Statistical Growth Modeling of Longitudinal DT-MRI for Regional Characterization of Early Brain Development

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Abstract. This paper presents a framework for modeling growth trajectories and determining significant regional differences in growth pattern characteristics applied to longitudinal neuroimaging data. We use nonlinear mixed effect modeling where temporal change is modeled by the Gompertz function. The Gompertz function uses intuitive parameters related to delay, rate of change, and expected asymptotic value; all descriptive measures which can answer clinical questions related to growth. Our proposed framework combines nonlinear modeling of individual trajectories, population analysis, and testing for regional differences. We apply this framework to the study of early maturation in white matter regions as measured with diffusion tensor imaging (DTI). Regional differences between anatomical regions of interest that are known to mature differently are analyzed and quantified. Although our framework can be applied to any image-derived measurements, we show statistical tests for axial diffusivity (AD) and radial diffusivity (RD) measurements as these are known to be sensitive to degree of myelination and axonal structuring. Experiments with image data from a large ongoing clinical study show that our framework provide descriptive, quantitative information on growth trajectories that can be directly interpreted by clinicians. To our knowledge, this is the first statistical analysis of growth functions to explain the trajectory of early brain maturation.

1 Introduction

Longitudinal imaging studies with repeated scans per subjects require appropriate analysis procedures that take into account the special nature of such study designs. These include correlation due to repeated measures, often with unbalanced spacing due to acquisitions at different time points and missing data at certain time points. Early development is characterized by large initial growth that flattens off, which favors nonlinear growth modeling. Typical clinical questions are addressing growth trajectory characterizations such as delayed or advanced growth, accelerated or slowed growth, or the question if groups can reach the same level of maturation if they have a delayed start.

Diffusion Tensor Imaging (DTI) provides a unique opportunity to assess the tissue structure of brain white matter in vivo, and has great potential to provide insight into early development. Previous studies have mostly focused on morphometry changes such as volume of gray and white matter, cortical thickness, and shape [7, 4, 13, 12]. There is also considerable research on DTI, however these are cross sectional studies and/or studies on children older than 2 years [1, 2]. The human brain undergoes the most significant change in the first and to a lesser extent in the second year, and studies of changes in white matter diffusivity that can be linked to cognitive development will be crucial to provide a better understanding of early growth. While longitudinal DTI of infants covering the few years of life are becoming available, analysis methodologies for assessing longitudinal changes of individuals and populations, to our knowledge, are not available. In this study, we focus on developing longitudinal models for diffusion parameters which are obtained from repeated scans of children imaged at 2 weeks, 1 year and at 2 years of age. DTI indices have been shown to provide relevant information about brain maturation and the underlying tissue changes as they indicate water content and myelination [4]. In this study, we focus on axial and radial diffusivity (AD and RD) as opposed to fractional anisotropy (FA) as FA is not a good indicator of myelination [6]. Describing and analyzing the non-linear changes of white matter are difficult as regions in the brain begin to mature at different times, with different rates [1]. We quantify these differences using Gompertz functions [3] that provide an intuitive parametrization representing delay, growth, and saturation rate in each region.

In contrast to previous studies, we analyze growth trajectories based on an explicit growth function and a nonlinear mixed effect modeling scheme [10]. Diffusion changes are modeled in a hierarchical fashion, with the global population trend as a fixed effect and individual trends as random effects. Mixed effect models are well suited for longitudinal data, where each time series constitutes an individual curve. Classical statistical approaches assume each observation is independent with equal distribution, which are not appropriate for repeated measures. We apply our framework to compare a set of white matter regions that are known to have different growth patterns and myelinate at different time periods. Quantitative analysis of these regions will provide further insight into brain maturation process and allow us to predict subject-specific growth trajectories with the potential of detecting pathological brain development related to brain disorders. We show that the statistical quantitative analysis results in parameters that use the clinician's vocabulary for assessment of growth trajectories.

2 Method

Non-linear Mixed Effects Modeling: We use a non-linear mixed effects (NLME) model to analyze the longitudinal DTI data. Compared to current statistical analysis on DTI which uses least-squares curve fitting, this is a true longitudinal model that can have unbalanced temporal data. The model can admit variable numbers of temporal observations in each subject; a significant advantage in real clinical data that often has missing observations. Also, the

model is robust to outliers as it accounts for the variabilities within individuals. In this subsection, we present a review of the non-linear mixed effects model. We will present our approach for analyzing longitudinal DTI data using NLME in the next subsection.

In the mixed effects model, the observed data is assumed to be a combination of both *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 [8] which is a hierarchical model, where the jth observation on the ith individual is modeled as:

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

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_{ij}, 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

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

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.

Regional Analysis of Longitudinal DTI Patterns: We perform quantitative analysis on a population of longitudinal DTI data within anatomical regions. We model DTI features as non-linear mixed effects, which combines regional population trends and individual subject trends. For this section, we assume that DT MR images have been registered to a standard reference space.

The primary goal for our analysis of growth trajectories is to determine whether patterns of growth are different among different regions, and if we can provide a descriptive, intuitive parametrization for each region that can be compared to other regions of brain. 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 DTI using the Gompertz function. Specifically, we model temporal growth for an individual i, time points t_{ij}, and region r by nonlinear mixed effect model of Gompertz function that is parametrized by asymptote ϕ_1^r, delay ϕ_2^r, and rate of change ϕ_3^r for a given region r:

$$y_{ij}^r = f(\phi_i^r, t_{ij}) + e_{ij} = \phi_{1i}^r \exp\{-\phi_{2i}^r {\phi_{3i}^r}^{t_{ij}}\} + e_{ij} \tag{3}$$

where the mixed effects are $\phi_i^r = [\phi_{1i}^r\ \phi_{2i}^r\ \phi_{3i}^r]^T = \beta^r + b_i$, the fixed effects for region r are $\beta^r = [\beta_1^r\ \beta_2^r\ \beta_3^r]^T$, and the random effects for each subject i are $b_i = [b_{1i}\ b_{2i}\ b_{3i}]^T$. In this model, p and q are same size vectors, and the design matrices A and B are identity. We note that an alternative representation for Gompertz function is $y = asymptote\ exp(-delay\ exp(-speed\ t))$ where $speed = -\log \beta_3$, thus higher β_3 implies lower speed.

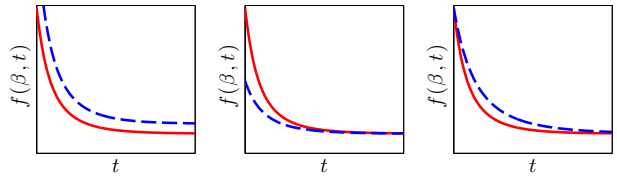


Fig. 1. Effect of varying the parameters of the Gompertz functions. The red curve show the reference curve that is held fixed. Left to right: the dashed blue curves show the effect of increasing values of β_1, β_2, and β_3 respectively. β_1 represents the asymptote, β_2 represents the delay, and speed is represented by $-\log \beta_3$.

The parameter ϕ_i^r combines the fixed effects of each region denoted by β^r that represents mean values of parameter ϕ_i in the population with random effect which denotes individual variation from the mean. The parametrization intuitively splits temporal changes as delay, growth and saturation (Fig. 1).

We obtain mixed effect model parameters using maximum likelihood estimation (MLE) on the marginal density of the respones y:

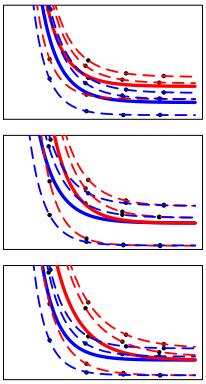
$$p(y|\beta, \Psi, \sigma^2) = \int p(y, |\beta, b, \Psi, \sigma^2) p(b) db$$

There is generally no closed form solution, so we use the approximation method proposed by Lindstrom and Bates [8], using the `nlme` function in R[4], to obtain model parameters, β, b, Ψ,σ. Once all the model parameters are estimated, we can conduct hypothesis testing and determine the significant modes of longitudinal changes in terms of asymptote, delay, and speed between regions. With N number of regions, we accomplish this through $\frac{N(N-1)}{2}$ pairwise fitting of nonlinear mixed effect model and test for fixed effect significance through t-test; corrected for multiple comparisons using Bonferroni correction. The parameters that are found to be significant can then be interpreted as the distinguishing feature between the longitudinal patterns of the two regions. For example, if the parameter β_2^r is found to be significantly different for two regions then the longitudinal growth for one region is delayed compared to the other.

3 Results and Conclusions

Validation on Synthetic Data: We use randomly generated synthetic longitudinal data to ensure our analysis methodology can capture underlying differences as presented in the synthetic data. Random data representing two regions is generated, and we verify that the overall trend of the subjects and each subject's specific growth trajectory matches the known ground truth. It is also important that the Gompertz parameters are verified to be significantly different between the two regions, matching the synthetic model. Synthetic random longitudinal data are generated following equation 3 where $\Psi = diag(0.0016, 0.0004, .000004)$

[4] `http://r-project.org`



	Truth R_1	Estimated R_1	Truth R_2	Estimated R_2	p-value
β_1	1	1.004	1.1	1.104	< 0.001
β_2	-2	-2.024	-2	-2.062	.24
β_3	.99	.991	.99	.991	.22

	Truth R_1	Estimated R_1	Truth R_2	Estimated R_2	p-value
β_1	1	1.005	1	1.004	.11
β_2	-1	-1.029	-2	-2.011	< 0.001
β_3	.99	.991	.99	.991	.28

	Truth R_1	Estimated R_1	Truth R_2	Estimated R_2	p-value
β_1	1	1.003	1	1.003	0.49
β_2	-2	-1.986	-2	-1.987	.96
β_3	.989	.990	.992	.993	< 0.001

Fig. 2. Example of randomly generated synthetic longitudinal data for two different regions colored blue (R_1) and red (R_2). Top to bottom: varying β_1 between two regions, varying β_2 between two regions, and varying β_3 between two regions. The significance values obtained from pairwise testing of different regions are shown on the right.

and $\sigma^2 = 0.000001$. Values for four time points of three subjects are generated while keeping some of the fixed parameters, β, the same in the two regions. We then vary one of the fixed parameters, and test for significant differences between two regions. Fig. 2 summarizes our experimental results. The results demonstrate that our approach can detect significant discriminatory features of growth patterns in a pair of regions in terms of the Gompertz asymptote, delay and speed parameters.

Analysis of Clinical Data: We perform analysis on a set of repeated scans of eight healthy subjects scanned at approximately 2 weeks, 1 year and 2 years of age. The images include T2W and DTI. We apply the unbiased atlas building framework by Joshi et al. [5] 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 nonlinear transformations. 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. In this study, we extract the axial and radial diffusivity features from the registered tensors, $AD = \lambda_1$ and $RD = \frac{\lambda_2+\lambda_3}{2}$ where λ_i are the sorted eigenvalues of the tensor.

For regional analysis, we select four anatomical regions in the unbiased atlas that are known to mature in distinctly different patterns and determine the characteristics of these differences. Since all DT images are registered to a common coordinate space, regions determined in this space can be automatically transferred to each individual image. We use regions defined by Mori et al. [9] that were registered to our unbiased atlas and modified through binary erosion for improved accuracy. The selection of regions in the atlas space allows automatic partitioning of the subjects' scans into different anatomical regions. Fig. 3 shows the estimated individual and population growth trajectories of AD and RD indices for Anterior and Posterior Limb of Internal Capsule (ALIC and PLIC re-

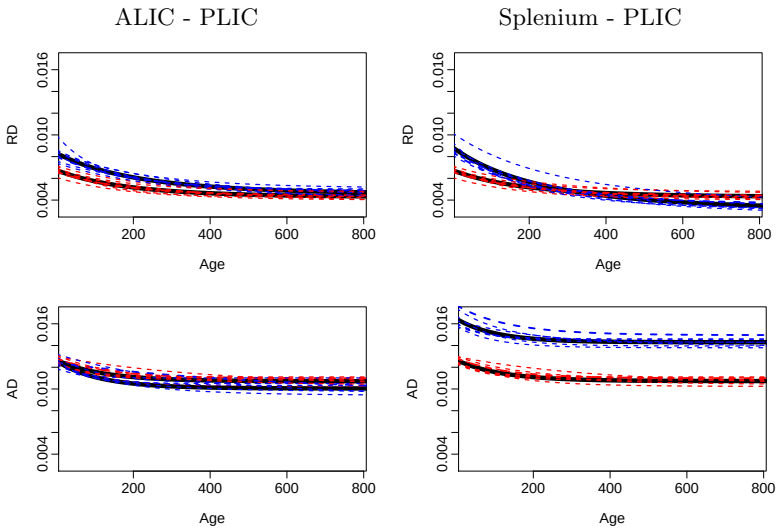


Fig. 3. Individual (dashed lines) and population curves (solid lines) for selected regions. Left: ALIC (blue) compared to PLIC (red). Right: Splenium (blue) compared to PLIC (red). Horizontal axis is age (since birth) in days.

spectively), and Splenium. The ALIC to PLIC comparison clearly demonstrates that PLIC has lower RD at birth due to initial myelination, but ALIC reaches the same level at 2 years. However, there were no significant differences in AD measurements between ALIC and PLIC, which may hint to the fact that RD is a better discriminatory factor for myelination compared to AD. Splenium also is not myelinated at birth, but then rapidly matures as it's shown in the RD plot.

Fig. 4 shows a summary of pairwise comparisons of Genu, Splenium, ALIC, and PLIC. We characterize the differences in an intuitive way using Gompertz asymptote, delay and speed parameters. Our findings confirm the temporal sequence of myelination of these selected regions provided by Rutherford et al. [11].
Conclusions: This paper presents a statistical methodology for characterizing longitudinal patterns of tissue properties in white matter regions. Our approach provides characterizations of the significant discriminating features of growth patterns, within a pair of regions, in terms of the Gompertz asymptote, delay, and speed parameters. The characterization using the Gompertz parameters provides an intuitive description of longitudinal trends, with potential for analyzing biological progression due to neurodevelopment or aging. This is in contrast to current modeling and analysis of DTI in early brain development where testing for regional or group differences does not directly reveal the type and nature of the difference. We have shown experimental results on the analysis of longitudinal DTI patterns in early development, where we performed quantitative comparisons and determine significant differences of growth patterns in certain anatomical white matter regions. Statistics on our growth function parameters provide a natural description of growth that can be easily interpreted in clinical

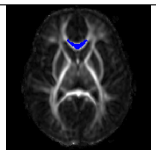
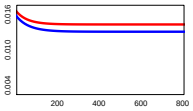
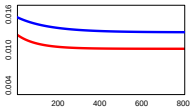
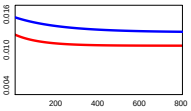
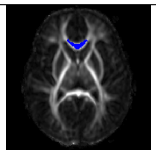
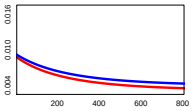
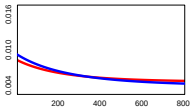
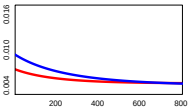
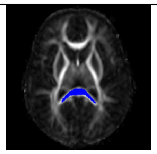
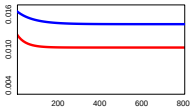
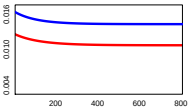
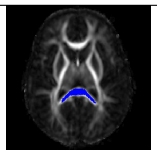
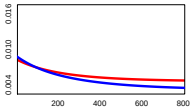
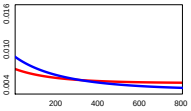
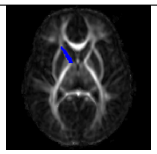
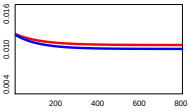
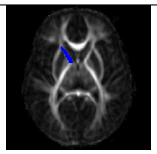
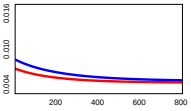
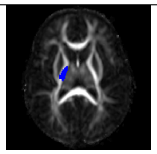
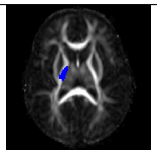
	Genu	Splenium	ALIC	PLIC
Genu-AD				
Genu-RD				
Sp-AD	β_1 : Genu< Sp			
Sp-RD	β_1 : Genu> Sp			
ALIC-AD	β_1 :Genu>ALIC	β_1 : Sp > ALIC		
ALIC-RD	β_1 :Genu<ALIC β_2 :Genu<ALIC	β_1 : Sp < ALIC β_2 : Sp < ALIC		
PLIC-AD	β_1 :Genu>PLIC	β_1 : Sp > PLIC	None	
PLIC-RD	β_1 :Genu<PLIC β_2 :Genu<PLIC β_3 :Genu>PLIC	β_1 : Sp < PLIC β_2 : Sp < PLIC	β_2 :ALIC<PLIC	

Fig. 4. Result of pairwise testing of different white matter regions, shown in the diagonal. Lower triangular: Gompertz parameters with significant differences ($p < 0.001$). Upper triangular: blue curves represent the population trajectory for a region denoted by the rows, and red curves represent growth trajectories of the population for regions denoted by the columns. Rows alternate between AD and RD values. When $\beta_1 : R_1 > R_2$, expected value of axial and radial diffusivity for R_1 is higher than R_2 after early development. When $\beta_2 : R_1 > R_2$, region R_2 is delayed in maturation compared to R_1. $\beta_3 : R_1 > R_2$ indicates accelerated growth for R_2 compared to R_1 as speed is $-\log \beta_3$.

studies, and they also confirm previous findings on neurodevelopment. The analysis can be extended to arbitrary number of regions, and can be performed on other diffusion invariants such as fractional anisotropy (FA) or mean diffusivity (MD), or even tissue features extracted from structural MRI. Future research is necessary towards a nonlinear mixed effect modeling of multi-variate growth functions following a strategy described in [12], for example. In addition, we plan to use models obtained from healthy subjects as normative data for comparison with predicted white matter changes in developmental disorders.

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