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QTL.gCIMapping.GUI v2.0: An R software for detecting small-effect and linked QTLs for quantitative traits in bi-parental segregation populations

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Abstract
The methodologies and software packages for mapping quantitative trait loci (QTLs) in bi-parental segregation populations are well established. However, it is still difficult to detect small-effect and linked QTLs. To address this issue, we proposed a genome-wide composite interval mapping (GCIM) in bi-parental segregation populations. To popularize this method, we developed an R package. This program with two versions (Graphical User Interface: QTL.gCIMapping.GUI v2.0 and code: QTL.gCIMapping v3.2) can be used to identify QTLs for quantitative traits in recombinant inbred lines, doubled haploid lines, backcross and F2 populations. To save running time, fread function was used to read the dataset, parallel operation was used in parameter estimation, and conditional probability calculation was implemented by C++. Once one input file with *.csv or *.txt formats is uploaded into the package, one or two output files and one figure can be obtained. The input file with the ICIM and win QTL cartographer formats is available as well. Real data analysis for 1000-grain weight in rice showed that the GCIM detects the maximum previously reported QTLs and genes, and has the minimum AIC value in the stepwise regression of all the identified QTLs for this trait; using stepwise regression and empirical Bayesian analyses, there are some false QTLs around the previously reported QTLs and genes from the CIM method. The above software packages on Windows, Mac and Linux can be downloaded from https://cran.r-project.org/web/packages/ or https://bigd.big.ac.cn/biocode/tools/7078/releases/27 in order to identify all kinds of omics QTLs.

1. Introduction

Linkage analysis has been the predominant statistical genetic mapping approach in the past decades. It has been widely used in the genetic dissection of quantitative traits in bi-parental segregation populations. Up to now numerous quantitative trait loci (QTLs) for quantitative traits have been identified, and some QTLs have been used to conduct marker-assisted selection in crop breeding and to clone genes in molecular biology. However, most of these QTLs have large effects.

At present the methodologies and software packages of mapping QTLs for quantitative traits in bi-parental segregation populations have been well established. At the early stage, Lander and Botstein [1] established a new framework, named interval mapping, for mapping QTLs in such populations, and its software is Mapmaker/QTL. However, this method does not consider the effect of other QTLs on the mapping of the current QTL. To overcome this issue, composite interval mapping (CIM) has been proposed [2–4]. Based on this CIM method, numerous software packages have been released, e.g., QTL PLABQTL [5], QGene [6], HAPPY [7], Map Manager [8], win QTL Cartographer [9], and QTL Express [10]. Similar to the CIM method, mixed linear model [11] and inclusive CIM (ICIM) [12] methods have been developed, and the corresponding software packages QTLNet [13] and QTL IciMapping [14] have also been released. As we know, multi-QTL mapping is now the state-of-the-art method for QTL mapping. Thus, a series of multi-QTL mapping approaches, including multiple-interval mapping [15], multi-marker analysis [16], Bayesian shrinkage estimation [17,18], penalized maximum likelihood [19], empirical Bayes [20], have been proposed, and some software packages have been released, for example, R/qtl [21,22], MapQTL [23], mpMap [24], win QTL Cartographer [25], and DOQTL [26]. These above methods and software packages have played an important role in the identification of QTLs in various populations.
important role in QTL mapping. However, there are still two short-
comings. First, it is difficult to detect small-effect QTLs. The reasons are as follows: the limited number of individuals or lines in the mapping population, large experimental error in field experiments, and low power of QTL mapping methods in the detection of small-
effect QTLs. Secondly, it is also difficult to detect the closely linked QTLs. If there are two linked QTLs with effects in the same direc-
tion, one false QTL between the two linked QTLs may be detected, whereas if there are two linked QTLs with effects in the opposite
directions, no QTL may be identified because the effects of the two linked QTLs may be canceled. To overcome the above two issues, Wang et al. [27] and Wen et al. [28] proposed genome-
wide composite interval mapping (GCIM), respectively, in back-
cross and F₂ populations.

In the GCIM, first, a single-locus random-SNP-effect mixed lin-
ear model in genome-wide association studies (GWAS) is used to
scan each putative QTL on the genome (File A.1). Here controlling
polygenic background via selecting background markers in CIM is
replaced by estimating polygenic variance in GWAS. Then, all the
peaks in the negative logarithm P-value curve are viewed as the
positions of multiple putative QTLs to be included in a multi-QTL
model, the QTL effects are estimated by empirical Bayes, and
non-zero effects are further evaluated by likelihood ratio test for
true QTL detection. Our Monte Carlo simulation studies and real
data analysis showed that the GCIM has high power in detecting
QTL, high accuracy in estimating QTL parameters and low false
positive rate as compared with the widely-used methods. To pop-
ularize the GCIM, it is necessary to develop its software package. In
this article, we introduce the R packages QTL.gCIMapping (File A.2)
or QTL.gCIMapping.GUI (File A.3).

2. Materials and methods

2.1. Genetic mapping population

There are two kinds of mapping populations available in this
software package. The first ones, including backcross (BC), doubled
haploid (DH) lines, recombinant inbred lines (RIL), F₂, and “immortal-
ized F₂ (IF₂)”, are primary segregation populations derived from the
cross between two homozygous lines. The second ones are sec-
ondary segregation populations derived from the cross between
two near iso-genic lines (intragenic lines or QTL isogenic lines).
Generally speaking, the accuracy of QTL mapping in primary map-
ping populations is lower than that in secondary mapping populat-
tions. The sample size is frequently more than 250 in primary
mapping and several thousands in fine mapping. All the dominant
and co-dominant markers are available.

In the genetic mapping populations, linkage maps, marker
genotypes and phenotypic values for quantitative traits are needed
in the QTL mapping. In the GCIM software package, the above three
kinds of information are incorporated into one input file. In addition,
covariate information can be considered and incorporated into the input file.

2.2. 1000-grain weight in rice

In this study, four datasets for 1000-grain weight in rice RILs
described in Yu et al. [29] are re-analyzed using the GCIM, CIM
and ICIM methods, which were implemented, respectively, by the
software packages QTL.gCIMapping.GUI v2.0, win QTL Cartogra-
pher v2.5 [25] and QTL IciMapping v4.1 [14]. The datasets Xing1997 and Xing1998 were downloaded from Xing et al. [30], while the datasets Hua1998 and Hua1999 were downloaded from Hua et al. [31,32]. All the four datasets have the same genotypes and different phenotypes. There were 1619 bin markers for all
the 210 RILs and these markers covered a length of 1625.509 cM
on the genome (Table A.1).

2.3. Development of the QTL.gCIMapping.GUI v2.0 software

QTL.gCIMapping.GUI v2.0 is an R package with graphical user
interface. Shiny is used to build interactive web applications in R
by automatic reactive binding between inputs and outputs and
extensive prebuilt widgets. The software mainly contains three
modules: dataset inputting, parameter settings and plot redrawing.
Once the dataset inputting and parameter settings are finished,
users may run the program and the results will be saved in the
directory that was set by the users. The plot redrawing is an addi-
tional module, and its function is to redraw the plot using the previ-
siously saved results, such as adjusting the color or thickness of the
curve and the resolution of the plot.

To reduce the running time, three approaches were adopted.
First, conditional probability calculation for the genotypes of puta-
tive QTL was implemented by C++ and Rcpp [33,34] is used for the
interface between R and C++. Then, parallel calculation was
adopted in parameter estimation. Parallel is used to detect
the number of CPU cores on the current host and create a set of copies
of R running in parallel and communicating over sockets, and
doParallel is used to register the parallel backend with the foreach
package. Finally, fread function was used to read dataset.

Once the software is successfully installed in the R environ-
ment, users can operate the software by clicking the mouse. If
users analyze the datasets on the server, the code version of this
software, QTL.gCIMapping v3.2, is also available. In this situation,
users need to write R script to call the function instead of clicking
the mouse directly.

2.4. Preparation of the input file

There are three kinds of input file formats available in this soft-
ware. The first one is the GCIM format with the “.csv” or “.txt” file.
This file consists of four parts: linkage maps, marker genotypes,
phenotypic values for quantitative trait, and covariates (Fig. 1).
Linkage maps, including marker names, chromosome number and
marker positions on chromosome (cM), are listed in the first
three columns. The marker genotypes are listed from the fourth
column. Each column represents one individual or line, the first
row shows the name of individual or line, and the other rows on
the right side of the linkage maps show marker genotypes. Each
marker genotype is encoded by a given single capital letter, “A”,
“H” and “B” indicate genotypes “AA”, “Aa” and “aa”, respectively,
while dominant marker genotypes “AA + Aa” or “Aa + aa” are rep-
resented by “D” or “C”, respectively. “-” means the absence of
marker genotypes. The phenotypic values for quantitative trait
and covariates are presented below both linkage maps and marker
genotypes. The phenotypic values for each trait are arranged in one
row and distinguished by “trait*”, where “*” is the serial num-
ber of the trait. The trait name is given on the next column with the
same row, and the phenotypic value of an individual or line is
placed at the intersection of the trait and the individual or line. If
some phenotypic values are missing, these values are indicated by “NA”. Each covariate is arranged into one row. The covariates are
distinguished by “Covar*”, where “*” is the serial number of
the covariate. The covariate name is presented on the next column
with the same row, and the covariate value of an individual or line is
placed at the intersection of the covariate and the individual. If
there are no covariates, this block is empty.

The second format for the input file is the Mt-MIM Control File
format of QTL Cartographer, and the third format is the EXCEL 2007
format for BIP of QTL IciMapping. The sample files for the two for-
mats are showed on Tables A.2 and A.3.
### 2.5. Statistical analysis

Stepwise regression is implemented by function “step” in R package “stats”. In the “step” function, we selected “both”, which does the forward and backward stepwise regression analysis. The introduction and deletion of a variable are based on the decrease of the AIC value for the model. Once the AIC value no longer decreases, the stepwise regression analysis terminates and the optimal regression equation is output.

### 2.6. Installation of the software package

This software can be installed in two ways: online installation and offline installation. For online installation, users can install directly using the below command:

```
install.packages('QTL.gCIMapping.GUI')
```

then all the add-on packages and QTL.gCIMapping.GUI v2.0 will install automatically. For offline installation, users first open R GUI, select “Packages” — “Install package(s) from local files...”, and then find and install the add-on packages, which include 39 packages:

- `cmprsk`
- `corpcor`
- `data.table`
- `digest`
- `doParallel`
- `Epi`
- `etools`
- `fdrtool`
- `foreach`
- `GeneNet`
- `glmnet`
- `htmltools`
- `httpuv`
- `iterators`
- `jstable`
- `longitudinal`
- `magrittr`
- `MASS`
- `mime`
- `numDeriv`
- `openxlsx`
- `parcor`
- `plyr`
- `ppls`
- `promise`
- `QTL.gCIMapping`
- `qtl`
- `R6`
- `Rcpp`
- `shiny`
- `sourcetools`
- `stringi`
- `stringr`
- `testthat`
- `utf8`
- `xtable`
- `zoo`

Finally, users install QTL.gCIMapping.GUI v2.0 package, which has been downloaded on your computer (Fig. 2).

### 2.7. Implementation of the software package

Once the software is installed, users can run the software by two commands:

```
library(QTL.gCIMapping.GUI) and QTL.gCIMapping.GUI()
```

Once the software is restarted, users use the above two commands as well.

The installation for the code version is almost the same as that for the above GUI version. The difference is that users need to write the below R scripts:

```
QTL.gCIMapping(file = "D:/Users/GCIM_Format_DH.csv", fileFormat = "GCIM", fileICIMcov = NULL, Population = "DH", Model = "Random", WalkSpeed = 1, CriLOD = 2.5, Likelihood = "REML", flagrqtl = TRUE, DrawPlot = TRUE, PlotFormat = "png", Resolution = "Low", Trait = 1:100, dir = "D:/Users")
```

The explanations for the above parameters are found in Table A.4. In the parameter setting module, users need to set fourteen parameters. Among these parameters, Likelihood and flagrqtl are specific to the F2 population, and eight may be default or set by users, including fileFormat, fileICIMcov, Model, Likelihood, flagrqtl, DrawPlot, PlotFormat, and Resolution (File A.3).

### 3. Results

#### 3.1. The description for the result files

If users run the code version of the software package, users will get one excel file with the .csv format (named “i_GCIM result.csv”) and one plot file with the png or jpeg or pdf formats (named “i_result.png”) in the directory that is set by users, where “i” represents the
If users run the GUI version, users will obtain one additional file, named "i_resultforplot.xlsx". Users may upload this additional file to the plot redrawing module of the software in order to draw one new plot, if users need to change the plot parameters, e.g., resolution and color. It is easy to change these plot parameters by clicking the mouse.

In the "i_GCIM result.csv" file for DH, RIL, BC1, BC2, there are nine parameters for each significant QTL and two parameters for each mapping population (Table A.5). These parameters are described as below. “Trait” is the trait name analyzed; “Chr” is the abbreviation for chromosome and its result is indicated by an integer number; “Position (cM)” is the position (cM) of each significant QTL on the chromosome; “Additive Effect” is the additive effect for each significant QTL; “LOD” is the LOD score for each significant QTL; “Left_Marker” and “Right_Marker” are respectively the left and right flanking marker names around each significant QTL; “Var_Genet” is the genetic variance for each significant QTL; “r² (%)” is the proportion of phenotypic variance explained by single QTL. “Var_Error” is the residual variance for the multi-QTL genetic model, and “Var_Phen (total)” is the variance for the phenotypic values of the trait in the mapping population. In the “i_GCIM result.csv” file for F2, the parameter “Additive Effect” for QTL effect is replaced by two parameters “Effect.a” and “Effect.d”, where “Effect.a” is additive effect and “Effect.d” is dominant effect for each significant QTL.

In the “i_res.tif” plot file for DH, RIL, BC1, BC2, horizontal (x) axis indicates marker position on the genome (cM); vertical axis on the right side means $-\log_{10}(P\text{-value})$ for all the putative QTLs on the genome, which are the results in the first step in GCIM, and vertical axis on the left side represents LOD scores for all the significant QTLs, which are the results in the second step in GCIM. In the “i_res.tif” plot file for F2, there are two $-\log_{10}(P\text{-value})$ curves. One is for an additive effect and another is for a dominant effect.

### 3.2. Real data analysis for 1000-grain weight in rice

Four datasets for 1000-grain weight in rice from Xing et al. [30] and Hua et al. [31, 32] were re-analyzed by the GCIM, CIM and ICIM methods. All the results are listed in the Tables A.6–A.9. A total of 13, 11 and 10 stable QTLs across the four datasets were detected by GCIM, CIM and ICIM, respectively (Table 1). Among the 18 stable QTLs, 10 are detected commonly by at least two methods and have the average $r^2$ of 5.40% from the GCIM, while 8 are identified by a single method and have the average $r^2$ of 2.82% (Tables A.6–A.9). This means that common QTLs have large effects and unique QTLs for each method have small effects. Meanwhile, a total of 8, 8, and 8 previously reported QTLs and 8, 5, and 7 previously reported genes around the above detected QTLs were found by the GCIM, CIM and ICIM methods, respectively, to be associated with the 1000-grain weight (Tables A.10–A.16; Figs. 3 and A.1–A.3; File A.4).

To compare the above three methods, we established multiple regression equations of all the QTLs, detected by each QTL mapping method, for the trait (model I), and then conducted stepwise regression (model II) and empirical Bayes (model III) analyses. As a result, the GCIM generates consistent results across the three models. Among all the 41 QTLs detected by the CIM, 10, 8, 9, and 10 were found in the model II not to be associated with 1000-grain weight, respectively, in the Xing1997, Xing1998, Hua1998 and Hua1999 datasets; 11, 8, 7, and 10 were found in the model...
Table 1. Stable QTLs for rice 1000-grain weight in multiple environments detected by composite interval mapping (CIM), genome-wide CIM (GCIM) and inclusive CIM (ICIM).

| QTL Chr | GCIM (Posc m) | CIM | ICIM | LOD | r^2 (%) |
|---------|---------------|------|------|-----|---------|
| 3       | 361.30–373.71 | 3.81 | 3.73 | 2.43 | 0.96    |
| 9       | 416.20–417.77 | 1.54 | 1.89 | 1.34 | 0.96    |
| 11      | 95.00–95.98   | 1.21 | 1.09 | 0.84 | 0.96    |
| 14      | 121.10–125.44 | 2.04 | 2.04 | 2.04 | 0.96    |
| 16      | 125.50–125.89 | 1.71 | 1.71 | 1.71 | 0.96    |
| 20      | 207.10–207.22 | 1.71 | 1.71 | 1.71 | 0.96    |
| 21      | 103.00–103.14 | 0.36 | 0.36 | 0.36 | 0.96    |
| 28      | 81.20–81.22   | 0.74 | 0.81 | 0.74 | 0.96    |
| 29      | 0.74–0.81     | 0.74 | 0.81 | 0.74 | 0.96    |

Based on the above results, we found that more small-effect known genes or QTLs are detected by the GCIM, for example, OsSec18 (r^2 = 0.96%) is detected only by the GCIM in the Hua1998 and Hua1999 datasets. ONAC106 (r^2 = 1.42%) is detected commonly by the GCIM and ICIM methods in the Hua1999 dataset, and RDD11 (r^2 = 1.44%) and gw7.1 (r^2 = 1.46%) are identified commonly by all the three methods in the Hua1998 dataset (Table A.10–A.13). Meanwhile, we also found two linked QTLs (kgw1a and RDD1) by all the three methods in the Hua1998 dataset (Fig. 3).

Among the above detected QTLs, we found two new candidate genes: LOC/Os12g44290 and LOC/Os11g04880. Based on the KEGG pathways at http://kobas.cbi.pku.edu.cn/ (KOBAS), these two genes are associated with steroid hormone biosynthesis, and some known genes for 1000-grain weight, such as SLG and GWS [36,37], can modulate brassinosteroid homeostasis in rice.

4. Discussion

The software package developed in this study has some advantages over similar packages. First, the GCIM can detect small-effect and linked QTLs. Secondly, all the QTLs identified by the GCIM are found to be associated with the trait of interest, and some QTLs identified by the CIM are found not to be associated with the trait of interest. Thirdly, the GCIM detects more QTLs than does the CIM. Finally, the current package considers the running time in three aspects. Read function is used to read the dataset, parallel operation is used in parameter estimation, and conditional probability calculation is implemented by C++.

As described by Krysmann and Mitchell-Olds [38] and Mackay et al. [39], detecting small and linked QTLs is a thorny issue in the genetic dissection of quantitative traits. However, this situation will change significantly since we propose the GCIM method and develop its software in this study. In the GCIM [27,28], there are two main improvements. On one hand, selecting background markers in the CIM and ICIM to control polygenic background has been replaced by estimating polygenic variance in GWAS. On the other hand, all the peaks in the negative logarithm P-value curve against genome position for each QTL effect are viewed as potential QTLs and these potential QTLs are placed into a multi-locus genetic model for true QTL identification. In our opinion, the difficulty of detecting small-effect and linked QTLs is due to their low LOD scores, although their peaks exist. Once all these peaks are viewed as potential QTLs in a multi-QTL genetic model, the power of detecting these QTLs increases. This is why the GCIM has higher power in identifying small-effect and linked QTLs than the other methods, including Bernardo [40] and Xu [41], which have the first improvement.

Based on previous and current studies, several peaks around one large-effect QTL are frequently observed when win QTL Cartographer (the CIM method) is used. In this case, we do not know whether there are multiple linked QTLs or only one single large-effect QTL. To address this issue, we optimized the regression equation of all the identified QTLs for the trait using stepwise regression and empirical Bayesian analyses. As a result, quite a
number of QTLs around large-effect QTLs in the CIM are found not to be associated with the trait of interest in real data analysis. This phenomenon does not happen in the GCIM. In other words, all the QTLs detected by the GCIM are significant. This result may explain why the number of QTLs detected by the CIM is more than those by the GCIM in some real data analyses.

Based on the number of stable QTLs detected by the above-mentioned three methods in real data analysis, the GCIM generates the most, and ICIM gives the least. However, the AIC values from the GCIM are the minimum, more known genes or previously reported QTLs are identified by the GCIM, and some QTLs identified by the CIM are found not to be associated with 1000-grain weight in step-wise regression and empirical Bayes. Thus, the GCIM should be widely adopted in the near future.

At present the methodologies and software packages of mapping main-effect QTL, and QTL-by-environment and QTL-by-QTL interactions for quantitative traits in bi-parental segregation populations have been well established. However, only main-effect QTLs can be detected in the software packages QTL.gCIMapping v3.2 and QTL.gCIMapping.GUI v2.0. Thus, it is necessary to extend the methodologies for detecting QTL-by-environment and QTL-by-QTL interactions in the near future.

5. Authors’ Contributions

YMZ conceived and designed the study. YWZ, YJW and YMZ wrote the codes, performed the data analyses, and wrote the draft. YMZ, JMD, and YWZ revised the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.csbj.2019.11.005.

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