

PROCEEDINGS

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# Robust PCA based method for discovering differentially expressed genes

Jin-Xing Liu<sup>1,2,4</sup>, Yu-Tian Wang<sup>2</sup>, Chun-Hou Zheng<sup>3</sup>, Wen Sha<sup>3</sup>, Jian-Xun Mi<sup>1,4</sup>, Yong Xu<sup>1,4\*</sup>

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## Abstract

How to identify a set of genes that are relevant to a key biological process is an important issue in current molecular biology. In this paper, we propose a novel method to discover differentially expressed genes based on robust principal component analysis (RPCA). In our method, we treat the differentially and non-differentially expressed genes as perturbation signals  $S$  and low-rank matrix  $A$ , respectively. Perturbation signals  $S$  can be recovered from the gene expression data by using RPCA. To discover the differentially expressed genes associated with special biological progresses or functions, the scheme is given as follows. Firstly, the matrix  $D$  of expression data is decomposed into two adding matrices  $A$  and  $S$  by using RPCA. Secondly, the differentially expressed genes are identified based on matrix  $S$ . Finally, the differentially expressed genes are evaluated by the tools based on Gene Ontology. A larger number of experiments on hypothetical and real gene expression data are also provided and the experimental results show that our method is efficient and effective.

## Background

One of the challenges in current molecular biology is how to find the genes associated with key cellular processes. Up to date, using microarray technology, these genes associated with a special biological process have been detected more comprehensively than ever before.

DNA microarray technology has enabled high-throughput genome-wide measurements of gene transcript levels [1,2], which is promising in providing insight into biological processes involved in gene regulation [3]. It allows researchers to measure the expression levels of thousands of genes simultaneously in a microarray experiment. Gene expression data usually contain thousands of genes (sometimes more than 10,000 genes), and yet only a small number of samples (usually less than 100 samples). Gene expression is believed to be regulated by a small number of factors (compared to the total number of genes), which act together to maintain the steady-state abundance of specific mRNAs. Some of these factors could represent the binding of one (or more) transcription

factor(s) (TFs) to the promoter region(s) of the gene [4]. So, it can be assumed that the genes associated with a biological process are influenced only by a small subset of TFs [5]. Although the expression levels of thousands of genes are measured simultaneously, only a small number of genes are relevant to a special biological process. Therefore, it is important how to find a set of genes that are relevant to a biological process.

Various methods have been proposed for identifying differentially expressed genes from gene expression data. These methods can be roughly divided into two categories: univariate feature selection (UFS) and multivariate feature selection (MFS). The commonest scheme of UFS is utilized as follows. First, a score for each gene is independently calculated. Then the genes with high scores were selected [6]. The main virtues of UFS are simple, interpretable and fast. However, UFS has some drawbacks. For example, if each gene is independently selected from gene expression data, a large part of the mutual information contained in the data will be lost.

To overcome the drawbacks of UFS, the methods of MFS use all the features simultaneously to select the genes. So far, many mathematical methods for MFS, such as principal component analysis (PCA), independent

\* Correspondence: laterfall2@yahoo.com.cn

<sup>1</sup>Bio-Computing Research Center, Shenzhen Graduate School, Harbin Institute of Technology, Shenzhen, China  
Full list of author information is available at the end of the article

component analysis (ICA), nonnegative matrix factorization (NMF), lasso logistic regression (LLR) and penalized matrix decomposition (PMD), have been devised to analyze gene expression data. For example, Lee *et al.* applied PCA to analyze gene expression data [7]. Liu *et al.* proposed a method of weighting principal components by singular values to select characteristic genes [8]. Probabilistic PCA was used to analyze gene expression data by Nyamundanda *et al.* [9]. Huang *et al.* used ICA to analyze gene expression data [10]. NMF was used to select the gene by Zheng *et al.* [11]. Liu *et al.* used LLR to select characteristic gene using gene expression data [12]. In [13], Witten *et al.* proposed penalized matrix decomposition (PMD), which was used to extract plant core genes by Liu *et al.* [14]. However, the brittleness of these methods with respect to grossly corrupted observations often puts its validity in jeopardy.

Recently, a new method for matrix recovery, namely robust PCA, has been introduced in the field of signal processing [15]. The problem of matrix recovery can be described as follows, assume that all the data points are stacked as column vectors of a matrix  $\mathbf{D}$ , and the matrix (approximately) have low rank:

$$\mathbf{D} = \mathbf{A}_0 + \mathbf{S}_0, \quad (1)$$

where  $\mathbf{A}_0$  has low-rank and  $\mathbf{S}_0$  is a small perturbation matrix. The robust PCA proposed by Candes *et al.* can recover a low-rank matrix  $\mathbf{A}_0$  from highly corrupted measurements  $\mathbf{D}$ [15]. Here, the entries in  $\mathbf{S}_0$  can have arbitrary large magnitude, and their support is assumed to be sparse but unknown.

Although the method has been successfully applied to model background from surveillance video and to remove shadows from face images [15], it's validity for gene expression data analysis is still need to be studied. The gene expression data all lie near some low-dimensional subspace [16], so it is natural to treat these genes data of non-differential expression as approximately low rank. As mentioned above, only a small number of genes are relevant to a biological process, so these genes with differential expression can be treated as sparse perturbation signals.

In this paper, based on robust PCA, a novel method is proposed for identifying differentially expressed genes. The differentially and non-differentially expressed genes are treated as perturbation signals  $\mathbf{S}$  and low-rank matrix  $\mathbf{A}$ . Firstly, the matrix  $\mathbf{D}$  of expression data is decomposed into two adding matrices  $\mathbf{A}$  and  $\mathbf{S}$  by using RPCA. Secondly, the differentially expressed genes are discovered according to the matrix  $\mathbf{S}$ . Finally, the differentially expressed genes are evaluated by the tools based on Gene Ontology. The main contributions of our work are as follows: firstly, it proposes, for the first time, the idea and method based on RPCA for discovery of differentially

expressed genes; secondly, it provides a larger number of experiments of gene selection.

## Methods

### The definition of Robust PCA (RPCA)

This subsection simply introduces robust PCA (RPCA) proposed by Candes *et al.* [15]. Let  $\|\mathbf{A}\|_* := \sum_i \sigma_i(\mathbf{A})$  denote the nuclear norm of the matrix  $\mathbf{A}$ , that is, the sum of its singular values, and let  $\|\mathbf{S}\|_1 := \sum_{ij} |S_{ij}|$  denote the  $L_1$ -norm of  $\mathbf{S}$ . Supposing that  $\mathbf{D}$  denotes the observation matrix given by Eq.(1), RPCA solves the following optimization problem:

$$\begin{aligned} & \text{minimize } \|\mathbf{A}\|_* + \lambda \|\mathbf{S}\|_1 \\ & \text{subject to } \mathbf{D} = \mathbf{A} + \mathbf{S} \end{aligned} \quad (2)$$

where  $\lambda$  is a positive regulation parameter. Due to the ability to exactly recover underlying low-rank structure in the data, even in the presence of large errors or outliers, this optimization is referred to as Robust Principal Component Analysis (RPCA).

For the RPCA problem Eq.(2), a Lagrange multiplier  $\mathbf{Y}$  is introduced to remove the equality constraint. According to [17], the augmented Lagrange multiplier method on the Lagrangian function can be applied:

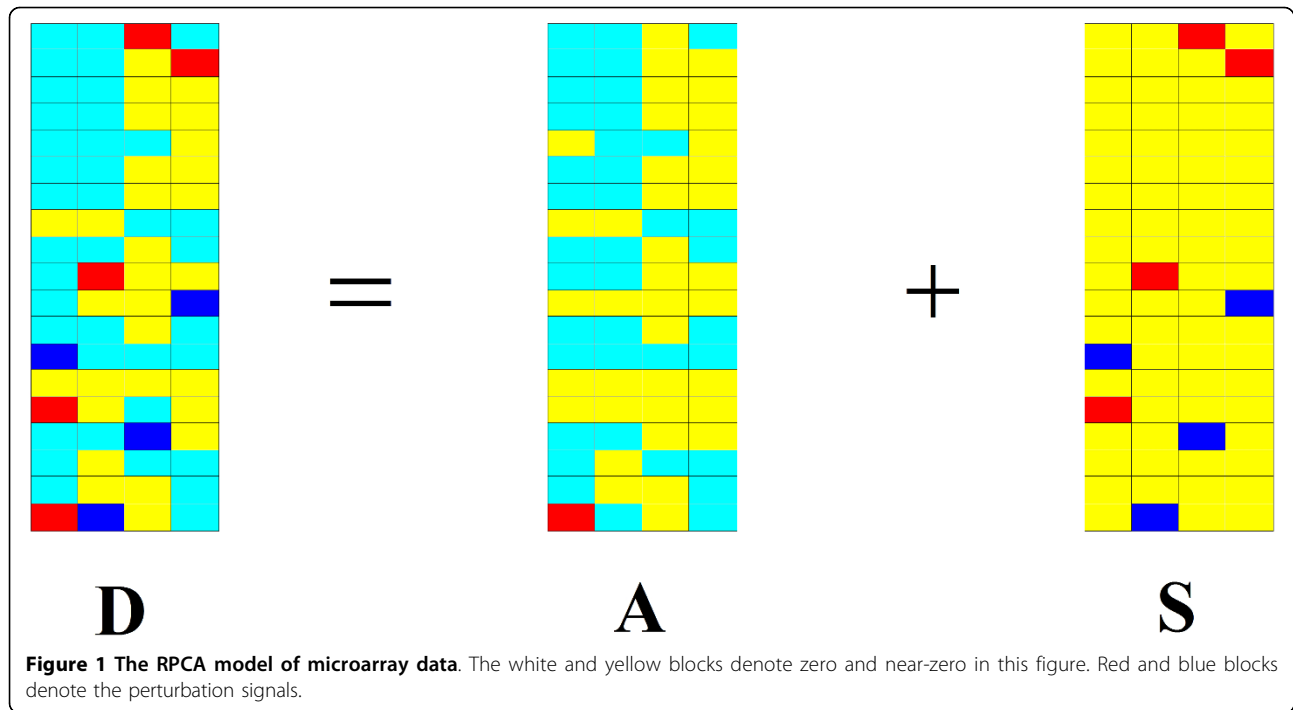
$$L(\mathbf{A}, \mathbf{S}, \mathbf{Y}, \mu) = \|\mathbf{A}\|_* + \lambda \|\mathbf{S}\|_1 + \langle \mathbf{Y}, \mathbf{D} - \mathbf{A} - \mathbf{S} \rangle + \frac{\mu}{2} \|\mathbf{D} - \mathbf{A} - \mathbf{S}\|_F^2, \quad (3)$$

where  $\mu$  is a positive scalar and  $\|\bullet\|_F^2$  denotes the Frobenius norm. Lin *et al.* gave a method for solving the RPCA problem, which is referred to as the inexact ALM (IALM) method [17]. The details of this algorithm can be seen in [17].

### The RPCA model of gene expression data

Considering the matrix  $\mathbf{D}$  of gene expression data with size  $m \times n$ , each row of  $\mathbf{D}$  represents the transcriptional responses of a gene in all the  $n$  samples, and each column of  $\mathbf{D}$  represents the expression levels of all the  $m$  genes in one sample. Without loss of generality,  $m \gg n$ , so it is a classical small-sample-size problem.

Our goal of using RPCA to model the microarray data is to identify these significant genes. As mentioned in Introduction, it is reasonable to view the significant genes as sparse signals, so the differential ones are viewed as the sparse perturbation signals  $\mathbf{S}$  and the non-differential ones as the low-rank matrix  $\mathbf{A}$ . Consequently, the genes of differential expression can be identified according to the perturbation signals  $\mathbf{S}$ . The RPCA model of microarray data is shown in Figure 1. The white and yellow blocks denote zero and near-zero in Figure 1. Red and blue blocks denote the perturbation signals. As shown in Figure 1, the matrix  $\mathbf{S}$  of differentially expressed genes (red or blue block) can be recovered from the matrix  $\mathbf{D}$  of gene expression data.



Suppose the matrix decomposition  $D = A + S$  has been done by using RPCA. By choosing the appropriate parameter  $\lambda$ , the sparse perturbation matrix  $S$  can be obtained, i.e., most of entries in  $S$  are zero or near-zero (as white and yellow blocks shown in Figure 1). The genes corresponding to non-zero entries can be considered as ones of differential expression.

#### Identification of differentially expressed genes

After observation matrix has been decomposed by using RPCA, sparse perturbation matrix  $S$  can be obtained. Therefore the differentially expressed genes can be identified according to sparse matrix  $S$ .

Denote the perturbation vector associated with  $i$ -th sample as:

$$S_i = [s_{1i}, s_{2i}, \dots, s_{mi}]^T, \quad i = 1, \dots, n. \quad (4)$$

Then the sparse matrix  $S$  can be expressed as follows:

$$S = [S_1, \dots, S_n]. \quad (5)$$

So the sparse matrix  $S$  can be denoted as:

$$S = \begin{bmatrix} s_{11} & s_{12} & \dots & s_{1n} \\ s_{21} & s_{22} & \dots & s_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ s_{m1} & s_{m2} & \dots & s_{mn} \end{bmatrix}. \quad (6)$$

The differentially expressed genes can be classified into two categories: up- and down-regulated ones [18],

which are reflected by the positive and negative entries in the sparse matrix  $S$ . Here, to discover the differentially expressed genes, only the absolute value of entries in  $S$  need to be considered. Then the following two steps are executed: firstly, the absolute values of entries in the sparse matrix  $S$  are found out; secondly, to get the evaluating vector  $\tilde{s}$ , the matrix is summed by rows. Mathematically, it can be expressed as follows:

$$\tilde{s} = \left[ \sum_{i=1}^n |s_{1i}| \dots \sum_{i=1}^n |s_{mi}| \right]^T. \quad (7)$$

Consequently, to obtain the new evaluating vector  $\hat{s}$ , which is sorted in descending order. Without loss of generality, suppose that the first  $c_1$  entries in  $\hat{s}$  are non-zero, that is,

$$\hat{s} = \left[ \hat{s}_1, \dots, \hat{s}_{c_1}, \underbrace{0, \dots, 0}_{m-c_1} \right]^T. \quad (8)$$

Generally, the larger the element in  $\hat{s}$  is, the more differential the gene is. So, the genes associated with only the first  $num$  ( $num \leq c_1$ ) entries in  $\hat{s}$  are picked out as differentially expressed ones.

#### Results and discussion

This section gives the experimental results. Firstly, in the first subsection, hypothetical data are exploited to clarify how to set the parameter  $\lambda$ . Secondly, in the second subsection, our method is compared with the



**Table 2 The recognition accuracy  $Acc_S$  with  $rank = 5$  and  $\mu = 0.05$**

$c$	$n$									
	10	20	30	40	50	60	70	80	90	100
0.1	1.00	0.30	0.96	0.02	1.00	0.64	1.00	0.07	1.00	0.71
0.2	1.00	1.00	1.00	0.92	1.00	1.00	1.00	0.99	1.00	1.00
0.3	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.4	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.5	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.6	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.7	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.8	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.9	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

**Experimental results on gene expression data of plants responding to abiotic stresses**

Along with other two state-of-the-art methods, namely PMD and SPCA, used as comparison, three methods, including RPCA, are used to discover the differentially expressed genes responding to abiotic stresses based on real gene expression data.

**Data source**

The raw data were downloaded from NASCArrays [http://affy.arabidopsis.info/] [21], which include two classes: roots and shoots in each stress. The reference numbers are: control, NASCArrays-137; cold stress, NASCArrays-138; osmotic stress, NASCArrays-139; salt stress, NASCArrays-140; drought stress, NASCArrays-141; UV-B light stress, NASCArrays-144; heat stress, NASCArrays-146. Table 6 lists the sample number of each stress type. There are 22810 genes in each sample. The data are adjusted for background of optical noise using the GC-RMA software by Wu et al. [22] and normalized using quartile normalization. The results of GC-RMA are gathered in a matrix for further processed.

**Table 3 The recognition accuracy  $Acc_S$  with  $rank = 5$  and  $\mu = 0.1$**

$c$	$n$									
	10	20	30	40	50	60	70	80	90	100
0.1	0.01	0.02	0.07	0.15	0.24	0.36	0.43	0.51	0.59	0.66
0.2	0.24	0.84	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.3	0.50	0.95	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.4	0.61	0.97	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.5	0.62	0.96	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.6	0.64	0.94	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.7	0.64	0.93	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.8	0.65	0.91	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.9	0.66	0.89	0.98	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1.0	0.67	0.86	0.97	0.99	1.00	1.00	1.00	1.00	1.00	1.00

**Table 4 The recognition accuracy  $Acc_S$  with  $rank = 10$  and  $\mu = 0.05$**

$c$	$n$									
	10	20	30	40	50	60	70	80	90	100
0.1	0.00	0.06	0.50	0.92	0.99	1.00	1.00	1.00	1.00	1.00
0.2	0.06	0.61	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.3	0.15	0.77	0.99	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.4	0.27	0.74	0.98	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.5	0.40	0.67	0.96	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.6	0.50	0.63	0.93	0.99	1.00	1.00	1.00	1.00	1.00	1.00
0.7	0.59	0.60	0.88	0.98	1.00	1.00	1.00	1.00	1.00	1.00
0.8	0.66	0.59	0.82	0.97	1.00	1.00	1.00	1.00	1.00	1.00
0.9	0.71	0.61	0.76	0.94	0.99	1.00	1.00	1.00	1.00	1.00
1.0	0.75	0.65	0.72	0.90	0.98	1.00	1.00	1.00	1.00	1.00

**Selection of the parameters**

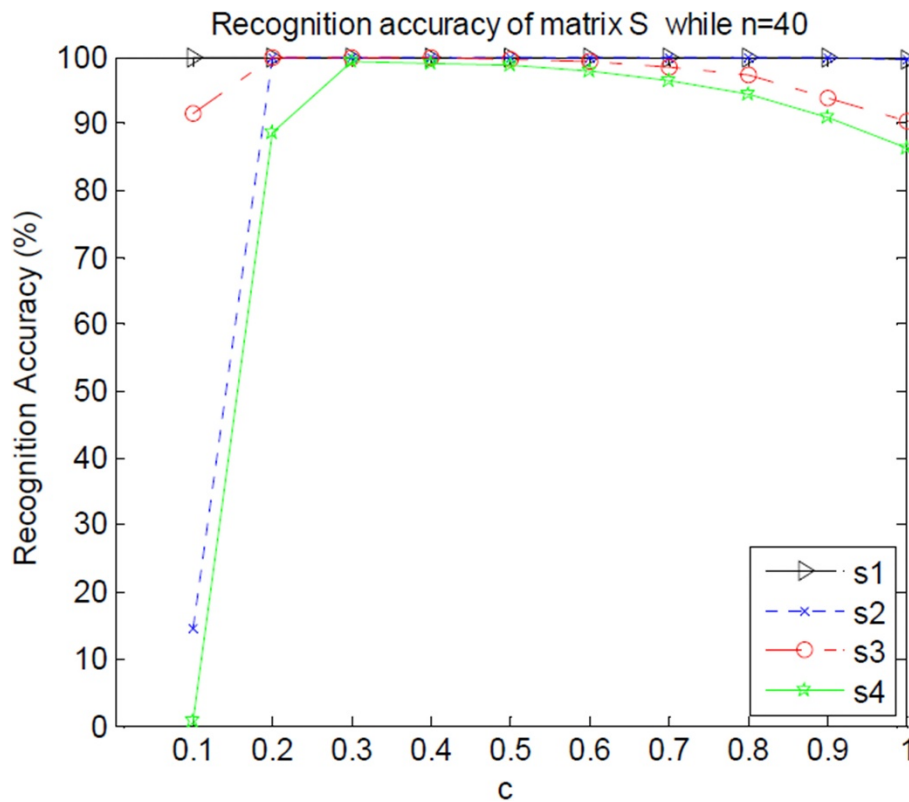
In this paper, for PMD method, the  $L_1$ -norm of  $\mathbf{u}$  is taken as the penalty function, i.e.  $\|\mathbf{u}\|_1 \leq \alpha_1$ . Because of  $1 \leq \alpha_1 \leq \sqrt{m}$ , let  $\alpha_1 = \alpha * \sqrt{m}$ , where  $1/\sqrt{m} \leq \alpha \leq 1$ . For simplicity, let  $p = 1$ , that is, only one factor is used. The results with  $L_1$ -norm ( $\|\mathbf{z}\|_1 = \sum_i |z_i|$ ) and  $L_0$ -norm ( $\|\mathbf{z}\|_0$ , i.e. the number of nonzero coefficients, or cardinality) penalty in SPCA are similar, which is also shown in [19], so  $L_0$ -norm penalty and the parameter  $\gamma$  are taken in SPCA. For a fair comparison, 500 genes are roughly selected by these methods via choosing appropriate parameters  $\alpha$  and  $\gamma$  of the two methods, PMD and SPCA, which are listed in Table 7 for different data set. As the first subsection of experiments mentioned, while  $c = 0.3$ , RPCA gives the optimization results. Then, according to methods section, the first 500 genes are selected.

**Gene ontology (GO) analysis**

Recently, many tools have been developed for the functional analysis of large lists of genes [23,24]. Most of them focus on the evaluation of Gene Ontology (GO)

**Table 5 The recognition accuracy  $Acc_S$  with  $rank = 10$  and  $\mu = 0.1$**

$c$	$n$									
	10	20	30	40	50	60	70	80	90	100
0.1	0.01	0.01	0.00	0.01	0.01	0.01	0.02	0.04	0.07	0.09
0.2	0.22	0.16	0.50	0.89	0.99	1.00	1.00	1.00	1.00	1.00
0.3	0.51	0.43	0.89	0.99	1.00	1.00	1.00	1.00	1.00	1.00
0.4	0.62	0.56	0.93	0.99	1.00	1.00	1.00	1.00	1.00	1.00
0.5	0.64	0.59	0.92	0.99	1.00	1.00	1.00	1.00	1.00	1.00
0.6	0.64	0.58	0.88	0.98	1.00	1.00	1.00	1.00	1.00	1.00
0.7	0.65	0.58	0.83	0.96	0.99	1.00	1.00	1.00	1.00	1.00
0.8	0.65	0.59	0.79	0.94	0.99	1.00	1.00	1.00	1.00	1.00
0.9	0.67	0.61	0.73	0.91	0.98	1.00	1.00	1.00	1.00	1.00
1.0	0.68	0.65	0.70	0.86	0.96	0.99	1.00	1.00	1.00	1.00



**Figure 2** The recognition accuracy of matrix *S* with different *c*. *s*1 denotes the recognition accuracy series with *rank* = 5 and  $\mu = 0.05$ . *s*2 denotes the recognition accuracy series with *rank* = 5 and  $\mu = 0.1$ . *s*3 denotes the recognition accuracy series with *rank* = 10 and  $\mu = 0.05$ . *s*4 denotes the recognition accuracy series with *rank* = 10 and  $\mu = 0.1$ .

annotations. GOTermFinder is a web-based tool that finds the significant GO terms shared among a list of genes, helping us discover what these genes may have in common. The analysis of GOTermFinder provides significant information for the biological interpretation of high-throughput experiments.

In this subsection, the genes identified by these methods, RPCA, PMD and SPCA, are sent to GOTermFinder [24], which is publicly available at <http://go.princeton.edu/cgi-bin/GOTermFinder>. Its threshold parameters are set as following: minimum number of gene products = 2 and maximum P-value = 0.01. Here, the key results are shown. Table 8 lists the terms of Response to abiotic stimulus (GO:0009628), whose background frequency in TAIR set is 1539/29556 (5.2%). Response to abiotic stimulus is the ancestor term of all the abiotic stresses.

**Table 6** The sample number of each stress type in the raw data

Stress Type	cold	drought	salt	UV-B	heat	osmotic	control
Number of Samples	6	7	6	7	8	6	8

In GOTermFinder, a p-value is calculated using the hyper-geometric distribution, its details can be seen in [24]. Sample frequency denotes the number of genes hit in the selected genes, such as 107/500 denotes 107 genes associated with the GO term in 500 ones selected by these methods. As listed in Table 8, all the three experimented methods, PMD, SPCA and RPCA, can extract the significant genes with very lower P-value, as well as very higher sample frequency. In Table 8, the superior results are in bold type. In the twelve items, there is only one of them (cold on root) that PMD is equal to our

**Table 7** The values of  $\alpha$  and  $\gamma$  on different data set

Stress	shoot	shoot	root	root
	PMD	SPCA	PMD	SPCA
	$\alpha$	$\gamma$	$\alpha$	$\gamma$
drought	0.0928	0.4224	0.0999	0.4065
salt	0.0924	0.4920	0.1057	0.5261
UV-B	0.1036	0.4505	0.0966	0.4329
cold	0.1026	0.4660	0.0983	0.4726
heat	0.0765	0.3770	0.0931	0.3710
osmotic	0.1049	0.5139	0.0946	0.5338

**Table 8 Response to abiotic stimulus (GO:0009628)**

Stress type		PMD		SPCA		RPCA	
		P-value	Sample frequency	P-value	Sample frequency	P-value	Sample frequency
drought	s	3.91E-34	107/500 (21.4%)	7.5E-21	87/500 (17.4%)	1.09E-45	<b>122/500 (24.4%)</b>
drought	r	1.78E-10	68/500 (13.6%)	4.14E-08	63/500 (12.6%)	1.03E-27	<b>98/500 (19.6%)</b>
salt	s	9.93E-39	113/500 (22.6%)	9.83E-33	105/500 (21.0%)	1.35E-55	<b>134/500 (26.8%)</b>
salt	r	1.36E-15	78/500 (15.6%)	6.18E-12	71/500 (14.2%)	1.65E-22	<b>90/500 (18.0%)</b>
UV-B	s	1.76E-13	74/500 (14.8%)	7.84E-23	90/500 (18.0%)	5.9E-41	<b>116/500 (23.2%)</b>
UV-B	r	5.3E-10	67/500 (13.4%)	8.00 E-4	52/500 (10.4%)	4.73E-29	<b>100/500 (20.0%)</b>
cold	s	5.82E-35	106/500 (21.6%)	1.17E-19	85/500 (17.0%)	2.13E-46	<b>123/500 (24.6%)</b>
cold	r	2.74E-23	<b>91/500 (18.2%)</b>	4.1E-19	84/500 (16.8%)	4.02E-23	<b>91/500 (18.2%)</b>
heat	s	1.44E-24	93/500 (18.6%)	4.64E-22	89/500 (17.8%)	7.46E-55	<b>133/500 (26.6%)</b>
heat	r	1.41E-15	78/500 (15.6%)	1.35E-08	64/500 (12.8%)	1.07E-34	<b>108/500 (21.6%)</b>
osmotic	s	6.55E-38	112/500 (22.4%)	2.02E-18	83/500 (16.6%)	6.83E-54	<b>132/500 (26.4%)</b>
osmotic	r	1.4E-14	76/500 (15.2%)	2.87E-17	81/500 (16.2%)	9.98E-35	<b>108/500 (21.6%)</b>

In this table, 's' denotes the shoot samples; 'r' denotes the root samples.

method. In other items, our method is superior to SPCA and PMD.

Figure 3 shows the sample frequency of response to abiotic stimulus (GO:0009628) given by the three methods. From Figure 3(a), RPCA method outperforms others in all the data sets of shoot samples with six different stresses. Figure 3(b) shows that only in cold-stress data set of root samples, PMD is equal to our method and they are superior to SPCA. In other data sets, our method is superior to the others.

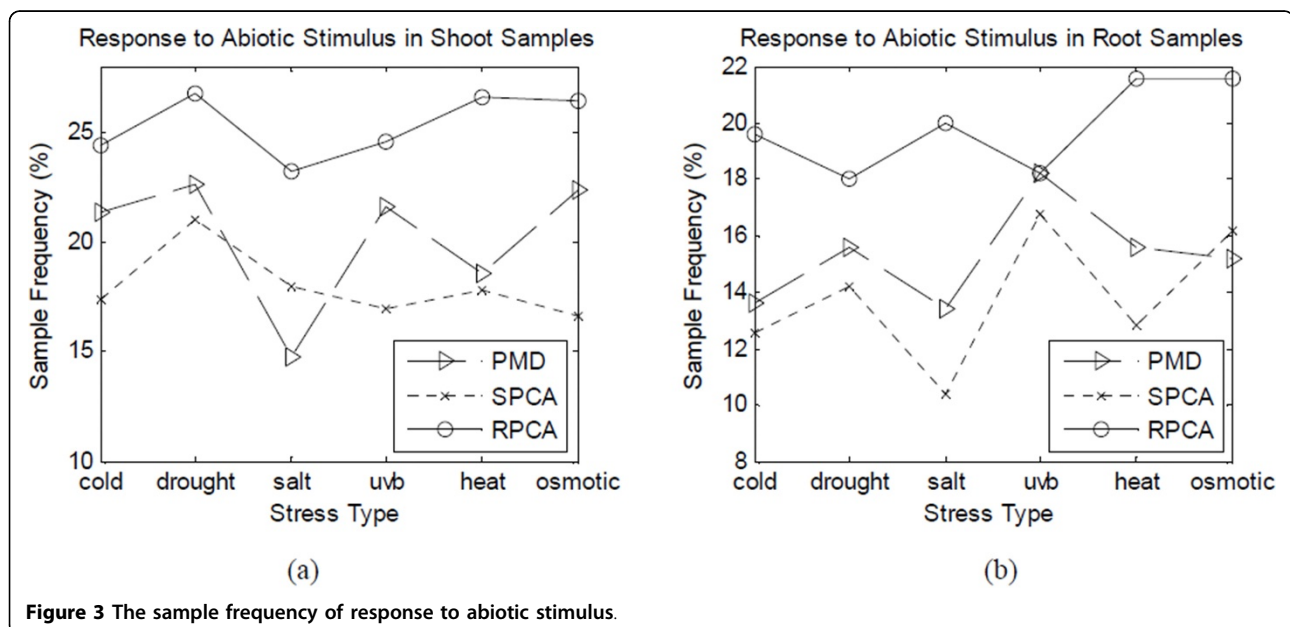
The characteristic terms are listed in Table 9, in which the superior results are in bold type. As listed in Table 9, PMD method outperforms SPCA and our method in three items, such as drought in shoot, salt in root and cold in

root, among the whole items. However, it shows that, on one of the twelve items (osmotic in shoot), our method has the same competitive result as PMD, while both methods are superior to SPCA. In other eight items, our method excels PMD and SPCA methods. In addition, on all the characteristic items, our method has superiority over SPCA.

From the results of experiments, it can be concluded that our method is efficient and effective.

**Experimental results on colon data**

The three methods, SPCA, PMD and RPCA, are compared on colon cancer data set [25]. Colon cancer is the fourth most common cancer for males and females and the second most frequent cause of death.



**Figure 3** The sample frequency of response to abiotic stimulus.

**Table 9 Characteristic terms selected from GO by algorithms**

Stress type	GO Terms	Background frequency	Sample frequency		
			PMD	SPCA	RPCA
drought	s GO:0009414 response to water deprivation	207/29887 (0.7%)	<b>47/500 (9.4%)</b>	23/500 (4.6%)	34/500 (6.8%)
drought	r GO:0009415 response to water deprivation	207/29887 (0.7%)	26/500 (5.2%)	24/500 (4.8%)	<b>30/500 (6.0%)</b>
salt	s GO:0009651 response to salt stress	395/29887 (1.3%)	41/500 (8.2%)	28/500 (5.6%)	<b>48/500 (9.8%)</b>
salt	r GO:0009651 response to salt stress	395/29887 (1.3%)	<b>33/500 (6.6%)</b>	22/500 (4.4%)	31/500 (6.2%)
UV-B	s GO:0009416Response to light stimulus	557/29887 (1.9%)	23/500 (4.6%)	30/500 (6.0%)	<b>42/500 (8.4%)</b>
UV-B	r GO:0009416Response to light stimulus	557/29887 (1.9%)	24/500 (4.8%)	none	<b>36/500 (7.2%)</b>
cold	s GO:0009409 response to cold	276/29887 (0.9%)	44/500 (8.8%)	34/500 (6.8%)	<b>58/500 (11.6%)</b>
cold	r GO:0009410 response to cold	276/29887 (0.9%)	<b>43/500 (8.6%)</b>	33/500 (6.6%)	38/500 (7.6%)
heat	s GO:0009408 response to heat	140/29887 (0.5%)	45/500 (9.0%)	30/500 (6.0%)	<b>47/500 (9.4%)</b>
heat	r GO:0009409 response to heat	140/29887 (0.5%)	43/500 (8.6%)	28/500 (5.6%)	<b>48/500 (9.6%)</b>
osmotic	s GO:0006970 response to osmotic stress	474/29887 (1.6%)	<b>55/500 (11.0%)</b>	29/500 (5.8%)	<b>55/500 (11.0%)</b>
osmotic	r GO:0006970 response to osmotic stress	474/29887 (1.6%)	39/500 (7.8%)	27/500 (5.4%)	<b>41/500 (8.2%)</b>

In this table, 's' denotes the shoot samples; 'r' denotes the root samples; 'none' denotes that the algorithm cannot give the GO terms.

#### Data source

The raw data were downloaded from <http://genomics-pubs.princeton.edu/oncology/affydata/I2000.html>, which include gene expression levels for 2000 gene and contain 40 tumor and 22 normal tissue samples.

#### Selection of the parameters

In this subsection, for PMD method, the  $L_1$ -norm of  $\mathbf{u}$  is taken as the penalty function, i.e.  $\|\mathbf{u}\|_1 \leq \alpha_1$ . Let  $\alpha_1 = \alpha * \sqrt{m}$ , where  $1/\sqrt{m} \leq \alpha \leq 1$ . For SPCA method, let  $p = 1$ , that is, only one factor is used.  $L_0$ -norm penalty and the parameter  $\gamma$  are taken in SPCA. For a fair comparison, 100 genes are roughly selected by these methods via choosing appropriate parameters. PMD and SPCA use the parameters  $\alpha = 0.2351$  and  $\gamma = 0.4306$  on colon data set, respectively. As the first subsection of experiments mentioned, while  $c = 0.3$ , RPCA gives the optimization results. Then, according to Methods section, the first 100 genes are selected using our method.

#### Gene ontology (GO) analysis

The genes identified by these methods, RPCA, PMD and SPCA, are evaluated by using AmiGO [26]. Its threshold parameters are set as following: minimum number of gene

products = 2 and maximum P-value = 0.1. A number of lines of evidence suggest that immune, stimulus and tumor have affinity, so Table 10 lists the key results: the terms of Response to stimulus (GO:0050896) and Immune system process (GO:0002376). As listed in Table 10, RPCA outperforms its competitive methods with higher sample frequency.

#### Function analysis

Table 11 lists the top 30 genes selected by using RPCA. To further study the biology functions of the selected genes, we also make the network analysis of the top 100 genes selected by our algorithm using the GeneMANIA tool [27] on the Web site <http://genemania.org/>. The result is listed in Table 12. From the table it can be seen that there are 215 genes of this chip participating in the cytokine-mediated signalling pathway, in which there are 21 genes discovered by our method. This pathway has the lowest p-value. It is considered as the most probable pathway with these top 100 genes. Recent findings also indicate that cytokine receptors can regulate immune cell functions by transcription-independent mechanisms [28]. Some other pathways with the most significance are also listed in Table 12.

**Table 10 Characteristic terms selected from GO on colon data**

GO Term	Response to stimulus	Immune system process
Accession No.	GO:0050896	GO:0002376
Background frequency	32294/155706 (20.7%)	7011/155706 (4.5%)
P-value(RPCA)	1.76E-10	5.74E-09
Sample frequency (RPCA)	38/57 (66.7%)	19/57 (33.3%)
P-value(SPCA)	8.71E-06	2.95E-04
Sample frequency (SPCA)	32/57 (56.1%)	14/57 (24.6%)
P-value(PMD)	7.93E-04	8.27E-01
Sample frequency (PMD)	27/51 (52.9%)	9/51 (17.6%)



**Table 11 The top 30 genes of colon data selected by RPCA**

Gene No.	Sequence	Gene Name
M27190	gene	Homo sapiens secretory pancreatic stone protein (PSP-S) mRNA, complete cds.
R89823	3' UTR	INORGANIC PYROPHOSPHATASE (Bos taurus)
M87789	gene	IG GAMMA-1 CHAIN C REGION (HUMAN).
T48904	3' UTR	HEAT SHOCK 27 KD PROTEIN (HUMAN).
M26383	gene	Human monocyte-derived neutrophil-activating protein (MONAP) mRNA, complete cds.
J00231	gene	Human Ig gamma3 heavy chain disease OMM protein mRNA.
X02761	gene	Human mRNA for fibronectin (FN precursor).
R80612	3' UTR	PHOSPHOLIPASE A2, MEMBRANE ASSOCIATED PRECURSOR (HUMAN).
M31994	gene	Human cytosolic aldehyde dehydrogenase (ALDH1) gene, exon 13.
T47377	3' UTR	S-100P PROTEIN (HUMAN).
X02492	gene	INTERFERON-INDUCED PROTEIN 6-16 PRECURSOR (HUMAN); contains L1 repetitive element.
M94132	gene	Human mucin 2 (MUC2) mRNA sequence.
X67325	gene	H.sapiens p27 mRNA.
D28137	gene	Human mRNA for BST-2, complete cds.
L05144	gene	PHOSPHOENOLPYRUVATE CARBOXYKINASE, CYTOSOLIC (HUMAN); contains Alu repetitive element; contains element PTR5 repetitive element.
X02874	gene	Human mRNA for (2'-5') oligo A synthetase E (1,6 kb RNA).
T55117	3' UTR	ALPHA-1-ANTITRYPSIN PRECURSOR (HUMAN).
M19045	gene	Human lysozyme mRNA, complete cds.
Y00711	gene	L-LACTATE DEHYDROGENASE H CHAIN (HUMAN);
X60489	gene	Human mRNA for elongation factor-1-beta.
T57780	3' UTR	IG LAMBDA CHAIN C REGIONS (HUMAN).
T60778	3' UTR	MATRIX GLA-PROTEIN PRECURSOR (Rattus norvegicus).
H58397	3' UTR	TRANS-1, 2-DIHYDROBENZENE-1, 2-DIOL DEHYDROGENASE (HUMAN).
L08044	gene	Human intestinal trefoil factor mRNA, complete cds.
M18216	gene	Human nonspecific cross reacting antigen mRNA, complete cds.
K03474	gene	Human Mullerian inhibiting substance gene, complete cds.
L33930	gene	Homo sapiens CD24 signal transducer mRNA, complete cds and 3' region.
T48014	3' UTR	HEMOGLOBIN ALPHA CHAIN (HUMAN).
H73908	3' UTR	METALLOTHIONEIN-IA (Bos taurus)
R70030	3' UTR	IG MU CHAIN C REGION (HUMAN).

## Conclusion

In this paper, a novel RPCA-based method of discovering differentially expressed genes was proposed. It combined RPCA and sparsity of gene differential expression to provide an efficient and effective approach for gene

identification. Our method mainly included the following two steps: firstly, the matrix *S* of differential expression was discovered from gene expression data matrix by using robust PCA; secondly, the differentially expressed genes were discovered according to matrix *S*.

**Table 12 Pathway analysis of the top 100 genes selected by RPCA on colon data**

rank	Go annotation	Q-value	Genes in network	Genes in genome
1	cytokine-mediated signalling pathway	2.27E-20	21	215
2	cellular response to cytokine stimulus	1.70E-19	21	244
3	response to cytokine stimulus	2.62E-18	21	283
4	type I interferon-mediated signalling pathway	1.61E-17	14	71
5	cellular response to type I interferon	1.61E-17	14	71
6	response to type I interferon	1.67E-17	14	72
7	interferon-gamma-mediated signalling pathway	2.60E-08	9	77
8	cellular response to interferon-gamma	3.64E-08	9	81
9	response to interferon-gamma	1.04E-07	9	92
10	response to other organism	3.69E-05	10	243

The experimental results on real gene data showed that our method outperformed the other state-of-the-art methods. In future, we will focus on the biological meaning of the differentially expressed genes.

#### Competing interests

The authors declare that they have no competing interests.

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#### Author details

<sup>1</sup>Bio-Computing Research Center, Shenzhen Graduate School, Harbin Institute of Technology, Shenzhen, China. <sup>2</sup>College of Information and Communication Technology, Qufu Normal University, Rizhao, China. <sup>3</sup>College of Electrical Engineering and Automation, Anhui University, Hefei, China. <sup>4</sup>Key Laboratory of Network Oriented Intelligent Computation, Shenzhen Graduate School, Harbin Institute of Technology, Shenzhen, China.

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