

RESEARCH ARTICLE

3D free-breathing cardiac magnetic resonance fingerprinting

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Funding information

Engineering and Physical Sciences Research Council, Grant/Award Numbers: EP/O001009/1, EP/P032311/1; National Institute for Health Research; Wellcome Trust, Grant/Award Number: NS/A000049/1

Purpose: To develop a novel respiratory motion compensated three-dimensional (3D) cardiac magnetic resonance fingerprinting (cMRF) approach for whole-heart myocardial T_1 and T_2 mapping from a free-breathing scan.

Methods: Two-dimensional (2D) cMRF has been recently proposed for simultaneous, co-registered T_1 and T_2 mapping from a breath-hold scan; however, coverage is limited. Here we propose a novel respiratory motion compensated 3D cMRF approach for whole-heart myocardial T_1 and T_2 tissue characterization from a free-breathing scan. Variable inversion recovery and T_2 preparation modules are used for parametric encoding, respiratory bellows driven localized autofocus is proposed for beat-to-beat translation motion correction and a subspace regularized reconstruction is employed to accelerate the scan. The proposed 3D cMRF approach was evaluated in a standardized T_1/T_2 phantom in comparison with reference spin echo values and in 10 healthy subjects in comparison with standard 2D MOLLI, SASHA and T_2 -GraSE mapping techniques at 1.5 T.

Results: 3D cMRF T_1 and T_2 measurements were generally in good agreement with reference spin echo values in the phantom experiments, with relative errors of 2.9% and 3.8% for T_1 and T_2 ($T_2 < 100$ ms), respectively. *in vivo* left ventricle (LV) myocardial T_1 values were 1054 ± 19 ms for MOLLI, 1146 ± 20 ms for SASHA and 1093 ± 24 ms for the proposed 3D cMRF; corresponding T_2 values were 51.8 ± 1.6 ms for T_2 -GraSE and 44.6 ± 2.0 ms for 3D cMRF. LV coefficients of variation were $7.6 \pm 1.6\%$ for MOLLI, $12.1 \pm 2.7\%$ for SASHA and $5.8 \pm 0.8\%$ for 3D cMRF T_1 , and $10.5 \pm 1.4\%$ for T_2 -GraSE and $11.7 \pm 1.6\%$ for 3D cMRF T_2 .

Conclusion: The proposed 3D cMRF can provide whole-heart, simultaneous and co-registered T_1 and T_2 maps with accuracy and precision comparable to those of clinical standards in a single free-breathing scan of about 7 min.

KEYWORDS

3D whole heart, low rank, MR fingerprinting, myocardial tissue characterization, quantitative cardiac MRI, T_1 map, T_2 map

1 | INTRODUCTION

Quantitative myocardial tissue characterization has emerged as an important tool for the diagnosis of cardiovascular disease. Tissue parameters such as T_1 , T_2 , T_2^* relaxation times and extracellular volume (ECV) have demonstrated sensitivity to several diseases.¹ These parameters detect underlying mechanisms of disease such as necrosis (T_1), edema (T_2), iron overload (T_2^*) or fibrosis (ECV), allowing disease progression to be monitored. Conventional myocardial mapping techniques map a single parameter per acquisition using two-dimensional (2D) breath-hold sequences such as modified Look-Locker inversion recovery (MOLLI)² and saturation recovery single-shot acquisition (SASHA)³ for T_1 , or T_2 prepared balanced steady-state free precession (T2prep-bSSFP)⁴ and T_2 gradient and spin echo (T_2 -GraSE)⁵ for T_2 . Multiple tissue parameters are generally sensitive to a given disease, and recently it has been suggested that simultaneous multi-parametric mapping could improve tissue characterization, as recommended in the updated diagnostic criteria for myocardial inflammation.⁶ For example, simultaneous T_1 and T_2 can lead to improved characterization of myocardial infarction,^{7,8} help distinguish between acute and chronic myocarditis (leading to improved diagnostic specificity)^{6,9} and potentially improve the understanding of the underlying disease.¹⁰ With conventional approaches, multi-parametric mapping requires sequential acquisitions under several breath-holds, often leading to non-registered maps as well as potential patient discomfort. Moreover, conventional mapping techniques provide limited coverage of the heart, and different methods have different confounding factors, including crossover dependencies between T_1 and T_2 if the two parameters are not simultaneously included in the model.^{4,11–13}

Due to T_1 's and T_2 's complementary diagnostic information and co-dependences in the signal model, joint parametric mapping methods have become of interest. An interleaved 2D T_1/T_2 encoding strategy based on inversion recovery (IR) and T_2 preparation (T2prep) pulses in free-breathing has been developed.¹⁴ Most cardiac mapping methods acquire data in a small cardiac acquisition window; however, 2D joint T_1/T_2 mapping has been achieved using IR interrupted b-SSFP readouts in CABIRIA.¹⁵ A combination of T2prep and saturation recovery pulses have also been employed for 2D joint T_1/T_2 mapping.¹⁶ Similarly, T2preps together with IR pulses have also been developed for this purpose.^{17,18} A hybrid T2prep-IR pulse is employed in MR multitasking for motion resolved simultaneous T_1/T_2 mapping.¹⁹ Extension to three dimensions for whole-heart coverage T_1/T_2 mapping has been considered using T2prep and IR pulses in three-dimensional (3D-)QALAS in a breath-hold; however, breath-hold duration can impose a limit on spatial resolution and/or coverage.²⁰ More recently, 3D free-breathing T_1/T_2 mapping has been achieved using T2prep, saturation recovery pulses and respiratory diaphragmatic navigators; however, this can lead to long and unpredictable scan times.²¹ All of the above are steady-state approaches, often sampling discrete points along the relaxation curves and relying on simplified exponential models.

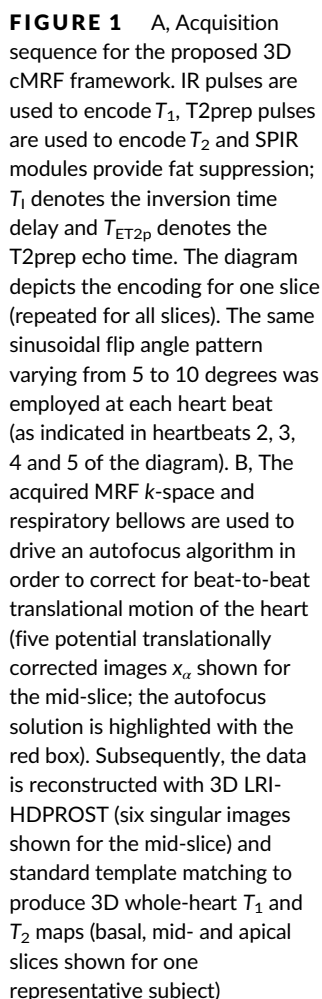
Magnetic resonance fingerprinting (MRF)²² is an established research technique for simultaneous and multi-parametric quantitative MR where system parameters (such as flip angle and repetition time) vary in time to sensitize the sequence to tissue parameters of interest (such as T_1 and T_2). MRF attempts to capture the parametric encoding within the transient state using directly the Bloch equations and can be extended to include not only additional parameters of interest (eg flow,²³ chemical exchange saturation transfer (CEST)²⁴), but also additional model corrections (eg B_1 ,²⁵ slice profile²⁶). Initially proposed for brain acquisitions, MRF has since been extended to 2D cardiac imaging (cMRF)²⁷ for simultaneous, co-registered T_1 and T_2 myocardial mapping in a single breath-hold. 2D breath-hold cMRF produces simultaneous and co-registered T_1/T_2 maps comparable to conventional methods, albeit in reduced scan time. Model corrections such as B_1 and slice profile for 2D cMRF have also been evaluated,²⁸ leading to reduced bias in the estimated parameters. Simultaneous multi-slice imaging has been combined with 2D cMRF²⁹ to increase the coverage of the heart; however, this is still limited to three slices and is sensitive to through-plane motion.

In this work we develop a novel respiratory motion compensated 3D cMRF approach for whole-heart coverage of T_1/T_2 myocardial mapping in a single free-breathing scan. Similarly to 2D cMRF, parametric encoding is primarily achieved with IR and T2prep pulses. The extension to three dimensions increases the scan time beyond a common breath-hold duration and free-breathing acquisitions are required. In-plane translational motion due to breathing is corrected with respiratory bellows driven localized autofocus^{30,31}, and a patch-based low-rank tensor regularized reconstruction³² is employed to accelerate the 3D cMRF scan. The proposed 3D cMRF was evaluated in a standardized phantom and in 10 healthy subjects, in comparison with gold standard spin echo measurements (phantom) and conventional MOLLI, SASHA and T_2 -GraSE mapping techniques (in vivo).

2 | EXPERIMENTS

2.1 | Acquisition

The proposed 3D cMRF uses a free-breathing, ECG-triggered acquisition with a variable density stack of spirals, where a different preparation pulse is applied in each heartbeat (Figure 1A). The preparation scheme was chosen heuristically, inspired by recent works in 2D cMRF.^{27,28} The acquisition is divided into blocks of 18 heartbeats with the following preparation scheme: IR15, NP, NP, NP, NP, IR150, NP, NP, NP, NP, IR300, NP, T2prep20, T2prep30, T2prep40, T2prep50, T2prep60, T2prep80, where NP denotes "no preparation pulse" and the numerical values after IR or T2prep denote the corresponding IR time delay (T_i) or T2prep echo time (T_{ET2p}), respectively. One block was used per slice encoding (with linear



ordering) and a minimum of a 4 s recovery period was employed between blocks to recover longitudinal magnetization (after 4 s the sequence resumed when the subsequent R wave was detected). A spectral presaturation with inversion recovery (SPIR)³³ pulse is used before data acquisition to suppress aliasing artefacts originating from the fat signal. The effective flip angle of the SPIR (which determines the zero crossing of the fat) was varied to account for the preparation pulse employed in each heartbeat. For IR delay < 200 ms, no SPIR pulse was employed, as the longitudinal fat magnetization is still negative. Otherwise, the SPIR flip angle θ at each heartbeat was given by

$$\theta = \cos^{-1} \left[\frac{e^{-T_H/T_{1f}} - 1}{e^{-T_{2\text{prep}}/T_{2f}} [e^{-T_H/T_{1f}} (1 - e^{-HR/T_{1f}})]} \right] \quad (1)$$

where T_{1f} and T_{2f} are the T_1 and T_2 relaxation times of fat, $T_{2\text{prep}}$ denotes the echo time of the T_2 preparation employed, T_{Hf} is the inversion time delay of the SPIR and HR is the nominal heartrate for a given subject. Adiabatic pulses were used for all 180° pulses in IR and T2prep modules to reduce sensitivity to potential B_1 errors^{34,35} and subsequent errors in the parametric maps.²⁸ In addition to ECG, respiratory bellows were used to record respiratory motion. The one-dimensional (1D) respiratory signal obtained from the bellows was later used for respiratory motion correction.

2.2 | Motion correction and reconstruction

The proposed 3D cMRF respiratory motion correction and reconstruction is summarized in Figure 1B. Respiratory motion of the heart is commonly monitored with diaphragmatic navigators³⁶ or self-navigation³⁷; however, these methods have generally been validated in steady-state imaging applications. Diaphragmatic navigator gating can lead to long and unpredictable scan time, since data is acquired only within a giving gating window. Moreover, the parametric encoding can deviate from the prescribed non-gated sequence (particularly for IR based sequences where T_1 is encoded across multiple shots), as data outside the gating window is rejected and re-acquired. Here, respiratory bellows are employed to be less sensitive to the variable contrasts employed in 3D cMRF, which could otherwise affect motion estimation. Respiratory bellows provide only a relative 1D signal of motion in arbitrary units, $r(t)$. In order to correct for translational respiratory motion this signal is used to drive a localized autofocus algorithm,³⁰ similar to previous work in abdominal³¹ and cardiac³⁸ imaging. This approach reconstructs a set of 3D images $\mathbf{x}_\alpha$ from all the acquired data and evaluates an image quality metric on these images to determine the optimal motion correction. To simplify the autofocus search space, we assume a linear relationship between the bellows signal and the respiratory motion of the heart, similar to previous works.^{31,38} Motion estimation is performed for each spatial dimension sequentially. Initially a set of $\alpha r(t)$ scaled respiratory bellows signals are considered. A corresponding bank of translationally corrected images $\mathbf{x}_\alpha$ is obtained by reconstructing k -space translationally corrected with $\alpha r(t)$ (using the inverse non-uniform Fourier transform). Following, the optimal scaling $\hat{\alpha}$ (which determines the estimated respiratory translational motion in millimeters) is obtained by solving $\hat{\alpha} = \text{argmin}_\alpha H(\mathbf{x}_\alpha)$. The localized gradient entropy $H(\mathbf{x}_\alpha)$ is given by $H(\mathbf{x}_\alpha) = - \sum_i h_\alpha(\mathbf{x}_\alpha(i)) \log_2 h_\alpha(\mathbf{x}_\alpha(i))$, where h_α is the normalized spatial gradient and $\mathbf{x}_\alpha(i)$ is the i th pixel intensity.³¹ The local gradient entropy is computed around a small region of interest, manually selected around the heart for each subject. The resulting optimal scaling for each dimension is used for global translation motion correction (ie corresponding phase shifts in k -space) prior to MRF reconstruction.

Although MRF initially used zero-filled reconstructions,²² it has been shown that some aliasing artefacts can propagate into the parametric maps for highly accelerated acquisitions such as those required in cMRF. More recently it has been shown that advanced reconstructions of the MRF time-series can improve the resulting T_1/T_2 estimates.^{32,39–43} In addition to parallel imaging,^{44,45} subspace modelled reconstructions^{41,42} and compressed sensing regularization^{32,43,46} have been applied to MRF reconstruction, improving accuracy and precision. For 3D cMRF, we use a low-rank inversion⁴¹ (LRI) regularized with a high-dimensionality undersampled patch based reconstruction³² (HDPROST). The LRI-HDPROST reconstruction solves the following problem:

$$\mathcal{L}(\hat{\mathbf{x}}, \hat{\mathcal{T}}_b) := \text{argmin}_{\mathbf{x}, \mathcal{T}_b} \frac{1}{2} \|\mathbf{A}\mathbf{U}_R \mathbf{F} \mathbf{C} \mathbf{x} - \mathbf{k}'\|_2^2 + \lambda \sum_b \|\mathcal{T}_b\|_* \text{ s.t. } \mathcal{T}_b = \mathbf{P}_b(\mathbf{x}) \quad (2)$$

where $\mathbf{A}$, $\mathbf{U}_R$, $\mathbf{F}$ and $\mathbf{C}$ are sampling, temporal compression (obtained from a truncated singular value decomposition of the MRF dictionary), non-uniform fast Fourier transform and coil sensitivity operators; $\mathbf{P}_b$ constructs a 3D local tensor $\mathcal{T}_b$ around voxel b by concatenating local (within a patch), non-local (between similar patches) and contrast (in the singular value domain) voxels along each dimension; $\mathbf{x}$ are the singular images reconstructed and $\mathbf{k}'$ is the translationally corrected k -space. The problem above was solved via the alternating direction method of multipliers (ADMM)⁴⁷; additional details can be found in Reference 32.

2.3 | Simulations

The sensitivity of the proposed sequence to variable heart rates was investigated in simulations. Extended phase graphs (EPGs)^{48,49} were employed to simulate the response of the magnetization to a sequence of 18 heartbeats, corresponding to a slice encoding (as depicted in Figure 1A). Four RR intervals were considered for the simulations: RR = [1500, 1000, 750, 600] ms (corresponding to [40, 60, 80, 100] beats per minute (bpm)). In each case, the RR intervals were further perturbed by random RR variations drawn for a Gaussian distribution of zero mean and standard deviation of [50, 300] ms. Finally, each simulated fingerprint was corrupted by Gaussian noise of zero mean and standard deviation of [0.05, 0.10, 0.20, 0.30] $\times D_m$, where D_m is the maximum absolute value of the dictionary. The simulated dictionary focused on tissues around the myocardium, considering the following values: T_1 = [700:5:1500] ms and T_2 = [5:0.5:90] ms, resulting in 27 531 fingerprints in total and a simulation time of approximately 5 h.

The signal-to-noise ratio (SNR) sensitivity of the proposed flip angle pattern was preliminarily investigated in a small simulation based on one representative subject. Ground-truth T_1 , T_2 and M_0 maps (obtained from in vivo 3D cMRF) were used to simulate cMRF acquisitions with three different flip angle patterns: (1) fixed flip angle of 5°, (2) variable flip angle in the range 5–10° (as used for phantom and in vivo data acquisition) and (3) fixed flip angle of 10°. Simulated acquisition parameters were the same as described in the following sections for phantom and data acquisition. The simulated MRF time-point images were undersampled with the same spiral trajectory and coil sensitivities as obtained from in vivo data. Zero-mean white Gaussian noise was added with a standard deviation of 2% of the maximum absolute dictionary value. This simulated MRF k -space was reconstructed without regularization (ie LRI reconstruction).

2.4 | Phantom acquisition

The proposed 3D cMRF was evaluated in a standardized phantom and in 10 healthy subjects (five males, age 30 ± 2 years) on a 1.5 T Ingenia MR system (Philips, Best, The Netherlands) using a 28-channel cardiac coil. The study was approved by the institutional review board and written informed consent was obtained from all subjects according to institutional guidelines.

A standardized T_1/T_2 phantom (T1MES)⁵⁰ was scanned with 3D cMRF with the following parameters: field of view (FOV) = $352 \times 352 \times 120$ mm³; resolution = $2 \times 2 \times 8$ mm³; 19 acquired slices (including slice oversampling of ~25%); echo time (T_E)/repetition time (T_R) = 1.25/6.80 ms; sinusoidal flip angle in the range 5–10°; gradient echo readout (gradient spoiling, ie FFE/FISP); variable density spiral sampling,⁵¹ ~35 $\times$ undersampled in the periphery of k -space (~18 $\times$ undersampled in the central 10% radius of k -space); spiral acquisition window = 3.6 ms; 30 spirals per shot; cardiac acquisition window = 204 ms; 540 time-points per slice encoding; acquisition time = 7 min. ECG information obtained from a healthy subject inside the scanner room was used to simulate heart rate variations during the phantom scan. Five 3D cMRF phantom acquisitions were performed in different sessions to investigate repeatability. 2D MOLLI, SASHA and T_2 -GraSE (parameters described below) were acquired in five transversal slice locations in a separate session. 3D cMRF was compared against 2D reference inversion recovery spin echo (IRSE) and spin echo for T_1 and T_2 , respectively. Key parameters for the IRSE included T_E/T_R = 15/15 000 ms and 15 T_1 values in the range of 50 to 5000 ms; key parameters for spin echo included eight echo times in the range of 10 to 640 ms.

2.5 | In vivo acquisition

Ten healthy subjects were scanned with the same 3D cMRF protocol as used in the phantom, in short axis orientation and with subject specific mid-diastolic triggering (determined by preceding CINE imaging). ECG and respiratory bellows signals were recorded for dictionary simulation and translational motion correction, respectively. Conventional 2D MOLLI, SASHA and T_2 -GraSE acquisitions were performed in basal, mid- and apical slices (for a total of nine breath-holds). All conventional mapping methods used FOV = 300×300 mm², resolution = 2×2 mm² and slice thickness = 8 mm. MOLLI (5(3)3 variant with beat intervals) parameters used were T_E/T_R = 1.19/2.40 ms, SENSE factor = 1.8, FA = 35° and acquisition window = 244 ms. SASHA used one infinity image and nine saturation prepared images with the following parameters: T_E/T_R = 1.19/2.40 ms; SENSE factor 1.8; FA = 70°; acquisition window = 244 ms. T_2 -GraSE used a double IR (for blood nulling) and nine echo times with the following parameters: T_E = 8.3:8.3:74.7 ms; EPI factor = 7; SENSE factor = 2.8; FA = 90°; acquisition window = 75 ms.

2.6 | Motion correction and reconstruction

Motion estimation was performed in vivo via respiratory bellows driven autofocus, as described above. The bellows signal ($r(t)$) was normalized to unity and a set of trial motion signals $ar(t)$ was obtained using α = [0 : 0.1 : 1] β ; consequently, the target motion state for correction was end-

expiration. The value of β represents the maximum expected physiological motion along a given dimension and was set to 8 mm based on a preliminary evaluation (not shown) of the data acquired in this study. Localized gradient entropy was evaluated on the data subset with T2prep for improved contrast. Preliminary results (Supporting Material Figure S6) estimated negligible motion along the slice dimension (presumably due to the 8 mm acquired resolution), and thus only in-plane motion correction was considered in this study.

All acquired data was reconstructed with LRI-HDPROST and solved with ADMM,⁴⁷ which requires three steps (iteratively): a Tikhonov regularized problem (solved via conjugate gradient (CG)), tensor denoising (via high-order singular value thresholding) and update of Lagrangian multipliers. Tensor denoising was performed slice by slice due to the anisotropy of the resolution ($2 \times 2 \times 8 \text{ mm}^3$). LRI-HDPROST used the following parameters: LRI rank $R = 6$, patch size = 4×4 , five CG iterations, six ADMM iterations, 20 similar patches, window size = 41 pixels and $\lambda = 3 \times 10^{-3}$. Coil sensitivity maps were derived from ESPIRiT⁵² using all the acquired data and density compensation functions obtained via Voronoi diagrams. Reconstruction parameters were determined experimentally by inspecting preliminary reconstructions in one subject (results not shown) and following parameters suggested in Reference³². Parametric maps were obtained via template matching in the singular value domain using a subject specific dictionary. Dictionaries were computed using EPG^{48,49} for each acquired dataset based on the implementation by Weigel.⁴⁸ The following values were considered: $T_1 = [200:30:900, 900:20:1200, 1200:30:1400, 1400:50:2000]$ ms and $T_2 = [20:1:60, 60:5:100, 100:20:300]$ ms. No slice profile, B_1 imperfections, magnetization transfer (MT) or $T_{1\rho}/T_{2\rho}$ effects were considered in the dictionary generation. Standardized phantom reference T_1 and T_2 values were also included in the phantom dictionary. Full 3D cMRF reconstruction took approximately 10 h, including 3 h for dictionary generation, 20 min for motion estimation and 6.5 h for LRI-HDPROST reconstruction on a Linux workstation with 12 Intel Xeon X5675 processors (3.07 GHz) and 200 GB RAM.

2.7 | Image analysis

Left ventricular myocardial T_1 and T_2 values were evaluated in regions of interest defined by the American Heart Association's (AHA's) 16-segment model.⁵³ 3D cMRF parametric maps were interpolated to $1 \times 1 \times 4 \text{ mm}^3$, for a total of 38 slices (2D reference methods were correspondingly interpolated to $1 \times 1 \text{ mm}^2$) using cubic interpolation. 3D cMRF slices corresponding to the basal, mid- and apical slices in the conventional 2D acquisitions were manually selected for analysis and comparison. The mean and coefficient of variation (CoV) over all subjects were evaluated for each of these slice positions, for T_1 and T_2 . Segments where the myocardium was not well depicted (eg due to remaining cardiac motion, respiratory motion or field inhomogeneities) were excluded from analysis. These included three segments for MOLLI and 20 segments for SASHA (out of 160 segments), primarily in apical and/or inferior regions. No segments were excluded for the proposed 3D cMRF.

3 | RESULTS

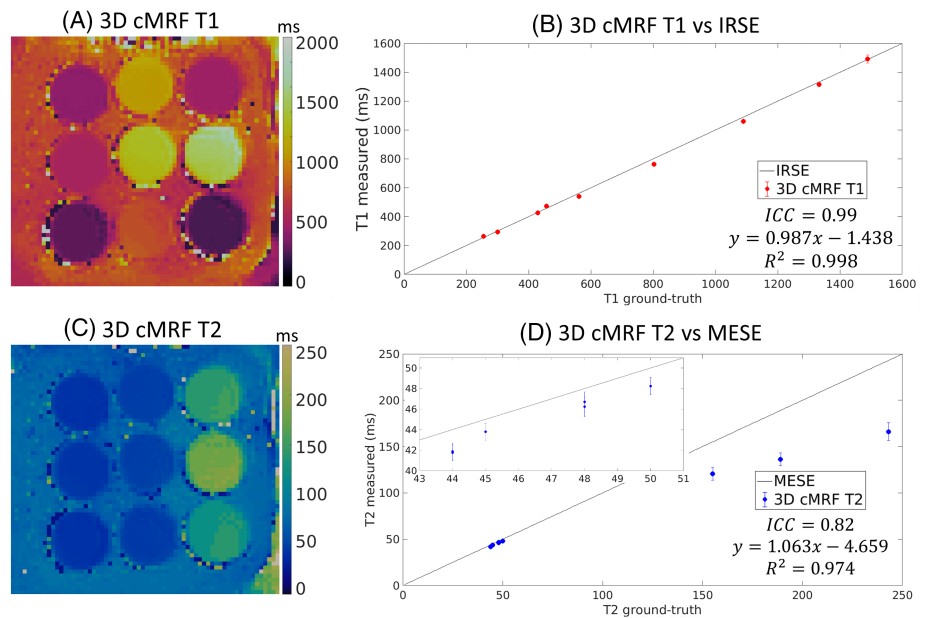
3.1 | Simulations

No significant variations of the (absolute) error in T_1 and T_2 were found when comparing RR intervals between 600 and 1500 ms (T_1 error increased by approximately 4.5 ms and T_2 error decreased by approximately 0.7 ms). No consistent bias was observed (average T_1 bias = -0.5 ms, average T_2 bias = -0.04 ms). The largest effect on the measured T_1 and T_2 error was due to the fingerprint noise considered (ranging from 5 to 30% of the maximum signal value), causing error variations of about 10–55 ms in T_1 and about 1.0–5.5 ms in T_2 . Plots showing the T_1 and T_2 errors as a function of heartrate are depicted in Supporting Material Figure S1. Simulated experiments on the choice of flip angle are shown in Supporting Material Figure S7. While all three flip angle patterns presented similar accuracy, an increase in standard deviation was observed for a fixed flip angle of 5° .

3.2 | Phantom

T_1 and T_2 values for the proposed 3D cMRF in the phantom were found to be in agreement with reference spin echo values. A slight negative bias in short T_2 (<100 ms) and a considerable negative bias for long T_2 (>100) was observed (Figure 2). Normalized errors in the phantom vials (in the format [minimum, mean, maximum]) were [0.2, 2.9, 5.1]%, [2.6, 3.8, 5.1]% and [22.1, 27.5, 31.6]% for (all) T_1 , short T_2 (<100 ms) and long T_2 , respectively. Normalized errors for MOLLI, SASHA and T_2 -GraSE were 5.5%, 2.3% and 1.8%, respectively. The CoV over five repeated phantom experiments (as a surrogate for repeatability) was 0.9% and 1.9% for T_1 and short T_2 , respectively. Slice variability was investigated in the phantom, resulting in an inter-slice CoV of 1.7% and 2.5% for T_1 and short T_2 , respectively. Larger CoVs were generally observed in edge slices,

FIGURE 2 T_1 and T_2 maps for the T1MES phantom using 3D cMRF over five scan sessions. A, One representative slice of the 3D cMRF T_1 map for the phantom. B, T_1 phantom values in comparison with reference IRSE. C, One representative slice of the 3D cMRF T_2 map for the phantom. D, T_2 phantom values in comparison with reference spin echo. Linear fit coefficients, adjusted coefficients of determination (R^2) and intra-class correlation coefficients (ICCs) are shown in the corresponding plots (computed with all vials for T_1 ; computed with only vials where $T_2 < 100$ ms for T_2). Error bars denote the standard deviation of the measurements over five scan sessions



particularly for T_2 . Corresponding slice variabilities for 2D MOLLI, SASHA and T_2 -GraSE were 0.6%, 0.7% and 2.2%, respectively. Plots showing repeatability and slice variability for phantom vials with short T_2 are shown in Supporting Material Figures S2 and S3 for T_1 and T_2 , respectively. Representative T_1 and T_2 maps obtained with 3D cMRF, 2D MOLLI, 2D SASHA and 2D T_2 -GraSE are depicted in Supporting Material Figure S4, revealing comparable quality between 3D cMRF and corresponding conventional methods.

3.3 | In vivo

3D cMRF was successfully acquired and reconstructed in all healthy subjects; the cohort's average heartrate was 61 ± 10 bpm; the cohort's acquisition time was 6.9 ± 1.1 min. The proposed 3D cMRF produced maps comparable to those of conventional 2D MOLLI, SASHA and T_2 -GraSE, as seen in representative subject A (Figure 3). Myocardium depiction is similar across different maps, except in apical slices, where MOLLI and especially SASHA present more artefacts (primarily at the inferolateral segment). Whole-heart T_1 and T_2 maps were obtained with 3D cMRF as seen in representative subject B (Figures 4 and 5, respectively). Myocardium and papillary muscles are well defined for all slices in the co-registered T_1 and T_2 maps obtained with 3D cMRF. T_1 measurements with the proposed 3D cMRF were generally higher than those with MOLLI and slightly lower than those with SASHA; 3D cMRF T_2 measurements were generally lower than those with T_2 -GraSE. The mean $\pm$ standard deviation of the mean over the subject cohort is depicted in the AHA 16-segment model shown in Figure 6A (as a surrogate for accuracy). 2D MOLLI, 2D SASHA and 3D cMRF T_1 values (mean $\pm$ standard deviation over all segments) were 1054 ± 19 ms, 1146 ± 20 ms and 1093 ± 24 ms, respectively. Corresponding 2D T_2 -GraSE and 3D cMRF T_2 values were 51.8 ± 1.6 ms and 44.6 ± 2.0 ms, respectively. Parametric values generally decreased from the septal to the lateral segments, with higher variations observed in 3D cMRF. In the format [mean septal, mean left ventricle (LV), mean lateral] the values for MOLLI, SASHA, 3D cMRF T_1 , T_2 -GraSE and 3D cMRF T_2 were [1065, 1054, 1040] ms, [1140, 1146, 1144] ms, [1113, 1093, 1068] ms, [52.3, 51.8, 50.7] ms and [46.5, 44.6, 42.7] ms, respectively. The CoV $\pm$ standard deviation of CoV over the subject cohort is shown in the AHA 16 segment model in Figure 6B (as a surrogate for precision). Corresponding measured CoVs for MOLLI, SASHA and 3D cMRF T_1 values were $7.6 \pm 1.6\%$, $12.1 \pm 2.7\%$ and $5.8 \pm 0.8\%$, respectively. For T_2 -GraSE and 3D cMRF the measured T_2 values were $10.5 \pm 1.4\%$ and $11.7 \pm 1.6\%$, respectively. Septal T_1 and T_2 values over basal, mid- and apical slices revealed slightly higher slice variations for 3D cMRF relative to MOLLI and T_2 -GraSE (Figure 7). Specifically, the septal slice standard deviation was 34.8 ms, 44.3 ms and 35.1 ms for MOLLI, SASHA and 3D cMRF T_1 , respectively, and 2.53 ms and 3.01 ms for T_2 -GraSE and 3D cMRF T_2 , respectively. Corresponding analysis in the lateral wall revealed standard deviations of 27.2 ms, 51.9 ms and 40.1 ms for MOLLI, SASHA and 3D cMRF T_1 , respectively, and 2.62 ms and 2.95 ms for T_2 -GraSE and 3D cMRF T_2 , respectively (Supporting Material Figure S5). Bland-Altman analysis was performed, where all measurements were within the 95% limits of agreement, with the exception of two cases in 3D cMRF versus MOLLI and one case for 3D cMRF T_2 versus T_2 -GraSE (Figure 8). When compared with MOLLI, 3D cMRF T_1 had a mean bias of 38.2 ms with 95% confidence interval (CI) of $[-4.6, 81.1]$ ms; compared with SASHA, 3D cMRF T_1 results in a mean bias of -54.5 ms and CI of $[-119.8, 10.9]$ ms. Comparing 3D cMRF T_2 with T_2 -

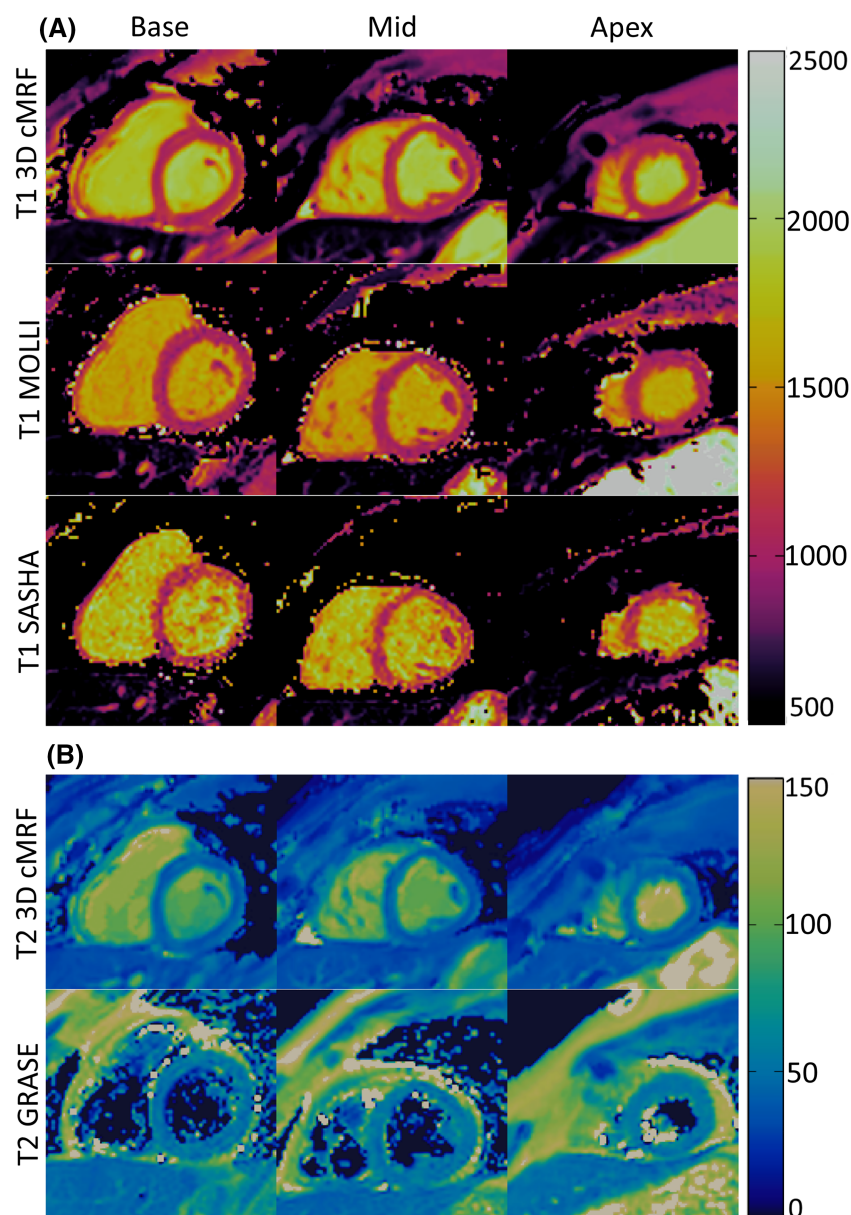


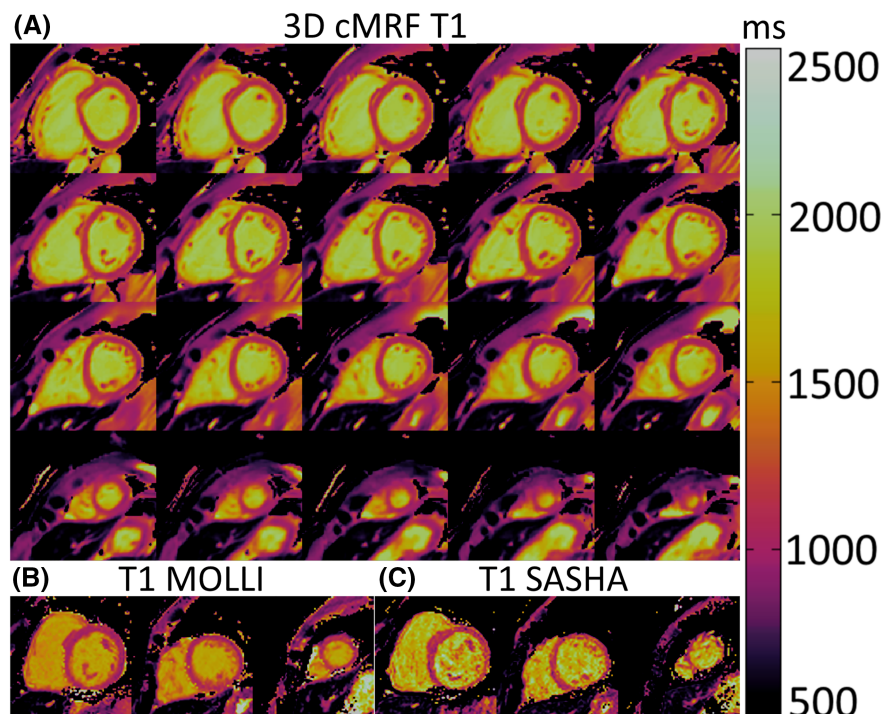
FIGURE 3 3D cMRF T_1 , 2D MOLLI, 2D SASHA, 3D cMRF T_2 and 2D T_2 -GraSE in three slices for representative subject A (RR interval = 930 ± 49 ms)

GraSE revealed a mean bias of -7.3 ms with a 95% CI of $[-11.2, -3.4]$ ms. Estimated motion amplitudes with 3D cMRF in the subject cohort (in the format [minimum, mean, maximum]) were $[2.1, 4.2, 8.3]$ mm. Figure 9 compares the proposed 3D cMRF with and without respiratory motion correction for subject C (~ 72 bpm, 8.3 mm motion amplitude), where residual blurring of the myocardium and papillary muscles is observed in the absence of translation motion correction. 3D translation motion correction was investigated in a preliminary study; however, no substantial differences were observed (Supplementary Material Figure S6). Key statistical results are summarized in Table 1.

4 | DISCUSSION

A framework for 3D free-breathing cMRF was developed and evaluated, showing comparable performance with 2D MOLLI, SASHA and T_2 -GraSE mapping techniques. In contrast to conventional 2D approaches, 3D cMRF does not require breath-holds, achieving whole-heart coverage and providing simultaneous and co-registered T_1 and T_2 parameter maps from a single scan. This approach helps streamline myocardial tissue

FIGURE 4 A, Whole-heart T_1 mapping (20 short-axis slices) produced with 3D cMRF for representative subject B (RR interval = 1069 ± 62 ms). B, C, Corresponding basal, mid- and apical slices for MOLLI (B) and SASHA (C)



characterization, potentially improving the experience of the radiographer (fewer scans to plan, higher throughput), the patient (fewer breath-holds, greater comfort) and the cardiologist (co-registered whole-heart maps, facilitated and comprehensive analysis).

3D cMRF T_1 values were generally higher than those of MOLLI (mean bias of +38 ms) and lower than those of SASHA (mean bias of -55 ms), which has also been observed in previous 2D cMRF studies.^{27,54} There are several confounding factors that may account for these differences,

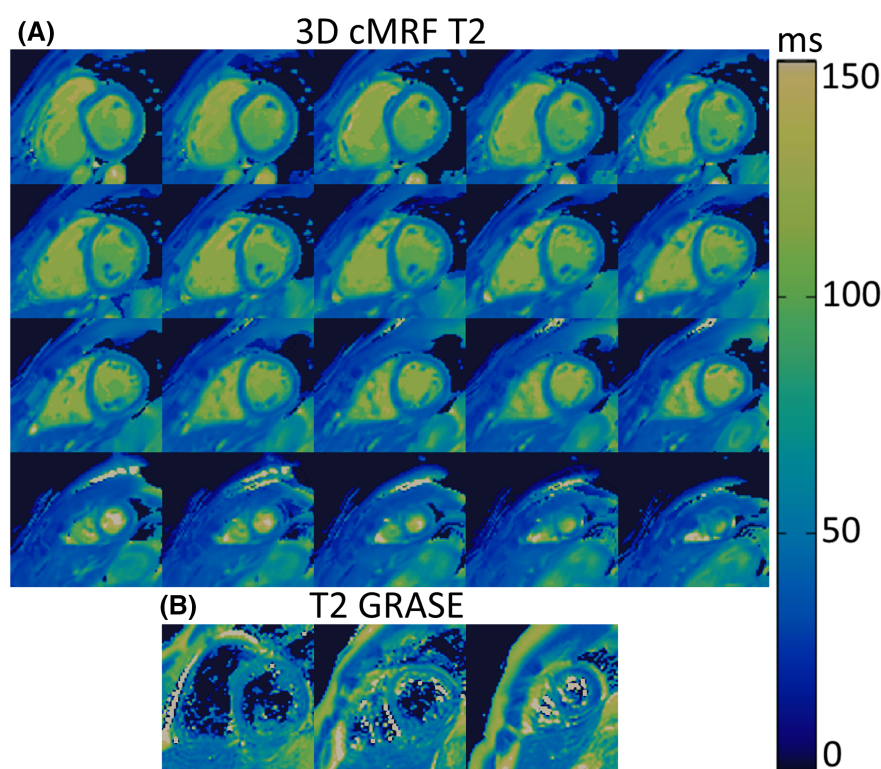


FIGURE 5 A, Whole-heart T_2 mapping (20 short-axis slices) produced with 3D cMRF for representative subject B (RR interval = 1069 ± 62 ms). B, Corresponding basal, mid- and apical slices for T_2 -GrASE

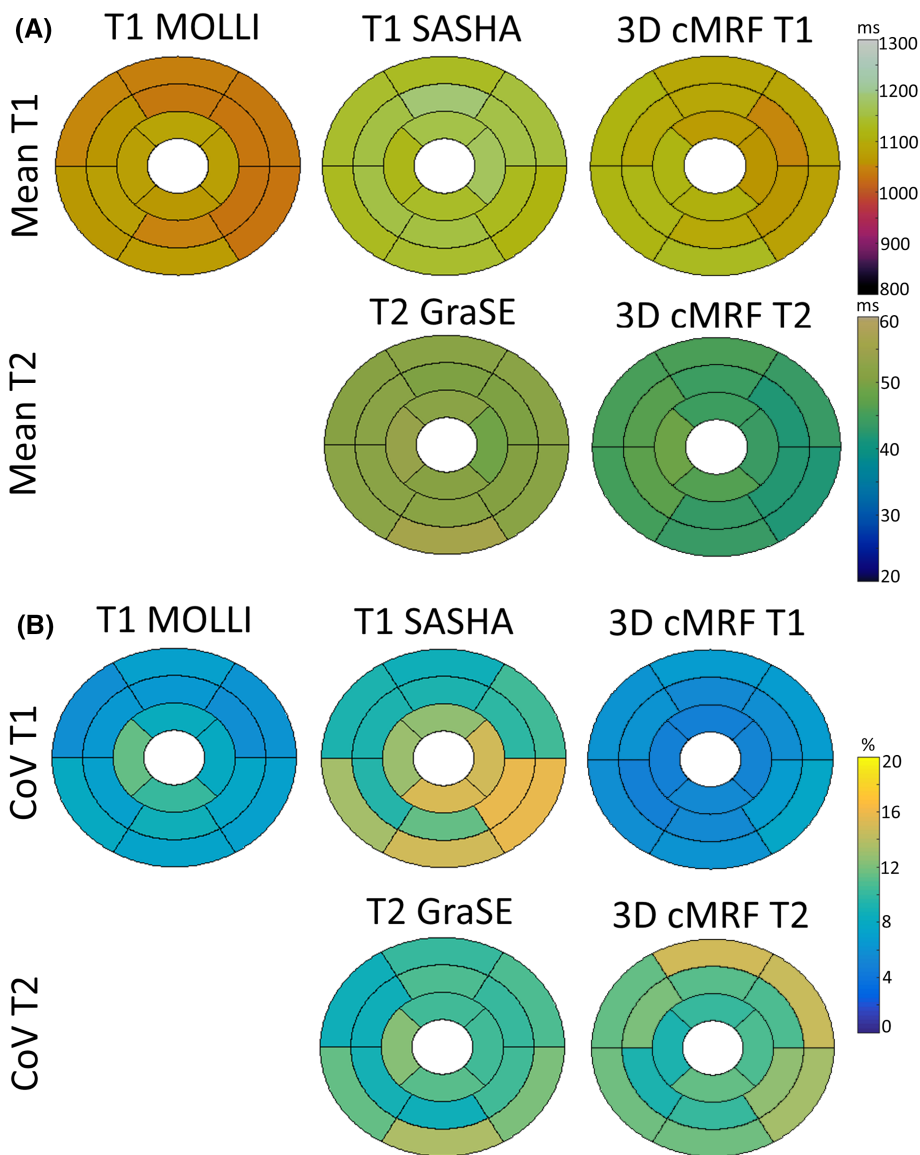
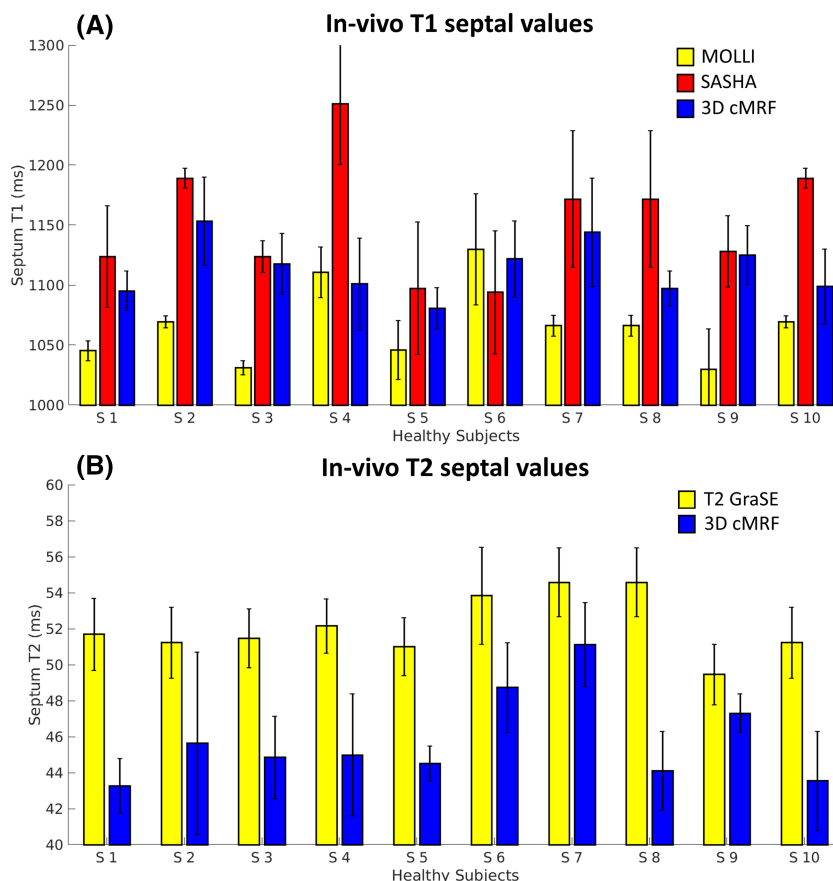


FIGURE 6 16-segment AHA bull's-eye plot for the mean and the CoV for 2D MOLLI, 2D SASHA, 2D T_2 -GraSE and 3D cMRF T_1 and T_2

such as T_2 dependences, partial volume and B_1 .¹² In particular, lack of magnetization transfer⁵⁵ in the current MRF model may account for the underestimation bias relative to SASHA. Similarly, 3D cMRF T_2 values were generally lower than T_2 -GraSE (mean bias -7.3 ms), also in agreement with previous studies in two dimensions.⁵⁶ 2D cMRF studies comparing against T2prep-bSSFP and T2prep-FLASH (fast low angle shot) have also reported an underestimation bias.^{27–29} T2prep methods and GraSE based methods have shown a negative and positive bias relative to multi-echo spin echo,⁵⁷ respectively. Underestimation was observed for high T_2 values (not relevant for myocardial characterization), likely due to the absence of long T2prep modules (to encode high T_2 values) in the proposed sequence. T_2 underestimation has been previously reported in brain,⁵⁸ abdominal⁵⁹ and cardiac⁶⁰ MRF, and confounding factors that may account for these differences should be further investigated in the future. Coefficients of variation were slightly lower for 3D cMRF T_1 than for MOLLI (and more so than for SASHA); for 3D cMRF T_2 these values were slightly higher (within one standard deviation) than for T_2 -GraSE. In all cases CoVs were measured on cubic interpolated data: the smoothness effect of the interpolation may lead to small reductions in CoV; however, the effect is consistent for all methods. A general decrease of parameter values from the septal to the lateral wall was observed with 2D MOLLI, T_2 -GraSE and more so with 3D cMRF for both T_1 and T_2 . Some slice variabilities were also observed with 3D cMRF; these were slightly higher than with MOLLI and T_2 -GraSE. These variations are likely due to B_0 and B_1 field inhomogeneities not accounted for in the respective models.

The proposed 3D cMRF achieves T_1 and T_2 encoding with IR pulses and T_2 preparation pulses, similar to the original 2D cMRF.²⁷ Here, sequence design was made heuristically, guided by results from previous studies (eg low flip angles to reduce B_1 sensitivity) in 2D cMRF.²⁸

FIGURE 7 A, T_1 values in the septum in each healthy subject (labelled from S1 to S10) for MOLLI, SASHA and 3D cMRF T_1 . B, Corresponding T_2 values for T_2 -GraSE and 3D cMRF T_2 . Reported values are averaged over basal, mid- and apical slices; error bars correspond to inter-slice standard deviations



Preliminary simulations in this work suggest that the flip angle pattern could affect precision at low flip angles and/or low SNR; however, further studies comparing variable and fixed flip angle patterns should be investigated. The proposed sequence differs from previous cMRF⁶¹ by separating IR and T2prep pulses (instead of interleaving them). This approach is expected to improve the dynamic range of the T_1 encoding at the expense of some SNR in T_2 encoding; however, it remains a heuristic solution. Comprehensive analysis on optimal sequence design for conventional (non-triggered) MRF has been developed previously.^{62–64} A similar analysis for (triggered) cMRF, possibly considering B_0/B_1 sensitivities, would be of interest and will be investigated in future studies. Optimal sequences would be expected to lead to reduced scan times and/or improved parametric maps. Fat signal can create strong undersampling artefacts and has been shown to bias T_1 estimation,⁶⁵ in addition to introducing blurring artefacts due to spiral readouts (no spiral blurring was considered in the proposed framework). Moreover, translational motion correction can introduce artefacts originating from (incorrectly motion corrected) static fat tissue.⁶⁶ A SPIR pulse is used in this framework for fat suppression, but alternative approaches such as water selective excitations⁶⁷ could be considered for similar effect. Corrections using more complex respiratory motion models can also help in this regard.⁶⁶

This study has several limitations. 3D cMRF has a predictable scan time of ~ 7 min, and, while adequate for clinical deployment, future work should consider additional strategies to reduce scan time. Higher resolution will also be desirable in the future and alternative 3D non-Cartesian trajectories could be considered, as recently proposed for T_1/T_2 mapping.⁶⁸ Although 3D cMRF was compared against three conventional approaches, it was not compared against T2prep-bSSFP at this time, due to unavailability on our system. As a proof of concept, no patients were included in this study, but should be considered in future studies. No in vivo repeatability was investigated in this study, primarily due to the long scan times associated with the experiment. Some residual blurring was observed with 3D cMRF, which could be primarily due to spiral (off-resonant) blurring and residual respiratory or cardiac (due to acquisition window or mistrigging) motion. Residual cardiac motion within the acquisition window of 204 ms could potentially lead to artificially enlarged wall thickness or reduced T_2 values⁶⁹; residual respiratory motion could occur due to errors in the bellows measurements (eg drift).⁷⁰ Minor blurring can also arise as an artefact of the undersampled reconstructions performed. SPIR modules will likely decrease the method's sensitivity to detect fat infiltration; however, 3D cMRF could potentially be combined with Dixon based readouts for simultaneous T_1 , T_2 and fat fraction estimation.⁵⁶ The proposed approach relies on a respiratory bellows driven autofocus algorithm to estimate the beat-to-beat translational motion of the heart. However, residual motion artefacts could also occur due to

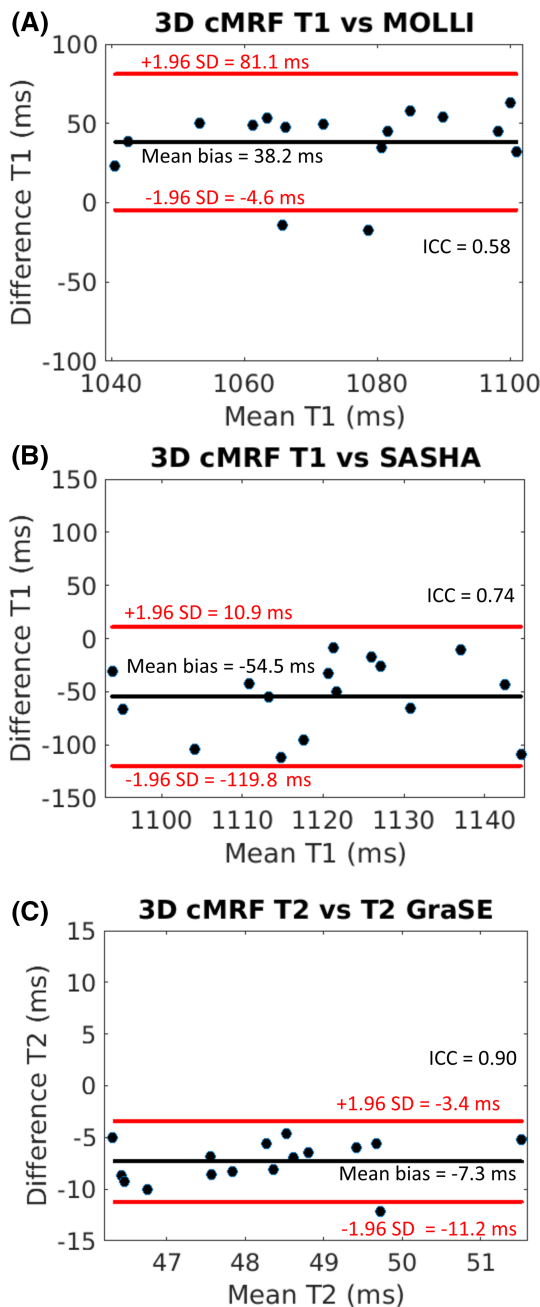


FIGURE 8 Bland-Altman plots comparing 3D cMRF T_1 versus MOLLI (A), 3D cMRF T_1 versus SASHA (B) and 3D cMRF T_2 versus T_2 -GRASE (C). ICCs are shown in each plot

the simplified (translational) motion model. Moreover, as the slice thickness is reduced, through-plane motion correction will increasingly be more important to avoid errors in T_1 and T_2 .^{71,72} Future work will consider generalized elastic motion compensated reconstructions to correct the remaining non-rigid components of motion.⁷³ A major limitation of the current approach, however, is the reconstruction time of approximately 10 h. 3D cMRF requires subject specific dictionaries and long iterative reconstructions. While patient tailored dictionaries are expected to grant higher heart rate insensitivity, they are also associated with long computation times (~ 3 h in this study) which can impose limitations on dictionary resolution. A GPU implementation of the method will considerably cut computational times.⁷⁴ In addition, recent developments in deep learning indicate that dictionary computation,⁷⁵ image reconstruction⁷⁶ and template matching⁷⁷ computational demands could be reduced by orders of magnitude, all of which could be combined with 3D cMRF to considerably reduce computational times. With the current approach, 3D cMRF is limited to simultaneous T_1/T_2 and has some residual biases in these measurements. cMRF can potentially be extended to map any combination of parameters and consider any combination of model corrections; however, dictionaries increase exponentially (in addition to increased acquisition and reconstruction times).⁷⁸ Deep learning solutions could also play a role in enabling acceptable computational times for truly multi-parametric fingerprinting (eg T_1 , $T_{1\rho}$, T_2 , T_2^* , B_0 , B_1 , MT and diffusion) from a single scan and should be investigated as future work.

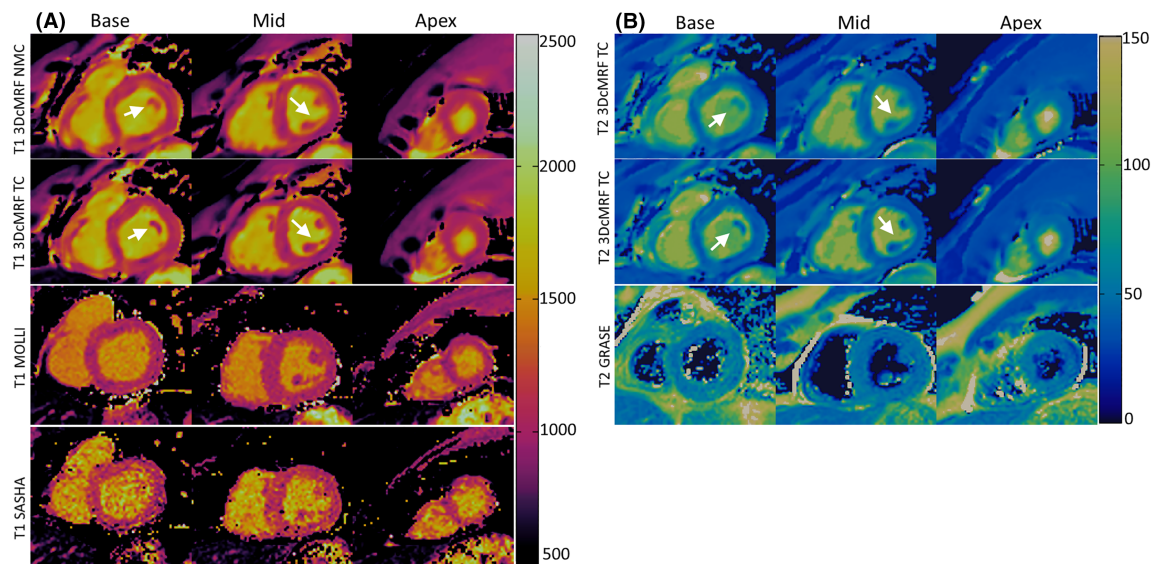


FIGURE 9 3D cMRF T_1 and T_2 parameter maps with no motion correction (NMC) and the proposed translation correction (TC), along with 2D MOLLI, SASHA and T_2 -GrASE for representative subject C (RR interval = 870 ± 55 ms). Blurring and ghosting motion artefacts in T_1 and T_2 maps are reduced after translation correction (arrows)

TABLE 1 Summary of the main statistical results. NRMSE, normalized root mean square error

Phantom	NRMSE (%)	Inter-scan repeatability CoV (%)	Inter-slice variability CoV (%)
3D cMRF T_1	2.9	0.9	1.7
MOLLI	5.5	N/A	0.6
SASHA	2.3	N/A	0.7
3D cMRF T_2	3.8	1.9	2.5
T_2 -GraSE	1.8	N/A	2.2
In vivo	LV value (ms)	LV spatial variability CoV (%)	Inter-slice septal variability (ms)
3D cMRF T_1	$1,093 \pm 24$	5.8 ± 0.8	35.1
MOLLI	$1,054 \pm 19$	7.6 ± 1.6	34.8
SASHA	$1,146 \pm 20$	12.1 ± 2.7	44.3
3D cMRF T_2	44.6 ± 2.0	11.7 ± 1.6	3.01
T_2 -GraSE	51.8 ± 1.6	10.5 ± 1.4	2.53

5 | CONCLUSION

A novel approach for 3D free-breathing respiratory motion compensated cMRF was proposed and validated in healthy subjects. The proposed method produces co-registered T_1 and T_2 maps with whole-heart coverage in a predictable scan time of ~ 7 min. Free-breathing 3D cMRF showed similar accuracy and precision to conventional 2D breath-hold methods; however, a slight underestimation of T_1 and T_2 values with cMRF was observed when compared with 2D SASHA and T_2 -GraSE, respectively.

ACKNOWLEDGEMENTS

The authors acknowledge financial support from (1) EPSRC EP/P001009/1, (2) EPSRC EP/P032311/1, (3) Wellcome EPSRC Centre for Medical Engineering (NS/A000049/1) and (4) the Department of Health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

ABBREVIATIONS

1D, one dimensional; 2D, two dimensional; 3D, three dimensional; ADMM, alternating direction method of multipliers; AHA, American Heart Association; bpm, beats per minute; bSSFP, balanced steady-state free precession; CG, conjugate gradient; cMRF, cardiac magnetic resonance fingerprinting; CoV, coefficient of variation; ECV, extracellular volume; EPG, extended phase graph; FOV, field of view; GraSE, gradient and spin echo; HDPROST, high-dimensionality patch based reconstruction; ICC, intra-class correlation coefficient; IR, inversion recovery; IRSE, inversion recovery spin echo; LRI, low-rank inversion; LV, left ventricle; MOLLI, modified Look-Locker inversion recovery; MRF, magnetic resonance fingerprinting; NP, no preparation pulse; SASHA, saturation recovery single-shot acquisition; SNR, signal-to-noise ratio; SPIR, spectral presaturation with inversion recovery; T₂prep, T₂ preparation; T_E, echo time; T_R, repetition time.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Cruz G, Jaubert O, Qi H, et al. 3D free-breathing cardiac magnetic resonance fingerprinting. *NMR in Biomedicine*. 2020;33:e4370. <https://doi.org/10.1002/nbm.4370>