RN-Cluster: Discovering coherent biclusters which is Robust to Noise

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Abstract

A bicluster is a subset of genes that show similar behavior within a subset of conditions. Biclustering algorithm is a useful tool to uncover groups of genes involved in the same cellular process and groups of conditions which take place in this process. We are proposing a polynomial time algorithm to identify functionally highly correlated biclusters. Our algorithm identifies 1) the gene set that follows additive, multiplicative, and combined patterns simultaneously that allow high level of noise, 2) the multiple, possibly overlapped, and diverse gene sets, 3) biclusters with negatively correlated as well as positively correlated gene set simultaneously, and 4) gene sets whose functional association is strongly high. We validated the level of functional association of our method, and compared with current methods using GO.

1. Introduction

Not all the genes in microarray dataset participate in a particular cellular process, and not all samples can be observed in a particular cellular process. We can expect subsets of genes to be co-regulated under certain experimental conditions, but to behave almost independently under other conditions [1]. Finding the set of co-regulated genes can lead to identify the functionality of the group of genes and eventually find the genetic pathways. Cheng [2] named the data mining technique that finds a submatrix of coherent gene set and sample set in a microarray as biclustering.

Many biclustering algorithms have been introduced, and biclustering is proven to be a NP-hard problem [2], so all these algorithms used heuristic methods or probabilistic approximation. Accordingly strengths and weaknesses of each algorithm are various and the patterns that each biclustering algorithm identified are also various. Biclustering algorithms could be divided into two groups largely by the patterns they find.

- *Algorithms that find additive or multiplicative patterns:*

δ-biclustering [2] uses mean squared residue of a submatrix to find biclusters. As a result, it finds additive or multiplicative co-regulation patterns. One weakness of δ-biclustering is that it allows only a small degree of noise. Thus it can identify strict patterns only. Also it can easily miss overlapping clusters due to the random value substitutions once a bicluster is identified.

p-Cluster [3] first scans the dataset to find all column-pair and row-pair maximal clusters called MDS. Then it does the pruning in turn using the row-pair MDS and the column-pair MDS. It then mines the final clusters based on a prefix tree. However, p-Cluster is not robust to noise, either.

Tri-Cluster [4] is the first algorithm that mines 3 dimensional microarray dataset. It makes a DFS(Depth First Search) tree whose node is the genes which show same range of fluctuation within user specified threshold ε. If ε is too big, DFS tree could grow too deep to complete the mining. However, Tri-Cluster with small ε does not allow high degree of noise. Moreover, its time complexity is exponential to the number of samples.

reg-Cluster [5] mines additive and multiplicative co-regulation patterns. It defines d_{ij} as a difference of the gene expression value between conditions c_i and c_j. Then it finds the gene set whose ratio of d01 and dij is within ε. Although the idea of mining additive and multiplicative patterns together is novel, it has a few problems. First, finding a proper ε is very difficult job. If ε is too big, the gene set in a bicluster would have many false positive genes. And if ε is too small, the gene set in a bicluster would have many false negative genes. Second, it constructs a DFS tree like Tri-Cluster. Thus it has same problems with Tri-Cluster.

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The number of nodes of DFS tree becomes exponential as the level grows. Therefore, the algorithms that construct DFS tree have common problem that the number of resulting biclusters are extremely many. That is because all the biclusters which are slightly different are accounted into result. It is a difficult problem to examine all these biclusters and to choose the one among the similar biclusters. The noise level that the previously mentioned algorithms allow is not enough to find all the meaningful patterns. Thus we could say that they commonly find strictly additive or multiplicative patterns.

- *Algorithms that find pattern by keeping ordered sequence:*

OPSM [1] defines a cluster as a submatrix of the original microarray matrix after performing column permutation separately for each row, whose gene expression values are in a non-decreasing pattern. Although OPSM shows good GO validation result [6], it is problematic that OPSM can find only one bicluster at a time. It could miss many meaningful biclusters hidden in the microarray data. OP-Cluster [7] and KiWi [8] use different algorithm with OPSM, but basically use same definition of OPSM. Commonly, OPSM based algorithms have possibility that the biologically significant patterns which do not preserve the order could be missed [9].

In this paper, we propose a new model for biclusters with functionally highly correlated gene expression data called RN-cluster. 1) RN-cluster identifies the gene set that follows additive, multiplicative, and combined patterns within user specified threshold simultaneously. Combined pattern of additive and multiplicative shape allows highly flexible patterns with specified level of noise tolerance and allowing high level of noise does not require exponential time or space complexity in RN-cluster, which means that RN-Cluster is robust to experimental noise. 2) RN-cluster identifies the multiple, possibly overlapped gene sets while guaranteeing gene-diversity in a bicluster by complying with user specified similarity threshold. 3) RN-cluster identifies biclusters with negatively correlated as well as positively correlated gene set simultaneously. 4) RN-cluster identifies biclusters whose functional association is strongly high. This functional association is validated using GO database.

2. PRELIMINARIES

This section describes the notations and preliminary concepts before we detail the algorithm.

2.1 Notations

G	A set of genes
S	A set of samples
(O, T)	A submatrix of the data set, where $O \subseteq G$, $T \subseteq S$
$g_0, g_1, \ldots$	Genes in O
$s_0, s_1, \ldots$	Samples in T
c_{ij}	Expression value of gene g_i on sample s_j
d^k_{ab}	$c_{kb} - c_{ka}$, difference of expression values of sample s_a and sample s_b on gene g_k
t^i_{cd}	d^i_{ab}/d^i_{cd}, ratio of gene g_i, where s_a and s_b are the first and second samples in RN cluster, respectively
δ	User-specified maximum ratio threshold (> 1)
mg	User-specified minimum # of genes of a RN cluster
ms	User-specified minimum # of samples of a RN cluster

2.2 Preliminary concepts

Let $O = \{g_0, g_1, \ldots, g_{m-1}\}$ and $T = \{s_0, s_1, \ldots, s_{n-1}\}$, then c_{ij} would be the expression level of gene g_i in sample s_j. Let C be a m x n submatrix (O, T) of the dataset (G, S), then we can write $C = (O, T) = \{c_{ij}\}$, $i \in [0, m-1]$ and $j \in [0, n-1]$.

Definition 1 (RN-cluster). Let $C = (O, T)$ be a bicluster, where $g_i, g_j, g_k \in O$ and $T = \{s_a, s_b, \ldots, s_c, s_d, \ldots\}$. C is a RN -cluster iff C satisfies the following properties:

1. $d^i_{ab} \neq 0$, $d^j_{ab} \neq 0$, $d^i_{cd} \neq 0$ and $d^j_{cd} \neq 0$
2. $\text{sign}(t^i_{cd}) = \text{sign}(t^j_{cd})$, where sign(x) returns -1 if x is negative and +1 if x is positive for all a > 1
3. $|t^i_{cd}| / \delta \leq |t^i_{cd}| \leq |t^k_{cd}| \times \delta$, where $|t^i_{cd}|$ and $|t^k_{cd}|$ are maximum and minimum $|t^h_{cd}|$ values for $g_h \in O$, respectively
4. $|O| \geq mg \geq 2$ and $|T| \geq ms \geq 3$

Definition 2 (p-RNC). When RN-Cluster $C = (O, T)$ and $|T| = p$, then we refer to C as p-RNC. p refers to the number of samples involved in the bicluster.

For example, suppose there are 10 x 6 microarray dataset (G, S) as shown in Table 1. Let 2-RNC be G x $\{s_0, s_2\}$ submatrix, $ms = 3$, $mg = 3$ and $\delta = 2$. If we examine sample s_3, then $T = \{s_0, s_2, s_3\}$. The d^k_{02} and d^k_{23} for gene g_k are shown in table 2.

Table 1. 10 x 6 microarray dataset

gene\sample	s_0	s_1	s_2	s_3	s_4	s_5
g_0	0.15	-0.07	-0.25	-0.3	-1.12	-0.67
g_1	0.21	0.03	0.18	-0.27	-0.32	0.62
g_2	-0.03	-0.07	0.28	0.32	-0.27	-0.36
g_3	-0.25	0.58	0.77	0.28	0.32	0.65
g_4	0.11	0.04	0.75	0.82	0.21	-0.2
g_5	0.24	0.31	0.95	0.12	0.18	0.69
g_6	-0.3	0.22	0.02	-0.64	0.06	-0.04
g_7	-0.15	-0.25	0.18	0.06	-0.15	-0.17
g_8	0	-0.74	-0.38	0.87	-0.34	0.12
g_9	-0.15	0.2	0.31	0.15	0.04	-0.22

Table 2. Difference values and ratio of difference values for gene set O

	g_0	g_1	g_2	g_3	g_4	g_5	g_6	g_7	g_8	g_9
d^k_{02}	-0.4	-0.03	0.31	1.02	0.64	0.71	0.32	0.33	-0.38	0.46
d^k_{23}	-0.05	-0.45	0.04	-0.49	0.07	-0.83	-0.66	-0.12	1.25	-0.16
$\lvert t^k_{23}\rvert$	8	0.067	7.75	2.08	9.14	0.86	0.48	2.75	0.30	2.88

We can see that bicluster B_1 with gene set $O = \{g_0, g_2, g_4\}$ and sample set $T = \{s_0, s_2, s_3\}$ satisfies all the properties: 1) d^k_{02} and d^k_{23} for k = 0, 2, 4 are not zero, 2) d^k_{02} and d^k_{23} for k = 0, 2, 4 have same sign, 3) the values $\max(|t^k_{23}|) = 9.14$ when k = 4, $\min(|t^k_{23}|) = 7.75$ when k = 2 and $|t^k_{23}| = 8$ when k = 0. Thus, 9.14 / 2(= 4.58) < 8 < 7.75 x 2(= 15.5), 4) $|O| = 3 \geq 3$ and $|T| = 3 \geq 3$. Thus B_1 can be said to be a 3-RNC. Similarly, we can see that bicluster B_2 with gene set $O = \{g_3, g_7, g_9\}$ and B_3 with gene set $O = \{g_5, g_6, g_8\}$ satisfies all the properties, thus B_2 and B_3 can be said to be a 3-RNC.

3. ALGORITHM

RN-Cluster mines a set of genes that behave similarly through a set of samples. RN-Cluster has two main steps: 1) get the initial 2-RNC set whose samples are all possible sample pairs, 2) for each p-RNC, get the (p+1)-RNC. We describe the details of each step.

3.1 Get the initial 2-RNC set

The set of samples $\{(s_i, s_j)\}$ where i < j and the set of genes $\{g_0, g_1, \ldots, g_{m-1}\}$ form a 2-RNC. The number of all the 2-RNCs is n(n-1) / 2, which are all possible sample pairs. For example, in Table 1, possible sample sets of 2-RNC are $\{s_0, s_1\}$, $\{s_0, s_2\}$, …, $\{s_0, s_3\}$. Note that if $ms = 3$, then $\{s_0, s_5\}$, $\{s_1, s_5\}$, $\{s_2, s_5\}$, $\{s_3, s_5\}$ and $\{s_4, s_5\}$ cannot form a 2-RNC, because it cannot grow up to 3 or more-RNC (e.g., G x $\{s_0, s_5, s_6\}$). Similarly, $\{s_0, s_4\}$, $\{s_1, s_4\}$, $\{s_2, s_4\}$ and $\{s_3, s_4\}$ cannot form a 2-RNC if $ms = 4$.

3.2 Get the (p+1)-RNCs from p-RNCs

For all 2-RNCs $C = (O, T)$, we make 3-RNC by examining the sample s_i such that l < i, where s_l is the last sample in sample set T. We can get 4-RNCs from 3-RNCs, 5-RNCs from 4-RNCs, and so on. In other words, we take the iterative method [10] by doing breadth first search to get (p+1)-RNCs from p-RNCs.

The examining process is composed of ranging and queuing process. Details of these parts are described in the following sub sections.

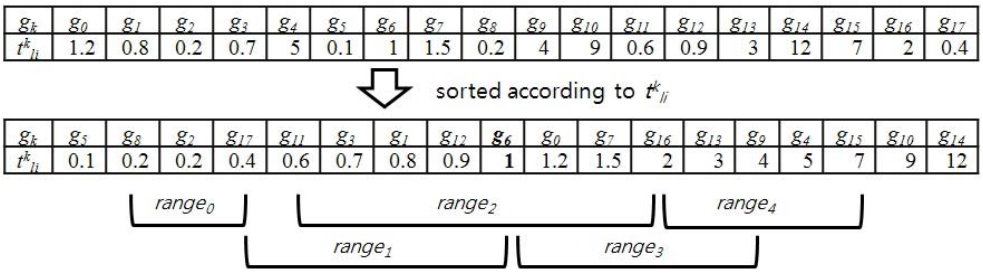
3.3 Ranging

The examining process first calculates t^k_{li} between s_l and s_i for all the genes g_k. Then genes in the gene set O are clustered into two sets: set of positive values, OP and set of negative values, ON according to the sign of t^k_{li}. If the sign of t^k_{li} is positive, g_k is included into OP, else g_k is included into ON. Keeping same signed ts in separate sets makes negatively correlated genes to be included in a bicluster.

First table of Figure 1 shows genes in OP and their t^k_{li} values. OP is sorted according to t^k_{li} in ascending order. Let $q = (|OP| / 2) - 1$. Then g_q is gene that is positioned in the middle of ordered OP. Second table of Figure 1 shows ordered OP of first table, and g_6 is positioned middle of ordered OP.

Then we heuristically get 5 sub-gene sets OP_0, OP_1, OP_2, OP_3 and OP_4 from OP with Definition 1 being satisfied. Each of sub-gene set OP_i contains genes whose t values are within $range_i$, where $i = 0, 1, 2, 3, 4$. Each $range_i$ are shown in Figure 1.

Once the ranges are derived, the sorted sequence of gene OP is linearly examined once. During examining, for each g_k in OP, if $|t^k_{li}| \in range_i$, then g_k is clustered into OP_i. All those OP_is except the ones whose size is less than mg become the gene set for new (p+1)-RNC whose new sample set is $T = T \cup \{s_i\}$.



When $\delta = 2$,

$range_0 = [t^a_{li} \times \delta^{-3}, t^a_{li} \times \delta^{-1}] = [0.125, 0.5] \rightarrow OP_0 = \{g_8, g_2, g_{17}\}$

$range_1 = [t^a_{li} \times \delta^{-2}, t^a_{li} \times \delta^{0}] = [0.25, 1] \rightarrow OP_1 = \{g_{17}, g_{11}, g_3, g_1, g_{12}, g_6\}$

$range_2 = [t^a_{li} \times \delta^{-1}, t^a_{li} \times \delta^{1}] = [0.5, 2] \rightarrow OP_2 = \{g_{11}, g_3, g_1, g_{12}, g_6, g_0, g_7, g_{16}\}$

$range_3 = [t^a_{li} \times \delta^{0}, t^a_{li} \times \delta^{2}] = [1, 4] \rightarrow OP_3 = \{g_6, g_0, g_7, g_{16}, g_{13}, g_9\}$

$range_4 = [t^a_{li} \times \delta^{1}, t^a_{li} \times \delta^{3}] = [2, 8] \rightarrow OP_4 = \{g_{16}, g_{13}, g_9, g_4, g_{15}\}$

Figure 1. Sub-gene sets and their ranges when δ = 2

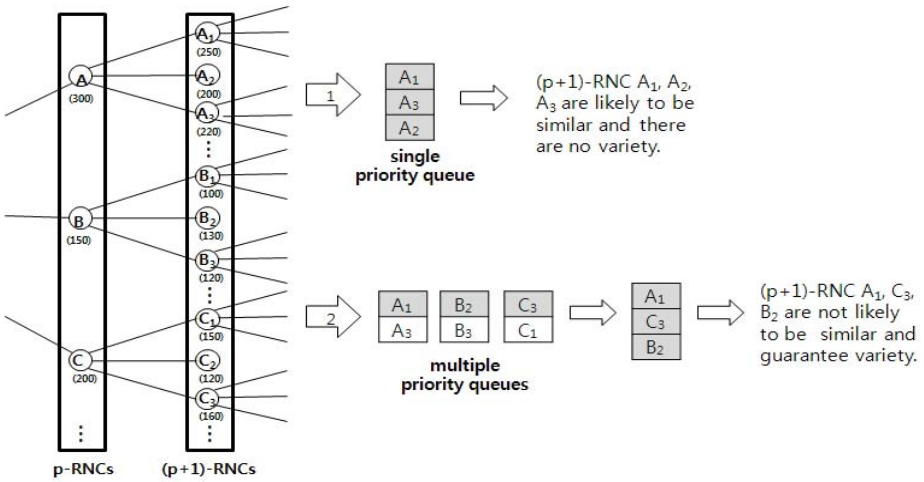


Figure 2. Queuing strategies

From the second table of Figure 1, we can see that the $t^q_{li} = 1$. When $\delta = 2$, $range_0 = [1 \times 2^{-3}, 1 \times 2^{-1}] = [0.125, 0.5]$. Likewise, $range_1$, $range_2$, $range_3$ and $range_4$ can be calculated as in Figure 1. Because OP_0 is composed of g_ks whose t^k_{li} is in $range_0$, $OP_0 = \{g_8, g_2, g_{17}\}$. OP_1, OP_2, OP_3 and OP_4 can be derived in a similar way. These processes are illustrated in Figure 1. We can apply the same process on ON. While generating (p+1)-RNCs, if we cannot get any OP_is or ON_is whose size is greater than or equal to minimum number of genes mg, for all the p-RNCs and all the samples s_i where $s_i \in S - T$, then there are no valid (p+1)-RNC, and the entire process ends.

3.4 Queuing

Let the number of the (p-1)-RNC be r. For each (p-1)-RNC, there are at most n samples to examine, and for each examination, at most 10 p-RNCs are generated (5 ranges from OP and ON). Thus there are O(nr) p-RNCs. We cannot keep all these p-RNCs due to limitation of memory, and examining all these p-RNCs is exponentially time consuming process. However we observe that 1) we are only interested in distinguished p-RNCs whose gene set is bigger than others, and 2) we only need to keep p-RNCs which have higher possibility to grow up to p'-RNC where p' > p.

To satisfy condition 1), we keep set of priority queues whose priority measure is the size of the gene set, $|O|$, to keep the p-RNCs. The p-RNCs in these queues form the output biclusters. Figure 2 compares two queuing strategies: single priority queue, and multiple priority queues. Ours is implemented using multiple priority queues. Each node in BFS tree of Figure 2 denotes the name of RNC and the size of its gene set, $|O|$.

Former strategy prunes the (p+1)-RNCs from p-RNCs B and C, that means it does not guarantee variety of genes. Thus we keep multiple priority queues to guarantee the variety of the p-RNCs. Every (p+1)-RNCs in each priority queues can be a result.

To satisfy condition 2), we need to keep another set of priority queues to keep the p-RNCs for next (p+1)-RNCs. The queuing strategy is same as the case above, but we heuristically set the priority measure as $|O| \times (n - last)$, where $last$ is the index of last sample of T (for example, when $T = \{s_0, s_2, s_3\}$, $last$ is 3). The strongholds for the priority measure $|O| \times (n - last)$ are followings: 1) it is generally true that p-RNC with bigger gene set grows up to a (p+1)-RNC with bigger gene set, and 2) as $last$ gets bigger, the possibility that the p-RNC grows up to larger-RNC gets smaller. For example, suppose that $S = \{s_0, s_1, s_2, s_3, s_4, s_5\}$ and there are two 3-RNCs SB_1 and SB_2 whose T is $\{s_0, s_1, s_2\}$ and $\{s_0, s_1, s_3\}$, respectively. SB_1 has more samples (s_3, s_4 and s_5) to examine than SB_2 (s_4 and s_5), which means SB_1 can grow up to three 4-RNCs with $T = \{s_0, s_1, s_2, s_3\}$, $T = \{s_0, s_1, s_2, s_4\}$ and $T = \{s_0, s_1, s_2, s_5\}$, while SB_2 can grow up to only two 4-RNCs with $T = \{s_0, s_1, s_3, s_4\}$ and $T = \{s_0, s_1, s_3, s_5\}$. Furthermore, SB_1 can grow up to 6-RNC with $T = \{s_0, s_1, s_2, s_3, s_4, s_5\}$, but SB_2 cannot grow up to 6-RNC. So we can say that, as $last$ gets bigger, the possibility of the p-RNC growing gets smaller. Accordingly, priority queues have p-RNCs which have bigger possibility to grow up to larger-RNC. After we examine all the p-RNCs, we can get two sets of (p+1)-RNCs, one is for output and another is the candidates for next (p+1)-RNCs.

Let the size of each priority queue and the total number of priority queues be $qsize$ and $qnum$, respectively. Both $qsize$ and $qnum$ can be input as a user-specified parameter. $qsize$ affects the diversity of results. We internally set the $qsize$ as 100, which is big enough, since $qsize$ is not directly proportional to the degree of diversity. Let $k = qnum \times qsize$, then k is the

total number of p-RNCs before eliminating duplicated RNCs. Accordingly, bigger *qnum* leads to bigger *k*. Generally, the bigger *k* leads to less pruning, thus prevents local optima. However, experimental results (Table 5) revealed that *qnum* does not affect the quality of biclusters once the value is bigger than 100.

4. EXPERIMENTAL RESULTS

The experimental environment is Windows XP operating system on AMD Athlon 64 X2 Dual, 2.81GHz, 1.93GB RAM machine. We used only real microarray datasets to evaluate RN-Cluster which is the Gasch [11] yeast dataset. The yeast dataset consists of 2944 genes over 173 samples. In all experiments, we used *ms* = 5, *mg* = 10, δ = 1.7, *rt* = 0.4 and *qnum* = 100 unless otherwise specified.

To show the quality of the RN-Cluster, we validated the results through GO, using FuncAssociate [12]. We compared GO validation result on OPSM, Bimax [6], ISA [13] and δ-biclustering [2]. According to Prelic [6], the proportion of biclusters enriched with significance level $\alpha = 0.001\%$ is about 88% in case of OPSM, when the same real data was used. OPSM shows best GO validation result among Bimax, ISA and δ-biclustering. Meanwhile, the proportion of RN-clusters enriched with significant level $\alpha = 0.001\%$ is 100%. That means every RN-Cluster is biologically meaningful.

To show more detailed result, we compared GO validation results of our bicluster with those of OPSM bicluster, which has approximately same number of genes with ours. We used BicAT v2.22 [14] to execute OPSM with iteration parameter = 10, on the same environment. Totally 14 biclusters were generated by OPSM, and we chose top 2 biclusters which show good GO validation result among them. Then we also chose biclusters with similar size of gene set from resulting RN-Clusters. Table 3-a), b), c) and d) show the top 5 p-values of biclusters from RN Cluster and OPSM and Table 3-e) is for the legends for other tables. We can see that p-values with same GO Attribute is generally much lower in RN Cluster than OPSM.

That means the significance of association is much bigger in the case of RN Cluster than OPSM. The graphs of Figure 3 show the RN-Clusters used in Table 3-a). We can easily find the negative correlation and the additive and multiplicative patterns in Figure 3.

Next we made experiments which guide the selection of default values for δ, *and qnum*. Firstly we made measurements of run-time while varying δ in seconds. Bigger δ means accommodation of higher level of noise. Figure 4 shows RN-Clustering's time complexity on varying δ. We can see that time complexity does not increase exponentially as δ increases and lowest p-

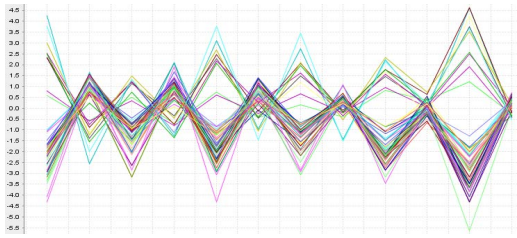


Figure 3. Gene curve graphs of 12-RNC

Table 3. GO validation results

Rank	N	X	P	GO Attribute
1	94	168	4.9e-90	GO:0005830: cytosolic ribosome
2	94	186	2.4e-84	GO:0044445: cytosolic part
3	106	276	3e-80	GO:0005840: ribosome
4	168	948	7.1e-76	GO:0043228: non-membrane-bound organelle
5	168	948	7.1e-76	GO:0043232: intracellular non-membrane-bound organelle

(a) 271 x 12 Bicluster from RN-Cluster (12-RNC)

Rank	N	X	P	GO Attribute
1	79	168	2.8e-67	GO:0005830: cytosolic ribosome
2	81	186	1.1e-65	GO:0044445: cytosolic part
3	91	276	2e-61	GO:0005840: ribosome
4	79	236	2.5e-53	GO:0033279: ribosomal subunit
5	78	230	4.2e-53	GO:0003735: structural constituent of ribosome

(b) 268 x 7 Bicluster from OPSM

Rank	N	X	P	GO Attribute
1	76	168	2.60E-120	GO:0005830: cytosolic ribosome
2	76	186	6.1e-116	GO:0044445: cytosolic part
3	81	276	1.1e-113	GO:0005840: ribosome
4	76	230	3e-107	GO:0003735: structural constituent of ribosome
5	76	236	3.2e-106	GO:0033279: ribosomal subunit

(c) 83 x 25 Bicluster from RN-Cluster (25-RNC)

Rank	N	X	P	GO Attribute
1	62	168	1.40E-82	GO:0005830: cytosolic ribosome
2	62	186	3.00E-79	GO:0044445: cytosolic part
3	66	276	1.50E-74	GO:0005840: ribosome
4	62	236	9.50E-72	GO:0033279: ribosomal subunit
5	61	230	1.30E-70	GO:0003735: structural constituent of ribosome

(d) 88 x 10 Bicluster from OPSM

Rank	Position in the GO attribute list ranked by significance of association (P-value) of the gene set of the bicluster
N	Number of genes in the gene set of the bicluster with this GO attribute
X	Number of genes overall with this GO attribute
P	Single hypothesis one-sided P-value of the association between GO attribute and the gene set of the bicluster (based on Fisher's Exact Test)

(e) Table legend

Table 4. lowest p-value of GO from randomly chosen 25-RNC on varying δ

δ	1.1	1.3	1.5	1.7	1.8	1.9	2.1	2.3	2.5	2.7
p-value	4.9e-25	1.7e-44	1.3e-76	4.3e-117	2.2e-110	1.2e-92	1.8e-99	2.5e-98	1.8e-101	1.4e-101

Table 5. lowest p-value of GO from randomly chosen 20-RNC on varying *qnum*

qnum	10	50	100	200	500	1000
p-value	1.4e-69	5.7e-83	1.1e-125	1.1e-125	1.1e-125	6.5e-87

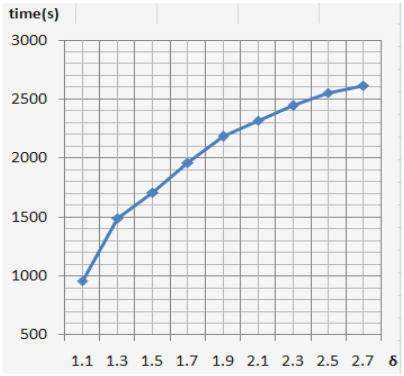


Figure 4. Time complexity on varying δ

value of GO from randomly chosen 25-RNC does not decrease substantially as δ increases as in Table 4.

Thus we can say that our algorithm is robust to the noise. Also we can see that allowing high level of δ is not necessary and 1.7 is sufficient as δ value. Secondly we measured the p-values while increasing *qnum* p-value does not decrease further, which means that *qnum* doesn't have to be bigger than 100. We recommend that *qnum* < 200 if the number of samples of microarray test dataset is less than 170.

5. CONCLUSION

RN-Clustering is robust to experimental noise by unique ranging, tree forming and queuing algorithm. These also guarantee the diversity of the results. RN-Clusters are proven to have significant level of functional association by GO validation.

The rapid increase in large-scale gene expression data provides us for tremendous chances to integrate many microarray datasets and identify a set of biclusters which are functional modules. For future works, we'll extend and apply RN-Clustering to integrated microarray datasets, and identify genetic regulation of specific biological pathways under a variety of conditions

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