Bayesian 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 the identification of latent clusters of infants who experience delayed motor 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 motor 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 finite mixture model for the analysis infant motor development. Our model has a number of attractive features. First, we adopt the multivariate skew normal distribution with cluster-specific parameters that accommodate the inherent correlation and skewness in the data. Second, we model the cluster membership probabilities using a novel application of the Pólya-Gamma data-augmentation scheme, thereby improving predictions of the cluster membership allocations. Lastly, we impute missing responses under the missing at random assumption by drawing from appropriate conditional multivariate skew normal distributions. Bayesian inference is achieved through straightforward Gibbs sampling, and can be implemented 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 clusters: one characterized by delayed U-shaped motor development and a higher percentage

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of male infants and another characterized by more steady motor development and a lower percentage of males. The clusters 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.

Key words: Mixture of Experts, Pólya-Gamma, Skew-Normal, Imputation, Latent Growth, Infant Development.

CONTENTS

1. Introduction

1.1 *Infant Development Clustering*

Heterogeneity of treatment effects (HTE) (Lanza and Rhoades, 2013).

1.2 *Existing Approaches*

Mixtures of multivariate non-symmetric distributions such as the multivariate skew-normal (MSN) distribution allow for the nuances of the marginal density to be captured with a more parsimonious set of mixture components. Mixtures of MSN distributions have been dealt with previously in a Bayesian context (Frühwirth-Schnatter & Pyne, 2010 and others), however in these models, focus lies primary on marginal density estimation, and inference on the mixture components (i.e. clusters) is often not discussed. More recently, the mixtures of skew-t factor analysis (MSTFA) model has been proposed for settings in which cluster-specific inference is of primary interest (Lin *et al.* 2018). However, an important feature not included in the MSTFA is the ability to explain individual-level cluster membership as a function of covariates of interest. Additionally, the parameter estimation procedure proposed by Lin et al. for the MSTFA relies on a prohibitively complex EM algorithm and does not enjoy the inferential benefits of a Bayesian approach, including the ability to incorporate prior information into a model and make posterior probability statements. Our proposed model improves on these previous works by estimating parameters in a Bayesian framework as well as including the ability to fit a multinomial logit regression to cluster membership probabilities using a novel application of data augmentation with the Pólya-Gamma distribution.

Polson et al. (2013) introduce a data augmentation scheme using the Pólya-Gamma distribution which allows for sampling of multinomial regression parameters using straightforward Gibb's updates from Gaussian full conditional distributions. In addition to more convinient parameter estimation, the Pólya-Gamma data augmentation method for logistic regression

has the advantage of direct sampling from the posterior distributions of multinomial parameters. This approach avoids the need for approximations of the posterior distribution, thus yeilding more stable sampling, especially when the number of parameters approaches the number of observations (Polson et al., 2013). Pólya-Gamma data augmentation for multinomial regression has not yet been applied to the analysis of longitudinally clustered data.

A ubiquitous feature of repeated measures studies is loss of data due to intermittent missingness and attrition. In the Bayesian setting, the standard approach to dealing with missing data is to perform multiple imputation, whereby m imputed data sets are generated from a specified imputation model. After m complete data sets are obtained, parameter estimates are combined across each data set to produce a final set of parameter estimates (Gelman *et al.* 2013). This approach is not only computationally burdensome, requiring storage and analysis of an $m \times n_{rows} \times n_{cols}$ data array in addition to multiplication of total model run time by a factor of m, but it has been shown to produce unreliable inferences (Zhou and Reiter, 2010). We instead include an "online" imputation imputation step in our Gibbs sampling procedure, whereby missing outcomes are updated at each iteration. This approach greatly increases the number of opportunities for exploration of the missing data parameter space and avoids the multiplication of total run time and number of parameters.

2. Nurture Study

2.1 *Baseline Demographics and Description of Variables*

2.2 *Statistical Challenges*

The analysis of infant motor development trends in the Nurture data presents a number of statistical challenges that motivate our proposed model. First, as depicted in Figure 1, the residuals from repeated measures models of Bayley composite scores exhibit skewness even after adjusting for covariates such as race, sex, and birthweight. This suggests that the assumption of conditional normality made by standard repeated measures models is violated, and a distinguishing feature of the data, skewness, is not being accounted for.

[Figure 1 about here.]

The Nurture data also feature intermittent missingness in Bayley composite scores throughout the study period. Of the total cohort (N = 666), 429 (64.4 %) observations were available at three months, 435 (65.3 %) observations were available at six months, 418 (62.8 %) observations were available at nine months, and 437 (65.6 %) observations were available at twelve months. As such, we require a modeling framework capable of dealing with missing data.

3. Model

3.1 *Multivariate Skew Normal Mixture Model*

A primary goal of the Nurture study is to identify clusters of infants characterized by distinct motor development trajectories throughout the first year of life. To address this aim, we propose a flexible finite mixture model that accommodates relevant features of the data, such as skewness, missing values, and dependence among the responses. For $i = 1, ..., n$, let $\mathbf{y}_i = (y_{i1}, \ldots, y_{iJ})^T$ be a $J \times 1$ vector of responses (i.e., Bayley composite scores) for subject i across the J measurement occasions. For analysis of the Nurture data, we propose a finite

mixture model of the form

$$f(\mathbf{y}_i) = \sum_{k=1}^{K} \pi_{ki} f(\mathbf{y}_i|\boldsymbol{\theta}_k), \tag{1}$$

where $\boldsymbol{\theta}_k$ is the set of parameters specific to cluster k ($k = 1, ..., K$) and π_{ki} is a subject-specific mixing weight representing the probability that subject i belongs to cluster k. For now we assume that K is fixed; in Section 3.4.3, we discuss model selection strategies for choosing the optimal value of K.

To facilitate posterior inference, we introduce a latent cluster indicator variable z_i taking the value $k \in \{1, ..., K\}$ with probability π_{ki}. Conditional on $z_i = k$, we assume $\mathbf{y}_i$ is distributed as

$$\mathbf{y}_i|(z_i = k) \sim \text{MSN}_J(\boldsymbol{\zeta}_{ki}, \boldsymbol{\alpha}_k, \boldsymbol{\Omega}_k), \tag{2}$$

where $\text{MSN}_J(\cdot)$ denotes the J-dimensional multivariate skew normal density, $\boldsymbol{\zeta}_{ki}$ is a $J \times 1$ vector of subject- and cluster-specific location parameters, $\boldsymbol{\alpha}_k$ is a $J \times 1$ vector of cluster-specific skewness parameters, and $\boldsymbol{\Omega}_k$ is a $J \times J$ cluster-specific scale matrix that captures dependence among the J responses for subject i. The vector $\boldsymbol{\alpha}_k$ has components α_{kj}, $j = 1, ..., J$, that control the skewness of outcome j in cluster k. When $\boldsymbol{\alpha}_k = \mathbf{0}$, the MSN distribution reduces to the multivariate normal distribution $\text{N}_J(\boldsymbol{\zeta}_{ki}, \boldsymbol{\Omega}_k)$, where $\boldsymbol{\zeta}_{ki}$ is a $J \times 1$ mean vector and $\boldsymbol{\Omega}_k$ is a $J \times J$ covariance matrix (Azzalini and Dalla Valle, 1996).

We can extend model (2) to the regression setting by modeling $\boldsymbol{\zeta}_{ki}$ as a function of covariates. Here we adopt a convenient stochastic representation of the MSN density (Azzalini and Dalla Valle, 1996):

$$\mathbf{y}_i|(z_i = k, t_i) = \mathbf{X}_i\boldsymbol{\beta}_k + t_i\boldsymbol{\psi}_k + \boldsymbol{\epsilon}_{ki}, \tag{3}$$

where $\mathbf{X}_i$ is a $J \times Jp$ design matrix that includes potential time-varying covariates (e.g., indicators denoting quarterly visits); $\boldsymbol{\beta}_k = (\beta_{k11}, \ldots, \beta_{k1p}, \ldots, \beta_{kJ1}, \ldots, \beta_{kJp})^T$ is a $Jp \times 1$ vector of cluster- and outcome-specific regression coefficients; $t_i \sim \text{N}_{[0,\infty)}(0, 1)$ is a subject-specific standard normal random variable truncated below by zero; $\boldsymbol{\psi}_k = (\psi_{k1}, \ldots, \psi_{kJ})^T$ is

a $J \times 1$ vector of cluster-specific skewness parameters; and $\boldsymbol{\epsilon}_{ki} \sim \mathrm{N}_J(\mathbf{0}, \boldsymbol{\Sigma}_k)$ is a $J \times 1$ vector of correlated error terms. Thus, conditional on t_i and $z_i = k$, $\boldsymbol{y}_i$ is distributed as $\mathrm{N}_J(\mathbf{X}_i\boldsymbol{\beta}_k + t_i\boldsymbol{\psi}_k, \boldsymbol{\Sigma}_k)$. Marginally (after integrating over t_i), $\mathbf{y}_i|(z_i = k)$ is distributed $\mathrm{MSN}_J(\boldsymbol{\zeta}_{ki}, \boldsymbol{\alpha}_k, \boldsymbol{\Omega}_k)$, where through back-transformation

$$\begin{aligned} \boldsymbol{\zeta}_{ki} &= \mathbf{X}_i\boldsymbol{\beta}_k, \\ \boldsymbol{\alpha}_k &= \frac{1}{\sqrt{1 - \boldsymbol{\psi}_k^T\boldsymbol{\Omega}_k^{-1}\boldsymbol{\psi}_k}}\boldsymbol{\omega}_k\boldsymbol{\Omega}_k^{-1}\boldsymbol{\psi}_k, \quad \text{and} \\ \boldsymbol{\Omega}_k &= \boldsymbol{\Sigma}_k + \boldsymbol{\psi}_k\boldsymbol{\psi}_k^T, \end{aligned} \tag{4}$$

where $\boldsymbol{\omega}_k = \mathrm{Diag}(\boldsymbol{\Omega}_k)^{1/2}$ is the $J \times J$ diagonal matrix containing the square root of the diagonal entries of $\boldsymbol{\Omega}_k$. Additional details can be found in Früwirth-Schnatter and Pyne (2010).

Of note, the MSN density can be expressed more compactly in terms of the matrix skew normal (MatSN) density (Chen and Gupta 2005). Let $\mathbf{Y}_k$ be an $n_k \times J$ response matrix with rows $\mathbf{y}_i^T$, $(i = 1, ..., n_k)$, where $n_k = \sum_{i=1}^{n} \mathbb{1}_{(z_i=k)}$ is the number of observations in cluster k. From equation (3), it follows that $\mathbf{Y}_k$ is distributed as

$$\begin{aligned} \mathbf{Y}_k &\sim \mathrm{MatSN}_{n_k \times J}(\mathbf{M}_k, \boldsymbol{\alpha}_k, \mathbf{I}_{n_k}, \boldsymbol{\Omega}_k) \\ \mathrm{vec}(\mathbf{M}_k) &= (\boldsymbol{\zeta}_{k1}^T, ..., \boldsymbol{\zeta}_{kn_k}^T)^T, \end{aligned} \tag{5}$$

where $\mathbf{M}_k$ is an $n_k \times J$ location matrix with rows $\boldsymbol{\zeta}_{ki} = \mathbf{X}_i\boldsymbol{\beta}_k$ as in equation (3), $\boldsymbol{\alpha}_k = (\alpha_{k1}, ..., \alpha_{kJ})^T$, $\mathbf{I}_{n_k}$ is the $n_k \times n_k$ identity matrix, and $\boldsymbol{\Omega}_k$ is the $J \times J$ scale matrix defined above in equation (2). From equation (3), it follows that $\mathbf{Y}_k$, conditional on the $n_k \times 1$ vector of random effects $\mathbf{t}_k = (t_1, ..., t_{n_k})^T$, is jointly distributed in matrix form as

$$\mathbf{Y}_k|\mathbf{t}_k \sim \mathrm{MatNorm}_{n_k \times J}(\mathbf{M}_k^*, \mathbf{I}_{n_k}, \boldsymbol{\Sigma}_k), \tag{6}$$

where $\mathrm{MatNorm}_{n_k \times J}(\cdot)$ denotes a $n_k \times J$ matrix normal density, $\mathbf{M}_k^*$ is an $n_k \times J$ matrix such that $\mathrm{vec}(\mathbf{M}_k^*) = \mathbf{X}_k\boldsymbol{\beta}_k + \mathbf{t}_k \otimes \boldsymbol{\psi}_k$ is an $n_kJ \times 1$ mean vector, $\mathbf{X}_k$ is an $n_kJ \times Jp$ design matrix, $\boldsymbol{\beta}_k$ is the $Jp \times 1$ vector of regression coefficients defined in equation (3), and $\boldsymbol{\Sigma}_k$ is the $J \times J$

conditional covariance of $\boldsymbol{\epsilon}_{ik}$ given in equation (3). As described in Section 3.6, the matrix representation of the MSN distribution admits convenient conjugate prior distributions for the regression parameters and scale matrices, which in turn leads to efficient Gibbs sampling for posterior inference.

3.2 *Multinomial Regression for the Cluster Indicators*

To accommodate heterogeneity in the cluster-membership probabilities, we model π_{ki} as a function of covariates using a multinomial logit model

$$\pi_{ki} = \Pr(z_i = k|\mathbf{w}_i) = \frac{\mathrm{e}^{\mathbf{w}_i^T \boldsymbol{\delta}_k}}{\sum_{h=1}^{K} \mathrm{e}^{\mathbf{w}_i^T \boldsymbol{\delta}_h}}, \; k = 1, \ldots, K, \tag{7}$$

where $\mathbf{w}_i$ is an $r \times 1$ vector of subject-level covariates, $\boldsymbol{\delta}_k$ is a $r \times 1$ vector of regression parameters associated with membership in cluster k. For identifiability purposes, we fix the reference category $k = K$ and set $\boldsymbol{\delta}_K = \mathbf{0}$. Under this model, $z_i|\boldsymbol{\pi}_i \sim$ Multinomial$(1, \boldsymbol{\pi}_i)$, where $\boldsymbol{\pi}_i = (\pi_{1i}, ..., \pi_{Ki})$. During MCMC estimation, the cluster labels z_i are updated from their multinomial full conditional distribution and used in the remaining MCMC steps as working cluster assignments, as detailed later in Section 3.4.2. By allowing the cluster probabilities to vary across subjects, our model can be viewed as a *mixture of experts* model, in which π_{ki} acts as a *gating function* controlling the prior probability of membership in cluster k, and $f(\mathbf{y}_i|\boldsymbol{\theta}_k)$ in equation (1) is the "expert" providing information on the within-cluster distribution of $\mathbf{y}_i$ (Bishop 2006).

To facilitate sampling, we adopt the efficient data-augmentation approach introduced by Polson et al. (2013), which expresses the inverse-logit function as a mixture Pólya–Gamma densities. By using Pólya–Gamma data augmentation for the multinomial model, we obtain a *Pólya–Gamma mixture of experts model* – a computationally efficient way to obtain inferences for the mixing weights in the Bayesian setting. A random variable w is said to follow a Pólya–

Gamma distribution with parameters $b > 0$ and $c \in \mathbb{R}$ if

$$w \sim \text{PG}(b, c) \stackrel{d}{=} \frac{1}{2\pi^2} \sum_{s=1}^{\infty} \frac{g_s}{(s - 1/2)^2 + c^2/(4\pi^2)}, \tag{8}$$

where $g_s \stackrel{iid}{\sim} \text{Ga}(b, 1)$ for $s = 1, ..., \infty$. Polson et al. establish that for $a, \eta \in \mathbb{R}$,

$$\frac{(\text{e}^{\eta})^a}{(1 + \text{e}^{\eta})^b} = 2^{-b} \text{e}^{\kappa\eta} \int_0^{\infty} \text{e}^{-w\eta^2/2} p(w|b, c = 0) dw, \tag{9}$$

where $\kappa = a - b/2$ and $p(w|b, c = 0)$ denotes a $\text{PG}(b, 0)$ density. Polson et al. further show that the conditional distribution $p(w|b, c)$ results from an "exponential tilting" of the $\text{PG}(b, 0)$ density, thus

$$p(w|b, c) = \frac{\text{e}^{-c^2 w/2} p(w|b, 0)}{E_w[\text{e}^{-c^2 w/2}]} = \frac{\text{e}^{-c^2 w/2} p(w|b, 0)}{\int_0^{\infty} \text{e}^{-c^2 w/2} p(w|b, 0) dw}. \tag{10}$$

Polson et al. use these results to show that, ~~in~~ the logistic model, the Bernoulli likelihood can be written ~~in terms of the kernel of a normal density and a PG$(b, 0)$ density,~~ resulting in a normal full conditional distribution for the logistic regression parameters. To extend the Pólya–Gamma data augmentation approach to the multinomial setting, we first introduce the binary indicators U_{ki}, such that $U_{ki} = \mathbb{1}_{(z_i = k)}$ – i.e., U_{ki} is an indicator variable taking the value 1 if subject i belongs to cluster k, and 0 otherwise. The full conditional distribution of $\boldsymbol{\delta}_k$ is then given as

$$p(\boldsymbol{\delta}_k | \mathbf{U}_k, \boldsymbol{\delta}_{h \neq k}) \propto p(\boldsymbol{\delta}_k) \prod_{i=1}^{n} \pi_{ki}^{U_{ki}} (1 - \pi_{ki})^{1 - U_{ki}},$$

where $p(\boldsymbol{\delta}_k)$ denotes the prior distribution of $\boldsymbol{\delta}_k$, and π_{ki} is defined as in equation (7). We can rewrite π_{ki} in terms of U_{ki} as

$$\pi_{ki} = P(U_{ki} = 1) = \frac{\text{e}^{\mathbf{w}_i^T \boldsymbol{\delta}_k - c_{ki}}}{1 + \text{e}^{\mathbf{w}_i^T \boldsymbol{\delta}_k - c_{ki}}} = \frac{\text{e}^{\eta_{ki}}}{1 + \text{e}^{\eta_{ki}}},$$

where $c_{ki} = \log \sum_{h \neq k} \text{e}^{\mathbf{w}_i^T \boldsymbol{\delta}_h}$ and $\eta_{ki} = \mathbf{w}_i^T \boldsymbol{\delta}_k - c_{ki}$. We note that the sum $\sum_{h \neq k} \text{e}^{\mathbf{w}_i^T \boldsymbol{\delta}_h}$ includes

the reference category, but since we fix $\boldsymbol{\delta}_K = \mathbf{0}$, we have $\mathrm{e}^{\mathbf{w}_i^T \boldsymbol{\delta}_K} = 1$, and hence

$$c_{ki} = \log \sum_{h \neq k} \mathrm{e}^{\mathbf{w}_i^T \boldsymbol{\delta}_h} = \log \left(1 + \sum_{h \notin \{k, K\}} \mathrm{e}^{\mathbf{w}_i^T \boldsymbol{\delta}_h} \right)^T .$$

We can use these quantities to re-express the full conditionals for $\boldsymbol{\delta}_k$ as

$$\begin{aligned} p(\boldsymbol{\delta}_k | \mathbf{U}_k, \boldsymbol{\delta}_{h \neq k}) &\propto p(\boldsymbol{\delta}_k) \prod_{i=1}^{n} \left(\frac{\mathrm{e}^{\eta_{ki}}}{1 + \mathrm{e}^{\eta_{ki}}} \right)^{U_{ki}} \left(\frac{1}{1 + \mathrm{e}^{\eta_{ki}}} \right)^{1 - U_{ki}} \\ &= p(\boldsymbol{\delta}_k) \prod_{i=1}^{n} \frac{(\mathrm{e}^{\eta_{ki}})^{U_{ki}}}{1 + \mathrm{e}^{\eta_{ki}}}, \end{aligned} \tag{11}$$

which is a logistic likelihood. We can thus apply the Pólya–Gamma sampler described by Polson et al. for logistic regression to update each $\boldsymbol{\delta}_k$ one at a time based on the binary indicators U_{ki}. To ~~accomplish this~~, we first define for $k = 1, ..., K$, the $n \times 1$ vector $\mathbf{U}_k^* = \left(\frac{U_{k1} - 1/2}{w_{k1}}, ..., \frac{U_{kn} - 1/2}{w_{kn}} \right)^T$. Polson et al. show that, conditional on $\boldsymbol{w} = (w_{k1}, ..., w_{kn})^T$, $\mathbf{U}_k^*$ follows a $\mathrm{N}_n(\boldsymbol{\eta}_k, \mathbf{O}_k^{-1})$ distribution with mean $\boldsymbol{\eta}_k = (\eta_{k1}, ..., \eta_{kn})^T$ and precision matrix $\mathbf{O}_k = \mathrm{Diag}(w_{k1}, ..., w_{kn})$. Thus, it follows that the full conditional distribution of $\boldsymbol{\delta}_k$ is given by

$$p(\boldsymbol{\delta}_k | \mathbf{z}, \mathbf{W}, \mathbf{O}_k) \propto p(\boldsymbol{\delta}_k) \exp \left[-\frac{1}{2} (\mathbf{U}_k^* - \mathbf{W}\boldsymbol{\delta}_k)^T \mathbf{O}_k (\mathbf{U}_k^* - \mathbf{W}\boldsymbol{\delta}_k) \right]. \tag{12}$$

As detailed in Section 3.4, if we assume $p(\boldsymbol{\delta}_k)$ to be multivariate normal, then $\boldsymbol{\delta}_k$ has a closed-form multivariate normal full conditional distribution that can be easily embedded within our proposed Gibbs sampling routine. For more details on the Pólya-Gamma Gibbs sampler for logistic and multinomial models, see Polson et al. (2013).

3.3 *Conditional MSN Imputation*

To accommodate intermittent missing at random (MAR) responses, we propose a convenient imputation algorithm that can be implemented "online" – that is, as part of the Gibbs sampler. In Section 6, we discuss extensions to allow for non-ignorable missingness (i.e., observations missing not at random). Suppose $\mathbf{y}_i$ has $q_i \in (1, \ldots, J)$ observed values, denoted $\mathbf{y}_i^{obs}$, and $J - q_i$ intermittent missing values, denoted $\mathbf{y}_i^{miss}$. We can make use of the stochastic

representation given in equation (3) to impute $\mathbf{y}_i^{miss}$ from its conditional multivariate normal distribution given $(z_i, t_i, \mathbf{y}_i^{obs})$:

$$\begin{aligned}
\mathbf{y}_i^{miss}|(z_i = k, t_i, \mathbf{y}_i^{obs}) &\sim \mathrm{N}_{J-q_i}(\boldsymbol{\mu}_{ki}^{cond}, \boldsymbol{\Sigma}_k^{cond}), \text{ where} \\
\boldsymbol{\mu}_{ki}^{cond} &= \boldsymbol{\mu}_{ki}^{miss} + \boldsymbol{\Sigma}_{k12}\boldsymbol{\Sigma}_{k22}^{-1}(\mathbf{y}_i^{obs} - \boldsymbol{\mu}_{ki}^{obs}) \\
\boldsymbol{\Sigma}_k^{cond} &= \boldsymbol{\Sigma}_{k11} - \boldsymbol{\Sigma}_{k12}\boldsymbol{\Sigma}_{k22}^{-1}\boldsymbol{\Sigma}_{k21}, \qquad (13) \\
\boldsymbol{\mu}_{ki} &= \begin{pmatrix} \boldsymbol{\mu}_{ki}^{miss} \\ \boldsymbol{\mu}_{ki}^{obs} \end{pmatrix}, \text{ and} \\
\boldsymbol{\Sigma}_k &= \begin{pmatrix} \boldsymbol{\Sigma}_{k11} & \boldsymbol{\Sigma}_{k12} \\ \boldsymbol{\Sigma}_{k21} & \boldsymbol{\Sigma}_{k22} \end{pmatrix}, \text{ where}
\end{aligned}$$

The location vector $\boldsymbol{\mu}_{ki}$ is defined as $\boldsymbol{\mu}_{ki} = \mathbf{X}_i\boldsymbol{\beta}_k + t_i\boldsymbol{\psi}_k$, and is partitioned into $\boldsymbol{\mu}_{ki}^{miss}$ and $\boldsymbol{\mu}_{ki}^{obs}$ with respect to the missing and observed indices of $\mathbf{y}_i$, respectively. The partition $\boldsymbol{\Sigma}_{k11}$ is a $(J-q_i)\times(J-q_i)$ matrix containing the rows and columns of $\boldsymbol{\Sigma}_k$ corresponding to $\mathbf{y}_i^{miss}$. Similarly, $\boldsymbol{\Sigma}_{k12}$ is a $(J-q_i)\times q_i$ matrix containing the rows of $\boldsymbol{\Sigma}_k$ that correspond to $\mathbf{y}_i^{miss}$, but columns of $\boldsymbol{\Sigma}_k$ that correspond to $\mathbf{y}_i^{obs}$. The remaining partitions $\boldsymbol{\Sigma}_{k21}$, and $\boldsymbol{\Sigma}_{k22}$ are defined in the same manner. These results follow from conventional multivariate normal theory, which we detail in the Web Appendix A. We note that, while conditional on t_i, $\mathbf{y}_i$ follows a MVN distribution, after marginalizing over t_i the vector $\mathbf{y}_i$ follows a MSN distribution. Thus, this proposed online conditional imputation method provides a ~~convinient~~ way of imputing MSN responses using samples from more standard densities.

An attractive practical feature of this imputation algorithm is that it avoids multiplicative run-time scaling in m, the number of imputations (Gelman et al. 2013; Zhou and Reiter, 2010). Our approach also provides more opportunities to explore the missing data parameter space than does multiple imputation, since each missing component is drawn once per MCMC iteration, and often in practice $n_{sim} >> m$, where n_{sim} is the total number of MCMC iterations (**find a reference**). In Section 4, we conduct simulation studies to demonstrate

that imputing the missing MSN responses with our online conditional imputation method improves inferences over standard Bayesian multiple imputation as outlined by Gelman et al. (2013).

3.4 *Bayesian Inference*

3.4.1 *Prior Specification.* We adopt a fully Bayesian inferential approach and assign prior distributions to all model parameters. Conveniently, all parameters admit conditionally conjugate priors, which greatly improves posterior computation via a data-augmented Gibbs sampler. To make use of the matrix normal representation introduced previously in Section 3, we define the matrix of regression parameters $\mathbb{B}_k^*$, where $\text{vec}(\mathbb{B}_k^*) = \boldsymbol{\beta}_k^* = (\boldsymbol{\beta}_k^T, \boldsymbol{\psi}_k^T)^T$. We assign $\mathbb{B}_k^* | \boldsymbol{\Sigma}_k$ a $\text{MatNorm}(\mathbf{B}_{0k}^*, \mathbf{I}_{p+1}, \boldsymbol{\Sigma}_k)$ prior, where $\mathbf{B}_{0k}^*$ is a matrix of location parameters such that $\text{vec}(\mathbf{B}_{0k}^*)$ is a vector of prior location parameters for the components of $\boldsymbol{\beta}_k^*$, $\mathbf{I}_{p+1}$ is the $(p+1)$-dimension identity matrix, and $\boldsymbol{\Sigma}_k$ is the covariance matrix defined in equation (2), for which we specify an $\text{IW}(\mathbf{V}_{0k}, \nu_{0k})$ prior. This leads to a matrix-normal-inverse-Wishart joint prior for $\mathbb{B}_k^*$ and $\boldsymbol{\Sigma}_k$, which is the conjugate joint prior for the regression parameters in the matrix normal model given in equation (5). This conjugate prior specification induces convenient closed-form full conditional distributions that can be easily updated within our proposed Gibbs sampler.

For the multinomial logit model, the regression parameters $\boldsymbol{\delta}_k = (\delta_{k1}, ..., \delta_{kr})^T$ are assigned a $\text{N}_r(\mathbf{d}_{0k}, \mathbf{S}_{0k})$ prior for $k = 1, ..., K-1$, which is conditionally conjugate under the Pólya-Gamma sampling scheme described in Section 3.2. We allow the normal-inverse-Wishart and multinomial hyperparameters (e.g., $\mathbf{B}_{0k}^*$ and $\mathbf{V}_{0k}$) to vary across clusters, though they may be shared across clusters in practice. An advantage of allowing for cluster-specific prior parameters is that *a priori* knowledge of motor development trends can be incorporated into certain clusters while allowing the priors for other clusters to be less informative. Addition-

ally, prior information regarding the effect of certain covariates on cluster membership can be incorporated in to the model by choosing informative values for $\mathbf{d}_{0k}$ and $\mathbf{S}_{0k}$

3.4.2 *Posterior Inference.* The above prior specification induces closed-form full conditionals for all model parameters, which can be efficiently updated as part of the Gibbs sampler outlined below. A programatic sketch of our MCMC algorithm is given in Web Appendix B. Additional details on derivations of full conditionals can be found in the Web Appendix A. We report MCMC diagnostics in Sections 4 and 5.

Step 1*: Conditional MSN Imputation.* The sampler begins by imputing missing values $\mathbf{y}_i^{miss}$ conditional on current values of $z_i = k$ and t_i as well as the associated $\mathbf{y}_i^{obs}$ observed data vector. Specifically, for $i = 1, ..., n$, we draw $\mathbf{y}_i^{miss}$ from $\mathrm{N}_{J-q_i}(\boldsymbol{\mu}_{ki}^{cond}, \boldsymbol{\Sigma}_k^{cond})$ as described in equation (13). We conclude by constructing a complete outcome vector $\mathbf{y}_i$ that merges $\mathbf{y}_i^{miss}$ with $\mathbf{y}_i^{obs}$.

Step 2: *Update of MSN Regression Parameters.* We begin the update of MSN regression parameters by updating t_i, the truncated normal random effect used in the stochastic representation ~~of $\mathbf{y}_i$ given~~ in equation (3). For cluster k, compute $A_k = (1 + \boldsymbol{\psi}_k^T \boldsymbol{\Sigma}_k^{-1} \boldsymbol{\psi}_k)^{-1}$ using current values of $\boldsymbol{\psi}_k$ and $\boldsymbol{\Sigma}_k$. Next, for $i = 1, ..., n_k$, compute $a_i = A_k \boldsymbol{\psi}_k^T \boldsymbol{\Sigma}_k^{-1} (\mathbf{y}_i - \boldsymbol{\zeta}_{ki})$, where $\boldsymbol{\zeta}_{ki} = X_i \boldsymbol{\beta}_k$. Finally, update t_i from $\mathrm{N}_{[0,\infty)}(a_i, \mathbf{A}_k)$. Repeat these updates for $k = 1, ..., K$.

The remaining MSN regression parameters are updated from their full conditionals as follows. First, we form the $n_k \times (p+1)$ matrix $\mathbf{X}_k^*$ by column-binding $\mathbf{X}_k$ and $\mathbf{t}_k$. For each cluster k ($k = 1, ..., K$), we update $\boldsymbol{\Sigma}_k$ from an $\mathrm{IW}(\nu_k, \mathbf{V}_k)$ density, where $\nu_k = \nu_{0k} + n_k$ and

$$\mathbf{V}_k = (\mathbf{Y}_k - \mathbf{X}_k^* \mathbf{B}_k^*)^T (\mathbf{Y}_k - \mathbf{X}_k^* \mathbf{B}_k^*) + (\mathbf{B}_k^* - \mathbf{B}_{0k}^*)^T \mathbf{I}_{p+1} (\mathbf{B}_k^* - \mathbf{B}_{0k}^*) + \mathbf{V}_{0k}.$$

We then make use of the matrix normal representation introduced in Section 3.2 to draw $\mathbb{B}_k^*$ from a $\mathrm{MatNorm}_{p+1,J}(\mathbf{B}_k^*, \mathbf{L}_k^*, \boldsymbol{\Sigma}_k)$ density, where $\mathrm{vec}(\mathbb{B}_k^*) = \boldsymbol{\beta}_k^* = (\beta_{k11}, ..., \beta_{kJp}, \psi_{k1}, ..., \psi_{kJ})^T$

and

$$\begin{aligned}\mathbf{B}_k^* &= \mathbf{L}_k^*(\mathbf{X}_k^{*T}\mathbf{Y}_k + \mathbf{I}_{p+1}\mathbf{B}_{0k}^*) \\ \mathbf{L}_k^* &= (\mathbf{X}_k^{*T}\mathbf{X}_k^* + \mathbf{I}_{p+1})^{-1}.\end{aligned}$$

Step 3:*Pólya–Gamma Data Augmentation for* z_i. The sampler concludes with updates of the multinomial regression parameters $\boldsymbol{\delta}_k$, for $k = 1, ..., K-1$, followed by updates of each latent cluster indicator z_i $(i = 1, \ldots, n)$ from its multinomial logit full conditional. First, we define $U_{ki} = 1_{z_i=k}$ for $i = 1, ..., n$ and $k = 1, ..., K-1$. Next, we update w_{ki} from a $\text{PG}(1, \eta_{ki})$ density, where $\eta_{ki} = \mathbf{w}_i^T\boldsymbol{\delta}_k - c_{ki}$, and $c_{ki} = \log\sum_{h\neq k} \text{e}^{\mathbf{w}_i^T\boldsymbol{\delta}_h}$. Next, define $U_{ki}^* = \frac{U_{ki}-1/2}{w_{ki}}$ and let $\mathbf{U}_k^* = (U_{k1}^*, ..., U_{kn}^*)^T$. Finally, for $k = 1, ..., K-1$, update $\boldsymbol{\delta}_k$ from a $\text{N}_r(\mathbf{d}_k, \mathbf{S}_k)$ density, where $\mathbf{S}_k = (\mathbf{S}_{k0} + \mathbf{W}^T\mathbf{O}_k\mathbf{W})^{-1}$, $\mathbf{O}_k = \text{Diag}(w_{k1}, ..., w_{kn})$, $\mathbf{d}_k = \mathbf{S}_k(\mathbf{S}_{k0}\mathbf{d}_{k0} + \mathbf{W}^T\mathbf{O}_k\mathbf{U}_k^*)$, and $\mathbf{W}$ is the $n \times r$ matrix of multinomial logit regression covariates such that the i^{th} row of $\mathbf{W}$ is $\mathbf{w}_i$.

Lastly, we update $z_1, ..., z_n$ by first computing $\boldsymbol{\pi}_i = (\pi_{1i}, ..., \pi_{Ki})$ as

$$\pi_{ki} = \frac{\text{e}^{\mathbf{w}_i\boldsymbol{\delta}_k}}{1 + \sum_{h=1}^{K-1}\text{e}^{\mathbf{w}_i\boldsymbol{\delta}_h}},$$

for $i = 1, ...n$ and $k = 1, ..., K$. We also compute, according to the multivariate normal density of $\mathbf{y}_i|t_i$, the probability $P(\mathbf{y}_i|\boldsymbol{\zeta}_{ki}^*, \boldsymbol{\Sigma}_k)$, where $\boldsymbol{\zeta}_{ki}^* = \mathbf{x}_i^*\boldsymbol{\beta}_k^*$. We use these quantities to compute $\boldsymbol{\upsilon}_i = (\upsilon_{1i}, ..., \upsilon_{Ki})$, where

$$\upsilon_{ki} = P(z_i = k|\mathbf{y}_i, \boldsymbol{\zeta}_{ki}^*, \boldsymbol{\Sigma}_k) = \frac{\pi_{ki}P(\mathbf{y}_i|\boldsymbol{\zeta}_{ki}^*, \boldsymbol{\Sigma}_k)}{\sum_{h=1}^{K}\pi_{hi}P(\mathbf{y}_i|\boldsymbol{\zeta}_{hi}^*, \boldsymbol{\Sigma}_h)}.$$

The cluster labels z_i are then updated from a $\text{Multinomial}(1, \boldsymbol{\upsilon}_i)$ density for $i = 1, ...n$. A schematic outline of the Gibbs sampler is given in the Web Appendix B. An `R` package for implementing the proposed model is currently in developlment. We provide `R` scripts for implementing the simulations and applications described below at `carter-allen.github.io/MVSN-FMM/`.

3.4.3 *Assessment of MCMC Convergence, Label Switching, and Model Selection.* We monitor convergence of the MCMC algorithm through the use of standard approaches such as

~~investigation of~~ trace plots and Geweke's (1992) Z-diagnostic, implemented in the `R` package `coda` (Plummer et al. 2006). In simulation studies under realistic parameter settings, we observed relatively fast convergence of all MCMC chains (i.e., within 1,000 iterations).

A common challenge for Bayesian mixture models is ~~the so-called~~ "label switching" ~~problem~~, in which draws of cluster-specific parameters may be ~~assigned~~ different cluster labels at various points during the MCMC simulation, rendering summaries of class-specific parameters incoherent. ~~After conducting simulation studies under a wide variety of realistic parameter settings, as detailed in Sections 4 and 5, we found little evidence of label switching in posterior draws of the model parameters.~~ When label switching was observed, we implemented *post hoc* relabling algorithms ~~as described in Papastamoulis 2016 and~~ implemented in the `label.switching` package in `R` (Papastamoulis 2016).

Because our primary objective is to identify a small number of clinically meaningful motor development clusters, we use Bayesian model selection criteria to choose the optimal K from among a small number of possible values (e.g., $K = 1, ...4$). To this end, we propose the use of the "widely applicable information criterion" (WAIC) introduced by Watanabe (2010) for model selection. WAIC has the desireable property of penalizing complexity in models – a feature congruent with our goal of explaining infant motor development heterogeneity with a parsimonious number of clusters. See Gelman et al. (2014) for a detailed discussion of WAIC and comparison to other popular model fit criteria, such as DIC. In Section 4, we show through a simulation study that this approach recovered the true value of K under realistic parameter settings.

4. Simulation Studies

4.1 *Simulation to Compare to Multivariate Normal*

Our first simulation study compares the MSN mixture model to a multivariate normal mixture model, with the primary goal being to validate our parameter estimation scheme in a setting that resembles the Nurture data. Our secondary goal is to investigate to what degree ignoring skewness in outcome components leads to poor posterior inferences. To emulate the Nurture study, we consider the following generative model

$$f(\mathbf{y}_i) = \sum_{k=1}^{3} \pi_{ki} f(\mathbf{y}_i|\boldsymbol{\theta}_k),$$

where $\boldsymbol{\theta}_k$ is the set of all parameters specific to cluster k for $k \in \{1, 2, 3\}$, and $\mathbf{y}_i|\boldsymbol{\theta}_k \sim \text{MSN}_4(\boldsymbol{\zeta}_{ki}, \boldsymbol{\alpha}_k, \boldsymbol{\Omega}_k)$, where $\boldsymbol{\zeta}_{ki} = (\zeta_{ki1}, \zeta_{ki2}, \zeta_{ki3}, \zeta_{ki4}) = \mathbf{x}_i\boldsymbol{\beta}_k$. We note from the above model specification that the number of clusters $K = 3$ and the number of measurement occasions $J = 4$. For the MSN regression model, we fit a main effect for time (i.e., measurement occasion) in addition to a baseline covariate, whose value does not vary with time, but whose effect does vary with time. Under this setting with $p = 2$ covariates, the design matrix $\mathbf{x}_i$ for subject i and the matrix of regression coefficients for cluster k, $\mathbf{B}_k$ are structured as

$$\mathbf{x}_i = \begin{bmatrix} 1 & 0 & 0 & 0 & x_i & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & x_i & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & x_i & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & x_i \end{bmatrix}, \text{ and } \mathbf{B}_k = \begin{bmatrix} \beta_{k11} & \beta_{k12} \\ \beta_{k21} & \beta_{k22} \\ \beta_{k31} & \beta_{k32} \\ \beta_{k41} & \beta_{k42} \end{bmatrix},$$

where $\text{vec}(\mathbf{B}_k) = \boldsymbol{\beta}_k$. Thus, for subject i in cluster k, the $J = 4$ measurements have location parameters given by

$$\begin{aligned}
\zeta_{ki1} &= \beta_{k11} + \beta_{k12} x_i \\
\zeta_{ki2} &= \beta_{k21} + \beta_{k22} x_i \\
\zeta_{ki3} &= \beta_{k31} + \beta_{k32} x_i \\
\zeta_{ki4} &= \beta_{k41} + \beta_{k42} x_i.
\end{aligned} \tag{14}$$

For cluster k, we collect all observations $\mathbf{y}_i$ $(i = 1, ..., n_k)$ into the $n_k \times 4$ matrix $\mathbf{Y}_k$ and all covariates ~~$\mathbf{x}_i$~~ into the $4n_k \times 8$ matrix $\mathbf{X}_k$ to utilize the matrix normal model specification detailed in Section 3, which allows for simultaneous updates of all MSN regression parameters in cluster k. For the multinomial regression model component of this simulation, we model the class labels z_i as a function of an intercept and one baseline covariate, ~~thus~~ $r = 2$. We leave the problem of missing data to simulation study ~~#2~~ and do not introduce missing data into this simulation.

~~For our~~ second goal in this simulation ~~–~~ to compare model performance when skewness is accounted for to model performance when skewness is ignored, we fit both the proposed MSN finite mixture model as well as a classic multivariate normal finite mixture model to data generated from an MSN distribution. We evaluate model fit in terms of absolute difference of parameter estimates as well as WAIC.

4.2 *Simulation to Compare Imputation Methods*

In ~~our~~ second simulation study, we compare our online conditional imputation approach to ~~standard~~ Bayesian multiple imputation ~~as defined in Gelman et al. (2013). For an argument against the use of data-discarding approaches such as available case analysis (ACA) or complete case analysis (CCA), we defer to Gelman and Hill (2006).~~ Our goal ~~with this simulation~~ is to demonstrate that our proposed online conditional imputation method performs ~~as well~~

as, if not better than standard Bayesian multiple imputation with respect to accuracy of parameter estimates. If the performance of the two imputation methods are held equal, we argue that our online conditional imputation method is preferable due to its computational efficiency and avoidance of a burdensome and often error-prone parameter aggregation step in the analysis.

To demonstrate the advantages of our proposed imputation method, we first generate $n = 1,000$ observations from a simple three-cluster ($K = 3$) MSN mixture model with $J = 4$ repeated measurements, one main effect for time ($p = 1$), and two multinomial regression predictors ($r = 2$). We then artificially ampute the simulated data using the `ampute` function provided by the `mice` package in `R` (Van Buuren and Groothuis-Oudshoorn 2010). Amputation occurs according to the missing at random (MAR) mechanism, whereby the occurence of missing data depends only on the values of the observed data (Gelman and Hill 2006). Additionally, we perform data amputation to simulatute intermittent missingness, as is consistent with the Nurture data. To this end, we specify that each of the 4 repeated measures for a given individual are equally likely to be missing. To further approximate the Nurture data, we set the frequency of missing data at each measurement occaision to be 30%. We fit our proposed MSN finite mixture model to the amputed data with an implementation of both our proposed online conditional imputation step and standard Bayesian multiple imputation as defined by Gelman et al. (2013).

4.3 *Simulation to Assess Sensitivity to Misspecified K*

Our final simulation is concerned with validating the use of WAIC for determining the number of clusters K. To this end, we simulate data from the same MSN mixture as in simulation study #2, that is – we simulate data from a $K = 3$ cluster model and fit MSN mixtures of $K \in \{2, 3, 4\}$, comparing the WAIC under each setting of K.

Need to start this simulation before writing more.

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
- Discuss other label switching approaches
- Discuss skew-t?

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7. Appendix

Put your final comments here.

Acknowledgements

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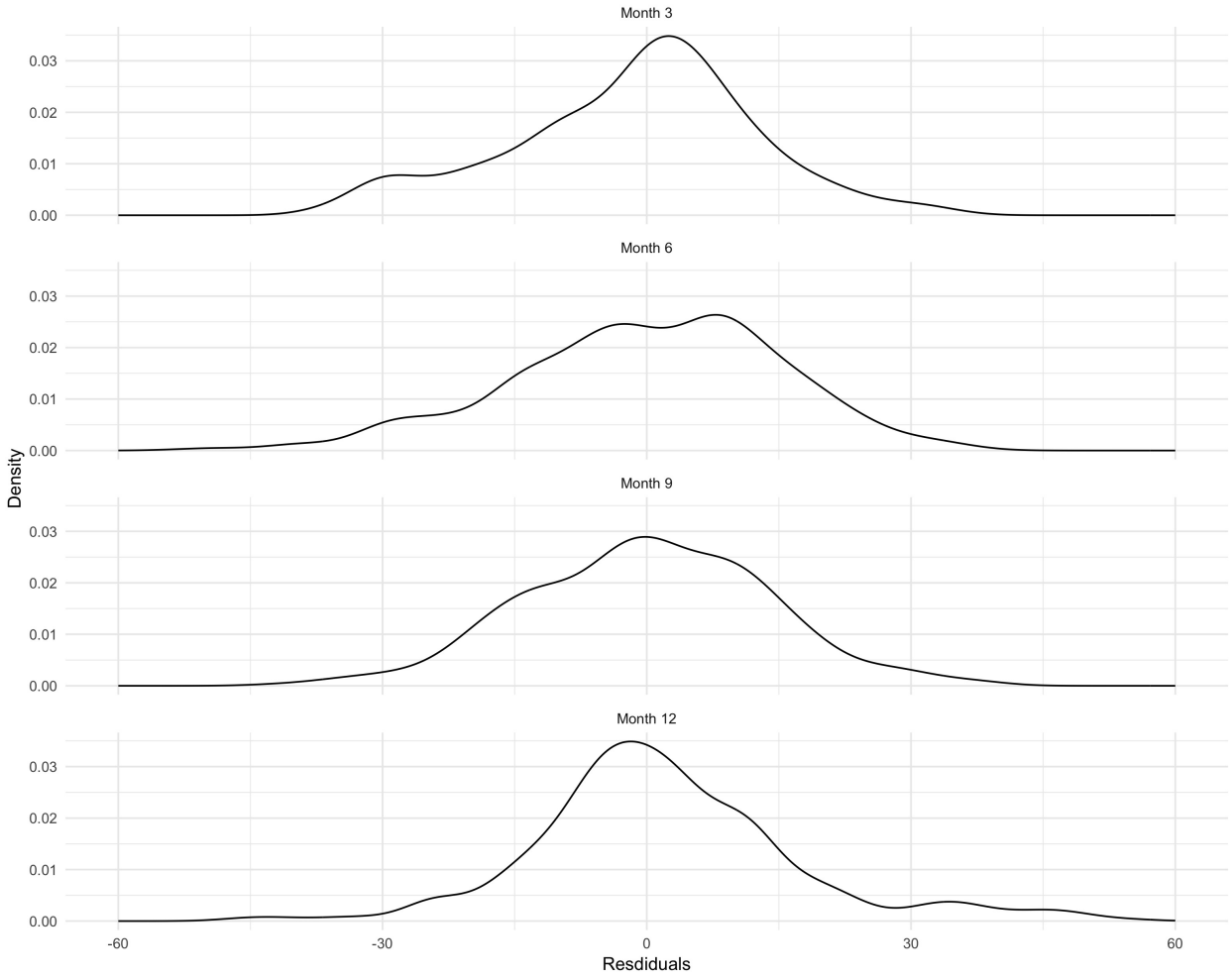
Month 3
Month 6
Month 9
Month 12
Density
0.00
0.01
0.02
0.03
-60
-30
0
30
60
Resdiduals