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 – Third 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).

For research activities, **funding** by the CNR Strategic Project "The Aging: Technological and Molecular Innovations Aiming to Improve the Health of Older Citizens" (http://www.progettoinvecchiamento.it) and by the Italian Ministry for Education, University and Research (Project MOLIM ONCOBRAIN LAB) is gratefully acknowledged.

Study and Training Activities

During the third year of PhD, I focused mainly on research activities and the analysis of the obtained results for the development of the PhD thesis and the writing of scientific publications. I attended an external course, seminars and a Spring School as reported below.

- ## Courses

The external course, included in the training plan of my third year of PhD, was organized and hosted by the association *Neocortex ETS, Advanced Neuroscience Course*.

External Course	Lecturer/s	Start-End	H	ECTS
Applied Statistics and Research Methodology for Medical and Social Sciences	E. Casula	November 20-22, 2020	24	4,8

- ## Seminars

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

Seminars	Lecturer/s	Host/s	Date	H	ECTS
How to Get Published with IEEE	E. Lukács	A. Scippa	April 20, 2020	2	0,4
Challenges and opportunity of medical imaging in the era of big data	M. Aiello	C. Sansone	July 10, 2020	2	0,4

In April 2020, I attended the *BCI & Neurotechnology Spring School,* organized and hosted by *g.tec medical engineering GmbH*. The School overall included 30 hours of lectures, equivalent to 5 ECTS, as summarized below:

Seminars from Schools	Start-End	H	ECTS
BCI & Neurotechnology Spring School	April 20-24, 2020	30	5

- ### Credits summary

Finally, I provide a table reporting a summary of the ECTS obtained in my third year of PhD. It shows an additional two-month period because I requested a two-month extension of the doctoral course, as per D.L. n. 34 of 19/05/2020, art. 236, comma 5. This period was fundamental to complete the writing of the PhD thesis after the interruption of the research activities in the CNR laboratories that hosted me, due to the COVID-19 pandemic in bimesters 3 and 4.

Credits year 3	Estimated	bimonth 1	bimonth 2	bimonth 3	bimonth 4	bimonth 5	bimonth 6	bimonth* 7	Summary
Modules	**5**	0	0	0	0	0	4,8	0	**5**
Seminars	**5**	0	5,4	0	0,4	0	0	0	**6**
Research	**50**	10	4	5	5	10	5	10	**49**
	60	10	9,4	5	5,4	10	9,8	10	**60**

*request for a two-month extension of the PhD program, as per D.L. n. 34 del 19/05/2020, art. 236, comma 5.

Research Activity

My last year of PhD was dedicated to improving the brain segmentation and 3D modelling techniques developed in the previous two years and consolidating my research skills, also thanks to my experience abroad. The first functional prototype of the anthropomorphic brain phantom presented in the TRAR_1-2 was obtained and tested, leading to the *proof-of-concept* of the project. Currently, we are facing the engineering phase of the developed techniques in order to ensure a future marketability of the product. In this regard, the project was also presented at the *Campania Start-up 2020* competition (application in September 2020 - selection not yet completed at the time of writing) in view of the creation of a start-up in the next year. During this year, the COVID-19 pandemic prevented me from spending a period abroad at the *Karolinska Institutet, Department of Clinical Neuroscience, Unit Head Human PET (PET Center for Psychiatry Research)*, during which I would be involved in characterizing the phantom, presented in TRAR_1-2, through advanced morpho-functional medical imaging equipment. These studies would have paved the way for prospective and multi-centric studies, which were necessarily postponed to the new year. However, that time was used to finalize the validation of the brain segmentation software presented in TRAR_1-2 and to complete the extension of the proposed method to the MRI sequences used in the routine protocols of clinical practice to adapt it also to 3D Printing (3DP) applications. 3DP technologies and applications in biomedical field were further investigated thanks to the period (4 months) of study and research abroad (carried out in smart-working mode as per m_pi.AOODGRIC.Registro Ufficiale.U.4179.20-03-2020) at *Reykjavik University, School of Technology, Department of Engineering, Medical Technology Center.*

The research activity of these years has led to the drafting/publication of scientific papers (listed in the dedicated section) and to my doctoral thesis work entitled *"Innovative Techniques to Devise 3D-printed Anatomical Brain Phantoms for Morpho-functional Medical Imaging".*

The Ph.D. thesis work addresses the development of innovative techniques for the realization of a realistic 3D-printed brain phantoms. 3DP is a disruptive technology that is paving the way for anatomical modelling in many biomedical applications ranging from surgical planning, to medical education and training, customised prosthesis design, medical imaging research, bioprinting and many others [1]. Despite the potential already expressed by 3DP in this field (especially, for presurgical planning), it is still little used for the realization of anthropomorphic phantoms of human organs with complex internal structures [2]. Furthermore, 3DP is still far from being a *plug-and-print* technology, and making an anthropomorphic phantom is very different from making a simple anatomical model. Hence the need to develop techniques, exploring the current limits of available 3DP technologies to try to overcome them by proposing innovative advanced solutions to create anatomical phantoms with unique characteristics, and greater *ease-of-use*. This test object can be used for quantitative technical assessments on morpho-functional imaging devices, providing simulation accuracy not obtainable with currently available brain phantoms. The prototyped anthropomorphic brain phantom consists of three brain compartments: grey matter (GM), white matter (WM) and striatum (caudate nucleus and putamen, part of the brain basal nuclei). The striatum is known to show a high uptake in nuclear medicine studies (PET/SPECT) and it is of great interest for brain imaging simulation. Having three separate chambers, which can be filled with tissue-appropriate solutions characterized by different concentrations of radioisotope for PET/SPECT, para-/ferro-magnetic metals for MRI, and iodine for CT imaging, the phantom can simulate three brain tissues simultaneously. The walls that separate the brain compartments have a uniform submillimetre thickness of about 0.5 mm, so as not to distort the result of the simulation. The design was achieved by developing a 3D modelling pipeline that took into account the printability requirements at each model manipulation step. The models for 3DP are typically described in STL (Standard Tessellation Language) format, which represents the shapes through the approximation in polygonal mesh (i.e., collection of triangles). In order to be printable the 3D STL model must be described by a *manifold* mesh (i.e., continuous, without holes and with a positive – not zero – volume). To create a model of the human brain phantom, it is first necessary to acquire and then segment MRI images using an accurate segmentation technique. To this end, an innovative multi-parametric segmentation approach based on brain relaxometry, applicable to the MRI acquisition sequences used in current routine clinical protocols (3D-GrE T1-weighted, FLAIR and fast-T2-weighted sequences with ≤ 3 mm slice thickness), was proposed [3]. The developed approach includes a preprocessing step to estimate relaxation parameter map (R1 = longitudinal relaxation rate, R2 = transverse relaxation rate, PD = proton density) from the signal intensities in T1w, T2w and FLAIR images of the subject. In the past, maps of R1, R2, and PD were obtained from Conventional Spin Echo (CSE) sequences no longer suitable for clinical practice due to long acquisition times. The estimation of pseudo-relaxation maps from signal intensity allowed rehabilitating the multi-parametric segmentation based on relaxometry [4], and to develop an innovative pipeline for the simultaneous segmentation of most of the brain structures (GM, WM, cerebrospinal fluid, thalamus, caudate nucleus, putamen, pallidus, nigra, red nucleus and dentate), including lesions due to pathologies characterized by focal signal changes in brain tissues [5]. Once the tissues were segmented, an automatic procedure allowed extracting a unique and connected voxelized surface, tracing the anatomical interface between the phantom's compartments directly on the segmented images. Furthermore, two tubes was designed for each compartment (one for filling and the other to facilitate the escape of air during filling). The procedure automatically checks the continuity of the voxelized surface, ensuring that the 3D model can be exported in STL format without errors, using a common image-to-STL conversion software [6]. Moreover, threaded junctions were added (for the hermetic closure of the phantom) using a mesh processing software. The phantom's 3D model resulted correct and ready for 3DP.

Finally, the most suitable 3DP technology was identified for the brain phantom's prototype materialization. In particular, the material extrusion technology, named Fused Deposition Modeling (FDM), and to the material jetting technology, named PolyJet, were investigated. According to our experience, FDM is the best candidate for our purposes. It allows materializing the phantom's hollow compartments in a single print, without having to print them in several parts to be reassembled later. Indeed, unlike PolyJet, FDM deposits completely removable soluble internal support structures. Another critical aspect, which required a considerable effort to optimize the printing parameters, is the submillimetre thickness of the phantom. Generally, 3D printer manufacturers recommend maintaining a uniform wall thickness of at least 1 mm. The optimization of printing path made it possible to obtain strong, but not completely waterproof walls, approximately 0.5 mm thick. A sophisticated technique, based on the use of a polyvinyl-acetate solution, was developed to waterproof the internal and external phantom walls (necessary requirement for filling). A special filling system was also designed to minimize the residual air bubbles, which could result in unwanted hypo-intensity (dark) areas in phantom-based imaging simulation.

The phantom was finally scanned trough CT and PET/CT to evaluate the realism of the brain simulation. None of the state-of-the-art brain phantoms allow such realism in the rendering of three brain compartments. Some represent only GM and WM, others only the striatum. Moreover, they typically have a poor anatomical yield, showing a reduced depth of the sulci and a not very faithful reproduction of the cerebral convolutions. The ability to simulate the three brain compartments simultaneously with greater accuracy, as well as the possibility of carrying out multimodality studies (PET/CT, PET/MRI), which represent the frontier of diagnostic imaging, give this device cutting-edge prospective characteristics. These will be quantifiable through multicentre comparative studies which may be completed in the next year. The effort to customize modelling processes and develop 3DP technology for these applications is expected to increase significantly in the coming years due to the growing need of realistic anatomical phantoms, useful for various morpho-functional imaging simulations.

Concurrently with the development of the segmentation software, I also developed a skull-stripping algorithm for the automatic removal of non-brain tissues from the images. The algorithm is based on the combination of T1w and T2w MRI images, commonly provided with any of the routine MRI imaging protocols and allows solving the lack of cerebrospinal fluid (CSF) on the images resulting from common skull stripping software. The procedure was successfully tested on a set of 76 patients with multiple sclerosis [3]. It allows preserving the CSF in the stripping procedure and therefore evaluating the natural cerebral atrophy due to aging, as well as that related to the pathology, by segmenting the CSF volumes. Due to its peculiarity, the same algorithm has been successfully applied for the determination of CSF volumes in paediatric patients with various brain pathologies that lead to an increase in CSF volume (e.g., in cases of hydrocephalus). The procedure is currently being validated by an expert neuroradiologist for the preparation of a further scientific publication.

• Collaborations

Below is the list of collaborations with other universities and research institutes. It refers to the collaborations established in the last year for common research interests and future developments.

- Reykjavik University, School of Technology, Department of Engineering, Medical Technology Center, Reykjavik, Iceland.
- Landspitaly – The National University Hospital of Iceland, Reykjavik, Iceland.
- Department of Advanced Biomedical Sciences, University of Naples “Federico II”, Naples, Italy.
- Department of Neurosciences and Reproductive and Odontostomatological Sciences, University of Naples “Federico II”, Naples, Italy.

Products

Below are the papers already published during the year, those submitted and those in the finalization phase for submission.

• International Conference Publications

1. **M.A. Pirozzi**, E. Andreozzi, M. Magliulo, P. Gargiulo, M. Cesarelli, B. Alfano (2020) “Automated Design of Efficient Supports in FDM 3D Printing of Anatomical Phantoms”. In: Henriques J., Neves N., de Carvalho P. (eds) XV Mediterranean Conference on Medical and Biological Engineering and Computing – MEDICON 2019. MEDICON 2019. IFMBE Proceedings, vol 76. Springer, Cham.

2. E. Andreozzi, **M.A. Pirozzi**, A. Sarno, D. Esposito, M. Cesarelli, P. Bifulco (2020) "A Comparison of Denoising Algorithms for Effective Edge Detection in X-Ray Fluoroscopy". In: Henriques J., Neves N., de Carvalho P. (eds) XV Mediterranean Conference on Medical and Biological Engineering and Computing – MEDICON 2019. MEDICON 2019. IFMBE Proceedings, vol 76. Springer, Cham.
3. E. Andreozzi, **M. A. Pirozzi**, A. Fratini, G. Cesarelli and P. Bifulco, "Quantitative performance comparison of derivative operators for intervertebral kinematics analysis," 2020 IEEE International Symposium on Medical Measurements and Applications (MeMeA), Bari, Italy, 2020, pp. 1-6, doi: 10.1109/MeMeA49120.2020.9137322.
4. E. Andreozzi, **M. A. Pirozzi**, A. Fratini, G. Cesarelli, M. Cesarelli and P. Bifulco, "A Novel Image Quality Assessment Index for EdgeAware Noise Reduction in Low-Dose Fluoroscopy:Preliminary Results," 2020 International Conference on e-Health and Bioengineering (EHB), Iasi, Romania, 2020, pp. 1-5, doi: 10.1109/EHB50910.2020.9280107.
5. **M.A. Pirozzi**, E. Andreozzi, M. Magliulo, P. Gargiulo, M. Cesarelli, B. Alfano, "3D-printed anatomical phantoms for medical imaging applications", Proceedings of the 18th Nordic-Baltic Conference on Biomedical Engineering (NBC), Reykjavik, Iceland, 2020 (Article in press).

- **Journal Publications**

1. **M.A. Pirozzi**, M. Tranfa, M. Tortora, V. Brescia Morra, A. Brunetti, B. Alfano, M. Quarantelli, "A polynomial regression-based approach to estimate relaxation rate maps suitable for multiparametric segmentation of clinical multiple sclerosis MRI studies". [Under Review - submitted to the *Medical Image Analysis* journal].
2. **M.A. Pirozzi**, M. Magliulo, M. Cesarelli, M. Quarantelli, B. Alfano (partial list), "3D-printed multicompartmental anthropomorphic brain phantom for morpho-functional imaging applications". [Being finalized for submission]
3. **M.A. Pirozzi**, M. Quarantelli, B. Alfano (partial list), "An innovative approach for automatic brain segmentation based on MRI relaxation parameter maps". [In preparation]

- **Book Chapter**

I have been involved in writing *Section A - 3D printing (3DP) in Healthcare, General Part* of a presurgical planning 3D printing handbook, which will be published by **Elsevier**, presumably in early 2022.

Conferences and Seminars

This year I attended an international conference, *NBC 2020 (https://www.nbc2020.is/)*, and I held a webinar for the *European Biotech Week – Innovation is in our genes (https://biotechweek.org/)*.

- **Conferences**

1. Oral presentation at 18th NORDIC BALTIC CONFERENCE on Biomedical Engineering and Medical Physics. The presented paper is ***M.A. Pirozzi****, E. Andreozzi, M. Magliulo, P. Gargiulo, M. Cesarelli, B. Alfano, "3D-printed anatomical phantoms for medical imaging applications", Proceedings of the 18th Nordic-Baltic Conference on Biomedical Engineering (2020)*.

- **Seminars**

1. "Biomedical signals. How can we read inside us?", *Discovery Lab 2.0: Ricerca per passione, VII edizione*, 28 Settembre – 2 Ottobre 2020.

Activity abroad

From July to November 2020 (**4 months** – July 1-31, August 20 – November 20) I carried out activities abroad (in smart-working mode as per m_pi.AOODGRIC.Registro Ufficiale.U.4179.20-03-2020) at Reykjavik University, School of Technology, Department of Engineering, Medical Technology Center, under the supervision of Prof. Paolo Gargiulo. The main study and research activities concerned the development of transversal skills on medical image segmentation software, on 3D modelling software for the creation of anatomical models for pre-surgical planning applications, and prototyping of anthropomorphic phantoms for medical imaging studies through PolyJet technology.

Tutorship

- Assistant for the BSc course of "Elaborazione dei Dati e Segnali Biomedici", held by Prof. Francesco Amato, **20 hours.**
- Assistant for the BSc course of "Ulteriori conoscenze: laboratorio di bioingegneria", held by Prof. Mario Cesarelli, **6 hours**.
- Assistant thesis supervisor for the BSc student in Biomedical Engineering Carmen Azzaro, supervisor Prof. Mario Cesarelli. Thesis title: "3D printing of anthropomorphic phantoms: from development to applications in medical imaging".

Reference:

[1] A. Aimar, A. Palermo, and B. J. Innocenti, "The role of 3D printing in medical applications: a state of the art", vol. 2019, 2019. X.

[2] M.A. Pirozzi, E. Andreozzi, M. Magliulo, P. Gargiulo, M. Cesarelli, B. Alfano, “3D-printed anatomical phantoms for medical imaging applications”, Proceedings of the 18th Nordic-Baltic Conference on Biomedical Engineering, NBC 2020 (Accepted).

[3] M.A. Pirozzi, M. Tranfa, M. Tortora, V. Brescia Morra, A. Brunetti, B. Alfano, M. Quarantelli, “A polynomial regression-based approach to estimate relaxation rate maps suitable for multiparametric segmentation of clinical multiple sclerosis MRI studies” (Under Review submitted to the *Medical Image Analysis* journal).

[4] B. Alfano, A. Brunetti, E.M. Covelli, M. Quarantelli, M.R. Panico, A. Ciarmiello, M. Salvatore, "Unsupervised, automated segmentation of the normal brain using a multispectral relaxometric magnetic resonance approach," Magnetic Resonance in Medicine, https://doi.org/10.1002/mrm.1910370113 vol. 37, no. 1, pp. 84-93, 1997/01/01 1997.

[5] M.A. Pirozzi, M. Quarantelli, B. Alfano (partial list), “An innovative approach for automatic brain segmentation based on MRI relaxation parameter maps” (Being finalized).

[6] M.A. Pirozzi, E. Andreozzi, M. Magliulo, P. Gargiulo, M. Cesarelli, B. Alfano (2020), “Automated Design of Efficient Supports in FDM 3D Printing of Anatomical Phantoms”. In: Henriques J., Neves N., de Carvalho P. (eds) XV Mediterranean Conference on Medical and Biological Engineering and Computing – MEDICON 2019. MEDICON 2019. IFMBE Proceedings, vol 76. Springer, Cham.