Gene expression

QUBIC: a bioconductor package for qualitative biclustering analysis of gene co-expression data

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Abstract

Motivation: Biclustering is widely used to identify co-expressed genes under subsets of all the conditions in a large-scale transcriptomic dataset. The program, QUBIC, is recognized as one of the most efficient and effective biclustering methods for biological data interpretation. However, its availability is limited to a C implementation and to a low-throughput web interface.

Results: An R implementation of QUBIC is presented here with two unique features: (i) a 82% average improved efficiency by refactoring and optimizing the source C code of QUBIC; and (ii) a set of comprehensive functions to facilitate biclustering-based biological studies, including the qualitative representation (discretization) of expression data, query-based biclustering, bicluster expanding, biclusters comparison, heatmap visualization of any identified biclusters and co-expression networks elucidation.

Availability and Implementation: The package is implemented in R (as of version 3.3) and is available from Bioconductor at the URL: http://bioconductor.org/packages/QUBIC, where installation and usage instructions can be found.

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Supplementary information: Supplementary data are available at Bioinformatics online.

1 Introduction

Advances in high-throughput technologies accelerated the generation of massive quantities of gene expression data. This data revolution is only partially paralleled by the development of new algorithms for its interpretation. Biclustering is a widely accepted approach for gene co-expression analysis to identify co-expressed genes under subsets of all the conditions in a gene expression dataset. Several biclustering algorithms such as Plaid (Lazzeroni and Owen, 2002), SAMBA (Tanay et al., 2002), FABIA (Hochreiter et al., 2010) have been published in the past two decades. It is noteworthy that our program, QUBIC (Li et al., 2009) is reviewed as one of the best programs due to its prediction performance on benchmark datasets and as the best in real biological dataset tests (Eren et al., 2013). To enable the biclustering users lacking comprehensive computational background, a web server of QUBIC was developed in 2012 (Zhou et al., 2012). Since gene expression datasets keep increasing in scale, we developed this user requested R package of QUBIC (QUBIC-R for short), to provide an efficient optimized implementation and to eliminate large-scale data submission to a webserver.

The unique features of QUBIC-R include: (i) biclustering is integrated with analyses functions, i.e. data discretization, query-based biclustering, bicluster expanding, biclusters comparison, heatmap
A bioconductor package of QUBIC

2 Implementation

QUBIC-R package is developed for the R statistical computing environment, and is released on Bioconductor (Gentleman et al., 2004). It depends on the biclust package developed by Kaiser et al. (2009) to be compatible with the biclust output. Its output format can also be used by network analysis software, such as Cytoscape (Smoot et al., 2011).

The original QUBIC program, written in GNU C with POSIX library, is limited in its portability. A memory leak may occur if the primary functions are called more than once. This problem was addressed by refactoring the C source code and transforming it into C++. Specifically, to avoid memory leak, we changed the majority of data structures and replaced C pointers by STL containers. We also optimized core function structures to facilitate future package updates and developments. The program efficiency has been significantly increased with the same predicting results (Fig. 1A). An input data as large as 30 000 × 30 000 can be finished within half an hour (detailed limits test are in Supplementary Fig. S1). All the computational experiments were conducted on a computer with Windows 7 × 64, Memory 48G, Intel Core i7-6700 3.4G.

3 Functions and examples

Nine functions are included in QUBIC-R. (i) qudiscretize creates a discrete matrix for a given matrix, i.e., the qualitative representation of input gene expression data; (ii) BCQU and (iii) BCQUD perform biclustering for continuous and discretized gene expression data, respectively; (iv) query-based biclustering allows users to input additional biological information to guide the biclustering progress (Method S1); (v) bicluster expanding expands existing biclusters under specified consistency level (Method S2); (vi) biclusters comparison compares biclusters obtained via different algorithms or parameters; (vii) quheatmap draws heatmap for any single or two predicted biclusters; (viii) qunetwork creates co-expression networks based on the identified biclusters (Method S3) and (ix) qunet2xml converts the constructed networks into XGMML format for further analysis in Cytoscape, Biomax and JNets. We use the genome-scale gene expression data collected under 466 conditions of E. coli (Faith et al., 2008) as an example to illustrate how these functions work. An installation of R package is required (Example S1). Details of the E. coli example are in Example S2 and synthetic data and yeast expression data are in Example S3-4.

i. qudiscretize is useful to obtain discrete gene expression matrix. This matrix can be used in other biclustering program, where -1 represents lowly express, 0 represents normally express, and 1 represents highly express. For example:

```r
> matrix1 <- ecoli[1:3,1:4]
> matrix1
```

```r
> matrix2 <- qudiscretize(matrix1)
> matrix2
```

ii. BCQU and (iii) BCQUD are used as the biclustering method from package ‘biclust’, for example:

```r
> res <- biclust (x = ecoli, method = BCQU(), f = 0.25)
> res1 <- biclust (x = qudiscretize(ecoli), method = BCQUD(), f = 0.25)
```

And QUBIC algorithm can be called independently via qubiclust and qubiclust_d for continuous and discrete data, respectively (res, res1, res2 and res3 are identical):

```r
> res2 <- qubiclust (x = ecoli, method = 0.25)
> res3 <- qubiclust_d (x = qudiscretize(ecoli), f = 0.25)
```

iv. Using the parameter weight, a user can conduct a query-based biclustering, with additional biological information.

```r
> file = S11145.protein.links.e10.txt
> graph = read.graph(file, format = ncol)
> get.edgelist(graph, names = TRUE)
> E(graph)$weight
> weight <- get.adjacency(graph, attr = weight)
> res4 <- biclust (x = ecoli, method = BCQU(), weight = weight, f = 0.25)
```

v. Using the seedbicluster parameter, a user can expand existing biclustering results to recruit more genes according to certain consistency level:

```r
> res5 <- biclust (x = ecoli, method = BCQU(), seedbicluster = res, f = 0.25)
> summary (res)
> summary (res5)
```

vi. Using the parameter showinfo, the biclustering results from different algorithms or from a same algorithm with different combinations of parameter can be compared:

```r
> test <- ecoli [1:50,]
```
vii. We can visualize the identified biclusters using heatmap in support of overall expression pattern analysis, either for a single bicluster or for two biclusters (Fig. 1C):

```r
par(mar = c(5, 4, 3, 5), cex.lab = 1.1, cex.axis = 0.5, cex.main = 1.1)
quheatmap(ecoli, res, number = 4)
par(mar = c(5, 4, 3, 5), cex.lab = 1.1, cex.axis = 0.5, cex.main = 1.1)
quheatmap(ecoli, res, number = c(3, 7))
```

viii. We can construct and visualize network for the identified biclusters, using the function `qunetwork`, either for a single bicluster or for two biclusters:

```r
library(qgraph)
net1 <- qunetwork(ecoli, res, number = 4, group = 4, method = "spearman")
qgraph(net1[[1]], groups = net1[[2]], layout = "spring", minimum = 0.6, color = cbind(rainbow(length(net1[[2]]) - 1), "gray"), edge.label = FALSE)
net2 <- qunetwork(ecoli, res, number = c(3, 7), group = c(3, 7), method = "spearman")
qgraph(net2[[1]], groups = net2[[2]], legend.cex = 0.5, layout = "spring", minimum = 0.6, color = c("red", "blue", "gold", "gray"), edge.label = FALSE)
```

ix. The function `qunet2xml` can convert the constructed networks into XGMML format, facilitating further functional enrichment analysis (e.g. DAVID) and advanced network visualization (e.g. Cytoscape, Fig. 1D):

```r
sink("tempnetworkresult.gr")
qunet2xml(net2, minimum = 0.6, color = c("red", "blue", "gray"))
sink()
```

4 Conclusion

Biclustering algorithms facilitate researchers in identification of co-expressed gene subsets in their gene expression dataset, and has become a useful approach for the interpretation of gene expression profile data. Our R package implements a well-cited biclustering algorithm, QUBIC. It provides more efficient source code and fully integrated functions to identify and analyze biclusters and visualize identified biclusters and corresponding co-expression networks. This package is a powerful tool for gene expression mining and co-expression network modeling.

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**References**


