Overview

1. Multivariate Models
   - GEE vs. GLMM
   - MANOVA vs. RM ANOVA

2. RM ANOVA Model

3. RM ANOVA Examples: SS & F-Tests

4. Sphericity
Familiar GLM, ANOVA assume independent residuals
- Correlated outcomes require multivariate extension
- Generalized Estimating Equations (GEE)
  - Only need mean model and working correlation matrix
  - Neither assumes nor estimates sources of variance
- Generalized Linear Mixed Model (GLMM)
  - Likelihood-based, need to specify random effects
  - In return, estimates variance due to each source
MANOVA vs. RM ANOVA

- ANOVA: Gaussian linear (mixed) model with categorical predictors
- How to extend to multivariate/correlated outcomes?
- Multivariate ANOVA (MANOVA)
  - Compares residual covariance matrix to model covariance
  - Allows multivariate outcomes across different scales
  - No assumptions about covariance except symmetric, pos. def.
  - Cost: More degrees of freedom $\rightarrow$ lower power
- Repeated Measures ANOVA (RM ANOVA)
  - Compares sums of squares including subject-level random effect
  - Only makes sense for repeated measures of same variable
  - Requires stronger assumptions about covariance matrix
  - Benefit: Greater power than MANOVA when assumptions are met
RM ANOVA (Mixed) Model:

\[ y_{ij} = \mu_{ij} + \pi_{ij} + e_{ij} \]

- \( y_{ij} \): continuous response of subject \( i = 1, \ldots, n \) at time \( j = 1, \ldots, t \)
- \( \mu_{ij} \): fixed population mean at time \( j \) for individuals like individual \( i \)
  - Includes covariates and (non-subject-specific) time effects
- \( \pi_{ij} \): random subject effect for subject \( i \) at time \( j \)
  - \( E(y_{ij} | \pi_{ij}) = \mu_{ij} + \pi_{ij} \)
- \( e_{ij} \): normally distributed random error for subject \( i \) at time \( j \)
- Crowder and Hand (1990) trichotomy:
  - \( \mu_{ij} \): "immutable constant of the universe"
  - \( \pi_{ij} \): "lasting characteristic of the individual"
  - \( e_{ij} \): "fleeting aberration of the moment"
RM ANOVA Model

Fundamental Assumptions:

- \( E(\pi_{ij}) = 0, \text{Var}(\pi_{ij}) = \sigma^2_{\pi j} \)
- \( E(e_{ij}) = 0, \text{Var}(e_{ij}) = \sigma^2_{e j} \)
- \( \text{Cov}(\pi_{ij}, \pi_{i'j'}) = \text{Cov}(\pi_{ij}, \pi_{i'j'}) = 0 \)
- \( \text{Cov}(\pi_{ij}, \pi_{ij'}) = \sigma_{\pi ij'} \text{ for } i \neq i', j \neq j' \)
- \( \text{Cov}(e_{ij}, e_{i'j'}) = 0 \text{ for } i \neq i', j \neq j' \)
- \( \text{Cov}(\pi_{ij}, e_{i'j'}) = 0 \text{ for all } i, i', j, j' \)
- Normality: \( \pi_{ij} \sim N(0, \sigma^2_{\pi j}), e_{ij} \sim N(0, \sigma^2_{e j}) \)

Common (but Not Necessary) Simplifying Assumptions:

- \( \sigma^2_{\pi j} = \sigma^2_{\pi} \text{ for all } j \)
- \( \sigma_{\pi jj'} \text{ constant for all } j, j' \)
- \( \sigma^2_{e j} = \sigma^2_{e} \text{ for all } j \)
Covariance:

\[
\text{Cov}(y_{ij}, y_{i'j'}) = E[(y_{ij} - \mu_{ij})(y_{i'j'} - \mu_{i'j'})]
= E[(\pi_{ij} + e_{ij})(\pi_{i'j'} + e_{i'j'})]
= E[\pi_{ij}\pi_{i'j'} + \pi_{ij} e_{i'j'} + e_{ij} \pi_{i'j'} + e_{ij} e_{i'j'}]
= E[\pi_{ij}\pi_{i'j'}] + 0 + 0 + E[e_{ij} e_{i'j'}]
= \begin{cases} 
\sigma^2_{\pi j} & \text{if } i = i', j = j' \\
\sigma_{\pi jj'} & \text{if } i = i', j \neq j' + \begin{cases} 
\sigma^2_{e j} & \text{if } i = i', j = j' \\
0 & \text{otherwise} 
\end{cases} \\
0 & \text{if } i \neq i'
\end{cases}
= \begin{cases} 
\sigma^2_{\pi j} + \sigma^2_{e j} & \text{if } i = i', j = j' \\
\sigma_{\pi jj'} & \text{if } i = i', j \neq j' \\
0 & \text{if } i \neq i'
\end{cases}
\]
Correlation:

- Observations are uncorrelated between subjects
- Within-subject (intraclass) correlation:
  \[
  \text{Corr}(y_{ij}, y_{ij'}) = \frac{\sigma_{\pi jj'}}{\left[(\sigma_{\pi jj} + \sigma_{ej}^2)(\sigma_{\pi jj'} + \sigma_{ej'}^2)\right]^{1/2}}
  \]
- Under simplifying assumptions that \( \sigma_{ej}^2 = \sigma_e^2 \) and \( \sigma_{\pi jj'} = \sigma_{\pi}^2 \):
  \[
  \text{Corr}(y_{ij}, y_{ij'}) = \rho = \frac{\sigma_{\pi}^2}{\sigma_{\pi}^2 + \sigma_e^2}
  \]
One Sample RM ANOVA

\[ y_{ij} = \mu + \pi_i + \tau_j + e_{ij} \]

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>E(MS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>( SS_T )</td>
<td>( t - 1 )</td>
<td>( MS_T = \frac{SS_T}{t-1} )</td>
<td>( \sigma_e^2 + n\sigma_{\tau}^2 )</td>
</tr>
<tr>
<td>Subjects</td>
<td>( SS_S )</td>
<td>( n - 1 )</td>
<td>( MS_S = \frac{SS_S}{n-1} )</td>
<td>( \sigma_e^2 + t\sigma_{\tau}^2 )</td>
</tr>
<tr>
<td>Residual</td>
<td>( SS_R )</td>
<td>( (n - 1)(t - 1) )</td>
<td>( MS_R = \frac{SS_R}{(n-1)(t-1)} )</td>
<td>( \sigma_e^2 )</td>
</tr>
</tbody>
</table>

- \( SS_T = \sum_{i=1}^{n} \sum_{j=1}^{t} (\bar{y}_{.j} - \bar{y}..)^2 = n \sum_{j=1}^{t} (\bar{y}_{.j} - \bar{y}..)^2 \)
- \( SS_S = \sum_{i=1}^{n} \sum_{j=1}^{t} (\bar{y}_{i.} - \bar{y}..)^2 = t \sum_{i=1}^{n} (\bar{y}_{i.} - \bar{y}..)^2 \)
- \( SS_R = \sum_{i=1}^{n} \sum_{j=1}^{t} (y_{ij} - \bar{y}_{i.} - \bar{y}_{.j} + \bar{y}..)^2 \)
- \( F = \frac{MS_T}{MS_R} \sim F_{t-1,(n-1)(t-1)} \) under \( H_0 : \tau_j = 0 \ \forall \ j \) and sphericity
Multiple Sample (Hierarchical) RM ANOVA

\[ y_{ij} = \mu + \gamma_h + \tau_j + (\gamma \tau)_{hj} + \pi_{i(h)} + e_{hij} \]

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<th>Source</th>
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<th>df</th>
<th>E(MS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>(SS_G)</td>
<td>(s - 1)</td>
<td>(\sigma_e^2 + t\sigma_\pi^2 + D_G)</td>
</tr>
<tr>
<td>Subjects (Group)</td>
<td>(SS_{S(G)})</td>
<td>(n - s)</td>
<td>(\sigma_e^2 + t\sigma_\pi^2)</td>
</tr>
<tr>
<td>Time</td>
<td>(SS_T)</td>
<td>(t - 1)</td>
<td>(\sigma_e^2 + D_T)</td>
</tr>
<tr>
<td>Group × Time</td>
<td>(SS_{GT})</td>
<td>((s - 1)(t - 1))</td>
<td>(\sigma_e^2 + D_{GT})</td>
</tr>
<tr>
<td>Residual</td>
<td>(SS_R)</td>
<td>((n - s)(t - 1))</td>
<td>(\sigma_e^2)</td>
</tr>
</tbody>
</table>

- \(D_G = \frac{nt}{s-1} \sum_{h=1}^{s} \gamma_h^2\)
- \(D_T = \frac{ns}{t-1} \sum_{j=1}^{t} \tau_j^2\)
- \(D_{GT} = \frac{n}{(s-1)(t-1)} \sum_{h=1}^{s} \sum_{j=1}^{t} (\gamma \tau)_{hj}^2\)
Multiple Sample (Hierarchical) RM ANOVA

- $SS_G = \sum_{s=1}^{s} \sum_{i=1}^{n_h} \sum_{j=1}^{t} (\bar{y}_{h..} - \bar{y}_{..})^2 = t \sum_{s=1}^{s} n_h (\bar{y}_{h..} - \bar{y}_{..})^2$
- $SS_{S(G)} = \sum_{s=1}^{s} \sum_{i=1}^{n_h} \sum_{j=1}^{t} (\bar{y}_{hi.} - \bar{y}_{h..})^2 = t \sum_{s=1}^{s} \sum_{i=1}^{n_h} (\bar{y}_{hi.} - \bar{y}_{h..})^2$
- $SS_T = \sum_{s=1}^{s} \sum_{i=1}^{n_h} \sum_{j=1}^{t} (\bar{y}_{..j} - \bar{y}_{..})^2 = n \sum_{j=1}^{t} (\bar{y}_{..j} - \bar{y}_{..})^2$
- $SS_{GT} = \sum_{s=1}^{s} \sum_{i=1}^{n_h} \sum_{j=1}^{t} (y_{h.j} - \bar{y}_{h..} - \bar{y}_{..j} + \bar{y}_{..})^2$
- $SS_R = \sum_{s=1}^{s} \sum_{i=1}^{n_h} \sum_{j=1}^{t} (y_{hij} - \bar{y}_{h.j} - \bar{y}_{hi.} + \bar{y}_{h..})^2$

- $F = \frac{MS_G}{MS_{S(G)}} \sim F_{s-1,n-s}$ under $H_0 : \gamma_h = (\gamma\tau)_{hj} = 0 \ \forall \ h,j$
  and within-group covariance matrices equal
- $F = \frac{MS_T}{MS_R} \sim F_{t-1,(n-s)(t-1)}$ under $H_0 : \tau_j = (\gamma\tau)_{hj} = 0 \ \forall \ h,j$
  and within-group covariance matrices equal, and sphericity
- $F = \frac{MS_{GT}}{MS_R} \sim F_{(s-1)(t-1),(n-s)(t-1)}$ under $H_0 : (\gamma\tau)_{hj} = 0 \ \forall \ h,j$
  and within-group covariance matrices equal, and sphericity
Sphericity

- Assumption needed for $F$ statistic to have $F$ distribution with right $df$
- Multiple ways to express sphericity:
  1. $\text{Var}(y_{ij} - y_{ij'})$ is constant for all $j, j'$
  2. $\epsilon = \frac{t^2(\bar{\sigma}_{ii} - \bar{\sigma}_{..})^2}{(t-1)(S - 2t \sum \bar{\sigma}_{i.}^2 + t^2 \bar{\sigma}_{..}^2)} = 1$, where
     - $\bar{\sigma}_{ii}$ is the mean of the entries on the main diagonal of $\Sigma$
     - $\bar{\sigma}_{..}$ is the mean of all the elements of $\Sigma$
     - $\bar{\sigma}_{i.}$ is the mean of the entries in row $i$ of $\Sigma$
     - $S$ is the sum of the squares of the elements of $\Sigma$
  3. Keselman, Algina & Kowalchuk: $C'\Sigma C = \lambda I_{t-1}$, where
     - $C$ is a normalized matrix of $t - 1$ orthogonal contrasts among $t$ times
     - $\lambda$ is a scalar
- Mauchly test of sphericity: sensitive to sample size, non-normality
Sphericity vs. Compound Symmetry

- Compound symmetry $\implies$ sphericity, but they are not equivalent
- $\text{Var}(y_{ij}) = \text{Var}(y_{ij'})$ for all $j, j'$ $+$ sphericity $\implies$ compound symmetry
- Though mathematically possible, hard to imagine $\text{Var}(y_{ij}) \neq \text{Var}(y_{ij'})$ but covariances all happen to work out to sphericity
- Conclusion: Compound symmetry not theoretically necessary for sphericity and valid $F$ tests, but practically it may as well be
Lack of Sphericity

How to proceed when sphericity does not hold?

- **MANOVA**
  - Sphericity replaced by equal within-group covariance matrices
  - Test whether the means of \( t - 1 \) differences are equal across groups
  - Four different test statistics summarize covariance matrix different ways
  - More degrees of freedom \( \implies \) lower power

- **Adjust degrees of freedom:**
  - \( F \approx F_{\epsilon(t-1),\epsilon(t-1)(n-1)} \)
  - Greenhouse & Geisser: Plug in MLE \( \hat{\epsilon} \) estimated from sample covariance matrix \( S \)
  - Huynh & Feldt: Plug in \( \tilde{\epsilon} = \min \left( 1, \frac{n(t-1)\hat{\epsilon}}{(t-1)(n-1-(t-1)\hat{\epsilon})} \right) \)
  - GG can be too conservative, especially for \( \epsilon > 0.75 \) and \( n < 2t \)
  - HF is less biased than GG, performs better when \( \epsilon > 0.75 \)

- **Go back to (G)LMM**
  - More flexibility to specify different covariance structures
  - So why try RM ANOVA at all? Adjusting \( df \) for valid \( F \)-test with near-sphericity may still be more powerful than GLMM with more \( df \)