



## Fundação para a Ciência e a Tecnologia

### Evaluation Reseach Unit 2013

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#### 1. IDENTIFICATION OF THE R&D UNIT

##### 1.0 Reference

645

##### 1.1 Name of the R&D Unit

Institute of Biophysics and Biomedical Engineering (IBEB)

##### 1.2 Acronym

IBEB

##### 1.3 Coordinator

Pedro Miguel Dinis de Almeida

##### 1.4 Multidisciplinary/interdisciplinary R&D Unit

No

##### Scientific areas

Physics

Bioengineering(Main Scientific Area)

##### 1.5 Profile of the R&D Unit

20% Basic research

80% Applied research and/or Experimental development

##### 1.6 Keywords

Disgnosis and therapy in oncology (breast, brain)

Neuronal biosignals and transcranial stimulation

Human-machine interfaces for rehabilitation

Medical Imaging reconstruction and processing

##### 1.7 Link to the R&D Unit's page on the Internet

www.ibeb.fc.ul.pt

##### 1.8 Unit registration options

#### Resultados Avaliação

#### Programas Doutoramento

#### Avaliação de Unidades 2013

Registo de Unidade

Confirmação na Equipa

Confirmação na Fusão

#### Submissão de Candidatura

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IBEB/FC/UL

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## 2. INSTITUTIONS AND THEIR ROLES

### 2.1 Main Host Institution

Fundação da Faculdade de Ciências da Universidade de Lisboa (FFC/FC/UL)

### 2.2 Other(s) Host Institution(s)

### 2.3 Participating Institution(s)

Institution Name	Host Institution
Faculdade de Ciências da Universidade de Lisboa (FC/UL)	

### 2.4 Institutional commitment

FCUL (Faculdade de Ciências da Universidade de Lisboa) created in 1911, is the participating institution for all its research units (formerly “Instituição de Acolhimento”). FCUL supplies space, general computing infrastructure, communications and, through its foundation (FFCUL - Fundação da FCUL), administrative and financial R&D (research and development) management.

Research units are associated to (one or several) FCUL departments, which are in charge of space allocation and may support interface with FCUL and/or FFCUL (see below) operational services. FCUL is also using space within the University of Lisbon Institute for Interdisciplinary Research, located at the Campo Grande university campus and at walking distance from FCUL, for some of its R&D units in mathematics and in physics.

FCUL associated R&D units have natural access to all FCUL labs and teaching areas to held meetings, seminars and workshops, especially during non-academic periods. R&D units also benefit from IT services, enabling most of them to locate their internet sites within the University servers. Legal, contractual and IP support is also directly provided by FCUL when requested by units.

Administrative and financial management are provided by FFCUL – the host Institution - a non-profit organization recently reclassified as a public institution created in 1993 as an initiative of the FCUL to promote and facilitate scientific research, technology and development services to society, and to organize qualified human resources training, offer consulting expertise and promote knowledge dissemination.

FFCUL acts as the legal front institution of multiple research units, from different scientific fields, carrying out research work and managing financial and administratively R&D (research and development) projects, with more than 400 ongoing projects. Many of these R&D activities are developed together with international teams and are funded both at national and European levels.

FFCUL provides the financial stability, the accounting support and the specialized human resources needed to comply with the overall project applications and financing programs and all different expenses reports required throughout project development. FFCUL human resources include a 12 person team in the financial department and 14 project managers.

The IBEB is located in its own building in the FCUL campus in Lisbon. The building is composed of 1 waiting area, a technical area hosting computer network access facilities, 8 offices, 4 computer rooms (with LINUX and Windows based systems), 2 laboratory areas, 1 seminar room with 25 seats, 1 meeting room, 1 library with approximately 300 titles and study locations and a secretary room. One of the laboratories houses a MEG system within the only magnetic shielded room in Portugal. The Unit also has a computer cluster located at the FCUL Informatics Center composed of 40 LINUX based processors.

## 3. R&D UNIT DESCRIPTION AND ACHIEVEMENTS

### 3.1 Description of the R&D Unit

The Institute of Biophysics and Biomedical Engineering (IBEB) is an autonomous Research Unit of the Faculty of Sciences of the University of Lisbon (FCUL) since 1992, and a research unit funded by the Fundação para a Ciência e a Tecnologia (FCT) since 2003. IBEB is legally represented by the FFCUL. IBEB has been evaluated as Excellent in 2003 and as Very Good in 2007, following independent evaluation by an FCT external international scientific committee. IBEB is located in its own building in the FCUL campus in Lisbon. The building is composed of 1 waiting area, a technical area hosting computer network access facilities, 8 offices, 4 computer rooms (with LINUX and Windows based systems), 2 laboratory areas, 1 seminar room with 30 seats, 1 meeting room, 1 library with approximately 300 titles and study locations and a secretary room. One of the laboratories houses a MEG system within the only magnetic shielded room in Portugal. The Unit also has a computer cluster located at the FCUL Informatics Center composed of 40 LINUX based processors. IBEB is a research unit in Biomedical Engineering with a strong focus on Neurosciences and Oncology. Between 2008 and 2012, the number of FTE Ph.D. members of IBEB increased from 14 to 17. Among these, 9 people had a working contract with FCUL (with tenure and invited) and shared their activities between teaching and research. During this period, the average number of teaching hours for these members has been close to ten hours per week. The other IBEB members had employment relationships with other higher education institutions with a direct relation to health technology. By the end of 2012 IBEB had 2 post-doctoral fellows (one FCT Ciência researcher and a Marie Curie fellow).

The main objectives for the period 2008-2012 were to continue to carry out high quality research and scientific training in Biophysics and Biomedical Engineering. This was pursued along existing lines of research, which have a clear focus on human health and brain function. The Institute also aimed to continue playing a major role in postgraduate training in Biophysics and Biomedical Engineering, through its close connection with the Faculty of Science of the University of Lisbon. The Faculty of Science offers an integrated MSc degree (3+2 years in accordance with Bologna rules) in Biomedical Engineering and Biophysics since September 2007, as well as a 3rd cycle (PhD) in the same area (3 to 4 years to obtain a PhD), since September 2008, providing a pool of high-quality students. IBEB's research work was planned to contribute to the improvement of knowledge in medical signal and medical image processing and in the modeling of data acquisition and physiological systems. The general areas of non-invasive electromagnetic brain stimulation, Magnetic Resonance Imaging (MRI) and Nuclear Medicine imaging, continued to deserve special attention as well as those of realistic physiological

modeling and physiological signal processing. A large part of this research work was done in collaboration with hospitals, clinics or other health institutions, in Portugal and abroad (the names of some of these institutions can be found later in this document) fulfilling the objectives outlined for this period, which in addition entailed increased attention to institutional collaboration with other national and international research institutes and/or universities. IBEB has been able to attract researchers (PhDs) from other institutions, and still seeks to increase the number of PhD members doing research at its facilities, particularly by recruiting new post-docs who can dedicate 100% of their time to research. The integration of new PhD and MSc students in ongoing projects also was (and still is) a major goal. Given the applied and technological nature of some of the research work carried out at IBEB, the concern to transfer technology and knowledge to society is an enduring one. IBEB has been managed by the Unit's scientific coordinator (Director) after listening to its scientific council, which has been composed by all of its integrated Ph.D. members. The unit's Director was responsible for the coordination of scientific activities. The Scientific committee (consisting of all PhD members) met regularly to discuss the scientific strategy. The unit also had an external advisory committee composed by well-recognized international scientists.

During 2008-2012, IBEB was organized into 2 research groups ("Functional Imaging" and "Signal and Image Processing"). The activities of these groups were autonomous but also submitted to common coordination efforts, in order to strike a balance between scientific cohesion and diversity that was deemed appropriate for the size and scope of the unit and for the common outlined goals. One of these groups has been studying image acquisition, reconstruction and quantification methods that use ionizing radiation (Positron and Single Photon Emission Tomography (PET and SPECT), X-ray. Recently (2011), the arrival of a Marie Curie fellow opened up a new line of research on the use of Ultra-Wide Band (UWB) Radar Waves in Breast Cancer detection. The activities of this group have been mainly focused on: the development of new imaging devices, (Clear-PEM and the Clear-PEM Sonic prototypes) and the development of new and more efficient strategies for image reconstruction and quantification.

The other group has been focused on studying the interaction of electromagnetic fields with neurons through the development of realistic models of the head and on implementing and applying brain connectivity methodology. The latter used newly developed MRI pulse sequences for susceptibility weighted imaging and diffusion kurtosis. More recently, we have introduced thematic lines on multimodal imaging, with a special emphasis on PET-MRI and PEM-UWB, Applied Photonics and Brain-Computer Interfaces. All research at IBEB was conducted with a strong collaboration with national and international research, medical and industrial institutions. In Portugal, these institutions include the Lisbon University Hospital, the Champalimaud Foundation, the Hospital da Luz, the University of Coimbra, among other. Internationally, these include the NIH (USA), the King's College London (UK), the Research Center Jülich (Germany), the CERN (France-Switzerland), the University of Ireland Galway (Ireland) among others.

IBEB's funding has been obtained so far using three different means:

- Through the FCT unit funding, indexed to the institute's scientific production and teaching impact and to the number of its FTE Ph.D. members.
- Through research projects, submitted either to the FCT, to QREN, to AdI and to the European Union.
- Through indirect funding from industrial partners, who have in some cases financed Ph.D. or Post-Doctoral fellows of IBEB.

This funding leveraged IBEB's research quality and visibility.

### 3.2 Major achievements

The major achievements of IBEB in the 2008-2012 period were the following:

2008

- Development of small animal Positron Emission Tomography data simulation using Monte Carlo approaches.
- Development of 2D and 3D statistical image reconstruction algorithms for a small PET dedicated system, named Clear-PET.
- Development of non-supervised automatic neural networks for pre-classification of nuclear medicine images.
- Development of a system to enhance stability of melanin incorporated into liposomes in layer-by-layer film.
- Prediction of the response of cortical neurons to Transcranial Magnetic Stimulation (TMS) stimuli taking into account the temporal waveform of the stimulus distribution of the electric field induced by TMS in a heterogeneous model of a cortical sulcus.
- Calculation of the effect of electrode size and separation on the distribution of the electric field and current stimulation (tDCS).
- A new post-doc was hired to work on a realistic head model for simulations of non-invasive brain stimulation, in the context of an EC funded project (HIVE).
- Implementation of a system for simultaneous tDCS/electroencephalography (EEG) for epileptic patients.
- Development of models to study the autonomic control of heart activity.
- Development of tools to study the correlation of EEG and Magnetoencephalography (MEG) signals over different brain areas.

2009

- Development and validation of tools for the measurement of brain effective connectivity.
- Development and validation of a procedure for automatic sleep staging based on polysomnography data.
- Development and validation of a procedure for fast diagnosis of obstructive sleep apnea, based on oronasal pressure data.
- Development and validation of a procedure for artifact removal applied to dermatological data.
- Development of a realistic head model based on MRI images for electric field calculations.
- Optimization of 2D and 3D image reconstruction algorithms for the Clear-PEM machine.
- First reconstructions of real clinical data issued from the Clear-PEM machine.
- A new researcher, recruited through the Ciência 2008 program, joined the group in December 2009.
- A new post-doctoral researcher joined the group in April 2009.
- New collaboration with Siemens and the DFFZ Center in Jülich on the acquisition and image reconstruction of data from a simultaneous PET/MRI system.

2010

- Development of a new method to allow the acquisition of Diffusion-Weighted MR images using Fast Spin Echo Pulse Sequences (collaboration with Imperial College, London).
- Development of a protocol to acquire resting-state functional MRI images of preterm babies (collaboration with Imperial College, London).
- A simulation study comparing eddy current levels of different Diffusion MR pulse sequences (collaboration with Oxford University and Imperial College, London).
- Development and validation of a method for the study of empirical mode decomposition phase-locking in brain (MEG) data with an application to fronto-temporal dementia (collaboration with MRC-Cognition and Brain Sciences Unit, Cambridge, UK).

- Study of the complexity of brain activity using the Multiscale Entropy Measure applied to EEG signals of autism patients (collaboration with CIDDR, Cambridge, UK).
- Improved realistic head model used for a variety of calculations of the electric field distribution for different electrode montages.
- Implementation of a procedure to map the results of electric field calculations onto cortical surface meshes with different resolutions for use in other software packages.
- Implementation of a procedure to place stimulation electrodes reproducibly on the scalp of the realistic head model.
- Implementation of geometry-specific image reconstruction algorithms for the Clear-PEM system, particularly for small animal imaging.
- Feasibility studies of new imaging prototypes for breast imaging using the Clear-PEM system in SPET mode.
- Implementation of novel statistical image reconstruction methods in digital radiology.
- Implementation and testing of novel Computed Assisted Detection systems for digital mammography.

2011 & 2012 (presented ensemble side they refer to a single strategic activity program submitted to the FCT):

- IBEB entered a COST initiative on PET/MR.
- IBEB proposed a new COST initiative in breast imaging methods that brings together 15 European and non-European countries.
- Industry connections within the HIVE project allowed for the recruitment of a post-doctoral researcher (effective 2013) at zero cost.
- New collaboration protocols with Champalimaud Foundation and Portuguese Oncology Institute (Lisbon).
- Collimator setups for Clear-PEM in SPET mode for scintimammography tested with appropriate image reconstruction algorithms.
- Simulations based on MR, PEM and radar breast imaging targeted to lesion detection.
- Testing of simulation algorithms for tomosynthesis.
- Refinement of the realistic head model for computation of electric field distribution.
- Large-scale simulation framework for benchmarking of brain connectivity methods, specifically Granger causality applied to fMRI.
- Graphical User Interface for the application of Wavelet Coherence analysis to brain functional data.
- Motion correction algorithm applicable to single-shot Fast Spin Echo Diffusion sequences.
- New software tools for the application of susceptibility weighted imaging and diffusion kurtosis imaging, with an application to breast MR imaging in the latter case.
- First version of a software tool for the analysis of brain connectivity with view to application to post-traumatic epilepsy.

Throughout these years, one of the main contributions of IBEB was the scientific training of the majority of the Portuguese scientific staff in its areas of expertise. Most of these people are now working in research or teaching institutions, ranging from Higher Education institutions in Portugal to Cambridge or Harvard Universities.

### Key Publications

Marquez-Ruiz, J., et al., Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits. *Proceedings of the National Academy of Sciences of the United States of America*, 2012. 109(17): p. 6710-6715. Times Cited: 14 Impact Factor: 9.737

Montez, T., et al., Altered temporal correlations in parietal alpha and prefrontal theta oscillations in early-stage Alzheimer disease. *Proceedings of the National Academy of Sciences of the United States of America*, 2009. 106(5): p. 1614-1619. Times Cited: 47 Impact Factor: 9.737

Peterchev, A.V., et al., Fundamentals of transcranial electric and magnetic stimulation dose: Definition, selection, and reporting practices. *Brain Stimulation*, 2012. 5(4): p. 435-453. Times Cited: 5 Impact Factor: 4.538

Rossi, S., et al., Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, 2009. 120(12): p. 2008-2039. Times Cited: 503 Impact Factor: 3.144

Catarino, A., et al., Atypical EEG complexity in autism spectrum conditions: A multiscale entropy analysis. *Clinical Neurophysiology*, 2011. 122(12): p. 2375-2383. Times Cited: 12 Impact Factor: 3.144

Salvador, R., et al., High permeability cores to optimize the stimulation of deeply located brain regions using transcranial magnetic stimulation. *Physics in Medicine and Biology*, 2009. 54(10): p. 3113-3128. Times Cited: 3 Impact Factor: 2.701

Nunes, R.G., et al., Performance of single spin-echo and doubly refocused diffusion-weighted sequences in the presence of eddy current fields with multiple components. *Magnetic Resonance Imaging*, 2011. 29(5): p. 659-667. Times Cited: 3 Impact Factor: 2.060

Herzog, H., et al., High resolution BrainPET combined with simultaneous MRI. *Nuklearmedizin-Nuclear Medicine*, 2011. 50(2): p. 74-82. Times Cited: 19 Impact Factor: 1.322

Oliveira, N., et al., Optimization of 2D image reconstruction for positron emission mammography using IDL. *Computers in Biology and Medicine*, 2009. 39(2): p. 119-129. Times Cited: 2 Impact Factor: 1.162

Janeiro, L., et al., Digital Breast Tomosynthesis, in *Mammography: Screening, Results and Risks*, A. Palmetti and R. Roux. 2011, Nova Science Publishers.

### 3.3 External Advisory Committee Reports

R&D Unit	File
Instituto de Biofísica e Engenharia Biomédica	 <a href="#">2012_External_Review_final.pdf</a>

### 3.4 Composition of the External Advisory Committee

R&D Unit	Member Name	Institution
Instituto de Biofísica e Engenharia Biomédica	Fernando Lopes da Silva	University of Amsterdam - The Netherlands

Instituto de Biofísica e Engenharia Biomédica	Peter Jezzard	University of Oxford - United Kingdom
Instituto de Biofísica e Engenharia Biomédica	Riitta Hari	Aalto University - Finland
Instituto de Biofísica e Engenharia Biomédica	Brian Hutton	University College London - United Kingdom

### 3.5 Brief description of the output indicators 2008/2012 of the research team of the new unit that support the vision and objectives of the strategic program

During the evaluation period (2008-2012), IBEB's researchers were able to produce a growing number of scientific and educational outputs that support the idea that this team will be able to fulfill the objectives proposed in the presently proposed strategic program. Please refer to PART B of this proposal for additional information on each objective for the 2015-2020 period (numbered O1 to O10).

Objective O1: "Support creative and ambitious research that addresses important scientific questions in Biomedical Engineering":

Between 2008 and 2012, IBEB researchers were able to increase not only the number of publications, but also the impact factor of those publications, publishing in the journals with high impact factors in the field of IBEB's expertise. This, together with the 5 five prizes awarded for "Best presentation" in conferences show that we are, in fact, able to tackle important scientific questions in Biomedical Engineering and that the international scientific community recognises thus effort. In particular, some of IBEB's Ph.D. members are included in referee and editorial boards of international scientific journals (e.g. Computers in Medicine and Biology, Medical Physics, Progress In Electromagnetics Research, Journal of Neural Engineering, Neuroimage).

Objectives O2, O3 and O6: "Emphasize multi- and inter-disciplinary approaches to Biomedical Engineering", "Contribute to the use of physical and engineering principles in Diagnostics and Therapy" and "Work to explore clinical, translational and multi-disciplinary research opportunities":

Although our team has been multidisciplinary, composed by Engineers in Physics, Biomedical Engineers and Mathematicians, almost all our publications and conference presentations are co-authored by medical doctors and many of our models are currently being used in clinical environment or in other research projects. Our publication track record clearly shows that we are able to contribute to translational from pre-clinical to clinical research. In fact, the vast majority of our publications resulted from projects developed in collaboration with international institutions which are among the most prestigious in the world (e.g. National Institute of Health (USA), CERN, University College of London, King's College of London, Cambridge University). As a result, IBEB's achievements increased its attractiveness for international researchers. During the evaluation period, IBEB hosted post-docs from China, Ethiopia and Austria, PhD students from Hungary and Iran and undergraduate students from different European countries and Brazil. IBEB's members have also been invited to participate in several international projects and are currently coordinating a COST Action funded by European Commission and participating in two others. All these indicators clearly indicate that we will be able to accomplish the objective O7: "Develop strategic partnerships that support and complement IBEB's scientific strengths". We have also stated as objectives to "Support Biomedical Engineering training of undergraduate, Ph.D. and postdoctoral researchers" and "Increase young people's enjoyment and aspirations in Biomedical Engineering"- respectively O5 and O10. Our indicators clearly show an increase in the number of thesis supervised and, with our research and presentations in high schools and national student forums, we have helped to maintain the master program in Biomedical Engineering and Biophysics in FCUL the highest ranked undergraduate program offered by FCUL.

We also aim to fulfil objectives O8 and O9, to "Develop close interactions with industry and facilitate innovation" and to "Engage effectively with the society":

Our recent history shows that we will be able to achieve these objectives. In fact, during the last years, we have been able to sign 10 collaboration protocols with companies and health institutions, confirming a high degree of confidence of these institutions on IBEB's research. Projects developed during the evaluation period were awarded in 2013 with significant innovation awards, namely the Vodafone Mobile Data Challenge, the ANACOM URSI Award and finally the BES Innovation award, which is probably the most prestigious innovation award attributed in Portugal. These awards clearly demonstrate the ability of IBEB to fulfil the above objectives. In addition, IBEB members are involved in the board or are acting as scientific consultants for different Medical Technology start-ups. IBEB members have also been consulting for one of the major hospitals in the Lisbon area. IBEB is the only research institution in Portugal working in topics such as Ultrawide Band (UWB) Radar for breast cancer detection, Transcranial Electromagnetic Stimulation (TMS, tDCS) or Image Reconstruction for Positron Emission Mammography (PEM). The coupling of this expertise, the creation of new state-of-the art research lines in BCI and MPI and multi-modality imaging and the housing of the only magnetic shielded room in Portugal, will help to make IBEB "a research infrastructure with unique facilities in Portugal" (objective O4). To fully accomplish this, IBEB must reinforced with state-of-the art experimental devices and human resources. This need is justified on Part B of this document.

## 4. FUNDING 2008/2012

### 4.1

Description	2008	2009	2010	2011	2012	TOTAL (€)
Pluriannual Programme/Strategic project	33750	47438	33206	7204	82351	203949
FCT-funded projects	215	18971	26316	18772	30868	95142
European Commission-funded projects	6895	61774	46916	32600	31905	180090
Other international projects	0	0	0	0	0	0
Other national projects	86877	16210	5114	0	0	108201
National industry projects	0	0	0	0	0	0
International industry projects	0	0	0	0	0	0
TOTAL (€)	127737	144393	111552	58576	145124	587382

## 5. GENERAL INDICATORS 2008/2012

### 5.1

Description	2008	2009	2010	2011	2012	TOTAL ( $\Sigma$ )
No. of researchers	36	37	33	27	24	157
No. of integrated researchers	14	17	17	17	17	82
No. of technicians and administrative staff	1	1	1	1	1	5
PhD theses under the supervision of integrated members	4	2	3	3	1	13
Publications in international peer reviewed journals	4	7	4	10	12	37
Books and chapters of international distribution	0	0	0	1	4	5
Models	4	6	4	4	8	26
Patents	1	0	0	0	0	1
Prototypes	0	2	0	0	0	2
Industry research contracts	1	0	0	0	0	1
Research contracts with national or international bodies	0	0	1	2	2	5
Master Thesis	8	5	2	5	24	44
Presentations at scientific conferences	15	18	19	35	60	147
Organisation of scientific meetings	1	1	1	1	2	6

### 5.2 Overall description of indicators and research outputs/Highlights

IBEB's track record during this evaluation period shows a consistent growing in all indicators. This is particularly notorious in indicators related with education (number of thesis supervised) and in knowledge dissemination indicators (e.g. number of conference presentations). Indicators from 2013 confirm this increase, e.g. the number of publications in peer-reviewed journals has already improved to 16. This consistent increase in scientific production has been followed by an increase of the recognition by scientific organizations and enterprises. During this period, IBEB's members were awarded with five prizes of "Best presentation" in conferences and projects developed during this period were awarded in 2013 with significant innovation awards, namely the Vodafone Mobile Data Challenge, the ANACOM URSI Award and finally the BES Innovation award, which is probably the most prestigious innovation award attributed in Portugal.

Furthermore, IBEB's members make a significant effort each year in transferring knowledge to society by organizing, together with the students from the Master in Biomedical Engineering and Biophysics, the "Workshop on Biomedical Engineering", which is probably the most attended scientific event on Biomedical Engineering that takes place in Portugal annually.

An indicator that must be highlighted is the number of models implemented. This indicator demonstrates the interaction between the Institute and hospitals and other research centers, since the majority of these models are currently being used in clinical environment or in other research projects.

IBEB was able to sign a considerable number of contracts with National Bodies, specifically two contracts in the context of programs Ciência 2008 and Ciência 2009 and an increasing number of contracts with FCT for research projects. With the financial limitations that presently affect Portuguese institutions, the number of financed projects obtained by IBEB must be stressed, since in the 2012 FCT call for R&D projects IBEB was responsible for 10% of all accepted projects submitted by FCUL's research centers. In 2013 IBEB has also been selected to be the host of an FCT funded Researcher for a period of 5 years.

IBEB's achievements increased its attractiveness for international researchers. During the evaluation period, IBEB hosted post-docs from China, Ethiopia and Austria, PhD students from Hungary and Iran and undergraduated students from different European countries and Brazil. IBEB's members have also been invited to participate in several international projects and are currently coordinating a COST Action funded by European Commission and participating in two others.

These merits are also acknowledged by national and international companies, with whom IBEB has signed research contracts and protocols, and by venture capital investors, who have recently invested in a company co-founded by FCUL and other institutions, as a result of scientific projects in which IBEB has participated.

In summary, during this period IBEB was able to fulfil its main objectives: to increase its scientific and educational outputs, to increase its internationalization and visibility, to diversify its funding sources and to contribute to the social and economic development.

## 6. SCIENTIFIC COMPONENT – STRATEGIC PROGRAMME 2015/2020

### 6.1 Abstract in Portuguese for publication

O principal objetivo do IBEB para os próximos anos é o de desenvolver-se de forma sólida como um centro de referência nacional e internacional na área da Engenharia Biomédica. Para isso, a investigação do IBEB será focada em duas áreas-chave: neurociências e oncologia. O IBEB participou já em importantes contribuições para os temas de investigação mencionados, por exemplo através do desenvolvimento de métodos de reconstrução de imagens em sistemas de PET dedicado à mama, da modelação numérica do processo de estimulação do cérebro com campos electromagnéticos e da implementação de algoritmos para estudar a conectividade do cérebro a partir de dados de MRI. Iniciámos recentemente novos tópicos de investigação relacionados com estes temas: a utilização de ondas de radar de banda ultra-larga aplicadas à detecção do cancro da mama, o

desenvolvimento de sistemas de imagem médica multimodal, o desenvolvimento de métodos de aquisição de imagens de MRI, a utilização de fotónica aplicada e a utilização de interfaces cérebro-computador. Recentemente a equipa do IBEB também incorporou novos membros com experiência na área da radioterapia externa, que complementam a experiência da unidade em imagem médica.

O IBEB possui uma organização científica simples, consistindo num único grupo de investigação que aborda várias linhas temáticas de modo complementar. Os membros do IBEB contribuirão para várias linhas de investigação tendo cada uma delas um investigador sénior, que será responsável pela coordenação de todos os projetos de investigação relacionados com essa linha. Com esta organização, a unidade consegue refletir de forma adequada a formação e treino científico da maior parte dos seus investigadores. O IBEB será dirigido por um diretor da unidade que será auxiliado por um conselho científico, composto por todos os seus membros doutorados. Terão lugar reuniões regulares entre o diretor e o conselho científico e entre os responsáveis pelas linhas temáticas de modo a que a estratégia da unidade possa ser continuamente discutida e adaptada em face de novos dados científicos.

Serão criadas novas oportunidades apoiadas por fontes de financiamento nacionais e internacionais, em particular as originadas das linhas temáticas do programa H2020. Até o final de 2020, o número de membros doutorados no IBEB deverá subir pelo menos para 20. Além disso, a aquisição e construção de equipamentos "state-of-the-art" alargará e fortalecerá o âmbito da investigação em áreas emergentes e competitivas da Engenharia Biomédica. Este equipamento potenciará de modo significativo a qualidade e quantidade da investigação realizada em áreas importantes para a estratégia científica do IBEB: espectroscopia cerebral no infravermelho próximo (fNIRS), TMS com EEG e neuronavegação simultânea, UWB para cancro da mama e imagens com partículas superparamagnéticas (MPI). Esta última linha tirará partido da sala blindada a campos magnético que existe no IBEB e que é a única instalação deste género em Portugal. Este equipamento também irá permitir novas oportunidades para investigadores de pós-doc. Fortaleceremos a tradição de ligações nacionais e internacionais fortes com centros de investigação e hospitais, através de um aumento das conexões com a indústria, tanto a nível nacional como internacional. Essas conexões serão estabelecidas através de protocolos de colaboração científica, acordos de compatibilidade, contratos de investigação e submissões de patentes.

O financiamento é crucial para que estas metas possam ser alcançadas. Um dos objetivos do IBEB é tornar-se menos dependente de fontes de financiamento nacionais através da participação em financiamentos internacionais, em particular no quadro da iniciativa H2020.

Outro objetivo importante da estratégia da IBEB para os próximos anos é continuar a ter um papel fundamental no ensino avançado em áreas relacionadas com a Engenharia Biomédica. O IBEB é a unidade de investigação associada ao curso de mestrado integrado Engenharia Biomédica e Biofísica que é oferecido desde há 6 anos na Faculdade de Ciências da Universidade Lisboa. Este curso encontra-se agora em processo de acreditação e continuará a acolher quarenta novos alunos a cada ano. O IBEB está ainda envolvido na proposta de um novo programa internacional de doutoramento em Engenharia Biomédica em conjunto com o University College London, o King's College London e a Universidade da Irlanda em Galway.

Por fim, o IBEB vai procurar desempenhar um papel importante na ligação entre a comunidade científica, a indústria e o público em geral. Para isso o website do IBEB será renovado e será criado um conselho consultivo empresarial do qual fará parte, entre outras empresas a Siemens Healthcare Portugal. As redes sociais (Facebook) continuarão a ser utilizadas como o meios de comunicação preferenciais para divulgar os principais acontecimentos da vida científica formativa do IBEB. Para além disso o IBEB continuará a organizar um workshop anual sobre Engenharia Biomédica, que tem tido, desde o seu início em 2006, uma média de presenças de cerca de duas centenas de pessoas.

## **6.2 Abstract in English for evaluation**

IBEB's main goal for the coming years is to strengthen its positioning as a national and international reference research and post-graduate training unit in the field of Biomedical Engineering. To do so IBEB's research efforts will be focused on two key areas: neuroscience and oncology. Investigation in these areas will follow four thematic lines: brain connectivity and dynamics, cancer therapy and drug-delivery, brain stimulation and neuro-rehabilitation, medical imaging and diagnosis. These lines have been defined since they are of key importance to the two chosen areas of research and they adapt well to the skills of the members that compose IBEB's research team. IBEB has already made important contributions to research topics related to these thematic lines, such as image reconstruction in PET systems, numerical modelling of brain stimulation techniques and implementation of algorithms to study brain connectivity from fMRI data. New research topics relevant to the aforementioned thematic lines have also started to be investigated: ultra-wide band radar waves in breast cancer detection, multimodal imaging, development of MRI acquisition methods, applied photonics and brain-computer interfaces. Recently IBEB's research team has also incorporated new members with expertise in the field of radiotherapy, which complements the unit's strong background on medical imaging.

To pursue these objectives, IBEB has chosen to simplify its organization. To reflect the similar background of most of the researchers, a single research group will be created. Its different members will contribute to one or more thematic lines. Each line will have one assigned senior investigator who will be responsible for coordinating all research projects related to that line. IBEB will continue to be governed by a unit's Director who will be aided by a scientific council, composed of all the PhD members. Monthly meetings between the Director and the scientific council will take place allowing for the unit's strategy to be continually discussed and adapted. Thematic line coordinators will meet each 2 weeks.

To become increasingly more competitive, IBEB needs to further increase the number of post-docs working in these areas. Thus new training opportunities will be offered in IBEB supported by national and international funding sources. By the end of 2020, the number of Ph.D. members in IBEB is expected to have risen to at least 20. Furthermore, the acquisition and construction of state-of-the-art equipment will widen the research's scope in emergent and competitive areas of Biomedical Engineering. This equipment will also allow IBEB to continue to be in line with research performed in areas important to IBEB's scientific strategy: near-infrared spectroscopy (NIRS) system for the brain, TMS with neural navigation and simultaneously recording EEG, UWB radar for breast cancer and magnetic particle imaging (MPI). The latter will take advantage of IBEB's magnetic shielded room which is the only facility of its sort in Portugal. The new equipment will also allow post-doc students to have advanced training opportunities in IBEB's labs. Expanding on IBEB's tradition of strong national and international connections with research centers and hospitals, an increase in the connections to the industry, both nationally and abroad, will also be sought. These connections will be established via scientific partnerships, non-confidentiality agreements, research contracts and patent submissions.

Funding is crucial for these goals to be reached. IBEB wants to increase its funding and to become less dependent on national funding sources by applying to international funding opportunities. The latter can be based either on the European community or specific research funds based on charity institutions, industry, or research funds available in countries like Brasil.

Another important goal of IBEB's strategy for the next years is to continue to have a key role in advanced teaching in areas related to Biomedical Engineering. IBEB leads a 6-year running Master's course on Biomedical Engineering and Biophysics at the Faculty of Sciences of the University of Lisbon. This course is now receiving quality accreditation and will continue to host forty new students each year. IBEB will also be proposing a new international PhD program in Biomedical Engineering together with University College London, King's College

London and the University of Ireland at Galway. The best performing students will be invited to continue their research in IBEB by means of public or private funding. Finally IBEB will seek to play an important role in the liaison between the scientific community, industry and with the general public. To do so IBEB's website will be renewed and an industrial advising committee with the participation of local and national industry representatives (Siemens Healthcare Portugal has already accepted) making information regarding research more easily available. Social networks (Facebook) will also continue to be used as the preferential media to publicize updates of IBEB's main accomplishments. This will also be done by adequately disseminating the obtained results through the appropriate platforms, which include the FCUL information system and mass media when relevant. IBEB will continue to organize a yearly workshop on Biomedical Engineering, which has an average attendance of about two hundred people and will host an annual series of scientific seminars open to the general public.

### 6.3 Strategy and vision of the unit and future management

IBEB's research will focus on the improvement of the understanding of physical and physiological aspects underlying human health and disease. This will be done with the help of imaging, modeling and simulation processes, which encompass human physiology and technology, relying on physical and engineering backgrounds.

IBEB's added value to its R&D areas will be in the development of new instruments and tools for:

The acquisition and processing of medical data from the following imaging modalities:

- Positron Emission Mammography.
- UWB radar imaging of the breast.
- MRI.
- Magnetic Particle Imaging (taking advantage of the magnetic shielded room facility existing at IBEB).
- Photonics (for breast reconstruction) and the study of the effects of brain stimulation.

The research on cancer therapy using:

- LASER light propagation on turbid media for drug delivery.
- High conformal radiotherapy and dose optimization.

The modeling of the interaction of Electromagnetic fields with the nervous system and its applications:

- The interaction of electrical and magnetic fields with neurons.
- The use of these interactions with therapeutic purposes.
- The use of Brain-Computer Interfaces and biomedical sensors for rehabilitation.
- The study of brain connectivity in health and disease.
- The brain plasticity and processing routes during cognitive tasks and its changes during disease.

We have defined 4 different thematic lines, ranging from medical imaging and therapy to specific aspects of brain functioning, which will be intertwined and will contribute to each other. The small number of team members led us to decide on defining only one research group within the unit. The scientific organization will therefore rely on a strong interconnection between members working on the various thematic lines. Each thematic line will have a scientific coordinator, which will monthly meet with the other thematic line's coordinators in order to develop and explore common direct lines of scientific interest. In addition we will continue to forge scientific connections in Portugal and abroad and have already secured national and international external scientific members to act as group members of IBEB. Some of these members will bring in additional international experience and will complement IBEB's core knowledge in all areas of research of the unit.

The research activities of each thematic line will contribute to the Unit's activities essentially in the two main areas of research of IBEB as follows:

The thematic lines Medical imaging and diagnosis and Cancer Therapy and drug delivery will be focused on research for the better use of imaging and therapy in Oncology. These two lines can feed basic imaging information to the other research lines. The research of these lines will be focusing on breast cancer using novel image reconstruction or imaging equipment. However, since there is expertise on areas like lung cancer (from radiotherapy) and dosimetry (an FCT approved project is running on Tomosynthesis dosimetry) this will also be explored. These thematic lines will explore different areas of assessing medical data through imaging, from X-ray imaging to Photonics as described latter in this document. New research themes will be pursued, in particular those related to Magnetic Particle Imaging and Drug delivery using LASER (which is running under an FCT approved research project).

Two other research lines have also been created: Brain connectivity and dynamics and Brain stimulation and neuro-rehabilitation. These two lines refer to the study of fundamental characteristics of the central nervous system that allow a better knowledge of its functioning and, in addition, research on ways in which its plasticity evolves under disease condition. Both research lines will have a strong connection with the Medical Imaging research line, since imaging modalities are currently evolving to morpho-functional techniques. These aspects are directly coupled to the research on new neuro-rehabilitation techniques using Brain-Computer Interfaces. The management of the Unit's activities will be done according to the following general governance structure:

An Executive Committee IBEB consisting of:

- a) The Unit's Director, elected by the Scientific Council of IBEB.
- b) One or two Sub - Directors, appointed by the Director from among integrated members of IBEB.

The Executive Committee:

- a. Establishes the annual plan for the Unit's activities, taking into account the general guidelines issued by FCT, FCUL and the External Scientific Advisory Council.
- b. Prepares an annual budget proposal.
- c. Ensures the management of human and material resources available to the Institute, including budget and its sharing by the different scientific thematic lines.
- d. Proposes the hiring of staff and the termination of their contracts.
- e. Ensures the conservation and maintenance of facilities, infrastructure, equipment and any other property of IBEB.
- f. Sets fees for services rendered by IBEB.
- g. Prepares the Unit's scientific activity reports, keeping track of the Unit's scientific production.
- j. Proposes the celebration of contracts, protocols and agreements with other institutions.

- The Director of IBEB:

- a. Administers and manages IBEB, ensuring that the general objectives of the Unit are achieved.
- b. Represents IBEB in and out of courts of law.
- c. Convenes and chairs meetings of the Executive Committee.
- d. Convenes and chairs meetings of the Scientific Council.
- e. Convenes and chairs meetings of the External Scientific Advisory Board.

The Director of IBEB has a final decision on the deliberations of the Executive Committee.

The Director may delegate to other members of the Executive Committee and will be replaced by them in his absence.

The Scientific Council of IBEB consists of all its integrated members and:

- a. Elects and dismisses the Unit's Director.
- b. Approves the activities of the Executive Commission producing necessary advice when needed.
- c. Approves the statutes of the IBEB.

d. Discusses the general strategy of the Unit with respect to science, budget, communication, etc.

The interaction between thematic lines will be promoted via:

- Regular scientific meetings, which will include a scientific journal survey specific to one of the thematic lines.
- A general IBEB scientific meeting, which will be held monthly. On each meeting, one of the thematic lines will present their latest results.
- Scientific seminars with invited speakers hosted by each one of the leaders of the thematic lines.
- Informal meetings.

Some of the IBEB's research lines (e.g. PEM, UWB - and the coupling of PEM and UWB - TMS and tDCs transcranial stimulation) are unique in Portugal. Strong connections exist with other research centers in Europe and the US and with European and non-European companies. We IBEB can contribute to Portuguese knowledge of cutting-edge medical technologies and their use

#### **6.4 Laboratory intensity level of the unit**

High

Laboratory intensity level Justification

IBEB has currently two laboratory spaces assigned on its building. In this application, we are asking for funding in order to strengthen these areas by reinforcing existing research strands and creating new ones. We strongly believe that this can introduce increased training and research opportunities in the areas where IBEB can excel internationally.

The acquisition of a simultaneous TMS stimulation system with EEG, neuronavigation, EMG and fNIRS, the construction of an optimized prototype for UWB imaging of the breast (recently awarded the ANACOM prize 2013 to IBEB team member Raquel Conceicao) and the launching of research in NIRS applied to the brain and Magnetic Particle Imaging for human use require a significant experimental effort and setup for which IBEB can allocate adequate space. This effort will complement the one being already done in Brain Computer Interface (BCI) applications. One of these applications has recently (November 2013) received the "BES Inovação" Prize, one of the most important Innovation Prizes in Portugal, providing privileged access to the market. In face of this, and taking into account the definitions of HIGH Laboratory Intensity Level (Equipment / laboratory and experimental component), the laboratory level of the proposed unit should be classified as HIGH.

#### **6.5 General objectives**

The EC has put forward a series of strategic areas of intervention for which R&D can significantly contribute, in particular those related to health challenges. Currently and in the near future, health challenges will be related, among other, with the improvement of disease understanding and management in areas like Oncology and Neuroscience. Provisional Eurostat figures indicate that in the EU-27 in 2010 there were 1.26 million deaths caused by cancer (malignant neoplasms), which equated to just over one quarter (25.9 %) of the total number of deaths. In addition, the largest increase in deaths between 2000 and 2010 were recorded for diseases of the nervous system and the sense organs and for mental and behavioral disorders. IBEB wishes to position its R&D and advanced training efforts to contribute with state-of-the-art research in cutting edge technological applications to the better understanding of disease progression and therapy in Oncology and Neurosciences.

Within this context, the main objectives of IBEB for 2015-2020 are the following:

- O1. Support creative and ambitious research that addresses important scientific questions in Biomedical Engineering.
- O2. Emphasize multi- and inter-disciplinary approaches to Biomedical Engineering.
- O3. Contribute to the use of physical and engineering principles in Diagnostics and Therapy.
- O4. Develop a research infrastructure with unique facilities in Portugal.
- O5. Support Biomedical Engineering training of undergraduate, Ph.D. and postdoctoral researchers.
- O6. Work to explore clinical, translational and multi-disciplinary research opportunities.
- O7. Develop strategic partnerships that support and complement IBEB's scientific strengths.
- O8. Develop close interactions with industry and facilitate innovation.
- O9. Engage effectively with the society.
- O10. Increase young people's enjoyment and aspirations in Biomedical Engineering.

In order to accomplish this, we will be committed:

- To obtain significant funding independent from local public funding sources:

IBEB's experience in participating and leading COST actions and Marie Curie post-doctoral fellowships will be used, in complement to the international connections already established, to apply for international funds. These can be based on European or non-European funding, originating on charity institutions or using the closer connections existing with Brazil, where the budget for scientific R&D has increased significantly in recent years. Recently, IBEB has applied to the "Human Brain Project" EC Flagship initiative with two projects on Cognitive Architectures along with national and international partners. During 2013, IBEB has also applied to the FCT Harvard Medical School - Portugal program in collaboration with the Champalimaud Foundation in Portugal and the Berenson-Allen Center for Noninvasive Brain Stimulation and the Martinos Center for Biomedical Imaging, both in Massachusetts, USA.

- To acquire or build and use state-of-the-art scientific instruments that help to consolidate an international leading edge of IBEB's research lines:

We propose to acquire and to build singular pieces of equipment for IBEB – to buy a fNIRS+TMS+EEG+EMG system with neuronavigation and to build a UWB radar breast prototype device and a MPI brain imaging prototype. The latter will take advantage of IBEB's Magnetic Shielded Room (a unique facility in Portugal). These pieces of equipment will significantly help leverage training and scientific opportunities.

-To increase the number of Ph.D. members to 20 (including post-doctoral fellows) by 2020 by recruiting national and international scientists.

We are aware that in order to become more competitive IBEB needs to integrate a higher number of post-doctoral fellows. We rely on international connections and the additional training opportunities created by new equipment at IBEB in order to be successful. National and international funding of projects will be used for this purpose.

-To increase the exposure to industry and knowledge transfer to society.

We will build up on previous successful connections with Siemens, PETsys, NOVOCURE, Starlab, Agilent, etc, in order to identify scientific R&D topics of mutual interest. Whenever possible, advanced training based on industry funding will be sought. An adequate connection with CBIOS of Lusófona University and IPATIMUP will be pursued which will bring additional connections to the Portuguese and international industry (in particular to the pharmaceutical industry).

-To continue to be a landmark in biomedical engineering teaching in Portugal and develop international teaching programs with leading Biomedical Engineering institutions in the world.

The 6-year running Master's in Biophysics and Biomedical Engineering led by IBEB at the Faculty of Sciences of the University of Lisbon is now receiving quality accreditation and will continue hosting 40 new students each

year. We will select the brightest among these and offer them an opportunity to pursue their scientific careers with us. For this, we will seek public and private funding within FCT and the industry. We will apply for an international Ph.D. program in Biomedical Engineering along with leading institutions in the world.

-To hire management support.

We will seek to hire a full time secretary in order to compensate for the probable retirement of the current one. This person will maintain adequate communication with IBEB's partners, keep IBEB's records up to date, support students and researchers (in particular with project writing reviewing and fund searching) and keep IBEB's web-pages updated.

-To continue organizing the Biomedical Engineering students meeting at FCUL, which has been under IBEB's responsibility for the last 6 years, joining around 200 attendees per year.

-To create a local industry counseling committee, which will allow an easier identification of Biomedical Engineering companies' needs in terms of R&D and student's abilities.

-To use Web-based approaches to rapidly disseminate IBEB's main achievements (scientific production, prizes, etc.) in particular through IBEB's web-page ([www.ibeb.fc.ul.pt](http://www.ibeb.fc.ul.pt)) and IBEB's Facebook page (currently followed by more than 600 users: ([www.facebook.com/InstitutoDeBiofisicaEEngenhariaBiomedica](http://www.facebook.com/InstitutoDeBiofisicaEEngenhariaBiomedica))).

- To have a flexible and operational management team.

The pursuing of these objectives has its support on the tackling of the following general scientific questions:

Q1. How can we use imaging to detect cancer at its early stages and predict its evolution more reliably?

Q2. How can we use innovative ways to treat cancer and reduce treatment side effects?

Q3. How can we stimulate the brain non-invasively and use this interaction for therapeutic purposes?

Q4. How are functional connections between the different parts of the brain structured in healthy and pathological conditions?

Specific input to these questions can be found on topic 10 of this document.

## 6.6 Implementation

During the 2015-2020 period IBEB will be a research unit with a focus on imaging and therapy aspects of cancer and on the basic understanding of brain functioning and its modulation. IBEB made a conscious choice to keep a relatively small team in order to achieve a maximum focus of its activities and anchor on strong external collaboration. IBEB members have been organized, according to their experience, into 4 different thematic lines of research. These lines are complementary and will be transversally fed by all of IBEB's members. In order to do so, the internal dynamics of IBEB's research will rely on journal survey and internal peer reviewing. This will act as an internal quality control methodology in order to keep IBEB focused on its general objectives. The driving force to do this will come from IBEB's Executive Board, Scientific Committee and from its Industrial and Scientific Advisory Boards which will determine IBEB's policy on research and financial spending. IBEB will have a strong interaction with the clinical community. IBEB's activity (80%) aims at producing usable knowledge at the clinical or at least pre-clinical setting. This is especially true for the research carried out on new methods for imaging disease but also for work done in more fundamental areas of research like brain connectivity. Innovative procedures for obtaining and processing data have already lead to the participation of IBEB on 4 international patents and to winning two national innovation awards. We hope to continue this effort. In fact, IBEB members are related (either through consultancy or direct participation on Boards) to SMEs in Health Research.

In addition and for each of the objectives stated above:

O1. Support creative and ambitious research that addresses important scientific questions in Biomedical Engineering.

IBEB is committed to attracting some of the best and most innovative young scientists working in the field of biomedical engineering. This is one of the main reasons why the IBEB wishes to initiate and build up a significant amount of expertise in areas like UWB cancer detection and MPI. We believe that these are areas from which we will be able to gain not only new technological weapons to fight cancer but also additional insights into the multidisciplinary characterization of cancer which are complementary to those already available at IBEB. In addition, the financing of young stage students, whom although without significant scientific maturity can more easily think "out-of-the box", aims at this objective. Moreover, in this proposal IBEB applies for some funding to host thematic seminars from recognized scientists in order to feed-in well-established research topics. We believe that by mingling scientific experience and scientific ingenuity, original, cutting-edge ideas can arise and can help to boost IBEB's research and its contribution to society in years to come. This will be complemented by obtaining advice from an international external advisory board composed by excellent scientists with a broad scientific view, ranging from basic science to its application and with great knowledge on science management. International funding, related to H2020 will be systematically pursued in particular, but not exclusively, in the Health topics.

O2. Emphasize multi- and inter-disciplinary approaches to Biomedical Engineering.

During 2015-2020 we will seek to connect to more biology-based research projects in the areas of Cancer and Neurosciences. The objective is to gain a broader vision of the underlying processes of cancer and to devise more accurate solutions for its diagnosis. In addition, this will potentiate the increase of the impact factor of the unit's publications. Reference institutions like IPATIMUP ([www.ipatimup.pt](http://www.ipatimup.pt)) have already been approached and the discussion of specific projects related to breast cancer and molecular imaging of the brain started.

O3. Contribute to the use of physical and engineering principles in Diagnostics and Therapy.

The great majority of IBEB's researchers are physicists with an engineering background. The use of engineering and physical principles to the design and application of biomedical engineering problems will come as natural. Therefore, aspects related to new equipment design and testing, simulation and knowledge transfer will be natural tasks within IBEB.

O4. Develop a research infrastructure with unique facilities in Portugal.

IBEB has a unique logistical infrastructure for its size. The logistical facilities, which include offices, a seminar room and a meeting room are put to the use of the local Biomedical Engineering community. Renewing its laboratory facilities in order to include competitive equipment in Biomedical Engineering like the one proposed in this document will be a pre-requisite for becoming more competitive and attractive internationally. The participation on international network initiatives will be a priority.

O5. Support Biomedical Engineering training for undergraduate and Ph.D. and postdoctoral researchers.

Increasing R&D and training relations with international leading partners: IBEB is proposing an international Ph.D. program in Biomedical Engineering along with the University College London, the King's College London (both participating in the Francis Crick Institute in London) and the University of Ireland at Galway.

IBEB has obtained financing in 2008, 2009, 2011 and now in 2013 to hire post-doctoral Marie Curie and FCT funded fellows. We will seek to continue this path and look deeper into industry funding opportunities (one post-doc in 2013 funded by NOVOCURE). This will allow reaching the objective of reaching 20 Ph.D. at IBEB by 2020.

O6. Work to explore clinical, translational and multi-disciplinary research opportunities.

IBEB has forged several collaboration protocols with clinical partners. These include the major hospitals in Lisbon, private clinical centers and also international partners like the Charite University in Germany. In addition, a significant number of the IBEB's collaborators are medical doctors, which will contribute in a decisive way to increase the translation of IBEB's research into the pre-clinical and clinical setting.

IBEB is not able to acquire the majority of the experimental equipment for developing independent research in all of its areas of influence due to its prohibitive costs (e.g PET). Nevertheless, we are a unit recognized by our international advisory committee as possessing specific strengths in TMS on and Hybrid Mammography (PEM-

UWB), areas on which IBEB is in the front edge of research and development. We therefore believe that IBEB should have unique experimental equipment in these areas and coordinate its research efforts by developing strategic partnerships with reference institutions whenever this is not the case.

Internationally: By continuing to carry out collaborative work with foreign partners. This will be supported on personal visits from several of IBEB's researchers and exchange of data and students as it already happens.

Nationally: By acting as a driving force for Biomedical Engineering research by seeking to obtain a multi-scale, engineering based approach to health and disease in the context of the University of Lisbon.

O8. Develop close interactions with industry and facilitate innovation.

IBEB has recently won two important Innovation Prizes (the VODAFONE Mobile Data Award 2013 and the BES Inovação National Contest). IBEB will continue this effort and has recently engaged with start-ups and spin-offs for scientific partnerships:

- Crowdprocess, S.A. for massive, parallel processing of medical data and Monte Carlo simulation.

- PETSys, S.A. and PETSys Electronics, S.A, for the application of novel photodetectors and electronics for medical purposes.

- NOVOCURE for the development of new strategies for the use of transcranial electromagnetic stimulation in health and disease.

- SwiftHockey and bioM spin-offs for the scientific consultancy on the development of targeted BCI applications.

Given the expertise of IBEB's members and their connections and the ever-growing market of Biomedical Engineering in specific application niches, we are confident that this effort will result in a significant increase of IBEB's publication numbers and success and in industrial property rights which can be protected.

O9. Engage effectively with society.

IBEB will organize scientific seminars open to the general public on Biomedical Engineering topics. These seminars will be tailored to non-specialized audiences and will be recorded and posted on IBEB's websites and on the YOUTUBE platform for generalized viewing and commenting. In addition, IBEB staff will contribute to the Annual Open Day initiative of the Faculty of Lisbon, by presenting its research activities and will participate in the Annual National Student University Forum (Futurália) taking place every year for the information of university candidates and their families. In addition, IBEB staff will, whenever plausible, produce comments on biomedical engineering topics which will be published through appropriate mass media means. In addition, we aim at obtaining significant input to research from non-profit organizations and patient's associations working in the IBEB's areas of influence (e.g. the Portuguese Association for research in Cancer - ASPIC (<http://www.aspic.pt>)) and similar national and international platforms.

O10. Increase young people's enjoyment and aspirations in Biomedical Engineering.

We will mentor Biomedical Engineering students, opening the doors of IBEB for them to make the Institute "their home". We will stimulate their critical appraisal of Biomedical problems, engage their participation in IBEB's projects and help them to pursue their careers, contributing their knowledge and skills to the local and national economy.

## **6.7 Contributions for the regional strategy**

The regional strategy for the Lisbon region has been prospectively put forward in the document "Plano de Acção Regional de Lisboa, 2014-2020, Diagnóstico Prospetivo - Setembro 2013" produced by the Council of Ministers of the Portuguese Government. One of the main bottlenecks identified for an increased "intelligent growing" of this area is the cooperation between Universities and Companies in research activities (pag 9 - n. 23). In addition, the document indicates that there is an opportunity to develop an international pole for excellent research and development (pag. 38) in the Lisbon area. IBEB will continue contributing to these efforts through the development of tight relationships with local companies like Siemens Portugal (Healthcare sector), Crowdprocess ([www.crowdprocess.com](http://www.crowdprocess.com)) and PETSys, S.A ([www.petsys.eu](http://www.petsys.eu)). The connection with foreign companies like NOVOCURE (<http://www.novocure.com>) or STARLAB (<http://starlab.es>) will enhance the probability of incorporating company knowledge and interest into IBEB's R&D activities and to Portuguese R&D structures and therefore contribute to lessen the recognized low participation of companies in research and development projects as university partners. As mentioned elsewhere in this proposal, the scientific connections within the Lisbon area include not only companies and scientific partners (e.g. the Portuguese Laboratory for Particle Physics with whom IBEB participates in the Portuguese PET-Mammography consortium) but also several private and public Hospitals and Universities (also abroad). Using these connections and through advanced training activities (Ph.D. and Post-Doc), the knowledge created therein will contribute to local specialization in the Health Technology domain. In addition, the connections to local industry will potentially contribute to mitigate the leakage of technical superior staff. In fact, Siemens, Phillips and some Consulting companies (like NOVABASE) frequently recruit IBEB's trainees. The joint effort put into all these aspects will contribute to the reinforcement of the impact of R&D in Biomedical Engineering in the Lisbon area. This effort will be in phase with the information put-out by FCT on the document "Diagnóstico do Sistema de Investigação e Inovação" which lists the areas of Health and Sciences of Engineering and Technology as those contributing the most to Portuguese scientific production. In this context, IBEB will contribute to the reinforcement of the international Portuguese contribution in Biomedical Engineering.

## **6.8 Opportunities for advanced training**

The opportunities for advanced training at IBEB for the period 2015-2020 are manifold:

1. Post-Doctoral opportunities.

The number of Post-Doctoral fellows at IBEB should increase significantly. In this respect, we will be offering new training opportunities using national (FCT) and international funding (H2020 related funding) related to the research topics of the unit. We expect that this would increase the number of Ph.D. members of IBEB to 20 by 2020. In order to accomplish this we are requesting funding to finance 4 post-docs within this proposal. The acquisition and building of new equipment, as detailed below in this proposal, is crucial for this.

2. Ph.D. projects linked to IBEB's research.

The research lines of IBEB for the next 6 years are of great actuality, linked to H2020 societal challenges on the Health topic. In this respect we will focus on cooperation with international institutes on MRI, PET, UWB, radiotherapy applications, MPI and BCI applications. Several research opportunities have already been identified in cooperation with national and international partners, which will lead to Ph.D. themes. We will seek financing for these either nationally or through international funding.

3. International Biomedical Engineering Ph.D. program.

IBEB will be promoting an International Ph.D. program in Biomedical Engineering joining International Institutions with similar or complementary research interests (e.g. UCL London, King's College London, Galway University Ireland). This program will be presented for funding to FCT. We expect to host at least 6 new Ph.D. students per year, leading to at least 18 Ph.D. thesis completed by 2020 by this reason alone. Additional opportunities will be related to on-going research projects under the responsibility of IBEB's Ph.D. members.

4. IBEB leads/participates in several COST Actions. These Actions provide funding for short term scientific missions and for topic specific scientific gatherings. IBEB will take advantage of these opportunities to further

promote scientific training for excellent students in specific areas.

5. The connections of IBEB with national- and abroad-based companies will be used to propose industry-based scholarships. This has already been done with Siemens and NOVOCURE and will be continued.
6. IBEB participates in the Portuguese Network for Brain imaging. This effort can offer advanced training opportunities in the areas of MRI, SPECT and PET imaging of the brain.
7. In addition to this, the wide range of connections of IBEB nationally and abroad can warrant a wide range of opportunities for training. This can be verified each year by the placement of approximately 40 students of FCUL to develop their final Master's dissertation either in Portugal or abroad. IBEB receives master students from neighbouring universities (usually 5-8 each year).

## 6.9 Internationalization

The efforts of IBEB on internationalization will continue in the future through:

COST actions:

- TD1301 "Development of a European-based Collaborative Network to Accelerate Technological, Clinical and Commercialization Progress in the Area of Medical Microwave Imaging" Action Leader - ongoing
  - TD1007 "Bimodal PET-MRI Molecular Imaging Technologies And Applications For In Vivo Monitoring Of Disease And Biological Processes" (MC Chair for Portugal) - ongoing
- Proposed COST oc-2013-2-16835, "Fast advanced Scintillator Timing" - lead by the CERN - Secondary proposer.

Other international collaborations:

- Institute of Neuroscience and Medicine - Medical Imaging Physics of the Julich Research Center
- CERN through the Crystal Clear Collaboration
- King's College London (Dr. Rita Nunes is a visiting scientist of this Institution).
- IBEB is currently awaiting decision on 2 Portugal-Germany cooperation actions: "MRI-guided Drug Delivery Systems based on Red Blood Cells and Biopolymer Microcarriers" with the Charité Universitätsmedizin Berlin and "PET-MRI brain connectivity and application to brain tumors" with the Institute of Neuroscience and Medicine (INM-4) – Julich research Centre.
- IBEB recently submitted a research proposal to the FCT Harvard Medical School - Portugal in collaboration with the Champalimaud Foundation in Portugal and the Berenson-Allen Center for Noninvasive Brain Stimulation and the Martinos Center for Biomedical Imaging, both in Massachusetts, USA.
- IBEB has recently participated in two calls in the context of the EU Flagship Project Human Brain Project in the context of Brain Connectivity.
- IBEB will lead a proposal for an international Ph.D. program in Biomedical Engineering joining institutions from the UK and Ireland.

IBEB has identified scientific partners abroad:

- The NIH, the Berenson-Allen Center for Noninvasive Brain Stimulation and the Martinos Center for Biomedical Imaging, both in Massachusetts, USA for the pursuing of scientific knowledge leading to TMS and TDCS applications to the brain.
- The University College London (UK) and the Julich Research Center (DE) for MRI, PET and simultaneous MRI-PET imaging related issues (hardware design, data acquisition, data procession and clinical applications).
- The University of Ireland Galway (IR) and the University of Calgary (CA) for the development and testing of UWB technology for imaging the breast.
- The Charite Universitätsmedizin Berlin for research on the applications of magnetic particles to imaging and therapy.
- The FOX Chase Cancer center in Philadelphia (USA) for radiotherapy applications.

These collaborations will be pursued through common visits, on-line meetings and the sharing of students when appropriate.

IBEB has also identified EC funded initiatives of interest (the Rather Project - <http://www.ratherproject.com>) with which we aim to join in the near future, bringing imaging expertise.

## 6.10 Knowledge transfer

IBEB has increased its direct connections with industrial partners and its participation on industry driven research through research contracts and patent submissions.

The strong interactions already existing with companies will be maintained by assigning research time from leaders of research thematic strands or Post-Doc members to lead continuing or foreseeable interactions:

- NOVOCURE in Israel for novel methods for cancer therapy using electromagnetic fields (Dr. Pedro Cavaleiro Miranda and Dr. Cornelia Wenger).
- PETsys, SA and PETsys Electronics S.A, for the testing of state-of-the art PET imaging using new, patent pending detection systems (Dr. Pedro Almeida is one of the company's directors). PETsys has produced a comfort letter in this respect, which we can provide to FCT.
- Agilent Technologies (Austria and Belgium), Cubresa (Canada), MITOS Medical Systems (Turkey) through COST 1301 Action led by Dr. Raquel Conceição.
- Siemens Medical (Portugal and Germany) with whom non-disclosure agreements are being signed on the field of X-ray tomosynthesis (Dr. Nuno Matela)
- Crowdprocess, S.A. for massive, parallel processing of data and Monte Carlo simulation.
- NOVOCURE for the development of new strategies for the use of transcranial electromagnetic stimulation in health and disease.
- SwiftHockey and bioM spin-offs (Dr. Hugo Ferreira is a consultant for both companies), for the scientific consultancy on the development of targeted BCI applications.

IBEB has recently won two important Innovation Prizes (the VODAFONE Mobile Data Award 2013 and the BES Inovação National Contest (in the category Information Technology and Services) with a biosensitive fabric allowing the interaction of people with electronic devices without touching them. There is a clear strategy of IBEB to continue this effort and we have recently engaged with a number of start-ups and spin-offs for scientific partnerships. Given the expertise of IBEB members and their connections to the ever-growing market of Biomedical Engineering in specific application niches, we are confident that this effort will result in a significant increase of IBEB's publication numbers and success and in industrial property rights which can be protected (not only through patents). Several different calculation and processing algorithms (radiotherapy, imaging acquisition, image processing, signal processing) will be developed by IBEB between 2015 and 2020. In every occasion, IBEB will make these tools available to scientific partners.

## 6.11 Ethical issues

IBEB will deal mostly with human data but occasionally it may also participate in projects using animal data.

Therefore, ethical issues will be dealt with in full respect to the following main principles:

- The World Medical Association (WMA) Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects (<http://www.wma.net/en/30publications/10policies/b3/>).

This will be complemented by enforcing the recommendations issued by local ethics committees. Confidentiality

issues related to the protection of human related data will be always enforced.

- The WMA Statement on Animal Use in Biomedical Research

(<http://www.wma.net/en/30publications/10policies/a18/>).

This will be complemented by the enforcement of Portuguese regulations specific to the manipulation of animals for research purposes. These regulations require that researchers should be certified by Portuguese National Veterinary Authorities before being allowed to carry out research using animals.

## 7. EXPECTED INDICATORS OF THE STRATEGIC PROGRAMME 2015/2020

### 7.1

Description	2015	2016	2017	2018	2019	2020	TOTAL ( $\Sigma$ )
Publications in peer-review international journals	15	16	17	20	22	24	114
Patents and performing patents	0	2	1	0	0	0	3
Books and chapters of international distribution	1	1	1	1	1	1	6
PhD theses under the supervision of integrated members	3	3	4	8	9	9	36
Conference proceedings	40	40	40	40	45	45	250
New materials, devices, products and processes, software, computer codes and algorithms	25	25	30	30	30	35	175
Books, including single-authored works (including scholarly editions of oral or written texts and translations with introduction and commentary)	0	0	0	0	0	0	0
Edited special issues of journals, with substantial research input on the part of the researcher	0	0	1	0	0	1	2
Chapters in books, including contributions to conference proceedings, essays in collections	0	0	0	0	0	0	0
Creative writing (to the extent that it embodies research)	0	0	0	0	0	0	0
Dictionary entries (forming part of investigation)	0	0	0	0	0	0	0
Encyclopedia entries (to the extent that they embody research)	0	0	0	0	0	0	0
Audio/visual and electronic/digital materials	0	0	0	0	0	0	0
Other categories, including web-based resources; video and audio recordings (to the extent that they embody research)	3	3	3	4	4	4	21
Performances and exhibitions to the extent that they embody research	0	0	0	0	0	0	0
Industrial research contracts	1	2	0	0	1	1	5
Research contracts with national or international bodies	2	2	3	3	4	4	18
Organisation of national and international scientific meetings	2	2	3	3	3	3	16
Master Thesis	25	25	25	30	30	30	165
Oral presentations in conferences	5	5	8	10	10	10	48

## 8. PROPOSED RESEARCH TEAM

### 8.1 Criteria adopted by the R&D unit for the definition of integrated member, if different from FCT reference table

We have adopted the FCT criteria.

### 8.2 List of Integrated Members / 10 nuclear CVs

Name	Nuclear CV
 Pedro Miguel Dinis de Almeida (Coordinator)	Yes
 Alexandre da Rocha Freire de Andrade	Yes

 Cornelia Wenger	No
 Grisel Margarita Mora Paula	Yes
 Hugo Alexandre Teixeira Duarte Ferreira	Yes
 João Miguel Pinto Coelho	Yes
 Lina da Conceição Capela de Oliveira Vieira	No
 Mónica Vieira Martins	No
 Nuno Miguel de Pinto Lobo e Matela	Yes
 Pedro Michael Cavaleiro de Miranda	Yes
 Raquel Cruz da Conceição	Yes
 Ricardo Nuno Braço Forte Salvador	Yes
 Rita Homem de Gouveia Costanzo Nunes	Yes

## 9. PROPOSED RESEARCH GROUPS

Reference	Name	Principal Investigator
RG-645-1499	Biomedical research in neurosciences and in oncology	Pedro Miguel Dinis de Almeida

### (RG-645-1499) Biomedical research in neurosciences and in oncology

#### 9.1. IDENTIFICATION OF THE RESEARCH GROUP

##### 9.1.1 Reference of the research group

RG-645-1499

##### 9.1.2 Name of the Research Group in portuguese

Investigação biomédica em neurociências e em oncologia

##### 9.1.3 Name of the Research Group in English

Biomedical research in neurosciences and in oncology

##### 9.1.4 Keyword(s)

Diagnosis and therapy in oncology  
 Neuronal biosignals and transcranial stimulation  
 Human-machine interfaces  
 Medical imaging reconstruction and processing

##### 9.1.5 Existed in 2008/2012

No

##### 9.1.6 Participating Institution(s) to which the Research Group belongs

Faculdade de Ciências da Universidade de Lisboa (FC/UL)

#### 9.2. RESEARCHERS IN THE GROUP

##### 9.2.1 List of Integrated Members / 3 nuclear CVs

Name	Principal Investigator	Nuclear CV
 Alexandre da Rocha Freire de Andrade	No	Yes
 Cornelia Wenger	No	No
 Grisel Margarita Mora Paula	No	No
 Hugo Alexandre Teixeira Duarte Ferreira	No	No
 João Miguel Pinto Coelho	No	No

🔍 Lina da Conceição Capela de Oliveira Vieira	No	No
🔍 Mónica Vieira Martins	No	No
🔍 Nuno Miguel de Pinto Lobo e Matela	No	No
🔍 Pedro Michael Cavaleiro de Miranda	No	Yes
🔍 Pedro Miguel Dinis de Almeida	Yes	Yes
🔍 Raquel Cruz da Conceição	No	No
🔍 Ricardo Nuno Braço Forte Salvador	No	No
🔍 Rita Homem de Gouveia Costanzo Nunes	No	No

### 9.2.2 List of current PhD students

#### NAME

João Pedro de Matos Rodrigues  
 ANA Lúcia Vital Belchior  
 Cláudia Sofia Marques Ferreira  
 Ricardo Miguel Ferreira Capote  
 Nuno Martins Dores de Oliveira  
 ANA ISABEL ANTUNES DIAS RODRIGUES GOUVEIA  
 Ana Maria Morais Cravo de Sá  
 Carina Isabel Bento Marques Coelho  
 Filipa Isabel Martins Borlinhas  
 Diana Queirós Carvalho Pinto de Faria  
 Ana Margarida Pires de Almeida Mota  
 Ricardo Jorge de Almeida Marques Maximiano

### 9.2.3 List of other researchers of the Research Group

#### NAME

Alberto Joao Rodrigues Leal  
 André Henrique Santos Correia Rodrigues Dias  
 Brian Forbes Hutton  
 Joseph Vilmos Hajnal  
 Liliana Lourenço Caldeira  
 Martin O Halloran  
 Bárbara Luz Custódio Santos de Oliveira  
 Durval Campos Costa  
 Nuno André Inácio da Silva  
 C-M Charlie Ma  
 Iraj Mohammadi Firouzjaei  
 Luis Manuel Carvalho Freire  
 Ana Catarina Beco Pinto Reis  
 Mamede Alves de Carvalho  
 Susana Cristina da Costa Pinto Candeias  
 Luis Manuel de Almeida Soares Janeiro  
 Luís Miguel Rosa Sousa Prado de Lacerda  
 André Filipe dos Santos Ribeiro  
 Rafael Neto Henriques  
 Nafiseh Mirzajani  
 Maria de Lurdes Geraldês Freire Raposo Orvalho  
 Reynaert Nick

## 9.5. ORGANISATIONAL STRUCTURE AND OBJECTIVES OF THE RESEARCH GROUP 2015/2020

### 9.5.1 Structure of the Research Group

The group has a very plastic structure, which is dominated by the thematic scientific lines pursued within the institute. This means that every Ph.D. member will be able to contribute to any thematic line even though it is focused in his/her specific topic. Although there is a number of core members on each thematic line, the commitment of each researcher to each thematic line may vary depending on the specific needs of the research taking place at a given point in time. This allows obtaining a high degree of cohesion and, at the same time, a very flexible structure, which is mandatory in a relatively small research unit. The group members of IBEB (the research group) and its collaborators have various scientific skills related to Biomedical Engineering research. In fact, there are group members, which are specialists on Magnetic Resonance Imaging (MRI), Brain-Computer Interfaces, Nuclear Medicine (mainly PET and SPECT), X-ray imaging, Magnetic and Electric Transcranial Brain Stimulation, Photonics, Radiotherapy, Microwave tumor detection, signal and image processing and Biomedical Technology. This expertise will be used to continue and deepen the work done in the areas of Imaging for Oncology and Neurosciences and to implement new areas of research (MPI and BCI applications). Additionally, the group has obtained the scientific collaboration of several members external to IBEB with complementary areas of expertise, namely those of Medical Doctors specialized on Neurosciences, Nuclear Medicine and Oncology from national research institutions. Also, researchers from international reference institutions like the UCL, King's College London and the FOX Chase Center, for example, have accepted to be associated to the IBEB as external members. IBEB relies upon strong scientific connections with its international partners (already referenced in this text). We believe that the scientific connections with sites of excellence in Portugal and abroad will continue to be one of the main objectives of IBEB and will secure a significant amount of its research highlights in the future.

### 9.5.2 Objectives of the Research Group

The objectives of the research group are those of the IBEB since the research group is composed by all of the IBEB Ph.D. integrated members.

Associate members will bring external expertise to IBEB, in particular in areas of research which depend extensively on unique data acquisition or processing methodologies (e.g. simultaneous PET/MRI, among others).

## 10. PROPOSED THEMATIC LINES

Reference	Name	Principal Investigator
TL-645-1299	Medical imaging and diagnosis	Pedro Miguel Dinis de Almeida
TL-645-1300	Brain connectivity and dynamics	Alexandre da Rocha Freire de Andrade
TL-645-1301	Cancer therapy and drug delivery	João Miguel Pinto Coelho
TL-645-1302	Brain stimulation and neuro-rehabilitation	Pedro Michael Cavaleiro de Miranda

### (TL-645-1299) Medical imaging and diagnosis

#### 10.1. IDENTIFICATION OF THE THEMATIC LINE

##### 10.1.1 Reference of Thematic Line

TL-645-1299

##### 10.1.2 Name of the Thematic Line in Portuguese

Imagem médica e diagnóstico

##### 10.1.3 Name of the Thematic Line in english

Medical imaging and diagnosis

##### 10.1.4 Principal Investigator

Pedro Miguel Dinis de Almeida

##### 10.1.5

##### Scientific areas

Physics

Bioengineering

Diagnostic, Therapies and Public Health

#### 10.2. DESCRIPTION OF THE THEMATIC LINE

##### 10.2.1 Description of the Thematic Line

Medical Imaging is a manifold domain ranging from the use of ionizing radiation (such as X-rays) to mechanical

waves (as in the case of Ultrasound) for medical diagnosis and health research purposes. The development of new diagnostic tools (more accurate and reproducible) for improved clinical practice demands the translation of multidisciplinary knowledge from diverse fields into clinical applications. In the last years, IBEB has become a national reference on research for improving the accuracy of medical imaging methods, such as in the MRI study of the brain, and developing new imaging devices such as the Clear-PEM system, among other examples. It is therefore natural that the renewed configuration of IBEB considers a thematic line on Medical Imaging. This thematic line is crucial to one of the main objectives of the unit: "...improve the understanding of physical and physiological aspects underlying human health and disease with the help of imaging, modeling and simulation processes relying on physical and engineering backgrounds." The scientific expertise of IBEB relies on people coming from the Physics and Biomedical Engineering and Technology areas. This expertise is complemented by a strong connection with medical doctors who use imaging as a tool. The synergies between IBEB's staff's competences will be extremely helpful to identify new state-of-the-art questions aimed at improving the quality of diagnostic techniques based on medical imaging. In addition, these synergies are expected to contribute to: i) increase the success of therapies relying on imaging data and ii) trigger ideas for creating new devices and acquisition strategies and evaluate their proof-of-concept through simulation.

We will carry out research on:

1. New methods:

- o New data processing techniques, allowing a more efficient use of the increasing amount of information obtained from imaging techniques (new visualization methods, multi-scale analysis, image classifiers such as machine learning algorithms), to support medical diagnosis and decision. For example, we are interested in using multi-scale analysis and graph-theory to enlighten connection paths within the brain.

- o New image reconstruction algorithms for UWB radar and tomographic modalities, taking advantage of the growing computation power (GPU, Cloud Computing, Parallel Programming):

These new algorithms are mainly statistical, and will be developed and optimized for large datasets using sparse-matrix properties and distributed computing. Such developments will foster interactions with local industry and clinicians as we will be able to offer them new and faster tools for image reconstruction.

- o Design and simulation of new acquisition methods:

This topic will comprise mainly the use of Monte Carlo simulation for radiation detection systems and specific software for the design of new MRI sequences. GATE and JEMRIS will be used, taking advantage of already established collaborations with the OpenGATE community and with the research center in Jülich, Germany.

- o Implementation of new MRI acquisition methods:

the aim is to quantify water diffusion in the human brain employing a novel strategy for quantitative MRI, Magnetic Resonance Fingerprinting (MRF), which has not previously been applied to diffusion. MRF relies on pattern recognition to extract tissue parameters, allowing for much more flexibility when designing acquisition strategies. From a single time-course it becomes possible to quantify multiple parameters. This topic will require programming the MRI scanners available at the Portuguese Brain Imaging Network and King's College London.

- o Development of new multi-modal imaging methods for the optimization of the acquired images (PET-MRI, PEM-UWB, PEM-US):

This topic will comprise the use of existing and development of novel multi-modal imaging analysis tools (e.g the Multimodal Brain Connectivity Analysis toolbox for MRI and PET connectivity data analysis, available at IBEB in the scope of previous projects.)

- o Development of new tools for the optical and UWB radar detection of sentinel lymph nodes:

Sentinel lymph nodes can be tagged with the use of nanocolloids using a light emitter and subsequent detection during surgery with a luminescence sensing system. Regarding UWB radar detection, anatomically-realistic phantoms of the underarm region will be developed and the detection of the sentinel nodes, based on differences between dielectric properties, will be simulated.

2. New devices and techniques:

- o Development of a pre-clinical prototype for UWB radar breast and axilla imaging equipment and associated imaging tools. Development of a new LASER based system for breast positioning detection in a hybrid PEM-UWB prototype.

Imaging of the underarm region has never been attempted with a microwave UWB radar approach. Also monitoring the position of the breast, during its examination with the multimodal PEM-UWB prototype, will make the examination faster and provide measurements of the breast surface, significantly improving the resulting breast image while avoiding breast compression, improving patient comfort. Microwave Imaging has also been proposed as a potential monitoring tool for neoadjuvant chemotherapy treatment of breast cancer, and this topic will also be considered in this line.

- o Development of a hardware based feasibility study for a Magnetic Particle Imaging (MPI) prototype system.

MPI is an emerging biomedical imaging technology that allows the direct quantitative mapping of the spatial distribution of superparamagnetic iron oxide nanoparticles. Contrast and sensitivity of MPI are believed to be better than those of other medical imaging modalities presently used, such as MRI, X-ray scans, ultrasound, Computed Tomography (CT), Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT). In particular, MPI allows novel real-time in vivo monitoring. All these opportunities and capabilities that MPI presents are now seen as potential breakthrough innovations in timely disease diagnosis, implant monitoring, and image-guided therapeutics.

- o Development of new imaging tools (image reconstruction and analysis) for Silicon Photomultiplier (Si-PM) Time-of-Flight PET systems.

Si-PM detectors are recognized as the next generation of PET detectors. Their use will foster applications of the simultaneous imaging of PET-MRI due to their ability to perform under strong magnetic fields. Coupled with adequate electronics, Si-PMs offer exciting new solutions for Time-of-Flight PET applications and dedicated PET systems.

- o Development of an fNIR imaging probe to characterize in vivo breast cancer tissue, which can be coupled with other imaging modalities.

This thematic line will be a transversal line in the unit, providing imaging data tailored to the unit's needs, either by processing it in a specific way or obtaining data using non-standard protocols.

### 10.3. RESEARCH GROUPS INVOLVED IN THE THEMATIC LINE

Reference	Name
RG-645-1499	Biomedical research in neurosciences and in oncology

### 10.4. ORGANISATIONAL STRUCTURE AND OBJECTIVES OF THE THEMATIC LINE

#### 10.4.1 Structure of the Thematic Line

The organization of this thematic line takes advantage of the expertise of the following IBEB members, which can be observed in their CV's - their contribution to the thematic cline will be the following:

Pedro Almeida (thematic line coordinator, nuclear medicine and multimodality applications)

Nuno Matela (image reconstruction algorithms and image quantification),

Rita Nunes (MRI imaging sequence development and data analysis).

Hugo Ferreira (MRI, MPI and PET-MRI applications).

Raquel Conceição, (UWB development and applications).

Mónica Martins (image reconstruction).

Lina Vieira (nuclear medicine modelling and technology assessment for new devices).

In addition to this expertise, the thematic line counts with the input of several external members, in particular Brian Hutton (for PET-MRI imaging), Martin O'Halloran and Elise Fear (for UWB), Joseph Hajnal (for MRI) and Lurdes Orvalho (for Tomosynthesis) allowing access to state-of-the art facilities and data collection.

The main interactions of this thematic line within IBEB will be with the Cancer Therapy and Drug Delivery thematic line. In fact, the adequate merging of complementary information issued from different imaging methodologies, its integrated understanding from the point of view of the pathophysiological processes under study, and the adequate rendering of this large amount of information is essential to help medical doctors becoming more effective in their diagnostic duties.

The thematic line scientific research will be significantly enhanced by strategic partnerships allowing:

a. Direct access to reference R&D Centers that will feed IBEB with state-of-the art data (PET-MRI, MRI, PET-CT) - e.g. the University College London, the Julich Research Center, King's College London or Champalimaud Foundation) and use IBEB's image processing and analysis skills.

b. Direct access to specialized medical doctors and to medical data (CT, MRI, PET) - e.g. the Hospital da Luz imaging department, Champalimaud Foundation.

c. Direct access to cooperation with local and international industry (e.g. Siemens Medical Solutions, PETSys, Phillips, Agilent technologies, MITOS Medical Systems, Micrima, Cubresa).

Similarly to other thematic lines within the unit, the research done will also be enhanced by a post-doctoral fellow and Ph.D. students working in areas like image reconstruction for pixelated and modular Si-PM PET systems or attenuation correction of simultaneous PET-MRI data. This thematic line will also have strong connections with the other IBEB's thematic lines. In particular with the "Cancer Therapy and Drug Delivery" thematic line, we will aim to maximize the relevant information obtained by imaging methods that can be considered during treatment planning. With the "Brain Dynamics and Connectivity" thematic line, we will work together to develop original visualization techniques, based on modern augmented reality technology. Amongst the thematic line researchers, synergies between parallel projects will be maximized, sharing methodologies used in image processing, visualization and image classification.

All the skills available to IBEB through the members of this thematic line will be used to fulfill the objectives of this thematic line, and the interaction between the integrated and associated members will be assured by trimestral meetings. In these meetings, the overall progress will be analyzed according to the established objectives, and possible changes in the program of work will be defined dynamically and as a result of new developments in the state of the art, new data, etc. The activities of this thematic line will join the expertise of IBEB, health institutions and, whenever possible, patients in order to contribute to the effective use of medical imaging state-of-the art in the clinical setting.

#### 10.4.2 Objectives of the Thematic Line

To develop imaging techniques and enhancing existing ones, with focus on oncology.

Objectives and Impact (I):

1. Constructing clinically useful image-based models of the aggressiveness of low-grade brain gliomas using PET-MRI simultaneous data.

(I): Better knowledge and characterization of the functional properties of brain gliomas.

2. Characterizing the effects of breast chemotherapy in the brain.

(I): Better knowledge of the cognitive effects resulting from the use of chemotherapy for breast cancer treatment.

3. Construction of fully operational image reconstruction and quantification algorithms for Si-PM PET systems.

(I): Contribution to a new generation of PET systems and application of state-of-the-art and cutting edge detector technology to cancer diagnosis.

Industry-driven research adding value to our unit and to the economical biomedical ecosystem.

4. Improve the diagnostic accuracy of X-ray tomosynthesis of the breast using statistically based image reconstruction algorithms, CAD and augmented reality technology.

(I): Direct benefit in patient management. Improved quality of life for patients (reduced radiation dose in tomosynthesis, faster diagnosis). Combination with other breast imaging modalities.

5. Quantification of functional and mechanical characteristics of breast cancer using the Clear-PEM Sonic prototype.

(I): Better understanding of imaging characteristics and pitfalls of dense and less dense breast tumors.

Combination with other breast imaging modalities.

6. Automatic methodology for discriminating between benign and malignant breast tumors in a simulation scenario for a UWB Radar system. Assessing and diagnosing lymph nodes in the axilla region.

(I): Development of new classification algorithms, to extract tumor response and classify each tumor according to its shape and size. Development of a system to diagnose the lymph nodes and to detect the sentinel node.

7. Construction and testing of a UWB radar adaptable to a PEM system for breast cancer diagnosis.

(I): Additional expertise on experimental development of medical devices and potential creation of Industrial Property on medical imaging.

8. Study of novel imaging biomarkers for breast cancer using MRI techniques and imaging genetics. Optimization and application of Diffusion Kurtosis Imaging for lesion subtype discrimination. Development of machine-learning algorithms for lesion classification based on the use of imaging as a phenotype: correlation between -omic (genomic, proteomic, etc) and histological information with MRI data.

(I): Identification of novel imaging biomarkers of disease and breast cancer subtypes. More accurate lesion classification will impact on treatment approach and prognosis. Avoid unnecessary biopsies and improve patients' quality of life.

9. Quantify water diffusion in the human brain employing Magnetic Resonance Fingerprinting.

(I): reducing exam durations while improving clinical information could make MRI much more cost-effective and accessible.

10. Construction of a one-end prototype for Magnetic Particle Imaging to image humans.

(I): Acquisition of expertise on this topic by leveraging and transferring knowledge from other areas of expertise within IBEB. Stronger positioning of IBEB on emergent imaging technologies for health. Increased training opportunities with a unique facility in Portugal. Strong connections with nanotechnology units in our country (3B's, CBIOS) and abroad (Charité University).

11. Development of new tools for the optical detection of sentinel lymph nodes.

(I): Detection and location of the sentinel node without exposing patients or technicians to radiation.

12. Development of fNIR-based imaging system to characterize in vivo breast cancer tissue. (I): Replacement of more invasive techniques or its integration with other imaging techniques.

Overall (I): More accurate, reliable, earlier and less invasive diagnosis or evaluation of therapy response.

## 10.1. IDENTIFICATION OF THE THEMATIC LINE

### 10.1.1 Reference of Thematic Line

TL-645-1300

### 10.1.2 Name of the Thematic Line in Portuguese

Dinâmica e conectividade cerebral

### 10.1.3 Name of the Thematic Line in english

Brain connectivity and dynamics

### 10.1.4 Principal Investigator

Alexandre da Rocha Freire de Andrade

### 10.1.5

#### Scientific areas

Physics

Bioengineering

Neurosciences, Ageing and Degenerative Diseases

## 10.2. DESCRIPTION OF THE THEMATIC LINE

### 10.2.1 Description of the Thematic Line

The non-invasive study of human brain function is one of the major scientific endeavors of current research in Medicine and Biomedical Engineering, as acknowledged by the substantial funding and high strategic priority awarded to brain-related research by the most relevant funding bodies within the European Union and the United States of America. The field of brain functional studies has expanded dramatically since the advent of functional Magnetic Resonance Imaging (fMRI) in the early 1990s, along with new developments in established modalities such as electroencephalography (EEG), magnetoencephalography (MEG) and traditional Magnetic Resonance Imaging (MRI). Other modalities, such as functional Near-Infrared Spectroscopy (fNIRS), Transcranial Magnetic Stimulation (TMS) and transcranial direct current stimulation (tDCS), have provided complementary capabilities. The early emphasis on strict localization of brain function has gradually been replaced by an attempt to probe the brain as a dynamic entity whose operation depends on the interaction between several loci. The term “connectivity” has come to encapsulate this view of the brain as a system of connected components that interact dynamically in order to support healthy brain function, and who tend to elicit pathological behavior when their communication is disturbed by a disease or injury. Connectivity may be studied from a strictly functional point of view and/or from a structural point of view. Since functional connectivity is dependent on the existence and integrity of neural structural pathways, it makes sense to cover both components in an integrated approach. “Dynamics” is a term with a broad meaning but which can be defined, in the context of brain research, as the study of how brain signals unfold in time, during rest (spontaneous oscillations) or in response to a stimulus, and the relation between temporal behavior and the underlying physiological mechanisms that support function. IBEB and several of its members have a long experience in the study of human brain function in health and disease. In recent years, brain connectivity, especially its dynamic component, has been a top priority. More specifically, IBEB members have experience in the design, computational implementation and validation of methods to acquire relevant data and assess the dynamic behavior, functional as well as structural connectivity patterns of the human brain using MRI, fMRI, EEG and MEG, and including application to diseases such as epilepsy, schizophrenia and autism. Given this solid previous experience and the importance that these topics have in current medical research, as well as the potential impact on the understanding of diseases with a very strong impact on healthcare and the quality of life of the populations, we believe that a thematic line centered on brain dynamics and connectivity is pertinent and strategically important for the Unit as a whole, and that it will be very important for the achievement of its main objectives.

Within this thematic line, the following lines of research will be explored:

- Design and implementation of new MRI and fMRI sequences specifically tailored for connectivity and dynamic studies, namely fast (multiband) fMRI and Diffusion Weighted Imaging (DWI) sequences targeted for structural connectivity/tractography approaches. Since both fMRI and DWI rely on multi-slice acquisitions, the simultaneous excitation of sets of slices will allow achieving full brain coverage within shorter times, improving the temporal resolution of fMRI and enabling the sampling of a larger number of diffusion directions and/or weightings within feasible scanning times.
- Implementation of an MRI pulse sequence for Point Spread Function calibration and of a reconstruction algorithm for the correction of geometric distortions typical of Echo Planar Imaging used for fMRI and DWI.
- Implementation of an Echo Volumar MRI sequence to perform resting-state fMRI of the fetal brain. The goal is to achieve improved robustness to motion taking advantage of the longer relaxation times of fetal brain compared to those of adult brains.
- Development of novel physical models and algorithms for diffusion kurtosis imaging (DKI)-based tractography in order to overcome existing Diffusion Tensor Imaging (DTI) limitations, and consequently improve structural connectivity estimates.
- Implementation of a simulation platform capable of recreating neural and hemodynamically filtered signals for M/EEG and fMRI simulations, respectively, based on large-scale spiking neuron models implemented in a Graphics Processing Unit (GPU).
- Development, computer implementation and validation of new signal processing methods for the study of functional connectivity, selectively fine-tuned for application to M/EEG, fMRI or fNIRS.
- Application to chosen pathological situations where connectivity is a key issue, most notably to epilepsy (tracking of seizure paths using effective connectivity methods that are sensitive to the direction of the information

flow along the neural pathways). To complement this information, structural connectivity studies based on tractography will also be performed.

- Application to the study of the interaction between resting-state networks in the healthy and pathological brain and to the study of low-frequency modulation of brain oscillations and its implications, including the disentangling of physiological (e.g. heart, breathing) components from neural ones using a multi-modal strategy (e.g. combining fNIRS, EEG and fMRI).
- Development of a software tool that integrates the validated methods and the simulation platform, in order to provide the researchers of the Unit and the external community with a workbench for conducting multi-modal connectivity studies (e.g. MRI, PET, EEG, fNIRS) using state-of-the-art methodologies in a user-friendly environment. The software tool will be particularly suitable for growing interest in multimodal studies such as simultaneous EEG/fMRI and PET-MRI.
- Interaction with the thematic line “Non-invasive brain stimulation and neuro-rehabilitation”: Simulation of the effect of electrical and magnetic stimulation in cortical circuits, using spiking neuron models and realistic models for the human cortex, including modeling of specific pathological phenomena such as dysfunction within the pathways involving basal ganglia in Parkinson’s disease.

It is our belief that this thematic line strikes an adequate and fruitful balance between past experience and know-how of the members involved and innovation targeted to cutting-edge research, multidisciplinary, support for high-quality graduate and undergraduate training, positive impact in public health and exploration of existing and new collaboration opportunities.

### 10.3. RESEARCH GROUPS INVOLVED IN THE THEMATIC LINE

Reference	Name
RG-645-1499	Biomedical research in neurosciences and in oncology

### 10.4. ORGANISATIONAL STRUCTURE AND OBJECTIVES OF THE THEMATIC LINE

#### 10.4.1 Structure of the Thematic Line

The structure of this thematic line relies directly on the expertise of the following IBEB members:

- Alexandre Andrade (Principal Investigator): experience in the development and implementation of novel methodologies for the analysis of biomedical signals and images, with emphasis on the study of brain function using M/EEG and fMRI, including applications to the study of diseases.
- Hugo Ferreira: experience in MRI scanner operation, functional and structural connectivity and complexity analysis using (f)MRI including applications to the study of diseases. Additionally, as a clinical consultant in neuroimaging he will foster the translation of research efforts into clinical practice (e.g. connectivity-based brain mapping for neurosurgical planning).
- Rita Nunes: experience in MRI sequence design and implementation (Philips and Siemens platforms) as well as scanner operation; has also focused on image reconstruction and processing including artifact reduction (motion, distortion) with emphasis on Diffusion Weighted Imaging. Experience in structural connectivity and tractography. Interaction with the thematic line “Non-invasive brain stimulation and neuro-rehabilitation” relies on the expertise and experience in magnetic and electric stimulation of the human brain and realistic model conception of the following IBEB members: Pedro Cavaleiro Miranda (Principal Investigator of the thematic line mentioned), Ricardo Salvador and Cornelia Wenger.

IBEB is currently involved in a significant number of partnerships and collaborative efforts which are relevant for this thematic line. This includes collaborations with clinical partners (e.g. Hospital de Santa Maria, Hospital da Luz, Hospital de São José) higher education institutions (e.g. King’s College, London, where Dr. Rita Nunes is a visiting scientist) and research labs (e.g. Jülich Forschungszentrum). This facilitates access to medical imaging equipment, to patient data and to expertise in relevant topics.

It is expected that this thematic line will benefit from the active participation of one of the post-doctoral researchers whose hiring is contemplated in the current strategic project. His/her profile should ideally include previous experience in brain functional studies with an emphasis on connectivity analysis.

Work within this thematic line will be coordinated by its Principal Investigator, who will promote regular meetings with the people involved in order to assess the ongoing progress and to ensure that the established objectives are being met. The participating researchers will have differentiated contributions towards the components involved (sequence design/hardware optimization, model building/simulation, computer implementation and validation of methods, data analysis, study design/interaction with subjects). It will be the duty of the Principal Investigator to ensure that individual contributions are steered towards specific tasks and landmarks that are compatible with the agreed objectives, without constraining the emergence of potentially relevant collateral projects guided by the initiative of individual researchers, and accommodating possible changes due to unexpected hurdles or opportunities that may arise during the period covered by this strategic project.

This thematic line is structured in a way that minimizes mutual dependence between different tasks and components. It is believed that running different sub-projects in parallel is the best way to achieve the proposed goals, since most of these depend on the convergence of different components (visualization, modeling, sequence design, methods development, and application). Although it is expected and desirable that different sub-lines will contribute towards the success of others (e.g. application to real data will benefit from the use of advanced fast fMRI sequences, computer modeling of cortical circuits will inform and contribute towards conclusions drawn from functional connectivity studies),

#### 10.4.2 Objectives of the Thematic Line

The objectives and expected impact of the activities of this thematic line for the period 2015-2020 are:

1. Implementation and testing of fast multiband fMRI and DWI sequences in order to achieve (respectively) higher temporal resolution and sampling of larger numbers of diffusion directions and/or weightings required for the application of complex diffusion models.
2. Implementation of an MRI pulse sequence for Point Spread Function measurement for the correction of geometric distortions typical of fast techniques.
3. Implementation of an Echo Volumar MRI sequence including selective excitation to perform resting-state fMRI of the fetal brain with improved robustness to motion.
4. Development of an expandable and user-friendly GPU-based simulation platform relying on spiking neuron models capable of recreating M/EEG and fMRI signals.
5. Development and implementation of analysis protocols targeted for seizure path tracking in epilepsy, based on effective connectivity techniques.
6. Development and implementation of a comprehensive protocol for fMRI connectivity analysis that explicitly includes amplitude and phase measures and is able to provide a full description of the dynamic spectral evolution of brain signals.

7. Application of connectivity protocol to patient studies. Given ongoing collaborations, schizophrenia, epilepsy, Parkinson's disease and gliomas are likely candidates.

8. Application of connectivity protocol and simulation platform to the study of the interaction between rest networks. The effects of disturbances induced by magnetic or electric stimulation will be covered, thanks to the incorporation of realistic models of the cortex (interaction with Stimulation thematic line).

9. Development of novel physical models and algorithms of DKI-based tractography for providing novel means for biomarker research and for improved structural connectivity analysis.

10. Development of a comprehensive software tool for multimodal structural and functional connectivity analysis able to integrate ongoing and future methodological innovations (such as correlation-purged Granger Causality, Phase-Amplitude Coupling). Integration of this tool with the simulation platform.

11. Study of connectivity using multimodal approaches (e.g. EEG/fMRI, PET-MRI) exploring collaborations with hospitals and the Jülich Forschungszentrum, focusing on the study of healthy subjects, but also epilepsy and glioma patients.

12. Study of brain complexity by using time-clustering, multi-scale entropy and detrended fluctuation analysis and also by applying network theory to connectivity matrices.

13. Development and implementation of machine-learning algorithms for classification of brain networks and diseases based on connectivity, complexity and imaging metrics (e.g. cortical thickness, mean diffusivity).

14. Adaptation and application of connectivity protocol to an fNIRS study of rest and task-induced activity in the human brain. The goal will be the disentanglement of vascular components (that are mixed up in fMRI studies) and thereby informing the interpretation of concurrent fMRI results.

A broader objective is to have a positive impact on the understanding of diseases and therefore on public health, as well as providing clinical partners with new tools that enable them to go beyond standard analyses and harness the full potential of their imaging equipment, with benefits for patients.

It will be our priority to translate research within this thematic line into publication in high impact journals, both methods-oriented and clinically- oriented.

The intended overall impact will be a significant contribution towards the understanding of specific aspects of human brain function that are relevant for major diseases, and a major contribution towards the expansion of the available methodological tools available to researchers in this field.

## (TL-645-1301) Cancer therapy and drug delivery

### 10.1. IDENTIFICATION OF THE THEMATIC LINE

#### 10.1.1 Reference of Thematic Line

TL-645-1301

#### 10.1.2 Name of the Thematic Line in Portuguese

Terapia oncológica e entrega de medicamentos

#### 10.1.3 Name of the Thematic Line in english

Cancer therapy and drug delivery

#### 10.1.4 Principal Investigator

João Miguel Pinto Coelho

#### 10.1.5

##### Scientific areas

Physics

Bioengineering

Nanoscience and Nanotechnology

Diagnostic, Therapies and Public Health

### 10.2. DESCRIPTION OF THE THEMATIC LINE

#### 10.2.1 Description of the Thematic Line

In recent years, new advances in the existing technologies have opened a range of opportunities regarding therapy. In particular, the application of advanced radiotherapy treatments, electromagnetic mediated thermotherapy and targeted laser hyperthermia of tumours is opening new possibilities in the fight against cancer. Also, new drug delivery systems are being developed based mainly on the application of light. Transdermal delivery makes use of laser beams to increase the permeability of the skin, and thermally-induced delivery is advancing with the development of new nano-carriers and advanced optical methods to allow light to have a better penetration in the tissues.

Making use of the existing skills, this thematic line is fundamental to achieve one of the goals of IBEB, as stated above: "(...) IBEB wishes to position its R&D and advanced training efforts on contributing with state-of-the-art research in cutting edge technological applications to the better understanding of disease progression and therapy in Oncology and Neurosciences."

Thus, the overall objective of this thematic line is to study, develop and implement techniques and methodologies for supporting or creating therapy and drug delivery systems. Three main fields are defined: radiotherapy, thermotherapy and photonics.

Advanced radiotherapy treatments with Intensive Modulated Radiation Therapy (IMRT) technique can deliver more conformal dose distributions to the tumour targets and thus allows higher doses to be administered to the intended target volumes while minimizing radiation damages to the surrounding normal tissues. IMRT may provide high tumour control and low toxicity, but it may also bring excessive leakage dose to the body compared to conventional radiotherapy. Therefore, the benefit of IMRT might be compromised because of the potential risk of increased radiation-induced malignancies. And hence, the design and optimization of the IMRT treatment

demands from the benefit-risk-analysis. Our research activities in radiotherapy aim to develop and implement calculation models as tools to properly validate the benefit-risk of the IMRT treatment. We will evaluate the overall benefit-risk ratio of advanced IMRT and existing therapy techniques by comparing physical and biological therapy endpoint parameters and the risk of radiation-induced malignancies, resulting from low doses, to the rest of the patient body. The Monte Carlo (MC) method and dosimetry techniques will be used to determine patient dose distributions and accelerator leakage radiation emerging from the linear accelerator (Linac). The clinical impact of Dose Mass Histogram for validation of IMRT plan will be evaluated in collaboration with Fox Chase Cancer Center of Philadelphia (FCCC). Multi-centre studies will be designed using clinical data from reference oncologic centres and the methodology from the previous study of the European Working Group on MC Treatment Planning (EWG-MCTP). For specific treatments, the neutron contamination of the clinical beams and their induced radioactivity will be investigated. The neutron induced radioactivity will be measured by gamma-neutron spectroscopy in collaboration with the University of Pisa.

With the study of detailed dosimetric aspects in radiotherapy and the participation in European multi-centre studies, the Unit will reinforce its Medical Physics component. This effort will be put into place to allow a strong connection with results produced in other thematic lines, in particular the one dealing with Medical Imaging. This effort will potentiate the recruitment of one post-doctoral fellow and the help of Ph.D. students in specific projects. With this in mind, the unit has applied for one FCT funded Post-Doctoral fellowship and has already two Ph.D. students in the specific area of Radiotherapy.

Recent developments on the use of thermotherapy based on microwaves increase the interest of the scientific community regarding the use of this kind of technology for cancer therapy. Localised temperature increased will: i) trigger controlled cell apoptosis, and/or ii) induce more sensitivity to pharmaceuticals. This thematic line will maintain a strong connection, in particular, with the Medical Imaging and Diagnostics thematic line.

As a therapeutic and drug delivery tool, photonics plays a direct role in:

- Assessing light interaction with nanoparticles
- Enhancing light penetration and maximizing irradiance

In fact, nanoparticles are being used with very positive results to locally destroy tumour tissues. Preliminary results show that it is possible to use light to increase nanoparticles temperature and thus effectively use them as drug delivery systems or as agents to hyperthermia effects. It is therefore important to ensure deliverance of the highest possible dose of radiation locally in order to avoid damaging the adjacent tissues to the tumours. A known difficulty is the small penetration depth due to the highly scattering properties of tissues.

In such context, main challenges of photonics research in this area are: for light interaction with nanoparticles, develop numerical models capable of studying the interaction of laser radiation with the different types of nanoparticles, mainly regarding the temperature distribution among the nanoparticles and the adjacent tissues, and to assess the impact on both tumour and normal tissues. These models will have to be validated by experimental implementation of irradiating methodologies and related metrology tools, which will pose a particular challenge due the scales being considered. For enhancing light penetration, we will study methods based on the correction of the incident wavefront, in order to minimize the effects of scattered light. Besides allowing higher depth activation capability, the processes will also allow higher concentration of light thus increasing the efficiency of the interaction processes and minimizing damage to adjacent tissues to the tumours by requiring lower incident energies. The first steps are already being taken in the framework of a FCT-funded project, but given the complexity of the problem, it is expected that it will take several years before achieving a product/technique with applications in the treatment of breast tumours in humans.

This line shares very significant synergies with research planned in the thematic line dealing with Medical Imaging and Diagnostics. In fact, adequate and precise imaging methodologies are essential for the delivery of effective therapy procedures. In this context, not only anatomical imaging like MRI or X-ray, but also molecular imaging such as PET, can provide useful information about the location and metabolic characteristics of tumors, in particular those within IBEB's main interests. In addition, imaging procedures, in particular those mastered by the unit are essential for the evaluation of therapy efficacy. These synergies will be used whenever desirable.

### 10.3. RESEARCH GROUPS INVOLVED IN THE THEMATIC LINE

Reference	Name
RG-645-1499	Biomedical research in neurosciences and in oncology

### 10.4. ORGANISATIONAL STRUCTURE AND OBJECTIVES OF THE THEMATIC LINE

#### 10.4.1 Structure of the Thematic Line

The thematic line of Cancer Therapy and Drug Delivery is organized according to four main skills: radiotherapy, radar fields, photonics and MRI. Its core is based on the expertise of the IBEB's integrated researchers associated to this thematic line:

- João Coelho, with expertise in photonic systems and lead researcher in a project to develop techniques to potentiate the therapy and drug delivery using laser radiation.
- Grisel Mora with the expertise in the application of the MC method for IMRT and clinical residence experience in radiotherapy, as a member of EWG-MCTP.
- Raquel Conceição with the expertise on the application of Ultra Wide Band Radar Technology to breast tumors.
- Hugo Ferreira with expertise in nanomedicine including nanoparticles, in MRI and also as a medical doctor.
- Rita Nunes, MRI including pulse sequence design and programming.

These competencies will be complemented with the participation of several associated members and also with cooperation with researchers of other units and institutes. As a follow up to already ongoing projects, first priority is to intensify collaborations with the partners like CBIOS/Lusófona or the 3B's research group in Minho and the Centrum for Tumor Medicine, Charité-Universitätsmedizin Berlin, regarding the development of nanoparticles and drug delivery nanocarriers. Ongoing work in the field of radiotherapy applications will be continued and an annual visit to the Philadelphia Fox Chase Center is foreseen for Dr. Grisel Mora in order to pursue collaborative work in this area, in particular with Dr. Charlie Ma. Collaborations with members of the EWG-MCTP will be reactivated and multi-centre studies for risk analysis will be performed using clinical data from oncologic centres of the EWG-MCTP (University of Berne, Université Lille, University of Cardiff and University of Seville). Ongoing work in the field of microwave medical applications, further training will be possible with the COST European network TD1301, which Dr. Raquel Conceição is chairing. Also, the existing cooperation with the Laboratory of Optics, Lasers and Systems of FCUL will complement the expertise in sensing and systems development, in particular in the field of optics.

The overall skills will be upgraded by one post-doc fellow proposed in this strategic plan to develop his/her activity in the field of instrumentation and sensing for the systems considered in this thematic line. The specificities of this work will be defined in detail according to the identified needs after the progress evaluation of the objectives during the first year.

All these skills will be used to fulfill the objectives of this thematic line, and the interaction between the integrated and associated members will be assured by trimestral meetings. In these meetings, the overall progress will be analyzed according to the established objectives, and possible changes in the program of work will be defined

#### **10.4.2 Objectives of the Thematic Line**

The overall objective of this thematic line is to study, develop and implement techniques and methodologies for supporting, and to create therapy and drug delivery systems. Four main areas are defined: radiotherapy, UWB, photonics and interventional MRI.

Regarding radiotherapy, the main scientific objectives are:

- To evaluate the overall benefit-risk ratio of advanced IMRT and conventional treatment techniques by comparing local tumor control, acute and late toxicities to nearby critical organs and the risk of radiation-induced malignancies resulting from low doses to the rest of the patient's body.
- To investigate the neutron dose component associated with the high energy clinical beams.
- To study the clinical impact of the Dose Mass Histogram as an alternative validation method for the radiotherapy treatment of the body sites including low density regions
- To determine the efficiency induced by commercial available nanoparticles for selected radiotherapy treatments.

The successful completion of the proposed research studies will provide reference data for the design, optimization and validation of the IMRT state of art techniques based on the overall benefit- risk ratio of the advanced radiation treatment. In addition, we will theoretically quantify the risk reduction of certain radiotherapy treatments using nanoparticles.

Regarding the use of UWB, we will seek to study the use of microwave fields for hyperthermia. We will begin by using anatomic models of tumours and then, if possible, real tissue from collaborators (e.g. IPATIMUP).

Regarding photonics, the main scientific objectives are:

- To develop numerical models as tools to study the interaction of laser radiation with tissues, drug carriers and nanoparticles, mainly regarding thermal effects.
- To contribute to the evaluation of emerging nanotechnologies in the development of therapy and drug delivery systems.
- Experimentally implement irradiating methodologies (for tissues, nanoparticles and drug carriers) and related metrology tools. This includes in vitro and in vivo studies.
- To develop phase-shaping methods for the correction of an incident wavefront in order to minimize the effects of scattered light.

Regarding interventional MRI, the main scientific objectives are in line with research started in 2012 in this field and include:

- To develop multifunctional magnetic devices (e.g. polymer+FeOx) and nanoparticles (e.g. gold+FeOx) for drug-delivery and hyperthermia together with the external partners mentioned above.
- To develop an apparatus for guiding magnetic devices and magnetic drug-delivery systems (DDS), related to the development of the magnetic particle imaging (MPI) system mentioned in the Medical Imaging and Diagnostics thematic line.
- To develop protocols for imaging and guiding magnetic devices and DDS to target sites using a MRI scanner and MPI system.
- To develop protocols for promoting drug-release at target sites using laser light stimulation and/or microwave by integration with the above research studies.
- To explore methods for magnetic device/particle-mediated hyperthermia for the future development of an apparatus which integrates magnetic device/particle imaging, guiding and hyperthermia.

These research fields will have impact in the development of targeted destruction of tumours by hyperthermia and on the study and development of radiation (microwave/laser/magnetic fields) mediated drug delivery systems.

All mentioned main scientific objectives will contribute to IBEB's global strategy of positioning itself as a R&D unit contributing to state-of-the-art research in cutting edge technological applications to the better understanding of disease progression and therapy in Oncology and Neurosciences. It makes use, not only of the skills existing at IBEB in the related areas, but also with the already existing cooperation network.

### **(TL-645-1302) Brain stimulation and neuro-rehabilitation**

#### **10.1. IDENTIFICATION OF THE THEMATIC LINE**

##### **10.1.1 Reference of Thematic Line**

TL-645-1302

##### **10.1.2 Name of the Thematic Line in Portuguese**

Estimulação cerebral e neuro-reabilitação

##### **10.1.3 Name of the Thematic Line in english**

Brain stimulation and neuro-rehabilitation

##### **10.1.4 Principal Investigator**

Pedro Michael Cavaleiro de Miranda

##### **10.1.5**

###### **Scientific areas**

Physics

Bioengineering

Neurosciences, Ageing and Degenerative Diseases

#### **10.2. DESCRIPTION OF THE THEMATIC LINE**

##### **10.2.1 Description of the Thematic Line**

Electric stimulation of excitable tissue was successfully applied to map out the representation of the body in the motor cortex back in the 1950's, to stimulate the heart using a pacemaker, and more recently to alleviate tremor in patients with Parkinson's disease using deep brain stimulation (DBS). The advantage of these techniques is that they achieve focal and effective stimulation; the disadvantage is that they are all invasive since they resort to implanted electrodes. Recently, non-invasive brain stimulation (NIBS) techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have found widespread use in neurophysiology and neuroscience studies. Their ability to stimulate the cortex or to modulate its excitability has been clearly demonstrated. In some conditions the effect can persist after the stimulation period is over, indicating that plastic changes have been induced. The dependence of the stimulation outcome on the brain state has also been established. Despite their inherent limited focality, the non-invasiveness and ease of use of these techniques has widened dramatically the scope of brain stimulation, particularly regarding potential therapeutic applications.

Brain-computer interfaces (BCIs) are used as a means of direct communication between the brain and a computer that could then be used to perform specific tasks. The use of implanted electrodes significantly enhances the performance of the interface but limits application in humans. Non-invasive BCIs, mostly based on EEG signals, have limited bit-rates and may require long training periods. BCIs are currently being explored as neurorehabilitation tools, used in a clinical setting as an adjunct to conventional rehabilitation methods such as physiotherapy. In this situation, issues related to BCI usability and user acceptance are particularly relevant. Cortical plasticity is another important determinant in the success of the neurorehabilitation program. The scientific goal of the "Brain stimulation and Neuro-rehabilitation" thematic line is to implement new techniques for brain stimulation and brain-computer interfaces, and to apply them in areas related to physiology, neuro-rehabilitation, and cognitive neuroscience. The common theme underlying this line of research is the non-invasive application of electric fields to the brain and the spinal cord, and the quantification of its effect on the central nervous system (CNS). This topic is addressed through a combination of computational modelling work, implementation of novel stimulation techniques and brain-computer interfaces (BCIs), and studies involving human subjects. The choice of thematic line serves two main purposes. The first is to organize within IBEB a group of researchers with common interests and complementary expertises. By deciding to work together on the thematic line, these researchers undertake to direct their activity to this shared endeavour. This entails broadening the scope of on-going projects and creating new projects that take advantage of the group's joint expertise. The second purpose is to promote collaborations with neuroscience and clinical partners outside IBEB, nationally and internationally, by increasing the visibility of the specific know-how that this group can bring to research projects in these areas. The combination of science and engineering skills with the ability to perform studies on human subjects will enable such collaborations to carry out innovative and high quality research. IBEB's mission is to carry out Biomedical Research in Neuroscience and Oncology of the highest quality by international standards. This thematic line contributes to IBEB's mission mainly in the Neuroscience area. IBEB is already an international reference in calculating the electric field distribution in non-invasive brain stimulation. The work that will be implemented in this line will allow IBEB to maintain this position and to make similarly important contributions in additional areas related to brain-computer interfaces, physiology, neuro-rehabilitation, and cognitive neuroscience. In the process, new national and international collaborations will be established and more researchers and students will be recruited to work on this line. Work with human subjects and patients will also increase the impact of the research carried out at IBEB. In line with the unit's objectives, this group will carry out innovative research at international level and publish its work in well-known journals, perform multidisciplinary research with clinical and neuroscience partners, attempt to increase the societal impact of its work by collaborating with SMEs, and train students at the MSc and PhD level.

### 10.3. RESEARCH GROUPS INVOLVED IN THE THEMATIC LINE

Reference	Name
RG-645-1499	Biomedical research in neurosciences and in oncology

### 10.4. ORGANISATIONAL STRUCTURE AND OBJECTIVES OF THE THEMATIC LINE

#### 10.4.1 Structure of the Thematic Line

The strategic objective of this thematic line is to establish a leading group in the application of non-invasive brain and spinal cord stimulation to neuro-rehabilitation and cognitive neuroscience. This group will address scientific questions such as how to optimize the delivery of the non-invasive application of electric fields to the central nervous system, or whether the performance of BCIs can be improved by combining it with brain stimulation. At present, this thematic line comprises three PhD members (P C Miranda, R Salvador and C Wenger), one PhD, MD member (Hugo Ferreira) and several PhD and MSc students. We can also rely on internal collaborators to carry out specific tasks, such as MRI data acquisition and processing (R Nunes) or connectivity analysis, neural network models (A Andrade). The work carried out so far has also involved collaborations with several national and international institutions, such as Santa Maria Hospital, Portugal (M Carvalho, A Mendonça), INSERM, Rennes, France (F Wendling), Universidad Pablo de Olavide, Spain (J Márquez-Ruiz), the Weizmann Institute of Science, Israel (A Zangen, Y Roth), and the NIH, USA (P J Basser, M Hallett). We are also currently working with two SMEs: Neuroelectrics Barcelona, Spain (G Ruffini) and Novocure, Israel (E Kirson).

The successful implementation of the proposed 6-year plan requires a significant increase in our work with clinical and neuroscience partners. This will increase the scope and impact of our work. One measure will be to reactivate existing collaborations and start new ones. We have already submitted a HMS-Portugal project proposal to the FCT on obsessive compulsive disorder and non-invasive brain stimulation in collaboration with the Champalimaud Foundation, Lisbon (A Oliveira Maia). We are also in the process of defining new projects related to multichannel brain stimulation and to spinal cord stimulation for the treatment of pain or spasticity with the Physiology Institute, Institute of Molecular Medicine, Lisbon (M Carvalho, S Pinto). Furthermore, we will seek to establish new European collaborations to address new topics and to apply for EU funds.

Another important aspect of this plan is the creation of a state of the art "Brain stimulation and Neuro-rehabilitation Laboratory" in IBEB. This lab will be equipped with non-invasive brain stimulation devices (TMS, tDCS), a neuronavigation system to accurately position the stimulation devices relative to the individual subjects' neuroanatomy, systems to monitor the response to stimulation (EMG, EEG, ECG, fNIRS), and devices for BCIs. The existence of this lab will enable IBEB to attract new collaborators and to propose highly innovative projects for funding. It would also lead to an increase in experimental work carried out at IBEB, which would be beneficial in several ways: increased scope for the participation of other IBEB members in this activity, more opportunities for advanced training, ability to organize hands-on courses on brain stimulation and on BCIs, etc..

This new structure requires a substantial increase in the number of researchers working specifically in this area. We will continuously monitor opportunities to apply for funds to recruit additional researchers through FCT, the European Commission, SMEs, and other organizations.

Researchers working on this thematic line will meet once a week to ensure that work progresses smoothly and to keep all members updated. The group's achievements will be disseminated via IBEB's website and public presentations.

#### 10.4.2 Objectives of the Thematic Line

One of the scientific objectives of this thematic line is to contribute to a better understanding of the biophysical and physiological processes underlying the non-invasive application of electric fields to the central nervous system, and to improve the delivery of such fields. This involves developing and refining computational models to predict the electric field distribution in the CNS, implementing models of the interaction between the applied electric field and the target cells or neural networks at various spatial scales, carrying out studies involving human subjects to validate our models and to test non-invasive CNS stimulation applications, and collaborating with SMEs that produce and sell this kind of equipment.

A second scientific objective is to set up a state of the art "Brain stimulation and Neuro-rehabilitation Laboratory", which would provide a unique facility in Portugal and in Europe, with a unique combination of technical expertise, state of the art equipment and access to human subjects and patients. This last point is linked to a third objective, which is to increase our collaborations with clinical and neuroscience partners. This will allow us to address new questions such as the ones already mentioned in the previous section and others such as the possible benefits of non-invasive brain stimulation in mild cognitive impairment (MCI) or in dementia, e.g., Alzheimer's Disease.

A fourth scientific objective is deeply related to the prior objectives and relates to further developing the field of BCIs at IBEB. Research will focus on user-BCI/BCI-user adaptation in order to find and develop means to facilitate and improve BCI usage by patients in neuro-rehabilitation and also by the general population within a growing number of existing applications and markets (e.g. entertainment/gaming) and other non-clinical applications (device communications and control in civilian and military settings, for instance). For this purpose, an innovative multimodal approach will be undertaken: knowledge derived from brain connectivity as well as from NIBS techniques such as tDCs and TMS will be used together with scalp EEG-based BCI devices. Brain connectivity data obtained from EEG and MRI (anatomical 3D T1-weighted, structural diffusion tensor imaging and fMRI based on blood-oxygen level dependent effect) will be used to evaluate brain networks' anatomical locations and relations. This information will then be used for optimal NIBS simulation and application using navigation methods and also for optimal BCI electrode positioning. Additionally, connectivity analysis will also be used to monitor the effects of NIBS and relate them to BCI performance. It is expected that by using this approach biomarkers for BCI performance will be identified and that NIBS neuro-modulation protocols for improving BCI usage will be designed tailor-made for specific patients and healthy subjects. This research will be complemented by the development of hybrid BCI devices, which will combine both stimulation and EEG-data acquisition together with a natural user interface for self-paced BCI training and optimal training signal classification.

We will also continue our current work in modelling the use of intermediate frequency alternating electric fields (~200 kHz) for the non-invasive treatment of brain tumours (glioblastomas). The long-term aim is to optimize treatment efficacy by improving field delivery and by understanding the relevant aspects of the electric field - cell interaction.

A final objective is to contribute to the advanced training of MSc, PhD students and post-doctoral fellows in this area.

## 11. BUDGET FOR THE STRATEGIC PROGRAMME 2015/2020

### 11.1 The unit is a candidate for evaluation and intend to apply for funding?

Yes

### 11.2

#### Host institution's budget

##### Fundação da Faculdade de Ciências (FFC/FC/UL)

Description	2015	2016	2017	2018	2019	2020	TOTAL (€)
Human Resources	52423	52423	52423	52423	52423	52423	314538
Missions	1200	2400	3600	4800	6000	8400	26400
Consultants	1500	1500	1500	1500	1500	1500	9000
Service Procurement and Acquisitions	20000	10000	0	0	0	0	30000
Patent Registration	0	0	1500	0	0	1500	3000
Adaptation of Buildings and Facilities	2500	2500	0	0	0	0	5000
Overheads	63275	13515	11805	11745	11985	12765	125090
Equipment	268000	0	0	0	0	0	268000
TOTAL (€)	408898	82338	70828	70468	71908	76588	781028

#### Overall budget

Description	2015	2016	2017	2018	2019	2020	TOTAL (€)
Human Resources	52423	52423	52423	52423	52423	52423	314538
Missions	1200	2400	3600	4800	6000	8400	26400
Consultants	1500	1500	1500	1500	1500	1500	9000
Service Procurement and Acquisitions	20000	10000	0	0	0	0	30000

Patent Registration	0	0	1500	0	0	1500	3000
Adaptation of Buildings and Facilities	2500	2500	0	0	0	0	5000
Overheads	63275	13515	11805	11745	11985	12765	125090
Equipment	268000	0	0	0	0	0	268000
TOTAL (€)	408898	82338	70828	70468	71908	76588	781028

## 12. STRATEGIC PROGRAMME AND BUDGET RATIONALE 2015/2020

### 12.1 Overall budget rationale

We strongly believe that the increase in IBEB's competitiveness on on-going research and the tackling of new and promising research areas, in particular in face of the H2020 challenges will require a significant increase in the number of post-doctoral fellows. On the other hand, this will be much easier to achieve through the leveraging done by the acquisition and/or development of state-of-the-art equipment associated with the thematic lines of the unit. This will allow complementing the research context of IBEB's activity, moving it from mainly data processing into a more balanced positioning which includes state-of-the-art data acquisition tools. The acquisition of this equipment is not trivial to pursue outside a strategically planned activity like the one described in this document. The values involved are the following: TMS Stimulator (78k€), Neuronavigation and EMG (65 k€), EEG recording (48k€), tDCS Stimulator (14k€), fNIRS (54k€), Parts (3k€), Maintenance (6k€) for a total of 267k€. Its acquisition will help attracting new post-doctoral fellows using funding sources which are independent from those asked for in this proposal and will add a significant additional probability for keeping bright students at IBEB, leading to Ph.D. thesis. In view of this, we foresee the financing of master's students through merit scholarships (one each year) and will try to capture the best finishing the Biomedical Engineering Masters at FCUL. These two main aspects of IBEB's planning are reflected on the proposed budget in which about two-thirds relate to equipment and human resources. Having the possibility of producing state-of-the-art data at IBEB will increase the unit's success probability for taking the scientific leadership of the projects on which it participates. In particular, the equipment proposed will allow IBEB to reinforce its scientific strengths in internationally recognized areas (e.g. TMS and tDCS and UWB) and to launch cutting-edge and transversal lines of research within the unit (MPI and brain fNIRS) which have a recognized scientific interest. We therefore believe that the investment done will have extremely benefic effects for the unit on the long run. UWB and MPI prototypes are not classified as equipment since we will develop hardware prototypes for this and so the required parts are included in the budget related to the Service Procurement and Acquisitions. One particularly important aspect of IBEB's activity relies on its connections with international partners. We have therefore foreseen a small annual budget of 1500€ for inviting scientists based abroad to visit IBEB. This will act as a catalyst for young students and will potentiate international participation of IBEB in transnational initiatives. In addition, we have foreseen a coupling of the number of missions to the increase of the unit's members, which is reflected in the Missions item (1200 € per mission).

In recent years, IBEB's members have won two entrepreneurship awards leading to the potential creation of spin-off companies. Therefore, we estimate that potential to the production of patented results will be possible and include budget allowing for 2 patent protection expenses within the Portuguese Patent Office and initial PCT submission. We rely on the University of Lisbon services to account for the additional expenses, (PCT, national evaluation phases, etc..) if judged relevant.

### 12.2 Human Resources rationale

Budget for human resources is directly coupled with the hiring of post-doctoral fellows. The unit is aware that this represents a significant financial effort but is strongly convinced that this spending is fundamental for the success of the strategic program presented in this proposal. Currently, most of the members of IBEB are also deeply involved in teaching and this represents a very heavy burden, which turns research and development efforts sub-optimal. Nevertheless, the scientific and intellectual outcome of IBEB during the last years shows that there has been a significant effort to increase scientific quality and visibility of the Institute. During these years the IBEB has been able to capture a significant amount of financing (circa 10k€/Ph.D. members/year). From the strategic point of view, IBEB sees spending in human resources at two different levels, concurring for a common objective:

1. We wish to attract bright Post-doctoral fellows issued from the Portuguese or the international stage that will commit 100% time to research. This will allow making the most of national and international cooperation connections already put forward during the last years. In addition, the hiring of new post-docs will allow taking advantage of new experimental equipment brought to IBEB and will enable an additional increase of the unit's availability for mentoring Ph.D. students. We should not forget that IBEB is directly coupled to a pool of approximately 30 Master students in Biomedical Engineering which finish their degree each year, after having had (in the majority of cases) an international experience on research during the 3rd year of their Master's course.
2. We plan on attracting the brightest among these students to stay at IBEB offering them a merit scholarship. As long as the unit can provide adequate training conditions, these students will have stronger reasons to stay in their own country instead of leaving and offer their training to foreign academia and economy. This has been a very serious problem in our country in recent years (it still is) and we believe that getting students involved in an early stage of their careers can contribute to minor it. We will encourage the participation of these students in small-scale projects belonging to the Units thematic lines, and especially those relying in the equipment that we plan to buy/build in the context of this proposal.

### 12.3 Equipment rationale

The funding will be used for equipment that will boost IBEB's positioning in an area where it can differentiate internationally (please see the report of the External Advisory Committee): that of transcranial stimulation with electromagnetic fields, its physiological modeling and the study of its effects on humans. Therefore, the acquisition of a TMS+EEG+Neuronavigation+EMG+tDCS+fNIRS equipment is deemed strategic. This unique piece of equipment fits the IBEB's current infrastructure with minor changes (foreseen as 5000€ in 2015-2016) associated with the reinforcement of the electrical network. Although expensive, the equipments price scales to about the same spending per year than that of hiring a post-doctoral fellow. The use of this equipment will allow validating in loco and in vivo most of the work that IBEB has been carrying out based on simulation and to additionally develop a new line of research supported on the use of photonics to study brain response to stimuli using functional Near Infrared Red Spectroscopy (fNIRS). This will have two direct effects in IBEB's research:

1. The possibility to secure industrial funding for research (prior will to invest in the results of this technology has been demonstrated by companies like STARLAB and NOVOCURE).

2. To secure IBEB as a leading unit in this field of research in the European panorama, with all the associated benefits. This desire is based in accumulated and recognized knowledge in this area (Prof. Pedro Miranda) and the possibility of hiring a post-doc fellow to deal with the applications of this equipment and its interactions with the other thematic lines of IBEB (therapy, imaging, brain connectivity).

The budget to acquire this unique piece of equipment is concentrated in the early part of the 2015-2020 period. This will allow IBEB to become rapidly more competitive in this area and to boost the attractiveness for high quality scientific personnel.

### 13. REVIEWERS PROPOSED BY THE R&D UNIT(S)

#### 13.1

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Peter Jezzard	Oxford University - United Kingdom	peterj@fmrib.ox.ac.uk	Bioengineering, Physics, Clinical Research, Neurosciences, Ageing and Degenerative Diseases
Jun Deng	Yale University School of Medicine	jun.deng@yale.edu	Clinical Research, Diagnostic, Therapies and Public Health