A novel biclustering approach with iterative optimization to analyze gene expression data

Sawannee Sutheeworapong\textsuperscript{1,2}, Motonori Ota\textsuperscript{4}, Hiroyuki Ohta\textsuperscript{1}, Kengo Kinoshita\textsuperscript{1,3}

\textsuperscript{1}Department of Biological Sciences, Graduate School of Biosciences and Biotechnology, Tokyo Institute of Technology, Tokyo, Japan; \textsuperscript{2}Graduate School of Information Sciences, \textsuperscript{3}Institute of Development, Aging and Cancer, Tohoku University, Miyagi, Japan; \textsuperscript{4}Graduate School of Information Sciences, Nagoya University, Nagoya, Japan

Objective: With the dramatic increase in microarray data, biclustering has become a promising tool for gene expression analysis. Biclustering has been proven to be superior over clustering in identifying multifunctional genes and searching for co-expressed genes under a few specific conditions; that is, a subgroup of all conditions. Biclustering based on a genetic algorithm (GA) has shown better performance than greedy algorithms, but the overlap state for biclusters must be treated more systematically.

Results: We developed a new biclustering algorithm (binary-iterative genetic algorithm [BIGA]), based on an iterative GA, by introducing a novel, ternary-digit chromosome encoding function. BIGA searches for a set of biclusters by iterative binary divisions that allow the overlap state to be explicitly considered. In addition, the average of the Pearson's correlation coefficient was employed to measure the relationship of genes within a bicluster, instead of the mean square residual, the popular classical index. As compared to the six existing algorithms, BIGA found highly correlated biclusters, with large gene coverage and reasonable gene overlap. The gene ontology (GO) enrichment showed that most of the biclusters are significant, with at least one GO term over represented.

Conclusion: BIGA is a powerful tool to analyze large amounts of gene expression data, and will facilitate the elucidation of the underlying functional mechanisms in living organisms.

Keywords: biclustering, microarray data, genetic algorithm, Pearson's correlation coefficient

Background

The complete sequencing of the genomes of many organisms has led to the launch of various omics studies. In one study, the advent of deoxyribonucleic acid (DNA) microarray technology has enabled the monitoring of the expression levels of numerous genes at a time, under many different growth conditions. This technique is now widely used in diverse types of biological research, such as identifying disease markers, reconstructing cellular signaling pathways, and inferring gene regulatory networks. DNA microarray technology has also provided numerous biological insights.\textsuperscript{1-3} Data generated from even a few array measurements are quite complex, and the amounts of microarray data available in public databases are dramatically increasing, due to the efficiency and rapid improvement of DNA microarray technologies. As a result, the interpretation of DNA microarray data obtained under a large number of conditions has become a challenging problem.

In the analyses of a large dataset, as the first step, researchers usually search for similar patterns appearing within the data. In the case of DNA microarray data, similar patterns of gene expression data are often investigated by using cluster analyses, such as K-means...
clustering and hierarchical clustering. Although clustering can provide considerable biological information, conventional clustering algorithms may not be suitable for some analyses of microarray data for the following two reasons. Firstly, there are many genes that encode proteins involved in several functional activities at a time, but the conventional clustering methods cannot identify these genes, because they only allow a gene to belong to one cluster at a time, instead of multiple clusters. Secondly, it is difficult to find the genes that are co-expressed under a few specific conditions but are differently expressed under other conditions because the similarity of the genes in conventional clustering is determined by the entire expression data.

In terms of the above shortcomings, biclustering is more effective than conventional clustering, since it can cluster both genes and conditions simultaneously, and a gene (or a condition) can be involved in multiple clusters at a time. The concept of biclustering was first proposed by Hartigan, and Cheng and Church applied it to search for the most homogeneously expressed genes over certain sets of conditions by using greedy search algorithms. Most biclustering algorithms have been implemented with greedy search algorithms to reduce the calculation costs. One such bicluster, a maximum bicluster, is known as a nondeterministic polynomial time (NP)-complete problem that can possibly be solved in polynomial time using a nondeterministic Turing machine, and a greedy search algorithm is required for actual applications to provide efficient approximations. Usually, one greedy search results in one bicluster, and the greedy search approach is repeatedly applied to the data, while preventing the reproduction of similar biclusters. The greedy search then tries to obtain a set of various biclusters as the final output.

Biclustering has also been implemented by using a genetic algorithm (GA) to find a practical solution to balance bicluster quality and calculation cost. A GA emulates evolutionary processes to obtain nearly optimal solutions. Initially, a set of candidate solutions is prepared; each solution being called a chromosome. The chromosomes evolve by exchanging their parts and changing some elements into a different state, and elite chromosomes are selected to survive as the parents of the next generation. This evolution and selection process is repeated over a number of generations to yield an optimal solution. Bleuler et al first applied GA to biclustering, whereby a binary string (representing a gene or a condition belonging to a bicluster, or not) was employed as a representation of chromosomes. To avoid any redundancy of the resulting biclusters, Bleuler et al introduced a special selection operator called environment selection. Chakraborty and Maka have generated a similar GA-based biclustering, but different in terms of chromosome initialization. Initial chromosomes are prepared by K-means clustering. These methods find an optimum set of biclusters from one GA search. For such methods, it would be difficult to obtain a set of various, nonredundant biclusters, because only better chromosomes can survive by the selection process of GA, and thus the resulting biclusters tend to converge into similar results in the later generations.

Another type of GA-based biclustering, Sequential Evolutionary Biclustering (SEBI), has a distinct strategy. SEBI initially applies GA to select the optimal bicluster, and then this process is repeated so that the genes and the conditions in the biclusters already selected are less likely to be selected again. In other words, although SEBI would generate a set of diverse biclusters, it de-emphasizes the overlap of biclusters, a significant feature of biclustering.

In the present study, we propose BIGA as the basis of a novel biclustering approach. In BIGA, an attempt is made to progressively divide the large amounts of input data into small datasets, by iteratively using GA, such as SEBI. Instead of evaluating a set of biclusters, GA is applied to each division process. Therefore, the resulting biclusters are substantially diverse. In addition, BIGA introduces the overlap state explicitly defined in the ternary digit (or trit) encoding chromosome. In this study, the algorithm is described, the performance of BIGA is compared with those of six existing biclustering algorithms, and the biological relevance of BIGA is evaluated by using gene ontology (GO) enrichment analyses. Finally, we conclude that BIGA is a powerful and practical solution for biclustering with high-dimensional data.

Material and methods

Definition of biclusters

BIGA accepts a set of gene expression data with the matrix form $D=(G, C)$, including $N$ rows of genes $G = \{g_1, g_2, \ldots, g_n\}$ and $M$ columns of conditions or samples $C = \{c_1, c_2, \ldots, c_m\}$, where $N$ and $M$ are the total numbers of genes and conditions, respectively. All genes will be clustered into $K$ overlapping biclusters $B = \{B_1, B_2, \ldots, B_K\}$, and each bicluster ($B_i$) corresponds to a submatrix $B_i = (X, Y)$ of $D$, where $X \subseteq G$ and $Y \subseteq C$. The sizes of $X$ and $Y$, ie, the numbers of genes and the conditions of a bicluster, are denoted by $n$ and $m$, in which $n \leq N$ and $m \leq M$, respectively.

Binary-iterative genetic algorithm

In order to decompose $D$ into $B$ systematically, a binary tree was introduced. Generally, a binary tree comprises nodes
and directed edges, in which each node can be extended to at most two child nodes. In this work, we regarded each bicluster and each edge as a node and a parent–child relationship between a bicluster pair, respectively. We designated the method as BIGA.

BIGA consists of the following three steps. A schematic diagram of BIGA is shown in (Figure 1).

Step 1: A division of microarray data is represented by a string, a sequence of trit (0, 1, 2) with the length of $n$ (number of genes in the parent bicluster) + $m$ (number of conditions in the parent bicluster). The trit 0, 1, and 2 means that an associated gene or condition is contained in either of two biclusters, $b_{left}$ or $b_{right}$, or both, respectively. This means that one string can encode the division of one bicluster into two biclusters, while allowing overlap. An example of this encoding is shown in (Figure 1A). The “|” symbol serves as a spacer of the genes and conditions for clarity. The string is equivalent to the division illustrated by the matrix (microarray data, or a bicluster) in the middle of (Figure 1A). In the matrix, the rows and the columns correspond to the genes and the conditions, respectively. The cell of the matrix belongs to either $b_{left}$ (blue cell), $b_{right}$ (red), or both (violet), under the decoding rule shown in (Figure 1B). The white cells are ignored because they are not coexpressed with color cells. Consequently, the bicluster shown in the middle of (Figure 1A) represents the division into two biclusters on the right of (Figure 1A).

Step 2: To search for the best chromosome (the best trit string) representing the optimal division of a bicluster, GA is performed (rectangles in Figure 1C). In the GA procedure, a mutation and a crossover are introduced into each chromosome. Each number on a chromosome is altered to 0, 1, or 2, for the mutation; whereas two chromosomes exchange corresponding parts with each other in the crossover. Chromosomes with higher fitness scores (described in the following section) survive in the next generation, and all other chromosomes are discarded. GA was implemented via Java Genetic Algorithm Product with a mutation rate of 0.01 and a crossover rate of 0.5. Finally, the best chromosome after 100 generations of GA (the underlined string in the rectangle) is selected, based on the fitness score (see the next section). The best chromosome is then decoded into two biclusters ($b_{left}$ and $b_{right}$). We decide whether to continue with further decompositions after the evaluation of the biclusters, as follows.

Step 3: Evaluation of biclusters. For each child bicluster, the numbers of genes and conditions, the average Pearson’s correlation coefficient (PCC), and the parent–child correlation coefficient (PCC), and the parent–child relationship are evaluated to determine their states: continue the decomposition (*), quit the decomposition and accept (+), or quit the decomposition and discard (-).

Figure 1 Schematic diagram of binary-iterative genetic algorithm. (A) Decomposition of a parent bicluster into two child biclusters encoded in a string (left panel). The string indicates that a parent bicluster (middle panel) is divided into two child biclusters (right panel). The red, blue, and violet cells in the biclusters belong to $b_{left}$, $b_{left}$, and both, respectively. (B) Decoding rule of a string. (C) Binary division performed by genetic algorithm (GA). The best string is underlined in the rectangle. For each GA, the generated biclusters ($b_{left}$ and $b_{right}$) are evaluated to determine their states: continue the decomposition (*), quit the decomposition and accept (+), or quit the decomposition and discard (-). (D) Flow diagram of the bicluster evaluation.
redundancy are examined to decide whether we should quit or continue the decomposition. Subsequently, the bicluster is either accepted as an element of the final biclusters, \( B \), or discarded. We calculate the PCC of every gene pair in a bicluster, and average them (the average PCC). The parent–child redundancy is defined as the ratio of the number of genes of the child bicluster \( n' \) to that of the parent bicluster \( n \). Therefore, a small parent–child redundancy indicates that the child bicluster contains a smaller number of genes than the parent, and a large parent–child redundancy means that the number of genes in the child bicluster is almost the same as that of the parent. The average PCC and the parent–child redundancy are abbreviated as \( C \) and \( R \), respectively. The decision process is illustrated in (Figure 1D). Briefly, the process employs four rules: (I) we quit the decomposition and accept the bicluster if \( C \) is higher than the threshold \( \tau_c \). (II) we quit the decomposition and discard the bicluster if the bicluster is “small,” which is judged by the thresholds \( \tau_n \) and \( \tau_m \) for \( n' \) and \( m' \), respectively. (III) we also quit the decomposition and discard the bicluster if the redundancy, \( R \), is small \( (R < \tau_r) \) or large \( (R > 1 - \tau_r) \). The latter rule was employed to reduce the calculation cost, because a child bicluster that is similar to its parent bicluster and has a low \( C \) is not considered to produce promising results. Using the forth rule: (IV) we continue the decomposition. Four thresholds, \( \tau_c, \tau_n, \tau_m, \) and \( \tau_r \), were empirically determined as 30, 10, 0.65, and 0.15, respectively (see Table S1). The Greek symbols in (Figure 1D) indicate the rule applied in each decision. In (Figure 1C), the accepted and discarded biclusters are marked by + and – symbols. The bicluster to be decomposed is marked by a * symbol. Figure 1C indicates that four biclusters are accepted.

**Fitness function**

In general, large biclusters including co-expressed genes across many specific conditions are preferable. The average PCC of a bicluster was employed to evaluate the gene co-expression. Furthermore, the relative area \( A \) of the bicluster, defined by \( (n'/n)^\alpha (m'/m)^\beta \), using the gene and condition numbers of the parent and child biclusters was used to evaluate the size of a bicluster. Two parameters were introduced for gene-weight \( (\alpha) \) and condition-weight \( (\beta) \), to control the balance between the number of genes and that of the conditions \( (0 < \alpha, \beta < 1) \) in a relative area, \( A \). The fitness function of a chromosome was defined as follows (Equation 1):

\[
f(c) = A(b_{left})C(b_{left}) + A(b_{right})C(b_{right}), \quad (1)
\]

where \( c \), \( b_i \) \( (i = \text{left or right}) \), \( A(b) \), and \( C(b) \) denote a chromosome, one of the child biclusters, the relative area of child bicluster \( b \), and the average PCC of child bicluster \( b \), respectively.

The balance between \( \alpha \) and \( \beta \) was important in order to select biologically meaningful biclusters when using \( f(c) \). Since a high average PCC for a large number of genes was obtained rather easily when only a small number of conditions were considered, a certain number of conditions should be required for each bicluster, to ensure the biological significance. The variation of \( \alpha \) and \( \beta \) was empirically estimated, and finally 0.3 and 0.5 were chosen, respectively (see the results in Table S1).

**Assessment procedure**

Six existing methods were compared to evaluate the performance of BIGA: Cheng and Church algorithm,2 Statistical-Algorithmic Method for Bicluster Analysis (SAMBA),19,20 order-preserving submatrix (OPSM),1 iterative signature algorithm (ISA),11 binary inclusion-maximal biclustering algorithm (BIMAX),21 and SEBI.16 SEBI is selected as a representative of the GA-based biclustering approaches,15,16 because SEBI adopts an outstanding system to reduce the redundancy of biclusters and performs iterative evolutionary searches like BIGA. The five other methods are based on greedy searches. Data provided by Gasch et al22 was used for the analyses of *Saccharomyces cerevisiae*. The analyses contained 2993 genes and 173 stress conditions, as a result the data size was large and abundant annotations were available. Prelic et al21 used this dataset to evaluate algorithms, and the resultant sets of biclusters for the five greedy-search algorithms are publicly available. These bicluster sets were obtained for comparison with our results. Neither the results of SEBI for the data nor SEBI itself is publicly available. The framework of SEBI was re-implemented in a second experiment.16 Note that there might be some minor differences between SEBI and the re-implemented SEBI. Henceforth, we denote mySEBI as our implementation.

The sets of biclusters were evaluated in terms of the following four points. Since PCC is a widely used parameter to assess the similarity of expression patterns, the distribution of the average PCC of all biclusters was examined. One may consider the mean square residual (MSR) of biclusters2 to be useful as an indicator of the coherence of biclusters, but PCC is better than MSR in terms of finding the functional relevance of genes,23–26 in much biological data, for example, the involvement of the same pathway or the participation in the same protein complex.27,28 The existing methods do not
necessarily optimize the correlation of biclusters, and some biclusters derived from other algorithms can contain biclusters showing strong anti-correlation (i.e., genes expressed inversely). The absolute value of PCC was used to estimate such biclusters for comparisons.

Coverage and overlap are also important measures to evaluate the biclustering, as higher coverage and lower overlap are preferable for further biological analyses. Previous studies\(^2\) used “cell coverage,” by calculating the percentages of area (genes × conditions) covered by the biclusters, and “cell overlap” by measuring the intersection areas of the biclusters. In this study, “gene coverage” and “gene overlap,” were adopted because higher cell coverage can be achieved even by a high coverage of conditions and a low coverage of genes, and this result is not biologically significant. In addition, cell overlap ignores the overlap of genes shared in any two biclusters, if the conditions in the biclusters are completely different. Gene coverage is defined as the ratio of genes that are assigned to any biclusters to all genes, and gene overlap is the ratio of total genes overlapping on multiple biclusters to the genes assigned to any biclusters (Equation 2):

\[
\text{Gene overlap} = \frac{\sum_{i=1}^{k} X_i - \bigcup_{i=1}^{k} X_i}{\bigcup_{i=1}^{k} X_i} \quad (2)
\]

Gene coverage can evaluate the ability of an algorithm to decide the cluster for each gene, and gene overlap can measure the ability of an algorithm to specify the clusters for genes that are not necessarily involved in multiple biological processes.

The biological significance of the results by measuring the GO enrichment was also evaluated. More precisely, FuncAssociate (2.0; Roth Laboratories, Harvard University, Boston, MA), a tool for finding overrepresented GO terms in a set of genes was utilised. Using this tool, we performed Fisher’s exact test to determine the probability of the appearance of genes associated with a GO term in each bicluster.\(^9\) FuncAssociate calculates an adjusted P-value (Padj) from the simulations, instead of the corrections of multiple tests. Padj is the probability of obtaining at least one false positive for any desired cutoff. We considered a biologically significant bicluster as one that is relevant to at least one GO term with a statistically significant appearance (namely, Padj less than significance level). The number of such biclusters, relative to the total number of biclusters (the GO enrichment), was used to estimate each algorithm. A previous study by Prelic et al\(^{27}\) evaluated the biological relevance of existing algorithms, using the GO enrichment.

**Results and discussion**

**Biclusters for the *Saccharomyces cerevisiae* microarray data**

With the selected parameters and thresholds, BIGA found 164 biclusters from the *S. cerevisiae* microarray data. The average numbers of genes and conditions in the biclusters are 92.25 and 23.65, respectively (Table 1). The detailed statistics of each bicluster are provided in Table S2. The properties of the biclusters obtained by other methods are also summarized in Table 1.

**Performance evaluation**

The distribution of the average PCCs of the biclusters obtained by each biclustering algorithm is shown in the boxplot (Figure 2A). The thick line around the middle of the box indicates the median of the average PCCs. The top and bottom of the box indicate the upper and the lower quartiles, respectively. The circles show the outliers (more than 1.5 times the upper quartile or less than 1.5 times the lower quartile from the median). The whiskers mean the range of data between the maximum and the minimum values, other than the outliers. According to the plots, OPSM performs the best with a very small deviation in the average PCCs. Apart from OPSM, BIGA can outperform the other methods when compared by the median of the average PCC. One may consider that the fitness function of BIGA takes the average PCC into account (Equation 1), and thus it is obvious that the average PCC of BIGA is good. However, note that the results are not necessarily satisfactory if the optimization procedure does not work well, or the balance between the average PCC and the area of the bicluster in (Equation 1) is inappropriate. Next, using the the Wilcoxon signed-rank test the study examined whether the distribution of the average PCCs of BIGA is significantly better than those of the other algorithms.\(^{31}\) The results showed that BIGA detects significantly more co-expressed genes in biclusters than the other methods, except for OPSM (the highest P-value is only 5.4 × 10^-6 against SAMBA). To clarify the performance, the expression profiles of the four best biclusters with higher average PCCs are demonstrated in Figure S1. Note: the reason for the highest performance of OPSM was related to the gene coverage and these analyses will be discussed later.

The gene coverage and the gene overlap are shown in (Figure 2B and 2C), respectively. As a result, BIGA achieved the fourth-highest gene coverage among the seven
Table 1 Comparing quantitative metrics among biclustering algorithms

| Properties                  | CC     | SAMBA  | ISA    | OPSM   | BIMAX  | mySEBI | BIGA   |
|-----------------------------|--------|--------|--------|--------|--------|--------|--------|
| Number of biclusters        | 100    | 100    | 66     | 12     | 101    | 100    | 164    |
| Average gene number         | 82.01  | 911.52 | 76.27  | 95.58  | 24.03  | 74.98  | 92.25  |
| Average condition number    | 19.85  | 25.15  | 8.71   | 12.50  | 3.00   | 80.5   | 23.65  |

Abbreviations: BIGA, binary-iterative genetic algorithm; BIMAX, binary inclusion-maximal biclustering algorithm; CC, Cheng and Church algorithm; ISA, iterative signature algorithm; OPSM, order-preserving submatrix; mySEBI, the Sequential Evolutionary Biclustering method used in this work; SAMBA, Statistical-Algorithmic Method for Bicluster Analysis.

algorithms (Figure 2B). SAMBA could classify almost 100% of the genes into biclusters, but each bicluster contained more than 900 genes (Table 1) with extremely high overlap (Figure 2C), which will make the succeeding experimental or bioinformatics analyses difficult. mySEBI could produce a set of biclusters that would include 95% of all genes with a small amount of overlap. CC showed the best gene coverage (highest) and overlap (lowest). The results indicate that the techniques to reduce redundancy of biclusters in SEBI and CC are efficient for gaining high coverage and low overlap. However, the average PCCs of the biclusters by both algorithms were very low (Figure 2A). OPSM produced biclusters with the highest correlation (Figure 2A), but failed to achieve higher gene coverage due to the small number of clusters (Table 1). The average PCCs of OPSM and BIGA are high, because both methods adopt gene co-expression in the target function. By contrast, CC and SEBI adopt MSR instead of PCC. Although MSR can sometimes identify coherent biclusters, it is not necessarily efficient to achieve higher correlations of genes.

BIGA yielded the second-largest gene overlap, with 6.29 (Figure 2C), which may imply that the biclusters of BIGA are mutually similar. The pairwise overlap (PO) of two biclusters defined by $X_i \cap X_j / X_i \cup X_j$, where $X_i$ and $X_j$ are genes in biclusters $B_i$ and $B_j$, respectively, was measured to examine the similarity of the biclusters more directly, and plotted in Figure 3A. The median of the POs for BIGA was not very large, as compared with those of the other methods, indicating that the biclusters determined by BIGA are not necessarily similar. Moreover, the variety of biclusters using the single-linkage clustering method, where the distance between two biclusters defined by $1.0 - PO$ was investigated. At each cut-off distance, the number of clusters was counted and normalized by the total number of biclusters, which we call the fraction of independent biclusters. When the cut-off distance is sufficiently small, no biclusters are merged and $FIB$ is 1.0. This state indicates that the biclusters are independent and diverse. On the other hand, when the cut-off distance is sufficiently large, most of the biclusters may be merged together, and $FIB$ will
converge to 0.0. This state means that all of the biclusters are judged as being similar to each other. We consider a higher FIB to be an indicator illustrating the variety of the resultant biclusters. According to the plot (Figure 3B), the FIBs of SAMBA and ISA are obviously low in almost the whole cut-off distance range, showing that their biclusters are rather similar. The FIBs of OPSM show that its ability to detect diverse biclusters is moderate. CC, mySEBI, BIMAX, and BIGA provided a wider variety of biclusters than the other algorithms, when the cut-off distance was less than 0.5. In summary, the average bicluster determined by BIGA contains many genes that are shared with other biclusters (Figure 2C): however, when focusing on each pair of biclusters, a small number of genes are shared (Figure 3A). Consequently, the biclusters determined by BIGA seem to be independent (Figure 3B), and cover most of the genes efficiently (Figure 2B).

Evaluation of biological relevance by gene ontology enrichment analyses

In the study by Prelic et al\textsuperscript{21} on the evaluation of existing methods using GO enrichment, OPSM showed the best performance (100% of the biclusters were significant at the 0.05 significance level). However, it only produced twelve biclusters (Table 1), and thus the gene coverage was the lowest (Figure 2B). Less than half of the biclusters produced by CC were judged to be significant,\textsuperscript{21} probably because CC cannot detect biclusters with a higher average PCC (Figure 2A). The percentages of significant biclusters from mySEBI are 93%, 81%, 69%, and 42% for the 0.05, 0.01, 0.005, and 0.001, respectively. By contrast, 94.5% of the biclusters produced by BIGA were judged to be significant at the 0.05 significance level. This value was changed to 88.4%, 86.0%, and 79.3% for the 0.01, 0.005, and 0.001 significance levels, respectively. The performance of BIGA is almost the same as those of BIMAX and ISA in GO enrichment,\textsuperscript{21} but BIGA outperforms them in the gene coverage (Figure 2B).

There was a functional relationship between the resultant biclusters by BIGA, based on the enriched GO terms at the 0.001 significance level. Among the 122 GO-enriched terms, ribosome-related terms (ribosome GO:0005840, ribosomal subunit GO:0033279, etc) are abundant in many biclusters (50 biclusters). This observation was consistent with the fact that 60% of transcription was devoted to ribosomal ribonucleic acid (RNA),\textsuperscript{32} because genes with higher expression levels tend to be clustered. Apart from the ribosome-related terms, primary metabolic (GO:0044238), translation (GO:0006412), protein-related (GO:0044267, GO:0019538), macromolecule-related (GO:0009059, GO:0034645, GO:0044260, GO:0043170), and biopolymer-related (GO:0043283, GO:0034960, GO:0043284, GO:0034961) processes also frequently appeared in several biclusters. This indicated that the genes involved in these terms are primary or essential in many biological processes. Five GO terms that are most enriched at the 0.001 significance level for each bicluster five specific GO terms among them are shown in Table S2.

Furthermore, the novel aspects of the biclusters identified by BIGA were examined. For each bicluster defined by BIGA, the PO against all biclusters identified by the other five methods was measured and the maximum PO was derived (Table S2). The highest value of the maximum POs was at most 0.12, indicating that the biclusters defined by BIGA are quite different from those determined by the other methods. To explore the relationships of the genes that were detected...
only by BIGA, on the study examined the biclusters of BIGA that were not similar to any of the other biclusters; that is, the biclusters with maximum pair-wise similarity scores < 0.05. In bicluster 109 (the maximum PO = 0.039 with bicluster 29 of CC), 16 out of 86 genes are involved in a cellular nitrogen metabolic process (GO:0034641), eg, SAS3 (YBL052C), TEF2 (YBR118W), and SWD3 (YBR175W), are co-expressed under twelve conditions. In bicluster 118 (0.037 with bicluster 56 of CC), 26 out of 66 genes, eg, RRN6 (YBL014C), ORC2 (YBR060C), and PAF1 (YBR279W), are involved in an RNA metabolic process (GO:0016070). In bicluster 160 (0.037, bicluster 24 of CC), 33 out of 74 genes, such as HEK2 (YBL032W), ROX3 (YBL093C), and SIF2 (YBR103W), are related to a nucleic acid metabolic process (GO:0090304). These results demonstrate that BIGA is useful to reveal the functional relevance underlying the biclusters. Furthermore, some genes belonged to the same bicluster, even though they lacked known co-functional evidence (see the biclusters in Table S2 without significant GO terms). These genes represent promising experimental targets that bridge biological processes exhibiting co-expression under specific conditions.

Conclusion

The development of biclustering algorithms has allowed biologists to start unraveling the underlying functional mechanisms in living organisms. We propose BIGA as an alternative biclustering technique, since it was designed to address the conventional problems of the pre-existing methods. Biclustering is obviously advantageous in accounting for the overlap state among clusters, but the suitable amount of overlap is still ambiguous and different algorithms often produce solutions with various degrees of overlap. We tried to develop a novel chromosome-encoding mode that explicitly defines the overlap between biclusters. BIGA revealed that the most frequently appearing genes express their functions in fundamental and essential biological processes, such as translation. A microarray often consists of relatively few conditions, with respect to a large number of genes. The weighting of genes and conditions diminishes the bias between the number of genes and conditions, which helps to eliminate unreliable results, such as biclusters with very few conditions. We also applied an alternative index, the average PCC, which impacts the biological meaning, rather than the MSR, to measure the goodness of a bicluster. The analysis of GO enrichment demonstrated that most of our biclusters were significant, with one or more enriched GO terms. When evaluated with the five pre-existing algorithms, BIGA performed well in most of the properties with good balance, although it did not show the best performance for all criteria. A pair-wise comparison of our biclusters with those obtained by the other algorithms revealed the novel aspects of the biclusters that are distinct from those of the other methods. Since biological systems are quite complicated, resulting in high-dimensional data, it is quite difficult to answer all biological questions with a single approach. For new discoveries, we recommend the application of several approaches, including BIGA.

Acknowledgments

We would like to thank the Human Genome Center for providing computational resources to analyze all of the data, as well as for a scholarship from the Ministry of Education, Culture, Sports, Science and Technology to Sawannee Sutheeworapong. We would like to acknowledge Prof Kenta Nakai for providing good facilities to Sawannee Sutheeworapong in the early stage of this work. We also thank Dr Takeshi Obayashi for useful discussions in the early stage of this work.

Authors’ contributions

SS, KK, and MO contributed to the overall research and the manuscript preparation. KK, MO, and HO were responsible for the project direction and financial support.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Ben-Dor A, Chor B, Karp R, Yakhini Z. Discovering local structure in gene expression data: the order-preserving submatrix problem. J Comput Biol. 2003;10:373–384.
2. Ma X, Salunga R, Tuggle T, et al. Gene expression profiles of human breast cancer progression. Proc Natl Acad Sci U S A. 2003;100:5974–5979.
3. Yamane D, Zahoor MA, Mohamed YM, et al. Microarray analysis reveals distinct signaling pathways transcriptionally activated by infection with bovine viral diarrhea virus in different cell types. Virus Res. 2009;142(1–2):188–199.
4. Wang RS, Wang Y, Zhang XS, Chen L. Inferring transcriptional regulatory networks from high-throughput data. Bioinformatics. 2007;23(22):3056–3064.
5. Hartigan JA, Wong MA. A k-means clustering algorithm. Appl Stat. 1979;28:100–108.
6. Sokal RR, Michener CD. A statistical method for evaluating systematic relationships. Univ Kansas Sci Bull. 1958;38:1409–1438.
7. Madeira SC, Oliveira AL. Biclustering algorithms for biological data analysis: a survey. IEEE/ACM Trans Comput Biol Bioinform. 2004;1(1):24–45.
8. Hartigan JA. Direct clustering of a data matrix. J Am Stat Assoc. 1972;67(337):123–129.
9. Cheng Y, Church GM. Biclustering of expression data. In: Proceedings of the Eighth International Conference on Intelligent Systems for Molecular Biology. ISMB 2000, San Diego, CA; August 19–12, 2000. AAAI Press; 2000:93–103.
10. Murali TM, Kasif S. Extracting conserved gene expression motifs from gene expression data. Proceedings of the Pacific Symposium on Biocomputing. PSB 2003, Lihue, HI, January 3–7, 2003. 2003;8:77–88.

11. Bergmann S, Ihmels J, Barkai N. Iterative signature algorithm for the analysis of large-scale gene expression data. Phys Rev E Stat Nonlin Soft Matter Phys. 2003;67:031902.

12. Peeters R. The maximum edge biclique problem in NP-complete. Discrete Appl Math. 2003;131(3):651–654.

13. Merz P, Zell A. Genetic Algorithms and Grouping Problems. Philadelphia, PA: John Wiley & Sons; 1998.

14. Bleuler S, Prelic A, Zitzler E. An EA framework for biclustering of gene expression data. Proceedings of Congress on Evolutionary Computation, Portland, OR, June 19–23. June 19–23, 2004;4: 166–173.

15. Chakraborty A, Maka H. Biclustering of gene expression data using genetic algorithm. Proceedings of the 2005 IEEE Symposium on Computational Intelligence in Bioinformatics and Computational Biology, 2005. CIBCB 2005. La Jolla, CA, November 14–14, 2005:1–8.

16. Divina F, Aguilar-ruiz JS. Biclustering of expression data with evolutionary computation. IEEE Trans Knowl Data Eng. 2006;18:590–602.

17. Donale K. The Art of Computer Programming, vol 1: Fundamental algorithms. 3rd ed Boston, MA: Addison-Wesley. 1997;Section 2.3:318–348.

18. Meffert K, Rotstan N. JGAP-Java Genetic Algorithms and Genetic Programming Package. Available from: http://jgaps.sf.net/. Accessed July 10, 2012.

19. Tanay A, Sharan R, Shamir R. Discovering statistically significant biclusters in gene expression data. Bioinformatics. 2002;18:S136–S144.

20. Tanay A, Sharan R, Kupiec M, Shamir R. Revealing modularity and organization in the yeast molecular network by integrated analysis of highly heterogeneous genomewide data. Proc Natl Acad Sci U S A. 2003;102(9):2981–2986.

21. Prelic A, Bleuler S, Zimmermann P, et al. A systematic comparison and evaluation of biclustering methods for gene expression data. Bioinformatics. 2006;22(9):1122–1129.
## Supplementary data

Table S1 Parameter determination

| Parameter | Genes | Conditions | Correlation | Biclusters | Coverage | Overlap |
|-----------|-------|------------|-------------|------------|----------|---------|
| $\alpha$  |       |            |             |            |          |         |
| 0.1       | 72.15 | 22.84      | 0.74        | 111        | 0.59     | 3.53    |
| 0.3       | 92.25 | 23.65      | 0.71        | 164        | 0.69     | 6.29    |
| 0.5       | 102.22| 24.42      | 0.7         | 252        | 0.67     | 11.82   |
| $\tau_r$  |       |            |             |            |          |         |
| 0.1       | 81.22 | 21.51      | 0.73        | 355        | 0.74     | 11.97   |
| 0.15      | 92.25 | 23.65      | 0.71        | 164        | 0.69     | 6.29    |
| 0.2       | 109.86| 25.07      | 0.69        | 57         | 0.58     | 2.59    |
| 0.25      | 128.13| 32.5       | 0.71        | 8          | 0.22     | 0.53    |
| 0.3       | 163   | 45         | 0.67        | 1          | 0.05     | 0       |
| $\tau_c$  |       |            |             |            |          |         |
| 0.60      | 100.62| 22.17      | 0.69        | 145        | 0.71     | 5.9     |
| 0.65      | 92.25 | 23.65      | 0.71        | 164        | 0.69     | 6.29    |
| 0.70      | 83.84 | 22.69      | 0.74        | 178        | 0.61     | 7.09    |

Notes: (A) Impact of gene-weight parameter on the goodness of biclusters ($\tau_r = 30, \tau_m = 10, \tau_c = 0.65, \tau = 0.15, \beta = 0.5$). (B) Impact of redundant threshold on the goodness of biclusters ($\tau_c = 30, \tau_m = 10, \tau_c = 0.65, \alpha = 0.3, \beta = 0.5$). (C) Impact of correlation threshold on the goodness of biclusters ($\tau_c = 30, \tau_m = 10, \tau_c = 0.15, \alpha = 0.3, \beta = 0.5$).

![Figure S1](image-url) (Continued)
Figure S1 Expression profiles of biclusters 1 (A), 2 (B), 3 (C), and 4 (D), in the descending order of the average Pearson's correlation coefficient.

Note: The x-axis represents the series of conditions; e.g., the number 8 denotes the 8th condition.
Table S2 Detailed statistics of resulting biclusters (sorted by descending order of average PCC)

| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms |
|--------------|-----------------|----------------------|-------------|-----------------------------------------------|----------------------------|
| 1            | 47              | 10                   | 0.87        | <0.001                                        | 2                          |
| 2            | 74              | 28                   | 0.81        | <0.001                                        | 3                          |
| 3            | 85              | 21                   | 0.80        | <0.001                                        | 14                         |
| 4            | 71              | 32                   | 0.80        |                                               | 12                         |
| 5            | 74              | 18                   | 0.80        | 0.001                                         | 1                          |
| 6            | 50              | 7                    | 0.80        | −                                             | 0                          |
| 7            | 79              | 24                   | 0.80        | <0.001                                        | 8                          |
| 8            | 52              | 16                   | 0.79        | −                                             | 0                          |
| 9            | 56              | 4                    | 0.79        | −                                             | 0                          |
| 10           | 87              | 21                   | 0.79        | <0.001                                        | 5                          |
| 11           | 72              | 20                   | 0.79        | <0.001                                        | 5                          |
| 12           | 78              | 26                   | 0.79        | <0.001                                        | 6                          |
| 13           | 74              | 14                   | 0.79        | <0.001                                        | 1                          |
| 14           | 83              | 33                   | 0.78        | <0.001                                        | 19                         |
| 15           | 86              | 23                   | 0.78        | <0.001                                        | 2                          |
| 16           | 49              | 18                   | 0.78        | <0.001                                        | 10                         |
### Table S2
Detailed statistics of resulting biclusters (sorted by descending order of average PCC)

| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms | Five most significant GO terms | Five most specific GO terms | Highest pairwise similarity score |
|--------------|-----------------|----------------------|-------------|-----------------------------------------------|-----------------------------|--------------------------------|-------------------------------|-------------------------------|
| 1            | 47              | 10                   | 0.87        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 2            | 74              | 28                   | 0.81        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 3            | 85              | 21                   | 0.80        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 4            | 71              | 32                   | 0.80        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 5            | 74              | 18                   | 0.80        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 6            | 50              | 7                    | 0.80        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 7            | 79              | 24                   | 0.80        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 8            | 52              | 16                   | 0.79        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 9            | 56              | 4                    | 0.79        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 10           | 87              | 21                   | 0.79        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 11           | 72              | 20                   | 0.79        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 12           | 78              | 26                   | 0.79        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 13           | 74              | 14                   | 0.79        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 14           | 83              | 33                   | 0.78        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 15           | 86              | 23                   | 0.78        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |
| 16           | 49              | 18                   | 0.78        | 0.001                                         |                             | GO:0003674 molecular_function | GO:0003674 molecular_function |                                |

(Continued)
| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms |
|-------------|-----------------|----------------------|-------------|-----------------------------------------------|---------------------------|
| 17          | 92              | 23                   | 0.78        | <0.001                                        | 12                        |
| 18          | 77              | 25                   | 0.78        | <0.001                                        | 4                         |
| 19          | 77              | 21                   | 0.78        | <0.001                                        | 5                         |
| 20          | 59              | 12                   | 0.78        | <0.001                                        | 1                         |
| 21          | 84              | 30                   | 0.77        | <0.001                                        | 10                        |
| 22          | 53              | 11                   | 0.77        | 0.001                                         | 1                         |
| 23          | 81              | 28                   | 0.77        | <0.001                                        | 11                        |
| 24          | 61              | 21                   | 0.77        | –                                              | 0                         |
| 25          | 82              | 13                   | 0.77        | <0.001                                        | 1                         |
| 26          | 103             | 24                   | 0.76        | <0.001                                        | 9                         |
| 27          | 93              | 27                   | 0.76        | <0.001                                        | 19                        |
| 28          | 65              | 11                   | 0.76        | <0.001                                        | 1                         |
| 29          | 78              | 32                   | 0.76        | <0.001                                        | 2                         |
| 30          | 62              | 19                   | 0.76        | <0.001                                        | 6                         |
| 31          | 89              | 19                   | 0.76        | <0.001                                        | 12                        |
| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms | Five most significant GO terms | Five most specific GO terms | Highest pairwise similarity score |
|--------------|-----------------|---------------------|-------------|---------------------------------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------|
| 17           | 92              | 23                  | 0.78        | 0.001                                       | 12                          | GO:0044238 primary metabolic process | GO:0034621 cellular macromolecular complex subunit organization | 0.072                         |
| 18           | 77              | 25                  | 0.78        | 0.001                                       | 4                           | GO:0003674 molecular_function | GO:0034621 cellular macromolecular complex subunit organization | 0.050                         |
| 19           | 77              | 21                  | 0.78        | 0.001                                       | 5                           | GO:0044238 primary metabolic process | GO:0003674 molecular_function | 0.062                         |
| 20           | 59              | 12                  | 0.78        | 0.001                                       | 1                           | GO:0044238 primary metabolic process | GO:0034621 cellular macromolecular complex subunit organization | 0.058                         |
| 21           | 84              | 30                  | 0.77        | 0.001                                       | 10                          | GO:0043228 nonmembrane-bounded organelle | GO:0015935 small ribosomal subunit | 0.073                         |
| 22           | 53              | 11                  | 0.77        | 0.001                                       | 1                           | GO:0044238 primary metabolic process | GO:0034621 cellular macromolecular complex subunit organization | 0.098                         |
| 23           | 81              | 28                  | 0.77        | 0.001                                       | 11                          | GO:0032991 macromolecular complex | GO:0044445 cytosolic part | 0.063                         |
| 24           | 61              | 21                  | 0.77        | 0.001                                       | 1                           | GO:0044238 primary metabolic process | GO:0003674 molecular_function | 0.056                         |
| 25           | 82              | 13                  | 0.77        | 0.001                                       | 1                           | GO:0044238 primary metabolic process | GO:0034621 cellular macromolecular complex subunit organization | 0.055                         |
| 26           | 103             | 24                  | 0.76        | 0.001                                       | 9                           | GO:0044238 primary metabolic process | GO:0003674 molecular_function | 0.077                         |
| 27           | 93              | 27                  | 0.76        | 0.001                                       | 19                          | GO:0044238 primary metabolic process | GO:0003674 molecular_function | 0.098                         |
| 28           | 65              | 11                  | 0.76        | 0.001                                       | 1                           | GO:0044238 primary metabolic process | GO:0034621 cellular macromolecular complex subunit organization | 0.045                         |
| 29           | 78              | 32                  | 0.76        | 0.001                                       | 2                           | GO:0044238 primary metabolic process | GO:0034621 cellular macromolecular complex subunit organization | 0.077                         |
| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms |
|-------------|------------------|----------------------|-------------|-----------------------------------------------|----------------------------|
| 32          | 91               | 30                   | 0.76        | <0.001                                        | 10                         |
| 33          | 105              | 34                   | 0.76        | <0.001                                        | 8                          |
| 34          | 105              | 28                   | 0.75        | <0.001                                        | 16                         |
| 35          | 110              | 25                   | 0.75        | <0.001                                        | 29                         |
| 36          | 66               | 16                   | 0.75        | <0.001                                        | 8                          |
| 37          | 71               | 10                   | 0.75        | 0.001                                         | 1                          |
| 38          | 59               | 14                   | 0.74        | <0.001                                        | 3                          |
| 39          | 58               | 16                   | 0.74        | <0.001                                        | 13                         |
| 40          | 83               | 36                   | 0.74        | <0.001                                        | 8                          |
| 41          | 78               | 23                   | 0.74        | <0.001                                        | 5                          |
| 42          | 113              | 26                   | 0.74        | <0.001                                        | 23                         |
| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms | Five most significant GO terms                                                                 | Five most specific GO terms                                                                 | Highest pairwise similarity score |
|-------------|-----------------|---------------------|-------------|-----------------------------------------------|---------------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|----------------------------------|
|             | 32              | 91                  | 30          | 0.76, 0.001                                   | 10                        | GO:0017111 nucleoside-triphosphatase activity                                                  | GO:0017111 nucleoside-triphosphatase activity                                              | 0.081                            |
|             | 33              | 105                 | 34          | 0.76, 0.001                                   | 8                         | GO:0009058 biosynthetic process                                                                | GO:0009058 biosynthetic process                                                          | 0.098                            |
|             | 34              | 105                 | 28          | 0.75, 0.001                                   | 16                        | GO:0032991 macromolecular complex                                                              | GO:0009987 cellular process                                                              | 0.088                            |
|             | 35              | 110                 | 25          | 0.75, 0.001                                   | 29                        | GO:0032991 macromolecular complex                                                              | GO:0006396 RNA processing                                                               | 0.085                            |
|             | 36              | 66                  | 8           | 0.75, 0.001                                   | 8                         | GO:0032991 macromolecular complex                                                              | GO:0034470 ncRNA processing                                                              | 0.085                            |
|             | 37              | 71                  | 10          | 0.75, 0.001                                   | 1                          | GO:0044085 cellular component biogenesis                                                        | GO:0044085 cellular component biogenesis                                                   | 0.068                            |
|             | 38              | 59                  | 14          | 0.74, 0.001                                   | 3                         | GO:0003674 molecular_function                                                                 | GO:0032991 macromolecular complex                                                        | 0.040                            |
|             | 39              | 58                  | 16          | 0.74, 0.001                                   | 13                        | GO:0044249 cellular biosynthetic process                                                        | GO:0044445 cytosolic part                                                               | 0.048                            |
|             | 40              | 83                  | 36          | 0.74, 0.001                                   | 8                         | GO:0044445 cytosolic part                                                                     | GO:0006913 nucleocytoplasmic transport                                                   | 0.080                            |
|             | 41              | 78                  | 23          | 0.74, 0.001                                   | 5                         | GO:0043229 intracellular organelle                                                             | GO:0043234 protein complex                                                               | 0.069                            |
|             | 42              | 113                 | 26          | 0.74, 0.001                                   | 23                        | GO:0043229 intracellular organelle                                                             | GO:0043234 protein complex                                                               | 0.076                            |

(Continued)
| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms |
|-------------|-----------------|---------------------|-------------|-----------------------------------------------|-----------------------------|
| 43          | 90              | 22                  | 0.74        | <0.001                                        | 18                          |
| 44          | 89              | 25                  | 0.74        | <0.001                                        | 6                           |
| 45          | 92              | 28                  | 0.74        | <0.001                                        | 8                           |
| 46          | 106             | 28                  | 0.74        | <0.001                                        | 12                          |
| 47          | 106             | 36                  | 0.74        | <0.001                                        | 14                          |
| 48          | 109             | 25                  | 0.74        | <0.001                                        | 23                          |
| 49          | 99              | 27                  | 0.74        | <0.001                                        | 24                          |
| 50          | 89              | 24                  | 0.73        | <0.001                                        | 10                          |
| 51          | 86              | 15                  | 0.73        | <0.001                                        | 3                           |
| 52          | 141             | 35                  | 0.73        | <0.001                                        | 18                          |
| 53          | 107             | 31                  | 0.73        | <0.001                                        | 20                          |
| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms | Five most significant GO terms | Five most specific GO terms | Highest pairwise similarity score |
|-------------|-----------------|---------------------|-------------|-----------------------------------------------|-----------------------------|-------------------------------|-----------------------------|-----------------------------|
| 43          | 90              | 22                  | 0.74        | 0.001                                         | 18                          | GO:0032991 macromolecular complex | GO:0044249 cellular biosynthetic process | 0.081                       |
| 44          | 89              | 25                  | 0.74        | 0.001                                         | 6                           | GO:0044238 primary metabolic process | GO:0005737 cytoplasm            | 0.057                       |
| 45          | 92              | 28                  | 0.74        | 0.001                                         | 8                           | GO:0019538 protein metabolic process | GO:0010608 posttranscriptional regulation of gene expression | 0.081                       |
| 46          | 106             | 28                  | 0.74        | 0.001                                         | 12                          | GO:0009987 cellular process | GO:0005622 intracellular | 0.083                       |
| 47          | 106             | 36                  | 0.74        | 0.001                                         | 14                          | GO:0030529 ribonucleoprotein complex | GO:0016462 pyrophosphatase activity | 0.100                       |
| 48          | 109             | 25                  | 0.74        | 0.001                                         | 23                          | GO:0032991 macromolecular complex | GO:0005488 binding | 0.083                       |
| 49          | 99              | 27                  | 0.74        | 0.001                                         | 24                          | GO:0032991 macromolecular complex | GO:0000166 nucleotide binding | 0.065                       |
| 50          | 89              | 24                  | 0.73        | 0.001                                         | 10                          | GO:0030529 ribonucleoprotein complex | GO:0005737 cytoplasm | 0.119                       |
| 51          | 86              | 15                  | 0.73        | 0.001                                         | 3                           | GO:0003674 molecular_function | GO:0005737 cytoplasm | 0.065                       |
| 52          | 141             | 35                  | 0.73        | 0.001                                         | 18                          | GO:0043228 nonmembrane-bounded organelle | GO:0006082 organic acid metabolic process | 0.083                       |
| 53          | 107             | 31                  | 0.73        | 0.001                                         | 20                          | GO:0033291 macromolecular complex | GO:0007010 cytoskeleton organization | 0.083                       |

(Continued)
Table S2 (Continued)

| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms |
|--------------|-----------------|----------------------|-------------|-----------------------------------------------|-----------------------------|
| 54           | 68              | 24                   | 0.73        | 0.001                                         | 6                           |
|              |                 |                      |             |                                               |                             |
| 55           | 128             | 26                   | 0.73        | <0.001                                        | 21                          |
|              |                 |                      |             |                                               |                             |
| 56           | 101             | 32                   | 0.73        | <0.001                                        | 15                          |
|              |                 |                      |             |                                               |                             |
| 57           | 107             | 32                   | 0.73        | <0.001                                        | 11                          |
|              |                 |                      |             |                                               |                             |
| 58           | 111             | 33                   | 0.72        | <0.001                                        | 11                          |
|              |                 |                      |             |                                               |                             |
| 59           | 92              | 27                   | 0.72        | <0.001                                        | 11                          |
|              |                 |                      |             |                                               |                             |
| 60           | 111             | 33                   | 0.72        | <0.001                                        | 7                           |
|              |                 |                      |             |                                               |                             |
| 61           | 76              | 15                   | 0.72        | <0.001                                        | 2                           |
| 62           | 94              | 20                   | 0.72        | <0.001                                        | 6                           |
|              |                 |                      |             |                                               |                             |
| 63           | 83              | 24                   | 0.72        | <0.001                                        | 13                          |
|              |                 |                      |             |                                               |                             |
| 64           | 126             | 28                   | 0.72        | <0.001                                        | 39                          |
|              |                 |                      |             |                                               |                             |
| 65           | 45              | 12                   | 0.72        | –                                             | 0                           |

(Continued)
Biclustering to analyze gene expression data

| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms | Five most significant GO terms | Five most specific GO terms | Highest pairwise similarity score |
|--------------|-----------------|----------------------|-------------|-----------------------------------------------|-----------------------------|-----------------------------|-----------------------------|---------------------------------|
| 54           | 68              | 24                   | 0.73        | 0.001                                         | 6                           | GO:0009987 cellular process  | GO:0043229 intracellular organelle | 0.045                           |
| 55           | 128             | 26                   | 0.73        | 0.001                                         | 21                          | GO:0009987 cellular process  | GO:0032991 macromolecular complex | 0.089                           |
| 56           | 101             | 32                   | 0.73        | 0.001                                         | 15                          | GO:0032991 macromolecular complex | GO:0006412 translation            | 0.089                           |
| 57           | 107             | 32                   | 0.73        | 0.001                                         | 11                          | GO:0032991 macromolecular complex | GO:0044445 cytosolic part       | 0.089                           |
| 58           | 111             | 32                   | 0.73        | 0.001                                         | 15                          | GO:0043228 nonmembrane-bounded organelle | GO:0043234 protein complex       | 0.099                           |
| 59           | 92              | 27                   | 0.72        | 0.001                                         | 11                          | GO:0009987 cellular process  | GO:0044445 cytosolic part       | 0.099                           |
| 60           | 111             | 33                   | 0.72        | 0.001                                         | 7                           | GO:0032991 macromolecular complex | GO:0006412 translation            | 0.078                           |
| 61           | 76              | 15                   | 0.72        | 0.001                                         | 2                           | GO:0003674 molecular_function | GO:0009987 cellular process       | 0.050                           |
| 62           | 94              | 27                   | 0.72        | 0.001                                         | 6                           | GO:0032268 regulation of cellular protein metabolic process | GO:0044445 cytosolic part       | 0.089                           |
| 63           | 83              | 24                   | 0.72        | 0.001                                         | 13                          | GO:0022627 cytosolic small ribosomal subunit | GO:0030686 90S preribosome      | 0.083                           |
| 64           | 126             | 28                   | 0.72        | 0.001                                         | 39                          | GO:0032991 macromolecular complex | GO:0030529 ribonucleoprotein complex | 0.099                           |
| 65           | 45              | 12                   | 0.72        | 0.001                                         | 13                          | GO:0022627 cytosolic small ribosomal subunit | GO:0044445 cytosolic part       | 0.099                           |

(Continued)
Table S2 (Continued)

| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms |
|--------------|-----------------|----------------------|-------------|-----------------------------------------------|----------------------------|
| 66           | 100             | 32                   | 0.72        | <0.001                                        | 8                          |
| 67           | 124             | 29                   | 0.72        | <0.001                                        | 15                         |
| 68           | 111             | 37                   | 0.72        | <0.001                                        | 9                          |
| 69           | 51              | 21                   | 0.71        | –                                             | 0                          |
| 70           | 106             | 30                   | 0.71        | <0.001                                        | 21                         |
| 71           | 46              | 12                   | 0.71        | –                                             | 0                          |
| 72           | 126             | 36                   | 0.71        | <0.001                                        | 17                         |
| 73           | 87              | 25                   | 0.71        | <0.001                                        | 8                          |
| 74           | 112             | 30                   | 0.71        | <0.001                                        | 18                         |
| 75           | 116             | 31                   | 0.71        | <0.001                                        | 13                         |
| 76           | 68              | 14                   | 0.71        | <0.001                                        | 7                          |
| 77           | 86              | 20                   | 0.71        | <0.001                                        | 3                          |
| 78           | 104             | 39                   | 0.71        | <0.001                                        | 23                         |
| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted \( P \)-value of GO enrichment | Number of enriched GO terms | Five most significant GO terms | Five most specific GO terms | Highest pairwise similarity score |
|-------------|-----------------|---------------------|-------------|--------------------------------------------------|-----------------------------|-------------------------------|-------------------------------|---------------------------------|
| 66          | 100             | 32                  | 0.72        | 0.001                                            | 8                           | GO:0005198 structural molecule activity | GO:0010608 posttranscriptional regulation of gene expression | 0.080                           |
| 67          | 124             | 29                  | 0.72        | 0.001                                            | 15                          | GO:0032991 macromolecular complex | GO:0034960 cellular biopolymer metabolic process | 0.097                           |
| 68          | 111             | 37                  | 0.72        | 0.001                                            | 9                           | GO:0032991 macromolecular complex | GO:0043284 biopolymer biosynthetic process | 0.099                           |
| 69          | 51              | 21                  | 0.71        | –                                                | –                           | GO:0032991 macromolecular complex | –                            | 0.059                           |
| 70          | 106             | 30                  | 0.71        | 0.001                                            | 21                          | GO:0032991 macromolecular complex | GO:0034960 cellular biopolymer metabolic process | 0.065                           |
| 71          | 46              | 12                  | 0.71        | –                                                | –                           | GO:0032991 macromolecular complex | –                            | 0.093                           |
| 72          | 126             | 36                  | 0.71        | 0.001                                            | 17                          | GO:0032991 macromolecular complex | GO:0034960 cellular biopolymer metabolic process | 0.070                           |
| 73          | 87              | 25                  | 0.71        | 0.001                                            | 8                           | GO:0032991 macromolecular complex | GO:0034960 cellular biopolymer metabolic process | 0.070                           |
| 74          | 112             | 30                  | 0.71        | 0.001                                            | 18                          | GO:0032991 macromolecular complex | GO:0034960 cellular biopolymer metabolic process | 0.085                           |
| 75          | 116             | 31                  | 0.71        | 0.001                                            | 13                          | GO:0032991 macromolecular complex | GO:0034960 cellular biopolymer metabolic process | 0.093                           |
| 76          | 68              | 14                  | 0.71        | 0.001                                            | 7                           | GO:0022627 cytosolic small ribosomal subunit | GO:0022627 cytosolic small ribosomal subunit | 0.080                           |
| 77          | 86              | 20                  | 0.71        | 0.001                                            | 3                           | GO:0003674 molecular_function | GO:0022627 cytosolic small ribosomal subunit | 0.052                           |
| 78          | 104             | 39                  | 0.71        | 0.001                                            | 23                          | GO:0032991 macromolecular complex | GO:0034960 cellular biopolymer metabolic process | 0.108                           |

(Continued)
Table S2 (Continued)

| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted \( P \)-value of GO enrichment | Number of enriched GO terms |
|--------------|-----------------|----------------------|-------------|-----------------------------------------------------|-----------------------------|
| 79           | 90              | 23                   | 0.71        | <0.001                                              | 9                           |
| 80           | 108             | 36                   | 0.71        | <0.001                                              | 7                           |
| 81           | 90              | 24                   | 0.71        | <0.001                                              | 11                          |
| 82           | 106             | 33                   | 0.71        | <0.001                                              | 21                          |
| 83           | 129             | 31                   | 0.71        | <0.001                                              | 18                          |
| 84           | 129             | 28                   | 0.71        | <0.001                                              | 22                          |
| 85           | 77              | 38                   | 0.71        | <0.001                                              | 12                          |
| 86           | 109             | 28                   | 0.70        | <0.001                                              | 6                           |
| 87           | 78              | 21                   | 0.70        | 0.001                                               | 8                           |
| 88           | 100             | 24                   | 0.70        | <0.001                                              | 19                          |
| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms | Five most significant GO terms                                                                 | Five most specific GO terms                                                                 | Highest pairwise similarity score |
|-------------|-----------------|----------------------|--------------|-----------------------------------------------|----------------------------|-----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|---------------------------------|
| 79          | 90              | 23                   | 0.71         | 0.001                                         | 9                          | GO:0006412 translation                                                                         | GO:0026265 cytosolic large ribosomal subunit                                             | 0.060                           |
| 80          | 108             | 36                   | 0.71         | 0.001                                         | 7                          | GO:0032991 macromolecular complex                                                                | GO:0043228 nonmembrane-bounded organelle                                                  | 0.067                           |
| 81          | 90              | 24                   | 0.71         | 0.001                                         | 11                         | GO:0032991 macromolecular complex                                                                | GO:0006139 “nucleobase, nucleoside, nucleotide and nucleic acid metabolic process”         | 0.084                           |
| 82          | 106             | 33                   | 0.71         | 0.001                                         | 21                         | GO:0032991 macromolecular complex                                                                | GO:0009058 biosynthetic process                                                          | 0.091                           |
| 83          | 129             | 31                   | 0.71         | 0.001                                         | 18                         | GO:0032991 macromolecular complex                                                                | GO:0005488 binding                                                                       | 0.098                           |
| 84          | 129             | 28                   | 0.71         | 0.001                                         | 22                         | GO:0032991 macromolecular complex                                                                | GO:0009059 macromolecule biosynthetic process                                           | 0.098                           |
| 85          | 77              | 38                   | 0.71         | 0.001                                         | 12                         | GO:0032991 macromolecular complex                                                                | GO:0009059 macromolecule biosynthetic process                                           | 0.090                           |
| 86          | 109             | 28                   | 0.70         | 0.001                                         | 6                           | GO:0009987 cellular process                                                                     | GO:0019222 regulation of metabolic process                                                  | 0.055                           |
| 87          | 78              | 21                   | 0.70         | 0.001                                         | 8                           | GO:0010468 regulation of gene expression                                                           | GO:0010556 regulation of macromolecule biosynthetic process                               | 0.055                           |
| 88          | 100             | 24                   | 0.70         | 0.001                                         | 19                         | GO:0032991 macromolecular complex                                                                | GO:0009889 regulation of biosynthetic process                                             | 0.073                           |

(Continued)
| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms |
|-------------|-----------------|----------------------|-------------|-----------------------------------------------|-----------------------------|
| 89          | 82              | 24                   | 0.70        | <0.001                                        | 13                          |
| 90          | 77              | 27                   | 0.70        | <0.001                                        | 5                           |
| 91          | 97              | 22                   | 0.70        | <0.001                                        | 17                          |
| 92          | 110             | 28                   | 0.70        | <0.001                                        | 6                           |
| 93          | 94              | 29                   | 0.70        | <0.001                                        | 15                          |
| 94          | 113             | 34                   | 0.70        | <0.001                                        | 32                          |
| 95          | 94              | 23                   | 0.70        | <0.001                                        | 4                           |
| 96          | 104             | 31                   | 0.70        | <0.001                                        | 10                          |
| 97          | 51              | 13                   | 0.70        | <0.001                                        | 1                           |
| 98          | 154             | 32                   | 0.70        | <0.001                                        | 14                          |
| 99          | 117             | 30                   | 0.70        | <0.001                                        | 11                          |
| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms | Five most significant GO terms | Five most specific GO terms | Highest pairwise similarity score |
|-------------|-----------------|---------------------|-------------|-----------------------------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------------|
| 89          | 82              | 24                  | 0.70        | 0.001                                         | 13                          | GO:0044445 cytosolic part   | GO:0009059 macromolecule biosynthetic process | 0.060                                         |
| 90          | 77              | 27                  | 0.70        | 0.001                                         | 5                           | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.050                                         |
| 91          | 97              | 22                  | 0.70        | 0.001                                         | 17                          | GO:0044445 cytosolic part   | GO:0044445 cytosolic part   | 0.090                                         |
| 92          | 110             | 28                  | 0.70        | 0.001                                         | 6                           | GO:0009987 cellular process  | GO:0009987 cellular process  | 0.062                                         |
| 93          | 94              | 29                  | 0.70        | 0.001                                         | 15                          | GO:0043291 macromolecular complex | GO:0044249 cellular biosynthetic process | 0.088                                         |
| 94          | 113             | 34                  | 0.70        | 0.001                                         | 32                          | GO:0009987 cellular process  | GO:0009987 cellular process  | 0.075                                         |
| 95          | 94              | 23                  | 0.70        | 0.001                                         | 4                           | GO:0006412 translation      | GO:0006412 translation      | 0.062                                         |
| 96          | 104             | 31                  | 0.70        | 0.001                                         | 10                          | GO:0006412 translation      | GO:0006412 translation      | 0.107                                         |
| 97          | 51              | 13                  | 0.70        | 0.001                                         | 1                           | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.043                                         |
| 98          | 154             | 32                  | 0.70        | 0.001                                         | 14                          | GO:0043228 nonmembrane-bounded organelle | GO:0043228 nonmembrane-bounded organelle | 0.115                                         |

(Continued)
### Table S2 (Continued)

| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms |
|--------------|-----------------|----------------------|-------------|-----------------------------------------------|-----------------------------|
| 100          | 110             | 28                   | 0.70        | <0.001                                        | 8                           |
| 101          | 139             | 34                   | 0.70        | <0.001                                        | 16                          |
| 102          | 98              | 28                   | 0.69        | <0.001                                        | 48                          |
| 103          | 71              | 18                   | 0.69        | <0.001                                        | 1                           |
| 104          | 105             | 21                   | 0.69        | <0.001                                        | 5                           |
| 105          | 140             | 32                   | 0.69        | <0.001                                        | 16                          |
| 106          | 41              | 12                   | 0.69        | –                                             | 0                           |
| 107          | 101             | 25                   | 0.69        | <0.001                                        | 24                          |
| 108          | 99              | 21                   | 0.69        | <0.001                                        | 9                           |
| 109          | 86              | 12                   | 0.69        | <0.001                                        | 7                           |
| 110          | 118             | 30                   | 0.69        | <0.001                                        | 17                          |
| 111          | 98              | 15                   | 0.69        | <0.001                                        | 5                           |
| 112          | 157             | 43                   | 0.69        | <0.001                                        | 38                          |
| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms | Five most significant GO terms | Five most specific GO terms | Highest pairwise similarity score |
|-------------|----------------|---------------------|-------------|-----------------------------------------------|---------------------------|-------------------------------|-------------------------------|-----------------------------|
| 100         | 110            | 28                  | 0.70        | 0.001                                        | 8                         | GO:0009987 cellular process   | GO:0044249 cellular biosynthetic process | 0.092                        |
| 101         | 139            | 34                  | 0.70        | 0.001                                        | 16                        | GO:0005198 structural molecule activity | GO:0032991 macromolecular complex | 0.100                        |
| 102         | 98             | 28                  | 0.69        | 0.001                                        | 48                        | GO:0044238 primary metabolic process | GO:0006333 chromatin assembly or disassembly | 0.085                        |
| 103         | 71             | 18                  | 0.69        | 0.001                                        | 1                         | GO:0009987 cellular process   | GO:0044249 cellular biosynthetic process | 0.085                        |
| 104         | 105            | 21                  | 0.69        | 0.001                                        | 5                         | GO:0044238 primary metabolic process | GO:0006333 chromatin assembly or disassembly | 0.080                        |
| 105         | 140            | 32                  | 0.69        | 0.001                                        | 16                        | GO:0005198 structural molecule activity | GO:0044249 cellular biosynthetic process | 0.098                        |
| 106         | 41             | 12                  | 0.69        | 0.001                                        | 1                         | GO:0044238 primary metabolic process | GO:0044249 cellular biosynthetic process | 0.080                        |
| 107         | 101            | 25                  | 0.69        | 0.001                                        | 24                        | GO:0044238 primary metabolic process | GO:0006333 chromatin assembly or disassembly | 0.080                        |
| 108         | 99             | 21                  | 0.69        | 0.001                                        | 9                         | GO:0005198 structural molecule activity | GO:0044249 cellular biosynthetic process | 0.080                        |
| 109         | 86             | 12                  | 0.69        | 0.001                                        | 7                         | GO:0044238 primary metabolic process | GO:0044249 cellular biosynthetic process | 0.080                        |
| 110         | 118            | 30                  | 0.69        | 0.001                                        | 17                        | GO:0005198 structural molecule activity | GO:0044249 cellular biosynthetic process | 0.098                        |
| 111         | 98             | 15                  | 0.69        | 0.001                                        | 5                         | GO:0005198 structural molecule activity | GO:0044249 cellular biosynthetic process | 0.085                        |
| 112         | 157            | 43                  | 0.69        | 0.001                                        | 38                        | GO:0005198 structural molecule activity | GO:0044249 cellular biosynthetic process | 0.108                        |

(Continued)
Table S2 (Continued)

| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms |
|--------------|-----------------|----------------------|-------------|-----------------------------------------------|-----------------------------|
| 113          | 116             | 34                   | 0.68        | <0.001                                        | 21                          |
| 114          | 69              | 13                   | 0.68        | 0.001                                         | 1                           |
| 115          | 96              | 21                   | 0.68        | <0.001                                        | 5                           |
| 116          | 38              | 9                    | 0.68        | –                                             | 0                           |
| 117          | 109             | 30                   | 0.68        | <0.001                                        | 9                           |
| 118          | 66              | 17                   | 0.68        | 0.001                                         | 1                           |
| 119          | 104             | 27                   | 0.68        | <0.001                                        | 5                           |
| 120          | 122             | 36                   | 0.68        | <0.001                                        | 38                          |
| 121          | 74              | 16                   | 0.68        | 0.001                                         | 8                           |
| 122          | 126             | 38                   | 0.68        | <0.001                                        | 35                          |
| 123          | 83              | 18                   | 0.68        | <0.001                                        | 3                           |
| 124          | 119             | 31                   | 0.67        | <0.001                                        | 8                           |
| 125          | 133             | 41                   | 0.67        | <0.001                                        | 27                          |
| 126          | 132             | 25                   | 0.67        | <0.001                                        | 18                          |
| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms | Five most significant GO terms | Five most specific GO terms | Highest pairwise similarity score |
|------------|----------------|---------------------|-------------|--------------------------------------------|--------------------------|----------------------------|--------------------------------|------------------------------|
| 113        | 116            | 34                  | 0.68        | 0.001                                       | 21                       | GO:0009987 cellular process  | GO:0000105 histidine biosynthetic process | 0.084                        |
| 114        | 69             | 13                  | 0.68        | 0.001                                       | 1                        | GO:0009987 cellular process  | GO:0000105 histidine biosynthetic process | 0.053                        |
| 115        | 96             | 21                  | 0.68        | 0.001                                       | 5                        | GO:0003674 molecular function | GO:0000105 histidine biosynthetic process | 0.037                        |
| 116        | 38             | 9                   | 0.68        | 0.001                                       | 0                        | GO:0009987 cellular process  | GO:0000105 histidine biosynthetic process | 0.041                        |
| 117        | 109            | 30                  | 0.68        | 0.001                                       | 9                        | GO:0003674 molecular function | GO:0000105 histidine biosynthetic process | 0.076                        |
| 118        | 66             | 17                  | 0.68        | 0.001                                       | 1                        | GO:0009987 cellular process  | GO:0000105 histidine biosynthetic process | 0.037                        |
| 119        | 104            | 27                  | 0.68        | 0.001                                       | 5                        | GO:0003674 molecular function | GO:0000105 histidine biosynthetic process | 0.072                        |
| 120        | 122            | 36                  | 0.68        | 0.001                                       | 38                       | GO:0009987 cellular process  | GO:0000105 histidine biosynthetic process | 0.097                        |
| 121        | 74             | 16                  | 0.68        | 0.001                                       | 8                        | GO:0000105 histidine biosynthetic process | GO:0000105 histidine biosynthetic process | 0.037                        |
| 122        | 126            | 38                  | 0.68        | 0.001                                       | 35                       | GO:0000105 histidine biosynthetic process | GO:0000105 histidine biosynthetic process | 0.072                        |
| 123        | 83             | 18                  | 0.68        | 0.001                                       | 3                        | GO:0000105 histidine biosynthetic process | GO:0000105 histidine biosynthetic process | 0.093                        |
| 124        | 119            | 31                  | 0.67        | 0.001                                       | 8                        | GO:0000105 histidine biosynthetic process | GO:0000105 histidine biosynthetic process | 0.093                        |
| 125        | 133            | 41                  | 0.67        | 0.001                                       | 27                       | GO:0000105 histidine biosynthetic process | GO:0000105 histidine biosynthetic process | 0.080                        |

(Continued)
**Table S2 (Continued)**

| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms |
|--------------|-----------------|----------------------|-------------|-----------------------------------------------|-----------------------------|
| 127          | 57              | 14                   | 0.67        | –                                             | 0                           |
| 128          | 51              | 18                   | 0.67        | <0.001                                        | 1                           |
| 129          | 77              | 25                   | 0.67        | <0.001                                        | 5                           |
| 130          | 75              | 22                   | 0.67        | <0.001                                        | 4                           |
| 131          | 106             | 26                   | 0.67        | <0.001                                        | 6                           |
| 132          | 133             | 25                   | 0.67        | <0.001                                        | 21                          |
| 133          | 128             | 35                   | 0.67        | <0.001                                        | 22                          |
| 134          | 107             | 28                   | 0.67        | <0.001                                        | 19                          |
| 135          | 109             | 24                   | 0.66        | <0.001                                        | 17                          |
| 136          | 72              | 16                   | 0.66        | <0.001                                        | 9                           |
| 137          | 113             | 24                   | 0.66        | <0.001                                        | 11                          |
| 138          | 48              | 12                   | 0.66        | –                                             | 0                           |
| 139          | 58              | 13                   | 0.66        | –                                             | 0                           |
| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms | Five most significant GO terms | Five most specific GO terms | Highest pairwise similarity score |
|-------------|-----------------|---------------------|--------------|-----------------------------------------------|-----------------------------|-------------------------------|-------------------------------|--------------------------------|
| 127         | 57              | 14                  | 0.67         | -                                             | 0                           | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.042                          |
| 128         | 51              | 18                  | 0.67         | 0.001                                         | 1                           | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.048                          |
| 129         | 77              | 25                  | 0.67         | 0.001                                         | 5                           | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.044                          |
|             |                 |                     |              |                                               |                             | GO:0003674 molecular_function |                              |                                |
| 130         | 75              | 22                  | 0.67         | 0.001                                         | 4                           | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.048                          |
| 131         | 106             | 26                  | 0.67         | 0.001                                         | 6                           | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.048                          |
| 132         | 133             | 25                  | 0.67         | 0.001                                         | 21                          | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.048                          |
|             |                 |                     |              |                                               |                             | GO:0003674 molecular_function |                              |                                |
| 133         | 128             | 35                  | 0.67         | 0.001                                         | 22                          | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.048                          |
|             |                 |                     |              |                                               |                             | GO:0003674 molecular_function |                              |                                |
| 134         | 107             | 28                  | 0.66         | 0.001                                         | 19                          | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.048                          |
|             |                 |                     |              |                                               |                             | GO:0003674 molecular_function |                              |                                |
| 135         | 109             | 24                  | 0.66         | 0.001                                         | 17                          | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.048                          |
|             |                 |                     |              |                                               |                             | GO:0003674 molecular_function |                              |                                |
| 136         | 72              | 16                  | 0.66         | 0.001                                         | 9                           | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.048                          |
|             |                 |                     |              |                                               |                             | GO:0003674 molecular_function |                              |                                |
| 137         | 113             | 24                  | 0.66         | 0.001                                         | 11                          | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.048                          |
|             |                 |                     |              |                                               |                             | GO:0003674 molecular_function |                              |                                |
| 138         | 48              | 12                  | 0.66         | -                                             | 0                           | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.048                          |
| 139         | 58              | 13                  | 0.66         | -                                             | 0                           | GO:0003674 molecular_function | GO:0003674 molecular_function | 0.048                          |

(Continued)
Table S2 (Continued)

| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms |
|--------------|-----------------|---------------------|-------------|---------------------------------------------|---------------------------|
| 140          | 135             | 37                  | 0.66        | <0.001                                      | 14                        |
| 141          | 103             | 21                  | 0.66        | <0.001                                      | 10                        |
| 142          | 164             | 32                  | 0.66        | <0.001                                      | 26                        |
| 143          | 90              | 18                  | 0.66        | <0.001                                      | 21                        |
| 144          | 101             | 20                  | 0.66        | <0.001                                      | 3                         |
| 145          | 122             | 4                   | 0.66        | <0.001                                      | 2                         |
| 146          | 121             | 32                  | 0.66        | <0.001                                      | 14                        |
| 147          | 121             | 30                  | 0.66        | <0.001                                      | 6                         |
| 148          | 104             | 22                  | 0.66        | <0.001                                      | 23                        |
| 149          | 140             | 19                  | 0.66        | <0.001                                      | 14                        |
| 150          | 116             | 30                  | 0.65        | <0.001                                      | 14                        |
| 151          | 61              | 21                  | 0.65        | <0.001                                      | 1                         |
| 152          | 62              | 15                  | 0.65        | <0.001                                      | 1                         |
| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P -value of GO enrichment | Number of enriched GO terms | Five most significant GO terms | Five most specific GO terms | Highest pairwise similarity score |
|-------------|-----------------|---------------------|-------------|-----------------------------------------------|-----------------------------|-----------------------------|-------------------------------|-----------------------------|
| 140         | 135             | 37                  | 0.66        | 0.001                                         | 14                          | GO:0044238 primary metabolic process | GO:0005488 binding          | 0.101                        |
| 141         | 103             | 21                  | 0.66        | 0.001                                         | 10                          | GO:0044238 primary metabolic process | GO:0005488 binding          | 0.063                        |
| 142         | 164             | 32                  | 0.66        | 0.001                                         | 26                          | GO:0044238 primary metabolic process | GO:0005488 binding          | 0.064                        |
| 143         | 90              | 18                  | 0.66        | 0.001                                         | 21                          | GO:0044238 primary metabolic process | GO:0005488 binding          | 0.091                        |
| 144         | 101             | 20                  | 0.66        | 0.001                                         | 3                           | GO:0044238 primary metabolic process | GO:0005488 binding          | 0.064                        |
| 145         | 122             | 4                   | 0.66        | 0.001                                         | 2                           | GO:0044238 primary metabolic process | GO:0005488 binding          | 0.052                        |
| 146         | 121             | 32                  | 0.66        | 0.001                                         | 14                          | GO:0044238 primary metabolic process | GO:0005488 binding          | 0.045                        |
| 147         | 121             | 30                  | 0.66        | 0.001                                         | 6                           | GO:0044238 primary metabolic process | GO:0005488 binding          | 0.041                        |
| 148         | 104             | 22                  | 0.66        | 0.001                                         | 23                          | GO:0044238 primary metabolic process | GO:0005488 binding          | 0.070                        |

(Continued)
### Table S2 (Continued)

| Bicluster ID | Number of genes | Number of conditions | Average PCC | The minimum adjusted P-value of GO enrichment | Number of enriched GO terms |
|--------------|-----------------|---------------------|-------------|-----------------------------------------------|----------------------------|
| 153          | 85              | 27                  | 0.65        | <0.001                                        | 5                          |
|              |                 |                     |             |                                               |                            |
| 154          | 142             | 33                  | 0.65        | <0.001                                        | 12                         |
|              |                 |                     |             |                                               |                            |
| 155          | 54              | 12                  | 0.65        | –                                             | 0                          |
| 156          | 71              | 15                  | 0.65        | <0.001                                        | 6                          |
|              |                 |                     |             |                                               |                            |
| 157          | 103             | 34                  | 0.65        | <0.001                                        | 21                         |
|              |                 |                     |             |                                               |                            |
| 158          | 84              | 19                  | 0.65        | <0.001                                        | 6                          |
|              |                 |                     |             |                                               |                            |
| 159          | 103             | 20                  | 0.65        | <0.001                                        | 10                         |
|              |                 |                     |             |                                               |                            |
| 160          | 74              | 7                   | 0.65        | 0.001                                         | 3                          |
|              |                 |                     |             |                                               |                            |
| 161          | 57              | 7                   | 0.64        | <0.001                                        | 1                          |
| 162          | 87              | 6                   | 0.63        | <0.001                                        | 1                          |
| 163          | 75              | 5                   | 0.61        | <0.001                                        | 2                          |
| 164          | 56              | 10                  | 0.54        | –                                             | 0                          |

Notes: The steps to select specific GO terms from each cluster. (1) We hypothesise if a GO term appears on only a small number of biclusters (ie, 1 of 4 biclusters), it is specific for the biclusters. (2) We have 164 biclusters. By the proportion test, 1 of 4 biclusters corresponds to 31 of 164 biclusters at 0.05 significance level. (3) Therefore, GO terms appear less than 32 times are specific terms.
| Five most significant GO terms                                      | Five most specific GO terms                                      | Highest pairwise similarity score |
|-------------------------------------------------------------------|-----------------------------------------------------------------|-----------------------------------|
| GO:00016070 RNA metabolic process                                 | GO:00034660 ncRNA metabolic process                             | 0.072                            |
| GO:0003674 molecular_function                                     | GO:0016070 RNA metabolic process                                |                                   |
| GO:0044238 primary metabolic process                             | GO:0009987 cellular process                                     |                                   |
| GO:0034660 ncRNA metabolic process                               | GO:0032991 macromolecular complex                               |                                   |
| GO:0030529 ribonucleoprotein complex                             | GO:00056222 intracellular                                     | 0.099                            |
| GO:0044445 cytosolic part                                        | GO:0032292 intracellular organelle                               |                                   |
| GO:0032991 macromolecular complex                                | GO:0044442 organelle part                                       |                                   |
| GO:0032279 ribosomal subunit                                     | GO:0044446 intracellular organelle part                         |                                   |
| GO:0043228 nonmembrane-bounded organelle                         | GO:0043226 organelle                                           |                                   |
| GO:0043283 biopolymer metabolic process                          | GO:0034960 cellular biopolymer metabolic process                | 0.052                            |
| GO:0044238 primary metabolic process                             | GO:0044260 cellular macromolecule metabolic process             |                                   |
| GO:0034621 cellular macromolecular complex assembly               | GO:0034622 cellular macromolecular complex assembly             |                                   |
| GO:0032991 macromolecular complex                                | GO:0015934 large ribosomal subunit                              | 0.079                            |
| GO:0009987 cellular process                                       | GO:0022625 cytosolic large ribosomal subunit                    |                                   |
| GO:0044445 cytosolic part                                        | GO:0051246 regulation of protein metabolic process              |                                   |
| GO:003228 nonmembrane-bounded organelle                          | GO:0044424 intracellular part                                   |                                   |
| GO:0032322 intracellular nonmembrane-bounded organelle           | GO:0032268 regulation of cellular protein metabolic process     |                                   |
| GO:0005198 structural molecule activity                           | GO:0005488 binding                                             | 0.074                            |
| GO:0004688 binding                                               | GO:0004688 binding                                             |                                   |
| GO:0003674 molecular_function                                     | GO:0003674 molecular_function                                   |                                   |
| GO:0003674 molecular_function                                     | GO:0003674 molecular_function                                   |                                   |
| GO:0003674 molecular_function                                     | GO:0003674 molecular_function                                   |                                   |
| GO:0003674 molecular_function                                     | GO:0003674 molecular_function                                   |                                   |

**Notes:** The steps to select specific GO terms from each cluster. (1) We hypothesise if a GO term appears on only a small number of biclusters (ie, 1 of 4 biclusters), it is specific for the biclusters. (2) We have 164 biclusters. By the proportion test, 1 of 4 biclusters corresponds to 31 of 164 biclusters at 0.05 significance level. (3) Therefore, GO terms appear less than 32 times are specific terms.