METHOD AND APPARATUS FOR IDENTIFYING COMPONENTS OF A SYSTEM WITH A RESPONSE CHARACTERISTIC

TECHNICAL FIELD OF THE INVENTION

The invention relates to a method and apparatus for identifying components of a system from data generated from the system, which components are capable of exhibiting a response pattern associated with a test condition and, particularly, but no exclusively, the present invention relates to a method and apparatus for identifying components of a biological system from data generated from the system, which components are capable of exhibiting a response pattern associated with a test condition.

BACKGROUND OF THE INVENTION

There are any number of "systems" in existence for which measurement of components of the system may provide a basis by which to analyse the system. Examples of systems include financial systems (such as stock markets, credit systems for individuals, groups, organisations, loan histories), geological systems, chemical systems, biological systems, and many more. Many of these systems comprise a substantial number of components which generate substantial amounts of data.

For example, recent advances in the biological sciences have resulted in the development of methods for large scale analysis of biological systems. An example of one such method is use of biotechnology arrays. These arrays are generally ordered high density grids of known biological samples (e.g. DNA, protein, carbohydrate) which may be screened or probed with test samples to obtain information about the relative quantities of individual components in the test sample. Use of biotechnology arrays

thus provides potential for analysis of biological and/or chemical systems.

An example of one type of biotechnology array is DNA microarrays for the analysis of gene expression. A DNA microarray consists of DNA sequences deposited in an ordered array onto a solid support base e.g. a glass slide. As many as 30,000 or more gene sequences may be deposited onto a single microarray chip. The arrays are hybridised with labelled RNA extracted from cells or tissue of interest, or cDNA synthesised from the extracted RNA, to determine the relative amounts of the RNA expression for each gene in the cell or tissue. The technique therefore provides a method of determining the relative expression levels of many genes in a particular cell or tissue. The method also has the potential to allow for the identification of genes that are expressed in a particular way, or in other words, have a particular response pattern in different cell types, or in the same cell type under different treatment or test conditions.

The ability to identify such genes would be useful, for example, in establishing diagnostic tests to distinguish between different cell types, to determine optimum conditions for expression of desired genes, or in assessing efficacy of drugs for targeting expression of particular genes.

A significant problem with the analysis of data generated from systems such as biotechnology arrays, however, is that response patterns in the data are often difficult to identify due to one or more of the following:

(a) the difficulty in manipulating large amounts of data generated by these types of methods or experiments;

(b) the inherent variation in the data;

(c) errors in the method which results in missing data (for example, areas on a biotechnology array from which data is missing).

The inventors have developed a method for analysis of data generated from systems which preferably permits identification of components of the system which exhibit a response pattern under a test condition.

DESCRIPTION OF THE INVENTION

In a first aspect, the invention provides a method for identifying components of a system from data generated from the system, which components exhibit a response pattern associated with a test condition applied to the system, comprising the steps of:

(a) specifying design factors to specify the type of response pattern for the test condition;

(b) identifying a linear combination of components from the input data which correlate with the response pattern.

Preferably, the method includes the step of defining a matrix of design factors.

The inventors have developed a method whereby linear combinations of components from a system can be computed from large amounts of data whereby the linear combination of components fits or correlates with a specified response pattern. Thus, using this method, specific patterns in the data can be searched for and components exhibiting this pattern identified. This facilitates rapid screening of the data from a system for significant components.

The linear combination of components is preferably of the form :

$$y = a_1X_1+a_2X_2+a_3X_3\ldots\ldots a_nX_n$$

Wherein y is the linear combination a_1-a_n are component weights and X_1-X_n are data values generated from the method applied to the system for components of the system.

Preferably, a linear combination of components is chosen such that a linear regression of the linear combination of components on the design factors has as much predictive power as possible. The component weights are assessed in a manner such that the values of the component weights for components which do not correlate with the design factors are eliminated from the linear combination.

The method of the present invention has the advantage that it requires usage of less computer memory than prior art methods. Accordingly, the method of the present invention can preferably be performed rapidly on computers such as, for example, laptop machines. By using less memory, the method of the present invention also allows the method to be performed more quickly than prior art methods for analysis of, for example, biological data.

The method of the present invention is suitable for use in the analysis of any system in which components which exhibit a response pattern are sought. Suitable systems include, for example, chemical systems, biological systems, geological systems, process monitoring systems and financial systems including, for example, credit systems, insurance systems, marketing systems or company record systems.

The method of the present invention is particularly suitable for use in the analysis of results obtained from methods applied to biological systems.

The data from the system is preferably generated from methods applied to the system. For example, the data may be a measure of a quantity of the components of the system, the presence of components in a system, or any other quantifiable feature of the components of a system. The data may be generated using any methods for measuring the components of a system. The data may be generated from, for example, biotechnology array analysis such as DNA array analysis, DNA microarray analysis (see for example, Schena et al., 1995, Science 270: 467-470; Lockhart et al. 1996, Nature Biotechnology 14: 1649; US Pat No. 5,569,588), RNA array analysis, RNA microarray analysis, DNA microchip analysis, RNA microchip analysis, protein microchip analysis, carbohydrate analysis, antibody array analysis, or analysis such as DNA electrophoresis, RNA electrophoresis, one dimensional or two dimensional protein electrophoresis, proteomics.

The components of the method of the present invention are the components of the system that are being measured. The components may be any measurable component of the system. The components may be, for example, genes, proteins, antibodies, carbohydrates. The components may be measured using methods for detecting the amount of, for example, genes or portions thereof, DNA sequences such as oligonucleotides or cDNA, RNA sequences, peptides, proteins, carbohydrate molecules or any other molecules that form part of the biological system. For example, in a DNA microarray, the component may be a gene or gene fragment. In an antibody array, the component may be a monoclonal antibody, polyclonal antibody, Fab fragment, or any other molecule that contains an antigen binding site of an antibody molecule.

It will be appreciated by those skilled in the art that the components need not be known, but merely identifiable in a manner to permit a correlation to be made between a

linear combination of the components and the design matrix. For example, each components may have a unique identifier such as an arbitrarily selected number or name.

The response pattern specified by the design factors may be any desired pattern. In one embodiment, the response pattern specified by the design factors is derived from known data. Thus, a response pattern derived from known data will identify response patterns that are significantly similar to a known response pattern. For example, a matrix of design factors may be provided for gene expression that correlates with a known gene expression pattern. For example, a particular expression pattern of a particular yeast gene over a particular growth period.

In another embodiment, the response pattern specified by the design factors is derived from the input array data. In this case, a response pattern derived from the input array data will group components of the array which exhibit significantly similar response patterns.

In yet another embodiment, the response pattern specified by the design factors is selected to identify any arbitrary response pattern.

The test conditions of the method of the invention may be any test conditions applied to a system. For example, in the case of a biological system, the test condition may be the growth conditions (such as temperature, time, growth medium, exposure to one or more test compounds) applied to an organism prior to measurement of the components of the system, the phenotype(such as a tumour cell, benign cell, advanced tumour cell, early tumour cell, normal cell, mutant cell, cell from a particular tissue or location)of an organism prior to measurement of the components of the system.

As discussed above, to identify a linear combination of components from input data, let $y^T = a^T X$ whereby y is a linear combination in which X is an input data matrix of data, preferably array data, having n rows of components and k columns of test conditions, and a is a matrix of values or weights to be applied to the input data. The significance of regression co-efficients of y on a matrix of design factors T may be determined by the ratio:

$$\lambda = \frac{\left(y^T P y\right)/r}{y^T (I-P) y/(n-r)} \qquad 1$$

Wherein

$P=T(T^TT)^{-1}T^T$; and

T is a kxr design matrix;

whereby values of a are selected to maximise λ.

Substituting $a^T X$ for y in equation 1 and ignoring the constant divisors provides the following equation:

$$\lambda = \frac{a^T X P X^T a}{a^T X (I-P) X^T a} \qquad 2$$

Thus, a linear combination of components $\underset{\sim}{a}$ may be computed by finding the maximum value of λ in equation 2. However, there are linear combinations ($\underset{\sim}{a}$) for which the denominator of equation 2 is zero and therefore λ is infinite. Thus, in one embodiment, the present invention provides algorithms for determining a whereby $a^T X(I-P)X^T a$ is not zero.

In one embodiment, the linear combination is computed by solving the generalised eigenvalue problem of:

$$\left(XPX^T - \lambda X(I-P)X^T\right)\underset{\sim}{a} = 0 \qquad 3$$

for λ and $\underset{\sim}{a}$

wherein X is a data matrix having n rows of components and k columns of test conditions and

$P = T(T^TT)^{-1}T^T$ wherein T is a matrix of k rows of design factors and r columns.

Equation 3 may be solved by the following algorithm:

Let $B = XPX^T$ and $W = X(I-P)X^T$

Then to maximise the ratio (equation 2) in the case that W is non-singular we would solve

$$(B - \lambda W)\underset{\sim}{a} = 0 \qquad 4$$

One approach for doing this is to rewrite equation 4 as

$$\left(W^{-\frac{1}{2}}BW^{-\frac{1}{2}} - \lambda I\right)W^{\frac{1}{2}}a = 0 \qquad 5$$

and solve this eigen equation.

If $W^{-\frac{1}{2}}$ in equation 5 is replaced in the singular case by

$$W^{-\frac{1}{2}} = U\begin{bmatrix}\Delta_1^{-\frac{1}{2}} & 0\\ 0 & 0\end{bmatrix}U^T \qquad 6$$

where Δ_1 is the diagonal matrix of 'non zero' eigen values of W it is easy to see that equation 5 becomes

$$\left(\begin{bmatrix} \Delta_1^{-\frac{1}{2}} U_1^T B U_1 \Delta_1^{-\frac{1}{2}} & 0 \\ 0 & 0 \end{bmatrix} - \lambda I\right)\begin{bmatrix} \Delta_1^{-\frac{1}{2}} U_1^T \underset{\sim}{a} \\ 0 \end{bmatrix} = 0 \qquad 7$$

where $U = [U_1 U_2]$ is partitioned conformable with Δ_1. Maximising equation 2 subject to $a = U_1 \underset{\sim}{\alpha}$ (i.e a is constrained to be in the range space of W) gives rise to the eigen equation defined by the top left hand block of the lefthand side of equation 7.

Equation 4 may be solved directly without requiring calculation of XPX^T or $X(I-P)X^T$ using the generalised singular value decomposition, see Golub and Van Loan (1989), Matrix Computations, 2nd Ed. Johns Hopkins University Press, Baltimore.

Alternatively, $X(I-P)X^T$ in equation 3 may be replaced with $X(I-P)X^T + \sigma^2 I$. Thus, in another embodiment, the linear combination may be identified by solving the equation:

$$\left(XPX^T - \lambda X(I-P)X^T + \sigma^2 I\right)\underset{\sim}{a} = 0 \text{ for } \lambda \text{ and a} \qquad 8$$

wherein X is a data matrix having n rows of components and k columns of test conditions; and
$P = T(T^T T)^{-1} T^T$ wherein T is a matrix of k rows of design factors and r columns and a is a weight matrix for the linear combination $y^T = \underset{\sim}{a}^T X$.

In a preferred embodiment, the invention provides a method for identifying components of a system from data generated from the system, which exhibit a response pattern associated with a set of test conditions applied to the system, comprising the steps of:

(a) specifying design factors to specify the type of response patterns for the test conditions;

(b) formulating a model for the residuals of a regression of the input data on the design factors;

(c) estimating parameters for the model;

(d) computing a linear combination of components using the model and its estimated parameters.

Preferably, the method includes the step of defining a matrix of design factors.

Preferably, the system is a biological system.
Preferably, the data generated from a method applied to the system is generated from a biotechnology array.

The inventors have found that the denominator of equation 2 may be replaced with the quantity a^TVa wherein V is the covariance matrix of the residuals from the regression model. Thus in one embodiment, the linear combination may be computed by maximising the ratio:

$$\lambda = \frac{a^T XPX^T a}{a^T Va} \qquad 9$$

Equation 9 may be used to give the following optimal a :

$$a = \lambda^{-1/2} XPu \qquad 10$$

wherein a is a weight matrix for the linear combination $y = a^T X$,
$P = T(T^TT)^{-1}T^T$,
u is an eigenvector of $P(XV^{-1}X^T)P$ or equivalently a left singular vector of $V^{-1/2}XP$;
and X is an nxk data matrix from data generated from a method applied to the system, the data being from n components and k test conditions.

This approach has the advantage that the method of the invention does not require storage of matrices larger than

nxk. Thus, an advantage of the method of the invention is that it permits analysis of data obtained from large numbers of components or large amounts of components and test conditions.

In a preferred embodiment, the covariance matrix V is replaced by its maximum likelihood estimator. Maximum likelihood estimates are obtained from a model for the microarray data. In this preferred embodiment, the data are modelled by a normal distribution, which is completely specified by the mean and variance.

The model of the method of the present invention may comprise a mean model and a variance model. The mean model may be defined by the equation:

$$E\left\{X^T\right\} = TB^T \qquad 11$$

wherein *X* is an *nxk* matrix of data, preferably array data, having *n* rows of components and *k* columns of test conditions, *T* is a *kxr* matrix of design factors having *k* rows and *r* columns and *B* is an *nxr* matrix of regression parameters.

The variance model may be defined by the equation:

$$Var\left\{vec\left\{X^T\right\}\right\} = I_k \otimes V \qquad 12$$

where V is a covariance matrix:

$$V = \Lambda\Phi\Lambda^T + \sigma^2 I,\ \Lambda_{nxs}$$

with constraints

$$\Phi_{sxs} \text{ diagonal and } \Lambda^T\Lambda = I\ .$$

The variance model and mean model together determine the likelihood. From (11) and (12) we may write twice the negative log likelihood as:

$$L = k\log|V| + tr\left\{\left(X^t - TB^t\right)V^{-1}\left(X - BT^t\right)\right\} \qquad 13$$

The parameters to be estimated in the model include Λ, Φ, σ^2 and the regression coefficient B. In one embodiment, an estimate of regression coefficients B for the mean model is computed using standard least squares:

$$\hat{B} = X^T T\left(T^T T\right)^{-1}$$

Substituting into Equation 13 we obtain the likelihood of V conditional on $B = \hat{B}$:

$$L = L(\hat{B}) = k\log|V| + tr\left\{V^{-1}RR^T\right\}$$
$$\text{where } R = X - \hat{B}T^T$$

In one embodiment, the parameters for the covariance matrix are estimated by computing the maximum likelihood estimates (MLE) for the covariance matrix, conditional on the regression parameters. The covariance matrix of the variance model may be defined by the equation:

$$V = \Lambda\Phi\Lambda^T + \sigma^2 I \qquad 14$$

To find the maximum likelihood estimate (MLE) of the parameters of V, we proceed as follows:

From $V = \Lambda\Phi\Lambda^T + \sigma^2 I$ we get

$$V = \left[\Lambda\Lambda^*\right]\begin{bmatrix}\Phi+\sigma^2 I_s & 0\\ 0 & \sigma^2 I_{n-s}\end{bmatrix}\left[\Lambda\Lambda^*\right]^T \qquad 15$$

where Λ^* is an orthonormal completion of Λ. It may be shown that

$$\begin{aligned} V^{-1} &= \left[\Lambda\Lambda^*\right]\begin{bmatrix}\left(\Phi+\sigma^2 I_s\right)^{-1} & 0\\ 0 & \sigma^{-2} I_{n-s}\end{bmatrix}\left[\Lambda\Lambda^*\right]^T \\ &= \Lambda\left(\Phi+\sigma^2 I_s\right)^{-1}\Lambda+\sigma^{-2}\left(I-\Lambda\Lambda^T\right). \end{aligned} \qquad 16$$

Hence:

$$\begin{aligned} |V| &= \left|\Phi+\sigma^2 I_s\right|\left(\sigma^2\right)^{n-s} \\ &= \prod_{i=1}^{s}\left(\Phi_{ii}+\sigma^2\right)\left(\sigma^2\right)^{n-s} \end{aligned}$$

so

$$k\log|V| = k\left\{\sum_{i=1}^{s}\log\left(\Phi_{ii}+\sigma^2\right)+(n-s)\log\sigma^2\right\} \qquad 17$$

Further, we may write:

$$\begin{aligned} tr\left\{V^{-1}RR^T\right\} &= tr\left\{\left(\Phi+\sigma^2 I_s\right)^{-1}\Lambda^T RR^T\Lambda\right\} \\ &\quad +\sigma^{-2}tr\left\{RR^T-\Lambda^T RR^T\Lambda\right\} \end{aligned} \qquad 18$$

Combining equation 17 and equation 18, the log likelihood function for $\Lambda, \Phi \text{ and } \sigma^2$ conditional on B may be obtained. We proceed to maximise this as a function of Λ subject to the constraint $\Lambda^T\Lambda = I$. Forming the Lagrangian and

differentiating this with respect to Λ we obtain the equation $\partial L/\partial\Lambda = 0$ where

$$\frac{\partial L}{\partial \Lambda} = \frac{\partial}{\partial \Lambda} tr\left\{\left[\left(\Phi+\sigma^2 I_s\right)^{-1} - \sigma^{-2} I_s\right]\Lambda^T R R^T \Lambda\right\} + tr\left\{\mathbf{L}\left(\Lambda^T\Lambda - I\right)\right\} \qquad 19$$

and L is a lower triangular matrix of Lagrange multipliers. Evaluating this and incorporating the constraint gives

$$RR^T\Lambda D + \Lambda L^T = 0$$

with $$\Lambda^T\Lambda = I$$

The first equation can be written as

$$RR^T\Lambda + \Lambda L^T D^{-1} = 0 \qquad 20$$

where $D = \left(\Phi+\sigma^2 I_s\right)^{-1} - \sigma^{-2} I_s$. Note that D is invertible provided all $\Phi_{ii} > 0$.

In one embodiment, the maximum likelihood estimate of σ is computed from the equation:

$$\hat{\sigma}^2 = \frac{1}{k(n-s)}\left\{tr\left\{RR^T\right\} - \sum_{i=1}^{s}\delta_{ii}\right\} \qquad 21$$

wherein s is the number of latent factors in the variance model.

In one embodiment, the maximum likelihood estimate of Φ is computed from the equation:

$$\hat{\Phi}_{ii} + \hat{\sigma}^2 = \delta_{ii}/k \qquad 22$$

In one embodiment, δ is defined by the equation:

$$\delta_{ii} = \left(\Lambda_i^T RR^T \Lambda_i\right) \qquad 23$$

wherein δ_{ii} is the i^{th} eigenvalue of RR^T.

Equations $\hat{\sigma}^2 = \frac{1}{k(n-s)}\left\{tr\left\{RR^T\right\} - \sum_{i=1}^{s}\delta_{ii}\right\}$ (21), $\hat{\Phi}_{ii} + \hat{\sigma}^2 = \delta_{ii}/k$ (22), and $\delta_{ii} = \left(\Lambda_i^T RR^T \Lambda_i\right)$ (23) are derived as follows:

Premultiplying $RR^T \Lambda D + \Lambda L^T = 0$ by Λ^T and using $\Lambda^T \Lambda = I$ shows that L is symmetric and hence diagonal. It follows that the columns of Λ are eigenvectors of RR^T.

Similarly we obtain

$$\frac{\partial L}{\partial \Phi_{ii}} = \frac{k}{\left(\Phi_{ii} + \sigma^2\right)} - \frac{\delta_{ii}}{\left(\Phi_{ii} + \sigma^2\right)^2}$$

$$\frac{\partial L}{\partial \sigma^2} = \sum_{i=1}^{s}\frac{k}{\left(\Phi_{ii} + \sigma^2\right)} + \frac{k(n-s)}{\sigma^2} - \sum_{i=1}^{s}\frac{\delta_{ii}}{\left(\Phi_{ii} + \sigma^2\right)^2}$$

$$-\frac{1}{\left(\sigma^2\right)^2}\left\{tr\left\{RR^T\right\} - \sum_{i=1}^{s}\delta_{ii}\right\}$$

where $\delta_{ii} = \left(\Lambda_i^T RR^T \Lambda_i\right)$ is the i^{th} eigenvalue of RR^T.

It follows that

$$\hat{\Phi}_{ii} + \hat{\sigma}^2 = \delta_{ii}/k$$

$$\hat{\sigma}^2 = \frac{1}{k(n-s)}\left\{tr\left\{RR^T\right\} - \sum_{i=1}^{s}\delta_{ii}\right\}$$

The number of latent factors in the model for the covariance matrix may be estimated by performing likelihood ratio tests, cross validation tests or Bayesian procedures. In one embodiment, the number of factors in the variance model is determined by performing a series of likelihood ratio tests, for increasing numbers of factors. The number of factors is chosen such that the test for further increase in the number of factors is not statistically significant. The likelihood ratio test statistic is computed using the equation:

$$-2\log L = k\left\{\sum_{i=1}^{s}\log(\delta_{ii}/k)+(n-s)\log\left\{\sum_{s+1}^{t}\delta_{ii}\Big/\left(k(n-s)\right)\right\}\right\} + kn \qquad 24$$

and the number of parameters is $ns+s+1-s(s+1)/2$.

In a preferred embodiment, the number of factors, s, in the variance model is determined by performing a Bayesian method, preferably based on a method for selecting the number of principle components given in Minka T.P. 2000, Automatic choice of dimensionality for PCA, MIT Media Laboratory Perceptual Computing Section Technical Report No. 514 (Minka (2000)). We note that the problem of choosing basis functions in the factor analysis model i.e. the number of left singular vectors in an singular value decomposition (SVD) of the residual matrix to include can be thought of as the problem of selecting the number of right singular vectors or principal components. Writing λ_i for the eigenvalues of R^TR, in Minka(2000) the number of principal components is chosen to maximise

$$\begin{aligned}\log P(R\,|\,s) = \log P(u) - 0.5n\sum_{j=1}^{s}\log(\lambda_j) \\ -0.5n(k-s)\log(v)+0.5(m+s)\log(2\pi) \\ -0.5\log\det(A_z)-0.5s\log(n)\end{aligned}$$

where m=ks-s(s+1)/2,

$$\log P(u) = -s\log(2) + \sum_{i=1}^{s} \log(\Gamma((k-i+1)/2)) - 0.5(k-i+1)\log(\pi)$$

$$v = (\sum_{j=s+1}^{k} \lambda_j)/(k-s)$$

and

$$\log\det(A_z) = \sum_{i=1}^{s}\sum_{j=i+1}^{k} \log((\hat{\lambda}_j^{-1} - \hat{\lambda}_i^{-1})(\lambda_i - \lambda_j)n)$$

where

$$\hat{\lambda}_j = \begin{cases} \lambda_j, for\ j \le k \\ v, otherwise. \end{cases}$$

More reliable results are obtained using the Bayesian approach if it is used on a subset of the genes, chosen to show high correlation with the response pattern specified by the design factors.

The present invention also provides a means to determine the shape of the relationship between the linear combination of components and the response pattern specified by the design factors. The inner product of the linear combinations with the data matrix results in a loading for each array. These loadings may be plotted against the columns of the design factors to reveal the shape of the response.

The present invention also provides for testing the significance of the components of a linear combination, and/or the overall strength of the relationship between the linear combination and the design factors. In one embodiment, the method comprises the further steps of:

(a) determining the significance of each weight of the linear combination; and

(b) setting non-significant weights to zero.

In a preferred embodiment, the significance of the weights of the linear combination is determined by a permutation test comprising the steps of:

(a) randomising the data, preferably biotechnology array data, within each row;

(b) Computing the weights and eigenvalues from the randomised data;

(c) repeating steps (a) and (b) a plurality of times; and

(d) determining a distribution for the weights and eigenvalues computed from the randomised data;

(e) determining the position of weights and eigenvalues computed from non-randomised data, preferably biotechnology array data, relative to the distribution of the weights and eigenvalues computed from randomised data;

(f) estimating the significance of each weight computed from the non-randomised data.

In a preferred embodiment, the significance of the relationship between the linear combinations of components and the response pattern specified by the design factors may be determined in an analogous way. For each randomisation step (a) above, the loadings are formed as inner products of the linear combinations with the data matrix. The multiple correlation between these loadings and the response pattern specified by the design factors is calculated. The significance of the overall relationship is evaluated by determining the position of the multiple correlation coefficient from non-randomised data with the distribution of the multiple correlation coefficient calculated from randomised data.

The present invention also provides methods for estimating missing values from the data. In one embodiment, missing values are estimated using an EM algorithm. In a

preferred embodiment, the method comprises estimating missing data values of array data by:

(a) estimating initial values of B,Γ,Φ,σ^2 by replacing missing values with simple estimates and calculating maximum likelihood estimates assuming the data was complete;

(b) Computing $E\{X|o_1,...o_k\}, E\{RR^T|o_1,...o_k\}$ the expected values of the data array and the residual matrix under the model given the observed data (where o_i is defined below);

(c) Substitute quantities for (b) into likelihood equations assuming complete data to obtain new estimates of B,Γ,ϕ and σ^2;

(d) Repeat steps (b) to (d) until convergence.

In one embodiment, the EM algorithm is performed as follows:

From equations 18 and 20:

$$R = X - BT^T, V = \Lambda\Phi\Lambda^T + \sigma^2 I$$

For the *ith* column of R, R_i say, we can partition R_i as

$$R_i = \begin{bmatrix} o_i \\ u_i \end{bmatrix}, V = \begin{bmatrix} V_{oo} & V_{ou} \\ V_{uo} & V_{uu} \end{bmatrix}, V^{-1} = \begin{bmatrix} V^{oo} & V^{ou} \\ V^{ou} & V^{uu} \end{bmatrix} \quad (25)$$

where o_i denotes the observed residual component and u_i denotes the missing residual component. To do the E step of the EM algorithm we need to compute the expected values

$$\mathrm{E}\{R_i|o_i\} \text{ and } E\{R_i R_i^T|o_i\} \quad (36)$$

Note that we are also conditioning on a set of parameter values, B,Λ,Φ and σ^2, however for easy of presentation we do not represent this in the following.

It can be shown that

$$E\{u_i|o_i\} = V_{u0}(V_{00})^{-1} o_i$$
$$= -(V^{uu})^{-1} V^{uo} o_i \qquad 27$$
$$= Co_i \text{ (say)}$$

Hence

$$E\{R_i|o_i) = \begin{bmatrix} I \\ C \end{bmatrix} o_i$$

From the definition of R we obtain

$$E(X_i|o_i) = \begin{bmatrix} I \\ C \end{bmatrix} o_i + BT^T e_i \qquad 28$$

where e_i is a kx1 vector with zeros except in the ith position which is a one.

Now writing V^{uu} *for* $V^{u_i u_i}$ we have

Let

$$E\{R_i R_i^T|o_i\} = \begin{bmatrix} I & 0 \\ C & I \end{bmatrix} \begin{bmatrix} o_i o_i^T & 0 \\ 0 & (V^{uu})^{-1} \end{bmatrix} \begin{bmatrix} I & C^T \\ 0 & I \end{bmatrix}$$
$$= \begin{bmatrix} I \\ C \end{bmatrix} o_i o_i^T \begin{bmatrix} I & C^T \end{bmatrix} + \begin{bmatrix} 0 & 0 \\ 0 & (V^{uu})^{-1} \end{bmatrix} \qquad 29$$
$$= R_i^* R_i^{*T} + \begin{bmatrix} 0 \\ L_i \end{bmatrix} \begin{bmatrix} 0 & L_i^T \end{bmatrix}$$

Where $(V^{uu})^{-1} = L_i L_i^T$.

It follows that

$$E\left[RR^T \middle| o_1 \ldots\ldots o_k\right] = \sum_{i=1}^{k} R_i^* R_i^{*T} + \sum_{i=1}^{k} S_i S_i^T \qquad 30$$

where $S_i = P_i^T \begin{bmatrix} 0 \\ L_i \end{bmatrix}$ is nxm_i. Here m_i is the number of missing values in column i and P_i is a permutation matrix with the property that $P_i R_i = \begin{bmatrix} o_i \\ u_i \end{bmatrix}$.

Define

$$m = \sum_i m_i \quad \text{and}$$

$$\hat{\mathrm{R}} = \left[\mathrm{R}_1^* \ldots . \mathrm{R}_k^* \vdots S_1 \ldots . S_K\right], \; nx(k+m) \qquad 31$$

then

$$E\left\{RR^T \middle| o_1, \ldots o_k\right\} = \hat{R}\hat{R}^T$$

A similar expression also follows from writing

$$\sum_i \begin{bmatrix} 0 & 0 \\ 0 & \left(V^{u_i u_i}\right)^{-1} \end{bmatrix} = \begin{bmatrix} 0 & 0 \\ 0 & D \end{bmatrix} = \begin{bmatrix} 0 & 0 \\ 0 & LL^T \end{bmatrix} \qquad 32$$

This requires only 1 (larger) matrix factorisation and the dimension of D may be much less than m if common genes are missing (across columns of X).

The above expressions enable the computation of maximum likelihood estimates by using the SVD of R, thus saving on storage requirements.

From equations 35 and 36 it can be seen that the matrix inversion $\left(V^{uu}\right)^{-1}$ is required. This may be a large matrix if there are many missing values in a column of R. In such cases we note the following:

$$V^{uu} = \Lambda_u \left(\Phi_s + \sigma^2 I_s\right)^{-1} \Lambda_u^T + \sigma^{-2}\left(I - \Lambda_u \Lambda_u^T\right) \qquad 33$$

where Λ_u denotes an appropriate subset of rows of Λ $(\Lambda_u \text{ is } m\text{x}s)$.

V^{uu} can be rewritten as

$$\Lambda_u\left\{\left(\Phi_s+\sigma^2 I_s\right)^{-1}-\sigma^2 I_s\right\}\Lambda_u^T+\sigma^{-2}I \qquad 34$$

Hence using the formula

$$\left(A+BDB^T\right)^{-1}=A^{-1}-A^{-1}B\left(B^TA^{-1}B+D^{-1}\right)^{-1}B^TA^{-1} \qquad 35$$

it can be shown that

$$\left(V^{uu}\right)^{-1}=\sigma^2 I-\sigma^2\Lambda_u\left(\sigma^2\Lambda_u^T\Lambda_u+\left\{\left(\Phi_s+\sigma^2 I_s\right)^{-1}-\sigma^{-2}I_s\right\}^{-1}\right)^{-1}\Lambda_u^{\sigma^2} \qquad 36$$

Note that this only requires the inverse of an sxs matrix where s is the number of basis functions in the variance model and is independent of m.

The EM algorithm discussed above requires the factorisation of the matrices V^{uu} which may be reasonably large if there are substantial numbers of missing values. An alternative algorithm which does not require this is as follows:

Write

$$R_i=X_i-BT^Te_i \quad \text{and}$$
$$\mathrm{R_i}=\begin{bmatrix}o_i\\u_i\end{bmatrix} \quad \text{for } i=1,\ldots,k. \qquad 37$$

Then assuming normality, we can write the log likelihood of the data as:

$$L = \log L = \sum_{i=1}^{k} \log f\left(u_i | o_i\, \theta\right) + \log g\left(o_i | o_i\, \theta\right) \qquad 38$$

where f is the conditional normally density function of u_i given o_i and g is the marginal density function of o_i. The vector of parameters θ is B, Λ, ϕ and σ^2.

Now writing $L = L\left(u_1, u_2, .., u_k, \sigma\right)$, an iterative algorithm can be specified for maximising equation 45 as follows:

(a) Specify initial values θ_o

(b) For iteration $n \geq 0$ maximise L as a function of $u_1, ..., u_k$. From the form of 45 we can do this independently for each u_i and since $\log f\left(u_i | o_i, \theta_n\right)$ is a (conditional) normal distribution the maximum occurs at $\hat{u}_i^{(n)} = \mathrm{E}\left\{u_i | o_i, \theta_n\right\}$. This of course is a calculation done in the E step of the original E-M algorithm.

(c) With $u_i = \hat{u}_i^{(n)}$ for $i = 1, ..., k$ maximise 45 as a function of θ ignoring the dependence of u_i on θ (i.e treating the u_i as now fixed) to produce θ_{n+1}

(d) Go to 2 until some stopping criteria is satisfied.

The above algorithm preferably produces a sequence with the property that for $n \geq 0$

$$L\left(\underset{\sim}{u}^{(n+1)}, \theta_{n+1}\right) \geq L\left(\underset{\sim}{u}^{(n)}, \theta_n\right) \qquad 39$$

where $\underset{\sim}{u}^{(n)} = \left(u_1^{(n)}, ..., u_k^{(n)}\right)$.

Step (c) of the algorithm corresponds to ignoring the V^{uu} terms in the calculation of $E\{RR^T|\sigma_1,...,o_k\}$ of the EM algorithm, and then doing the M step of the EM algorithm. (Note that the estimation of B can be done independently of the other parameters in θ.)

We can completely remove the need to calculate $(V^{uu})^{-1}$ in step (b) of the above algorithm by noting that we can use a cyclic ascent algorithm to maximise $\log f(u_i|o_i,\theta)$ as follows:

Let the components of u_i be $(u_{ji}, j=1,...m_i)$

Maximising over u_{li} (say) with $u_{-li}=(u_{ji}, j\neq l)$ fixed, corresponds to computing $E\{u_{li}|u_{-li},o_i\theta\}$

To see this write:

$$\log f(u_i|o_i\theta)=\log f(u_{li}\,|\,u_{-li},o_i,\theta)+\log h(u_{-li}|o_i,\theta) \qquad 40$$

where h is a conditional normal density. Now note that the first term in equation 15 has a maximum at $E\{u_{li}|u_{-li},o_i,\theta\}$ and this can be computed purely from the elements of V^{-1} given earlier.

Iterating over $l=1...,m_i$ will produce the (unique) maximum of $\log f(u_i|o_i,\theta)$ namely $E\{u_i|o_i,\theta\}$.

This method requires only one matrix factorisation and therefore reduces storage requirements. In a preferred embodiment, the missing values are estimated at the same time that parameters for the model are estimated.

The identification method of the present invention may be implemented by appropriate computing systems which may include computer software and hardware.

In accordance with a second aspect of the present invention, there is provided a computer program, arranged, when run on a computing device, to control the computing device to identify linear combinations of components from input data which correlate with a response pattern defined by a matrix of design factors specifying types of response patterns for a set of test conditions in a system.

The computer program may implement any of the preferred algorithms and method steps of the first aspect of the present invention which are discussed above.

In accordance with a third aspect of the present invention, there is provided a computer readable medium providing a computer program in accordance with the second aspect of the present invention.

In accordance with a fourth aspect of the present invention, there is provided a computer program, which, when run on a computing device, is arranged to control the computing device, in a method of identifying components from a system which exhibit a pre-selected response pattern to test conditions applied to the system, and wherein a matrix of design factors specifying the response patterns for the test conditions is defined, to formulate a module for the residuals of a regression of the input array data on the design factors, to estimate parameters for the model and compute a linear combination of components using the model and the estimated parameters.

The computer program may be arranged to implement any of the preferred method and calculation steps discussed above in relation to the second aspect of the present invention.

In accordance with a fifth aspect of the present invention, there is provided a computer readable medium providing a computer program in accordance with the fourth aspect of the present invention.

In accordance with a sixth aspect of the present invention there is provided an apparatus for identifying components from a system which exhibit a response pattern(s) associated with test conditions applied to the system, and wherein a matrix of design factors to specify the type of response patterns for the set of tests and conditions is defined, the apparatus including a calculation device for identifying linear combinations of components from the input data which correlate with the response pattern.

In accordance with an seventh aspect of the present invention, there is provided an apparatus for identifying components from a system which exhibit a preselected response pattern to a set of test conditions applied to the system, wherein a matrix of design factors to specify the response pattern(s) for the test conditions is defined, the apparatus including a means for formulating a model for the residuals of a regression of the input array data on the design factors, means for estimating parameters for the model and means for computing a linear combination of components using the model and the estimated parameters.

A computing system including means for identifying components including means for implementing any of the preferred algorithms and method steps of the first aspect of the present invention which are discussed above.

Where aspects of the present invention are implemented by way of a computing device, it will be appreciated that any

appropriate computer hardware e.g. a PC or a mainframe or a networked computing infrastructure, may be used.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a graphical plot of a matrix of design factors of a preferred method of the invention (top) and gene expression patterns of the genes of yeast from microarray data that correlate to the response pattern specified by those design factors (bottom). The x-axis is the time of growth of the yeast at which gene expression was measured. The y-axis is the value design factor given for each time (top) or the level of gene expression (bottom).

Figure 2 shows a graphical plot of a matrix of design factors of a preferred method of the invention (top) and gene expression patterns of the genes of yeast from microarray data that correlate to the response pattern specified by the design factors (bottom). The x-axis is the time of growth of the yeast at which gene expression was measured. The y-axis is the value design factor given for each time (top) or the level of gene expression (bottom).

Figure 3 shows a graphical plot of a matrix of design factors of a preferred method of the invention (top) and gene expression patterns of the genes of yeast from microarray data that correlate to the response pattern specified by the design factors (bottom). The x-axis is the time of growth of the yeast at which gene expression was measured. The y-axis is the value design factor given for each time (top) or the level of gene expression (bottom).

Figure 4 shows a graphical plot of a matrix of design factors of a preferred method of the invention (top) and

gene expression patterns of the genes of GC B-like diffuse large B cell lymphoma and activated B-like diffuse large B cell lymphoma from microarray data that correlate to the response pattern specified by the design factors (bottom). The x-axis is the class of lymphoma. The y-axis is the value design factor given for each class (top) or the level of gene expression (bottom).

Figure 5 shows a graphical plot of a matrix of design factors of a preferred method of the invention (top) and gene expression patterns of the genes of yeast from the microarray data listed in table 1 that correlate to the response pattern specified by those design factors (bottom). The x-axis is the time of growth of the yeast at which gene expression was measured. The y-axis is the value design factor given for each time (top) or the level of gene expression (bottom).

Figure 6 shows a graphical plot of a matrix of design factors of a preferred method of the invention (top) and gene expression patterns of the genes of yeast from the microarray data listed in table 1 that correlate to the response pattern specified by the design factors (bottom). The x-axis is the time of growth of the yeast at which gene expression was measured. The y-axis is the value design factor given for each time (top) or the level of gene expression (bottom).

Figure 7 shows a graphical plot of a matrix of design factors of a preferred method of the invention (top) and gene expression patterns of the genes of yeast from the microarray data listed in table 1 that correlate to the response pattern specified by the design factors (bottom). The x-axis is the time of growth of the yeast at which gene expression was measured. The y-axis is the value design factor given for each time (top) or the level of gene expression (bottom).

Figure 8 shows a graphical plot of a matrix of design factors of a preferred method of the invention (top) and gene expression patterns of the genes of GC B-like diffuse large B cell lymphoma (GC) and activated B-like diffuse large B cell lymphoma (activate) from the microarray data listed in table 2 that correlate to the response pattern specified by the design factors (bottom). The x-axis is the class of lymphoma (GC or activated). The y-axis is the value design factor given for each class (top) or the level of gene expression (bottom).

EXAMPLES

EXAMPLE 1

The data set for this example is the results from a DNA microarray experiment and is reported in Spellman, P. and Sherlock, G., et al. (1998) Comprehensive identification of cell cycle-regulated genes of the yeast Saccharomyces cerevisiae by Microarray Hybridization. Mol. Biol. Cell 9(12):3273-3297.

The data set generated from the microarray experiments described in the above paper can be obtained from the following web site:

http://genome-www4.stnford.edu/MicroArray/SMD/publications.html

The array data consists of n=2467 genes and k=18 samples (times). The matrix of design facors T (design matrix)has r=6 columns defined by the terms $\cos(l\theta)$, $\sin(l\theta)$ for $l=1...3$ and $\theta = (7m\pi)/119$, $m=0,1,\ldots,17$.

This example illustrates how the method of the present invention can be used to discover sets of genes which exhibit periodic variation within the cell cycle. For this data set, the pattern of periodic variation is a by

product of the analysis given the choice of the matrix of design factors T. A search for a priori response pattern could also be specified by choosing r=1 and placing the appropriate pattern in the single column of the design matrix. For this data set we have six canonical vectors a. Note that $a=\lambda^{-1/2}XPu$ where u is the design factor and a denotes the scores. Two basis functions were used in the factor analysis model. Results for the first three canonicalvariates are given below. The design factor axis is time. Each component has a calculated p value which is highly significant. A list of genes forming a group with a similar pattern of variation over time is given below for the first three canonical vectors. The size of this group can be varied by choosing the significance level applied to the scores (the level here was set at 0.001). Group sizes will tend to be smaller for smaller significance levels.

The results for each canonical vector might be interpreted as implying a similar pattern of variation for each of the three groups but with a phase shift for each group. The low to low cycle period is of the order of 70 minutes which agrees with the results in the paper.

The genes identified are shown below. Results of the gene expression from these genes is shown in Figures 1, 2 and 3.

1. Canonical Variate1 (see Figure 1)

d is:0.9932 p Value is:0

Spellman Cell Cylcle Data

Gene	Score	P Value
YCL040W:	-0.6096	0
YPL092W:	-0.4394	0
YEL060C:	-0.434	0
YDR343C:	-0.4239	0

YGR008C:	-0.4047	0
YOR347C:	-0.3978	0
YLR178C:	-0.3853	0
YCL018W:	-0.332	0
YMR008C:	-0.3011	0
YKL148C:	-0.299	0
YGR255C:	-0.2745	0
YDR178W:	-0.2454	0
YMR152W:	-0.1967	0
YMR023C:	-0.1408	0
YOL028C:	0.0956	0
YGL244W:	0.1202	0
YIR023W:	0.1645	0
YKL015W:	0.1809	0
YOR330C:	0.1937	0
YPL212C:	0.2026	0
YJL076W:	0.2201	0
YCR034W:	0.2373	0
YFR028C:	0.2393	0
YPL128C:	0.2482	0
YHR170W:	0.2513	0
YBL014C:	0.2515	0
YML123C:	0.2523	0
YGL097W:	0.2531	0
YOR340C:	0.2677	0
YMR274C:	0.2683	0
YFL037W:	0.2966	0
YML065W:	0.3194	0
YOL109W:	0.3451	0
YPR124W:	0.3752	0
YBR142W:	0.3777	0
YBL069W:	0.4035	0
YPL155C:	0.4282	0
YBR243C:	0.4564	0
YLR056W:	0.4738	0
YJR092W:	0.5137	0
YMR058W:	0.5362	0
YGL021W:	0.6822	0
YGR108W:	0.7574	0

YMR001C:	0.7806	0
YBR038W:	0.8433	0
YPR119W:	1.1639	0

2. Canonical Variate2 (see Figure 2)

d is:0.9874 p Value is:0

Spellman Cell Cycle Data

Gene	Score	p-Value
YCL040W	-0.6096	0
YBR067C	-0.5403	0
YPL092W	-0.4394	0
YEL060C	-0.4340	0
YDR343C	-0.4239	0
YGR008C	-0.4047	0
YOR347C	-0.3978	0
YLR178C	-0.3853	0
YCL018W	-0.3320	0
YMR008C	-0.3011	0
YKL148C	-0.2990	0
YGR255C	-0.2745	0
YDR178W	-0.2454	0
YMR152W	-0.1967	0
YBL079W	0.1295	0
YIR023W	0.1645	0
YKL015W	0.1809	0
YOR330C	0.1937	0
YJL076W	0.2201	0
YNL216W	0.2330	0
YBR222C	0.2357	0
YFR028C	0.2393	0
YPL128C	0.2482	0
YHR170W	0.2513	0
YBL014C	0.2515	0
YGL097W	0.2531	0
YMR274C	0.2683	0
YAL059W	0.2848	0
YBL082C	0.3054	0

YML065W	0.3194	0
YBR142W	0.3777	0
YPL155C	0.4282	0
YBR243C	0.4564	0
YLR056W	0.4738	0
YJR092W	0.5137	0
YGR108W	0.7574	0
YMR001C	0.7806	0
YPR119W	1.1639	0

3. Canonical Variate 3 (see Figure 3)

d is:0.9773 p Value is:0.001

Spellman Cell Cylcle Data

Gene	Score	p-Value
Gene	Score	p-Value
YKL127W	-0.3295	0
YNL280C	-0.3154	0
YJL034W	-0.2972	0
YCR069W	-0.2856	0
YOR079C	-0.2786	0
YOR075W	-0.2702	0
YOR237W	-0.2587	0
YLR299W	-0.2569	0
YMR238W	-0.2451	0
YOR219C	-0.2103	0
YDL207W	-0.2078	0
YDL131W	0.2301	0
YNR050C	0.3180	0
YDL182W	0.3254	0
YCR065W	0.3736	0
YGL038C	0.3944	0
YER145C	0.4387	0
YPL256C	0.6011	0
YMR179W	0.6136	0
YPR019W	0.6201	0
YIL009W	0.6512	0
YJL196C	0.6680	0

YDL179W	0.7498	0
YLR079W	0.7639	0
YGR041W	0.9150	0
YJL159W	0.9385	0
YKL185W	1.1207	0
YNL327W	2.0384	0

EXAMPLE 2

The data set for this example is the results from a DNA microarray experiment and is reported in

Alizadeh, A.A., et al. (2000) Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 403:503-511.

The data set generated from the microarray experiments described in the above paper can be obtained from the following web site:

http://genome-www4.stnford.edu/MicroArray/SMD/publications.html

There are n=4026 genes and n=36 samples. In the following DLBCL refers to "Diffuse large B cell Lymphoma". The samples have been classified into two disease types GC B-like DLBCL (21 samples) and Activated B-like DLBCL (15 samples). The design matrix T has 1 column with values -1 if the sample is in group 2 and +1 if the sample is in group 1. This array data is used to illustrate the potential use of the method of the present invention in discovering genes which are diagnostic of different disease types.

The results of applying the above methodology are given below along with a (partial) list of potentially diagnostic genes. Figure 4 shows factor loadings calculated for each array, with a Box plot showing the

distribution of factor loadings from each disease type. Note the distinct factor loadings for each grouping in the plot.

The genes identified are shown below. Results of the gene expression from these genes is shown in figure 4.

Canonical Variate1

$d = 0.923$ p-value $= 0.128$

Gene	Score	p-Value
GENE3608X:	0.1363	0
GENE3326X:	0.1495	0
GENE3261X:	0.2013	0
GENE3327X:	0.2104	0
GENE3330X:	0.2109	0
GENE3259X:	0.2217	0
GENE3328X:	0.2361	0
GENE3329X:	0.2465	0
GENE3258X:	0.2534	0
GENE1719X:	0.3064	0
GENE1720X:	0.3197	0
GENE3332X:	0.4509	0

EXAMPLE 3

The data set for this example is listed in Table 1 and is an extract of the data set described in Spellman, P. and Sherlock, G., et al. (1998) Comprehensive identification of cell cycle-regulated genes of the yeast Saccharomyces cerevisiae by Microarray Hybridization. Mol. Biol. Cell 9(12):3273-3297.

The array data consists of n=100 genes and k=18 samples (times). The matrix of design facors T (design matrix)has

r=6 columns defined by the terms cos(lθ), sin(lθ) for l=1...3 and θ = (7mπ)/119 , m=0,1,…,17.

This example illustrates how the method of the present invention can be used to discover sets of genes which exhibit periodic variation within the cell cycle. For this data set, the pattern of periodic variation is a by product of the analysis given the choice of the matrix of design factors T. A search for a priori response pattern could also be specified by choosing r=1 and placing the appropriate pattern in the single column of the design matrix. For this data set we have six canonical vectors a. Note that $a=\lambda^{-\frac{1}{2}}XPu$ where u is the design factor and a denotes the scores. The Bayesian criterion was minimised with 1 basis functions in the factor analysis model. Results for the first three of these are given below. The design factor axis is time. Each component has a calculated p value which is highly significant. A list of genes forming a group with a similar pattern of variation over time is given below for the first three canonical vectors. The size of this group can be varied by choosing the significance level applied to the scores (the level here was set at 0.001). Group sizes will tend to be smaller for higher significance levels.

The results for each canonical vector might be interpreted as implying a similar pattern of variation for each of the three groups but with a phase shift for each group. The low to low cycle period is of the order of 70 minutes which agrees with the results in the paper.

The genes identified are shown below. Results of the gene expression from these genes is shown in Figures 5, 6 and 7.

1. Canonical Variate1 (see Figure 1)

d is:0.p Value is:0

Spellman Cell Cylcle Data

Gene	Score	p-Value
YPL092W	-1.0041	0.007
YER015W	-0.2681	0.008
YGL237C	0.3235	0.009
YKR010C	0.5801	0.000
YNR023W	0.5849	0.001
YCR034W	0.6459	0.000
YAL023C	0.8632	0.000
YBL001C	0.8943	0.001
YPL127C	1.9008	0.000
YNL031C	2.1047	0.000
YNL030W	2.6658	0.000
YBR009C	2.9482	0.000

YPR119W 0.17948 0

2. Canonical Variate2 (see Figure 2)

d is:0.98320 p Value is:0

Spellman Cell Cycle Data

Gene	Score	p-Value
Gene	Score	p-Value
YOR074C	-1.8064	0.000
YIL066C	-1.7692	0.000
YCL040W	-1.6460	0.000
YJL073W	-1.0510	0.000
YOR321W	-0.9528	0.000
YKL148C	-0.7819	0.000
YDL093W	-0.6411	0.007
YJL201W	-0.5744	0.009
YOR132W	-0.4864	0.009
YKR010C	-0.3184	0.009
YFR028C	0.5224	0.006
YKR054C	0.5821	0.007
YNL062C	0.5910	0.005
YHR170W	0.6916	0.000
YNL061W	0.8039	0.001
YLR098C	1.0517	0.001

YOR153W	1.0690	0.001
YOL109W	1.0760	0.000
YAL040C	1.1198	0.000
YGL008C	1.1682	0.002
YMR058W	1.6489	0.000
YMR001C	2.1982	0.000

3. Canonical Variate 3 (see Figure 3)

d is:0.8870 p Value is:0.01

Spellman Cell Cylcle Data

Gene	Score	p-Value
YMR065W	-1.57783303	0.000
YJL099W	-0.72894484	0.000
YJL044C	0.515497036	0.010
YDR292C	0.654473229	0.010
YIL066C	1.383495184	0.005
YGL038C	1.617149735	0.000
YLR079W	2.689484257	0.000
YKL185W	3.434889201	0.000

Table 1

Gene	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
YAL001C	0.68	0.68	0.65	0.94	0.53	0.51	0.68	1.13	0.73	0.86	0.96	1.54
YAL002W	0.74	0.91	0.84	0.87	0.86	0.64	0.86	1.84	0.66	0.67	0.93	1.01
YAL023C	0.51	0.3	0.74	1	1.72	1.36	1.28	0.67	0.74	0.67	0.82	1.04
YAL040C	3.71	1.57	2.1	0.47	0.7	0.66	1.45	1.11	2.23	2.59	2.16	1.07
YBL001C	0.23	0.86	0.22	0.94	1.03	1.04	1.17	1.68	0.76	0.96	0.48	0.74
YBL016W	7.92	1.26	0.37	0.34	0.49	0.71	0.5	2.46	0.41	0.51	0.61	0.87
YBR009C	0.06	0.04	0.14	0.53	2.83	3.22	1.22	1.62	0.45	0.44	0.3	0.61
YBR169C	1.17	1.32	1.55	0.96	0.8	0.8	1.12	1.7	0.91	1.57	0.9	1.04
YCL040W	0.86	3.78	5.31	2.89	1.57	0.7	0.67	0.38	0.5	0.75	0.87	1.06
YCR034W	0.51	0.53	0.57	0.84	1.11	1.4	1.12	1.06	1.13	1.11	1.21	0.89
YCR088W	1.08	1.12	1.34	1.38	1.15	1.48	0.96	1.45	1.32	0.84	1.16	1.45
YDL087C	0.79	0.53	0.82	1.38	0.79	0.67	0.94	0.89	0.91	1	0.8	0.78
YDL093W	0.6	0.57	0.8	1.08	1.58	1.04	1.2	0.66	0.63	0.74	0.7	1.11
YDL205C	0.65	0.42	0.82	0.39	0.9	0.45	0.53	0.4	0.82	0.42	1.27	0.84
YDR039C	1.38	1.45	1.99	1.2	2.12	1.52	2.08	1.38	1.63	1.23	1.36	1.26
YDR041W	1.34	0.96	1.22	0.99	1.08	0.84	1.17	1	1.07	0.94	0.94	0.86
YDR092W	1.07	0.61	1.01	0.65	1.13	1.08	1.2	1.27	1.22	0.82	0.96	1.27
YDR188W	0.57	0.54	0.55	0.65	0.68	0.76	0.64	0.73	1.32	1.12	1.36	0.8
YDR292C	0.64	0.73	0.65	0.96	0.67	0.97	0.65	0.91	1.12	1.13	1.43	0.99

YDR345C	1.48	1.27	1.26	0.79	1	0.63	1.23	0.73	0.97	1.06	1.39	1.17
YDR457W	1.01	0.5	0.91	0.91	1.28	1.23	0.84	0.67	0.93	0.91	1.68	1.07
YER008C	0.57	0.75	0.86	0.7	0.93	0.79	0.97	0.89	0.99	0.78	0.78	1.2
YER015W	1.23	1.28	0.91	0.79	1.08	0.71	1.01	0.82	1	0.84	0.91	0.99
YER091C	0.73	2.08	1.3	0.6	0.38	1.86	2.01	2.18	1.36	0.84	0.96	0.84
YER178W	1.34	0.86	1.2	0.96	1.11	0.84	1.35	1.08	1.22	0.89	1.28	1.04
YFL029C	0.86	0.74	1.34	0.71	0.86	0.73	0.87	1.07	1.11	0.79	0.84	0.71
YFR028C	0.53	0.47	0.4	0.55	0.5	1.04	0.79	0.76	0.97	1.07	0.73	0.7
YGL008C	0.51	0.51	0.5	0.53	0.51	0.96	0.94	1.39	1.8	2.18	1.65	1.06
YGL027C	0.94	0.67	1.34	1.27	2.25	1.51	1.93	1.03	1	0.87	1.28	1.3
YGL038C	0.42	0.8	1.65	1.77	0.7	1.06	0.5	0.65	0.66	1.22	1.38	1.88
YGL237C	1.13	0.63	0.74	0.84	1.23	1.34	1.01	1.03	0.84	0.84	0.97	0.89
YGR080W	1.11	1.03	1.17	0.76	0.71	0.67	1.15	0.91	1	0.79	0.91	0.9
YGR195W	1.16	0.74	0.87	0.73	1.15	0.82	1.2	0.93	0.96	1.11	0.82	0.94
YGR274C	1.06	1	1.3	1.11	1.13	1.06	0.97	1.21	1.26	0.97	1.8	1.12
YHL038C	0.93	0.67	1.12	0.74	1.16	1.12	1.22	0.67	1.23	0.97	1.16	0.87
YHR026W	0.93	0.71	0.84	0.97	0.9	1.08	1	1.01	1.08	0.74	1.03	0.79
YHR170W	0.84	0.64	0.36	0.64	0.78	1.16	0.84	1.06	1.21	1.35	0.99	1
YIL066C	0.36	0.74	2.41	3	2.61	1	0.86	0.61	0.54	0.45	1.57	2.61
YIL101C	0.89	1.38	1.36	0.9	1.03	0.94	0.73	0.99	1.13	0.66	2.66	0.8
YIR018W	0.82	2.77	0.8	0.8	0.84	0.94	1.03	1.06	1.22	0.86	0.9	0.71
YIR022W	0.93	0.84	1	1.03	1.07	0.99	1.4	1.08	0.94	0.65	0.84	0.76
YJL008C	1.11	0.63	0.86	0.79	1.16	0.8	1.34	0.97	1.11	0.63	1.04	1
YJL044C	0.84	0.75	0.54	0.51	0.35	0.38	0.41	0.51	0.82	0.87	0.74	0.6
YJL073W	0.97	0.82	2.16	2.61	1.28	1	0.84	0.66	0.63	0.79	0.84	1.27
YJL099W	1.01	1.11	0.84	0.86	1.06	1.23	1.3	1.4	1.03	0.94	0.64	0.76
YJL110C	0.53	0.51	0.44	0.58	0.53	0.74	0.56	0.71	0.74	0.89	0.6	0.8
YJL173C	0.5	0.5	0.84	1.23	1.57	1.21	1.48	1.01	0.7	0.55	0.79	0.78
YJL201W	0.41	0.44	1.11	1.08	1.06	0.91	1.07	0.68	0.61	0.56	0.66	0.76
YJR106W	0.7	0.84	0.8	0.71	0.7	1.03	0.82	0.66	0.86	1.06	0.82	0.9
YJR131W	0.89	0.7	1	1	1.01	1.12	0.89	0.99	1.01	1	0.99	1
YKL117W	1.22	1.4	1.21	1.75	1.17	1.7	1.16	1.62	1.51	1.12	1.46	1.21
YKL148C	0.76	1.26	1.88	1	0.87	0.66	0.73	0.53	0.54	0.67	0.7	0.7
YKL182W	1.03	0.51	0.6	0.39	0.39	0.31	0.35	0.26	0.33	0.37	0.57	0.89
YKL185W	0.57	0.26	0.54	0.2	0.18	0.15	0.11	0.15	0.53	3.78	4.18	1.57
YKR010C	0.45	0.47	0.64	0.87	1.03	1.03	0.91	0.66	0.74	0.53	0.55	0.73
YKR054C	0.57	0.39	0.54	0.5	0.63	0.47	0.68	0.67	1.01	0.86	0.9	0.63
YLR079W	0.3	0.64	0.33	0.47	0.37	0.38	0.27	0.34	0.36	1.28	2.36	1.57
YLR098C	0.51	0.54	0.42	0.47	0.43	0.82	1	1.2	1.48	1.68	0.86	0.87
YLR155C	1.11	1.08	1.65	1.11	1.52	0.79	1.54	1.16	1.06	1.39	1.08	0.73
YML035C	0.96	0.66	1.36	1.12	1.35	0.94	1.32	0.93	1.32	1.15	1.23	0.91
YML104C	0.87	0.94	0.93	1.15	1.08	1.34	1.2	1	1.23	1.7	1.01	1.15
YMR001C	0.25	0.2	0.18	0.14	0.32	0.7	1.82	1.52	2.25	1.34	0.78	0.54
YMR015C	1.04	0.5	0.42	0.6	0.73	0.93	1.23	0.93	1.01	0.86	1.04	0.71
YMR023C	1.11	1.63	1.17	1.13	1.01	1.07	0.97	0.91	0.97	0.84	0.97	0.94
YMR058W	2.27	0.86	1.04	1.17	2.1	2.27	4.26	3.22	5.42	5.21	7.1	5.47
YMR065W	6.42	1.46	0.65	0.51	0.7	0.4	0.89	0.97	0.89	0.89	0.65	0.61
YMR070W	0.75	0.8	0.9	0.93	1	0.76	1.16	1.03	1	0.87	1.27	0.91
YMR129W	0.68	0.41	0.49	0.53	0.73	0.73	0.87	0.75	0.96	0.84	0.94	0.76

YMR231W	0.68	0.9	0.71	0.87	0.8	0.87	0.79	0.86	0.87	0.94	0.7	1.04
YNL012W	0.78	1.15	0.94	1.08	0.76	0.65	0.97	0.91	0.86	0.79	0.64	0.73
YNL030W	0.06	0.08	0.1	0.73	1.97	2.27	1.45	0.7	0.48	0.21	0.27	0.51
YNL031C	0.11	0.15	0.14	0.65	1.49	2.27	1.21	0.55	0.45	0.29	0.23	0.58
YNL059C	0.79	0.65	0.61	0.54	0.61	0.87	0.9	0.73	0.84	0.89	0.73	0.79
YNL061W	0.89	0.44	0.27	0.49	0.68	0.82	0.99	0.96	1.03	1.07	0.8	0.94
YNL062C	0.96	0.61	0.37	0.57	0.91	0.76	1.21	0.96	1.22	0.76	0.87	0.87
YNL073W	0.79	0.76	0.96	0.7	0.96	0.65	1.01	0.64	0.84	0.79	0.76	0.84
YNL188W	0.31	0.47	0.84	0.71	0.45	0.55	0.76	0.54	0.57	1.13	1.12	0.73
YNL272C	1.36	1.13	1.4	1.84	1.2	1.32	1.15	1	0.93	0.99	1.12	1.62
YNR023W	0.56	0.5	0.49	0.87	1.06	1.17	1.45	1	0.74	0.89	0.74	0.71
YOL028C	0.82	0.75	0.76	0.86	0.78	0.97	1.08	0.99	1	0.87	1.01	0.94
YOL067C	1.07	0.67	1.28	0.84	0.8	1.06	1.23	1.07	1.07	1	1.11	0.78
YOL109W	0.84	0.44	0.41	0.4	0.67	0.68	1.16	1.36	1.27	0.96	1.38	1.07
YOR037W	0.96	0.84	1.17	0.89	1.39	1.15	1.07	0.68	0.73	1.03	0.87	0.8
YOR074C	0.24	0.55	1.32	2.2	2.41	1.32	1.01	0.36	0.38	0.67	0.51	1.57
YOR132W	0.94	1.26	1.65	1.52	1.26	0.91	0.96	0.71	0.78	0.93	1	1.13
YOR153W	0.61	0.42	0.35	0.34	0.49	0.78	1.11	1.01	1.04	0.66	0.61	0.53
YOR167C	1.34	0.86	0.87	1.13	1.04	1.08	1.16	0.94	1.15	0.8	1.2	0.71
YOR259C	0.86	0.61	1.13	0.97	1.07	1.23	1.07	0.96	1.08	0.93	1.22	0.99
YOR261C	0.9	0.57	0.9	1	0.96	1.23	0.87	0.78	1.03	0.86	1.21	0.76
YOR321W	0.61	0.66	1.06	2.1	1.57	1.34	1.32	0.76	0.66	0.54	0.8	1.17
YPL040C	0.68	0.75	0.79	1.12	0.94	0.75	0.9	0.71	0.9	0.99	0.9	0.99
YPL050C	0.86	0.64	1.16	1.11	1.34	1.07	1.36	1.07	1	0.86	0.86	0.84
YPL061W	1	2.66	5.42	2.89	1.46	0.91	0.87	1.04	1.23	1.4	1.97	1.11
YPL072W	0.93	0.99	1.06	1.17	1.04	1.68	1.52	1.48	1.01	0.86	0.66	0.87
YPL086C	0.91	0.48	0.37	0.64	0.76	1.04	1.22	1.17	1.13	0.9	0.66	0.82
YPL092W	1.35	4.39	2.18	1.28	1	0.61	0.66	0.66	0.79	0.75	0.7	0.54
YPL127C	0.12	0.14	0.64	1.54	2.18	2.36	2.05	1.21	0.74	0.47	0.41	0.91
YPL234C	0.78	0.58	0.44	0.7	0.7	0.57	0.94	0.64	0.76	0.41	0.6	0.45
YPR056W	0.6	0.51	0.68	0.54	0.86	0.84	0.89	0.68	0.73	0.78	0.86	0.67
YPR102C	1.15	0.84	1.03	1.08	1.06	1.16	1.13	1.23	1.51	0.99	1.51	0.89

Gene	A13	A14	A15	A16	A17	A18
YAL001C	0.63	0.97	0.7	1.46	0.65	1.06
YAL002W	0.64	0.61	1.03	1.48	0.57	0.94
YAL023C	1.01	1.17	1.35	1.08	1.04	0.7
YAL040C	0.93	0.73	0.96	1.01	1.46	2.01
YBL001C	1	1.06	1.08	1.11	0.82	0.8
YBL016W	0.84	0.96	0.8	1.15	0.58	1.2
YBR009C	1.65	1.7	2.41	1.21	0.67	0.48
YBR169C	0.94	0.86	1.08	1.79	0.75	1.49
YCL040W	1.16	0.48	0.78	0.73	0.84	0.63
YCR034W	1.22	1.08	1.21	1.22	1.12	1
YCR088W	1.03	1.01	1.07	1.79	0.97	1.26
YDL087C	1	0.84	0.82	0.78	0.79	0.71
YDL093W	1.32	0.97	0.89	0.68	0.53	0.61
YDL205C	0.75	0.57	0.49	1.58	0.34	0.71
YDR039C	1.3	1.43	1.32	1.22	0.74	1.15

YDR041W	0.87	0.78	0.89	0.78	0.79	0.67
YDR092W	0.93	1.21	0.96	1.03	1.11	1.13
YDR188W	0.78	0.65	0.79	1.07	0.74	0.8
YDR292C	0.84	0.84	0.71	1.06	0.79	1.17
YDR345C	1.68	1	1.15	0.71	1.06	0.82
YDR457W	0.78	0.74	1.28	1.15	1.15	1.34
YER008C	0.87	0.86	1.07	0.99	0.91	0.89
YER015W	0.97	0.67	0.84	0.71	0.94	0.8
YER091C	0.64	0.61	0.94	1.77	0.89	1.04
YER178W	1.06	1.03	1.39	1.01	1.36	0.76
YFL029C	0.75	0.82	0.94	0.73	1.13	1.13
YFR028C	0.84	0.76	0.86	0.96	0.68	0.9
YGL008C	0.73	0.84	0.87	1.79	0.97	1.65
YGL027C	1.4	1.13	1.65	1.23	1.23	0.68
YGL038C	1.36	1.15	0.9	0.89	0.64	0.73
YGL237C	0.89	1.21	1.2	1.07	1.28	1.12
YGR080W	0.9	0.66	0.9	0.78	0.22	0.75
YGR195W	0.89	0.79	0.84	0.79	1.01	0.87
YGR274C	1.13	1.01	1.26	1.54	0.78	0.94
YHL038C	1.01	0.86	0.86	0.73	1.12	0.99
YHR026W	1.06	0.79	0.96	0.84	0.8	0.79
YHR170W	0.93	0.96	0.99	1.16	1.03	1.12
YIL066C	2.25	1.27	1.34	0.99	0.35	0.55
YIL101C	0.75	0.55	1.08	1.21	0.65	1
YIR018W	0.93	0.84	0.87	1.15	0.76	1
YIR022W	1.07	0.71	1.08	0.7	1.4	0.79
YJL008C	0.99	0.74	1.21	0.84	1.04	0.78
YJL044C	0.73	0.48	0.53	0.56	0.5	0.7
YJL073W	1.03	0.82	0.74	0.68	0.57	0.74
YJL099W	0.86	0.8	0.97	0.99	1.57	1
YJL110C	0.73	0.57	0.61	0.8	0.71	0.82
YJL173C	1.32	0.76	1.35	0.71	1.23	0.49
YJL201W	0.97	0.68	0.99	0.76	0.86	0.51
YJR106W	0.86	0.67	0.74	0.87	0.53	0.86
YJR131W	0.9	0.84	0.97	1.04	0.75	0.78
YKL117W	1.22	0.93	1.21	1.22	1.16	1.01
YKL148C	0.74	0.49	0.67	0.58	0.43	0.56
YKL182W	0.84	0.79	0.87	0.87	0.43	0.48
YKL185W	0.75	0.51	0.33	0.36	0.29	1.16
YKR010C	1.04	0.89	1	1.03	0.66	0.73
YKR054C	0.64	0.58	0.93	0.84	0.82	0.79
YLR079W	1.13	0.71	0.55	0.53	0.43	0.75
YLR098C	0.65	0.49	0.63	0.89	1	1.16
YLR155C	1.2	1.01	1.23	1.2	1.67	0.73
YML035C	0.96	0.67	1	0.82	1.13	0.82
YML104C	1.12	1.11	1.2	1.62	1.23	1.12
YMR001C	0.39	0.54	0.91	1.34	2.01	1.34
YMR015C	0.9	0.63	1.06	0.87	0.76	0.82
YMR023C	0.94	0.7	0.8	0.9	0.75	0.8

YMR058W	4.76	3.35	6.82	5.7	8.25	5.21
YMR065W	0.54	0.39	0.57	0.7	1	0.84
YMR070W	1	0.96	1.36	1.26	0.71	1.07
YMR129W	0.54	0.84	0.97	1.11	0.7	0.68
YMR231W	0.8	0.58	0.63	0.82	0.86	0.99
YNL012W	1.12	0.97	0.79	0.74	0.68	0.8
YNL030W	1.75	1.46	2.27	0.97	0.63	0.4
YNL031C	1.43	1.79	1.7	0.78	0.74	0.44
YNL059C	0.84	0.63	0.73	0.66	0.68	0.84
YNL061W	1	0.79	0.7	0.79	0.73	1.04
YNL062C	1.06	0.96	0.87	1.08	0.91	0.99
YNL073W	0.8	0.55	0.67	0.71	0.74	0.66
YNL188W	0.73	0.49	0.56	0.4	0.7	0.74
YNL272C	1.21	0.99	0.87	0.84	1.15	1.03
YNR023W	0.8	0.63	1.04	1.01	1.51	1.22
YOL028C	0.87	0.84	0.96	0.99	1.26	0.97
YOL067C	0.73	0.65	0.94	0.96	1.15	1.16
YOL109W	1.07	0.91	1.93	1.26	1.38	0.93
YOR037W	0.89	0.68	0.75	0.75	1.06	1.38
YOR074C	1.55	0.82	0.57	0.6	0.4	0.34
YOR132W	1.16	0.65	0.96	0.8	1.06	1.04
YOR153W	0.47	0.57	1.06	1.7	1.11	1.26
YOR167C	1.3	0.7	1.48	0.84	1.46	0.8
YOR259C	0.82	0.55	0.8	0.74	0.82	0.8
YOR261C	0.76	0.49	0.76	0.6	0.9	0.65
YOR321W	1.4	0.96	1.04	0.87	0.79	0.54
YPL040C	1.01	0.64	0.61	0.84	0.61	0.79
YPL050C	1.07	0.87	1.01	0.75	0.94	1.04
YPL061W	0.63	0.34	0.35	0.43	0.64	0.71
YPL072W	1.01	0.78	1.11	0.96	1.43	1.48
YPL086C	0.8	0.82	0.64	0.68	0.84	0.86
YPL092W	0.6	0.54	1	0.68	0.51	0.67
YPL127C	1.38	1.57	1.34	1.38	1.17	0.73
YPL234C	0.71	0.45	0.84	0.41	0.53	0.44
YPR056W	0.79	0.65	0.76	0.76	0.99	0.9
YPR102C	1.12	0.76	1.7	1.13	1.9	1.08

EXAMPLE 4

The data set for this example is listed in Table 2 and is an extract of the data set described in Alizadeh, A.A., et al. (2000) Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 403:503-511.

The data set generated from the microarray experiments described in the above paper can be obtained from the following web site:

http://genome-www4.stnford.edu/MicroArray/SMD/publications.html

There are n=100 genes and n=42 samples. In the following DLBCL refers to "Diffuse large B cell Lymphoma". The samples have been classified into two disease types GC B-like DLBCL (21 samples) and Activated B-like DLBCL (21 samples). The design matrix T has 1 column with values -1 if the sample is in group 2 and +1 if the sample is in group 1. This array data is used to illustrate the potential use of the method of the present invention in discovering genes which are diagnostic of different disease types.

The results of applying the above methodology are given below along with a (partial) list of potentially diagnostic genes. The plot shows factor loadings calculated for each array, with a Box plot showing the distribution of factor loadings from each disease type. Note the distinct factor loadings for each grouping in the plot.

The genes identified are shown below. Results of the gene expression from these genes is shown in figure 8.

Canonical Variate1

$d = 0.912$ p-value $= 0.000$

Gene	Score	p-Value
GENE2238X	0.4491	0.027
GENE2943X	0.4102	0.045
GENE2977X	0.3827	0.024
GENE1246X	0.4157	0.030
GENE124X	0.4213	0.012

GENE122X	0.3318	0.038
GENE1614X	-0.4406	0.038

Table 2

RowNames	DLCL0001	DLCL0002	DLCL0003	DLCL0004	DLCL0005	DLCL0006	DLCL0007	DLCL0008
GENE3950X	-0.2049	0.6574	-0.3501	1.1837	0.3306	0.1310	1.5559	-0.4136
GENE2531X	-0.2116	1.0063	-0.4699	1.1355	0.5358	0.0929	1.2739	-0.5714
GENE918X	-0.1815	0.9708	-0.3538	1.1432	0.3901	0.4990	1.2520	-0.6532
GENE3511X	-1.2609	-0.3673	0.2774	0.6506	0.2095	-0.6501	-0.0393	-1.9622
GENE3496X	-1.5438	0.2235	0.3742	0.6152	0.0026	0.4043	0.7658	-2.1362
GENE3484X	-1.5441	0.2644	0.3324	0.5755	0.3227	0.3810	0.6922	-2.0400
GENE3789X	-0.8190	0.8721	-0.4551	-0.3695	0.5510	0.8935	-0.5408	-1.8466
GENE3692X	1.5834	-1.3890	0.2694	0.3204	-0.9297	-0.8659	-0.0240	1.2389
GENE3752X	-0.5429	0.0079	1.0622	1.0307	0.4799	0.3226	-0.0708	-1.5657
GENE3740X	-0.1202	0.3514	-0.2352	0.5584	-0.7183	1.7546	1.1220	-2.1561
GENE3736X	-1.0454	0.1940	0.1413	1.0247	0.4182	1.0642	0.0622	-2.0475
GENE3682X	0.0352	-0.5229	-1.0198	-1.0882	-0.7605	1.2054	0.8310	-1.0306
GENE3674X	0.0919	-0.3555	-1.1076	-0.8632	-1.0361	0.9907	1.1110	-0.8782
GENE3673X	0.4663	-0.7188	-1.0865	-1.3763	-0.7102	0.9291	0.8167	-1.3677
GENE3644X	1.2679	1.0367	-0.2156	0.4202	0.5551	-0.1771	0.5743	-1.2367
GENE3472X	-0.5140	0.4945	0.5546	0.2904	-0.0097	1.2149	1.1549	-2.0388
GENE2530X	-0.3729	-0.7347	-0.5176	-0.0474	0.2601	0.0612	-0.2102	-1.2411
GENE2287X	-0.7046	-0.7689	-0.4475	0.4799	-0.3006	0.6084	0.8196	-1.2739
GENE2328X	-0.4273	0.4495	-1.8079	-1.0243	0.4682	0.7853	-2.0504	-0.9683
GENE2417X	-1.1810	1.0531	0.1474	0.1021	0.4644	2.0191	0.7210	-1.1055
GENE2238X	0.6934	-0.2178	0.8979	0.6190	-0.3294	0.2843	-0.3294	-0.0319
GENE1971X	-0.1957	1.3122	-0.3276	-0.2145	1.4441	0.3132	0.8221	-0.9873
GENE3086X	0.0236	-1.4920	-0.3702	0.2026	-0.0600	-0.7521	-0.6089	-0.1674
GENE1009X	1.4548	-0.6280	0.7398	0.2580	0.1025	-0.3483	-0.5970	-0.3793
GENE1947X	0.4856	-0.5274	0.1845	0.1023	-0.5000	-0.1441	1.4713	0.9237
GENE3190X	2.0024	-0.8814	0.8489	-0.6571	-0.3047	-0.2299	-1.0417	1.4577
GENE3379X	0.7059	-0.4788	1.6020	0.0224	-0.3117	0.2351	-0.6762	1.2223
GENE3184X	1.3782	-0.6784	0.9336	0.8335	-0.5783	-0.7117	-0.1337	0.7334
GENE3122X	1.1454	-0.5556	-0.3894	1.2236	-0.4089	-0.4676	0.9890	0.6175
GENE1099X	0.5601	-0.8521	-0.7039	0.5133	-0.5634	-1.0082	-0.8521	1.3871
GENE3032X	0.5833	-1.4015	-0.4815	0.6600	-0.4134	-0.9415	-0.9245	1.4352
GENE2675X	0.3661	-1.0045	0.6262	1.8668	-0.7244	-1.1245	-0.3842	2.1269
GENE2481X	0.4123	-0.8389	0.7840	1.8267	-0.5487	-1.0111	-0.3130	2.0443
GENE2878X	1.0922	-0.8274	0.2785	0.9566	0.3202	-0.5875	-1.2238	1.3530
GENE2943X	1.5951	-0.6212	0.3013	1.0551	0.7063	-0.5649	-1.1162	1.6288
GENE2977X	1.2805	-1.2491	1.1314	1.1262	-0.6527	-1.1000	-0.8275	0.9463
GENE3014X	1.9501	-1.2171	0.4584	0.7935	-0.2875	0.0476	-1.2603	2.0582
GENE2006X	0.3456	-1.0625	0.2272	1.4378	-0.1939	-0.6677	-0.6414	-0.6545
GENE1368X	0.5254	-0.4359	1.7741	1.1000	-0.2591	-1.3642	0.3928	0.7243
GENE1184X	0.5950	-0.5359	1.7039	0.8914	-0.0308	-1.3154	0.4962	0.7487

GENE1226X	1.1537	-1.1220	-0.3129	-0.0769	-0.5994	-0.2454	-0.8944	1.6342
GENE1228X	1.1347	-0.3684	1.9013	-0.9074	0.7934	-0.1948	0.1286	-0.6140
GENE1231X	0.2407	-1.2858	0.0103	1.6088	-0.8538	0.2551	-0.3785	0.5575
GENE1246X	0.3136	-1.0667	0.3136	1.6182	-0.6627	0.4567	-0.7553	0.9449
GENE1172X	0.0021	-0.6792	0.5580	1.1317	0.0918	0.4862	-1.3336	0.5938
GENE1164X	-0.3385	-0.6039	-0.3053	1.0383	0.6568	0.1923	-2.0636	0.3914
GENE3029X	0.9558	-1.8240	-0.4890	-0.0318	-0.2512	0.4803	-0.1415	0.6997
GENE1027X	0.3195	-0.8192	-0.0407	1.1561	-0.7030	1.1329	-0.1220	1.5396
GENE1354X	1.0921	0.3968	0.5090	0.4192	-0.3883	-0.0967	-0.7247	0.4641
GENE62X	-1.7087	-0.3336	-0.2409	0.6397	0.5470	-0.1173	0.0063	2.1229
GENE932X	-1.6636	0.1194	-0.3264	-1.7472	-0.6050	-0.4935	-0.1592	-1.4407
GENE3611X	-1.3618	0.5350	-0.5350	0.3161	-0.1702	-0.7052	1.4590	-1.3131
GENE3631X	-0.5379	0.4721	-0.9278	0.0823	0.0291	1.3404	-0.0418	-1.7783
GENE330X	0.8497	0.6081	-1.5880	-0.7095	-0.9511	1.1132	0.5422	-0.9731
GENE331X	-0.8855	0.8435	-0.4014	-0.4878	-0.0037	1.0510	0.1519	-1.3870
GENE808X	1.5424	-0.0178	-0.2335	0.7125	0.4137	0.4469	-0.1672	-0.5157
GENE487X	1.1631	-0.5281	0.2915	0.0053	1.2932	-0.5802	-0.3330	0.3565
GENE621X	0.8961	-0.7734	0.2879	-0.0341	1.1465	-0.1772	-0.6422	0.3117
GENE622X	1.2278	-0.3796	0.3532	0.2113	0.6132	-0.4269	0.2350	-0.6751
GENE634X	-1.6102	0.9498	-0.4669	0.6888	0.7261	0.1296	0.8877	-2.0328
GENE659X	-1.0282	2.0564	-0.1360	0.7435	0.1317	0.1062	1.2916	-1.7165
GENE669X	-0.7541	1.9543	-0.0171	0.8396	0.2500	0.1487	1.4108	-1.9056
GENE674X	-0.7844	2.0333	0.2374	0.7844	0.6606	0.1858	0.8567	-1.9094
GENE675X	-1.8669	-0.3961	0.5014	0.2751	-0.2528	0.2676	1.0520	-2.2591
GENE676X	0.1521	2.9355	-0.8281	-0.0536	0.0553	3.1896	-0.4045	-0.6466
GENE704X	-0.2724	0.8058	-0.6828	-0.4656	0.0977	0.0253	-1.2139	-1.2219
GENE734X	-0.1106	0.8918	-0.7138	-0.3740	-0.0512	0.0593	-1.0536	-1.4104
GENE738X	-0.3670	1.1934	-0.4616	-0.9817	2.0445	1.2643	-0.2488	-2.2347
GENE456X	0.2548	1.4336	0.2701	-0.8322	0.1017	0.1936	-1.5211	-1.4752
GENE744X	-0.1761	1.0752	0.2892	-1.2991	0.9309	-0.1440	-1.1066	-1.5237
GENE179X	-1.5071	-0.2186	-3.7390	-0.3566	-0.8398	0.7018	0.2416	-0.7248
GENE124X	-1.3867	1.3179	-0.7428	-0.7714	-0.5997	0.5595	-0.1704	-2.4027
GENE122X	-1.2443	1.2153	-0.7888	-0.4396	-0.7736	0.4410	-0.1815	-2.6107
GENE111X	-0.7042	0.8689	-1.0433	-0.3245	-1.0840	0.6790	0.7469	-2.1418
GENE97X	-0.1985	1.1612	0.2602	-0.4770	-0.5589	0.0472	0.5223	-1.8532
GENE2645X	-1.0298	1.1902	0.0604	-0.3955	0.6749	-0.0585	-0.7324	-1.5055
GENE3408X	0.6893	-0.4665	0.5792	-0.5766	-0.3748	0.2306	-1.0719	-0.7600
GENE3854X	0.6938	-0.9260	0.4181	-0.2884	-0.2884	0.3492	-0.8399	-0.6331
GENE1406X	0.0021	-0.9105	0.4473	-0.3540	-0.1314	0.6254	-1.7563	-0.0647
GENE1401X	1.7535	-0.9049	0.7783	1.4704	-0.8419	-0.1655	0.2749	2.0839
GENE3462X	-0.3011	0.2070	0.1129	-0.3952	-0.6774	-1.0914	1.2231	-0.0376
GENE3173X	-0.5215	-0.2846	0.3418	-0.2168	-0.0476	-0.4369	0.9681	-1.3849
GENE3971X	1.5198	-0.5224	-0.2014	0.6154	-1.5434	0.1486	-0.4640	-0.2306
GENE1756X	1.0949	-1.9916	1.4067	-0.1054	-1.3369	-0.7134	1.0326	0.5181
GENE1533X	1.5099	-1.6932	1.1189	0.3219	-1.7534	-0.4601	0.6527	0.7430
GENE1757X	0.6631	-0.7090	0.0789	0.0382	-0.6275	-0.2607	0.0518	1.4647
GENE3572X	0.5991	-0.5067	1.0958	0.6151	0.3106	-1.5484	-0.6509	0.6952
GENE3571X	-0.5755	-0.4997	0.6209	-0.8935	0.7269	-0.0303	-0.4392	-1.4841
GENE385X	-1.2426	0.7899	-0.2381	-0.2614	-0.7287	0.9300	0.3693	-2.0603

GENE1614X	-1.7405	1.2328	0.2134	-0.9335	-0.0627	1.0204	-0.2114	-1.6131
GENE1623X	-0.9216	0.5149	0.6527	-1.4136	1.2233	0.0623	0.2197	-0.1935
GENE1646X	-1.0213	0.3776	-0.5812	-0.7383	-0.0939	0.6291	-0.8641	-1.1941
GENE1660X	0.9611	-0.4493	-0.6750	0.3687	-0.9711	-0.6891	-0.1672	0.8200
GENE1721X	0.9852	-0.1574	-0.3398	0.4503	-1.3366	-0.2668	-0.2547	0.1586
GENE1573X	-0.0220	0.9123	-0.0901	-0.1485	0.1434	0.7079	0.4646	-1.4721
GENE1553X	-0.7350	2.0362	0.5313	-0.4230	-0.2211	0.9167	-0.3863	-1.1938
GENE1773X	-1.1428	2.1206	0.1544	-0.7780	-0.3726	0.7625	-0.7982	-1.6698
GENE913X	1.0593	1.2244	1.0593	0.4492	0.2195	-1.2880	-0.7568	-0.4768
GENE3980X	0.9547	1.3890	1.1508	0.3454	0.2613	-1.1745	-0.9644	-0.3480
GENE3X	-0.0042	2.4527	-0.8465	0.0485	0.6276	0.9786	-0.0744	-2.2329

RowNames	DLCL0009	DLCL0010	DLCL0011	DLCL0012	DLCL0013	DLCL0014	DLCL0015	DLCL0016
GENE3950X	0.8026	0.0583	-0.0415	-1.3484	0.6846	-0.7494	-0.1686	0.1582
GENE2531X	0.3974	-0.0178	0.2498	-1.6693	0.6096	-1.1711	-0.4330	0.0837
GENE918X	1.0615	0.2813	-0.1996	-1.6149	0.7077	-0.9254	-0.3448	0.1452
GENE3511X	-0.3786	-1.3288	-0.0167	0.3113	0.9334	0.2435	-0.6162	-0.5370
GENE3496X	0.2235	0.0930	0.1131	-0.0175	0.6352	0.8963	-1.6743	0.4645
GENE3484X	0.5074	-0.0857	0.3713	-0.2315	0.5852	0.6241	-1.6802	0.3130
GENE3789X	0.5510	0.3155	0.6152	-0.5194	1.7283	-0.9261	-1.3542	1.0861
GENE3692X	-0.3046	1.0093	-0.3812	-0.0623	-2.2564	-0.0240	1.8385	-1.6824
GENE3752X	-0.0393	-1.8490	-0.2439	-0.9048	0.4957	1.1094	-1.7073	-0.9363
GENE3740X	-0.2697	-1.1094	0.0178	-0.1547	-0.9484	-0.6953	-1.5120	-0.2122
GENE3736X	-0.0697	-1.2827	0.1940	-0.4389	-0.2411	-0.4125	-1.0718	-0.9399
GENE3682X	-0.4040	-0.5625	-1.1098	0.7770	2.0876	-0.2384	-0.9801	-0.5265
GENE3674X	-0.1675	-0.6977	-0.5699	0.6898	2.2127	-0.0660	-0.9609	-0.4759
GENE3673X	-0.3598	-0.7707	-0.9265	1.0286	0.3668	0.0511	-0.9005	-1.0086
GENE3644X	-0.2349	-1.4101	0.5551	-1.4872	0.8248	-1.5257	-1.1211	0.6514
GENE3472X	-0.6340	-0.9102	0.8667	-0.6941	1.1189	-1.1503	-0.5620	0.9628
GENE2530X	-0.2825	-1.4401	-0.4091	-0.0474	-0.2463	0.4048	-0.0835	-0.2282
GENE2287X	0.2228	-1.0995	-0.0894	0.5442	-0.4567	-0.3098	-0.3741	0.0024
GENE2328X	-0.0915	0.2816	0.2443	-0.4646	2.0913	0.3562	-0.1288	0.4682
GENE2417X	-0.9546	-2.2226	2.1701	0.6757	1.6418	-0.0791	-0.9395	0.5096
GENE2238X	0.8979	-0.2550	0.8794	0.5818	-0.5898	-1.9287	0.9909	-0.3294
GENE1971X	0.0494	-1.0815	0.0117	-0.8365	1.1048	-0.6480	-0.9119	-0.0072
GENE3086X	0.7873	1.5034	-0.6686	-0.4776	-0.7760	-0.1793	1.3005	-1.0504
GENE1009X	-0.5659	1.1750	-1.1876	0.8642	-0.9389	-0.0063	1.0352	0.4600
GENE1947X	0.7321	0.8689	-0.1714	2.2105	0.1023	-1.3214	1.0880	-0.4452
GENE3190X	0.0585	1.5218	-0.3794	0.1760	-0.4969	-0.0270	0.9130	-0.5824
GENE3379X	0.6451	0.9489	0.2806	0.0832	0.9793	-0.9496	0.9185	-0.4029
GENE3184X	0.3777	-1.3232	-0.6784	2.7901	-0.2782	-0.1448	-1.3121	0.6890
GENE3122X	0.9694	0.8619	0.2949	0.9205	-0.3894	-1.6700	-0.2819	-0.9662
GENE1099X	0.6927	0.7786	0.0139	-0.4620	0.6771	0.0607	0.8644	-0.6805
GENE3032X	0.7111	0.7793	0.0381	-0.7030	-0.1152	0.1830	0.6600	-0.8052
GENE2675X	-0.5743	2.0568	-0.4642	-0.3742	0.2361	-0.5843	-0.1041	-1.0945
GENE2481X	-0.1498	2.1078	-0.4943	-0.2949	0.3398	-0.9930	-0.2042	-0.9205
GENE2878X	1.3008	0.2367	-0.6188	0.0594	-0.4727	-0.9735	0.4558	-0.2223
GENE2943X	1.3026	0.2226	-0.6774	0.8188	-0.9474	-0.4637	0.6388	-0.2274
GENE2977X	-0.1129	0.1905	-0.7298	0.6584	-1.4702	-0.5756	1.4656	-0.1900

GENE3014X	0.5665	-1.4441	-0.8712	-0.8063	-0.0064	-0.1037	1.7123	-0.6766
GENE2006X	0.0298	2.6616	-0.7335	0.5561	-0.3782	0.0298	1.0957	-0.3782
GENE1368X	0.2271	1.4978	0.2271	0.7906	-0.7564	-0.6127	-0.2260	0.2160
GENE1184X	0.2107	1.3306	0.1778	0.7267	-0.7225	-0.5249	-0.0199	0.1558
GENE1226X	0.9514	0.6480	0.5131	1.3054	-1.8132	-0.2370	-0.4983	-0.4140
GENE1228X	-0.8176	2.3265	0.9072	0.5718	0.2184	0.0268	1.3383	-0.9973
GENE1231X	0.5575	0.0823	1.3640	-0.0761	-0.8970	-1.4730	-0.5801	-0.1913
GENE1246X	0.3136	-0.1998	0.2968	0.1285	-1.4118	-2.0767	0.0695	-1.0162
GENE1172X	-0.0875	0.5221	-0.3923	0.6566	-2.1136	-2.9653	0.6118	-1.3964
GENE1164X	0.1758	0.7729	-0.3551	0.2587	-1.6323	-0.6371	2.1331	-1.4831
GENE3029X	0.6997	1.4861	0.2060	0.5900	0.9740	0.3705	1.1569	0.0597
GENE1027X	-0.0639	0.8656	0.0871	1.3304	-1.0748	1.2026	1.1097	-1.5512
GENE1354X	-0.0742	0.0379	-0.3883	0.0603	-0.4780	0.7108	0.6660	-0.5677
GENE62X	0.8869	-1.0752	-0.1019	0.6551	-0.4572	-1.0752	2.5246	0.7478
GENE932X	-1.0786	-0.7721	-0.1035	0.3701	-0.0199	0.2587	-0.3542	0.9273
GENE3611X	-0.5836	-2.9911	0.5107	-1.4834	0.7052	0.6566	-0.5836	-0.3891
GENE3631X	-0.2898	-0.8923	0.3126	-1.3708	-0.0772	0.1354	-0.8746	0.0114
GENE330X	0.7179	-1.2366	1.2669	-2.6860	-0.0946	-1.1048	-1.2586	0.1469
GENE331X	0.6706	-1.3524	1.5179	-1.7155	2.8839	-0.5570	-0.8855	0.5496
GENE808X	1.0278	1.0444	1.2104	-0.2833	-0.4659	-0.8145	0.1648	-0.6983
GENE487X	-0.1378	1.1761	-1.1786	1.4493	-0.5281	-0.8664	1.3843	1.3712
GENE621X	-0.4395	1.4088	-0.9403	1.3611	-0.8330	-0.5468	1.8500	1.4446
GENE622X	-0.1669	1.6533	-1.1360	1.1923	-0.8051	-0.8642	1.4051	1.5705
GENE634X	0.2663	0.5770	0.5024	-0.6782	0.1793	0.0675	-0.9764	0.7385
GENE659X	-0.2634	-1.3723	1.8652	-0.5821	1.4828	1.0877	-1.0919	0.4249
GENE669X	-0.0724	-1.0673	1.7701	-1.0120	1.4016	1.0147	-0.8278	0.4067
GENE674X	-0.3716	-1.5379	1.4656	-0.8360	1.4553	1.1663	-0.3922	0.5264
GENE675X	-0.4037	-0.5998	0.0790	-0.3358	0.9539	1.0972	-1.6557	0.3581
GENE676X	-0.7192	-0.7676	0.1642	-0.0899	0.4063	-0.1262	-0.1988	-0.0778
GENE704X	0.1782	0.0575	-0.4977	-0.9484	0.0253	-0.4253	-0.3770	0.0333
GENE734X	0.3566	-0.3485	-0.2551	-1.3254	-0.0087	-0.3060	-0.4844	0.0932
GENE738X	0.7914	-1.1472	1.1461	-0.2488	0.4605	-1.3127	-0.7216	0.1058
GENE456X	0.2395	-1.3068	0.3007	-0.7097	1.1274	0.2701	-0.8475	0.1936
GENE744X	-0.3526	-0.9622	0.1448	-0.7536	1.3801	0.4014	-0.3044	-0.1921
GENE179X	-0.5177	-1.4381	0.2186	-0.0575	0.0805	-0.9319	0.0345	-0.4487
GENE124X	-0.1560	-0.8000	0.2446	-0.3135	1.4753	-0.1274	-1.2150	0.2303
GENE122X	-0.0296	-1.1076	0.4410	-0.8799	1.3975	0.3044	-1.4265	0.4562
GENE111X	-0.0262	-0.9483	0.6112	-0.7449	1.5606	0.4892	-1.5857	0.5299
GENE97X	-0.1822	-1.7549	-0.6409	-1.1651	0.3912	0.3912	-1.4927	1.1284
GENE2645X	0.7145	-1.6046	0.5163	-0.2567	1.2893	1.1704	-0.2567	0.2983
GENE3408X	-0.2830	1.9551	-0.0079	0.2123	-1.2187	-1.6589	1.5515	-0.1363
GENE3854X	-0.5814	1.8312	0.0734	0.6421	-1.1845	-2.1668	1.4003	0.3319
GENE1406X	0.3805	0.0689	-0.9105	0.7589	-1.0886	-0.1760	1.2709	-0.0201
GENE1401X	-0.5903	0.0861	-1.1251	1.1558	-0.8419	-1.2824	1.1558	0.0547
GENE3462X	-0.5269	-1.1478	-0.9785	-1.1102	1.0726	0.3199	-1.3172	-0.3387
GENE3173X	-1.9774	-0.7247	-0.4200	0.7311	0.1217	0.3249	-1.1479	-0.2676
GENE3971X	0.7613	1.3156	0.7321	0.0903	-0.2598	-0.8724	0.5571	-0.0847
GENE1756X	-1.1498	1.4846	-1.0563	0.1908	-1.2122	-0.8225	0.7676	-0.7601
GENE1533X	-0.2646	1.4949	-0.6105	0.0963	-0.9263	-1.0315	-0.0992	-0.4451

GENE1757X	0.1061	1.8722	-0.3286	1.1658	-1.4019	-0.6547	1.0435	0.0925
GENE3572X	-0.2663	1.8330	-0.0420	0.1984	-1.2279	0.1984	-0.2343	-0.1381
GENE3571X	-0.9238	-1.3932	0.0454	0.2120	1.4841	-0.1817	-0.3029	-0.6058
GENE385X	-0.7754	0.0656	-0.1446	0.5095	0.9768	0.4394	0.2993	0.2292
GENE1614X	-1.0821	0.0647	-0.2963	1.0204	0.7656	0.1922	0.9780	0.2771
GENE1623X	-0.0164	-0.4100	0.2788	1.1053	1.0462	0.3378	-0.8232	1.0462
GENE1646X	-0.1882	-1.1784	0.4090	0.0161	2.2794	0.1890	-0.4711	-0.2511
GENE1660X	-0.2236	1.8073	-0.9288	0.7072	-0.9994	-0.5480	2.5830	0.4392
GENE1721X	0.0249	1.5808	-1.3001	0.6327	-0.6923	-0.8260	2.1035	0.3774
GENE1573X	-0.8298	0.7371	-0.6351	-1.0244	0.8539	-0.5475	0.5619	-0.2361
GENE1553X	-1.5425	0.1643	-0.0192	1.3572	1.1003	-0.2211	-0.1660	0.7332
GENE1773X	-0.9401	0.3774	0.4382	0.7220	0.7220	-0.6563	0.1544	-0.0483
GENE913X	0.4635	0.3056	0.6717	0.5353	-1.1588	-0.5414	1.0234	0.7291
GENE3980X	0.1913	0.3664	0.3314	0.7166	-1.2586	-0.2360	1.0738	0.6325
GENE3X	-0.3727	1.1541	-0.1972	-0.7237	0.6802	0.2415	-0.7588	0.4170

RowNames	DLCL0017	DLCL0018	DLCL0020	DLCL0021	DLCL0023	DLCL0024	DLCL0025	DLCL0026
GENE3950X	0.8207	-0.0959	0.5847	0.3942	-1.0761	-0.3501	0.7300	-1.5572
GENE2531X	1.1909	-0.0732	0.4712	0.2313	-1.2726	-0.3869	0.7849	-1.3741
GENE918X	1.2248	-0.1633	0.5534	0.4173	-1.4063	-0.3266	0.7712	-1.1795
GENE3511X	2.2002	-0.7180	-0.8876	1.8270	0.5602	0.3453	0.9221	-0.6840
GENE3496X	2.5230	-1.4735	0.4645	-0.3689	0.0930	-0.1480	1.4486	-0.7003
GENE3484X	2.3548	-1.5149	0.3227	-0.4454	-0.1148	-0.4065	1.2464	-0.7468
GENE3789X	2.9271	-0.6264	0.4439	1.1289	-0.8405	-0.4551	0.3583	0.2727
GENE3692X	-1.2869	1.1879	0.3970	1.2517	-0.6873	0.0015	0.4225	0.7159
GENE3752X	3.1393	-0.1967	0.1338	-0.4170	-1.7703	0.2596	0.7160	0.6530
GENE3740X	2.0537	-0.2122	1.1565	1.1910	-1.5925	-1.0749	0.4434	-2.0871
GENE3736X	3.1475	-1.5069	1.0379	0.5368	-0.2411	-0.3598	0.0753	-0.2147
GENE3682X	0.5465	0.3485	-1.2034	0.9282	-1.0378	0.9570	0.5717	-0.9981
GENE3674X	-0.1600	0.4191	-1.1565	0.7011	-1.0324	0.7500	0.6071	-1.2505
GENE3673X	0.4317	0.7475	-1.4498	1.2319	-0.7232	0.7215	0.9032	-0.8616
GENE3644X	1.7303	0.5358	0.5743	0.4587	-0.5624	-1.2753	-0.6973	-1.4872
GENE3472X	0.8427	-0.1418	1.5991	0.5546	-0.4059	-0.9342	0.0383	-1.6546
GENE2530X	2.4848	0.0250	-0.0655	0.7665	-0.3006	0.7846	1.6709	0.1878
GENE2287X	1.1043	0.1860	0.1860	1.2328	-1.0903	0.7645	1.6368	-0.7414
GENE2328X	1.6062	-0.7072	0.1324	0.1324	-1.0616	-0.0915	0.8413	0.4682
GENE2417X	0.4342	-1.8301	1.4606	1.0682	-0.1696	0.2983	0.1926	0.0417
GENE2238X	-0.8129	1.7534	1.5302	-2.0217	-0.9431	-0.0691	-1.0547	1.5116
GENE1971X	2.4807	-0.5161	0.4640	1.0294	-1.4773	-0.5349	0.7279	-1.2888
GENE3086X	-0.1077	0.5725	0.5606	0.0713	1.3363	-0.5134	-0.7163	2.7445
GENE1009X	-1.0322	1.0196	-0.4260	0.0870	0.5844	-0.0840	-0.5503	2.1232
GENE1947X	0.2940	0.0750	0.6225	-2.2248	-0.5547	-0.2810	-0.2810	-0.0893
GENE3190X	-1.3087	-0.0376	0.5712	-0.9455	-0.1658	0.5605	-0.1872	-0.0910
GENE3379X	-2.2407	0.9641	-0.7218	-0.9345	-0.2054	-0.4636	-1.4660	2.0729
GENE3184X	-0.8896	1.1892	0.2999	-0.2337	-0.2893	0.2777	-0.6450	0.7112
GENE3122X	-0.0766	0.5002	0.0505	-0.2232	-0.4578	0.1092	1.1552	-0.2232
GENE1099X	-1.8586	0.7005	0.2480	-0.7039	-0.5478	-0.1655	-0.3996	-0.7585
GENE3032X	-0.8478	0.8219	0.7622	-1.3504	-0.4645	-0.0385	-0.3282	-0.7371
GENE2675X	-1.8648	0.8963	0.9464	-1.5147	-0.0241	0.8363	-0.7344	-0.6743

GENE2481X	-1.7274	0.9019	0.9563	-1.2650	-0.3946	0.6027	-0.9477	-0.6031
GENE2878X	-1.1508	0.4036	-0.1389	-0.9526	1.3008	-0.0032	-0.8900	1.4365
GENE2943X	-1.2512	1.1451	0.1776	-0.9924	0.8188	0.0876	-0.6212	2.0338
GENE2977X	-0.0666	0.2059	0.4013	-0.3134	0.9874	0.7406	-0.5139	1.5941
GENE3014X	-1.1738	1.6150	-1.0225	-0.0605	0.9880	1.3772	-0.0064	-0.0497
GENE2006X	-1.2467	-0.5492	-0.4308	1.2931	0.5035	0.1614	-0.3124	0.0429
GENE1368X	-1.4968	0.2823	-0.7564	0.3597	-0.1265	1.2768	-0.0602	0.3818
GENE1184X	-1.0629	0.2327	-0.7555	0.4522	-0.0089	1.1000	0.0021	0.3754
GENE1226X	-2.3779	0.5216	1.2717	-0.3213	0.0411	0.4036	0.1254	2.4770
GENE1228X	-1.4883	0.9311	-0.0570	-0.6499	0.9491	-0.4044	-0.7517	0.2723
GENE1231X	-2.5674	0.1543	0.8743	-0.8682	-0.1049	-0.7962	-0.9258	0.8311
GENE1246X	-2.6827	1.0206	0.5914	-0.6290	0.1790	-0.4523	-0.6711	1.2226
GENE1172X	-1.2171	1.1765	0.2083	-0.3027	0.7014	0.0649	-0.6882	1.9475
GENE1164X	-1.6987	1.5360	-0.4214	-0.8693	1.1213	0.9388	-0.3385	1.8843
GENE3029X	-3.4516	1.4861	-0.0135	-0.0866	0.6997	-0.3244	0.2608	-0.3610
GENE1027X	-1.9346	1.1097	0.2963	-0.1104	-0.7495	-0.9818	-0.9586	-0.7727
GENE1354X	0.5538	1.0921	0.0828	-0.0069	0.0603	-0.8817	0.4865	1.3389
GENE62X	-1.7550	0.5315	1.5512	0.5315	-0.0246	-0.4263	-1.7705	0.2380
GENE932X	0.9273	-0.6050	1.0388	-0.4657	-0.4935	0.7044	1.3731	0.1751
GENE3611X	0.2675	-1.7265	-0.8511	0.7052	0.0973	-0.0243	-0.2918	0.1459
GENE3631X	3.2187	-0.0949	0.5430	0.4721	-0.9632	-0.7860	-0.1126	-0.2367
GENE330X	0.6520	-0.3801	0.1689	0.6301	-0.6217	0.4983	0.0152	-0.0288
GENE331X	1.2585	-1.0930	0.5323	-1.3697	-0.1074	-1.2141	0.5496	-0.8164
GENE808X	-0.7813	-0.1340	0.6461	-1.3622	-0.4327	-0.7813	-0.5987	0.0154
GENE487X	-1.4128	1.0981	0.8769	-1.9591	0.4996	-0.0468	-0.8143	1.0330
GENE621X	-1.2623	0.7768	0.8364	-1.5962	0.1209	-0.0698	-1.2385	1.2299
GENE622X	-1.4906	0.5541	0.8968	-1.5615	0.2704	-0.3914	-0.9351	0.8141
GENE634X	1.6582	-1.2623	-0.0568	-0.3551	0.0302	-0.5912	-0.8770	-1.1753
GENE659X	0.2082	-1.3596	0.2974	-0.2252	0.0297	-0.9390	-0.0977	-1.2704
GENE669X	0.0934	-1.3345	0.2224	-0.4040	0.1579	-0.3764	0.0566	-0.9383
GENE674X	-0.5367	-0.6709	0.1755	-0.0310	0.4541	0.0619	0.1135	-0.7122
GENE675X	1.3386	-2.0404	-0.2453	0.7654	0.6975	0.0941	0.5693	-0.1171
GENE676X	-0.3198	0.2610	0.7814	0.7572	-0.8039	-0.1867	0.8056	-0.0173
GENE704X	2.6244	-0.7794	-0.4575	-0.4012	-0.1035	-0.2403	1.1679	-0.6748
GENE734X	2.0981	-0.9601	-0.3995	-0.3400	-0.1191	-0.4759	1.0872	-0.6798
GENE738X	0.6496	-1.1708	1.1224	0.3422	-0.9344	-1.1708	0.2477	-1.2181
GENE456X	1.3418	-0.0208	0.1170	0.2242	-1.0771	-0.8934	0.1170	-0.9700
GENE744X	1.5886	0.1287	-0.0959	0.3212	-0.4649	-0.2723	0.4175	-0.4328
GENE179X	0.9089	-0.6788	-1.0699	0.1726	0.7248	-0.4717	0.2416	0.3566
GENE124X	2.5199	0.0729	-0.0129	-0.6426	-0.1704	-0.0129	0.7026	-0.9288
GENE122X	2.0049	0.0766	0.1222	-0.2726	-0.2422	-0.0145	0.6840	-1.0469
GENE111X	1.4521	-0.1889	0.0959	-0.4466	-0.4737	-0.8534	0.7333	-1.6535
GENE97X	2.2424	-0.9194	0.4240	-0.5589	-0.8866	-0.4770	0.3748	-0.0347
GENE2645X	1.8642	-0.4549	-0.9505	-0.3360	0.1397	0.2190	1.6263	-1.1289
GENE3408X	1.0562	-0.8701	0.5058	-0.8884	0.8177	-0.1546	0.1389	2.8540
GENE3854X	0.1768	-0.9605	0.7972	-1.3052	0.4353	-0.1506	0.0734	3.4338
GENE1406X	-0.2427	0.5809	-1.5783	-1.9789	1.0705	-0.3985	-0.1092	0.2692
GENE1401X	-0.4959	1.6749	-0.0712	-1.6756	-0.8262	0.0075	-0.8105	0.5738
GENE3462X	2.4462	-0.2446	-0.8656	0.5269	-1.0161	0.5833	-0.3387	-0.9032

GENE3173X	2.6610	0.3926	-0.9448	0.7142	-0.2168	0.4603	0.8835	-0.7416
GENE3971X	-0.5224	0.5571	0.4696	0.4696	-0.1139	-1.6601	-0.9891	-0.1431
GENE1756X	0.8299	1.0949	-0.7290	-1.7266	-0.3081	-0.5419	-0.1989	1.3132
GENE1533X	0.0662	1.0136	-0.4451	-1.9790	-0.6406	-0.8812	-0.4451	0.0211
GENE1757X	-0.0433	0.7854	-0.2200	-0.2471	0.2284	-0.0705	-0.5868	-0.1928
GENE3572X	0.2465	0.0221	-0.2984	-0.3304	0.4708	-0.7150	-1.0356	1.8490
GENE3571X	2.3473	-0.9541	-0.6512	2.4079	-0.2726	-0.1060	-0.0454	0.1212
GENE385X	-0.2614	-0.3549	-0.4951	0.7431	0.1124	-1.3127	-0.1446	-1.0557
GENE1614X	1.8700	-0.4875	-0.6998	0.6169	-0.6149	-0.7848	0.1072	-0.2751
GENE1623X	1.6366	-0.2722	0.3772	0.4559	-0.6264	-0.7445	1.3611	-2.2991
GENE1646X	0.7077	-0.7383	-0.8169	0.1733	0.3462	-0.4711	0.2676	-0.7855
GENE1660X	0.1007	1.0598	0.6085	-1.9302	0.4251	0.0584	-0.9006	0.1289
GENE1721X	0.3409	0.8150	0.9852	-2.0173	0.5841	-0.2668	-1.0448	0.5233
GENE1573X	0.1824	0.1337	-0.1583	0.6008	0.3673	-0.5086	0.4841	-0.6546
GENE1553X	1.3021	-0.2578	0.8066	1.1920	-1.0836	-1.2855	0.9534	-1.0653
GENE1773X	0.7423	-0.4131	0.4382	0.4787	-0.2712	-0.9604	1.3909	-1.0009
GENE913X	-0.2400	-0.1682	1.2531	-2.2284	0.3630	-0.2112	-0.8429	1.9925
GENE3980X	-0.1799	-0.2360	1.1999	-1.9660	0.5905	0.1703	-0.7403	1.8862
GENE3X	2.2246	-0.4429	0.2766	0.9961	0.2064	-1.1273	0.3117	-0.8465

RowNames	DLCL0027	DLCL0028	DLCL0029	DLCL0030	DLCL0031	DLCL0032	DLCL0033	DLCL0034
GENE3950X	0.1491	0.5847	0.2126	0.7753	1.1111	-0.7766	-0.5316	-1.3847
GENE2531X	0.1944	0.4897	0.2313	0.8772	1.0709	-0.6452	-0.8297	-1.5309
GENE918X	0.1996	0.6442	0.0998	0.6351	0.9889	-0.7984	-0.8619	-1.5061
GENE3511X	1.1257	1.1483	-0.1185	0.1530	-0.6954	-0.2429	-1.6794	0.4018
GENE3496X	0.4043	0.6252	0.1030	-0.2183	1.0771	-0.1580	0.9767	-1.0216
GENE3484X	0.2060	0.8575	0.1963	-0.0079	0.9644	0.1380	1.4603	-0.9996
GENE3789X	0.3583	0.8721	-0.6264	0.4439	-0.2839	-0.5622	-1.2044	-0.9475
GENE3692X	-1.0318	-0.1771	-0.3939	-0.0495	0.2311	0.3460	-0.0878	-1.1849
GENE3752X	0.1338	0.8419	0.4327	0.4013	0.8576	-1.0464	-0.5429	-1.6601
GENE3740X	0.9495	0.6274	0.1558	0.5699	1.2830	-0.1777	-1.0864	-0.7183
GENE3736X	0.6951	0.9324	-0.8081	0.3654	1.1697	0.2731	-1.0059	-0.6367
GENE3682X	-0.4076	1.6339	-1.2610	1.1010	0.9102	0.2837	-1.0198	-0.4833
GENE3674X	-0.4571	1.4419	-1.1640	1.1711	1.3065	0.6221	-1.5099	-0.0998
GENE3673X	-0.4247	1.4655	-1.3979	1.2060	0.9248	0.8859	-1.2379	-0.3512
GENE3644X	0.5165	0.7670	-0.8321	-0.1385	0.3239	-0.5817	-0.5046	-1.0826
GENE3472X	0.2784	0.2544	-0.1058	1.0588	0.6146	-0.2979	-0.9462	-1.4385
GENE2530X	0.5857	1.0740	0.4772	0.6942	0.4952	-0.6442	-1.1868	-1.5124
GENE2287X	-0.2272	1.1318	0.0575	0.7921	0.5717	-1.1270	-1.6504	-1.4392
GENE2328X	-1.3974	-0.0542	-0.2408	0.0204	1.3077	-0.5392	-2.3862	-0.6885
GENE2417X	0.4945	1.1134	0.1474	0.1323	0.3134	0.0115	-0.4413	-1.0904
GENE2238X	-1.5940	-0.5898	0.5446	1.1211	-0.1063	1.3071	-0.8501	1.2141
GENE1971X	-0.8553	0.4263	0.4075	-0.1768	1.0294	0.0682	-1.4396	-0.5538
GENE3086X	-0.9550	0.3935	0.3339	-0.2867	0.2742	-0.1077	3.3650	-0.2748
GENE1009X	-0.1928	-0.8612	-0.1617	0.9263	-1.9182	-0.5348	-1.5607	0.7398
GENE1947X	-1.8963	0.2940	0.3214	0.7868	-1.8415	0.6773	-1.1297	0.9237
GENE3190X	-0.0376	-0.2406	1.1373	3.3376	-0.5076	1.3402	-0.4435	-0.2833
GENE3379X	-0.9648	-1.8609	-0.2054	0.5996	-0.0080	1.0552	-1.5420	1.1312
GENE3184X	-0.2560	-0.3782	0.4111	0.7446	-1.7456	0.4889	-0.3894	0.9113

GENE3122X	-0.4383	0.4611	0.7739	1.1747	-0.0766	-0.5263	-0.4481	1.8590
GENE1099X	0.1466	-0.4230	0.4899	1.0282	-0.6961	1.1062	-0.7195	1.1609
GENE3032X	0.2767	-0.5326	0.4130	1.0774	-0.6860	1.1285	-0.3622	0.7111
GENE2675X	0.7263	-0.1341	0.6562	0.5162	-1.3446	0.4061	0.4862	0.5262
GENE2481X	0.3035	-0.0954	0.7115	0.8475	-1.1199	0.5030	0.8112	0.6934
GENE2878X	-0.5040	-0.4101	2.1354	0.7375	-1.0986	1.7599	-0.7439	0.3932
GENE2943X	-0.5424	-0.1937	2.1013	0.6388	-0.8012	1.2913	-0.7112	0.2676
GENE2977X	-0.7607	-0.4059	0.8794	0.5710	-1.0743	0.8229	-1.0435	1.7843
GENE3014X	-0.1470	-0.2226	1.0853	-0.0064	-1.2819	0.3395	-0.8063	0.2530
GENE2006X	-0.1545	-0.3782	0.8983	-0.1281	-0.7466	0.4509	0.3587	1.7800
GENE1368X	0.3155	-0.3033	0.6249	-0.0492	-1.2316	0.4370	-0.0934	1.6967
GENE1184X	0.2766	-0.3712	0.5181	-0.1846	-1.1398	0.5181	-0.0967	1.3965
GENE1226X	-0.5826	-1.2822	0.3867	0.4289	-0.1106	0.4289	1.0273	1.2380
GENE1228X	-1.3147	-0.5781	-1.1829	0.5059	-0.8835	0.2664	1.1766	-0.4762
GENE1231X	-0.6521	-1.6314	1.0327	1.2631	0.7303	0.9895	1.6232	0.9175
GENE1246X	-1.5212	-0.8226	1.4583	1.0206	-0.6375	1.0459	1.2479	1.0879
GENE1172X	-1.5578	0.0739	1.0690	0.3607	-1.3605	0.5400	0.9614	0.4145
GENE1164X	-0.8693	-0.9191	1.7516	-0.0067	-1.3006	0.1094	0.8061	0.1758
GENE3029X	-0.6353	-1.1839	0.3157	0.1145	-0.5621	0.0779	0.0231	1.7604
GENE1027X	-0.8076	-1.3304	0.6797	-0.0871	0.2382	-0.5635	1.7022	0.7611
GENE1354X	-0.2312	-1.3079	1.2267	0.5987	-1.1284	0.5090	0.5987	1.7650
GENE62X	-1.3997	-0.5499	0.4852	0.8714	-1.3688	0.1299	0.1453	0.5006
GENE932X	0.8437	2.1253	-0.3542	0.5373	-0.3264	-0.5492	-1.9143	-0.9950
GENE3611X	0.9484	-0.2675	0.7295	0.3161	1.5563	-0.7782	-0.4620	0.8025
GENE3631X	0.2949	0.6139	-0.3430	-0.4316	0.0646	-0.9455	-1.9201	-0.2898
GENE330X	1.0254	-0.1605	0.1689	-0.2044	-0.1825	-0.0727	-1.3025	-0.9950
GENE331X	-0.0729	0.8263	-0.5224	-0.1593	-0.2804	-0.1939	-0.2112	-0.1420
GENE808X	-0.9638	-0.1506	0.5797	0.4469	-0.6983	1.8411	-0.0676	-0.3165
GENE487X	-0.4631	-0.9314	-0.9054	0.5517	-1.6860	-0.2289	0.7598	1.7095
GENE621X	-0.3918	-0.7018	-0.7138	0.8126	-1.5843	-0.7853	1.1226	1.7069
GENE622X	-0.8642	-1.0888	-0.8287	0.8141	-1.6679	-0.3205	1.3342	1.7951
GENE634X	0.4403	0.6143	-0.1562	-0.2059	0.8628	0.0302	0.0799	-0.0941
GENE659X	0.8965	-0.3399	0.1062	-0.0850	1.0877	0.6033	0.4376	-1.0919
GENE669X	0.9318	-0.1553	0.3606	-0.1000	1.1068	0.6738	0.3606	-1.5464
GENE674X	1.1560	0.0826	0.2787	-0.4232	0.8670	0.5057	0.1755	-1.8475
GENE675X	-0.1397	0.8634	0.1469	0.3279	1.2028	-0.1699	-0.9392	-0.3358
GENE676X	-0.2351	0.9266	-0.4892	-1.2879	0.0674	-0.4408	-0.4408	-0.2230
GENE704X	-0.6104	0.4518	-0.3127	-1.1173	1.0633	-0.1035	-0.8277	-1.1093
GENE734X	-0.4929	0.2971	-0.1191	-0.6203	1.2316	-0.1956	-0.8072	-0.8242
GENE738X	-0.1779	1.3589	-0.5325	-0.7453	1.2406	-0.2488	-0.1070	-0.7216
GENE456X	-0.4648	-0.8628	0.4385	-0.3117	1.9082	-0.5413	-1.5517	-0.8934
GENE744X	-0.3205	-0.1600	0.0966	-0.6895	1.6047	-0.6253	-2.4221	-1.1226
GENE179X	-0.1265	0.6558	0.0575	0.0345	0.6788	-0.3796	-0.3106	0.2646
GENE124X	0.1302	0.8313	-1.3009	0.1874	0.6024	-0.7571	-0.0416	-0.0416
GENE122X	0.4410	0.3044	-0.9254	0.2285	0.5169	-0.8647	-0.2878	0.2892
GENE111X	0.8689	0.3943	-0.8399	0.4349	0.7604	-1.1111	-0.2025	0.6926
GENE97X	0.2602	0.2438	-1.0996	-0.3460	-0.1002	0.0308	-0.8374	0.5550
GENE2645X	1.0515	0.8334	-0.1378	0.1992	-0.2171	-1.4064	-0.2171	-1.5055
GENE3408X	-0.5215	-0.3381	-0.5215	0.3040	-1.6589	0.6159	0.6709	0.6709

GENE3854X	0.1424	-0.4263	-0.0816	0.1768	-1.2879	0.5043	-0.1506	0.7800
GENE1406X	-0.4876	0.4473	1.4712	0.1134	-0.5098	0.8034	1.9386	0.8925
GENE1401X	-1.5498	-0.3543	1.4389	0.3693	-0.3700	0.2434	-0.3858	0.5109
GENE3462X	0.1694	1.1855	-0.0188	-0.3387	2.2580	-0.6962	-1.8064	0.0941
GENE3173X	-0.0476	1.0358	-1.1817	-0.7755	0.4434	-0.5046	-0.5893	1.5268
GENE3971X	-0.4348	-0.9016	0.7613	0.9655	-1.6310	-0.1431	1.1114	1.3740
GENE1756X	-1.2122	-0.1210	-1.0563	0.7364	-0.3081	0.3311	1.7340	0.5025
GENE1533X	-1.1519	-0.8210	-0.6706	1.1189	0.1114	0.5324	1.8558	1.1941
GENE1757X	-0.5732	-0.5460	0.1197	0.5408	-0.4509	0.2555	0.2827	1.7500
GENE3572X	-0.4907	-1.1157	0.0221	0.6311	-1.2920	0.5029	1.6247	1.4164
GENE3571X	0.7118	0.9238	-0.2574	-0.5603	0.2877	-0.3029	0.3483	-1.0298
GENE385X	0.6263	0.8366	-1.2193	-0.0979	-0.3549	-0.7287	-1.4996	-0.1213
GENE1614X	0.4045	0.9355	-1.9741	-0.7636	-0.8697	-0.8697	-1.8255	-0.6574
GENE1623X	-0.1935	1.7153	-1.0594	0.4362	0.0230	-0.6658	-0.3313	-0.9216
GENE1646X	0.0632	0.3462	-0.5183	-0.7698	-0.0153	-0.6598	0.4876	-0.0468
GENE1660X	0.5803	-0.7596	1.5534	1.2008	-0.8301	0.4392	-0.0685	-0.3083
GENE1721X	0.1343	-0.4978	0.1586	0.4625	-0.8868	0.2802	0.4747	-0.6801
GENE1573X	0.5522	-0.0707	-0.6546	-0.0512	0.6787	-1.2191	-0.8200	-1.5986
GENE1553X	-0.5698	0.0358	-1.8544	0.0175	1.0452	-0.7350	-0.7533	-1.1571
GENE1773X	-0.5753	1.2085	-1.4671	0.5801	1.1679	-0.4739	-0.8388	-1.3455
GENE913X	0.3774	-0.8142	0.0400	0.8942	-0.6922	0.9014	1.1957	0.2195
GENE3980X	0.3734	-0.8663	-0.0118	0.7446	-0.8943	0.8917	0.9337	0.3314
GENE3X	-1.1624	0.2766	-0.9167	-0.8641	0.0836	-0.6359	-0.8992	-0.9869

RowNames	DLCL0036 OCT	DLCL0037	DLCL0039	DLCL0040	DLCL0041	DLCL0042	DLCL0048	DLCL0049
GENE3950X	0.8298	-1.2395	1.4560	0.5575	-1.0489	2.1821	-0.7403	0.6392
GENE2531X	0.7572	-0.3684	1.6061	0.6557	-0.7559	2.2981	-0.7651	0.5635
GENE918X	0.8528	-0.7349	1.5061	0.5807	-0.7077	2.0686	-1.2793	0.4355
GENE3511X	-0.6162	-0.9555	0.7864	2.4038	0.6846	-0.5144	0.6054	1.1031
GENE3496X	0.7357	-1.0116	0.6553	0.6654	-1.3329	1.5088	-0.9111	0.0328
GENE3484X	0.9158	-0.7176	0.9644	0.7797	-1.3107	1.3533	-1.0288	-0.3482
GENE3789X	-0.2625	-0.9261	0.9149	0.3583	0.4439	0.0158	0.3155	1.5785
GENE3692X	-0.9170	1.8895	0.7159	-1.0573	-0.5725	0.0398	-0.3174	0.0143
GENE3752X	0.7160	-0.8733	0.8576	0.7632	-0.1810	1.2667	-0.3383	0.6688
GENE3740X	0.6389	-0.2122	0.7769	0.1788	-0.3273	1.7546	-0.0512	0.0408
GENE3736X	0.4841	-0.9267	1.2752	0.6423	-0.4125	0.5105	-0.0829	1.0774
GENE3682X	1.8896	-0.2600	1.8824	0.7158	0.4889	0.5681	-0.9981	0.6689
GENE3674X	1.8781	-0.3781	1.4757	0.4379	0.5695	0.9380	-0.9985	0.7011
GENE3673X	1.1324	-0.1133	1.2579	1.0676	1.3401	1.2016	-0.3166	0.9075
GENE3644X	-0.7165	-0.0615	1.9615	1.4028	0.6707	2.0000	-0.3890	0.8633
GENE3472X	0.6506	-1.1383	0.8908	0.4465	-1.2704	2.8718	-0.0457	0.2064
GENE2530X	1.3815	-0.6623	1.1825	0.7304	0.6038	0.1516	-1.8199	1.7794
GENE2287X	0.7921	-0.0986	0.8013	1.2053	0.4707	1.8113	-1.5402	1.5909
GENE2328X	0.3376	-0.6325	1.0652	1.2704	-0.0915	1.3823	-0.4833	1.7741
GENE2417X	-0.9848	-1.1357	0.7059	-0.4263	-0.6527	0.5247	-0.6376	0.0417
GENE2238X	-1.7986	0.8794	0.7120	-0.9803	-1.3336	0.2285	-0.7571	-0.4038
GENE1971X	0.9917	-0.4030	0.0494	-1.0438	-0.4972	2.8577	-0.1203	0.7844
GENE3086X	-1.0624	0.5129	-1.2414	-1.4562	0.5606	-0.4299	-0.4299	-0.7998

GENE1009X	-1.0944	2.2476	-1.1099	-0.3949	-1.7161	-0.5037	0.5688	-0.3638
GENE1947X	-0.5274	1.2249	-0.5821	-1.6499	0.9511	0.7047	-1.5404	-1.1297
GENE3190X	-0.9242	-1.3087	-0.4008	-0.7105	-0.5396	-1.1592	-0.7212	-0.1765
GENE3379X	-0.1447	0.5085	-0.9800	-1.3597	0.2047	0.2654	-0.6762	-0.0991
GENE3184X	-1.7678	1.6228	-0.5561	-1.2565	-0.6450	-0.2782	-0.5005	-1.2342
GENE3122X	-0.0668	0.8228	-1.2203	-0.0472	-3.2243	-2.2663	-1.1519	-0.0179
GENE1099X	-1.7104	2.0269	-1.4997	0.8566	1.6368	-2.0069	0.5211	-1.2734
GENE3032X	-2.0916	2.0060	-1.9638	0.0807	1.6226	-1.4015	0.5152	-0.8393
GENE2675X	-1.1345	0.0960	-0.3442	-1.4247	1.5366	-1.2946	0.2861	0.4361
GENE2481X	-0.9386	0.2400	-0.4127	-1.6367	1.4731	-1.4735	-0.6666	-0.2677
GENE2878X	-1.1091	2.5319	-0.9735	-0.8796	-1.2447	-0.1180	-0.9526	-0.8065
GENE2943X	-1.2849	0.9763	-1.2849	-0.2049	-0.9362	-1.1049	-0.9812	-1.4199
GENE2977X	-1.3468	1.6250	-0.8944	0.4116	-1.0486	-1.5525	-0.6424	-0.7144
GENE3014X	0.7286	1.8852	-0.0172	-0.5361	-0.1253	-1.5306	-1.0874	-0.5793
GENE2006X	-0.1150	2.9775	-0.4177	-0.8519	-0.7335	-1.1941	-1.6941	-1.6941
GENE1368X	-1.5189	1.0448	-0.6127	-0.3807	-2.9443	0.4702	-1.1211	-1.2095
GENE1184X	-1.5680	1.7698	-0.6018	-0.2724	-3.3027	0.3754	-1.2276	-1.1727
GENE1226X	-1.2569	0.9430	-1.1726	-0.8692	0.1254	-1.2737	-1.2063	-0.0179
GENE1228X	-0.8416	1.3563	-0.6679	-0.6559	-1.1410	-1.0452	0.0687	-0.7577
GENE1231X	-1.0410	0.3559	-0.3209	-1.1130	-1.1130	0.9895	0.1543	-0.4361
GENE1246X	-0.2587	0.6334	0.2968	-1.0751	-0.5533	0.7176	-0.2250	-0.6038
GENE1172X	-0.1503	1.5262	0.2442	-0.8854	-0.2399	0.1904	-0.2847	-0.1323
GENE1164X	-0.0233	1.5028	0.4743	-0.8693	0.4246	-0.3717	-0.5873	0.4578
GENE3029X	0.3705	0.5169	-1.0010	-1.5131	0.8277	-1.3851	-1.4034	-0.2330
GENE1027X	-1.2259	1.2375	-0.9237	-0.0407	-0.7959	-1.1561	-0.0174	-0.1104
GENE1354X	0.1276	0.8230	-0.5228	-0.7247	-2.1602	-3.9322	-1.0836	0.5090
GENE62X	-0.9980	1.4585	0.0681	-1.3070	-0.8898	-0.5036	0.2534	0.3925
GENE932X	1.6795	0.6209	0.4259	0.2587	0.2308	2.0138	0.5652	1.4845
GENE3611X	0.5350	0.3891	0.4620	0.7538	0.6809	2.9181	0.2432	-0.0730
GENE3631X	0.4544	-0.2721	0.6316	0.1000	2.2973	0.9683	-0.3607	1.5530
GENE330X	-0.4240	-0.1605	-0.0946	-0.0068	1.3987	2.6065	0.7179	2.1893
GENE331X	0.9300	-0.8164	0.9127	0.6015	-0.0037	0.8781	0.2557	0.1865
GENE808X	-0.7979	0.0984	-1.4286	-1.5779	-0.9804	0.0486	-0.3331	-0.4825
GENE487X	-1.0615	1.0720	0.0833	-0.7883	-0.2939	-2.1543	0.7078	0.5517
GENE621X	-1.2981	0.8245	0.0733	-1.0954	-0.2487	-1.8705	0.8603	0.3833
GENE622X	-1.2306	0.2468	0.5659	-1.0297	-0.1432	-1.8452	0.6368	0.6014
GENE634X	0.4900	-0.8149	0.6267	0.2663	-2.0576	3.1122	1.4966	0.0178
GENE659X	0.6416	-0.7478	0.3102	-0.4801	-1.9459	1.5975	0.8582	-0.6840
GENE669X	0.3422	-0.6528	0.5817	-0.1829	-2.0991	1.4016	0.6278	-0.4961
GENE674X	0.2993	-0.7431	0.4645	-0.2684	-2.1262	1.3005	0.9599	-0.4438
GENE675X	1.4366	-0.8638	0.4712	0.5843	-0.4489	1.5497	0.8483	0.2977
GENE676X	-0.0657	-1.1185	-1.0822	1.7374	-1.3969	0.5273	1.0960	0.9266
GENE704X	1.2967	0.2506	0.9587	0.9185	3.1152	0.8219	0.8058	1.1438
GENE734X	1.2061	-0.7902	0.9597	1.0277	3.2704	1.0956	1.0532	1.3250
GENE738X	0.6496	-0.0124	2.0445	0.6260	-1.1472	1.3589	0.1768	0.6496
GENE456X	1.2499	-0.8934	1.1887	0.7753	2.0766	2.3063	0.1017	0.4844
GENE744X	1.1394	-0.8820	1.7811	0.8025	2.1982	1.7170	-0.0477	0.1929
GENE179X	1.0929	1.1389	1.6681	1.3690	0.7018	1.6221	1.7602	0.4717
GENE124X	0.3305	-0.8000	0.9172	1.7615	1.1032	1.5755	0.4020	0.1731

GENE122X	0.3044	-1.0621	0.8206	1.9593	1.0787	1.2002	1.0332	0.5018
GENE111X	0.7197	-1.1518	0.5027	1.1944	1.1808	1.8047	0.6655	-0.2296
GENE97X	-0.4934	-0.6572	-0.0183	0.9482	-0.3951	3.1435	1.8820	0.4404
GENE2645X	0.5361	0.4370	-1.1685	1.9434	-1.2676	0.2190	1.2893	0.9325
GENE3408X	1.6983	-0.2464	-0.5215	-0.8884	-1.4205	-0.1730	-0.8517	-1.1269
GENE3854X	0.9695	-0.4263	-0.9433	-1.4775	-0.5814	0.5387	-0.6331	-0.5125
GENE1406X	0.4028	2.2058	-1.0663	-0.7102	0.6031	-1.3334	-1.2666	-1.1108
GENE1401X	-0.8891	0.0075	-1.3925	-0.3071	0.2120	-0.0240	-0.0554	-0.7318
GENE3462X	0.9408	-1.0161	-0.3011	0.5833	0.8279	2.6908	0.0188	-0.3763
GENE3173X	1.8484	-0.4708	0.3418	2.1023	0.8158	1.0189	-0.2507	-1.1140
GENE3971X	-2.2436	1.6365	0.9072	-0.6099	-2.0394	1.3740	-0.4057	-0.9308
GENE1756X	-0.0119	1.3443	-0.4016	-0.2301	1.1105	-1.3525	0.5649	-0.6510
GENE1533X	-0.2496	0.2166	-0.8661	-0.5202	0.8181	-0.6105	0.9685	-0.7759
GENE1757X	-1.1302	0.3099	-0.7498	-1.1030	-2.3529	-1.3204	0.2555	-0.1520
GENE3572X	-0.3785	0.2305	-1.2920	-1.4843	-1.1477	-0.7631	0.4869	-0.7952
GENE3571X	2.8319	-0.4543	0.8329	-0.3635	-0.5906	1.4841	-0.5603	0.4240
GENE385X	2.7289	-2.2939	0.7665	1.1403	-0.5184	0.5329	1.1403	0.6497
GENE1614X	2.4646	0.4045	0.6382	1.0842	-0.4450	-0.2963	0.6594	0.2559
GENE1623X	1.0462	-2.8304	-0.5871	1.3021	-0.4100	0.8495	0.3968	-0.3509
GENE1646X	3.8354	0.2676	0.9906	2.5623	0.0947	-0.8484	-0.7698	-0.2825
GENE1660X	-0.3365	-0.4352	0.2136	0.4110	-1.7469	-2.5790	-0.8160	0.2277
GENE1721X	-0.0845	1.8847	0.3166	0.8272	-1.3366	-3.0870	-0.8625	0.2194
GENE1573X	0.0753	1.1166	1.0485	2.8976	1.5838	0.1337	-0.5378	1.4573
GENE1553X	0.4029	-0.3496	0.4212	1.4306	-1.0836	1.6692	0.8984	0.3662
GENE1773X	0.6814	0.8436	0.8639	1.7963	-1.1834	1.4720	0.1139	0.3977
GENE913X	-1.8551	1.0880	0.5927	-0.8788	-1.7761	-1.8048	-0.2687	-1.3526
GENE3980X	-1.8189	1.1788	0.4574	-0.9854	-2.0990	-1.8189	-0.1729	-1.3986
GENE3X	0.6276	0.7329	1.2594	1.5928	-0.6008	0.9786	-0.6008	0.8206

RowNames	DLCL0051	DLCL0052
GENE3950X	-1.7024	-2.8096
GENE2531X	-2.0292	-2.2322
GENE918X	-2.0232	-2.1684
GENE3511X	-1.2043	-1.4193
GENE3496X	-1.6643	-1.7446
GENE3484X	-1.6899	-1.8163
GENE3789X	-1.6753	-1.8037
GENE3692X	-0.1133	2.3233
GENE3752X	-0.9678	-0.4957
GENE3740X	-0.8103	0.8574
GENE3736X	0.6951	-2.2716
GENE3682X	-1.1782	-1.3402
GENE3674X	-1.2693	-1.4610
GENE3673X	-1.3244	-1.6575
GENE3644X	-0.2156	-1.7376
GENE3472X	-0.9702	-1.1023
GENE2530X	-2.4891	-1.2592
GENE2287X	-2.6513	-0.6220
GENE2328X	0.7294	-0.8751

GENE456X	-1.2762	-0.2657
GENE744X	-1.3312	-0.5290
GENE179X	-0.4027	-0.9779
GENE124X	0.4593	-2.2024
GENE122X	0.5929	-2.2160
GENE111X	0.8553	-2.0875
GENE97X	1.0629	-0.3624
GENE2645X	-1.7830	-0.7919
GENE3408X	1.3313	0.8544
GENE3854X	1.2453	0.8317
GENE1406X	-0.1537	2.0054
GENE1401X	-0.5903	2.4299
GENE3462X	-0.0941	0.6774
GENE3173X	-0.9786	-1.4865
GENE3971X	0.0903	1.4907
GENE1756X	0.5493	1.3911
GENE1533X	1.4046	2.0814
GENE1757X	-0.8721	3.4890
GENE3572X	3.0670	-0.3625
GENE3571X	-0.9238	-1.4084
GENE385X	-0.0979	2.1215
GENE1614X	-0.3388	1.6363
GENE1623X	-1.4332	0.4165
GENE1646X	0.2676	-1.0055
GENE1660X	0.8482	0.8200
GENE1721X	0.8515	0.7664
GENE1573X	-1.8127	-2.6010
GENE1553X	-1.9462	-0.3312
GENE1773X	-2.2779	-0.4131
GENE913X	0.0974	0.5999
GENE3980X	0.1422	0.8567
GENE3X	-1.2151	-1.4783

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprising" is used in the sense of "including", i.e. the features specified may be associated with further features in various embodiments of the invention.

It is to be understood that a reference herein to a prior art document does not constitute an admission that

GENE2417X	-1.1206	-1.5131
GENE2238X	-0.2736	0.9537
GENE1971X	-0.8365	-1.4208
GENE3086X	0.7993	-0.3583
GENE1009X	1.5015	1.2683
GENE1947X	0.7868	1.0058
GENE3190X	-0.9562	1.8209
GENE3379X	0.2502	1.9969
GENE3184X	0.3777	2.1342
GENE3122X	0.2167	1.4484
GENE1099X	1.0126	1.4027
GENE3032X	1.0604	1.9037
GENE2675X	-0.2241	1.5166
GENE2481X	0.0043	1.7542
GENE2878X	-0.5562	0.7062
GENE2943X	-1.0712	0.2113
GENE2977X	-1.1463	1.6095
GENE3014X	-1.1955	0.6637
GENE2006X	-0.0097	0.5167
GENE1368X	-0.6901	1.8846
GENE1184X	-0.8433	1.7039
GENE1226X	0.3867	0.6733
GENE1228X	2.4403	-0.5182
GENE1231X	1.0471	1.6664
GENE1246X	0.9617	1.3825
GENE1172X	0.2532	1.4007
GENE1164X	-0.3717	-0.7366
GENE3029X	-0.4341	1.1935
GENE1027X	2.2832	-0.1104
GENE1354X	-0.2088	0.7781
GENE62X	-0.1946	1.0105
GENE932X	-1.8029	-0.4099
GENE3611X	-0.3161	-0.8268
GENE3631X	1.3227	-1.3708
GENE330X	0.0591	-0.1386
GENE331X	1.8637	-1.7847
GENE808X	3.9324	0.9117
GENE487X	-0.6842	0.1484
GENE621X	-0.6422	0.4310
GENE622X	-0.1078	0.9678
GENE634X	-0.4048	-1.6227
GENE659X	0.6925	-1.4998
GENE669X	0.0290	-2.2004
GENE674X	-0.2684	-2.3635
GENE675X	0.0262	-2.7342
GENE676X	-1.5179	-1.2516
GENE704X	-1.3668	-1.6323
GENE734X	-1.7332	-1.0536
GENE738X	-0.8399	-0.7216

the document forms part of the common general knowledge in the art in Australia or in any other country.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for identifying components of a system from data generated from the system, which exhibit a response pattern associated with a test condition applied to the system, comprising the steps of:

   a) specifying design factors to specify a response pattern for the test condition;
   b) identifying a linear combination of components from the input data which correlate with the response pattern.

2. The method of claim 1 including the step of defining a matrix of design factors.

3. The method of claim 1 wherein the linear combination is computed by solving the equation:

$$(XPX^T-\lambda X(I-P)X^T)a=0 \text{ for } \lambda \text{ and } a$$

wherein X is a data matrix having n rows of components and k columns of test conditions and $P = T(T^TT)^{-1}T^T$ wherein T is a matrix of k rows of design factors and r columns.

4. The method of claim 1 wherein the linear combination is computed by solving the equation:

$$(XPX^T-\lambda X(I-P)X^T +\sigma^2 I)a=0 \text{ for } \lambda \text{ and } a$$

wherein X is a data matrix having n rows of components and k columns of test conditions; and $P = T(T^TT)^{-1}T^T$ wherein T is a matrix of k rows of design factors and r columns and a is a weight matrix for the linear combination $y^T=a^TX$.

5. A method for identifying components of a system from data generated from the system, which exhibit response patterns to a test condition applied to the system, comprising the steps of:

a) specifying design factors to specify a response pattern for a test condition;
b) formulating a model for the residuals of a regression of the input data on the design factors;
c) estimating perimeters for the model; and
d) computing a linear combination of components using the model and the estimated perimeters.

6. The method of claim 5 wherein the linear combination may be computed from the equation:

$$a=\lambda^{-1/2}XPu$$

wherein a is a weight matrix for the linear combination $y^T=a^TX$,
$P = T(T^TT)^{-1}T^T$,
u is an eigenvector of $P(XV^{-1}X^T)P$ or equivalently a right singular vector of $V^{-1/2}XP$;
and X is an nxk data matrix of data generated from a method applied to a system, wherein the data is from n components and k test conditions.

7. The method of claim 5 wherein the residual covariance matrix is computed from the model:

$$V=\Lambda\Phi\Lambda+\sigma^2I$$

8. The method of claim 7 wherein the estimate of Λ may be computed from the singular vectors of R, wherein

$$R=X-\hat{B}\,T^T$$

9. The method of claim 8 wherein the estimate of σ is computed from the equation:

$$\sigma^2=1/(k(n-s))\{tr\{RR^T\}-\sum_{i=1}^{s}\delta_{ii}\},$$

10. The method of claim 8 wherein the estimate of ϕ is computed from the equation:

$$\Phi_{ii}+\sigma^2=\delta_{ii}/k$$

11. The method of claim 8 wherein the number of factors is computed using the Bayesian method whereby the number of factors is chosen to maximise

$$\log P(R|s)=\log P(u)-0.5n\sum_{j=1}^{s}\log(\lambda_j)$$
$$-0.5n(k-s)\log(v)+0.5(m+s)\log(2\pi)$$
$$-0.5\log\det(A_z)-0.5s\log(n)$$

where m=ks-s(s+1)/2,

$$\log P(u)=-s\log(2)+\sum_{i=1}^{s}\log(\Gamma((k-i+1)/2))$$
$$-0.5(k-i+1)\log(\pi)$$
$$v=(\sum_{j=s+1}^{k}\lambda_j)/(k-s)$$

and

$$\log\det(A_z)=\sum_{i=1}^{s}\sum_{j=i+1}^{k}\log((\hat{\lambda}_j^{-1}-\hat{\lambda}_i^{-1})(\lambda_i-\lambda_j)n)$$

where

$$\hat{\lambda}_j=\begin{cases}\lambda_j, for\ j\le k\\ v, otherwise.\end{cases}$$

12. The method of any one of claims 1 to 11 comprising the further step of:

a) determining the significance of each weight of the linear combination; and

b) setting non-significant weights to zero.

13. The method of any one of claims 1 to 12 wherein the significance of the weights of the linear combination is determined by a permutation test comprising the steps of:

a) randomising the data for the components of a linear combination;

b) computing the weights and eigenvalues from the randomised data;

c) repeating steps a) and b) a plurality of times;

d) determining a distribution for the weights and eigenvalues computed from the randomised data;

e) determining the position of weights and eigenvalues computed from non-randomised data relative to the distribution of the weights and eigenvalues computed from randomised data; and

f) estimating the significance of each weight computed from the non-randomised data.

14. The method of any one of claims 1 to 12 wherein the significance of the overall linear combination is determined by a permutation test comprising the steps of:

(a) randomising the data for the components of a linear combination;

(b) computing the weights and eigenvalues from the randomised data, and from these computing the squared multiple correlation coefficient of the linear combination with the columns of the design basis;

(c) repeating steps a) and b) a plurality of times;

(d) determining a distribution for squared multiple correlation coefficient computed from the randomised data;

(e) determining the position of the squared multiple correlation coefficient from non-randomised data relative to the distribution of the squared multiple correlation coefficient computed from randomised data; and estimating the significance of the squared multiple correlation coefficient computed from the non-randomised data.

15. A method for estimating missing values from the results of the method applied to the system of any one of claims 1 to 14 comprising the steps of:

a) estimating initial values of B, Λ, Φ and σ by replacing missing values with simple estimates and calculating maximum likelihood estimates assuming the data was complete;

b) computing $E\{X|o_1,\ldots o_k\}$ and $E\{RR^T|o_1,\ldots,o_k\}$ the expected values of the data array and the residual matrix under the model given the observed data;

c) substitute quantities for (b) into likelihood equations to obtain estimates of B, Λ, Φ and σ^2;

d) repeat steps (b) to (d) until convergence.

16. The method of any one of claims 1 to 15 wherein the response pattern as specified by the design factors is derived from known data.

17. The method of any one of claims 1 to 15 wherein the response pattern as specified by the design factors is derived from the input array data.

18. The method of any one of claims 1 to 15 wherein the response pattern as specified by the design factors

is selected to identify an arbitrary response pattern.

19. The method of any one of claims 1 to 18 wherein the data is generated from the system using a method selected from the group consisting of DNA array analysis, DNA microarray analysis, RNA array analysis, RNA microarray analysis, DNA microchip analysis, RNA micrchip analysis, protein microchip analysis, carboydrate analysis, DNA electrophoresis, RNA electrophoresis, one dimensional or two dimensional protein electrophoresis, proteomics, antibody array analysis.

20. A computer program, arranged, when run on a computing device, to control the computing device to identify linear combinations of components from input data which correlate with a response pattern in a defined matrix of design factors specifying types of response patterns for a set of test conditions in a system.

21. A computer readable medium providing the computer medium of claim 20.

22. A computer program which, when run on a computing device, is arranged to control the computing device, in a method of identifying components from a system which exhibit a response pattern to a test condition applied to the system, and wherein a matrix of design factors specifying the response patterns for the test conditions is defined, to formulate a module for the residuals of a regression of the input data on the design factors, to estimate parameters for the model and compute a linear combination of components using the estimated parameters.

23. A computer readable medium providing the computer program of claim 22.

24. An apparatus for identifying components from a system which exhibit a response pattern associated with test conditions applied to the system, and wherein a matrix of design factors to specify the type of response

patterns for the set of tests and conditions is defined, the apparatus including a calculation device for identifying linear combinations of components from the input data which correlate with the response pattern.

25. An apparatus for identifying components from a system which exhibit a preselected response pattern to a set of test conditions applied to the biotechnology array, wherein a matrix of design factors to specify the response pattern(s) for the test conditions is defined, the apparatus including a means for formulating a model for the residuals on a regression of the input array data on the design factors, means for estimating perimeters for the model and means for computing a linear combination of components using the estimated perimeters.

26. A computer program which when run on a computing device is arranged to control the computing device to implement the method of any one of claims 1 to 19.

27. A computing system including means for identifying components including means for implementing the method of any one of claims 1 to 19.

Dated this 11th day of July 2002

CSIRO

By their Patent Attorneys

GRIFFITH HACK