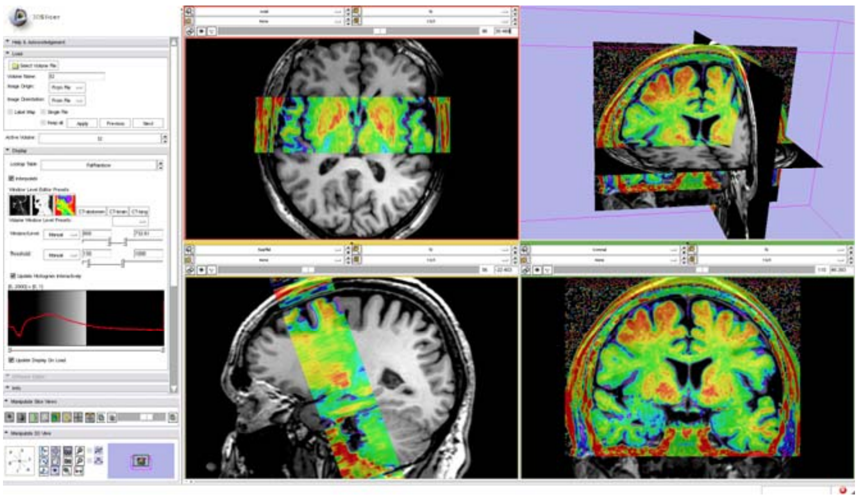
Anciano 85 años Sano

Anciano 84 años Alzheimer

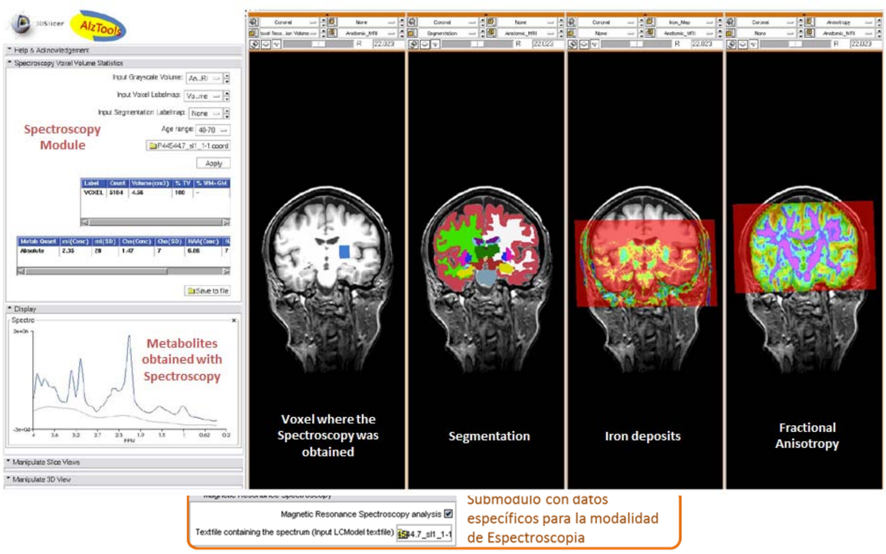
Arterial Spin Labeling (ASL) using gold standards.

Second row: an 84-year old healthy male. Left: caption obtained with PET; right: equivalent image obtained with ASL. Third row: images an 85-year old male with Alzheimer's disease.

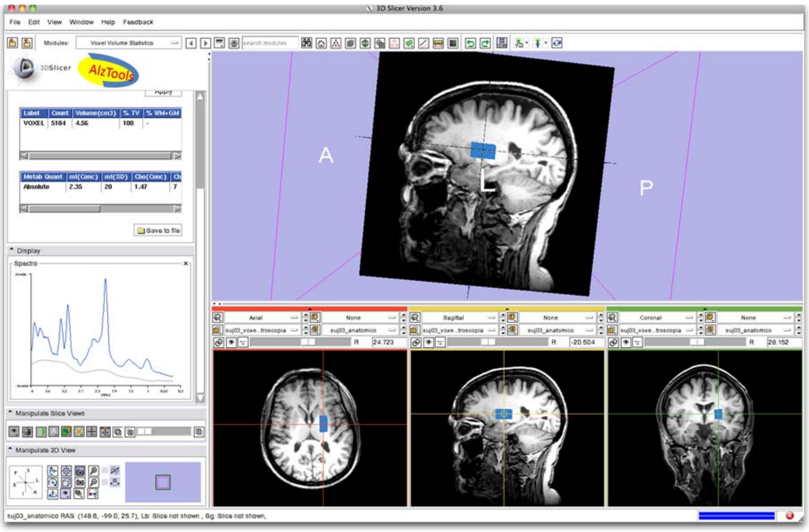
Iron deposit quantification



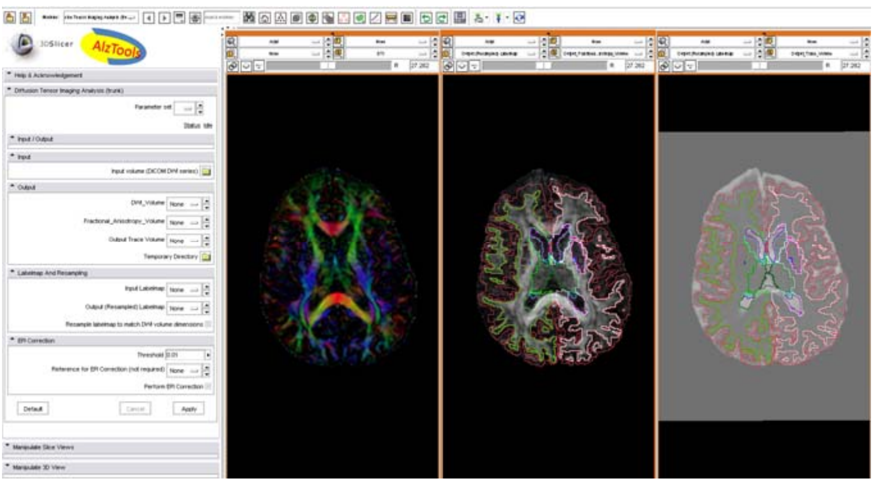
Integration. Multimodality



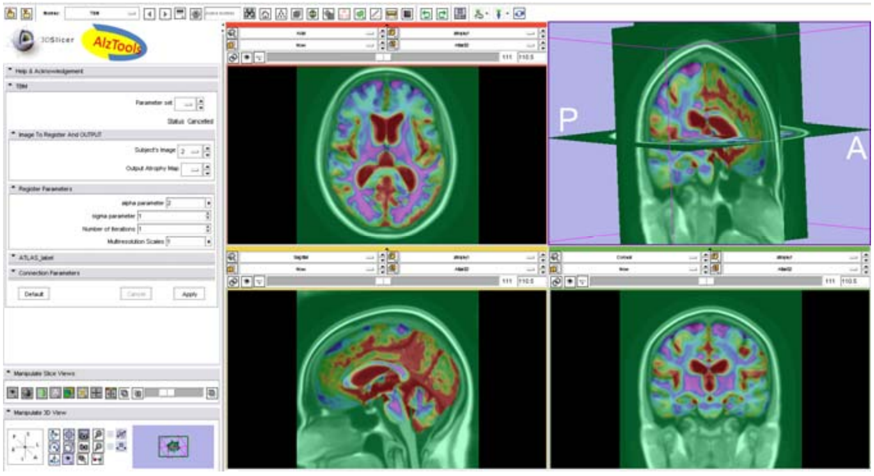
Spectroscopy. Molecular imaging



Difussion imaging



Tensor-based morfometry



Brain synchronization analysis

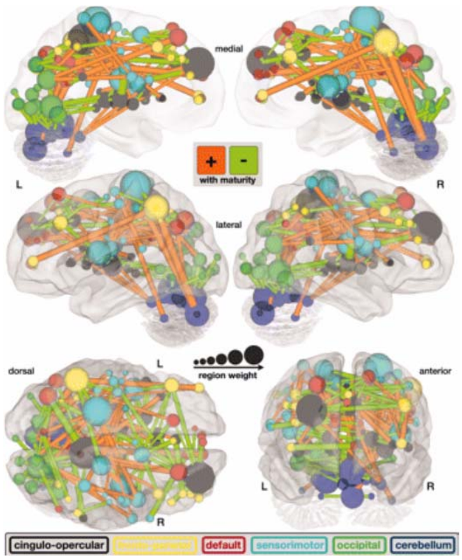
Target: MEG-based imaging and biomarker development. Application to neurological diseases

•MEG imaging, multimodality, simulation tools and multivariate and non-linear analysis for cognitive neuroscience and clinical neurology;
•Study of the brain connectivity and synchronization phenomena for cognitive neuroscience and clinical applications. Biomarkers for the early detection of dementia. Functional connectivity in AD and MCI
•Reorganization of functional connectivity as a correlate of recovery in acquired brain injury. Traumatic brain injury and stroke
•Study of emotions and depression
•Working memory and attentional process
•Advanced classification tools to aid decision making
•Source analysis. Inverse problem
•Advanced Technology for MRI-EEG studies with high temporal and spatial resolution. Application to Epilepsy

Laboratories:
Cognitive and Computational Neuroscience
Advanced Mathematics applied to Biomedicine
Computational System Biology

Describing the brain

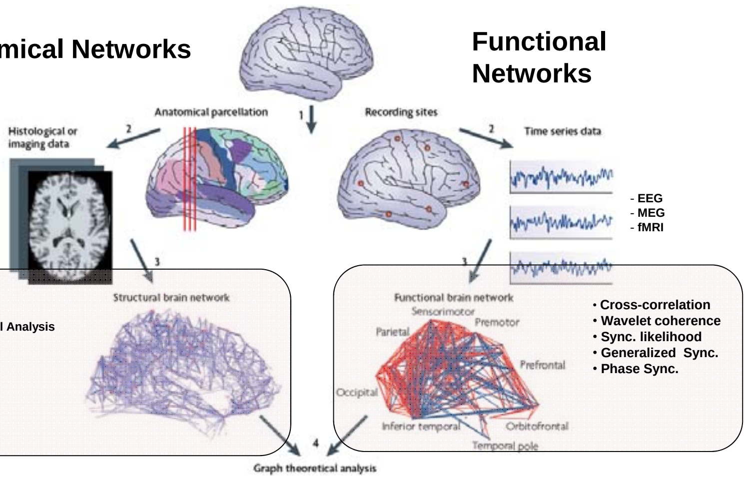
- Functional segregation
- Functional integration:
  - Functional connectivity
  - Effective communication



Describing brain connectivity

Anatomical Networks

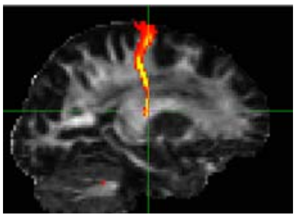
Functional Networks



From Bullmore & Sporns, Nature Rev. 10, 186 (2009)

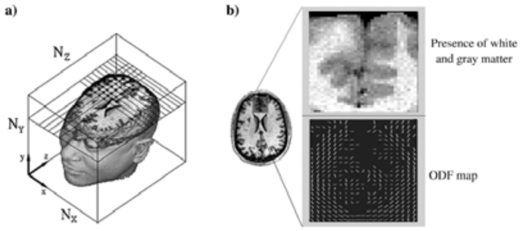
Estructural connectivity. Some methods

Probabilistic tractography: indicates the probability that two nodes/voxels are connected by a brain tract.



Behrens et al. FMRIB Technical Report TR03TB1

Graph Theory can also be used to search for patterns of anatomical connectivity between regions of grey matter.



Iturria-Medina et al. NeuroImage 36 (2007) 645-660

Functional connectivity

Definition: The functional connectivity represents the statistical interdependence between two physiological signals, providing information on the functional interactions between different brain regions[1].

Note: long-range synchronization between signals has been proposed as the mechanism for communication and information integration in the brain[2].

fMRI

- PROs: Good spatial resolution
- CONs: Information is not directly related to neuronal activity
- CONs: Only very low frequency bands

EEG/MEG

- PROs: It covers a higher frequency range
- PROs: It measures neuronal activity in a direct form, through the measurement of electrical or magnetic fields.
- CONs: Solution of the reverse problem

[1] Bajo et al. Journal of Alzheimer's Disease 22 (2010) 183-193

[2] Fries et al.Trends Cogn Sci 9 (2005) 474-480

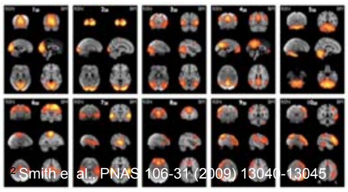
Functional connectivity (fMRI)

BOLD (Blood Oxygenation Level Dependent) contrast. Indirectly related to neuronal activity. Signal dependent on the blood level oxygenation.

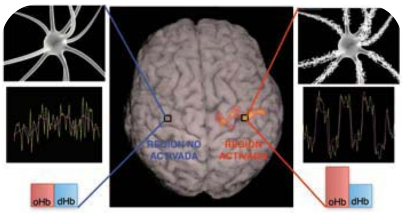
Resting neuronal networks

Functional connectivity
Brain regions that work together in the absence of external stimulation

FMRI studies "resting - state"
Spontaneous fluctuations in BOLD signal



Smith et al., PNAS 106-31 (2009) 13040-13045



Neuronal networks task evoked

Functional connectivity
of brain regions that work together with a specific purpose

fMRI studies “task - evoked”
Changes in BOLD signal evoked by task

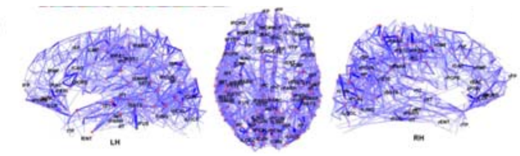
Related

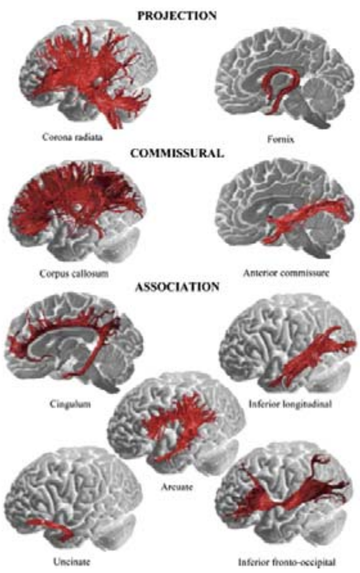
Functional-structural Connectivity

Signal-image integration

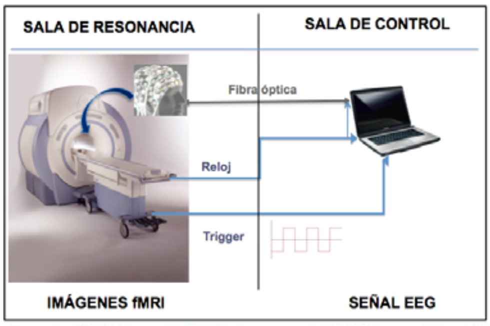
EEG/iEEG/MEG/BOLD → Search for statistical interdependencies (FC) between signals

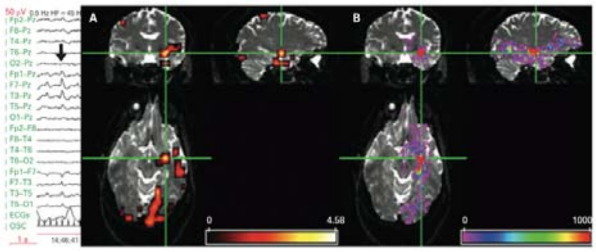
dMRI/SEM → Tracking algorithms. SC extraction





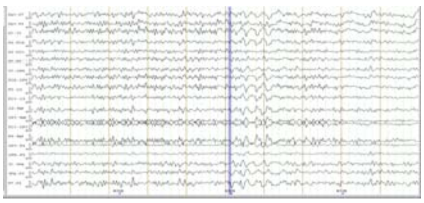
Functional connectivity (MRI/EEG)



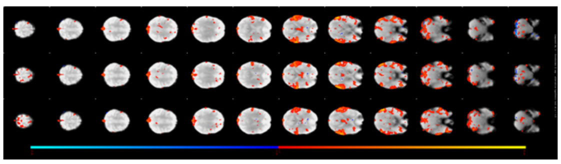


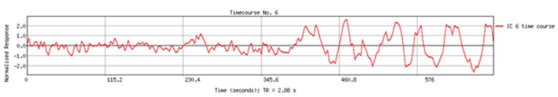
EEG/fMRI: resting state

Estudy of an epilepsy patient (vision focus loss)



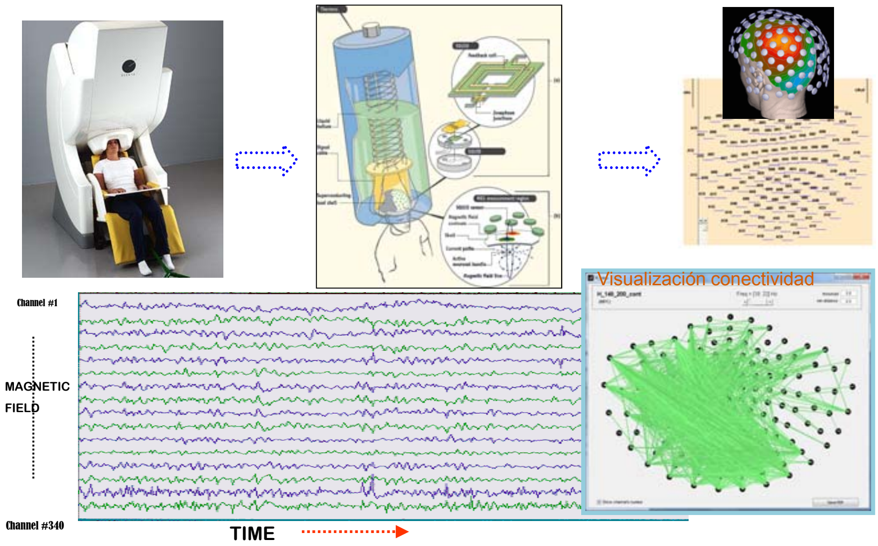
BETA abnormal activity (16 Hz) with eyes closed…





…network that does not appear synchronized while the patient remains with her eyes open.

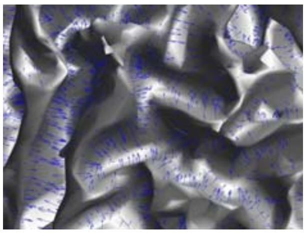
MEG recordings

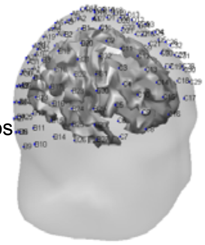


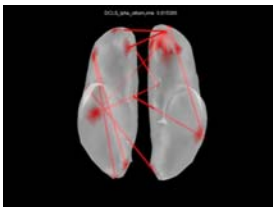
MEG: The inverse problem

Estudio de la conectividad funcional mediante parámetros de sincronización entre pares de señales, "*Synchronization Likelyhood", "Phase Locking Values"*

En el espacio de sensores
• 306 sensores
• Magnetómetros y gradiómetros
• Problemas en la integración con la conectividad estructural al ser espacios distintos.







Para integrar la conectividad funcional observada mediante MEG, será necesario trabajar en el espacio de fuentes
• Del orden de 7000 dipolos, necesario clustering
• Mas de una solución al problema inverso

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Alzheimer disease

Normal

Memory complaints with normal scores on neuropsychological test: no medical evidence of disease

SMC
SUBJECTIVE MEMORY COMPLAINTS

ild cognitive mpairment

** William Utermohlen es un pintor al que en 1995, le diagnosticaron Alzheimer y decidió utilizar la pintura para reflejar el deterioro paulatino de su mente*

Alzheimer's disease

Cognitive Continuum

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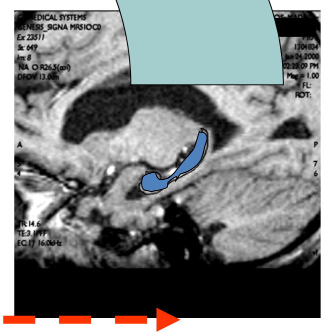
Alzheimer disease: Who will develop dementia?

MCI subjects are at higher risk of developing dementia: **10-15% per year**, 2-3% healthy elders

Looking back to the biomagnetic profiles of those patients that develop or not dementia

Predict the progression to dementia

AD



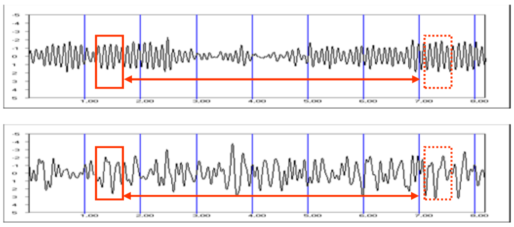
2´5 years

Biosignal analysis: Funtional connectivity

Many options for time-series analysis and dimensionality reduction (classification)

a) Linear algorithms
- Correlation
- Covariance
- Coherence

b) Non linear algorithms: Information based
- Mutual information
- Transfer Entropy

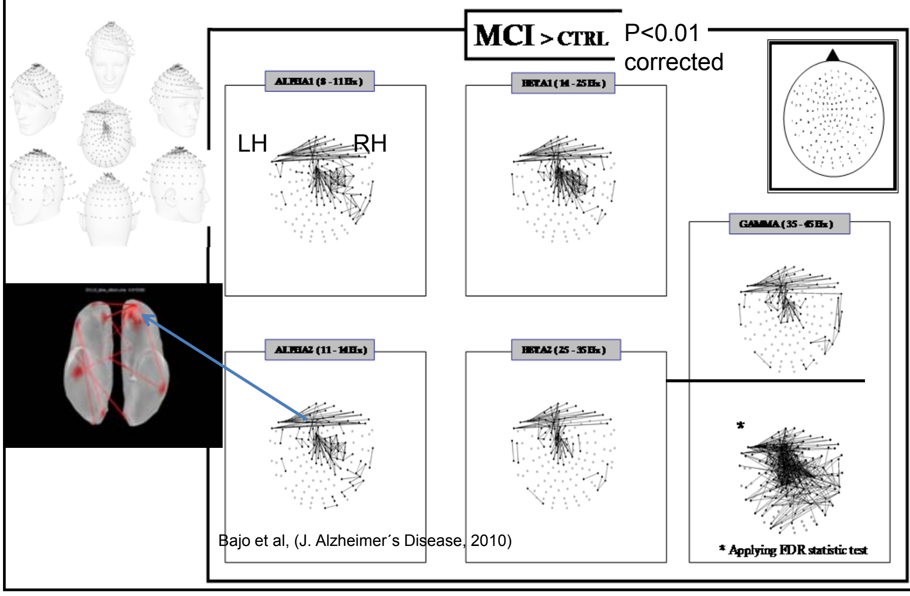


(*) Synchronization Likelihood
Stam & van Dijk, 2002

c) Non linear algorithms: Generalized Synchronization
- Mutual prediction
- Synchronization Likelihood (*)

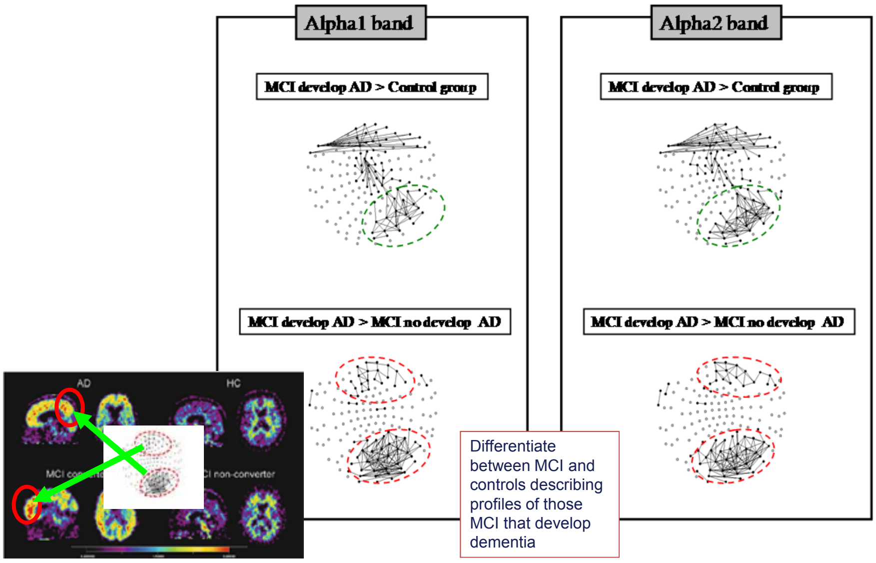
d) Non linear algorithms: Phase Synchronization
- Phase coherence
- Phase Lag Index

Alzheimer disease: Biomarkers (MCI)



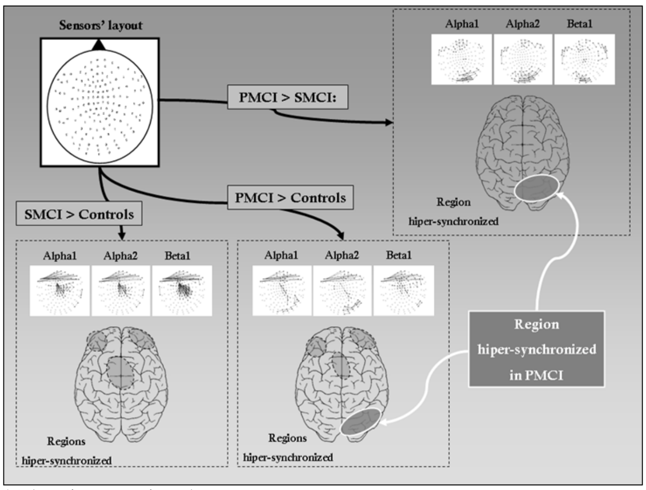
Bajo et al, (J. Alzheimer´s Disease, 2010)

MCI-AD: Synchronization Analysis → Biomarkers



Differentiate between MCI and controls describing profiles of those MCI that develop dementia

Alzheimer disease: Biomarkers (SMC)



* *Bajo et al., 2011, under review*

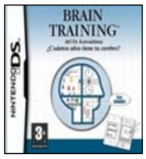
Cognitive recovery in acquired brain injury

Trauma recovering therapy

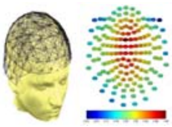
Accident

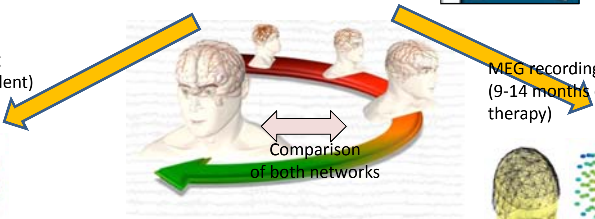
Head Trauma

Cognitive Therapy

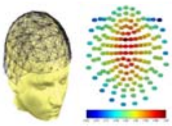


MEG recording
(after the accident)





MEG recording
(9-14 months of
therapy)

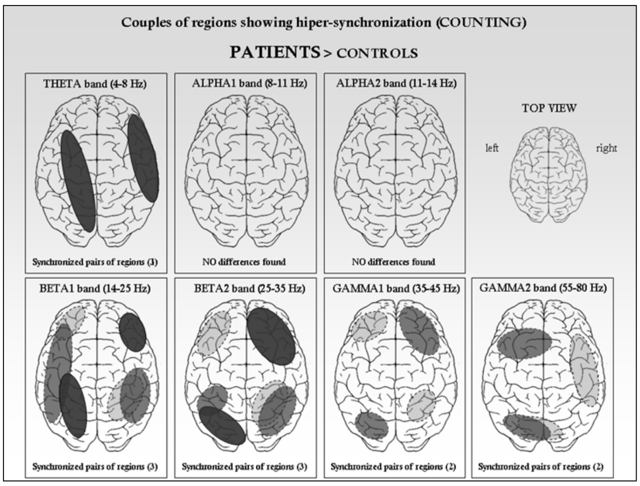


Abnormal synchrony could be one of the causes of the cognitive dysfunction

Correlation between abnormal synchronization and cognitive deficits

Funct. Connectivity biomarkers: Many other applications

* EEG- drug-dependencies effects . *Centro Terapéutico Barajas . Ayto. Madrid*



Clinical Neuroscience

Target: Multimodal approach to human memory formation in health and disease
Detailed description
Medial temporal lobe epilepsy
Clinical Neuroscience.Post-traumatic stress disorder (PTSD)

Laboratories:
Clinical Neuroscience

Bioinstrumentation and biosensors

Target: Design of new technologies based sensors and medical devices.

•Biosensors based on nanoparticles for early diagnosis of bacterial diseases and contamination (food, environment).
•New sensors and instruments to measure physiologic variables (glucaemia, vascular pressure, etc.)
•Developing of methodologies for the detection and identification of nanoparticles non-intentional contaminants in humans tissues and the environment.

Laboratories:
Bioinstrumentation
Nanotechnology
Advanced Mathematics applied to Biomedicine

CTB center for biomedical technology

Nanomedicine

POLITÉCNICA CAMPUS DE EXCELENCIA INTERNACIONAL

Target: Design and manufacture of biocompatible and stable nanostructures for RMI contrast agents for in vivo early diagnosis of Alzheimer disease, labeling of human neural precursor cells for cellular therapies, and tumor hyperthermia based therapies and drug delivery.

Detailed description

•Design and development of nanostructures, biocompatible and stable in the biological media and their physical and biological characterization

•Development of selective markers, contrast agents, for RMI and MEG. Molecular imaging technology for Alzheimer Disease: Magnetic nanomarkers for in vivo early diagnosis and progression of AD

•Labeling of human neural precursor cells with MNPs for in vivo cell tracking to be used in cellular therapies against neurodegenerative disease (i.e. Parkinson disease)

•Development of nanomarkers for early tumor therapy and diagnosis. Design and fabrication of nanostructures and the supporting instrumentation for hyperthermia and drug delivery applications

•Development of devices based on the guidance and focusing of MNPs for new therapies.

Laboratories:

Bioinstrumentation and nanotechnology

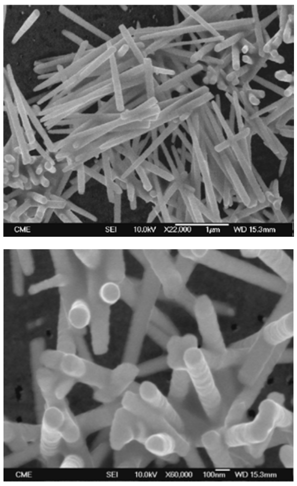
Molecular Biology and Biochemistry

Bioelectromagnetism

CTB center for biomedical technology

Design and fabrication of nanostructures, biocompatible and stable in the biological media: Electrodeposición

POLITÉCNICA

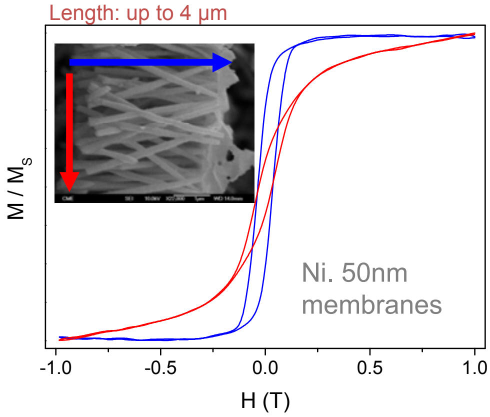


Co. 50nm membranes

Fe, Co, Ni, CoFe, CoNiFe

Diameter: 10,30,50 y 100nm

Length: up to 4 µm



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Physical and biological characterization of nanostructures, and nanoconjugates

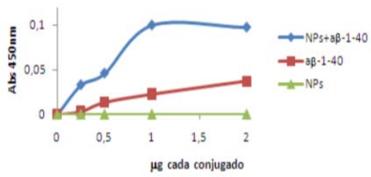
T1 and T2 Nuclear Magnetic Resonance Relaxometry (Stelar SmarTRACER + Bruker 2 T electromagnet)

Alternating Gradient Magnetometer: MicroMag, M²900-4 AGM (Princeton Measurements Corporation

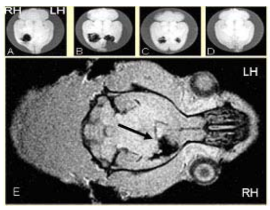
CIBER-bbn www.ciber-bbn.es

Development of selective contrast agents (RMI).
Molecular Imaging Technology for Alzheimer Disease

Different peptides have been conjugated with the magnetic nanoparticles to achieve a specific marker of the amyloid plaque. *in vitro* tests to evaluate the specific binding, affinity and toxicity of the conjugates.



Results obtained by an ELISA test carried out in P96 wells that have been previously treated with 1 µg of aβ1-42 peptide. The nanoconjugate NP-aβ shows an even higher affinity to bind to aβ1-42 than the aβ peptide alone. Interestingly NPs alone do not show any affinity to binding to aβ1-42.

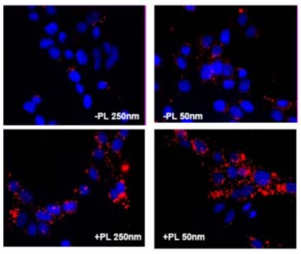


Dextran coated magnetic nanoparticles (MNPs) can be detected efficiently by MRI in *ex vivo* and *in vivo* brains.

Challenges: highly stable in vivo; cross the Blood - Brain Barrier (BBB) non-destructively following intravenous injection; bind specifically to plaques with high affinity and produce local changes in tissue contrast detectable by MRI. Animal models: transgenic mice for AD (5xFAD)

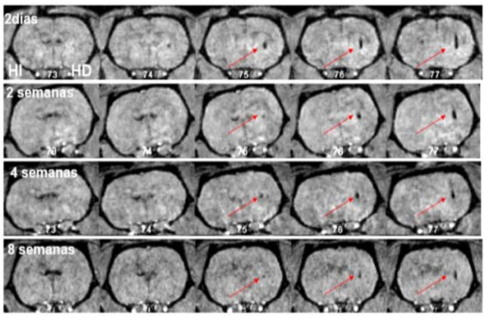
Labeling of human neural precursor cells with MNPs for in vivo cell tracking to be used in cellular therapies against neurodegenerative disease (i.e. Parkinson disease)

Replacing damaged or lost neural cells by transplanting *in vitro*-expanded neural precursor cells (NPCs). MR images indicate the specific place where the transplanted cells are located. PET images will show the maturation and functional state of the transplanted cells, previously labeled with MNPs. The mature and functional cells can replace dopaminergic neuron loss during the progress of Parkinson's disease.

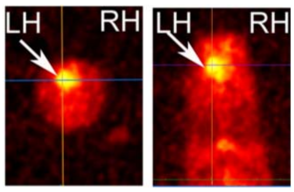


Uptake of MNPs by hNPCs. Protocol developed to label human NPCs using poli-Lysine to improve the internalization of the MNPs by human precursor cells.

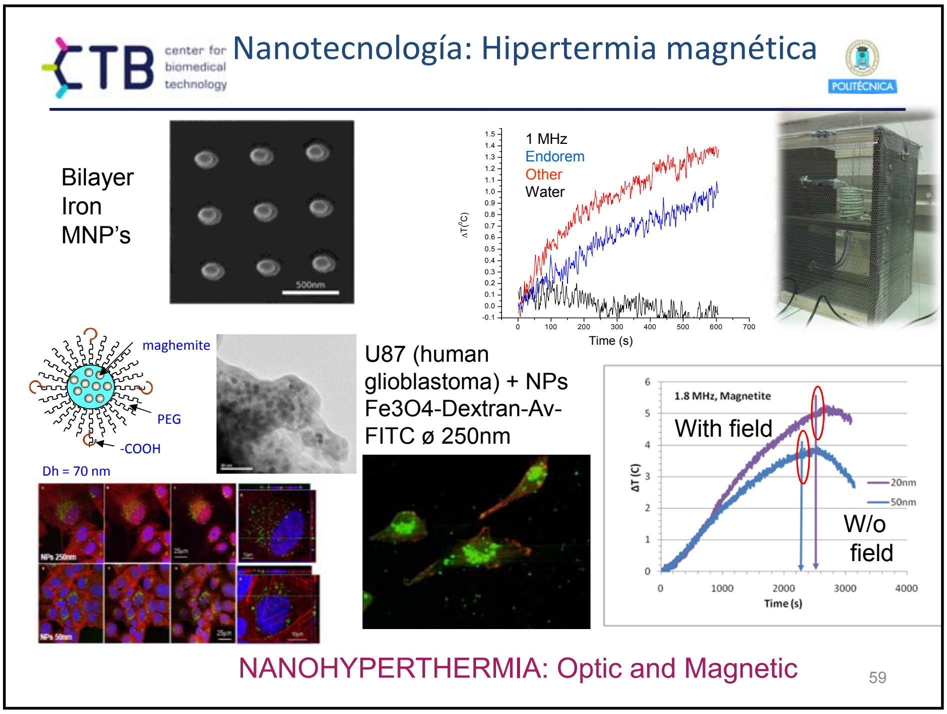
Labeling of human neural precursor cells with MNPs for in vivo cell tracking to be used in cellular therapies against neurodegenerative disease (i.e. Parkinson disease)

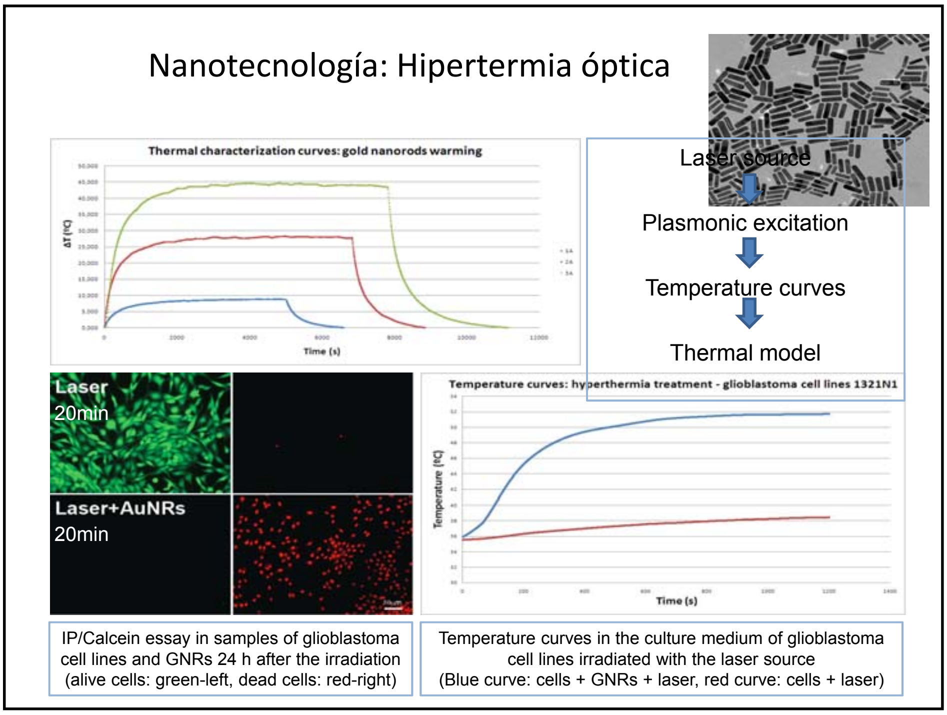


MRI Studies. MNPs-labeled hNPCs stereo-tactically injected into the rat's brain. MNPs-labeled cells were resuspended, washed and transplanted into the right caudate putamen brain. For MR detection 400,000 cells were transplanted into the right striatum. *In vivo* longitudinal MRI studies were carried out using a 4,7T MR scanner. The MNPs-labeled cells (red-arrow) can be reliably detected by MR from early points in time (2 days) to 8 weeks after transplantation.



PET studies. Representative summary images (coronal and transversal planes) of studies carried out on the same animal with 11C-DTBZ. The arrows indicate the uptake of 11C-DTBZ by the healthy left striatum (Left hemisphere, LH), no signal is detected in the right lesioned striatum (right hemisphere, RH) demonstrating the validity of this technique to visualize the dopaminergic innervations.


CTB center for biomedical technology
Nanotecnología: Hipertermia magnética
POLITÉCNICA
Bilayer
Iron
MNP's
500nm
1 MHz
Endorem
Other
Water
ΔT(°C)
Time (s)
maghemite
PEG
-COOH
Dh = 70 nm
U87 (human
glioblastoma) + NPs
Fe3O4-Dextran-Av-
FITC ø 250nm
1.8 MHz, Magnetite
With field
W/o
field
20nm
50nm
ΔT (C)
Time (s)
NANOHYPERTHERMIA: Optic and Magnetic
59


Nanotecnología: Hipertermia óptica
Thermal characterization curves: gold nanorods warming
ΔT (°C)
Time (s)
Laser source
Plasmonic excitation
Temperature curves
Thermal model
Laser
20min
Laser+AuNRs
20min
Temperature curves: hyperthermia treatment - glioblastoma cell lines 1321N1
Temperature (°C)
Time (s)
IP/Calcein essay in samples of glioblastoma cell lines and GNRs 24 h after the irradiation (alive cells: green-left, dead cells: red-right)
Temperature curves in the culture medium of glioblastoma cell lines irradiated with the laser source (Blue curve: cells + GNRs + laser, red curve: cells + laser)

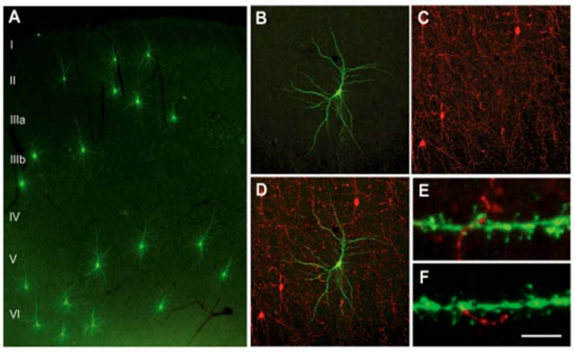
Ramón y Cajal Blue Brain Project

Target: Study of the brain cortex microrganization and the alterations of cortical circuits in Alzheimer disease.

Detailed description
•Study of the structural and functional microrganization of the cortical column as the building block of the cerebral cortex
•Study of the alterations of cortical circuits in Alzheimer disease

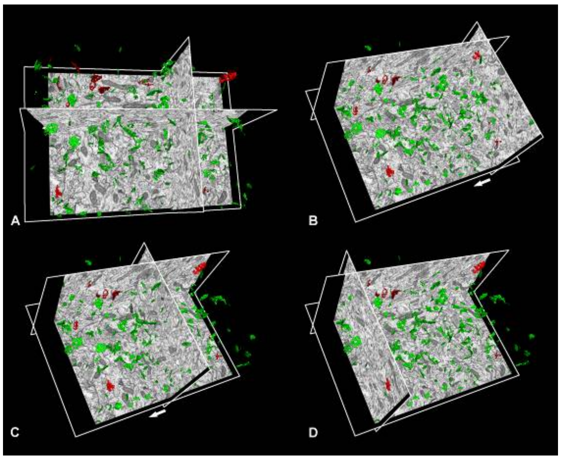
Laboratories:
Blue Brain
Cognitive and Computational Neuroscience
Advanced Mathematics applied to Biomedicine
MIDAS

Brain cortex microrganization. Ramon y Cajal Blue Brain Project



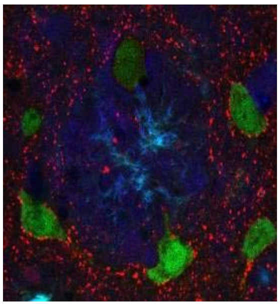
Confocal by catecholaminergic fibers (immunocytochemical labeling with antibodies against tyrosine hydroxylase; TH). The pyramidal cells in paraformaldehyde fixed tissue were intracellularly injected with Lucifer yellow, which diffuses throughout the neuron as a result of the direct negative current applied, allowing us to visualize the morphology of the entire cell, including the dendritic spines. *A*, Panoramic view obtained by confocal microscopy showing pyramidal cells in different layers of the cortex. *B, C*, Higher magnification confocal microscopy images from layer VI of the same section and field, showing an injected pyramidal cell (*B*), and TH-positive neurons and fibers (*C*). *D*, when merged, both images (*B* and *C*) show the localization of TH-positive axons with respect to the pyramidal cell. *E*, *F*, higher magnifications of sections in panel *D* showing the possible contacts between TH-positive axons and dendritic spines (*E*), or the dendritic shaft (*F*) of the pyramidal cell labeled with Lucifer yellow.

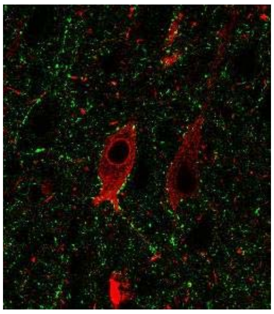
Brain cortex microrganization. Ramon y Cajal Blue Brain Project



Three-dimensional visualization of synaptic densities within a tissue block reconstructed from a series of images obtained by (FIB/SEM). The segmented asymmetric synapses are represented in green and the symmetric synapses in red. Images A to D show different ways to rotate the virtual tissue block in 3D and different positions of the perpendicular planes of the section. In this respect, every synapse present within the sample can be visualized and located.

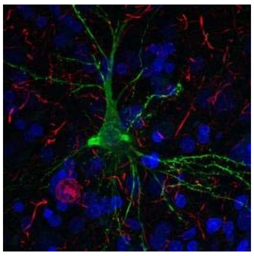
Study of the alterations of cortical circuits in Alzheimer disease

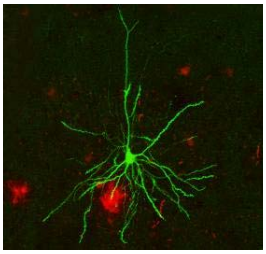




The human cerebral cortex triple stained (left) to study the relationship between plaques (thioflavin; blue), neurons (NeuN; green) and GABAergic axon terminals (vGAT; red). Dual immunocytochemical staining (right) to study the somatic innervation of tau-positive neurons (red) by GABAergic axon terminals (vGAT; green).

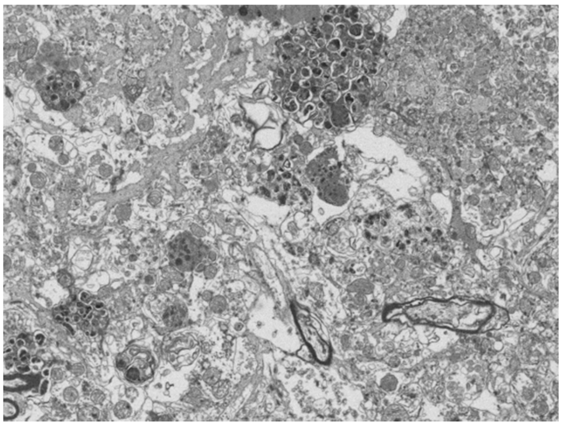
Study of the alterations of cortical circuits in Alzheimer disease





Confocal microscopy images showing the spiny dendrites (green) of cortical pyramidal cells from a transgenic mouse (left) and from a patient with Alzheimer's disease (right). Pyramidal cells were intracellularly injected with Lucifer yellow (a fluorescent marker, green). *Left;* These transgenic mice develop plaques that contain beta amyloid (red, stained with Congo red) and they are used as a model to study Alzheimer's disease. *Right;* a pyramidal cell intracellularly labeled to study the relationship between tau (anti-tau immunocytochemical staining, red) and the microanatomical alterations in pyramidal cells. Cell nuclei of neurons and glia are stained in blue with DAPI to analyze the possible neuronal loss and/or gliosis. The alterations to pyramidal cells are related to cognitive impairment

Study of the alterations of cortical circuits in Alzheimer disease



Human cerebral cortex from an autopsy of a patient with Alzheimer's disease, part of a series of images obtained by FIB/SEM that show numerous dystrophic neurites, as well as bundles of amyloid, especially in the upper left corner.

Computational Systems Biology

Target: Computational System Biology applied to neuroscience

Detailed description
•Research on classification methods to define objective biomarkers of neurodegenerative diseases
•Complex networks based multivariate and non-linear analysis of neurophysiology signals (MEG)
•Neuronal cell cultures experimental study of the relationship between structure and function of networks. Application to the analysis of feasibility in cell implantation. Applications of neurodegenerative diseases

Laboratories:
Computational System Biology
Biological Networks
Cognitive and Computational Neuroscience
Advanced Mathematics applied to Biomedicine

Modeling Brain Networks

Advantages

- We have information of the brain as a whole and not only of its isolated components.
- We can relate the information contained in the topology with the dynamical processes occurring in it.
- We can try to identify differences between healthy and impaired brains in order to understand and prevent different brain diseases.

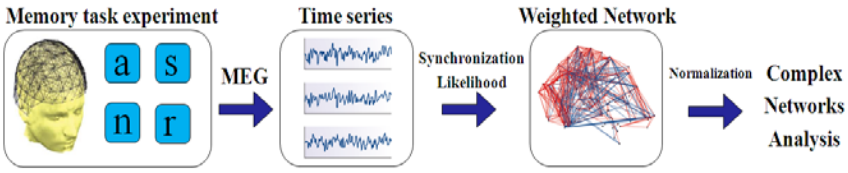
GOOD NEWS
Possibility of clinical applications

Drawbacks

- We are projecting the activity of billions of neurons into a few nodes.
- The activity at each position is strongly influenced by its neighbors.
- Experiments are expensive and it is difficult to find volunteers.
- There exists a great variability of the recorded activity between individuals (and even in the same individual).
- Anatomical and, specially, functional networks are not static.

CAUTION! High risk of GIGO
(Garbage In, Garbage Out)

Modeling Brain Newtworks. Application to MCI/AD



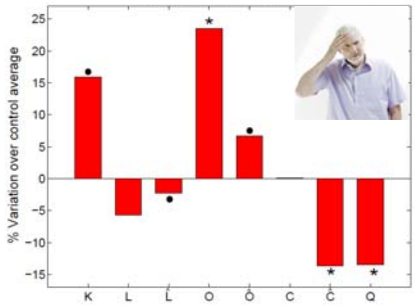


Fig. 4. Percentage of variation and statistical significance. Percentage of variation of the average degree K, average shortest path L and its normalized value $\hat{L} = \frac{L}{L_{ran}}$, network outreach O and normalized outreach $\hat{O} = \frac{O}{O_{ran}}$, clustering C and normalized clustering $\hat{C} = \frac{C}{C_{ran}}$ and network modularity. Circles correspond to $p < 0.03$ and stars to $p < 0.001$, specifically: O ($p = 0.007$), $\hat{C}$ ($p = 0.002$), Q (p = 0.0033), K ($p = 0.018$), L_z ($p = 0.025$) and $\hat{O}$ ($p = 0.027$).

- The network strength *K* increases (+15.9%)
- Network outreach increases (+23.4%)
- The network modularity decreases (-13.5%)
- Normalized clustering decreases (-13.6%)
- Normalized outreach increases (+6.7%):

Modeling Brain Newtworks. Application to MCI/AD

- ❑ **Degree, clustering, outreach and *knn* distributions:**
  - ❑ **MCI networks have nodes with higher connectivity.**
  - ❑ **The clustering increases with the degree (in both Control and MCI).**
  - ❑ **For the same degree, outreach is higher at the MCI group.**
  - ❑ **Networks are assortative**

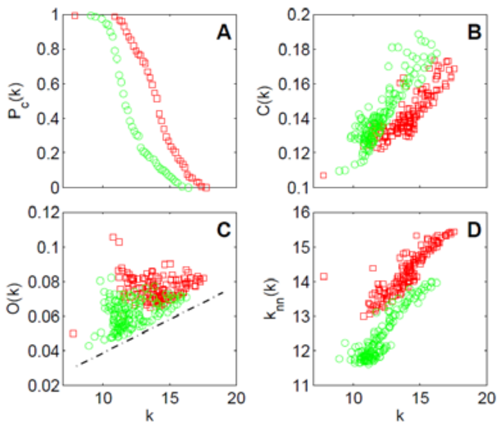


Fig. 3. Several network parameter distributions for the control (green circles) and MCI (red squares) groups. (*A*) Probability distribution of finding a node with a degree higher than k, (*B*) clustering coefficient $C(k)$, (*C*) outreach $O(k)$ and (*D*) average nearest neighbors degree $k_{nn}(k)$.

Modeling Brain Newtworks. Application to MCI/AD

From macroscopic (network) to microscopic (node) analysis

❑ Within module degree:

$$z_i = \frac{k_i - \bar{k}_{c_i}}{\sigma_{k_{c_i}}}$$

❑ Participation coefficient:

$$p_i = 1 - \sum_{c=i}^{N_c} \left(\frac{k_{c_i}}{k_i} \right)^2$$

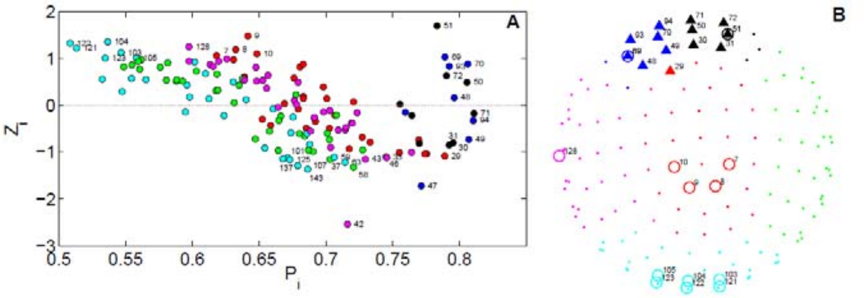
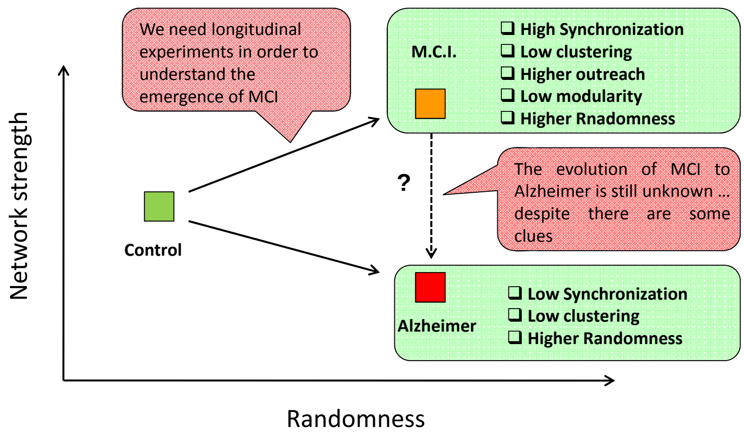


Fig. 6. Community structure and roles. (*A*) Within-module degree z_i for each node in the network of the control group as a function of its corresponding participation coefficient p_i. Only the first 13 nodes with the highest z_i and p_i are labelled. Their positions within the corresponding lobe are marked in (*B*) with circles for those with the highest z_i and with triangles for those with the highest p_i.

MCI/AD. Complex networks methods give useful information (from another perspective) about functional brain networks

We have to be cautious since there is a high variability in the results

Network parameters give hints about how brain functional connectivity is affected by different diseases. In the case of Mild Cognitive Impairment:



CTB center for biomedical technology

Another step further: Network models to explain spontaneous emergence and adaptation of modularity and heterogeneity in complex networks

Balance of segregation and integration processes:

•Segregation (tendency to cluster synchronization) is necessary for maximizing the parallel functioning;
•Integration is essential to perform the different parallel tasks in a coordinated way.

Simultaneously, these networks exhibit peculiar structural properties: they are very heterogeneous (displaying in most cases a scale-free distribution in the connectivity), and they are generally modular (displaying the formation of community structures).

The question: Is it possible to encompass all these features as emergent structures in a simple model of networking units?

CTB center for biomedical technology

Adaptation and spontaneous emergence of modularity and heterogeneity in complex networks

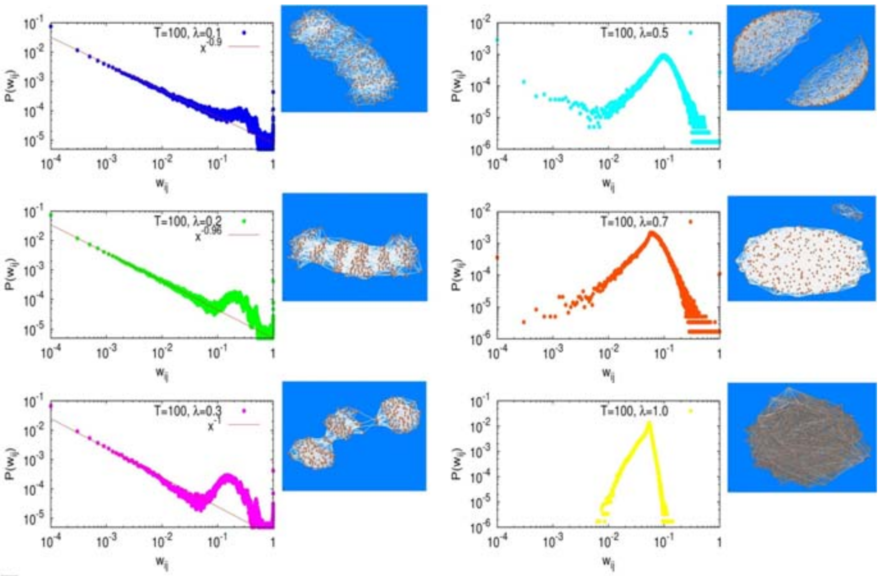
The scales of a network:

Microscale - The scale of a node and its neighborhood
Statistical property of the graph connectivity
Major adaptation mechanisms (Hebbian learning, homeostatic plasticity)
Mesoscale – The scale of a cluster, or community structure
Modules and motifs
Clustering properties, loop properties
Segregation processes and cluster synchronization
Macroscale – The scale of the whole network
Diameter, shortest path, small world properties
Efficiency, vulnerability
Integration mechanisms

The result: Local adaptation processes and coevolution of nodes and links yield spontaneous emergence of modularity and scale-free properties (inhomogeneity)!

CTB center for biomedical technology

Adaptation and spontaneous emergence of modularity and heterogeneity in complex networks



CTB center for biomedical technology

Adaptation and spontaneous emergence of modularity and heterogeneity in complex networks

In the brain, **synchronization** is at the core of the physical mechanisms governing **the transfer and processing of information** at the level of neuronal synapses as well as in the development of cognitive tasks. Synchronization phenomena also **affect the structural features** of the brain, thus playing a crucial role in shaping the neuronal circuitry and in the organization of the axonal pathways.

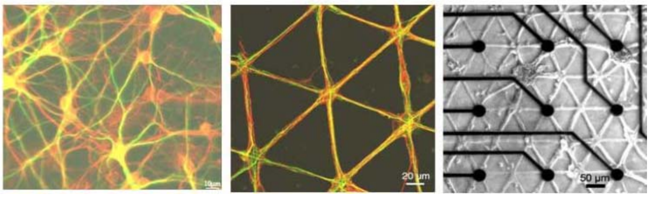
In classical approaches, the ties between units strengthen as their dynamical states become more and more correlated. In theoretical neuroscience this mechanism is known as **Hebbian learning**.

In fact, in real systems the enhancement of some synapses is seen to be counter-balanced by the weakening of others. Such competition, usually denoted as **homeostatic plasticity**, plays a crucial role in counter-acting the positive feedback effects associated with Hebbian learning, as well as in conferring stability to neuronal networks during their development.

We demonstrated that a model of an adaptive network of phase oscillators, in which both mechanisms of Hebbian learning and competition are taken into account, reproduces all at once the typical features of real brain dynamics

Neuronal cell cultures: regeneration, learning

Study of the relationship between structure and function of networks. Application to the analysis of feasibility in cell implantation applications of neurodegenerative diseases



Random and patterned networks. Double-immunostaining of dendrites (red) and axons (green). (Left) – Example of free-forming (random) cultured neural network. (Middle) Patterned cultured networks with 6-fold lattice-like symmetry generated using a novel lithography technique. A few neurons are located at each node of the network and the links are composed of dendrites and axons. (Right) Similar patterned network grown on multi-electrodes-array for recording of the electrical activity. Courtesy of Prof. Eshel Ben Jacob (Tel Aviv University).

Connexinopathies

Target: Human diseases caused by dysfunction in connexins

Detailed description

•Role of Connexin-36 in Epilepsy and Genesis of Brain Rhythms upon Physiological and Pathological conditions

•Pathogenic Mechanism in Myelin Disorders caused by Mutations in Connexin-46.6 and Connexin-43

•Role of Connexins in the Hematopoietic Stem Cell Niches . Neurogenic potential of Bone Marrow Mesenchymal Stem Cells . Explore the pluripotential ability of mesenchymal stem cells and progenitors (MSC/P) to re-establish functional recovery in a model of brain injury.

Laboratories:

Experimental and Computational Neurology

Biomechanics, Biomaterial and Tissue Engineering

Bioelectromagnetism

Bioelectromagnetism

Target: Research on brain communication mechanisms with very low frequency and intensity pulsed magnetic fields. Neurophysiologic basis of pain

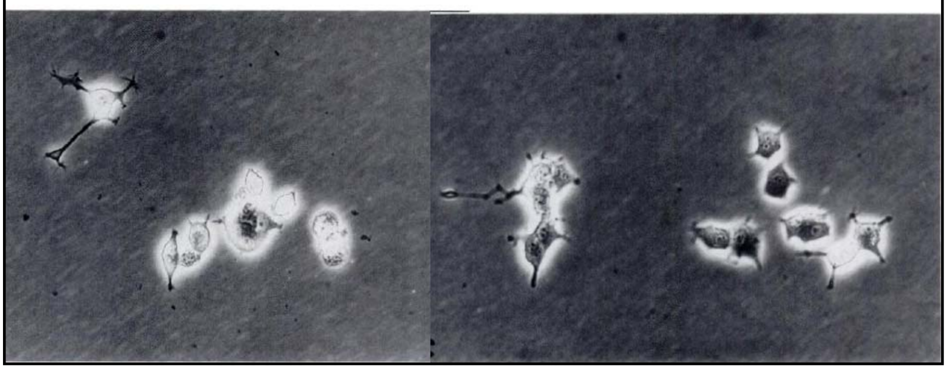
Detailed description
•Research on brain communication mechanisms with very low frequency and intensity pulsed magnetic fields
•New devices and magnetic actuators, fMRI compatible, for clinical applications of low electromagnetic fields: Fibromyalgia, trigeminal neuralgia, migraine, etc.
•Pulsed Magnetic Field Stimulation to enhance Neurite Growth.
•Environmental EMF Dosimetry

Laboratories:
Bioelectromagnetism
Molecular Biology and Biochemistry
Neuroimaging

Contac: Ceferino Maeztú Unturbe

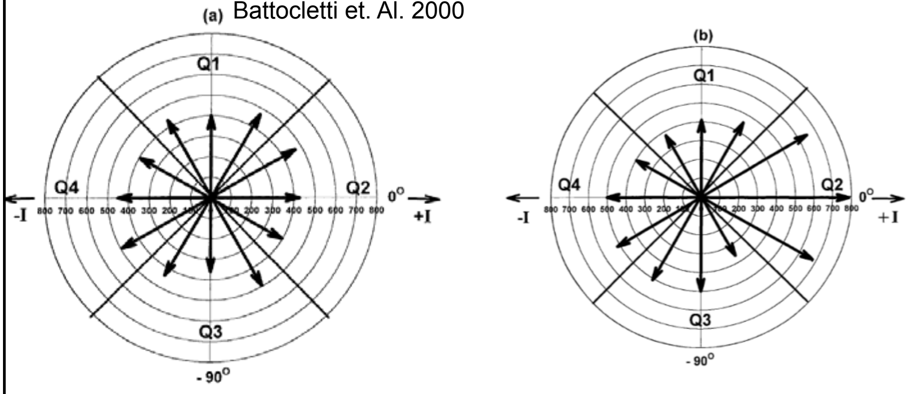
Crecimiento axonal inducido con campos electromagnéticos

"Evidence For Direct Effect Of Magnetic Fields On Neurite Outgrowth",
Blackman et Al. 1993



Resultados previos

"Directed and Enhanced Neurite Growth with Pulsed Magnetic Field Stimulation", Macias, Battocletti et. Al. 2000

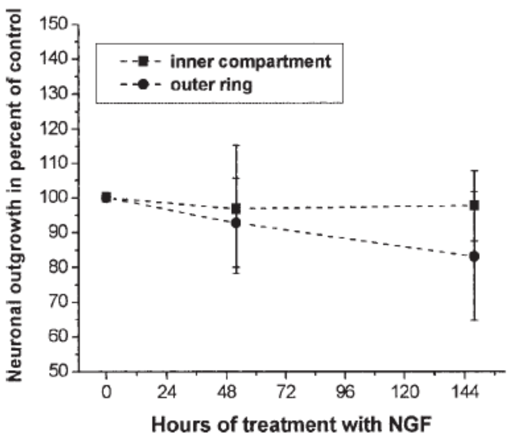


No magnetic field

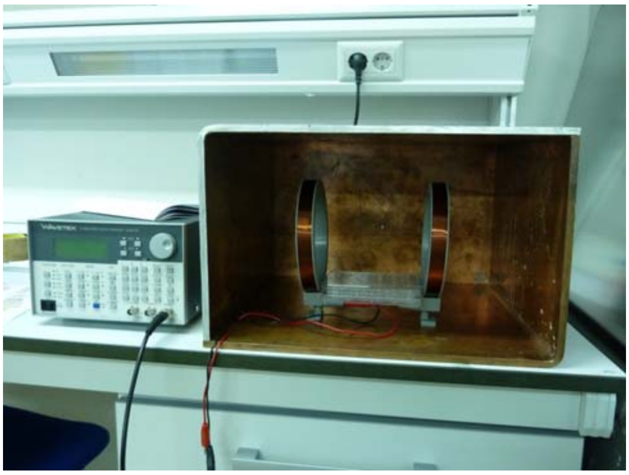
With pulsed magnetic field

Resultados previos

"Neuronal Outgrowth of PC-12 Cells After Combined Treatment With Nerve Growth Factor and a Magnetic Field: Influence of the Induced Electric Field Strenght", Schimmelpfeng et. Al. 2004



Set experimental para la estimulación celular



Biomechanics, Biomaterial and Tissue Engineering

Target: New bioinspired fibers for biomedical applications, collagen-based materials applied to biostructural prosthesis and cell mechanics. Scaffolds to package stem cells

•New bioinspired fibers for biomedical applications
•Collagen-based materials applied to biostructural prosthesis
•Cell mechanics
•Design and manufacturing of biocompatible materials with controlled topologies (single fibers, arrays and networks) derived from both natural (silkworm silk fibroin) and synthetic materials (PLA-PGA copolymers) as method to encapsulate and packaging bone marrow mesenchymal stem cells and progenitors

Laboratories:
Biomechanics, Biomaterial and Tissue Engineering
Experimental and Computational Neurology

Biomedical informatics: Data Mining and Simulation

Target: Integración de información heterogénea multiescala y técnicas de inteligencia artificial para la ayuda al diagnóstico y diagnóstico precoz de patología neurodegenerativas..

•Learning Health System development
•Integration of genomic and clinical databases
•Medical Artificial Intelligence
•Mathematical and computational tools to extract biologically and clinically relevant information from large data sets
•Web services for medical applications

Laboratories:
MIDAS
Cognitive and Computational Neuroscience
Ramón y Cajal Blue Brain Project

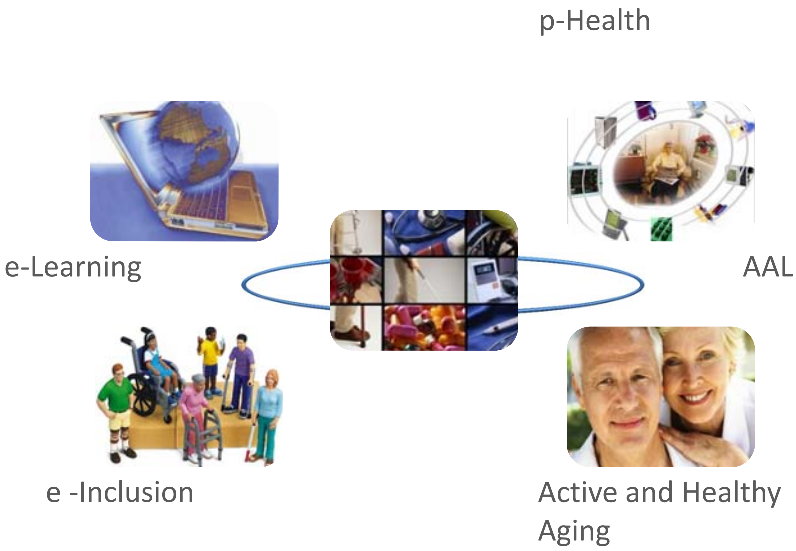
Personalised Care: Chronic disease management and wellness support

Target: Novel devices and systems for habits and daily activities monitoring, and intelligent environments for personalized and ubiquitous health care.

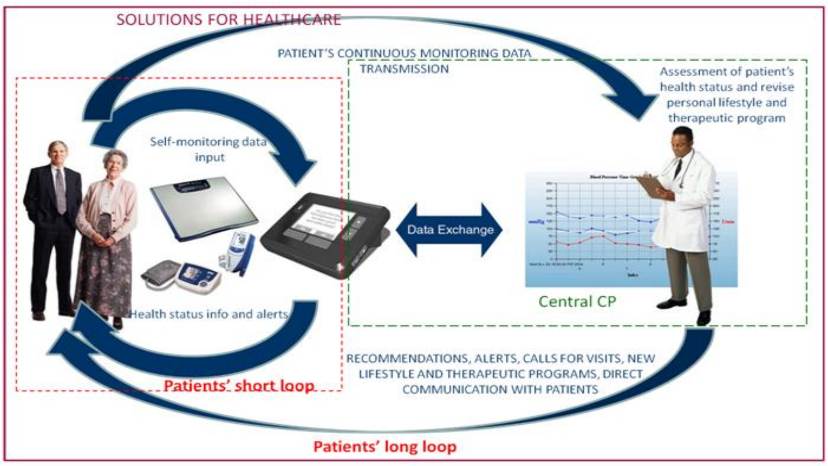
•Novel devices for habits and daily activities monitoring
•Intelligent environments for personalized and ubiquitous health care
•Knowledge extraction. Pattern assessment. Habit assessment
•Personalized health services
•Low cost technologies to support the health of rural isolated communities (EHAS program)

Laboratories:
Personal Health Care Systems (PHealth)
Internet of things and social networks

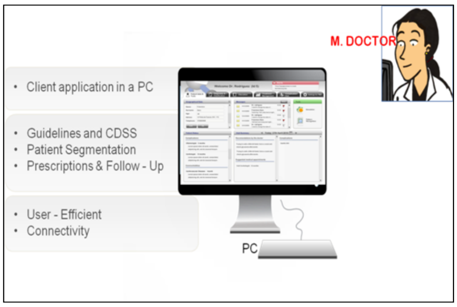
Inteligencia ambiental



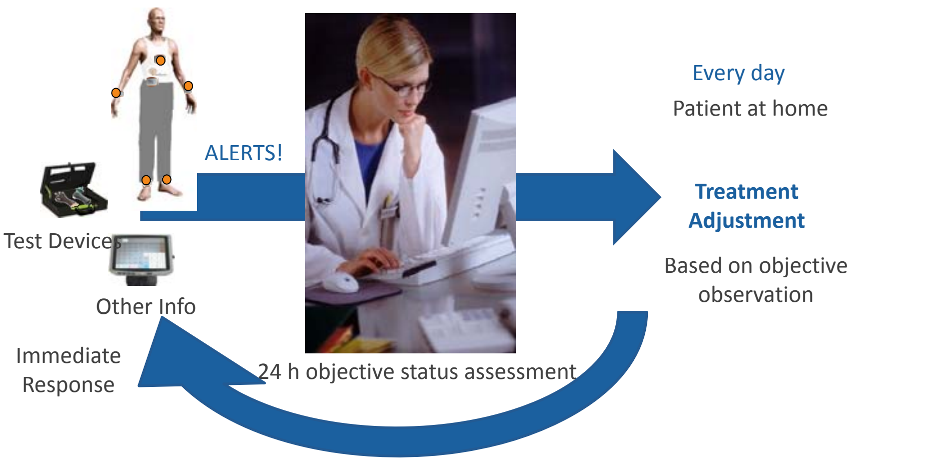
Tecnología para la gestión de pacientes crónicos



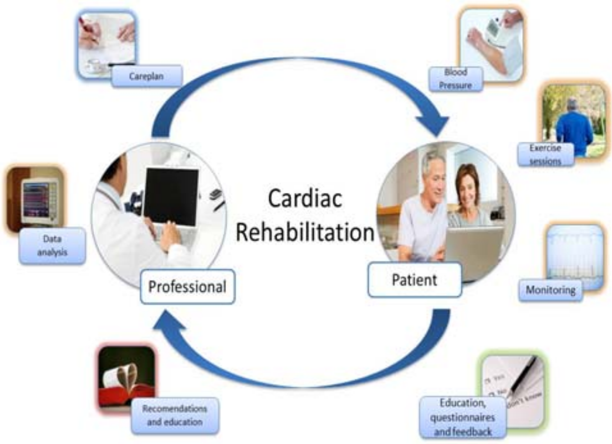
Tecnología para la gestión de pacientes crónicos:Diabetes



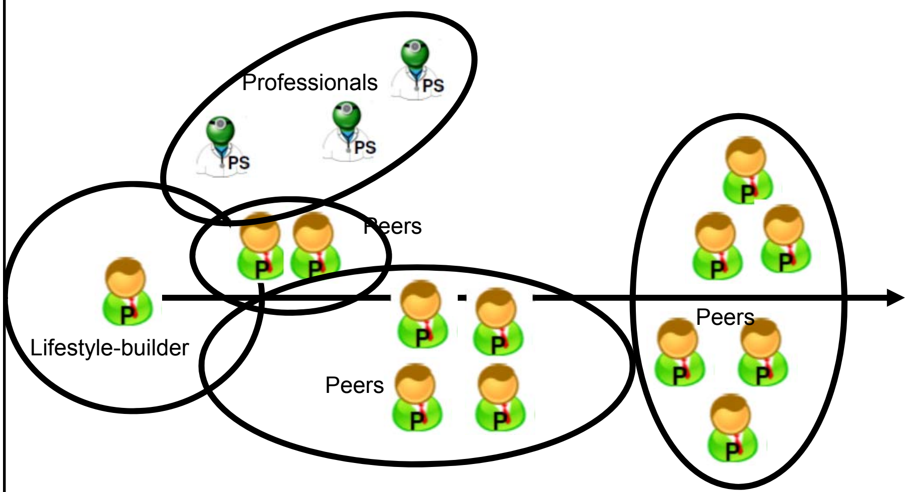
Tecnología para la gestión de pacientes crónicos: Parkinson



Tecnología para la gestión de pacientes crónicos: Cardio



Usos de las Redes Sociales en sanidad



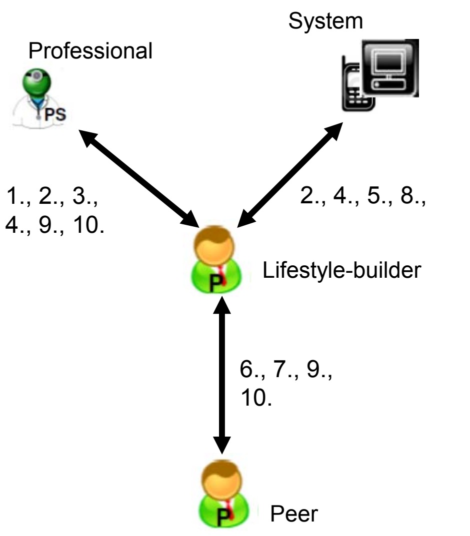
Funciones

1. Prescribe lifestyle and action plan.
2. Configure lifestyle and action plan.
3. Contact with professional.
4. Exchange encouraging guidance.
5. Learn from sound sources
6. Contact with peer.
7. Exchange challenges.
8. Make healthy daily choices.
9. Get involved into healthy groups.

Supervision / non-supervision.

Mobile scenario / home scenario.

On-line mode / off-line mode.



Homomorphic analysis of speech

Target:

Detailed description

Laboratories:

Contact: Pedro Gómez Vilda

Diabetes technologies

Target: Telemedical artificial pancreas and closed/semi closed-loop algorithms and glucose predictive models and prevention of Diabetes Mellitus and cardio metabolic risk.

•Telemedical Artificial Pancreas
•Closed and semi closed-loop algorithms and Glucose predictive models
•Risk management and decision support tools
•Prevention of Diabetes Mellitus and Cardio Metabolic Risk
•Computational modeling of autoimmune response of type 1 diabetes

Laboratories:
Diabetes technologies

Tele-rehabilitation technology

Target: Neurorehabilitation processes modeling, dysfunctional models and hybrid bionics, smart monitoring of cognitive and physical rehabilitation, interactive virtual environments, telemedicine.

•Neurorehabilitation processes modeling, dysfunctional models and hybrid bionics
•Smart monitoring of cognitive and physical rehabilitation
•Interactive virtual environments and content creation and management technologies in neurorehabilitation
•Modeling and smart adaptation of upper-limb neurorehabilitation therapies
•Knowledge management and Data Mining in Neurorehabilitation for the generation of clinical evidence
•Medical imaging based analysis and standardization of structural alterations in acquired brain injury
•Neurorehabilitation Telemedicine

Laboratories:
Simulation, virtual reality and image guiding technologies