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Title: Magnetic Resonance Fingerprinting Review Part 2: Technique and Directions

Magnetic Resonance Fingerprinting Review Part 2: Technique and Directions

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Abstract

Magnetic Resonance Fingerprinting (MRF) is a general framework to quantify multiple MR-sensitive tissue properties with a single acquisition. There have been numerous advances in MRF in the years since its inception. In this work, we highlight some of the recent technical developments in MRF, focusing on sequence optimization, modifications for reconstruction and pattern matching, new methods for partial volume analysis, and applications of machine and deep learning.

Keywords: Magnetic resonance fingerprinting, optimization, reconstruction, machine learning, deep learning

Introduction

Magnetic resonance fingerprinting (1) (MRF) was introduced as a novel quantitative MR technique, which is used to generate maps of MR related tissue properties using a single acquisition. The inception of MRF has sparked numerous research projects in the MR community, ranging from repeatability and clinical applications to sequence design and reconstruction. Indeed, it was only a few years since the publication of (1) that review papers were written (2, 3) to summarize the many improvements and extensions that had been made to MRF. In this work, we focus on the technical developments made to the MRF framework, specifically in terms of optimization, reconstruction, partial volume, and machine learning. Both optimization and machine learning are active research areas in their own right, and the techniques themselves are constantly evolving.

To appreciate many of the recent developments in MRF, it is imperative to understand the proposed framework for MRF from the initial works, such as in (1), (4), (5), and (6), and how this approach is different from conventional methods. Quantitative mapping in MRI generally involves a long acquisition in which one tissue property is mapped at a time. The signal models to quantify T1 or T2 are typically described using 1) exponential models of signal recovery or decay (e.g, inversion recovery for T1 (7), and Carr-Purcell-Meiboom-Gill (CPMG) for T2 (8, 9)) 2) steady state signal models (e.g variable flip angle FLASH,(10) and DESPOT1 (11) for T1, DESPOT2 (11), Partial Spoiling SSFP (12), and DESS (13) for T2) , or 3) from driven equilibrium or transient state of the steady state sequences (e.g. Look-Locker (14)). There have been many approaches that propose to quantify multiple tissue properties simultaneously using a more complex signal model. Such approaches, which use one acquisition to quantify multiple properties, include inversion recovery True-FISP (15, 16) for T1, T2, and proton density and QRAPMASTER (17) to quantify T1, T2, proton density, and B1 field amplitude. Other quantitative methods for multiple properties include MRF spin tomography in the time domain (18) to quantify T1, T2, and B1, and the multipathway multi-echo imaging method (19) for 3D quantification of T1, T2, T2*, B0 and B1. Quantification of additional properties, including T1, T2* and magnetic susceptibility was demonstrated in (20), and magnetization transfer was quantified along with R1 and R2 in (21).

MRF recognizes that modern computation allows for much more complex signal models, which can provide higher quality mapping than previous methods (1). As such, it typically relies on a variable acquisition scheme to generate pixel-wise signal evolutions that are unique and distinct from the exponential recovery curves typically used in T1 or T2 mapping. In MRF, multiple tissue properties are quantified using a single scan, eliminating the need for registration between multiple, long acquisitions. Coupled with the variable sequence parameters, the data are typically highly undersampled in the Fourier domain, resulting in an accelerated acquisition; however, this acceleration also leads to signal evolutions which are heavily corrupted by aliasing artifacts. Instead of fitting these acquired pixel signal evolutions to an exponential model, pattern matching with a predefined dictionary of simulated signal evolutions is typically used and has been shown to be an efficient and accurate method to determine properties such as T1 and T2 relaxation times (1, 5).

The variable excitation and sampling patterns that are so important in MRF are also not unique to it. Variable repetition times were previously used in balanced steady state free precession imaging to improve the frequency response and reduce banding artifacts (22, 23), and simulated annealing was used to optimize the repetition time for this case in (24). Randomized sampling was previously used in (25, 26), and is in the spirit of the idea of compressed sensing for MRI (27). Earlier works, including (28, 29), and later (30) utilized randomized excitation for NMR spectroscopy. MRF is unique in that the

sequence parameters and sampling trajectories are varied together to create spatial and temporal incoherence in the signal evolutions.

Though initially implemented as a 2D acquisition, MRF was quickly modified for both for simultaneous multislice acquisitions (31–33) and 3D excitations (6, 34, 35), to obtain volumetric coverage in the brain. Example T1 and T2 maps from simultaneous multislice and 3D MRF acquisitions are shown in Figure 1. Additionally, sequences have been modified for areas beyond neuro, including applications in the abdomen (36), breast (37, 38), prostate (39), cardiac (40–42), knee and hip (43, 44), among others. Examples from several of these works are presented in Figure 2.

This work is the second part of a two-part review on MRF. Part I (45) focuses in detail on the clinical applications to which MRF has been applied, along with repeatability studies for MRF and the potential challenges faced for the clinical implementation of the technique. In this part of the review, we focus on technical developments made in the field of MRF, specifically on developments related to sequence optimization, reconstruction, and partial volume quantification, as well as applications of machine learning and deep learning to MRF. Each of these new techniques look to improve some facet of the MRF framework, resulting in faster acquisition times, reduction in aliasing artifacts, dictionary compression, faster pattern matching and better accuracy and precision.

Sequence Optimization

Besides clinical applications, much of the recent work on MRF focuses on improving the framework in some way, from optimizing the sequence structure, to improving the reconstruction performance, or simply finding ways to collect data more quickly. All of these types of improvements fall under the broad umbrella of optimization. To design an optimization problem, first it must be determined which aspect of MRF we want to improve, such as T1, T2 accuracy or precision, minimizing acquisition time, or sensitizing the sequence to additional properties. To understand which directions to take in this process, however, it is necessary to establish the goal of optimization and analyze the sources of error in the method, and which are most significant. To this end, appropriate metrics that will best predict and quantify the overall performance of a new MRF sequence should be used. These metrics should be highly correlated to the cost function used to find these optimal sequences, if not used directly as part of the cost function themselves. Since the MRF framework extends beyond sequence design, metrics and methods of analysis for each step in the process must be implemented, including those that account for sampling trajectories and undersampling factors, range and step size of dictionary tissue properties, and aspects of the reconstruction.

Direct Sequence Optimization and Metrics

There are many degrees of freedom available when optimizing MRF sequences, and thus many variables that can be optimized, including flip angle and repetition time, echo time, RF phase, sampling patterns, and so on. While flexibility in sequence design is a

main tenant of the MRF framework, it can lead to a prohibitively large optimization problem. Designing a cost function for such a problem may not be simple, and can include factors such as variance of quantitative results, signal magnitude, or value of the inner product. However, the complexity of the cost function will affect both the optimization landscape of the problem and the computational techniques that are able to provide a solution.

Quantification of tissue properties was initially achieved in MRF using the inner product between the acquired signal evolutions and the precomputed dictionary (1). For this type of pattern matching in particular, the ideal set of dictionary entries would be orthogonal in the tissue dimension, though the idea of dictionary entries being different from each other is important in other reconstruction techniques. For easier separation between signals with different relaxation properties, the inner product between different signals should be very small or zero, even in the presence of noise or artifacts from undersampling. However, signal evolutions generated from similar relaxation properties are highly correlated, resulting in a difficult partial volume problem for tissues such as white matter and gray matter (46, 47). Orthogonality would aid in separating a mixed signal in the case of a voxel containing multiple and different tissues, as we will discuss more in Section 3.3.

Three different metrics were tested as predictors of MRF performance in Sommer, et al (48). Two metrics were related to the inner product between dictionary entries. The first

of these was a local inner product measure, comparing the inner product value between adjacent dictionary entries. The other was a global metric, using a wide range of dictionary entries for inner product comparison. The third metric used Monte Carlo simulations to add simulated complex Gaussian noise to dictionary signal evolutions. The inner product was then calculated to obtain the error between the ground truth T1 and T2 values and the computed ones. All three metrics were tested against a set of randomly generated MRF sequences. The error metric using Monte Carlo noise simulation was most successful in predicting which sequences had the best performance, as opposed to the local and global dot product metrics, and this was shown in both phantom and in vivo studies.

The inner product metric was also used in Cohen, et al (49) where the cost function was designed to maximize the orthogonality of the dictionary, by comparing the matrix $D^H D$ to the identity matrix, where D is the matrix representation of the dictionary. Four different optimization techniques were examined; including a) simulated annealing, b) branch-and-bound, c) interior-point, and d) brute force, in their performance to produce an optimal sequence using this particular cost function. The interior-point algorithm produced the best sequences, in terms of scan time and T2 accuracy. The optimal flip angle and TR patterns produced from the interior-point optimization are shown in Figure 3, with the initialization for the interior-point algorithm shown in blue and the optimized

patterns shown in red. For both the FA and TR, piecewise linear patterns were calculated from the optimization, unlike the randomized patterns used for initialization.

The Cramér-Rao bound is a statistical tool which places a lower bound on the variance of an unbiased estimator, and has recently been applied to derive optimal sequence parameters for T1 mapping (50), and separately to increase the precision for the relaxation values estimated with DESPOT (11, 51). A rigorous derivation of a cost function to characterize the signal to noise ratio (SNR) efficiency of the MRF sequence is presented in Zhao, et al, (52), using the Cramér -Rao lower bound. SNR efficiency is defined in terms of the variance in the estimated tissue properties from the MRF sequence. White Gaussian noise is assumed in the derivation and the Cramér-Rao bound is used to define a lower bound for the variance of the calculated T1 and T2 values using MRF. The cost function, which is the trace of the Cramér-Rao matrix, is optimized to determine FA and TR patterns that will produce optimal SNR efficiency. Two patterns are calculated, using different numbers of time points to vary the sequence length. In the first pattern, the constraints for the optimization include only upper and lower bounds for the FA and TR values. In the second, however, a constraint is placed on the maximum change allowed in consecutive flip angles, to force the FA pattern to be piecewise smooth. Without this additional constraint, the FA pattern produced from the optimization has rapid changes over the first hundred or so TRs, but with a constraint on the maximum flip angle change, both FA and TR patterns are

structured, smoothly varying, and flat (i.e., staying at either the maximum or minimum constraints) for large portions of the sequence. The FA and TR patterns from this optimization are shown in Figure 3. The calculated FA patterns are considerably different from the sinusoidal FA pattern in (5).

In Kara, et al (53), a cost function and optimization metric are derived in terms of a quality factor for each tissue property in MRF-FISP. The quality factors relate the variance from noise and aliasing artifacts to the variance of the computed tissue properties. By optimizing the quality factors for T1 and T2 simultaneously, the effects of noise and undersampling on the resulting quantitative maps can be minimized. A genetic algorithm (54) is applied to produce optimal FA patterns with fixed TR, TE, and RF phase for fewer TRs than are typically used in MRF-FISP, with the resulting FA pattern shown in Figure 3. In contrast to the FA patterns found in (52), there are no constraints placed on consecutive flip angle changes, resulting in a FA pattern with large variations and rapid changes. However, in both cases (52, 53), the point is made that by rigorously optimizing the sequence structure for MRF-FISP, shorter sequences with improved efficiency may be possible, than have previously demonstrated.

Each of these approaches to MRF sequence optimization attempt to modify the current MRF framework for a measurable gain, whether it be in accuracy, precision, or efficiency, though each also focus specifically on the problem of sequence design. More recently, (55) examined the spiral sampling patterns and spatial biases which result

from the undersampling patterns commonly used in MRF. Both variable and constant-density spirals were studied, each with 48 sequentially rotated spiral interleaves, and the order of the single-shot sampling was varied to determine an optimal spacing and ordering of the spirals. As opposed to a sequential ordering, {1, 2,… 48, 1, 2,…}, the authors found that by using an increment of eleven for spiral ordering, that is, {1, 12, 23,…}, shading artifacts were reduced in both T1 and T2 maps.

Other sampling trajectories for MRF have also been implemented and studied, including echo planar imaging (49), Cartesian (56) and radial k-space acquisitions (43, 57), though optimization of the trajectory is still an open problem. Another recent work (58) proposes an analytical model which includes both effects from sequence design and k-space sampling as an error analysis tool for MRF. This tool may be useful in assessing and predicting the performance of MRF sequences going forward. Other recent assessment and error analysis methods include error propagation analysis from nuisance parameters in quantitative MR (59) and an automatic image-quality assessment in (60). While neither were originally designed for MRF, they may prove to be beneficial for the MRF community.

Other improvements/modification to the MRF sequence

Beyond implementation of optimization algorithms to determine optimal sequence patterns, there have been numerous methods that modify existing MRF sequence structures to increase sensitivity to additional tissue properties, many of which were

outlined in Part I of this review (45). However, adding tissue or system properties can complicate the quantification process, for example, this may result in extra dimensions in the dictionary. Some examples include sequences that are sensitive to T2* (61–64), perfusion (65, 66), and water-fat quantification (43, 67). A more complicated model is needed in the case of MRF for chemical exchange, or MRF-X (68), in which six properties are quantified, including two relaxation properties to characterize two exchanging components within one voxel, volume fraction, and exchange rate.

There are still many other sequence modifications that have been made in MRF. Cardiac MRF involves modifying the sequence to an individual patient's cardiac cycle with ECG triggering (40), which necessitates a patient-specific MRF dictionary. The MRF framework is additionally modified in (57) to achieve a pseudo steady-state precession of the spins, reducing the impact from intravoxel dephasing on tissue property quantification. More recent work combines the MRF framework of chemical exchange saturation transfer (CEST) for quantification of volume fraction and exchange rate (69, 70). Beyond sensitizing the sequence to in vivo tissue properties, it is possible to also quantify system properties, as in (71) where a combination of sequence types are used to quantify T1, T2, B0 and the external B1+ field. B1 field estimation is also included in the MRF sequence in (56). Adding tissue or system properties as in any of these cases can complicate the quantification process simply due to the exponential

increase in dictionary size required for matching. Solutions to the problem of dictionary size are addressed in the next section.

Reconstruction and Quantification

Dictionary Size and Matching Time

Besides sequence optimization, another challenge in MRF is the size of the dictionary. When the dictionary is large, this can cause problems with storage and memory. Another issue is the exhaustive matching process, and when coupled with a large dictionary, can take too much time to compute. The MRF dictionary can be represented as a two-dimensional matrix. The columns of this matrix represent simulated signal evolutions generated by the Bloch equations using different combinations of tissue properties, such as T1 and T2. The rows of the dictionary matrix are the number of time points, or TRs, used in the MRF sequence. Depending on the sequence type used and the granularity of the tissue property values desired, the tissue property dimension of the dictionary can easily grow from tens of thousands to millions. For example, in the case of MRF-FISP (5), the sequence is used to quantify two properties: T1 and T2 relaxation times. However, in the case of MRF-bSSFP, off-resonance is another property that is quantified, increasing the size of the required dictionary. In a breast MRF study using MRF-FISP (37), a dictionary with 20,059 columns representing possible T1, T2 combinations was used, whereas in a brain tumor study using MRF-bSSFP (72), the additional dimension of off-resonance increases the dictionary size to

287,709 columns. In the case where the sequence is also sensitized to quantify T1, T2, off-resonance, and T2*, the number of columns in the dictionary was reported to be over 30 million in Wang, et al (61), and 64 million in Hong, et al (63).

Inner product pattern matching has been shown to be accurate and robust to the high degree of aliasing artifacts due to undersampling in several of the initial MRF studies, including Ma, et al (1) and Jiang, et al (5). Also shown in both (1, 5), the number of time points used in the sequence will have a direct impact on the quality and accuracy of the T1 and T2 maps. Therefore, for the sequences in these initial studies, the number of time points was generally between 1000 to 3000. Strategies to handle the time and tissue property dimensions in the dictionary can lead to both reduced storage requirements and faster matching times.

To mitigate the size of the dictionary, the singular value decomposition (SVD) was used as a compression tool to reduce the time dimension in the dictionary (73), enabling a compression of 80-99% by projecting the dictionary onto a subspace spanned by the first few singular vectors. In this way, after projecting the dictionary onto a low rank subspace, the size of the dictionary is reduced in the time dimension, resulting in fewer points to compare, and the inner product matching is between 3-5 times faster (73).

This idea of projecting the dictionary onto a low rank subspace has spread into many reconstruction algorithms that use the low rank property of the dictionary to speed up reconstruction or mitigate effects from undersampling in the reconstruction, such as in

(74–76). Additionally, the SVD can be applied prior to image reconstruction, significantly reducing the size of the reconstruction problem, and has been used, for example, in the 3D MRF reconstruction (6) in which the raw k-space data are projected onto the SVD space. By projecting the data in this way, the reconstruction problem is reduced from 1440 3D volumes to only 25. Computing the SVD of a large matrix can be memory-intensive, and in the case where the dictionary may be too large to efficiently store and retrieve, a randomized SVD (77) approach can be applied to approximate the singular vectors of the dictionary, without needing to store the full dictionary in memory (78). Multi-channel transmit MRF, also called 'Plug-and-Play MRF' (43) requires a different compression scheme for the dictionary due to the multiple transmit channels used. Phase unwinding is proposed to aid in dictionary compression in this particular case (79), by reconstructing the multi-channel data separately, and combining after phase correction. SVD compression can then be applied to the data.

Dictionary size is the most problematic in the tissue property domain, and this dimension will grow exponentially as the number of tissue properties that the sequence is sensitized to increases, as previously described. Since the pattern matching that is used to find the best dictionary match is exhaustive, a group matching strategy was proposed (80) and was able to significantly reduce the time it takes to match acquired signal evolutions to the dictionary with minimal impact on accuracy. Reported matching times were up to 70 times faster compared to exhaustive direct matching, reducing the

time from 178 seconds to 2.5 seconds for MRF-bSSFP. This work on fast group matching accelerated the procedure by using correlations between entries with similar relaxation properties to create subgroups within the dictionary, reducing the search space used in the matching. Acquired pixel signal evolutions were first matched to the mean signal of each group, and subgroups were eliminated when this initial inner product value was below a fixed threshold. Grouping the dictionary does not reduce the overall number of tissue property combinations, but by performing an initial match with representative signals, matching time was reduced. Other works have incorporated the idea of a fast search for the dictionary pattern matching, including (81) in which the dictionary is structured as a k-dimensional tree on which an approximate nearest neighbor search can be performed. In MRF-ZOOM (82), the separability of tissue properties based on the inner product model is used to develop a fast dictionary searching algorithm to reduce the matching time.

Beyond fast matching strategies, other works have focused on reducing the number of dictionary entries required for accurate quantification of tissue properties. In Yang, et al, (78) a coarse version of the dictionary in the tissue property dimension is used, meaning that the step size in properties such as T1 and T2 is relatively large. Pattern matching is first done using the coarse dictionary. The dictionary is projected to a low rank subspace where polynomial interpolation is applied to determine more accurate T1 and T2 values. By applying interpolation to the coarse dictionary, the discretized nature of

the tissue properties can be circumvented. A similar idea is proposed in (76), using linear interpolation between dictionary to overcome the dictionary step size in the quantification problem. When combining this method with compression in the time domain, the storage requirements for the dictionary are greatly reduced.

Reconstruction Techniques

A great deal of work on MRF in recent years has focused on improving the reconstruction process, specifically on how to best transform the highly undersampled k-space data into the image domain or directly into quantitative tissue property maps. A direct method which is commonly used for reconstruction is the non-uniform fast Fourier transform (83), in which the non-Cartesian data are first resampled to a Cartesian grid and then the fast Fourier transform is applied. Once the data are reconstructed, pattern matching is applied, though artifacts from undersampling will still impact the matching. Most iterative algorithms for MRF attempt to reduce the effect of aliasing artifacts in the image domain, and can also have the effect of reducing the number of TRs needed for the sequence, shortening the overall time for the scan, for example, in (84) and (85).

Iterative approaches for MRF solve the problem by iterating between k-space to enforce data consistency, and the image domain, where the reconstructed signals are projected onto the MRF dictionary. Due to the application of multiple gridding and non-uniform Fourier transform iterations, the reconstruction time for such iterative algorithms can be

much greater as compared to a direct gridding and reconstruction. The iterative methods aim to solve a problem of the general form

$$\min_x \|y - Fx\| + \lambda T(x)$$

where x is the reconstructed image series corresponding to the acquired k-space data y. The operator F represents the encoding function used to transform the image series to k-space, the operator T can represent any number of penalty functionals that act on the image series, to emphasize a desired feature in the solution, for example, a wavelet transform, or total variation, and λ is a regularization parameter. Additionally, constraints are sometimes placed on the above problem by which the signal evolutions are projected onto the dictionary subspace for matching. This matching step can be included in the iterative process, for example to ensure data consistency (84), or completed upon convergence of the algorithm.

Low rank reconstructions

Many reconstruction algorithms, such as (41, 74–76, 86) leverage the fact that the MRF dictionary can be compressed without significant loss of information (73). While iterative reconstruction algorithms may have advantages, they may require more sophisticated computational techniques. In Assländer, et al, (75), the reconstruction alternates between data consistency in k-space, and then dictionary matching in the image domain. The SVD of the dictionary is applied in the Fourier domain to solve the problem

in a low rank subspace and improve the conditioning of the problem. Variable splitting and the alternating direction method of multipliers (87, 88) are applied to solve the linear inverse problem for data consistency. These computational techniques (variable splitting and alternating direction method of multipliers) are also applied in the maximum likelihood approach in (85).

The low rank subspace of the dictionary is also used by Zhao, et al, in (74), but an additional low rank constraint is also placed on the reconstructed time series. The reconstruction problem is approximated using linear least squares, which is then solved using the conjugate gradient algorithm. Pattern matching with the dictionary is used after convergence of the algorithm to generate the quantitative tissue property maps, with examples of in vivo results from this work shown in Figure 4. Aliasing artifacts are significantly reduced in this reconstruction, which in turn shortened the number of time points required for the acquisition, to as few as 700.

Similar to the previously described approaches, a low rank approach is proposed in Hamilton, et al (41). In this work, the reconstruction is performed in the SVD space to significantly reduce the time dimension of the problem. A wavelet transform is also applied, which can have the effect of smoothing the tissue property maps. Though designed for the application of simultaneous multislice cardiac MRF, this method could be applied to a single slice acquisition as well. Example T1 and T2 maps from the multislice cardiac acquisition and low rank reconstruction are in Figure 2.

In (76), a low rank constraint is placed on the reconstructed time series. A data consistency step is applied, similar to the iterative approach in (89); however, instead of forcing each pixel signal evolution to match to one dictionary entry, this constraint is relaxed, allowing a linear combination of multiple entries to fit each signal evolution.

A slightly different approach is taken in (86). Similar to previous methods, SVD compression for the time domain using the dictionary is applied; however, there is a spatial low rank assumption additionally made in the image domain. Small patches of 7x7 pixels in the reconstructed singular images are assumed to have low rank. Sparse regularization is also used by applying a wavelet transform to the singular images. Example T1 and T2 maps from this reconstruction technique are shown in Figure 4.

Finally, in a unique approach to the iterative reconstruction problem, Doneva et al, (90) use the low rank property of the acquired data in the k-t domain, unlike the previous methods which all use the low rank property of the dictionary or reconstructed image series. The SVD is applied to a small, fully sampled calibration data set in k-space, and this is used as a projection matrix to recover missing k-space data. An advantage of this method is that the iterations are performed only in k-space, eliminating the repeated gridding and Fourier transform operations, which make the algorithm computationally more efficient, with reconstruction times as low as ten seconds.

Other reconstruction techniques and improvements

Apart from the aforementioned low rank iterative approaches, other aspects of the reconstruction are varied to improve upon the MRF framework in various ways. One correction directly deals with blurring artifacts from B0 inhomogeneity that are a result from the accelerated spiral undersampling used in MRF. By applying a multi-frequency interpolation approach to correct the MRF reconstruction, blurring is significantly reduced in MRF-FISP (91). As undersampling artifacts from a highly accelerated MRF scan can be severe, it is advantageous to develop methods that can mitigate these artifacts without sacrificing speed in the acquisition. View sharing is a technique which is used to further accelerate the acquisition by requiring fewer time points in the MRF sequence (56). Using a high undersampling factor, data points that are not acquired in the edges of k-space are filled in with those from adjacent time frames as in key-hole acquisition (92). A similar concept is used in soft-weighted key-hole MRF, or MRF SOHO (93), in which parallel imaging, soft-gating, and the key-hole technique are combined to accelerate the scan. The sliding window reconstruction for MRF (94) combines the highly undersampled frames in k-space to instead reconstruct fully sampled images free from aliasing artifacts. As fewer time points are used in the reconstruction, the MRF dictionary is modified prior to matching. Data acquisition time is reduced by up to one third, by reducing the number of acquired time points from 1000 to as few as 300.

Parameters from the reconstruction methods discussed in this section are outlined in Table 1, including reconstruction time, number of time points used in the acquisition, image resolution, and MRF sequence used. It is interesting to note the variation in many of these parameters; for example, reconstruction methods were performed on sequences using as few as 400 time points to as many as 3000. Many works report testing on only one variant of the MRF sequence as well. Reproducibility and assessment of reconstruction techniques will be an important consideration going forward, and is discussed more in part 1 (45).

Partial Volume

Partial volume can be problematic in any MR technique where the voxel size is larger than the tissue structures being imaged, which can cause blurring and degraded boundaries in the image. Many techniques have been proposed to solve the partial volume problem in MR (95), we will focus on the proposed solutions to partial volume with MRF in this section. For MRF, the unique signal evolution structure may be an advantage for partial volume, however the problem is still ill-posed and difficult to solve in this context. Though partial volume is, in some sense, similar to the problem of fat/water separation, it does not necessitate a new sequence design or reconstruction processes to obtain an accurate solution. While a benefit from a direct sequence optimization may be that voxels with multiple components are more easily identified and separated, the few works on partial volume in MRF have focused finding an optimal

solution to a linear inverse problem, using the MRF sequence structures that are already in place.

In (1), a linear model was proposed to decompose the MRF pixel signal into weights corresponding to a few, predefined dictionary signal evolutions. For example, in the brain, these predefined signal evolutions could correspond to white matter, gray matter, and cerebrospinal fluid (CSF). Using three representative dictionary signal evolutions, each pixel signal could be decomposed into a sum of the three, with corresponding weights, using linear least squares. An improvement on this method was made in the recent work (46), which deals specifically with how to solve this predefined linear model. As MRF signal evolutions are complex-valued, and the weights from a linear least squares model will be complex, a more realistic tissue model was proposed in the form of a partial volume dictionary, which is formed with linear combinations using only positive, real-valued weights for each predefined tissue type. Quantification of weights is done by pattern matching with this partial volume dictionary using the inner product. Another modification included in this work is a subject-specific partial volume dictionary, which reflects the fact that there is some natural variation in the relaxation properties in the brain between subjects (96). To this end, k-means is applied to single component MRF relaxometry maps for each subject, to determine the appropriate tissue properties to include in the partial volume dictionary. Shown in Figure 5(a) and (b) is a comparison of the two aforementioned methods, applied to a normal volunteer, showing relative

fractions of white matter, gray matter, and CSF. The method has also been applied to brain tumor patients, in which case, more tissue components are used in the model to create tissue fraction maps, for example, white matter, gray matter, CSF, tumor, and peritumoral white matter.

A limitation of using a fixed tissue model, for example, assuming that brain tissue is only composed of white matter, gray matter, and CSF, may be evident in the case of pathology, where a diseased or unhealthy tissue may not be composed of these three tissues. If the diseased tissue has relaxation properties different from those represented in the model, then forcing a fixed model on the voxel signals will result in erroneous tissue fraction calculations and diseased tissue will not properly characterized. There have been works on partial volume for MRF that remove the fixed tissue model and apply the full dictionary to mixed voxel signals. In McGivney, et al, (47), the Bayesian paradigm for inverse problems is used to solve the problem in terms of the maximum a posterior estimator, assuming a probabilistic model for the tissue weights, and with additional post-processing, the resulting values can be combined into relative tissue fraction maps, shown in Figure 5(c) for a glioblastoma brain tumor patient. The work by Tang, et al (97) also does not require a fixed tissue model, but instead encourages sparsity of the weight vector by using reweighted ℓ_1 regularization. Though these methods are computationally more complex than the dictionary based approach (46),

they allow a more flexible tissue model when relaxation values are not known a priori, which may be the case in diseased or abnormal tissues.

Applications of Machine and Deep Learning to MRF

In recent years, machine learning and deep learning have become increasingly popular topics for research, and applications in MRI are frequent (98). Machine and deep learning may be a natural fit to solve some of the challenges in MRF, such as image reconstruction and pattern matching. Indeed, several of the deep learning applications to MRF aim to either speed up the Bloch simulation calculation of a large dictionary or remove the need for a dictionary altogether by directly learning the tissue property mappings from the signal evolutions. In (99), unsupervised learning methods are used to rapidly generate the MRF dictionary within several seconds, which could be valuable when performing sequence optimization or modification. Rapid dictionary generation is also the goal in (100), where neural networks are used to generate a dictionary that is based on a patient-specific cardiac rhythm, 100 times faster than using Bloch simulation. In (101), the relationship between the tissue property values and the dictionary is learned through regression, eliminating the exhaustive search from pattern matching. Neural networks are applied to learn tissue properties and also to directly generate synthetic qualitative images (102), bypassing the dictionary matching step. It is likely that the number of works published in this area applied to MRF will continue to grow dramatically, rapidly increasing over the coming months and years.

In the work entitled MRF-DRONE by Cohen, et al (103), deep learning is applied to MRF signal evolutions, after image reconstruction, to learn the T1 and T2 values without direct dictionary matching. The TensorFlow framework (104) was used to construct a fully connected neural network with four layers and two hidden layers, and the method was tested on both MRF-EPI (49) and MRF-FISP (5) sequences. Compared to direct dictionary matching, the application of the neural network to the MRF data was between 300 to 5000 times faster. Though network training can take a considerable amount of time in these types of methods (10 to 74 minutes in this work), this is considered a preprocessing step that only needs to be computed once. A similar method in (105) trains a convolutional neural network with three layers to learn the tissue properties from a dictionary, resulting in faster quantification of T1 and T2 and eliminating the need to store the dictionary after training.

Another deep learning method, named spatially-constrained quantification, is applied in (106) to learn the T1 and T2 values directly from the MRF signal evolutions. A two-step process is used. First, the time dimension of the signal evolutions is reduced using two fully connected neural networks to learn a nonlinear mapping for feature extraction, as opposed to using SVD compression. The next step uses a convolutional neural network to quantify T1 and T2 values at each pixel, using the spatial features of neighboring pixels calculated in the first step. T1 and T2 maps generated using this framework are shown in Figure 6, using both 576 and 288 time points for the quantification. This

framework allows a significant reduction in the MRF acquisition time, by requiring as few as one fourth the number of acquired time points compared to MRF-FISP (5).

One aspect to point out in the above works is the problem of the inherent complex-valued property of the MRF data. In (103), the absolute value of signal evolutions is taken for the input into the neural network, where as in (106), the signal evolution is split into its real and imaginary parts, resulting in a vector that is twice as long as the original. An neural network is designed, using the full complex-valued data in (107), specifically with the application to MRF in mind.

Although not MRF, the recent works of (108) and (109) demonstrate the power of machine learning to directly quantify tissue properties from MRI data. In the case of (108), tissue properties are learned using the MR signal model with nonlinear regression and application of a nonlinear kernel function. Application of the method allows for quantification of T1 and T2 relaxation times using both spoiled gradient-recalled echo and dual-echo steady-state sequences. The AUTOMAP method (109) is a comprehensive deep learning technique to replace the image reconstruction step and can be applied to various imaging methodologies to directly learn the encoding method. These works highlight the impact that machine learning can have on MR, in particular, applying these ideas to MRF may open the door for more comprehensive optimization of the framework.

Discussion

MR Fingerprinting is a flexible framework that allows fast and simultaneous quantification of multiple tissue and system properties. Because the reconstruction and pattern matching do not require a particular signal shape, the framework is able to reduce the constraints on MR acquisition design and signal modeling. This flexibility can provide more rapid, robust, repeatable and specific tissue properties for tissue characterization and clinical usage. A thorough discussion of the repeatability and reproducibility of MRF, clinical applications, and potential barriers for clinical adaptation was presented in Part 1 of this review (45), which highlights the advantages and potential problems with using the MRF framework in a clinical setting. We focus our discussion here on the topics highlighted in this portion of the review, namely the technical developments that have been made to MRF and the challenges that still remain.

The increased flexibility and degrees of freedom of MRF can pose challenges for optimization. Current studies typically optimize MRF acquisition and reconstruction separately, as evidenced in Sections 2 and 3. Sequence optimization mainly focuses on improving signal separability and precision of the results, assuming perfect sampling with Gaussian white noise. Though some initial optimization methods have been studied, the global optimum for MRF sequence design has yet to be proven. The number of degrees of freedom available in designing an MRF sequence are numerous, including sequence parameters such as flip angle, repetition time, echo time, and RF

phase. While sequences have been designed that optimize several of these, a comprehensive design that optimizes all of these variables simultaneously does not yet exist. MRF reconstruction methods are typically developed based on existing sequences and sampling strategies and the main goal has been to reduce image artifacts and noise. The MRF sequence design, k-space sampling and reconstruction may be incorporated in a comprehensive framework for optimization in the future, and this would be a significant step in optimizing the full MRF method. However, the optimization landscape for MRF is not well understood and has not been well studied, and it is likely that the landscape is not convex and is high dimensional, and this will add additional modeling and computational complexity, as finding a global optimum is difficult with even state of the art optimization techniques. Having an accurate model that can be solved using current computational methods in real time is a clear barrier for MRF to being optimized thoroughly and rapidly, for application in the clinic.

By decreasing the correlations of the signal evolutions from different tissue types, MRF may provide a unique opportunity to effectively separate multiple tissue properties from a single voxel, leading to better multi-parametric mapping, partial volume separation and microstructure characterization. For example, reducing the similarity between white matter and gray matter signal evolutions in the dictionary could result in more accurate volume fraction estimations for this common partial volume occurrence in the brain. The challenges associated with such a partial volume separation problem include multi-

dimensional data modeling and solving inverse problems, and both of these fields are being studied and constantly evolving. An additional challenge with partial volume is validation and establishment of a ground truth is difficult, however the resulting multi-dimensional and multi-scale tissue properties has the potential to make the tissue/disease characterization more specific.

There may be different metrics to assess the overall performance of the various MRF designs, including accuracy and precision of tissue property maps or total scan time, and it is likely a combination of factors such as these will need to be used. While metrics such as SNR and image quality of each individual time point may be applicable, their relationship to the final image quality, accuracy, and precision of the tissue property maps are nonlinear due to the pattern matching. Therefore, metrics regarding the tissue property maps are better choices for both optimization and results validation. Both phantom and in vivo validation are required for these types of metrics, and these studies have been outlined in detail in Part 1 of this review (45). Scan time is another applicable metric for clinical translation of MRF. For example, reducing the total scan time is a desirable goal for MRF, as it will reduce scanner time for patients. Current 3D MRF scan times for whole brain coverage with 1 mm isotropic resolution are reported to be 7.5 minutes (35), and 5 minutes (34). Metrics that have been used in sequence optimization, such as accuracy or image quality can also be used to evaluate the applications of machine and deep learning to MRF.

In addition to explicitly solving optimization problems of the MRF framework, deep learning has been implemented in reconstruction, dictionary generation and matching steps, and has shown promising results for solving nonlinear, nonconvex, and high dimensional problems. With the significant interest in deep learning from both engineering and clinical fields, the techniques will likely be further developed for MRF quantification, image analysis and clinical validations.

Conclusions

MRF is a unique framework for quantitative MRI and provides multiple registered tissue property maps from a single acquisition. Recent technical developments for MRF, including sequence optimization, improved reconstruction algorithms, partial volume separation, and deep learning have been summarized in this review as important techniques to move the field of MRF forward. By developing a comprehensive optimization framework for MRF, including optimization across sequence design, reconstruction, and pattern matching, MRF will be even more widely applicable and impactful for clinical practice.

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Reference	MRF Sequence type	Scan time	Sampling Pattern	Number of TRs	Reconstruction time	Resolution
Low Rank ADMM Reconstruction for MRF [75]	Pseudo steady-state free precession [57]	4.1 s (1 radial spoke per TR) 7.35 min (32 radial spokes per TR)	Radial	841	43 s	1mm x 1mm, 3mm slice thickness
Maximum Likelihood for MRF [85]	FISP [5]	13.1 s for 1000 TRs	Spiral, R = 48	Varies, between700 and 1400	32 min for 1000 TRs	1.18 mm x 1.18 mm, 5 mm slice thickness
Improved MRF reconstruction with low rank and subspace modeling [74]	FISP [5]	11.8 s for 900 TRs	Spiral, R = 48	900	22 min for 700 TRs	1.18 mm x 1.18 mm, 5 mm slice thickness
Low rank MRF [76]	bSSFP [1] (retrospective)	--	Spiral, R = 48	400	205 min	2.3 mm x 2.3 mm, 5 mm slice thickness
Sparsity and locally low rank regularization for MRF [86]	FISP [5], MRF-SOHO [93]	2.6 s for 600 TRs 9.6 s for 1750 TRs	Radial	600, 1750	~ 60 min	2 mm x 2 mm, 1 mm x 1mm, both with 10 mm slice thickness
Simultaneous multislice cardiac MRF using low rank reconstruction [41]	SMS cardiac MRF [41], [42]	Variable per patient, 16 heartbeat acquisition	Spiral, R = 48	768	10.9 min for one slice, 47.3 min for three	8 mm slice thickness
Multiscale reconstruction for MRF [84]	bSSFP [1]	3 s for 300 TRs	Spiral, R = 48	Varied: 300, 500,1000, and 3000	30 min for 300 TRs, 63 min for 1000 TRs	1.18 mm x 1.18 mm, 5 mm slice thickness
Matrix completion-based reconstruction for undersampled MRF data [90]	FISP [5]	--	Cartesian, R = 8; Spiral, R = 48	200, 1000	10.1 s for 200 TRs, 40.3 s for 1000 TRs	1.96 mm x 1.96 mm, 8 mm slice thickness
Accelerated MRF using soft-weighted key-hole [93]	MRF-SOHO [93]	6 s for 2x2 mm^2 18 s for 1x1 mm^2 23 s for 0.7x0.7mm^2	Radial	Varied: between 200 and 1000	10 min for 2x2 mm^2, 30 min for 1x1 mm^2, 120 min for 0.7x0.7mm^2	Varied, 2 mm x 2mm, 1mm x 1mm, 0.7 mm x 0.7 mm, 10 mm slice thickness
Robust sliding-window reconstruction for accelerating the acquisition of MRF [94]	FISP [5]	--	Spiral	300, 500	--	1.3 mm x 1.3 mm

Table 1.

Table Captions

Table 1. Summary of reported in vivo scan parameters for the iterative reconstruction techniques discussed in this review. All items listed in the table are reported in each individual reference. Scan time and reconstruction time listed are for in vivo scans presented in each respective reference.

Figure Captions

Figure 1. Neuro applications of MRF. Shown in a) are 2D multislice T1, T2 maps from a normal volunteer, scanned with MRF-FISP (5, 32). In b) are T1, T2, and proton density maps shown in axial, coronal, and sagittal views from three slices in a 3D MRF-FISP acquisition (6). All units for T1 and T2 maps are in ms. *The multislice figure is reprinted with permission from* (32).

Figure 2. Examples of applications of MRF to different parts of the body, including a) abdomen maps from a patient with lung adenocarcinoma metastatic to the liver using a 2D MRF scan (36), b) cardiac multislice maps from a normal volunteer using a simultaneous multislice scan (41), and c) breast maps from a patient with invasive ductal carcinoma in left breast using a 3D MRF scan (37). Units for all T1, T2 maps are shown in ms. *Figures of abdomen and breast T1, T2 maps are reprinted with permission, with new color maps applied, from* (36) *and* (37)*, respectively*.

Figure 3. Flip angle (FA) and repetition times (TR) produced from the optimization techniques discussed in Section 2. The FA and TR patterns in a) are from (49) using the interior-point optimization, applied to a cost function which emphasizes the orthogonality

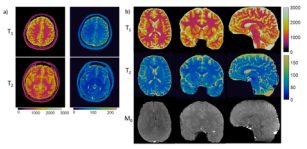
of the dictionary matrix. In b) are FA and TR patterns from (52), which are based on the Cramér-Rao lower bound for unbiased estimators. ‘Optimized I’ and ‘Optimized II’ refer to the constraints put on the FA pattern. In Optimized I, upper and lower bounds are placed on FA and TR, whereas in in Optimized II, changes in neighboring FA values are additionally constrained. In c) is the FA pattern from (53), which is calculated using the genetic algorithm to optimize T1 and T2 quality factors. The FA and TR patterns used in MRF-FISP (5) are shown in d). *Figures reprinted with permission from* (49, 52, 53).

Figure 4. T1 and T2 maps obtained from reconstruction techniques outlined in Section 3. Units for all maps are in ms. In a) the maps are reconstructions using 700 TRs from the low rank method from Zhao, et al (74), compared also to direct reconstruction and matching, as well as the maximum likelihood approach (85). Error maps are computed by comparing to a full-sampled reconstruction as the gold standard. In b) are maps using the sparsity and locally low rank method from Lima da Cruz, et al (86), shown from two different volunteers. *Figures reprinted with permission, and new color maps applied, from* (74, 86).

Figure 5. Partial volume fraction calculation from three of the discussed methods. In a) and b) are fraction maps representing white matter, gray matter, and CSF in a normal volunteer, using a 3D MRF-FISP (6) acquisition. The method used in part a) is from the pseudoinverse calculation with a fixed three component dictionary, whereas in b), linear combinations of this three component dictionary are used to generate a larger partial

volume dictionary, to which pattern matching is applied (46). In c) the method from (47) is applied to a glioblastoma brain tumor patient. Tissues shown in this decomposition include white matter, two gray matter components, CSF, tumor and regions surrounding the tumor. Shown on the right are the T1 and T2 maps obtained from 3D MRF-FISP (6) in this patient.

Figure 6. T1 and T2 maps generated from the deep learning method of Fang, et al (106). DM represents the results from applying direct reconstruction and pattern matching, SCQ represents the deep learning method, spatially-constrained quantification. Different number of time points were used, as noted in the figure. Maps are compared to an MRF with 2304 time points used for the ground truth, with relative error maps shown and total percent error shown in each figure. *Figure reprinted with permission, and new color maps applied, from* (106).



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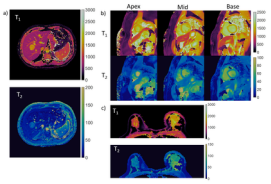

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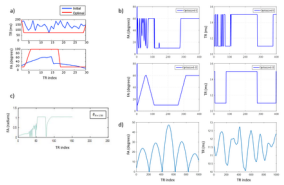

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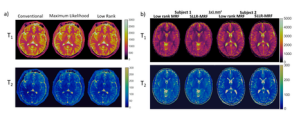

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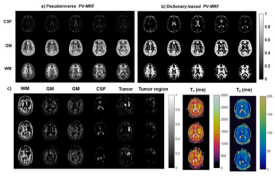

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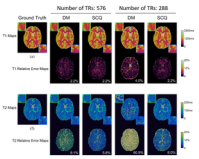

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Magnetic Resonance Fingerprinting Review Part 2: Technique and Directions

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