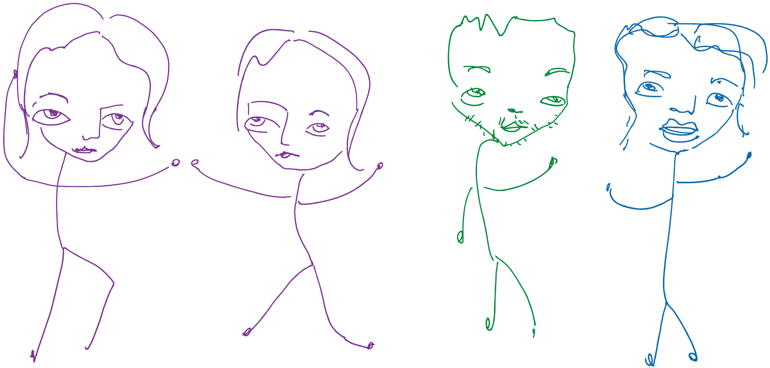
Research question

Power to detect a difference in correlations between samples of identical (monozygotic) and non-identical (dizygotic) twin pairs



Background

Let's assume that...

- each pair of twin siblings share the same environmental history
- zygosity doesn't influence environmental interactions
- trait is normally distributed
- accurate classification of zygosity
- accurate measurement of trait
- No dominant genetic variance (where one allele reliably masks the expression of the other when the two co-occur at a particular locus)
- mz and dz twins have been sourced from equivalent populations

Background

Let x_{zjk} be the value of trait x in the kth member of the jth twin pair having zygosity $z \in \{\mathrm{mz}, \mathrm{dz}\}$

$$(x_{z\cdot 1}, x_{z\cdot 2}) \sim \mathcal{N}(\boldsymbol{\mu}, \Sigma)$$

$$r_z = \hat{\rho}_z = \frac{Cov(x_{z\cdot 1}, x_{z\cdot 2})}{\hat{\sigma}_{x_{z\cdot 1}} \hat{\sigma}_{x_{z\cdot 2}}}$$

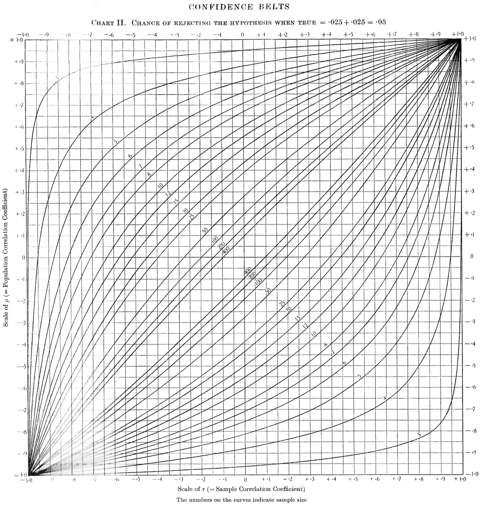
$$\hat{\delta} = r_{mz} - r_{dz}$$

$$\text{heritability} = 2\delta$$

Trait etiology	**Correlation in twin pairs**	
	Monozygotic (mz)	**Dizogotic (dz)**
genetic	$r_{mz} = 1$	$r_{dz} = 0.5$
shared env.	$r_{mz} = 1$	$r_{dz} = 1$
individual env.	$r_{mz} = 0$	$r_{dz} = 0$
combination	$0 < r_{mz} < 1$	$0 < r_{dz} < 1$

A skip through the literature

- Galton, F. 1888
- Pearson, K. 1895
- Fisher, RA. 1915
- David, FN. 1938
- Falconer, DS. 1960
- Cohen, J. 1988
- Neale, M. et al. 1994
- Visscher, PM. 2004
- Verhulst, B. 2017



Power for difference in correlations[1]

Frequentist NHST paradigm

α (Type I error) and β (Type II error); Power is $1 - \beta$

Fisher's Z formula approach

$$\text{power} = 1 - \Phi\left(\Phi^{-1}_{\alpha/2} - \text{abs}\left(\frac{\text{arctanh}(r_{mz}) - \text{arctanh}(r_{dz})}{\sqrt{(n_{mz}-3)^{-1} + (n_{dz}-3)^{-1}}}\right)\right)$$

Simulation approach

- implement hypothesis test(s) for difference in correlations
- take m draws from simulated bivariate mz and dz populations
- run hypothesis test(s) on each pair of draws
- power given parameters is proportion of tests where $p < \alpha$

[1] **Cohen1988**.

Simulations

Using r_{mz} and r_{dz} derived from simulated bivariate normal and non-normal populations with covariance $\begin{bmatrix} 1 & \rho \\ \rho & 1 \end{bmatrix}$, the following hypothesis tests were run:

- Fisher's Z: $\frac{\operatorname{arctanh}(r_{mz}) - \operatorname{arctanh}(r_{dz})}{\sqrt{(n_{mz}-3)^{-1} + (n_{dz}-3)^{-1}}}$
- Generalized Variable Test (GVT)[2]
- Signed log-likelihood ratio test[3]
- Permutation test[4]
- Zou's confidence interval[5]

Plan 1000 simulations of all mz dz combinations of *rho* and *n* using three distinct distributions and re-run using Spearman correlation (rank based, non-parametric)...

[2] **Krishnamoorthy2014**.
[3] **Krishnamoorthy2014**.
[4] **Efron1994**.
[5] **Zou2007**.

Preliminary results: simulation times

$1000 \times 39^2 \times 7^2 \times 6 \times 3 \times 2 = 2,234,400,000$ simulations...

Optimisation approach[6]

- hand coded
- functions compiled using either JIT compiler or RCCP

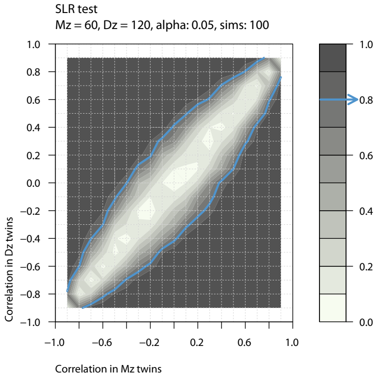
Test	Time/1000 runs (secs)	
	as is	**compiled**
Fisher's z (no sim)	0.03	0.02
Fisher's Z	0.56	0.36
GTV (r)	18.65	16.55
GTV (R C++)		12.08
Permutation (PT)	2473.18	2341.62
SLR	0.49	0.33
Zou's CI	0.38	0.28
Total (sans r-compiled GTV)	2493.29	2354.69
$\times 1520 \times 49 \times 3 \times 2/60/60/24/365$	35 years	33 years
$-$PT : $\times 361 \times 49 \times 3 \times 2/60/60/24$	25 days	16 days

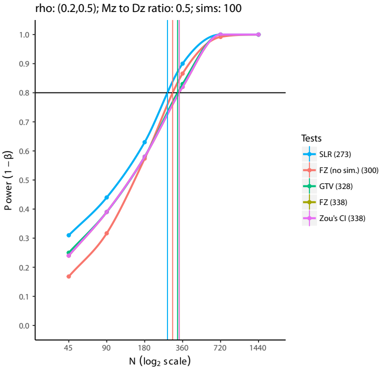
Main findings

106,134 sets of power estimates comparing 5 tests (wide form)

Example

Power to detect $\hat{\delta}_\rho$ in Mz and Dz twins $\sim \mathcal{N}\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 1 & \rho \\ \rho & 1 \end{bmatrix} \right)$



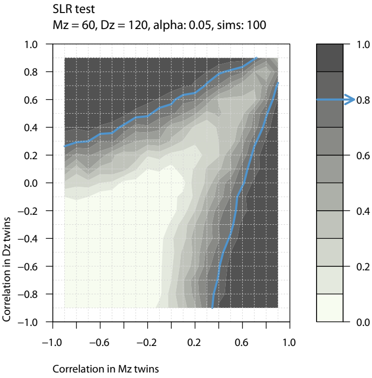


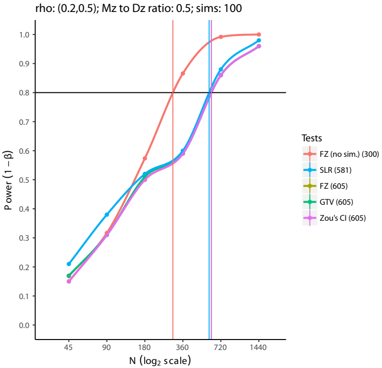
Main findings

106,134 sets of power estimates comparing 5 tests (wide form)

Example

Power to detect $\hat{\delta}_\rho$ in Mz and Dz twins $\sim \mathcal{G}\left(\begin{bmatrix} 1 \\ 1 \end{bmatrix}, \begin{bmatrix} 5 & \rho \\ \rho & 5 \end{bmatrix} \right)$





Limitations

- Analysis not yet complete
- 100 simulations for each parameter combinations
  - 1000 is currently processing
- ICC not currently implemented
- Partial correlations are important, and not yet covered
  - incorporation of evaluation of correlation using mixed effects regression approaches could address above two issues
- Included tests are not exhaustive
- Code could be more efficient, allowing higher resolution estimation
  - e.g. original intent of -0.95 through 0.95 in 0.05 increments

Sum up and next steps