Publishable Summary for 18HLT05 QUIERO
Quantitative MR-based imaging of physical biomarkers

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 have a qualitative nature (i.e. they display a contrast between different tissues, which must be interpreted by a specialist on visual inspection) that limits their objectivity and comparability. The project will evaluate the suitability of two MR-based emerging techniques, **Electrical Properties Tomography** (EPT) and **Magnetic Resonance Fingerprinting** (MRF), to bring a “quantitative revolution” in MRI, so that each image pixel is associated with the measurement (including uncertainty) of one or more tissue parameters.

Need

Traditional MRI is qualitative and MRI results obtained at different times and locations are difficult to compare. In addition, conventional MRI does not provide direct information about the nature of the pathology. Quantitative imaging approaches like EPT and MRF are being developed to eliminate interobserver variability and reduce the need for invasive procedures (e.g. biopsies). EPT and MRF should enable new biomarkers to be identified and boost early disease detection. These approaches could be used to optimise the clinical path, to improve the quality of life of patients and to reduce the associated economic burden.

At the state of the art, a comprehensive characterisation of the reliability of these innovative procedures has not yet been achieved. In order to start using them effectively, the medical community needs to know the level of confidence associated with EPT and MRF results, but this can be achieved only through a systematic analysis of their performance.

In particular, a specific characterisation of EPT and MRF is 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.

Performance characterisation of MRI relies on artificially constructed test objects, known as "phantoms". Characterisation of EPT and MRF in terms of repeatability and reproducibility requires 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) must be taken into account. From this viewpoint, the possible synergy between EPT and MRF, as well as the use of artificial intelligence to analyse the corresponding biomarkers, should be explored to maximise the diagnostic power of quantitative MRI.

Objectives

The overall objective of the project is 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 are:

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 will be considered and compared; for MRF, statistical template-free methods will be evaluated as an alternative to traditional dictionary-based techniques.

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2. **To make EPT and MRF suitable for practical use in the analysis of “high impact” clinical conditions**. Basic EPT techniques will 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 will be extended to the heart region through 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), will be specifically developed and used for this purpose. The target uncertainties required are 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 will be taken into account and advanced statistical techniques and *in vivo* assessments will be applied. The synergistic use of EPT and MRF will be explored to optimise diagnosis and specific computer-aided diagnostics approaches will 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).

Progress beyond the state of the art

Most authors of EPT and MRF algorithms have the exclusive use of their computational codes. This consortium will implement its own codes, some of which will be released as freeware. This will allow comparison of the performances of different EPT/MRF approaches under identical conditions and **their characterisation against theoretically modelled data**.

Traditional EPT and MRF implementations do not address some of the specific technical challenges required by “high impact” pathologies (e.g. cerebral and cardiac diseases). **The project will overcome such restrictions**, by producing: 1) MRF procedures designed to address the heart motion and novel approaches that do not require a pre-calculated “dictionary” of MR signals; 2) more efficient EPT implementations. In addition, the project will explore the possibility to “hybridise” the two techniques.

Most test objects (phantoms) currently available on the market do not replicate the heterogeneity of real tissues; moreover, metrological support for characterisation of tissue mimicking materials and MRI phantoms is still lacking. The project will improve this unsatisfactory state of the art, through the preparation and characterization of materials that mimic realistic tissue properties and the development of 3D-printed anthropomorphic phantoms. Such phantoms will be used to test EPT/MRF algorithms multiple times in the same scanner and, then, in different scanners, to obtain **a characterisation of the results in terms of repeatability and reproducibility**.

To become clinical tools, EPT and MRF must be able to spot anomalous values of the parameters in the presence of a physiological variability. Therefore, *in vivo* acquisitions will be performed to quantify the dispersion of the parameters in healthy humans. Then, this information will be exploited to evaluate the **suitability of the investigated parameters to act as biomarkers**. Finally, the project will go further by exploiting artificial intelligence to interpret the distribution of such biomarkers automatically.

Results

Objective 1

For MRF, standard dictionary-based methods have been implemented, using both Bloch simulations and the Extended Phase Graph (EPG) formalism. Moreover, 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) has been implemented. In addition, the project has developed a specific Bayesian MRF approach that goes beyond the simple evaluation of the relaxation times of the imaged biological tissues. This provides them with a whole probability distribution, permitting calculation of the uncertainty associated with any given evaluation. Comparisons, for different sampling schemes, of the MRF methods implemented up to now show that k-space–based approaches are promising and improve the estimation at low signal-to-noise ratios, however they still require reconstruction times that are too long to be readily adopted into clinical practice.

The project has originated an extensible, open-source, C++ library collecting the EPT methods that are under study within the project itself. The library, named *EPTlib* (https://eptlib.github.io/), is publicly available through an open-access repository on GitHub (https://github.com/eptlib) and, for the first time ever, gives access to open implementations of EPT algorithms. At the moment, the library contains implementations of the standard Helmholtz-based EPT algorithm, the gradient EPT and the convection-reaction EPT. The library provides a stand-alone executable file able to apply, with parameters set by the user, each implemented EPT algorithm on a given spatial distribution of the radiofrequency magnetic flux density (B1) that takes place during MRI. To have a benchmark to test the EPT algorithms, synthetic B1-mapping can be produced using *b1map-sim*. The latter is a novel tool, made available together with *EPTlib*, which generates virtual MR acquisitions which realistically mimic the actual measurement process that occurs in MRI scanners performing common B1-mapping techniques. By virtue of its low computational cost, this virtual measurement system can be used to generate the noisy inputs required to test EPT algorithms in a Monte Carlo framework.

In order to test the EPT and MRF algorithms in a completely controlled virtual environment, the digital models of a number of simple-geometry phantoms and anatomical human bodies (with focus on the brain and heart regions) have been prepared. Realistic simulations have been performed, exposing such models to the electromagnetic field produced by birdcage body coils (working at 1.5 T or 3 T) and a head coil (suitable for parallel transmission at 7 T), obtaining a dataset of transmit and receive sensitivities that, in turn, have been used to carry out realistic Bloch simulations.

Objective 2

Specific work is in progress, within the project, to tailor MRF and EPT to investigate “high impact” clinical conditions, with special reference to the pathologies that may affect the brain and heart regions.

Starting from clinical input, a preliminary analysis of the sequences used for cardiac MRF has been carried out. Among them, fast gradient echo sequences, improved by suitable preparation pulses, have been selected for cardiac MRF acquisitions of the relaxation times, because they allow for fast imaging, are robust to field inhomogeneity and applicable at different field strengths.

A specific MRF approach to provide both the traditional MRF parameters and carry out B1-mapping of the scanned region has been developed. The latter is suitable to provide the input required by EPT algorithms even in the presence of physiological motion (heartbeat and breathing), allowing their application to the thoracic region.

Since MRF can provide information useful to improve the quality of EPT reconstructions (in particular, an independent segmentation of the biological tissues, useful to overcome the difficulty exhibited by some EPT methods when imaging strongly heterogeneous/irregular body regions, such as the gyri of the brain), the *EPTlib* library has been equipped with a specific post-processing algorithm. The algorithm applies a median filter, whose window is shaped to fit the anatomy previously identified by MRF, to the values of the parameters measured via EPT, improving their accuracy.

Objective 3

Regarding the preparation of tissue mimicking materials (TMM), the project has focused its attention on three target tissues: white matter, grey matter and the cardiac muscle. 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) has been developed and used to produce simple-geometry homogeneous and heterogeneous phantoms exhibiting the properties of the target tissues. In particular, large heterogeneous phantoms have been prepared, exploiting suitable sealing and storage techniques to prevent diffusion and ensure stability. 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 has been produced.

Parallel to the realization of simple-geometry phantoms, the development of an anthropomorphic brain phantom via 3D-printing is on-going. To this end, rheological characterization of different hydrogel-based materials has been performed. For these different “inks”, printing processes, gelling processes and strand geometry have been tested. Besides first monophasic prototypes, anatomically shaped bi-phasic (white and grey matter) test specimens of around 30 ml have been prepared, making use of multichannel plotting, and their stability has been already proved over several weeks. The possibility to add a further layer made of a calcium-phosphate–based bone cement, which could mimic the properties of the surrounding cranial/calvarial bone, is under investigation. Some pictures and a video showing the printing process are available on a dedicated page of the project website (https://quiero-project.eu/project-structure/developments-in-soft-matter-and-hydrogel-printing). The experience gained through the activities mentioned above has allowed the identification of tools and strategies for the realization of a new low-cost soft-matter printer. For this purpose, a 3D-robot based on an open-source design has been built and equipped with syringe extruders for two-component silicone printing. Moreover, a novel custom-made extrusion system for larger volumes has been designed and developed for a computer-numerical-control–based 3D printing device.

The characterization of the relaxation times of the tissue mimicking materials has been carried out using both MRI scanners and spectrometers. At the same time, the characterization of the dielectric properties has been performed through the measurement of their complex electrical reflectance, over the frequency range 50 MHz – 300 MHz, and used as a feedback to improve the tuning with the target values. In order to monitor the stability of the relaxation and dielectric properties of the phantoms, these measurements are repeated periodically.

First MRF acquisitions have already been performed at 1.5 T and 7 T on some of the phantoms developed within the project. Further measurements, as well as MR acquisitions suitable to provide input for EPT, have been planned and will be used to develop a complete repeatability and reproducibility characterization of the MRF and EPT techniques when applied to experimental data, collected under controlled conditions.

Objective 4

The selection of the most appropriate patients for the clinical study of brain diseases was finalised in the first part of the project and the corresponding ethical approval to acquire MR data on both patients and healthy volunteers was obtained. The patient group involves people with quite severe lesion burden and, more specifically, young children with white matter diseases, who will be followed up clinically within the project timeline. Data accrual has already started, with the MR acquisition, performed at 1.5 T, of 43 patients (among them, 10 patients have been already scanned also at 7 T). The first 3D MRF dataset of 23 subjects, classified as aged-matched controls, is already available. In addition, some project partners have participated in a repeatability and reproducibility study, involving eight different sites and applied to 12 healthy volunteers, the outcome of which is publicly accessible.

The pathologies to be investigated in the clinical study on cardiac diseases have also been identified and the local ethical committee has approved the proposal. Patients with cardiomyopathies and known fibrosis, systemic disorders and coronary artery diseases with different stages of myocardial infarction will be included in the study.

The characterisation of EPT and MRF techniques under real-world conditions will involve the interpretation of their results by modern artificial intelligence solutions, which will be trained and tested first *in silico* and then *in vivo*. In order to produce a dataset of virtual data that is large enough for this purpose, electromagnetic and Bloch simulations will be conducted on various anatomically accurate human models, reproducing a realistic clinical set-up in a completely controlled virtual environment.

Impact

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

A newsletter summarizing the project achievements is regularly provided to the stakeholder committee, whose members represent 17 different affiliations, including relevant international societies and committees, MRI scanner manufacturers, scientific and clinical institutes. Members of the advisory board (a sub-set of the stakeholders, covering 10 affiliations) have participated at the three formal project meetings held up to now, where specific time slots were devoted to round table discussions.

Since the kick-off, four scientific papers have been published in the form of open access articles; one of them has also originated a dataset made available under the project community on the Zenodo repository. In addition, seven presentations (two posters and five oral, one of which invited) have been presented at scientific conferences. A number of new contributions have been recently submitted for possible presentation at the next meeting of the International Society of Magnetic Resonance in Medicine (ISMRM), to be held in May

2021.

The project coordinator will co-chair the next *Joint Workshop on MR Phase, Magnetic Susceptibility and Electrical Properties Mapping* (https://qmrlucca.org/), where the project results will be promoted to the scientific community working on quantitative MRI. In addition, an oral session dedicated to the project has been planned within the next workshop *Mathematical and Statistical Methods for Metrology* (MSMM), which will take place in spring 2021 (http://www.msmm2021.polito.it/).

Impact on industrial and other user communities

The project consortium has cooperation with all three main manufacturers of MRI scanners, i.e. GE Healthcare, Siemens Healthcare and Philips Healthcare, who are members of the advisory board and therefore have prior access to the project results. In addition, the gain in objectivity of the measured data and the availability of new, well-characterised, tissue-mimicking phantoms obtained through the project will contribute to the activities of multi-centre studies, clinical laboratory intercomparisons and production of commercial test objects in MRI.

As a result of receiving the first project newsletter, the Chairperson of the European Imaging Biomarkers Alliance (EIBALL), one of the most influential institutions on quantitative MR worldwide, invited the project coordinator to give a presentation on the project work plan during their business meeting held in May 2020.

Impact on the metrology and scientific communities

Five consortium members belong to MATHMET, the European Metrology Network for Mathematics and Statistics, and regularly update this community on the project outcomes. Periodic reports on the progress of the project are provided by consortium members to the Working Group on the Expression of Uncertainty in Measurement of the Joint Committee for Guides in Metrology. The successful cooperation between two project partners on the development of tissue mimicking materials has had an important role in conceiving the new EMPIR project 20NRM05 iMET-MRI, which will deal with specific aspects of standardization in quantitative MRI.

The publication of the *EPTlib* library, gives public access to EPT algorithms for the first time. By virtue of this feature, *EPTlib* has been recognised on the website of the Electro-Magnetic Tissue Properties Study Group of ISMRM as the first and only EPT package currently available on the internet (see https://www.emtphub.org/electrical-software-packages/). Shortly after its publication on GitHub, *EPTlib* was used in the framework of the EMPIR project 17NRM05 EMUE, where it was employed as the computational “engine” to develop an example of evaluation of the uncertainty associated with the repeatability of EPT experiments (available at https://zenodo.org/record/4248879#.X_iUyNhKjIW).

The work performed within the project has created the occasion for the development of a Master thesis on the segmentation of MR data to produce anthropomorphic phantoms. A lecture on electromagnetic dosimetry in MRI was delivered in December 2020 to an external audience. Furthermore, to assist NMI capacity building, a short online training course for project partners has been provided to transfer knowledge on the use of EPT methods.

Impact on relevant standards

To date, EPT and MRF are not subject to specific standards. Thus, 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 has 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 are all periodically informed of the project’s progress.

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. From this viewpoint, the project has the potential to facilitate the implementation of IEC 60601-2-33, the international standard on MRI equipment and safety, which prescribes limits of exposure.

Longer-term economic and social 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.

List of publications

1) A. Arduino, O. Bottauscio, M. Chiampi, L. Zilberti, *Uncertainty propagation in phaseless electric properties tomography*, Proceedings of the 2019 International Conference on Electromagnetics in Advanced Applications (ICEAA), https://arxiv.org/abs/1911.02809.

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 **65**, 2020, https://doi.org/10.1088/1361-6560/ab7eee.

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 **226**, 2021, https://doi.org/10.1016/j.neuroimage.2020.117573. A dataset linked to this publication is publicly available on the Zenodo repository, at http://doi.org/10.5281/zenodo.3989799.

4) P. A. Gómez, M. Cencini, M. Golbabaee, R. F. Schulte, C. Pirkl, I. Horvath, G. Fallo, L. Peretti, M. Tosetti, B. H. Menze, G. Buonincontri, *Rapid three-dimensional multiparametric MRI with quantitative transient-state imaging*, Scientific Reports **10**, 2020, https://doi.org/10.1038/s41598-020-70789-2.

This list is also available here: https://www.euramet.org/repository/research-publications-repository-link/

<table>
<tr><td colspan="2">Project start date and duration:</td><td>01 June 2019, 36 months (+6 months extension due to COVID-19)</td></tr>
<tr><td colspan="3">Coordinator: Luca ZILBERTI, INRIM Tel: +39 011 3919 848 E-mail: l.zilberti@inrim.it
Project website address: https://quiero-project.eu/</td></tr>
<tr><td>Internal Funded Partners:
1. INRIM, Italy
2. IMBiH, Bosnia and Herzegovina
3. LGC, United Kingdom
4. LNE, France
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6. TUBITAK, Turkey</td><td>External Funded Partners:
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