Bivariate Genetic Analysis

Boulder Workshop 2018

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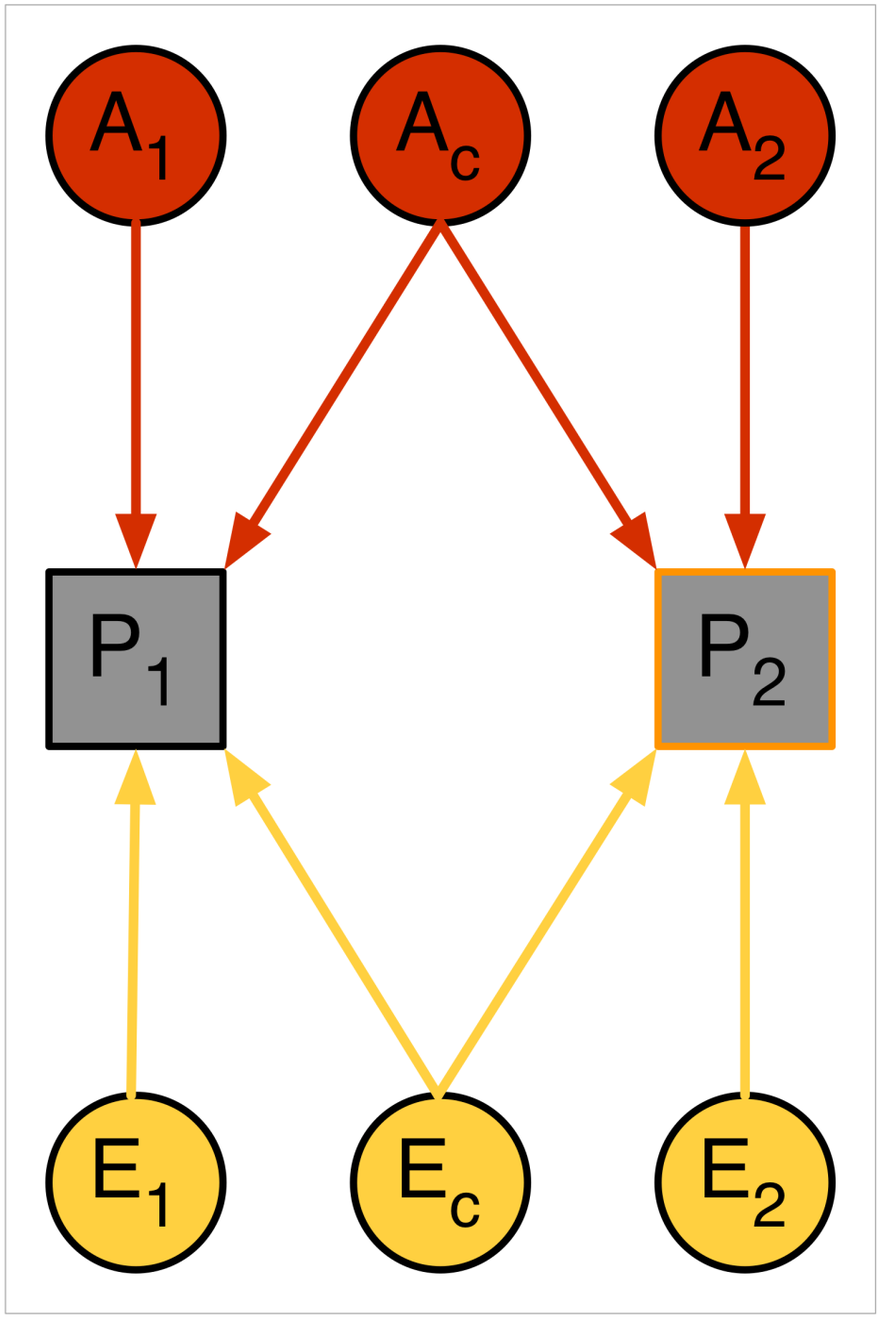
Questions

- 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



Causes of covariation

- Two or more traits can be correlated because they share common genes or common environmental influences
  - same genetic/environmental factors influencing traits?
- With twin data on multiple traits it is possible to partition the covariation into its genetic and environmental components
- Goal is 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	(within-twin cross-trait) covariance	cross-twin cross-trait covariance

Sources of Information

- Within-twin Cross-trait covariance: phenotypic covariance
- Cross-twin Cross-trait covariance: between twins
- MZ:DZ ratio of Cross-twin Cross-trait covariance
- Ratio of Cross-twin to Within-twin Cross-trait covariance

Variances Phenotype 1 (P1)

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	Variance $P1_{T1}$			
	$P2_{T1}$				
twin 2	$P1_{T2}$			Variance $P1_{T2}$	
	$P2_{T2}$				

Variances Phenotype 2 (P2)

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	Variance $P1_{T1}$			
	$P2_{T1}$		Variance $P2_{T1}$		
twin 2	$P1_{T2}$			Variance $P1_{T2}$	
	$P2_{T2}$				Variance $P2_{T2}$

Phenotypic Covariance P1-P2
Within-Twin Cross-Trait

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	Variance $P1_{T1}$	Covariance $P1_{T1}P2_{T1}$		
	$P2_{T1}$	Covariance $P1_{T1}P2_{T1}$	Variance $P2_{T1}$		
twin 2	$P1_{T2}$			Variance $P1_{T2}$	Covariance $P1_{T2}P2_{T2}$
	$P2_{T2}$			Covariance $P1_{T2}P2_{T2}$	Variance $P2_{T2}$

Cross-Twin Within-Trait P1

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	Variance $P1_{T1}$	Covariance $P1_{T1}P2_{T1}$	Within-Trait $P1_{T1}P1_{T2}$	
	$P2_{T1}$	Covariance $P1_{T1}P2_{T1}$	Variance $P2_{T1}$		
twin 2	$P1_{T2}$	Within-Trait $P1_{T1}P1_{T2}$		Variance $P1_{T2}$	Covariance $P1_{T2}P2_{T2}$
	$P2_{T2}$			Covariance $P1_{T2}P2_{T2}$	Variance $P2_{T2}$

Cross-Twin Within-Trait P2

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	Variance $P1_{T1}$	Covariance $P1_{T1}P2_{T1}$	Within-Trait $P1_{T1}P1_{T2}$	
	$P2_{T1}$	Covariance $P1_{T1}P2_{T1}$	Variance $P2_{T1}$		Within-Trait $P2_{T1}P2_{T2}$
twin 2	$P1_{T2}$	Within-Trait $P1_{T1}P1_{T2}$		Variance $P1_{T2}$	Covariance $P1_{T2}P2_{T2}$
	$P2_{T2}$		Within-Trait $P2_{T1}P2_{T2}$	Covariance $P1_{T2}P2_{T2}$	Variance $P2_{T2}$

Cross-Twin Cross-Trait X1Y2

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	Variance $P1_{T1}$	Covariance $P1_{T1}P2_{T1}$	Within-Trait $P1_{T1}P1_{T2}$	Cross-Trait $P1_{T1}P2_{T2}$
	$P2_{T1}$	Covariance $P1_{T1}P2_{T1}$	Variance $P2_{T1}$		Within-Trait $P2_{T1}P2_{T2}$
twin 2	$P1_{T2}$	Within-Trait $P1_{T1}P1_{T2}$		Variance $P1_{T2}$	Covariance $P1_{T2}P2_{T2}$
	$P2_{T2}$	Cross-Trait $P1_{T1}P2_{T2}$	Within-Trait $P2_{T1}P2_{T2}$	Covariance $P1_{T2}P2_{T2}$	Variance $P2_{T2}$

Cross-Twin Cross-Trait X2Y1

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	Variance $P1_{T1}$	Covariance $P1_{T1}P2_{T1}$	Within-Trait $P1_{T1}P1_{T2}$	Cross-Trait $P1_{T1}P2_{T2}$
	$P2_{T1}$	Covariance $P1_{T1}P2_{T1}$	Variance $P2_{T1}$	Cross-Trait $P2_{T1}P1_{T2}$	Within-Trait $P2_{T1}P2_{T2}$
twin 2	$P1_{T2}$	Within-Trait $P1_{T1}P1_{T2}$	Cross-Trait $P2_{T1}P1_{T2}$	Variance $P1_{T2}$	Covariance $P1_{T2}P2_{T2}$
	$P2_{T2}$	Cross-Trait $P1_{T1}P2_{T2}$	Within-Trait $P2_{T1}P2_{T2}$	Covariance $P1_{T2}P2_{T2}$	Variance $P2_{T2}$

Bivariate Twin Covariance Matrix

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	$VP1_{T1}$	$CP1_{T1}P2_{T1}$	$CP1_{T1}P1_{T2}$	$CP1_{T1}P2_{T2}$
	$P2_{T1}$	$CP1_{T1}P2_{T1}$	$VP2_{T1}$	$CP2_{T1}P1_{T2}$	$CP2_{T1}P2_{T2}$
twin 2	$P1_{T2}$	$CP1_{T1}P1_{T2}$	$CP2_{T1}P1_{T2}$	$VP1_{T2}$	$CP1_{T2}P2_{T2}$
	$P2_{T2}$	$CP1_{T1}P2_{T2}$	$CP2_{T1}P2_{T2}$	$CP1_{T2}P2_{T2}$	$VP2_{T2}$

Within Twin Covariances

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	$VP1_{T1}$	$CP1_{T1}P2_{T1}$	$CP1_{T1}P1_{T2}$	$CP1_{T1}P2_{T2}$
	$P2_{T1}$	$CP1_{T1}P2_{T1}$	$VP2_{T1}$	$CP2_{T1}P1_{T2}$	$CP2_{T1}P2_{T2}$
twin 2	$P1_{T2}$	$CP1_{T1}P1_{T2}$	$CP2_{T1}P1_{T2}$	$VP1_{T2}$	$CP1_{T2}P2_{T2}$
	$P2_{T2}$	$CP1_{T1}P2_{T2}$	$CP2_{T1}P2_{T2}$	$CP1_{T2}P2_{T2}$	$VP2_{T2}$

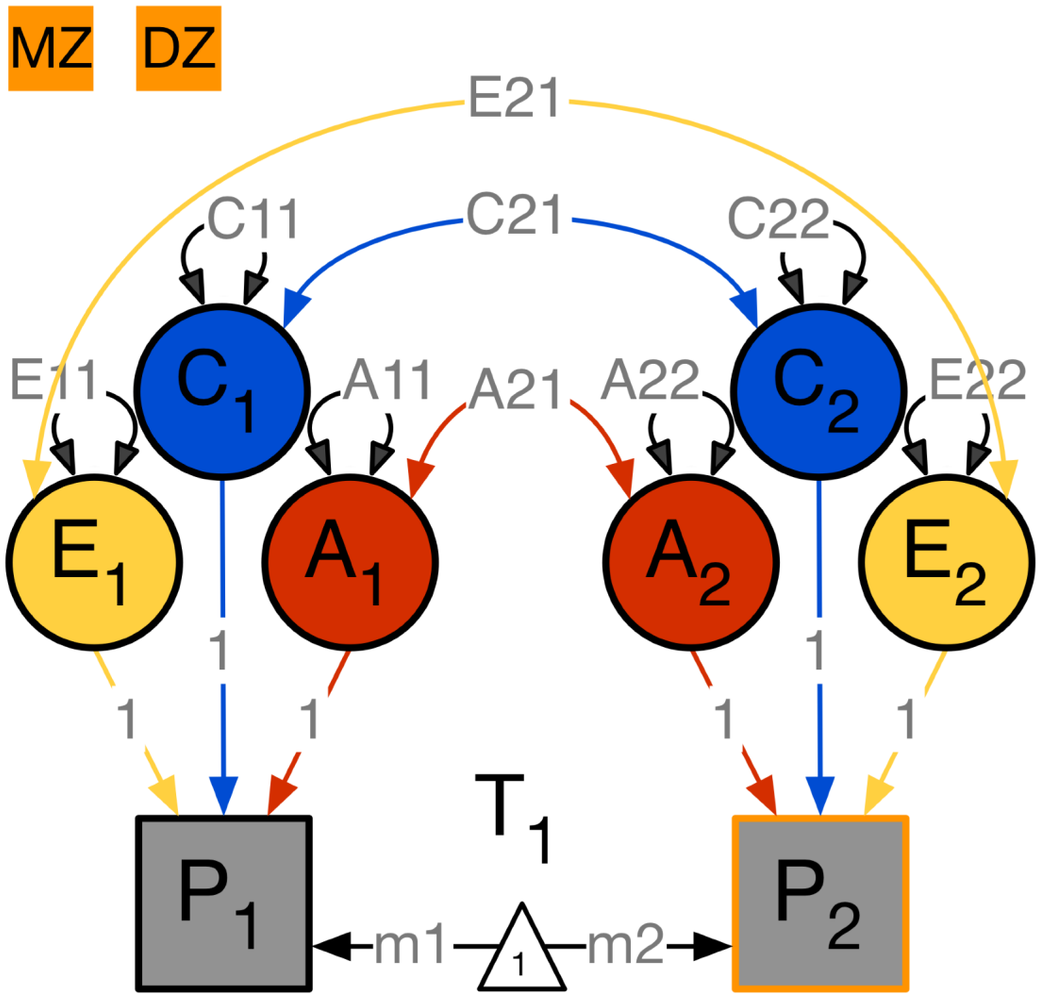
Within-Twin Covariance

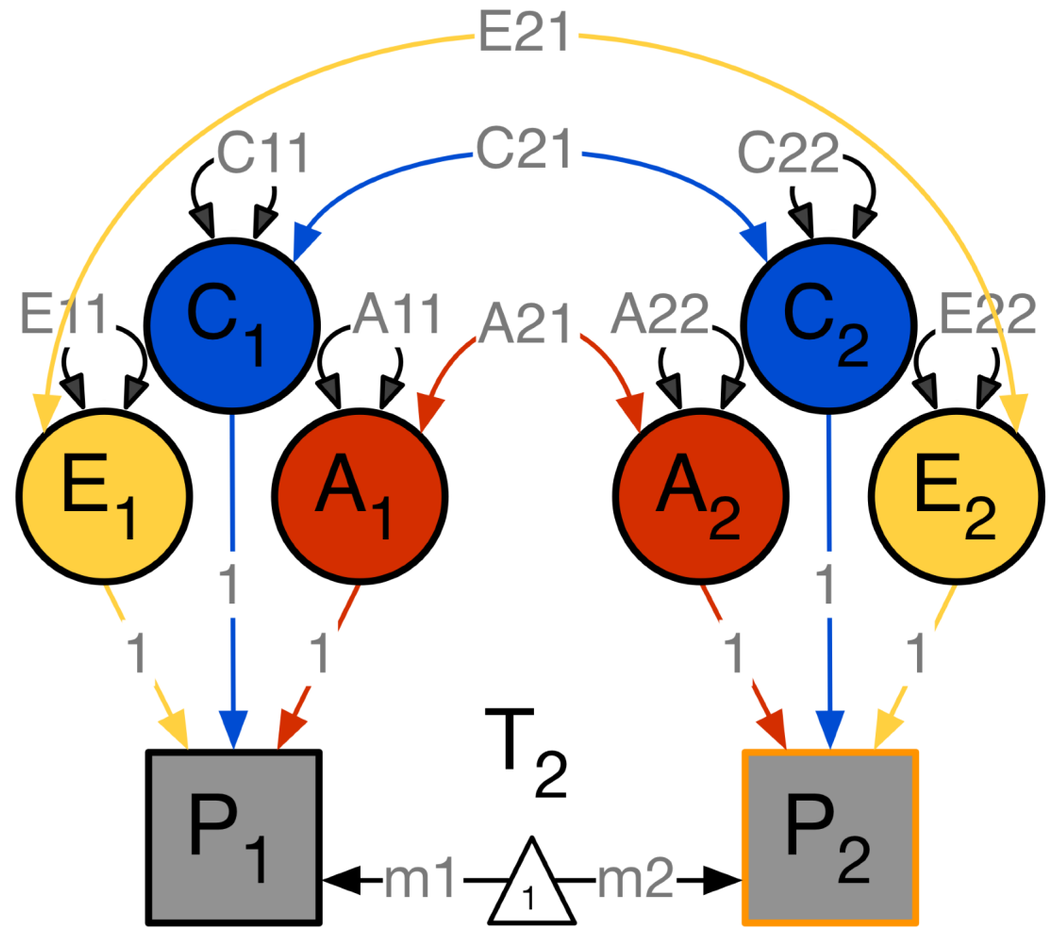
Within-Twin Covariance

Cross-Twin Covariances

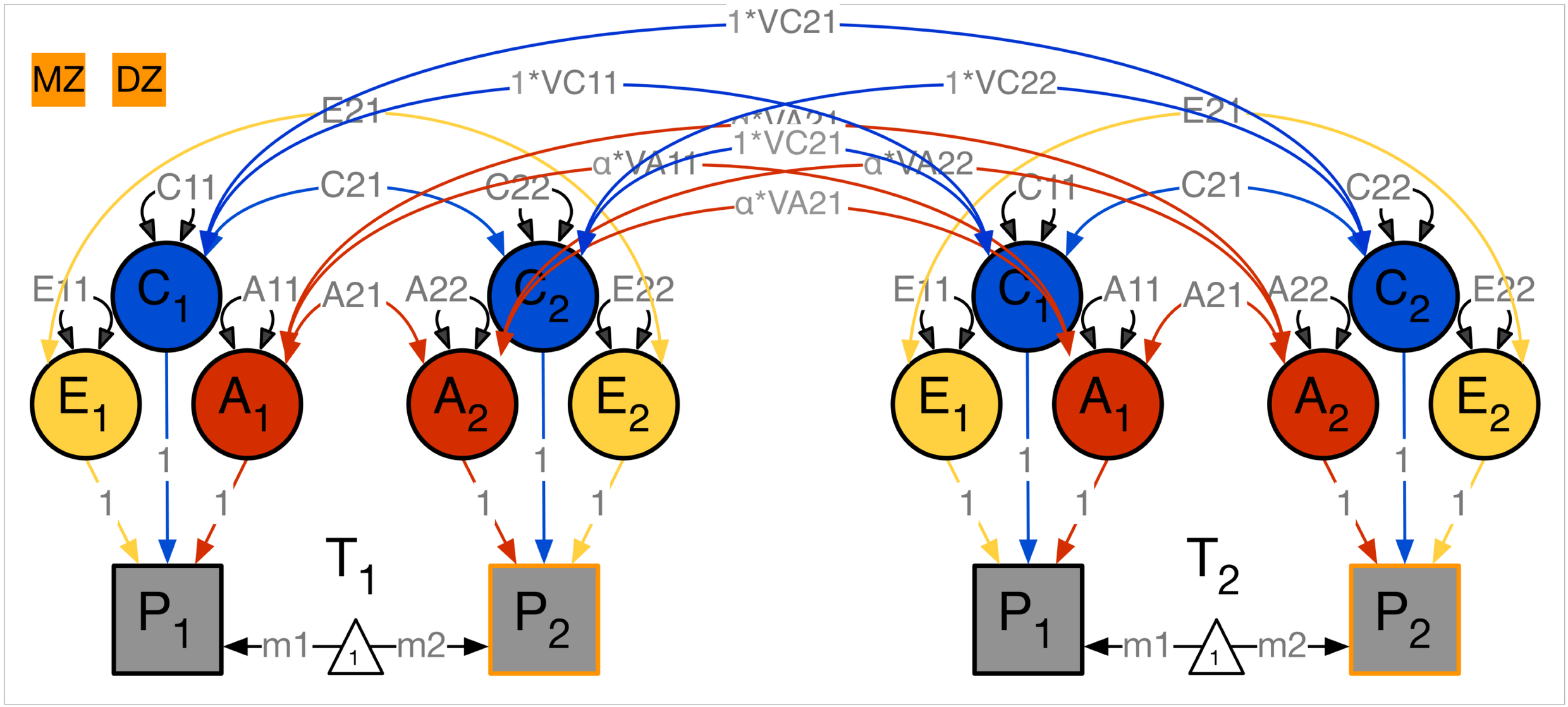
		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	$VP1_{T1}$ Within-Twin	$CP1_{T1}P2_{T1}$ Covariance	$CP1_{T1}P1_{T2}$ **Cross-Twin**	$CP1_{T1}P2_{T2}$ **Covariance**
	$P2_{T1}$	$CP1_{T1}P2_{T1}$	$VP2_{T1}$	$CP2_{T1}P1_{T2}$	$CP2_{T1}P2_{T2}$
twin 2	$P1_{T2}$	$CP1_{T1}P1_{T2}$ **Cross-Twin**	$CP2_{T1}P1_{T2}$ **Covariance**	$VP1_{T2}$ Within-Twin	$CP1_{T2}P2_{T2}$ Covariance
	$P2_{T2}$	$CP1_{T1}P2_{T2}$	$CP2_{T1}P2_{T2}$	$CP1_{T2}P2_{T2}$	$VP2_{T2}$

Two Phenotypes/Twin - Within-Twin Covariances

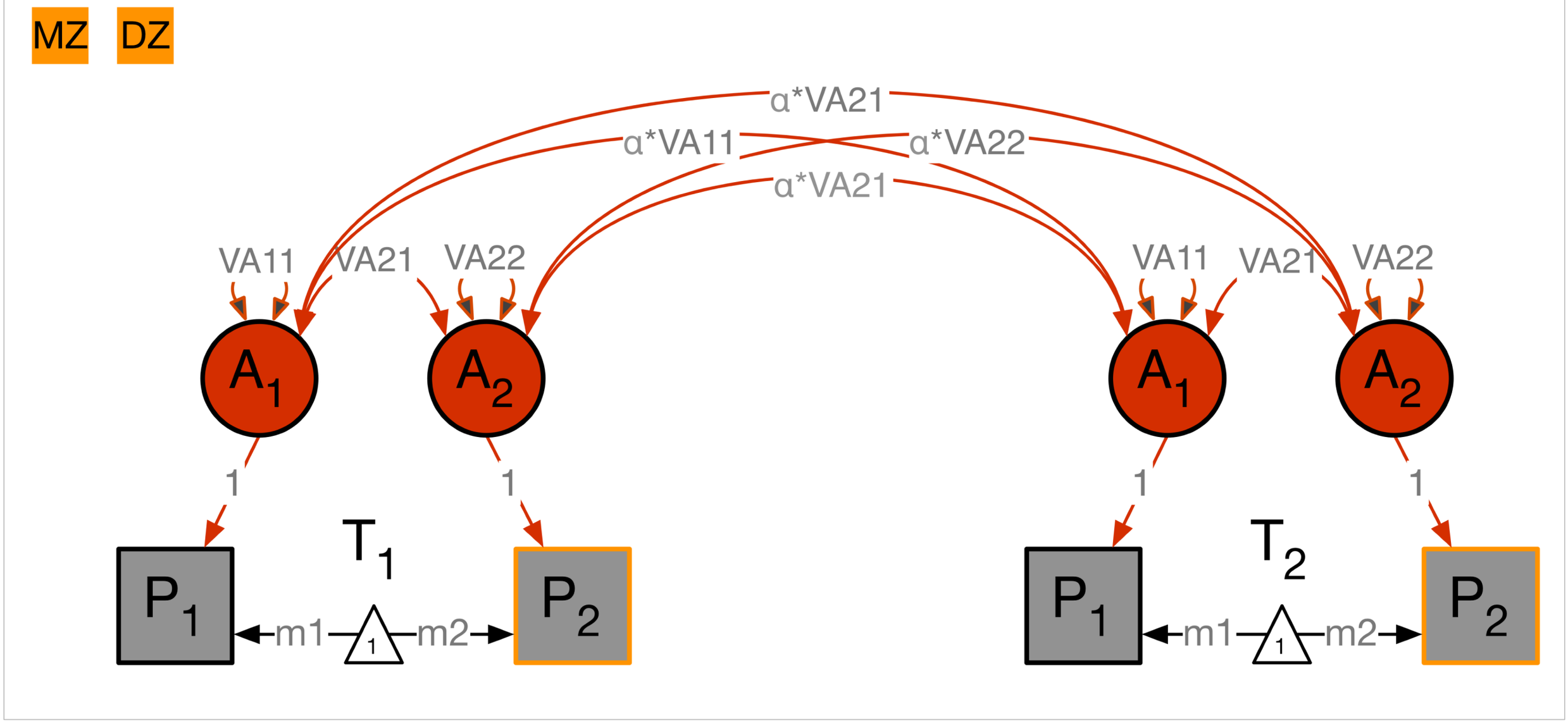




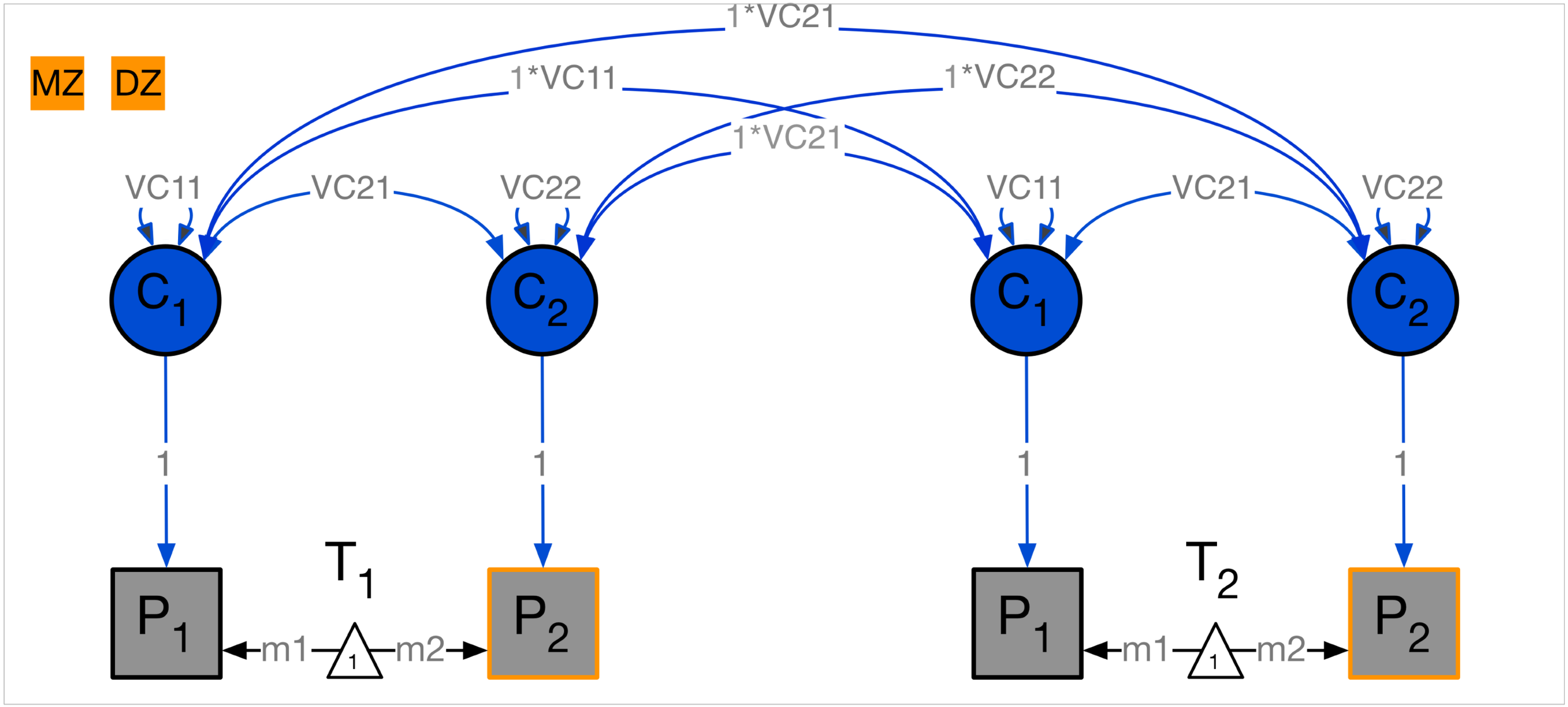
Cross-Twin Covariances



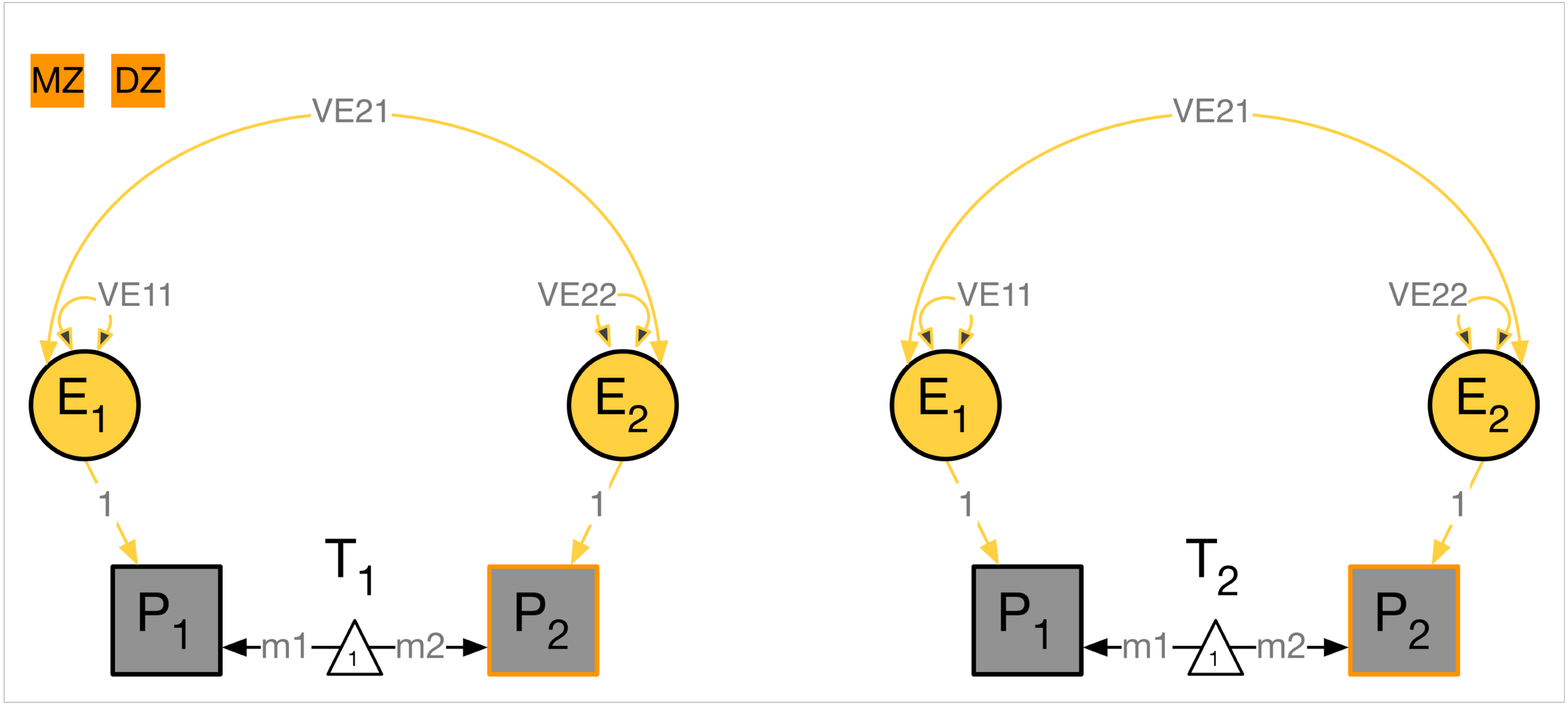
A Cross-Twin Covariances



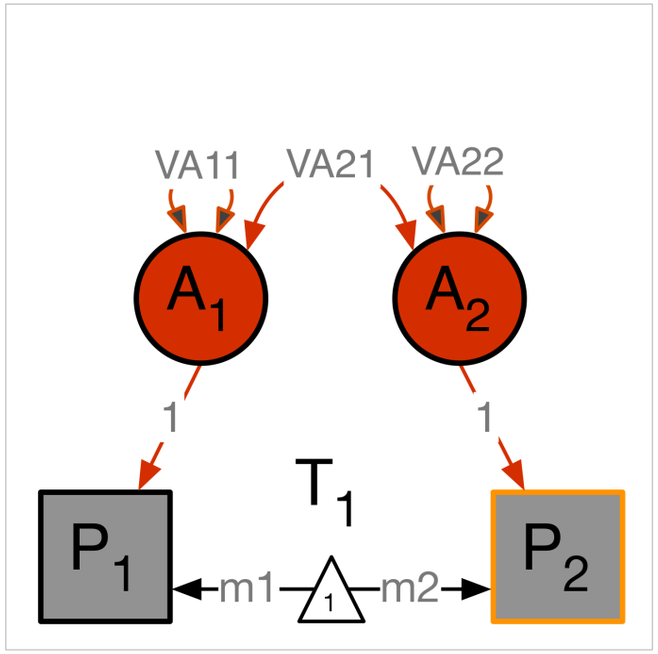
C Cross-Twin Covariances



E Cross-Twin Covariances



Bivariate Twin Covariance Matrix

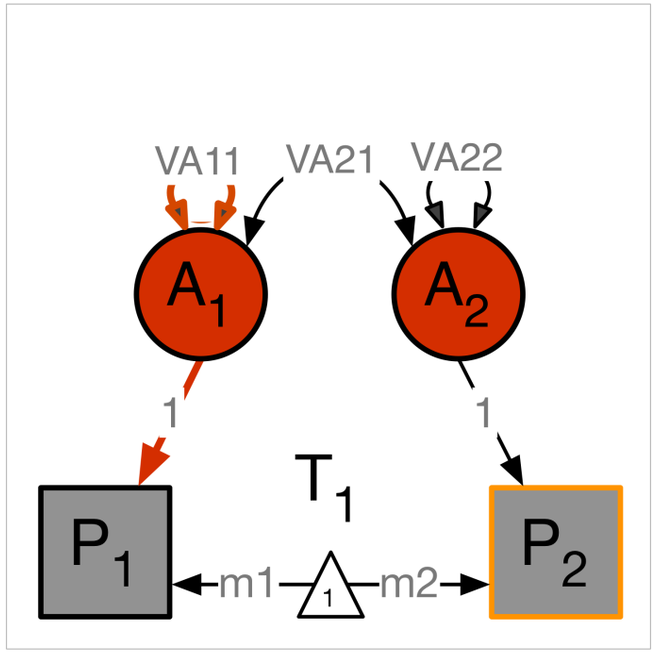


twin 1

	$P1_{T1}$	$P2_{T1}$
$P1_{T1}$	Variance $P1_{T1}$	Covariance $P1_{T1}P2_{T1}$
$P2_{T1}$	Covariance $P1_{T1}P2_{T1}$	Variance $P2_{T1}$

twin 1

Bivariate Twin Covariance Matrix

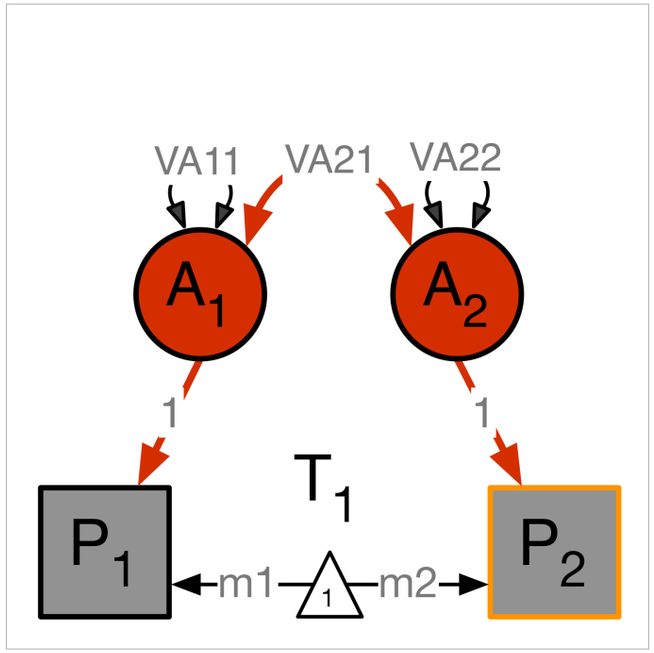


twin 1

	$P1_{T1}$	$P2_{T1}$
$P1_{T1}$	VA11	Covariance $P1_{T1}P2_{T1}$
$P2_{T1}$	Covariance $P1_{T1}P2_{T1}$	Variance $P2_{T1}$

twin 1

Bivariate Twin Covariance Matrix

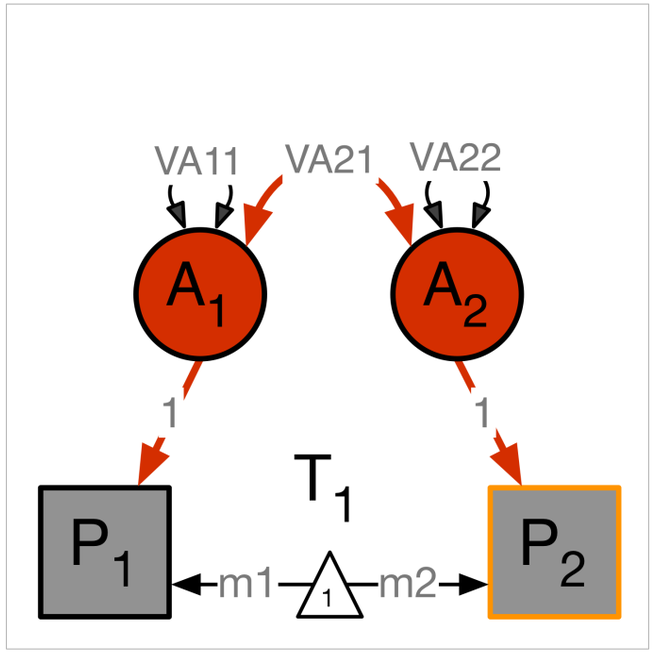


twin 1

	$P1_{T1}$	$P2_{T1}$
$P1_{T1}$	VA11	Covariance $P1_{T1}P2_{T1}$
$P2_{T1}$	VA21	Variance $P2_{T1}$

twin 1

Bivariate Twin Covariance Matrix

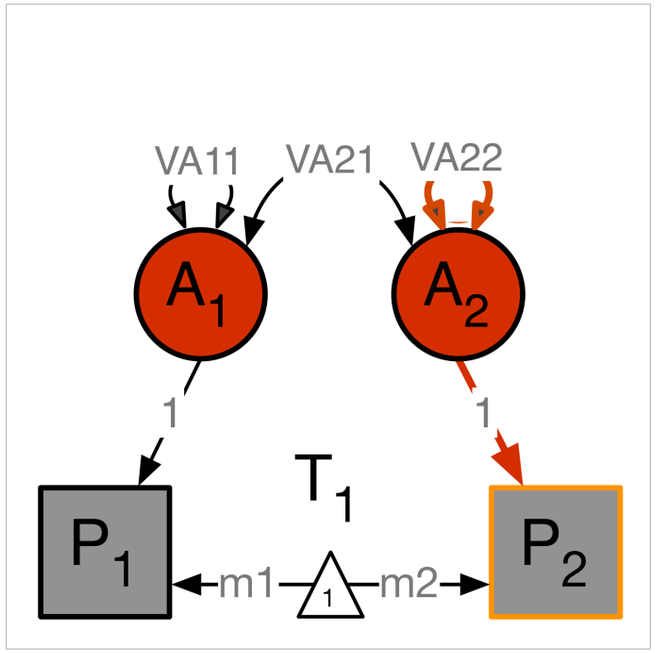


twin 1

	$P1_{T1}$	$P2_{T1}$
$P1_{T1}$	VA11	VA21
$P2_{T1}$	VA21	Variance $P2_{T1}$

twin 1

Bivariate Twin Covariance Matrix



twin 1

	$P1_{T1}$	$P2_{T1}$
$P1_{T1}$	VA11	VA21
$P2_{T1}$	VA21	VA22

twin 1

Bivariate Twin Covariance Matrix

twin 1

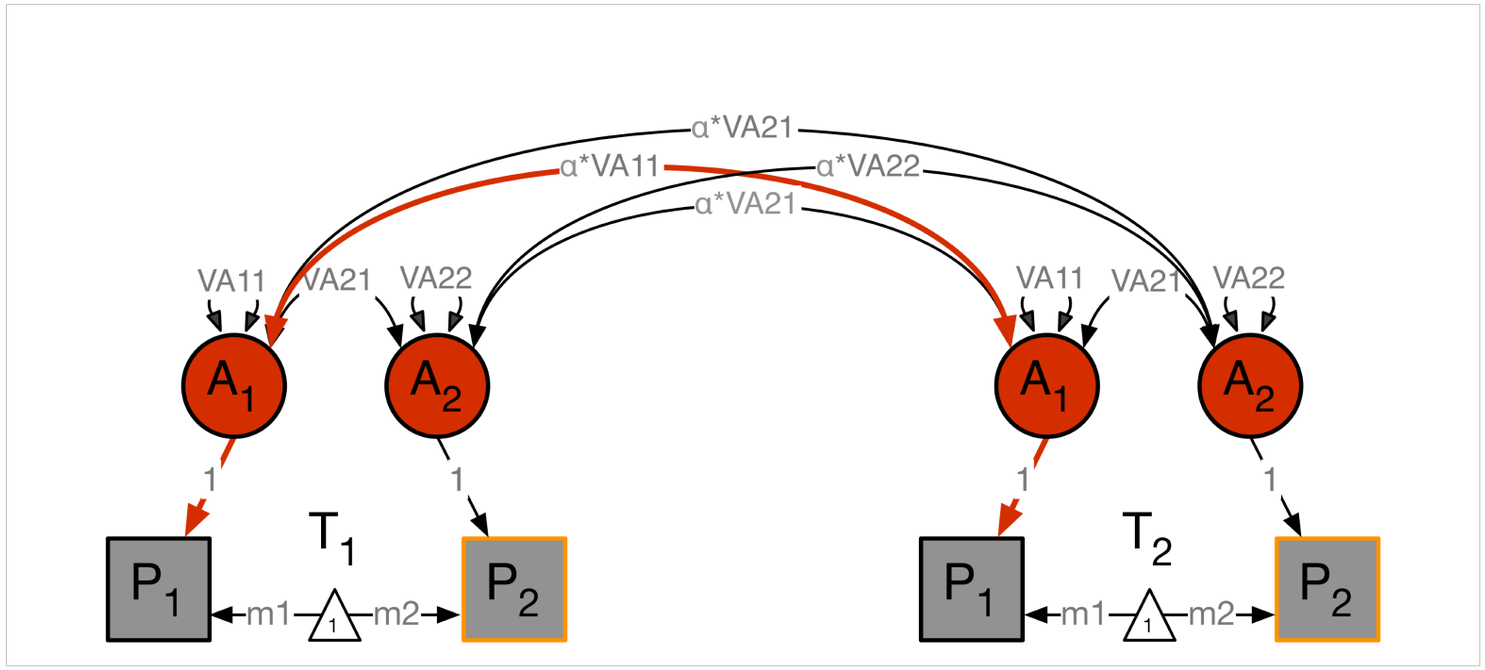
twin 1	$P1_{T1}$	$P2_{T1}$
$P1_{T1}$	VA11 + VE11	VA21 + VE21
$P2_{T1}$	VA21 + VE21	VA22 + VE22

Bivariate Twin Covariance Matrix

twin 1

twin 2	$P1_{T1}$	$P2_{T1}$
$P1_{T2}$	Within-Trait $P1_{T1}P1_{T2}$	Cross-Trait $P1_{T1}P2_{T2}$
$P2_{T2}$	Cross-Trait $P2_{T1}P1_{T2}$	Within-Trait $P2_{T1}P2_{T2}$

Bivariate Twin Covariance Matrix

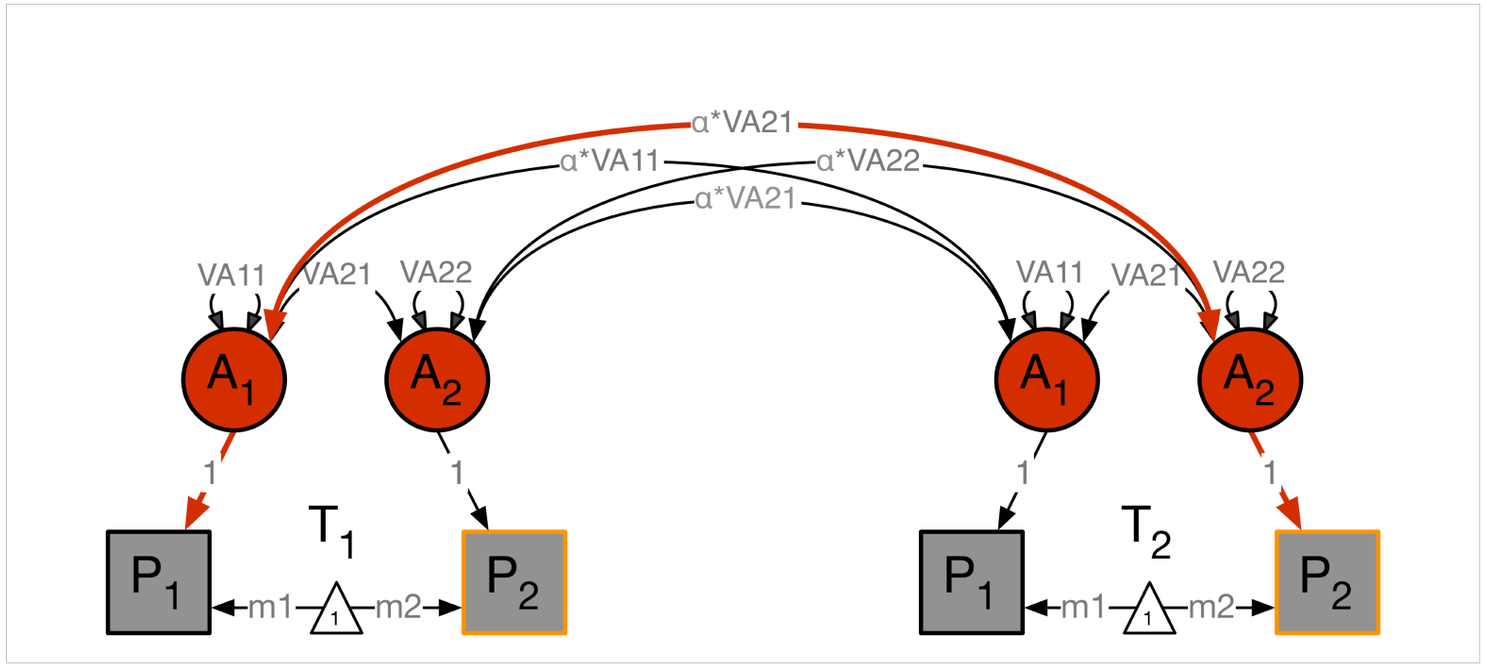


twin 1

twin 2

	$P1_{T1}$	$P2_{T1}$
$P1_{T2}$	1/0.5 * VA11	Cross-Trait $P1_{T1}P2_{T2}$
$P2_{T2}$	Cross-Trait $P2_{T1}P1_{T2}$	Within-Trait $P2_{T1}P2_{T2}$

Bivariate Twin Covariance Matrix

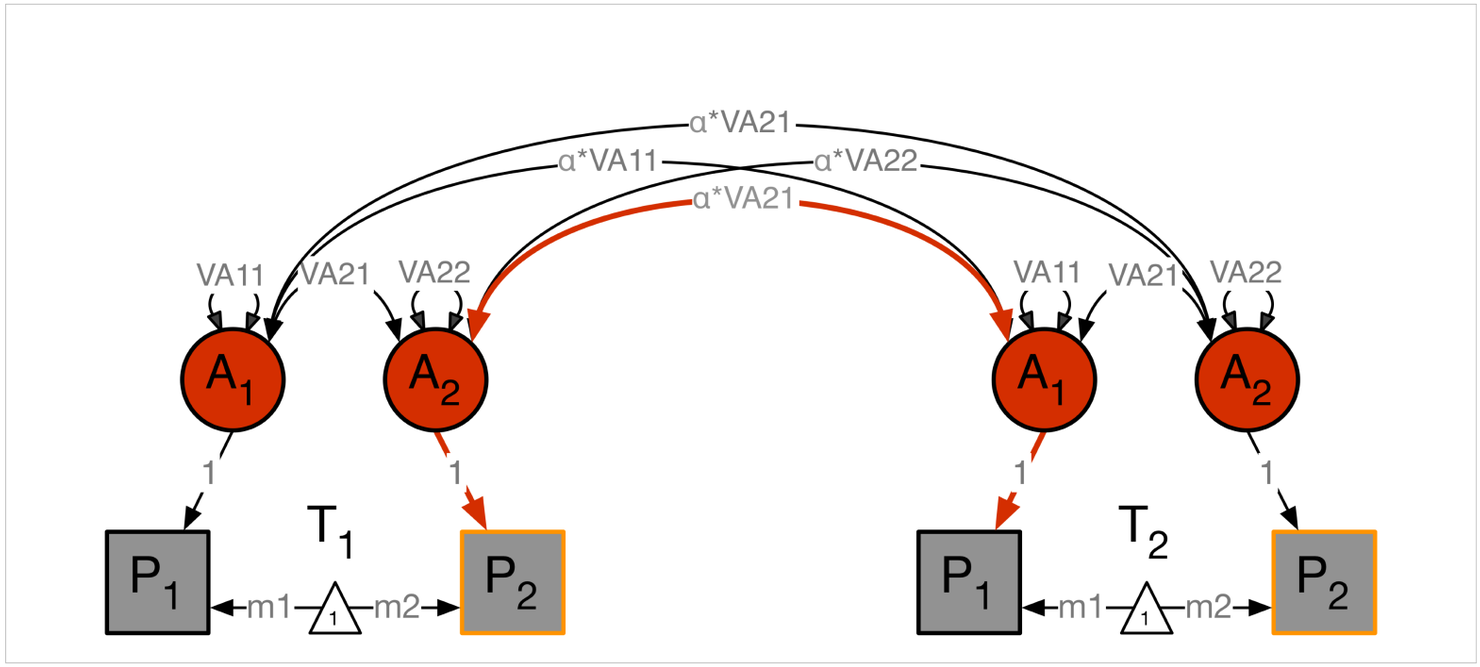


twin 1

twin 2

	$P1_{T1}$	$P2_{T1}$
$P1_{T2}$	1/0.5 * VA11	Cross-Trait $P1_{T1}P2_{T2}$
$P2_{T2}$	1/0.5 * VA21	Within-Trait $P2_{T1}P2_{T2}$

Bivariate Twin Covariance Matrix

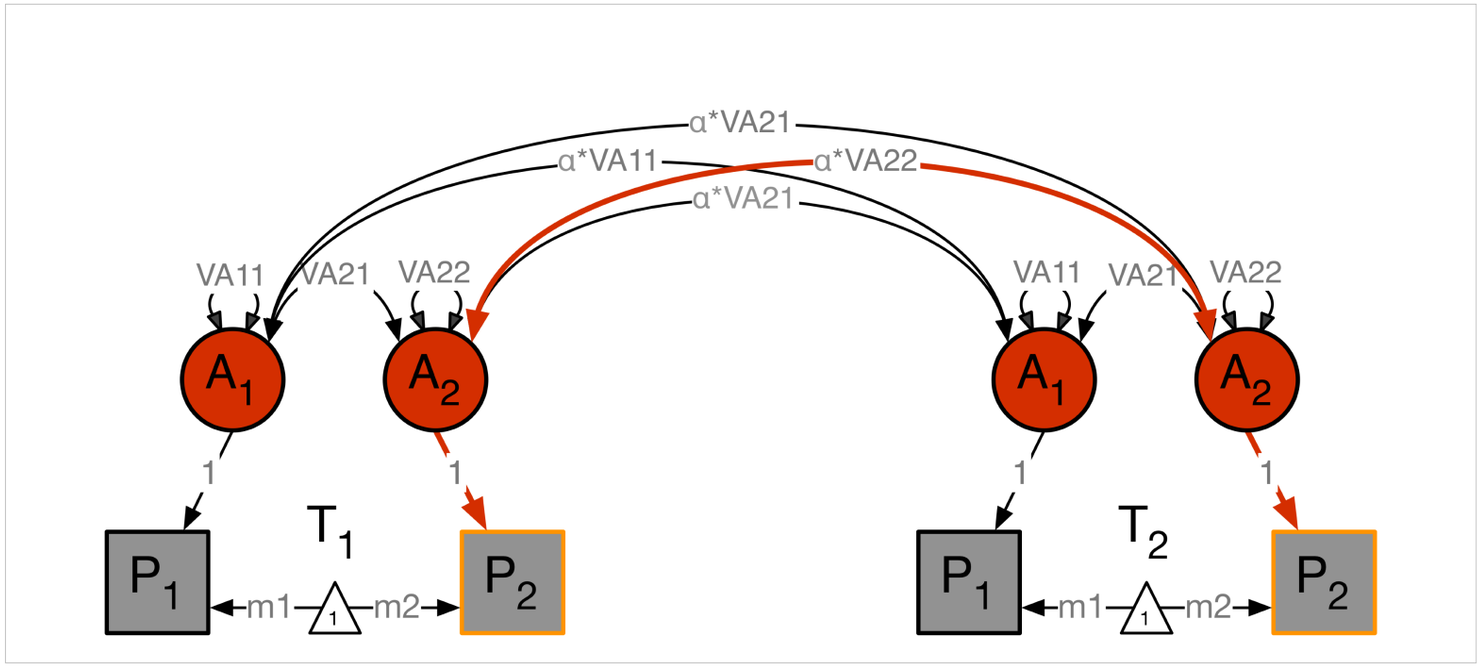


twin 1

twin 2

	$P1_{T1}$	$P2_{T1}$
$P1_{T2}$	1/0.5 * VA11	1/0.5 * VA21
$P2_{T2}$	1/0.5 * VA21	Within-Trait $P2_{T1}P2_{T2}$

Bivariate Twin Covariance Matrix



twin 1

twin 2

	$P1_{T1}$	$P2_{T1}$
$P1_{T2}$	1/0.5 * VA11	1/0.5 * VA21
$P2_{T2}$	1/0.5 * VA21	1/0.5 * VA22

Predicted Twin Covariance Matrix

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	VA11 +VC11 +VE11	VA21 +VC21 +VE21	1/0.5 * VA11 +VC11	1/0.5 * VA21 +VC21
	$P2_{T1}$	VA21 +VC21 +VE21	VA22 +VC22 +VE22	1/0.5 * VA21 +VC21	1/0.5 *VA22 +VC22
twin 2	$P1_{T2}$	1/0.5 * VA11 +VC11	1/0.5 * VA21 +VC21	VA11 +VC11 +VE11	VA21 +VC21 +VE21
	$P2_{T2}$	1/0.5 * VA21 +VC21	1/0.5 *VA22 +VC22	VA21 +VC21 +VE21	VA22 +VC22 +VE22

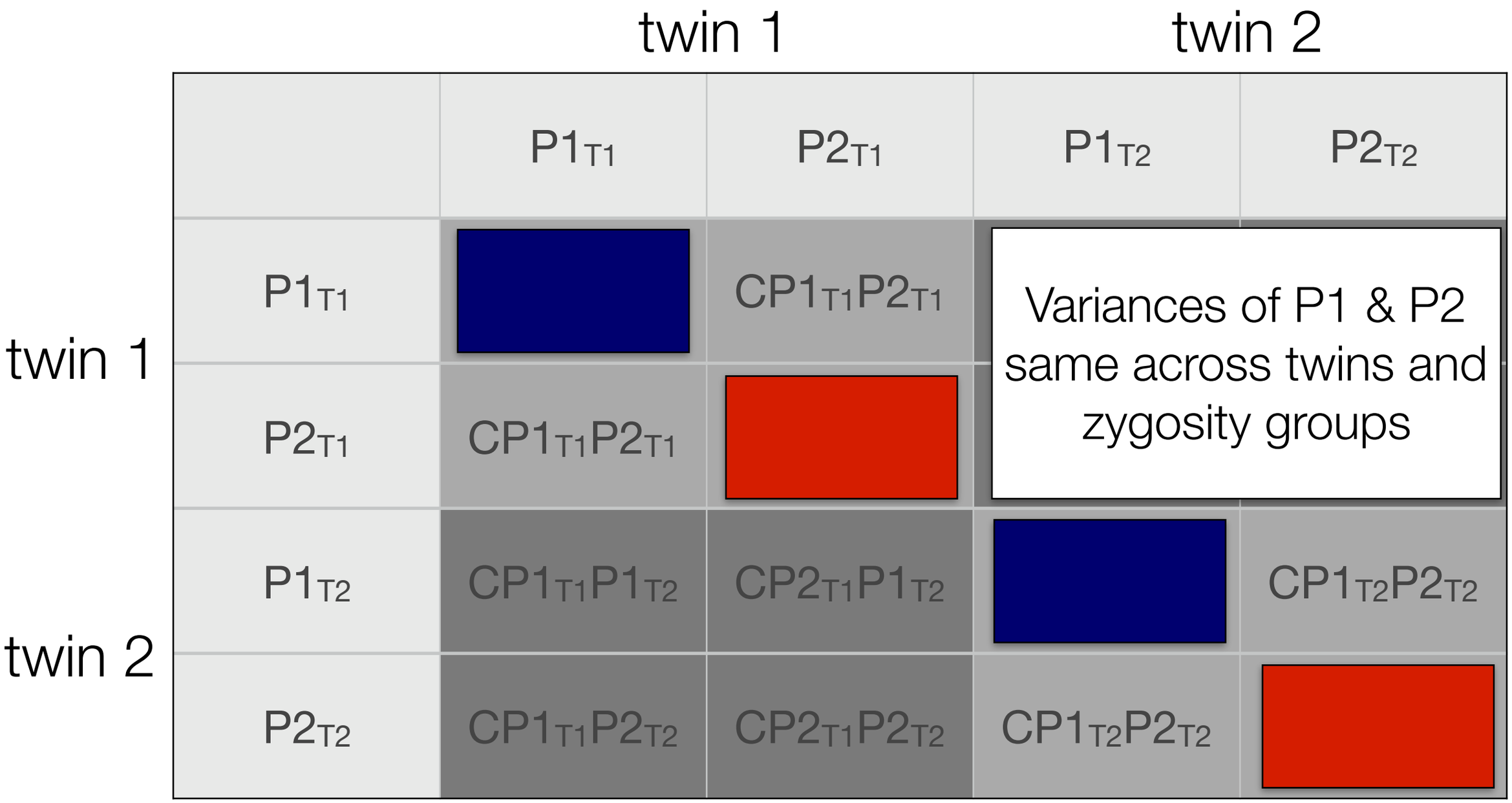
Predicted MZ Twin Covariance

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	VA11 +VC11 +VE11	VA21 +VC21 +VE21	VA11 +VC11	VA21 +VC21
	$P2_{T1}$	VA21 +VC21 +VE21	VA22 +VC22 +VE22	VA21 +VC21	VA22 +VC22
twin 2	$P1_{T2}$	VA11 +VC11	VA21 +VC21	VA11 +VC11 +VE11	VA21 +VC21 +VE21
	$P2_{T2}$	VA21 +VC21	VA22 +VC22	VA21 +VC21 +VE21	VA22 +VC22 +VE22

Predicted DZ Twin Covariance

		twin 1	twin 2	
	$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1 $P1_{T1}$	VA11 +VC11 +VE11	VA21 +VC21 +VE21	0.5 * VA11 +VC11	0.5 * VA21 +VC21
twin 1 $P2_{T1}$	VA21 +VC21 +VE21	VA22 +VC22 +VE22	0.5 * VA21 +VC21	0.5 *VA22 +VC22
twin 2 $P1_{T2}$	0.5 * VA11 +VC11	0.5 * VA21 +VC21	VA11 +VC11 +VE11	VA21 +VC21 +VE21
twin 2 $P2_{T2}$	0.5 * VA21 +VC21	0.5 *VA22 +VC22	VA21 +VC21 +VE21	VA22 +VC22 +VE22

Bivariate Twin Covariance Matrix



Bivariate Twin Covariance Matrix

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	$VP1_{T1}$		Covariances of P1& P2 same across twins and zygosity groups	
	$P2_{T1}$		$VP2_{T1}$		
twin 2	$P1_{T2}$	$CP1_{T1}P1_{T2}$	$CP2_{T1}P1_{T2}$	$VP1_{T2}$	
	$P2_{T2}$	$CP1_{T1}P2_{T2}$	$CP2_{T1}P2_{T2}$		$VP2_{T2}$

Bivariate Twin Covariance Matrix

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	$VP1_{T1}$	$CP1_{T1}P2_{T1}$	Cross-Twin Within-Trait Covariances differ by zygosity	
	$P2_{T1}$	$CP1_{T1}P2_{T1}$	$VP2_{T1}$		
twin 2	$P1_{T2}$		$CP2_{T1}P1_{T2}$	$VP1_{T2}$	$CP1_{T2}P2_{T2}$
	$P2_{T2}$	$CP1_{T1}P2_{T2}$		$CP1_{T2}P2_{T2}$	$VP2_{T2}$

Bivariate Twin Covariance Matrix

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	$VP1_{T1}$	$CP1_{T1}P2_{T1}$	Cross-Twin Cross-Trait Covariances differ by zygosity	
	$P2_{T1}$	$CP1_{T1}P2_{T1}$	$VP2_{T1}$		
twin 2	$P1_{T2}$	$CP1_{T1}P1_{T2}$		$VP1_{T2}$	$CP1_{T2}P2_{T2}$
	$P2_{T2}$		$CP2_{T1}P2_{T2}$	$CP1_{T2}P2_{T2}$	$VP2_{T2}$

Example MZ Covariance Matrix

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	1			
	$P2_{T1}$	0.26	1		
twin 2	$P1_{T2}$	0.64	0.21	1	
	$P2_{T2}$	0.25	0.7	0.31	1

Example DZ Covariance Matrix

		twin 1		twin 2	
		$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
twin 1	$P1_{T1}$	1			
	$P2_{T1}$	0.31	1		
twin 2	$P1_{T2}$	0.2	0.12	1	
	$P2_{T2}$	0.12	0.53	0.27	1

Cross-Trait Covariances

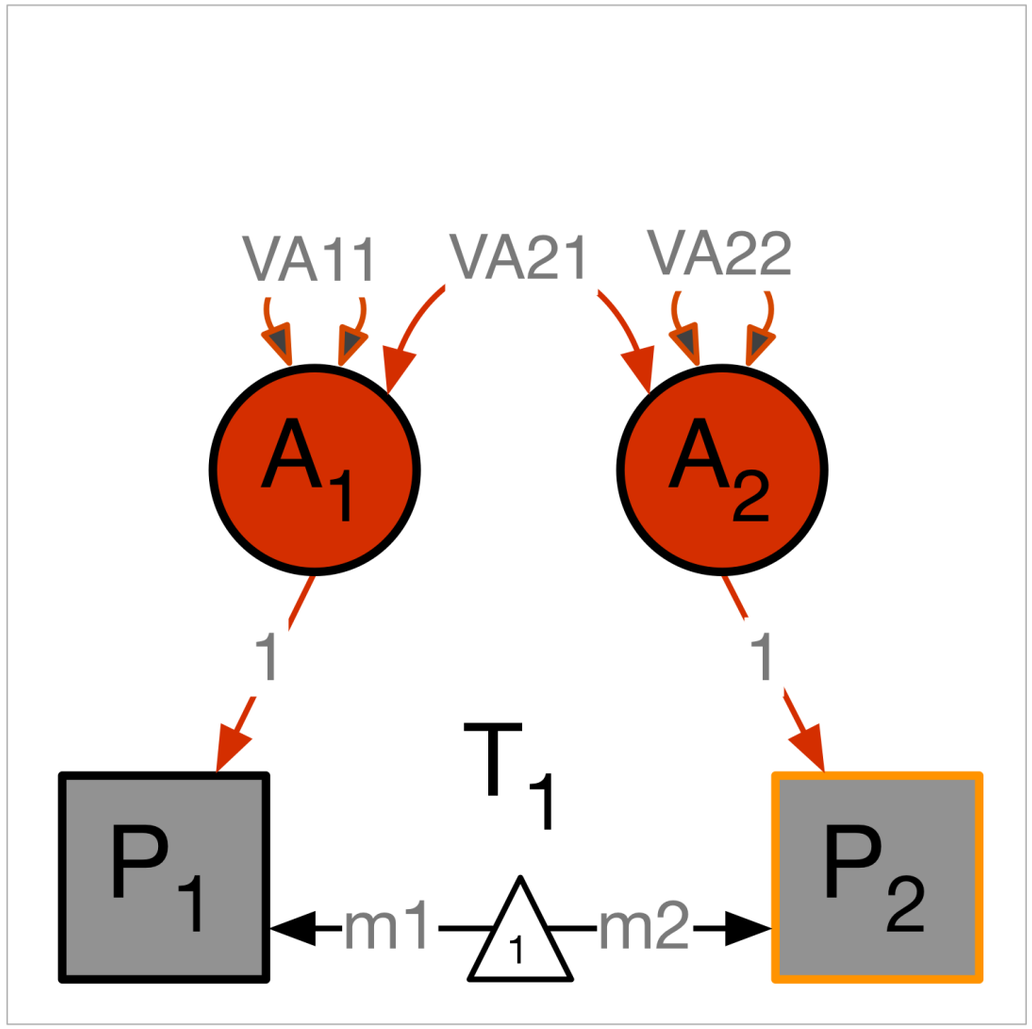
- Within-twin Cross-trait covariances imply common etiological influences (phenotypic covariance)
- Cross-twin Cross-trait covariances imply familial common etiological influences
- MZ/DZ ratio of Cross-twin Cross-trait covariances reflects whether common etiological influences are genetic or environmental
- Ratio of Cross-twin to Within-twin Cross-trait covariance reflects on role of unique environment

Genetic Covariance to Genetic Correlation

calculated by dividing genetic covariance by square root of product of genetic variances of two variables

$$\begin{bmatrix} 1 & r_g \\ r_g & 1 \end{bmatrix} = \begin{bmatrix} \frac{1}{\sqrt{\sigma^2_{A_{11}}}} & 0 \\ 0 & \frac{1}{\sqrt{\sigma^2_{A_{22}}}} \end{bmatrix} * \begin{bmatrix} \sigma^2_{A_{11}} & \sigma^2_{A_{12}} \\ \sigma^2_{A_{21}} & \sigma^2_{A_{22}} \end{bmatrix} * \begin{bmatrix} \frac{1}{\sqrt{\sigma^2_{A_{11}}}} & 0 \\ 0 & \frac{1}{\sqrt{\sigma^2_{A_{22}}}} \end{bmatrix}$$

Contribution to Phenotypic Correlation

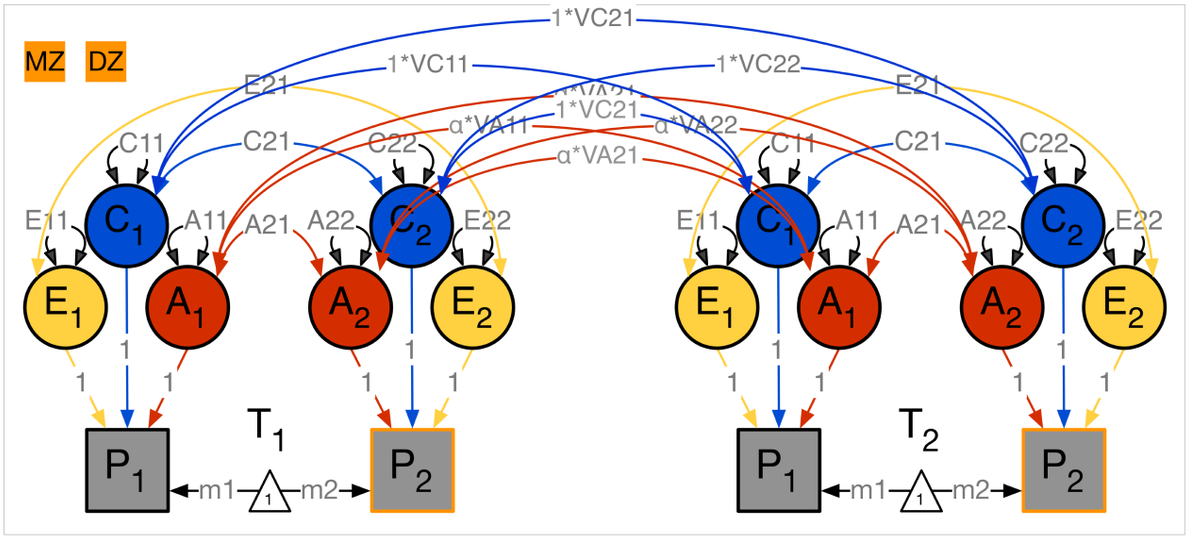


if VA21=~VA11 & VA22, then two sets of genes overlap completely

if however VA11 & VA22 are near zero, genes do not contribute much to phenotypic correlation

contribution to phenotypic correlation is function of both heritabilities and rg

OpenMx Specification



	$P1_{T1}$	$P2_{T1}$	$P1_{T2}$	$P2_{T2}$
$P1_{T1}$	$VP1_{T1}$	$CP1_{T1}P2_{T1}$	$CP1_{T1}P1_{T2}$	$CP1_{T1}P2_{T2}$
$P2_{T1}$	$CP1_{T1}P2_{T1}$	$VP2_{T1}$	$CP2_{T1}P1_{T2}$	$CP2_{T1}P2_{T2}$
$P1_{T2}$	$CP1_{T1}P1_{T2}$	$CP2_{T1}P1_{T2}$	$VP1_{T2}$	$CP1_{T2}P2_{T2}$
$P2_{T2}$	$CP1_{T1}P2_{T2}$	$CP2_{T1}P2_{T2}$	$CP1_{T2}P2_{T2}$	$VP2_{T2}$

OpenMx script