Modeling/Estimating Genetic and Environmental Components

40th International Statistical Genetics Online Workshop 2026

Hermine HM Maes et al.

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Running Day 3 Practical on YOUR COMPUTER

- You will need R (or RStudio) installed on your computer
- You will need the following R packages: OpenMx and mvtnorm
- Login to your account using
  - `ssh student@workshop.colorado.edu` (with your username in place of "`student`")
  - `cp /home/hmaes/2026/Day3/oneSACEvcrH.R .` (include the .)
  - `scp student@workshop.colorado.edu:oneSACEvcrH.R .`
- Run R script locally using R or RStudio

Schedule for Day 3 Practical

- Introduction (Recap of Video's): 20 minutes
- **First Breakout Session**: 20-25 minutes
- Brief review of testing model assumptions: 10 minutes
- Break: 10 minutes

- **Second Breakout Session**: 20-25 minutes
- Brief review of interpreting ACE model results: 10 minutes
- **Third Breakout Session**: 20-25 minutes
- Final Review: 10 minutes

Learning Objectives for Day 3 Practical

- How to test basic assumptions prior to genetic modeling
- How to fit an ACE model, interpret results and get an estimate of the twin heritability using the classical twin design
- How to setup the ACE model using the actual relatedness of twins
- What you can learn from adding genotypic data on DZ twins, with or without analyzing MZ twins

Estimating heritability

- Understanding causes of variation in phenotype & partitioning it in genetic and environmental variance components
  - Genetically informative designs -> **twin heritability**
    - infer genetic (and environmental) contributions to variance from phenotypic covariances (correlations) among family members, often twins, using expected relatedness
  - Genomically informative designs -> **SNP heritability**
    - infer genetic contributions to variance from genetic relationship matrices (correlations) based on measured genotypes of individuals, using actual relatedness

- "*Remember that all models are wrong; the practical question is how wrong do they have to be to not be useful*"

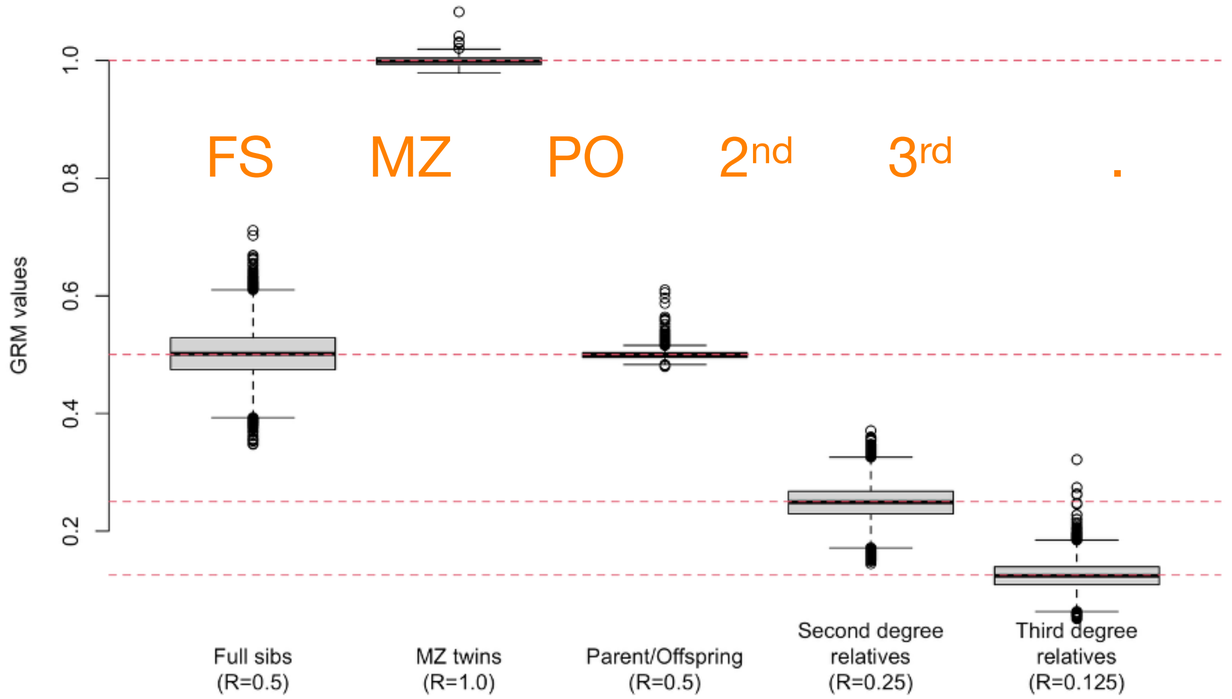
George E P Box and Norman R Draper. 1986. Empirical Model-Building and Response Surface. John Wiley & Sons, Inc., New York, NY, USA

Coefficient of Genetic Relationship > GRMs

How to estimate genetic relatedness from SNP data?

- Coefficient of genetic relationship $\mathbf{R_{jk}}$ = 2x probability that two alleles picked at random in individuals **j** and **k** are Identical-By-Descent (IBD)
- Genetic Relationship Matrix (GRM) is matrix of $\mathbf{R_{jk}}$'s and can be quantified based on expected IBD sharing (e.g., 0.5 for full sibs) or using actual SNP data

- $\hat{\pi}_{jk}$ is an estimate of $\mathbf{R_{jk}}$
- Expectation of $\hat{\pi}_{jk}$ is exactly $\mathbf{R_{jk}}$
- Observed relatedness varies by relationship



Yang, 2011

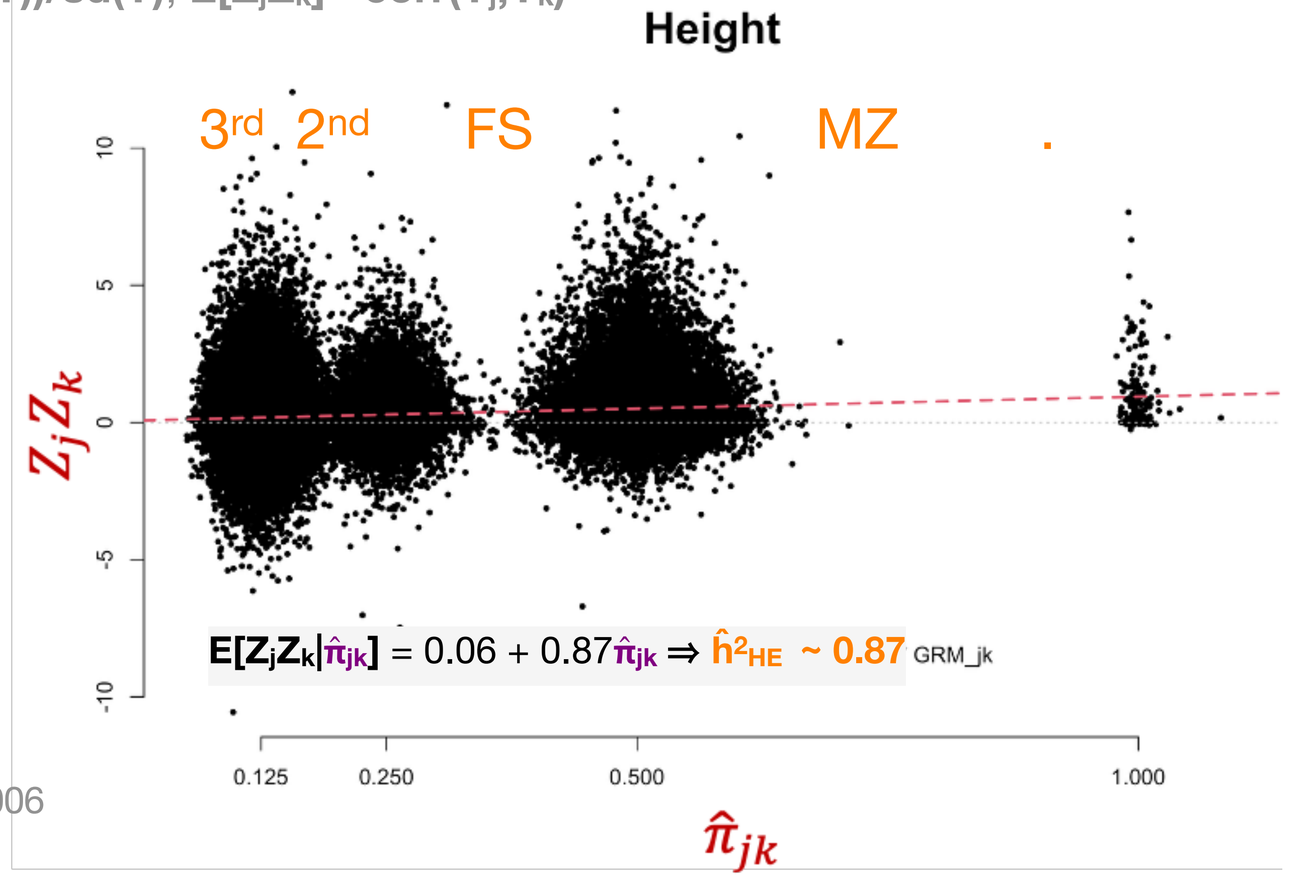
Haseman-Elston Regression

How do we use the genetic relationship coefficient to estimate SNP heritability?

- relies on association between phenotypic similarity and genetic sharing
- estimates h^2 by regressing Z_jZ_k [phenotypic similarity] onto $\hat{\pi}_{jk}$ [genetic similarity]

  where $Z_j=(Y_j-\text{mean}(Y))/\text{sd}(Y)$ & $Z_k=(Y_k-\text{mean}(Y))/\text{sd}(Y)$, $E[Z_jZ_k]=\text{corr}(Y_j,Y_k)$

- Cross-Product (CP) method:
  $Z_jZ_k = \beta_0 + \beta_1\hat{\pi}_{jk} + \varepsilon$
- Slope β_1 directly estimates heritability h^2



Haseman & Elston, 1972; Elston et al, 2000; Visscher at al, 2006

HE Regression vs Classical Twin Design

How does SNP heritability relate to Twin heritability?

- Shared goal of partitioning phenotypic variance to estimate h^2, by analyzing how phenotypic similarity between individuals relates to their genetic relatedness, with HE-regression using DNA-based relatedness rather than inferred pedigree relationships in the twin design

- **Heritability Estimation**:
  - Haseman-Elston Regression **HE** (Molecular): regresses phenotypic cross-product (CP) of siblings (or pairs of unrelated individuals) on shared proportion of alleles, estimated via Identity-By-State (IBS) or Identity-By-Descent (IBD)

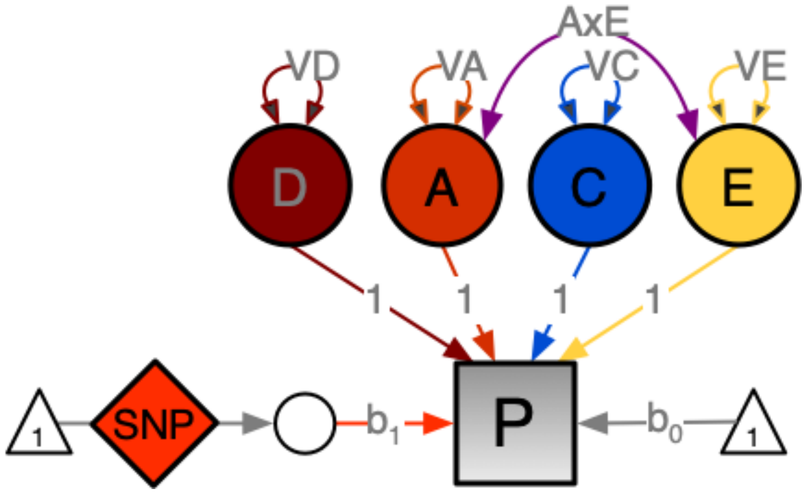
$$\mathbf{corr(Yi,Yj) = h^2 R_{jk} + Residual}$$

  - Classical Twin Design **CTD** (Traditional): compares monozygotic **MZ** twins to dizygotic **DZ** twins to partition variation in a phenotype into additive genetic **A**, common environmental **C**, and unique environmental **E** components

$$\mathbf{cov = VA \otimes rA + VC \otimes rC + VE \otimes rE}$$

Path Analysis

How to specify models using path diagrams?



- Path Diagram **Conventions**:
  - Squares or rectangles denote observed variables
  - Circles or ellipses denote latent (unmeasured) variables
  - Single-headed arrows or paths (–>): causal relationships between variables where variable at tail has influence on variable at head
  - Double-headed arrows (<–>): covariance between two variables, through common causes not in modeled; or variance of a variable
  - Triangles denote means; Diamonds denote definition variables (variables on paths)

- Path Analysis **Tracing Rules**:
  - Trace backwards, change direction at a 2-headed arrow, then trace forwards (never trace through two-headed arrows in same chain)
  - Expected covariance between two variables, or variance of a variable, is computed by multiplying together all coefficients in a chain, and summing over all possible chains

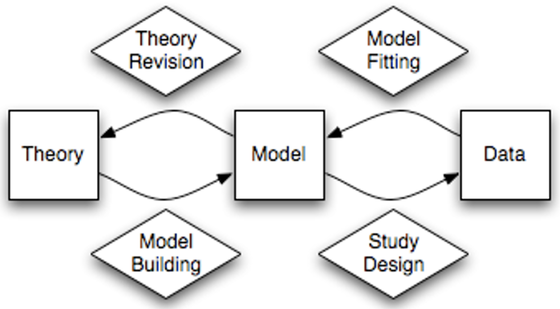
Sewall Wright, 1918; https://en.wikipedia.org/wiki/Path_analysis_(statistics)

The Classical Twin Study

How to estimate twin heritability?

- Partition phenotypic variance (V) in genetic and environmental components
  - $\mathbf{V}_{total}$ = **VG**enetic + **VE**nvironmental
  - Assumptions: additivity & independence of effects
  - Heritability ($\mathbf{h^2}$): proportion of variance due to genetic influences ($\mathbf{h^2}$ = **VG**enetic / $\mathbf{V}_{total}$)
  - Property of a group (not an individual), thus specific to that group in place & time

- Classical Twin Study/Design (CTS/CTD): monozygotic (MZ) and dizygotic (DZ) twins reared together
  - **MZ** twins share **100%** of their genes
  - **DZ** twins share on average **50%** of their genes
- Genetic factors are assumed to contribute to a phenotype when MZ twins are more similar for that phenotype than DZ twins



Eaves et al, 1978; Boomsma et al, 2002; Van Dongen et al, 2012; Polderman et al, 2015

Sources of Variance

Which factors make people different from one another?

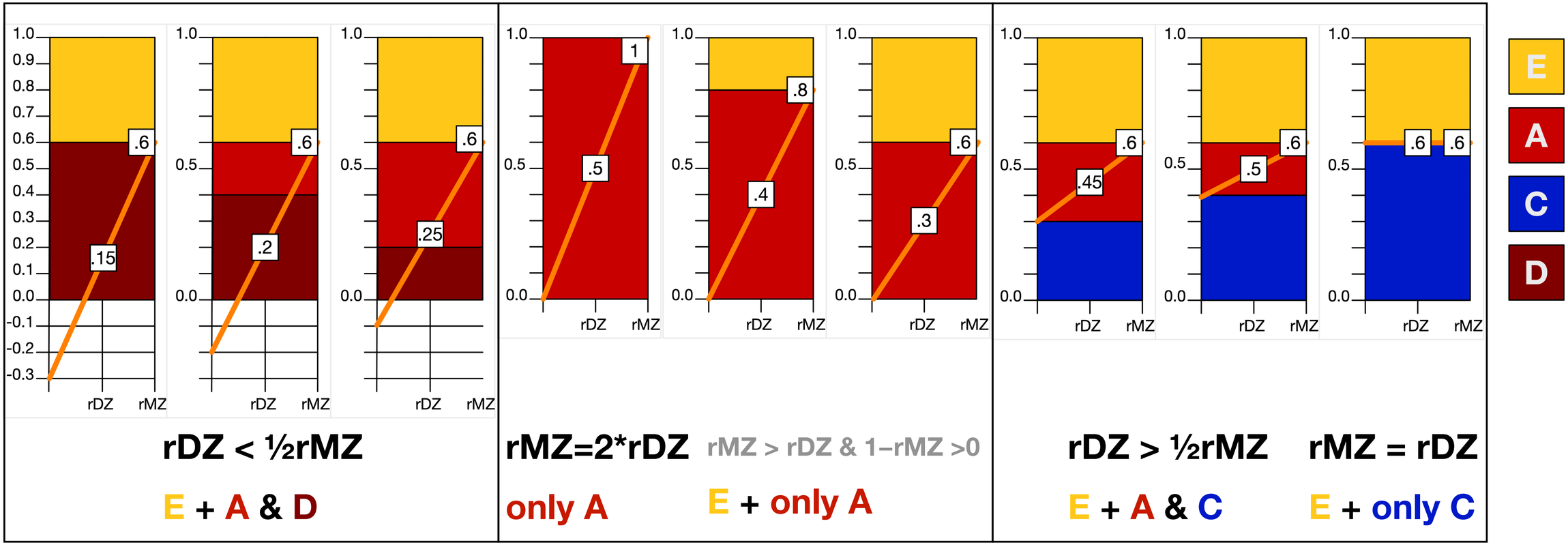
- Additive Genetic factors (**VA**, **A**, a^2): sum of all average effects of single alleles at individual loci
- Genetic Dominance (**VD**, **D**, d^2): result of interactions between alleles at same locus
- Common Environment: (**VC**, **C**, c^2): aspects of environment shared by family members, which contribute to similarity between relatives [shared]
- Unique Environment (**VE**, **E**, e^2): unique to individual, contribute to variation within family [specific, unique or within-family]

Fisher, 1918; Mather & Jinks, 1972; Martin & Eaves, 1977; Neale & Cardon, 1992

Patterns of Twin Correlations

Where does the information come from to estimate **A**, **C**, **D** & **E**?

From twin correlations to expected sources of variance



rDZ < ½rMZ

E + A & D

rMZ=2*rDZ rMZ > rDZ & 1–rMZ >0

only A **E + only A**

rDZ > ½rMZ **rMZ = rDZ**

E + A & C **E + only C**

rMZ: monozygotic twin correlation; **rDZ**: dizygotic twin correlation

A: additive genetic variance; **E**: unique environmental variance: **C**: common environmental variance; **D**: dominance genetic variance

Twin Model Assumptions

What assumptions are we making?- Important Quality Control Step!

- Equal Environments of MZ and DZ pairs (EEA)
  - MZ & DZ twins equally correlated in exposure to environmental events of etiologic importance for trait
- Random Mating, No rGE Correlation, No G x E Interaction
- No Sex Limitation, No G x Age Interaction

- **Basic Data Assumptions**: MZ & DZ twins sampled from same population, therefore we expect
  - Equal means/variances in Twin 1 and Twin 2 [twin order]
  - Equal means/variances in MZ and DZ twins [zygosity]
  - Further assumptions possibly needed when testing for heterogeneity by sex or adding other relatives [full siblings etc.]

Evans et al, 1999

Saturated Models

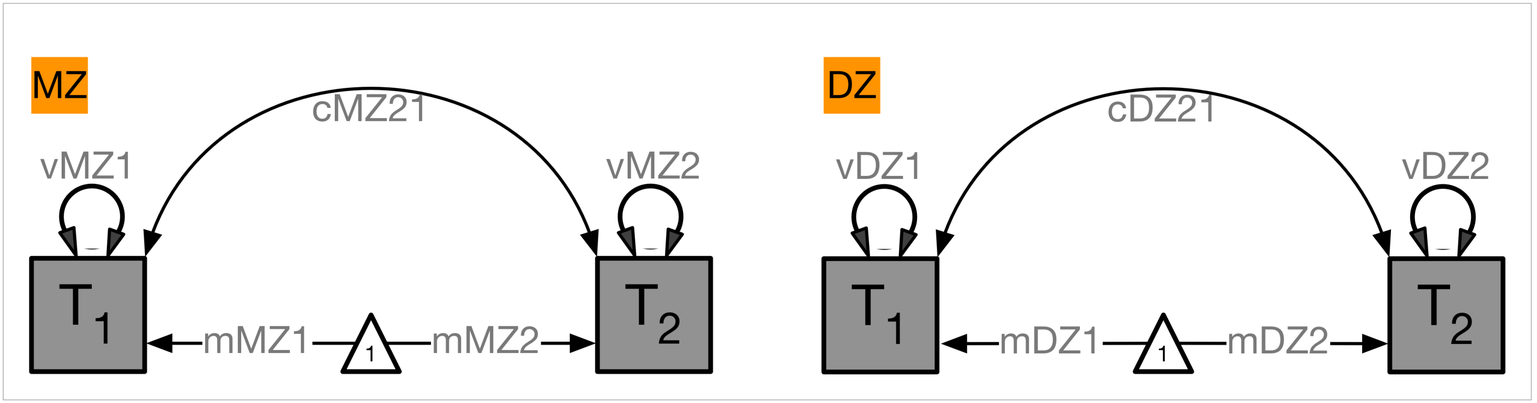
Are data assumptions valid: can we equate means/variances?

- Data: BMI in young OZ female MZ & DZ twins: observed means & variances [NH&MRC 1981 Q]

MZf twins pairs N=534		
cov	**T1**	**T2**
T1	0.73	0.59
T2	0.59	0.79
mean	21.34	21.35

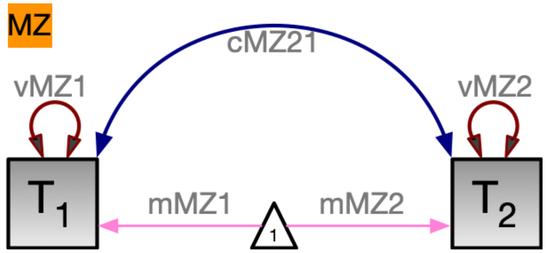
DZf twins pairs N=328		
cov	**T1**	**T2**
T1	0.77	0.24
T2	0.24	0.82
mean	21.45	21.46

- Model: as many free parameters as statistics

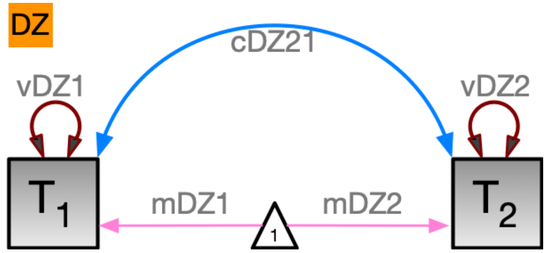


Specification of Data & Model in OpenMx

What are the key commands for OpenMx script of saturated twin model?



covMZ *2x2*	vMZ1	cMZ21
	cMZ21	vMZ2
meanMZ *1x2*	mMZ1	mMZ2



covDZ *2x2*	vDZ1	cDZ21
	cDZ21	vDZ2
meanDZ *1x2*	mDZ1	mDZ2

```
dataMZ     <- mxData( observed=mzData, type="raw" )
meanMZ     <- mxMatrix( type="Full", nrow=1, ncol=ntv, free=TRUE, values=svm, labels=c("mMZ1","mMZ2"),name="meanMZ" )
covMZ      <- mxMatrix( type="Symm", nrow=ntv, ncol=ntv, free=TRUE, values=c(svv,0,svv), labels=c("vMZ1","cMZ21","vMZ2"),
 name="covMZ" )
```

```
dataDZ     <- mxData( observed=dzData, type="raw" )
meanDZ     <- mxMatrix( type="Full", nrow=1, ncol=ntv, free=TRUE, values=svMe, labels=c("mDZ1","mDZ2"),name="meanDZ" )
covDZ      <- mxMatrix( type="Symm", nrow=ntv, ncol=ntv, free=TRUE, values=c(svv,0,svv), labels=c("vDZ1","cDZ21","vDZ2"),
 name="covDZ" )
```

Goodness of Fit Statistics - Likelihood Ratio Tests

Are data assumptions met?

		os	ep	-2ll	df	AIC	Δ-2ll	Δdf	p
	saturated	1777	10	4055.93	1767	521.93			
m1	**meanT1=meanT2**	1777	8	4056.00	1769	518.00	0.07	2	0.97
m2	**+ varT1=varT2**	1777	6	4058.94	1771	516.94	3.01	4	0.56
m3	**+ mean/varMZ=DZ**	1777	4	4063.45	1773	517.45	7.52	6	0.28

os	observed statistics
ep	estimated parameters

-2ll	-2 LogLikelihood	
df	degrees of freedom	os - ep
AIC	Akaike's Information Criterion	-2ll -2df

Δ-2ll	likelihood ratio Chi-square
Δdf	difference in df
p	probability of Chi-square

- BMI in young OZ females (age 18-30)
  - means [m1] & variances [m2] of twin 1 & 2 not significantly different in MZ & DZ pairs
  - means & variances of MZs and DZs [m3] not significantly different from one another
- Basic data assumptions of classical twin study [CTD] met

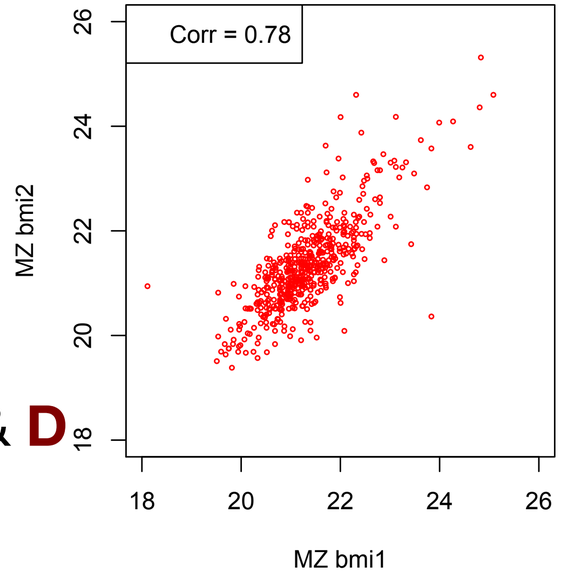
Parameter Estimates & ML Correlations

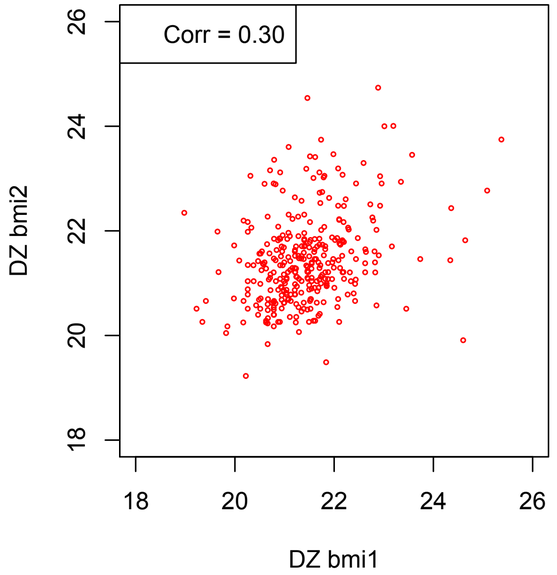
What does the pattern of MZ/DZ correlations predict about h^2?

- 4 parameters estimated in reduced model: `mZ,vZ,cMZ21 cDZ21`

MZf twins pairs N=534		
cov	**T1**	**T2**
T1	0.78	r=0.78
T2	0.61	0.78
mean	21.39	21.39

DZf twins pairs N=328		
cov	**T1**	**T2**
T1	0.78	r=0.30
T2	0.23	0.78
mean	21.39	21.39





- rMZ < 1: **E**
- rMZ > rDZ: **A** (+**D**)
- rDZ < 1/2rMZ: **A** & **D**

Practical 1

Setup data/model & Test data assumptions

- oneSACEvcrH.R
  - one: univariate script analyzing one phenotype in pairs of twins
  - S: Saturated model: freely estimating all model parameters: means, variances, covariance
  - ACE: ACE model: A:additive genetic, C:common/shared environment, E:unique/specific environment
  - v: direct variance estimation
  - c: continuous data
  - r: relatedness (both expected: rel & actual: piH)

- Section 1: Load Libraries & Functions
- Section 2: Simulate Data
- Section 3: Prepare Data
- Section 4: Prepare & Run Saturated Model
  - Section 4b: Test Data Assumptions

Simulated Data

Are data assumptions valid: can we equate means/variances?

- Data: Simulated data for 1000 pairs of MZ & 1000 pairs of DZ twins

```
> head(tDat)
  fid zyg rel piH      age sex1 sex2         T1         T2
1   1   1   1   1 57.69656    1    1  0.8076685 -1.0082586
2   2   1   1   1 46.70106    1    1  1.3422981  1.9681887
3   3   1   1   1 62.84351    1    1 -0.7068754 -1.0471504
4   4   1   1   1 66.18861    0    0  0.7987861  1.2378847
5   5   1   1   1 55.21314    0    0  0.7816142  1.1039350
6   6   1   1   1 52.16464    1    1 -0.4011456  0.4619979
> head(tDat[1000:1007,])
      fid zyg rel       piH      age sex1 sex2          T1         T2
1000 1000   1 1.0 1.0000000 63.13769    0    0  0.36294721  1.1613742
1001 1001   2 0.5 0.4597417 53.50322    0    1  0.31238999  0.8749122
1002 1002   2 0.5 0.5084421 37.28565    0    0  0.54484969 -0.2001131
1003 1003   2 0.5 0.5065984 22.86921    1    0  0.28314825  0.7468084
1004 1004   2 0.5 0.5068894 25.50235    0    0 -0.44437191 -0.5376371
1005 1005   2 0.5 0.4639071 58.63402    1    1  0.09119432 -1.2091367
```

- Variables:
  - Family number: fid
  - Phenotypes: **T1 T2**
  - Age: age
  - Sex (0=male, 1=female): sex1 sex2
  - Assigned Zygosity (1=MZ, 2=DZ): zyg
  - Expected relatedness ((1=MZ, .5=DZ): rel
  - Genomic relatedness: piH

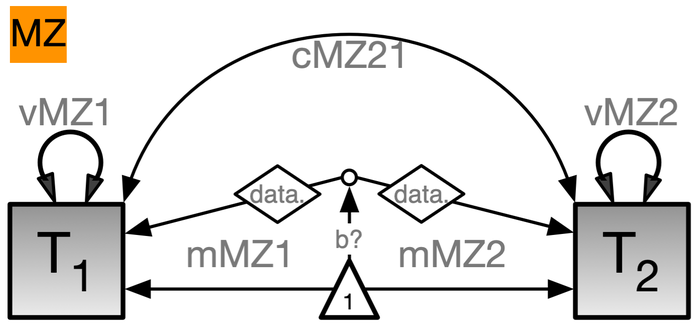
Saturated Models

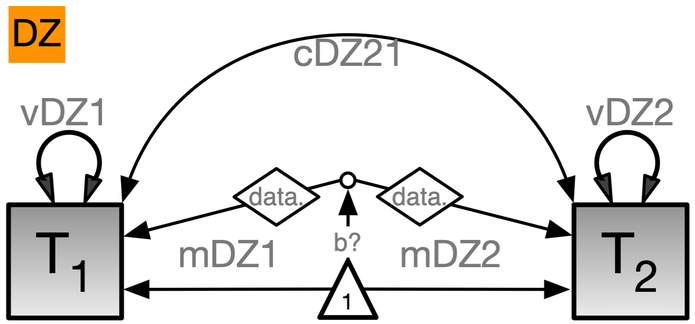
Are data assumptions valid: can we equate means/variances?

- Data: Simulated data for MZ & DZ twins: observed means & variances

MZ twins pairs N=1000		
cov	**T1**	**T2**
T1	0.97	0.67
T2	0.66	0.99
emean	*0.12	*0.15
mean	0.00	0.03

DZ twins pairs N=1000		
cov	**T1**	**T2**
T1	1.01	0.41
T2	0.40	0.93
emean	*0.01	*0.15
mean	0.01	0.03





*value of expected mean for last observation in data set

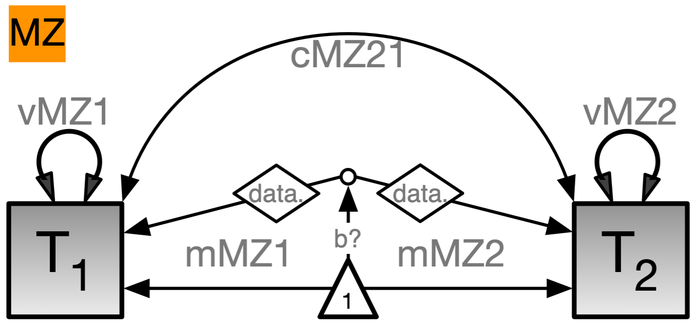
Definition Variables

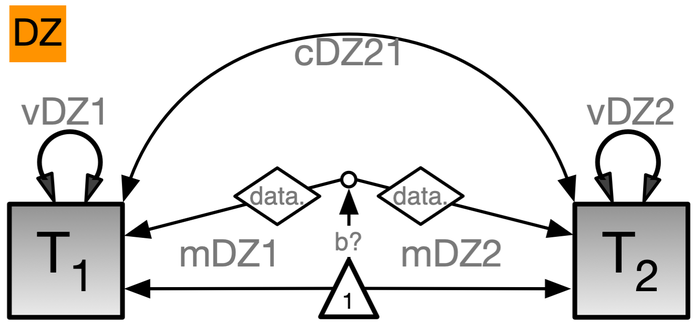
Are data assumptions valid: can we equate means/variances?

- "data.varName" in label argument of mxMatrix indicates definition variable
- matrix element updated dynamically with value from dataset when calculating row likelihood

```
> head(tDat[2000:2001,])
      fid zyg rel       piH      age sex1 sex2       T1        T2
1000 1000   1 1.0 1.0000000 63.13769    0    0 0.36294721 1.1613742
1001 1001   2 0.5 0.4597417 53.50322    0    1 0.31238999 0.8749122

betaS     <- mxMatrix( type="Full", nrow=1, ncol=1, free=TRUE, values=svBe, labels="betaS", name="bS" )
defSex    <- mxMatrix( type="Full", nrow=1, ncol=ntv, free=FALSE, labels=c("data.sex1","data.sex2"), name="Sex" )
intercept <- mxMatrix( type="Full", nrow=1, ncol=ntv, free=TRUE, values=svMu, labels="interC", name="intercept" )
expMean   <- mxAlgebra( expression= intercept +bS*Sex, name="expMean" )
```



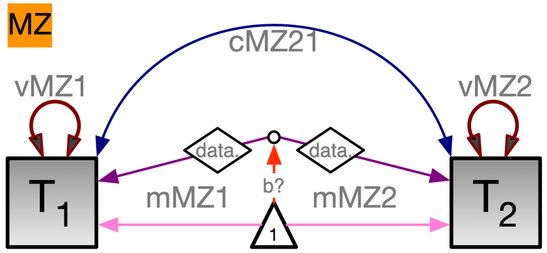


	Twin 1	Twin 2
1	μ	μ

	Twin 1	Twin 2
1	μ + b(def$_i$)	μ + b(def$_i$)

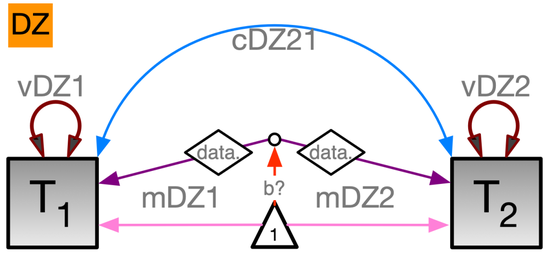
Specification of Data & Model in OpenMx

What are the key commands for OpenMx script of saturated twin model?



covMZ *2x2*	vMZ1	cMZ21
	cMZ21	vMZ2

meanMZ *1x2*	mMZ1	mMZ2



covDZ *2x2*	vDZ1	cDZ21
	cDZ21	vDZ2

meanDZ *1x2*	mDZ1	mDZ2

```
defSex     <- mxMatrix( type="Full", nrow=1, ncol=2, free=FALSE, labels=c("data.sex1","data.sex2"), name="defSex" )
defAge     <- mxMatrix( type="Full", nrow=1, ncol=1, free=FALSE, labels=c("data.age"), name="defAge" )
betaS      <- mxMatrix( type="Full", nrow=1, ncol=1, free=TRUE, labels="bS", name="betaS" )
betaA      <- mxMatrix( type="Full", nrow=1, ncol=1, free=TRUE, labels="bA", name="betaA" )
```

```
dataMZ     <- mxData( observed=mzData, type="raw" )
meanMZ     <- mxMatrix( type="Full", nrow=1, ncol=ntv, free=TRUE, values=svm, labels=c("mMZ1","mMZ2"),name="meanMZ" )
emeanMZ    <- mxAlgebra( expression= meanMZ +betaS%*%defSex +betaA%*%cbind(defAge,defAge), name="emeanMZ" )
covMZ      <- mxMatrix( type="Symm", nrow=ntv, ncol=ntv, free=TRUE, values=c(svv,0,svv), labels=c("vMZ1","cMZ21","vMZ2"),
 name="covMZ" )
```

```
dataDZ     <- mxData( observed=dzData, type="raw" )
meanDZ     <- mxMatrix( type="Full", nrow=1, ncol=ntv, free=TRUE, values=svMe, labels=c("mDZ1","mDZ2"),name="meanDZ" )
emeanDZ    <- mxAlgebra( expression= meanDZ +betaS%*%defSex +betaA%*%cbind(defAge,defAge), name="emeanDZ" )
covDZ      <- mxMatrix( type="Symm", nrow=ntv, ncol=ntv, free=TRUE, values=c(svv,0,svv), labels=c("vDZ1","cDZ21","vDZ2"),
 name="covDZ" )
```

Goodness of Fit Statistics - Likelihood Ratio Tests

Are data assumptions met?

		os	ep	-2ll	df	AIC	Δ-2ll	Δdf	p
	saturated	4000	12	10463.66	3988	10487.66	NA	NA	NA
m1	**meanT1=meanT2**	4000	10	10464.79	3990	10484.79	1.13	2	0.57
m2	**+ varT1=varT2**	4000	8	10466.57	3992	10482.57	2.91	4	0.57
m3	**+ mean/varMZ=DZ**	4000	6	10466.62	3994	10478.62	2.95	6	0.81

os	observed statistics
ep	estimated parameters

-2ll	-2 LogLikelihood	
df	degrees of freedom	os - ep
AIC	Akaike's Information Criterion	-2ll -2df

Δ-2ll	likelihood ratio Chi-square
Δdf	difference in df
p	probability of Chi-square

- Simulated data
  - means [m1] & variances [m2] of twin 1 & 2 not significantly different in MZ & DZ pairs
  - means & variances of MZs and DZs [m3] not significantly different from one another
- Basic data assumptions of classical twin study [CTD] met

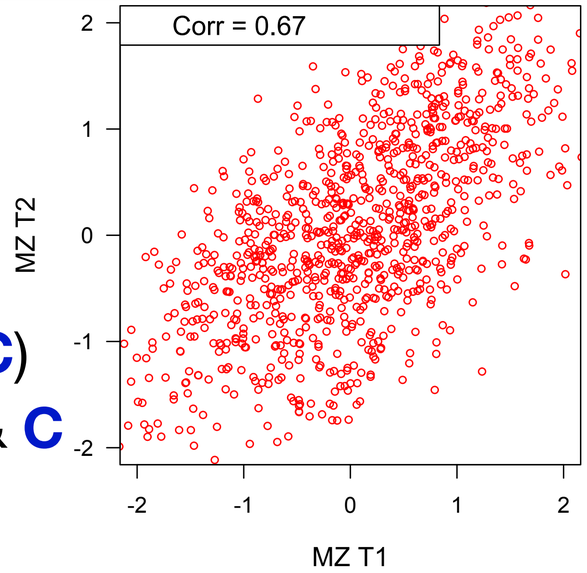
Parameter Estimates & ML Correlations

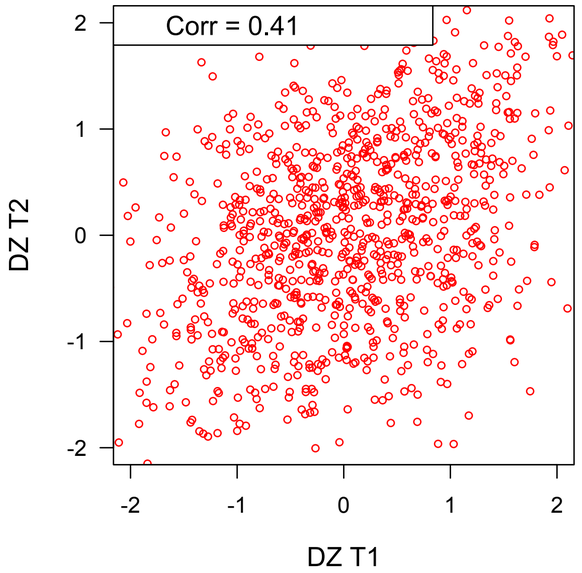
What does the pattern of MZ/DZ correlations predict about h^2?

- 4 parameters estimated in reduced model: `mZ,vZ,cMZ21 cDZ21`

MZ twins pairs N=1000		
cov	**T1**	**T2**
T1	0.97	r=0.67
T2	0.65	0.97
mean	0.02	0.02

DZ twins pairs N=1000		
cov	**T1**	**T2**
T1	0.97	r=0.41
T2	0.41	0.97
mean	0.02	0.02





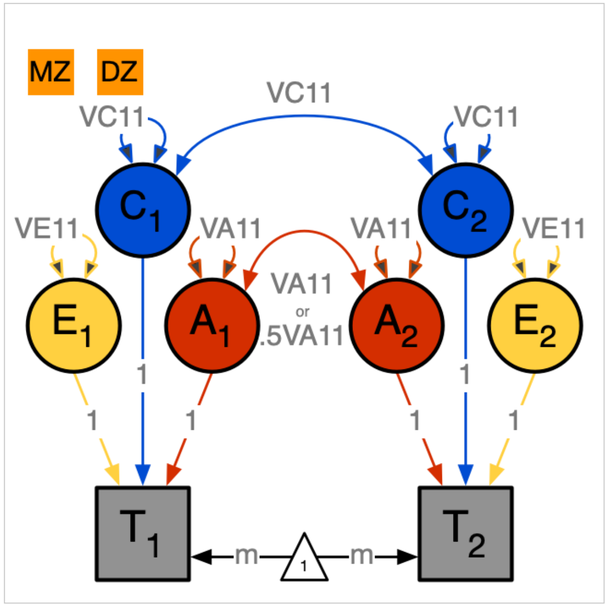
- rMZ < 1: **E**
- rMZ > rDZ: **A** (+**C**)
- rDZ > ½rMZ: **A** & **C**

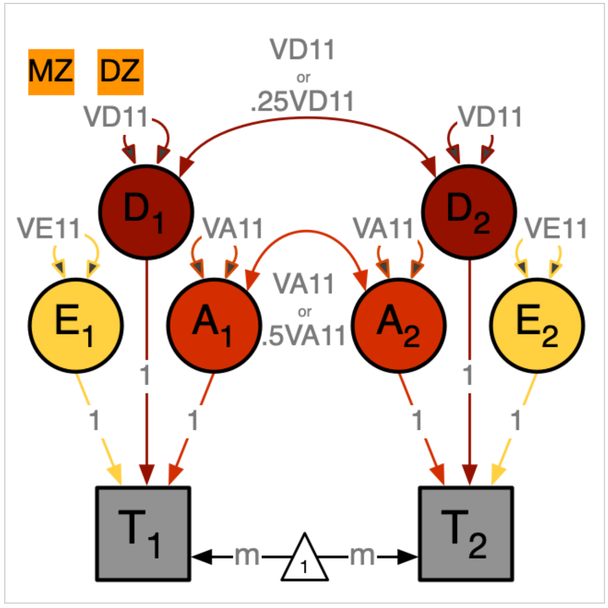
The ACE vs ADE Model

E= VE11
A= VA11
C= VC11
D= VD11

What are contributions of **A**, **C**, **D** & **E** factors to the variance?

- Classical Twin Design has three unique statistics: variance & MZ & DZ covariance, allowing estimating of three parameters: **A**, **C** & **E** or **A**, **D** & **E**
- **C** and **D** are confounded as they have opposite expectations





MZ	T1	T2
T1	A+C+E	A+C
T2	A+C	A+C+E

DZ	T1	T2
T1	A+C+E	½⊗A+C
T2	½⊗A+C	A+C+E

MZ	T1	T2
T1	A+D+E	A+D
T2	A+D	A+D+E

DZ	T1	T2
T1	A+D+E	½⊗A+¼⊗D
T2	½⊗A+¼⊗D	A+D+E

Univariate

- 1-rMZ: **E**
- rMZ > rDZ: **A** (+**D**)
- rMZ = 2*rDZ: only **A**
- rMZ = rDZ: only **C**
- 1/2rMZ < rDZ: **A** & **C**
- 1/2rMZ > rDZ: **A** & **D**

Path Coefficients vs Direct Variance Estimation

Why is Direct Symmetric Variance Estimation preferred?

- Path Estimation bounds variance components to be positive
  - May make incorrect inferences when comparing alternative models
- Direct (Symmetric) Variance Estimation allows variances to be estimated as negative
  - Makes correct inferences when comparing alternative models
  - Allows calculating **VD** when fitting **ACE** or calculating **VC** when fitting **ADE**

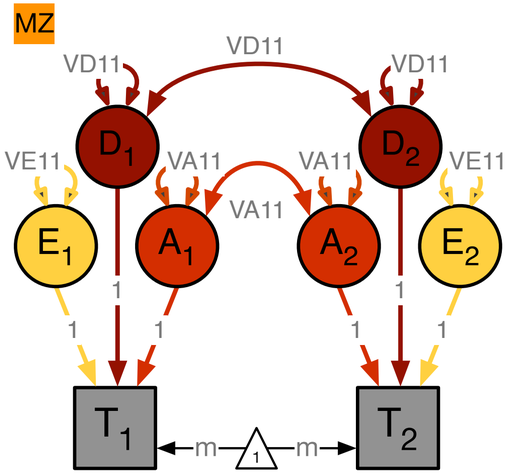
- Get **VD** when fitting **ACE** with direct variance estimation
- Three unique observed statistics
  - V = VA+VC+VE
  - cMZ = VA+VC
  - cDZ = .5VA+VC
- Three unknown parameters
  - V – cMZ = (VA+VC+VE) – (VA+VC) = VE
  - 2(cMZ – cDZ) = 2(VA+VC) – 2(.5VA+VC) = VA
  - VC = –cMZ +2cDZ, or V – VA – VE = VC
- What if negative VC?
  - VD' = –2VC
  - VA' = cMZ +2VC = VA+3VC

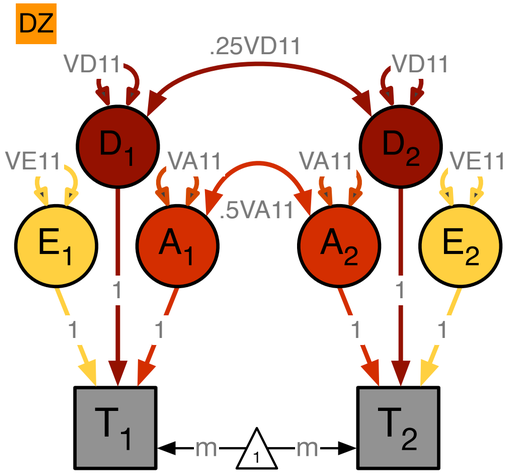
- Get **VC** when fitting **ADE** with direct variance estimation
- Three unique observed statistics
  - V = VA+VD+VE
  - cMZ = VA+VD
  - cDZ = .5VA+.25VD
- Three unknown parameters
  - V – cMZ = (VA+VD+VE) – (VA+VD) = VE
  - –(cMZ – 4cDZ) = –(VA+VD) + (2VA+VD) = VA
  - VD = 2cMZ – 4cDZ, or V – VA – VE = VD
- What if negative VD?
  - VC' = –1/2VD
  - VA' = cMZ +1/2VD = VA+3/2VD

Verhulst et al, 2019

One Trait - Univariate Twin Model Script

How to specify **ADE** model in OpenMx?





VA *1x1*	VA_{11}	***V*** *1x1*	VA+VD+VE	***expCovMZ*** *2x2*	V | cMZ cMZ | V
VC *1x1*	VD_{11}	***cMZ*** *1x1*	VA+VD	***expCovDZ*** *2x2*	V | cDZ cDZ | V
VE *1x1*	VE_{11}	***cDZ*** *1x1*	.5VA+.25VD	***meanG*** *1x2*	m | m

```
meanG    <- mxMatrix( type="Full", nrow=1, ncol=ntv, free=TRUE, values=svm, labels=labVars("mean",vars), name="meanG" )
covA     <- mxMatrix( type="Symm", nrow=nv, ncol=nv, free=TRUE, values=svp, label="VA11", name="VA" )
covD     <- mxMatrix( type="Symm", nrow=nv, ncol=nv, free=TRUE, values=svp, label="VD11", name="VD" )
covE     <- mxMatrix( type="Symm", nrow=nv, ncol=nv, free=TRUE, values=sve, label="VE11", name="VE" )
covP     <- mxAlgebra( expression= VA+VD+VE, name="V" )
covMZ    <- mxAlgebra( expression= VA+VD, name="cMZ" )
covDZ    <- mxAlgebra( expression= 0.5%x%VA+ 0.25%x%VD, name="cDZ" )
ecovMZ   <- mxAlgebra( expression= rbind( cbind(V, cMZ), cbind(t(cMZ), V)), name="ecovMZ" )
ecovDZ   <- mxAlgebra( expression= rbind( cbind(V, cDZ), cbind(t(cDZ), V)), name="ecovDZ" )
```

`nv <- 1`; `svm`, `svp`, `sve`: start values for means, VA, VD, VE; `labVars`: functions in `miFunctions.R`

Interpreting Goodness of Fit - Parameter Estimates

What is the best fitting/ most parsimonious genetic model?

		os	ep	-2ll	df	AIC	Δ-2ll	Δdf	p
	saturated	1777	10	4055.93	1767	521.93			
m1	**ADE model**	1777	4	4063.45	1773	517.45	7.51	6	0.27
m2	**AE model**	1777	3	4067.66	1774	519.66	4.21	1	0.04
m3	**E model**	1777	2	4591.79	1775	1041.79	528.34	2	0.00

- ADE model fits data not significantly worse than saturated model, is most parsimonious

		variance components			standardized components		
		VA	**VD**	**VE**	**SA**	**SD**	**SE**
m1	**ADE**	0.32 0.02-0.61	0.29 0.01-0.60	0.17 0.15-0.19	0.41	0.37	0.22
m2	**AE**	0.62 0.56-0.68	-	0.17 0.17-0.19	0.78	-	0.22
m3	**E**	-	-	0.78 0.73-0.83	-	-	1.00

- Broad heritability [**VA**+**VD** / **V**] estimated at 78%, narrow heritability [**VA** / **V**] at 41%

Practical 2

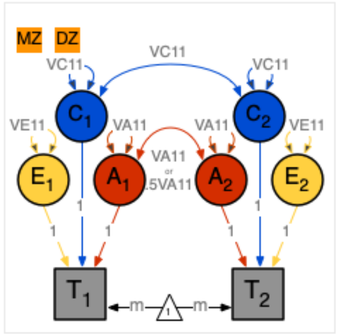
Fit multi-group ACE modeling

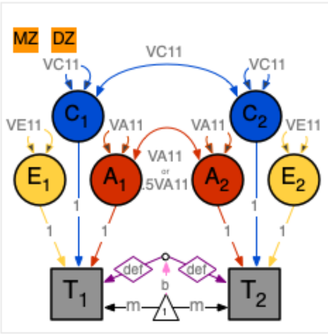
- oneSACEvcrH.R
  - one: univariate script analyzing one phenotype in pairs of twins
  - S: Saturated model: freely estimating all model parameters: means, variances, covariance
  - ACE: ACE model: A:additive genetic, C:common/shared environment, E:unique/specific environment
  - v: direct variance estimation
  - c: continuous data
  - r: relatedness (both expected: rel & actual: piH)

- Section 5: Prepare and Run ACE Model 1
  - Section 5b: Test Significance of A & C
- Section 6: Prepare and Run ACE Model 2: Alternate parameterization

Standard ACE Model

How to specify ACE model in OpenMx?






```
nv        <- 1
covA      <- mxMatrix( type="Symm", nrow=nv, ncol=nv, free=TRUE, values=svp, label="VA11", name="VA" )
covC      <- mxMatrix( type="Symm", nrow=nv, ncol=nv, free=TRUE, values=svp, label="VC11", name="VC" )
covE      <- mxMatrix( type="Symm", nrow=nv, ncol=nv, free=TRUE, values=sve, label="VE11", name="VE" )
covP      <- mxAlgebra( expression= VA+VC+VE, name="V" )
covMZ     <- mxAlgebra( expression= VA+VC, name="cMZ" )
covDZ     <- mxAlgebra( expression= 0.5%x%VA+ VC, name="cDZ" )
ecovMZ    <- mxAlgebra( expression= rbind( cbind(V, cMZ), cbind(t(cMZ), V)), name="ecovMZ" )
ecovDZ    <- mxAlgebra( expression= rbind( cbind(V, cDZ), cbind(t(cDZ), V)), name="ecovDZ" )
```

Object: covA covC covE covP covMZ covDZ

Matrix

VA + VC + VE = VA+VC+VE

VA + VC = VA+VC

.5⊗VA + VC = .5⊗VA+VC

MZ	T1	T2
T1	VA+VC+VE	VA+VC
T2	VA+VC	VA+VC+VE

	T1	T2
T1	V	cMZ
T2	cMZ'	V

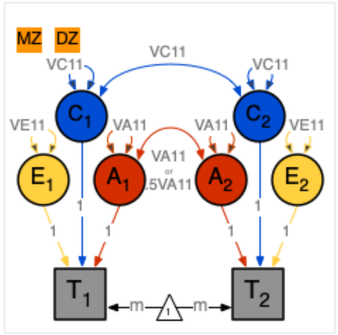
DZ	T1	T2
T1	VA+VC+VE	.5⊗VA+VC
T2	.5⊗VA+VC	VA+VC+VE

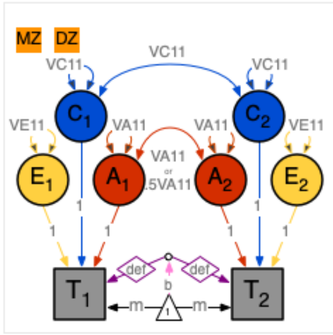
	T1	T2
T1	V	cDZ
T2	cDZ'	V

`nv <- 1`; `svm`, `svp`, `sve`: start values for means, VA, VC, VE

Output of ACE Model

How to get output from OpenMx?






```
> fitGofs(fitACE)
Mx:ACE1  os=4000  ns=2000   ep=6   co=0  df=3994  ll=10466.6152  cpu=26.6803  opt=SLSQP  ver=2.21.11  stc=0
```

```
> fitECIs(fitACE,fitACE$stVC)
   mean      bS      bA    VA11    VC11    VE11
 0.0179  0.1258 -0.0001  0.4933  0.1584  0.3229

            VA     VC     VE     SA     SC     SE      V
stVC    0.4933 0.1584 0.3229 0.5061 0.1626 0.3313 0.9747
lbound  0.3858 0.0561 0.2964 0.3972 0.0586 0.3016 0.9278
ubound  0.6066 0.2564 0.3527 0.6198 0.2597 0.3641 1.0251
```

```
> mxCompare( fitSAT, fitACE)
  base comparison ep minus2LL   df      AIC   diffLL diffdf         p
1  SAT       <NA> 12 10463.66 3988 10487.66       NA     NA        NA
2  SAT       ACE1  6 10466.62 3994 10478.62 2.951332      6 0.8149299
```

p-value > α (=0.05) thus LRT NOT significant which means that the submodel (the ACE model) is not significantly worse than full model (the Saturated model) and is more parsimonious

```
> summary(fitACE)
Summary of ACE1

free parameters:
  name matrix row col      Estimate  Std.Error A
1 mean  meanG   1   1  1.791298e-02 0.06556890
2   bS  betaS   1   1  1.257758e-01 0.03306412
3   bA  betaA   1   1 -7.507312e-05 0.00133027
4 VA11     VA   1   1  4.932850e-01 0.05603520
5 VC11     VC   1   1  1.584394e-01 0.05079627
6 VE11     VE   1   1  3.229377e-01 0.01427239

confidence intervals:
                       lbound  estimate    ubound note
ACE1.stVC[1,1] 0.38577648 0.4932850 0.6065836
ACE1.stVC[1,2] 0.05614056 0.1584394 0.2564429
ACE1.stVC[1,3] 0.29640099 0.3229377 0.3527466
ACE1.stVC[1,4] 0.39723042 0.5061087 0.6198362
ACE1.stVC[1,5] 0.05858223 0.1625583 0.2597419
ACE1.stVC[1,6] 0.30161504 0.3313330 0.3640669
ACE1.stVC[1,7] 0.92777849 0.9746621 1.0251410

Model Statistics:
               |  Parameters  |  Degrees of Freedom  |  Fit (-2lnL units)
       Model:              6                  3994               10466.62
   Saturated:             NA                    NA                     NA
Independence:             NA                    NA                     NA
Number of observations/statistics: 2000/4000

Information Criteria:
      |  df Penalty  |  Parameters Penalty  |  Sample-Size Adjusted
AIC:       2478.615              10478.62                10478.66
BIC:     -19891.389              10512.22                10493.16
CFI: NA
TLI: 1   (also known as NNFI)
RMSEA:  0  [95% CI (NA, NA)]
Prob(RMSEA <= 0.05): NA
To get additional fit indices, see help(mxRefModels)
timestamp: 2026-06-01 01:33:50
Wall clock time: 27.65012 secs
optimizer:  SLSQP
OpenMx version number: 2.21.11
Need help?  See help(mxSummary)
```

Interpreting Goodness of Fit - Parameter Estimates

What is the best fitting/ most parsimonious genetic model?

		os	ep	-2ll	df	AIC	Δ-2ll	Δdf	p
	saturated	4000	12	10463.66	3988	10487.66			
m1	**ACE model**	4000	6	10466.62	3994	10478.62	2.95	6	0.81
m2	**AE model vs m1**	4000	5	10475.70	3995	10485.70	9.08	1	0.00
m3	**CE model vs m1**	4000	5	10552.81	3995	10562.81	86.19	1	0.00
m4	**E model vs m1**	4000	4	11250.80	3996	11258.80	784.19	2	0.00

- ACE model fits data not significantly worse than saturated model, is most parsimonious

		variance components			standardized components		
		VA	**VC**	**VE**	**SA**	**SC**	**SE**
m1	**ACE**	0.49 0.39-0.61	0.16 0.06-0.26	0.32 0.30-0.35	0.51 0.40-0.62	0.16 0.06-0.26	0.33 0.30-0.36
m2	**AE**	0.65 0.60-0.71	-	0.31 0.29-0.34	0.68 0.65-0.70	-	0.32 0.30-0.35
m3	**CE**	-	0.53 0.48-0.58	0.45 0.42-0.47	-	0.54 0.51-0.57	0.46 0.43-0.49
m4	**E**			0.97 0.93-1.02			1.00

- Broad heritability [**VA**+**VD** / **V**] estimated at 51%, narrow heritability [**VA** / **V**] at 51%

One Trait - VA ⊗ Genetic Relatedness

How to specify **ACE** model in an alternative way?

cMZ *2x2*	**VA**+VC+VE	**1**⊗**VA**+VC
	1⊗**VA**+VC	**VA**+VC+VE
cDZ *2x2*	**VA**+VC+VE	**.5**⊗**VA**+VC
	.5⊗**VA**+VC	**VA**+VC+VE
	VA+**VC**+VE	α⊗VA+**VC**
	α⊗VA+**VC**	VA+**VC**+VE
	VA+VC+**VE**	α⊗VA+VC
	α⊗VA+VC	VA+VC+**VE**

VA⊗ ***rAmz*** *2x2*	1	1
	1	1
VA⊗ ***rAdz*** *2x2*	1	.5
	.5	1
VC⊗ ***rC*** *2x2*	1	1
	1	1
VE⊗ ***rE*** *2x2*	1	0
	0	1

```
rAmz: type="Stand", nrow=2, ncol=2, free=F, values=c(1,1,1)
rAdz: type="Stand", nrow=2, ncol=2, free=F, values=c(1,.5,1)
rC: type="Unit", nrow=2, ncol=2, free=F
rE: type="Iden", nrow=2, ncol=2, free=F
ecovMZ: VA%x%rAmz +VC%x%rC +VE%x%rE
ecovDZ: VA%x%rAdz +VC%x%rC +VE%x%rE
```

Alternative

ecovMZ= VA⊗rAmz + VC⊗rC + VE⊗rE

ecovDZ= VA⊗rAdz + VC⊗rC + VE⊗rE

VA *1x1*	VA_{11}	***V*** *1x1*	VA+VC+VE	***ecovMZ*** *2x2*	VA+VC+VE	VA+VC
					VA+VC	VA+VC+VE
VC *1x1*	VC_{11}	***cMZ*** *1x1*	VA+VC	***ecovDZ*** *2x2*	VA+VC+VE	.5⊗VA+VC
					.5⊗VA+VC	VA+VC+VE
VE *1x1*	VE_{11}	***cDZ*** *1x1*	.5⊗VA+VC			

ecovMZ *2x2*			***ecovDZ*** *2x2*		
V	cMZ		V	cDZ
cMZ	V		cDZ	V

```
covA: type="Symm", nrow=1, ncol=1, free=T, values=svp, label="VA11", name="VA"
covC: type="Symm", nrow=1, ncol=1, free=T, values=svp, label="VC11", name="VC"
covE: type="Symm", nrow=1, ncol=1, free=T, values=sve, label="VE11", name="VE"
covP: VA+VC+VE, name="V"
covMZ: VA+VC, name="cMZ"
covDZ: 0.5%x%VA+VC, name="cDZ"
ecovMZ: rbind( cbind(V, cMZ), cbind(t(cMZ), V))
ecovDZ: rbind( cbind(V, cDZ), cbind(t(cDZ), V))
```

Traditional

```
ecovMZ= rbind(cbind(VA+VC+VE, VA+VC),
              cbind(VA+VC,    VA+VC+VE)
ecovDZ= rbind(cbind(VA+VC+VE, .5VA+VC),
              cbind(.5VA+VC,  VA+VC+VE)
```

One Trait - VA ⊗ Expected Genetic Relatedness

How to specify **ACE** model in an alternative way with a definition variable?

cMZ *2x2*

VA+VC+VE	1⊗VA+VC
1⊗VA+VC	VA+VC+VE

cDZ *2x2*

VA+VC+VE	.5⊗VA+VC
.5⊗VA+VC	VA+VC+VE

VA+**VC**+VE	α⊗VA+**VC**
α⊗VA+**VC**	VA+**VC**+VE

VA+VC+**VE**	α⊗VA+VC
α⊗VA+VC	VA+VC+**VE**

VA⊗ ***rAmz*** *2x2*

1	1
1	1

VA⊗ ***rAdz*** *2x2*

1	.5
.5	1

VC⊗ ***rC*** *2x2*

1	1
1	1

VE⊗ ***rE*** *2x2*

1	0
0	1

```
rAmz: type="Stand", nrow=2, ncol=2, free=F, values=c(1,1,1)
rAdz: type="Stand", nrow=2, ncol=2, free=F, values=c(1,.5,1)
rC: type="Unit", nrow=2, ncol=2, free=F
rE: type="Iden", nrow=2, ncol=2, free=F
ecovMZ: VA%x%rAmz +VC%x%rC +VE%x%rE
ecovDZ: VA%x%rAdz +VC%x%rC +VE%x%rE
```

Alternative

ecovMZ= VA⊗rAmz + VC⊗rC + VE⊗rE

ecovDZ= VA⊗rAdz + VC⊗rC + VE⊗rE

VA+VC+VE	rel⊗VA+VC
rel⊗VA+VC	VA+VC+VE

VA+**VC**+VE	α⊗VA+**VC**
α⊗VA+**VC**	VA+**VC**+VE

VA+VC+**VE**	α⊗VA+VC
α⊗VA+VC	VA+VC+**VE**

VA⊗ ***rA*** *2x2*

1	1
rel	1

VC⊗ ***rC*** *2x2*

1	1
1	1

VE⊗ ***rE*** *2x2*

1	0
0	1

```
rA: type="Stand", nrow=2, ncol=2, free=F, labels="data.rel"

rC: type="Unit", nrow=2, ncol=2, free=F
rE: type="Iden", nrow=2, ncol=2, free=F
ecovTW: VA%x%rAmz +VC%x%rC +VE%x%rE
```

rel = 1 for MZs
rel = .5 for DZs

Alternative 2

ecovTW= VA⊗rA + VC⊗rC + VE⊗rE

One Trait - VA ⊗ Actual Genetic Relatedness

How to specify ACE model in an alternative way using pihat information?

cMZ 2x2	VA+VC+VE	1⊗VA+VC
	1⊗VA+VC	VA+VC+VE
cDZ 2x2	VA+VC+VE	.5⊗VA+VC
	.5⊗VA+VC	VA+VC+VE
	VA+VC+VE	α⊗VA+VC
	α⊗VA+VC	VA+VC+VE
	VA+VC+VE	α⊗VA+VC
	α⊗VA+VC	VA+VC+VE

VA⊗ *rAmz* 2x2	1	1
	1	1
VA⊗ *rAdz* 2x2	1	.5
	.5	1
VC⊗ *rC* 2x2	1	1
	1	1
VE⊗ *rE* 2x2	1	0
	0	1

```
rAmz: type="Stand", nrow=2, ncol=2, free=F, values=c(1,1,1)
rAdz: type="Stand", nrow=2, ncol=2, free=F, values=c(1,.5,1)
rC: type="Unit", nrow=2, ncol=2, free=F
rE: type="Iden", nrow=2, ncol=2, free=F
ecovMZ: VA%x%rAmz +VC%x%rC +VE%x%rE
ecovDZ: VA%x%rAdz +VC%x%rC +VE%x%rE
```

Alternative

ecovMZ= VA⊗rAmz + VC⊗rC + VE⊗rE

ecovDZ= VA⊗rAdz + VC⊗rC + VE⊗rE

	VA+VC+VE	π̂⊗VA+VC
	π̂⊗VA+VC	VA+VC+VE
	VA+VC+VE	α⊗VA+VC
	α⊗VA+VC	VA+VC+VE
	VA+VC+VE	α⊗VA+VC
	α⊗VA+VC	VA+VC+VE

VA⊗ *rA* 2x2	1	1
	π̂	1
VC⊗ *rC* 2x2	1	1
	1	1
VE⊗ *rE* 2x2	1	0
	0	1

```
rA: type="Stand", nrow=2, ncol=2, free=F, labels="data.piH"

rC: type="Unit", nrow=2, ncol=2, free=F
rE: type="Iden", nrow=2, ncol=2, free=F
ecovTW: VA%x%rAmz +VC%x%rC +VE%x%rE
```

Alternative 3

ecovTW= VA⊗rA + VC⊗rC + VE⊗rE

One Trait - VA ⊗ Actual Genetic Relatedness

How to specify ACE model in an alternative way using pihat information?

VA+VC+VE	π̂⊗VA+VC
π̂⊗VA+VC	VA+VC+VE

VA⊗ *rA* *2x2*

1	1
π̂	1

VA+VC+VE	α⊗VA+VC
α⊗VA+VC	VA+VC+VE

VC⊗ *rC* *2x2*

1	1
1	1

VA+VC+VE	α⊗VA+VC
α⊗VA+VC	VA+VC+VE

VE⊗ *rE* *2x2*

1	0
0	1

```
rA: type="Stand", nrow=2, ncol=2, free=F, labels="data.piH"

rC: type="Unit", nrow=2, ncol=2, free=F
rE: type="Iden", nrow=2, ncol=2, free=F
ecovTW: VA%x%rAmz +VC%x%rC +VE%x%rE
```

Alternative 3

corr(Yi,Yj) = h^2 R_{jk} + Residual

ecovTW= VA⊗rA + VC⊗rC + VE⊗rE

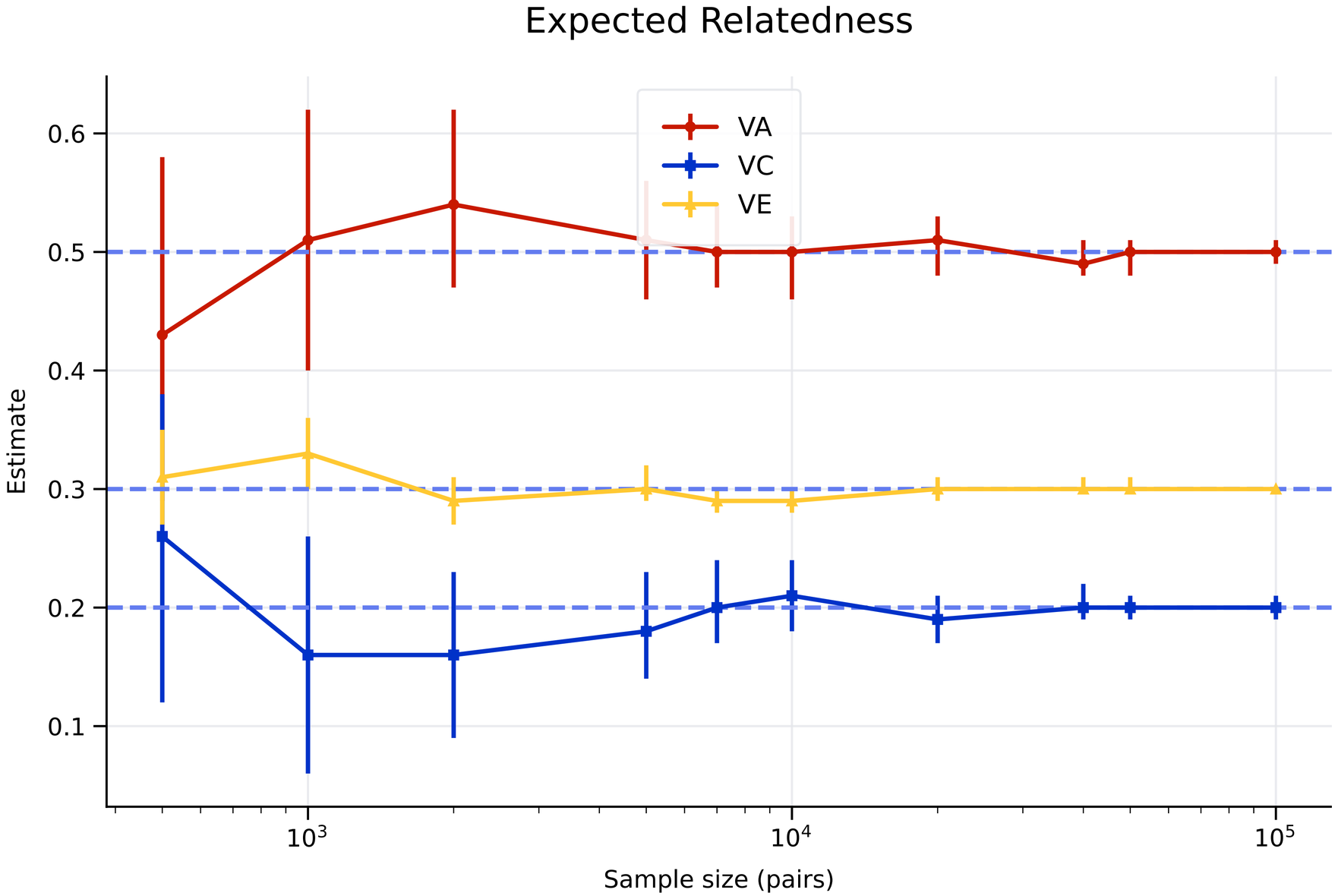
Practical 3

Fit single group ACE modeling

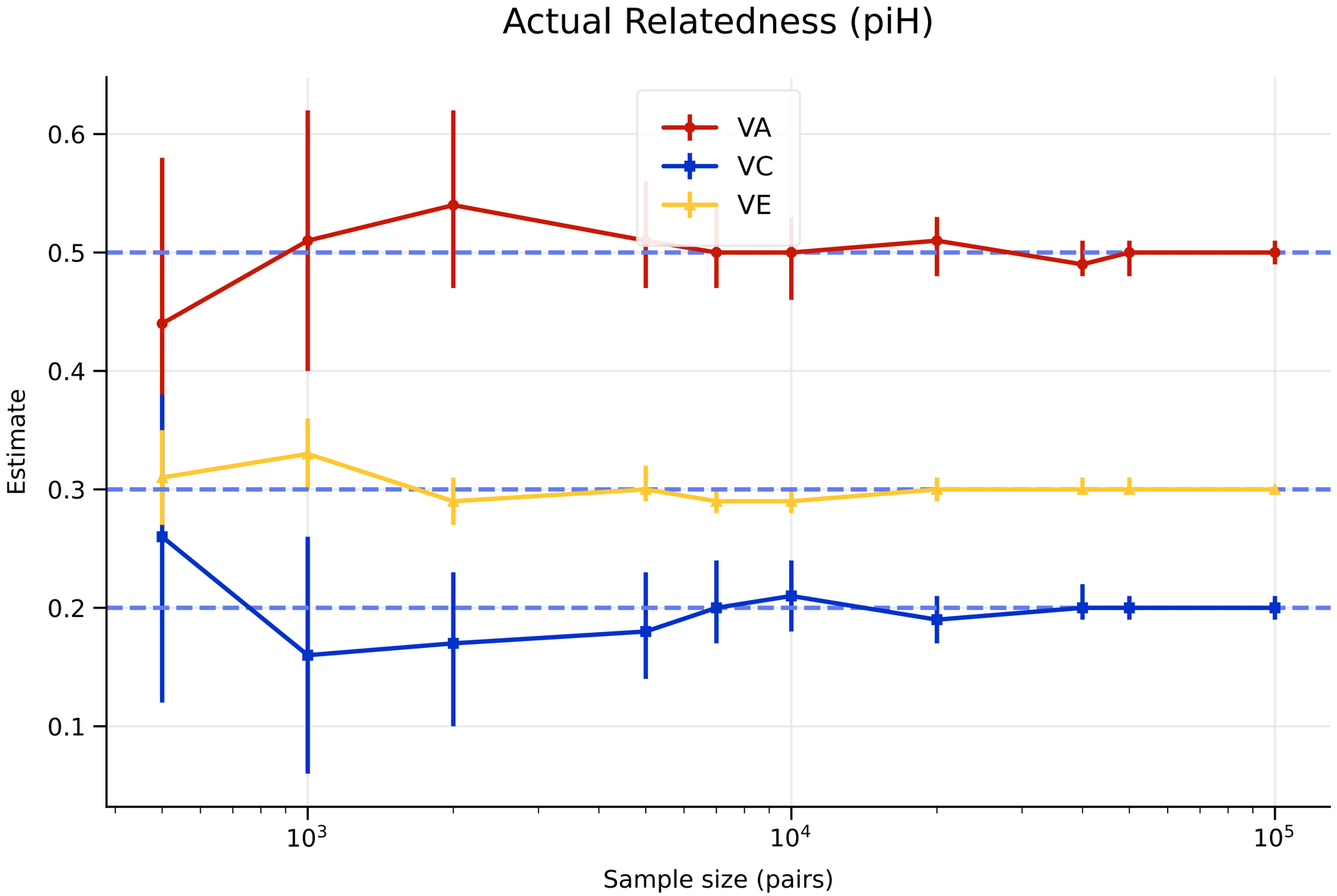
- oneSACEvcrH.R
  - one: univariate script analyzing one phenotype in pairs of twins
  - S: Saturated model: freely estimating all model parameters: means, variances, covariance
  - ACE: ACE model: A:additive genetic, C:common/shared environment, E:unique/specific environment
  - v: direct variance estimation
  - c: continuous data
  - r: relatedness (both expected: rel & actual: piH)

- Section 7: Prepare and Run ACE Model 3: Expected Relatedness as definition variable
- Section 8: Prepare and Run ACE Model 4: Actual Relatedness as definition variable
- Section 9: Prepare and Run ACE Model 3: Actual Relatedness for DZ's only
- Section 10: Summarize Results

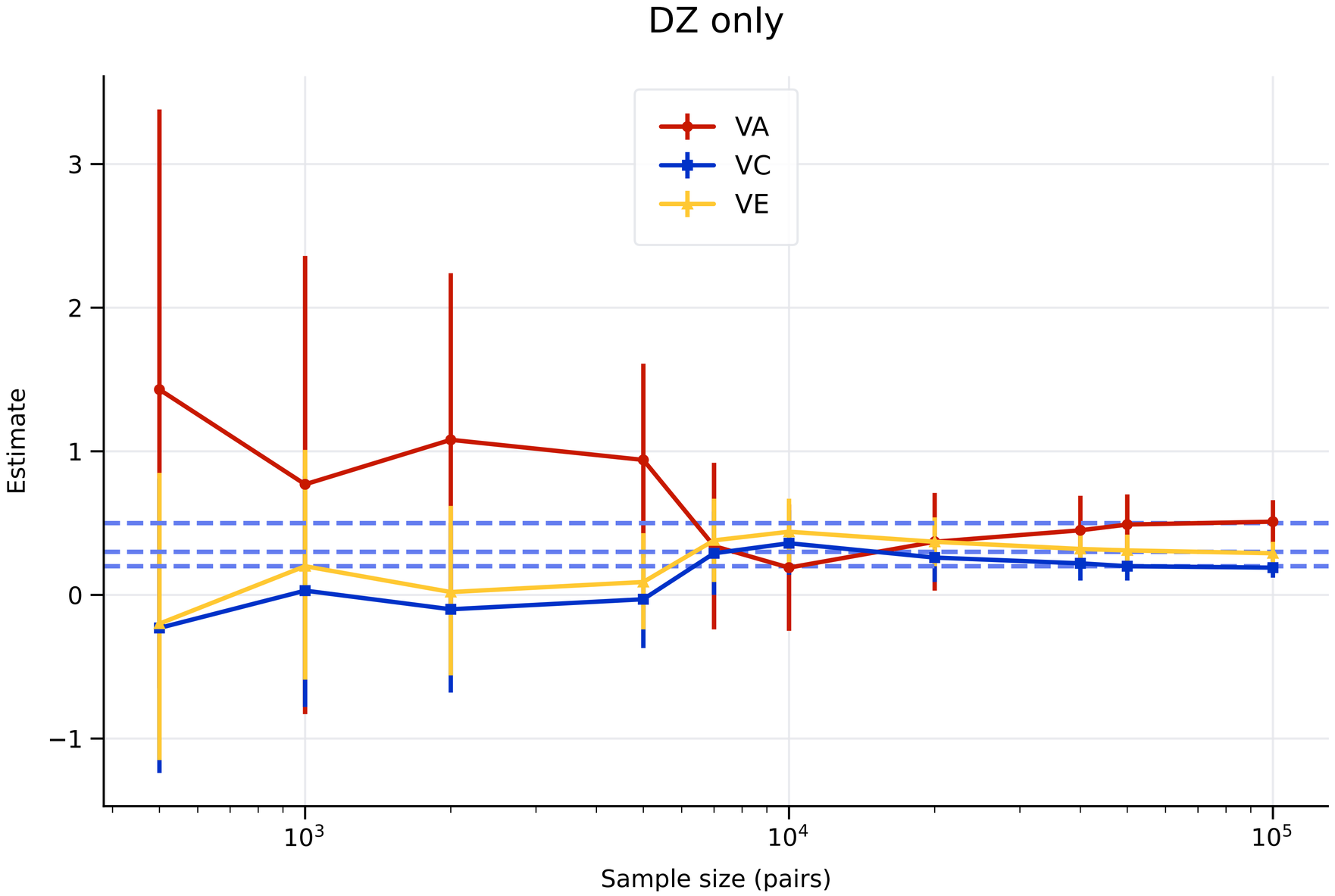
Expected Relatedness



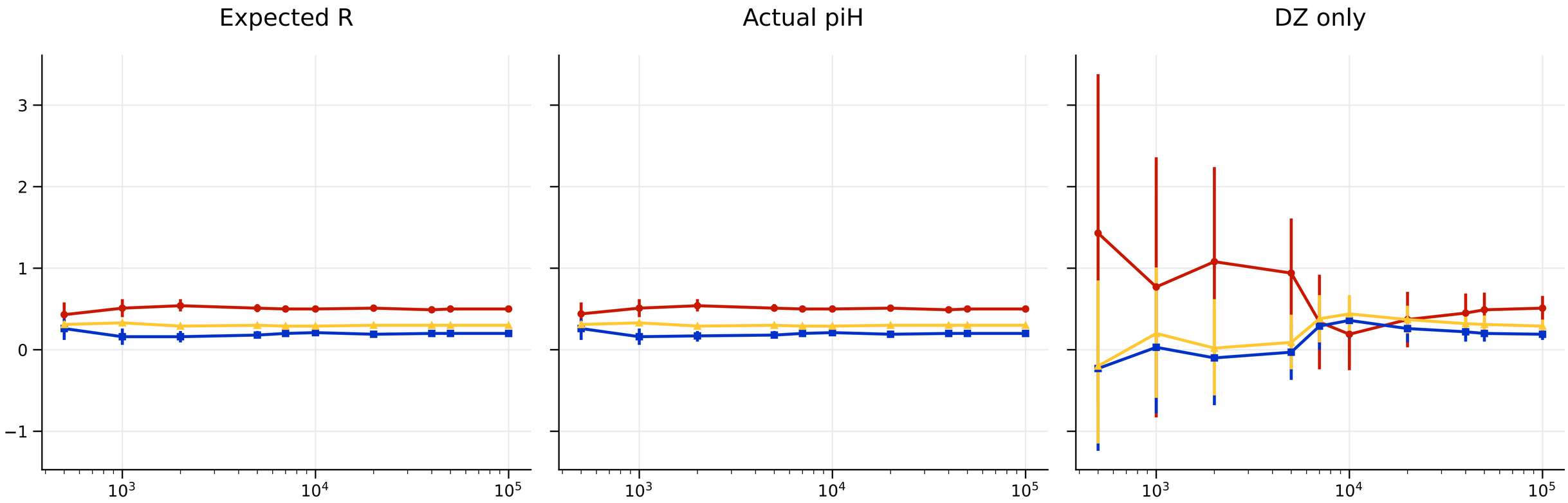
Actual Relatedness



Actual Relatedness DZs



Comparison of Three Scenarios



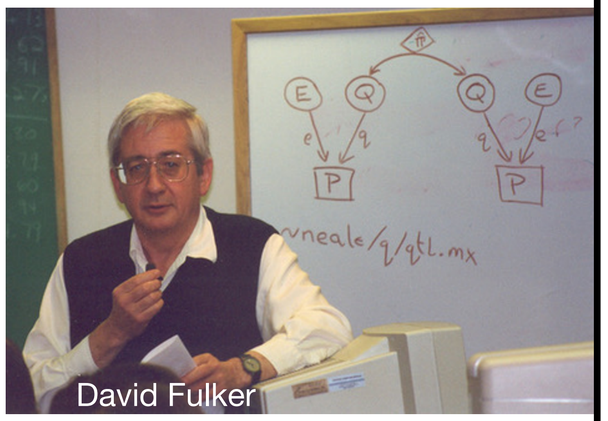
Day 3 Take Home Messages

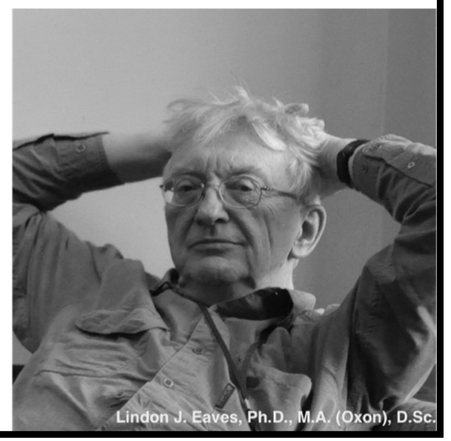
- The Classical Twin Design is a powerful design to estimate heritability, while also estimating shared and unique environmental sources of variation
- The estimate of twin heritability based on genotypic data used to calculate the actual relatedness (pihat) is similar to that using the expected relatedness when MZ data are included
- Large sample sizes are needed to get a stable estimate of the twin heritability from the actual relatedness genotyped of DZ twins (or siblings)
- Much more will be covered in the 2027 Boulder workshop

1987-2026

40th workshop

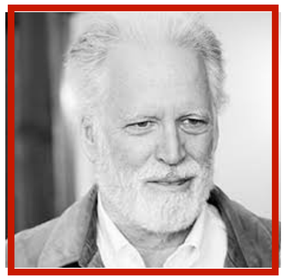
from left to right: Robert Derom†, Walter Nance†, Michael Neale, me, Joanne Meyer, Robert Vlietinck, Peter Molenaar, Andrew Heath, Karl Joreskog, Catherine Derom, Dorret Boomsma, Nick Martin, John Hewitt, Lindon Eaves†, David Fulker† [founders]





Thank you

OpenMx Development Team & International Statistical Genetics Team



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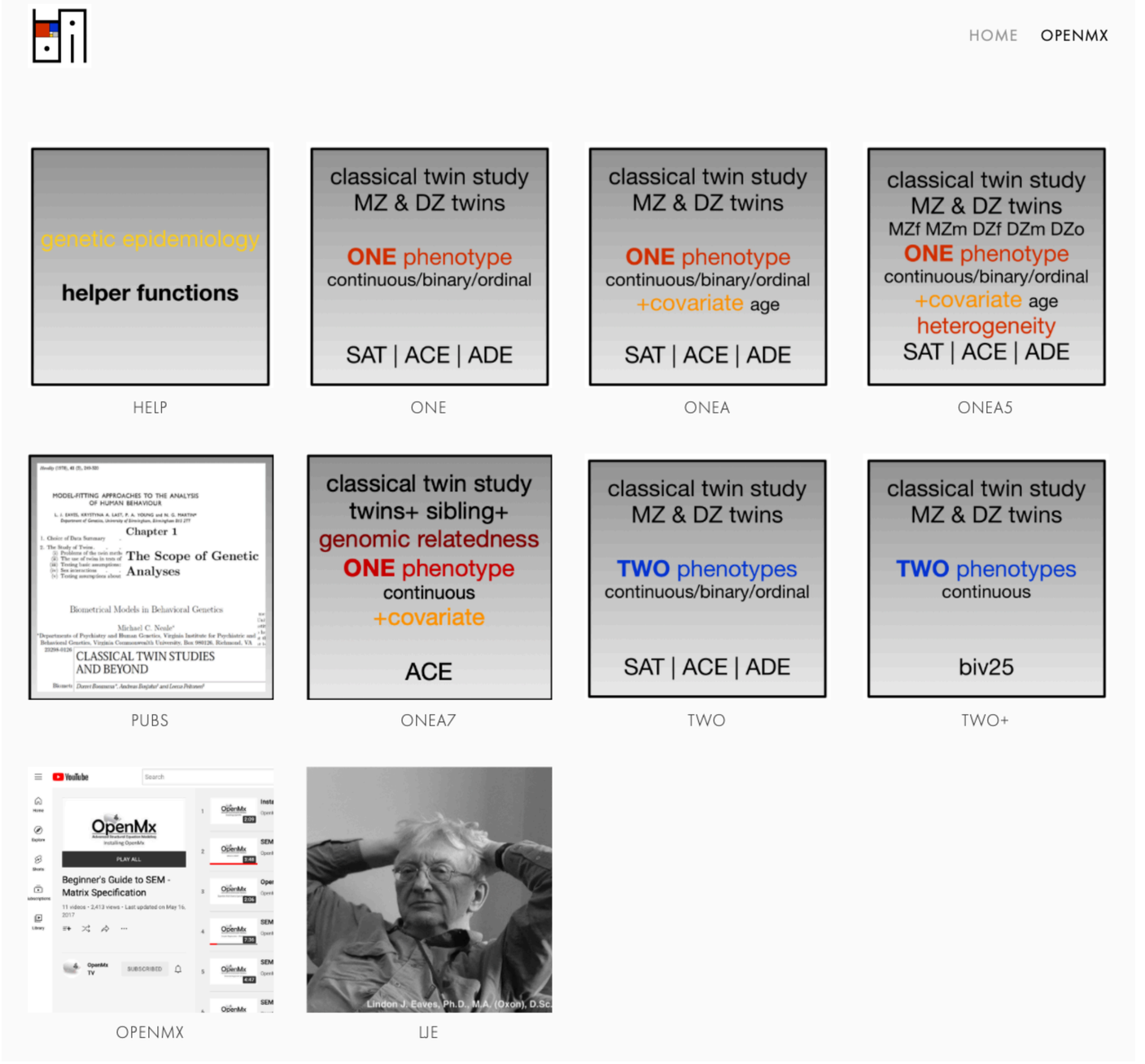

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