Univariate modeling

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Starting at the beginning…

- Data preparation
  - The algebra style used in Mx expects 1 line per case/family
  - (Almost) limitless number of families and variables
  - Missing data
    - Default missing code is now **NA**
    - **No missing covariates/definition variables!**
  - Quick R - http://www.statmethods.net/

Selecting and sub-setting data

- Make separate data sets for the MZ and DZ

```
> mzData <- as.data.frame(subset(data, zyg<3, c(bmi1,bmi2)))
> dzData <- as.data.frame(subset(data, zyg>2, c(bmi1,bmi2)))
> head(dzData)
       bmi1    bmi2
843 21.9642      NA
844 21.8791 21.2112
845 22.2321 22.6044
846 19.8491 20.1743
847 20.1743      NA
848 21.7050 21.2905
```

- Check data is numeric and behaves as expected

```
> cov(mzData,use="complete")
          bmi1      bmi2
bmi1 0.8779390 0.6734489
bmi2 0.6734489 0.8987715
> cov(dzData,use="complete")
          bmi1      bmi2
bmi1 0.8908474 0.2872594
bmi2 0.2872594 0.8657751
> colMeans(mzData,na.rm=TRUE)
    bmi1     bmi2
21.75089 21.73471
> colMeans(dzData,na.rm=TRUE)
    bmi1     bmi2
21.68689 21.88095
```

Common problem

- Problem: data contains a non numeric value

```
> cov(dzData,use="complete")
          bmi1      bmi2
bmi1 0.8908474 0.2872594
bmi2 0.2872594 0.8657751
Warning message:
In cov(dzData, use = "complete") : NAs introduced by coercion
> colMeans(mzData,na.rm=TRUE)
Error in colMeans(mzData, na.rm = TRUE) : 'x' must be numeric
> colMeans(dzData,na.rm=TRUE)
Error in colMeans(dzData, na.rm = TRUE) : 'x' must be numeric
```

20171	1	0.35	5	2	51	79	1.5999	1.7998	19.9219	24.3827	20.9427	22.3571
20188	1	0.37	5	2	53	65	1.5698	1.73	21.5019	21.7181	21.477	21.547
20204	1	0.53	5	1	58	64	1.6299	NA	21.83	NA	A	NA
20390	1	0.37	5	2	64	73	1.6499	1.8298	23.5078	21.7982	22.1013	21.5728
20398	1	0.52	5	2	60	77	1.6299	1.73	22.5827	25.7276	21.8203	22.7329

- Equivalent Mx Classic error - *Uh-oh... I'm having trouble reading a number in D or E format*

Important structural stuff

- openMx has a very fluid and flexible stucture
- Each code snippet is being saved as a variable
- We tend to reuse the variable names in our scripts
- This makes it very important to create a new project for each series of analyses
- Remember the project also contains the data so these files can become very large.

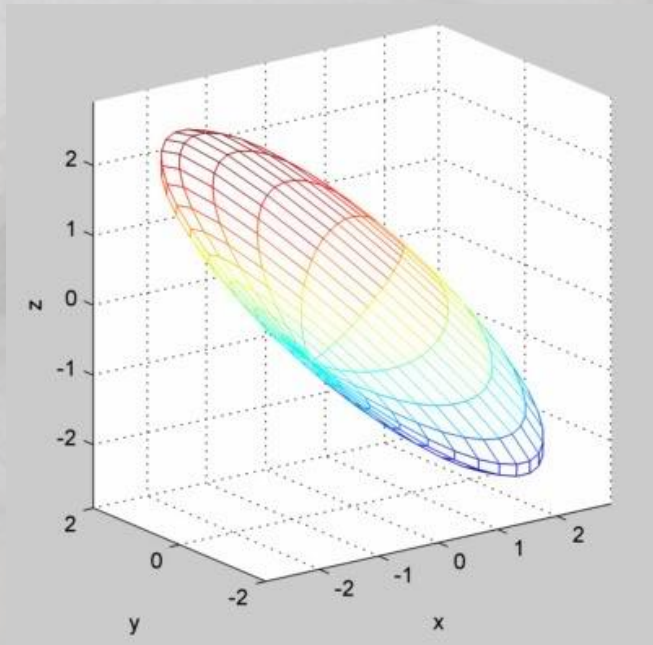
Matrices are the building blocks

```
mxMatrix( type="Lower", nrow=nv, ncol=nv, free=TRUE,
values=.6, label="a11", name="a" ), #X
```

- Many types eg. type="Lower"
- Denoted by names eg. name="a“
- Size eg. nrow=nv, ncol=nv
- All estimated parameters must be placed in a matrix & Mx must be told what type of matrix it is

Choosing the model

- Thinking about parameter space…
- Imagine an ACE model
- Solution space bounded by CIs



Choosing the model

- ACE vs ADE
  - With twins alone can't joint estimate ACDE
  - Options
    - Add in an extra relationship
    - Fix one of these parameters and estimate the other 3
    - Accept this limitation
      - All models are wrong some are useful (George E. P. Box)
    - Reject the twin model, pretend genes have no influence and interpret biological inheritance as a social phenomenon
  - No 1 size fits all solution

Quantifying and Addressing Parameter Indeterminacy in the Classical Twin Design

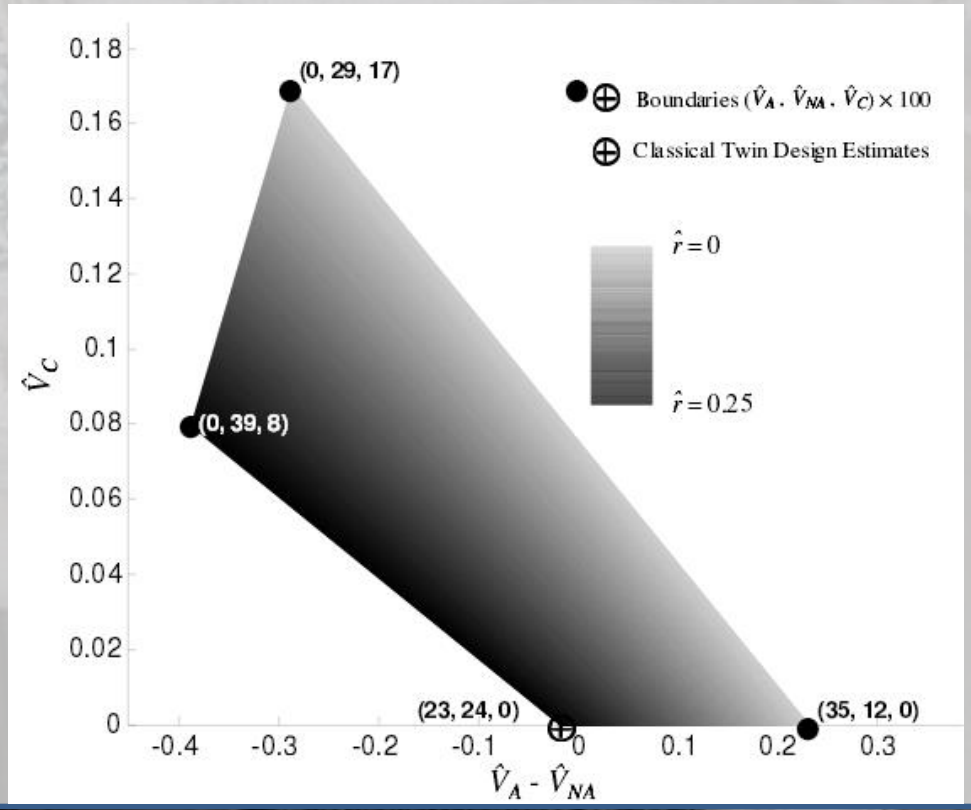
Matthew C. Keller[1] and William L. Coventry[2,3]

[1] Center for Society and Genetics, University of California, Los Angeles, United States of America
[2] Queensland Institute of Medical Research, Brisbane, Australia
[3] School of Psychology, University of New England, Armidale, Australia

Table 1

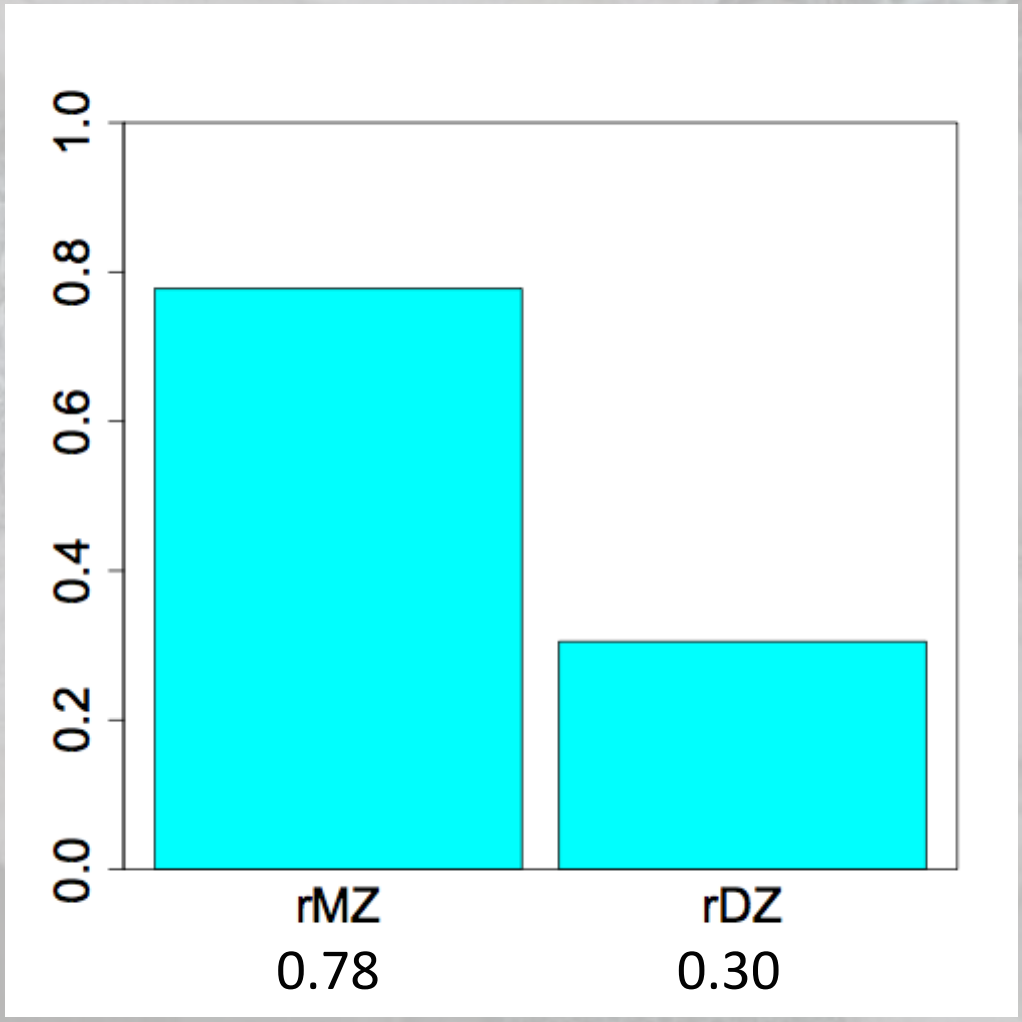
Methods of Obtaining $\hat{V}_A$, $\hat{V}_C$, and $\hat{V}_{NA}$ from $C\hat{V}_{NZ}$ and $C\hat{V}_{OZ}$ and the Boundaries of the Parameter Space Given Eight Different Pairs of Fixed Parameters Possible in Twin-Only Designs

Fixed Parameters	$\hat{V}_A$	$\hat{V}_{NA}$	$\hat{V}_C$
$C\hat{V}_{OZ}/C\hat{V}_{NZ} > 1/2$			
1. $\hat{r} = 0$, $\hat{V}_A = 0$	0 *min*	$C\hat{V}_{NZ} - C\hat{V}_{OZ}$ *inter*	$C\hat{V}_{OZ}$ *max*
2. $\hat{r} = 0$, $\hat{V}_{NA} = 0$	$2(C\hat{V}_{NZ} - C\hat{V}_{OZ})$ *max*	0 *min*	$2C\hat{V}_{OZ} - C\hat{V}_{NZ}$ *min*
3. $\hat{r} = .25$, $\hat{V}_A = 0$	0 *min*	$4/3(C\hat{V}_{NZ} - C\hat{V}_{OZ})$ *max*	$4/3C\hat{V}_{OZ} - 1/3C\hat{V}_{NZ}$ *inter*
4. $\hat{r} = .25$, $\hat{V}_{NA} = 0$	$2(C\hat{V}_{NZ} - C\hat{V}_{OZ})$ *max*	0 *min*	$2C\hat{V}_{OZ} - C\hat{V}_{NZ}$ *min*
$C\hat{V}_{OZ}/C\hat{V}_{NZ} < 1/2$			
5. $\hat{r} = 0$, $\hat{V}_A = 0$	0 *min*	$C\hat{V}_{NZ} - C\hat{V}_{OZ}$ *inter*	$C\hat{V}_{OZ}$ *max*
6. $\hat{r} = 0$, $\hat{V}_C = 0$	$2C\hat{V}_{OZ}$ *max*	$C\hat{V}_{NZ} - 2C\hat{V}_{OZ}$ *min*	0 *min*
7. $\hat{r} = .25$, $\hat{V}_A = 0$	0 *min*	$4/3(C\hat{V}_{NZ} - C\hat{V}_{OZ})$ *max*	$4/3C\hat{V}_{OZ} - 1/3C\hat{V}_{NZ}$ *inter*
8. $\hat{r} = .25$, $\hat{V}_C = 0$	$4C\hat{V}_{OZ} - C\hat{V}_{NZ}$ *inter*	$2C\hat{V}_{OZ} - 4C\hat{V}_{NZ}$ *inter*	0 *min*



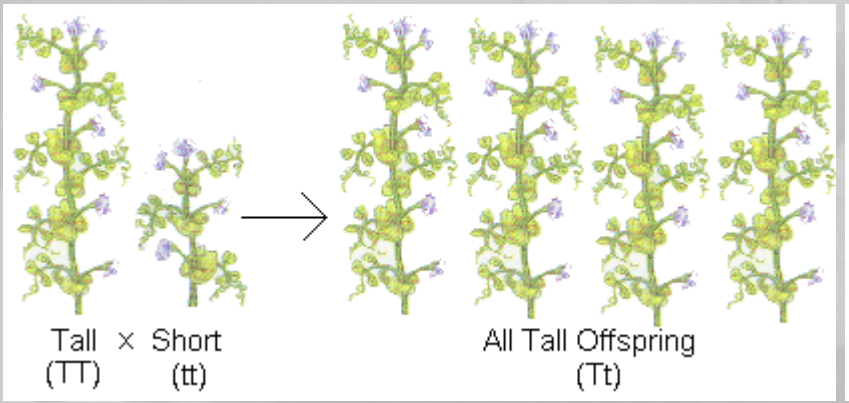
Yesterday we ran an ADE Model

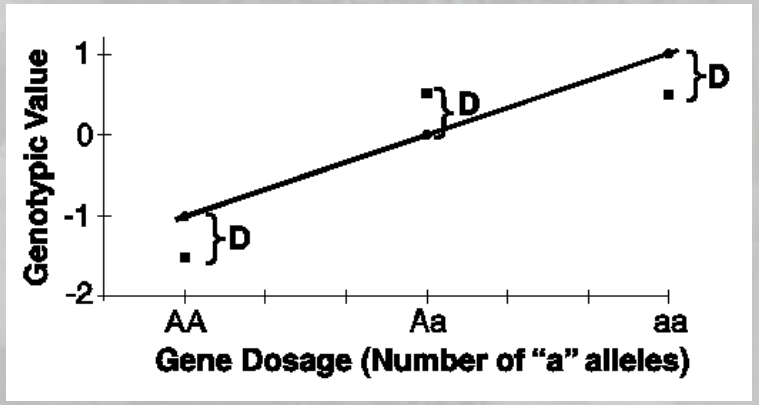
- Why?



What is D again?

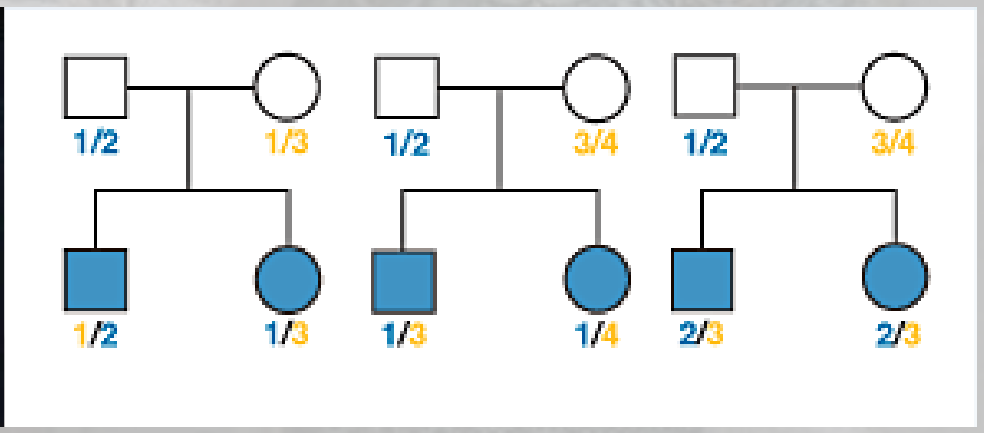
- Dominance refers to non-additive genetic effects resulting from interactions between alleles at the same locus or different loci (epistasis)





What is D again?

- DZ twins/full siblings share
  - ~50% of their segregating DNA &
  - for ~25% loci they share not only the genotype but also the parental origin of each allele



- DZ twins/full siblings share
  - ~50% of their segregating DNA &
  - for ~25% loci they share not only the genotype but also the parental origin of each allele

This is where the .5A comes from

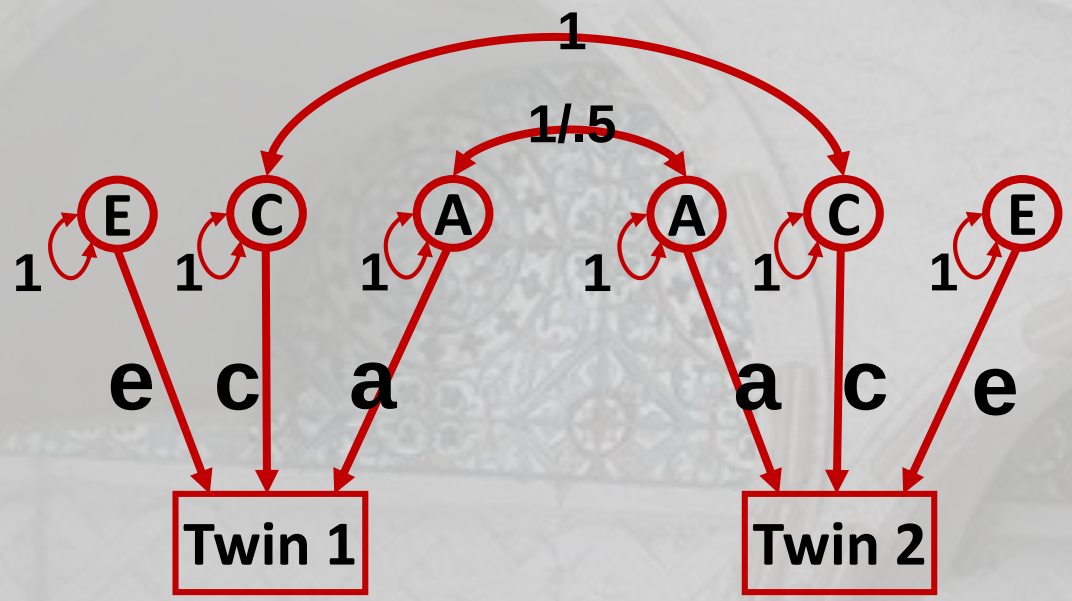
This is where the .25D comes from

Consider a mating between mother AB x father CD:

		Sib1			
		AC	**AD**	**BC**	**BD**
Sib 2	**AC**	2	1	1	0
	AD	1	2	0	1
	BC	1	0	2	1
	BD	0	1	1	2

IBD 0 : 1 : 2 = 25% : 50% : 25%

Today we will run an ACE model

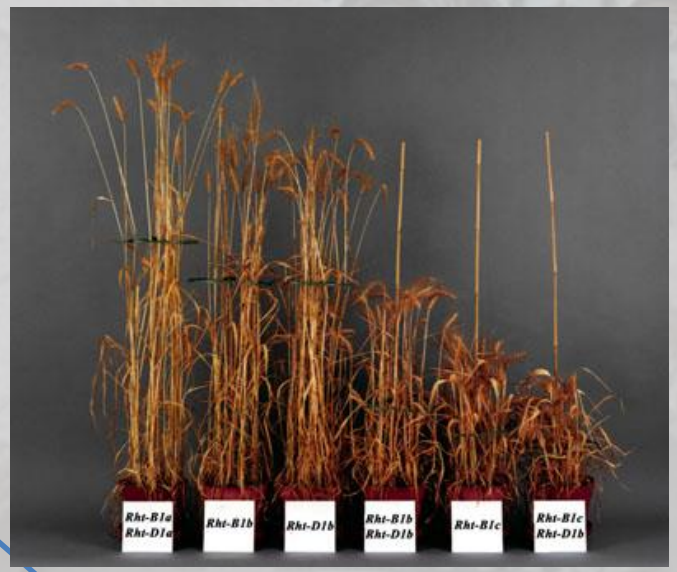


MZ		DZ	
$a^2+c^2+e^2$	a^2+c^2	$a^2+c^2+e^2$	$.5a^2+c^2$
a^2+c^2	$a^2+c^2+e^2$	$.5a^2+c^2$	$a^2+c^2+e^2$

Today we will run an ACE model

Additive genetic effects

- Why is the coefficient for DZ pairs .5?
- Average genetic sharing between siblings/DZ twins



Sib 2 \ Sib1	AC	AD	BC	BD
AC	2	1	1	0
AD	1	2	0	1
BC	1	0	2	1
BD	0	1	1	2

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

Today we will run an ACE model

Common environmental effects

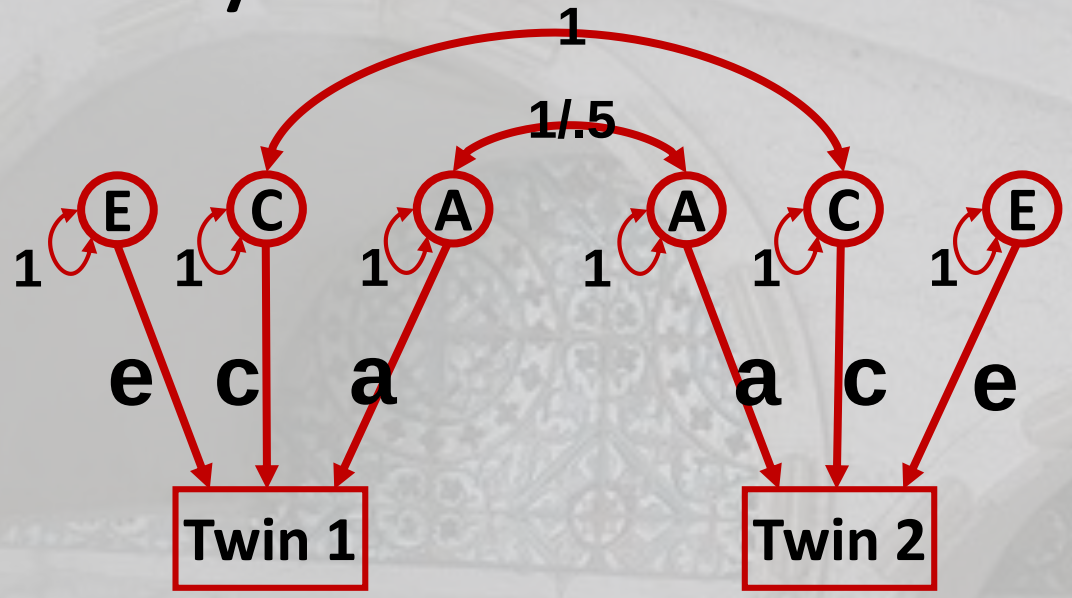
- Coefficient =1 for MZ and DZ pairs
- Equal environment assumption – for all the environmental influences THAT MATTER there is ON AVERAGE no differences in the degree of environmental sharing between MZ and DZ pairs

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

Today we will run an ACE model

- Open RStudio
- faculty/sarah/tues_morning
- Copy everything

Today we will run an ACE model




```
pathA     <- mxMatrix( type="Full", nrow=nv, ncol=nv, free=TRUE,
                       values=.6, label="a11", name="a" )
pathC     <- mxMatrix( type="Full", nrow=nv, ncol=nv, free=TRUE,
                       values=.6, label="c11", name="c" )
pathE     <- mxMatrix( type="Full", nrow=nv, ncol=nv, free=TRUE,
                       values=.6, label="e11", name="e" )
```

```
meanG     <- mxMatrix( type="Full", nrow=1, ncol=ntv, free=TRUE,
                       values= 20, label="mean", name="expMean" )
```

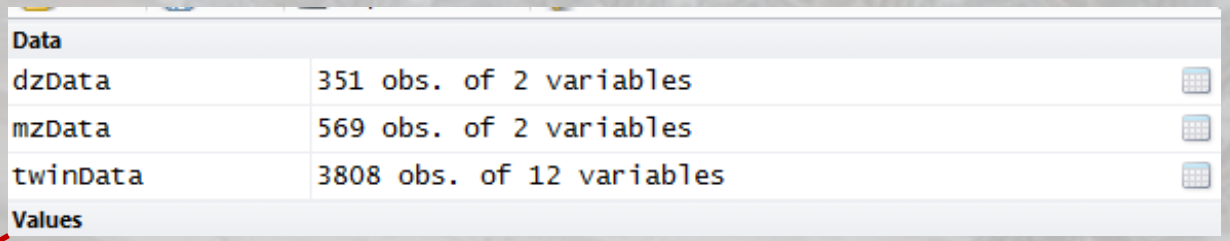
Today we will run an ACE model

```
covA      <- mxAlgebra( a %*% t(a), name="A" )
covC      <- mxAlgebra( c %*% t(c), name="C" )
covE      <- mxAlgebra( e %*% t(e), name="E" )
```

```
covMZ      <- mxAlgebra(
  rbind( cbind(A+C+E , A+C),
         cbind(A+C   , A+C+E)), name="expCovMZ" )
```

```
covDZ      <- mxAlgebra(
  rbind( cbind(A+C+E, 0.5%x%A+C),
         cbind(0.5%x%A+C , A+C+E)), name="expCovDZ" )
```

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




```
# Data objects for Multiple Groups
dataMZ     <- mxData( observed=mzData, type="raw" )
dataDZ     <- mxData( observed=dzData, type="raw" )

# Objective objects for Multiple Groups
objMZ      <- mxFIMLObjective( covariance="expCovMZ",
                               means="expMean", dimnames=selVars )

objDZ      <- mxFIMLObjective( covariance="expCovDZ",
                               means="expMean", dimnames=selVars )
```

To fit a model to data, the differences between the observed covariance matrix and model-implied expected covariance matrix are minimized.
Objective functions are functions for which free parameter values are chosen such that the value of the objective function is minimized.
mxFIMLObjective() uses full-information maximum likelihood to provide maximum likelihood estimates of free parameters in the algebra defined by the covariance and means arguments.

```
modelMZ   <- mxModel( pars, defAge, meanG, expMean, expCovMZ, dataMZ, objMZ,
               name="MZ" )
modelDZ   <- mxModel( pars, defAge, meanG, expMean, expCovDZ, dataDZ, objDZ,
               name="DZ" )
minus2ll  <- mxAlgebra( expression=MZ.objective + DZ.objective, name="m2LL" )
```

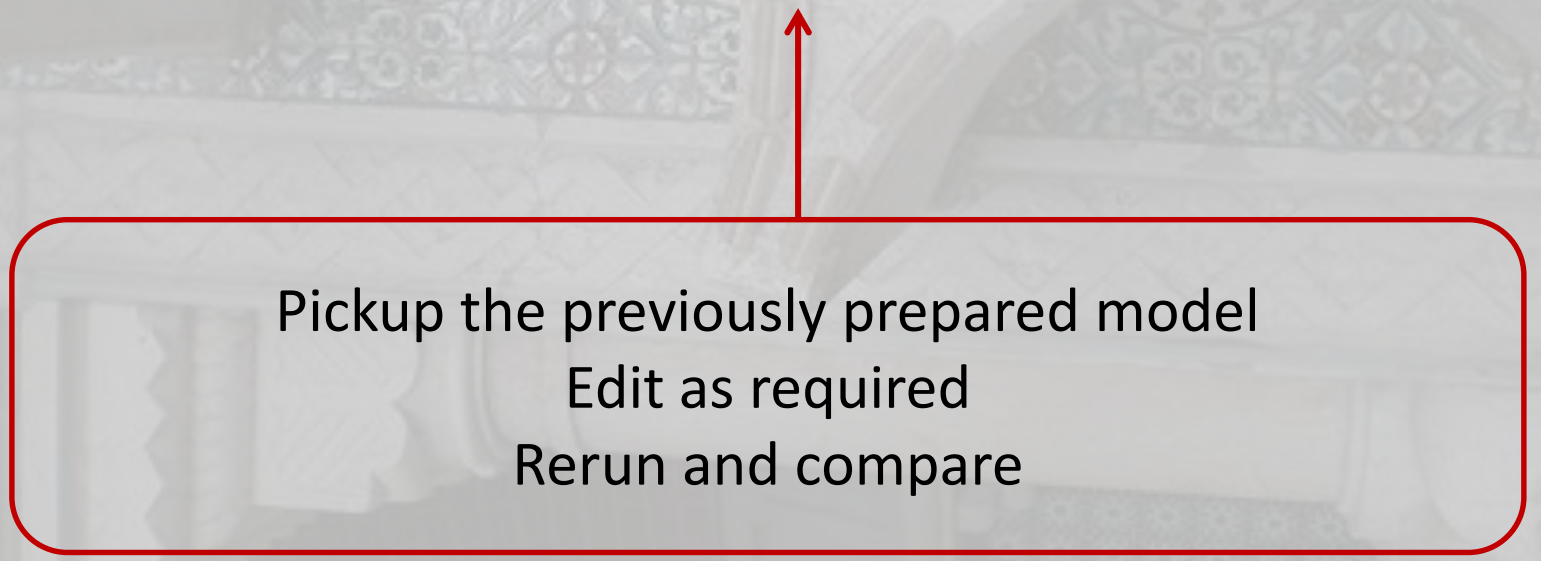
This models requires path parameters, means, covariance, data and objectives

Automatic naming – you don't need to predefine this

```
# Run ACE model
aceFit    <- mxRun(aceModel)
aceSumm   <- summary(aceFit)
aceSumm
```

Submodels

```
# Run AE model
aeModel    <- mxModel( aceFit, name="AE" )
aeModel    <- omxSetParameters( aeModel, labels="c11",
                                free=FALSE, values=0 )
aeFit      <- mxRun(aeModel)
round(aeFit@output$estimate,4)
```



Saving your output

- Save the R workspace
  - On closing click yes
  - Very big
  - Saves everything
- Save the fitted model
  - Equivalent to save in classic Mx
  - save(univACEFit, file="test.omxs")
  - load("test.omxs") – need to load OpenMx first

What to report

- Summary statistics
  - Usually from a simplified ‘saturated’ model
- Standardized estimates
  - Easier to conceptualise
    - ie 40% of the phenotypic variance vs a genetic effect of 2.84
    - Can easily be returned to original scale if summary statistics are provided

What to report

- Path coefficients
  - Very important in multivariate analyses
    - Gives a much clearer picture of the directionality of effects
- Variance components/proportion of variance explained
- Genetic correlations

General Advice/Problem solving

- Scripting styles differ
- Check the sample description
- Learn to love the webpage
- Comments are your friends

Bus shelter on the road to Sintra (Portugal)