

Magnetic Resonance Fingerprinting for Precision Imaging in Neuro-Oncology

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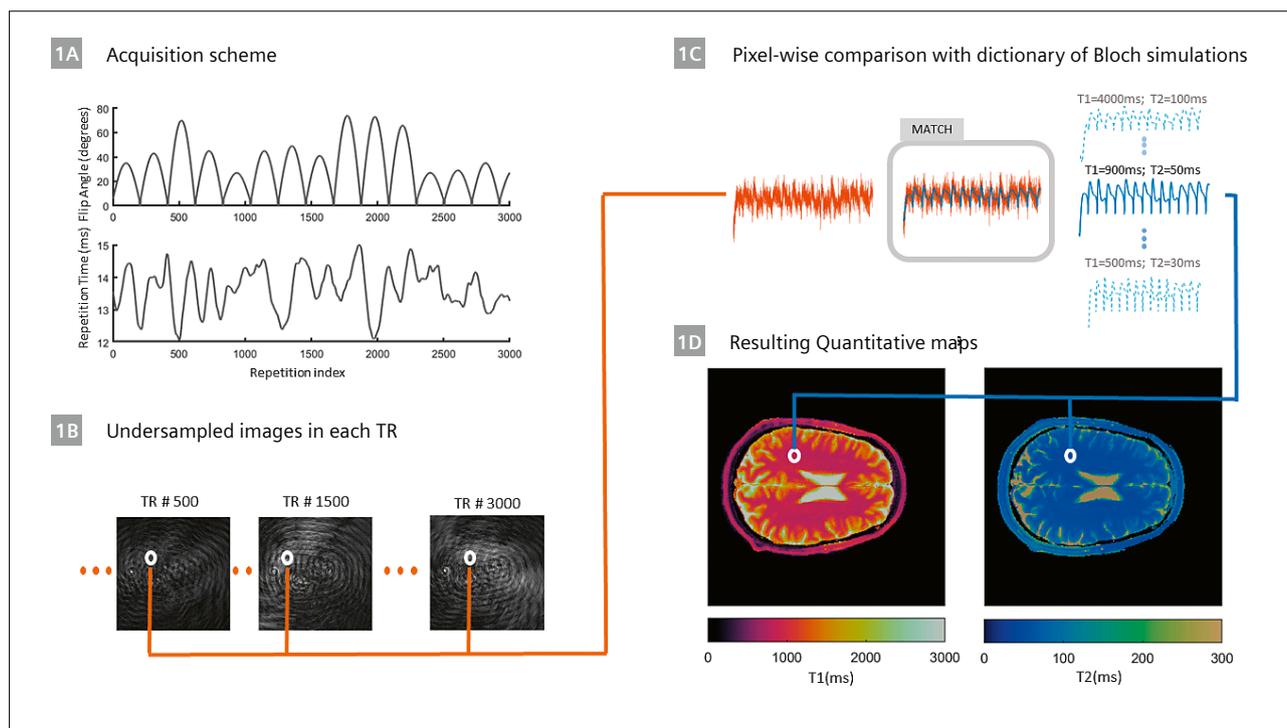
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Introduction

Brain tumors are one of the greatest health afflictions of our time. Although less prominent than other cancers, affecting around 4 in 100,000 people every year globally, it puts a great burden on patients, carers, and healthcare systems [1]. Recent advances have brought a better understanding of brain-tumor biochemistry, as well as the introduction of new treatments. However, for the most aggressive tumors, many challenges remain – for example, average life expectancy for glioblastoma is still under two years [1]. The standard of care for aggressive tumors includes surgical resection followed by adjuvant treatment and rehabilitation [2]. For effective surgical planning, as well as for treatment evaluation, neuroimaging methods are of primary importance. In this context, precision

imaging requires accurate assessment of the disorder *in situ*, accounting for the often-observed tumor heterogeneity [3], disease progression, presentation after initial treatment, and follow-up during treatment cycles [4]. Due to its superior soft-tissue contrast and the use of non-ionizing radiation, MRI is key to precision imaging. MR exams are repeated often, serving as a major source of information for individualized therapeutic paths, enabling diagnosis, treatment, control, and follow-up tailored to the individual characteristics of each patient [5].

Magnetic resonance imaging is essential in guiding, assisting, and monitoring treatment strategy. Currently, structural MR sequences at fields of 1.5T or above are the standard for brain-tumor imaging. T1-weighted,



1 In Magnetic Resonance Fingerprinting (MRF)¹, acquisition parameters are varied at each TR to keep the magnetization in the transient state (1A). Next, highly undersampled images are acquired in each TR (1B). For each voxel, the acquired data is compared with the clean simulation (1C) to find a match using pattern recognition, then matching results from all voxels are combined to form parameter maps (1D).

¹Work in progress. MR Fingerprinting is not commercially available in some countries. Due to regulatory reasons its future availability cannot be ensured. Please contact your local Siemens Healthineers organization for further details.

T2-weighted, FLAIR, and diffusion-weighted sequences are commonly included in protocols [6]. The images obtained with these sequences provide information about lesion location, brain tissue infiltration, and lesion cellularity. In addition, when contrast media are administered, images become sensitive to processes such as blood-brain barrier infiltration, a phenomenon typical of biologically aggressive neoplasms.

When combined with a patient's clinical history and symptoms, these data are commonly used by the radiologist to perform a differential diagnosis. In addition to a confident diagnosis, accurate delineation of tumor margins has a primary role in therapy planning [7]. Discriminating primary vasogenic edema seen in metastases from the edema with neoplastic cellular infiltration seen in glioblastoma is important to guide surgery and therapy, with a positive impact on patient outcome [8]. To that end, many studies have aimed at probing the underlying tumor microstructure and differentiating the biological characteristics of the tissue. Advanced MR imaging techniques including diffusion tensor imaging, perfusion, and spectroscopy have been used to discriminate glioblastomas from brain metastases and identify areas of peritumoral infiltrations [9]. More specifically, a multiparametric approach combining and comparing the features obtained with basic and advanced techniques could improve both sensitivity and specificity in identifying areas of gliomas that are not contrast enhancing but biologically active [10]. For example, applying machine learning algorithms on hundreds of features extracted from T1, T2, FLAIR, diffusion, and perfusion images has been shown to differentiate between vasogenic edema and tumor infiltration in patients with high grade gliomas with a sensitivity of 86% and a specificity of 89 % [11].

Advanced multiparametric procedures, however, require long scan times since the acquisition of many different basic and advanced sequences is necessary and needs specific postprocessing currently performed offline by dedicated personnel with specific technical expertise. To aid this, many automatic tools for quantitative analysis of neoplastic structures have been developed. Despite many improvements, this remains a challenge [10], owing to the large variability of qualitative MR data commonly used in the clinic. Recent advances have allowed automatic segmentation of brain MR images, achieving robust modelling and segmentation of volumetric data based on Artificial Intelligence (AI). Among these methods, the AI-Rad Companion for brain MR morphometry from Siemens Healthineers recently received 510k and CE labeling [11].

As AI-based medical computer vision enters the field of diagnostic imaging, several tools are needed to achieve automatic classification and interpretation of images, or tumor growth modelling and prediction. Reliable, repro-

ducible, quantitative image data becomes critical – determining the accuracy of decision support and the predictive quality of derived disease models. Consequently, AI-based methods require a rich set of consistent imaging data. Such consistency can be obtained with quantitative MRI methods. In this regard, conventional multiparametric assessments are currently far from entering the clinical arena due to lengthy acquisition and the complexity of processing, as well as questions over their repeatability and reproducibility [12].

MR Fingerprinting in neuro-oncology

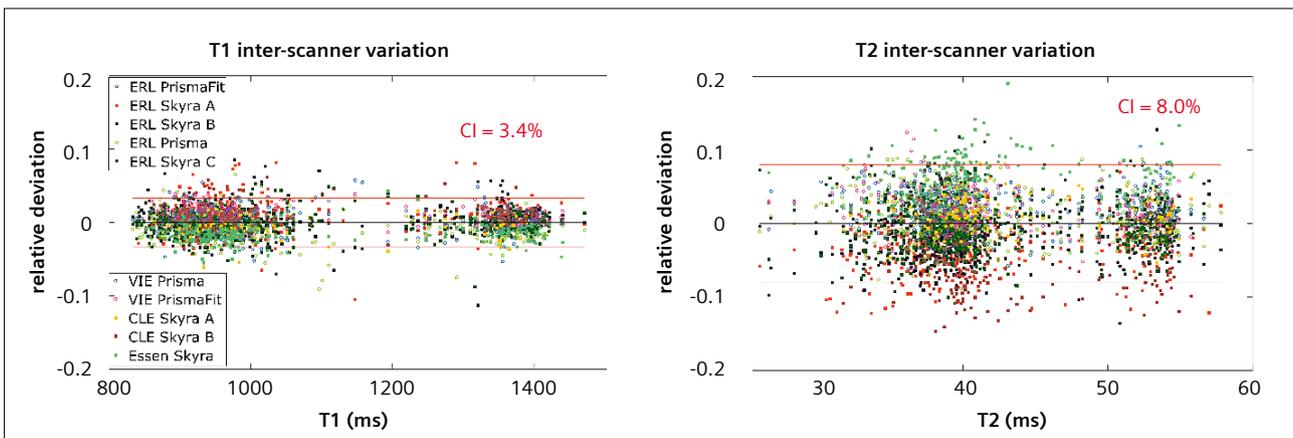
New tools for fast multiparametric estimation have recently been developed, achieving fast multiparametric mapping in a short acquisition time [13]. Among these methods, Magnetic Resonance Fingerprinting (MRF) has now been developed into a Siemens Healthineers product, in partnership with Case Western Reserve University [14]. MRF is a framework for multiparametric mapping relying on transient-state acquisitions [15], achieving multiparametric maps in under 30s. While conventional methods for parameter quantification acquire only one parameter at a time, MRF uses a holistic approach to the signal, including all the relevant information within a single model. This makes it possible to derive many individual parameters at once in an efficient manner.

A scheme of a typical MRF algorithm is shown in Figure 1. Rather than achieving a magnetization steady-state, acquisition parameters are purposely varied in each TR to generate unique tissue responses. For each pulse, an undersampled snapshot is acquired, typically with a non-Cartesian k -space acquisition, such as a spiral. In a typical MRF implementation, a dictionary is calculated with the possible physical responses obtained by simulating the transient-state response via the Bloch equations over a range of meaningful tissue parameters (T1, T2, PD, etc.) and system imperfections (e.g., field inhomogeneity). Patterns of acquisition parameters, such as flip angle and TR, are optimized to encode specific magnetization properties at pixel level. After acquisitions, measured signals in individual pixels are compared with calculated dictionary elements. This approach, including multiple parameters within the same model, has the advantage of producing highly accurate maps, with repeatability and reproducibility matching or outperforming other literature methods yet requiring a much shorter scan time [16, 17]. Exemplary 95% confidence intervals for MRF repeatability are reported in Figure 2.

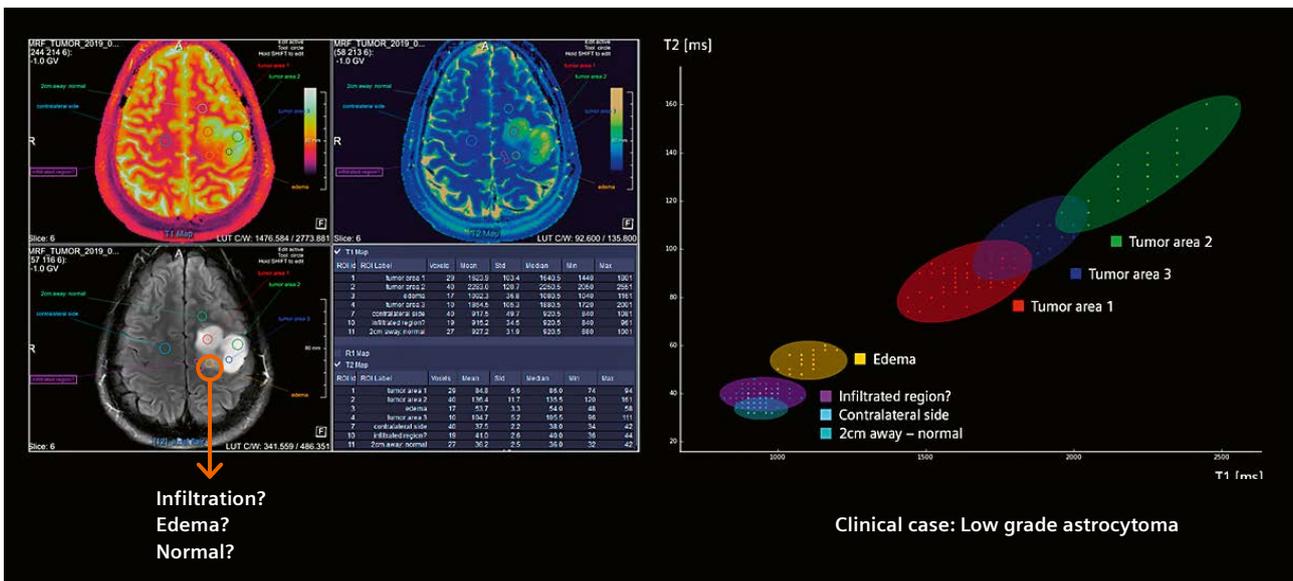
Quantitative relaxometry assessments for neuro-oncology require accurate and reliable tools for confident tissue characterization. Despite initial promise, studies on relaxometry in the early days of MRI found significant overlap between different tumor grades. The results on

tumor tissue characterization were not consistent between studies [18], and more significant diagnosis markers were later found with perfusion and diffusion assessments [19]. However, precise measurements of relaxometry have recently been re-introduced in research studies to complement information from more conventional tumor imaging protocols, as they provide valuable and objective information. For instance, in anti-angiogenic therapy, differentiating response from non-response can be difficult, as enhancement may be faint or subtle due to the decreased vessel wall permeability resulting from therapy. T1 subtraction maps have been used in this setting to improve inter-observer variability and better identify progression [20].

In addition to T1 subtraction maps, native T2 mapping has also provided important findings. In non-enhancing tumors, Response Assessment in Neuro-Oncology (RANO) requires assessment of FLAIR abnormalities, which provide separate information when compared with the enhancement pattern. Here, objective criteria are difficult to establish due to the various sources of pathology, including radiation effects, ischemia, edema, and post-operative gliosis. Recently, studies have found that objective T2 measurements are more specific than T2w images for tumor identification after anti-angiogenic treatments [21], more precisely characterize edema [22], and show a better outcome prediction [23].



2 Graphs show inter-scanner variation of mean T1 and T2 values in all solid matter compartments. Different colors indicate different scanners. Symmetric confidence intervals (CIs) of 1.96 standard deviations are shown. For T1 mean value in solid tissue, CI half-width is 3.4%. For T2 it is 8.0% [data from [16]].



3 Image visualization (left) and scatter plot (right) of the different areas of a low grade astrocytoma, showing a neat discrimination of the various components based on two-dimensional histograms. Courtesy of Professor Siegfried Trattnig, Medical University of Vienna, Austria.

New, more efficient approaches such as MRF, capable of acquiring multiparametric maps in under 30 seconds, are aiding the transition of these findings towards clinical protocols. Initial experiences with MRF in neuro-oncology studies have shown its ability to distinguish different tissue characteristics in both adult and pediatric brain tumors. In a group of 31 adult patients with intra-axial brain tumors, T2 maps were shown to be significantly different between solid tumor regions of lower-grade gliomas and metastases [24]. Likewise, T1 maps of Peritumoral White Matter (PWM) surrounding lower-grade gliomas differed from maps of PWM around glioblastomas [24]. Similar results were obtained in a group of 23 pediatric² and young adult patients [25]. Specifically, the authors reported statistically significant difference in T1 and T2 between low and high grade gliomas as well as between peritumoral and contralateral white matter. These results, although preliminary and yet to be replicated in larger studies, build upon findings showing the value of relaxometry for discriminating different molecular subtypes of tumors and evaluating anti-angiogenic treatment [20]. MRF allows this information to be obtained with a rapid and reproducible acquisition protocol.

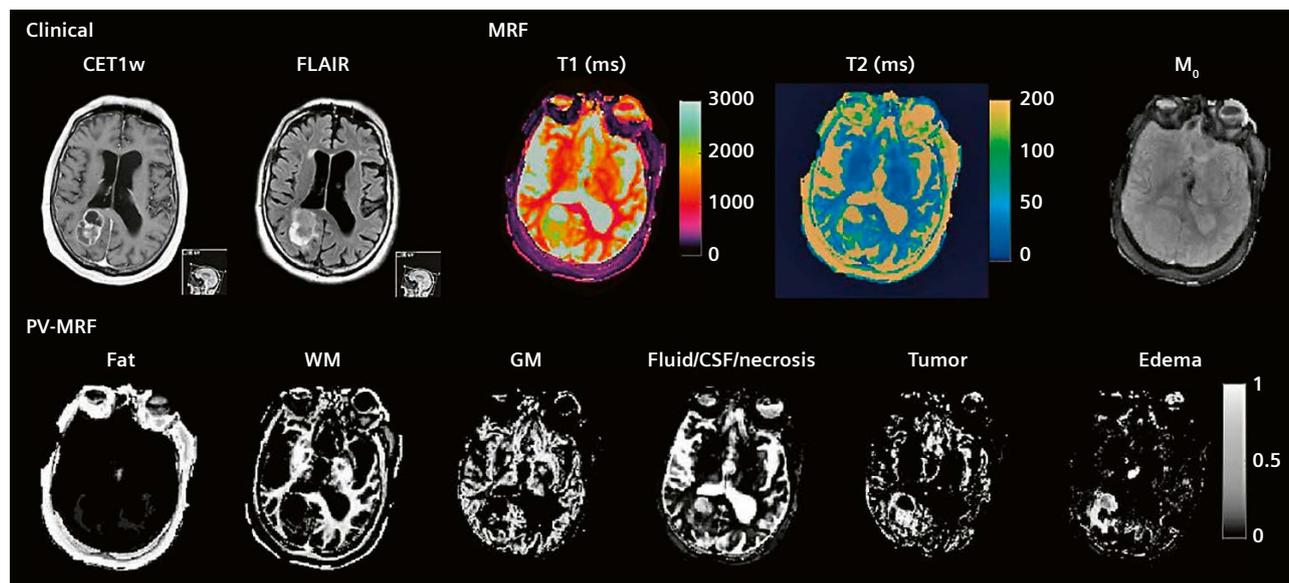
Challenges and opportunities for MRF in neuro-oncology

In addition to analyses based on a single value of T1 and T2 within each voxel, studies are looking into more sophisticated multicomponent analyses to assess tissue microstructure. These include a wealth of information

related to subtle features such as pore size, distribution, and exchange between compartments. While DESPOT modelling and diffusion are established methods to achieve this [26], they often suffer from long acquisition times and complex processing procedures.

With the recent emergence of fast, multiparametric acquisition schemes such as MRF, studying tissue microstructure with more realistic acquisition times has become feasible. In addition to speed, MRF has other inherent advantages for partial-volume modelling. Conventional partial-volume modelling of T1 and T2 mapping involves multi-exponential fits, which are difficult to perform mathematically. In contrast, MRF acquisition generates signals from mixtures which are distinct from pure tissue, allowing for a better discrimination of microstructural components [27]. An example can be seen in Figure 4, showing a segmentation of a small-cell lung cancer metastasis in the brain using dictionary-based partial volume MRF (PV-MRF) and 3D MRF acquisition. Recently, a similar approach has also been used to characterize developmental changes relating to myelination in children from birth² to five years old [28]. This was done by modelling white matter as composed by myelin water, intracellular/extracellular water, and free water, allowing to generate precise myelination trajectories. Similar models could be used to discriminate and follow-up myelin integrity in other disease and treatment cases.

²MR scanning has not been established as safe for imaging fetuses and infants less than two years of age. The responsible physician must evaluate the benefits of the MR examination compared to those of other imaging procedures.



4 Segmentation of a small-cell lung cancer metastasis in the brain using dictionary-based PV-MRF and 3D MRF acquisition. Dictionary matching enables the use of expanded multi-component models and segmentation of more tissue types than conventional partial-volume analysis [from [27]].

Future applications of MRF may include synergistic approaches for treatment planning. In this context, the feasibility of integrating accurate and precise MRF protocols in MR-guided radiation therapy planning has been recently demonstrated [29]. The MRF strategy employed showed increased repeatability and reproducibility for quantification, which is promising for longitudinal quantitative assessment of treatment response for better adaptive therapy, and for large-scale, multi-center clinical trials. There is also promise in including MRF in intraoperative MR solutions such as the Nexaris MR Combi Suite Neurosurgery. Intraoperative MR solutions have recently been shown to significantly improve the management of brain tumor patients by maximizing the extent of resection, and achieving five times more total resection than lightweight surgery [30, 31].

Another advance for treatment planning could be combined PET and multiparametric MRI. The combination of these two modalities for tissue segmentation has recently been shown to provide novel integrated segmentations for effective gamma knife treatment [32]. In this context, optimal combinations of quantitative features from MRF with complementary metabolic information from PET protocols could yield sophisticated tissue characterizations in neuro-oncological applications, with many opportunities for combined MR-PET systems [33], such as the BIOGRAPH mMR. Due to its capability for multi-component estimation in white matter, MRF could also help in the definition of more efficient and less toxic treatment plans. Common findings in patients treated with radiotherapy include vascular damage, hemorrhage, edema, neuroinflammation, astrogliosis, and neuronal cell damage [34,35]. These adverse effects can generate diffuse damage and lead to cognitive decline with a significant impact on the quality of life.

The potential of MRF for oncology is not limited to brain imaging. Research is investigating MRF in other areas of the body, such as chest [36], prostate [37, 38], breast [37], and musculoskeletal system [39–41]. Optimized MRF protocols may aid tumor detection, characterization, and treatment planning in many different applications.

In conclusion, MRF represents a paradigm shift for reliable, repeatable, and consistent signal acquisition and modelling. The recent availability of this technique in the clinical realm may have a significant impact on tumor detection, characterization, and effective treatment planning. Importantly, the clinical MRF sequence uses a standardized implementation, facilitating the pooling of data from different sites and different scanners. This could potentially enable larger scale clinical trials, producing large and consistent datasets. The increased consistency in signal outputs from MRF, compared with more conventional contrast-weighted images, holds great potential for radiomics.

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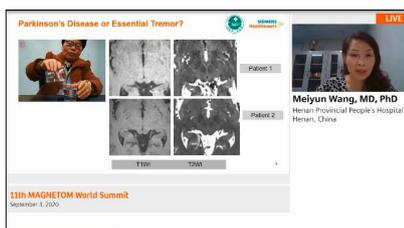
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