Published in final edited form as:

Proc SPIE Int Soc Opt Eng. 2015 February 21; 9412: . doi:10.1117/12.2075687.

An Example-Based Brain MRI Simulation Framework

Qing He^a, Snehashis Roy^a, Amod Jog^b, and Dzung L. Pham^a

^aCenter for Neuroscience and Regenerative Medicine, Henry M. Jackson Foundation for the Advancement of Military Medicine, Bethesda, MD, USA

^bDepartment of Computer Science, Johns Hopkins University, Baltimore, MD, USA

Abstract

The simulation of magnetic resonance (MR) images plays an important role in the validation of image analysis algorithms such as image segmentation, due to lack of sufficient ground truth in real MR images. Previous work on MRI simulation has focused on explicitly modeling the MR image formation process. However, because of the overwhelming complexity of MR acquisition these simulations must involve simplifications and approximations that can result in visually unrealistic simulated images. In this work, we describe an example-based simulation framework, which uses an “atlas” consisting of an MR image and its anatomical models derived from the hard segmentation. The relationships between the MR image intensities and its anatomical models are learned using a patch-based regression that implicitly models the physics of the MR image formation. Given the anatomical models of a new brain, a new MR image can be simulated using the learned regression. This approach has been extended to also simulate intensity inhomogeneity artifacts based on the statistical model of training data. Results show that the example based MRI simulation method is capable of simulating different image contrasts and is robust to different choices of atlas. The simulated images resemble real MR images more than simulations produced by a physics-based model.

Keywords

brain MRI simulation; example based method; regression ensemble; inhomogeneity field

INTRODUCTION

The simulation of MR images plays an important role in the validation of image analysis algorithms such as image segmentation, since there is usually lack of ground truth in real MR images. Previous work on MRI simulation has attempted to simulate the physical process of MR image formation. Two popular types of methods are based on the Bloch equations and k-space integration [1–5]. In [1], a 3D MRI simulator was described based on Bloch equation resolution that takes into account T_2^* effects, chemical shift, and static field inhomogeneities. In [2], a new technique was proposed to address the problem related to the finite number of isochromats used in Bloch equation based MRI simulation. A hybrid simulation approach using Bloch equation and tissue templates was proposed in [3]. In [4], the use of analytical models for the anatomy and coil sensitivity maps was proposed for simulating parallel imaging. Arguably the most commonly simulation approach is the publicly available BrainWeb phantom [5], which has been used for evaluating a large

number of image analysis algorithms. A challenge in these simulation algorithms is incorporating scanner artifacts such as radio frequency inhomogeneities and susceptibility artifacts, both of which generate non-uniform tissue intensities. Most current MRI simulation methods, however, inevitably resort to approximations and simplifications of the physical model due to practical limitations. Thus the simulated images can appear artificial; simulating realistic looking MR images remains a challenging problem.

Recently, we proposed an example-based brain MRI simulation method [6] and showed preliminary results on T1-weighted MPRAGE image simulation. The MR image and its anatomical models are used as the example or atlas, and the relationships between the MPRAGE image intensities and its anatomical models are learned using a patch-based regression. The novelty of the example-based method is that the physics of MR image formation is not explicitly modeled but is rather learned implicitly through the regression. Given the anatomical models of a new subject, the MR image can be predicted by the learned regression. In this work, we aim to extend the example-based simulation framework by (1) employing anatomical models based on partial volume fractions, (2) demonstrating simulation of multiple image contrasts, and (3) imposing intensity non-uniformity on the simulated images. The non-uniformity or inhomogeneity field is statistically modeled from training data. Results show that the example-based MRI simulation method is capable of simulating different image contrasts and is robust to different choices of atlas. Because the underlying anatomy is known, the simulated MR images are potentially useful for validating image analysis algorithms such as brain segmentation, intensity inhomogeneity correction, skull stripping, and many others.

METHODS

Overview

The simulation framework contains three main components. The first component is the construction of the anatomical models of the head. Section 2.2 describes the method to construct the anatomical models of the atlas subject, and the same method can be used for the anatomical models of any given subject. The second component is the patch based regression to predict the MR image of the given subject, which is described in Section 2.3. The third component is the simulation of inhomogeneity field from a set of training data, which is described in Section 2.4.

Atlas anatomical models

In this work, we include cerebrospinal fluid (CSF), cortical gray matter (GM), subcortical GM, white matter (WM), and non-brain regions of the head (consisting of skull, meninges, and extra-cranial tissue) in the anatomical models. Additional structures are possible but not considered here. In order to provide accurate simulation of partial volume effects, the anatomical model consists of structures represented by partial volume fractions [7]. Since partial volume fractions are typically not available, they must be computed from a label image provided by manual delineation or other ground truth segmentation. Alternatively in [6], the tissue labels were derived from the fusion of a set of automatic segmentation results. To transform the hard labels to partial volume fractions, we apply 1 iteration of a partial

volume estimation algorithm [7], using the hard segmentation as an initialization. Because the subcortical GM has overlapping intensities with cortical GM, partial volume estimation is performed separately on the brain image I and the masked brain image $I_N = I * (1 - M)$, where M is the binary mask of subcortical GM. 4-class partial volume estimation is performed on the brain image I , resulting in four partial volume images: F_1 (CSF), F_2 (cortical GM), F_3 (WM), F_4 (subcortical GM). 3-class partial volume estimation is performed on the masked brain image I_N , resulting in three partial volume images: T_1 (CSF), T_2 (total GM), T_3 (WM). $\{F_i\}$ and $\{T_i\}$ are then combined to generate $P_i = T_i + F_i * M$, $i = 1 \dots 4$, $T_4 = 0$. The final results are four partial volume images: P_1 (CSF), P_2 (cortical GM), P_3 (WM), and P_4 (subcortical GM).

For the non-brain area of the atlas, the specific anatomical composition is typically not of interest and unavailable. We employ a 4-class representation computed using a multispectral fuzzy c-means algorithm. Figure 1 shows an example atlas data set, including the MPRAGE image (a), hard segmentation of the brain (b), partial volume images of the brain (c–f) and the non-brain area (g–j). The atlas subject is randomly chosen from the Multimodal MRI Reproducibility Resource (MMRR) [8]. The partial volume representations of the head (Figure 1(c–j)) constitute the entire anatomical models of this atlas subject, which will be used for training a regression ensemble described in the next section. Additional contrasts such as T2-weighted, proton density (PD) weighted images, and FLAIR image contrasts are possible, allowing for simulation of these available contrasts. All MR images within the atlas are corrected for intensity non-uniformity [9].

Multi-contrast MRI simulation using patch based regression

A training step is first required to build the regression model. To simulate an image with the desired contrast C , the MR image with contrast C of the atlas subject is required, along with the anatomical models described in 2.2. Generally, a T1-weighted image of the atlas subject is also required if the methods in 2.1 are used to construct the anatomical models. To build the simulation, a mapping from the anatomical model to the MR image must be learned. For the atlas MR image of the desired contrast C , we perform a regression from its partial volume image set $\{P_j\}$. At each voxel location (x_i, y_i, z_i) , a $3 \times 3 \times 3$ patch centered at (x_i, y_i, z_i) is extracted from each of the partial volume images P_j . The patches are then concatenated into a vector $\vec{p}_i$ of length $27 \times n$, where n is the number of partial volume images. Let q_i denote the intensity of the atlas MR image at voxel (x_i, y_i, z_i) . A bagged regression ensemble [10] is trained to learn the relation between the vector $\vec{p}_i$ and the intensity q_i at each voxel location (x_i, y_i, z_i) . 15 regression trees each having 5 minimum observations per leaf node are used in our experiment. To avoid any confusion of the intensity, separate training is performed on the brain area and the non-brain area respectively, resulting in two regression ensembles R_B and R_N .

Once the model has been trained, to simulate the MR image of a different brain anatomy, the only required input is the anatomical models of this subject, i.e., the partial volume image set $\{P'_j\}$. They can be constructed either using the methods in 2.2 given that the T1-weighted image of this subject is available, or through other alternative ways. Applying non-linear spatial transformations to the atlas anatomical model would therefore potentially offer

limitless variations of brain anatomy and simulated images. At each voxel location (x'_i, y'_i, z'_i) , image patches are extracted from $\{P'_i\}$ and concatenated into a vector $\vec{p}_i$ as described above. Depending on the voxel location (x'_i, y'_i, z'_i) , the learned regression ensemble R_B or R_N is applied on $\vec{p}_i$ to predict the intensity q'_i of the simulated image.

Simulation of intensity non-uniformity

Intensity non-uniformities, caused by inhomogeneities in the RF field during acquisition, are common in MRI, particularly at higher magnetic field strengths. These artifacts are useful to include in simulations for evaluating the robustness of processing algorithms. Intensity non-uniformities are usually modeled as a multiplicative field with smooth, spatially varying intensities. We built a statistical model of the non-uniformity based on a multivariate Gaussian distribution. Non-uniformity fields from N ($N=40$ in our experiment) data sets were extracted using the N3 algorithm [9]. The corresponding MR images were then affine registered to a common space and the spatial transformations were applied to the corresponding inhomogeneity fields to generate N fields in the same space. A cubic B-spline function was fitted to each field, resulting in a coefficient vector $\vec{b}_i (i=1 \dots N)$ for each field. The interval between knot points of the B-spline function controls the smoothness of the simulated inhomogeneity field. We set the interval equal to one third of the smallest dimension of the image size, which is the value used in the N3 algorithm. The N vectors $\vec{b}_i$ were assumed to follow a multivariate Gaussian distribution $G(\vec{\mu}, \Sigma)$ as follows.

$$\vec{b}_i \sim G(\vec{\mu}, \Sigma) = \frac{1}{\sqrt{(2\pi)^k |\Sigma|}} \exp\left(-\frac{1}{2} (\vec{b}_i - \vec{\mu})^T \Sigma^{-1} (\vec{b}_i - \vec{\mu})\right) \quad (1)$$

where k is the dimension of $\vec{b}_i$. The mean vector $\vec{\mu}$ and the covariance matrix Σ are estimated from the N samples $\vec{b}_i$. To simulate a new field, a random sample $\vec{b}_s$ is drawn from the estimated Gaussian distribution G , and the inhomogeneity field is reconstructed from the B-spline coefficients $\vec{b}_s$.

The estimated field is transformed to the space of a simulated image with the inverse affine transformation, and then multiplied. The non-uniformity field is random each time it is generated, but follows the pattern captured from the real fields. Increasing the effect of the field can be applied simply by scaling its magnitude.

RESULTS

Results of MPRAGE image simulation

MPRAGE image simulation was performed on subjects from the OASIS project (<http://www.oasis-brains.org/>) with manual segmentations provided by the MICCAI 2012 Grand Challenge and Workshop on Multi-Atlas Labeling (<https://masi.vuse.vanderbilt.edu/workshop2012>). One subject was randomly selected as the atlas (Figure 2(a)) and another subject as the test subject (Figure 2(b)). The atlas and the test subjects have different image dimensions. The brain labels of both subjects were grouped into four tissue classes, followed

by partial volume estimation to generate brain anatomical models. The non-brain anatomical models of each subject were generated according to 2.2. For comparison, a separate simulation is run on the same test subject using the MMRR atlas shown in Figure 1. Little difference is apparent between the simulated MPRAGE images using the two atlases (Figure 2(c,d)), and both look similar to the real image in appearance. Figure 2(e) shows an image simulated using a physics-based approach based on the same anatomical model, but employing the NMR tissue parameters, pulse sequence parameters within an explicit MPRAGE imaging equation [11]. The contrast properties of the physics based simulation are clearly different from the real MR image, which make the simulated image appear more artificial.

To quantitatively measure how the simulated MR images resemble the real MR images, we choose to compute the symmetric KL divergence between the histograms of the simulated image and the real image. A simulated image with realistic appearance should have similar intensity distribution as the real image of the same subject, and the KL divergence between histograms can measure such similarity, with a smaller value indicating larger similarity. Simulation experiment was performed on a mixture of nine test subjects randomly selected from both OASIS project and MMRR. Let K_E denote the KL divergence between the histograms of the example based simulation result and the real MPRAGE image, and K_P the KL divergence between the histograms of the physics based simulation result and the real MPRAGE image. Only the voxels within the head area of each image are considered for the histogram computation, and 128 bins are used for each histogram. The ratio K_E/K_P was computed for each test subject. The mean and standard deviation of K_E/K_P over the nine subjects was 0.449 and 0.141. This result shows that the example-based method generates images more similar to the real images, since K_E is only around half of K_P for each subject. To take into account the effect of histogram quantization, different numbers of histogram bins were used to compute K_E and K_P and similar results were obtained.

Results of multi-contrast image simulation

Figure 3 demonstrates the simulation of different image contrasts using the proposed method. Simulated FLAIR, PD-weighted, and T2-weighted images of a test subject from MMRR (different from the atlas subject shown in Figure 1) are compared with the real MR images from which the corresponding anatomical had been derived. Visual inspection shows that the simulated images are similar to the real images. Note that hypointense regions around the globus pallidus due to iron deposition are not well represented in the simulated FLAIR image. This could be due to differences in the atlas MR image or also the fact that the globus pallidus is not explicitly modeled in the simulation.

Results of intensity non-uniformity simulation

Figure 4 focuses on the simulation of intensity non-uniformity fields. The randomly simulated field (Figure 4(b)) shows similar properties to the field extracted from a real MR image (Figure 4(a)). The MPRAGE image of the same test subject as shown in Figure. 3 is simulated using the example based method (Figure 4(c)) and then multiplied by the simulated non-uniformity field (Figure 4(d)). To demonstrate the effect of the simulated inhomogeneity field on brain segmentation, a 3-tissue classification is performed on the

brain area of the simulated MPRAGE image before and after multiplying the simulated non-uniformity field. Figure 4(f) shows poor segmentation of subcortical structures resulting from the inhomogeneity field, which is a common problem in real tissue classification applications.

Figure 4(g,h) compare the intensity distributions of 40 simulated non-uniformity fields against 40 real fields used as training data in 2.4. Figure 4(g) shows the mean intensity plots of the simulated (blue) and real (red) inhomogeneity fields, sorted in ascending order. The fields generated by our method have similar mean intensity values (1.014 ± 0.027) to the real fields (1.012 ± 0.022). Figure 4(h) depicts a similar relationship regarding the standard deviation of the intensity, where the simulated fields have standard deviation of 0.096 ± 0.016 and the real fields have standard deviation of 0.090 ± 0.013 . Only voxels within the head are considered in the calculation of mean and standard deviation of the intensity, since the estimated inhomogeneity in the background area can vary unexpectedly.

CONCLUSION AND DISCUSSION

This work proposes a new example-based framework to simulate brain MR images with different contrasts and intensity non-uniformity artifacts. The anatomical models are represented by partial volume fractions, and the intensity inhomogeneity field is statistically modeled from training data. This simulation approach differs from previous work in that the physics of the MR image acquisition are implicitly modeled using a patch-based regression that captures the nuanced relationship between the anatomical structure and the image intensities. Results show that our method can generate realistic looking brain MR images. Such images are useful for evaluating the performance of image segmentation and other processing algorithms.

There are many choices of anatomical models used for the simulation, as long as it is consistent for the atlas and test subjects. The four-class brain anatomical model used in our experiment is a relatively coarse representation of the brain anatomy. Although it is generally sufficient for a typical T1-weighted brain MR image, it may not work well for some other contrasts such as the FLAIR image shown in Figure 3. The distinct intensity of the globus pallidus is lost in the simulated image because the globus pallidus is not modeled as a separate tissue class in our anatomical model. Anatomical models representing a higher level of details of the brain may better address such problems. The tradeoff is the increased computation time for the training of the regression ensemble as well as the simulation, since more partial volume images are contained in a higher level anatomical model. Currently, our simulation code is written in Matlab R2012 and run on a server with 12×2.73GHz processors and 48GB RAM. For an atlas image with dimension 176×256×256, it takes around 9 minutes to train the regression ensemble for the brain area and 15 minutes for the non-brain area including the background. To simulate an image with the same size, it takes around 4 minutes for the brain area and 13 minutes for the non-brain area.

Noise is not directly addressed within the simulation framework. Since the atlas MR images already have some noise, it is regenerated in the simulated images. However, the current framework is not able to control the noise level of the simulated images. Future work

includes seeking a systematic way to simulate realistic looking noise images from the noise patterns in real noisy MR images. Similar to the simulation of the inhomogeneity fields in 2.4, the noise image should be random each time it is simulated but reflecting the noise patterns in real MR images.

In summary, the example based simulation framework shows its capability of simulating realistic looking brain MR images with different contrasts and inhomogeneity effects. Including anatomical models at a finer detail level is possible in order to better accommodate certain image contrasts. Noise simulation is to be performed in the future to complete this framework.

Acknowledgments

This work was partially supported by NINDS grant R01 NS070906. Support for this work also included funding from the Department of Defense in the Center for Neuroscience and Regenerative Medicine.

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Figure 1.

(a) atlas MPRAGE image; (b) brain segmentation of (a) derived from the fusion of a set of automatic segmentation results; (c–f) partial volume images of CSF, cortical GM, WM, subcortical GM; (g–j) membership images of the non-brain area

Figure 2.

Axial, sagittal and coronal views of (a) real MPAGE image of OASIS atlas subject; (b) real MPAGE image of OASIS test subject; (c) simulated MPAGE image using an OASIS atlas; (d) simulated MPAGE image using an MMRR atlas; (e) physics-based simulation

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Figure 3.

Axial, sagittal and coronal views of real FLAIR, PD, T2 images (a, c, e,) of the MMRR test subject and the corresponding simulated images of the same subject (b, d, f)

Figure 4.

(a) non-uniformity field extracted from a real MR image; (b) randomly simulated non-uniformity field; (c) a simulated MPRAGE image; (d) simulated image multiplied by the simulated field; (e) 3-class tissue classification of the brain without non-uniformity; (f) tissue classification of the brain with non-uniformity; (g) mean intensity plots of the simulated (blue) and real (red) inhomogeneity fields, sorted in ascending order; (h) same as (g) regarding the standard deviation of the intensity