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

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considered and compared; for MRF, statistical template-free methods will be 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 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; in particular, no software for EPT is publicly available at present. 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**.

Current 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 be the first to explore the possibility to "hybridize" 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 automatically interpret the distribution of such biomarkers.

Results

Objective 1

The development of an extensible, open-source, C++ library collecting relevant EPT algorithms has started. The library, named EPTlib, is made 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.

Both local and global EPT algorithms are being implemented. During the project lifetime, they will be characterized in terms of performances and compared to each other. The library already contains the classical Helmholtz-based EPT algorithm; other approaches, like the gradient EPT, the dictionary-based EPT and the convection-reaction EPT will be added in the near future. In order to provide a metrological characterisation of the implemented EPT algorithms, the uncertainty and the intrinsic bias of the B1-mapping sequences used to produce the EPT input will be evaluated and then propagated through the EPT algorithms. To this end, a novel approach based on synthetic virtual B1-mapping acquisitions has been developed and will be extended to include the effects of complex uncertainty sources (e.g. non-ideal spoiling). Moreover, realistic electromagnetic simulations in the presence of homogeneous and heterogeneous phantoms, as well as anatomically accurate human models, have been conducted in order to have the most realistic experimental set-up in a completely controlled virtual environment.

Standard dictionary-based MRF approaches have been implemented using both Bloch simulations and the Extended Phase Graph (EPG) formalism. In addition, the consortium has started working on the implementation of a MRF-based parameter estimation approach that does not rely on a pre-calculated dictionary but directly estimates the parameters from MR raw data.

Objective 2

The EPTlib library, which is under development, will collect state of the art EPT algorithms, implemented and possibly optimized to handle the partial knowledge that EPT input can provide in practical “high impact” clinical conditions. The implementation of classical algorithms, like the Helmholtz-based EPT, is being carried out to adapt their execution to the actual available knowledge. Cutting-edge algorithms, like the dictionary-based EPT, will be implemented as well, in order to exploit the advantages of the most recent technical advancements in this field. Since EPTlib is the first public collection of EPT algorithms, its design towards practical clinical applications has been specifically conceived to help in the adoption of EPT as a quantitative imaging technique in clinical routine.

Starting from clinical input, an analysis of the sequences used for cardiac MRI has been carried out. Among them, gradient echo sequences have been selected for future cardiac MRF acquisitions, because they allow for fast imaging, are robust to field inhomogenities and applicable at different field strengths.

Objective 3

As regards the preparation of tissue mimicking materials, the consortium has decided to focus 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 prototypes of homogeneous and heterogeneous phantoms.

Parallel to the realization of simple-geometry phantoms, the development of an anthropomorphic brain phantom via 3D-printing has started. To this end, rheological characterization of different hydrogel-based materials has been performed. Moreover, printing processes, gelling processes and strand geometry have been tested for the different “inks” mentioned above. First anatomically shaped test specimens of around 30 ml, in monophasic and bi-phasic design, have been prepared making use of a commercial 3D extrusion printer. This activity 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 (www.opensourceimaging.org/project/cosi-measure) has been built and equipped with syringe extruders for two-component silicone printing (www.opensourceimaging.org/project/syringe-pump-library).

The characterization of the electrical conductivity and permittivity of the tissue mimicking materials has started. In particular, the influence of NaCl and sucrose for tuning electrical properties has been tested in homogenous agar-based phantoms, whose stability is monitored periodically. Future measurements will be performed on Gellan gum-based phantoms as well. Based on these first characterizations, further tuning of the relevant parameters is being performed. The effect of the concentration of gelling agents on both the stability and the relaxation times of the produced gels has been also investigated. Uncertainty evaluation and further time stability checks are in progress. Magnetic characterization of 3D-printed samples has been carried out at 3 T; further characterizations will be performed at 1.4 T and 7 T.

Objective 4

The selection of the most appropriate patients for the clinical study of brain diseases has been finalized. This selection involves patients with quite severe lesion burden and, more specifically, young children with white matter diseases, that will be followed up clinically within the project timeline.

The pathologies to be investigated in the clinical study on cardiac diseases have been identified too. Patients with cardiomyopathies and known fibrosis, systemic disorders and coronary artery diseases with different stages of myocardial infarction will be involved.

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

Impact

The progress of the project is being popularized via the project website (https://quiero-project.eu/) and two dedicated pages opened 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). Direct information is regularly provided to the stakeholder committee, whose members represent 14 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 two formal project meetings held up to now. Since the kick-off, five papers have been presented at scientific conferences; one of which led to an open-access publication.

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-characterized, tissue-mimicking phantoms obtained through the project will contribute to the activities of multi-centre studies, clinical laboratory intercomparisons and producers of commercial test objects in MRI.

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 with regard to the relevant project outcomes (including the analysis of uncertainty propagation through very complex and multivariate processes and the use of artificial intelligence to manage critical decision-making situations). Moreover, periodic reports on the progress of the project in this field 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 project's activities were last presented to the group in December 2019.

Besides the dissemination activity carried out through presentations at scientific conferences and publications, an account has been opened on GitHub (https://github.com/eptlib) to make the extensible, open-source, C++ library (EPTlib) available and to facilitate its spread within the scientific community involved in quantitative MRI. Further promotion of the project will be achieved at the next Joint Workshop on MR phase, magnetic susceptibility and electrical properties mapping (Lucca, Italy, October 2021), where a whole scientific session will be devoted to the project scope and results. The workshop has received formal endorsement by the International Society for Magnetic Resonance in Medicine (ISMRM) and will be attended by many experts of quantitative MRI.

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 personalized 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

- 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.

<table>
<tr><td colspan="2">Project start date and duration:</td><td>01 June 2019, 36 months</td></tr>
<tr><td colspan="3">Coordinator:
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<tr><td>Internal Funded Partners:
1. INRIM, Italy
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