SPATIO-TEMPORAL ANALYSIS OF EARLY BRAIN DEVELOPMENT

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***Abstract*—Analysis of human brain development is a crucial step for improved understanding of neurodevelopmental disorders. We focus on normal brain development as is observed in the multimodal longitudinal MRI/DTI data of neonates to two years of age. We present a spatio-temporal analysis framework using Gompertz function as a population growth model with three different spatial localization strategies: voxel-based, data driven clustering and atlas driven regional analysis. Growth models from multimodal imaging channels collected at each voxel form feature vectors which are clustered using the Dirichlet Process Mixture Models (DPMM). Clustering thus combines growth information from different modalities to subdivide the image into voxel groups with similar properties. The processing generates spatial maps that highlight the dynamic progression of white matter development. These maps show progression of white matter maturation where primarily, central regions mature earlier compared to the periphery, but where more subtle regional differences in growth can be observed. Atlas based analysis allows a quantitative analysis of a specific anatomical region, whereas data driven clustering identifies regions of similar growth patterns. The combination of these two allows us to investigate growth patterns within an anatomical region. Specifically, analysis of anterior and posterior limb of internal capsule show that there are different growth trajectories within these anatomies, and that it may be useful to divide certain anatomies into subregions with distinctive growth patterns.**

***Index Terms*—Brain development, MRI, Diffusion tensor imaging, Longitudinal analysis, Growth trajectory**

I. INTRODUCTION

Magnetic Resonance Imaging (MRI), both structural and diffusion tensor imaging (DTI), provide insight into brain structure in vivo. Histological studies have described a temporo-spatial brain maturation, which has been investigated qualitatively by radiologists [1]. However, there is still a lack of quantification of the normal brain maturation process. Understanding of normal brain maturation is of a great clinical importance and a crucial step in understanding developmental abnormalities. Previous studies have shown rapid growth in the first 2 years followed by more subtle changes [2].

In this study we focus on developmental changes of white matter from neonatal period to 2 years of age as is reflected in MRI/DTI parameters. The brain undergoes significant changes during this period, and little is known about normal developmental growth pattern for this age group. Previous studies on brain development have been mainly focused on the morphometric measures such as volume [3], [4], [5], and shape [6]. There has also been studies of diffusion parameters such as fractional anisotropy FA, mean diffusivity MD, axial AD, and radial diffusivity RD [7], [8], [9], [10]. However, quantification results of T1-weighted (T1W) and T2-weighted images (T2W) are limited [10], [11]. In contrast to previous work where the analysis of MRI/DTI parameters are done through discrete time points, we propose a longitudinal data analysis through continuous functions that preserve temporal relationships. This longitudinal data analysis can be done voxel-wise or based on regions of interests (ROI). In the voxel-based approach, images are all aligned to a template, and growth model trajectories are estimated for each voxel. Voxel-based analysis assumes that the normalization procedure (aligning all the images to the template) is accurate. An alternative approach is to group voxels into regions, and model growth trajectories for each regions. However, defining regions of interest can be a time consuming and user dependent task. To overcome these shortcomings, we use an expert defined white matter label atlas [12] to automatically group voxels into regions via registration of atlas labels to images. We also propose a data driven approach to group voxels with similar growth patterns into a region. This method does not make use of prior anatomical knowledge, and such a region defined by an atlas can include different growth patterns. The data driven approach can also define ROIs by grouping voxels that have similar growth trajectories. In this approach, a given structure may be divided into many smaller regions, where each subregion has a unique growth trajectory. Further, different anatomical structures may be grouped into one region if they have similar growth patterns. Both atlas-based and data driven regional analysis can provide new insight into the trajectory of early brain development as measured by longitudinal neuroimaging.

II. METHOD

We characterize brain development through analysis of contrast changes in MRI and DTI of children undergoing healthy brain development. We discuss spatio-temporal brain development using voxel-based analysis, atlas-based ROI analysis and data driven analysis to gain a better understanding at this crucial developmental stage.

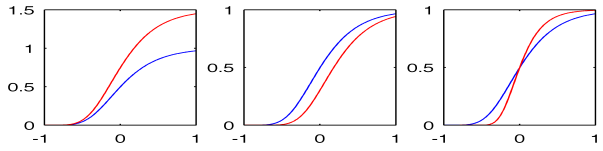

Fig. 1. Graph of Gompertz function. Red: original curve. Blue: Left to right: shows effect of varying parameters a, b, and c.

We assume that we have a set of longitudinal co-registered multimodal MR data (T1W, T2W, PD, AD, and RD) from infants scanned at approximately two weeks, 1 year, and 2 years. Co-registration of multiple image modalities and of images over time has been accomplished by applying existing nonlinear registration methodologies [10], [13].

A. Modeling of Longitudinal Intensity Changes by Gompertz Function

Normal cognitive development follows a temporal sequence that is assumed to be correlated with structural maturation of underlying brain tissue. Different regions in the brain reach maturity at different times, also the rate of maturation varies among different regions. Our goal is to model these longitudinal changes as observed in MRI/DTI to gain a better understanding of growth trajectories. We are also interested in finding regions of the brain with similar patterns of growth.

We create a population model for the nonlinear contrast changes as observed in longitudinal MRI and DTI data where temporal growth is modeled using the Gompertz function:

$$Z_{a,b,c}(t) = ae^{be^{ct}} \tag{1}$$

where a is the asymptote, b is the displacement in time t, and c is the growth rate. Fig. 1 shows the effect of varying one parameter, while keeping the other two parameters fixed. The parameter a corresponds to the final values of a region/voxel at the end of time period. The parameter b can be thought of as a shift in time, and parameter c indicates a given region to mature faster/slower compared to others. The Gompertz function is appropriate for time series data where growth is slow at the later stages, which is the case for the human brain in early development that undergoes rapid changes in the first year and stabilizes after 2 years. In analysis of growth patterns, either a logistic model or the Gompertz model is typically chosen. Both of these functions have asymptotic behavior at the beginning and end of the time interval, however the logistic model is symmetric around its inflection point. We choose the Gompertz model as we assume that the rate of change may vary around the inflection point and thus growth may not be symmetric.

Specifically, the temporal growth model for the population is created by computing the least squares fit of the Gompertz function to temporal data points extracted from different subjects, which can be done for each voxel or within an ROI. Given a collection of data points (image intensities) $y_{i,j}$ observed at time points $t_{i,j}$ where i indexes the different locations and subjects, and j indexes the number of time measurements ($j = 1, 2, 3$), the Gompertz function parameters that represents the data is computed as follows:

$$(a, b, c) = \underset{(\hat{a},\hat{b},\hat{c})}{\operatorname{argmin}} \sum_{i,j} ||Z_{\hat{a},\hat{b},\hat{c}}(t_{i,j}) - y_{i,j}||^2. \tag{2}$$

We use nonlinear optimization [1] to fit the Gompertz function $Z_{a,b,c}$ to the observed data.

B. Atlas Based Region Analysis

In this study we use a stereotactic white matter atlas (ICBM-DTI-81) which is in the space of ICBM-152 [12] datasets for definition of anatomical regions of interest. This atlas was created by manual segmentation of a standard space average of diffusion MRI tensor maps of 81 subjects. By using an expert defined atlas and mapping it to the space of pediatric subjects, we remove the need for manual segmentation of each scan and thus reduce errors due to limited reproducibility.

We apply the unbiased atlas building framework [14] to a set of T2W images of eight 1-year old subjects to build a T2W atlas at the reference age of 1-year and the required mappings. The mappings are subsequently used to create a corresponding T1W atlas from the T1W images of each subject. The adult ICBM-152 T1W atlas is registered to this 1-year T1W atlas, by cascading linear and nonlinear transformations [15]. Even though the brain goes through significant changes during the early years of life, the shape and contrast in T1W and T2W regions of brain appear well defined at 1-year which allows us to register the adult brain to infant brain and at the same time to register the white matter atlas to the infant images.

Subjects' scans including all modalities and time points are registered to the 1-year atlas space, which also includes the labeled white matter atlas. This allows automatic partitioning of white matter of each subject into different anatomical regions, that are used in modeling of growth trajectories by Gompertz functions for each region and each modality.

C. Data Driven Region Analysis

An alternative approach to studying brain development is a data driven approach, where we do not make use of prior anatomical knowledge. Here, we are interested in finding spatial regions with similar patterns of growth as is represented by Gompertz parameters. As mentioned in Sec. II-A, each parameter of the curve has an intuitive description of growth. The parameter a is the asymptote value, while b and c are growth parameters governing delay and speed. We propose the use of a nonparametric Bayesian framework to cluster brain voxels into regions that have similar Gompertz parameters. Clustering is performed in the parameter space of the Gompertz functions in each modality, with M modalities then there would be $3\times M$ values in our feature space.

Nonparameteric Bayesian models using Dirichlet processes as priors have been widely used due to their capability to capture the inherent number of clusters from the data. They have been used in brain tissue classification [16], and brain

[1] http://www.r-project.org/

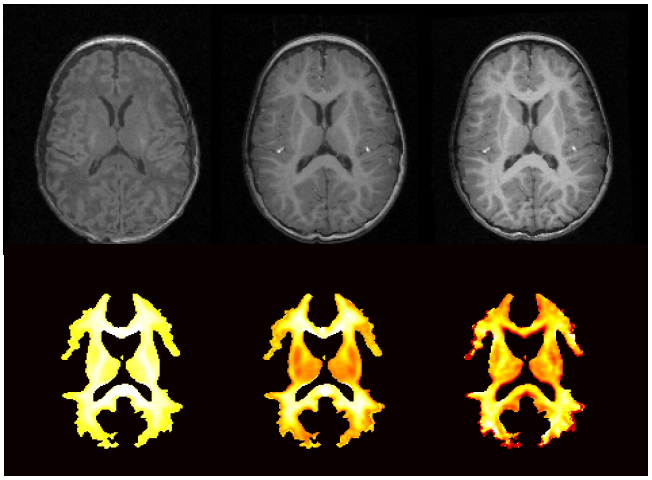

Fig. 2. Top, left to right: Co-registered T1W scans of a subject at 2 weeks, 1 year and 2 years of age. Bottom, left to right: spatial maps of parameter a, b, and c of the Gompertz functions fitted to T1W data. Areas with high intensity in a correspond to higher maturity level at 2-years of age. Areas with high intensity in b correspond to areas with a delayed onset in maturation. Areas with high intensity in c correspond to areas with higher growth rate.

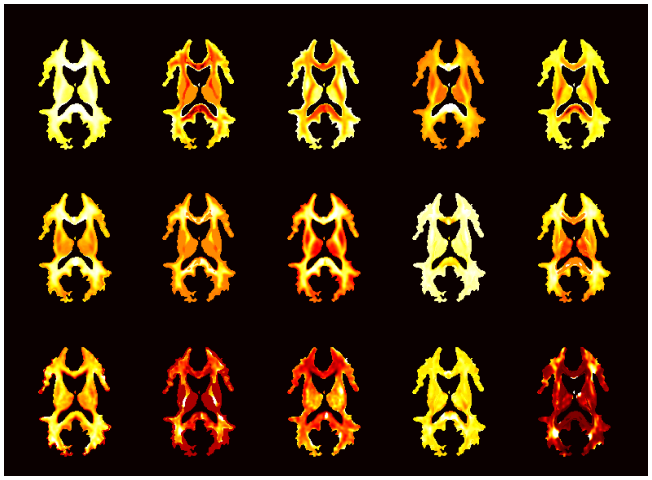

Fig. 3. Voxel-based analysis, where parameters of Gompertz functions representing the population growth are displayed at each voxel. Top to bottom: a, b, and c parameters of Gompertz function. Left to right: Gompertz function parameters obtained from nonlinear regression of T1W, TW2, PD, AD, and RD. Areas with high intensity in a for T1W and AD and low intensity in T2, PD, and RD correspond to higher maturity level at 2-years of age. Areas with high intensity in b correspond to areas with a delayed onset in maturation. Areas with high intensity in c correspond to areas with higher growth rate.

image analysis [13]. We use the Dirichlet Process Mixture Models (DPMM) [17] to automatically determine the number of clusters, and estimate the representative parameters using a publicly available code[2]. We assume that the feature vectors are drawn from mixtures of Gaussian distributions. Specifically, each feature vector θ in $\Re^{3\times M}$ is distributed following

$$p(\theta) = \sum_{k=1}^{N} G_{\Sigma_k}(||\theta - \mu_k||) \tag{3}$$

where N is the estimated number of mixtures of different Gaussians parametrized by means μ_k and covariances Σ_k. This model uses Euclidean distances between the feature vectors, which is an approximation of the non-Euclidean distances. This approximation will still yield distinct growth patterns within the data, although with reduced accuracy.

III. ANALYSIS OF WHITE MATTER MATURATION IN EARLY BRAIN DEVELOPMENT

A. Dataset and Image Preprocessing

We used a subset of data that was obtained as part of a large longitudinal infant neuroimaging study [3], [11]. This subset includes repeated scans of eight subjects scanned at approximately 2 weeks, 1 year and 2 years of age. The images include T1W, T2W, PD, and diffusion tensor images. The intensity inhomogeneity of the structural images were corrected using the N3 software [18]. We apply the unbiased atlas building procedure of Joshi et al. [14] to the set of T2W images at 1-year to obtain spatial mappings between each subject. Scans of other modalities and 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) image to T2W images. Tensors are resampled using finite strain reorientation and Riemannian interpolation strategy. Scalar diffusion measurements such as axial diffusivity (AD=λ_1) and radial diffusivity (RD=$\frac{\lambda_2+\lambda_3}{2}$) were computed for each scan. Intensity levels of T1W scans were normalized using the fat region which has high intensity, and T2W intensities were normalized using CSF region which has high intensity.

[2]http://www.kyb.tuebingen.mpg.de/bs/people/dilan/dpcode/

B. Results

1) Voxel-based Analysis: The Gompertz function at each voxel was calculated as described in Sec. II-A. Fig. 2 shows contrast changes of T1W images of one subject that was scanned at approximately 2 weeks, 1 year, and 2 years of age, and the corresponding Gompertz parameters from regression of population longitudinal changes through this period.

Fig. 3 shows parameters a, b, and c of Gompertz functions for all the modalities that we used in this study: T1W, T2W, PD, AD, and RD. Areas with high intensity in parameter a of T1W and AD images, and low intensity in T2 and RD images (splenium, genu, anterior and posterior internal capsule) confirms previous findings that the central white matter tracts are more mature compared to the peripheral tracts at this age. Parameter b of Gompertz function, which can be interpreted as the delay in maturation have high intensity in frontal and occipital white matter regions compared to the central regions of white matter, and these areas are known to be myelinated after central white matter regions [1]. Parameter c corresponds to the speed of the Gompertz function, areas with high intensity are maturing faster compared to regions with lower intensity values. Most of areas with high speed correspond to the regions that were identified with the b parameter as having a late start, although there are exceptions.

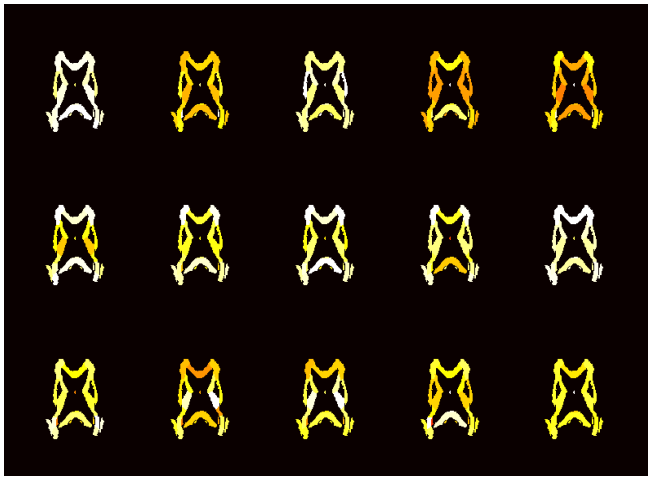

Fig. 4. Atlas-driven analysis, where Gompertz population models are generated within anatomical regions defined by the atlas. Top to bottom: spatial maps of the parameters a, b, c of the Gompertz functions. Left to right: Gompertz function parameters obtained from nonlinear regression of T1W, TW2, PD, AD, and RD modalities. Areas with high intensity in a for T1W and AD and low intensity in T2W, PD, and RD correspond to higher maturity level at 2 years of age. Areas with high intensity in b correspond to areas that have a delayed onset in maturation. Areas with high intensity in c correspond to areas that have higher growth rate.

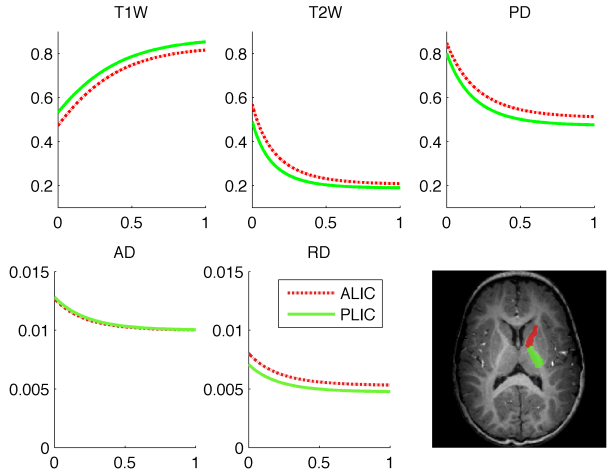

Fig. 5. Growth trajectories of PLIC and ALIC.

2) ROI Analysis: Fig. 4 displays the estimated parameters of Gompertz function for atlas-based ROI selection of different modalities as was described in Sec. II-B. Our result show asynchronous contrast changes of white matter in different modalities, which might underlie the complex white matter maturation such as dendritic growth and myelination. As a proof of concept, we focus on two regions for further analysis. Fig. 5 displays the growth trajectories of posterior limb of internal capsule (PLIC) and anterior limb of internal capsule (ALIC). PLIC is known to myelinate earlier compared to ALIC [1], and this is evident from growth trajectories represented by different modalities, except AD. Axial diffusivity (AD) may not be a good indicator for the degree of myelination but of a more general structuring of axonal bundles.

In the data-driven approach, spatial regions with similar

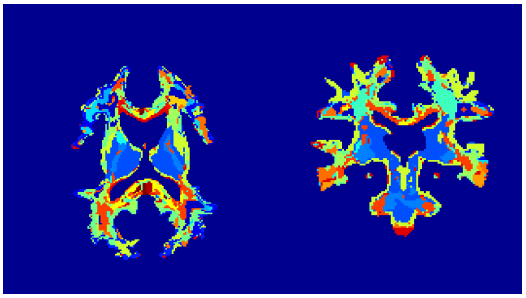

Fig. 6. Axial and coronal views of data-driven clustering.

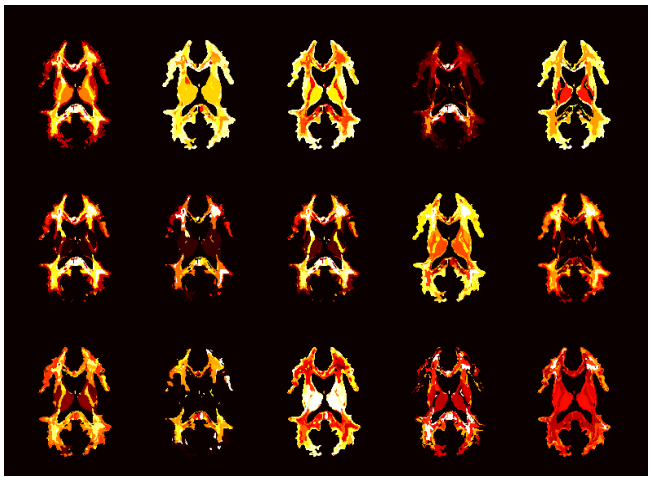

Fig. 7. Data-driven analysis using clustering, where we estimate the Gompertz population growth model from the data without the use of a spatial anatomical prior. Top to bottom: spatial maps of the parameters a, b, c of the Gompertz functions. Left to right: Gompertz function parameters obtained from nonlinear regression of T1W, T2W, PD, AD, and RD modalities.

Gompertz parameters of multimodal data are clustered together without regard for anatomical partitioning. Fig. 6 shows the axial and coronal views of the data clusters. The data driven approach converges to 21 clusters. Fig. 7 displays the parameters of Gompertz function corresponding to these clusters. Growth trajectories of 2 data driven clusters explain

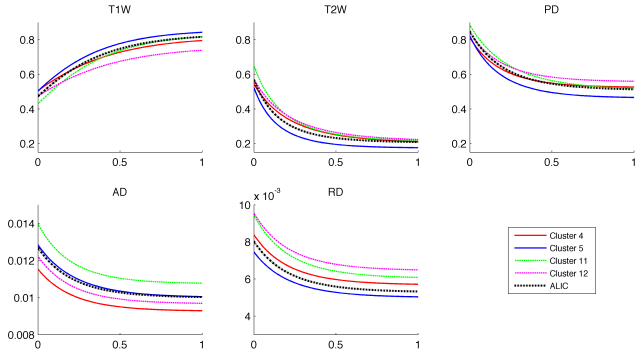

Fig. 8. Comparison of data-driven vs. user-driven estimation of growth trajectory of ALIC. Color trajectories display four data-driven clusters. 78% of ALIC is part of these four clusters. The dashed black trajectory is the growth trajectory of the ALIC based on the atlas defined region.

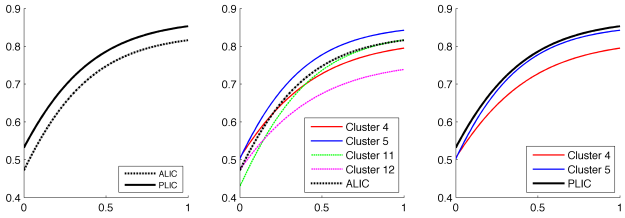

Fig. 9. Comparison of data-driven vs. user-driven growth trajectory of ALIC and PLIC shown for the T1 modality. Left: Trajectories of ALIC and PLIC based on the atlas driven approach. Middle: Trajectories of four data driven clusters that represent 78% of ALIC, shown in color, with overlay of the ALIC growth pattern calculated from the atlas region. Right: Trajectories of two data driven clusters that represent 95% of PLIC, shown in color, with overlay of the PLIC growth pattern calculated from the atlas region. Note that the two clusters which include PLIC are shared with the ALIC set of clusters.

about 95% of growth pattern that is observed in PLIC, whereas more clusters are needed to explain ALIC as is shown in Fig. 8 and 9. Fig. 8 displays the growth trajectories of 4 different clusters that explain 78% of growth trajectories within ALIC. There are distinct patterns of growth within ALIC, where one growth pattern may not be sufficient to explain the underlying white matter changes.

IV. CONCLUSIONS

In this work, we have presented a method for estimating Gompertz population growth models through nonlinear regression of longitudinal multi-modality MR data. We have also presented three different spatial localization strategies for analyzing and visualizing dynamic progression of white matter development. The resulting maturation maps of white matter shows that different MR modalities capture different properties of the maturation process, however they all highlight a growth pattern that decreases from central to peripheral regions. Voxel-based approaches can highlight more detailed changes with age, however they need to be smoothed and corrected for multiple test comparison if voxel-based hypothesis testing would be applied. Regional based approaches overcome some of the voxel-based shortcomings by creating a single statistic for a defined region. Some of the drawbacks of ROIs are the time consuming manual segmentation of regions, however by using a predefined atlas we can overcome this issue as demonstrated in this paper. Another short coming of atlas ROIs is that a selected region may not have similar patterns of growth and obtaining one measurement for the whole region may not be correct. On the other hand, data driven approach may be better suited for defining regions that have similar patterns of growth.

There are some limitations to our proposed analysis framework. We assume a correct registration and intensity normalization across all subjects, which may be difficult to obtain for some outlier cases. Another limitation is that the nonlinear regression of Gompertz function is sensitive to the choice of the initial parameters. This may be problematic as it is not guaranteed to converge to the true underlying model. In our future research, we will develop a strategy to combine the complex set of change patterns across several imaging modalities (here five) into a small set that will inform clinical researchers about regional maturation patterns, its associations with cognitive development, and differences of such patterns in neurodevelompmental disorders.

V. ACKNOWLEDGMENT

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