The *Funmap2* Package

Version 2.4

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1. Introduction

The Funmap2 package is developed to identify quantitative trait loci (QTL) for a longitudinal, or vectorized, phenotypic trait as based on the Funmap2 model [1]. This guide gives some brief instructions on how to perform the tasks of QTL detection by the Funmap2 package. The outline of this guide is as follows.

We refer to Ma et al. (2002) and Wang et al. (2017) for the theoretical foundation of this package. If you benefited from this software, then please cite the following paper in your work:

1. Ma, C. X., G. Casella, and R. L. Wu, Functional mapping of quantitative trait loci underlying the character process: A theoretical framework. Genetics 161: 1751-1762.

2. Nating Wang, Hongxiao Tian, Yongci Li, Rongling Wu, Jiangtao Luo, Zhong Wang. Fast computation of significance threshold in QTL Mapping of Dynamic Quantitative Traits, Journal of Biometrics and Biostatistics.

2. Installation

The Funmap2 package depends on the ***mvtnorm***, ***parallel*** package (available on CRAN), so these packages should be installed firstly. To install Funmap2, download the package file and type the appropriate command below or click the menu item "Install packages from local zip files".

Windows OS:

```
>install.packages("C:/yourpath/Funmap2_2.4.zip", repos=NULL)
```

Linux/Mac OS:

```
>install.packages("/yourpath/Funmap2_2.4.tar.gz", repos=NULL)
```

Or you can install the package from the GitHub from the LINUX command line:

```
$ git clone https://github.com/wzhy2000/Funmap2.git
$ cd Funmap2
$ R CMD INSTALL Funmap2
```

Before the package is used in R, the package importation is necessary by the following command:

```
> library(Funmap2)
```

After it is loaded, all functions within Funmap2 will be readily available to the user.

3. Data format

The Funmap2 package can indentify QTL loci and perform hypothesis testing on the basis of data files containing the appropriately formated marker, genotype and phenotype information. The appropriate formatting for these three files is described below.

3.1. Marker file

```
Id, Marker, Distance, chromosome(group) index, chromosome(group)name
1, D1Mit3,   0,   1, G1
2, D1Mit20, 9.4, 1, G1
…
```

In the marker file, the distance field is a distance (in cM) in one chromosome or linkage group. The header row should be included.

3.2. Genotype file

```
Individual ID, Marker1, Marker2, Marker3, Marker4, Marker5……
1, 2,  -1, 1, 1, 0, -1……
2, -1, 2,  2, 1, 0,  1,……
3, 2,  2,  0, 0, 1,  1,……
……
```

Three genotypes (aa=0,Aa=1,AA=2) and missing data (coded as -1 or NA) are valid marker values.

3.3. Phenotype file

```
Id, point1, point2, point3, point4, point5……
1,  data1, data2, data3, data4, data5……
2, ……
```

The phenotype table should be filled with numerical values and missing values recorded as NA.

3.4. Measured time file

```
Id, point1, point2, point3, point4, point5……
1,  time1, time2, time3, time4, time5……
2, ……
```

The measured time table should be filled with numerical values and missing values recorded as NA.

There are only limited data checks in the current version, and the package requires individual ids in the genotype file and phenotype file to be consistent.

4. Methodological Framework

Statistical model, hypothesis test and permutation will be explained in this section.

4.1. Statistical Model

The Funmap2 is QTL mapping methodology which has two fundamental points. The phenotypical trendency of the trait follows a mathematic curve. In statistical view, the phenotypes of the trait at all time points follow a multivariate normal density. It can be described by the following equation. y is measure values at all time points,

g can be considered a mathematic curve.

$$f_j(\mathbf{y}) = \frac{1}{(2\pi)^{m/2}|\Sigma|^{1/2}}\exp[-(\mathbf{y}-\mathbf{g}_j)^T\Sigma^{-1}(\mathbf{y}-\mathbf{g}_j)/2]$$

The 2nd point for the Funmap2 is based on genetical law which QTL between any two markers has different possibility for 3 genotypes depending on the position. The Funmap2 tries to find a position where the minimum cumulation for the gap between measure value and curve value is achieved according to the genotype possibility. The calculation methods of the maximum-likelihood estimates are shown in the following equation, where p_{ij} is the genotypical possibility for QQ, Qq and qq, $f_j(y)$ is the gap between measure value and curve value.

$$\log L(\mathbf{\Omega}) = \sum_{i=1}^{N}\log\left[\sum_{j=1}^{2}p_{ij}f_j(\mathbf{y}_i)\right]$$

Genotype possibility at any QTL position is decided by cross type. Three cross types are provided in the Funmap2, including Backcross, F2 and RILs selfing. In the package, we use the constant of "BC", "F2" and "RIL" to indicate cross type.

The Funmap2 software implements 5 curves in current version. In other words, in the Funmap2 package, we can use six types of g function, including logistic growth curve [1], nonparametric method [2] and composite curve [3]. The Appendix A shows the details of 9 curves. In the Funmap2, we use the curve type to indicate curve type, such as, "Logistic", "Legendre3" and "Exponential".

MLE algorithm is employed to estimate likelihood value and find QTL position for these curves. In addition, MLE algorithm also gives the estimation of the curve parameter for each chromosome (linkage group) of genotype at QTL position. So the Funmap2 can give the QTL position and estimated parameters at that QTL position. During the computation of MLE, multivariate normal distribution is involved to predict the probability of individual curve associated with the covariance structure which presents the correlation between the measured values at the two time points. In the Funmap2 package, 13 covariance structures [4] have been implemented, including the most frequently used structure, "AR1", "SAD1". The Appendix B shows the details of 13 covariance structures.

4.2. Hypothesis Test

The purpose of hypothesis test is to justify the existence of QTL position and the difference between genotype expressions. The Funmap2 implements the basic hypothesis test of QTL position for all curves.

Hypothesis test
All parameters are identical for any genotype. e.g. for logistic curve, $a_1 = a_2, b_1 = b_2, r_1 = r_2$

In pratical computations, four source data sets, including phenotype data, time points, genotypy data and marker data, are loaded into a data object in R environment firstly.Then hypothesis tests are performed on the data object to justify the existence of QTL position and do other evaluations. In other words, hypothesis test estimates likelihood ratio and all parameters for each genotype at every 1 or 2 cM position on a map interval bracketed by two markers throughout the entire linkage map. According to likelihood ratio value, the Funmap2 selects siginificant QTL positions which likelihood ratios are reached to maximum value at its chromosome (linkage group). These siginificant QTL positions and corresponding parameters will be made into a result object at last.

Data object and result object can be summarized into figures and PDF reports or displayed in the console. The contents of PDF report will be described in the following section.

4.3. Permutation

The permutaion is necessary to decide the significant threshold for likelihood ratio value (LR2) calculated in the hypothesis test. From the consuming time to consider, permutation loop is set to 100 defaultly. If you want to get the precise thresholds, 1000 permutations are recommended to obtain the p-value of 0.05 and 0.01.

It takes long time to do QTL scaning more than 100 times in permutation process. To improve the computational efficiency of a permutation test of mixture models used in Functional Mapping, version 2.4 has proposed a new optimized method [5]. New method first quantified the correlation between QTL and longitudinal data, using a curve clustering method. Then, the QTLs which are highly correlated with the outcome were computed in the improved permutation tests.

5. Examples

The main function for the Funmap2 is *FM2.pipe()* which can execute all tasks and output the summary report and figures to help the user understand the result. The typical syntax to run this function is shown below.

```
# Load the pre-installed data for the example
file.pheno.csv <- system.file("extdata","populus.BC.pheno.csv",
package="Funmap2")
file.geno.csv <- system.file("extdata","populus.BC.geno.csv", package="Funmap2")
file.marker.csv <- system.file("extdata","populus.BC.marker.csv",
package="Funmap2")

# Call the pipeline in parallel computing.
r <- FM2.pipe( file.pheno.csv, NULL, file.geno.csv, file.marker.csv, "BC",
   curve.type="logistic",
   covar.type="auto",
   options=list(n.cores=10) );

# Show the summary information for the data object
show(r$dat)

# Show the summary information for the result object
show(r$ret)

# Export all QTL positions into a CSV file
write.csv(r$ret$full.res, file="funmap2.qtl.csv", quote=F, row.names=F);
```

FM2.pipe () function has 5 required parameters and other optional parameters, including

1) Phenotype file name, *required*.
2) Measured time file name, *required*.
3) Genotype file name, *required*.
4) Marker definiation file name, *required*.
5) Cross type: three cross types are available in this version, “BC”, “F2” or “RIL”, *required*.
6) Curve type, several types are available, if it is not specified, curve type is determined through curve fitting procedure.
7) Covariance type, several types are available, if it is not specified, covariance structure is determined by the MLE method.
8) Options: A list of control option, including step size of QTL scaning, permutation loop, optimized permutation based on the QTL filter method, multiple CPU cores in parall compuating and QTL peak count, it will be discussed in the manual.

Normally the function loads four data files, checks data validity, runs the hypothesis tests, and finally performs permutation to identify significant threshold for the likelihood ratio (LR) values. While this pipeline is executed, progress information, summary information and figures are shown in the console continuously. It maybe takes a long time to finish these flows unless the function is incorrectly interrupted.

If the multiple processors are available, they can be utilized with the Funmap2 in the non-Windows operating systems. The Funmap2 can use the *parallel* package to support the parallel computation. If the paralle package needs to be installed in the R (< 2.14.0) before the power of parallel computation is revealed.

The LR values obtained from the hypothesis test are referred to the permutation result to make a conclusion whether QTL positions are significant or not.

The above pipeline can be executed by sequential functions in the R codes as the following:

```
# Loading the experiment data file and return a data object
dat <- FM2.load.data( file.pheno.csv, NULL, file.geno.csv, file.marker.csv, "BC",
    curve.type="auto",
    covar.type="auto");

# Show summary information for data object
show(dat);

# Draw the figures to show phenotypic curves and genotypic data in PDF file
plot(dat, pdf.file="plot.data.pdf");
```

In the calling of *FM2.load.data(),* the curve type and covariance structure are not assigned to specific values, the function *FM2.estimate.data()* is invoked to determine the curve type and covariance structure and estimate the parameter of these objects. After data loading, QTL scaning can be executed as the following codes.

```
# Hypothesis test on each QTL position and return a result object
res <- FM2.qtlscan( dat, options=list(scan.step=1, peak.count=5) );

# Show summary information for result object
show(res);

# Draw the figures to show the results in PDF file
plot(res, pdf.file="plot.res.pdf");
```

FM2.qtlscan() scans each genotype at every 1 cM position based on the curve object and covariance object. Because threshod is unavailable to determine the QTL significance without permutation test, this function uses *peak.count* to select the top peaks from the QTL scaning results. On the ultimate ppurpose, the results still need permutation tests to make the further selection. The following codes show how to do permutation and how to use the threshold to select the significant QTL.

```
# 500 Permutation tests on 10 CPU cores using the optimized method with QTL filter
ratio: 0.01,
res <- FM2.permutation( dat, res, options=list(n.cores=10, permu.loop=500,
permu.filter.ratio=0.01) );

# Show summary information for permutation result object
show(res$obj.permu);

# Draw the figures to show the permutation in PDF file
plot(res$obj.permu, pdf.file="plot.res.permu.pdf");
```

FM.permutation() takes long time to do whole genome tests even in the parallel computing. In order to reduce the computational intensity, an optimized method based on QTL filter [5] has been applied in this function since version 2.4. In general, all QTL positions on genome wide are tested in the permutation procedure. If top QTLs with strong correlation between QTL gene and phenotypic trails only are employed to do permutation tests, definitely it decrease the computational time at large scale.In this example, we only select top 1% QTLs at each permutation using the optional parameter *permu.filter.ratio.*

Permutation results are attached in the result object. We can use the threshold obtained from permutation tests to determine the significant QTLs as following codes. Generic *plot()* function also exports QTL profile and curves for different genes at these QTLs positions

```
# Select significant QTLs with p-value less than 0.05
res <- FM2.select.qtl ( res,  threshold=0.05, threshold.type="pvalue")

# Show summary information for result object
show(res);

# Draw the figures to show the results in PDF file, including QTL profile,
# curves of different genes for QTL postion.
plot(res, pdf.file="plot.res.pdf");
```

FM2.select.qtl() return a update result object with significant QTL index. We can check and export the parameters of these significant QTL as following codes.

```
# List the parameters of significant QTLs
# 'qtl.peaks' stores the index of significant QTLs in full table('full.res')
show(res$full.res[res$qtl.peaks, ]);

# Export the significant QTLs into the CSV file
write.csv( res$full.res[res$qtl.peaks, ], file="funmap2.sig.qtl.csv", quote=F,
row.names=F);
```

6. Results

As set forth herein, progress information is continuously displayed to the console while program is running. They include percentage of complete and remaining time which is estimated by the elapsed time.

Besides progress information, the outputs include some summaries for the data objects, result objects of the hypothesis tests and permutation objects. In some summaries, figures are exported to PDF files and data are exported into CSV files. We will introduce these summary formats as the following.

6.1. Raw data object

The summary of a data object includes the following:
1) The estimated parameters for mean curve.
2) A figure with tiled curves (At most 8*8 tile sub-graph can be drawn in one figure.)
3) A figure with overlapped curves (At the same time the fit curve is drawn)

```
The data set for Funmap2 model:
-----------------------------------
         Date: 2010-04-16 18:17:44
        Model: Logistic Curve
        Cross: BC
   Pheno. file: LC.populus.pheno.csv
    Geno. file: LC.populus.geno.csv
    Maker file: LC.populus.marker.csv
   Sample size: 78
  Sample times: 11
  Marker count: 275
        LC  a: 25.38983
            b: 16.17701
            r: 0.62963
          rho: 0.75430
       sigma2: 8.86295
-----------------------------------
```

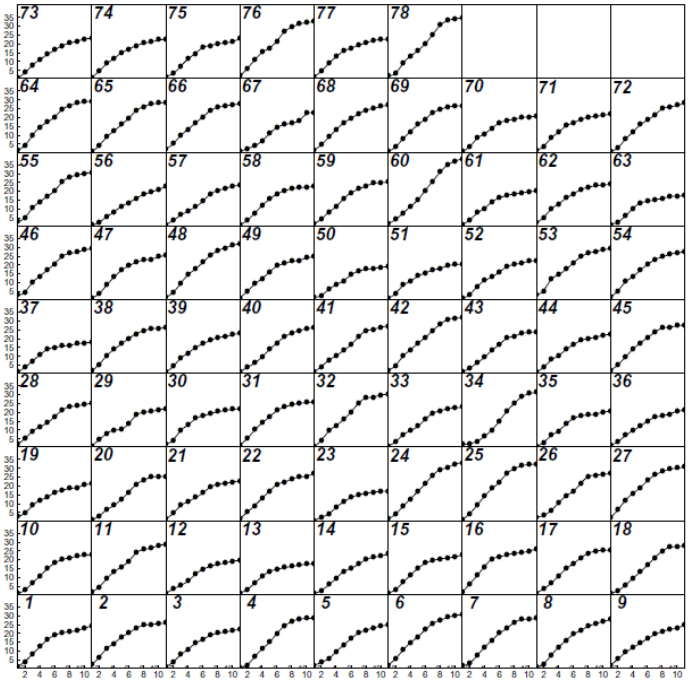


Figure 1: The figure with tiled curves

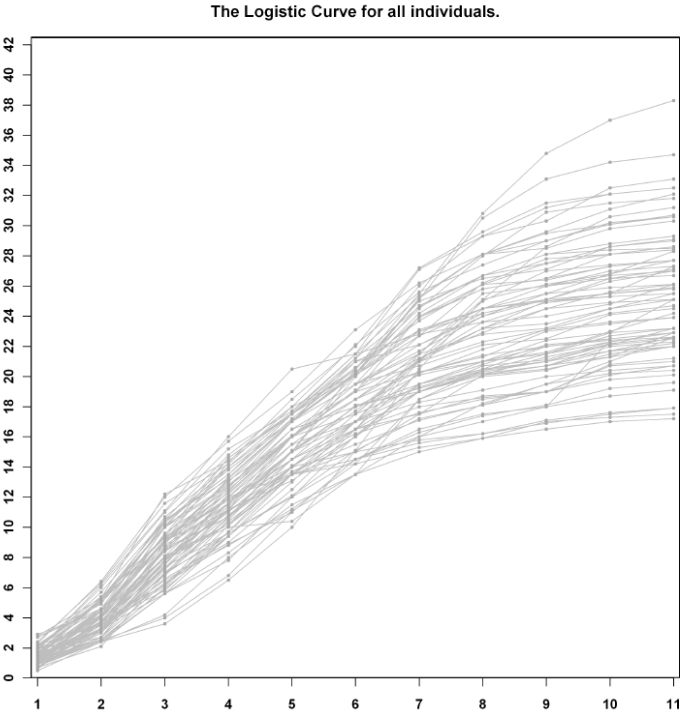


Figure 2: The figure with overlapped curves.

6.2. Hypothesis test

The hypothesis test scans every marker by the specified step (2cm or 1cm). It takes a long time, so the Funmap2 displays its progress for each chromosome (linkage group).

```
Execute the hypothesis test LGC.BC.T10...
Group:1/19, 00:03:18  has elapsed, left time:  00:59:18 .
Group:2/19, 00:06:31  has elapsed, left time:  00:55:20 .
```

```
Group:3/19, 00:09:42  has elapsed, left time:  00:51:42 .
...
Group:19/19,00:42:03  has elapsed, left time:  00 seconds .
The hypothesis test is done
```

After the marker scanning, the Funmap2 identifies the 5 (default value) significant QTLs. In one choromosome (linkage group) at most one significant QTL is selected. The most significant QTLs are strongly displayed at the head of summary.

```
    a2=a1 and b2=b1 and r2=r1
-----------------------------------
         Curve: Logistic Curve
         Cross: Backcross
      QTL pos.: 50.1  (Group:8)
        QTL LR: 66.516
    QTL p-value: 0.000
Grwoth para(Qq): a2=  30.615, b2=  10.776, r2=   0.538
Grwoth para(qq): a1=  23.707, b1=   9.449, r1=   0.615
           rho: 0.953
        sigma2: 8.637
-----------------------------------
 No.  Grp      Pos.       LR       a1       b1       r1       a0       b0       r0
   1    8   50.100    66.516   30.615   10.776    0.538   23.707    9.449    0.615
   2   12  113.100    55.190   29.865    9.736    0.528   25.207    8.725    0.586
   3   13   12.000    50.963   29.518    9.723    0.526   24.926    8.906    0.602
   4   18   10.000    25.684   29.236    9.550    0.536   25.523    8.963    0.584
   5    1  151.300    24.162   25.998    8.520    0.575   28.801    9.672    0.536
```

In the summary, besides the list of 5 QTL positions, three kinds of figures are drawn on the basis of the results, including:
1) The LR profile for all chromosomes (linkage group).
2) The LR profile for QTL postion.
3) The curve for QTL postion.

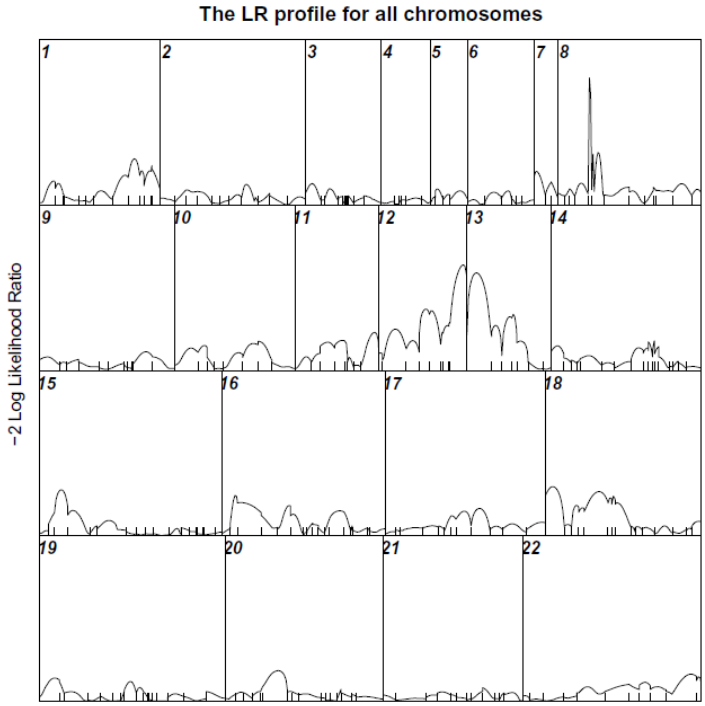


Figure 3: The LR profile for all chromosomes.

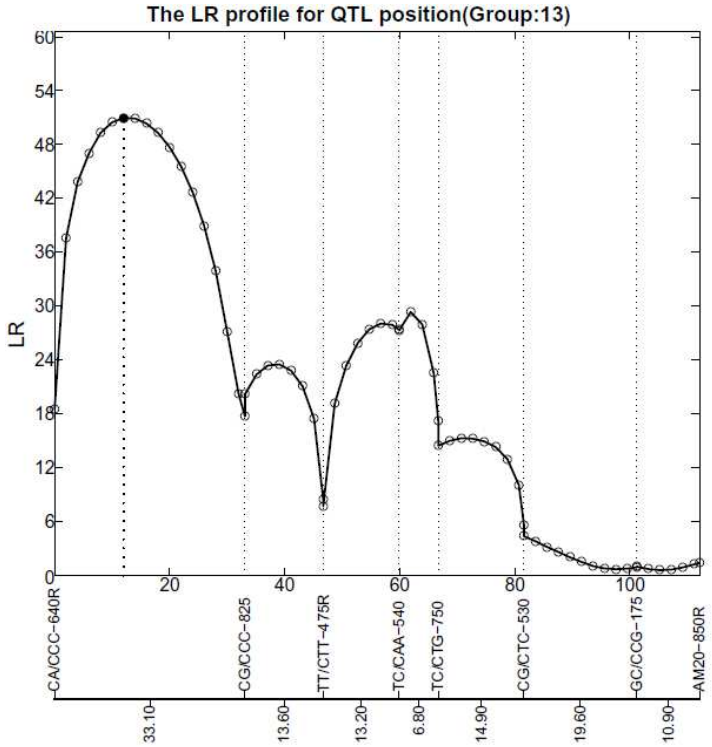


Figure 4: The LR2 profile for QTL position.

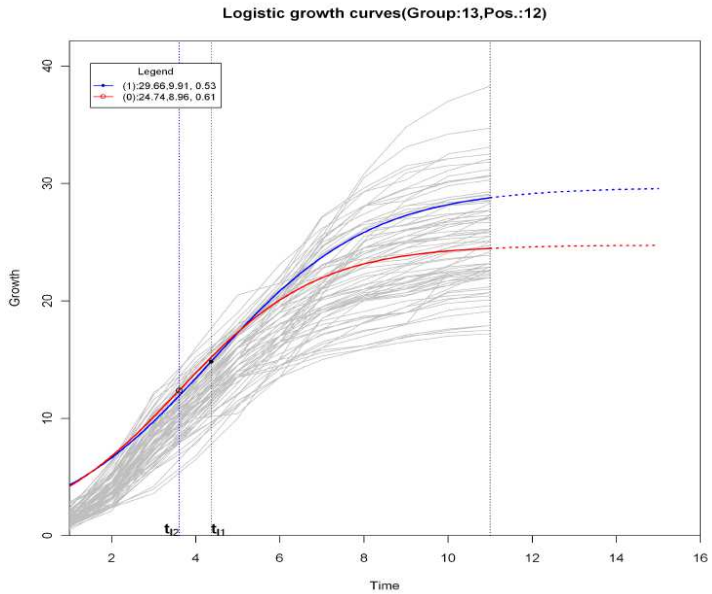


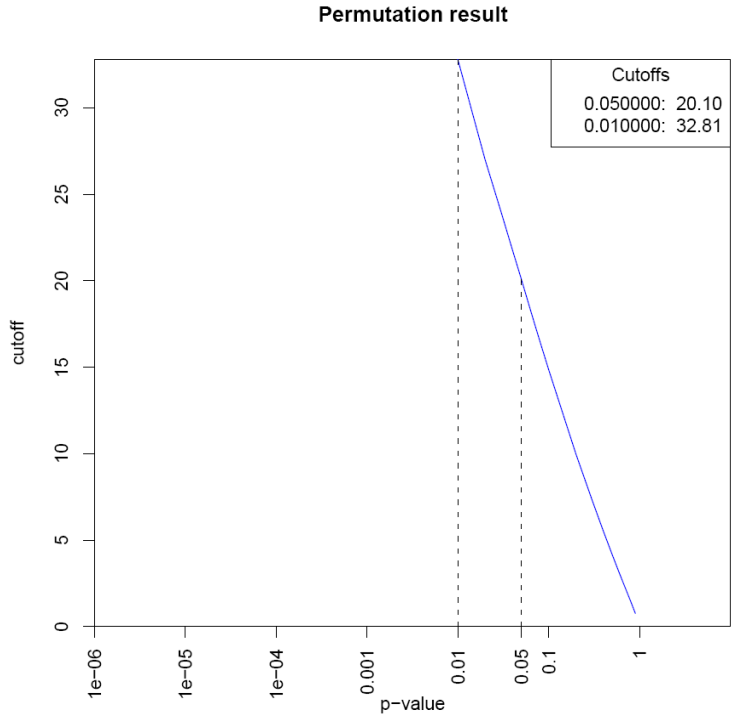
Figure 5: The curve for QTL position.

6.3. Permutation object

Permutation object can be obtained for a long time because the permutataion is to do hypothesis test on at least 1000 random samples. But the summary is very short and pithy. It just shows cutoff values for marked p-values. The following summary information just shows a permutation results on 100 random samples.

```
Permutation result:
 ----------------------------------
        Curve: Logistic Curve
        Cross: BC
         Loop: 100
----------------------------------

 p-value       Cutoff
0.90000    0.76583
0.80000    1.45845
0.70000    2.21657
0.60000    3.09488
0.50000    4.16930
0.40000    5.52038
0.30000    7.33172
0.20000    9.97031
0.10000   14.86003
0.09000   15.63818
0.08000   16.50743
0.07000   17.51136
0.06000   18.68964
0.05000   20.09660
0.04000   21.77278
0.03000   23.96467
0.02000   26.98845
0.01000   32.80592
```



7. Report

Although the Fumap2 can output summary information and figures for the result objects in the console, we also need a neat output format. From version 2.2, *FM2.report()* function provides a report function which can embed the summary information and multiple figures into a PDF file. *FM2.report()* can be called by the following format.

```
>FM2.report("report_demo.pdf", dat, ret);
```

The following link shows a PDF report.
https://github.com/wzhy2000/Funmap2/blob/master/demo/report_demo.2.4.pdf

8. Simulation

Simulation is a good way to understand the functions and learn how to use them. Simulation uses the pre-defined parameters to create a data object. This data object has same structure as real data object which loads phenotype data, genotype data and maker data from CSV files. After simulation, hypothesis tests and other procedures are same as real data analysis. The following codes show a hypothesie test and report output for simulation data.

```
> dat <- FM2.simulate();
> ret <- FM2.qtlscan(dat);
> FM2.report( "test.pdf", dat, ret);
```

All pre-defined parameters in the function *FM2.simulate()* can be customized. The following table shows the required parameters and optional paramaters for all curves and covariance structure.

Table 1: Common part of a parameter object.

Parameters	Description
simu.obs	Integer, sample_size, default: 800
simu.times	Vector, sample_times, default: 8
simu.mrkdist	Vector, maker position , default: c(0,20,40,60,80,⋯,200)
simu.qtlpos	Ineteger, QTL position,default:95
cross.type	String, default: "BC"
curve.type	String, default: "Logistic"
covar.type	String, default: "AR1"
par.X	Vector, covariate coefficient, not supported currently
par0	Vector, curve parameters for gene QQ, default is NULL, indicating the values are extracted from curve object.
par1	Vector, curve parameters for gene Qq, default is NULL, indicating the values are extracted from curve object.
par2	Vector, curve parameters for gene qq, default is NULL, indicating the values are extracted from curve object.
par.covar	Vector, covariance parameters, default is NULL, indicating the values are extracted from covariance object.
phe.missing	Missing rates in the phenotypic data
marker.missing	Missing rates in the genotypic data

9. Function list

FM2.pipe() function provides the default pipeline to analyze the data files. Actually it is composed by the basic functions provided by this package. The following lists all of them. The user can use these functions to customize the procedure of data analysis.

No	escription
1	***FM2.pipe(phenol.csv, time.csv, geno.csv, marker.csv, cross.type, curve.type, cova.type, ...)*** The QTL mapping pipeline to analyze the data files.
2	***FM2.simulate(...)***

	Simulate a data object based on a parameter object. A data object can be returned by this function.
3	***FM2.load.data(pheno.csv, time.csv, geno.csv, marker.csv, cross.type, curve.type, covar.type,...)*** Load the data from four files and return a data object. This data object can be summarized by *summary()* method in R.
4	***FM2.estimate.data(dat.obj,...)*** Estimate the parameters of curve and covariance for given data object. Besides the parameter estimate, if the curve type or the covariance structures are not specified, curve ftting or MLE are used to determine the type. An updated data object can be returned by this function.
5	***FM2.qtlscan(dat.obj,...)*** Perform the hypothesis test on the data object. A result object can be obtained from this function.
6	***FM2.permutation(dat.obj, res.obj, ...)*** Execute the permutation by the specified data object. An updated data object with permutation results can be returned by this function.
7	***FM2.select.qtl(res.obj,...)*** Select the significant QTL position on the basis of selecting method and criteria. An updated result object can be returned by this function.
8	***FM2.report (pdf.file, dat.obj, res.obj)*** Output a PDF report for data object and result object of hypothesis test.
9	***FM2.simu.pipe(cross.type, curve.type, covar.type,...)*** Demonstrate the pipeline by the simulation data.

10. Empirical data

In Funmap2 package, two empirical datasets are included, populus data[1] (logistic curve, backcross) and mice data[6] (logistic curve, F2). Please check the examples in manual to find how to use it.

11. References

1. Ma, C. X., G. Casella, and R. L. Wu, 2002. Functional mapping of quantitative trait loci underlying the character process: A theoretical framework. Genetics 161: 1751-1762.

2. Yang, J., R. L. Wu and G. Casella. Nonparametric functional mapping of quantitative trait loci. Biometrics 65: 30-39.

3. Lin, M. and R. L. Wu, 2006. A joint model for nonparametric functional mapping of longitudinal trajectories and time-to-events. BMC Bioinformatics 7(1):138.

4. IBM SPSS Advanced Statistics 20, p162-165.
https://www.csun.edu/sites/default/files/advanced-statistics20-64bit.pdf

5. Nating Wang, Hongxiao Tian, Yongci Li, Rongling Wu, Jiangtao Luo, Zhong Wang. Fast computation of significance threshold in QTL Mapping of Dynamic Quantitative Traits, Journal of Biometrics and Biostatistics.

6. Wu, R. L., C.-X. Ma, W. Hou, P. Corva and J. FM2..edrano, 2005.Functional mapping of quantitative trait loci that interact with the hg gene to regulate growth trajectories in mice. Genetics 171: 239-249.

12. Appendix A: Curves

Curve	Equation	Parameter
Logistic	$g = \frac{a}{1+be^{rt}}$	a, b, r
Bi- Logistic	$g = \frac{a_1}{1+b_1e^{r1*t}} + \frac{a_2}{1+b_2e^{r2*t}}$	a_1, b_1, r_1,a_2, b_2, r_2
Pharmacology	$g = E_0 + \frac{E_{\max} * t}{E_{c50} + t}$	E_0, E_{c50}, E_{max}
Exponential	$g = a * e^{-rt}$	a,r
Bi-exponential	$g = a_1 * e^{-r1*t} + a_2 * e^{-r2*t}$	a_1,r_1,a_2,r_2
Power	$g = a_1 * e^{-r1*t} + a_2 * e^{-r2*t}$	a_1,r_1,a_2,r_2
Legendre2 Legendre Polynomial(2rd-order)	$g = u_0 + u_1 * x + u_2 * (3x^2 + 1)/2$	u_0, u_1,u_2, u_3,
Legendre3 Legendre Polynomial(3rd-order)	$g = u_0 + u_1 * x + u_2 * (3x^2 + 1)/2 + u_3 * (5x^3 - 3x)/2$	u_0, u_1,u_2, u_3,
Legendre4 Legendre Polynomial(4rd-order)	$g = u_0 + u_1 * x + u_2 * (3x^2 + 1)/2 + u_3 * (5x^3 - 3x)/2$	u_0, u_1,u_2, u_3,u_4

13. Appendix B: Covariance Structures

Covariance	Matrix structure	Parameter
AR1 First-order autoregressive structure with homogenous variances	$\sigma^2 \begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 \\ \rho & 1 & \rho & \rho^2 \\ \rho^2 & \rho & 1 & \rho \\ \rho^3 & \rho^2 & \rho & 1 \end{bmatrix}$	σ^2,ρ
ARH1 First-order autoregressive structure with heterogenous variances	$\begin{bmatrix} \sigma_1^2 & \sigma_2\sigma_1\rho & \sigma_3\sigma_1\rho^2 & \sigma_4\sigma_1\rho^3 \\ \sigma_2\sigma_1\rho & \sigma_2^2 & \sigma_3\sigma_2\rho & \sigma_4\sigma_2\rho^2 \\ \sigma_3\sigma_1\rho^2 & \sigma_3\sigma_2\rho & \sigma_3^2 & \sigma_4\sigma_3\rho \\ \sigma_4\sigma_1\rho^3 & \sigma_4\sigma_2\rho^2 & \sigma_4\sigma_3\rho & \sigma_4^2 \end{bmatrix}$	σ_1^2, σ_2^2,…,ρ
ARMA(1,1) First-order autoregressive structure with heterogenous variances	$\sigma^2 \begin{bmatrix} 1 & \phi\rho & \phi\rho^2 & \phi\rho^3 \\ \phi\rho & 1 & \phi\rho & \phi\rho^2 \\ \phi\rho^2 & \phi\rho & 1 & \phi\rho \\ \phi\rho^3 & \phi\rho^2 & \phi\rho & 1 \end{bmatrix}$	σ^2, ϕ,ρ
VS Variance Components	$\begin{bmatrix} \sigma_1^2 & 0 & 0 & 0 \\ 0 & \sigma_2^2 & 0 & 0 \\ 0 & 0 & \sigma_3^2 & 0 \\ 0 & 0 & 0 & \sigma_4^2 \end{bmatrix}$	σ_1^2, σ_2^2,…

SI Scaled Identity.	$\sigma^2 \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$	σ^2
CS Compound Symmetry with constant variance and constant covariance	$\sigma^2 \begin{bmatrix} 1 & \rho & \rho & \rho \\ \rho & 1 & \rho & \rho \\ \rho & \rho & 1 & \rho \\ \rho & \rho & \rho & 1 \end{bmatrix}$	σ^2,ρ
CSH Heterogeneous Compound Symmetry with heterogenous variances and constant correlation between elements	$\begin{bmatrix} \sigma_1^2 & \sigma_2\sigma_1\rho & \sigma_3\sigma_1\rho & \sigma_4\sigma_1\rho \\ \sigma_2\sigma_1\rho & \sigma_2^2 & \sigma_3\sigma_2\rho & \sigma_4\sigma_2\rho \\ \sigma_3\sigma_1\rho & \sigma_3\sigma_2\rho & \sigma_3^2 & \sigma_4\sigma_3\rho \\ \sigma_4\sigma_1\rho & \sigma_4\sigma_2\rho & \sigma_4\sigma_3\rho & \sigma_4^2 \end{bmatrix}$	σ_1^2, σ_2^2,…,ρ
FA1 Factor Analytic: First-Order	$\begin{bmatrix} \lambda_1^2+d & \lambda_2\lambda_1 & \lambda_3\lambda_1 & \lambda_4\lambda_1 \\ \lambda_2\lambda_1 & \lambda_2^2+d & \lambda_3\lambda_2 & \lambda_4\lambda_2 \\ \lambda_3\lambda_1 & \lambda_3\lambda_2 & \lambda_3^2+d & \lambda_4\lambda_3 \\ \lambda_4\lambda_1 & \lambda_4\lambda_2 & \lambda_4\lambda_3 & \lambda_4^2+d \end{bmatrix}$	λ_1^2, λ_2^2,…,d,
FAH1 Heterogenous Factor Analytic First-Order	$\begin{bmatrix} \lambda_1^2+d_1 & \lambda_2\lambda_1 & \lambda_3\lambda_1 & \lambda_4\lambda_1 \\ \lambda_2\lambda_1 & \lambda_2^2+d_2 & \lambda_3\lambda_2 & \lambda_4\lambda_2 \\ \lambda_3\lambda_1 & \lambda_3\lambda_2 & \lambda_3^2+d_3 & \lambda_4\lambda_3 \\ \lambda_4\lambda_1 & \lambda_4\lambda_2 & \lambda_4\lambda_3 & \lambda_4^2+d_4 \end{bmatrix}$	λ_1^2, λ_2^2,…,d_1, d_2, …,
HF Huynh-Feldt.	$\begin{bmatrix} \sigma_1^2 & \frac{\sigma_1^2+\sigma_2^2}{2}-\lambda & \frac{\sigma_1^2+\sigma_3^2}{2}-\lambda & \frac{\sigma_1^2+\sigma_4^2}{2}-\lambda \\ \frac{\sigma_1^2+\sigma_2^2}{2}-\lambda & \sigma_2^2 & \frac{\sigma_2^2+\sigma_3^2}{2}-\lambda & \frac{\sigma_2^2+\sigma_4^2}{2}-\lambda \\ \frac{\sigma_1^2+\sigma_3^2}{2}-\lambda & \frac{\sigma_2^2+\sigma_3^2}{2}-\lambda & \sigma_3^2 & \frac{\sigma_3^2+\sigma_4^2}{2}-\lambda \\ \frac{\sigma_1^2+\sigma_4^2}{2}-\lambda & \frac{\sigma_2^2+\sigma_4^2}{2}-\lambda & \frac{\sigma_3^2+\sigma_4^2}{2}-\lambda & \sigma_4^2 \end{bmatrix}$	σ_1^2, σ_2^2,… λ
TOEP Toeplitz with homogenous variances and heterogenous correlations	$\sigma^2 \begin{bmatrix} 1 & \rho_1 & \rho_2 & \rho_3 \\ \rho_1 & 1 & \rho_1 & \rho_2 \\ \rho_2 & \rho_1 & 1 & \rho_1 \\ \rho_3 & \rho_2 & \rho_1 & 1 \end{bmatrix}$	σ^2,ρ_1,ρ_2,…
TOEPH Heterogenous Toeplitz with heterogenous variances and heterogenous correlations between elements	$\begin{bmatrix} \sigma_1^2 & \sigma_2\sigma_1\rho_1 & \sigma_3\sigma_1\rho_2 & \sigma_4\sigma_1\rho_3 \\ \sigma_2\sigma_1\rho_1 & \sigma_2^2 & \sigma_3\sigma_2\rho_1 & \sigma_4\sigma_2\rho_2 \\ \sigma_3\sigma_1\rho_2 & \sigma_3\sigma_2\rho_1 & \sigma_3^2 & \sigma_4\sigma_3\rho_1 \\ \sigma_4\sigma_1\rho_3 & \sigma_4\sigma_2\rho_2 & \sigma_4\sigma_3\rho_1 & \sigma_4^2 \end{bmatrix}$	σ_1^2, σ_2^2,…, ρ_1,ρ_2,…
SAD1 First-order Structured Antedependence		

14. Appendix C: version history.

2012/10/05 Version 2.2 has been released.
2017/01/12 Version 2.4 has been released.