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Coordinator: Luca Zilberti, INRIM Project website address: <u>https://quiero-pr</u>	Tel: +39 011 3919 484 <u>pject.eu/</u>		E-mail: I.zilberti@inrim.it		
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1 Overview

With more than 30 million scans per year in European countries, Magnetic Resonance Imaging (MRI) is one of the most important tomographic tools adopted in clinical practice. Nevertheless, standard MRI results mostly had a qualitative nature, to be interpreted by a specialist on visual inspection, that limited their objectivity and comparability. The project evaluated the suitability of two promising MR-based techniques, **Electrical Properties Tomography** (EPT) and **Magnetic Resonance Fingerprinting** (MRF), to bring a "quantitative revolution" in MRI, so that each image pixel could be associated with the measurement (including uncertainty) of one or more tissue parameters.

The project implemented EPT and MRF algorithms (some of which were distributed as open source software), characterized them both on synthetic data and on the phantoms developed in the project itself, and used such algorithms to identify minimum thresholds for the detection of a selection of brain and cardiac pathologies.

2 Need

Traditional MRI was qualitative and MRI results obtained at different times and locations were difficult to compare. In addition, conventional MRI could not provide direct information about the nature of the pathology. The development of quantitative imaging approaches like EPT and MRF started some years ago with the aim to eliminate interobserver variability and reduce the need for invasive procedures (e.g. biopsies). The idea behind this field of research was to enable new biomarkers to be identified and boost early disease detection, optimising the clinical path, improving the quality of life of patients and reducing the associated economic burden.

At the beginning of the project, a comprehensive characterisation of the reliability of EPT and MRF procedures had not yet been achieved. To start considering their clinical use, the medical community needed to know the level of confidence associated with EPT and MRF results, but this required a systematic analysis of their performance.

In particular, a specific characterisation of EPT and MRF was required for those contexts that have significant implications for health and, at the same time, are challenging from the imaging viewpoint (e.g. the cardiac region, where the physiological motion of the tissues affects the image acquisition).

Characterisation of EPT and MRF in terms of repeatability and reproducibility required artificially constructed test objects, known as "phantoms", with traceable, validated, and monitored components.

For *in vivo* applications, the physiological variability of parameters from subject to subject (which could act as a misleading element in the diagnostic phase) required to be carefully evaluated. From this viewpoint, the possible synergy between EPT and MRF, and the use of artificial intelligence to analyse the corresponding biomarkers, were worth exploring to maximise the diagnostic power of quantitative MRI.

3 Objectives

The overall objective of the project was to promote the development and possible combination of EPT and MRF, two MR-based techniques able to produce objective, quantitative and traceable images, and their adoption in clinical practice through a systematic characterisation of their reliability.

The specific objectives of the project were:

1. To develop, improve and implement numerical algorithms for use in EPT and MRF and to characterise their performance. For EPT, both local relationships and global inversion methods were considered and compared; for MRF, statistical template-free methods were evaluated as an alternative to traditional dictionary-based techniques.

2. To make EPT and MRF suitable for practical use in the analysis of "high impact" clinical conditions. Basic EPT techniques had to be improved to handle the partial knowledge of the phase of the magnetic field and mainly applied to the analysis of diseases that cause significant changes in dielectric properties (e.g. cerebral ischemia). The application of MRF to the heart region required methods able to suppress artefacts caused by physiological motion and moving fluids.

3. To evaluate the accuracy of EPT and MRF procedures in magnetic resonance experiments under controlled conditions. Heterogeneous phantoms, composed of soft semisolid materials mimicking the properties of human tissues (e.g. conductivity, relative permittivity, longitudinal and transverse relaxation times





in the order of 1 S/m, 50, 1000 ms and 50 ms respectively), had to be specifically developed and used for this purpose. The target uncertainties were 20 % for EPT and 10 % for MRF.

4. To fully characterise EPT and MRF as diagnostic tools under real-world conditions, including determining, for the target organs selected, the inter- and intrasubject physiological variability and minimum threshold for the detection of anomalies due to diseases. The variability of tissue properties had to be taken into account and advanced statistical techniques and *in vivo* assessments applied. The synergistic use of EPT and MRF was worth exploring to optimise diagnosis, and specific computer-aided diagnostics approaches had to be developed.

5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (accredited laboratories, MRI manufacturers), the relevant technical committees and end users (e.g. hospitals and health centres).

4 Results

4.1. Development and implementation of EPT and MRF algorithms

Relevance of the work carried out to meet the first objective

A number of EPT and MRF implementations existed at the beginning of the project, but they had not been compared systematically and, more importantly, typically they were under the exclusive use of their owners. Thus, the cornerstone of the project was the creation of libraries of EPT and MRF implementations, under full control of the consortium, suitable to be characterized and adapted to the purposes of the project itself.

The consortium implemented its own codes, some of which were then released as freeware, and went on improving them throughout the project lifetime. This allowed comparison of the performance of different EPT and MRF approaches under identical conditions. For EPT, both local relationships and global inversion methods were initially considered. Then, in order to concentrate the effort on techniques more suitable to be adopted into clinical practice, most of the work was focused on Helmholtz-EPT (H-EPT) and Convection-Reaction EPT (CR-EPT). For MRF, the consortium worked not only on traditional dictionary-based techniques, but also on a novel technique that estimates the relaxation times of biological tissues directly from raw MR data, and also on a Bayesian approach able to provide the output along with a whole probability distribution (and hence the uncertainty).

Work undertaken by the partners

EPT approaches

During the project, INRIM created an extensible, open-source, C++ library collecting the EPT methods that were under study. The library, named EPTlib (https://eptlib.github.io/; see its logo in Fig. 4.1.1), has been made publicly available through an open-access repository on GitHub (https://github.com/eptlib) and, for the first time ever, gave access to open implementations of EPT algorithms. The library contains implementations of the Helmholtz- EPT (H-EPT), the Convection-Reaction EPT (CR-EPT) and the gradient-EPT (gEPT) methods. The latter works only with parallel transmission (pTx) scanners, whereas the other two techniques work also with traditional systems. The library provides also a stand-alone application that directly applies the EPT algorithms on a given spatial distribution of the radiofrequency magnetic flux density (B1) that takes place during MRI, with parameters set by the user. To facilitate the uptake of EPTlib by external users, INRIM issued a user guide (available on the website of the library) that explains in detail its use. Moreover, an educational lecture on the usage of EPTlib through Python scripts was held in October 2022, during the Joint Workshop on MR phase, magnetic susceptibility and electrical properties mapping. To have a benchmark for testing the EPT algorithms, a novel tool, called b1map-sim, was made available together with EPTlib. This tool is able to produce synthetic B1-mapping and generate virtual MR acquisitions that mimic the actual measurement process in a realistic way. By virtue of its low computational cost, b1map-sim can be used to generate the noisy inputs required to test EPT algorithms via Monte Carlo method. EPTlib was used in the framework of the EMPIR project 17NRM05 EMUE to produce an example of application of the Guide to the expression of Uncertainty in Measurement (GUM).







Figure 4.1.1 – Logo of the EPTlib library.

A first characterization of the implemented EPT algorithms was performed through virtual EPT experiments carried out by INRIM, LNE and IMBiH, under completely controlled conditions. The virtual experiments were carried out based on the result of electromagnetic simulations involving a homogeneous cylindrical phantom. a heterogeneous cylindrical phantom with spherical inclusions (with radiuses ranging from 1 mm to 5 mm), and body portions of some anatomical models from the Virtual Population (Duke and Ella models) and XCAT (male #93 model) datasets. The simulations, performed by INRIM, were conceived to model the electromagnetic field produced by different types of radiofrequency antennas, namely a low-pass bird-cage body coil working at 64 MHz, a high-pass bird-cage body coil working at 128 MHz and an 8-channel head coil working at 300 MHz, designed for parallel transmission (pTx) purposes. In the experiments, the intrinsic bias produced by the algorithms was evaluated for different choices of the operative parameters to determine the set of parameters that generates the best results with noiseless input. Then, the parameters of each EPT algorithm were further optimised to deal with noisy input, for different levels of the signal-to-noise ratio. For the selected optimal parameters, the propagation of the uncertainty was finally assessed. The results of the virtual experiments were summarized in a report, which put in evidence complementary features in the performances of the analysed EPT techniques and highlighted how the accuracy and precision of the results may vary significantly, from point to point, within the same EPT map. Additional electromagnetic simulations were carried out in the framework of the Researcher Mobility Grant (RMG) performed by a researcher from INRIM and hosted by PTB. In these simulations, a 16-channel pTx body coil (used to radiate the model of a homogeneous body-phantom) and an 8-channel pTx head coil (used to radiate either the model of a homogeneous cylindrical phantom or a realistic model of a human head) were modelled. The simulations were performed with the aim of producing data suitable for investigating the potential of static shimming techniques to improve the performance of EPT algorithms. As a collateral outcome of the research on EPT, INRIM investigated the possibility to estimate subject-specific local SAR based on B1-mapping sequences and EPT algorithms, with reference to brain imaging with a 16-leg birdcage body-coil operated at 64 MHz. The analysis showed that, when using only the B1+ component of the radiofrequency magnetic field to calculate SAR, a large systematic error takes place. However, the investigation showed that it is possible to improve the results significantly, using a suitable tissue-dependent correction factor. The latter was calibrated based on numerical results, following a bootstrapping approach based on twenty-seven simulations of different anatomical human subjects. The robustness of the correction factor was assessed against different levels of the signal-to-noise ratio.

MRF approaches

PTB and SM implemented standard dictionary-based MRF methods, using both Bloch simulations and the Extended Phase Graph (EPG) formalism. Moreover, PTB implemented a new technique that does not rely on a pre-calculated dictionary but estimates the parameters (in particular, the relaxation times) directly from "k-space" (i.e. raw MR data). In addition, PTB developed an original Bayesian MRF approach that goes beyond the simple evaluation of the relaxation times of the imaged biological tissues, but provides them with a whole probability distribution, permitting calculation of the uncertainty associated with any given evaluation.

In order to test the MRF approaches through virtual experiments, Bloch simulations for simple and anatomically realistic models with different T1/T2 combinations were carried out, also including the transmit and receive sensitivities produced through the electromagnetic simulations mentioned above (for the chest of the male #93 XCAT model).

Comparisons of dictionary-based and k-space-based MRF for Cartesian, radial and spiral sampling schemes (depicted in Fig. 4.1.2) were carried out. Cartesian sampling schemes benefited most from k-space-based approaches but the overall performance was best for radial sampling patterns. The analysis also showed that





k-space-based approaches were promising and improved the estimation at low signal-to-noise ratios, but they still required reconstruction times that were too long to be readily adopted into clinical practice. In terms of accuracy and precision, a parametric analysis of the performances of the MRF techniques has shown that a combination of high maximum flip angles (FA) without T2 preparation pulses allowed for accurate T1 and T2 estimation.



Figure 4.1.2 – Overview of the MRF acquisition design. Pattern of variable flip angles used for the successive acquisitions (A). Sequence diagram showing the excitation pulses, slice selection and readout gradients (B). Trajectory in the k-space, for each repetition time, for the spiral, radial and Cartesian sampling schemes (C).

In order to create a synergy between different projects, the MRF acquisition scheme for T1 mapping was specifically adapted to meet the requirements of the 18HLT09 Neuromet2 project, in which patients with brain diseases were scanned. Data were acquired and a k-space-based approach for parameter estimation was applied.

Summary of key outputs and conclusion

For EPT, different approaches were implemented within a library made publicly available along with a user guide and some ancillary tools. In parallel, MRF approaches were implemented as well. The performance of both families of techniques were checked on synthetic data through virtual experiments based on realistic simulations, and the best operative configurations were identified. A cross fertilization took place between QUIERO and other concurrent projects in which the EPT and MRF algorithms were applied. A dosimetric analysis performed in silico showed that EPT can play an important role in the evaluation of subject-specific local SAR during MRI exams. Having these results, the project successfully achieved the objective.





4.2. Adaptation of EPT and MRF algorithms for use in "high impact" clinical conditions

Relevance of the work carried out to meet the second objective

To maximise the clinical relevance of the research, the consortium chose the brain and the heart as the main targets for the quantitative MRI approaches under analysis. In particular, the work done on EPT was mainly oriented on the measurement of the dielectric properties of the white matter, while the activities on MRF were mainly conceived to allow monitoring the relaxation times of the myocardium. Hence, the second objective of the project required to adapt "basic" EPT and MRF techniques to the specific target mentioned above, and check their performance. For EPT, special attention was paid to the analysis of the complicated shape of brain tissues. To this end, in addition to more traditional EPT techniques, an EPT technique that extrapolates the dielectric properties from the knowledge of the water content of biological tissues (wEPT) was also implemented because of the possibility to apply it starting from MRF measurements of the longitudinal relaxation time T1. For cardiac MRF, the acquisition and reconstruction approaches were specifically designed to work in the presence of the heartbeat and respiratory motions, which may create significant artefacts in the images.

Work undertaken by the partners

EPT approaches

Since the post-processing of EPT results can benefit from an independent segmentation of the biological tissues, useful when imaging strongly heterogeneous/irregular body regions, such as the gyri of the brain, a median filter (whose window is shaped dynamically according to the geometry of the anatomy) was implemented in EPTIib by INRIM. This feature allows for a synergistic use of EPT and MRF, in case the latter is used to provide the required segmentation. Moreover, in addition to "traditional" EPT approaches, SM implemented an EPT technique able to estimate the dielectric properties of brain tissues starting from the knowledge of the longitudinal relaxation time T1, which can be measured via MRF. This technique exploits an empirically-observed correlation exhibited by the water fraction in the brain tissues with both T1 and the dielectric properties, without making use of a physical model. Thus, the technique represents another "bridge" between MRF and EPT, which exports towards EPT the short acquisition time and the high image resolution typical of MRF. In addition to this work, the RMG organized by INRIM and PTB allowed to investigate the possibility to improve brain EPT reconstructions using the pTx technology. To this end, the RMG researcher simulated an 8-channel head-coil and used the obtained results both to test gEPT algorithms, available within EPTlib, and to implement different static shimming strategies to improve the H-EPT performance. Promising results were obtained, in particular for the phase-based version of H-EPT, which suggest that the investigation is worth deepening in the future.

A preliminary investigation of the usefulness of EPT as a diagnostic tool for brain pathologies was performed on synthetic data. To this end, starting from a set of anatomical human models (males/females, adults/children) belonging to the Virtual Population and XCAT libraries, an extended population including about 150 healthy variants (obtained by changing the properties of the brain tissues within a physiological range) and 200 pathological models (obtained by introducing a pathological region in the white matter, with variable size, irregular shape and conductivity higher than the physiological range) was prepared by INRIM. H-EPT and CR-EPT were applied to the data from electromagnetic simulations of the extended population, including versions that were intentionally corrupted by a realistic level of additive noise, and the results of these EPT algorithms were processed, looking for a reliable way to "diagnose" the presence of the pathology in the virtual models. First, traditional statistical approaches were employed by LGC to try to discriminate between the pathological region and the healthy white matter. In particular, a logistic regression model was built with the EPT data as predictor, with the aim to identify if a voxel belonged to the pathological or the healthy tissue, given its conductivity estimated through EPT. The guality of the model was evaluated using the AUC (area under the curve) metric. The H-EPT results were quite noisy and the regression model was not able to reliably identify the pathological voxels. The CR-EPT results, instead, led to a regression model with a satisfactory capability of discriminating pathological and healthy voxels (AUC > 0.6). Besides statistical approaches, convolutional neural networks (CNN) or similar approaches were tried, but they did not lead to good results because of the relatively large amount of noise in the data. Hence, a different solution was developed. The H-EPT and CR-EPT results were combined by UL in a smart post-processing approach, in which the voxels where the two algorithms (taking into account the propagated noise and the systematic errors) agreed were selected as seed points for a subsequent median filter. As indicated in Fig. 4.2.1, the output was then





thresholded (increased conductivity values were candidates for anomaly) and searched for connected components; a large enough component indicated the presence of the anomaly. The improvement in the final conductivity map was large enough to allow for the detection of the pathology in a large number of cases, overcoming the logistic regression model.



Figure 4.2.1 – The leftmost image shows the EPT reconstruction after the post-processing based on agreement between H-EPT and CR-EPT; lighter colour means higher value of electrical conductivity. The medium-sized anomaly is in the top left corner. The other images show "candidate voxels" for the anomaly as the threshold value progressively increases. In an ideal case, as the threshold is increased only the anomaly is left – at this stage connected components algorithm is employed to only retail the largest (or several largest) groups of voxels. Here the underlying assumption is that the anomaly is mass-like (e.g. a tumour).

MRF approaches

Specific work was done by PTB to tailor the MRF approaches for cardiac applications. In this regard, PTB developed a numerical simulation environment (see Fig. 4.2.2) suitable to model the acquisition around the heart region in the presence of non-rigid respiratory and cardiac motion fields, useful to assess the uncertainties in MRF results due to the motion patterns. Different heart rates, cardiac cycle events (e.g. ectopic beats) and respiratory motion patterns can be provided to the software, which then transforms the underlying anatomy prior to the simulation of MRF signals, to obtain motion corrupted information. Arbitrary scan orientations are possible and are independent of the orientation of the anatomical segmentation and motion fields. The simulation also provides ground truth motion fields for evaluation. The simulation environment package developed by PTB was released as an open-source software on GitHub, (https://github.com/johannesmayer/SIRF/tree/petmr-simulation) and a range of different tutorials were written Jupyter Notebooks also available as open-source (https://github.com/johannesmayer/SIRFas Exercises/tree/simulation-notebooks). The use of the simulation framework was explained within a user guide and presented during an online workshop organized by PTB and Charité in July 2022, open to external stakeholders. Finally, PTB developed a motion-correction approach, which corrects for cardiac motion and minimizes motion-related artefacts in the obtained T1 and T2 maps of the myocardium, for a wide range of heart rates. Cardiac triggering combined with breath holding was identified as the most reliable reference method for cardiac parameter mapping.



Figure 4.2.2 - Scheme of the simulation environment for cardiac MRF.





The possibility to feed EPT with a B1-mapping produced through MRF was investigated, with the aim of extending the application of EPT to the cardiac region. To this end, a B1-mapping approach based on MRF was specifically developed by PTB. Unfortunately, it was observed that the B1 maps provided by MRF were affected by artefacts that made their quality too low for being adopted as input for EPT (which is very sensitive to input noise).

Using clinical inputs from Charité, gradient echo sequences with a T1 preparation pulse were selected for cardiac MRF acquisition, because they allow for fast imaging, are robust to field inhomogeneities (important for field strengths greater than 1.5 T) and applicable at different field strengths. A comprehensive evaluation of the accuracy and precision of the MRF techniques was carried out by PTB and LGC. Based on the existing literature, several parameters were identified for the evaluation: maximum value of the flip angle, pattern frequency of flip angles and additional preparation pulses. Central composite designs were carried out. The different MRF acquisition approaches were evaluated based on the root-mean-square-error calculated over a range of realistic T1 and T2 combinations. This analysis showed that a combination of high maximum flip angles without T2 preparation pulses allows for accurate T1 and T2 estimation. The results of the investigation were described in a technical report. In short, the studies of PTB and LGC achieved an accuracy, expressed in terms of relative error, of (5.6 ± 3.4) % for T1 and (8.3 ± 8.4) % for T2. Using T2-preparation pulses did not lead to a strong improvement in T2 estimation. The temporal pattern of the flip angle was important to achieve accurate T1 and T2 estimation. The results of a factorial design for different parameters of the flip angle pattern suggested that large flip angles and high number of flip angle lobes allow for most accurate parameter estimation.

In order to evaluate the effectiveness of MRF parameters to be used as biomarkers for cardiac diseases, the myocardium region of one XCAT model was selected as a reference. Then, geometrical deformations were applied to get myocardium models of three different sizes. For each model, many pathological variants, with an alteration of the myocardium that resembles fibrosis, were produced by PTB. The resulting extended population of myocardium models, resulting in about 200 pathological models and 3 healthy models, was used for analysing the MRF techniques. Bloch simulations reproducing the sequences needed to apply the MRF techniques were carried out in the extended population of myocardium models. Motion artefacts due to heartbeat and respiration were not introduced for this analysis. MRF was applied to these data altered by the presence of noise. Traditional statistical approaches were applied to study the capability of MRF techniques to identify lesions. Generalised linear modelling was used to fit classification models for both voxel-level classification (identification of a single voxel as fibrosis) and for classification based on mean T1 and T2 values for designated regions. Receiver operating characteristic (ROC) curve analysis was used to determine the efficacy of classification, using area under curve (AUC) as a performance indicator. Models showed good to excellent classification for the data sets examined. The best model, based on mean relaxation times for designated regions and using both T1 and T2, attained AUC of 0.992. A model for classification at the voxel level, using both T1 and T2, attained AUC of 0.966 (for comparison, a common threshold for useful clinical classification is 0.8). The simulations showed that MRF offers a potentially powerful tool for identification of lesions in myocardial tissue, especially where it is possible to designate a suspect region for which a mean relaxation time can be determined. In addition to traditional statistical analysis, a convolutional neural network (CNN) operating on T1 and T2 images provided by MRF was implemented by UL. The CNN, whose flowchart is shown in Fig. 4.2.3, led to good results in predicting the presence and the location of the fibrosis.







Figure 4.2.3 – Identification of a cardiac fibrosis using a convolutional neural network (simulated data).

Summary of key outputs and conclusion

The possibility to refine EPT maps based on an independent segmentation of the tissues was introduced. Moreover, an EPT technique that estimates the dielectric properties from T1 maps obtained through MRF was implemented. A simulation framework that allows simulating MRF acquisitions in the presence of physiological motion (heartbeat and respiration) was created and made publicly available, and a motion correction strategy to improve cardiac MRF results was developed. A population of virtual human models, including healthy subjects and patients with brain or heart diseases, was created and used to investigate, in silico, the suitability of EPT and MRF parameters to act as biomarkers. Promising results were obtained.

4.3. EPT and MRF experiments under controlled conditions

Relevance of the work carried out to meet the third objective

The third objective of the project was to evaluate the accuracy of EPT and MRF procedures through experiments carried out using MRI systems under controlled conditions, scanning suitable test objects ("phantoms"). To this purpose, heterogeneous phantoms, composed of soft semisolid materials mimicking the properties of human tissues, had to be developed. For the preparation of the tissue mimicking materials, a number of recipes were explored and samples of these materials were characterized, in terms of dielectric and relaxation properties, before using them in the quantitative imaging experiments. Moreover, specific effort was made to monitor periodically the stability of such properties over time. Regarding the manufacturing of the phantoms, both mould-based approaches and 3D-printing techniques were investigated and tested. The phantoms produced within the project were used to check the performance of the implemented EPT and MRF algorithms, with particular attention on the repeatability of the measurements.

Work undertaken by the partners

Regarding the preparation of tissue mimicking materials (TMM), the project focused its attention mainly on white matter and grey matter. INRIM, PTB, TUD and TUBITAK agreed on a protocol for the production of new phantoms, based on different additives, such as Gellan Gum, Carrageenan and Agarose polysaccharides, synthetic polymers and inorganic salts. GdCl₃ have been chosen as T1-modifier, NaCl as electrical conductivity modifier, Polyvinylpyrrolidone (PVP) and Glycerol as permittivity modifiers, and NaN₃ as antifungal to preserve the stability. The protocol was used by INRIM to produce simple-geometry homogeneous and heterogeneous phantoms exhibiting the properties of the target tissues. Large heterogeneous phantoms were then prepared, in which the independent tuning of relaxation times and dielectric properties was obtained by exploiting the proyents or limit diffusion processes). Suitable sealing and storage techniques were applied to prevent long term variations and ensure stability of the multilayer phantoms. Moreover, as a preliminary step towards the preparation of phantoms with embedded "lesions", a structure including five vials filled with TMM





exhibiting contrast with respect to the background was produced. Then, a first generation of brain phantoms with anthropomorphic structures (some of which include "pathological lesions") was produced using custom moulds. Based on feedbacks from the experimental characterization of the first generation, another generation of phantoms were prepared by INRIM using silicone moulds obtained from 3D-printed plastic structures of the white and grey matter. This included one homogenous phantom representing the white matter only, a heterogeneous anthropomorphic phantom mimicking a slice of the brain (including both white and grey matter), and a third phantom consisting of a plexiglass cylinder in which a slab of the upper part of the white matter was inserted in a grey matter matrix. Two of these phantoms are shown in Fig. 4.3.1, with their T1 and T2 characterization. For each of the three phantoms, two "twins" were realized to allow reproducibility analyses among different sites. Finally, INRIM realised also one biphasic anthropomorphic phantom mimicking the whole volume of a brain, using realistic 3D-printed brain-shaped moulds.



Fig 4.3.1 – T1 and T2 parametric maps of first series of anthropomorphic phantoms measured with a 3 T (A-B, in seconds) and a 1.5 T (C-D, in milliseconds) scanner.

Parallel to the realization of mould-based phantoms, the development of anthropomorphic brain phantoms via 3D-printing was pursued by TUD (see Fig. 4.3.2). To this end, rheological characterization of different pasty, hydrogel-based materials were performed. For these different "inks" mainly based on natural biopolymers, printing processes, gelling processes and strand geometry were tested and optimized. Besides first monophasic prototypes, anatomically shaped bi-phasic (white and grey matter) test specimens were prepared, making use of multichannel plotting, and their stability was monitored over several weeks. Some limitations regarding homogeneity and reproducibility of relaxation times over an entire geometry due to the void structure of the 3D-printed phantoms were identified. These issues were fixed by adjusting material viscosity (lower agarose/carrageenan content) and internal layer-to-layer orientation within the printed samples. Based on the experience gained through these activities, TUD identified tools and strategies for the realization of a new lowcost soft-matter 3D printer, developed starting from a construction kit for a CNC (computerised numerical control) machine. The new 3D printer was equipped with two pneumatic valves, extrusion modules, additional motor axes and 30 ml-cartridge holders. After a preliminary test using a blend based on alginate/ methylcellulose to test fabrication protocols, large GdCl₃-doped phantom samples consisting of one or more material phases were prepared through the new printer, with dimensions up to 100 mm x 60 mm x 44 mm. In particular, a triphasic anthropomorphic phantom including a 3D-printed hydrogel grey/white matter-shaped structure, in combination with 350 mL of added CaCl₂ solution (mimicking the cerebrospinal fluid), was fabricated.

The characterization of the relaxation times of the tissue mimicking materials was carried out by PTB and UNITO using MRI scanners, and by TUBITAK using spectrometers. The effect of the concentration of gelling agents on both the stability and the relaxation times of the gels was investigated. It was observed that the





presence of agar helped both with the stability of the gels and with the tuning of the transverse relaxation time T2. The effect of the concentrations of Gellan Gum and $GdCl_3$ on T1 was confirmed through the characterization in different 3 T MRI scanners. T1 and T2 measurements made by TUBITAK in a 1.4 T NMR spectrometer showed consistency with the expected values. The characterization of the dielectric properties was performed by INRIM and PTB through the measurement of the complex electrical reflectance of the TMM, over the frequency range 50 MHz – 300 MHz, and used as feedback to improve the tuning with the target values. In particular, the influence of NaCl and sucrose for tuning electrical properties was tested in homogenous agar-based phantoms. Significant work was done to compare and determine the variation of the frequency range the comparison indicated deviations below 5 % and, for the complete range, well below 10 %. By repeated measurements on one TMM sample, it was shown that the uncertainty margin was well below 2 % for each system. However, differences as large as 15 % were observed on jellylike samples, suggesting the presence of systematic errors. The dielectric characterisation was extended, for two selected TMM, in the framework of the RMG hosted by PTB, by repeating the measurements at different temperatures.



Figure 4.3.2 – Components of the developed low-cost 3D printer: two-channel extrusion system consisting of two ink-loaded 30 mL cartridges (a) and novel large volume extrusion system for continuous material supply and ink deposition (b).
Example of an anthropomorphic 3D-printed brain phantom (c). Characterization of the relaxation times *T*₁ and *T*₂ for a triphasic 3D-printed phantom (grey matter, white matter, CaCl₂ as surrounding CSF) (d).

Stability of both the dielectric and relaxation properties of some of the TMM and phantoms was monitored over the whole project lifetime. Good stability was observed for the dielectric parameters (variation within the uncertainty of the measurements) after more than 2 years. For cylindrical phantoms, after more than 2 years from preparation the change of the relaxation times was found between 5 % and 10 % in the grey matter compartment and some of the inclusions. In some cases, larger variations were observed and ascribed to the very small size of the inclusions in this phantom. Anthropomorphic phantoms revealed a similar stability, although a general drift for all the phantoms towards longer relaxation values was observed. The latter was probably due to water condensation in void subregions within the phantom and put in evidence that the way of realisation and conservation of the phantoms themselves is crucial to reduce drift phenomena. Stability studies on T1 and T2 relaxation times with a bench-top NMR spectrometer at 1.4 T NMR were also performed. Relaxation values remained to a large extent stable, exhibiting variations below 2 % after more than 3 years.

Acquisitions suitable to perform MRF and EPT on the phantoms produced in the project were performed in the MRI scanners available within the consortium. The acquisitions were repeated multiple times in order to allow both repeatability and reproducibility analyses. INRIM and LNE applied H-EPT and CR-EPT to the





experimental data, observing that certain acquisitions were affected by small imaging artefacts that, despite being negligible in many common MRI applications, were amplified by the EPT procedure leading to estimations of the electric properties with an unsatisfactory spatial resolution. In particular, the phase maps acquired for the cylindrical heterogeneous phantom were affected by a structured noise (that the consortium ascribed to the relatively small size of the phantoms) that propagated through the EPT algorithms. leading to large artefacts in the recovered distribution of the electrical conductivity. The global average value of the estimated conductivity was within the range of the expected value, anyway. The structured noise was not present in the 3 T acquisition of the brain-shaped mould-based heterogeneous phantom, whose EPT was good enough to recognize the boundary between the two materials precisely, and a good agreement with the reference values of the parameters was observed (see Fig. 4.3.3). The results of MRF experiments were analysed by PTB and LGC, observing that the reproducibility was dependent on the flip angle, with a higher flip angle leading to a better reproducibility (this effect was observed both for T1 and T2). In the case of the 3D-printed phantoms, the measured values varied more strongly for different regions in the same phantom compared to the phantoms produced using custom moulds. The analysis of the problem suggested that it was due to a more heterogeneous structure, for which accurate identification of homogeneous regions (i.e. white matter) was more challenging. The results of the EPT and MRF experiments were collected and discussed in a technical report. Further EPT experiments were conducted by INRIM on phantoms developed outside the project, in the framework of two collaborations with external stakeholders. The first was an experimental repeatability and reproducibility analysis of the conductivity estimated through H-EPT, conducted in cooperation with Philips Healthcare on a saline phantom. This analysis showed that, for a homogeneous target, the spatial dispersion of the values of the conductivity provides a good quantification of the reproducibility uncertainty. The second of these activities, performed together with the University Medical Centre in Utrecht, aimed at exploring the possibility to develop an H-EPT method able to produce, along with the EPT maps, also the corresponding pixel-wise uncertainty maps, starting from the same input. The procedure was tested on a heterogeneous phantom and produced promising results. Thus, it will be further explored in the future.



Figure 4.3.3 – Map of the conductivity (S/m) estimated through EPT on a mould-based heterogeneous brain phantom, with (a) and without (b) segmentation. The inset puts in evidence the consistency between the conductivity image and the magnitude image in terms of identification of the boundary that separates different TMM.

Summary of key outputs and conclusion

Recipes and techniques for the preparation of tissue mimicking materials and phantoms (including simple mould-based phantoms, phantoms based on anthropomorphic 3D-printed moulds, and anatomically realistic 3D-printed phantoms), suitable for use in quantitative imaging experiments, were identified and tested. The characterization of the dielectric and relaxation properties of these materials was performed over time, showing good stability. EPT and MRF experiments were performed and allowed to identify some issues. For EPT, the quality of the acquisition is crucial and requires special care. For MRF, the experiments are useful to optimize the parameters of the algorithms and, in turn, allow the identification of defects in the text objects. Having these results, the project successfully achieved the objective.

4.4. In vivo EPT and MRF





Relevance of the work carried out to meet the fourth objective

To envisage future clinical applications of EPT and MRF, the physiological variability of parameters from subject to subject (which could act as a misleading element in the diagnostic phase) required to be carefully evaluated. According to the fourth objective of the research, two clinical studies were carried out to collect in vivo data acquired on the two target organs (brain and heart). Based on the acquired data, the consortium quantified the inter- and intra-subject physiological variability of the selected biomarkers and identified the minimum threshold for the detection of the pathological anomalies under study.

In order to explore the possibility to perform (semi)automatic computer-aided diagnostic processes, advanced statistical techniques and machine learning approaches were applied to the quantitative maps produced through EPT and MRF, and their effectiveness in spotting pathological changes in the biological tissues was evaluated.

Work undertaken by the partners

In vivo brain scans

A clinical study of brain diseases was performed, with main focus on children with white matter diseases, including: myelin disorders due to a primary defect in oligodendrocytes or myelin, i.e. leukodystrophies (hypomyelination and demyelination, and with myelin vacuolization); astrocytopathies; leuko-axonopathies; microgliopathies; leukovasculopathies. Globally, the study involved 53 patients (32 males, 21 females; aged 0y-60y) and 32 age-matched healthy controls (19 males, 13 females; aged 0y-55y), scanned at 1.5 T by SM. Within the patient cohort, five subjects underwent two different MR sessions. A subset composed of ten patients was also acquired at 7 T, leading to a total number of MR scans equal to 100. Three-dimensional MRF data of these subjects were collected at 1.125 mm resolution. Using the novel wEPT technique that estimates the dielectric properties from MRF-based T1 maps, SM calculated conductivity and permittivity for the whole dataset. Then, taking into account that the two dielectric parameters originate from the same MRF measurement, the analysis was focused on the conductivity only (whose measured data are provided in Fig. 4.1.1), which is the typical parameter provided by most of the traditional EPT approaches. For a subset of the age-matched control cohort (seven people), conventional phase-based EPT was also carried out for comparison. In addition to this clinical study, 3D MRF maps of the brain of twelve healthy volunteers were obtained by SM in the framework of a repeatability/reproducibility study involving eight different sites (1.5 T and 3.0 T scanners, single vendor). Each subject/site dataset included two acquisitions, to assess repeatability of the measurements. The analysis of these datasets demonstrated high repeatability and reproducibility of MRF measurements in grey and white matter. The corresponding parametric maps have been made publicly available on Zenodo. Segmentation of wEPT data allowed to compute the median conductivity of white and grey matter in a subset of the people involved in the clinical study (45 patients with pathologies of the white matter and 27 healthy volunteers, whose scans exhibited high quality).



Figure 4.4.1 – Median values of the conductivity of white and grey matter calculated via wEPT in 45 patients and 27 healthy controls involved in the clinical study.





A statistical analysis performed by LNE with support from INRIM provided a quantification of the intra- and inter-subject variability of the conductivity of white and grey matter, and showed that the evolution with the age of this parameter can be modelled through an exponential decay in healthy people. Correcting the effect of the age in the data allowed to quantify a significant patient-control effect (standard deviation equal to 20.9 mS/m). Based on these findings, a threshold for the detection of anomalies in white matter with 95 % confidence level was computed. In particular, a minimum contrast equal to +34.3 mS/m with respect to the median conductivity of the white matter (after correction of the age effect) was identified as a requirement for a reliable EPT-based detection of the pathologies under study. Using this rule, 25 subject out of the 45 considered patients would have been correctly classified as pathological cases (see an example in Fig. 4.4.2), whereas the other 20 patients would have not been correctly recognized. The false negative outcomes could be ascribed to the stage of progress or the spatial extent of the pathology. These results were collected and discussed within a technical report.



(a)

(b)

Figure 4.4.2 – Map of the conductivity (mS/m) obtained via wEPT on a transverse section of the brain of a patient (a) and the corresponding violin plot of the conductivity measured in the voxels, with indication of the median values (b). The median value for the white matter is above the range (indicated by the two black lines) of values considered as physiological taking into account the age of the patient and therefore the biomarker successfully suggests the presence of a pathology.

The quality of the in vivo scans was not good enough to allow for standard EPT reconstructions. Thus, the classification of the maps could not be performed using the smart post-processing strategy previously developed and tested on synthetic data for this class of EPT algorithms. As an alternative, a convolutional neural network (CNN) was trained by UL using wEPT data. However, despite the use of data augmentation techniques, the training of the CNN could not be performed in a satisfactory way, because of the large variability of the diseases under study and of the relatively small size of the training set. In the light of the promising results obtained in silico, the automatic location of brain diseases using EPT maps remains an interesting topic for future developments of the research on quantitative imaging, anyway.

In vivo cardiac scans

The clinical study of heart diseases involved scans of four healthy volunteers (two at 1.5 T and two at 3 T) and 15 patients (all at 3 T) performed by Charité. The patient cohort included 7 people with hypertrophic cardiomyopathy, 4 with muscular dystrophies and 4 with severe aortic stenosis. Both conventional quantitative MRI and the MRF-based mapping acquisitions of the relaxation times developed by PTB were carried out. Maps corresponding to three patients are reported in Fig. 4.4.3. All cardiac measurements were analysed by PTB and LGC. In short, the observed mean and standard deviation values were: for the conventional T1-mapping sequence (MOLLI-based), (1288 \pm 64) ms, vs (1219 \pm 41) ms for the MRF-based approach; for the conventional T2-mapping sequence (FLASH-based), (42 \pm 3) ms, vs (31 \pm 9) ms for the MRF-based





sequence. These results, combined with those collected on healthy volunteers, allowed to conclude that the pathologies under study can be reliably detected if the average values of the parameters in the myocardium are larger than 1478 ms and 52 ms, or smaller than 1062 ms and 16 ms, for T1 and T2 respectively (the change can be present in either just T1, or just T2, or both). The results of the in vivo cardiac experiments were collected and discussed within a technical report.



Figure 4.4.3 – Resulting quantitative maps for three different patients. References for T1 and T2 were respectively acquired with a MOLLI and a T2-prepared bSSFP sequences.

For cardiac MRF, the automatic location of lesions via machine learning was not pursued, because of the small amount of available data (that was significantly hampered by the pandemic). This lack was partially compensated by the work done by UL on a deep learning approach developed on synthetic data, with over 200 cases available for training. Even if this approach could not be tested in vivo (because its parameters would have needed specific tuning and partial re-learning), it is expected that its extension on clinical data will be quite straightforward as soon as a suitable amount of cardiac MRF measurements will become available.

Summary of key outputs and conclusion

Two clinical studies were carried out within the project. Even if they suffered some difficulties due to the pandemic (that hampered the possibility to perform in vivo experiments, limiting the development of clinical decision support systems based on artificial intelligence), they corroborated the idea that EPT and MRF can provide useful clinical information and paved the way to future investigations of the sensitivity and specificity associated with the biomarkers measured through these techniques. In particular, for both brain EPT and cardiac MRF, the physiological variability of such parameters was quantified and thresholds for the detection of pathological anomalies based on quantitative imaging were identified. Having these results, the project successfully achieved the objective.

5 Impact

The progress of the project was publicised via the project website (<u>https://quiero-project.eu/</u>) and two dedicated pages on <u>LinkedIn</u> and <u>ResearchGate</u>. In addition, a short video describing the work plan of the project was made available on YouTube (<u>https://youtu.be/I3wNZpzUoog</u>), and was promoted on the EURAMET website and by DG Science & Innovation.

A newsletter summarising the project achievements was regularly provided to the stakeholder committee, whose members represented 17 different affiliations, including relevant international societies and committees, MRI scanner manufacturers, scientific and clinical institutes. Members of the stakeholder committee participated at the formal project meetings, where specific time slots were devoted to round table discussions.

To date, thirteen scientific papers have been published in the form of open access articles; one of them originated a dataset made available under the <u>project community on the Zenodo repository</u>. Other scientific articles are currently accepted, under review and in preparation. In addition, 45 presentations (20 posters and 25 orals, six of which invited) were presented at scientific conferences, including the Mathematical and





Statistical Methods for Metrology (MSMM) workshop in 2021 (where a special session was devoted to the project) and the 2020, 2021 and 2022 editions of the annual meeting of the International Society for Magnetic Resonance in Medicine. Moreover, in 2022 the project coordinator chaired the Joint Workshop on MR Phase, Magnetic Susceptibility and Electrical Properties Mapping, where seven technical presentations were given by members of the consortium.

Impact on industrial and other user communities

The project consortium has cooperated with all three main manufacturers of MRI scanners, i.e. GE Healthcare, Philips Healthcare and Siemens Healthcare. The latter, based on the work done in the project to produce and characterise tissue mimicking materials and phantoms, asked to be periodically informed about the progress of the consortium in this field and attended some of the official project meetings. More in general, the expertise in the characterisation of the dielectric and relaxation properties of tissue mimicking materials will allow INRIM, PTB and TUBITAK to offer corresponding measurement services to their external customers. Other uptake by external users could originate from the new low-cost soft-matter 3D printer designed and built by TUD, whose development, in order to promote open science, was described within an open access scientific article.

The dissemination activities carried on by the consortium during the project lifetime attracted the attention of some potential end users of the investigated quantitative methods. Among them, we may cite the University of Verona and the Istituto Neurologico "C. Besta", that showed interest in applying EPT to clinical data. The evaluation of uncertainty in EPT experiments will be the subject of a scientific paper under preparation, co-authored by consortium members and a researcher from Philips Healthcare.

A summary of the values of the parameters measured in vivo through EPT and MRF will be made available shortly after the end of the project (as soon as the data will be published in open access scientific articles) on the project website and other widely accessible repositories. Relevant stakeholders (e.g. the IT'IS Foundation, that maintains a popular online database of tissue properties) will be specifically informed about this action, to encourage uptake of this research product.

Impact on the metrology and scientific communities

The EPTlib library developed within the project gave public access to EPT algorithms for the first time. In particular, it was recognised as the first EPT package available on the internet by the Electro-Magnetic Tissue Properties Study Group of ISMRM, which represents the reference community for EPT. The adoption of EPTlib by external users was promoted in many occasions, including the 2021 edition of the ISMRM congress (where a work describing EPTlib was awarded with the ISMRM Magna Cum Laude Merit Award) and the 2022 Joint Workshop on MR Phase, Magnetic Susceptibility and Electrical Properties Mapping (where a specific educational lecture, attended by about 100 scientists, was given). Similarly, the MRF approaches developed and made available as open source software by consortium members allowed external users to access the MRF world. To facilitate this kind of uptake, a tutorial on the use of the simulation framework for cardiac MRF was held during an online workshop, with more than 20 participants (mainly early career researchers), organised in July 2022 by PTB and Charité. The work done in the project created the opportunity to start a number of scientific collaborations with research groups that did not belong to the project consortium. Among them, we may cite a cooperation with the University Medical Centre in Utrecht, which manages a Dutch national project on EPT (for whose advisory board, QUIERO's coordinator was invited to become a member). The exploitation of the freeware developed and made available during the project took place also in the framework of other EMPIR projects. In particular, EPTlib was exploited within the 17NRM05 EMUE project to develop an example of evaluation of the uncertainty associated with the repeatability of EPT experiments, whereas MRF approaches were used in the 18HLT09 Neuromet2 project to acquire in vivo brain data.

Five consortium members belong to MATHMET, the European Metrology Network for Mathematics and Statistics, and regularly updated this community on the project outcomes. Moreover, specific presentations were held by consortium members at the conferences organised by MATHMET in 2019 and 2022. Periodic reports on the progress of the project were also provided by consortium members to the Working Group on the Expression of Uncertainty in Measurement of the Joint Committee for Guides in Metrology.

The work performed within the project created the occasion for the development of four Master theses and two Bachelor theses. A specific lecture on EPT was given within a course on MR dosimetry, for PhD students, at Politecnico di Torino (April 2021). EPT was also presented during lectures on MR dosimetry within a qualifying course in health physics at the University of Torino (December 2020 and 2021). One seminar on EPT, held by a consortium member, was hosted within INRIM's program of internal seminars. Furthermore, to assist NMI





capacity building, a short online training course for project partners was provided to transfer knowledge on the use of EPT methods.

Impact on relevant standards

To date, EPT and MRF are still not subject to specific standards. The route to their standardisation requires a number of preparatory steps, involving those organisations responsible for the relevant standards and good practice. To promote long-term uptake of EPT and MRF and pave the way for the creation of future standards, the consortium established contacts with targeted bodies, including the European Imaging Biomarkers Alliance (EIBALL), the Quantitative Imaging Biomarkers Alliance (QIBA) and the International Society for Magnetic Resonance in Medicine (ISMRM), which were periodically informed of the project's progress. After receiving the first project newsletter, the Chairperson of the EIBALL invited the project coordinator to give a presentation on the project work plan during their business meeting held in May 2020. Moreover, members of the consortium have been invited to join the advisory board that will supervise the first international "challenge" organised with the aim of performing an extended intercomparison of EPT implementations in the framework of the ISMRM Study Group on Electro-Magnetic Tissue Properties.

In terms of MRI safety, EPT is the key to assessing the subject-specific, local exposure to radiofrequency electromagnetic fields, which depends on the spatial distribution of the actual electrical properties throughout the body. Working in this direction, the consortium informed the committee that maintains standard IEC 60601-2-33 (the international standard on MRI equipment and safety, which prescribes limits of exposure) about the investigation performed in the project on subject-specific SAR assessments based on EPT reconstructions.

Longer-term economic, social and environmental impacts

Patients will be the principle long-term beneficiaries of the full characterisation of EPT and MRF as diagnostic tools. MR-based quantitative imaging will boost early disease detection, fundamental to increased survival rates. Besides their intrinsic value for the detection, characterisation and monitoring of pathologies, fast and quantitative MRI methods will also cut down the use of (unnecessary) invasive procedures, reducing patients' stress and the corresponding cost for the healthcare system.

For **clinicians**, the use of biomarkers provided by EPT and MRF will pave the way for new diagnostic strategies. Furthermore, the exploitation of EPT and MRF will foster personalised medicine. Finally, the increasing availability of images bringing reliable quantitative information will contribute to the development of large databases of reference clinical data at an international level, promoting knowledge transfer, training and decision-making in a global context.

From the **economic** viewpoint, the use of MRF has the potential to reduce scan times and allow a larger number of exams to be performed in one day (or, equivalently, to cut the cost of each single exam). Due to the increased confidence in the results of quantitative MRI, the number of redundant scans will be also reduced. In addition, quantitative MRI will stimulate the extended use of artificial intelligence in diagnostics, with further time and money savings in the longer-term.

6 List of publications

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2) J. Mayer, R. Brown, K. Thielemans, E. Ovtchinnikov, E. Pasca, D. Atkinson, A. Gillman, P. Marsden, M. Ippoliti, M. Makowski, T. Schaeffter, C. Kolbitsch, *Flexible numerical simulation framework for dynamic PET-MR data*, Physics in Medicine and Biology, 2020, <u>https://doi.org/10.1088/1361-6560/ab7eee</u>.

3) G. Buonincontri, J. W.Kurzawski, J. D. Kaggie, T. Matys, F. A. Gallagherd, M. Cencini, G. Donatelli, P. Cecchi, M. Cosottini, N. Martini, F. Frijia, D. Montanaro, P. A. Gómez, R. F. Schulte, A. Retico, M. Tosetti, *Three dimensional MRF obtains highly repeatable and reproducible multi-parametric estimations in the healthy human brain at 1.5T and 3T*, NeuroImage, 2021, <u>https://doi.org/10.1016/j.neuroimage.2020.117573</u>. A dataset linked to this publication is publicly available on the Zenodo repository, at <u>http://doi.org/10.5281/zenodo.3989799</u>.

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7) S. Metzner, G. Wubbeler, C. Kolbitsch, C. Elster, *A comparison of two data analysis approaches for quantitative magnetic resonance imaging*, Measurement Science and Technology, 2022, <u>https://doi.org/10.1088/1361-6501/ac5fff</u>.

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