GeneCorr v0.82

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## Introduction

This package is an HE implementation to calculate genetic and/or any other correlation between pairs of variables that are related via some relatedness matrices. Essentially this calculation will answer the question: “What fraction of the correlation between variables is due to the relatedness”.

For any significant number of traits these computations require a computing cluster. This version works with the LSF scheduler although any other can be easily implemented. Because of the cluster-related steps, this is organized as a pipeline with several steps that need to be executed one after another.

The general approach is you construct one config file for the whole process and then pass it to the different R scripts in this package. Some of them will generate run-files which are needed to be run on the cluster.

## Inputs

1. R dataframe with phenotypes, covariates and ID field
2. An R matrix (or multiple ones) with colnames=rownames=ID and representing some similarity between subject *i* and *j*
3. Various Parameters (See “Configuration File” section for specific description)

## Outputs

1. Spearman correlation between phenotypes
2. Spearman correlation p-value between phenotypes
3. Number of people in each phenotype pair
4. Total (Phenotypic ) model correlation. Different from Spearman if the subjects are related
5. Total model correlation pvalue (Fisher)
6. Genetic correlation
7. Genetic correlation p-value (Blocked Bootstrap)
8. Genetic correlation SD
9. Genetic Correlation filtered (according to provided filter values)
10. Heritability-normalized Genetic Correlation
11. Heritability-normalized Genetic Correlation filtered (according to provided filter values)
12. Household correlation
13. Household correlation p-value (Blocked Bootstrap)
14. Household correlation SD
15. Household correlation filtered (according to provided filter values)
16. Heritability-normalized Household correlation
17. Heritability-normalized Household correlation filtered (according to provided filter values)
18. Residual correlation
19. Heritabilities (Genetic)
20. Household variance components (analogue for heritabilities for Household distance matrix)
21. PDF with figures for all of the above

## Required packages

Make sure you have these installed. Run on erisOne:  
[user@eris1n3 ~]$ module load R/4.0.2  
[user@eris1n3 ~]$ R  
> library(RColorBrewer)

> library(corrplot)

> library(plotrix)

> library(ggchicklet)

> library(qgraph)

> library(corpcor)

> library(gdata)

> library(reshape2)

> library(ggpattern)

> library(igraph)

> library(ggplot2)

> library(config)  
> library(gtools)  
> library(tidyr)

> library(tidyverse)

> library(hash)

> library(R.utils)

> library(GENESIS)

If any of these gives errors, for example :  
> library(hash)

Error in library(hash) : there is no package called ‘hash’

Then run:

> install.packages(“hash”)

After it finishes, run:

> q()  
n

And you can continue with the pipeline. If some of the scripts in the pipeline crash with similar error, install the missing package in a similar fashion.

## Pipeline

The main steps are:

1. Prepare data files (phenotypes and relatedness matrices), decide upon covariates.
2. Prepare the configuration file
3. Convert the data to GCTA format and run variance components estimation (Heritability in the case of genetics) in batches on the cluster
4. Run the Genetic Correlation estimation in batches on the cluster
5. Combine the Genetic Correlation batches and Heritability estimates to the final dataset
6. Generate Figures

### Step 1 - Prepare a configuration file

This configuration file is used by all scripts in the pipeline. See “Configuration File” section for specific description.

Example:  
/yourdir/Code/runGenCor\_ALL\_Base\_v1.config

### Step 2 - Generate Blocked-Bootstrap helper file.

Run: “/yourdir/Code/1\_Generate\_blocked\_bootstrap\_distmatr\_v2.R”  
with the config file as a parameter. Very fast. Two ways you can do it.

First way - from interactive shell :  
[user@eris1n3 ~]$ bsub -Is -q interact-big -R "rusage[mem=128000]" -n 8 csh

Job <341649> is submitted to queue <interact-big>.

<<Waiting for dispatch ...>>

<<Starting on celeste>>

[user@celeste ~]$ Rscript /yourdir/Code/1\_Generate\_blocked\_bootstrap\_distmatr\_v2.R /yourdir/Code/runGenCor\_ALL\_Base\_v1.config

Or create a script file: “/yourdir/Code/runBootstrap\_v1.sh”

#!/bin/sh

#BSUB -o /yourdir/DataProc/output\_bootstrap\_cluster.out

#BSUB -e /yourdir/ DataProc/output\_bootstrap\_cluster.err

#BSUB -q normal

#BSUB -R "rusage[mem=30000]"

#BSUB -J bootstrap1

module load R/4.0.2

Rscript /yourdir/Code/1\_Generate\_blocked\_bootstrap\_distmatr\_v2.R /yourdir/Code/runGenCor\_ALL\_Base\_v1.config

And run it:

[user@eris1n3 ~]$ bsub < /yourdir/Code/runBootstrap\_v1.sh

### Step 3 - Convert genotype and phenotype files to GCTA format

This is done to calculate heritabilities. Run from command line: “/yourdir/Code/2\_convert\_grm\_RData\_GCTA\_v2.R”  
with the config file as a parameter (Same as in Step 2).  
\*\*Note – you need to this for every phenotype file, but different phenotype files can use the same genotype file (if the genotype file includes all the participants from the phenotype file). The genotype conversion is slow - multiple minutes. So you can run it once for the combined model and then just use it for the sex-specific modules.

1. Step (3) will generate a shell-script file which name you define in the config file under:  
   “run\_GCTA\_script\_filename”  
   You now need to run it on the cluster from command line. So if the file is:  
   /yourdir/DataProc/run\_GCTA\_VCs\_reml\_2mat\_Base\_All.sh  
   run this line via the command line.  
   [user@eris1n3 ~]$ /yourdir/DataProc/run\_GCTA\_VCs\_reml\_2mat\_Base\_All.sh  
     
    This will submit as many jobs as you have phenotypes in the file. Need to wait for it to finish. May take up to several hours depending on cluster availability. Wait till all finish.
2. Some runs may fail. You will need to check which failed and re-run them. Failing, meaning a missing “.hst” file. The way you do it is via   
   /yourdir/Code/3\_rerun\_miising\_GCTA\_v1.R  
   with the config file as a parameter.
   1. Step (3-2) will generate a shell-script file which name you define in the config file under:  
      “rerun\_GCTA\_script\_filename”  
      You now need to run it on the cluster from command line (Same as Step 3-1). So if the file is:  
      /yourdir/DataProc/rerun\_GCTA\_VCs\_reml\_2mat\_Base\_All.sh  
      run this line via the command line. This will submit as many jobs as have failed in the previous step. Need to wait for it to finish. May take up to several hours depending on cluster availability. Wait till all finish.

### Step 4 – Calculate Genetic Correlations in batches on the cluster

Now we get to the actual genetic correlation calculation. First run   
/yourdir/Code/4\_SOFER\_GenCor\_distrib\_Kinship\_Household\_v8.R  
with the config file as a parameter (Same as Step 2). Very fast.

* 1. This will generate a shell-script file which name you define in the config file under:  
     “run\_Gencor\_script\_filename”  
     You now need to run it on the cluster from command line. If the file is   
     "/yourdir/DataProc/runRscript\_distrib\_Kinship\_Household\_BaseModel\_All\_v8.sh"  
     then you run it like this:  
     [user@eris1n3 ~]$ bsub < /yourdir/DataProc/runRscript\_distrib\_Kinship\_Household\_BaseModel\_All\_v8.sh  
     This will submit as many jobs as you have genetic correlations in the file. Need to wait for it to finish. May take minutes to days depending on cluster availability. Wait till all finish

### Step 5 – Combine Genetic Correlations batches

Run from command line: “/yourdir/Code/5\_SOFER\_GenCor\_combine\_Kinship\_Household\_v8.R”  
with the config file as a parameter (Same as Step 2). Very fast

### Step 6 – Combine Genetic Correlations and Heritability from GCTA

Run from command line: “/yourdir/Code/6\_merge\_GenCor\_GCTA\_VCs\_v2.R”  
with the config file as a parameter (Same as Step 2). Very fast

### Step 7 – Generate Figures

Run from command line: “/yourdir/Code/7\_make\_figure\_gencor\_twomat\_v8.R”  
with the config file as a parameter (Same as Step 2). Very fast

## Data Files Example

Phenotypes file:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ID | SEX | AGE | Phenotype1 | Phenotype2 |
| 1523 | Female | 57 | 1 | 32 |
| 1100 | Male | 48 | 3 | 24 |
| 1052 | Female | 56 | 13 | 25 |
| 1102 | Female | 45 | 15 | 25 |
| 1973 | Female | 50 | 19 | 24 |
| 1026 | Female | 53 | 18 | 30 |
| 1558 | Male | 58 | 5 | 22 |
| 1268 | Male | 46 | 3 | 33 |
| 1553 | Female | 56 | 6 | 21 |
| 1130 | Female | 67 | 6 | 15 |

Relatedness Matrix:

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **1523** | **1100** | **1052** | **1102** | **1973** | **1026** | **1558** | **1268** | **1553** | **1130** |
| **1523** | 1 | 0.06 | -0.41 | -0.11 | -1.24 | 0.32 | 1.38 | 2.2 | -0.28 | -1.09 |
| **1100** | 0.05 | 1 | 1.65 | -0.1 | 0.86 | 0.3 | 0.49 | -0.36 | -1.48 | 0.48 |
| **1052** | 0.23 | -0.31 | 1 | -1.65 | -1.05 | 0.12 | 0.33 | 0.25 | -1.8 | -0.38 |
| **1102** | -0.96 | -0.15 | -1.61 | 1 | 1.06 | -0.58 | -0.17 | 1.6 | 1.18 | 1.46 |
| **1973** | 1 | -0.53 | -0.44 | -0.22 | 1 | -0.18 | 0.82 | 0.53 | 1.5 | -0.9 |
| **1026** | -1.11 | 1.58 | -0.68 | -0.33 | 0.1 | 1 | -1 | 0.38 | 2.04 | 1.58 |
| **1558** | -1.18 | -0.35 | 1.4 | 0.48 | -0.84 | -0.04 | 1 | 0.55 | -0.01 | -1.06 |
| **1268** | 1.01 | 1.97 | -0.28 | -2.08 | -1.65 | -0.53 | -0.34 | 1 | -0.92 | -1.67 |
| **1553** | -0.07 | -1.01 | -0.31 | -0.05 | -0.56 | 0.54 | -0.31 | -1.1 | 1 | 0.82 |
| **1130** | 1.1 | -1.29 | 0.4 | -0.22 | -0.02 | -2.07 | 1.42 | -0.74 | -2.26 | 1 |

## Configuration File

# keep this structure – default:…

default:

# Name of this config file

this\_config\_filename : "/yourdir/Code/runGenCor\_ALL\_Base\_v1.config"

# cluster parameters

LSF\_QUEUE\_NAME : "normal" #name of the queue you want to use

LSF\_MEMORY : "30000" #amount of memory available in queue

# relatedness matrices names

kinship\_matrix\_filename : "/yourdir/Data/genetic\_cor\_kinship\_matrix.RData"

household\_matrix\_filename : "/yourdir/Data/genetic\_cor\_household\_matrix.RData"

# phenotypes file name – has to include ID, covariates and the phenotypes themselves

phenotypes\_filename :

/yourdir/Data/20210511\_genetic\_cor\_phenotype\_baseline.RData

# list of non-quantitative covariates

factor\_covariates : ["SEX","Education","CENTER","BMI\_cat","ALCOHOL\_intake"]

# list of quantitative covariates

numeric\_covariates : ["AGE","weights\_baseline\_log","FRAME\_CVD\_RISK\_10YR","CESD10","STAI10","EV1","EV2","EV3","EV4","EV5"]

# Name of ID field

idfield\_name : "HCHS\_ID"

# list of phenotype fields

phenotypes\_fieldnames : ["SLPA54","WHIIRS","SLPDUR","ESS","EDS","global\_cog\_score","TOTAL\_6ITEM","SEVLT\_3TRIALS","SEVLT\_RECALL","WORDFREQ","DIGITSYMBOL","short\_slp","long\_slp","AHI\_GE15","SDB5","Avg\_event\_length","SLPA92","SLPA91","SLPA97","SLEA4","SLEA5","SLEA6","SLEA7","SLEA8"]

#what phenotypes to compare to what other ones. Group1 <-> Group2.

phenotypes\_group1 : ["SLPA54","WHIIRS","SLPDUR","ESS","EDS","short\_slp","long\_slp","AHI\_GE15","SDB5","Avg\_event\_length","SLPA92","SLPA91","SLPA97","SLEA4","SLEA5","SLEA6","SLEA7","SLEA8"]

phenotypes\_group1\_Name : "Sleep"

phenotypes\_group2 : ["global\_cog\_score","TOTAL\_6ITEM","SEVLT\_3TRIALS","SEVLT\_RECALL","WORDFREQ","DIGITSYMBOL"]

phenotypes\_group2\_Name : "Cognition"

# Genetic Correlation - provide directory name for output files

workdirname : "/yourdir/Result/"

# Genetic Correlation - provide basis for file names to be generated

outfileprefix : "GenCor\_CogSleep\_Kinship\_Household\_BaseModel\_All\_v8"

ONEBATCH : 2 # Number of genetic correlations to calculate per batch

BOOTSTRAP\_REPEATS : 100 # Number of repeats for Bootstrap per correlation. determines final possible pvalue. If 0 then only Fisher pvalues will be calculated

#relatedness degree - used for blocked\_bootstrap (to divide into groups), heritabilities (to exclude relatives when calculating).

relatedness\_distance : 0.0625 #3rd degree relatives

# Figure generation parameters

pvalueThreshold : 0.05 # do not display any correlations with pvalue less than this

peopleNumThreshold : 1000 # do not display any correlations calculated for less people than this

correlationThreshold : 0.05 # # do not display any correlations with absolute value less than this

#filtering and figures

CALC\_ORDER : False # calculate order by clustering for corrplots

CALC\_ORDER\_QGRAPH : True # calculate order by clustering for qgraphs

QGRAPH\_LAYOUT\_FILE : "/yourdir/Result/GenCor\_CogSleep\_Kinship\_Household\_BaseModel\_All\_v8\_combine\_SOL\_qgraph\_res\_v3.RData"

#Filename for script to run on the cluster - GCTA Heritability calculations

run\_GCTA\_script\_filename : "/yourdir/DataProc/run\_GCTA\_VCs\_reml\_2mat\_Base\_All.sh"

#Filename for script to run on the cluster - Distributed Genetic Correlation calculation

run\_Gencor\_script\_filename : "/yourdir/DataProc/runRscript\_distrib\_Kinship\_Household\_BaseModel\_All\_v8.sh"

#############################################################################################################

#### From here its internal filenames required for work

#############################################################################################################

# blocked lookup generation - provide file names to be generated for kinship and household matrices

kinship\_matrix\_filename\_blocked\_lookup : "/yourdir/DataProc/genetic\_cor\_kinship\_matrix\_Base\_All\_lookup.RData"

household\_matrix\_filename\_blocked\_lookup : "/yourdir/DataProc/genetic\_cor\_household\_matrix\_Base\_All\_lookup.RData"

#convert data to GCTA format from R data - provide file names to be generated

phenotypes\_GCTA\_prefix : "/yourdir/DataProc/20210511\_genetic\_cor\_phenotype\_baseline\_GCTA"

GCTA\_cluster\_filename\_prefix : "/yourdir/DataProc/GCTA\_VCs\_pheno\_NoRel3rdDeg\_PCs5\_2mat\_Base\_All"

# provide run-scripts file names to be generated

rerun\_GCTA\_script\_filename : "/yourdir/DataProc/rerun\_GCTA\_VCs\_reml\_2mat\_Base\_All.sh"

CONVERT\_MATRICES\_toGCTA : True #if this is false, matrices generation will be skipped

# provide name for non-related individuals file names to be generated

Unrelated\_individuals\_filename : "/yourdir/DataProc/genetic\_cor\_kinship\_matrix\_Unrelated3rdDeg.RData"

kinship\_matrix\_filename\_GCTA : "/yourdir/DataProc/genetic\_cor\_kinship\_matrix\_NoRel3rdDeg.GCTA"

household\_matrix\_filename\_GCTA : "/yourdir/DataProc/genetic\_cor\_household\_matrix\_NoRel3rdDeg.GCTA"

two\_matrix\_GCTA\_filename : "/yourdir/DataProc/20210511\_genetic\_cor\_phenotype\_baseline\_GCTA\_mgrm\_K\_HH.txt"

# Prtial correlations - need to provide precalculated pairs and group file. These files can be created after regular run

PARTIAL : False

pairfile : ""

grpfile : ""