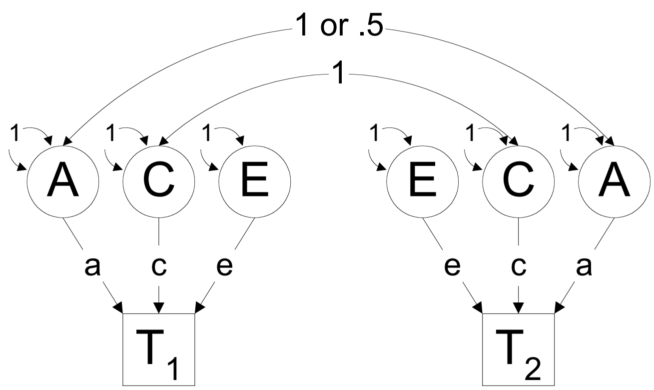
Bivariate analysis

HGEN619 class 2007

Univariate ACE model



Expected Covariance Matrices

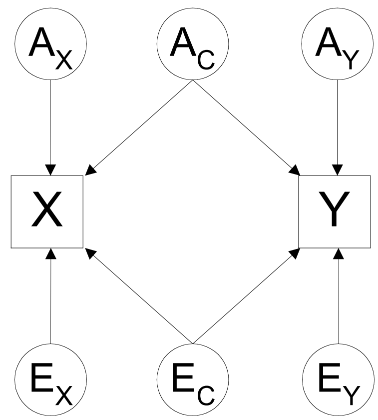
$$E\ MZ = \begin{bmatrix} a^2+c^2+e^2 & a^2+c^2 \\ a^2+c^2 & a^2+c^2+e^2 \end{bmatrix} \quad 2 \times 2$$

$$E\ DZ = \begin{bmatrix} a^2+c^2+e^2 & .5a^2+c^2 \\ .5a^2+c^2 & a^2+c^2+e^2 \end{bmatrix} \quad 2 \times 2$$

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



Bivariate Questions II

- 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

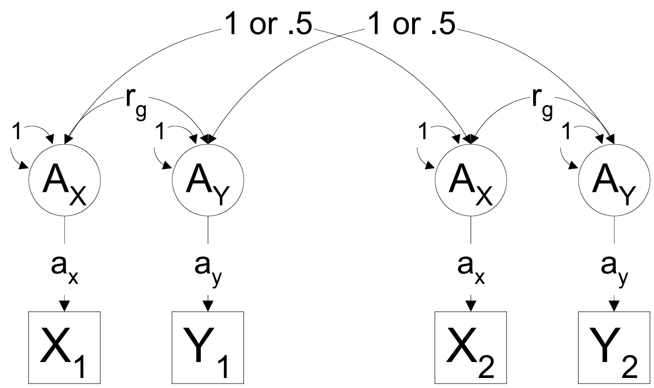
Bivariate Twin Data

		individual twin	
		within	between
trait	within	(within-twin within-trait co)variance	(cross-twin within-trait) covariance
	between	(cross-twin within-trait) covariance	cross-twin cross-trait covariance

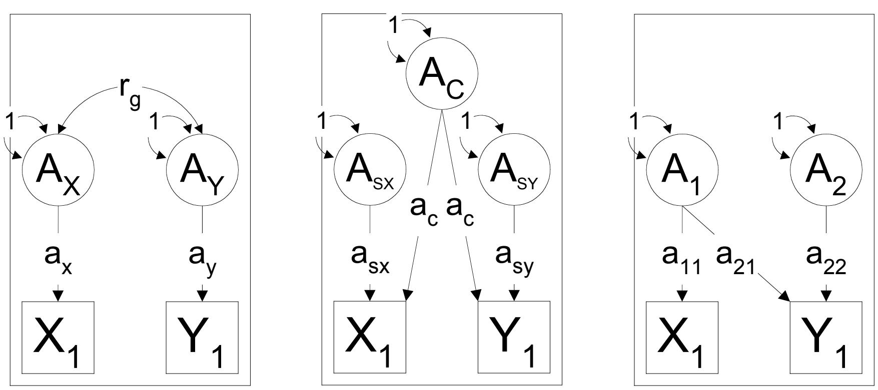
Bivariate Twin Covariance Matrix

	X_1	Y_1	X_2	Y_2
X_1	V_{X1}	C_{X1Y1}	C_{X1X2}	C_{X1Y2}
Y_1	C_{Y1X1}	V_{Y1}	C_{Y1X2}	C_{Y1Y2}
X_2	C_{X2X1}	C_{X2Y1}	V_{X2}	C_{X2Y2}
Y_2	C_{Y2X1}	C_{Y2Y1}	C_{Y2X2}	V_{Y2}

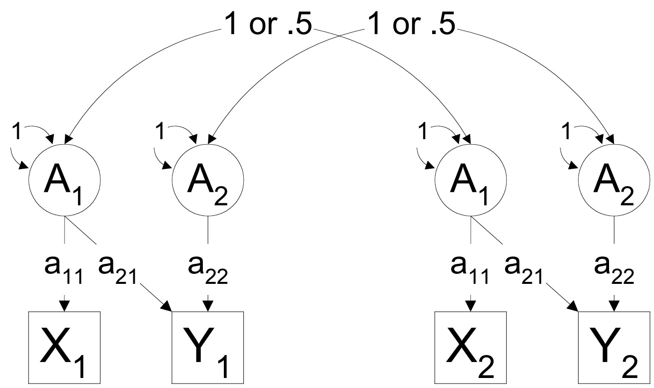
Genetic Correlation



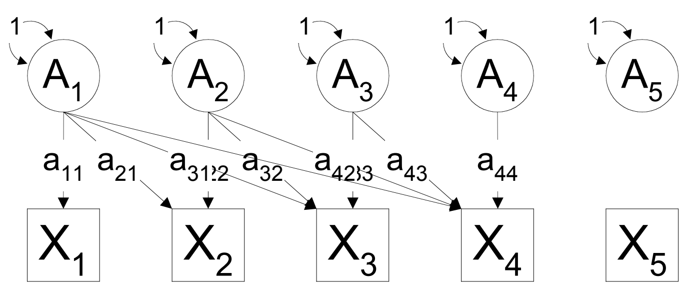
Alternative Representations



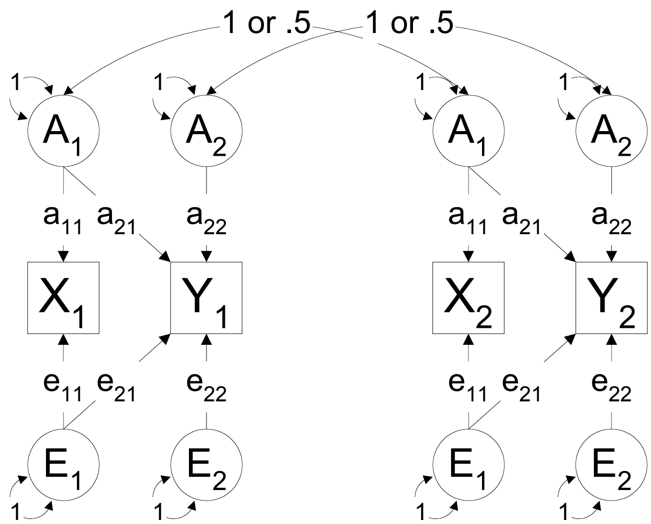
Cholesky Decomposition



More Variables



Bivariate AE Model



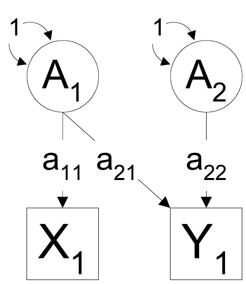
MZ Twin Covariance Matrix

	X_1	Y_1	X_2	Y_2
X_1	$a_{11}^2+e_{11}^2$		a_{11}^2	
Y_1	$a_{21}*a_{11}+e_{21}*e_{11}$	$a_{22}^2+a_{21}^2+e_{22}^2+e_{21}^2$	$a_{21}*a_{11}$	$a_{22}^2+a_{21}^2$
X_2				
Y_2				

DZ Twin Covariance Matrix

	X_1	Y_1	X_2	Y_2
X_1	$a_{11}^2+e_{11}^2$		$.5a_{11}^2$	
Y_1	$a_{21}*a_{11}+$ $e_{21}*e_{11}$	$a_{22}^2+a_{21}^2+$ $e_{22}^2+e_{21}^2$	$.5a_{21}*a_{11}$	$.5a_{22}^2+$ $.5a_{21}^2$
X_2				
Y_2				

Within-Twin Covariances [Mx]



X Lower 2 2

$$\begin{array}{c} \\ X_1 \\ Y_1 \end{array} \begin{array}{cc} A_1 & A_2 \\ \left[\begin{array}{c} a_{11} \\ a_{21} \end{array}\right. & \left.\begin{array}{c} 0 \\ a_{22} \end{array}\right] \end{array}$$

A=X*X'

$$EA=\begin{bmatrix} a_{11} & 0 \\ a_{21} & a_{22} \end{bmatrix} * \begin{bmatrix} a_{11} & a_{21} \\ 0 & a_{22} \end{bmatrix} = \begin{bmatrix} a_{11}^2 & a_{11}*a_{21} \\ a_{21}*a_{11} & a_{22}^2+a_{21}^2 \end{bmatrix}$$

Within-Twin Covariances

$$EA = \begin{bmatrix} a_{11}^2 & a_{11}*a_{21} \\ a_{21}*a_{11} & a_{22}^2+a_{21}^2 \end{bmatrix}$$

$$EE = \begin{bmatrix} e_{11}^2 & e_{11}*e_{21} \\ e_{21}*e_{11} & e_{22}^2+e_{21}^2 \end{bmatrix}$$

$$EP = EA+EE = \begin{bmatrix} a_{11}^2+ e_{11}^2 & a_{11}*a_{21} + e_{11}*e_{21} \\ a_{21}*a_{11} + e_{21}*e_{11} & a_{22}^2+a_{21}^2 +e_{22}^2+e_{21}^2 \end{bmatrix}$$

Cross-Twin Covariances

MZ $$EA = \begin{bmatrix} a_{11}^2 & a_{11}*a_{21} \\ a_{21}*a_{11} & a_{22}^2+a_{21}^2 \end{bmatrix}$$

DZ $$.5@EA = \begin{bmatrix} .5a_{11}^2 & .5a_{11}*a_{21} \\ .5a_{21}*a_{11} & .5a_{22}^2+.5a_{21}^2 \end{bmatrix}$$

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

E MZ =

$a^2+c^2+e^2$	a^2+c^2
a^2+c^2	$a^2+c^2+e^2$

2 x 2

E DZ =

$a^2+c^2+e^2$	$.5a^2+c^2$
$.5a^2+c^2$	$a^2+c^2+e^2$

2 x 2

Univariate Expected Covariances II

E MZ =

EA+EC+EE	EA+EC
EA+EC	EA+EC+EE

2 x 2

E DZ =

EA+EC+EE	.5@EA+EC
.5@EA+EC	EA+EC+EE

2 x 2

Bivariate Expected Covariances

E MZ =

EA+EC+EE	EA+EC
EA+EC	EA+EC+EE

4 x 4

E DZ =

EA+EC+EE	.5@EA+EC
.5@EA+EC	EA+EC+EE

4 x 4

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                        ! N dependent variables per twin

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
  V= A+C+E;                           ! total 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
```

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! 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 zyg mem1 gm1 wm1 mem2 . .
  Select if  zyg =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   | A+C+E  ;
 Options RSiduals
End
```

```
G3: DZ twins
Data NInputvars=8

  Missing=-2.0000

  Rectangular File=mri.rec
  Labels fam zyg mem1 gm1 wm1 mem2 . .
  Select if  zyg =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 _
  H@A+C | A+C+E  ;
 Options RSiduals
End
```

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! Bivariate ACE model
! NL mri data III

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

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