



# Spatio-Temporal Motion Correction and Iterative Reconstruction of In-Utero Fetal fMRI

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**Abstract.** Resting-state functional Magnetic Resonance Imaging (fMRI) is a powerful imaging technique for studying functional development of the brain *in utero*. However, unpredictable and excessive movement of fetuses have limited its clinical applicability. Previous studies have focused primarily on the accurate estimation of the motion parameters employing a single step 3D interpolation at each individual time frame to recover a motion-free 4D fMRI image. Using only information from a 3D spatial neighborhood neglects the temporal structure of fMRI and useful information from neighboring timepoints. Here, we propose a novel technique based on four dimensional iterative reconstruction of the motion scattered fMRI slices. Quantitative evaluation of the proposed method on a cohort of real clinical fetal fMRI data indicates improvement of reconstruction quality compared to the conventional 3D interpolation approaches.

**Keywords:** Fetal fMRI · Image reconstruction · Motion-compensated recovery · Regularization

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## 1 Introduction

Functional magnetic resonance imaging (fMRI) offers a unique means of observing the functional brain architecture and its variation during development, aging, or disease. Despite the insights into network formation and functional growth of the brain, *in utero* fMRI of living human fetuses, and the developmental functional connectivity (FC), however, remain challenging. Since the fMRI acquisition takes several minutes, unconstrained and potentially large movements of the fetuses, uterine contractions, and maternal respiration can cause severe artifacts such as in-plane blurring, slice cross-talk, and spin-history artifacts that likely vary over time. Without mitigation, motion artifacts can considerably affect the image quality, leading to a bias of subsequent conclusions about the FC of the developing brain.

Standard motion correction approaches, including frame-by-frame spatial realignment along with discarding parts of data with excessive motion, have been adopted so far to address motion artifacts of *in utero* fMRI [9, 16, 19]. More recently, cascaded slice-to-volume registration [12] combined with spin history correction [4], and framewise registration based on the 2<sup>nd</sup> order edge features instead of raw intensities [10] were suggested. These studies used 3D linear interpolation of motion scattered data at each volume independently to reconstruct the entire time series. Since *in utero* motion is unconstrained and complex, the regular grid of observed fMRI volumes becomes a set of irregularly motion scattered points possibly out of the field-of-view of the reconstruction grid, which might contain gaps in regions with no points in close proximity. Therefore interpolation in each 3D volume cannot recover the entire reconstruction grid.

Here we propose a new reconstruction method that takes advantage of the temporal structure of fMRI time series and rather than treating each frame independently, it takes both the spatial and the temporal domains into account to iteratively reconstruct a full 4D *in utero* fMRI image. The proposed method relies on super-resolution techniques that attracted increasing attention in structural fetal T2-weighted imaging, aiming to estimate a 3D high-resolution (HR) volume from multiple (semi-)orthogonal low resolution scans [3, 5, 14]. In case of fMRI, orthogonal acquisitions are not available, instead the reconstruction of a 4D image from a single sequence acquired over time is desired (An illustration of the problem is shown in Fig. 1). Currently, existing single-image reconstruction methods are generally proposed for 3D structural MR images with isotropic voxels, while the effect of motion is implicitly modeled via blurring the desired HR image [13]. None of these methods have been tailored for 4D fMRI with high-levels of movement such as the fetal population.

Our contribution is threefold: (1) we develop a 4D optimization scheme based on low-rank and total variation regularization to reconstruct 4D fMRI data as a whole (2) we explicitly model the effect of motion in the image degradation process since it is the main source of gaps between interpolated slices; (3) we show the performance of our algorithm on the highly anisotropic *in utero* fMRI images. Experiments were performed on 20 real individuals, and the proposed method was compared to various interpolation methods.

## 2 Method

We first describe the fMRI image acquisition model and then its corresponding inverse problem formulation to recover a 4D artifact-free fMRI from a single scan of motion corrupted image, using low-rank and total variation regularizations.

### 2.1 The Reconstruction Problem

fMRI requires the acquisition of a number of volumes over time (fMRI time-series, bold signal) to probe the modulation of spontaneous (or task-related) neural activity. This activity is characterized by low frequency fluctuations ( $<0.1$  Hz) of bold signals and therefore temporal smoothing is often applied as a pre-processing step in fMRI analysis. We aim at estimating the motion-compensated reconstruction of fMRI time series ( $\mathcal{X} \in \mathbb{R}^{\hat{B} \times \hat{K} \times \hat{H} \times N}$ ) from observed motion-contaminated fMRI volumes ( $\mathcal{T} \in \mathbb{R}^{B \times K \times H \times N}$ ) that integrates temporal smoothing within a full 4D iterative framework. Both  $\mathcal{X}$  and  $\mathcal{T}$  are composed of  $N$  3D volumes  $\mathbf{X}_n, \mathbf{T}_n$  acquired over  $N$  timepoints. In MR image acquisition, a degradation process yields a low-resolution image from the latent high-resolution image:

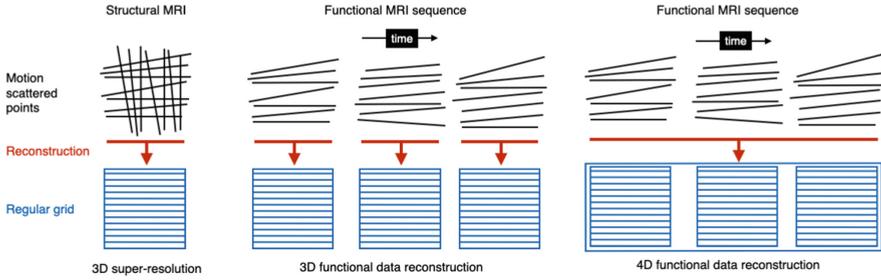
$$\mathbf{T}_n = DSM_n \mathbf{X}_n + z \quad (1)$$

where  $D$  is a 3D downsampling operator,  $S$  is a 3D blurring operator,  $M$  is the set of estimated motion parameters (three rotation and three translation parameters for each slice  $\mathbf{t}_{n,h} \in \mathbb{R}^{B \times K}$  of the volume  $\mathbf{T}_n$ , estimated prior to optimization (Sect. 3.1)), and  $z$  represents the observation noise. The application of  $M_n$  in the model here is equivalent to transforming each slice by the motion followed by resampling them on a 4D regular grid. Successful recovery of  $\mathcal{X}$  from the  $\mathcal{T}$  not only ensures the compensation of motion but also smoother bold signals due to the implicit temporal structure present in the data. However, since the Eq. (1) is ill-posed, direct recovery of  $\mathcal{X}$  is not possible without enforcing a prior. Hence, the reconstruction of the latent desired 4D image  $\mathcal{X}$  is achieved by minimizing the following cost function based on the inverse problem formulation:

$$\min_{\mathcal{X}} \sum_{n=1}^N \|DSM_n \mathbf{X}_n - \mathbf{T}_n\|^2 + \lambda \mathfrak{R}(\mathcal{X}) \quad (2)$$

where  $\mathfrak{R}(\mathcal{X})$  is a spatio-temporal regularization term, and  $\lambda$  balances the contributions of the data fidelity and regularization terms. We propose two regularization terms in this context, 4D low-rank for missing data recovery and total variation for preserving local spatial consistency.

**4D Low-Rank Regularization.** Rank as a measure of nondegenerateness of the matrix, is defined by the maximum number of linearly independent rows or columns in the matrix. Since self-similarity is widely observed in fMRI images, low rank prior has been successfully used in matrix completion of censored fMRI



**Fig. 1.** Illustration of the image reconstruction using super-resolution technique. Over-sampling exists in case of 3D structural MRI (left panel), however, there is not enough data for separate reconstruction of each 3D fMRI volume (middle panel). Here we propose to reconstruct the whole 4D fMRI at once using both spatial and temporal data structure (right panel).

time series [1]. Here we use low rank as a regularization term to help retrieve relevant information from all image regions. To compute the rank for a 4D image  $\mathcal{X}$ , we first unfold it into a 2D matrix along each dimension [6]. Specifically, suppose the size of  $\mathcal{X}$  is  $B \times K \times H \times N$ , we unfold it into four 2D matrices  $\{X_{(i)}, i = 1, 2, 3, 4\}$  with size of  $B \times (K \times H \times N)$ ,  $K \times (B \times H \times N)$ ,  $H \times (B \times K \times N)$ , and  $N \times (B \times K \times H)$  where  $X_{(i)}$  means unfold  $\mathcal{X}$  along dimension  $i$ . Then we compute the sum of the singular values in each matrix for their trace norms  $\|X_{(i)}\|_{tr}$ . Finally, the rank of  $\mathcal{X}$  is approximated as the combination of trace norms of all unfolded matrices [13]:

$$\mathfrak{R}_{rank}(\mathcal{X}) = \sum_{i=1}^4 \alpha_i \|X_{(i)}\|_{tr} \tag{3}$$

where  $\{\alpha_i\}$  are parameters satisfying  $\alpha_i \geq 0$ , and  $\sum_{i=1}^4 \alpha_i = 1$ . By minimizing this term, we obtain a low-rank approximation of  $\mathcal{X}$ . The low rank regularization is applied in the entire 4D data retrieving useful information for the reconstruction task from both spatial and temporal domains.

**Total Variation Regularization.** Total variation (TV) is defined as integrals of absolute gradient of the signal. For a 4D functional image  $\mathcal{X}$ :

$$\mathfrak{R}_{tv}(\mathcal{X}) = \sum_{n=1}^N \int |\nabla \mathbf{X}_n| dbdkdh \tag{4}$$

where the gradient operator is performed in 3D spatial space. TV regularization has been largely adopted in image recovery because of its powerful ability in edge preservation [13, 14]. Here, we use TV in 3D space instead of 4D space based on the notion that primarily the spatial neighborhood exhibits consistency and thus TV in temporal domain may not be effective.

**Algorithm 1.** 4D motion-compensated reconstruction of fMRI time series**Input:** Single scan fMRI image  $\mathcal{T}$ , realignment parameters**Initialize:** The desired  $\mathcal{X}$  by resampling motion-transformed image  $\mathcal{T}$  with linear interpolation. Set auxiliary variable  $Y_i^{(0)} = 0, U_i^{(0)} = 0, i = 1, 2, 3, 4$ **while**  $\|\mathcal{X}^k - \mathcal{X}^{k-1}\| / \|\mathcal{T}\| > \varepsilon$  **do**  Update  $\mathcal{X}^k$  by using gradient descent:

$$\arg \min_{\mathcal{X}} \sum_{n=1}^N \left\| DSM_n \mathbf{X}_n^{(k-1)} - \mathbf{T}_n \right\|^2 + \sum_{i=1}^4 \frac{\rho}{2} \left\| \mathcal{X}^{(k-1)} - Y_i^{(k-1)} + U_i^{(k-1)} \right\|^2 + \lambda_{tv} \sum_{n=1}^N \int |\nabla \mathbf{X}_n^{(k-1)}| dbdhdk \quad (7)$$

  Update  $Y_i^{(k)}$  by using Singular Value Thresholding:

$$Y_i^{(k)} = \text{fold}_i \left[ SVT_{\lambda_{rank} \alpha_i / \rho} \left( \mathcal{X}_{(i)}^{(k-1)} + U_{i(i)}^{(k-1)} \right) \right] \quad (8)$$

  with  $\text{fold}_i (Y_{i(i)}) = Y_i$ 

$$\text{Update } U_i^{(k)} = U_i^{(k-1)} + \left( \mathcal{X}^{(k)} - Y_i^{(k)} \right) \quad (9)$$

**end while**

## 2.2 Optimization

The proposed 4D single acquisition reconstruction is thus formulated as below:

$$\min_{\mathcal{X}} \sum_{n=1}^N \left\| DSM_n \mathbf{X}_n - \mathbf{T}_n \right\|^2 + \lambda_{rank} \mathfrak{R}_{rank}(\mathcal{X}) + \lambda_{tv} \sum_{n=1}^N \mathfrak{R}_{tv}(\mathbf{X}_n) \quad (5)$$

We employ the alternating direction method of multipliers (ADMM) algorithm to minimize the cost function in Eq. (5). ADMM has been proven efficient for solving optimization problems with multiple non-smooth terms [2]. Briefly, we first introduce redundant variables  $\{Y_i\}_{i=1}^4$  with equality constraints  $\mathcal{X}_{(i)} = Y_{i(i)}$ , and then use Lagrangian dual variables  $\{U_i\}_{i=1}^4$  to integrate the equality constraints into the cost function:

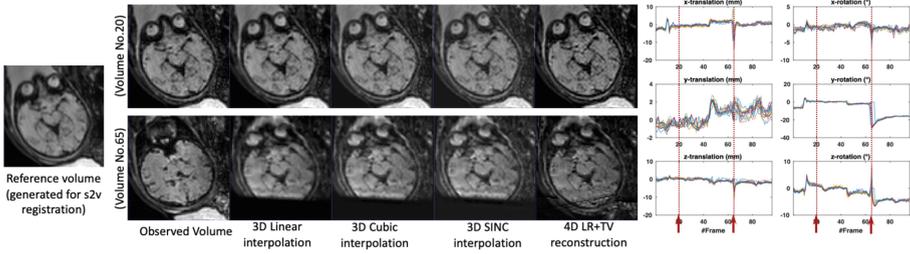
$$\min_{\mathcal{X}, \{Y_i\}_{i=1}^4, \{U_i\}_{i=1}^4} \sum_{n=1}^N \left\| DSM_n \mathbf{X}_n - \mathbf{T}_n \right\|^2 + \lambda_{rank} \sum_{i=1}^4 \alpha_i \left\| Y_{i(i)} \right\|_{tr} + \sum_{i=1}^4 \frac{\rho}{2} \left( \left\| \mathcal{X} - Y_i + U_i \right\|^2 - \left\| U_i \right\|^2 \right) + \lambda_{tv} \sum_{n=1}^N \int |\nabla \mathbf{X}_n| dbdkdh \quad (6)$$

We break the cost function into subproblems for  $\mathcal{X}$ ,  $Y$ , and  $U$ , and iteratively update them. The optimization scheme is summarized in Algorithm 1.

## 3 Experiments and Results

### 3.1 Data

**Data Acquisition:** Experiments in this study were performed on 20 *in utero* fMRI sequences obtained from fetuses between 19 and 39 weeks of gestation. None of the cases showed any neurological pathology. Pregnant women were scanned on a 1.5T clinical scanner (Philips Medical Systems, Best, Netherlands) using single-shot echo-planar imaging (EPI), and a sensitivity encoding



**Fig. 2.** Reconstruction of *in-utero* fMRI for a typical fetus, and the estimated slice-wise realignment parameters. When motion is small (volume No. 20) all interpolation methods recovered a motion compensated volume, and our approach resulted in a sharper image. In contrast, with strong motion relative to the reference volume (volume No. 65), single step 3D interpolation methods are not able to recover the whole brain, and parts remain missing, whereas the proposed 4D iterative reconstruction did recover the entire brain.

(SENSE) cardiac coil with five elements. Image matrix size was  $144 \times 144$ , with  $1.74 \times 1.74 \text{ mm}^2$  in-plane resolution, 3 mm slice thickness, a TR/TE of 1000/50 ms, and a flip angle of  $90^\circ$ . Each scan contains 96 volumes obtained in an interleaved slice order to minimize cross-talk between adjacent slices.

**Preprocessing:** For preprocessing, a binary brain mask was manually delineated on the average volume of each fetus and dilated to ensure it covered the fetal brain through all ranges of the motion. A four dimensional estimate of the bias field for spatio-temporal signal non-uniformity correction in fMRI series was obtained using N4ITK algorithm [17] as suggested previously [11]. Intensity normalization was performed as implemented in mialSRTK toolkit [15]. Finally, motion parameters were estimated by performing a hierarchical slice-to-volume registration based on the interleaved factor of acquisition to a target volume created by automatically finding a set of consecutive volumes of fetal quiescence and averaging over them [12]. Image registration software package NiftyReg [7] was used for all motion correction steps in our approach. Demographic information of all 20 subjects as well as the maximum motion parameters estimated were reported in Supplementary Table S1.

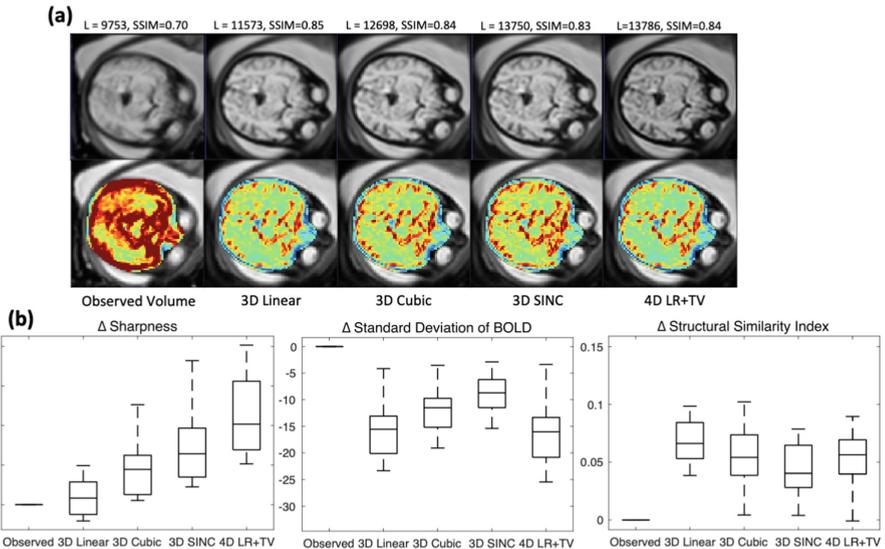
### 3.2 Experimental Setting and Low-Rank Representation

We first evaluated to which extent *in utero* fMRI data can be characterized by its low-rank decomposition. The rapid decay of the singular values for a representative slice of our cohort is shown in Supplementary Figure S1. We used the top 30, 60, 90, and 120 singular values to reconstruct this slice and measured signal-to-noise ratio (SNR) to evaluate the reconstruction accuracy. The number of used singular values determines the rank of the reconstructed image. Using the top 90 or 120 singular values (out of 144), the reconstructed image does not show visual differences compared to the original image while it has a relatively high SNR (Fig. S1).

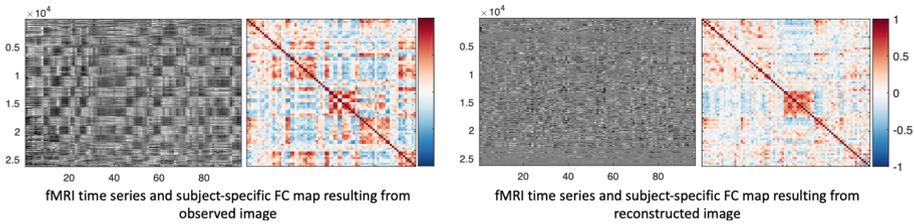
For the full 4D fMRI data of our cohort with the size of  $144 \times 144 \times 18 \times 96$ , four ranks, one for each unfolded matrix along one dimension is computed. Each is less than the largest image size 144. These ranks are relatively low in comparison to the total number of elements, implying *in utero* fMRI images could be represented using their low-rank approximations. We set  $\alpha_1 = \alpha_2 = \alpha_3 = \alpha_4 = 1/4$  as all dimensions are assumed to be equally important,  $\lambda_{\text{rank}} = 0.01$ ,  $\lambda_{\text{TV}} = 0.01$  were chosen empirically. The algorithm stopped when the difference in iterations was less than  $\varepsilon = 1e - 5$ .

### 3.3 Evaluation of Image Reconstruction

A number of interpolation methods was employed to be compared with our reconstructed image including linear, cubic spline, and SINC interpolation. For each method, we applied the same realignment parameters as the ones used in our model, and in accordance with standard motion correction techniques, each 3D volumes of fMRI time series was interpolated separately. We quantified sharpness [8] of the average recovered image, standard deviation of bold signal fluctuations (SD) through-out the sequence, and the Structural Similarity Index (SSIM) which correlates with the quality of human visual perception [18]. Higher values of sharpness and SSIM, and lower values of SD are indicative of better recovery.



**Fig. 3.** Evaluation metrics for a typical fetus (a) and the whole cohort (b). Panel (a) shows an example slice in the average volume (top row) and voxel-wise standard deviation of the bold signal during fMRI acquisition. Higher Laplacian (sharpness) and SSIM, and lower standard deviation are indicative of better recovery. Panel (b) demonstrates these metrics in our fetal dataset.



**Fig. 4.** Carpet plot and functional connectivity maps achieved for an example subject using the observed fMRI time series and the time series recovered by 4D iterative reconstruction.

Figure 2 shows, from left to right, the reference volume, two corresponding slices in the observed image, and the results of different reconstruction methods. Volume No.20 exhibits minor motion, volume No.65 exhibits strong motion. The motion estimate plots on the right show their respective time points. The figure shows the recovered slices of these two volumes using 3D linear, cubic, SINC, and the proposed 4D LR+TV method, respectively. In the case of excessive complex motion ( $30^\circ$  out of the plane combined with in-plane rotation and translation), the 3D interpolation methods cannot recover the whole slice as they utilize information only from the local spatial neighborhoods. The reconstructed slice by the proposed 4D iterative reconstruction approach recovers the image information, is sharper, and preserves more structural detail of the brain. Figure 3 shows a qualitative and quantitative comparison of reconstruction approaches. Figure 3 (a) shows the average volume (top row), and the standard deviation of intensity changes over time (bottom row) for one subject. 4D reconstruction achieves sharper structural detail, and overall reduction of the standard deviation, which is primarily related to motion as described earlier. Although linear interpolation results in signals as smooth as the proposed method, severe blurring is observed in the obtained image by this approach. Figure 3 (b) provides the quantitative evaluation for the entire study population. The proposed method significantly ( $p < 0.01$ , paired-sample t-tests for each comparison) outperforms all comparison methods. The average gain of sharpness over the observed image is 2294 in our method compared to 1521 for 3D SINC, 959 for 3D Cubic, and 294 for 3D Linear, and the average reduction of SD relative to the observed image is  $-17$  in our method compared to  $-9.34$  for 3D SINC,  $-12.70$  for 3D Cubic, and  $-16.50$  for 3D Linear. The difference between linear interpolation and our approach did not reach the statistical significance level for SSIM ( $p = 0.28$ ). In summary, 4D iterative reconstruction reduces standard deviation over time, while increasing sharpness and recovered structure, which the 3D approaches failed to achieve.

### 3.4 Functional Connectivity Analysis

Figure 4 illustrates the impact of the accurate motion correction and reconstruction for the analysis of functional connectivity (FC) in the fetal population.

The details of the pipeline employed for extracting subject-specific FC maps is explained in the supplementary material. When using the time series recovered by our proposed approach for FC analysis, the number of motion-corrupted correlations decreased significantly as visible in the *carpet plot* of signals, and the associated connectivity matrix.

## 4 Conclusion

In this work, we presented a novel spatio-temporal iterative 4D reconstruction approach for *in-utero* fMRI acquired while there is unconstrained motion of the head. The approach utilizes the self-similarity of fMRI data in the temporal domain as 4D low-rank regularisation together with total variation regularization based on spatial coherency of neighboring voxels. Comparative evaluations on 20 fetuses show that this approach yields a 4D signal with low motion induced standard deviation, and recovery of fine structural detail, outperforming various 3D reconstruction approaches.

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