Small example of use of OmicABEL

Yurii Aulchenko for the OmicABEL developers

July 1, 2013

Contents

1 Important note on data format for OmicABEL

The example of use provided below make use of the data provided together with the GenABEL-package. Note that when working with your data you

do NOT need to have the data in the GenABEL-package format, and you do not need to follow this procedure to get data usable for OmicABEL; this is a simple example explaining the input and output files and usage of OmicABEL.

The major fact you need to remember is that OmicABEL makes use of the 'filevector' (aka 'DatABEL') "DOUBLE" format for input. Hence, again, you do NOT have to have your data in GenABEL format, but you do need to get files into filevector/DatABEL "DOUBLE".

The major issue is getting the (usually vast amounts of) genotypic data in right format. To get to right format, in real life we recommend that you use one of the GenABEL conversion procedures to convert your data from IMPUTE, MACH, or MiniMac to DatABEL/filevector. The corresponding GenABEL-package functions are `impute2databel`, `mach2databel`, and `minimac2databel`. Make, however, sure that you use the dataOutType = "DOUBLE" argument when argument when doing the genotype data conversion! For example (in R),

```
mach2databel(imputedgenofile = "f1.mldose", mlinfofile = "f1.mlinfo",
        outfile="f1", dataOutType = "DOUBLE")
```

This argument is added to the GenABEL-package since version >=1.7-7.

If you have already have genotypic data in filevector/DatABEL format, but these are in the "FLOAT" format (default option for the `xxx2databel` procedures), you can use the `float2double` utility provided together with OmicABEL to convert to "DOUBLE". For example, if you have your genotypic data in (filevector-FLOAT) files `myData.fvi` and `myData.fvd`, you can convert them to DOUBLE by using (from command line):

```
float2double myData myDataDouble
```

After which you will get files `myDataDouble.fvi` and `myDataDouble.fvd` (note that the size of these files is roughly double the size of floats - take care you have enough HDD space).

2 Outline of the example

In this example, we will use the data set distributed with GenABEL to show the use of OmicABEL. Hence you need to have GenABEL package installed on your system. You will also need the DatABEL package for data manipulations and 'mvtnorm' package (simulation of traits) installed.

For conversion of files to the FaST-LMM format, you will need PLINK installed, you will also need FaST-LMM if you'd like to run the comparison.

3 Prepare the data for analysis

Note that you do NOT need to follow this procedure to get data usable for OmicABEL. The trick is to get your data in tables and then dump these tables in 'filevector' (aka 'DatABEL') format. You do NOT need to have your data in GenABEL format for that!

Please start R and ...

3.1 Load the libraries and necessary data

We will load the 'ge03d2.clean' data set

```
library(mvtnorm)
library(DatABEL)
library(GenABEL)
data(ge03d2.clean)
df <- ge03d2.clean[,autosomal(ge03d2.clean)]
```

```
 DatABEL v.0.9-4 (March 12, 2013) loaded
 Loading required package: MASS
 GenABEL v. 1.7-4 (February 22, 2013) loaded
```

and check how many individuals and SNPs are there

```
nids(df)
nsnps(df)
```

```
 [1] 822
 [1] 6826
```

3.2 Compute genomic relationship

Compute genomic KINSHIP

```
gkin <- ibs(df,weight="freq")
gkin[1:3,1:3]
```

```
               id4          id10          id25
 id4   0.447279504 6.683000e+03 6687.0000000
 id10  0.007856257 4.657045e-01 6678.0000000
 id25 -0.007928409 6.881990e-03    0.4815139
```

Now transform this into relationship matrix

```
grel <- gkin
grel[upper.tri(grel)] <- t(grel)[upper.tri(grel)]
grel <- 2*grel
grel[1:3,1:3]
```

```
              id4       id10        id25
 id4   0.89455901 0.01571251 -0.01585682
 id10  0.01571251 0.93140902  0.01376398
 id25 -0.01585682 0.01376398  0.96302789
```

3.3 Simulate some traits

```
set.seed(10)
nTraits <- 10
model.h2 <- runif(nTraits,min=0.3,max=0.7)
myPhenos <- matrix(NA,ncol=nTraits,nrow=nids(df))
s2 <- 3
j <- 1
for (current.h2 in model.h2) {
  Sigma <- s2*(current.h2*grel + (1-current.h2)*diag(rep(1,nids(df))))
  myPhenos[,j] <- rmvnorm(1,sigma=Sigma)
  j <- j + 1
}
colnames(myPhenos) <- paste("tra",1:dim(myPhenos)[2],sep="")
myPhenos[1:2,]
```

```
           tra1      tra2      tra3      tra4      tra5       tra6       tra7
 [1,] -0.137185 -1.507003 3.2995679 -1.181792 0.2607997 -0.8527273 -2.3883019
 [2,] -2.177526 -0.442744 0.1585556  1.784114 1.5286974  2.5535508 -0.9764274
            tra8       tra9     tra10
 [1,] -0.3908143 -1.0160779 -2.773482
 [2,]  2.0045780 -0.1445038  2.448823
```

Let us also compute all ratios between the traits:

```
tmp <- myPhenos
for (i in 1:(nTraits-1)) {
  for (j in (i+1):nTraits) {
    cRatioIJ <- tmp[,i]/tmp[,j]
    cRatioJI <- tmp[,j]/tmp[,i]
    tmp <- cbind(tmp,cRatioIJ)
    colnames(tmp)[dim(tmp)[2]] <- paste("rat_",i,"_",j,sep="")
    tmp <- cbind(tmp,cRatioJI)
    colnames(tmp)[dim(tmp)[2]] <- paste("rat_",j,"_",i,sep="")
  }
}
dim(tmp)
myPhenos <- tmp
```

```
 [1] 822 100
```

3.4 Export the data in DatABEL format

Make sure you always use the DOUBLE type!

Need to make sure there are no 'older' filevector files around

```
killFiles <- c("pheno?.???","genos.???","covars.???","grel.???")
unlink(killFiles)
```

Export traits. We first export one trait

```
tmp <- matrix2databel(from=myPhenos[,1,drop=FALSE],filename="pheno1",type="DOUBLE")
```

and then all traits – this is handy to show the use of different options

```
tmp <- matrix2databel(from=myPhenos,filename="phenos",type="DOUBLE")
```

Export covariates - note you need '1' as the first covariate!

```
myCovariates <- phdata(df)[,c("sex","age")]
myCovariates <- cbind(1,myCovariates)
myCovariates[1:3,]
tmp <- matrix2databel(from=as.matrix(myCovariates),filename="covars",type="DOUBLE")
```

```
      1 sex      age
 id4  1   0 51.63771
 id10 1   1 53.73938
 id25 1   0 66.01148
```

Export relationship

```
tmp <- matrix2databel(from=grel,filename="grel",type="DOUBLE")
```

Export genotypes. Note that you do NOT need to have genotypes in the GenABEL format to do this operation.

```
tmp <- matrix2databel(from=as.numeric(gtdata(df)),filename="genos",type="DOUBLE")
```

Remove the 'tmp' object and 'gc' to keep things clean:

```
rm(tmp)
gc()
```

```
           used (Mb) gc trigger  (Mb) max used  (Mb)
 Ncells  364098 19.5     667722  35.7   467875  25.0
 Vcells 3105774 23.7   17089802 130.4 20039530 152.9
```

3.5 Export the data in format for FaST-LMM

We are going to compare the OmicABEL results with FaST-LMM, and therefore will export the results in a format usable for FaST-LMM as well. Note this part is NOT necessary to run the OmicABEL!

Start with genotypic files, to be exported in TPED format

```
export.plink(df,transpose=TRUE)
```

Export covariates

```
falmmCov <- cbind(1:nids(df),idnames(df),phdata(df)[,c("sex","age")])
falmmCov[1:3,]
write.table(falmmCov,file="plink.cov",col.names=FALSE,row.names=FALSE,
        quote=FALSE)
```

```
      1:nids(df) idnames(df) sex      age
 id4           1         id4   0 51.63771
 id10          2        id10   1 53.73938
 id25          3        id25   0 66.01148
```

Export phenotypes

```
falmmPhe <- cbind(1:nids(df),idnames(df),myPhenos)
write.table(falmmPhe,file="plink.phe",col.names=FALSE,row.names=FALSE,
        quote=FALSE)
```

Export genomic relationship

```
falmmRel <- grel
nms <- paste(1:nids(df),idnames(df))
colnames(falmmRel) <- nms
falmmRel <- cbind(var=nms,falmmRel)
write.table(falmmRel,file="plink.sim",col.names=TRUE,row.names=FALSE,
        quote=FALSE,sep="\t")
```

Now, you can leave R.

Let us switch to the shell and convert the TPED into binary PLINK format (so our 'timing' comparison is more fair)

```
plink --tfile plink --make-bed


@----------------------------------------------------------@
|        PLINK!       |     v1.07      |   10/Aug/2009     |
|----------------------------------------------------------|
|  (C) 2009 Shaun Purcell, GNU General Public License, v2  |
|----------------------------------------------------------|
|  For documentation, citation & bug-report instructions:  |
|        http://pngu.mgh.harvard.edu/purcell/plink/        |
@----------------------------------------------------------@

Web-based version check ( --noweb to skip )
Recent cached web-check found... OK, v1.07 is current

Writing this text to log file [ plink.log ]
Analysis started: Fri Mar 15 01:40:55 2013

Options in effect:
        --tfile plink
        --make-bed

Reading pedigree information from [ plink.tfam ]
822 individuals read from [ plink.tfam ]
```

```
0 individuals with nonmissing phenotypes
Assuming a disease phenotype (1=unaff, 2=aff, 0=miss)
Missing phenotype value is also -9
0 cases, 0 controls and 822 missing
438 males, 384 females, and 0 of unspecified sex
6826 (of 6826) markers to be included from [ plink.tped ]
Before frequency and genotyping pruning, there are 6826 SNPs
822 founders and 0 non-founders found
Total genotyping rate in remaining individuals is 0.990041
1 )
0 SNPs failed frequency test ( MAF < 0 )
After frequency and genotyping pruning, there are 6826 SNPs
After filtering, 0 cases, 0 controls and 822 missing
After filtering, 438 males, 384 females, and 0 of unspecified sex
Writing pedigree information to [ plink.fam ]
Writing map (extended format) information to [ plink.bim ]
Writing genotype bitfile to [ plink.bed ]
Using (default) SNP-major mode

Analysis finished: Fri Mar 15 01:40:59 2013
```

4 Run OmicABEL analysis

Let us check that all files are present in the current directory:

```
ls *.fv?
```

```
covars.fvd
covars.fvi
genos.fvd
genos.fvi
grel.fvd
grel.fvi
pheno1.fvd
pheno1.fvi
phenos.fvd
phenos.fvi
```

Make sure that the executables 'CLAK-GWAS' and 'reshuffle', or make sure they are in your path. We can now run the OmicABEL analysis with (also using 'time' to time the run).

We first run analysis of single trait using the option 'chol'

```
CLAK-GWAS -var chol -nths 3 -cov covars -phi grel \
          -snp genos -pheno pheno1 -out myres1


Running a Genome-Wide Association Study of the following size:
  sample size:      822
  # of covariates:  2
  # of SNPs:        6826
  # of phenotypes:  1

Will use CLAK-Chol with the following parameters
  x_b: 3072
  y_b: 1
  o_b: 3072
  x_tile: 160
  y_tile: 160
  # of threads: 3
  Available memory 3.107723 GBs (out of 3.873131 GBs)

Estimating GWAS parameters: heritability and variance... Done ( took 0.287 secs )
Performing the study... Done ( took 0.888 secs )
```

(this takes about 3 seconds)

Now, for analysis of multiple traits it is suggested to use the option 'eigen':

```
CLAK-GWAS -var eigen -nths 3 -cov covars -phi grel \
          -snp genos -pheno phenos -out myres


Running a Genome-Wide Association Study of the following size:
  sample size:      822
  # of covariates:  2
  # of SNPs:        6826
  # of phenotypes:  100

Will use CLAK-Eig with the following parameters:
  x_b: 3200
  y_b: 100
```

```
  o_b: 3072
  x_tile: 160
  y_tile: 160
  # of threads: 3
  Available memory 3.105980 GBs (out of 3.873131 GBs)

Estimating GWAS parameters: heritability and variance... Done ( took 2.088 secs )
Performing the study... Done ( took 5.996 secs )
```

(this takes about 20 seconds)

Easy, ergh?! Note that time does not add up - doing N phenotypes is much faster then doing N time one phenotype!

4.1 Extract the data in text format

This command will dump ALL results into single large text file (danger! danger! - check the reshuffle options for more targeted extracts)

```
reshuffle myres --chi2
```

```
myres--chi2--
finish iout_file read 0.003161
TRAITS VALUE SET CHANGED TO ALL
SNPS VALUE SET CHANGED TO ALL
startwritetxt=0.004497
endwritechitrait tra1 0.126704
[OUTPUT TRUNCATED]
```

Let us have a look at the first few lines of the output:

```
head -n 3 chi_data.txt
```

```
 SNP   Trait   beta_1  beta_sex        beta_age        beta_SNP        se_1    se_sex
 rs1646456     tra1    0.0915423184633255      0.122388660907745       -0.0007078118505
 rs7950586     tra1    -0.0256201047450304     0.11798419803381        -0.0008740884368
```

5 Explore the results

Start R again and ...

5.1 Load data into R

```
myRes <- read.table("chi_data.txt",head=TRUE,stringsAsFactors=FALSE)
myRes$Pvalue <- pchisq(myRes$Chi2,1,low=FALSE)
dim(myRes)
myRes[1:2,]
```

```
[1] 682600     18
        SNP Trait      beta_1  beta_sex      beta_age   beta_SNP      se_1
1 rs1646456  tra1  0.09154232 0.1223887 -0.0007078119 -0.2248352 0.2267392
2 rs7950586  tra1 -0.02562010 0.1179842 -0.0008740884 -0.1955265 0.2193964
     se_sex      se_age    se_SNP    cov_sex_1     cov_age_1    cov_SNP_1
1 0.1071139 0.004135856 0.1023784 -0.006057684 -0.0008482659 -0.006096948
2 0.1071970 0.004135147 0.2361242 -0.006151666 -0.0008531595 -0.003884701
    cov_age_sex   cov_SNP_sex   cov_SNP_age     Chi2     Pvalue
1 -5.950255e-07 -4.163674e-05 -1.022416e-05 4.822943 0.02808336
2 -9.072596e-07  1.001256e-03 -1.512502e-05 0.685694 0.40763289
```

5.2 Explore the results

Let us check GC λ's and $\max(\chi^2)$ for all the traits:

```
for (cTrait in unique(myRes$Trait)) {
  condition <- which(myRes$Trait==cTrait)
  lambda <- median(myRes[condition,"Chi2"])/qchisq(.5,1)
  maxChi2 <- max(myRes[condition,"Chi2"])
  cat(cTrait,"'s Lambda = ",lambda,"; max chi2 = ",maxChi2,"\n")
}
```

```
 tra1 's Lambda =  1.040671 ; max chi2 =  11.51143
tra2 's Lambda =  1.001553 ; max chi2 =  14.37402
tra3 's Lambda =  1.005891 ; max chi2 =  12.72925
[OUTPUT TRUNCATED]
```

6 Run alternative analysis and compare the results

6.1 Run FaST-LMM analysis

Let us analyze trait number 1 (and on the way we will also store the eigen-decomposition)

```
fastlmmc -bfile plink -sim plink.sim -covar plink.cov \
              -pheno plink.phe -mpheno 1 \
              -REML -simLearnType ONCE -MaxThreads 3 \
              -eigenOut flmmEigenRes -out flmmOutT1.txt
```

(this takes about 3 seconds)

Now, we can fairly time how long does it take to analyze all 10 phenotypes. For this, we will arrange an 'sh' file which will run all phenotypes analysis (and time it). This perl script generates the 'runFaST-LMM.sh':

```
open OUF,">runFaST-LMM.sh" or die $!;
for ($i=1;$i<=100;$i++) {
  print OUF "
fastlmmc -bfile plink -sim plink.sim -covar plink.cov \\
              -pheno plink.phe -mpheno $i \\
              -REML -simLearnType ONCE -MaxThreads 3 \\
              -eigen flmmEigenRes -out flmmOutT$i.txt
";
}
```

Let us run it and check few first lines if the batch file:

```
head runFaST-LMM.sh
```

```
fastlmmc -bfile plink -sim plink.sim -covar plink.cov \
              -pheno plink.phe -mpheno 1 \
              -REML -simLearnType ONCE -MaxThreads 3 \
              -eigen flmmEigenRes -out flmmOutT1.txt

fastlmmc -bfile plink -sim plink.sim -covar plink.cov \
              -pheno plink.phe -mpheno 2 \
              -REML -simLearnType ONCE -MaxThreads 3 \
              -eigen flmmEigenRes -out flmmOutT2.txt
```

Finally, let us run (and time) the analysis of all 10 traits:

```
sh runFaST-LMM.sh &> runFaST-LMM.out
```

(this takes about 220 seconds)

6.2 Compare the results

Time-wise, you can easily see that OmicABEL outperforms other implementations. Let us now check how close are the results.

Let us first extract OmicABEL results for a specific trait, "tra3", so we do not need to load everything into R:

```
head -n 1 chi_data.txt > chi_data_tra3.txt
grep "tra3" chi_data.txt >> chi_data_tra3.txt
```

Load OmicABEL results

```
myRes <- read.table("chi_data_tra3.txt",head=TRUE,stringsAsFactors=FALSE)
myRes$Pvalue <- pchisq(myRes$Chi2,1,low=FALSE)
dim(myRes)
myRes[1:2,]
```

```
[1] 6826   18
        SNP Trait      beta_1   beta_sex      beta_age   beta_SNP      se_1
1 rs1646456  tra3 -0.03245008 0.01006570 -0.0006363846 -0.0116124 0.2320724
2 rs7950586  tra3 -0.08013462 0.02045402 -0.0007954766  0.5805020 0.2243592
     se_sex      se_age    se_SNP    cov_sex_1     cov_age_1    cov_SNP_1
1 0.1095037 0.004230591 0.1063008 -0.006363481 -0.0008876185 -0.006569172
2 0.1095915 0.004229751 0.2449815 -0.006463339 -0.0008930187 -0.004231980
    cov_age_sex   cov_SNP_sex   cov_SNP_age       Chi2     Pvalue
1 -4.002032e-09 -4.097003e-05 -1.114071e-05 0.01193359 0.91301138
2 -3.186624e-07  1.078362e-03 -1.526427e-05 5.61488639 0.01780854
```

and results from FaST-LMM - say, trait 3:

```
falmmRes <- read.table("flmmOutT3.txt",head=TRUE,stringsAsFactors=FALSE)
falmmRes$Chi2 <- qchisq(falmmRes$Pvalue,1,low=FALSE)
dim(falmmRes)
falmmRes[1:2,]
```

```
[1] 6826   19
        SNP Chromosome GeneticDistance Position       Pvalue    Qvalue   N
1  rs245122          1               0   366653 0.0003820629 0.9383752 822
2 rs5547541          3               0 10955677 0.0004055348 0.9383752 822
  NullLogLike AltLogLike  SNPWeight SNPWeightSE WaldStat NullLogDelta
1   -1579.886  -1586.850  0.2664040  0.07468547 12.72358  -0.08197409
```

```
2   -1579.886  -1586.996 -0.2423752  0.06825339 12.61037  -0.08197409
  NullGeneticVar NullResidualVar    NullBias NullCov01Weight NullCov02Weight
1       1.711163        1.576488 -0.06623389   -0.0006507778     -0.06623389
2       1.711163        1.576488 -0.06623389   -0.0006507778     -0.06623389
      Chi2
1 12.61794
2 12.50652
```

The results are perfectly correlated:

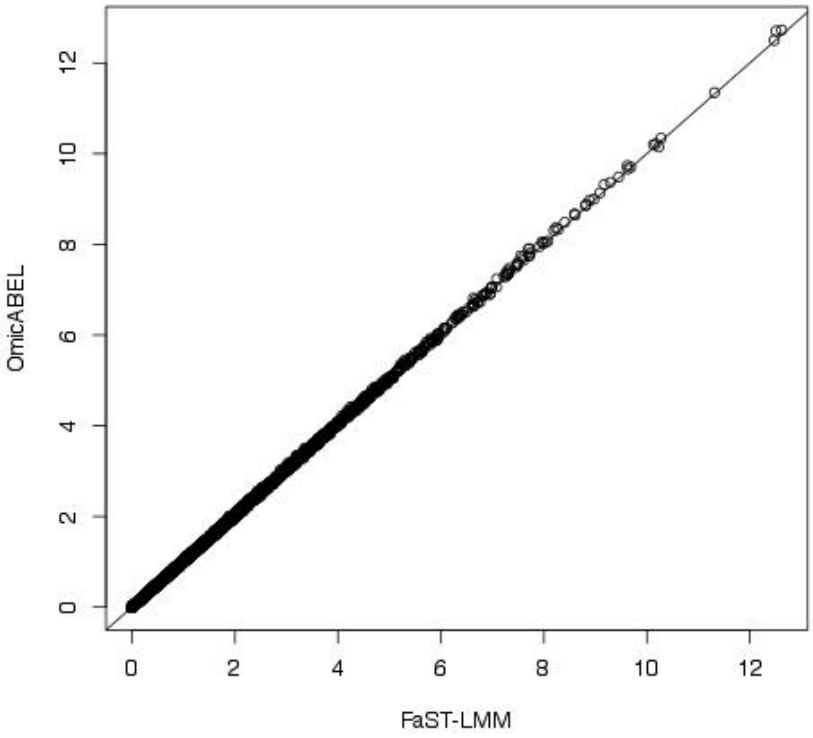
```
rownames(falmmRes) <- falmmRes$SNP
table(rownames(falmmRes) %in% myRes[,"SNP"])
falmmRes <- falmmRes[myRes[,"SNP"],]
cor(falmmRes$Chi2,myRes[,"Chi2"])^2
```

```
 TRUE
 6826
 [1] 0.9998198
```

Cross-plot the results:

```
jpeg("OmicAvsFaST.jpeg")
plot(falmmRes$Chi2,myRes[,"Chi2"],xlab="FaST-LMM",ylab="OmicABEL")
abline(a=0,b=1)
dev.off()
```

```
  null device
            1
```


OmicABEL
FaST-LMM
0
2
4
6
8
10
12