A multivariate skew-normal finite mixture model for analysis of infant development trajectories

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SUMMARY: In studies of infant motor development, a crucial research goal is to identify latent classes of infants that experience delayed development, as this is a known risk factor for adverse outcomes later in life. However, there are a number of statistical challenges in modeling infant development: the data are typically skewed, exhibit intermittent missingness, and are highly correlated across the repeated measurements collected during infancy. Using data from the Nurture study, a cohort of over 600 mother-infant pairs followed from pregnancy to 12 months postpartum, we develop a flexible Bayesian latent class model for the analysis infant motor development. Our model has a number of attractive features. First, we adopt the multivariate skew normal distribution with class-specific parameters that accommodate the inherent correlation and skewness in the data. Second, we model the class membership probabilities using a novel Plya-Gamma data-augmentation scheme, thereby improving predictions of the class membership allocations. Lastly, we impute missing responses under missing at random assumption by drawing from appropriate conditional skew normal distributions. Bayesian inference is achieved through straightforward Gibbs sampling, and can be carried out in available software such as R. Through simulation studies, we show that the proposed model yields improved inferences over models that ignore skewness. In addition, our imputation method yields improvements compared to conventional missing data methods, including multiple imputation and complete or available case analysis. When applied to Nurture data, we identified two distinct development classes: one characterized by delayed U-shaped development and a higher percentage of male infants and another characterized by more steady development and a

lower percentage of males. The classes also differed in terms of key demographic variables, such as infant race and maternal pre-pregnancy body mass index. These findings can aid investigators in targeting interventions during this critical early-life developmental window.

CONTENTS

1. Introduction

2. Nurture Study

2.1 *Baseline Demographics and Description of Variables*

2.2 *Statistical Challenges*

2.2.1 *Skewness of Bayley score residuals.*

2.2.2 *Attrition and Intermittent Missingness.*

3. Model

3.1 *Multivariate Skew Normal Regression*

We model the effect of covariates on longitudinal development outcomes through the use of a MSN regression model. The MSN distribution can be represented as the superposition of a MN random variable with a latent truncated normal random effect. Let $\mathbf{Y}_{n \times k}$ be the observation matrix such that Y_{ij} is the observation for subject i at timepoint j.

$$\mathbf{Y}_{n \times k} = \mathbf{X}_{n \times p} \boldsymbol{\beta}_{p \times k} + t_{n \times 1} \psi_{1 \times k} + \boldsymbol{\epsilon}_{n \times k}$$

where X_i is the $1 \times p$ vector of covariate values for subject i, β_j is the $i \times k$ vector of fixed effects coefficients for timepoint j, $t_i \overset{iid}{\sim} N_{[0,\infty)}(0,1)$ is a truncated normal random effect, ψ is the vector containing skewness parameters for each timepoint, and $\boldsymbol{\epsilon}_i \sim N_k(0, \boldsymbol{\Sigma}_{k \times k})$ is the correlated error term.

3.2 *Multinomial Regression on Class Probabilities*

A primary concern of our model is with identification of latent infant development clusters. We accomplish this via multinomial logit regression model on cluster membership, which utilizes Pólya-Gamma data-aumentation to allow for updating of all parameters using Gibbs sampling. The multinomial logit model is as follows for $l = 1, ..., h$.

$$P(Z_i = l | w_i) = \pi_{il} = \frac{e^{w_i^T \delta_l}}{\sum_{r=1}^h e^{w_i^T \delta_r}}$$

where w_i is the vector of class probability covariates for subject i, δ_l contains the multinomial regression parameters for class l, and h is the number of putative clusters specified *a priori*.

During our MCMC estimation procedure, the class labels z_i are updated from their multi-

nomial full conditional distribution and used in the remaining MCMC steps as class assignments.

3.3 *Conditional MVSN Imputation*

We allow for missingness of outcomes in the MSN mixture model by imputing missing values from their conditional multivariate normal distributions. We note that

$$Y_i | X_i, t_i, \boldsymbol{\beta}, \psi \sim N_k(X_i \boldsymbol{\beta} + t_i \psi, \boldsymbol{\Sigma})$$

This allows us to appeal to standard conditional forms of the multivariate normal distribution. Let $Y_i = [Y_{i_{q \times 1}}^{miss} | Y_{i_{k-q \times 1}}^{obs}]^T$. We have

$$Y_i^{miss} | Y_i^{obs}, X_i, t_i, \boldsymbol{\beta}, \psi \sim N(\mu^{miss}, \boldsymbol{\Sigma}^{miss})$$

where μ^{miss} and Σ^{miss} take standard forms. Each missing outcome is imputed "online", i.e. once per MCMC iteration. This provides more opportunities to explore the parameter space than multiple imputation and avoids multiplicative run-time scaling in m, the number of imputations.

3.4 *Bayesian Inference*

- Emphasize that PG data augmentation for the multinomial model results in a PG mixture of experts model, which is a computationally efficient way to model edge weights.

3.4.1 *Prior Choice.*

3.4.2 *MCMC Algorithm.*

3.4.3 *Assessment of MCMC Convergence.*

3.4.4 *Label Switching.*

4. Simulation Studies

4.1 *Simulation to Compare to Multivariate Normal*

4.2 *Simulation to Compare Imputation Methods*

4.3 *Simulation to Assess Sensitivity to Mispecified K*

5. Application

- Include both time varying and non-time varying covariates for the within cluster covariate set.

6. Discussion

- Discuss how we handle non-ignorable missingness

7. Appendix

Put your final comments here.

Supplementary Materials

7.1 *Glossary of Notation*

- **Y**: A $N \times J$ matrix containing all multivariate skew-normal outcomes such that y_{ij} is the jth outcome observed for subject i, where $i = 1, ..., n$ and $j = 1, ...J$.

- **X**: A $n \times p$ matrix containing all multivariate skew-normal regression covariates such that x_{ij} is the jth covariate value for subject i.

- **B**: A $m \times p$ matrix containing all multivariate skew-normal regression coefficients such that $\mathbf{B} = [\boldsymbol{\beta}_1, ..., \boldsymbol{\beta}_p]$, where β_{ij} is interpreted as the effect of covariate i on outcome j for $i = 1, ..., m$ and $j = 1, ..., p$.

- **E**: A $n \times p$ matrix of error terms in the multivariate skew-normal regression model component. **E** is made up of row vectors $\boldsymbol{\epsilon}_i = (\epsilon_{i1}, ..., \epsilon_{ip})$, where $\boldsymbol{\epsilon}_i \overset{iid}{\sim} N_p(0, \boldsymbol{\Sigma})$ for $i = 1, ..., n$.

- **$\boldsymbol{\Sigma}$**: A $p \times p$ covariance matrix that defines the correlation between the p multivariate normal outcomes.

- **$\boldsymbol{\Omega}$**: A $p \times p$ covariance scale matrix that defines the correlation between the p multivariate skew-normal outcomes.

- **$\boldsymbol{\psi}$**: A $p \times 1$ vector containing the skewness parameter for each outcome.

- **$\boldsymbol{\alpha}$**: A $p \times 1$ vector containing the skewness parameter for each outcome.

- **t**: An $n \times 1$ vector of truncated normal random effects used in the stochastic representation of the multivariate skew-normal distribution. For $i = 1, ..., n$, $t_i \overset{iid}{\sim} T_{[0,\infty)}(0, 1)$

- **$\mathbf{X}^*$**: A $n \times (m + 1)$ matrix constructed by column binding **t** to **X**

- **$\mathbf{B}^*$**: A $(m + 1) \times p$ matrix constructed by row binding $\boldsymbol{\psi}^T$ to **B**.

7.2 Derivation of Full Conditional Distributions

7.2.1 *Multivariate Skew-Normal Regression.*   Without loss of generality, we derive the full conditional distributions for the multivariate skew-normal regression model component under the assumption that all observations belong to a single cluster. To make the extension to the case where more than one cluster is specified, simply apply these distributional forms to cluster specific parameters and data. Finally, we assume for the moment that we have complete data for all outcomes for each subject. We extend consider the case of missing data in section (INSERT SECTION).

The multivariate skew-normal regression model can be written as follows in matrix form.

$$\mathbf{Y} = \mathbf{X}\mathbf{B} + \mathbf{t}\boldsymbol{\psi}^T + \mathbf{E} = \mathbf{X}^*\mathbf{B}^* + \mathbf{E}$$

The matrix $\mathbf{Y}$ is of dimension $n \times p$. For convenience, we define $\mathbf{X}^*$ as a $n \times (m+1)$ matrix constructed by column binding $\mathbf{t}$ to $\mathbf{X}$, and $\mathbf{B}^*$ as a $(m+1) \times p$ matrix constructed by row binding $\boldsymbol{\psi}^T$ to $\mathbf{B}$. We assume that $t_i \overset{iid}{\sim} T_{[0,\infty)}(0,1)$ and that $\mathbf{E}$ is made of row vectors $\boldsymbol{\epsilon}_i = (\epsilon_{i1}, ..., \epsilon_{ip})$ for $i = 1, ..., n$, where $\boldsymbol{\epsilon}_i \overset{iid}{\sim} N_p(0, \boldsymbol{\Sigma})$.

The conditional likelihood for this model is given below.

$$p(\mathbf{Y}|\mathbf{X}^*, \mathbf{B}^*, \boldsymbol{\Sigma}) \propto |\boldsymbol{\Sigma}|^{-n/2} \exp\left\{ -\frac{1}{2}\text{tr}(\mathbf{Y} - \mathbf{X}^*\mathbf{B}^*)^T(\mathbf{Y} - \mathbf{X}^*\mathbf{B}^*)\boldsymbol{\Sigma}^{-1} \right\}$$

We choose conjugate priors for $\mathbf{B}^*$ and $\boldsymbol{\Sigma}$ as follows.

$$\boldsymbol{\Sigma} \sim \text{inverse-Wishart}(\mathbf{V}_0, \nu_0)$$

$$\mathbf{B}^*|\boldsymbol{\Sigma} \sim MatNorm_{(m+1),p}(\mathbf{B}_0^*, \mathbf{L}_0^{-1}, \boldsymbol{\Sigma})$$

We now dervive the joint posterior distribution of the parameters $\mathbf{B}^*$ and $\boldsymbol{\Sigma}$.

$$p(\mathbf{B}^*, \boldsymbol{\Sigma}|\mathbf{X}^*, \mathbf{Y}) \propto p(\mathbf{Y}|\mathbf{X}^*, \mathbf{B}^*, \boldsymbol{\Sigma})p(\mathbf{B}^*|\boldsymbol{\Sigma})p(\boldsymbol{\Sigma})$$

$$\propto |\boldsymbol{\Sigma}|^{-n/2}\exp\left\{-\frac{1}{2}\text{tr}\left[(\mathbf{Y}-\mathbf{X}^*\mathbf{B}^*)^T(\mathbf{Y}-\mathbf{X}^*\mathbf{B}^*)\boldsymbol{\Sigma}^{-1}\right]\right\}$$

$$\times |\boldsymbol{\Sigma}|^{-(m+1)/2}\exp\left\{-\frac{1}{2}\text{tr}\left[(\mathbf{B}^*-\mathbf{B}_0^*)^T\mathbf{L}_0(\mathbf{B}^*-\mathbf{B}_0^*)\boldsymbol{\Sigma}^{-1}\right]\right\}$$

$$\times |\boldsymbol{\Sigma}|^{(\nu_0+p+1)/2}\exp\left\{-\frac{1}{2}\text{tr}(\mathbf{V}_0\boldsymbol{\Sigma}^{-1})\right\}$$

7.2.2 *Multinomial Logit Regression.*

7.2.3 *Multivariate Normal Conditional Imputation.* The multivariate normal conditional imputation derivations are given for a single cluster without loss of generality. In practive, the data and parameters in this section would be replaced by cluster specific estimates in the case of clustering.

For a given observation vector $\mathbf{y} \sim N_p(\boldsymbol{\mu}, \boldsymbol{\Sigma})$, we allow for missingness in at most $p-1$ of the multivariate outcomes through the use of a conditional imputation step embedded within our Gibbs sampler. Suppose $\mathbf{y}$ contains q missing observations and can be partitioned into two vectors $\mathbf{y_1}$ and $\mathbf{y_2}$ such that $\mathbf{y_1}$ is a $q \times 1$ vector of missing observations and $\mathbf{y_2}$ is a $(p-q) \times 1$ vector of complete observations. Similarly, partition $\boldsymbol{\mu}$ and $\boldsymbol{\Sigma}$ as follows.

$$\boldsymbol{\mu} = \begin{bmatrix} \boldsymbol{\mu}_1 \\ \boldsymbol{\mu}_2 \end{bmatrix} \qquad \boldsymbol{\Sigma} = \begin{bmatrix} \boldsymbol{\Sigma}_{11} & \boldsymbol{\Sigma}_{12} \\ \boldsymbol{\Sigma}_{21} & \boldsymbol{\Sigma}_{22} \end{bmatrix}$$

We will use these quantities to derive the conditional distribution $f(\mathbf{y_1}|\mathbf{y_2}, \boldsymbol{\mu}, \boldsymbol{\Sigma})$.

$$f(\mathbf{y_1}|\mathbf{y_2}, \boldsymbol{\mu}, \boldsymbol{\Sigma}) \propto f(\mathbf{y_1}, \mathbf{y_2}|\boldsymbol{\mu}, \boldsymbol{\Sigma})$$

$$\propto \exp\left\{-\frac{1}{2}(\mathbf{y} - \boldsymbol{\mu})^T \boldsymbol{\Sigma}^{-1}(\mathbf{y} - \boldsymbol{\mu})\right\}$$

$$= \exp\left\{-\frac{1}{2}\begin{bmatrix}\mathbf{y}_1 - \boldsymbol{\mu}_1 \\ \mathbf{y}_2 - \boldsymbol{\mu}_2\end{bmatrix}^T \boldsymbol{\Sigma}^{-1} \begin{bmatrix}\mathbf{y}_1 - \boldsymbol{\mu}_1 \\ \mathbf{y}_2 - \boldsymbol{\mu}_2\end{bmatrix}\right\}$$

$$= \exp\left\{-\frac{1}{2}\begin{bmatrix}\mathbf{y}_1 - \boldsymbol{\mu}_1 \\ \mathbf{y}_2 - \boldsymbol{\mu}_2\end{bmatrix}^T \begin{bmatrix}\boldsymbol{\Sigma}_{11} & \boldsymbol{\Sigma}_{12} \\ \boldsymbol{\Sigma}_{21} & \boldsymbol{\Sigma}_{22}\end{bmatrix}^{-1} \begin{bmatrix}\mathbf{y}_1 - \boldsymbol{\mu}_1 \\ \mathbf{y}_2 - \boldsymbol{\mu}_2\end{bmatrix}\right\}$$

$$= \exp\left\{-\frac{1}{2}\begin{bmatrix}\mathbf{y}_1 - \boldsymbol{\mu}_1 \\ \mathbf{y}_2 - \boldsymbol{\mu}_2\end{bmatrix}^T \begin{bmatrix}\boldsymbol{\Sigma}_{11}^* & \boldsymbol{\Sigma}_{12}^* \\ \boldsymbol{\Sigma}_{21}^* & \boldsymbol{\Sigma}_{22}^*\end{bmatrix} \begin{bmatrix}\mathbf{y}_1 - \boldsymbol{\mu}_1 \\ \mathbf{y}_2 - \boldsymbol{\mu}_2\end{bmatrix}\right\}$$

$$= \exp\left\{-\frac{1}{2}\left[(\mathbf{y}_1 - \boldsymbol{\mu}_{cond})^T \boldsymbol{\Sigma}_{cond}^{-1}(\mathbf{y}_1 - \boldsymbol{\mu}_{cond})\right]\right\}$$

$$\Rightarrow \mathbf{y_1}|\mathbf{y_2}, \boldsymbol{\mu}, \boldsymbol{\Sigma} \sim N_q(\boldsymbol{\mu}_{cond}, \boldsymbol{\Sigma}_{cond})$$

$$\boldsymbol{\mu}_{cond} = \boldsymbol{\mu}_1 + \boldsymbol{\Sigma}_{12}\boldsymbol{\Sigma}_{22}^{-1}(\mathbf{y}_2 - \boldsymbol{\mu}_2), \qquad \boldsymbol{\Sigma}_{cond} = \boldsymbol{\Sigma}_{11} - \boldsymbol{\Sigma}_{12}\boldsymbol{\Sigma}_{22}^{-1}\boldsymbol{\Sigma}_{21}$$

The blockwise inversion formula was used to invert $\boldsymbol{\Sigma}$ according to the following reparameterizations.

$$\boldsymbol{\Sigma}_{11}^* = \boldsymbol{\Sigma}_{11}^{-1} + \boldsymbol{\Sigma}_{11}^{-1}\boldsymbol{\Sigma}_{12}(\boldsymbol{\Sigma}_{22} - \boldsymbol{\Sigma}_{21}\boldsymbol{\Sigma}_{11}^{-1}\boldsymbol{\Sigma}_{12})^{-1}\boldsymbol{\Sigma}_{21}\boldsymbol{\Sigma}_{11}^{-1}$$

$$\boldsymbol{\Sigma}_{12}^* = -\boldsymbol{\Sigma}_{11}\boldsymbol{\Sigma}_{12}(\boldsymbol{\Sigma}_{22} - \boldsymbol{\Sigma}_{21}\boldsymbol{\Sigma}_{11}^{-1}\boldsymbol{\Sigma}_{12})^{-1}$$

$$\boldsymbol{\Sigma}_{21}^* = -(\boldsymbol{\Sigma}_{22} - \boldsymbol{\Sigma}_{21}\boldsymbol{\Sigma}_{11}^{-1}\boldsymbol{\Sigma}_{12})^{-1}\boldsymbol{\Sigma}_{21}\boldsymbol{\Sigma}_{11}^{-1}$$

$$\boldsymbol{\Sigma}_{22}^* = (\boldsymbol{\Sigma}_{22} - \boldsymbol{\Sigma}_{21}\boldsymbol{\Sigma}_{11}^{-1}\boldsymbol{\Sigma}_{12})^{-1}$$