An Integrated Genetic Analysis Package Using R

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1 Introduction

This package was initiated to integrate some C/Fortran/SAS programs I have written or used over the years. As such, it would rather be a long-term project, but an immediate benefit would be something complementary to other packages currently available from CRAN, e.g. **genetics**, **hwde**, etc. I hope eventually this will be part of a bigger effort to fulfill most of the requirements foreseen by many, e.g. Guo and Lange (2000), within the portable environment of R for data management, analysis, graphics and object-oriented programming. My view has been outlined more formally in Zhao and Tan (2006b) and Zhao and Tan (2006a) in relation to other package systems. Also reported are Zhao (2005) and Zhao (2006) on package **kinship**.

The number of functions are quite limited and experimental, but I already feel the enormous advantage by shifting to R and would like sooner rather than later to share my work with others. I will not claim this workas exclusively done by me, but would like to invite others to join me and enlarge the collections and improve them.

2 Implementation

The following, extracted from the package INDEX, shows the data and functions currently available.

aldh2 ALDH2 markers and Alcoholism

apoeapoc APOE/APOC1 markers and Schizophrenia
bt Bradley-Terry model for contingency table
ccsize Power and sample size for case-cohort design

chow.test Chow's test for heterogeneity in two

regressions

cf Cystic Fibrosis data
crohn Crohn disease data
fa Friedreich Ataxia data

fbsize Sample size for family-based linkage and

association design

fsnps A case-control data involving four SNPs with

missing genotype

gc.em Gene counting for haplotype analysis

gcontrol genomic control

gcp Permutation tests using GENECOUNTING
genecounting Gene counting for haplotype analysis
gif Kinship coefficient and genetic index of

familiality

hap Haplotype reconstruction

hap.em Gene counting for haplotype analysis
hap.score Score Statistics for Association of Traits

with Haplotypes

hla HLA markers and Schizophrenia htr Haplotype trend regression

hwe Hardy-Weinberg equlibrium test for

multiallelic marker

hwe.hardy Hardy-Weinberg equlibrium test using MCMC kbyl LD statistics for two multiallelic loci kin.morgan kinship matrix for simple pedigree makeped A function to prepare pedigrees in

 ${\tt post-MAKEPED} \ {\tt format}$

mao A study of Parkinson's disease and MAO gene

mia multiple imputation analysis for hap mtdt Transmission/disequilibrium test of a

multiallelic marker

muvar Means and variances under 1- and 2- locus

(biallelic) QTL model

nep499 A study of Alzheimer's disease with eight SNPs and APOE

pbsize Power for population-based association design

pedtodot Converting pedigree(s) to dot file(s)

pfc Probability of familial clustering of disease pfc.sim Probability of familial clustering of disease

pgc Preparing weight for GENECOUNTING

plot.hap.score Plot Haplotype Frequencies versus Haplotype

Score Statistics

print.hap.score Print a hap.score object

s2k Statistics for 2 by K table

snca A study of Parkinson's disease and SNCA makers

tbyt LD statistics for two SNPs

tscc Power calculation for two-stage case-control design

twinan90 Classic twin models

whscore Whittemore-Halpern scores for allele-sharing

Assuming proper installation, you will be able to obtain the list by typing library(help=gap) or view the list within a web browser via help.start().

You can cut and paste examples at end of each function's documentation.

Both genecounting and hap are able to handle SNPs and multiallelic markers, with the former be flexible enough to include features such as X-linked data and the later being able to handle large number of SNPs. But the latter is able to recode allele labels automatically, so functions gc.em and hap.em are in haplo.em format and used by a modified function hap.score in association testing.

It is notable that multilocus data are handled differently from that in **hwde** and elegant definitions of basic genetic data can be found in **genetics** package.

Incidentally, I found my C mixed-radixed sorting routine as in Zhao and Sham (2003) is much faster than R's internal function.

With exceptions such as function pfc which is very computer-intensive, most functions in the package can easily be adapted for analysis of large datasets involving either SNPs or multial-lelic markers. Some are utility functions, e.g. muvar and whscore, which will be part of the other analysis routines in the future.

For users, all functions have unified format. For developers, it is able to incorporate their C/C++ programs more easily and avoid repetitive work such as preparing own routines for matrix algebra and linear models. Further advantage can be taken from packages in **Bioconductor**, which are designed and written to deal with large number of genes.

3 Examples

Examples can be found from most function documentations. You can also try several simple examples via demo:

library(gap) demo(gap)

4 Known bugs

Unaware of any bug. However, better memory management is expected.

5 Bibliographic note

The main references are Chow (1960), Guo and Thompson (1992), Williams et al. (1992), Gholamic and Thomas (1994), Risch and Merikangas (1996), Spielman and Ewens (1996), Risch and Merikangas (1997), Miller (1997), Sham (1997), Sham (1998), Devlin and Roeder (1999), Zhao et al. (1999), Guo and Lange (2000), Hirotsu et al. (2001), Zhao et al. (2002), Zaykin et al. (2002), Zhao (2004), Skol et al. (2006).

References

- G. C. Chow. Tests of equality between sets of coefficients in two linear regression. *Econometrica*, 28:591–605, 1960.
- B. Devlin and K. Roeder. Genomic control for association studies. *Biometrics*, 55(4):997–1004, 1999.
- K. Gholamic and A. Thomas. A linear time algorithm for calculation of multiple pairwise kinship coefficients and genetic index of familiality. *Comp Biomed Res*, 27:342–350, 1994.
- S. W. Guo and K. Lange. Genetic mapping of complex traits: promises, problems, and prospects. *Theor Popul Biol*, 57:1–11, 2000.
- S. W. Guo and E. A. Thompson. Performing the exact test of hardy-weinberg proportion for multiple alleles. *Biometrics*, 48:361–372, 1992.
- C. Hirotsu, S. Aoki, T. Inada, and Y. Kitao. An exact test for the association between the disease and alleles at highly polymorphic loci with particular interest in the haplotype analysis. *Biometrics*, 57:769–778, 2001.
- M. B. Miller. Genomic scanning and the transmission/disequilibrium test: analysis of error rates. *Genet Epidemiol*, 14:851–856, 1997.
- N. Risch and K. Merikangas. The future of genetic studies of complex human diseases. *Science*, 273(September):1516–1517, 1996.
- N. Risch and K. Merikangas. Reply to scott el al. Science, 275:1329–1330., 1997.
- P. C. Sham. Transmission/disequilibrium tests for multiallelic loci. Am J Hum Genet, 61: 774–778, 1997.
- P. C. Sham. *Statistics in Human Genetics*. Arnold Applications of Statistics Series. Edward Arnold, London, 1998. 11-1-1999.
- A. D. Skol, L. J. Scott, G. R. Abecasis, and M. Boehnke. Joint analysis is more efficient than replication-based analysis for two-stage genome-wide association studies. *Nat Genet*, 38(2): 209–13, 2006.
- R. S. Spielman and W. J. Ewens. The TDT and other family-based tests for linkage disequilibrium and association. Am J Hum Genet, 59(5):983–9, 1996.

- C. J. Williams, J. C. Christian, and J.A. Jr. Norton. Twinan90: A fortran programfor conducting anova-based and likelihood-based analyses of twin data. Comp Meth Prog Biomed, 38(2-3):167–76, 1992.
- D. V. Zaykin, P. H. Westfall, S. S. Young, M. A. Karnoub, M. J. Wagner, and M. G. Ehm. Testing association of statistically inferred haplotypes with discrete and continuous traits in samples of unrelated individuals. *Hum Hered*, 53(2):79–91, 2002.
- J. H. Zhao. 2LD. GENECOUNTING and HAP: computer programs for linkage disequilibrium analysis. *Bioinformatics*, 20:1325–6, 2004.
- J. H. Zhao. Mixed-effects Cox models of alcohol dependence in extended families. *BMC Genet*, 6(Suppl):S127, 2005.
- J. H. Zhao. Pedigree-drawing with R and graphviz. Bioinformatics, 22(8):1013-4, 2006.
- J. H. Zhao, S. Lissarrague, L. Essioux, and P. C. Sham. GENECOUNTING: haplotype analysis with missing genotypes. *Bioinformatics*, 18(12):1694–5, 2002.
- J. H. Zhao and P. C. Sham. Generic number systems and haplotype analysis. *Comp Meth Prog Biomed*, 70:1–9, 2003.
- J. H. Zhao, P. C. Sham, and D. Curtis. A program for the Monte Carlo evaluation of significance of the extended transmission/disequilibrium test. *Am J Hum Genet*, 64:1484–1485, 1999.
- J. H. Zhao and Q. Tan. Genetic dissection of complex traits in silico: approaches, problems and soluations. *Current Bioinformatics*, 1(3):in press, 2006a.
- J. H. Zhao and Q. Tan. Integrated analysis of genetic data with R. *Hum Genomics*, 2(4): 258–65, 2006b.