Bivariate analysis

HGEN619 class 2007

Univariate ACE model
Expected Covariance Matrices

\[
E_{MZ} = \begin{bmatrix}
a^2+c^2+e^2 & a^2+c^2 \\
a^2+c^2 & a^2+c^2+e^2
\end{bmatrix} \quad 2 \times 2
\]

\[
E_{DZ} = \begin{bmatrix}
a^2+c^2+e^2 & 0.5a^2+c^2 \\
0.5a^2+c^2 & a^2+c^2+e^2
\end{bmatrix} \quad 2 \times 2
\]

Bivariate Questions I

- Univariate Analysis: What are the contributions of additive genetic, dominance/shared environmental and unique environmental factors to the variance?
- Bivariate Analysis: What are the contributions of genetic and environmental factors to the covariance between two traits?
Two Traits

- Two or more traits can be correlated because they share common genes or common environmental influences
  - e.g. Are the same genetic/environmental factors influencing the traits?
- With twin data on multiple traits it is possible to partition the covariation into its genetic and environmental components
- Goal: to understand what factors make sets of variables correlate or co-vary

Bivariate Questions II
**Bivariate Twin Data**

<table>
<thead>
<tr>
<th>individual twin</th>
<th>within</th>
<th>between</th>
</tr>
</thead>
<tbody>
<tr>
<td>trait</td>
<td>within</td>
<td>between</td>
</tr>
<tr>
<td>trait</td>
<td>within</td>
<td>(within-twin within-trait covariance)</td>
</tr>
<tr>
<td>trait</td>
<td>between</td>
<td>(cross-twin within-trait covariance)</td>
</tr>
</tbody>
</table>

**Bivariate Twin Covariance Matrix**

<table>
<thead>
<tr>
<th></th>
<th>(X_1)</th>
<th>(Y_1)</th>
<th>(X_2)</th>
<th>(Y_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(X_1)</td>
<td>(V_{X1})</td>
<td>(C_{X1Y1})</td>
<td>(C_{X1X2})</td>
<td>(C_{X1Y2})</td>
</tr>
<tr>
<td>(Y_1)</td>
<td>(C_{Y1X1})</td>
<td>(V_{Y1})</td>
<td>(C_{Y1X2})</td>
<td>(C_{Y1Y2})</td>
</tr>
<tr>
<td>(X_2)</td>
<td>(C_{X2X1})</td>
<td>(C_{X2Y1})</td>
<td>(V_{X2})</td>
<td>(C_{X2Y2})</td>
</tr>
<tr>
<td>(Y_2)</td>
<td>(C_{Y2X1})</td>
<td>(C_{Y2Y1})</td>
<td>(C_{Y2X2})</td>
<td>(V_{Y2})</td>
</tr>
</tbody>
</table>
**Genetic Correlation**

![Diagram of genetic correlation]

**Alternative Representations**

![Alternative representations diagrams]
Cholesky Decomposition

More Variables
Bivariate AE Model

MZ Twin Covariance Matrix

<table>
<thead>
<tr>
<th></th>
<th>$X_1$</th>
<th>$Y_1$</th>
<th>$X_2$</th>
<th>$Y_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X_1$</td>
<td>$a_{11}^2 + e_{11}^2$</td>
<td>$a_{11}^2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Y_1$</td>
<td>$a_{21}a_{11} + e_{21}e_{11}$</td>
<td>$a_{22}^2 + a_{21}^2 + e_{22}^2 + e_{21}^2$</td>
<td>$a_{21}a_{11}$</td>
<td>$a_{22}^2 + a_{21}^2$</td>
</tr>
<tr>
<td>$X_2$</td>
<td></td>
<td></td>
<td>$a_{11}^2$</td>
<td></td>
</tr>
<tr>
<td>$Y_2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### DZ Twin Covariance Matrix

<table>
<thead>
<tr>
<th></th>
<th>(X_1)</th>
<th>(Y_1)</th>
<th>(X_2)</th>
<th>(Y_2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(X_1)</td>
<td>(a_{11}^2 + e_{11}^2)</td>
<td>.5(a_{11}^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Y_1)</td>
<td>(a_{21}a_{11} + e_{21}e_{11})</td>
<td>(a_{22}^2 + a_{21}^2 + e_{22}^2 + e_{21}^2)</td>
<td>.5(a_{21}a_{11})</td>
<td>.5(a_{22}^2 + a_{21}^2)</td>
</tr>
<tr>
<td>(X_2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Y_2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Within-Twin Covariances \([Mx]\)

\[A = X^*X'\]

\[EA = \begin{bmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{bmatrix} \ast \begin{bmatrix} a_{11} & a_{21} \\ a_{21} & a_{22} \end{bmatrix} = \begin{bmatrix} a_{11}^2 & a_{11}a_{21} \\ a_{21}a_{11} & a_{22}^2 + a_{21}^2 \end{bmatrix}\]
Within-Twin Covariances

\[ \text{EA} = \begin{bmatrix} a_{11}^2 & a_{11}a_{21} \\ a_{21}a_{11} & a_{22}^2 + a_{21}^2 \end{bmatrix} \]

\[ \text{EE} = \begin{bmatrix} e_{11}^2 & e_{11}e_{21} \\ e_{21}e_{11} & e_{22}^2 + e_{21}^2 \end{bmatrix} \]

\[ \text{EP} = \text{EA} + \text{EE} = \begin{bmatrix} a_{11}^2 + e_{11}^2 & a_{11}a_{21} + e_{11}e_{21} \\ a_{21}a_{11} + e_{21}e_{11} & a_{22}^2 + a_{21}^2 + e_{22}^2 + e_{21}^2 \end{bmatrix} \]

Cross-Twin Covariances

\[ \text{MZ EA} = \begin{bmatrix} a_{11}^2 & a_{11}a_{21} \\ a_{21}a_{11} & a_{22}^2 + a_{21}^2 \end{bmatrix} \]

\[ \text{DZ} \cdot 0.5@\text{EA} = \begin{bmatrix} 0.5a_{11}^2 & 0.5a_{11}a_{21} \\ 0.5a_{21}a_{11} & 0.5a_{22}^2 + 0.5a_{21}^2 \end{bmatrix} \]
Cross-Trait Covariances

- Within-twin cross-trait covariances imply common etiological influences
- Cross-twin cross-trait covariances imply familial common etiological influences
- MZ/DZ ratio of cross-twin cross-trait covariances reflects whether common etiological influences are genetic or environmental

Univariate Expected Covariances

\[
\begin{align*}
E_{MZ} &= \begin{bmatrix}
a^2 + c^2 + e^2 & a^2 + c^2 \\
a^2 + c^2 & a^2 + c^2 + e^2
\end{bmatrix} \\
E_{DZ} &= \begin{bmatrix}
a^2 + c^2 + e^2 & 0.5a^2 + c^2 \\
0.5a^2 + c^2 & a^2 + c^2 + e^2
\end{bmatrix}
\end{align*}
\]
### Univariate Expected Covariances II

\[ \begin{align*}
E_{MZ} &= \begin{pmatrix}
EA+EC & EA+EC+EE \\
EA+EC & EA+EC+EE
\end{pmatrix} \quad 2 \times 2 \\
E_{DZ} &= \begin{pmatrix}
EA+EC+EE & .5@EA+EC \\
.5@EA+EC & EA+EC+EE
\end{pmatrix} \quad 2 \times 2
\end{align*} \]

### Bivariate Expected Covariances

\[ \begin{align*}
E_{MZ} &= \begin{pmatrix}
EA+EC+EE & EA+EC \\
EA+EC & EA+EC+EE
\end{pmatrix} \quad 4 \times 4 \\
E_{DZ} &= \begin{pmatrix}
EA+EC+EE & .5@EA+EC \\
.5@EA+EC & EA+EC+EE
\end{pmatrix} \quad 4 \times 4
\end{align*} \]
Practical Example I

- Dataset: MCV-CVT Study
- 1983-1993
- BMI, skinfolds (bic,tri,calf,sil,ssc)
- Longitudinal: 11 years
- N MZF: 107, DZF: 60

Practical Example II

- Dataset: NL MRI Study
- 1990’s
- Working Memory, Gray & White Matter

- N MZFY: 68, DZF: 21
Bivariate ACE model
NL mri data I

- #NGroups 4
- #define nvar 2
- G1: Model Parameters
- Calculation
- Begin matrices;
- X Lower nvar nvar Free ! additive genetic path coefficient
- Y Lower nvar nvar Free ! common environmental path coefficient
- Z Lower nvar nvar Free ! unique environmental path coefficient
- H Full 1 1
- G Full 1 nvar Free ! means
- End matrices;
- Matrix H .5
- Start .5 X 1 1 1 Y 1 1 1 Z 1 1 1
- Start .7 X 1 2 2 Y 1 2 2 Z 1 2 2
- Matrix G 6 7
- Begin algebra;
- A= X*X'; ! additive genetic variance
- C= Y*Y'; ! common environmental variance
- E= Z*Z'; ! unique environmental variance
- S= A+V | C+V | E+V ; ! standardized variance components
- End algebra;
- Labels Row V WM BBGM
- Labels Column V A1 A2 C1 C2 E1 E2
- End

Bivariate ACE model
NL mri data II

- G2: MZ twins
- Data NInputvars=8
- ! N inputvars per family
- Missing=-2.0000
- ! missing values ='-2.0000'
- Rectangular File=mri.rec
- Labels fam sgy mem1 gm1 wm1 mem2 ..
- Select if sgy=1 ;
- Select gm1 wm1 gm2 wm2 ;
- Begin Matrices = Group 1;
- Means G| G;
- ! model for means, assuming mean t1=t2
- Covariances
- ! model for MZ variance/covariances
- A+C|E >
- A+C | A+C|E ;
- Options R|S|iduals
- End

- G3: DZ twins
- Data NInputvars=8
- ! N inputvars per family
- Missing=-2.0000
- ! missing values ='-2.0000'
- Rectangular File=mri.rec
- Labels fam sgy mem1 gm1 wm1 mem2 ..
- Select if sgy=2 ;
- Select gm1 wm1 gm2 wm2 ;
- Begin Matrices = Group 1;
- Means G| G;
- ! model for means, assuming mean t1=t2
- Covariances
- ! model for DZ variance/covariances
- A+C|E | H|A+C | A+C|E | H|A+C | A+C|E ;
- Options R|S|iduals
- End
! Bivariate ACE model
! NL mri data III

- G4: summary of relevant statistics
- Calculation
- Begin Matrices = Group 1
- Begin Algebra ;
  Re \stnd{(A)}| \stnd{(C)}| \stnd{(E)}; ! calculates rg|rc|re
- End Algebra ;
- Interval @95 $1 1 1 1 1 3 1 1 5$ ! CI's on A,C,E for first phenotype
- Interval @95 $1 2 2 1 2 4 1 2 6$ ! CI's on A,C,E for second phenotype
- Interval @95 $R 4 2 1 R 4 2 3 R 4 2 5$ ! CI's on rg, rc, re
- End

nlmribiv.mx