

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 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

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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.

KEY WORDS: A key word; But another key word; Still another key word; Yet another key word.

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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), however in these models, focus lies primary on marginal density estimation and inference on the mixture components (i.e. clusters) is 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, parameter estimation 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, namely the ability to incorporate prior information into a model and make posterier 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.

Put lit review of Bayesian PG multinomial logistic regression here

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 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.

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 Generic Mixture

Let \mathbf{y}_i be the $J \times 1$ observation vector for subject i such that y_{ij} is the observation for subject i at timepoint j . We assume for now that \mathbf{y}_i is fully observed. Later, we relax this assumption by allowing for missingness in the components of \mathbf{y}_i . The general formulation of the multivariate skew normal mixture model is as follows.

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

Here $\boldsymbol{\theta}_k$ is the set of parameters shared by subjects belonging to class k ($k = 1, \dots, K$). The probability of subject i ($i = 1, \dots, n$) belonging to class k ($k = 1, \dots, K$) is denoted π_{ik} . Note that π_{ik} is not indexed by time and we do not allow for subjects switching classes over the study period. This feature of the model is a result of our interest in clustering based on development patterns rather than time-specific development scores. Later, we detail a multinomial logit regression model placed on π_{ik} to allow for flexible modeling of class membership probabilities as a function of covariates of interest.

In each development class, we assume that a subject's $J \times 1$ outcome vector follows a multivariate skew normal (MSN) distribution. We define a latent variable $Z_i \in \{1, \dots, K\}$ to denote the cluster membership of subject i for $i = 1, \dots, n$. We model $\mathbf{y}_i | Z_i$ as

$$\mathbf{y}_i | Z_i = k \sim MSN_J(\boldsymbol{\zeta}_k, \boldsymbol{\alpha}_k, \boldsymbol{\Omega}_k)$$

where $\boldsymbol{\zeta}_k$ is a $J \times 1$ vector of class specific location parameters, $\boldsymbol{\alpha}_k$ is a $J \times 1$ vector of class specific skewness parameters, and $\boldsymbol{\Omega}_k$ is a $J \times J$ class specific scale matrix.

3.2 Multivariate Skew Normal Regression

We model the effect of covariates on longitudinal development outcomes through the use of a MSN regression model. We adopt a standard stochastic representation of a MSN random variable as the sum of a latent truncated normal random effect and a correlated multivariate normal random error term. The MSN stochastic representation is as follows.

$$\mathbf{y}_i = \boldsymbol{\beta}^T \mathbf{x}_i + t_i \boldsymbol{\psi} + \boldsymbol{\epsilon}_i$$

where \mathbf{x}_i is the $P \times 1$ vector of covariate values for subject i , $\boldsymbol{\beta}$ is the $P \times J$ vector of fixed effects coefficients, $t_i \stackrel{iid}{\sim} N_{[0,\infty)}(0, 1)$ is a conditional truncated normal random effect, $\boldsymbol{\psi}$ is the $J \times 1$ vector containing cluster-specific skewness parameters, and $\boldsymbol{\epsilon}_i \sim N_J(0, \boldsymbol{\Sigma}_{J \times J})$ is the correlated error term. It can be shown that under these conditions \mathbf{y}_i is multivariate skew normal with location. For conciseness, we present the MSN distribution here outside of the finite mixture context. When using this stochastic representation in our finite mixture model, the parameters $\boldsymbol{\beta}$, $\boldsymbol{\psi}$, and $\boldsymbol{\Sigma}$ are replaced with class-specific counterparts $\boldsymbol{\beta}_k$, $\boldsymbol{\psi}_k$, and $\boldsymbol{\Sigma}_k$.

3.3 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-augmentation to allow for updating of all parameters using Gibbs sampling. The multinomial logit model is as follows for $k = 1, \dots, K$.

$$P(Z_i = k | \mathbf{w}_i) = \pi_{ik} = \frac{e^{\mathbf{w}_i^T \boldsymbol{\delta}_k}}{\sum_{k'=1}^K e^{\mathbf{w}_i^T \boldsymbol{\delta}_{k'}}}$$

where \mathbf{w}_i is the vector of class probability covariates for subject i , $\boldsymbol{\delta}_k$ contains the multinomial regression parameters for class k , and K is the number of putative clusters specified *a priori*. For identifiability purposes, we fix the reference category $k = K$ and set $\boldsymbol{\delta}_K = \mathbf{0}$.

$$P(Z_i = k | \mathbf{w}_i, \boldsymbol{\delta}_k) = \begin{cases} \pi_{ik} = \frac{e^{\mathbf{w}_i^T \boldsymbol{\delta}_k}}{1 + \sum_{k'=1}^{K-1} e^{\mathbf{w}_i^T \boldsymbol{\delta}_{k'}}} & k < K \\ \pi_{ik} = \frac{1}{1 + \sum_{k'=1}^{K-1} e^{\mathbf{w}_i^T \boldsymbol{\delta}_{k'}}} & k = K \end{cases}$$

Under this model, $Z_i | \mathbf{w}_i \sim \text{Multinom.}(1, \boldsymbol{\pi}_i)$, where $\boldsymbol{\pi}_i = (\pi_{i1}, \dots, \pi_{iK})$

During MCMC estimation, the class labels z_i are updated from their multinomial full conditional distribution and used in the remaining MCMC steps as class assignments.

3.4 Conditional MVN 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

$$\mathbf{y}_i | Z_i, \mathbf{x}_i, t_i, \boldsymbol{\beta}_{Z_i}, \boldsymbol{\psi}_{Z_i}, \boldsymbol{\Sigma}_{Z_i} \sim N_J(\boldsymbol{\beta}_{Z_i}^T \mathbf{x}_i + t_i \boldsymbol{\psi}_{Z_i}, \boldsymbol{\Sigma}_{Z_i})$$

This allows us to appeal to standard conditional forms of the multivariate normal distribution to specify the distribution of missing observations. For subject i , we use q_i to denote the number of the total J possible repeated measurements are missing. We partition the full $J \times 1$ outcome vector \mathbf{y}_i into the $(J - q_i) \times 1$ observed data vector \mathbf{y}_i^{obs} and the $q_i \times 1$ missing data vector \mathbf{y}_i^{miss} . $Y_i = [Y_{i_{q \times 1}}^{miss} | Y_{i_{k-q \times 1}}^{obs}]^T$. We have

$$\mathbf{y}_i^{miss} | \mathbf{y}_i^{obs}, \mathbf{x}_i, t_i, Z_i, \boldsymbol{\beta}_{Z_i}, \boldsymbol{\psi}_{Z_i}, \boldsymbol{\Sigma}_{Z_i} \sim N(\boldsymbol{\mu}^{miss}, \boldsymbol{\Sigma}^{miss})$$

where $\boldsymbol{\mu}^{miss}$ and $\boldsymbol{\Sigma}^{miss}$ take standard forms detailed in the Appendix.

An attractive feature of this imputation approach is that 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.

Discuss non-ignorable missingness here

3.5 *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.

3.5.1 *Prior Choice.*

3.5.2 *MCMC Algorithm.*

3.5.3 *Assessment of MCMC Convergence.*

3.5.4 *Label Switching.*

Algorithm 1 Gibbs Sampler

Define n_{iter} ; n_{burn} ; K ; θ_{init} ; θ_0
 $n_{sim} := n_{iter} - n_{burn}$
 $\theta := \theta_{init}$
for $\iota = 1, \dots, n_{sim}$ **do**
 I. CONDITIONAL IMPUTATION
 for $i = 1, \dots, n$ **do**
 Draw \mathbf{y}_i^{miss} from $N_q(\boldsymbol{\mu}_i^{miss}, \boldsymbol{\Sigma}_i^{miss})$
 $\mathbf{y}_i := \mathbf{y}_i^{miss} \cup \mathbf{y}_i^{obs}$
 end for
 II. MSN REGRESSION
 for $k = 1, \dots, K$ **do**
 $n_k := \sum_{i=1}^n \mathbb{1}_{Z_i=k}$
 for $i_k = 1, \dots, n_k$ **do**
 Draw t_i from $N_{[0,\infty)}(a_i, A)$
 end for
 $\mathbf{X}_k^* := \text{cbind}(\mathbf{X}_k, \mathbf{t}_k)$
 Draw \mathbf{B}_k^* from $\text{MatNorm}(\mathbf{B}_k, \mathbf{L}_k^{-1}, \boldsymbol{\Sigma}_k)$
 Draw $\boldsymbol{\Sigma}_k$ from $\text{InvWish}(\nu_k, \mathbf{V}_k)$
 end for
 III. MULTINOMIAL LOGIT
 for $i = 1, \dots, n$ **do**
 for $k = 1, \dots, K$ **do**
 $\pi_{ik} := P(Z_i = k | \mathbf{w}_i, \boldsymbol{\delta}_k)$
 $p_{ik} := P(\mathbf{y}_i | \boldsymbol{\beta}_k^{*T} \mathbf{x}_i^*, \boldsymbol{\Sigma}_k)$
 end for
 $\mathbf{p}_{Z_i} := \frac{\mathbf{p}_i \odot \boldsymbol{\pi}_i}{\mathbf{p}_i \cdot \boldsymbol{\pi}_i}$
 Draw Z_i from $\text{Categorical}(\mathbf{p}_{Z_i})$
 for $k = 1, \dots, K - 1$ **do**
 Draw $\boldsymbol{\delta}_k$ from $N(\mathbf{M}, \mathbf{S})$
 end for
 end for
 $\theta := \{\mathbf{B}^*, \boldsymbol{\Sigma}, \mathbf{Z}, \boldsymbol{\delta}\}$
 Store θ
end for

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 Misspecified 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.

ACKNOWLEDGEMENTS

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 j^{th} outcome observed for subject i , where $i = 1, \dots, n$ and $j = 1, \dots, J$.
- **X**: A $n \times p$ matrix containing all multivariate skew-normal regression covariates such that x_{ij} is the j^{th} covariate value for subject i .
- **B**: A $m \times p$ matrix containing all multivariate skew-normal regression coefficients such that $\mathbf{B} = [\beta_1, \dots, \beta_p]$, where β_{ij} is interpreted as the effect of covariate i on outcome j for $i = 1, \dots, m$ and $j = 1, \dots, p$.
- **E**: A $n \times p$ matrix of error terms in the multivariate skew-normal regression model component. **E** is made up of row vectors $\epsilon_i = (\epsilon_{i1}, \dots, \epsilon_{ip})$, where $\epsilon_i \stackrel{iid}{\sim} N_p(0, \Sigma)$ for $i = 1, \dots, n$.
- **Σ**: A $p \times p$ covariance matrix that defines the correlation between the p multivariate normal outcomes.
- **Ω**: A $p \times p$ covariance scale matrix that defines the correlation between the p multivariate skew-normal outcomes.
- **ψ**: A $p \times 1$ vector containing the skewness parameter for each outcome.
- **α**: 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 $i = 1, \dots, n$, $t_i \stackrel{iid}{\sim} T_{[0, \infty)}(0, 1)$
- **X***: A $n \times (m + 1)$ matrix constructed by column binding **t** to **X**
- **B***: A $(m + 1) \times p$ matrix constructed by row binding ψ^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.

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

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 $t_i \stackrel{iid}{\sim} T_{[0,\infty)}(0, 1)$ and that \mathbf{E} is made of row vectors $\boldsymbol{\epsilon}_i = (\epsilon_{i1}, \dots, \epsilon_{ip})$ for $i = 1, \dots, n$, where $\boldsymbol{\epsilon}_i \stackrel{iid}{\sim} N_p(0, \boldsymbol{\Sigma})$.

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.

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

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

We now derive the joint posterior distribution of the parameters \mathbf{B}^* and Σ .

$$\begin{aligned}
p(\mathbf{B}^*, \Sigma | \mathbf{X}^*, \mathbf{Y}) &\propto p(\mathbf{Y} | \mathbf{X}^*, \mathbf{B}^*, \Sigma) p(\mathbf{B}^* | \Sigma) p(\Sigma) \\
&\propto |\Sigma|^{-n/2} \exp \left\{ -\frac{1}{2} \text{tr} [(\mathbf{Y} - \mathbf{X}^* \mathbf{B}^*)^T (\mathbf{Y} - \mathbf{X}^* \mathbf{B}^*) \Sigma^{-1}] \right\} \\
&\times |\Sigma|^{-(m+1)/2} \exp \left\{ -\frac{1}{2} \text{tr} [(\mathbf{B}^* - \mathbf{B}_0^*)^T \mathbf{L}_0 (\mathbf{B}^* - \mathbf{B}_0^*) \Sigma^{-1}] \right\} \\
&\times |\Sigma|^{(\nu_0 + p + 1)/2} \exp \left\{ -\frac{1}{2} \text{tr} (\mathbf{V}_0 \Sigma^{-1}) \right\}
\end{aligned}$$

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 practice, the data and parameters in this section would be replaced by cluster specific estimates in the case of clustering.

For a given observation vector $\mathbf{y} \sim N_p(\boldsymbol{\mu}, \Sigma)$, 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 Σ as follows.

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

We will use these quantities to derive the conditional distribution $f(\mathbf{y}_1|\mathbf{y}_2, \boldsymbol{\mu}, \boldsymbol{\Sigma})$.

$$\begin{aligned}
f(\mathbf{y}_1|\mathbf{y}_2, \boldsymbol{\mu}, \boldsymbol{\Sigma}) &\propto f(\mathbf{y}_1, \mathbf{y}_2|\boldsymbol{\mu}, \boldsymbol{\Sigma}) \\
&\propto \exp \left\{ -\frac{1}{2}(\mathbf{y} - \boldsymbol{\mu})^T \boldsymbol{\Sigma}^{-1}(\mathbf{y} - \boldsymbol{\mu}) \right\} \\
&= \exp \left\{ -\frac{1}{2} \begin{bmatrix} \mathbf{y}_1 - \boldsymbol{\mu}_1 \\ \mathbf{y}_2 - \boldsymbol{\mu}_2 \end{bmatrix}^T \boldsymbol{\Sigma}^{-1} \begin{bmatrix} \mathbf{y}_1 - \boldsymbol{\mu}_1 \\ \mathbf{y}_2 - \boldsymbol{\mu}_2 \end{bmatrix} \right\} \\
&= \exp \left\{ -\frac{1}{2} \begin{bmatrix} \mathbf{y}_1 - \boldsymbol{\mu}_1 \\ \mathbf{y}_2 - \boldsymbol{\mu}_2 \end{bmatrix}^T \begin{bmatrix} \boldsymbol{\Sigma}_{11} & \boldsymbol{\Sigma}_{12} \\ \boldsymbol{\Sigma}_{21} & \boldsymbol{\Sigma}_{22} \end{bmatrix}^{-1} \begin{bmatrix} \mathbf{y}_1 - \boldsymbol{\mu}_1 \\ \mathbf{y}_2 - \boldsymbol{\mu}_2 \end{bmatrix} \right\} \\
&= \exp \left\{ -\frac{1}{2} \begin{bmatrix} \mathbf{y}_1 - \boldsymbol{\mu}_1 \\ \mathbf{y}_2 - \boldsymbol{\mu}_2 \end{bmatrix}^T \begin{bmatrix} \boldsymbol{\Sigma}_{11}^* & \boldsymbol{\Sigma}_{12}^* \\ \boldsymbol{\Sigma}_{21}^* & \boldsymbol{\Sigma}_{22}^* \end{bmatrix} \begin{bmatrix} \mathbf{y}_1 - \boldsymbol{\mu}_1 \\ \mathbf{y}_2 - \boldsymbol{\mu}_2 \end{bmatrix} \right\} \\
&= \exp \left\{ -\frac{1}{2} [(\mathbf{y}_1 - \boldsymbol{\mu}_{cond})^T \boldsymbol{\Sigma}_{cond}^{-1}(\mathbf{y}_1 - \boldsymbol{\mu}_{cond})] \right\} \\
&\Rightarrow \mathbf{y}_1|\mathbf{y}_2, \boldsymbol{\mu}, \boldsymbol{\Sigma} \sim N_q(\boldsymbol{\mu}_{cond}, \boldsymbol{\Sigma}_{cond})
\end{aligned}$$

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

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

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

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

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

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

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