Latent Factor Regression Models for Grouped Outcomes

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Outline

Overview

- Multiple-outcome regression models pool information across outcomes, for higher power to detect a covariate effect
- Two traditional approaches:
  - **Random effect models:** random effects induce correlations between outcomes (cf. Sammel, Lin, & Ryan 1999; Roy, Lin, & Ryan 2003)
  - **Latent factor models:** continuous latent variables manifested by outcomes (cf. Muthén 2002; Sanchez et al. 2005)
- Our focus: **Multiple outcomes nested in domains** such as motor function, intelligence, and attention
- Motivating example: Relating sexually dimorphic traits in male infants to factors including exposure to phthalates (industrial chemicals)

Overview

- We show **the random effect models are a special case of the continuous latent factor framework, even when the multiple outcomes are nested in domains**
- Not surprising since the continuous latent factor framework is extremely general, and non-identifiable in unrestricted case.
- Allows us to view modeling options as a spectrum between parsimonious random effect models and flexible latent factor models
- We **introduce a set of models along this spectrum, and show that they are identifiable**

Overview

- **Gives a set of general-purpose tools for modeling and sensitivity analysis in the case of outcomes nested in domains**
- Yields estimates of the exposure/covariate effect both at the domain and outcome levels
- Shares information across outcomes, in part by **shrinkage of the estimated effect across outcomes**.
- Models **differ in degree of shrinkage**

Modeling Grouped Outcomes

Random effect regression model for outcomes nested in domains

(Thurston, Ruppert, Davidson 2009). Subjects $i \in \{1, \ldots, n\}$, (standardized) outcomes $j \in \{1, \ldots, p\}$:

$$Y_{ij} = (\mathbf{b}_{o,j} + \mathbf{b}_{\mathcal{D},d(j)} + \mathbf{b})\mathbf{X}_i + \phi_i + \psi_{i,d(j)} + \epsilon_{ij}$$

$d(j) \in \{1, \ldots, D\}$: domain of outcome j
$\mathbf{b}$: common covariate effect
$\mathbf{b}_{\mathcal{D},d(j)}$: random domain-level covariate effect
$\mathbf{b}_{o,j}$: random outcome-level covariate effect
ϕ_i: subject random effect
$\psi_{i,d(j)}$: subject-domain random effect

Modeling Grouped Outcomes

$$Y_{ij} = (\mathbf{b}_{o,j} + \mathbf{b}_{\mathcal{D},d(j)} + \mathbf{b})\mathbf{X}_i + \phi_i + \psi_{i,d(j)} + \epsilon_{ij}$$

- Captures positive correlation between outcomes even after accounting for covariates
- Shrinks covariate effect across domains and across outcomes within a domain

Modeling Grouped Outcomes

Continuous latent factor framework (non-identifiable)
(cf. Sammel & Ryan 1996; Muthén 2002; Sanchez et al. 2005)

$$\mathbf{Y}_i = \boldsymbol{\alpha} + \boldsymbol{\beta}_o \mathbf{X}_i + \boldsymbol{\Lambda}\boldsymbol{\xi}_i + \boldsymbol{\epsilon}_i$$
$$\boldsymbol{\xi}_i = \boldsymbol{\beta}_{\mathcal{D}} \mathbf{X}_i + \mathbf{B}\boldsymbol{\xi}_i + \boldsymbol{\zeta}_i.$$

$\mathbf{Y}_i$: outcomes vector
$\boldsymbol{\beta}_o$, $\boldsymbol{\beta}_{\mathcal{D}}$: regression coefficients matrices
$\boldsymbol{\Lambda}$: factor loadings matrix
$\boldsymbol{\xi}_i$: latent factors vector
$\mathbf{B}$: matrix relating latent factors
$\boldsymbol{\epsilon}_i$, $\boldsymbol{\zeta}_i$: independent residuals

Modeling Grouped Outcomes

- Take the # latent factors = D
- Take nonzero elements of $\mathbf{\Lambda}$ to be the $(j, d(j))$ elements. E.g., with $D = 2$ and $p = 4$ where $d(1) = d(2) = 1$ and $d(3) = d(4) = 2$ then

$$\mathbf{\Lambda} = \begin{pmatrix} \lambda_1 & \lambda_2 & 0 & 0 \\ 0 & 0 & \lambda_3 & \lambda_4 \end{pmatrix}^T.$$

- Induce **B** by setting $\boldsymbol{\xi}_i = \boldsymbol{\beta}_{\mathcal{D}}\mathbf{X}_i + \phi_i + \boldsymbol{\psi}_i$

Yields

$$Y_{ij} = \alpha_j + \boldsymbol{\beta}_{o,j}\mathbf{X}_i + \lambda_j \xi_{i,d(j)} + \epsilon_{ij}$$
$$\xi_{ik} = \boldsymbol{\beta}_{\mathcal{D},k}\mathbf{X}_i + \phi_i + \psi_{ik}$$

Modeling Grouped Outcomes

$$
\begin{aligned}
Y_{ij} &= \alpha_j + \boldsymbol{\beta}_{o,j}\mathbf{X}_i + \lambda_j \xi_{i,d(j)} + \epsilon_{ij} \\
\xi_{ik} &= \boldsymbol{\beta}_{\mathcal{D},k}\mathbf{X}_i + \phi_i + \psi_{ik}
\end{aligned} \tag{1}
$$

- This model is identifiable so long as $\boldsymbol{\beta}_{o,j}$ are random effects and $\lambda_j = 1$ for the first outcome in each domain
- Additionally taking $\lambda_j = 1$ for all j and making $\boldsymbol{\beta}_{\mathcal{D},k}$ random effects yields the random effect model of Thurston et al. (2009)
- We investigate models of the form (1)

Modeling Grouped Outcomes

$$Y_{ij} = \alpha_j + \boldsymbol{\beta}_{o,j}\mathbf{X}_i + \lambda_j \xi_{i,d(j)} + \epsilon_{ij}$$
$$\xi_{ik} = \boldsymbol{\beta}_{\mathcal{D},k}\mathbf{X}_i + \phi_i + \psi_{ik}$$

- We obtained this from the latent factor framework by making assumptions about $\mathbf{\Lambda}$ and $\mathbf{B}$
- Contrast our choice of $\mathbf{B}$ (induce via subject random effect ϕ_i) with more standard choice: assign latent factors particular interpretations, like "motor function" and "intelligence", then manually select a small number of nonzero elements in $\mathbf{B}$ corresponding to hypothesized associations among the factors

Modeling Grouped Outcomes

$$Y_{ij} = \alpha_j + \boldsymbol{\beta}_{o,j}\mathbf{X}_i + \lambda_j \xi_{i,d(j)} + \epsilon_{ij}$$
$$\xi_{ik} = \boldsymbol{\beta}_{\mathcal{D},k}\mathbf{X}_i + \phi_i + \psi_{ik}$$

Our models (identifiable):

A. As above

B. Make $\boldsymbol{\beta}_{\mathcal{D},k}$ random effects

C. Like **A** but sets $\boldsymbol{\beta}_{o,j} = 0$

D. Like **C** but sets $\lambda_j = 1$ for all j

Use Bayesian inference and MCMC computation

Simulation Study

Vary:

- Models used to simulate & fit data
- sample size n
- # outcomes per domain
- factor loading (λ_j) values
- ...

Evaluate bias and RMSE for:

- domain-specific covariate effects $\beta_{\mathcal{D},k}$
- outcome-specific covariate effects $\text{OS}_j \triangleq \beta_{o,j} + \lambda_j \beta_{\mathcal{D},d(j)}$

Simulation Study

λ_j	Some $\lambda_j = 0.5$		All $\lambda_j = 1$						
Simulated	Model A		Model A			Model B		Model D	
Estimation	A	D	A	B	D	A	B	A	D
bias $\beta_{\mathcal{D},k}$	-.011	-.041	-.014	-.017	-.001	-.002	-.005	-.008	.000
bias OS_j	-.001	.002	-.005	-.005	-.003	.001	.000	-.004	-.001
RMSE $\beta_{\mathcal{D},k}$	.054	.063	.039	.041	.036	.039	.039	.033	.026
RMSE OS_j	.041	.061	.040	.040	.050	.040	.041	.035	.025

Even when the model is misspecified:

RMSE is an order of magnitude smaller than the parameter range (.5) for OS_j, and $\approx$5$\times$ smaller than the range (.2) for $\beta_{\mathcal{D},k}$

Bias is 2 orders of magnitude smaller than the range for OS_j and 5-25$\times$ smaller for $\beta_{\mathcal{D},k}$.

Simulation Study

λ_j	Some $\lambda_j = 0.5$		All $\lambda_j = 1$						
Simulated	Model A		Model A			Model B		Model D	
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bias $\beta_{\mathcal{D},k}$	-.011	-.041	-.014	-.017	-.001	-.002	-.005	-.008	.000
bias OS_j	-.001	.002	-.005	-.005	-.003	.001	.000	-.004	-.001
RMSE $\beta_{\mathcal{D},k}$	.054	.063	.039	.041	.036	.039	.039	.033	.026
RMSE OS_j	.041	.061	.040	.040	.050	.040	.041	.035	.025

The highest error occurs if we fit too simple of a model (D) when the data are simulated from a more complex model (A)

The lowest error occurs if the model is simple (D) and we fit the simple model (D)

Fitting Model B does not yield lower error than fitting Model A, even if the data are from Model B.

Study for Future Families

Study for Future Families:

Relate sexually dimorphic traits in male infants to factors including phthalate exposure

7 outcomes, in 3 domains:

- 4 skinfold thickness metrics
- body mass index and weight percentile-for-age
- head circumference percentile-for-age

Predictors including:

- phthalate score
- infant age
- gestational age
- mother's age & race

Study for Future Families

- Applied Models A, C, and D (Model B not appropriate because phthalate effect not hypothesized to be similar, or even have the same sign, in all domains)
- Find no evidence of a phthalate effect in any model
- Estimated covariate effects show differences between models

Study for Future Families

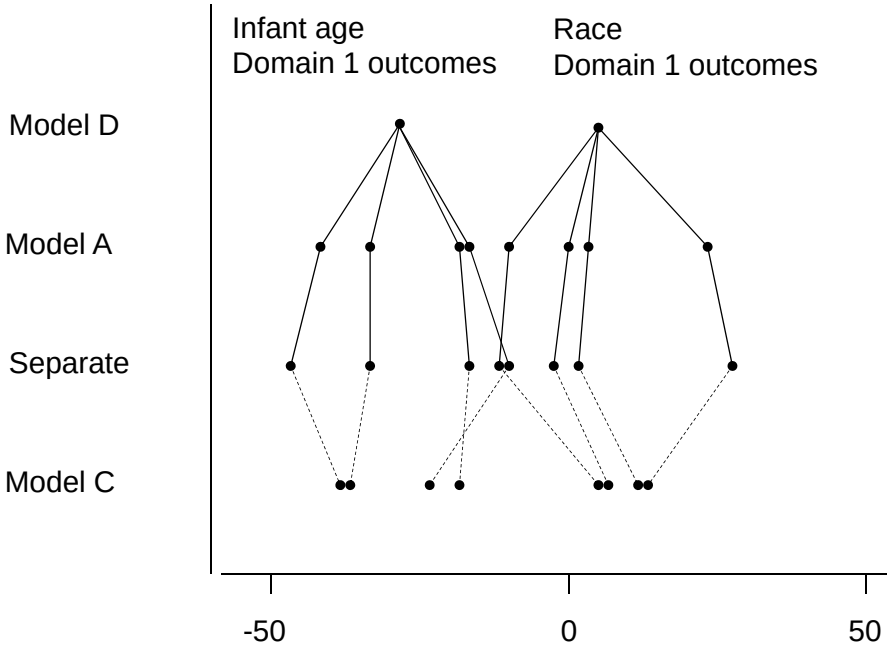
Model D coefficient estimates (common within a domain):

Covariate	Domain 1	Domain 2	Domain 3
Infant Age	$\mathbf{-28.0}$ $(\mathbf{-41.5}, \mathbf{-14.9})$	$\mathbf{-19.5}$ $(\mathbf{-36.0}, \mathbf{-3.3})$	16.1 $(-2.7, 34.9)$
Mother's Age	-11.3 $(-24.9, 1.9)$	0.13 $(-13.2, 13.4)$	9.97 $(-9.4, 29.5)$
Gestational Age	8.36 $(-4.9, 21)$	$\mathbf{18.1}$ $(\mathbf{2.0}, \mathbf{34.1})$	10.4 $(-8.3, 29.1)$
Race (Cauc./Non)	5.06 $(-7.9, 18.0)$	4.56 $(-8.1, 17.3)$	-12.3 $(-31.1, 6.4)$

- positive relationship between gest. age and BMI/weight
- negative relationship between infant age and both skinfold thickness and BMI/weight

Study for Future Families

Some coefficient point estimates ($\times$ 100) for Models A, C, D and separate regressions:



Model A estimates are shrunk relative to separate regressions, and Model D estimates are shrunk relative to Model A. Model C estimates are very different.

Study for Future Families

Although interval estimates get wider Model D $\rightarrow$ C $\rightarrow$ A, there are as many significant covariate effects in Models C & A as in D.

Slightly different set in Model A, which allows covariate effects to have different significance within a domain

Conclusions

- Showed that random-effect models for multiple outcomes nested in domains are a special case of the continuous latent factor framework
- Introduced identifiable models extending the random-effect models
- Simulations show excellent accuracy in point estimation of outcome-specific and domain-specific covariate effects, even in misspecified cases
- Applied to the Study for Future Families to understand factors relating to sexually dimorphic traits in male infants
- We recommend the use of Models A & D, which showed complementary strengths in the simulation study and different degrees of shrinkage in the data analysis

Paper available at: http://people.orie.cornell.edu/woodard/