Modeling multiple longitudinal outcomes

ADC Data Core meeting

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Section 1

Outline

Section 2

Introduction

Introduction

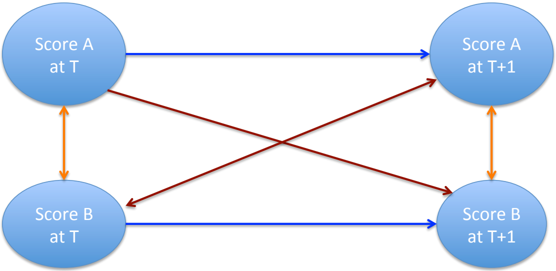
- When a single characteristic is measured longitudinally, we refer to *univariate* longitudinal data.
- A collection of multiple chracteristics measured at each moment in time is called *multivariate* longitudinal data.
- We will review the following multivariate longitudinal models:
  1. Shared random effects.
  2. Multivariate random effects

  and compare them with indepedent random effect models.
- We will present SAS codes and show results from each model.
- We will compare the models through simulations.

Section 3

Multivariate models

Relationships



Shared-parameter random-effects models

The shared parameter models may imply very strong assumptions for the association structure between outcomes. For example, let $\mathbf{Y}_{i1}$ and $\mathbf{Y}_{i2}$ be two longitudinal continuous outcomes that share a common random intercept

$$
\begin{aligned}
y_{i1t} &= \beta_1 + b_{1i} + \beta_2 t + e_{i1t} \qquad e_{i1t} \sim N(0, \sigma_1^2) \\
y_{i2t} &= \beta_3 + \gamma b_{1i} + \beta_4 t + e_{i2t} \qquad e_{i2t} \sim N(0, \sigma_2^2)
\end{aligned}
$$

with $\mathrm{Var}(b_{0i}) = \sigma_b^2$.Then

$$
\begin{aligned}
Corr(Y_{1s}, Y_{1t}) &= \frac{\sigma_b^2}{\sigma_b^2 + \sigma_1^2} \\
Corr(Y_{2s}, Y_{2t}) &= \frac{\gamma^2\sigma_b^2}{\gamma^2\sigma_b^2 + \sigma_2^2} \\
Corr(Y_{1s}, Y_{2t}) &= \frac{\gamma\sigma_b^2}{\sqrt{\sigma_b^2 + \sigma_1^2}\sqrt{\gamma^2\sigma_b^2 + \sigma_2^2}} \\
&= \sqrt{Corr(Y_{1s}, Y_{1t})}\sqrt{Corr(Y_{2s}, Y_{2t})}
\end{aligned}
$$

Multivariate random-effect models I

The joint random-effects imply more flexible correlation patterns. For example, we allow $\mathbf{Y}_{i1}$ and $\mathbf{Y}_{i2}$ to depend on separate random effects $\mathbf{b}_1$ and $\mathbf{b}_2$ which are themselves correlated.

$$\begin{aligned} y_{i1t} &= \beta_1 + b_{1i} + \beta_2 t + e_{i1t} \qquad e_{i1t} \sim N(0, \sigma_1^2) \\ y_{i2t} &= \beta_3 + b_{2i} + \beta_4 t + e_{i2t} \qquad e_{i2t} \sim N(0, \sigma_2^2) \end{aligned}$$

with $\begin{pmatrix} b_{1i} \\ b_{2i} \end{pmatrix} \sim \mathrm{N}(\mathbf{0}, \mathbf{G})$. Then

$$\begin{aligned} Corr(Y_{1s}, Y_{1t}) &= \frac{Var(b_1)}{Var(b_1) + \sigma_1^2} \\ Corr(Y_{2s}, Y_{2t}) &= \frac{Var(b_2)}{Var(b_2) + \sigma_2^2} \end{aligned}$$

Multivariate random-effect models II

$$
\begin{aligned}
Corr(Y_{1s}, Y_{2t}) &= \frac{Cov(b_1, b_2)}{\sqrt{Var(b_1) + \sigma_1^2}\sqrt{Var(b_2) + \sigma_2^2}} \\
&= \frac{Cov(b_1, b_2)}{\sqrt{Var(b_1)}\sqrt{Var(b_2)}} \frac{\sqrt{Var(b_1)}\sqrt{Var(b_2)}}{\sqrt{Var(b_1) + \sigma_1^2}\sqrt{Var(b_2) + \sigma_2^2}} \\
&= Corr(b_1, b_2)\sqrt{Corr(Y_{1s}, Y_{1t})}\sqrt{Corr(Y_{2s}, Y_{2t})} \\
&\leq \sqrt{Corr(Y_{1s}, Y_{1t})}\sqrt{Corr(Y_{2s}, Y_{2t})}
\end{aligned}
$$

This demonstrates explicitly the role of the correlation between the outcome-specific random effects in dictating the between-process outcome correlation at any two time points. Moreover, the restriction imposed by the shared-parameter model is relaxed in the sense that the model no longer assumes that the product of the within process correlations equals the between-process correlation, thus allowing a more general dependence structure.

Section 4

Results

Example dataset

Journal of Alzheimer's Disease 59 (2017) 251–263
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IOS Press

The Effect of Traumatic Brain Injury History with Loss of Consciousness on Rate of Cognitive Decline Among Older Adults with Normal Cognition and Alzheimer's Disease Dementia

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Study sample

- Case-control study using data from the NACC dataset using UDS visits between September 2005 and September 2014.
- The study sample was restricted to participants 50 years or older, with English as their primary language, available APOE genotype data, no history of alcohol or substance abuse, no reported TBI after their first visit and at least two UDS visits.
- The sample included 432 with normal cognition.

SAS code for independent random effect: Memory

```
title 'Memory: Independent random effects';
proc mixed data=tbi.normal_memory covtest;
class trauma_dich sex naccid test;
model outcome=test test*time test*trauma_dich
 test*sex test*educ test*demageb test*time*sex
test*time*educ test*time*demageb
test*time*trauma_dich/solution;
random test test*time/sub=naccid type=un G;
parms (1)  (0)(1)(0)(0)(1)(0)(0)(0)(1)(1)(1)/
hold=2,5,7,9;
repeated /type=VC grp=test sub=naccid;
run;
```

Covariance parameters for independent random effects

Estimated G Matrix							
Row	Effect	NACCID	Test	Col1	Col2	Col3	Col4
1	Test	NACC001008	LM:Delayed	0.3556		-0.05705	
2	Test	NACC001008	LM:Immediate		0.5933		-0.04761
3	time*Test	NACC001008	LM:Delayed	-0.05705		0.02050	
4	time*Test	NACC001008	LM:Immediate		-0.04761		0.02010

SAS code for independent random effect: Attention


```
title 'Attention: Independent random effects';
proc mixed data=tbi.normal_Attention covtest;
class trauma_dich sex naccid test;
model outcome=test test*time test*trauma_dich
 test*sex test*educ test*demageb test*time*sex
test*time*educ test*time*demageb
test*time*trauma_dich/solution;
random test test*time/sub=naccid type=un G;
parms (1) (0) (1) (0) (0) (1) (0) (0) (0) (1) (0) (0) (0) (0) (1)
 (0) (0) (0) (0) (0) (1) (0) (0) (0) (0) (0) (0) (1) (0) (0) (0) (0)
 (0) (0) (0) (1) (1) (1) (1) (1) /hold=2,4,5,7,8,9,12,13,14,
18, 19,20,22,23,25, 26,27,29,30,31,33,34,35;
repeated /type=VC grp=test sub=naccid;
run;
```

SAS code for multivariate random effect: Memory


```
title 'Memory: Multivariate model';
proc mixed data=tbi.normal_memory covtest;
class trauma_dich sex naccid test;
model outcome=test test*time test*trauma_dich
 test*sex test*educ test*demageb test*time*sex
test*time*educ test*time*demageb
test*time*trauma_dich/solution;
random test test*time/sub=naccid type=un G;
repeated /type=VC grp=test sub=naccid;
run;
```

Covariance parameters for multivariate random effects

Estimated G Matrix							
Row	Effect	NACCID	Test	Col1	Col2	Col3	Col4
1	Test	NACC001008	LM:Delayed	0.3599	0.4103	-0.05732	-0.05723
2	Test	NACC001008	LM:Immediate	0.4103	0.6152	-0.07146	-0.05953
3	time*Test	NACC001008	LM:Delayed	-0.05732	-0.07146	0.02449	0.02993
4	time*Test	NACC001008	LM:Immediate	-0.05723	-0.05953	0.02993	0.03292

SAS code for shared random effect: Memory

```
title 'Memory: shared random effects';
proc mixed data=tbi.normal_memory covtest;
class trauma_dich sex naccid test;
model outcome=test test*time test*trauma_dich
 test*sex test*educ test*demageb test*time*sex
test*time*educ test*time*demageb
test*time*trauma_dich/solution;
random intercept time/sub=naccid type=un;
repeated /type=VC grp=test sub=naccid;
run;
```

Covariance parameters for shared random effects

Estimated G Matrix				
Row	**Effect**	**NACCID**	**Col1**	**Col2**
1	Intercept	NACC001008	0.3818	-0.05752
2	time	NACC001008	-0.05752	0.02237

Covariance Parameter Estimates						
Cov Parm	**Subject**	**Group**	**Estimate**	**Standard Error**	**Z Value**	**Pr Z**
UN(1,1)	NACCID		0.3818	0.02991	12.77	<.0001
UN(2,1)	NACCID		-0.05752	0.008769	-6.56	<.0001
UN(2,2)	NACCID		0.02237	0.003834	5.83	<.0001
Residual	NACCID	Test LM:Delayed	0.09519	0.005969	15.95	<.0001
Residual	NACCID	Test LM:Immediate	0.3367	0.01617	20.83	<.0001

Parameter estimates

Domain	Test	Independent Random Effects Estimate (SE)	Independent Random Effects p-value	Multivariate Random Effects Estimate (SE)	Multivariate Random Effects p-value	Shared Random Effects Estimate (SE)	Shared Random Effects p-value
Memory	Logical Memory: Delayed	-0.005 (0.004)	0.2495	-0.004 (0.004)	0.383	-0.004 (0.004)	0.294
	Logical Memory: Immediate	-0.012 (0.005)	0.030	-0.010 (0.005)	0.055	-0.011 (0.006)	0.059
Attention	Digit Span: Backward	-0.002 (0.007)	0.811	-0.008 (0.0068)	0.214	-0.009 (0.006)	0.149
	Digit Span: Forward	0.000 (0.007)	0.987	-0.001 (0.007)	0.903	0.001 (0.007)	0.872
	TRAILS A	-0.074 (0.024)	0.002	-0.077 (0.023)	0.001	-0.029 (0.024)	0.183
	WAIS	-0.027 (0.010)	0.006	-0.030 (0.010)	0.002	-0.011 (0.010)	0.262
Language	Animals	-0.002 (0.006)	0.751	-0.004 (0.005)	0.411	-0.005 (0.005)	0.339
	Vegetables	-0.008 (0.006)	0.168	-0.006 (0.005)	0.299	-0.007 (0.006)	0.257
	Boston Naming Test	-0.015 (0.014)	0.292	-0.016 (0.014)	0.235	0.004 (0.015)	0.793

Fit statistics

	Independent Random Effects		Multivariate Random Effects		Shared Random Effects	
Domain	-2log lik	AIC	-2log lik	AIC	-2log lik	AIC
Memory	4353.6	4369.6	3933.9	3957.9	4141.9	4151.9
Attention	14672.8	14704.8	13716.8	13796.8	15228.0	15242
Language	10039.1	10063.1	9242.6	9290.6	10299.8	10311.8

Section 5

Simulations

Simulation Scheme

1. Select $n/2$ matched pairs with replacement.
2. Generate randomly a binary exposure with probability 40%
3. For a given effect of exposure calculate a new test score:

$$\text{New Test Score}_{it} = \text{Old Test Score}_{it} + \mathit{Effect}_i \times t$$

4. Run the following mixed effect models
   1. Independent random effects model
   2. Multivariate random effects model
   3. Shared random effects model
5. Repeat for 1000 times.

Simulation study results: Memory

Test		Independent Random Effects		Multivariate Random Effects		Shared Random Effects	
		Effect=0.01	Effect=0.07	Effect=0.01	Effect=0.07	Effect=0.01	Effect=0.07
LM: Delayed	Estimate	0.01	0.07	0.01	0.07	0.01	0.07
	RMSE	0.001	0.001	0.001	0.001	0.001	0.001
	power	7.5	82.4	6.3	82.0	6.5	81.6
	coverage	94.0	94.9	95.1	94.6	95.0	94.5
LM: Immediate	Estimate	0.01	0.07	0.01	0.07	g 0.01	0.07
	RMSE	0.001	0.001	0.001	0.001	0.001	0.001
	power	6.2	59.2	6.1	55.9	8.6	53.1
	coverage	95.2	94.2	94.8	93.9	92.2	92.2

Simulation study results: Language

Test		Independent Random Effects		Multivariate Random Effects		Shared Random Effects	
		Effect=0.01	Effect=0.07	Effect=0.01	Effect=0.07	Effect=0.01	Effect=0.07
Animals	Estimate	0.01	0.07	0.01	0.07	0.01	0.07
	RMSE	0.001	0.001	0.001	0.001	0.001	0.001
	power	7.3	56.2	8.2	58.8	6.3	58.9
	coverage	94.2	94.2	94.1	94.1	93.9	93.9
BNT	Estimate	0.01	0.07	0.01	0.07	g 0.01	0.07
	RMSE	0.003	0.003	0.003	0.003	0.003	0.003
	power	6.1	14.2	6.0	14.3	10.3	19.0
	coverage	94.2	94.2	94.5	94.5	89.7	89.7
Vegetables	Estimate	0.01	0.07	0.01	0.07	g 0.01	0.07
	RMSE	0.001	0.001	0.001	0.001	0.001	0.001
	power	6.7	53.3	7.6	59.8	5.1	54.0
	coverage	94.0	94.0	93.7	93.7	96.2	96.2

Section 6

Conclusions

Conclusions and further work

- Multivariate models for small number of characteristics are easy to implement in current software
- Multivariate models can be used to test hypotheses for cross-correlations over time between neuropsychological scores
- Despite the increased complexity of the models, no loss of power is evident.
- More research is needed for implementing models for a larger number of characteristics