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 (Objective 1).

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 (Objective 2).

Performance characterisation of MRI relies on artificially constructed targets, known as "phantoms". Characterisation of EPT and MRF in terms of repeatability and reproducibility requires phantoms with traceable, validated, and monitored components. (Objective 3).

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 (Objective 4).

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.

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 and results

Currently, most authors of EPT and MRF algorithms have the full ownership and exclusive use of these computational codes, and no software for EPT in particular is publicly available at present. As part of this project, the consortium will implement its own codes, which will be released as freeware. This will allow comparison of the performances of different EPT/MRF approaches under identical conditions and **the characterisation of such approaches against theoretically modelled data** (Objective 1).

Quantitative MRI has a strong potential for the diagnosis of certain “high impact” pathologies (e.g. cerebral and cardiac diseases). However, current EPT and MRF implementations have not yet been conceived to address the specific technical challenges required by these situations. For instance, the physiological motion occurring in the heart may impair the accuracy and precision of the MRF maps. As for EPT, local implementations typically lack accuracy at the interface between different tissues; therefore, their application to regions with irregular boundaries (e.g. the brain) is challenging. On the other hand, global methods result in greater accuracy but are time-consuming and their application to real 3D problems remains challenging. **The project aims to overcome these restrictions**, by producing: 1) MRF procedures designed to address the presence of the heart motion and novel MRF approaches that do not require a pre-calculated “dictionary” of MR signals; 2) more efficient EPT implementations, where the (typically limited) information about the phase of the radiofrequency magnetic field is properly managed. In addition, the project will explore the potential to “hybridize” the two techniques, using MRF as a fast method to measure the magnetic field distribution required to perform EPT (Objective 2).

With the development of quantitative imaging, demands on test objects have increased, but metrological support for characterisation of tissue mimicking materials is still lacking. During the project lifetime, specific attention will be devoted to the preparation of materials that mimic realistic tissue properties (including the presence of a pathology within a healthy background), as well as to the development of anthropomorphic phantoms through 3D printing technology. Such phantoms (with traceable properties and checked for stability over time) will be used to acquire MR data and test EPT/MRF algorithms. All acquisitions will be repeated multiple times in the same scanner and then repeated in different scanners, to obtain **a characterisation of the results in terms of repeatability and reproducibility** (Objective 3).

Most applications of EPT/MRF procedures have aimed to verify their ability to quantify the value of the investigated parameters against a point of reference. However, to become clinical tools, EPT and MRF must be able to spot anomalous values in the presence of the physiological variability of such parameters. Therefore, a specific effort will be made to obtain, through in vivo acquisitions, a quantification of the dispersion of the parameters in healthy humans. This information will be exploited to evaluate the **suitability of the investigated parameters to act as biomarkers**. In addition, the exploitation of artificial intelligence to automatically interpret the values and distribution of each biomarker (or a combination of them) will be explored (Objective 4).

Impact

Impact on industrial and other user communities

Three European manufacturers cover most of the worldwide MRI market: GE Healthcare (UK), Siemens Healthcare (Germany) and Philips Healthcare (Netherlands). The consortium has a consolidated cooperation with these industrial partners, who will be invited to join the project advisory board and to have prior access to the solutions developed by the consortium. This will allow them to implement the proposed algorithms in their scanners, with no need for specific changes to their hardware.

Besides MRI manufacturers, the main end user of the project results will be the medical community, who will benefit from the quantification of EPT and MRF reliability as diagnostic tools. In addition, medical and technical staff working on MRI will have direct access to the research outputs (e.g. software for EPT, made available free of charge), which can be used for diagnostic as well as for training purposes. In the short term, this will allow staff to become familiar with EPT and MRF, prior to the possible adoption of these techniques into clinical practice.

The availability of well-characterised assessment tools for quantitative MRI will contribute to the traditional activities of multi-centre studies and clinical laboratory intercomparisons, as a result of the gain in objectivity of the measured data and the availability of new, well-characterised, phantoms composed of tissue mimicking materials. The latter will be taken up by the producers of commercial test objects in MRI, which will have the opportunity to incorporate the new processes and characterisation tools within their productive processes.

Impact on the metrology and scientific communities

For researchers working on EPT and MRF, the project will provide a comprehensive and systematic characterisation of these techniques, from the intrinsic accuracy of the algorithms to their sensitivity and specificity.

From a metrological point of view, the contribution given by the NMIs in the consortium will pave the way to new calibration services, fundamental to guarantee the traceability of the measurements associated with the imaging process. This will give them a privileged position as independent advisors for the certification of innovative MRI platforms before their adoption in clinics.

Given its strong multidisciplinarity (which requires, for instance, capabilities in the fields of modelling, data analysis, uncertainty quantification, phantom preparation and characterisation), the project will facilitate cross-fertilisation and knowledge transfer among participant NMIs, in particular towards emerging institutes, with specific reference to the strategic sector of health. Most participant NMIs are members of MATHMET, the European Metrology Network for Mathematics and Statistics. This project will address state-of-the-art mathematical and computational challenges, such as the analysis of uncertainty propagation through very complex and multivariate processes and the use of artificial intelligence to manage critical decision-making situations.

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, such as ISMRM (International Society of Magnetic Resonance in Medicine), QIBA (Quantitative Imaging Biomarkers Alliance).

To promote long-term uptake in standardisation, the consortium will actively exchange information with targeted bodies within these organisations, for example, the study groups on Electro-Magnetic Tissue Properties or on Quantitative MR organised within ISMRM, that aim to facilitate the development, evaluation and clinical application of EPT and MRF, paving the way for the creation of future standards.

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, EPT has the potential to facilitate the implementation (and continuous improvement) of IEC 60601-2-33, the international standard on MRI equipment and safety, which prescribes limits of exposure. The same applies, more generally, to electromagnetic dosimetry, where EPT can provide a way to check the accuracy of traditional methods for exposure evaluation.

Longer-term economic and social impacts

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. Considering that the total annual cost of MRI investigations for the European healthcare system is in excess of € 3 billion, each percentage point of avoided scans will allow savings of more than € 30 million every year. In addition, quantitative MRI will stimulate the extended use of artificial intelligence in diagnostics, with further time and money savings in the longer-term.

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. It is worth noting that cancer (in young people) and cardiovascular diseases or dementia (among the elderly) are among the main causes of death in Europe. The general aptitude of EPT/MRF to spot oncological lesions, together with the specific focus of this project on brain and heart, will contribute to the detection and treatment of these "high impact" clinical conditions.

Once EPT and MRF have been demonstrated to be suitable as diagnostic tools, the algorithms developed and made publicly available by the consortium, together with the reports analysing their performance in detail, will contribute to the wider adoption of EPT and MRF in the clinical community. For **clinicians**, the use of biomarkers provided by MR-based quantitative imaging will pave the way for new diagnostic strategies for pathologies that currently cannot be detected on a physical (and therefore objective) basis. The exploitation of EPT and MRF will foster personalized medicine; for example, EPT will underpin an optimised, subject-specific, therapeutic use of radiofrequency electromagnetic fields. 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.

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