EMPIR Call 2018 – Health, SI Broader Scope, Normative and Research Potential

Selected Research Topic number: **SRT-h08**
Version: 1.0

Title: Quantitative MR-based imaging of physical biomarkers

Abstract

Magnetic Resonance Imaging (MRI) is a widely used qualitative medical technique that is used to image the anatomy and physiological processes of patients. However, MRI has limited diagnostic capabilities and it does not allow the course of a disease to be followed quantitatively over time. To address these issues, two quantitative imaging approaches, Electric Properties Tomography (EPT) and Magnetic Resonance Fingerprinting (MRF), need to be further developed. This should include a full metrological characterisation of their sensitivity and specificity under real-world conditions. Once developed, these approaches could be routinely used to provide quantitative MR-based imaging of physical biomarkers, eliminating interobserver variability and reducing the need for invasive quantitative procedures (e.g. biopsies).

Keywords

Magnetic resonance imaging, quantitative imaging, electric properties tomography, magnetic resonance fingerprinting, biomarkers, machine learning.

Background to the Metrological Challenges

Despite its widespread use, traditional MRI is qualitative meaning that the acquired images have to be interpreted by a specialist and this does not allow results obtained at different times and locations to be quantitatively compared. In addition, conventional MRI does not provide direct information about the nature of the pathology nor does it quantify biomarkers. To address these issues, quantitative imaging approaches including EPT and MRF, are being developed, which should eliminate interobserver variability and reduce the need for invasive quantitative procedures (e.g. biopsies). In addition, EPT and MRF should enable new biomarkers to be identified for a plethora of pathologies that cannot be physically diagnosed and they should 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.

EPT can be used to quantitatively image the dielectric properties (i.e. the electric conductivity and permittivity) of tissue using conventional MRI sequences. Therefore, EPT could be used to quantitatively measure physical biomarkers allowing disease progression to be monitored over time. However, EPT needs to be further developed, including the use of surrogates for the phase of the magnetic field, for use in the analysis of “high impact” clinical conditions that cause significant changes in dielectric properties (e.g. cerebral ischemia). Both local and global EPT methods can be used. Local methods are straightforward and fast, but they amplify the measurement noise considerably and their accuracy is limited as approximations such as the local homogeneity assumption are used. Global methods such as the contrast source inversion method can overcome some of these problems and can provide additional information including an estimate of the local rate at which energy is absorbed by the human body (i.e. the specific absorption rate (SAR)). Unfortunately, global methods require a longer computational time, therefore their application to real 3D problems remains challenging. Both methods can be improved by using multi-channel coils, but this increases the image acquisition time. At the moment some field components cannot be directly retrieved by the MR scanner, therefore alternative image reconstruction strategies, based on new and improved algorithms, need to be developed, implemented and characterised. EPT also needs to be metrologically characterised under real-world conditions before it enters routine clinical use. The occurrence of false positives/negatives needs to be investigated, the inter-subject variability of the electric properties of tissues needs to be considered and advanced statistical techniques and in vivo assessment methods need to be applied. The accuracy of EPT and the experimental uncertainties also need to be determined using heterogeneous phantoms.

MRF can achieve fully quantitative multiparametric imaging by obtaining all of the parameters that contribute to the MR signal, including the proton density and the relaxation times, in a single acquisition. This requires novel data acquisition, post processing and visualisation approaches that rely on compressed measurements,

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pattern recognition and dictionary learning. As with EPT, MRF could also be used to quantitatively monitor disease progression over time. One application for MRF could be in the detection of heart diseases (e.g. diffuse myocardial fibrosis). However, MRF needs further improvement. One example, would be to prevent the significant aliasing effects that are caused by the undersampling that is used to manage the signal acquisition. In addition, some phenomena including physiological motion (i.e. breathing and heartbeat) and the presence of internal fluids moving through the scanned region can results in artefacts that reduce the accuracy of the MRF process, therefore methods need to be developed to suppress these artefacts. The partial volume effect, i.e. the presence of heterogeneities within a single resolution unit, also needs to be addressed. MRF uses large dictionaries, which require significant memory and there is a heavy computational burden in the matching phase. Therefore, new and improved algorithms, need to be developed, implemented and characterised so that MRF can be optimised for use in clinical applications. MRF also needs to be metrologically characterised under real-world conditions and the occurrence of false positives/negatives needs to be investigated. The inter-subject variability of the electric properties of tissues needs to be considered and advanced statistical techniques and in vivo assessment methods need to be applied. The accuracy of MRF and the experimental uncertainties need to be determined using heterogeneous phantoms.

The synergistic use of EPT and MRF also needs to be explored to optimise diagnosis, and specific computer-aided diagnostics approaches (e.g. machine learning) need to be developed to enable the handling of big data.

Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the protocol.

The JRP shall focus on the traceable measurement and characterisation of the sensitivity and specificity of two Magnetic Resonance-based imaging techniques, Electric Properties Tomography (EPT) and Magnetic Resonance Fingerprinting (MRF), which can be used to quantify physical biomarkers of disease in clinical settings.

The specific objectives are

1. To develop, improve and implement numerical algorithms for use in EPT and MRF and to characterise their performance. This should focus on both local relationships and global inversion methods for EPT and on techniques that rely on a pre-calculated dictionary and on statistical template-free methods for MRF.
2. To make EPT and MRF suitable for use in the analysis of “high impact” clinical conditions. EPT should be applied to the analysis of diseases that cause significant changes in dielectric properties (e.g. cerebral ischemia) and this technique should be further developed to use surrogates of the phase of the magnetic field. MRF should be applied to the detection of heart diseases (e.g. diffuse myocardial fibrosis) and methods should be developed to suppress artefacts caused by physiological motion and fluids moving in the scanned region.
3. To evaluate the accuracy of EPT and MRF procedures in magnetic resonance experiments under controlled conditions. Heterogeneous phantoms, composed of reference materials that mimic the properties of human tissues (e.g. conductivity, relative permittivity, longitudinal and transverse relaxation times in the order of 1 S/m, 50 S/m, 1000 ms and 50 ms respectively), should be used. 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 the frequency of occurrence of false positives/negatives. The variability of tissue properties should be taken into account and advanced statistical techniques and in vivo assessments should be applied. The synergistic use of EPT and MRF should be explored to optimise diagnosis and specific computer-aided diagnostics approaches should 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), standards developing organisations (CEN, ISO) and end users (e.g. hospitals and health centres).

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical

practitioners, hospitals and industry is strongly recommended, both prior to and during methodology development.

Proposers should establish the current state of the art, and explain how their proposed project goes beyond this.

In particular, proposers should outline the achievements of the EMRP project HLT06 MRI Safety and how their proposal will build on those.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.8 M€, and has defined an upper limit of 2.1 M€ for this project.

EURAMET also expects the EU Contribution to the external funded partners to not exceed 35 % of the total EU Contribution across all selected projects in this TP.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the “end user” community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the “end user” community (e.g. letters of support) is also encouraged.

You should detail how your JRP results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Transfer knowledge to the medical imaging sector.

You should detail other impacts of your proposed JRP as specified in the document “Guide 4: Writing Joint Research Projects (JRPs)”

You should also detail how your approach to realising the objectives will further the aim of EMPIR to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. Specifically, the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work

Time-scale

The project should be of up to 3 years duration.