Joint longitudinal modeling of brain appearance in multimodal MRI for the characterization of early brain developmental processes

Avantika Vardhan[1], Marcel Prastawa[2], Neda Sadeghi[1], Clement Vachet[1], Joseph Piven[3], Guido Gerig[1] ⋆

SCI Institute, University of Utah, Salt Lake City, UT, USA[1];
GE Global Research, USA[2];
Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA[3]

Abstract. Early brain maturational processes such as myelination manifest as changes in the relative appearance of white-gray matter tissue classes in MR images. Imaging modalities such as T1W (T1-Weighted) and T2W (T2-Weighted) MRI each display specific patterns of appearance change associated with distinct neurobiological components of these maturational processes. In this paper we present a framework to jointly model multimodal appearance changes across time for a longitudinal imaging dataset, resulting in quantitative assessment of the patterns of early brain maturation not yet available to clinicians. We measure appearance by quantifying contrast between white and gray matter in terms of the distance between their intensity distributions, a method demonstrated to be relatively stable to interscan variability. A multivariate nonlinear mixed effects (NLME) model is used for joint statistical modeling of this contrast measure across multiple imaging modalities. The multivariate NLME procedure considers correlations between modalities in addition to intra-modal variability. The parameters of the logistic growth function used in NLME modeling provide useful quantitative information about the timing and progression of contrast change in multimodal datasets. Inverted patterns of relative white-gray matter intensity gradient that are observable in T1W scans with respect to T2W scans are characterized by the SIR (Signal Intensity Ratio). The CONTDIR (Contrast Direction) which measures the direction of the gradient at each time point relative to that in the adult-like scan adds a directional attribute to contrast. The major contribution of this paper is a framework for joint multimodal temporal modeling of white-gray matter MRI contrast change and estimation of subject-specific and population growth trajectories. Results confirm qualitative descriptions of growth patterns in pediatric radiology studies and our new quantitative modeling scheme has the potential to advance understanding of variability of brain tissue maturation and to eventually differentiate normal from abnormal growth for early diagnosis of pathology.

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1 Introduction

Early brain development involves a complex sequence of biophysical and chemical changes occurring in systematic progression. These changes including cortical folding, premyelination changes in white matter, and myelination, can be clearly seen in brain MR (Magnetic Resonance) images [1]. Several qualitative studies have attributed significant changes in MR image appearance seen in the first two years of life to myelination [2, 3]. Myelination manifests as changing relative contrast between white matter and gray matter tissues in T1W (T1-Weighted) and T2W (T2-Weighted) MR images. MR studies of neurodevelopment confirm that these appearance changes are highly modality-specific. Each modality captures different phases of myelination resulting in differential timing of contrast change trajectories [2, 3, 1].

Most quantitative studies of the early brain have focused on volumetric and morphometric indicators, as well as microstructural parameters such as diffusion [4, 5]. The usage of image appearance as a complementary indicator of brain maturation is relatively much less explored although a key feature in pediatric radiological exams. A few recent studies have modeled spatiotemporal changes in signal intensity (SI) to better understand neurodevelopmental processes [6, 7]. However, using SI for appearance analysis increases dependence on effective normalization schemes to account for variability in intensity range between scans. The primary goal of this work is to jointly model appearance changes in MR images of the developing brain across multiple modalities using relative white-gray matter contrast. The usage of the distance between white matter and gray matter intensity distributions to quantify white-gray contrast provides greater stability to inter-scan variations compared with signal intensity analysis [8]. We apply this method to imaging studies of early brain development that are longitudinal and multimodal by design.

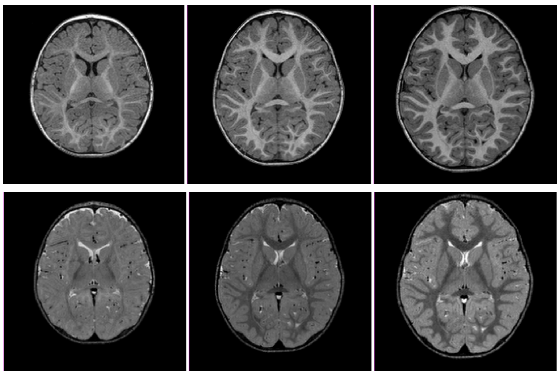


Fig. 1. Infant MRI: (from left to right) scans at 6, 12, and 24 months of age. The modalities of scans are T1W (top row) and T2W (bottom row).

Most imaging studies use a combination of different modalities of MRI such as T1W and T2W to study the early developing brain. Patterns of appearance change seen in commonly used MPRAGE (Magnetization Prepared Rapid Acquisition GRE) T1W and FSE (Fast Spin Echo) T2W scans of the early developing brain are shown in Fig. 1.

The T1W scans show increasing brightness of white matter relative to gray matter with progression of age while the T2W scans show the reversed pattern (decreasing brightness of white matter). The signal intensities and tissue properties captured by T1W and T2W scans depend on T1 and T2 relaxation times. The shortening of T1 relaxation time occurs in relation to an increase in cholesterol and glycolipids during the early phase of myelin formation, while the shortening of T2 relaxation time is associated with later stages of myelination involving processes including tightening of spiral myelin around the axon [1]. This knowledge that each modality captures a distinct maturational phase highlights the need for joint multimodal analysis.

SI values in MR images also depend on the pulse sequences used for imaging, along with factors such as scanner type, scanning conditions, and strength of the main magnetic field. The framework presented here is generic since the method for joint multimodal analysis of appearance that the authors propose is not limited to the pulse sequences and modalities discussed in this paper.

This paper applies multivariate nonlinear mixed effects modeling (NLME) to the problem of joint modeling of white-gray matter contrast in multimodal scan sets. The NLME modeling uses a nonlinear growth function to estimate population and subject-specific trajectories of contrast change [9]. The growth function parameters are jointly estimated for all modalities by taking into account correlations between them, and provide timing and progression information related to contrast change in different modalities [6, 10], and have future potential as clinical descriptors of population trends. The study of appearance change in multimodal image sets also requires quantification of direction of relative white-gray matter contrast. This is especially true for T1W and T2W images since the signal intensity gradient of white matter with respect to gray matter in these modalities is inverted. We characterize the direction of relative white-gray intensity gradient using SIR (Signal Intensity Ratio). The gradient direction at each time point is compared with the gradient direction in the adult-like image of the same modality to capture contrast reversal using a measure named CONTDIR (Contrast Direction). The CONTDIR measure is used to assign a directional attribute or sign to the contrast measure. Overall, this paper proposes a method to longitudinally model white-gray matter contrast change jointly across multimodal image sets, in terms of both magnitude and direction. The multivariate NLME procedure and the resulting parametrized growth functions enable characterization of differences between contrast change trajectories of multiple modalities and have the potential to deepen our understanding of neurodevelopmental processes.

2 Methodology

The proposed framework for joint multimodal modeling of appearance change in MRI is outlined in Fig. 2. The framework consists of four major components : (i) Spatio-temporal image processing pipeline consisting of co-registration of entire image data to a common coordinate space, segmentation of images into tissue classes (gray, white matter, etc.) and parcellation of the brain into major cortical regions; (ii) generation of white matter and gray matter intensity distributions and quantification of regional contrast in terms of the Hellinger Distance (HD) between these distributions; (iii) charac-

terizing contrast direction using SIR and adding a directional attribute to contrast using CONTDIR; and (iv) multivariate NLME for joint modeling of multimodal appearance change.

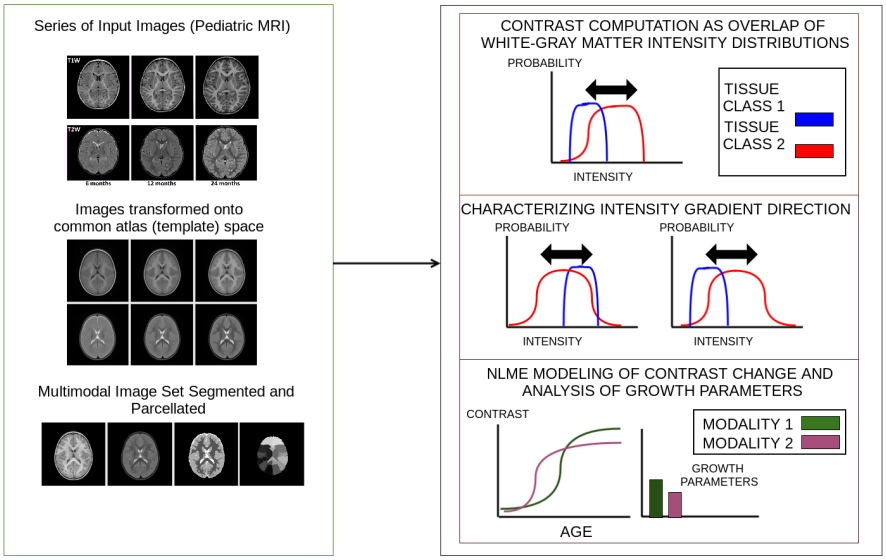


Fig. 2. Complete framework for image-processing (left) and statistical analysis of contrast (right).

2.1 Spatio-Temporal Image Processing Pipeline

A joint registration-segmentation pipeline which removes variability due to factors such as shape, structure, and volume is implemented such that appearance changes alone remain to be studied. This pipeline consists of intra subject registration using non-rigid free form deformations [11] followed by inter subject registration using LDDMM (Large Deformation Diffeophomorphic Metric Mapping) based algorithms [12] for unbiased atlas building. The result of these registrations is that all images in the dataset share the common coordinate space of the atlas. Mapping of a parcellation atlas onto the constructed atlas enables extraction of major cortical regions. An expectation-maximization (EM) based procedure for segmenting the brain into major tissue classes is implemented [13]. Improved segmentation of early time point scans is obtained using subject-specific priors in the EM procedure. These priors are obtained from probabilistic tissue segmentation maps of the latest time-point scan of each subject [14].

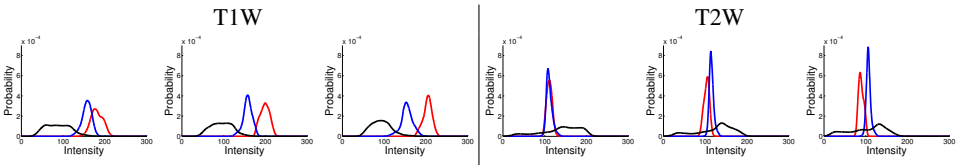
2.2 Quantification of contrast

Contrast between two tissue classes with intensities represented by probability density distributions requires a measure of similarity. Statistics suggest the use of the Hellinger

distance (HD) which knows solutions for discrete and parametric distributions and satisfies the properties of a metric. The HD can be expressed in terms of the Bhattacharyya coefficient (BC) given any two intensity distributions $P1$ and $P2$ as :

$$BC(P1, P2) = \int_y \sqrt{P1(y)P2(y)}dy. \tag{1}$$

$$HD(P1, P2) = \sqrt{2(1 - BC(P1, P2))}. \tag{2}$$



a) 6 months b) 12 months c) 24 months (d) 6 months (e) 12 months (f) 24 months

Fig. 3. Intensity Distributions of gray matter (blue), white matter (red), and cerebrospinal fluid or csf (black) in the left frontal lobe for T1W (a-c) and T2W (d-f) images of a single subject scanned at approximately 6 months (a and d), 12 months (b and e) and 24 months (c and f) of age.

Kernel Density Estimation (KDE) with a Gaussian kernel G is used to obtain smooth and continuous distributions for the intensities of each tissue class c_k. For an image $I_{i,m}$ belonging to subject i and of modality m, the intensity distribution over the entire intensity range Int is denoted by $P_{i,m}(Int|c_k)$. Intensity distributions for the multimodal image set of a single subject are shown in Fig. 3.

In the following, contrast measured in terms of HD between white and gray matter intensity distributions is named $CONT$, and defined according to the notation given above becomes :

$$CONT_{i,m} = HD(P_{i,m}(Int|c = WM), P_{i,m}(Int|c = GM)). \tag{3}$$

Contrast computed in our analysis is region-specific and time point-specific in addition to being modality-specific. The tissue intensity distributions and contrast measures are independently generated and studied for each major cortical region of the brain to better capture spatial variability. Subject i's contrast in the region R, for the jth scan obtained at time point $t_{i,j}$ of modality m, is denoted as $CONT^R_{i,m}(t_{i,j})$.

2.3 Direction of Relative Intensity Gradient of White-Gray Matter Tissue

The relative white-gray matter intensity gradients in T1W and T2W scans have opposite directions. Generally, the intensity of white matter is greater than gray matter in adult-like T1W scans, while the reverse applies to adult-like T2W scans. In this paper, we use the Signal Intensity Ratio (SIR) of white matter to gray matter to characterize this gradient direction and hence distinguish between reversed appearance patterns seen in

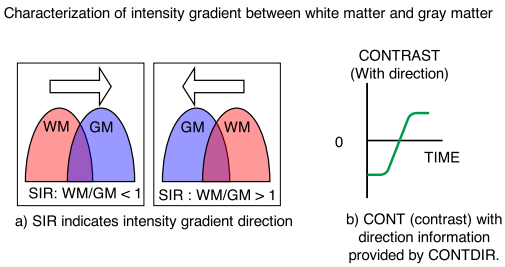


Fig. 4. a) Examples of two histograms with the same contrast value, but inverted white-gray intensity gradient directions. The SIR values capture gradient direction. b) Contrast change trajectory with directional information of intensity gradient relative to the adult-like scan provided by CONTDIR.

different modalities, as shown in Fig. 4. Regional SIR is the ratio of the mean intensity of WM voxels to the mean intensity of GM voxels in a region. Consider the SIR for the modality m scan of the ith subject taken at time $t_{i,j}$, such that the intensity of a voxel x in this scan is given by $Int_{i,m}(x, t_{i,j})$. If the SIR in a region R is greater than 1, it implies that the mean intensity of WM is greater than the mean intensity of GM in that region.

$$SIR^R_{i,m}(t_{i,j}) = \frac{\frac{\sum_{x \epsilon WM,R} Int_{i,m}(x,t_{i,j})}{N^R(WM)}}{\frac{\sum_{x \epsilon GM,R} Int_{i,m}(x,t_{i,j})}{N^R(GM)}} \tag{4}$$

The terms $N^R(WM)$ and $N^R(GM)$ in the above equation denote the total number of voxels in a region R belonging to WM and GM tissue classes respectively.

It has also been observed that the direction of white-gray intensity gradient undergoes a reversal during early development. A quantity $CONTDIR$ characterizes this reversal by comparing direction of intensity gradient at each time instant to gradient direction in the adult-like scan. Consider the regional SIR value for the image scanned at a time point t' when image appearance is adult-like. If SIR of the adult-like image satisfies the inequality $SIR^R_{i,m}(t') - 1 > 0$, then contrast values at all time points which satisfy the same inequality $SIR^R_{i,m}(t) - 1 > 0$ are assigned a positive sign. The contrast values which do not satisfy the same inequality as the adult-like image are assigned a negative sign. The same rule is applicable if the SIR of the adult-like image satisfies the inequality $SIR^R_{i,m}(t') - 1 < 0$. The direction of contrast for region R, for a modality m scan belonging to subject i, taken at time instant t, relative to adult-like contrast observed at time t' is denoted by $CONTDIR$ and defined using the signum function:

$$CONTDIR^R_{i,m}(t) = signum\left(\frac{SIR^R_{i,m}(t) - 1}{SIR^R_{i,m}(t') - 1}\right). \tag{5}$$

To summarize, the SIR encodes the actual direction of relative white-gray matter intensity gradient, while the $CONTDIR$ helps determine if reversal in gradient direction takes place. For multimodal mixed effect analysis, the SIR-based directional attributes are modeled independently from contrast. The $CONTDIR$ value, however, is used to provide a sign to the contrast measure defined in the earlier section in all

subsequent analysis. Therefore only reversals in contrast are characterized in the HD-based contrast analysis by adding a sign using CONTDIR. The actual direction of the intensity gradient is independently modeled using the SIR with LME (Linear Mixed Effects) analysis. If the SIR-based directional attributes were used to add a sign to the contrast measure, contrast values of images belonging to different modalities would have opposite signs and their ranges would not be comparable.

2.4 Nonlinear Mixed Effects Modeling of Contrast

Our study data is longitudinal, i.e. repeated images of each subject are obtained over time. Taking into account correlations of repeated measures, different time spacing and varying number of timepoints per subject, as well as resistance to noise, statistics is offering the methodology of mixed-effect modeling. Unlike regression of the set of measures assuming independence, mixed effect modeling correctly includes intra-subject correlations and estimates temporal trajectories of the whole group (fixed effect) and of each individual (random effects). Accounting for nonlinear temporal changes of contrast, we apply a nonlinear mixed-effects modeling technique (NLME) [9, 15]. The NLME framework we use is well established and has several advantages including robustness to noise and outliers, and the ability to work with datasets that include missing and unevenly spaced data. The NLME model uses mixed effects parameters consisting of a linear combination of population-based fixed effects and subject-specific random effects to estimate growth trajectories. The observation of the ith individual at the jth time point $t_{i,j}$ is hence modeled using NLME as :

$$y_{ij} = f(\boldsymbol{\phi}_i, \mathbf{t}_{ij}) + e_{ij}. \tag{6}$$

Here $i = 1, ..., N_{ind}$ refers to subject indices and $j = 1, ..., T_{ind}$ are indices of time points of scan. The function f is the nonlinear growth function of choice that is used to model the contrast change trajectory. This function is dependent on the covariate vector t_{ij} as well as the mixed effect parameter vector $\boldsymbol{\phi}_i$. The error term e_{ij} refers to the residual i.i.d error which follows the normal distribution $e_{ij} \sim N(0, \sigma^2)$. The parameter vector $\boldsymbol{\phi}_i$ which has fixed and random effect components can be written as :

$$\boldsymbol{\phi}_i = \boldsymbol{A_i}\boldsymbol{\beta} + \boldsymbol{B_i}\boldsymbol{b_i} \text{ , where } \boldsymbol{b_i} \sim N(0, \boldsymbol{\psi}). \tag{7}$$

The vector of fixed effects is given by $\boldsymbol{\beta}$ and the vector of random effects by $\boldsymbol{b_i}$. The design matrices associated with fixed effects and random effects vectors are given by $\boldsymbol{A_i}$ and $\boldsymbol{B_i}$ respectively. The random effects which contribute to parameter $\boldsymbol{\phi}_i$ are assumed to be normally distributed with variance-covariance matrix $\boldsymbol{\psi}$ over all subjects.

Since we want to model the highly nonlinear trends seen in contrast change a parametric growth function is adopted for NLME modeling [5]. Parametric growth models provide concise description of the data and show greater flexibility compared with linear models. After testing various choices for parametric functions with low number of parameters based on the Akaike Information Criterion (AIC), we decided on using the logistic growth model. We use the four parameter logistic growth model defined by the parameters $(\phi_1, \phi_2, \phi_3, \phi_4)$ as :

$$f(\boldsymbol{\phi}, t) = \phi_1 + \frac{\phi_2}{1 + exp^{\frac{\phi_3 - t}{\phi_4}}}. \tag{8}$$

The parameters of the logistic model can be interpreted as follows : (i) ϕ_1 is the left horizontal asymptotic parameter which is the value taken by the model for very small values of input t, (ii) ϕ_2 is the right horizontal asymptotic parameter at which the model saturates for large values of input t, (iii) ϕ_3 is the inflection point parameter which indicates the time taken to reach half the difference between left and right asymptotic values, and (iv) ϕ_4 is a rate parameter denoting a scaling function on the time axis which indicates the curvature of the model at the inflection point.

To generate an individual i's trajectory using NLME modeling with the logistic function, mixed effects parameters $\boldsymbol{\phi}_i$ consisting of the sum of fixed effect β and subject-specific random effect b_i are used (by setting values of design matrices $\boldsymbol{A}$ and $\boldsymbol{B}$ appropriately). The response y_{ij}^R for a region R and subject i at the jth time instant t_{ij} can be written as :

$$y_{ij}^R = {\boldsymbol{\phi}^R}_{i1} + \frac{{\boldsymbol{\phi}^R}_{i2}}{1 + exp^{\frac{{\boldsymbol{\phi}^R}_{i3} - t_{ij}}{{\boldsymbol{\phi}^R}_{i4}}}} + e_{ij} = {\beta^R}_1 + {b^R}_{i1} + \frac{{\beta^R}_2 + {b^R}_{i2}}{1 + exp^{\frac{{\beta^R}_3 + {b^R}_{i3} - t_{ij}}{{\beta^R}_4 + {b^R}_{i4}}}} + e_{ij}. \quad (9)$$

Since we lack information about contrast at the time of birth, the first parameter ${\phi^R}_{i1}$ is set to 0 in our analysis. Based on study of variability across subjects and information criteria, we assume that the right-asymptotic parameter ϕ_2 and inflection point parameter ϕ_3 have non-zero random effects, while the remaining parameters don't have a random effects component.

Extension of statistical analysis to multimodal data We now extend the univariate model to the multivariate case of multimodal data. Here, the response y_{ij}^R defined above is now considered for a particular modality m to be:

$$y_{ij,m}^R = f({\boldsymbol{\phi}^R}_{i,m}, t_{ij}) = {\beta^R}_{1,m} + {b^R}_{i1,m} + \frac{{\beta^R}_{2,m} + {b^R}_{i2,m}}{1 + exp^{\frac{{\beta^R}_{3,m} + {b^R}_{i3,m} - t_{ij}}{{\beta^R}_{4,m} + {b^R}_{i4,m}}}} + e_{ij} \quad (10)$$

The responses for the entire set of multimodal images can be modeled as :

$$\begin{bmatrix} y_{ij,m}^R \\ . \\ . \\ . \end{bmatrix} = \begin{bmatrix} f({\boldsymbol{\phi}^R}_{i,m}, t_{ij}) \\ . \\ . \\ . \end{bmatrix} + e_{ij}. \quad (11)$$

In order to jointly study both variability within a modality (between individuals), and across modalities, the random effects belonging to all modalities are assumed to follow a multivariate normal distribution [10, 6]. The parameters of this multivariate normal distribution are estimated by taking into account inter-modality covariance. In this manner, the growth patterns of scans from different modalities are associated and estimated jointly rather than separately. For a set of modalities $[m = 1, 2, ..., M]$, the joint random effects parameters $b_{i2,m}$ and $b_{i3,m}$ (corresponding to mixed effects parameters ϕ_2 and ϕ_3, i.e. right horizontal asymptote and inflection point) are jointly modeled across all M modalities as:

$$\boldsymbol{b}_i = \begin{bmatrix} b_{i2,1} \; b_{i3,1} \; . \; . \; b_{i2,M} \; b_{i3,M} \end{bmatrix}^T \sim N(0, \boldsymbol{\psi}). \quad (12)$$

Inferences relating to appearance change trends in multiple modalities can be made by (i) studying the estimated mixed effects parameters and resulting growth trajectories, and (ii) hypothesis testing to find significant differences in parameters belonging to different modalities. The details about computation of estimated parameters ($\boldsymbol{\beta}, \boldsymbol{\phi}, \boldsymbol{\psi}, \boldsymbol{\sigma^2}$) as well as hypothesis testing can be found in [6] and [10].

3 Results

NLME Modeling of Synthetic Data

Longitudinal changes in bivariate data were simulated with synthetic data generated using the logistic growth model to better understand multivariate NLME analysis. The random effects parameters (right horizontal asymptote and inflection point) underlying the logistic growth function were generated from a multivariate Gaussian distribution. The left horizontal asymptote was set to zero as explained in the section above and the rate parameter was assumed to only have a fixed effect component. In two independent experiments, the random effects parameters of the two variables were designed to be (i) strongly correlated, and (ii) uncorrelated. The fixed effects were the same for both experiments. The individual and subject specific trends were estimated using NLME based mixed effects analysis. A univariate NLME model fit was first done separately for each variable, followed by a joint modeling for both variables using multivariate NLME. We first consider (i), the case where the variable parameters are strongly correlated. Here, the multivariate NLME fit for all variables resulted in a significantly lower AIC (Akaike Information Criterion) value compared with the sum of AIC values of univariate fits for each variable. This indicates that multivariate NLME provides a better fit for the data in case (i). In case (ii) where the parameters are uncorrelated, the usage of multivariate NLME had no major effect on the AIC as seen in Table 1. This synthetic data experiment reinforces the necessity of the multivariate fit for modeling multimodal data, particularly when correlation exists between modalities.

Relation between growth parameters of variables	AIC(Var.1) + AIC(Var.2)	AIC(Var.1 + Var.2)
Strong Correlation	-869.751	-1015.242
No Correlation	-866.006	-864.939

Table 1. AIC comparisons for separate and joint fits of multivariate synthetic data

3.1 Multimodal Contrast Modeling and Analysis on Infant Clinical Data

The framework outlined in Section 2 is applied to 22 healthy controls scanned at approximately 6 months, 12 months, and 24 months of age. Registration removes all volumetric and morphometric differences and segmentation classifies each voxel into one of the major tissue classes. Intensity distributions for white and gray matter tissue classes are computed. Four major cortical regions in left and right hemispheres (eight brain

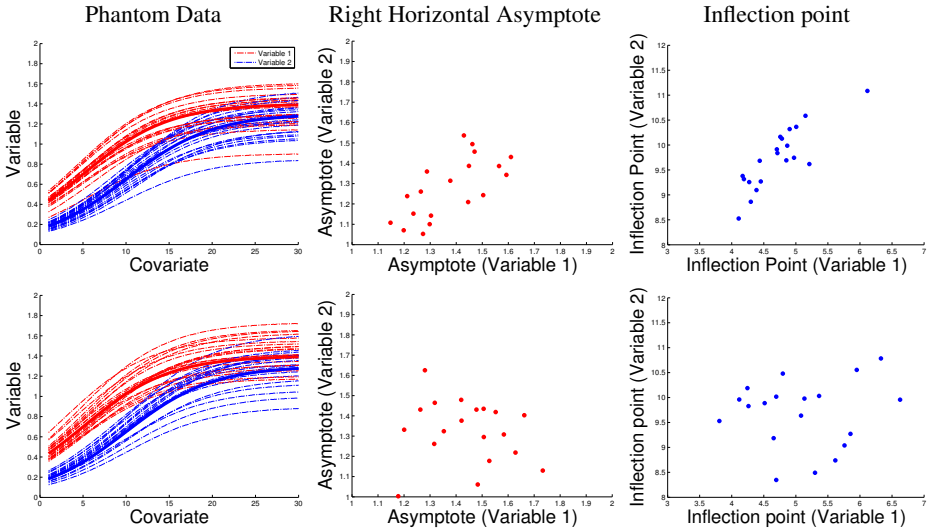


Fig. 5. (Leftmost column) Trajectories of change plotted with respect to the covariate for two synthetically generated variables. These variables (1 and 2) have strongly correlated (top row) and uncorrelated (bottom row) random effects parameters for the underlying logistic growth function. (Middle and right columns) Experimentally designed values of mixed effects parameters (fixed + random effects) for variable 2 vs. variable 1 are shown in 2D scatter plots : (middle column) right horizontal asymptote ϕ_2 and (right column) inflection point ϕ_3. The parameters in the top row show strong correlation between the two variables while the parameters in the bottom row show no correlation. The inflection point assumes same unit as the covariate while the asymptote assumes the unit of the variable modeled.

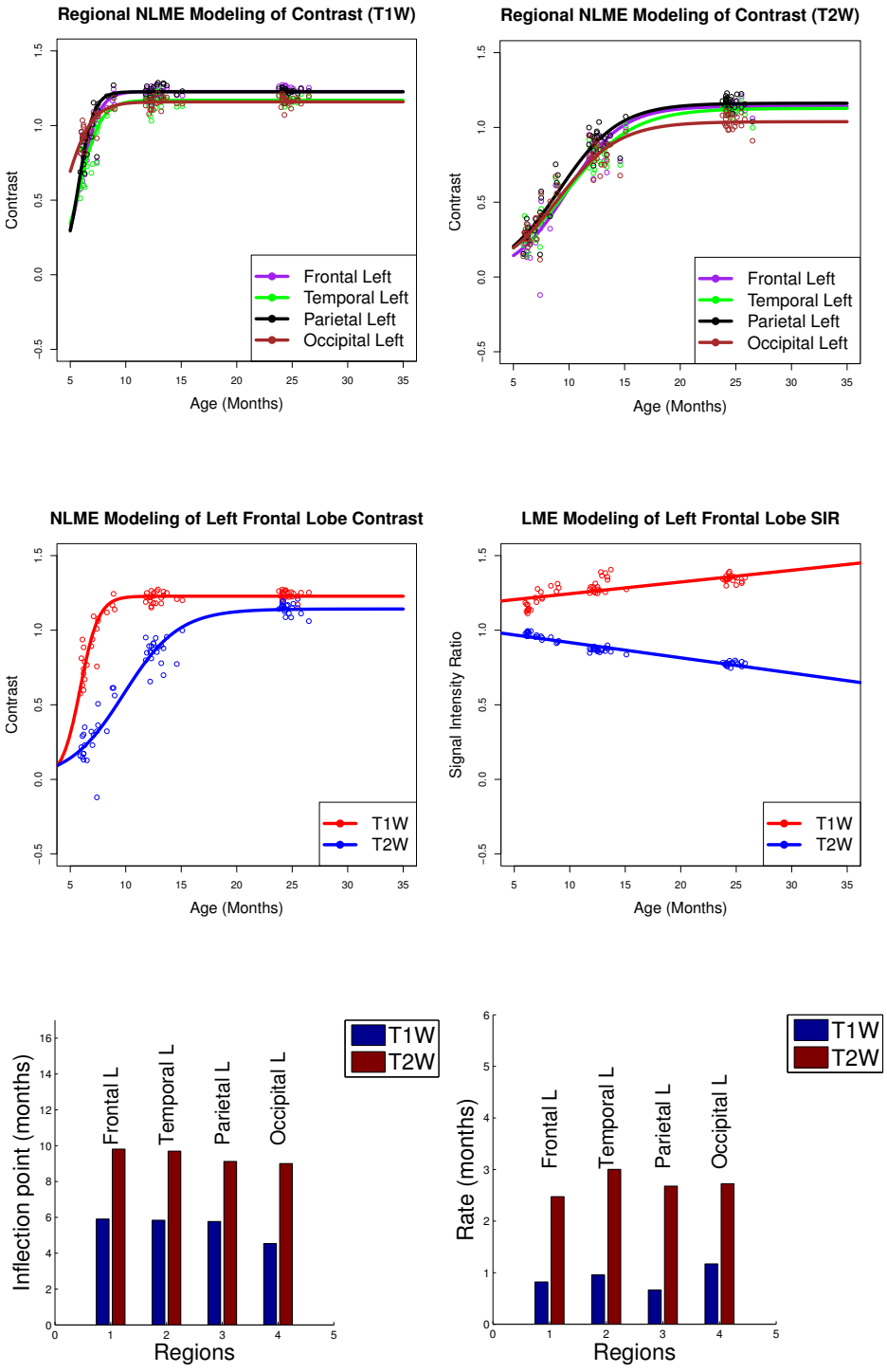


Fig. 6. (Top row) Mean contrast change Trajectories in the major cortical lobes of the left hemisphere for T1W (top row, left column) and T2W (top row, right column) modalities. (Middle row, left column) Mean contrast change trajectories for both modalities in the left frontal lobe modeled using NLME. (Middle row, right column) Mean linear trend for left-frontal lobe SIR ratios changing with time modeled using LME. (Bottom row, left column) Mean (fixed effect) inflection point parameter in months, which measures the time at which half the right horizontal asymptotic value is reached. (Bottom row, right column) Mean (fixed effect) rate parameter in months which is a scaling factor on the time axis and is representative of the curvature at the time point at which half the right asymptotic value is reached.

regions in total) are chosen to explore spatially dependent brain maturation patterns. Contrast in T1W and T2W modalities are jointly modeled for each lobe using multivariate NLME. The contrast value modeled also has a direction attribute (relative to adult-like image) given by CONTDIR. Results shown are for left hemispheric cortical lobes, although similar patterns are replicated in the right hemisphere as well.

As seen in Fig. 6, we infer that contrast change in T1W scans takes place more rapidly as compared with T2W scans. From visual analysis of the growth trajectories it is observed that the white-gray contrast in T1W scans becomes close to adult-like at around 10 months of age. In comparison, contrast in T2W scans continues increasing until two years of age. Since myelination is known to be one of the key processes contributing to contrast in T1W and T2W images, this pattern is in conformity with the well-established knowledge that in general, changes associated with myelination are apparent earlier and proceed faster on T1W images than on T2W images [1]. The contrast change trajectories of different cortical regions are also known to follow the trend of contrast first appearing in parietal/occipital lobes, followed by temporal and frontal lobes. Quantitative results from the applied framework are consistent with qualitative radiological observations : the contrast value is seen to reach early saturation in occipital and parietal lobes while temporal and frontal lobes undergo contrast change over a longer time period.

Analysis of logistic growth function parameters describing contrast change Statistical inferences based on the non-zero parameters (right-asymptote, inflection point, and rate) of the logistic function of the form defined earlier, quantify the established qualitative knowledge that regional contrast change takes place with varying rates in different modalities. Statistical hypothesis testing using the Student's t-test confirms significant differences in both the inflection point and rate parameters between T1W and T2W modalities for all lobes (results not shown). These timing parameters plotted in Fig. 6 numerically exemplify differences seen in the appearance of white-gray matter contrast between T1W and T2W modalities. Although absolute values of these parameters might vary depending on the type of pulse sequence used, they can still be compared to assess delay in appearance of adult-like white-gray contrast for certain modalities. The inflection point is particularly crucial to this finding since it indicates the time taken to reach half the right asymptotic value (assuming that the left asymptote is zero). While the inflection point lies in the range from 4 to 6 months for T1W images, it takes on a much higher value of over 9 months for T2W images. Analysis of the inflection point parameter also numerically confirms the visual finding that temporal and frontal lobes follow delayed maturation trajectories compared with occipital and parietal lobes. The rate parameter is a numerical scale parameter on the input time axis. This parameter approximates to the time taken in months for change from 50 percent to 73 percent of the maximum value [16]. The rate parameter ranges between half and 1 month for T1W images and between 2 and 3 months for T2W images, indicating that the rate of change after the inflection point in T1W images is much higher than the rate of change in T2W images. The SIR (Signal Intensity Ratio) of major brain regions is used in addition to NLME modeling of contrast magnitude to characterize directionality of relative intensity gradient between white and gray matter tissue classes. A linear

mixed effects model is used to estimate the general population trend observed in SIR as seen in Fig. 6. This LME model is similar to the NLME model described above except that the nonlinear growth function is replaced by a linear function. It can be observed that for T1W images the SIR is predominantly greater than 1, indicating that white matter is of higher intensity compared with gray matter on average. The SIR is less than 1 for most T2W images, indicating the inverted nature of white-gray matter contrast. The slope of the SIR trends for T1W and T2W scans further illustrates the knowledge that contrast changes in these two modalities take place in opposite directions. The CONTDIR value which measures gradient relative to intensity gradient in the adult-like image is also computed at each time point and adds the sign for the contrast value.

4 Discussion and Conclusions

The multivariate NLME modeling of multimodal contrast change demonstrates that T1W and T2W modalities show distinctly different patterns of contrast change. The average growth function parameters estimated using NLME serve as numerical indicators of these differential patterns and conform to existing studies of the developing brain [1]. Statistical hypothesis testing further substantiates the claim that the timing parameters of contrast change are significantly different for the two modalities studied. Our choice of the logistic function to model contrast change is based on comparison of AIC values with a few other commonly used biological growth functions. Prior knowledge that maturation takes place in a highly asymptotic manner and reaches a saturation value around 2 years of age further strengthens our choice. Our method faces limitations since contrast as a measure of appearance could be adversely affected by intensity inhomogeneities. In this study contrast is analyzed in a regional manner but a voxel-level appearance measure could give rise to new interesting insights at a finer anatomical scale, particularly since large variability can exist even within a lobar region as applied here.

This work presents a complete framework for the joint modeling of multimodal MR image appearance change in longitudinal datasets using multivariate NLME. The usage of multivariate NLME for contrast modeling enables joint estimation of appearance change parameters in T1W and T2W modalities, hence accounting for correlations between multimodal scans. The timing parameters extracted from this model and statistical inferences from the same quantify lag in appearance of white-gray matter contrast observed in T2W scans compared with T1W, confirming the utility of the method in early brain developmental studies. Modeling of SIR enables the inclusion of information about the direction of white-gray intensity gradient. CONTDIR assigns a directional value to contrast and captures contrast reversals by finding the relative direction of the white-gray intensity gradients compared to the adult-like image. Future studies would involve multimodal estimation of time of contrast reversal using neonate scans, extending the current analysis to several other modalities, and exploring applications of this work in detecting developmental abnormalities. The effect that switching from univariate to multivariate modeling has on prediction of abnormal trajectories of appearance change also holds interest.

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