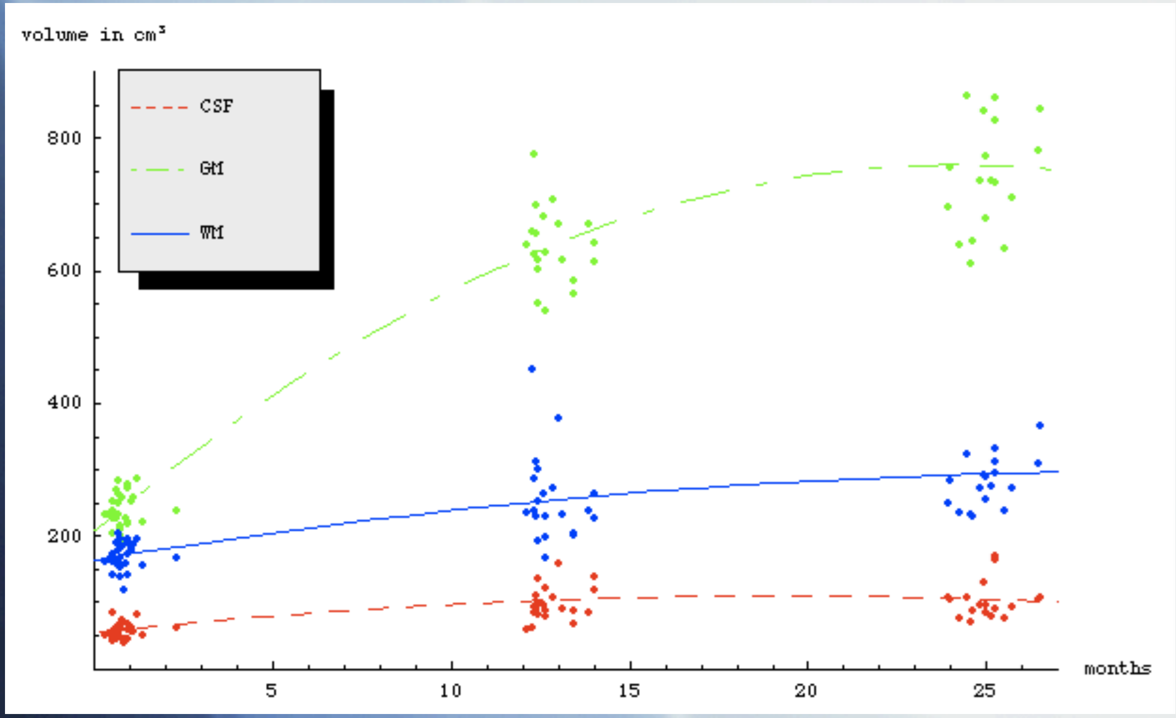
Multivariate Longitudinal Statistics for Neonatal-Pediatric Brain Tissue Development



Christine Xu

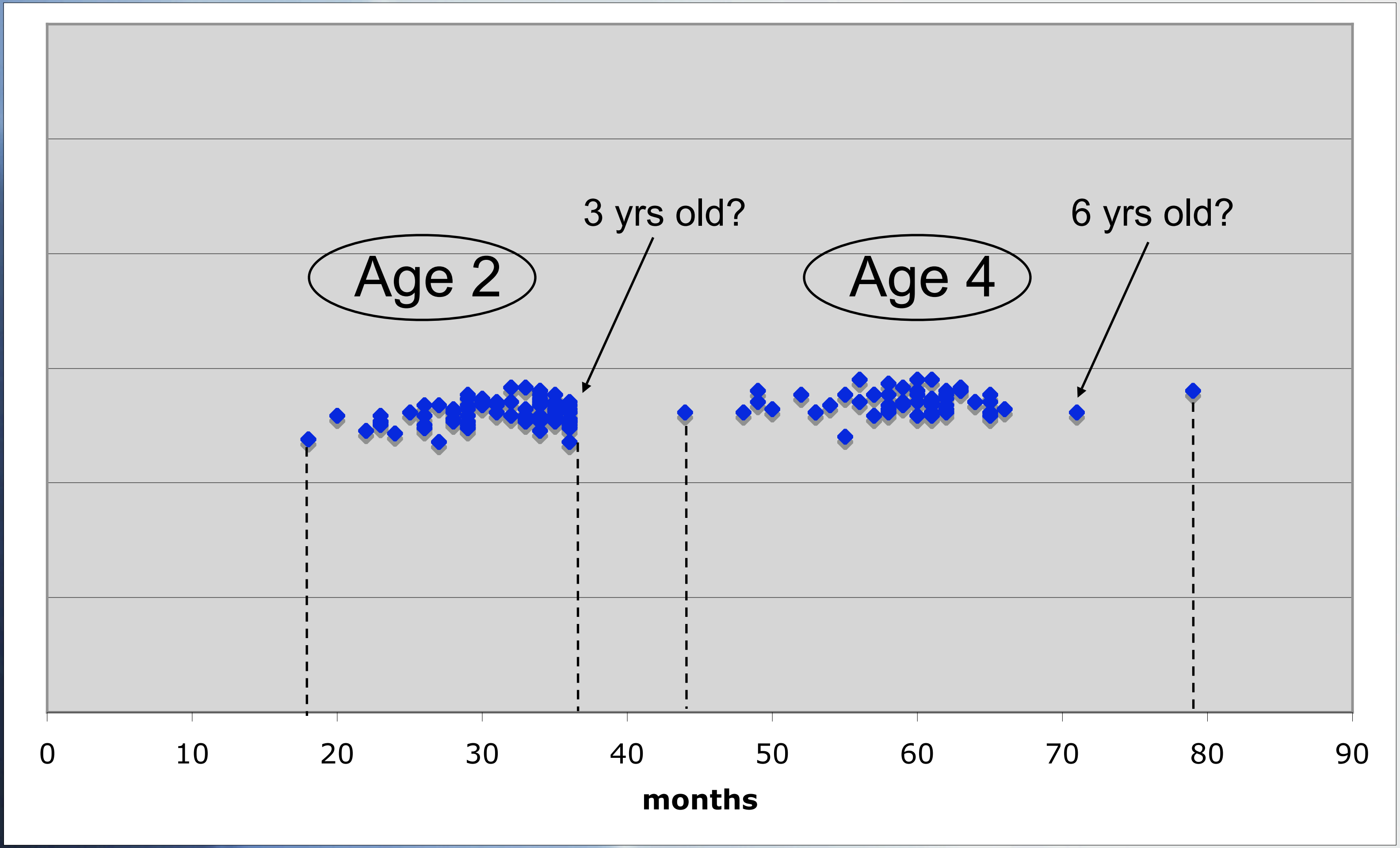
Goal

- The goal 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 neonatal-pediatric data from birth to 2 years of age.

Related Work

- Cross-sectional studies on age differences
- Regression analysis to study growth

Age Plot of Cross-sectional Studies



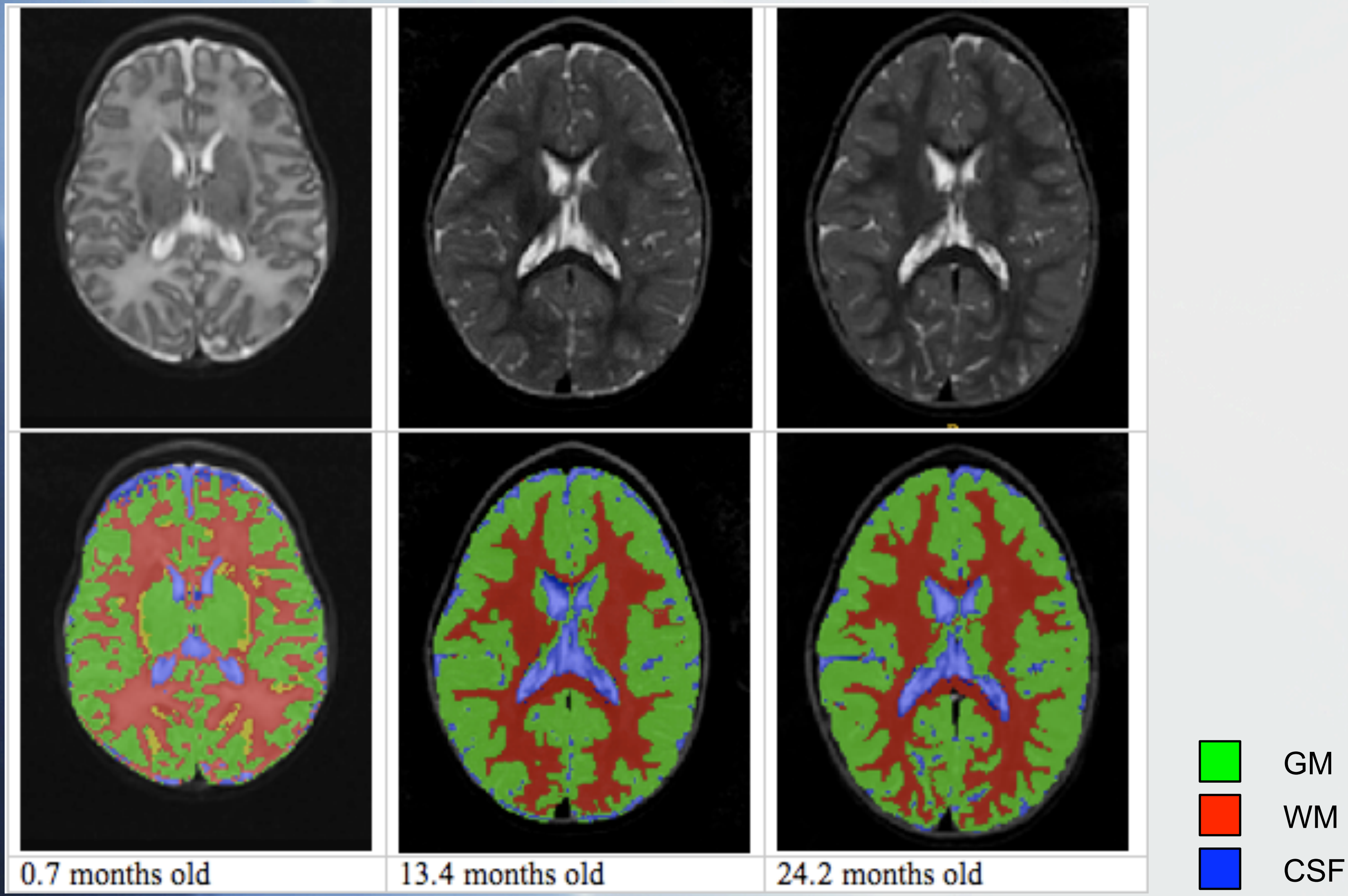
Regression

- Markov-Gauss assumption: independence of all data points, homoscadastic
  - not suitable for longitudinal data
- Is regression suitable for growth studies?
  - Yes and no
  - Remember: the true hidden population growth trajectory should be the average of all individual growth trajectories.

Subjects and Datasets

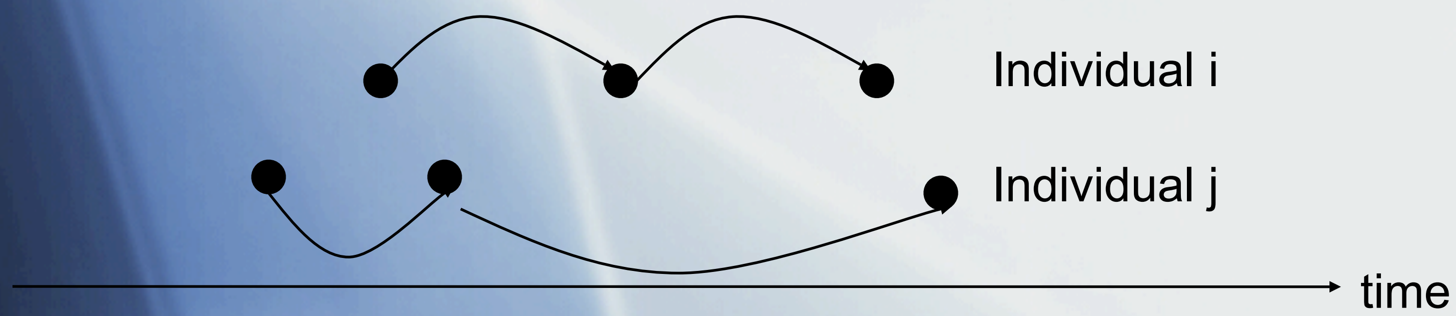
- 41 neonatal/pediatric subjects that have baseline and follow-up MR scans at around age 0, 1, and 2.
- Time axis: number of months since birth
- Atlas-based expectation maximization segmentation method for tissue segmentation
- Volumes of three brain tissue in cm^3

Longitudinal changes of MR images of one child



Property 1: Correlation

- Positive correlation between repeated measurements
- The value of correlation depends on the distance in time
  - Closer in time, larger correlation
  - Further in time, smaller correlation
- Correlations different for different children
  - Different measuring schedules



Property 2: Irregularity

- Given n_i repeated measurements of the ith child

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

$n_i \neq n_j$?

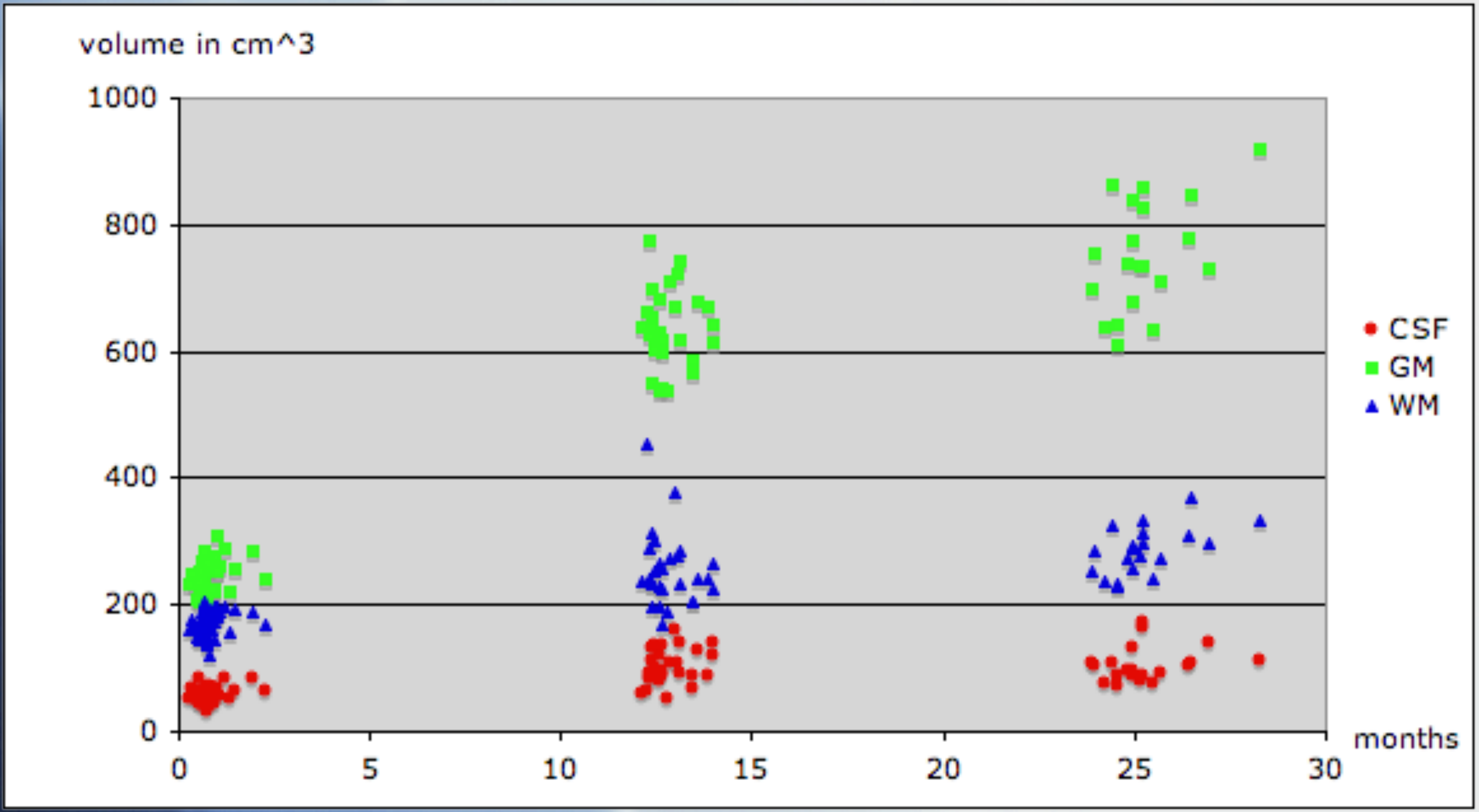
Child movement during scan?

Miss an appointment?

Have different time points?

Irregular Data Set

Uneven sampling of time axis



Property 3: Multiple Responses

- What about more than one response, e.g. WM, GM, CSF?

$$y_{CSF,i} = \begin{pmatrix} y_{CSF,i1} \\ y_{CSF,i2} \\ \vdots \\ y_{CSF,in_{i1}} \end{pmatrix} \quad y_{GM,i} = \begin{pmatrix} y_{GM,i1} \\ y_{GM,i2} \\ \vdots \\ y_{GM,in_{i2}} \end{pmatrix} \quad y_{WM,i} = \begin{pmatrix} y_{WM,i1} \\ y_{WM,i2} \\ \vdots \\ y_{WM,in_{i3}} \end{pmatrix}$$

Use multivariate longitudinal analysis to jointly study growth pattern of multiple responses.

Linear Mixed Model

- Study the growth pattern of a single response
- Two-level model
  - Individual level: unique trajectory for each individual
  - Population level: average of parameters characterizing individual trajectories

Individual Level

$$y_{ij} = \beta_{0i} + \beta_{1i}t_{ij} + \beta_{2i}t_{ij}^2 + e_{ij}$$ i: child, j: time point

- No matter how many measurement time points each individual have, or how close or far apart the measurements are, the number of parameters used (β_{0i}, β_{1i}, β_{2i}) to characterize the trajectory is always the same.

Population Level

- Individual intercepts and slopes varying around a "centered" average intercept β_0 and slope β_1:

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

b_{0i}, b_{1i} are *random effects*: how the intercept and slope for the i^{th} subject deviate from the mean values

Linear Mixed Model

- Simple substitution, we get:

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

- We assume:

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

$$e_{ij} \sim N(0, \sigma^2)$$

Linear Mixed Model

- Variance/covariance between two repeated measurements for subject i is:

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

If j and k are far apart in time, the correlation is smaller than that if they are close to each other.

- If j=k:

$$\operatorname{var}(y_{ij}) = \sigma_{11} + 2\sigma_{12} t_{ij} + \sigma_{22} t_{ij}^2 + \sigma^2$$

Increasing variance of y_{ij} over time

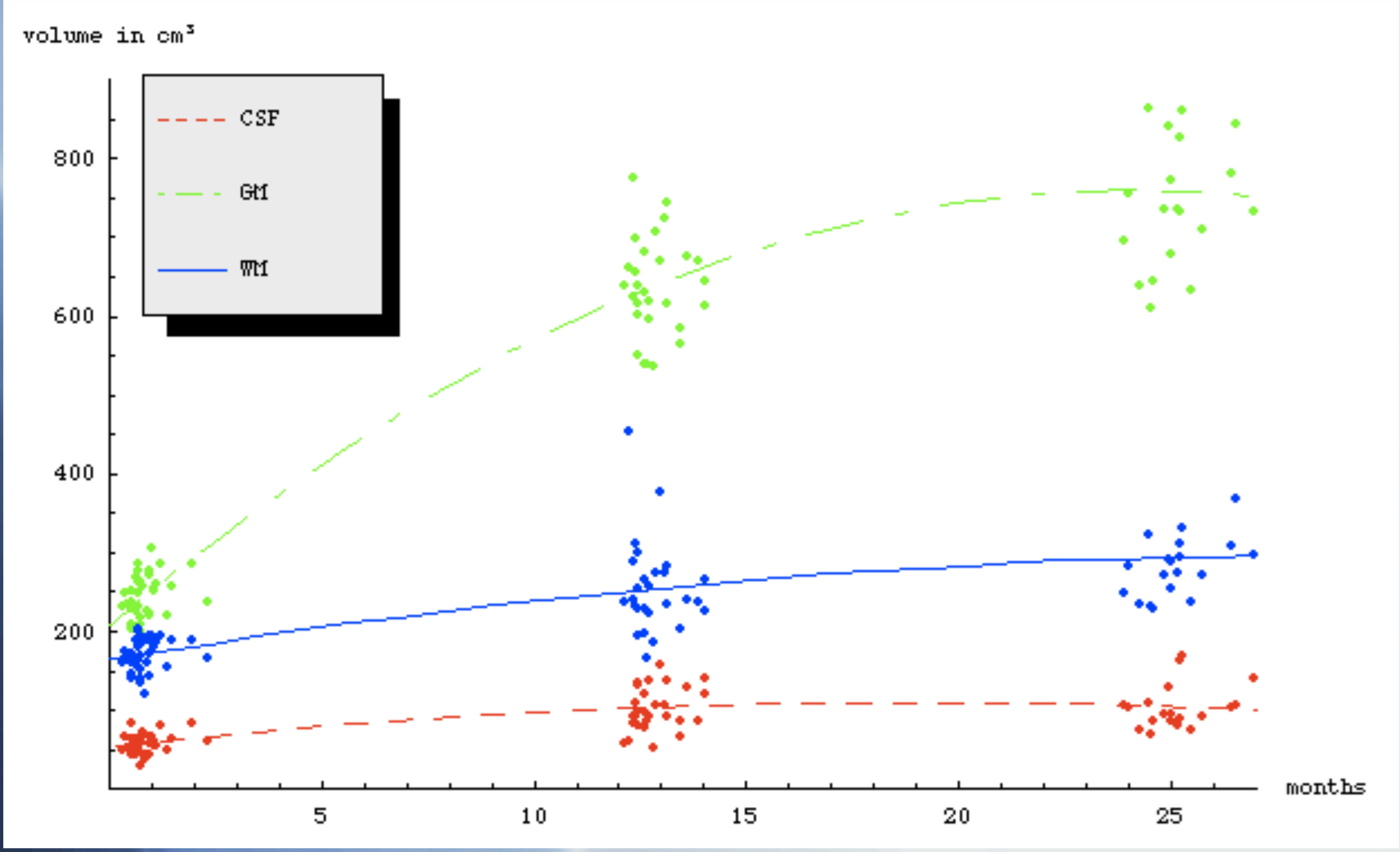
Joint Modeling of Mixed Model

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

- Impose a joint multivariate distribution on the joint random effects, so the growth patterns of the three tissue volumes are associated

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

Parametric Growth Curves



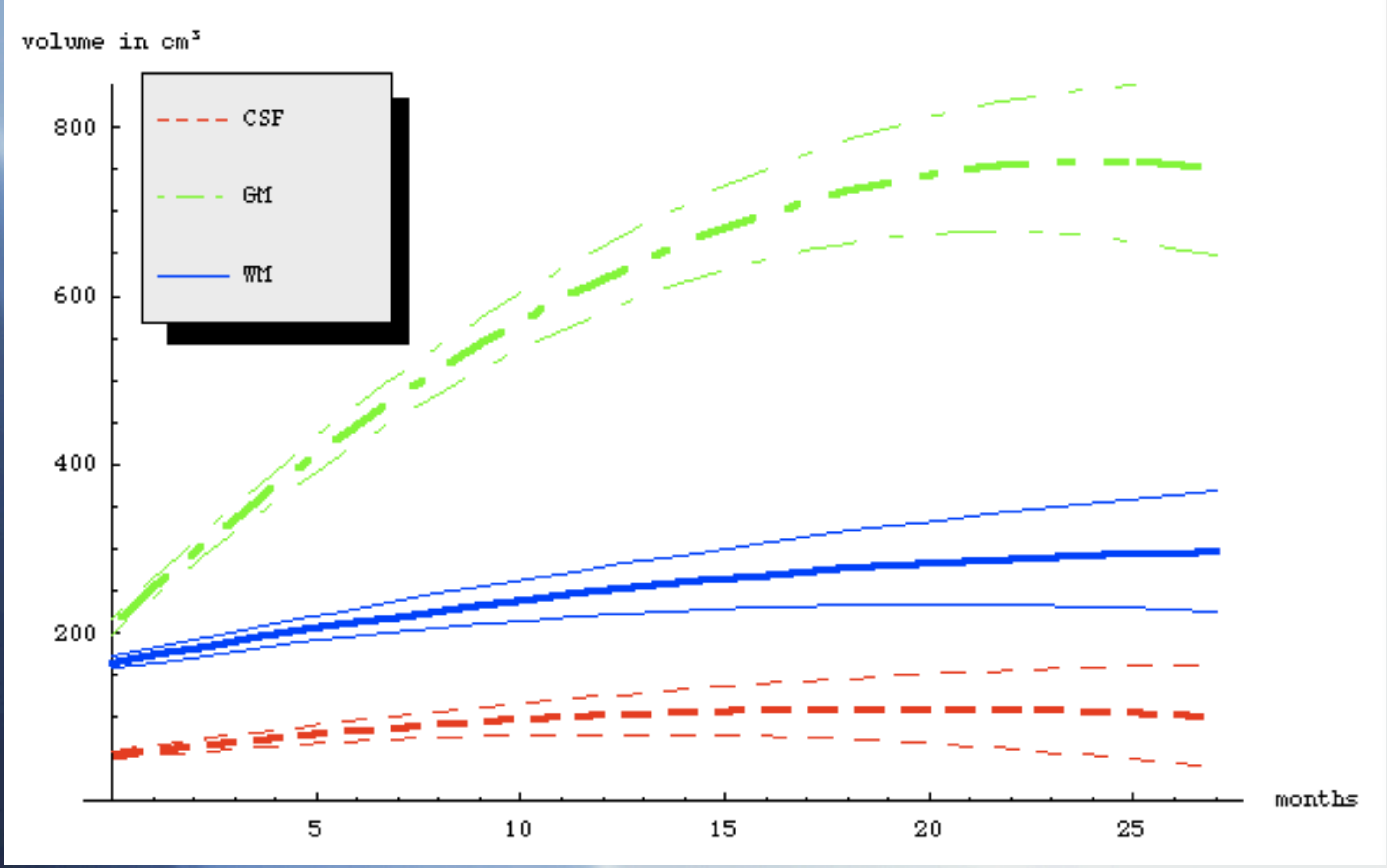
Parametric Growth Curves

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|	**	**	**	**	**	**	**	**	**

- Statistics also showed the slopes of all three tissues are significantly different from each other: GM>WM>CSF
- All three quadratic terms were tested to be significant
- Quadratic terms of WM, CSF were tested to be not statistically different from each other

Confidence Intervals

95% confidence interval of growth curves



Confidence Intervals

- Inter-individual variance increases over time for all three tissue types

Standard deviation	neonates	1 yr old	2 yrs old
CSF	11.88	27.27	27.57
GM	28.28	61.70	87.45
WM	20.42	58.5	38.12

Individual Correlation Matrix

- Different individual correlation matrix
  - different size
  - different value
- Multiple responses
  - correlation within tissues over time
  - correlation between tissues

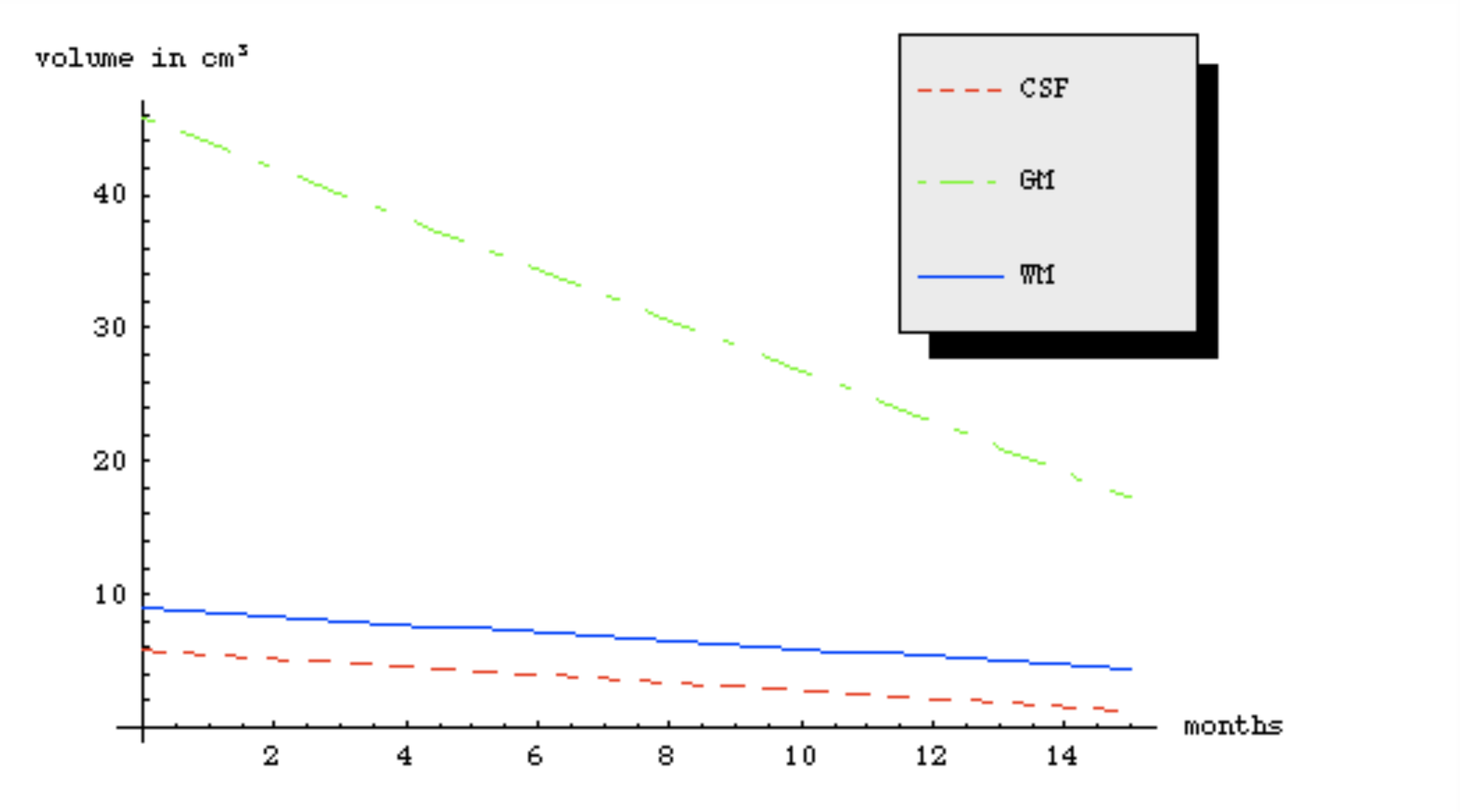
Individual Correlation Matrix

- 9x9 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, 24.2.

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

Growth Velocity

Take the derivatives of parametric growth curve functions



Growth Velocity

- The speed of growing decreases over time for all three tissues
- The growth speed of GM is much larger than those of CSF and WM for the first 2 years, but it also decreases faster.
  - GM: significant growth, slow down over time
  - CSF, WM: significant growth, less dramatic compared to GM

Conclusion

- Applied a joint modeling schema of mixed model to neonatal/pediatric brain tissue data;
- Obtained growth curves as a quadratic function of time;
- Computed confidence bands of growth trajectories;
- Computed correlation within and between different brain tissues;
- Studied the growth patterns of all brain tissues; GM fastest;
- The first multivariate longitudinal analysis of brain tissue for the early developing brain.