PhD in Information Technology and Electrical Engineering

Università degli Studi di Napoli Federico II

PhD Student: Maria Agnese Pirozzi

XXXIII Cycle

Training and Research Activities Report – First Year

Tutor: Prof. Mario Cesarelli

co-Tutors: Dr. Mario Quarantelli (MD), Ing. Mario Magliulo (PhD)

Information

I am **Maria Agnese Pirozzi** and I received a **M.Sc. degree cum laude in Biomedical Engineering** from the University of Naples "Federico II" on January 31, 2017. From April 2017 I am the grantee of a **research fellowship at the Italian National Research Council – Institute of Biostructure and Bioimaging (CNR-IBB)** of Naples. From January 2018 to today I am also a **PhD Student of XXXIII cycle in Information Technology and Electrical Engineering (ITEE)** at Department of Electrical Engineering and Information Technology (DIETI) of University of Naples "Federico II" **without fellowship**. My tutor is Prof. **Mario Cesarelli** and I have two **co-tutors** at CNR-IBB, Dr. Mario Quarantelli (MD) and Ing. Mario Magliulo (PhD).

Study and Training Activities

During the first year of PhD, I attended courses and seminars within the ITEE program and external as reported below.

• Courses and External Courses

Below are the courses included in the training plan of my first year of PhD. Both the modules organized and provided by DIETI Department and those organized and provided in other Departments are listed. Next to each item is reported the Department that provided the course, the lecturer(s), the start and end dates, the total amount of hours and ECTS.

Master's Degree Modules	Department	Lecturer/s	Semester	H	ECTS
Biomedical Imaging	DicMaPI, Università degli Studi di Napoli "Federico II"	M. Cesarelli	Second of a.y. 17/18 (examination July 11, 2018)	30	6
Computer Interface for Biological Systems (CIBS)	DicMaPI, Università degli Studi di Napoli "Federico II"	P. Bifulco	Second of a.y. 17/18 (examination October 08, 2018)	30	6

Ad-Hoc Modules	Department	Lecturer/s	Start-End	H	ECTS
Green Economy and Managment in Engineering Projects	DII, Università degli Studi di Napoli "Federico II"	G. Zollo, L. Iandoli, G. Bruno, P. Rippa, A. Castiglione, G. Ferruzzi, C. Piccolo, I. Quinto	June 6, 2018 - June 27, 2018	10	3
Morphic Sensing	DIETI, Università degli Studi di Napoli "Federico II"	G.D. Gargiulo	July 4, 2018 - July 5, 2018	12	2.4

Research Capacity Enhancement Modules	Department	Lecturer/s	Start-End	H	ECTS
How to publish a scientific paper	DIETI, Università degli Studi di Napoli "Federico II"	A. Birukou, E. Magistrelli	November 26, 2018 - November 26, 2018	2	0.4

In June 2018, I also attended the *SIE2018 PhD School* held in Napoli (Italy). The PhD School overall included 16 hours of lectures plus final examinations, equivalent to a module of 4 ECTS.

Modules from PhD Schools	Short Name	Start-End	H	ECTS
SIE2018 PhD School organized within the 50th Annual Meeting of Associazione Società Italiana di Elettronica (SIE)	SIE'18	June 18, 2018 - June 20, 2018	13	4

• Seminars

Below are the seminars part of my first-year training plan.

Seminars	Lecturer/s	Host/s	Date	H	ECTS
From medical imaging to surgical planning: new directions for Bone and Muscle Assessment	P. Gargiulo	M. Cesarelli, P. Bifulco	May 29, 2018	2	0.4
Using electroencephalography (EEG) to investigate the role of neocortical brain in postural control and postural adaptation when exposed to vibratory proprioceptive stimulation	P. Gargiulo	M. Cesarelli, P. Bifulco	May 29, 2018	2	0.4
Parallel and Distributed Computing with Matlab	S. Marrone	A. D'Alessio	November 21, 2018	2	0.4
Network Analysis, Data Sciences and Control in Computational NeuroScience	P.M. Pardalos	M. Guarracino, L. Mallozzi	Decembre 10, 2018	1	0.2

In September 2018, I attended the *XXXVII Annual School of Bioengineering* held in Bressanone (Italy) organized by the Italian National Bioengineering Group (GNB). The PhD School overall included 30 hours of lectures, equivalent to 5 ECTS.

Seminars from PhD Schools and Workshops	Start	End	H	ECTS
XXXVII Annual School of Bioengineering organized by the Italian National Bioengineering Group (GNB)	September 10, 2018	September 13, 2018	30	5

- ## Credits summary

Finally, I provide a table reporting a summary of the ECTS obtained in my first year of PhD.

	Credits year 1							
		1	2	3	4	5	6	
	Estimated	bimonth	bimonth	bimonth	bimonth	bimonth	bimonth	Summary
Modules	22	0	0	7	8,4	6	0,4	**21,8**
Seminars	6	0	0	0,8	0	5	0,6	**6,4**
Research	32	8	8	2,2	1,6	3	9	**31,8**
	60	8	8	10	10	14	10	**60**

Research Activity

Title

Development of innovative techniques to create anthropomorphic brain phantoms for morpho-functional imaging.

Introduction

Anthropomorphic phantoms are realistic three-dimensional models of the human body and organs used in the computerized analysis for clinical applications. These phantoms, originally created from the radiological and nuclear medicine science community for ionizing radiation dosimetry measurements [1], are still among the most developed objects for technical evaluations on medical imaging devices (such as CT, MRI, PET or SPECT). Having a phantom containing the physical, geometrical and physiological information of a subject is indispensable for the development and testing of the same medical imaging methods. Therefore, the most advanced phantoms reproduce the exact human anatomy from medical images [2]. Imaging studies obtained on phantom are crucial for reducing quantitative variability due to differences in the acquisition setting and intrinsic imaging characteristics. Phantom studies are also carried out to verify that each scanner is properly calibrated and has adequate capabilities to support imaging, such as brain imaging. Brain imaging is particularly challenging in many aspects and in functional imaging is currently hampered by low-resolution issues, which lead to image "contamination" from surrounding structures. This problem becomes more prominent in cases where atrophy is present, such as Alzheimer's disease. Functional images can be corrected for shape and size, based on corresponding brain structures. This need to validate these functional images and their analysis has led

to the use of anthropomorphic brain phantoms, because of an intuitive and real disparity between the images usually obtained with simple geometric test brain phantoms and activity distributions seen in *in vivo* images [3].

The most widespread brain phantom is the *Hoffmann 3D-Brain Phantom*. This phantom, realised with shaped thin plastic levels inserted in a plastic cylinder, comprises only one compartment simulating the brain [3], [4]. Another widely used brain phantom is the *RSD Striatal Head Phantom*. An original anthropomorphic two-compartment phantom of the human brain suitable for PET/SPECT and CT/MRI imaging is the *STEPBrain Phantom*, created and patented in 2006 by three Italian National Research Council (CNR-IBB) researchers [6]. No other phantom with these characteristics has been described in the refereed literature before or is currently commercially available. The phantom was designed as composed by two separate compartments for GM and WM, which can be filled by solutions with different isotope (PET/SPECT), metal (MRI) or iodine (CT) concentrations.

Goals to achieve

The aim of research activity is to explore the possibilities of designing and producing a complex brain anthropomorphic phantom using innovative design and manufacturing techniques. The human brain is both a functionally and a topologically complex organ. Generally, the phantoms attempting to emulate the external anatomy of the brain have a reduced depth of the cerebral sulci or render only the superficial shape of the brain, obtaining it with various types of moulds. Despite the superficial resemblance, these phantoms cannot represent exactly the anatomy and the variety of the brain tissues, which is what we want to achieve with our designed phantom. This phantom is a unique part, anatomically accurate in shape and proportions that, at the same time, can simulate three compartments of the human brain: GM, WM and *Striatum*. The *Striatum* is a high-uptake structure in NM studies and, for this reason, it is interesting to emulate it.

Methodologies and activities

Thanks to advanced mathematical techniques of solid modelling and computer-aided design (CAD) that obtaining the information from the voxel data then allows to extract 3D models of the organs in a suitable format of vector graphics, once the virtual model has been obtained, it must be transformed into a physical phantom. This phantom can be filled with radioactive tracers or with solutions mimicking magnetic resonance signals of brain tissues to explore quantitative aspects of imaging systems under quite similar conditions to those in which the subject is physically present [6]. However, with traditional production techniques of *Subtractive Manufacturing* it is very difficult to create such complex objects and so, on the wide tendency to digitalization of the manufacturing of the last two decades, modern *Additive Manufacturing* (AM) techniques, recently better known as *3D printing*, have been introduced. The latter, being able to create an object in an additive way, layer by layer, allow developing products no longer bound by design complexity [7].

To realize the brain anthropomorphic phantom, I started from images of Magnetic Resonance (MRI) of a normal volunteer detailed in segmentation by means of a segmentation software developed by the researchers of the Institute of Biostructure and Bioimaging [8], [9]. The software segments normal brain studies in 17 compartments and has already allowed the realization of the digital MRI brain phantom, called *Phantomag* [10]. I have been designing the physical counterpart of this digital phantom with only 3 compartments: one for GM, one for WM and one for Striatum. To design a printable model, further automatic processing and manual editing have been carried out on the images of the digital model, aimed at correcting small imperfections of *Phantomag* and connecting the left and right parts of Striatum, respectively. Then, I have moved from raster graphics to vector graphics. The vector STL format (*Stereo Lithography interface format*) is among the most used in the world of 3D printing and AM to describe the geometry of a 3D model: a solid whose surface is discretized in triangles, more commonly called polygonal meshes. I have derived the interface surfaces between the three compartments of the phantom (GM, WM, Striatum) to create empty and fillable compartments. The vertical wall thickness of phantom compartments should be less than 1 mm, preferably between 0.4 mm and 0.6 mm, because it should be at the same time not less than the diameter of the printer nozzle (to be able to print it) and less than the resolution of the imaging methods (not visible to the imaging).

The AM technology chosen for this application is the *Fused Deposition Modelling* (FDM), among the most advanced and effective available today, for the strength, durability and stability of the final parts. The material (in the form of the filament) is extruded through a heated nozzle. The nozzle releases overlaid layers of a melted polymer, predisposing also, if necessary, removable support structures. Supports are required to print the phantom, precisely because it is internally hollow and because of the complexity of the shapes of the model.

Intermediate results and future perspectives of research activity

Our experimental tests carried out to date highlight two critical issues for our application, due to the current limits of the FDM technology. A first problem is represented by the minimum vertical wall thickness that can be materialized with FDM, generally required at least 1 mm thick, even for high-end printers. Our brain phantom requires a submillimetre wall thickness (between 0.4 mm and 0.6 mm), sturdiness and impermeability. The impermeability is very difficult to obtain and requires optimizing the printing parameters setting. However, the water-tightness is not real because even according to the internal pressure the water could creep into the weft deposited during the printing process. To overcome the water-tightness problem, we have been developing an appropriate waterproofing technique. A problem we have been facing is that both external and internal supports are needed to print the phantom. These latter are particularly insidious and difficult to manage. Unlike external ones, they cannot be removed manually and when automatically generated by slicing software they are not perfectly efficient. The phantom's compartments are very convoluted, and this results in numerous critical points for 3D printing. These points are located mainly in correspondence of deep ripples and sulci that

characterize the compartments of GM and WM. In these and other points, holes may be created during 3D printing due to a verisimilar absence or inadequacy of supports. Therefore, we have designed ad hoc supports to support exactly and only the critical points. We are testing the possibility of making them using soluble material to free the phantom from internal supports, but, in the meanwhile, we printed the first prototype of the designed phantom with a semi-professional 3D printer. To print the phantom, we used a common plastic (PET-G) and we chose to adopt supports, automatically generated by the slicing software, made of the same material. We modified the support structure parameters of the slicing software to ensure that these were permeable and "invisible" to Nuclear Medicine imaging.

In the next year, we will have a professional printer for greater reliability in successful printing of complex objects, shorter printing time and less man-hour wasted in solving the problems of not professional printing. Once the waterproofing is permanent, a system for filling the phantom will then be developed. The greatest criticality of the filling phase is the need to avoid that air bubbles are trapped inside the phantom. These would result in unwanted hypointense areas in imaging. By defining suitable filling procedures for Nuclear Medicine (PET/SPECT) and Magnetic Resonance studies it will be possible to use the phantom for the applications reported in this document. The optimization of all these aspects could also open the way to the creation of brain phantoms with other and different compartments of interest.

Title

Development of a brain segmentation software from QMCI maps and a digital brain phantom.

Introduction

The segmentation of brain MRI images is very useful for the quantitative assessment of brain volumes, both for the characterization of normal brain ageing and for the study of chronic degenerative disorders of the brain (such as Parkinson's disease, Alzheimer's disease, Multiple Sclerosis, etc.). These pathologies require repeated checks over long periods to evaluate the evolution of the disease and effects of treatments. Most of the MRI images segmentation algorithms reported in the literature are based on the signal intensity of MR data (T1-, T2-, PD-, weighted) and require operator intervention at different levels. *Quantitative Magnetic Color Imaging* (QMCI)[1] maps based on physical MRI parameters (R1, R2, PD) instead provide a standardized approach for the

[1] Magnetic resonance imaging technique using a single colour image (RGB) to simultaneously represent the spin-echo information. The relaxation rate maps (R1 = 1/T1 and R2 = 1/T2) and proton-density (PD) are calculated on studies obtained in standard spin-echo sequences and merged into a single colour image with R1, R2, PD coded respectively as red, green and blue. An unequivocal and reproducible chromatic characterization of normal brain structures and lesions is obtained. ((CNR has filed international patent application PCT/IT92/00112 for the QMCI technique).

evaluation of MRI data. In fact, unlike the intensity signal maps, the calculated relaxation rate maps provide a reproducible position of voxel clusters of tissue in the multi-parametric space (R1, R2, PD) [11]. The distribution of pixels in the feature space (R1, R2, PD) allows separating a greater number of tissue components than the distribution of pixels in signal intensity space (T1, T2, PD). The relaxation rates are quantitative physical data, therefore the preliminary calculation of these parametric maps in a segmentation algorithm can overcome also the problems created by the variable gain of MR imager on signal intensity obtained at different times in different subjects [12], [13], [14].

Goals to achieve

The brain segmentation software that we are developing aims to recognize most of the brain tissues, as well as possible lesions, exploiting *a priori* knowledge contained in the digital brain phantom *Phantomag* (http://lab.ibb.cnr.it/ Phantomag Desc.htm) [10] and in look-up tables describing the tissues that define the physical and geometrical properties of the tissue to be segmented. The digital model replicates the real anatomy and tissue inhomogeneities reproduced from MRI images of a normal volunteer, representing both the anatomy and the relaxation rate and PD distribution of 17 different healthy compartments, plus an eighteenth compartment that goes to simulate lesions (abnormal white matter).

Methodologies and activities

The tissues to be segmented are: GM (Grey Matter), WM (White Matter), CSF (Cerebrospinal Fluid), basal ganglia (Pallidus, Putamen, Thalamus, Nucleus Caudatus, Substantia Nigra, Red Nucleus, Nucleus Dentatus), ICC (IntaCranial Connective tissue), Low PD, Fat, Muscle, Vitreous Humor, ECC(ExtraCranial Connective tissue), ECF (ExtraCranial Fluid) e AWM (Abnormal WM). The automatic and unsupervised segmentation procedure has been developed in Matlab® and it is based on the following steps.

Loading data. The QMCI images of the study to be segmented and the model are loaded. Information is uploaded from the brain tissue look-up tables. The model of the classified tissues is loaded and transformed into a model with natural labels (from 1 to 20). These are information that will be used during the classification.
Realignment of model distributions and adjustment of model's QMCIs. The distribution of the model is realigned to that of the patient applying a shift, calculated by an affine transform iteratively algorithm. The calculated shift serves to go to "correct" the QMCI maps, i.e. the relaxation rates (R1, R2) and PD of the model, modifying the values in line with the realignments of the distributions.

Co-registration of the model to the patient. The model is co-registered by proceeding in two main steps: in the first step all the endocranial tissues of the model are co-registered with those of the patient; in the second step the co-registration is finished only for the tissues of basal ganglia.
Pre-segmentation. The final segmentation is preceded by a pre-classification of patient's tissues obtained by composing a given voxel's probability to be of one tissue in the feature-space (R1, R2, PD) and the same voxel's probability to be the same tissue for the spatial position.
Final segmentation. Firstly, any voxels of topologically incompatible contiguous tissue in pre-segmentation are removed. Then, the voxels to be segmented are classified according to the "local occurrences" in a window around the unknown voxel and based on the 4D-histogram of the model tissues. Any incompatible voxels are eliminated again by contiguity and then any supernumerary (than those anatomically possible) tissue agglomerates and those with a total number of pixels less than the minimum for a given tissue cluster are eliminated. Then the few remaining voxels are classified based on local occurrences, the 4D-histogram and taking account of incompatibilities between tissues.

Intermediate results and future perspectives of research activity

The software is currently under testing, optimization and revision of procedures and code. Tests conducted on studies of pathological patients have been allowing to optimize the whole co-registration phase and we are currently testing the classification phase. It is still under discussion whether the pre-segmentation methodology to put "seeds" on the image presented is the best, or if it can still be improved by exploiting the barycentre of each model tissues' groups in the feature space. In both cases, the implemented solutions show that the segmentation result is already much better than that obtained with other currently available brain segmentation software.

In the next year, I will optimize the pre-segmentation and final classification procedure. I will insert an algorithm that will improve the recognition and segmentation of AWM and another one to consider the statistics of contiguity between the tissues to improve compartments' boundaries. I will apply the software to disparate studies of pathological and healthy patients to estimate the actual reproducibility and goodness of the results obtained.

• Collaborations

I collaborated with researchers of the University of Salerno, Department of Medicine, Surgery & Dentistry "Scuola Medica Salernitana" for the realization of a 3D-printed mouthpiece for a low-cost open-architecture taste delivery system for gustatory fMRI and BCI experiments.

Products

I am preparing a journal publication on this year's research activities and a conference publication.

- ## Journal Publications

1. Antonietta Canna, Anna Prinster, Michele Fratello, Luca Puglia, Mario Magliulo, Elena Cantone, **Maria Agnese Pirozzi**, Francesco Di Salle, Fabrizio Esposito, «A low-cost open-architecture taste delivery system for gustatory fMRI and BCI experiments», *Journal of Neuroscience Methods*, Volume 311, 2019, Pages 1-12, ISSN 0165-0270, https://doi.org/10.1016/j.jneumeth.2018.10.003.

- ## Conference Publications

1. [Under Review] Emilio Andreozzi, **Maria Agnese Pirozzi**, Antonio Sarno, Daniele Esposito, Mario Cesarelli, Paolo Bifulco, «A Comparison of Denoising Algorithms for Effective Edge Detection in X-ray Fluoroscopy», *Nordic Baltic Conference on Biomedical Engineering and Medical Physics* (NBC2019).
2. [In preparation – Provisory Title] **Maria Agnese Pirozzi**, Emilio Andreozzi, Mario Magliulo, Anna Prinster, Mario Cesarelli, Bruno Alfano, «An Automated Method to Design Efficient Support Structures for FDM 3D Printing of Complex Anatomical Models Based on Medical Imaging Data».

Conferences and Seminars

- ## Presentation made

1. «Brain Imaging. What if we could print a brain?», *Discovery Lab 2.0 – Ricerca per passione*, V Edition, Napoli 24-28 Settembre 2018, CNR-Edificio di Biotecnologie, Via De Amicis, 95.

Activity abroad

I do not have carried out any activity abroad in my first year of PhD.

Tutorship

- Assistant for the BSc course of "Elaborazione dei Dati e Segnali Biomedici", held by Prof. Mario Cesarelli, **26 hours.**

- Assistant for the MSc course of "Elaborazione di Segnali e Immagini Biomediche", held by Prof. Mario Cesarelli, **6 hours.**
- Assistant for the laboratory lessons of MSc course of "Computer Interfaces for Biological Systems", held by Prof. Bifulco, **4 hours.**

Reference:

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[2]. M. Caon, «Voxel-based computational models of real human anatomy: a review», Radiat Environ Biophys, vol. 42, pp. 229-235, 2004.

[3]. E. J. Hoffman, P. D. Cutler, W. M. Digby e J. C. Mazziotta, «3-D Phantom to Simulate Cerebral Blood Flow and Metabolic Images for PET», IEEE TRANSACTIONS ON NUCLEAR SCIENCE, vol. 37, n. 2, 1990.

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[6]. H. Zaidi e B. M. W. Tsui, «Review of Computational Anthropomorphic Anatomical and Physiological Models», Proceedings of the IEEE, vol. 97, n. 12, 2009.

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[10]. B. Alfano, M. Comerci, M. Larobina, A. Prinster, J. P. Hornak, S. E. Selvan, U. Amato, M. Quarantelli, G. Tedeschi, A. Brunetti, M. Salvatore, «An MRI digital brain phantom for validation of segmentation methods», Medical Image Analysis 15 (2011) 329–339.

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[14]. R.K. Breger, F.W. Wehrli, H.C. Charles, J.R. MacFall, V.M. Haughton, «Reproducibility of relaxation and spin-density parameters in phantoms and the human brain measured by MR imaging at 1.5 T», Magn. Reson. Med. 3, 649-662 (1986).