Published in final edited form as:

Med Image Anal. 2009 February ; 13(1): 36–48. doi:10.1016/j.media.2008.05.003.

Restoration of MRI data for intensity non-uniformities using local high order intensity statistics

Stathis Hadjimetriou^{a,*}, Colin Studholme^b, Susanne Mueller^b, Michael Weiner^b, and Norbert Schuff^b

^a NCIRE/VA UCSF, Department of Radiology, Center for Imaging of Neurodegenerative Diseases, 4150 Clement Street, San Francisco, CA 94121, United States

^b VA UCSF, Department of Radiology, Center for Imaging of Neurodegenerative Diseases, 4150 Clement Street, San Francisco, CA 94121, United States

Abstract

MRI at high magnetic fields (>3.0 T) is complicated by strong inhomogeneous radio-frequency fields, sometimes termed the “bias field”. These lead to non-biological intensity non-uniformities across the image. They can complicate further image analysis such as registration and tissue segmentation. Existing methods for intensity uniformity restoration have been optimized for 1.5 T, but they are less effective for 3.0 T MRI, and not at all satisfactory for higher fields. Also, many of the existing restoration algorithms require a brain template or use a prior atlas, which can restrict their practicalities. In this study an effective intensity uniformity restoration algorithm has been developed based on non-parametric statistics of high order local intensity co-occurrences. These statistics are restored with a non-stationary Wiener filter. The algorithm also assumes a smooth non-uniformity and is stable. It does not require a prior atlas and is robust to variations in anatomy. In geriatric brain imaging it is robust to variations such as enlarged ventricles and low contrast to noise ratio. The co-occurrence statistics improve robustness to whole head images with pronounced non-uniformities present in high field acquisitions. Its significantly improved performance and lower time requirements have been demonstrated by comparing it to the very commonly used N3 algorithm on BrainWeb MR simulator images as well as on real 4 T human head images.

Keywords

Image intensity restoration; MRI bias field correction; Co-occurrence statistics; High order image statistics; Non-stationary Wiener filtering

1. Introduction

In vivo human magnetic resonance imaging (MRI) is a non-invasive imaging technique that provides good quality volumetric data sets. It is used in clinical practice and research for studying anatomy and pathology such as brain injury and neurodegenerative diseases. Longitudinal MRI can also be used to monitor the progression of these conditions or their potential reversal with treatment. The qualitative interpretation of such data or the user-driven quantitative interpretation is very limited and cumbersome due to the data size. Qualitative analysis is also not reproducible. To take advantage of the imaging data the quantification must be done automatically.

The accurate acquisition of MRI data requires a homogeneous radio-frequency field, which is not possible to achieve. The inhomogeneity is sometimes termed the “bias field”. The non-uniform radio-frequency field results in non-biological intensity non-uniformities across the image. While a new generation of high field MRI scanners (>3.0 T) has significantly improved the resolution of MR imaging, it suffers from more pronounced intensity non-uniformities. In high fields the radio-frequency wavelength gets shorter, approaching the dimension of the human head or body (Sled and Pike, 1998). The local dielectric properties of these regions lead to non-uniformity of image intensity, greatly complicating further automatic analysis such as registration and tissue segmentation.

There have been several attempts to correct for non-uniformity during acquisition based on its physical properties. The non-uniformity of the transmission coil has been estimated from its frequency response to parameterized acquisition sequences (Stollberger and Wach, 1996; Vita et al., 2004; Noterdaeme and Brady, 2008). In addition, the non-uniformity of transmission and receiver coil(s) combined has been approximated using phantoms (Axel et al., 1987; Wang et al., 2005). However, the physical correction methods are valid only for particular MRI sequences and do not account for the complicated interaction between the radio-frequency fields and the human body. It is not obvious how the combined non-uniformities can be accounted for during acquisition, especially for higher magnetic fields. Thus, existing methods for correction of the non-uniformities during acquisition are incomplete, time consuming, and clinically impractical.

As an alternative to physical corrections, several post-acquisition image restoration methods have also been proposed to account for the effect of the non-uniformities. Their main advantage are that they do not require additional acquisitions and are applicable to a range of MRI contrast mechanisms (Arnold et al., 2001; Belaroussi et al., 2006; Hou, 2006; Vovk et al., 2007). They make regularity assumptions about the field non-uniformity as well as about the anatomy and treat the non-uniformity in the same way irrespective of its sources. Typically, they operate on the logarithm of image intensities (Guillemaud and Brady, 1997; Leemput et al., 1999a; Zhang et al., 2001) and assume that the non-uniformity can be approximated by basis functions such as Gaussians, splines, polynomials, or sinusoids. Existing methods for intensity uniformity restoration have been optimized for 1.5 T images, but they are less effective for 3.0 T MRI, and not at all satisfactory for higher fields. The simplest type of restoration has been homomorphic filtering (Brinkmann et al., 1998; Cohen et al., 2000). This is based on the assumption that the non-uniformity corresponds to spatial frequencies lower than those of the anatomy. Thus, the non-uniformity is computed by smoothing an image in the spatial or frequency domain. Smoothing has also been applied to statistics of local histograms computed over image tiles (DeCarli et al., 1996; Brinkmann et al., 1998). The basic assumption of homomorphic filtering, that the spatial frequencies of the non-uniformity are lower than those of the anatomy, can be problematic for high field MR images. In such images the non-uniformity can extend from the low frequency part of their spectrum until the intermediate frequency range.

Another class of image restoration approaches estimates the non-uniformity based on a registered reference image directly (Studholme et al., 2004) or indirectly through registered tissue templates, which are used as priors (Leemput et al., 1999a; Pohl et al., 2002). Non-uniformity estimation has also been combined with tissue classification. Several such approaches require initialization with manual presegmentation (Dawant et al., 1993; Wells et al., 1996; Held et al., 1997; Styner et al., 2000) while others are automatic (Meyer et al., 1995; Prima et al., 2001). Some of these approaches perform tissue classification from the intensity histogram using a variety of methods such as expectation maximization (Dempster et al., 1977; Wells et al., 1996; Held et al., 1997; Guillemaud and Brady, 1997; Leemput et al., 1999a; Ashburner and Friston, 2000), fuzzy c-means classification (Pham and Prince, 1999;

Ahmed et al., 2002), as well as energy minimization (Styner et al., 2000). Intensity tissue classification has also been enhanced by breaking an image spatially into subregions (Gilles et al., 1996; Lee and Vannier, 1996) as well as by using Markov random fields (Held et al., 1997; Leemput et al., 1999b; Zhang et al., 2001). Estimating the non-uniformity with prior tissue images necessitates an accurate registration of the image to their space. The accuracy of registration, particularly in the non-rigid case (Pohl et al., 2002), can be affected by a pronounced non-uniformity such as that present in >3 T images. This poses a problem when registration is used to extract the brain region from a head image during preprocessing. Also, the tissue template priors may be unable to represent the intensity variations of anatomy or pathology in an image.

Several non-parametric image restoration approaches have been suggested that are more robust to intra and inter subject variability as well as pathology. One such class of non-parametric techniques is based on the retinex algorithm (Brainard and Wandell, 1986; Kimmel et al., 2003; Rising, 2004). This algorithm operates on the logarithm of the intensities and normalizes them to their geometric mean within a neighborhood. Thus, it enhances the components of the non-uniformity whose wavelengths are close to the size of the neighborhood considered and introduces overshooting contours at the borders between different tissue regions (Brainard and Wandell, 1986). This problem can be alleviated but not resolved with a multiresolution image representation computed with Gaussian or wavelet bases (Han et al., 2001; Rising, 2004). Another class of non-parametric approaches assumes that the image is a piecewise union of extensive regions of constant intensity. These methods compute a derivative of an image such as the gradient or the Laplacian and threshold the low values, which are attributed exclusively to non-uniformities. The thresholded derivative image is incorporated into a regularized cost functional whose minimization estimates the non-uniformity (Vokurka et al., 1999; Lai and Fang, 1999; Luo et al., 2005). The assumption of extensive homogeneous regions is inappropriate for many anatomical regions including the brain cortices, which are regions of great interest in a variety of neurological studies. Both the retinex algorithm as well as the variational methods operate locally and do not necessarily restore global image statistics. They are also based on the distinction between low frequency non-uniformity and high frequency anatomy. More generally, the use of differential image properties (Vovk et al., 2004) may lead to intensity uniformity restorations which are correlated with image structure.

Another class of non-parametric techniques uses directly the global intensity histogram of an image (Viola, 1995; Sled et al., 1998; Likar et al., 2001). These techniques assume that the non-uniformity widens the intensity distributions of the various tissues. Thus, the sharpening of the histogram is assumed to restore intensity uniformity. This is achieved by also obtaining a smooth estimate of the non-uniformity. Such a histogram based technique, N3 (Sled et al., 1998), was found to have a performance superior to homomorphic filtering (Arnold et al., 2001). An extensively used criterion for histogram sharpness has been the minimum entropy (Viola, 1995; Mangin, 2000; Likar et al., 2001; Bansal et al., 2004). The statistics of different regions corrupted by high spatial non-uniformity may have a considerable overlap in the intensity histogram.

A non-parametric approach for intensity uniformity restoration is being described that is effective for high field MRI especially for brain imaging (Hadjidemetriou et al., 2007). It is based on local high order intensity coincidence or co-occurrence statistics. The non-parametric processing increases the robustness of the approach to subject anatomy, pathology, as well as intensity variations within a tissue. The co-occurrence statistics represent the intensities of different tissues as well as the joint intensities of adjacent tissues. The high order of coincidences favors the dominant distributions and selectively decreases the contribution of noise to their variance. The effect of the image intensity distortion on the co-occurrence statistics is assumed to be equivalent to linear filtering with a physically motivated smooth

point spread function. It is used to design a non-stationary Wiener filter (Kuan et al., 1985; Haykin, 2002) to restore the statistics. The algorithm is also based on the reasonable assumption that the non-uniformity is smoothly varying in space. The restoration algorithm is iterative with a robust stopping criterion based on the entropy of the co-occurrence distribution normalized with respect to the effective dynamic range, namely, the scaled entropy. This algorithm is shown to effectively perform intensity uniformity restorations of human head data acquired under high field with an emphasis on the brain region that gives rise to the dominant distributions of the white matter and of the region around the interface between white matter and gray matter. The co-occurrence algorithm was compared to the commonly used N3 algorithm (Sled et al., 1998) with phantom as well as with real images. The algorithm developed in this work has been found to have a superior performance.

2. Methods

The image model emphasizes the effect of spatial intensity non-uniformity. This distortion is also assumed to be spatially smooth. Thus, image noise, which has high spatial frequencies, is not considered. The restoration is iterative with a stable stopping criterion. An overview of the algorithm is sketched in Fig. 5.

2.1. Model of the intensity non-uniformity

The relation between the measured image I and the true anatomic image I_A is assumed to be

$$I = BI_A + N_I, \quad (1)$$

where matrix B contains the unknown non-uniformity field and the image noise N_I is additive. The statistics of I_A are assumed to consist of distributions that can be discriminated. The Taylor series expansion of the non-uniformity, B , around a voxel $\mathbf{x}_0$ gives

$$B(\mathbf{x}) = B(\mathbf{x}_0) + \nabla B(\mathbf{x})|_{\mathbf{x}_0} (\mathbf{x} - \mathbf{x}_0) + O(\mathbf{x}^2). \quad (2)$$

Approximation up to the first-order term leads to a non-uniformity which is locally linear within a sphere of radius $\rho = |\mathbf{x} - \mathbf{x}_0|$ around $\mathbf{x}_0$. Thus, quadratic and higher-order terms are assumed to be negligible within distance ρ from $\mathbf{x}_0$. The non-uniformity is recovered within a scale factor which does not affect the discriminability between tissues. The image noise N_I in Eq. (1) is also assumed to be Gaussian, stationary, and white (Gudbjartsson and Patz, 1995).

2.2. Preprocessing for selection of the valid intensity range of an image

The non-uniformity assumption of Eq. (1) does not hold in areas of an MR image with very bright artifacts such as those caused by instrumental imperfections or blood flow. The dynamic range they correspond to is detected and removed and only the valid dynamic range of the MR contrast mechanism is retained. This is achieved using the histogram h of the original image I and its cumulative histogram $\mathcal{H} = \int_u h du$. The intensity value $u^{0.9}$ that corresponds to the upper 0.9 percentile of $\mathcal{H}$, $\mathcal{H}(u^{0.9}) = 0.9$ is computed. The intensity range up to $1.5 \times u^{0.9}$ is preserved, whereas the intensity range beyond that value is linearly compressed to the range $(1.5 \times u^{0.9}, 3.0 \times u^{0.9}]$ with maximum intensity $u'_{\max} = 3.0 \times u^{0.9}$. In an MR image with two bytes per voxel the value of $u'_{\max}$ can be a very large number. In such cases the intensity range up to $u'_{\max}$ is further subsampled linearly to a smaller maximum value $u_{\max}$ to improve the efficiency of the restoration. The resulting intensity range $[0, u_{\max}]$ of the initial image I_0 is preserved during the iterations t . An image is the map from its three-dimensional domain $D \in \mathbf{x}$ to its intensity range, $I_t: D \rightarrow [0, u_{\max}]$.

2.3. High order intensity co-occurrence statistics

The statistics of image I_t used in this work are the n th-order coincidences or co-occurrences between pairs of intensities within spherical neighborhoods of radius ρ . The non-uniformity in windows of this size is assumed to be linear. The count of intensities in the range $u \in [0, u_{\max}]$ in a sphere of radius ρ around voxel $\mathbf{x}_0$ is given by

$$h_t(\mathbf{x}_0, \rho, u) = \int_{I_t^{-1}(u) \cap \|\mathbf{x} - \mathbf{x}_0\| \leq \rho} d\mathbf{x}. \quad (3)$$

In an n th-order co-occurrence between intensity u_0 and intensity u_1 the center of the spherical neighborhood has intensity u_0 and the remaining window contains at least $n - 1$ voxels of the same intensity and at least n voxels of intensity u_1 . Additional voxels of any of the two intensities within the spherical window π give the co-occurrence:

$$c_t(\mathbf{x}_0, \rho, u_0, u_1) = \begin{cases} h_t(\mathbf{x}_0, \rho, u_0) + h_t(\mathbf{x}_0, \rho, u_1) - 2n \\ \text{if } I_t(\mathbf{x}_0) = u_0 \cap h_t(\mathbf{x}_0, u_0) \geq n \cap h_t(\mathbf{x}_0, u_1) \geq n \\ 0 \text{ otherwise,} \end{cases} \quad (4)$$

where $c_t(\mathbf{x}_0, \rho, u_0, u_1)$ are the co-occurrences with intensity u_0 at $\mathbf{x}_0$ for radius ρ and iteration t . The intensity co-occurrences are integrated over the entire image domain to give a 2D matrix. In images with a subsampled intensity range the direct computation of these statistics can lead to indentation artifacts. This problem is addressed using a two-dimensional Gaussian Parzen window $G(\sigma_c)$ during the integration of the statistics to give the probability distribution:

$$C_t(\rho, u_0, u_1) = \int_{D_{u'_1, u'_0}} C_t(\mathbf{x}, \rho, u'_0, u'_1) G(u'_0 - u_0; \sigma_c) \times G(u'_1 - u_1; \sigma_c) du'_0 du'_1 d\mathbf{x}. \quad (5)$$

The 2D matrix, C_t , is not necessarily symmetric for high order of co-occurrences with $n > 1$. The co-occurrences in a region with a contiguous tissue lie close to the diagonal of matrix C_t . The co-occurrences at an interface of different tissues lie farther from the diagonal. To examine the properties of the restoration the co-occurrence distributions of an intensity uniform image are assumed to be Gaussian. In Appendix A.1 it is shown that regions of contiguous tissue in an image have intensity co-occurrence statistics whose variance is lower than the statistics in the intensity histogram.

2.4. Effects of image distortions on the co-occurrence statistics

Fig. 1 shows the effects of some types of image intensity distortions on the co-occurrence statistics using BrainWeb T1 phantom images (Cocosco et al., 1997; Collins et al., 1998). In the first row is the true uncorrupted T1 phantom image. The distributions in its co-occurrence matrix are sharp. The horizontal and vertical streaks are caused by the partial volume artifact simulated in the phantom. The second row shows an image without intensity non-uniformity, but with high Gaussian noise $N_1 = 5\%$. The distributions in its co-occurrence matrix are Gaussians. The presence of additive zero mean Gaussian noise N_1 in an image increases the variances of the distributions in the statistics C of the image. The third row in Fig. 1 shows a phantom with low noise $N = 3\%$ and high intensity non-uniformity $B = 40\%$. The effect of the non-uniformity is primarily to elongate the distributions along lines passing from the origin.

Image intensity non-uniformity affects intensity co-occurrences between u_0 and u_1 , where u_0 is the intensity of the central voxel at $\mathbf{x}_0$ in a hypothetical anatomic image I_A . The effect is to

scale and rotate the co-occurrences about the origin of C_{I_A} . The zero-order term $B(\mathbf{x}_0)$ in Eq. (2) scales the co-occurrences around the origin. The first-order term $\nabla B(\mathbf{x}_0)$ in Eq. (2) rotates them around the origin. The geometry of the angular distortion in the statistics is demonstrated in Fig. 9a. The effect of the non-uniformity on the co-occurrence statistics C is simpler to

examine in polar coordinates (r, ϕ) , where $r = \sqrt{u_0^2 + u_1^2}$ and $\tan \phi = u_1/u_0$. The effect of the non-uniformity B on the co-occurrence statistics of the true image C_{I_A} is assumed to be equivalent to linear filtering with a Gaussian point spread function both along the radial dimension r as well as along the angular dimension ϕ . The co-occurrence statistics of the initial image C_{I_0} are also assumed to be corrupted by additive Gaussian noise N_C . Thus, the effect of the image distortion in Eq. (1) on the co-occurrence statistics is given by $C_{I_0} = C_{I_A} * G(\sigma_r) * G(\sigma_\phi) + N_C$, where σ_r and σ_ϕ are the standard deviations of the point spread functions in the radial and angular directions, respectively.

The standard deviation σ_r of the radial point spread function $G(\sigma_r)$ depends on the mean value of the non-uniformity, $B(\mathbf{x}_0)$. It is shown in Appendix A.2 to be

$$\sigma_r \propto B(\mathbf{x}_0) r. \quad (6)$$

The standard deviation σ_ϕ of the angular point spread function $G(\sigma_\phi)$ depends on the mean value of the gradient of the non-uniformity, $\mu_{\nabla B} = \nabla B(\mathbf{x}_0)$. It is shown in Appendix A.3 that

$$\sigma_\phi = 2 \sin^{-1} \left[\frac{1}{\sqrt{2}} \sqrt{1 - \frac{1 + \tan^2 \phi (1 + \mu_{\nabla B})}{\sqrt{(1 + \tan^2 \phi) (1 + \tan^2 \phi (1 + \mu_{\nabla B})^2)}}} \right]. \quad (7)$$

The value of σ_ϕ as a function of ϕ for a fixed value of $\mu_{\nabla B}$ is plotted in Fig. 9b.

2.5. Restoration of the co-occurrence statistics for image intensity uniformity

At each iteration t of the algorithm the effect of the non-uniformity on C_t is unmixed. This is achieved by considering the point spread functions of the distortion whose statistics are given by Eqs. (6) and (7). They are used to compute non-stationary Wiener restoration filters for the image statistics. The radial and angular restoration filters are the inverses of the Gaussian point spread functions of the distortions:

$$f_r = \frac{G(\sigma_r)}{\|G(\sigma_r)\|_2^2 + \epsilon} \quad \text{and} \quad f_\phi = \frac{G(\sigma_\phi)}{\|G(\sigma_\phi)\|_2^2 + \epsilon} \quad (8)$$

bounded by ϵ . This parameter represents the inverse signal to noise, N_C , ratio of the statistics. The shape of the Wiener restoration filters is shown in Fig. 2. In Eq. (6) the radial distortion is proportional to r . Thus, the size of the radial restoration filter has the same linear dependence, $\sigma_r \propto r$. The size of the radial restoration filter in the algorithm is its standard deviation normalized with respect to the dynamic range to give its normalized standard deviation:

$$\sigma_r^n = \frac{\sigma_r}{u_{\max}}. \quad (9)$$

The angular restoration filter is represented in terms of radians, and hence it is inherently normalized to the radius r in C_t , which is the dynamic range. The normalized standard deviation of the angular restoration filter, σ_ϕ^n , is determined from Eq. (7). The total Wiener restoration filter is the convolution of the two filters $f_q = f_r * f_\phi$, where $*$ is convolution, and is two-dimensional. A figure with different sizes for the non-stationary Wiener filter is in Fig. 3. The restoration filter f_q is applied to the co-occurrence matrix C_t and maps every co-occurrence (u_0, u_1) in polar coordinates (r, ϕ) to an expected one (r^q, ϕ^q) given by

$$(r^q, \phi^q) = \frac{\int_{r'} \int_{\phi'} f_r(r' - r, \sigma_r) f_\phi(\phi' - \phi, \sigma_\phi) (r', \phi') dr' d\phi'}{\int_{r'} \int_{\phi'} f_r(r' - r, \sigma_r) f_\phi(\phi' - \phi, \sigma_\phi) dr' d\phi'}. \quad (10)$$

The expected polar coordinates (r^q, ϕ^q) are transformed to the expected rectangular ones to give (u_0^q, u_1^q) . The mapping in Eq. (10) gives a restoration matrix R_t with a gain factor for each intensity co-occurrence, which is the ratio of the expected restored intensity u_0^q of the central voxel over its initial intensity u_0 . Thus, the restoration factor or gain is $R_t(u_0, u_1) = u_0^q / u_0$. The co-occurrence statistics of the T1 BrainWeb phantom images in Fig. 1b are used to compute the restoration matrices shown in Fig. 1c.

2.6. Estimation of the spatial non-uniformity and image restoration

The product in Eq. (1) is decomposed to estimate I_t as well as a smooth estimate of the non-uniformity B at iteration t , B_t . To this end the restoration matrix R_t is first backprojected to the image. The backprojection to a voxel $\mathbf{x}_0$ is performed using a sphere of radius ρ around it. The size of this neighborhood is the same as the size of the neighborhood that is used to compute

the co-occurrence statistics C_t . The sphere gives $(\frac{4}{3}\pi\rho^3 - 1)$ intensity co-occurrences with intensity u_0 of voxel $\mathbf{x}_0$. These co-occurrences index the restoration matrix R_t to obtain an equal number of gain factors. Their expected value gives a rough estimate of the restoration image W_t^{rough} at $\mathbf{x}_0$:

$$\begin{aligned} W_t^{\text{rough}}(\mathbf{x}_0) &= E_{\mathbf{x}_1}(R_t(I_t(\mathbf{x}_0), I_t(\mathbf{x}_1))) \\ &= \frac{1}{(\frac{4}{3}\pi\rho^3 - 1)} \sum_{|\mathbf{x}_1 - \mathbf{x}_0| \leq \rho} R_t(I_t(\mathbf{x}_0), I_t(\mathbf{x}_1)). \end{aligned} \quad (11)$$

The rough estimate of the spatial restoration given by this equation is the inverse of the rough estimate of the non-uniformity $W_t^{\text{rough}}(\mathbf{x}_0) = 1/B_t^{\text{rough}}(\mathbf{x}_0)$. The non-uniformity is assumed to be smooth. Thus, the restoration image W_t^{rough} is filtered with a spatial Gaussian filter $G(\sigma_w)$ to give $W_t^{\text{smooth},t} = W_t^{\text{rough}} * G(\sigma_w)$. In the first row of Fig. 4 is a T1 BrainWeb phantom image with $B = 40\%$ and $N = 5\%$. The rough estimate of the non-uniformity in this image is in the second row of this figure. In the third row of Fig. 4 is a smooth estimate of the non-uniformity.

The Wiener filtering can contract the effective dynamic range of an image. The dynamic range is renormalized at each iteration t to preserve the relative size of the Wiener restoration filter given in Eq. (9). The re-normalization is done by rescaling the intensity range to ensure that the upper 0.9 percentile, $u^{0.9,t}$, of the cumulative histogram $\mathcal{H}_t$, $\mathcal{H}_t(u^{0.9,t}) = 0.9$ remains constant with iterations t . The correction for the non-uniformity at iteration t is given by

$$W_t^{\text{smooth}} = W_t^{\text{smooth},t} \frac{u^{0.9,0}}{u^{0.9,t}}. \text{ It is applied to the restored image at iteration } t \text{ pixelwise,}$$

$$I_{t+1} = I_t \times W_t^{\text{smooth}}, \quad (12)$$

to improve its estimate. The correction of the non-uniformity is initialized at $t = 0$ to unity $W_0^{\text{smooth}} = 1 \forall \mathbf{x}$.

2.7. Condition for the end of the iterations

The steps of the algorithm described in Sections 2.3, 2.5, 2.6 are repeated iteratively. The effect of the spatial non-uniformity on the co-occurrence statistics is assumed to be equivalent to filtering with a Gaussian point spread function. The Shannon entropy of the co-occurrence statistics of a corrupted image is larger than the one of the assumed underlying anatomic image, $S(C_{I_0}) > S(C_{I_A})$. The Shannon entropy of the co-occurrence statistics of the image decreases monotonically with iterations as a result of Wiener filtering, $S(C_{I_{t+1}}) < S(C_{I_t})$. However, the Shannon entropy of the co-occurrence statistics of an image computed over the normalized effective dynamic range, namely, the scaled entropy of the co-occurrence matrix is a non-monotonic function of the iterations t . Thus, the scaled entropy can be used directly in the stopping criterion of the iterations. In iterations t in which the scaled entropy increases or is stationary $S_{sc}(C_{t+1}) \geq S_{sc}(C_t)$, the size of the restoration filter is halved $\sigma_{q,t+1}/2$. The iterations end when the size of the restoration filter becomes unity, $\sigma_{q,t} = 1$ or at an upper bound on the allowed number of iterations $t_{\max}$. The restored image is the one whose co-occurrence matrix has minimum scaled entropy $t_{\text{restored}} = \min_{t \in [0, t_{\max}]} S_{sc}(C_t)$.

2.8. Implementation and efficiency of the algorithm

The level of sensitivity of the algorithm to its parameters' settings varies with three being the most significant for its performance. These are the size of the Wiener filter for the restoration of the statistics σ_q^n , the size of the smoothing filter for the spatial uniformity σ_w , and the size of the co-occurrence window ρ . The parameter of the Parzen window σ_c is selected together with the number of intensity levels so that the co-occurrence statistics do not contain indentation artifacts. The elimination of this artifact improves the robustness of the algorithm to the value of ϵ , which represents the regularization for the presence of noise in the statistics. The Wiener restoration filter f_q of the co-occurrences C_t is separable. Its size is bounded to improve the robustness of the restoration with respect to high intensity artifacts due to instrumental imperfections and blood flow. A bound on the size of the Wiener filter also avoids an unnecessary increase of the computational cost. The maximum radial size $\sigma_{r,\max}$ of the filter corresponds to radial distance in C_t equal to $u^{0.9,0}$ of the histogram of the original image

I_0 , $\sigma_{r,\max} = \sigma_r^n u^{0.9,0}$. The size of the angular restoration filter $\sigma_{\phi,\max}$ is also bounded for similar reasons. It is obtained for $u^{0.9,0}$ in the radial coordinate of C_t and for $\phi = 45^\circ$ in the angular coordinate of C_t with a certain value of $\mu_{\nabla B}$ in Eq. (7). The small value of the spatial window of radius ρ required for the computation of the local co-occurrence statistics limits the value of σ_ϕ^n and makes the significance of the radial standard deviation σ_r^n greater. The computation of the co-occurrence matrix C_t with the discretized version of Eq. (5) can be accelerated with minimal loss of accuracy by spatially subsampling the voxels in the spherical neighborhood considered of radius ρ either randomly or regularly in steps of Δx_1 , Δx_2 , and Δx_3 . The same subsampling can be used to compute the rough non-uniformity correction W_t^{rough} in the discretized version of Eq. (11).

The rough spatial estimate of the non-uniformity is smoothed using a spatial Gaussian multiresolution pyramid (Burt and Adelson, 1983). The rough spatial estimate is first subsampled with a Gaussian pyramid to a fraction of its size. The smoothing with $G(\sigma_w)$ is performed in the low resolution. It is then upsampled with a Gaussian filter as well to give the

smooth non-uniformity in the original resolution. During the first $t_{\max}/3$, $[0, t_{\max}/3)$, iterations the rough estimate is subsampled to 25% in each of its three dimensions x_1 , x_2 , and x_3 . If the subsequent $t_{\max}/3$, $[t_{\max}/3, 2t_{\max}/3)$, iterations are performed, the rough estimate is subsampled to 50% in each of its dimensions. If the last $t_{\max}/3$, $[2t_{\max}/3, t_{\max})$, iterations are performed, the rough estimate is not subsampled and is smoothed in its original resolution. The Gaussian filtering that was used to both compute the pyramid of W_t^{rough} and to smooth the non-uniformity was performed separably along the axes to improve efficiency. The algorithm can be accelerated further, however, with some loss of accuracy. The effect of the smooth non-uniformity correction W_t^{smooth} in Eq. (12) can be accentuated with a multiplicative factor $\kappa > 1$ to give $I_{t+1} = I_t \times (1 + \kappa (W_t^{\text{smooth}} - 1))$. The algorithm was implemented in the C++ programming language.

3. Evaluation

The co-occurrence algorithm has been evaluated with phantom images from the BrainWeb MR simulator (Cocosco et al., 1997; Collins et al., 1998) as well as with real head images acquired at 4 T. The processing was performed on whole head images. The co-occurrences in Eqs. (4) and (11) were computed in a sphere of $\rho = 9\text{mm}$ with regular subsampling factors $\Delta x_1 = \Delta x_2 = \Delta x_3 = 3\text{mm}$. The order of the statistics was $n = 2$ which favors the restoration of whole head images. The mean value of the gradient of the non-uniformity in Eq. (7) was $\mu_{\nabla B} = 0.3$ and the standard deviation of the Parzen window in Eq. (5) was $\sigma_c = 1.5$. The maximum number of the iterations was set to $t_{\max} = 40$. The two image sets were also processed with N3 (Sled et al., 1998), a very commonly used technique for bias field correction (Arnold et al., 2001). It was applied with the least spatial decimation factor of two and with a maximum of 1000 iterations. The distance d_{N3} between the knots of the spline bases was set to the value recommended by the authors $d_{N3} = 200\text{mm}$ (Sled et al., 1998). The real images were acquired with fields higher than those with which the N3 algorithm was originally evaluated. Thus, the N3 corrections were also performed with the additional settings $d_{N3} = 110\text{mm}$ and $d_{N3} = 20\text{mm}$.

The restorations of both the phantom as well as the real images were evaluated with a measure of the contrast between the intensity statistics of the gray matter (GM) and the white matter (WM). The contrast was quantified with the coefficient of joint variation (CJV) (Likar et al., 2001; Vovk et al., 2004):

$$\text{CJV}(\text{GM}, \text{WM}) = \frac{\sigma_{\text{GM}} + \sigma_{\text{WM}}}{|\mu_{\text{GM}} - \mu_{\text{WM}}|}, \quad (13)$$

where μ_{GM} and μ_{WM} are the means of the tissue intensities, and σ_{GM} and σ_{WM} are their standard deviations. This measure has been used extensively for the evaluation of the performance of intensity uniformity restoration algorithms (Vovk et al., 2004). It represents both the uniformity of the intensity within individual tissue regions as well as the contrast between the intensity distributions of different tissue regions. The N3 correction with the minimum CJV over the three settings for parameter d_{N3} was compared with the co-occurrence correction to give the relative improvement in the performance of the co-occurrence algorithm as $(\text{CJV}_{N3} - \text{CJV}_{\text{co-oc}})/\text{CJV}_{N3}$. The experiments were performed on a Xeon processor of 3.6 GHz and 8 GB of RAM.

3.1. Preprocessing for the extraction of the signal region in an image

An image is first preprocessed to remove regions of low signal that correspond to background or noise, such as those present in the whole head images used in this work. The signal regions

are extracted using the one-dimensional diagonal self-co-occurrence statistics of the intensities. The noise in these statistics corresponds to a distribution of low variance in the low intensity range. The noise due to the acquisition in a magnitude MR image is given by a Rayleigh

distribution, $P(N_I) \propto \left(u/\sigma_{N_I}^2\right) e^{-u^2/2\sigma_{N_I}^2}$ (Rice, 1945; Gudbjartsson and Patz, 1995), where σ_{N_I} is the standard deviation. This distribution is fit using the intensity and density value of the peak noise density. The computed noise distribution is subtracted from the image distribution to give the remainder distribution. The intensity range where the noise density is greater than the remainder density gives the intensity range of the noise.

The spatial locations that correspond to noise intensities are assigned to the background. The remaining region, the signal region, is processed to compute its largest connected component. It is computed at a low image resolution for efficiency with a limited loss of accuracy and is then upsampled to the original image resolution. The non-uniformity is first computed only over the signal region and is subsequently extrapolated to the low signal or no signal regions. The extrapolation is performed by solving numerically Laplace's equation $\nabla^2 B = 0$ over the low signal domain. The boundary conditions are Dirichlet with the non-uniformity kept fixed over the signal region.

3.2. Phantom images

The algorithm was tested on images from the most commonly used MRI contrast mechanisms T1, T2, and proton density (PD), which were available from the BrainWeb MR simulator. The nominal resolution of the images is $1 \times 1 \times 1 \text{ mm}^3$ at a matrix size of $181 \times 217 \times 181$ voxels. The data for the three contrasts are the true images with noise level $N_I = 0\%$ and non-uniformity level $B = 0\%$ as well as images corrupted with noise level $N_I = 5\%$ and non-uniformity levels of $B = 0\text{--}20\text{--}40\%$. The parameter FWHM of N3 was set to 0.15 as suggested by the authors for this set of images (Sled et al., 1998). In the co-occurrence algorithm the size of the Wiener restoration filter was $\sigma_r^n = 0.03$ and the spatial smoothing of the non-uniformity was set to $\sigma_w = 75 \text{ mm}$.

The restorations of the whole head phantom images were first evaluated with the intensity statistics of the gray matter and white matter regions using the coefficient of joint variation (CJV) given in Eq. (13) (Likar et al., 2001; Vovk et al., 2004). The ground truth image regions occupied by each of the two tissues were obtained from the BrainWeb simulator (Cocosco et al., 1997; Collins et al., 1998). The coefficients of joint variation for all T1, T2, and PD phantom image corrections are given in Tables 1-3, respectively. In the last row of these tables is the relative improvement in the performance of the co-occurrence algorithm compared to that of N3 for each image. The co-occurrence algorithm performs clearly better than N3 for the T2 and PD images corrupted with non-uniformity level 40%. This demonstrates the robustness of the co-occurrence algorithm to the low contrast between the intensity statistics of gray matter and white matter tissues present in T2 and PD images. The performance of the two algorithms for non-uniformities of very low levels 0–20% is comparable. The corruption of the images by noise also affected the values of the CJV.

The performance of the algorithm for this data set was also evaluated by comparing directly the estimated intensity non-uniformities with the true intensity non-uniformities available from the BrainWeb MR simulator. Even though the corrections were performed over the whole head, the evaluations were only done over the brain region. This is the region occupied by white matter, gray matter, glial matter, and cerebrospinal fluid in the BrainWeb anatomical model. The non-uniformities are computed and are defined within a scale factor. Thus, they were first normalized to a unit average value, $\bar{B}$. The L_1 norm of their difference per pixel gives the measure of the error in the non-uniformity estimate:

$$e = \frac{1}{m} \|\bar{B}_{\text{est}} - \bar{B}_{\text{true}}\|_1, \quad (14)$$

where m is the total number of pixels in the brain mask, $\bar{B}_{\text{est}}$ is the normalized estimated non-uniformity, and $\bar{B}_{\text{true}}$ is the normalized true non-uniformity. The performance of the N3 algorithm with the least error over the three settings for parameter d_{N3} was compared to the performance of the co-occurrence algorithm to give the improvement achieved with the latter algorithm, $e_{N3} - e_{\text{co-oc}}$.

The computed errors in the non-uniformity estimates for the T1, T2, and PD images in the phantom set are given in Tables 4-6, respectively. The relative improvement in the performance of the co-occurrence algorithm is given in the last row of these tables. The co-occurrence algorithm performs better than N3 for the images corrupted with intensity non-uniformities, both for level 20% and for level 40%. The performance of the two algorithms for the images without intensity non-uniformity is comparable. The improvement with the co-occurrence algorithm is greater for the T2 and for the PD images than for the T1 images. This demonstrates the greater robustness of the co-occurrence algorithm with respect to the lower contrast between the tissue statistics present in the T2 and the PD images.

The results for the restorations of the phantom images corrupted with the highest amount of non-uniformity used 40% and noise level of 5% are in Fig. 6a-c for the T1, T2, and PD images, respectively. The first column shows the original corrupted images. The second column shows the true intensity non-uniformity. The remaining two columns show the absolute value of the difference, as it is given in Eq. (14), between the non-uniformity estimates and the true non-uniformity. In the third column is the error image for the N3 estimate and in the fourth column is the error image for the co-occurrence estimate. The largest error with the N3 algorithm is demonstrated by the largest magnitude of the intensity in its error images.

3.3. Human head images

The algorithm was evaluated with human head images of elderly subjects acquired at 4 T with an 8-channel array head coil. The 8-channel receiver coil had a larger field non-uniformity than a conventional birdcage coil but provided a better signal to noise ratio, especially at the outer brain regions close to the coils. A T1-weighted magnetization prepared rapid gradient echo (MPRAGE) sequence was used. The parameters of the sequence were TR/TE = 2300/3.37 ms, TI = 950 ms, and a flip angle of 7°. The nominal resolution of MPRAGE is $1.0 \times 1.0 \times 1.0$ mm³ at a matrix size of $256 \times 256 \times 176$ voxels. In the co-occurrence algorithm the size of the Wiener restoration filter was $\sigma_r^n = 0.015$ and the spatial smoothing of the non-uniformity was $\sigma_w = 30$ mm. A relatively small value for σ_r^n was selected for this image set to emphasize performance and a relatively small value of σ_w was selected due to the high level of non-uniformity present in the 4 T images.

The corrections were also performed with N3. The FWHM was set to a small value 0.1 to emphasize accuracy. The coefficients of joint variation were computed for all images with regions of interest selected from their white matter and their gray matter. The selections were manual and blind to the algorithm outputs. The regions of interest in each image were selected from all lobes of the brain, subcortical regions, and the cerebellum. The regions of interest for the white matter are located in the corpus callosum, subcortical white matter, deep white matter, and the cerebellum. The regions of interest for the gray matter are located in the thalamus as well as in the frontal, parietal, and occipital lobes of the brain. Gray matter regions from the medial temporal cortex were also selected due to their significance in studies of neurodegenerative diseases with elderly subjects. Regions with partial volume artifacts or brain

lesions were not selected. The coefficients of joint variation of the restorations with the two algorithms are given in Table 7. The best performing knot distance for N3 is $d_{N3} = 20$ mm. The corrections with the co-occurrence algorithm are significantly more accurate for all images. This demonstrates the robustness of the algorithm developed to the strong non-uniformities present in high field images as well as its ability to take advantage of the improved resolution present in these images.

The corrections of four representative images from those in Table 7 are shown in Fig. 7. In each example the first row shows the acquired image, the second row shows the restoration with N3, and in the last row is the restoration with the co-occurrence algorithm. The images are shown with their dynamic ranges windowed to those of their white matter intensities. The N3 restorations contain a considerable residual of the non-uniformity and in some images the non-uniformity is even accentuated. N3 also decreases image contrast by darkening the white matter and introducing overshooting contours around the borders between different regions such as between gray matter and white matter at the cortex. The white matter regions in the images restored with the co-occurrence algorithm are more intensity uniform. The artifacts of the N3 correction are strong in Fig. 7a. The high relative improvement achieved with the co-occurrence correction for that image is given in column 10 of Table 7.

Brain images of elderly subjects are particularly challenging to restore. They may have enlarged ventricles, lower contrast to noise ratio, lower cortical thickness, and many of them may have a white matter lesion load as well as some motion artifacts. They are a very good testing ground for the co-occurrence algorithm. Its high performance on these images demonstrates its robustness and reliability. The duration of the restoration depends on the amount of non-uniformity present in an image. The time duration of a correction was on average 1:23 h with the co-occurrence algorithm and 2:21 h with N3. The N3 restorations with the best performing parameter $d_{N3} = 20$ mm were much more costly. The time required to restore high field real images with the co-occurrence algorithm is significantly lower than that required by N3.

4. Discussion and conclusion

The contrast mechanism used to acquire an MR image affects its valid dynamic range. The intensity correction algorithm first detects this range and scales it linearly. Most intensity uniformity restoration algorithms scale the entire dynamic range logarithmically. Even though this intensity transformation makes the non-uniformity additive, it also warps the dynamic range in a non physical way. As a result the log transformation may decrease the ratio of tissue contrast to noise in the discretized statistics. The noise in the MR images used in this work is modeled by a Rayleigh distribution (Rice, 1945; Gudbjartsson and Patz, 1995). It is used during preprocessing for the detection of a lower bound for the valid intensity range as well as for the subsequent extraction of the signal region. The non-uniformity estimation is performed only over the signal region where the image noise can be approximated as Gaussian. The computation of the non-uniformity only over the signal region justifies the assumptions that both the noise and the effect of the non-uniformity in the co-occurrence statistics are given by zero mean Gaussian distributions as well. The assumption that the Gaussian distribution of the non-uniformity is unimodal may not be representative for high field images. Multimodal statistics for the non-uniformity are effectively represented by increasing the size σ_r^n of the Wiener filter. The performance of the algorithm is sensitive to regions that are close both spatially as well as in their co-occurrence statistics.

A pivotal assumption of the algorithm is that the intensity non-uniformity is spatially smooth. In spin echo sequences the non-uniformity may have abrupt variations at the borders between different tissue regions. However, for the purposes of image processing these abrupt changes can be absorbed into the tissue statistics (Sled et al., 1998; Mangin, 2000). The smoothing of

the non-uniformity correction is performed with a Gaussian filter, which has a local spatial effect. The smoothing constraint imposed with global bases functions such as polynomials or splines can be very drastic and may even accentuate the non-uniformity in some parts of the image. Some intensity correction algorithms smooth the non-uniformity field exclusively at a low resolution for efficiency (Sled et al., 1998; Leemput et al., 1999a). In this study the smoothing of the non-uniformity is performed with a pyramid. At the final iterations the non-uniformity estimate is refined by smoothing at the full image resolution.

The evaluation of the co-occurrence algorithm with the Brain-Web phantom images demonstrated its robustness to high levels of non-uniformity as well as its improved performance compared to N3 for low contrast between tissue statistics. The co-occurrence algorithm was also evaluated with real T1 images, which are very useful in measuring the thickness of the cortex of elderly subjects in studies of neurodegenerative conditions. The images were acquired at 4 T and suffered from high levels of intensity distortion. The restoration of these images is very challenging. The high performance of the co-occurrence algorithm on these images demonstrates its robustness and reliability. The time requirements of the algorithm are lower than those of N3 for these real high field images. The restorations of high field images have relatively higher computational requirements due to the higher spatial resolution as well as the higher amount of non-uniformity present. The time requirements of the restoration can be decreased by taking advantage of the fact that all the steps of the algorithm are fully parallelizable. In conclusion, a new algorithm has been developed and validated that uses local intensity co-occurrences for effective image restoration from intensity non-uniformity distortion in MR images.

Appendix

Appendix A

A.1. Effect of additive image noise on the co-occurrence statistics

The effect of the noise is analyzed by considering a single contiguous tissue assumed to be intensity uniform. Section 2.1 presents the assumption that the superimposed noise N_1 is Gaussian, independently, and identically distributed with zero mean and variance Σ . Thus, the variance of the tissue distribution in the histogram is $\Sigma_h = \Sigma$. The noise in different voxels is assumed to be independent, and hence the conditional co-occurrence statistics reduce to the product of the densities of the two Gaussians, one for each of the voxels of the same intensity. The product must be renormalized to give a new distribution, the product of two Gaussians distribution, whose variance Σ_c is (Gales and Airey, 2005)

$$\Sigma_c = (\Sigma^{-1} + \Sigma^{-1})^{-1} = (2\Sigma^{-1})^{-1} = \frac{\Sigma}{2} \quad (15)$$

$$= \frac{\Sigma_h}{2}, \quad (16)$$

Thus, the variance of the distribution of a contiguous tissue in the diagonal self-co-occurrence statistics is half of that of the same tissue in the histogram $\Sigma_c = \Sigma_h/2$.

A number of co-occurrences with each of the voxels is considered in Eq. (4). This summation is a linear transformation of random variables with identical mean and variance. Hence, the variance is not affected by the summation. The mean value of the tissue statistics is the same

in both the histogram and the self-co-occurrence statistics. Thus, the discriminability of the latter is higher. This analysis emphasizes the noise and ignores the spatial intensity non-uniformity. The algorithm minimizes the variation of the non-uniformity by selecting co-occurrences that lie within a small sphere of radius ρ . The effect of the intensity non-uniformity on the co-occurrences is examined in the following two sections.

A.2. Effect of image non-uniformity along the radial dimension of the co-occurrence statistics

This analysis is for the effect of the intensity non-uniformity on the co-occurrence statistics of a single anatomic tissue. Both the distribution of the tissue as well as the distribution of the non-uniformity are assumed to be Gaussian. The distribution of the tissue has parameters μ_A and σ_A and the distribution of the non-uniformity has parameters μ_B and σ_B . The two distributions are sampled spatially to give two images, which are multiplied to give image I . The distribution of the product image I is a normal product distribution, which is a modified Bessel function of the second kind P_I (Weisstein, 2008). The moment generating function of this distribution gives (Ware and Lad, 2003)

$$E(P_I) = \mu_B \mu_A + \rho \sigma_B \sigma_A \quad (17)$$

and

$$V(P_I) = \mu_B^2 \sigma_A^2 + \mu_A^2 \sigma_B^2 + \sigma_B^2 \sigma_A^2 + 2\rho \mu_B \mu_A \sigma_B \sigma_A + \rho^2 \sigma_B^2 \sigma_A^2. \quad (18)$$

It is assumed that the spatial samples of the Gaussian distribution of the anatomy and of the Gaussian distribution of the non-uniformity are uncorrelated with $\rho = 0$. This assumption simplifies the expression for the variance in Eq. (18) to

$$V(P_I) = \mu_B^2 \sigma_A^2 + \mu_A^2 \sigma_B^2 + \sigma_B^2 \sigma_A^2. \quad (19)$$

. As described in Section 2.1 $\sigma_A = 0$ and for a specific value of anatomic intensity u_A the variance of the total distribution is $V(P_I|u_A) = u_A^2 \sigma_B^2$. The square root of this relation gives

$$\sigma(P_I|u_A) = u_A \sigma_B. \quad (20)$$

. This relation holds for each of the two axes of the co-occurrence statistics. The geometry of the co-occurrence between intensities u_{A0} and u_{A1} in Fig. 8 gives

$$\sigma(C|u_{A0}, u_{A1}) \propto \sigma_B \sqrt{u_{A0}^2 + u_{A1}^2} = \sigma_B r, \quad (21)$$

where r is the distance of the co-occurrence from the origin of their matrix.

A.3. Effect of image non-uniformity along the angular dimension of the co-occurrence statistics

As shown in Appendix A.2 the zero-order term $B(\mathbf{x}_0)$ of the expansion of the field of the non-uniformity locally causes only a radial deviation of the co-occurrences in C_I . This analysis is

for the angular deviation caused by the first-order term $\nabla B(\mathbf{x}_0)$ and ignores the effects of higher-order terms. Thus, the intensity of the central pixel is not affected and a co-occurrence (u_0, u_1) is mapped to $(u_0, u_1 + \Delta u_1)$.

The cosine law for angle $\Delta\phi$ over triangle ABD gives the cosine of the angle as a function of u_0 , u_1 , and Δu_1 :

$$\Delta u_1^2 = (u_0^2 + u_1^2) + (u_0^2 + (u_1 + \Delta u_1)^2) - 2\sqrt{u_0^2 + u_1^2} \times \sqrt{u_0^2 + (u_1 + \Delta u_1)^2} \cos \Delta\phi \Rightarrow \quad (22)$$

Line BC of length v forms the isosceles triangle ABC . The cosine law for that triangle gives

$$v^2 = 2(u_0^2 + u_1^2) - 2(u_0^2 + u_1^2) \cos \Delta\phi. \quad (23)$$

The cosine $\cos \Delta\phi$ is eliminated from Eqs. (22) and (23) to give

$$v^2 = \frac{2(u_0^2 + u_1^2) - 2(u_0^2 + u_1^2)}{-2\sqrt{u_0^2 + u_1^2} \sqrt{u_0^2 + (u_1 + \Delta u_1)^2} \cos \Delta\phi} \times \frac{\Delta u_1^2 - 2u_0^2 - 2u_1^2 - \Delta u_1^2 - 2u_1 \Delta u_1}{-2\sqrt{u_0^2 + u_1^2} \sqrt{u_0^2 + (u_1 + \Delta u_1)^2} \cos \Delta\phi}. \quad (24)$$

The substitution $\Delta u_1 = \alpha u_1$ in this equation, where $\alpha = \nabla B$ gives

$$v^2 = 2(u_0^2 + u_1^2) \left[1 - \frac{u_0^2 + (1 + \alpha) u_1^2}{\sqrt{u_0^2 + u_1^2} \sqrt{u_0^2 + u_1^2 (1 + \alpha)^2}} \right]. \quad (25)$$

The substitution $\tan \phi = u_1/u_0$ in Eq. (25) leads to:

$$\frac{v^2}{4(u_0^2 + u_1^2)} = \frac{1}{2} \left[1 - \frac{1 + \tan^2 \phi (1 + \alpha)}{\sqrt{1 + \tan^2 \phi} \sqrt{1 + \tan^2 \phi (1 + \alpha)^2}} \right]. \quad (26)$$

The midpoint E of line segment BC provides the right triangle ABE with $\sin \frac{\Delta\phi}{2} = \frac{v}{2\sqrt{u_0^2 + u_1^2}}$. This relation can be substituted in Eq. (26) to give

$$\sin^2 \frac{\Delta\phi(\phi, \nabla B)}{2} = \frac{1}{2} \left[1 - \frac{1 + \tan^2 \phi (1 + \alpha)}{\sqrt{1 + \tan^2 \phi} \sqrt{1 + \tan^2 \phi (1 + \alpha)^2}} \right]. \quad (27)$$

In this equation the substitution of α with the mean value of the gradient $\mu_{\nabla B} = \nabla B(\mathbf{x}_0)$ gives the standard deviation $\Delta\phi(\phi, \alpha) = \sigma_\phi$ of the unimodal Gaussian point spread function $G(\sigma_\phi)$ in the angular dimension of the co-occurrence statistics. This leads to Eq. (7) in Section 2.4.

References

- Ahmed M, Yamany S, Mohamed N, Farag A, Moriarty T. A modified fuzzy c-means algorithm for bias field estimation and segmentation of MRI data. *IEEE Transactions on Medical Imaging* 2002;21(3): 193–199. [PubMed: 11989844]
- Arnold J, Liow J, Schaper K, Stern J, Sled J, Shattuck D, Worth A, Cohen M, Leahy R, Mazziota J, Rottenberg D. Qualitative and quantitative evaluation of six algorithms for correcting intensity nonuniformity effects. *NeuroImage* 2001;13:931–943. [PubMed: 11304088]
- Ashburner A, Friston K. Voxel-based morphometry—the methods. *NeuroImage* 2000;11:805–821. [PubMed: 10860804]
- Axel L, Costantini J, Listerud J. Intensity correction in surface-coil MR imaging. *American Journal of Roentgenology* 1987;148:418–420. [PubMed: 3492123]
- Bansal, R.; Staib, L.; Peterson, B. Correcting nonuniformities in MRI intensities using entropy minimization based on an elastic model; *Proceedings of MICCAI*; 2004.
- Belaroussi B, Milles J, Carme S, Zhu Y, Cattin H. Intensity non-uniformity correction in MRI: existing methods and their validation. *Medical Image Analysis* 2006;10:234–246. [PubMed: 16307900]
- Brainard D, Wandell B. Analysis of the retinex theory of color vision. *Journal of the Optical Society of America A* 1986;3(10):1651–1661.
- Brinkmann B, Manduca A, Robb R. Optimized homomorphic unsharp masking for MR grayscale intensity correction. *IEEE Transactions on Medical Imaging* 1998;17(2):161–171. [PubMed: 9688149]
- Burt P, Adelson E. The Laplacian pyramid as a compact image code. *IEEE Transactions on Communication* 1983;COM-31:532–540.
- Cocosco C, Kollokian V, Kwan R-S, Evans A. BrainWeb: online interface to a 3D MRI simulated brain database. *Neuroimage* 1997;5(4–24):S425.
- Cohen M, DuBois R, Zeineh M. Rapid and effective correction of RF inhomogeneity for high field magnetic resonance imaging. *Proceedings of Human Brain Mapping* 2000;10:204–211.
- Collins D, Zijdenbos A, Kollokian V, Sled J, Kabani N, Holmes C, Evans A. Design and construction of a realistic digital brain phantom. *IEEE Transactions on Medical Imaging* 1998;17(3):463–468. [PubMed: 9735909]
- Dawant B, Zijdenbos A, Margolin R. Correction of intensity variations in MR images for computer aided tissue classification. *IEEE Transactions on Medical Imaging* 1993;12(4):770–781. [PubMed: 18218473]
- DeCarli C, Murphy D, Teichberg D, Campbell G, Sobering G. Local histogram correction of MRI spatially dependent image pixel intensity nonuniformity. *Journal of Magnetic Resonance Imaging* 1996;6:519–528. [PubMed: 8724419]
- Dempster A, Laird N, Rubin D. Maximum likelihood from incomplete data via the EM algorithm (with discussion). *Journal of the Royal Statistical Society B* 1977;39:1–38.
- Gales M, Airey S. Product of Gaussians for speech recognition. *Computer Speech and Language* 2005;20:22–40.
- Gilles, S.; Brady, M.; Declerck, J.; Thirion, J.; Ayache, N. Bias field correction of breast MR images; *Proceedings of the 4th International Conference on Visualization in Biomedical Computing*; 1996. p. 153–158.
- Gudbjartsson H, Patz S. The Rician distribution of noisy MRI data. *Magnetic Resonance in Medicine* 1995;34:910–914. [PubMed: 8598820]
- Guillemaud R, Brady M. Estimating the bias field of MR images. *IEEE Transactions on Medical Imaging* 1997;16:238–251. [PubMed: 9184886]
- Hadjidemetriou S, Studholme C, Mueller S, Weiner M, Schuff N. Restoration of MRI data for field nonuniformities using high order neighborhood statistics. *Proceedings of SPIE Medical Image Processing* 2007;6512
- Han C, Hatsukami T, Yuan C. A multi-scale method for automatic correction of intensity non-uniformity in MR images. *Journal of Magnetic Resonance Imaging* 2001;13:428–436. [PubMed: 11241818]
- Haykin, S. *Adaptive Filter Theory*. Prentice-Hall; Upper Saddle River, NJ: 2002.

- Held K, Korps E, Krause B, Wells W III, Kikinis R, Gartner H-WM. Markov random field segmentation of brain MR images. *IEEE Transactions on Medical Imaging* 1997;16:878–886. [PubMed: 9533587]
- Hou Z. A review on MR image intensity inhomogeneity correction. *International Journal of Biomedical Imaging* 2006;49515:1–11.
- Kimmel R, Elad M, Shaked D, Keshet R, Sobel I. A variational framework for retinex. *International Journal of Computer Vision* 2003;52(1):7–23.
- Kuan D, Sawchuk A, Strand T, Chavel P. Adaptive noise smoothing filter for images with signal dependent noise. *IEEE Transactions on Pattern Analysis and Machine Intelligence* 1985;7(2):165–177.
- Lai S, Fang M. A new variational shape-from-orientation approach to correcting intensity inhomogeneities in magnetic resonance images. *Medical Image Analysis* 1999;3(4):409–424. [PubMed: 10709704]
- Lee S, Vannier M. Post-acquisition correction of MR inhomogeneities. *Magnetic Resonance in Medicine* 1996;36:275–286. [PubMed: 8843382]
- Leemput K, Maes F, Vandermeulen D, Suetens P. Automated model-based bias field correction of MR images of the brain. *IEEE Transactions on Medical Imaging* 1999a;18(10):885–896. [PubMed: 10628948]
- Leemput K, Maes F, Vandermeulen D, Suetens P. Automated model-based tissue classification of MR images of the brain. *IEEE Transactions on Medical Imaging* 1999b;18(10):897–908. [PubMed: 10628949]
- Likar B, Viergever M, Pernus F. Retrospective correction of MR intensity inhomogeneity by information minimization. *IEEE Transactions on Medical Imaging* 2001;20(12):1398–1410. [PubMed: 11811839]
- Luo J, Zhu Y, Clarysse P, Magnin I. Correction of bias field in MR images using singularity function analysis. *IEEE Transactions on Medical Imaging* 2005;24(8):1067–1085. [PubMed: 16092338]
- Mangin, J. Entropy minimization for automatic correction of intensity nonuniformity; *Proceedings of IEEE Workshop on MMBIA*; 2000. p. 162–169.
- Meyer C, Bland P, Pipe J. Retrospective correction of intensity inhomogeneities in MRI. *IEEE Transactions on Medical Imaging* 1995;14(1):36–41. [PubMed: 18215808]
- Noterdaeme, O.; Brady, M. A fast method for computing and correcting intensity inhomogeneities in MRI; *Proceedings of International Symposium of Biomedical Imaging*; 2008. p. 1525–1528.
- Pham D, Prince J. An adaptive fuzzy c-means algorithm for image segmentation in the presence of intensity inhomogeneities. *Pattern Recognition Letters* 1999;20:57–68.
- Pohl, K.; Wells, W.; Guimond, A.; Kasai, K.; Shenton, M.; Kikinis, R.; Grimson, W.; Warfield, S. Incorporating nonrigid registration into expectation maximization algorithm to segment MR images; *Proceedings of MICCAI*; 2002.
- Prima, S.; Ayache, N.; Barrick, T.; Roberts, N. Maximum likelihood estimation of the bias field in MR brain images: investigating different modelings of the imaging process; *Proceedings of MICCAI*; 2001. p. 811–819.
- Rice S. Mathematical analysis of random noise. *Bell System Technical Journal* 1945;24:100–103.
- Rising H. Analysis and generalization of retinex by recasting the algorithm in wavelets. *Journal of Electronic Imaging* 2004;13(1):93–99.
- Sled J, Pike G. Standing-wave and RF penetration artifacts caused by elliptic geometry: an electrodynamic analysis of MRI. *IEEE Transactions on Medical Imaging* 1998;17(4):653–662. [PubMed: 9845320]
- Sled J, Zijdenbos A, Evans A. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Transactions on Medical Imaging* 1998;17(1):87–97. [PubMed: 9617910]
- Stollberger R, Wach P. Imaging of the active B1 field in vivo. *Magnetic Resonance in Medicine* 1996;35:246–251. [PubMed: 8622590]
- Studholme C, Cardenas V, Song E, Ezekiel F, Maudsley A, Weiner M. Accurate template based correction of brain MRI intensity distortion with application to dementia and aging. *IEEE Transactions on Medical Imaging* 2004;23(1):99–110. [PubMed: 14719691]

- Styner M, Brechbuhler C, Szekely G, Gerig G. Parametric estimate of intensity inhomogeneities applied to MRI. *IEEE Transactions on Medical Imaging* 2000;19(3):153–165. [PubMed: 10875700]
- Viola, P. Alignment by maximization of mutual information. 1995. p. 137-142. Ph.D. Thesis
- Vita, E.; Thomas, D.; Deichmann, R.; Turner, R.; Oldidge, R. Fast B1 mapping with EPI; *Proceedings of ISMRM*; 2004.
- Vokurka E, Thacker N, Jackson A. A fast model independent method for automatic correction of intensity nonuniformity in MRI data. *Journal of Magnetic Resonance Imaging* 1999;10:550–562. [PubMed: 10508322]
- Vovk U, Pernus F, Likar B. MRI intensity inhomogeneity correction by combining intensity and spatial information. *Institute of Physics Publishing* 2004;49:4119–4133.
- Vovk U, Pernus F, Likar B. A review of methods for correction of intensity inhomogeneity in MRI. *IEEE Transactions on Medical Imaging* 2007;26(3):405–421. [PubMed: 17354645]
- Wang J, Qiu M, Yang Q, Smith M, Constable R. Measurement and correction of transmitter and receiver induced nonuniformities in vivo. *Magnetic Resonance in Medicine* 2005;53(2):408–417. [PubMed: 15678526]
- Ware, R.; Lad, F. Research report. Vol. 15. University of Caterbury, UCDMS; 2003. Approximating the distribution for sums of products of normal variables.
- Weisstein, E. Normal Product Distribution. 2008. MathWorld,
<<http://mathworld.wolfram.com/NormalProductDistribution.html>>
- Wells W, Grimson W, Kikinis R, Jolesz F. Adaptive segmentation of MRI data. *IEEE Transactions on Medical Imaging* 1996;15:429–442. [PubMed: 18215925]
- Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Transactions on Medical Imaging* 2001;20(1):45–57. [PubMed: 11293691]

Fig. 1.

Example phantom T1 images from the BrainWeb MR simulator. In the first row in (a) is the true phantom, in the second row is a phantom image without intensity non-uniformity but with high superimposed noise, and in the third row is a phantom with high non-uniformity and some superimposed noise. Next to each image in (b) is its co-occurrence density matrix. In (c) are their corresponding restoration matrices where the gain factors are linearly proportional to the intensities.

Fig. 2.
The shape of the Wiener restoration filter in both the radial r and angular ϕ dimensions.

Fig. 3.
The radial and angular sizes of the non-stationary Wiener restoration filter f_q depend on the position of its center point in the co-occurrence matrix.

Fig. 4.

The first row shows a BrainWeb phantom with both high non-uniformity $B = 40\%$ and high noise $N_I = 5\%$. The second row shows the rough estimate of its non-uniformity and in the third row is the smooth estimate of its non-uniformity.

Fig. 5.
A block summary of the algorithm.

Fig. 6.

The error images of the restorations of the BrainWeb MR phantoms corrupted with a non-uniformity of 40% and a noise level of 5% for T1, T2, and PD are in (a), (b), and (c), respectively. The first column shows the original corrupted phantom. In the second column is the true non-uniformity field. The remaining two columns show the error images for the N3 and the co-occurrence restorations, respectively. The dynamic range used for the display of both error images is the same. In all cases the error images resulting from the N3 restorations are brighter which correspond to higher error.

(a) Row ten in table 7.

(b) Row two in table 7.

(c) Row four in table 7.

(d) Row five in table 7.

Fig. 7.

Examples of restorations of four of the 4 T human head images given in Table 7. In each example the first row shows the acquired image, the second row shows the correction with N3, and in the third row is the restoration with the co-occurrence algorithm. The N3 restoration contains a considerable residual of the non-uniformity and sometimes it even accentuates the non-uniformity. It also darkens the white matter and introduces overshooting contours around the borders between regions with different intensities such as between the gray matter and the white matter at the cortex. The higher uniformity of the white matter intensity seen in the images corrected with the co-occurrence algorithm is an indication of its improved performance.

Fig. 8.
Radial standard deviation of a tissue distribution due to intensity non-uniformity.

(a) An intensity co-occurrence (u_0, u_1) as a result of the non-uniformity gradient $\alpha = \nabla B$ becomes $(u_0, u_1(1 + \alpha))$. The angle ϕ of (u_0, u_1) with the horizontal axis becomes $\phi + \Delta\phi$.

(b) The effect of a constant non-uniformity $\alpha = 0.3$ on the rotational angle $\Delta\phi = \sigma_\phi$ as a function of angle ϕ . The effect on co-occurrences close to the diagonal $\phi = 45^\circ$ is greater.

Fig. 9.

The effect of intensity non-uniformity on the angular spread of the co-occurrences and the size of the Wiener restoration filter.

Table 1

The coefficient of joint variation (CJV) and the relative improvement of the co-occurrence algorithm compared to N3 for T1 images of the BrainWeb MR simulator

Processing\image	$N_I = 0\%$ $B = 0\%$	$N_I = 5\%$ $B = 0\%$	$N_I = 5\%$ $B = 20\%$	$N_I = 5\%$ $B = 40\%$
Original (10^{-2})	44.729	61.666	64.809	74.913
N3 (10^{-2}): fwhm = 0.15				
$d = 20$ mm	45.677	63.353	62.525	63.098
110 mm	46.361	62.615	61.917	62.329
200 mm	46.805	62.651	61.763	62.026
Co-occurrence (10^{-2})	44.729	62.162	61.745	61.423
Co-occurrence improvement (%)	2.1	0.7	0.0	1.0

Table 2

The coefficient of joint variation (CJV) and the relative improvement of the co-occurrence algorithm compared to N3 for T2 images of the BrainWeb MR simulator

Processing\image	$N_I = 0\%$ $B = 0\%$	$N_I = 5\%$ $B = 0\%$	$N_I = 5\%$ $B = 20\%$	$N_I = 5\%$ $B = 40\%$
Original (10^{-2})	66.785	103.60	111.79	126.42
N3 (10^{-2}): fwhm = 0.15				
$d = 20$ mm	67.424	103.63	108.55	120.30
110 mm	67.239	103.60	108.11	119.04
200 mm	67.177	103.59	108.02	119.40
Co-occurrence (10^{-2})	66.785	104.94	106.02	110.20
Co-occurrence improvement (%)	0.6	-1.3	1.9	7.4

Table 3

The coefficient of joint variation (CJV) and the relative improvement of the co-occurrence algorithm compared to N3 for PD images of the BrainWeb MR simulator

Processing\image	$N_I = 0\%$ $B = 0\%$	$N_I = 5\%$ $B = 0\%$	$N_I = 5\%$ $B = 20\%$	$N_I = 5\%$ $B = 40\%$
Original (10^{-2})	40.159	96.866	110.03	144.95
N3 (10^{-2}): fwhm = 0.15				
$d = 20$ mm	42.625	108.80	112.90	122.43
110 mm	40.900	102.16	105.81	113.85
200 mm	40.353	99.509	102.17	109.78
Co-occurrence (10^{-2})	40.159	101.02	95.569	98.330
Co-occurrence improvement (%)	0.5	-1.5	6.5	10.4

Table 4

The error in the intensity non-uniformity estimates (e) and the relative improvement of the co-occurrence algorithm compared to N3 for T1 images of the BrainWeb MR simulator

Processing\image	$N_I = 0\%$ $B = 0\%$	$N_I = 5\%$ $B = 0\%$	$N_I = 5\%$ $B = 20\%$	$N_I = 5\%$ $B = 40\%$
N3 (10^{-2}): fwhm = 0.15				
$d = 20$ mm	1.413	1.462	1.441	1.884
110 mm	1.508	1.042	1.138	1.632
200 mm	1.561	0.9924	0.9808	1.509
Co-occurrence (10^{-2})	0.000	0.8286	0.8502	1.267
Co-occurrence improvement (10^{-3})	14.1	1.6	1.3	2.4

Table 5

The error in the intensity non-uniformity estimates (e) and the relative improvement of the co-occurrence algorithm compared to N3 for T2 images of the BrainWeb MR simulator

Processing\image	$N_I = 0\%$ $B = 0\%$	$N_I = 5\%$ $B = 0\%$	$N_I = 5\%$ $B = 20\%$	$N_I = 5\%$ $B = 40\%$
N3 (10^{-2}): fwhm = 0.15				
$d = 20$ mm	0.9814	1.259	3.074	6.655
110 mm	0.8680	0.6819	2.757	6.345
200 mm	0.7955	0.5872	2.703	6.427
Co-occurrence (10^{-2})	0.000	1.554	2.433	4.015
Co-occurrence improvement (10^{-3})	8.0	-9.7	2.7	23.3

Table 6

The error in the intensity non-uniformity estimates (e) and the relative improvement of the co-occurrence algorithm compared to N3 for PD images of the BrainWeb MR simulator

Processing\image	$N_I = 0\%$ $B = 0\%$	$N_I = 5\%$ $B = 0\%$	$N_I = 5\%$ $B = 20\%$	$N_I = 5\%$ $B = 40\%$
N3 (10^{-2}): fwhm = 0.15				
$d = 20$ mm	1.141	1.919	3.500	4.993
110 mm	0.6890	1.162	3.034	4.597
200 mm	0.4946	0.7573	2.686	4.223
Co-occurrence (10^{-2})	0.000	1.329	2.302	3.905
Co-occurrence improvement (10^{-3})	4.9	-5.7	3.8	3.2

The coefficient of joint variation (CJV) and the relative improvement of the co-occurrence algorithm compared to N3 for real T1 MPRAGE 4T images of elderly subjects

Processing image	1	2	3	4	5	6	7	8	9	10
Original (10^{-2})	106	83.0	74.1	86.1	96.5	108	118	85.2	80.0	104
N3 (10^{-2}); fwhm = 0.10										
$d = 20$ mm	64.2	49.1	42.5	50.9	55.1	49.5	57.5	47.1	57.8	85.5
110 mm	74.6	64.4	70.0	82.1	73.6	74.7	88.0	64.2	74.0	69.0
200 mm	84.0	73.0	71.9	85.2	79.7	89.0	109	67.0	76.2	77.4
Co-occurrence (10^{-2})	47.9	45.3	40.0	46.1	41.8	44.6	48.9	43.6	51.7	52.1
Co-occurrence improvement (%)	25.4	7.7	5.9	9.5	24.1	9.9	15.0	7.4	10.6	24.5

The co-occurrence algorithm improves performance significantly.