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A Method for Handling Intensity Inhomogeneities in fMRI Sequences of Moving Anatomy of the Early Developing Brain

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Abstract

This paper presents a method for intensity inhomogeneity removal in fMRI studies of a moving subject. In such studies, subtle changes in signal as the subject moves in the presence of a bias field can be a significant confound for BOLD signal analysis. The proposed method avoids the need for a specific tissue model or assumptions about tissue homogeneity by making use of the multiple views of the underlying bias field provided by the subject's motion. A parametric bias field model is assumed and a regression model is used to estimate the basis function weights of this model. Quantitative evaluation of the effects of motion and noise in motion estimates are performed using simulated data. Results demonstrate the strength and robustness of the new method compared to explicit segmentation based methods that estimate bias within individual timeframes, as well as the state of the art 4D nonparametric bias estimator (N4ITK). We also qualitatively demonstrate the impact of the method on resting state neuroimage analysis of a moving adult brain with simulated motion and bias fields, as well as on in-vivo moving fetal fMRI.

Keywords

fMRI; Fetal imaging; Bias Correction

1. Introduction

The measurement of BOLD signal fluctuations with functional magnetic resonance imaging (fMRI) has been widely used to study connectivity in the adult brain. A typical study

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involves data acquisition, several preprocessing steps to account for various artifacts, followed by analysis. Although there is currently no standardized processing pipeline, several packages (Ashburner (2012); Cox (1996); Goebel (2012); Smith et al. (2004)) with flexible pipelines have been designed for carrying out these studies in adults. The typical steps in a processing pipeline include motion correction, susceptibility artifact removal, brain-nonbrain segmentation, intensity bias correction and spatial and temporal filtering (Strother (2006)).

Recently, fMRI has been used to study the early developing brain (young children and fetuses) (Schopf et al. (2011); Seshamani et al. (2012); Studholme (2011)). The adult pipelines however cannot be directly applied to the fMRI studies of young children/ fetuses due to several challenges that this data poses. One of the leading challenges is that unlike the adult, it is often difficult or impossible (as in the case of the fetus) to control large movements of the subject. This can cause the distance between the coil and the head to vary as data is acquired. Preprocessing, visualization, as well as neuroscientific analysis are greatly impacted by these issues. Most of the preliminary work in the area addresses the challenge of subject motion by complete exclusion of subjects who are moving or by omitting of parts of the time sequence when the subject is moving (scrubbing - Power et al. (2012)). These approaches however may limit the applicability of BOLD signal analysis in the early developing brain. Postprocessing methods for addressing the effects of motion therefore greatly impact the ability to perform functional analysis in this domain.

Large subject motion between acquisitions not only introduces challenges in registration, but also introduces effects such as spin history artifacts (Friston et al. (1996)) which can degrade the signal. In addition, inhomogeneities in the magnetic field can introduce artifacts that can affect the functional analysis of the moving subject. Figure 1 shows an example of this effect in an fMRI time series of a moving fetal head. It can be observed that the intensities near the top of the image are always higher as the fetus is imaged in different positions. Note that these inhomogeneities will not affect correlation based analysis of a stationary subject (which is how the majority of adult studies have been carried out thusfar) since the signal is mean centered before any analysis.

Intensity inhomogeneity correction in MRI data has been a very active area of research in the last few decades. Several retrospective techniques (Belaroussi et al. (2006); Vovk et al. (2007)) that make only a few assumptions about the acquisition process have been proposed. These include filtering methods (Haselgrove and Prammer (1986); Cohen et al. (2000); Zhou et al. (2001); Lewis and Fox (2004)) which assume that the inhomogeneity is a low frequency artifact, parametric surface fitting methods (Dawant et al. (1993); Lai and Fang (1999); Vemuri et al. (2005); Vokurka et al. (2001)), segmentation methods (Ashburner and Friston (2005); Van Leemput et al. (1999); Wells et al. (1996); Gerig et al. (2003); Zhu and Jiang (2003)), histogram based methods (Sled et al. (1998); Likar et al. (2001); Solanas and Thiran (2001); Learned-Miller and Ahammad (2004); Vovk et al. (2004)) and parallel imaging (Lin et al. (2003)) based methods. However, almost all of them have focused primarily on correcting structural images for static bias for the purpose of tissue segmentation and analysis. When applied to fMRI data, each frame is treated independently and hence no information about the varying time signal is utilized.

In this paper, we address this problem of intensity inhomogeneity in fetal fMRI time series data acquired during motion (multiple views). Our aim is to remove the artifact from time series for accurate detection of changes in MRI signals that are needed in functional imaging studies. The new approach we propose in this paper aims to directly estimate a single underlying bias field from the different views of that bias field provided by the moving anatomy. To the best of our knowledge the only other prior work that has been applied to

addressing intensity inhomogeneities of multiple images of fetuses under motion is that of Kim et al. (2011). This method was focussed on simply estimating bias field inconsistencies, rather than estimating the underlying bias field as we aim for here. In addition, in this new work we focus on faster EPI acquisitions used in functional or diffusion imaging, where volume motion is the key factor as opposed to slice to slice imaging in slower structural imaging sequences. We derive a regression technique called MuVIE (Multi-View Intensity Inhomogeneity Estimation), that estimates the underlying bias using all the acquired time series. In the experimental section, we simulate fetal fMRI time series to compare MuVIE with a single volume based segmentation method as well as N4ITK, and demonstrate that our algorithm outperforms these techniques for moving fetal data. We also demonstrate its robustness to registration estimates and show that the proposed method in fact can greatly enhance fMRI analysis in adult data in the presence of BOLD activation. Finally, we show how signal correction can impact ICA based BOLD analysis of in-vivo fetuses.

2. Methods

2.1. Preliminaries

Let $\mathcal{I}$ be a 4D spatio-temporal image containing the observed intensities of a time series of N volumes, each containing K voxels, and let $\mathcal{I}^*$ be the 4D spatio-temporal image containing ideal (unbiased) intensities of the same time series. Let x_k denote a 3D voxel location and $x_{k,n} = [x_k^T, n]^T$ denote a 4D voxel location (voxel k at time n). Assuming a multiplicative signal model, the effect of the bias field B_{true} at $x_{k,n}$ can be expressed as:

$$\mathcal{I}(x_{k,n}) = \mathcal{I}^*(x_{k,n}) B_{true}(x_{k,n}) \quad (1)$$

Under a logarithmic transformation, the bias field can be treated as an additive artifact:

$$\widehat{\mathcal{I}}(x_{k,n}) = \widehat{\mathcal{I}}^*(x_{k,n}) + \widehat{B}_{true}(x_{k,n}), \quad (2)$$

where $\widehat{\mathcal{I}}(x_{k,n}) = \log(\mathcal{I}(x_{k,n}))$, $\widehat{\mathcal{I}}^*(x_{k,n}) = \log(\mathcal{I}^*(x_{k,n}))$, and $\widehat{B}_{true}(x_{k,n}) = \log(B_{true}(x_{k,n}))$. We model the logarithm of the estimated bias field B_{est} at voxel $x_{k,n}$ as a weighted sum of M basis functions $G_1 \dots G_M$:

$$\widehat{B}_{est}(x_{k,n}) = \sum_{m=1}^M w_m G_m(x_{k,n}) \quad (3)$$

Assuming a set of basis functions, the objective therefore is to estimate the set of weights $w_1 \dots w_M$ which models the bias field. Examples of basis functions include polynomial bases, fourier bases, etc. The specific bases we use are outlined in the experiments section.

2.2. Multi-View Intensity Inhomogeneity Estimation

In order to estimate the bias field, we assume that the intensity of any piece of anatomy should vary as little as possible from other views given the assumption of slow spatial variation of bias. This assumption holds even in the case of fMRI time sequences since the intensity variation due to the BOLD effect can be assumed to occur at a spatially and temporally higher frequency than the variation due to motion and coil sensitivity. To this end, we minimize the sum of squared differences between the time series of all voxels.

Let $\{T_1, T_2, T_3 \dots T_N\}$ be a set of precomputed motion estimates that transforms each view of the anatomy (time frame) to a reference coordinate system. Let $\mathcal{T}$ be a function such that $\mathcal{T}(x_{k,n}) = T_n(x_k)$. We can then use $\mathcal{T}$ to describe voxel correspondences between all views and hence define an energy function, E , as follows:

$$E = \sum_{n=1}^N \sum_{p=1, p \neq n}^N \sum_{k=1}^K [(\widehat{\mathcal{J}}(\mathcal{T}(x_{k,n})) - \widehat{B}_{est}(\mathcal{T}(x_{k,n}))) - (\widehat{\mathcal{J}}(\mathcal{T}(x_{k,p})) - \widehat{B}_{est}(\mathcal{T}(x_{k,p})))]^2 \quad (4)$$

This can be rewritten as:

$$E = \sum_{n=1}^N \sum_{p=1, p \neq n}^N \sum_{k=1}^K [(\widehat{\mathcal{J}}(\mathcal{T}(x_{k,n})) - \widehat{\mathcal{J}}(\mathcal{T}(x_{k,p}))) + (\sum_{m=1}^M w_m (G_m(\mathcal{T}(x_{k,p})) - G_m(\mathcal{T}(x_{k,n}))))]^2 \quad (5)$$

Minimizing this with respect to the weights $w_1 \dots w_M$ gives us the system:

$$\mathbf{G}^T \mathbf{G} \mathbf{w} = \mathbf{G}^T \mathbf{v} \quad (6)$$

where:

$$\mathbf{G} = \begin{bmatrix} G_1(\mathcal{T}(x_{1,1})) - G_1(\mathcal{T}(x_{1,2})) & \dots & G_M(\mathcal{T}(x_{1,1})) - G_M(\mathcal{T}(x_{1,2})) \\ \vdots & & \vdots \\ G_1(\mathcal{T}(x_{K,1})) - G_1(\mathcal{T}(x_{K,2})) & \dots & G_M(\mathcal{T}(x_{K,1})) - G_M(\mathcal{T}(x_{K,2})) \\ G_1(\mathcal{T}(x_{1,1})) - G_1(\mathcal{T}(x_{1,3})) & \dots & G_M(\mathcal{T}(x_{1,1})) - G_M(\mathcal{T}(x_{1,3})) \\ \vdots & & \vdots \\ \vdots & & \vdots \\ G_1(\mathcal{T}(x_{K,N-1})) - G_1(\mathcal{T}(x_{K,N})) & \dots & G_M(\mathcal{T}(x_{K,N-1})) - G_M(\mathcal{T}(x_{K,N})) \end{bmatrix}$$

$$\mathbf{v} = \begin{bmatrix} \mathcal{J}(\mathcal{T}(x_{1,2})) - \mathcal{J}(\mathcal{T}(x_{1,1})) \\ \vdots \\ \mathcal{J}(\mathcal{T}(x_{K,2})) - \mathcal{J}(\mathcal{T}(x_{K,1})) \\ \mathcal{J}(\mathcal{T}(x_{1,3})) - \mathcal{J}(\mathcal{T}(x_{1,1})) \\ \vdots \\ \vdots \\ \mathcal{J}(\mathcal{T}(x_{K,N})) - \mathcal{J}(\mathcal{T}(x_{K,N-1})) \end{bmatrix}$$

We can solve for the weight vector $\mathbf{w}$ with least squares regression (assuming additive gaussian noise) and calculate the estimated bias field using equation 3. We call this method the **Multi-View Intensity Inhomogeneity Estimation - MuVIE**. Note that when motion is very small (such as jitter in adult fMRI studies), this system cannot be solved since the motion would not provide enough distinct views of the bias from which the underlying field can be estimated. However, in such a case, time series analysis is not affected since there are no signal changes being induced by motion within the bias field.

The estimated bias field B_{est} can then be used to compute the bias corrected time frames $\mathcal{I}_{out}$ with the following equation:

$$\widehat{\mathcal{I}}_{out}(x_{k,n}) = \widehat{\mathcal{I}}(x_{k,n}) - \widehat{B}_{est}(x_{k,n}), \quad (7)$$

where $\widehat{\mathcal{I}}_{out}(x_{k,n}) = \log(\mathcal{I}_{out}(x_{k,n}))$.

2.3. Algorithm Summary

A summary of the proposed algorithm is shown in figure 2. The input is a set of images acquired during motion of the subject, under a bias field. The first image of the sequence is manually aligned with an age specific head mask synthesized from a spatio-temporal model of the fetal brain. This mask is then used to rigidly register all volumes to one of the volumes by maximization of Normalized Mutual Information with respect to the 6 rigid transformation parameters, and these estimates are used for computing the bias field as described in the previous section. The resulting field can then be used to correct the input images for the bias. Finally, the output image sequence is scaled such that its mean intensity (within the brain) is the same as the mean intensity of the input image sequence.

3. Validation

In this section, we validate our model on real fetal data. Our current fetal fMRI database consists of scans of healthy fetuses (ages of 31 and 36 wks), scanned 1-2 times using a 1.5T GE Scanner. Each scan is a multishot EPI consisting of 60-160 frames, acquired with a 2-interleave, flip angle=80, TE=40-50, TR=2000. We select a short dataset containing 50 frames and apply three different methods:

1. MuVIE 4D: Here, we assume a 4D bias field model (ie: the bases functions G_m are 4D functions)
2. MuVIE 3D: Here, we assume a 3D bias field model (ie: bases functions G_m are 3D functions. This can be thought of as a special case of a 4D function where $B_{est}(x_{k,1}) = B_{est}(x_{k,2}) = \dots B_{est}(x_{k,n})$.) and refer to it as MuVIE 3D. For MuVIE 3D, we can keep changing the reference frame within the sequence, and obtain a 3D bias field corresponding to each frame.
3. N4ITK: This is a current state of the art method for bias correction within MRI which generates a 4D bias field estimate.

We then evaluate how the field changes over time by computing the Normalized Cross Correlation of the 3D fields with the field corresponding to the first frame. Figure 3 shows these values across all 50 frames. We make a few observations from this. The first is that the correlation values across time are very close to 1, thus implying that the fields do not change significantly over time. The second is that even when computed independently with MuVIE 3D, the fields still correlate very highly.

Finally, we compare the fields estimated by MuVIE 3D and MuVIE 4D for three different subjects. Figure 4 shows three views of the field for three different subjects. Subject 1 is the subject used above, with 50 frames. Subject 2 and 3 were sequences with 160 frames each. The middle rows show the field generated by MuVIE 3D and the bottom rows show the fields generated by MuVIE 4D. We observe that these fields are very similar and do not change significantly over time. Hence, for the rest of the experiments in this paper, we use MuVIE 3D and simply refer to it as MuVIE.

Note: The fetal datasets contained rotation motion in the range of 0-20 degrees with standard deviations of 2.95 degrees, 4.59 degrees, 5.94 degrees in x,y and z rotations, and translational motion with a maximum of 10mm with standard deviations of 0.87mm, 1.95mm and 1.37mm along the x,y and z axes. The condition numbers of the system solved by MuVIIIE for these datasets were well above 100 which made them stable systems.

4. Experiments on Simulated Data

We carried out three sets of experiments to examine the sensitivity, robustness and applicability of our method. In all the experiments, we generated simulated data by applying a known bias field to a fetal dataset, performed bias correction and then compared the result of bias correction with the original data. In our experiments, MuVIIIE uses polynomial bases and N4ITK uses a B-spline model for the bias field. In order to be fair to both methods, the experiments in this section are performed with 3 kinds of bias fields: a bias field modelled with polynomial bases (P), a bias field modelled with B-Splines (S) and a bias field modelled with Discrete Cosine Bases (D) which is an independent model. The following subsections outline our experiments towards these goals.

4.1. Simulation

Each simulated dataset containing 100 volumes was created using the following steps:

1. We selected a real fetal dataset and first applied N4ITK to remove any extra bias in the data. Next, we registered each frame of the data to the first frame to obtain gross motion estimates. We then selected and averaged 10 frames from this dataset where the motion parameters indicated the fetal head motion was minimal. This gave us an average frame (figure 5 - Column 1).
2. For each frame in the simulated sequence, gaussian noise and motion were applied. In each experiment, we report the noise parameters and standard deviations of motion that were applied.
3. Three types of bias fields were generated: a polynomial field, a B-spline field and a DCT field. The polynomial fields were described by 9 second order polynomial bases ($x, y, z, x^2, y^2, z^2, xy, xz, yz$), the spline fields were described with 4X4X4 control points placed over the whole view of the brain and the DCT fields were described by 3 first order discrete cosine bases. In each case, bias fields were obtained by applying MuVIIIE and N4ITK algorithms on a real fetal dataset. (The Discrete Cosine bias field was obtained by applying MuVIIIE with cosine bases on a fetal dataset.) This gives us a realistic bias field at a realistic strength level. Figure 5 (Column 2) shows the **polynomial field : P**, Figure 5 (Column 3) shows the **spline field : S** and Figure 5 (Column 4) shows the **DCT field : D**.
4. Finally, these bias fields were applied as in equation 2:

$$\widehat{\mathcal{F}}(x_{k,n}) = \widehat{\mathcal{F}} * (x_{k,n}) + s\widehat{B}_{true}(x_{k,n}),$$

where s is a parameter that controls the strength of the added bias. Note that $s=1$ would indicate no change in strength from the field estimated from a real dataset.

Fields generated by such bases are not uniquely defined and hence comparing two sets of coefficients is not an adequate way of comparing two bias fields. In addition, it is not possible to compare fields generated with the polynomial model with those generated with

the spline model simply by their parameters. In the next subsection, we describe how we evaluate our methods.

4.2. Evaluation

We compared our algorithm with a state of the art method N4ITK Tustison et al. (2010). N4ITK is an extension of the well known N3 method Sled et al. (1998), with the substitution of a faster and more robust B-spline approximation routine, and a modified hierarchical optimization scheme for improved bias field correction over the original N3 algorithm. For the sake of clarity, we assign a name to the different ways in which we apply the algorithm and the proposed method:

- **N4ITK:** This is the baseline method. Here, for each frame, the mask is transformed to the frame's coordinate system by applying the registration estimate so that only the voxels inside the brain are used for field estimation. The method computes multiple bias fields (one for each frame).
- **MuVIIE:** This is the proposed method, which uses the same mask and all the frames in the time series to estimate one bias field in the coordinate system of the frame that all the volumes in the time series were registered to.

Once the bias fields were computed from any of the methods, they were used to correct the input images for the artifact (Equation 7). The resulting bias corrected images could then be compared to the original input image (before any bias field was applied) using the Normalized Sum of Squared Differences. (Note that a normalized metric is necessary here since the bias field does not correct for global scaling between frames). The results of N4ITK could hence be evaluated and compared to the results of MuVIIE using this metric.

We also measured the run time of both algorithms. On average, for a dataset consisting of 100 frames that was processed on a 24 core (2.67GHz) system, N4ITK required **103** seconds whereas MuVIIE required only **16** seconds.

4.3. Experiment 1: Evaluating the Effect of Motion

The objective of this experiment is to investigate the effect of motion on the proposed method and compare resulting estimates to those computed by the baseline method (N4ITK). In particular, we are interested in determining the relationship between the amount of subject motion and the performance of the methods.

First, we computed estimates for typical fetal head motion. We selected an in-vivo fetal dataset containing 160 frames where the subject was moving (Subject 2 from Section 3 - Validation), and computed rigid head motion between every volume and the first volume in the time series. This provided a realistic motion trajectory of a fetal head imaged with a fast EPI sequence. Figure 6 shows the rotation and translation estimates of this trajectory. We observed that the maximum movement from the initial position was in the range of about 20 degrees and the maximum translation was in the range of 8mm.

Hence, we generated data with noise parameters mean = 0, std = 1% of the intensity range and applied simulated motion that consisted of only of a series of rotations with standard deviations varied from 4 degrees (small motion) - 22 degrees (very large motion) in steps of 2 degrees. (Translation was not applied to ensure that the whole fetal head remains within view throughout the sequence.)

The objective of this experiment was to compare the performance of the multi field models when motion estimation is accurate. However, since N4ITK does not use a polynomial

model, it would be unfair to test only with a simulated polynomial field. Therefore, we perform three experiments:

- Experiments with polynomial field P (Figure 5, Column 2) with varying the amount of motion in data.
- Experiments with a spline field S (Figure 5, Column 3) with varying the amount of motion in data.
- Experiments with a DCT field D (Figure 5, Column 4) with varying the amount of motion in data.

In each case, we generated 5 datasets with the noise and motion parameters described above and applied bias at a strength $s=1$. We then estimated the fields and corrected the images with both methods: N4ITK and MuVIIE. We compared the results of N4ITK and MuVIIE by evaluating the Normalized SSD between corrected images and the ground truth. Figure 7 (Top Left) shows the results with the polynomial field, Figure 7 (Top Right) shows the same experiment with the spline field and Figure 7 (Bottom) shows results with the DCT field. The mean Normalized SSD of all 5 runs of the experiment has been plotted. In addition the error bars show the standard deviation of the error.

The following observations can be made from this:

- As the amount of motion increases, both methods are better at estimating the bias field. This is an expected behavior for MuVIIE since increased motion means that more views of the bias field are obtained. However, what is interesting to note is that the increased motion seems to improve N4ITK as well. This can possibly be explained by the fact that N4ITK estimates a field for every frame and then performs smoothing. Hence, obtaining more varied views of the bias field has also improved the performance of this method.
- The mean error for MuVIIE is less than that for N4ITK. However, as the motion increases, the standard deviations of MuVIIE also increase. N4ITK however is more stable even as the amount of motion increases. In the case of the polynomial and DCT fields however, even with the higher standard deviations, MuVIIE still outperforms N4ITK. However in the spline case it is difficult to conclude if either method outperforms the other.

In summary, MuVIIE performs better when the simulated field is polynomial (which favors MuVIIE) or DCT (an independent model) and performs comparably with N4ITK for the B-spline model case, even when the model favors N4ITK. This demonstrates the strength of the proposed method. One reason for this could be that at different development stages, the anatomy of the developing brain can naturally exhibit intensity gradients which do not arise from the scanner and therefore should not be removed. Hence, a non-parametric method such as N4ITK may not perform as well for this type of application.

4.4. Experiment 2: Evaluating the Effect of Bias Strength

Next, we investigated the effect of the bias strength on the estimation. In all datasets, noise parameters mean = 0, std = 1% and motion parameters with standard deviation of 12 degrees (only rotation) were used. We generated three types datasets which differed only by the type of bias field that was applied and performed three kinds of experiments:

- Experiments with polynomial field P (Figure 5, Column 2) with varying bias strength.
- Experiments with a spline field S (Figure 5, Column 3) with varying bias strength.

- Experiments with a DCT field D (Figure 5, Column 4) with varying bias strength.

Again, we evaluated MuVIIE and N4ITK by executing 5 runs and computing the mean Normalised SSD values. Figure 8 shows these results. In the case of the polynomial field, we observe that MuVIIE performs better than N4ITK till a bias strength of 2 after which N4ITK improves. With the spline and DCT fields, N4ITK overtakes MuVIIE after bias strength 1.5. It is also evident that the average error of MuVIIE greatly varies with changes in bias strength whereas N4ITK seems to vary a little less. Again this can be due to the fact that N4ITK estimates multiple fields and smooths across them. However, it is interesting to note that at $s=1$, which is a realistic estimate of the amount of bias in a dataset, MuVIIE is the clear winner.

4.5. Experiment 3: Evaluating Robustness to Noisy Motion Estimates

Finally, we evaluated the robustness of our method with noisy motion estimates. Again, we compared the use of the polynomial field P and the spline field S. We used the dataset generated with 1% noise and motion parameters of 0 mean and std 12 degrees and introduced noise into the motion estimates. We conducted twelve experiments by varying the strength of the bias field, type of field and the type of registration error, shown in Table 1.

The error in motion estimates was modelled as gaussian noise with standard deviations ranging from 0.5 degrees to 5 degrees in steps of 0.5 degrees. For N4ITK, we explicitly computed and input a mask transformed by the noisy motion estimates. We computed the mean Normalized SSD between the corrected images and ground truth. In addition, we also computed the mean normalized SSD between the uncorrected image and the ground truth. (This uncorrected image is the simulated image that has been generated with the addition of noise, motion and bias.) We refer this normalized SSD as the **base** and plot it as a black dotted line on all our graphs.

Figures 9(a), 9(b), 9(c), 9(d), 9(e) and 9(f) show the results of the first six experiments (bias strength $s = 1$). We observe that with the polynomial field P, MuVIIE performs better than N4ITK at this bias strength level. In particular, we note that the Normalized SSD resulting after N4ITK correction is higher than that of the base. Upon examination of the result, we noticed that N4ITK slightly overcorrects the images at this bias level which removes actual structure in the image. We also note that in the spline field case (second row), both methods seem to do worse than the base line at this bias strength but perform comparably. Finally, with the DCT field, we note that both methods overcorrect again but MuVIIE outperforms N4ITK.

To examine the effect of the strength, we performed experiments at bias strength $s=2$. Figures 10(a), 10(b), 10(c), 10(d), 10(e) and 10(f) show the results of these next six experiments (bias strength $s = 2$). Here we observe that neither of the methods overcorrects, except for a slight overcorrection in the DCT field case. N4ITK outperforms MuVIIE for the spline case. In the polynomial field case, MuVIIE outperforms N4ITK for the rotation error case and for translation errors that are less than (2.5mm). The difference in error between MuVIIE and N4ITK is much larger for the polynomial case than the spline case when the errors are small. This suggests that MuVIIE is greatly advantageous over N4ITK for the polynomial field model but does not suffer greatly for the spline model with favors N4ITK. However, in the case of the DCT field, N4ITK outperforms MuVIIE. We would like to note however that this bias strength level is much greater than what is expected in a real fetal dataset. Hence, although we can see that N4ITK does have its merit for higher field strengths, it suffers from the problem of overcorrection at a more realistic strength level of 1.

Finally, we observe that both methods are quite robust to rotation error. MuVIIE consistently degrades in performance with increase in translation error as expected. However N4ITK seems to improve slightly. This can again be due to the fact that N4ITK performs the slight overcorrection. Upon visual examination of the fields, we observe that with higher error in the motion estimates, the overcorrection is reduced, which thus improves the numeric result.

5. Analysis of the effect of bias correction on signal analysis of BOLD data

In the previous section, we evaluated the performance of the algorithm only in the presence of noise and a bias field. However, a crucial question that arises is if the method is applicable to data containing BOLD activation. Since functional connectivity in the developing brain with BOLD is still not well established, we address this question with experiments on an adult brain in resting state in this section.

5.1. Data

Data was first collected on a stationary adult in resting state using a GE scanner with parameters TE= 40 TR = 2800, Number of voxels: 64X64X35, Slice Thickness: 3.75 X 3.75 X 4, 110 time points. Single-subject resting state analysis was then carried out with ICA, extracting 20 components and computing a Z-map (number of standard deviations from the mean). This Z-map was thresholded at 3.0 to show components that were significant. One of these components highlighting the occipital cortex was selected and a seed was generated by choosing all voxels in this component (Figure 11, top row). A correlation analysis of the seed was then carried out with all other voxels in the brain. The result of this is shown in the bottom row of Figure 11.

Next, volume motion and bias fields were introduced to the dataset. The trajectory of motion introduced involved motion in the coronal plane, as if the subject was starting facing the front, moving his head to the right and returning back to the original position.

Three types of polynomial bias fields of degree 1 (Top rows of Figure 12) with a magnitude of 4% of the signal were generated and applied to all frames of this data, resulting in three test datasets. Figure 13 shows the difference between the original volume and volumes with the bias field added in all cases.

5.2. Evaluation

Volume motion correction and correlation analysis with the same seed described in Figure 11 was then applied to these images. In the left column of Figure 14, the top rows show the ground truth (same as Figure 11). The middle rows of each of the subfigures show the correlation analysis on the data after the addition of each of these bias fields, and the bottom rows show the difference between the ground truth and the correlation analysis of the data with the added bias. This illustrates how the correlation analysis changes in the presence of bias.

We then estimated the bias fields for each of these datasets with the MuVIIE algorithm and corrected these images with the estimates. The bottom rows of each subfigure in Figure 12 show the estimated bias fields. Observe that the shape of these estimated fields are similar to the ground truth (top rows of Figure 12). We computed the normalized SSD between the estimated and applied fields to quantify the difference between the two. The last column of Table 2 shows these values.

Volume correction and correlation analysis with the seed in Figure 11 was carried out on these bias corrected images. The middle rows of each subfigure in the right column of

Figure 14 show how the correction affected the analysis in each of the datasets. Observe how these results are much closer to the ground truth (top row) compared to the figures in the left column. The bottom rows of these subfigures visualize the difference between the ground truth correlation map and the correlation map after bias correction.

We then quantified the difference between the resulting correlation maps and the ground truth correlation map by computing the mean sum of squared differences between each map and the ground truth. Column 2 and 3 of Table 2 shows these values. There is a significant drop of the normalized SSD between the ground truth and the bias corrected images even when the normalized SSD between the two fields varies. This demonstrates that bias field estimation can in fact drastically impact BOLD analysis, that correction with the MuVIIE algorithm is not affected by the presence of a BOLD signal and that the MuVIIE algorithm can indeed estimate the underlying bias field present in maternal coordinates such that the BOLD signal detection can be improved.

6. Applications to In-vivo Fetal fMRI

Finally, we demonstrate the impact of our method on in-vivo fetal data. Due to the lack of ground truth the objective of this section is only to show the feasibility of our method on in-vivo fetal data and its impact on analysis. BOLD fMRI studies of the fetal brain are still in an exploratory stage and seed-based correlation analysis (used in the previous section) requires a priori knowledge of the brain's functional organization and depends on consistent seed placement. Therefore, it is not viable to carry out such an analysis on the fetal brain at this stage. We therefore evaluate the algorithm with data driven analysis (ICA) and demonstrate how bias correction affects this analysis.

6.1. Evaluation

We use the database described in the Validation section. Subject 1 contains only 50 frames that is not sufficient for a data driven fMRI analysis. Therefore, we show results on Subject 2 and Subject 3. For each of these subjects, we applied N4ITK and MuVIIE. We show the effect of bias correction on the two subjects in Figure 15. In each of the figures, the left column shows the original data and the following four columns show the result after bias correction with N4ITK and MuVIIE respectively. Observe that the high intensities present in the original images disappear in all the bias-corrected images.

We then demonstrate the effect of bias correction on BOLD signal analysis. We performed single subject ICA on each subject separately (ITPP FastICA library Hyvarinen (1999)) and extracted 14 components. Figure 16 shows the results on Subject 2 and figure 17 shows the results on Subject 3. The top row in each figure shows all components extracted before any correction has been applied. The remaining rows show the components extracted after applying N4ITK and MuVIIE respectively. The bias correction greatly affects the type of components that are extracted. Of particular interest is the observation that some components disappear and new components may appear after bias correction. In Figure 16, component 11 in the top row (without bias correction) completely disappears after N4ITK or MuVIIE is applied. In their place, new components appear such as component 11 and 12 in row four (N4ITK) and component 13 and 14 in row five (MuVIIE). In Subject 3, again we see a difference after bias correction, particularly the presence of component 13 in row four and component 6 in row five.

Note that the purpose of the ICA analysis was only to demonstrate the impact of our method on signal analysis. The results presented in this section show that it is a crucial and necessary step in the preprocessing pipeline for fetal fMRI analysis which would also

address other artifacts such as spin history correction and slice motion correction which need to be considered before a proper neuroscientific analysis can be carried out.

7. Discussion and Conclusion

We presented a method MuVIEE (Multi-View Intensity Inhomogeneity Estimation) for correcting intensity changes in MRI data of moving subjects. This method computes a bias field by using registration estimates and minimizing the difference in the intensities of corresponding voxels from multiple views. We demonstrate that this algorithm has some significant advantages over the baseline N4ITK method with simulated data and that although it is dependent on registration, it is robust enough to deal with small errors in registration estimates that may arise because of the presence of the bias field. We also demonstrate that the proposed method can be applied to fMRI data in the presence of a BOLD signal and can in fact improve signal analysis, as verified by our experiments with resting state adult data. Finally, we investigated the applicability of the method on real in-vivo MRI data and show that this correction constitutes a significant step in the preprocessing pipeline of moving anatomy by demonstrating its effect on resting state analysis of fetal fMRI.

There are several future directions that this work opens up. From a technical perspective, we have presented a method that depends on registration estimation and is robust to small errors. The next step could be exploring how the bias correction could in turn affect the accuracy of registration and developing an iterative procedure that can improve both bias correction as well as registration. One could also pursue the idea of incorporating slice motion estimates into the framework. From an experimental point of view, we plan to compare the method with more methods such as that of Vovk et al. (2006). From an application perspective, the method can be applied to event related fetal studies, other types of moving MRI data such as adults or young children who may not be able to stay still in the MRI scanner as well as other modalities that acquire multiple volumes such as DTI.

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Highlights

A parametric method for bias correction of moving subjects in fMRI is proposed.

The algorithm relies on modeling the bias field in the spatial domain and then estimation of a field by minimizing the intensity variance across the timeseries.

Although the method relies on registration, it is robust to small errors in registration.

Experiments are presented demonstrating improved performance compared to state of the art techniques: PABIC and N4ITK.

The algorithm is able to estimate the bias field even in the presence of BOLD activation and improve analysis.

Removal of bias with this method in fetal fMRI can greatly affect analysis.

Figure 1.
The effect of motion of a fetus on signal changes in an fMRI time series.

Figure 2.

Multi-View Intensity Inhomogeneity Estimation (MuViIE) Algorithm Summary: The input is a set of volumes containing different views of the anatomy. These views are registered to a template and the registration estimates are used to compute the bias field which is then applied for correction.

Figure 3.

Correlation of bias fields to bias field of first frame. Red: Each bias field was computed as a single underlying 3D field, with the reference frame as the frame number (x axis). Green: 4D field computed with MuVIE. Blue: 4D field computed with N4ITK.

(a) Subject 1

(b) Subject 2

(c) Subject 3

Figure 4.

Top Row of each Subject: Original fMRI data , Middle row: Bias field computed by estimation of one 3D field, Bottom Row of each Subject: Bias field computed by estimation of one 4D field (first frame). Observe that the shapes of the two fields are quite similar.

Figure 5.

From Left to Right, Column 1: Frame averaged from 10 frames from in-vivo fetal data set with very little motion. The three views are axial, sagittal and coronal in the mothers coordinate system. Column 2: Polynomial field used in experiments. Column 3: Spline Field used in experiments. Column 4: DCT Field used in experiments.

Figure 6.

Estimated head motion trajectory of an in-vivo fetus. The six graphs show the variation in the rigid registration parameters estimated over 160 frames in the fMRI time series.

Figure 7.

Experiment showing the effect of Varying the amount of motion in data. Top Left: Plot showing results of experiment where the applied bias field was modelled with polynomials. Top Right: Plot showing results of experiment where the applied bias field was modelled with splines. Bottom: Plot showing results of experiment where the applied bias field was modelled with DCT bases.

Figure 8.
Experiment with Varying the bias strength.

Figure 9.

Results with polynomial P (top row), spline S (middle row) and DCT D (bottom row) fields at bias level $s=1$. Graphs show Normalised SSD between ground truth and corrected images and the base which is the Normalized SSD between the ground truth and the uncorrected images. Top: Results with varying rotation error. Bottom: Results with varying translation error.

Figure 10.

Results with polynomial P (top row), spline S (middle row) and DCT D (bottom row) fields at bias level $s=2$. Graphs show Normalised SSD between ground truth and corrected images and the base which is the Normalized SSD between the ground truth and the uncorrected images. Top: Results with varying translation error. Bottom: Results with varying rotation error.

Figure 11.

Top: ICA Component Extracted in the Occipital Cortex and delineation of Seed region in green. Bottom: Correlation analysis of the brain using the seed extracted from this component. Red regions show high correlation.

(a) Bias Fields for Set 1

(b) Bias Fields for Set 2

(c) Bias Fields for Set 3

Figure 12.

Top Row of each figure: Bias fields applied to data, Bottom row of each figure: Bias fields estimated by MuVIIIE. In each field: Left - Axial View, Middle - Sagittal View, Right - Coronal View

(a) Difference of Set 1

(b) Difference of Set 2

(c) Difference of Set 3

Figure 13.
Differences between original and biased images of the three different experiments.

(a) Dataset 1

(b) Dataset 2

(c) Dataset 3

Figure 14.

Seed Analysis of Datasets 1,2 and 3. In each sub-figure, the top row shows the ground truth, the middle row shows correlation analysis on the uncorrected data (left) and data that is bias corrected with MuVIIIE (right) and the bottom row shows the difference between the ground truth and the obtained correlations. Brighter indicates larger differences.

(a) Subject 2

(b) Subject 3

Figure 15. Left to right: Original Frame, Bias Corrected Frames with N4ITK and MuVIIE. Top to bottom: rows show Axial, Sagittal and Coronal views.

Figure 16.

14 ICA components extracted from Subject 2 using single subject analysis. Each component is overlaid on an axial and sagittal view of the subject's brain. Top Row: No Bias Correction, Second Row: N4ITK, Third Row: MuVIIIE

Figure 17.

14 ICA components extracted from Subject 3 using single subject analysis. Each component is overlaid on an axial and sagittal view of the subject's brain. Top Row: No Bias Correction, Second Row: N4ITK, Third Row: MuVIE

Table 1
Settings for 12 different experiments for evaluating robustness to noisy registration estimates

Strength Value (s)	Type of Field	Registration Error
1	Polynomial	Rotation
1	Polynomial	Translation
1	Spline	Rotation
1	Spline	Translation
1	Dct	Rotation
1	Dct	Translation
2	Polynomial	Rotation
2	Polynomial	Translation
2	Spline	Rotation
2	Spline	Translation
2	Dct	Rotation
2	Dct	Translation

Table 2

Mean Normalized SSD for each dataset. The second column shows the difference between the ground truth and the images after the bias field has been applied. The third column shows the difference to the ground truth after bias correction with MuVIIE. The last column shows the difference between the applied field and estimated field.

Dataset	Without Correction	After Correction	Field Distance
1	0.0171	0.0076	0.832
2	0.0401	0.0074	1.042
3	0.0483	0.0084	3.064