Simulated Half-Fourier Acquisitions Single-shot Turbo Spin Echo (HASTE) of the Fetal Brain: Application to Super-Resolution Reconstruction

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Abstract. Accurate characterization of *in utero* human brain maturation is critical as it involves complex interconnected structural and functional processes that may influence health later in life. Magnetic resonance imaging is a powerful tool complementary to the ultrasound gold standard to monitor the development of the fetus, especially in the case of equivocal neurological patterns. However, the number of acquisitions of satisfactory quality available in this cohort of sensitive subjects remains scarce, thus hindering the validation of advanced image processing techniques. Numerical simulations can mitigate these limitations by providing a controlled environment with a known ground truth. In this work, we present a flexible numerical framework for clinical T2-weighted Half-Fourier Acquisition Single-shot Turbo spin Echo of the fetal brain. The realistic setup, including stochastic motion of the fetus as well as intensity non-uniformities, provides images of the fetal brain throughout development that are comparable to real data acquired in clinical routine. A case study on super-resolution reconstruction of the fetal brain from synthetic motion-corrupted 2D low-resolution series further demonstrates the potential of such a simulator to optimize post-processing methods for fetal brain magnetic resonance imaging.

Keywords: Fetal brain Magnetic Resonance Imaging (MRI) · Numerical phantom · Half-Fourier Acquisition Single-shot Turbo spin Echo (HASTE) sequence · Super-Resolution (SR) reconstruction

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1 Introduction

Brain maturation involves complex intertwined structural and functional processes that can be altered by various genetic and environmental factors. As such, early brain development is critical and may impact health later in life [1–3].

Magnetic resonance imaging (MRI) may be required during pregnancy to investigate equivocal situations as a support for diagnosis and prognosis, but also for postnatal management planning [4]. In clinical routine, T2-weighted (T2w) fast spin echo sequences are used to scan multiple 2D thick slices that provide information on the whole brain volume with a good signal-to-noise ratio (SNR) while minimizing the effects of random fetal motion during the acquisition [5]. Contrary to periodic movements that can be directly related to physiological processes such as breathing or a heartbeat, and may therefore be compensated during post-processing, stochastic movements of the fetus in the womb cause various artifacts in the images and impede the repeatability of measurements [6], thus hindering retrospective motion correction. The difficulty of estimating such unpredictable movements results in the lack of any ground truth, yet necessary for the validation of new methods [7]. Post-processing approaches built on motion estimation and correction can compensate for motion artifacts. Especially, super-resolution (SR) reconstruction techniques take advantage of the redundancy between low-resolution (LR) series acquired in orthogonal orientations to reconstruct an isotropic high-resolution (HR) volume of the fetal brain with reduced intensity artifacts and motion sensitivity [8–11]. The development and validation of such advanced image processing strategies require access to large-scale data to account for the subject variability, but the number of good quality exploitable MR acquisitions available in this sensitive cohort remains relatively scarce. Therefore, numerical phantoms are an interesting alternative that offers a fully scalable and flexible environment to simulate a collection of data in various controlled conditions. As such, they make it possible to conduct accurate, robust and reproducible research studies [6,12], especially to evaluate post-processing techniques with respect to a synthetic ground truth.

In this work, we present a simulation framework for T2w Half-Fourier Acquisition Single-shot Turbo spin Echo (HASTE) of the fetal brain based on segmented HR anatomical images from a normative spatiotemporal MRI atlas of the fetal brain [4]. It relies on the extended phase graph (EPG) formalism [13,14] of the signal formation, a surrogate for Bloch equations to describe the magnetization response to various MR pulse sequences. EPG simulations are particularly relevant in the case of multiple radiofrequency pulses that are responsible for stimulated echoes [13], as in the HASTE acquisition scheme. The proposed pipeline is highly flexible and built on a realistic setup that accounts for intensity non-uniformities and stochastic fetal motion. A case study on SR fetal brain MRI further explores the value of such a numerical phantom to evaluate and optimize an SR reconstruction algorithm [11,15].

2 Methods

2.1 Numerical Implementation of HASTE Acquisitions

Fig. 1 provides an overview of the workflow implemented in MATLAB (MathWorks, R2019a) to simulate clinical HASTE acquisitions of the fetal brain. We have developed this numerical phantom with the idea of keeping the framework as general as possible to enable users a large flexibility in the type of simulated images. As such, multiple acquisition parameters can be set up with respect to the MR contrast (effective echo time, excitation/refocusing pulse flip angles, echo spacing, echo train length), the geometry (number of 2D slices, slice orientation, slice thickness, slice gap, slice position, phase oversampling), the resolution (field-of-view, matrix size), the resort to any acceleration technique (acceleration factor, number of reference lines), as well as other settings related to the gestational age (GA) of the fetus, the radiofrequency transmit field inhomogeneities, the amplitude of random fetal motion in the three main directions, and the SNR. The entire simulation pipeline is described in detail in the following.

Fetal Brain Model and MR Properties. Our numerical phantom is based on segmented 0.8-mm-isotropic anatomical images (Fig. 1-i) from the normative spatiotemporal MRI atlas of the developing brain built by Gholipour and colleagues from normal fetuses scanned between 19 and 39 weeks of gestation [4]. Due to the lack for ground truth relaxometry measurements in the fetal brain, all thirty-four segmented tissues are merged into three classes: gray matter, white matter and cerebrospinal fluid (Fig. 1-ii and Table 1). Corresponding T1 and T2 relaxation times at 1.5 T [16–20] are assigned to these anatomical structures to obtain reference T1 and T2 maps, respectively (Fig. 1-iii).

Table 1. Classification of segmented brain tissues [4] as gray matter, white matter and cerebrospinal fluid.

Gray matter	Amygdala, Caudate, Cortical plate, Hippocampus, Putamen, Subthalamic nuclei, Thalamus
White matter	Cerebellum, Corpus callosum, Fornix, Hippocampal commissure, Intermediate zone, Internal capsule, Midbrain, Miscellaneous, Subplate, Ventricular zone
Cerebrospinal fluid	Cerebrospinal fluid, Lateral ventricles

Intensity Non-Uniformities (INU). Non-linear slowly-varying INU fields are based on BrainWeb estimations from real scans to simulate T2w images [21]. The available 20% INU version is resized to fit the dimensions of the atlas images and normalized by 1.2 to provide multiplicative fields from 0.8 to 1.2 over the brain area.

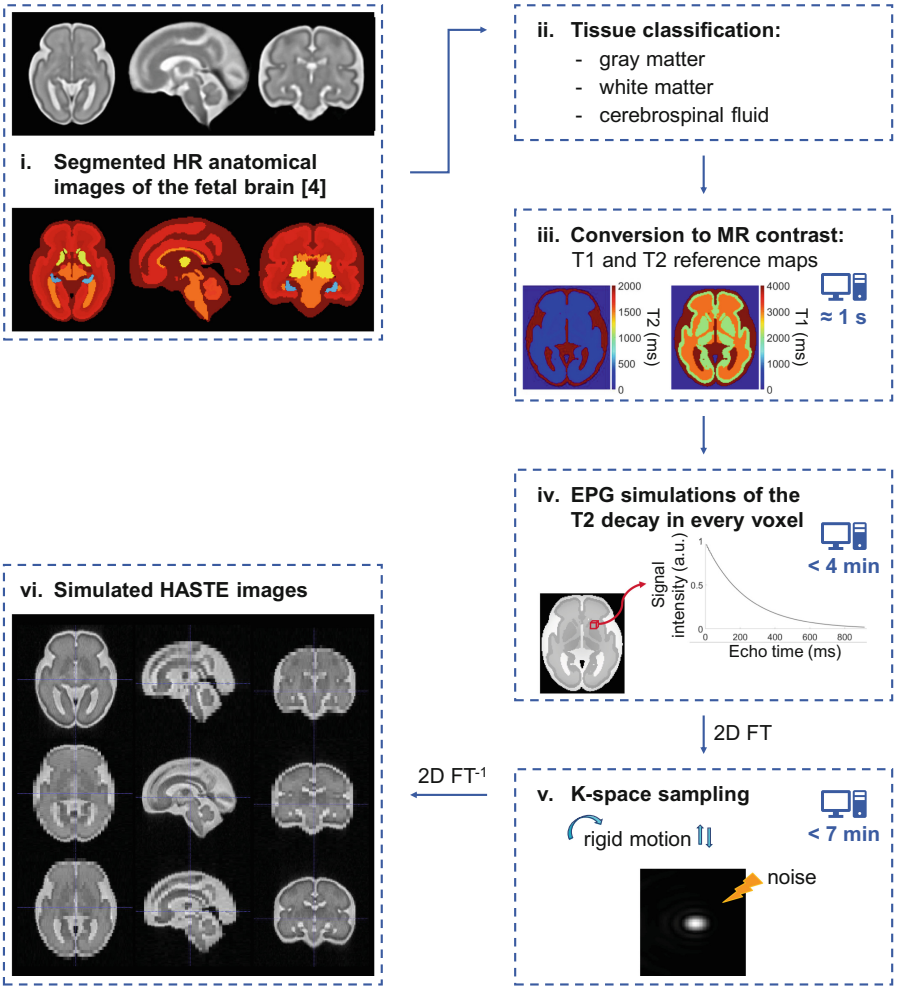

Fig. 1. Workflow for simulating HASTE images of the fetal brain (i) from segmented HR anatomical MR images [4], illustrated for a fetus of 30 weeks of GA. (ii) Brain tissues are organized into gray matter, white matter and cerebrospinal fluid. (iii) Anatomical structures are converted to the corresponding MR contrast to obtain reference T1 and T2 maps of the fetal brain at 1.5 T. (iv) The T2 decay over time is computed in every brain voxel by the EPG algorithm and subsequently used (v) to sample the Fourier domain of the simulated HASTE images of the moving fetus. After the addition of noise to match the SNR of real clinical acquisitions, (vi) HASTE images of the fetal brain are eventually recovered by 2D inverse Fourier transform.

EPG Formalism. From the HASTE sequence pulse design, the T1 and T2 maps of the fetal brain and the realistic INU, the EPG algorithm [14] computes the T2 decay in every voxel of the anatomical images over each echo train

(Fig. 1-iv). The resulting 4D matrix that combines information about both the anatomy and the magnetic relaxation properties of the fetal brain is hereafter referred to as the T2 decay matrix.

K-Space Sampling and Image Formation. The T2 decay matrix is Fourier-transformed in the spatial dimensions and subsequently used for k-space sampling of the simulated HASTE images. For a given echo time (TE), at most one line from the associated Fourier domain of the T2 decay matrix is used, with the central line corresponding to the effective TE. Forty-two reference lines are consecutively sampled around the center of k-space. Beyond, one line out of two is actually needed to simulate an acceleration factor of two resulting from the implementation of GRAPPA interpolation in the clinical HASTE acquisitions. As a first approximation, these sampled lines are copied to substitute the missing lines. As HASTE is a partial Fourier imaging technique, the properties of Hermitian symmetry in the frequency domain are used to fill the remaining unsampled part of k-space. While intra-slice motion can be neglected, inter-slice random 3D translation and rotation of the fetal brain are implemented during k-space sampling (Fig. 1-v). Complex Gaussian noise (mean, 0; standard deviation, 0.15) is also added to simulate thermal noise generated during the acquisition process and qualitatively match the SNR of clinical data. The simulated images are eventually recovered by 2D inverse Fourier transform (Fig. 1-vi).

With the aim of replicating the clinical protocol for fetal brain MRI, HASTE acquisitions are simulated in the three orthogonal orientations. Besides, the position of the field-of-view is shifted by ± 1.6 mm in the slice thickness orientation to produce additional partially-overlapping datasets in each orientation.

Fetal Motion. The amplitude of typical fetal movements is estimated from clinical data [22]. Three levels are defined accordingly for little, moderate and strong motion of the fetus. They are characterized by less than 5%, 10% and 25% of corrupted slices respectively, and simulated by a uniform distribution of $[-2, 2]$ mm, $[-3, 3]$ mm and $[-3, 3]$ mm for translation in every direction and $[-2, 2]^\circ$, $[-4, 4]^\circ$ and $[-4, 4]^\circ$ for 3D rotation respectively (Fig. 1-v).

Computational Performance. Since the addition of 3D motion during k-space sampling is expensive in computing memory, the simulations are run on 16 CPU workers in parallel with 20 GB of RAM each. In this setup and for a fetus of 30 weeks of GA whose brain is covered by twenty-five slices, the computation time to convert segmented HR images of the fetal brain to MR contrast and to run EPG simulations in every voxel of the 3D HR anatomical images is in the order of one second, respectively less than four minutes. K-space sampling takes less than seven minutes for one axial series with the different levels of motion.

2.2 Clinical Protocol

Typical fetal brain acquisitions are performed on patients at 1.5 T (MAGNETOM Sola, Siemens Healthcare, Erlangen, Germany) with an 18-channel body coil and a 32-channel spine coil at our local hospital. At least three T2w series of 2D thick slices are acquired in three orthogonal orientations using an ultra-fast multi-slice HASTE sequence (TR/TE, 1200 ms/90 ms; excitation/refocusing pulse flip angles, 90°/180°; echo train length, 224; echo spacing, 4.08 ms; field-of-view, $360 \times 360\,mm^2$; voxel size, $1.13 \times 1.13 \times 3.00\,mm^3$; inter-slice gap, 10%). The position of the field-of-view is slightly shifted in the slice thickness orientation to acquire additional data with some redundancy. In clinical practice, six partially-overlapping LR HASTE series are commonly acquired for subsequent SR reconstruction of the fetal brain.

2.3 Datasets

Six subjects in the GA range of 21 to 33 weeks were scanned at our local hospital as part of a larger institutional research protocol with written consent approved by the local ethics committee.

These clinical cases are used as representative examples of fetal brain HASTE acquisitions: the corresponding sequence parameters are replicated to simulate HASTE images of the fetal brain at various GA, and with realistic SNR. The amplitude of fetal movements in clinical acquisitions is assessed by an engineer expert in MR image analysis to ensure a similar level of motion in the simulated images. The original real cases are also used to visually compare the quality and realistic appearance of the synthetic images generated.

A 3D HR 1.1-mm-isotropic HASTE image of the fetal brain is simulated without noise or motion to serve as a reference for the quantitative evaluation of SR reconstructions from simulated LR 1.1-mm-in-plane HASTE images.

2.4 Qualitative Assessment

Two medical doctors specialized in neuroradiology and pediatric (neuro) radiology respectively, provided qualitative assessment of the fetal brain HASTE images simulated in the GA range of 21 to 33 weeks, in the three orthogonal orientations with various levels of motion. Special attention was paid to the MR contrast between brain tissues, to the SNR, to the delineation and sharpness of the structures of diagnostic interest that are analyzed in clinical routine, as well as to characteristic motion artifacts.

2.5 Application Example: Parameter Fine-Tuning for Optimal SR Reconstruction

Implementation of SR Reconstruction. Orthogonal T2w LR HASTE series from clinical examinations, respectively simulated images, are combined into

a motion-free 3D image $\hat{\mathbf{X}}$ using the Total Variation (TV) SR reconstruction algorithm [11,15] which solves:

$$\hat{\mathbf{X}} = \arg\min_{\mathbf{X}} \frac{\lambda}{2} \sum_{kl} \| \underbrace{\mathbf{D}_{kl}\mathbf{B}_{kl}\mathbf{M}_{kl}}_{\mathbf{H}_{kl}} \mathbf{X} - \mathbf{X}_{kl}^{LR} \|^2 + \|\mathbf{X}\|_{TV}, \tag{1}$$

where the first term relates to data fidelity with k being the k-th LR series $\mathbf{X}^{LR}$ and l the l-th slice, $\|\mathbf{X}\|_{TV}$ is a TV prior introduced to regularize the solution, and λ balances the trade-off between data fidelity and regularization terms. $\mathbf{D}$ and $\mathbf{B}$ are linear downsampling and Gaussian blurring operators given by the acquisition characteristics. $\mathbf{M}$ encodes the rigid motion of slices.

Both clinical acquisitions and the corresponding simulated images are reconstructed using the SR reconstruction pipeline available in [15].

Regularization Setting. LR HASTE images of the fetal brain are simulated to mimic clinical MR acquisitions of three subjects of 26, 30 and 33 weeks of GA respectively, with particular attention to ensuring that the motion level is respected. For each subject, a SR volume of the fetal brain is reconstructed from the various orthogonal acquisitions, either real or simulated, with different values of λ (0.1, 0.3, 0.75, 1.5, 3) to study the potential of our simulation framework in optimizing the quality of the SR reconstruction in a clinical setup. A quantitative analysis is conducted on the resulting SR reconstructions to determine the value of λ that provides the sharpest reconstruction of the fetal brain with high SNR, namely the smallest normalized root mean squared error (NRMSE) with respect to a synthetic ground truth.

3 Results and Discussion

3.1 Qualitative Assessment

Fig. 2 illustrates the close resemblance between simulated HASTE images of the fetal brain and clinical MR acquisitions for two representative subjects of 26 and 30 weeks of GA respectively, in terms of MR contrast between tissues, SNR, brain anatomy and relative proportions across development, as well as typical out-of-plane motion patterns related to the interleaved slice acquisition scheme. Experts in neuroradiology and in pediatric (neuro)radiology report a good contrast between gray and white matter, which is important to investigate cortex continuity and identify the deep gray nuclei as well as any migration anomaly. They also notice good SNR in the different series and report proper visualization of the main anatomical structures: the four ventricles, the corpus callosum, the vermis, the cerebellum, even sometimes the fornix. Besides, they are able to monitor the evolution of normal gyration throughout gestation. However, they point out that small structures such as the hypophyse, the chiasma, the recesses of the third ventricle, and the vermis folds that look part of the cerebellum, are

more difficult to observe. The cortical ribbon is clearly visible but quite pixelated, which is likely to complicate the diagnosis of polymicrogyria. White matter appears too homogeneous, which makes its multilayer aspect barely distinguishable, with an MR signal that is constant across GA, thus preventing physicians from exploring the myelination process throughout brain maturation. For these reasons, experts feel confident in performing standard biometric measurements on the simulated images and in evaluating the volume of white matter, but not its fine structure.

These limitations in the resemblance of the simulated HASTE images as compared to typical clinical acquisitions may be explained by the origin of the simulated images and the lack of T1 and T2 ground truth measurements, both in the multiple fetal brain tissues and throughout maturation. HASTE images are simulated from a normative spatiotemporal MRI atlas of the fetal brain [4] where representative images at each GA correspond to an average of fetal brain scans across several subjects, thus resulting in smoothing of subtle inter-individual heterogeneities, especially in the multilayer aspect of the white matter. As a first approximation because of the lack of detailed literature on the changes that result from maturation processes in finer structures of the brain, we consider average T1 and T2 relaxation times of the various fetal brain tissues labeled as gray matter, white matter or cerebrospinal fluid (see Table 1) over gestation. As a result, our simulated images may fail to capture the fine details of the fetal brain anatomy throughout development.

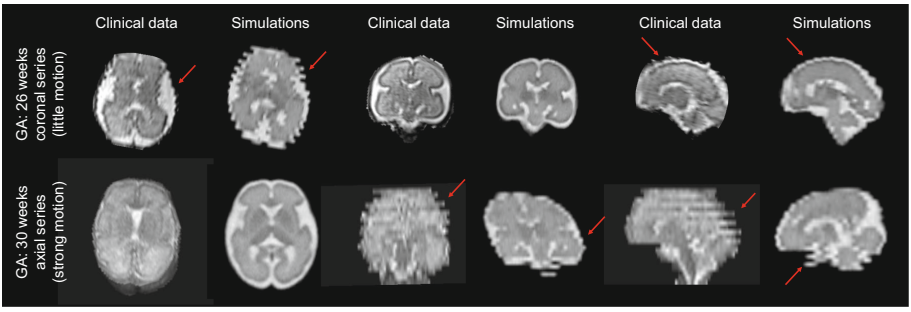

Fig. 2. Comparison between motion-corrupted clinical MR acquisitions and corresponding simulated HASTE images at two GA (26 and 30 weeks). Images are shown in the three orthogonal planes. Red arrows point out typical out-of-plane motion patterns.

3.2 Application Example: Parameter Fine-Tuning for Optimal SR Reconstruction

In fetal MRI, the level of regularization is commonly set empirically based on visual perception [8–10]. Thanks to its controlled environment, the presented framework makes it possible to adjust the parameter λ for optimal SR reconstruction with respect to a synthetic 3D isotropic HR ground truth of the fetal

brain. Of note, in-plane motion artefacts like signal drops are not accounted for in the simulation pipeline at this stage, as heavily corrupted slices are commonly removed from the reconstruction.

Figure 3 explores the quality of SR fetal brain MRI depending on the weight of TV regularization. Based on the simulations, a high level of regularization ($\lambda = 0.1$) provides a blurry SR reconstruction with poor contrast between the various structures of the fetal brain, especially in the deep gray nuclei and the cortical plate. In addition, the cerebrospinal fluid appears brighter than in the reference image. A low level of regularization ($\lambda = 3$) leads to a better tissue contrast but increases the overall amount of noise in the resulting SR reconstruction. A fine-tuned regularization ($\lambda = 0.75$) provides a sharp reconstruction of the fetal brain with a high SNR and a tissue contrast close to the one displayed in the reference image. In the SR images reconstructed from clinical LR HASTE series altered by a little-to-moderate level of motion, as in the simulations, the structure of the corpus callosum and the delineation of the cortex are especially well defined for appropriate TV regularization ($\lambda = 0.75$), leading to high-SNR HR images of the fetal brain. Although the NRMSE between SR reconstructions from simulated HASTE images and the ground truth are close to each other in the three configurations studied, the error is minimal for $\lambda = 0.75$, which further supports this parameter setting for optimal SR reconstruction.

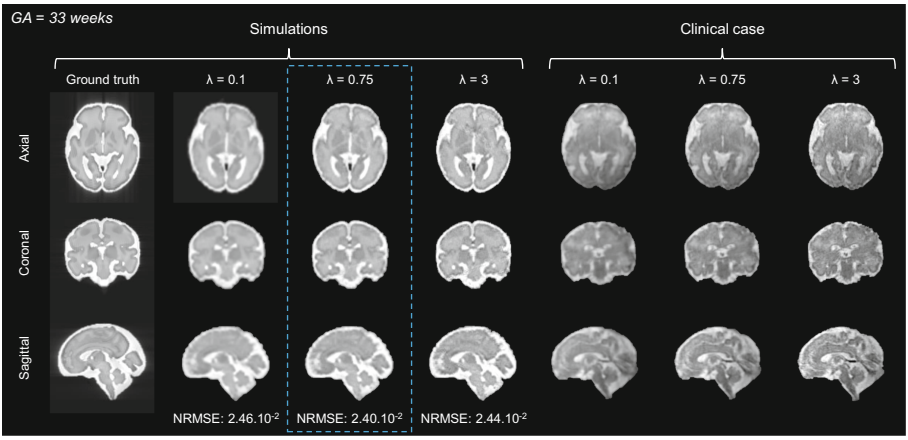

Fig. 3. Appreciation of the quality of SR reconstruction depending on the weight λ that controls the strength of the TV regularization. The potential of our framework to optimize the reconstruction quality through parameter fine-tuning in the presence of motion is illustrated for a fetus of 33 weeks of GA with three values of λ. A representative clinical case from which the synthetic HASTE images are derived is provided for comparison. The blue box highlights that the NRMSE between SR reconstructions from simulated data and a simulated 3D HR ground truth is minimal for $\lambda = 0.75$.

4 Conclusions and Perspectives

In this work, we present a novel numerical framework that simulates as closely as possible the physical principles involved in HASTE acquisitions of the fetal brain, with great flexibility in the choice of the sequence parameters and anatomical settings, resulting in highly realistic T2w images of the developing brain throughout gestation. Thanks to its controlled environment, this numerical phantom makes it possible to explore the optimal settings for SR fetal brain MRI according to the image quality of the input motion-corrupted LR HASTE series. It also enables quantitative assessment of the robustness of any SR reconstruction algorithm depending on various parameters such as the noise level, the amplitude of fetal motion in the womb and the number of series used for SR reconstruction [23]. Future work aims at investigating the ability of such synthetic images to generalize post-processing tools like fetal brain tissue segmentation to datasets acquired on other MR systems and with other parameters using domain adaptation techniques. Therefore, the developed pipeline will be extended to simulate fast spin echo sequences from other MR vendors, both at 1.5 T and 3 T. It will then be made publicly available to support reproducibility studies and provide a common framework for the evaluation and validation of post-processing strategies for fetal brain MRI.

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