Multivariate Longitudinal Statistics for Neonatal-Pediatric Brain Tissue Development

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ABSTRACT

The topic of studying the growth of human brain development has become of increasing interests in the neuroimaging community. Cross-sectional studies may allow comparisons between means of different age groups, but they do not provide any growth model that integrates the continuum of time, nor do they present any information about how individuals/population change over time. Longitudinal data analysis method arises as a strong tool to address these questions. In this paper, we use longitudinal analysis methods to study tissue development in early brain growth; a novel approach of multivariate longitudinal analysis is applied to study the associations between the growth of different brain tissues.

We present in this paper the methodologies to statistically study scalar (univariate) and vector (multivariate) longitudinal data, and our exploratory results in the study of neonatal-pediatric brain tissue development. We obtained growth curves as a quadratic function of time for all three tissues. The quadratic terms were then tested to be statistically signicant, showing that there was indeed a quadratic growth of tissues in early brain development. Moreover, our result shows that there is a positive correlation between repeated measurements of any single tissue, and among those of different tissues.

Our approach is generic in natural and thus can be applied to any longitudinal data with multiple outcomes, even brain structures. Also, our joint mixed model is flexible enough to allow incomplete and unbalanced data, i.e. subjects do not need to have the same number of measurements, or be measured at the exact time points.

Keywords: early brain development, multivariate longitudinal analysis, mixed model, statistical analysis

1. INTRODUCTION

The topic of studying the growth of human brain development has become of increasing interests in the neuroimaging community, especially early brain growth of the first two years of life.[1–3] Because it is the most dynamic and perhaps the most important phase of postnatal brain development. Therefore, the ability to study brain development at a period when it undergoes a rapid and critical modification is absolutely essential to shed light on our understanding of brain development.

With the advances of medical imaging techniques and the expansion of data acquisition of the studies, longitudinal image data, in which subjects are scanned and measured repeatedly over time, becomes available. However, such longitudinal image data, especially in the age range between neonates up to 2 years old, are so far rarely studied in its entirety.[4] The purpose of this paper is to jointly study the growth patterns of gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) volumes segmented from longitudinal brain MR images of neonate-pediatric data from birth to 2 years of age.

Traditionally, cross-sectional studies were conducted to compare the mean measurements of two or more age groups, and to find whether there are any significant differences among the age groups.[5] However, this type of studies does not provide any growth model that integrates the continuum of time, nor does it tell us the trend of how individuals and population change over time. Some other researchers tried to apply regression methods to retrieve growth information of the population, which is a reasonable way to approximates the true population growth. But we need to realize that the effect of growth or aging is really an inherently within-individual

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effect, and the true hidden population growth trajectory should really be the average of all individual growth trajectories. On the other hand, the Gauss-Markov assumption of regression requires the participating subjects and measurements to be independent, thus making regression methods not suitable for longitudinal data with repeated measurements, which is obviously not independent. Mixed model theory[6–8] thus arises as a strong tool to address existing problems of traditional methods, providing a growth model as a function of time to truly model the underlining change processes of individuals in longitudinal data.

While most longitudinal analyses focus on studying change over time in a single outcome variable, e.g. total cerebral volume, this paper uses a multivariate longitudinal approach to jointly model the association between the growth trajectories of multiple outcome variables, e.g. volumes of GM, WM, and CSF. Besides characterizing the growth pattern of each of the outcome variables, we also look at the associations between repeated measurements, between the volumes of different tissues, and between the growth rates of different brain tissues.

The method of multivariate longitudinal analysis is generic in natural and thus can be applied to any longitudinal data with multiple outcomes, even brain structures or DTI tracts. However, the purpose of this paper is not trying to solve all the problems in completion; some results are still limited by the sample size of the study. Instead, it serves as an scientific exploration into applying multivariate longitudinal methods to image data, which has not been done so far in the field of medical imaging.

2. LONGITUDINAL DATA

The defining feature of longitudinal data is that subjects are measured repeated over time. For example, in our study, we need to take the brain MR images of one cohort of neonates at birth, followed by the images taken again for the same cohort of children at around one and/or two years old. These measuring occasions are called different time points. It is essential to understand properties of our longitudinal data or just longitudinal data in general, because they determine what kind of model we use, explain why such model as discussed in section 3 is suitable, and what we can expect from the analysis.

2.1. Subjects and Datasets

The input of our study involves 41 neonatal/pediatric subjects that have baseline and follow-up MR scans at about age 0, 1 and 2. They are drawn from an ongoing longitudinal neonatal/pediatric brain MRI project at the Department of Psychiatry of UNC-Chapel Hill,[9] and the size of our data set will keep growing for the years to come. We use the number of months since birth as a measurement of time. Each individual does not need to have the same number of MR scans, nor does one have to assume that the scans be taken at the same time points, which means that the time points for one child are different from those of another. Out of the 41 subjects, 4 have all three scans, the others have just two scans, resulting in 86 MR scans at different time points.

We then used an atlas-based expectation maximization segmentation system (EMS)[10] for tissue segmentation of newborn brains, due to their low intensity contrast and the growth process of the white matter tissue. For scans of one and two year olds, we used a probabilistic atlas for automatic tissue segmentation. For any given child, when we compare side by side its baseline and follow-up MR scans and their corresponding tissue segmentations, as showed in figure 1, it is clear that there are indeed noticeable longitudinal tissue growth in early brain development.

Upon segmentation, we compute the volumes (as in cubic centimeter cm^3) of three brain tissue types WM, GM, and CSF, and consider them to be three outcome variables. We would like to statistically study their inherent growth pattern and the association between them.

2.2. Correlation

It is an inescapable feature in longitudinal studies that there are positive correlation between repeated measurements of any given subject, because they are measured from the same subject over time. And it is very likely to predict the outcome at the next time point based on the measurements at the previous time points. This correlation breaks the Gauss-Markov assumption of traditional regression analysis, which assumes all the measurements are independent and have the same variances.

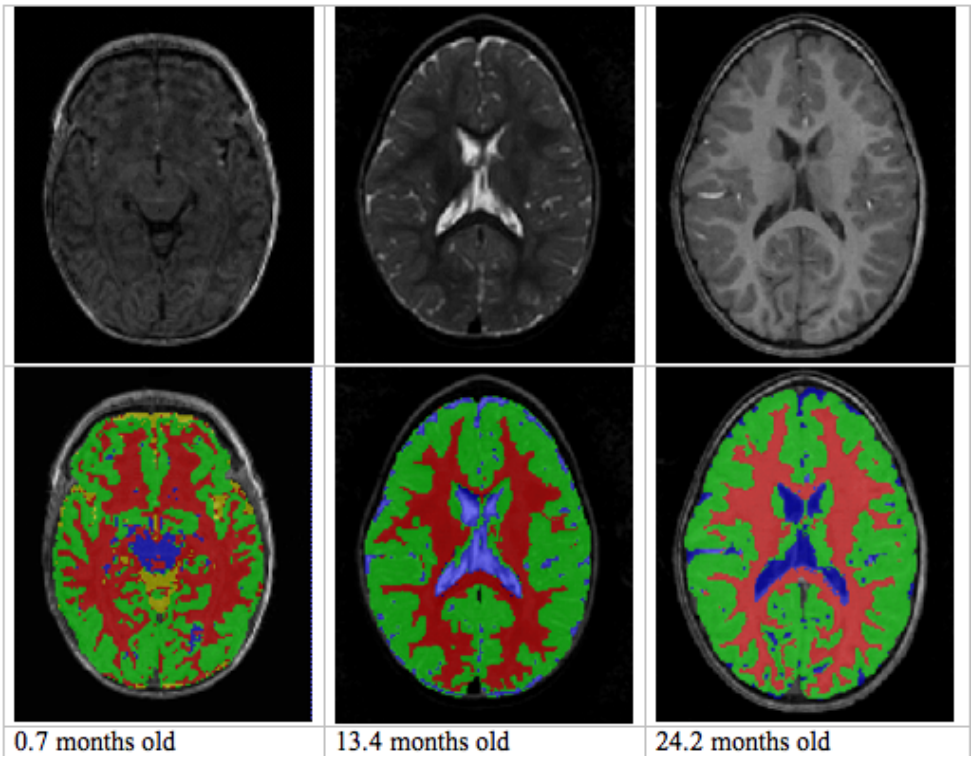

Figure 1. Illustration of longitudinal changes of MR images of one child and their corresponding tissue segmentation. The child was scanned at age of 0.7 months, 13.4 months and 24.2 months old. GM, WM, and CSF are colored with green, red, and blue, respectively. In the neonate case, red is non-myelinated white matter, and yellow is myelinated white matter.(subject ID=0106)

Another important aspect of correlation is that the value of it depends on the distance in time between two measurements. For example, we would expect two measurements that are close in time to have a larger correlations than those that are far apart. Moreover, as will be discussed in the next section 2.3, measuring time schedules vary from subject to subject. It is almost unlikely to have an equally-spaced and complete clinical data set where each individual has exactly the same time points. As a result, the correlation between repeated measurements of different individuals should be different, and we will show that the mixed model as discussed in section 3 is able to capture this property.

2.3. Irregularity

Knowing the above correlation property of longitudinal data, it is natural for us to think of grouping the repeated measurements of the same subject together, e.g. given n_i repeated measurements of the ith subject, we group them into a $n_i \times 1$ response vector (in this study, n_i=2 or 3, because children have up to 3 MR scans):

$$y_i = \begin{pmatrix} y_{i1} \\ y_{i2} \\ \vdots \\ y_{in_i} \end{pmatrix}$$

By doing this, it is easier for us to consider their correlation. However, it introduces new problems: what if different subjects have different number of repeated measurements, i.e. $n_i \neq n_j$? In clinical studies, it is quite often for an individual to miss a couple of appointments. In our neonate-pediatric brain development study, certain MR images of some babies are not usable because of uncontrollable motions of the babies during image

capture. Thus we have y_i's that are of different length. What is more, even if none of the children miss a single appointment, or none of the babies move during the MR scans, i.e. all the y_i's are of the same length, we cannot guarantee they come on the same day, i.e. two different y_i vectors correspond to different time points. Thus, we need a statistical model that is flexible enough to handle these irregularities, i.e. uneven sampling at the time axis for different subjects.

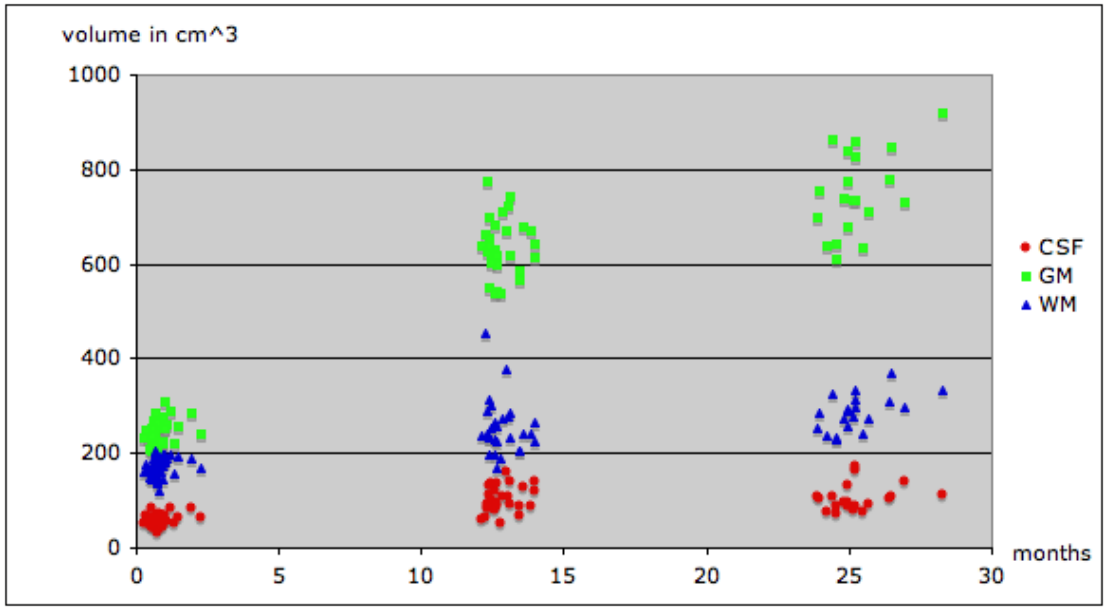

Figure 2. Scatter plot of our WM, GM, CSF data versus time. An illustration of irregular data that has uneven sampling at time axis for different subjects. CSF: red dot, GM: green box, WM: blue triangle.

2.4. Multiple Responses

A more challenging problem in longitudinal studies is that there are multiple responses of one individual at any time. In this study, we want to study the growth pattern of WM, GM, CSF volumes at the same time. To express it mathematically, if each individual has k responses, e.g. $k = 3$ when we study the WM, GM, CSF volume, each of which has n_{ik} repeated measurements over time, we have k response vectors for child i:

$$y_{(CSF)i} = \begin{pmatrix} y_{(CSF)i1} \\ y_{(CSF)i2} \\ \vdots \\ y_{(CSF)in_{i1}} \end{pmatrix}, y_{(GM)i} = \begin{pmatrix} y_{(GM)i1} \\ y_{(GM)i2} \\ \vdots \\ y_{(GM)in_{i1}} \end{pmatrix}, y_{(WM)i} = \begin{pmatrix} y_{(WM)i1} \\ y_{(WM)i2} \\ \vdots \\ y_{(WM)in_{ik}} \end{pmatrix},$$

where $y_{(CSF)i1}, y_{(CSF)i2}$, etc. are CSF volumes of child i measured at different time points, the same for $y_{(GM)i1}$ and $y_{(WM)i1}$ etc.. To distinguish this longitudinal analysis of multiple responses, we called it *multivariate longitudinal analysis*, while the longitudinal analysis of a single response is called *univariate longitudinal analysis*. Thus, we need a statistical model that is expandable to handle the multiple response case, which will be discussed in the next section.

3. STATISTICAL ANALYSIS

3.1. Linear Mixed Model

The linear mixed model is used to study the growth patterns of a single outcome. It is a two-level model.[6–8,11] The first level is the individual level, which lets us think of a unique trajectory for each individual. It is

then reasonable to think that the within-individual variances are the fluctuations around the individual-specific trajectory, and the among-individual variances can be described as differences of parameters characterizing these trajectories, e.g. intercepts and slopes in the case of the simplest linear model.

3.1.1. Individual (First Stage) Model

For the ith child, if its measuring time points are $t_{i1}, \cdots, t_{in_i}$, and the corresponding GM volumes, for example, are $y_{i1}, \cdots, y_{in_i}$, then the model for child i, $i = 1, \cdots, m$, is

$$y_{ij} = \beta_{0i} + \beta_{1i} t_{ij} + \beta_{2i} t_{ij}^2 + e_{ij}, j = 1, \cdots, n_i. \tag{1}$$

We can see that no matter how many time points (e.g. n_i) each individual have, or how close or far apart the measurements are, the number of parameters used (e.g. $\beta_{0i}, \beta_{1i}, \beta_{2i}$) to characterize the trajectory is always the same (it is 3 in this illustrating case). We can study among-individual variability based on variation of these three parameters, thus perfectly handle the irregularity/imbalance problem of longitudinal data described in 2.3.

3.1.2. Population (Second Stage) Model

In the population level, we think of individuals observed arising from a population of all such individuals, each has its own intercept and slope, varying around a "centered" average intercept β_0 and slope β_1:

$$\begin{pmatrix} \beta_{0i} \\ \beta_{1i} \end{pmatrix} = \begin{pmatrix} \beta_0 \\ \beta_1 \end{pmatrix} + \begin{pmatrix} b_{0i} \\ b_{1i} \end{pmatrix}. \tag{2}$$

Here b_{0i} and b_{1i} are called *random effects* describing how the intercept and slop for the ith subject deviate from their mean values. We do not consider the quadratic term as a random effect here because from visualization of the data we do not see subjects vary a lot in the 2nd order of the growth trend. As a result, we consider all the subjects share the same quadratic terms β_2. Then, doing simple substitution from equations 1 and 2, we get:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + b_{0i} + b_{1i} t_{ij} + e_{ij}. \tag{3}$$

It is often reasonable to assume that populations of intercepts and slopes are approximately normally distributed, i.e.

$$\begin{pmatrix} b_{0i} \\ b_{1i} \end{pmatrix} \sim N_2(0, D), \text{ where } D = \begin{pmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{21} & \sigma_{22} \end{pmatrix}.$$

As a result, variance/covariance between two (repeated) measurements for subject i are:

$$cov(y_{ij}, y_{ik}) = \sigma_{11} + \sigma_{21} t_{ij} + \sigma_{12} t_{ik} + \sigma_{22} t_{ij} t_{ik}. \tag{4}$$

When $i = k$, variance of the jth measurement is $var(y_{ij}) = \sigma_{11} + 2\sigma_{12} t_{ij} + \sigma_{22} t_{ij}^2 + \sigma^2$. It is easy to show that when j and k are far apart in time, the correlation of the two repeated measurement is smaller than if they are close to each other. Thus this linear mixed model perfectly solves the correlation problem as discussed in 2.2.

3.1.3. Estimation and Inference

The estimations of β (the vector for $\beta_0, \beta_1, \beta_2$) and D are done by iterative likelihood-based methods, such as maximum likelihood or restricted maximum likelihood.[11–13] Having the estimation for β and its sampling distribution $\hat{V}_\beta$, it is straightforward to conduct hypothesis testings, compute confidence intervals, and determine whether certain parameter is statistically significant or not. We can specify appropriate matrices L to represent various questions of interest. For example, if we want to study whether the rate of change, e.g. slope, is statistically significant, we let $L = (0, 1, 0)$. When L consists of a single row, a general t-statistic can be constructed as follows[13,14]

$$t = \frac{L\hat{\beta}}{\sqrt{L\hat{V}_\beta L'}}. \tag{5}$$

3.2. Joint Modeling of Mixed Model

To study the joint evolution of growth trajectories among three brain tissues, an approach of jointly modeling the random effects for different tissue volumes is adopted.[15–17] First, the average evolution of each tissue volume is described using the aforesaid linear mixed model in 3.1 as a quadratic function of time, and individual-specific parameters (e.g. slopes) deviate from the average by the introduced random effects:

$$\begin{aligned} y_{ij,CSF} &= \beta_{0,CSF} + \beta_{1,CSF}t_{ij} + \beta_{2,CSF}t_{ij}^2 + b_{0i,CSF} + b_{1i,CSF}t_{ij} + e_{ij,CSF} \\ y_{ij,GM} &= \beta_{0,GM} + \beta_{1,GM}t_{ij} + \beta_{2,GM}t_{ij}^2 + b_{0i,GM} + b_{1i,GM}t_{ij} + e_{ij,GM} \\ y_{ij,WM} &= \beta_{0,WM} + \beta_{1,WM}t_{ij} + \beta_{2,WM}t_{ij}^2 + b_{0i,WM} + b_{1i,WM}t_{ij} + e_{ij,WM} \end{aligned}$$

Then, random effects for different tissues are jointed together. By imposing a joint multivariate distribution on the joint random effects, the different growth patterns of three tissue volumes are associated.

$$\begin{pmatrix} b_{0i,CSF} \\ b_{0i,GM} \\ b_{0i,WM} \\ b_{1i,CSF} \\ b_{1i,GM} \\ b_{1i,WM} \end{pmatrix} \sim N_6(0, D),$$

where D is the covariance matrix of all the random effects of all three tissues. The off-diagonal elements of D represent the association between the growth pattern of different tissues.

4. RESULTS

4.1. Parametric Growth Curves

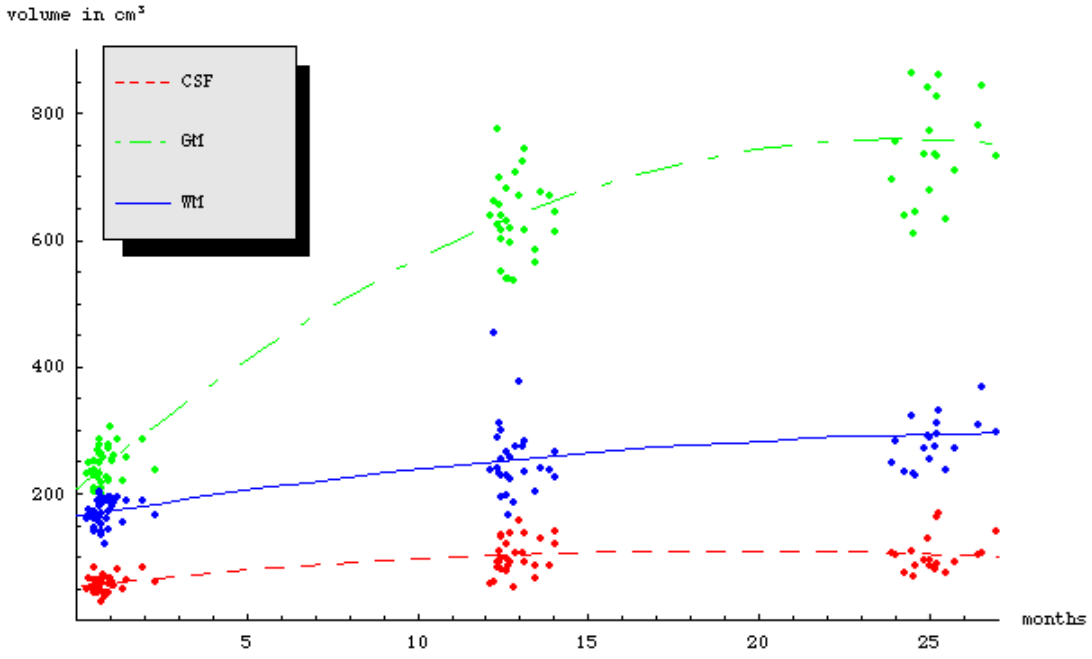

Figure 3. Parametric growth curves of 3 tissues resulting from the joint mixed modeling described in section 3.2. CSF: red dash line, GM: green dot-dash line, and WM: blue solid line.

We applied the joint mixed model described in the previous section, and obtain the parametric growth curves of all three brain tissues as a quadratic function of time. Statistics showed that the quadratic terms of CSF and WM are not statistically different from each other. The quadratic terms of all three tissues were tested to be statistically significant, as in table 1, showing that there was indeed a quadratic growth of tissues in early brain development.

Parameters	$\beta_{0,CSF}$	$\beta_{1,CSF}$	$\beta_{2,CSF}$	$\beta_{0,GM}$	$\beta_{1,GM}$	$\beta_{2,GM}$	$\beta_{0,WM}$	$\beta_{1,WM}$	$\beta_{2,WM}$
Estimate	54.7	5.8	-0.15	208	45.9	-0.95	164.7	8.9	-0.15
$\Pr > \|t\|$	**	**	**	**	**	**	**	**	**

Table 1. Estimation and test statistics of growth curve parameters using joint mixed model. ** represents significant results with t score < 0.01.

4.2. Confidence Intervals

Then, we used the statistical method described in 3.1.3 to obtain the 95% upper and lower bounds of all the nine growth parameters in table 1. In figure 4, we can see that for all three brain tissues, the confidence bands start out narrow at age 0 and become wider and wider over time. In order to better understand this, we compare the confidence interval bands in figure 4 with the original data in figure 2. We find out that it is inherent in the data that the variance of data, i.e. inter-individual differences, increase over time, which is quite typical seen in most of the longitudinal data.

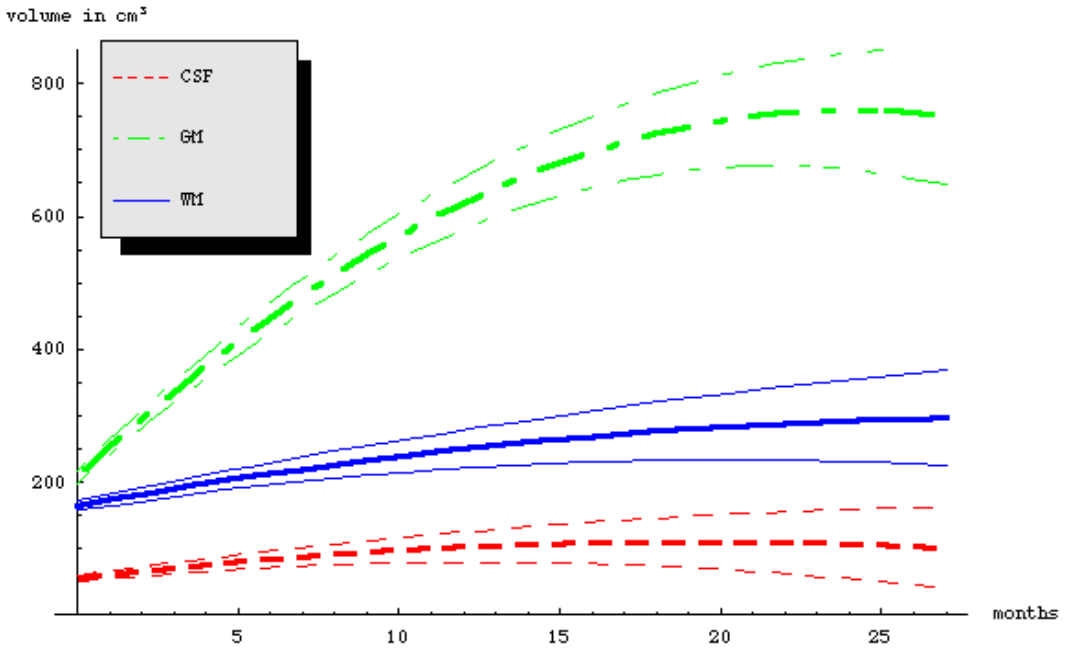

Figure 4. 95 % confidence interval of the growth curves of three brain tissues. CSF: red dash line, GM: green dot-dash line, and WM: blue solid line.

Furthermore, in order to quantitatively justify our result, we compute the variances of the tissue volumes for three age groups: neonates, 1 year old, and 2 year old, as shown in table 2. We find that the variances of different brain tissues did increase over time from neonates to 2 year olds, so we can conclude that our result of confidence intervals shown in figure 4 is indeed a reasonable estimate of the hidden truth according to the properties of the original data. Actually, it is this exact property of increasing variances that makes

traditional regression model not appropriate for longitudinal analysis. Because the Gauss-Markov assumption states independent measurements with the same variance at all occasions. The mixed model, on the other hand, can handle the correlation between measurements, as well as increasing variance over time, which makes it preferable for longitudinal analysis.

Variance	neonates	1 yr old	2 yrs old
CSF	11.88	27.27	27.57
GM	28.28	61.70	87.45
WM	20.42	58.50	38.12

Table 2. Variance of brain tissue volumes for three different age groups: neonates, 1 year old, 2 year old.

4.3. Individual Correlation Matrix

As discussed in section 2.2, different subjects would have different correlation matrices, because they might have different number of MR scans, and the scans might not have the same distance in time. Thus the size of the correlation matrix and the value of it are unique for each individual. What is more, since we are studying longitudinal data with multiple responses: volumes of CSF, GM, and WM, not only do we need to consider correlation within the same tissue, we also have to think about correlations between measurements from different tissues. Size of the correlation matrix increases dramatically along with the number of multiple responses. For a child that have 3 MR scans, it would have a 9×9 correlation matrix, as shown in figure 5.

Estimated Correlation Matrix for case 0106									
Row	CSF_0	CSF_1	CSF_2	GM_0	GM_1	GM_2	WM_0	WM_1	WM_2
CSF_0	1.00	0.45	0.31	0.87	0.56	0.38	0.56	0.34	0.22
CSF_1		1.00	0.95	0.44	0.53	0.48	0.27	0.18	0.12
CSF_2			1.00	0.27	0.45	0.44	0.16	0.12	0.09
GM_0				1.00	0.59	0.41	0.48	0.29	0.19
GM_1					1.00	0.94	0.30	0.28	0.23
GM_2						1.00	0.20	0.23	0.21
WM_0							1.00	0.30	0.22
WM_1								1.00	0.84
WM_2									1.00

Figure 5. Correlation matrix for one child who had 3 MR scans in the first two years of life. The scans were taken at month 0.7, 13.4, and 24.2. This is the same case as shown in figure 1. (Subject ID=0106)

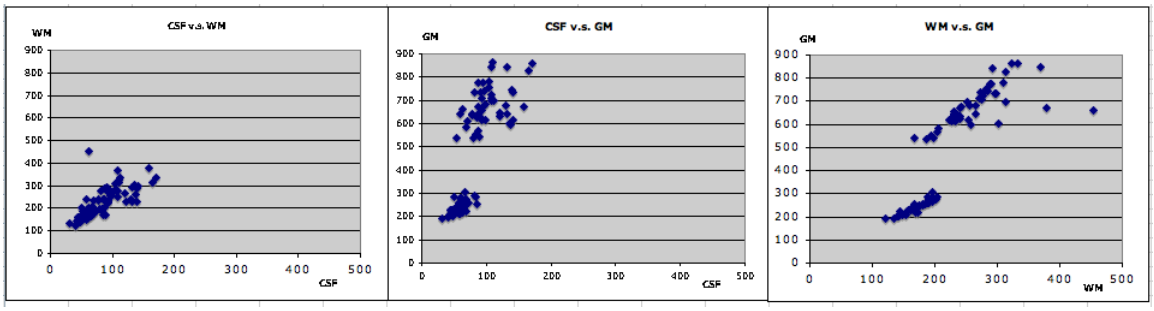

Figure 6. Scatter plot of different tissues. Left: CSF v.s. WM, middle: CSF v.s. GM, right: WM v.s. GM.

From figure 5, we can see that within the same tissue, correlation decreases as the two measurements become further apart in time, which conforms to our discussion in section 2.2. Also, we can see that there are

positive correlation between measurements of different tissues, and the correlation again decreases with the two measurements of different tissues becoming further in time.

What is more, we notice that for subject 0106, the correlation between CSF and GM seems to be larger than that between CSF and WM at the same time point. In order to qualitatively justify this, we generate the scatter plots of different tissues from all the subjects, regardless of their measure time points, as shown in figure 6. And it seems the cluster of CSF v.s. GM appears to be steeper than that of CSF v.s. WM, which shows the result in figure 5 is consistent with the data. But as to whether this conclusion is general in nature, it is yet to be determined, because we will need much larger data set for our experiments.

4.4. Derivatives of Growth Curves

Since we obtain from the joint mixed modeling the parametric growth curves of three brain tissue volumes, we can take the derivatives of the function and look at the trend of the growing speed over time, as shown in figure 7. Even though in reality, the change of growing speed might not be linear in natural, but for a short period of time as 2 years, it is a reasonable approximation. By doing this we can, for the first time, get a continuous quantitative understanding of how the growth speed change over time, and compare them between different tissues. We can see from the figure that the speed of growing decreases over time for all three tissues. The growing speed of GM is much larger than those of CSF and WM for the first 2 years, but it also decreases faster. It indicates that there is a dramatic growth for gray matter tissues in the neonate brains for the first two years, and the growth slows down gradually over time. There are also significant growth of the CSF and WM tissues, but in a much less dramatic way compared to the GM. Currently, because of the lack of longitudinal data beyond 2 years in our study, we cannot draw further conclusion of the growth pattern and growth speed of this data. But it is an ongoing project, and we will have a better understanding of the change processes of early human brains in the future.

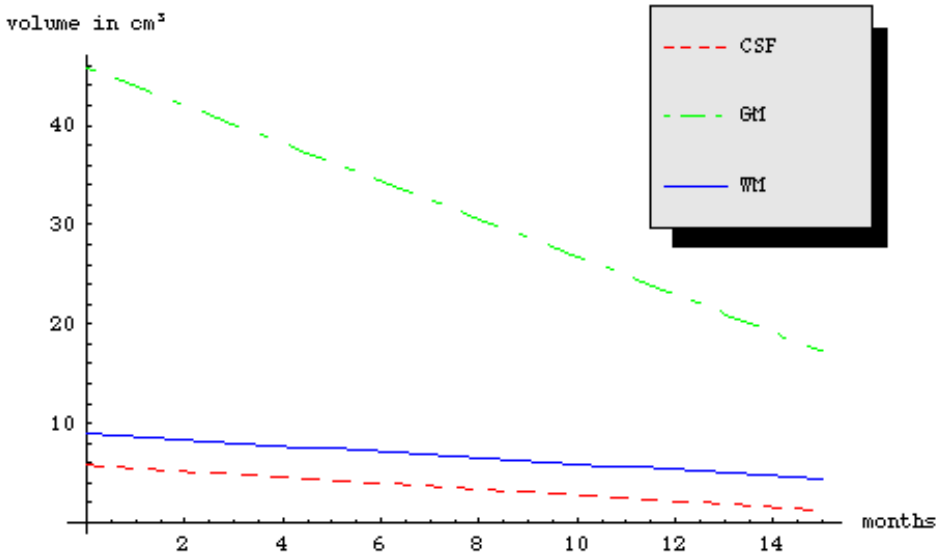

Figure 7. Derivatives of the parametric growth curves of three brain tissues. CSF: red dash line, GM: green dot-dash line, and WM: blue solid line.

5. CONCLUSION

We have successfully applied the joint modeling schema of mixed models to our neonatal/pediatric brain tissue data, and obtained growth curves as a quadratic function of time for all three tissues. Therefore, we can estimate

the average tissue volume at any time during age 0 to 2, even at time points where we do not have any input data. The quadratic terms of the growth function were tested to be statistically significant in all three curves, showing that there was indeed a quadratic growth of tissues in early brain development.

We computed confidence bands of the growth curves of three brain tissues, and verify it is consistent with the data. Because the tissue volumes are of increasing variance over time, the confidence bands start out narrower at around age 0, and become wider and wider over time. Our result also shows that correlation between measurements (both repeated measurements of the same brain tissue or two measurements from different tissues) decreases as as they become further apart in time. Positive correlation were detected among CSF, GM, and WM tissue volumes.

We studied the growth patterns of all three brain tissues, and found that GM has the fastest growth in the first two years, compared to those of CSF and WM, but the speed of GM growth also slows down faster.

Our work is exploratory and still in progress, but it should be able to raise the attention to the importance of multivariate longitudinal analysis in image analysis, through which we can gain insights and new perspectives in understanding our own brain development.

6. ACKNOWLEDGEMENT

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