MULTIVARIATE MODELING OF LONGITUDINAL MRI IN EARLY BRAIN DEVELOPMENT WITH CONFIDENCE MEASURES

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ABSTRACT

The human brain undergoes rapid organization and structuring early in life. Longitudinal imaging enables the study of these changes over a developmental period within individuals through estimation of population growth trajectory and its variability. In this paper, we focus on maturation of white and gray matter as is depicted in structural and diffusion MRI of healthy subjects with repeated scans. We provide a framework for joint analysis of both structural MRI and DTI (Diffusion Tensor Imaging) using multivariate nonlinear mixed effect modeling of temporal changes. Our framework constructs normative growth models for all the modalities that take into account the correlation among the modalities and individuals, along with estimation of the variability of the population trends. We apply our method to study early brain development, and to our knowledge this is the first multimodel longitudinal modeling of diffusion and signal intensity changes for this growth stage. Results show the potential of our framework to study growth trajectories, as well as neurodevelopmental disorders through comparison against the constructed normative models of multimodal 4D MRI.

1. INTRODUCTION

The human brain undergoes significant changes during infancy and early development. Advances in the medical imaging have allowed us to track these changes in vivo through longitudinal imaging, that provides a more accurate picture of development compared to cross-sectional analysis. Growth modeling of longitudinal data yields a better average trajectory as the population model is based on individual temporal trajectories. This results in significantly improved model of growth and growth variability, especially when inter-subject variability is greater than the temporal change [1].

Previous neuroimaging studies have substantially increased our understanding of early brain development. Previous studies of DTI and MRI have shown changes in early brain development. Some of these studies have looked at changes of diffusion parameters over time [2, 3]. Others have looked at contrast changes as is depicted in T1W and T2W [4]. There are relatively few studies that have looked at both DTI and MRI [5]. However, most of these studies have been cross-sectional, and only consider one of the modalities. In this paper, we focus on multivariate longitudinal modeling where growth model is jointly estimated based on all the modalities.

We present a new method to generate models of temporal changes in multimodal MRI taken at non-uniformly sampled, discrete time points. Our proposed method estimates nonlinear models of the growth trajectories of individual subjects, the population, and the confidence intervals around the average trajectory. This is accomplished using non-linear mixed effects modeling (NLME) where multimodal changes are described using Gompertz functions. The Gompertz growth function provides a representation of asymptotic growth using intuitive parameters such as delay, rate of change, and expected asymptotic value. We have demonstrated the utility of such modeling in our recent paper that presents a method for unimodal analysis [6], where we compare growth in white matter regions. In this paper, we demonstrate and apply our new method to longitudinal multimodal MRI data containing both structural (T1w and T2w) and diffusion imaging modalities. We analyze and construct normative models in anatomical regions of interest in white matter and gray matter. Results indicate that the quantitative modeling of early brain development through MRI generates normative models with confidence intervals that have potential for detecting abnormal growth due to disease.

2. METHOD

Non-linear Mixed Effects Modeling: We use a non-linear mixed effects (NLME) model to analyze the longitudinal structural and diffusion tensor imaging (DTI) data. The mixed effect model is robust to outliers as it accounts for the variabilities within individuals. In the mixed effects model, the observed data is assumed to be a combination of both

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fixed effects, parameters associated with the entire population or at least within a sub-population, and *random effects* that are specific to an individual drawn at random. In non-linear mixed effects models, some or all of the fixed and random effects parameters present nonlinear responses. This makes nonlinear mixed effects model a natural and common choice for longitudinal data. We use the NLME model proposed by Lindstrom and Bates [7], where the jth observation on the ith individual is modeled as:

$$y_{ij} = f(\phi_i, t_{ij}) + e_{ij} \qquad i = 1, \cdots, M;\ j = 1, \cdots, n_i \quad (1)$$

where M is the number of individuals, n_i is the number of observations on the ith individual, f is a nonlinear function of the covariate vector t_{ij} and parameter vector ϕ_i, and $e_{ij} \sim N(0, \sigma^2)$ is an i.i.d. error term. The parameter vector can vary among individuals. This is incorporated into the model by writing ϕ_i as

$$\phi_i = A_i\beta + B_i b_i \qquad b_i \sim N(0, \Psi) \quad (2)$$

β is a p-vector of fixed effects, and b_i is a q-vector of random effects associated with individual i with variance-covariance Ψ. A_i and B_i are design matrices.

Multivariate Analysis of Longitudinal MRI: We perform quantitative analysis on a population of longitudinal multi-modal MRI data within anatomical regions. We model the multimodal image features as non-linear mixed effects, which combines regional population trends and individual subject trends. For this section, we assume that all MR images have been registered to a standard reference space. The primary goal for our analysis of growth trajectories is to determine the multivariate growth patterns and study the variation of different imaging modalities in space and time, using intuitive parametrization of growth trajectories. As the human brain undergoes rapid changes in the first year of development and slows considerably in later years, we model early development patterns in longitudinal, multimodal MRI using the Gompertz function. Specifically, we model temporal growth for an individual i, time points t_{ij}, and image channel/modality c by nonlinear mixed effect model of the Gompertz function

$$\begin{bmatrix} y_{ij}^c \\ \vdots \end{bmatrix} = \begin{bmatrix} f(\phi_i^c, t_{ij}) \\ \vdots \end{bmatrix} + e_{ij} = \begin{bmatrix} \phi_{1i}^c \exp\{-\phi_{2i}^c \phi_{3i}^{c\,t_{ij}}\} \\ \vdots \end{bmatrix} + e_{ij} \quad (3)$$

where the mixed effects are $\phi_i^c = [\phi_{1i}^c\ \phi_{2i}^c\ \phi_{3i}^c]^T = \beta^c + b_i^c$, the fixed effects, $\beta^c = [\beta_1^c\ \beta_2^c\ \beta_3^c]^T$, for modality c represent mean values of parameter ϕ_i^r in the population and the random effects for each subject i, $b_i^c = [b_{1i}^c\ b_{2i}^c\ b_{3i}^c]^T$, explains individual variation from the mean. By imposing joint multivariate distribution on random effects of all the modalities, we capture both inter individual variability within a modality as well as association between the growth pattern seen in different modalities. This parametrization intuitively decomposes the mean of temporal changes of a population as saturation (β_1), delay (β_2), and speed ($-\log \beta_3$).

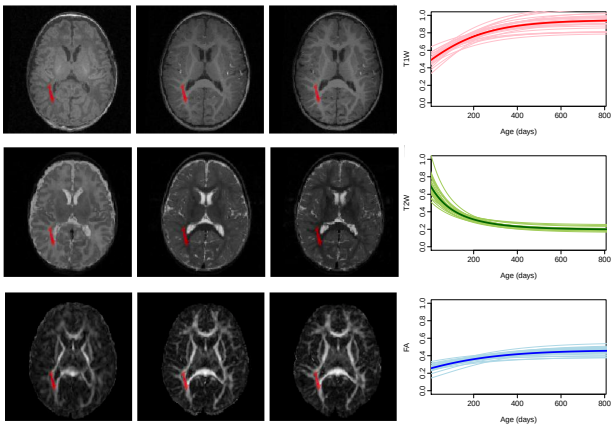

Fig. 1. Co-registered multi-modal MRI data are shown on the left. Left to Right: Images taken at two weeks, 1 year and 2 years. Top to Bottom: T1W, T2W and FA. Posterior thalamic radiation is shown as red label on the images. Population and individual growth trajectories for this region is shown to the right. Thick curves are the average growth trajectories for normalized T1W, T2W and FA.

Constructing Normative Models with Confidence Measures: The mixed effect model parameters provide descriptions of population trends as well as individual trends, along with the variability within the population. We use the NLME model to construct normative models that not only describe the expected trends, but also the expected deviations from the trends. Due to the non-linear modeling using Gompertz parameters, the computed deviations from the expected parameters do not generate multimodal trajectories with upper and lower bounds. We construct confidence intervals that bound the population trends through Monte Carlo simulations based on the mean and covariance matrix of the fixed effects, where we generate confidence bands at the 95% level. We also generate 95% predicted intervals based on the mean and covariance matrix of the fixed effects and random effects.

3. RESULTS AND CONCLUSIONS

Analysis of Clinical Data: We perform analysis on a set of repeated scans of 26 healthy subjects scanned at approximately 2 weeks, 1 year and 2 years of age. Four of the subjects had suboptimal DTI scans at 1 year that were removed, but their scans for other time points and modalities were included. The images include T1W, T2W and DTI. We apply the unbiased atlas building framework [8] to the set of T2W images at 1 year to obtain spatial mappings between each subject through the estimated atlas. Scans of other time points of each subject are registered to this atlas via linear and non-

linear transformations [1]. Tensor maps are calculated for each DTI scan, and are registered to the atlas using transformations obtained by registering the DTI baseline (B0) images to T2W images. T1W images were normalized using intensity value of fatty tissue between the skull and skin. For T2W, the csf region of ventricles was used for normalization. Fractional anisotropy feature from the registered tensors was used for the joint analysis between DTI and structural MRI.

We analyze growth trajectories in white and gray matter anatomical regions, using atlases developed and disseminated by Mori et al. [9] and Harvard Center for Morphometric Analysis [2]. Figure 1 shows the right posterior thalamic radiation (PTR) overlaid on longitudinal T1W, T2W and FA image of one subject, along with the population and individual trajectories estimated using multivariate nonlinear mixed effect model. PTR includes optic radiation and it is one of the white matter tracts that matures early [10]. There is a rapid change in T1W and T2W in the first year followed by slower maturation during second year. FA also increases during the first two years.

Fig. 3 show the population trends and confidence intervals for white matter regions of interest. This includes the body of corpus callosum (BCC) that is known to have a very limited myelination at birth, whereas Posterior limb of internal capsule (PLIC) is known to be one of the regions that shows early myelination. This pattern is evident as PLIC has a higher FA and T1W values, with lower T2W values compared to BCC and superior longitudinal fasciculus (SLF). However, BCC and SLF show a quick maturation during first year, specially in T2W. Figure 3 also shows the predicted 95% confidence interval of the expected average growth trajectory. We observe that T2W has a higher variability at birth whereas T1W has a high variability at 2 years.

We also analyze growth trajectories in gray matter, even though DTI analysis has been typically performed only in white matter. We observe small changes in FA values in these regions as gray matter matures, however the changes of T1W and T2W are greater as expected. Figure 2 shows the changes of white and gray matter in different lobes. Overall, T1W intensities increase with age and T2W intensities decrease with age. FA values for gray matter are low as gray matter does not contain fiber structure. We observe high variability for T1W at birth and also at 2 years, however T2W has high variability only at birth. We noted higher degree of maturation as is depicted in average T1W and T2W curves for occipital lobe as compared to frontal and temporal lobes. Intensity changes are higher for white matter compared to gray matter as shown in the right part of Figure 2. Higher FA values are observed in white matter compared to gray matter, due to the fiber structure in white matter. We also observe high variability of FA and T2W at birth for white matter, while T1W has high variability throughout the early development stages.

[1] http://www.doc.ic.ac.uk/~dr/software

[2] http://www.cma.mgh.harvard.edu/fsl_atlas.html

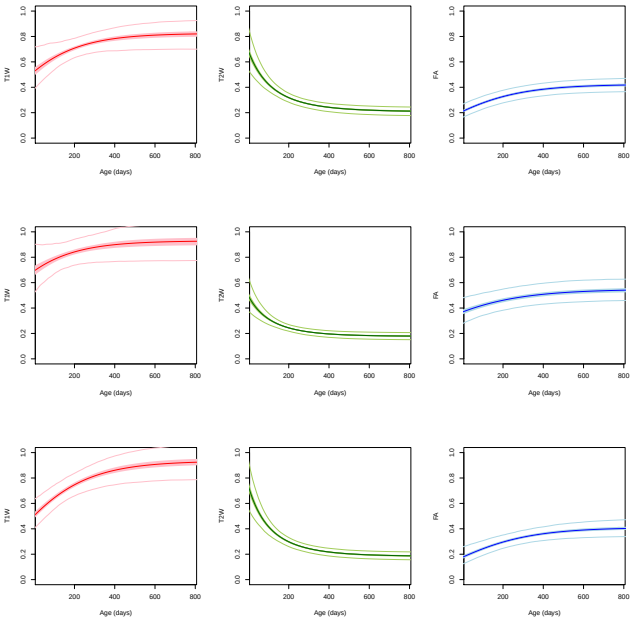

Fig. 3. Population growth trajectories (bold) and confidence intervals (light). From top to bottom: Body of Corpus Callosum (BCC), Posterior Limb of Internal Capsule (PLIC), and Superior Longitudinal Fasciculus (SLF). Thick curves are the average growth trajectories for normalized T1W (red), T2W (green) and FA (blue).

Conclusions: We have presented a new method for generating normative models of growth from multimodal, longitudinal MR images. The method utilizes non-linear mixed effects modeling using Gompertz parametrization of longitudinal changes. We applied and evaluated our method to clinical data on early brain development to obtain normative growth models in anatomical regions of interest in white and gray matter. These models describe the expected trends of the population, as well as the expected deviations from these trends. Results suggest that our approach has potential for detecting abnormalities in growth trajectories of a patient by direct comparison to the constructed normative models. In the future, we will explore the application of our approach to subjects with developmental delay or degenerative disorders such as Krabbe's disease.

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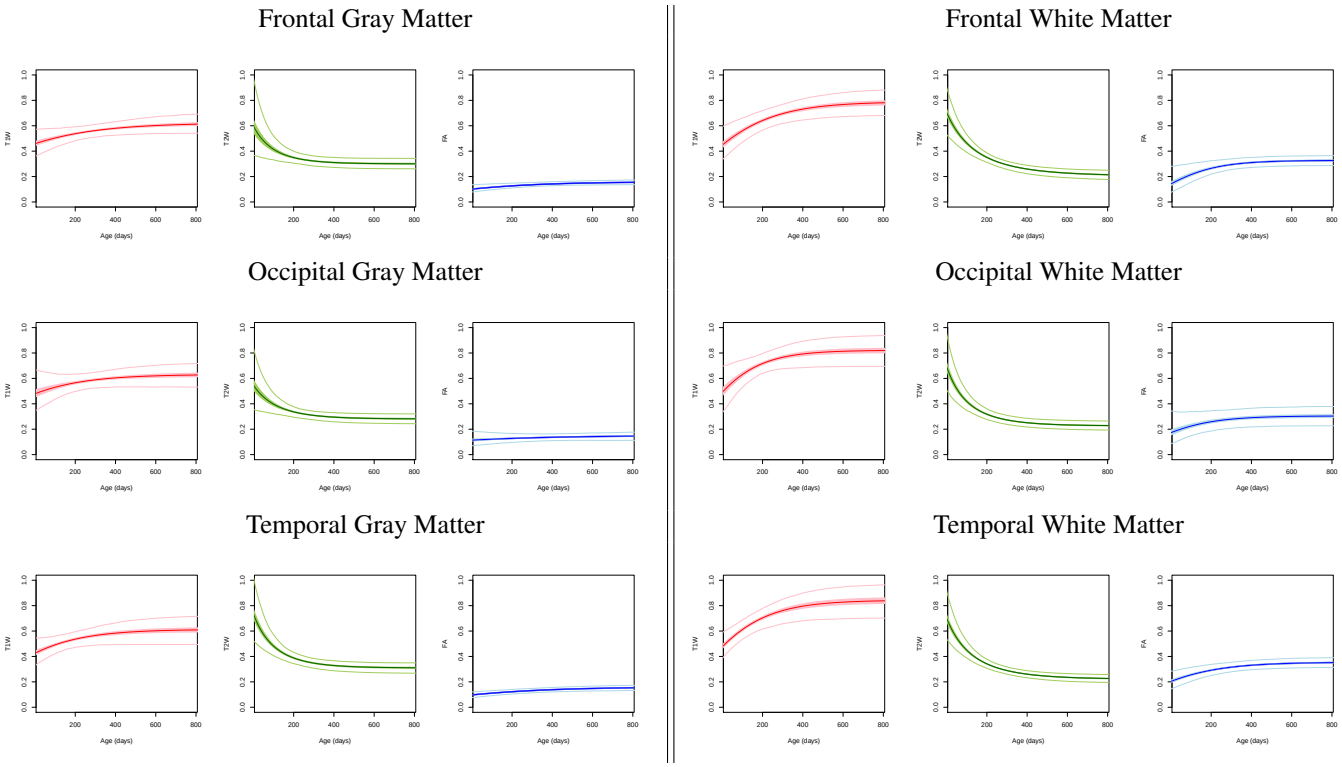

Fig. 2. Population trends and confidence intervals for gray matter and white matter in the frontal, occipital, and temporal lobes. Red denotes normalized T1W, green is T2W and blue is FA. Bold color curves are the estimated population growth trajectories, while the 95% confidence interval of the curves are shown as shaded regions bounded by transparent color curves. Light color curves show the 95% predicted intervals for each region.

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