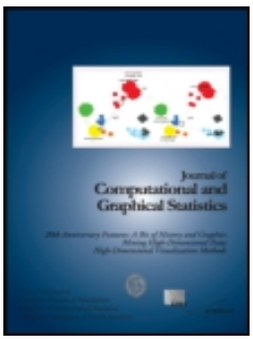

Journal of Computational and Graphical Statistics

ISSN: 1061-8600 (Print) 1537-2715 (Online) Journal homepage: https://www.tandfonline.com/loi/ucgs20

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To cite this article: Beiying Ding & Robert Gentleman (2005) Classification Using Generalized Partial Least Squares, Journal of Computational and Graphical Statistics, 14:2, 280-298, DOI: 10.1198/106186005X47697

To link to this article: https://doi.org/10.1198/106186005X47697

Published online: 01 Jan 2012.

Classification Using Generalized Partial Least Squares

Beiying DING and Robert GENTLEMAN

Advances in computational biology have made simultaneous monitoring of thousands of features possible. The high throughput technologies not only bring about a much richer information context in which to study various aspects of gene function, but they also present the challenge of analyzing data with a large number of covariates and few samples. As an integral part of machine learning, classification of samples into two or more categories is almost always of interest to scientists. We address the question of classification in this setting by extending partial least squares (PLS), a popular dimension reduction tool in chemometrics, in the context of generalized linear regression, based on a previous approach, iteratively reweighted partial least squares, that is, *IRWPLS*. We compare our results with two-stage PLS and with other classifiers. We show that by phrasing the problem in a generalized linear model setting and by applying Firth's procedure to avoid (quasi)separation, we often get lower classification error rates.

Key Words: Cross-validation; Firth's procedure; Gene expression; Iteratively reweighted partial least squares; (Quasi)separation; Two-stage PLS.

1. INTRODUCTION

The wealth of gene expression data now available poses numerous statistical questions ranging from image analysis and variability analysis of gene expression levels (Chen, Dougherty, and Bitterner 1997; Newton et al. 2001), to the study of biochemical pathways. The huge number of genes relative to the moderate sample size renders many of the statistical modeling approaches inappropriate and hence efficient methods for dimension reduction and information extraction are of great interests. In this article, we adapt a technology prevalent in chemometrics to the analysis of gene expression data. Our methodology easily extends to other settings, such as proteomic investigation through mass spectrometry or more classical problems such as Fisher's Iris data (Fisher 1936).

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Journal of Computational and Graphical Statistics, Volume 14, Number 2, Pages 280–298
DOI: 10.1198/106186005X47697

1.1 PARTIAL LEAST SQUARES (PLS) IN CHEMOMETRICS

Similar data structures have been seen in the field of chemometrics, which has recently focused on analyzing observational data, originating mostly from organic and analytical chemistry, food research, and environmental studies. In these areas the number of observations tends to be many fewer than the number of measured variables and there is usually a high degree of collinearity among the variables, for example, digitizations of analog signals or signals for different wavelengths in predicting chemical composition of a compound in spectroscopy. The similarity of these problems to those in computational biology suggests that the methodology developed for chemometrics may be appropriate for computational biology.

Over the years, chemometricians have developed techniques for predictive modeling based on heuristic reasoning and the empirical evidence which have shown generally good performance. Both partial least squares (PLS) and principal component regression (PCR) have been popular regression methods in chemometrics (Wold 1975; Massy 1965). There are a wealth of articles on regression applications to chemical problems available in the *Journal of Chemometrics* (John Wiley) and *Chemometrics and Intelligent Laboratory Systems* (Elsevier). An introduction to PLS regression was given by Geladi and Kowalski (1986) and the use of PLS in calibration can be found in Martens and Naes (1989). A statistical view of PLS was given by Frank and Friedman (1993).

1.2 APPLICATION OF PLS FOR GENE EXPRESSION DATA

In this article, we propose a procedure for two-group and multigroup (> 2 group) classification (prediction) of human tumor samples based on microarray gene expression data. The procedure involves incorporating PLS within the iteratively reweighted least squares (IRWLS) steps for multinomial or binary logistic regression. Our approach is based on iteratively reweighted partial least squares (*IRWPLS*) first proposed by Marx (1996) and a procedure by Firth (1992a, b, 1993) which is applied to remedy and avoid the frequently encountered nonconvergence and infinite parameter estimate problems in logistic regression (Albert and Anderson 1984; Santner and Duffy 1986). This problem is usually present when the sample size is small relative to the number of parameters. Infinite parameter estimates can occur even when there is only one highly predictive covariate. For binary logistic regression, Heinze and Schemper (2002) showed that Firth's procedure ensures finite parameter estimates.

More recently, effort has been devoted to using penalized likelihood to tackle high-dimensional problems, for example, ridge penalized logistic regression (Eilers, Boer, van Ommen, and van Houwelingen 2001). Fort and Lambert-Lacroix (2003) also proposed combining PLS with logistic regression penalized with a ridge parameter. Comparisons of our results with their approaches are of interest and will be explored in future research.

2. METHODS

We first introduce PLS in its original form, that is, for a continuous response. We then consider the extension of PLS to generalized linear models (GPLS), specifically for categorical data in classification problems. A more detailed description is first devoted to the two-group classification problem where we also address separation problems in logistic regression. We then generalize the approach to multigroup classification.

2.1 PARTIAL LEAST SQUARES (PLS)

Originating from general systems-analysis models and developed as a calibration method to predict chemical variables, PLS is usually presented as an algorithm.

Let $\mathbf{X} = (\mathbf{x}_1, \mathbf{x}_2 \ldots, \mathbf{x}_p)$ be the n by p matrix of predictors and $\mathbf{y}$ be the n by 1 response vector. $\mathbf{X}$ can often be written as a bilinear form (Kruskal 1978):

$$\begin{aligned} \mathbf{X} &= \mathbf{T}\mathbf{P}' + \mathbf{E}_K \\ &= \mathbf{t}_1\mathbf{p}_1' + \mathbf{t}_2\mathbf{p}_2' + \cdots + \mathbf{t}_K\mathbf{p}_K' + \mathbf{E}_K, \end{aligned}$$

where $\mathbf{T} = [\mathbf{t}_1, \mathbf{t}_2, \ldots, \mathbf{t}_K], \mathbf{P} = [\mathbf{p}_1, \mathbf{p}_2, \ldots, \mathbf{p}_K]$. The $\mathbf{t}_k$'s are called *latent variables* or *scores*, and the $\mathbf{p}_k$'s are called *loadings*. The residual matrix is $\mathbf{E}_K$ and $\mathbf{K}$ is the number of PLS components. Moreover, we usually assume that the $\mathbf{X}$ matrix is standardized so that each column has mean 0 and standard deviation 1 (although the latter is not necessary). We further assume that

$$\begin{aligned} \mathbf{y} &= \mathbf{X}\boldsymbol{\beta} \\ &= \mathbf{T}\mathbf{Q} + \mathbf{f}_K \\ &= \mathbf{t}_1 q_1 + \mathbf{t}_2 q_2 + \cdots + \mathbf{t}_K q_K + \mathbf{f}_K, \end{aligned}$$

where $\mathbf{Q} = [q_1, q_2, \ldots, q_K]$ and $\mathbf{f}_K$ is the residual. Thus, $\mathbf{X}$ and $\mathbf{y}$ are linked via the latent variables $\mathbf{T}$.

Usually the criterion for constructing components in PLS is to sequentially maximize the covariance between the response $\mathbf{y}$ and $\mathbf{X}\mathbf{g}$, subject to the constraint that $\mathbf{g}'\mathbf{X}'\mathbf{X}\mathbf{g} = 0$. The PLS components $\mathbf{t} = \mathbf{X}\mathbf{g}^*$ are orthogonal, where $\mathbf{g}^* = \text{argmax}_{\mathbf{g}'\mathbf{g}=\mathbf{1}} \text{cov}(\mathbf{X}\mathbf{g}, \mathbf{y})$. If $\mathbf{K}$ is chosen to be the rank of $\mathbf{X}$ (i.e., the minimum of the row rank and the column rank of $\mathbf{X}$) and $\mathbf{X}$ is of full rank, then the PLS estimates of $\boldsymbol{\beta}$ are identical to ordinary least squares (OLS) estimates. However, because PLS is usually applied in cases where p is larger than n, a value of K smaller than the rank of $\mathbf{X}$ is often used. Hence, K can be viewed as a hyperparameter that also needs to be optimized. K is often selected by cross-validation as the number of PLS components for which the predicted sum of errors is minimized.

2.2 TWO-STAGE PLS LOGISTIC REGRESSION

When the outcome variable is not continuous, the ordinary PLS method does not apply directly. Wang et al. (1999) proposed a probability-based multivariate algorithm combining

partial least squares and logistic regression for identification of the development stages of oral cancer through analysis of autofluorescence spectra of oral tissues. Classification of the four stages of cancer development (normal, hyperplasia, dysplasia and early cancer) is carried out in two steps (we will call this two-stage PLS regression in later sections). First, the PLS components are obtained using the original covariates and coded response matrix (where three dummy variables of values 0 or 1 are used to represent the categorical response, which is treated as unordered). Second, they assumed that

$$\log\left(\frac{p_k}{p_1}\right) = \beta_{0k} + \boldsymbol{\beta}_k' \mathbf{s}_k,$$

where $k = 1, \ldots, 4$, that is, $p_k = P(\text{class } k|\mathbf{s}_k)$, and $\mathbf{s}_k$ is the vector of PLS components for an observation belonging to class k. The maximum likelihood estimates for the regression coefficients can be obtained and the samples were classified into the category which has the highest predicted probability from the logistic regression based on the extracted components. The authors used leave-one-out cross-validation (LOOCV) to determine the number of PLS components and for evaluating the performance of the algorithm.

Nguyen and Rocke (2002b) applied a similar approach to problems of two-group tumor classification using two-stage PLS regression on microarray gene expression data. The original PLS procedure was first used for dimension reduction where the response variable was either 0 or 1, and logistic discrimination (LD) was applied to the chosen PLS components for classification. Quadratic discriminant analysis (QDA) was also tested as a comparison with LD. They applied their method to various datasets involving human tumor samples and stability of the classification results was assessed by rerandomization. They used a similar approach for multigroup classification (Nguyen and Rocke 2002a). Later we compare our results with theirs.

Although their results for two-group classification appear good, their approach may not be ideal because the original PLS algorithm was designed for a continuous outcome $\mathbf{y}$ with constant variance, and a linear relationship with $\mathbf{X}$. Analogous to the development of generalized linear models to accommodate regression of nonnormal responses on a set of covariates, we consider the extension of PLS from the linear model to the generalized PLS setting.

2.3 ITERATIVELY REWEIGHTED PARTIAL LEAST SQUARES (IRWPLS)

McCullagh and Nelder (1989) showed that the maximum likelihood estimation of the parameters $\boldsymbol{\beta}$ of generalized linear models via Fisher scoring method can be rephrased as iteratively reweighted least squares (IRWLS) as follows,

$$\begin{aligned} \mathbf{A}\,\mathbf{b}^{t+1} &= \mathbf{A}\mathbf{b}^t + \mathbf{U} \\ &= \sum W\mathbf{x}\left(\eta + (y-\mu)\frac{\partial \eta}{\partial \mu}\right), \end{aligned}$$

where $\mathbf{b}^t$ are the regression coefficient estimates for $\boldsymbol{\beta}$ at tth iteration, $\mathbf{U}$ is the score vector, and $\mathbf{A}$ is the expected value of Fisher information. The ijth element of $\mathbf{A}$ is, $A_{ij} = -E(\frac{\partial U_i}{\partial \beta_j})$

where $i, j = 1, \ldots p$. The dependent variable here is a linearized form of the link function applied to the response variable,

$$z = \eta + (y - \mu)\frac{\partial \eta}{\partial \mu},$$

and the weights, W, are functions of the fitted values $\hat{\mu}$. Estimates are obtained by iteratively updating the adjusted dependent variable and weights until the convergence criterion is met.

Marx (1996) proposed an iteratively reweighted PLS algorithm which incorporates PLS into the framework of generalized linear models. His approach embeds the weighted PLS steps within the iterative steps, treating and updating the adjusted dependent variable $\mathbf{z}$ as the response rather than working with the original outcome. The two nested loops are iterated until the stopping criterion is satisfied. In the high-dimensional problems we are addressing, separation often occurs and Marx did not directly address this problem. We give more detailed description of the problem in the following section and discuss one remedy.

2.4 FIRTH'S PROCEDURE

For classification problems using logistic regression, it is well-known that convergence poses a long-standing problem. Infinite parameter estimates can occur depending on the configuration of the sample points in the observation space (Albert and Anderson 1984; Santner and Duffy 1986). There are three categories of configurations of the sample points: complete separation, quasi-complete separation, and overlap. For both complete and quasi-complete separation, there exists a vector $\mathbf{b}$ that correctly classifies all observations to their groups. Thus, the MLE for $\boldsymbol{\beta}$ does not exist and the log-likelihood goes to zero and/or the dispersion matrix becomes unbounded as iterations proceed. Only under the *overlap* configuration do finite regression coefficient estimates exist. We note that although separation is an indication of perfect prediction and hence could be considered positively, it is problematic for logistic model fitting because it is in contradiction to the assumptions of the model. In high-dimensional problems, such as analysis of gene expression data we find that separation is common. Since we want to make use of a logistic model as the basis for analyzing these data we must find some way to overcome the separation problem.

Firth (1992a, b, 1993) developed a procedure to remove the first-order term of the asymptotic bias of maximum likelihood estimates in GLMs based on a modification of the score function,

$$U(\beta_j)^* = U(\beta_j) + .5 \times \text{trace}\{I(\boldsymbol{\beta})^{-1}[\partial I(\boldsymbol{\beta})/\partial \beta_j]\} = 0, \quad j = 1 \ldots p,$$

where $U(\boldsymbol{\beta})$ is the original score function and $I(\boldsymbol{\beta})^{-1}$ is the inverse Fisher's information matrix evaluated at $\boldsymbol{\beta}$. When applying Firth's procedure to logistic regression, Heinze and Schemper (2002) showed that in the modified score function for logistic regression, each original observation, y_i, is split into two pieces, a *response* and a *nonresponse*. This guarantees finite estimates since for every covariate pattern there are some responses and some nonresponses which is the *overlap* configuration. So this procedure provides a solution to separation problems in logistic regression.

We can readily modify the original IRWPLS, by incorporating the Firth's procedure, to deal with two-group classification problems with large number of covariates (e.g., genes). Specifically,

$$\begin{aligned} U(\beta_j)^* &= \sum_{i=1}^{n} \{(y_i + h_i/2) - p_i(1+h_i)\} x_{ij} \\ &= \sum_{i=1}^{n} (y_i^* - p_i^*) x_{ij} \\ &= \sum_{i=1}^{n} w_i^* x_{ij} \frac{\partial \eta_i}{\partial p_i^*} (y_i^* - p_i^*), \end{aligned}$$

where w_i^* is the ith diagonal term of weight matrix

$$\begin{aligned} W^* &= W \times \text{diag}(h_i + 1) \\ y_i^* &= y_i + h_i/2 \\ p_i^* &= p_i \times (1 + h_i) \\ z_i^* &\doteq \eta_i + (y_i^* - p_i^*) \frac{\partial \eta_i}{\partial p_i^*}, \end{aligned}$$

now the pseudo response is z^*.

Although h_i's are functions of $\boldsymbol{\beta}$, they are treated as fixed when derivatives of the score functions with respect to $\boldsymbol{\beta}$ are taken, to make the problem more tractable. Hence the last equation above is actually an approximation. We call this approach *IRWPLSF* procedure in later sections.

When separation occurs in IRWPLS, ad-hoc criteria can be used to get estimates of the coefficients. For example, one can use the estimates that changed least from the iteration before separation occurred. However, these criteria may actually invalidate other aspects of model fitting, for example, they have impact on the selection of the hyperparamter K. The IRWPLSF procedure, however, avoids this problem. For example, it can properly evaluate the difference among convergent models for all values of K without resorting to data-dependent procedures.

2.5 IRWPLS FOR MULTIGROUP CLASSIFICATION

In this section, we extend the IRWPLS procedure to the multigroup classification scenario. It is a generalization of logit models for binary responses (see Fahrmeir et al. 2001, chap. 3 for a discussion). In our application, we always treat the classes as nominal with no special ordering. It would be straightforward to use any other model deemed appropriate, such as an adjacent logit model. And it is this ability to generalize and to accommodate complex multigroup relationships that makes classification procedures based on a GLM framework so appealing.

We assume that the counts at each configuration of the covariates are fixed, independent multinomials and we will refer to this model as the multinomial logit model. Let the cate-

gorical outcome Y have $C+1$ classes labeled $0, 1, \ldots, C$. We illustrate our model under the *common-baseline categorical* model that is commonly used. Suppose the baseline class is always labeled class 0, and for each $j = 1, \ldots C$, the logit model holds:

$$\log\left(\frac{p_{ij}}{p_{i0}}\right) = \boldsymbol{\beta}_j' \mathbf{x}_i,$$

where $i = 1, \ldots, n$, indexes samples. Note here that the most general case, that is, different $\boldsymbol{\beta}_j$'s for each of the C logits, is considered. With the following constraints,

$$\sum_{j'=0}^{C} p_{ij'} = 1, \ \sum_{j'=0}^{C} y_{ij'} = 1,$$

where $y_{ij} = I(\text{sample}\, i \in \text{class}\, j)$, with $I(\cdot)$ being an indicator function and using the standard form of the likelihood, the score functions are:

$$\begin{aligned} \mathbf{U}(\boldsymbol{\beta}) &= \mathbf{X}'(\mathbf{Y} - \mathbf{P}) \\ &= \mathbf{X}'\mathbf{W}\frac{\partial \boldsymbol{\eta}}{\partial \mathbf{P}}(\mathbf{Y} - \mathbf{P}). \end{aligned}$$

In the above formula, $\boldsymbol{\beta} = (\boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \ldots, \boldsymbol{\beta}_C)'$, where $\boldsymbol{\beta}_j$, $j = 1, \ldots, C$ is the $p \times 1$ regression coefficient vector corresponding to the jth logit. $\mathbf{Y} = (\mathbf{y}_1', y_2', \ldots, \mathbf{y}_n')'$ where $\mathbf{y}_i = (y_{i1}, y_{i2}, \ldots, y_{iC})'$, which is the $C \times 1$ response vector for the ith sample. Similarly $\mathbf{P} = (\mathbf{p}_1', \mathbf{p}_2', \ldots, \mathbf{p}_n')'$ where $\mathbf{p}_i = (p_{i1}, p_{i2}, \ldots, p_{iC})'$, and $\mathbf{X} = (\mathbf{X}_1', \mathbf{X}_2', \ldots, \mathbf{X}_n')'$ where

$$\mathbf{X}_i = \begin{pmatrix} \mathbf{x}_{i1} & \mathbf{0} & \mathbf{0} & \ldots & \mathbf{0} \\ \mathbf{0} & \mathbf{x}_{i2} & \mathbf{0} & \ldots & \mathbf{0} \\ & & \ldots & & \\ \mathbf{0} & \mathbf{0} & \ldots & 0 & \mathbf{x}_{iC} \end{pmatrix}$$

in which $\mathbf{x}_{ij}$ is the covariate vector corresponding to the jth logit, $j = 1, \ldots, C$. Usually $\mathbf{x}_{i1} = \mathbf{x}_{i2} = \cdots = \mathbf{x}_{iC} = \mathbf{x}_i$. Note that the baseline level, that is, class 0, is now only implicitly modeled as a result of conforming to the linear constraints for uniqueness of the estimates. $\mathbf{W}$ is a block diagonal matrix with the ith diagonal block being:

$$\mathbf{W}_i = \begin{pmatrix} p_{i1}(1-p_{i1}) & -p_{i1}p_{i2} & \ldots & -p_{i1}p_{iC} \\ -p_{i1}p_{i2} & p_{i2}(1-p_{i2}) & \ldots & -p_{i2}p_{iC} \\ & \ldots & & \\ -p_{i1}p_{iC} & -p_{i2}p_{iC} & \ldots & p_{iC}(1-p_{iC}) \end{pmatrix}.$$

It can then be shown that the pseudo-response vector for the ith sample is,

$$\mathbf{z}_i = \boldsymbol{\eta}_i + \frac{\partial \boldsymbol{\eta}_i}{\partial \mathbf{P}_i}(\mathbf{y}_i - \mathbf{p}_i).$$

Now the IRWPLS procedure can be carried out as before with the necessary changes, and we refer to this model fitting procedure as *MIRWPLS*.

For the multinomial logit model, the problem of (quasi-)complete separation still exists. Firth's procedure can be extended to multinomial case, which we will denote by *MIRWPLSF*. The pseudo response vector can be expressed in a similar form as before:

$$\mathbf{z}_i^* = \boldsymbol{\eta}_i + \frac{\partial \boldsymbol{\eta}_i}{\partial \mathbf{p}_i^*}(\mathbf{y}_i^* - \mathbf{p}_i^*),$$

where $\mathbf{p}_i^*$ and $\mathbf{y}_i^*$ are functions of the original $\mathbf{p}_i$ and $\mathbf{y}_i$, as in the description of MIRWPLS. The last equality illustrates that the problem can be rephrased as a multinomial logit model with an adjusted response vector $\mathbf{y}_i^*$ and mean vector $\mathbf{p}_i^*$ for each sample. For a detailed derivation refer to Appendix A. Note, however, that even though MIRWPLSF tends to shrink $\boldsymbol{\beta}$ towards zero (Firth 1993), and hence provides a more stable model than MIRWPLS, finite estimates are no longer guaranteed due to the multiplicity of classes.

Prediction of outcome is simply based on polytomous discrimination (PD), which is essentially classifying an observation into the class with highest predicted probability, based on the fitted model. This prediction rule is also commonly referred as *softmax* (Ripley 1996).

2.6 ASSESSING PREDICTION

We use classification error rates to assess the performance of the IRWPLS-based procedures and to compare them with other classifiers. When a test set is available, the out-of-sample test set classification error rate is estimated using the model built on the training set. When a test set is not available, we use leave-one-out cross-validation (LOOCV) which is described next. For each iteration, one of the n samples is reserved as a test set and the remaining $n - 1$ form the training set. A model is constructed using the training set, and the test set, that is, the one left out, is classified using the model. After iterating through all n samples, the number of incorrect predictions divided by n is an estimate of the error rate.

The optimal number of PLS components, K, is selected by choosing that value of K which minimizes the LOOCV error rate for the training set. We employ this technique for other procedures that involve hyperparameters, such as selecting k in the k-nearest neighbors (KNN) procedure.

3. RESULTS

In this section, we compare the classification results from IRWPLS-based procedures with other classifiers including two-stage PLS, Fisher's linear discriminant analysis (FLDA), diagonal LDA (DLDA), quadratic discriminant analysis (QDA) (Dudoit, Fridlyand, and Speed 2002), k-nearest neighbors (KNN), random forests (RF) (Breiman 2001, 2002) and support vector machines (SVM) (Furey et al. 2000; Guyon, Weston, Barnhill, and Vapnik 2002). Dudoit, Fridlyand, and Speed (2002) found that simple classifiers such as DLDA and KNN were better than other more sophisticated classifiers in a large scale comparison of discrimination methods. All examples presented in this section were run on publicly available data. The data sources are listed in Appendix B. All software is available as

Table 1. % Misclassification for Pima Data using IRWPLS(F)

	Training set (n = 200) CV error				*Test set (n = 332) out-of-sample error*			
	IRWPLS	*IRWPLSF*			*IRWPLS*	*IRWPLSF*		
K	*Overall*	*Overall*	*N*	*D*	*Overall*	*Overall*	*N*	*D*
1	.2500	.2500	.1364	.4706	.2199	.2199	.1345	.4037
2	.2500	.2500	.1515	.4412	.2078	.2048	.1166	.3853
3	.2800	.2800	.1591	.5147	.2229	.2229	.1031	.3945
4	.2600	.2650	.1515	.4853	.2048	.2078	.1031	.3945
5	.2600	.2550	.1439	.4706	.2078	.2018	.1031	.3945
6	.2650	.2550	.1364	.4853	.2018	.2078	.1031	.3945
7	.2350	.2350	.1288	.4412	.1988	.1988	.1031	.3945

R packages through either CRAN or the Bioconductor Project. See Appendix B for the appropriate URLs.

3.1 TWO-GROUP CLASSIFICATION

3.1.1 Pima Data

We first test our procedure on a simple dataset where the number of covariates is smaller than the number of samples available. We use the Pima data as reported by Venables and Ripley (2002). There are 532 complete records, 200 of which are used as training set and the remaining 332 as the test set. The goal of the study was to establish a link between the seven covariate measurements collected and whether or not the woman has diabetes (Smith et al. 1988). For both the training and test set, about 1/3 are from the diabetic group.

Results on applying IRWPLS-based procedures to the Pima diabetes data are shown in Table 1. K stands for the number of PLS components used. *Overall* refers to the overall misclassification rate, whereas *N* and *D* refer to the class specific conditional error rates for nondiabetic and diabetic samples, respectively. Due to the simple structure of the data and the abundance of samples, the best performance is achieved when using seven PLS components, that is, full rank, which is essentially logistic discrimination. The LOOCV error rate for the training set is .2350 and the test set error is .1988 for both IRWPLS and IRWPLSF. The class specific training set CV error rates for *N* and *D* are similar for IRWPLS and IRWPLSF, hence only the latter are shown (Table 1). In general, the diabetic patients are more likely to be misclassified, possibly as a result of there being fewer cases in the data or they may be more variable.

The misclassification results from some other commonly used classification procedures are listed in Table 2. For KNN, $k = 6$ is the optimal number of k-nearest neighbor based on the lowest LOOCV misclassification rate of the training set. The performance of IRWPLS and IRWPLSF is comparable with that of the other classifiers for this simple dataset, in terms of both overall and class specific error rates. This is true even when IRWPLS or IRWPLSF are based on fewer than full rank PLS components. This example indicates that IRWPLS-based procedures are reasonable classifiers for standard low-dimensional data.

Table 2. Comparison of % Misclassification for Pima Data

	Training set (CV error)			*Test set (out-of-sample error)*		
Classifier	*Overall*	*N*	*D*	*Overall*	*N*	*D*
FLDA	.2450	.1364	.4559	.2018	.1883	.2294
DLDA	.2400	.2197	.2794	.2470	.2242	.5046
QDA	.2750	.1667	.4853	.2289	.2108	.2661
KNN	.2550	.1591	.5735	.2169	.2063	.2936
RF	.2800	.1667	.4853	.2469	.1973	.3119
SVM	.2800	.1515	.5294	.2319	.2287	.2385

3.1.2 Gene Filtering

Even though PLS can handle more covariates than there are samples, the number of genes in a gene expression dataset (often in the tens of thousands) is still too large for practical use, especially given the fact that typically a considerable percentage of the genes do not show differential expressions across groups. Hence, filtering is often applied before classification to remove such genes. For the two-class problem reported here, we choose the m genes with the largest absolute t statistics. Gene selection is carried out as a part of the CV procedure, that is, every time we leave one sample out, both gene selection and model building are done using only the $n - 1$ samples and then prediction of the left out sample is done (Ambroise and McLachlan 2002).

3.1.3 Colon Data

The classification of colon cancer was discussed by Alon et al. (1999). Gene expression data from 40 tumor and 22 normal colon tissue samples were analyzed with an Affymetrix oligonucleotide array. Using two-way clustering, Alon et al. (1999) were able to cluster 19 normal and 5 tumor samples into one group and 35 tumor and 3 normal tissues into the other. The 2,000 genes with highest minimal expression intensity across the 62 tissues were used in the analysis. Several ESTs were replicated on the arrays and some replicates for the same EST have exactly the same expression measurements. Because of this, in all cases where there were replicate probe sets, we used the mean expression profile of the replicates, leaving 1,911 nonredundant genes.

The number of misclassifications based on LOOCV for IRWPLS and IRWPLSF as well as DLDA, KNN, RF, and SVM, are shown in Table 3. The numbers in brackets for IRWPLS and IRWPLSF are the optimal numbers of PLS components chosen by lowest LOOCV classification error rates of the two IRWPLS-based procedures respectively. Those for KNN are the optimal numbers of nearest neighbors, again chosen by LOOCV.

The minimum number of six misclassifications is achieved by IRWPLSF with $m = 30$ genes and KNN with $m = 20$ genes. This result is comparable with Furey et al. (2000), who also misclassified six cases using a support vector machine (SVM). However, Furey

Table 3. Comparison of Misclassification for Colon Data, $n = 62$ (Tumor $= 40$, Normal $= 22$)

m	*IRWPLS*		*IRWPLSF*		*DLDA*	*KNN*		*RF*	*SVM*
5	11	(1)	12	(2)	11	12	(8)	16	13
10	9	(2)	8	(2)	8	8	(10)	12	10
20	7	(1)	7	(1)	7	6	(10)	8	9
30	8	(1)	6	(15)	8	8	(3)	9	8
40	8	(1)	8	(1)	8	9	(3)	9	9
50	8	(1)	8	(2)	7	8	(3)	9	8
100	8	(2)	7	(4)	11	7	(4)	10	10
200	8	(8)	6	(6)	14	8	(3)	10	9
500	10	(1)	7	(5)	18	8	(5)	10	10
1000	9	(4)	6	(5)	22	10	(2)	10	10

et al. (2000) used a slightly different feature selection procedure:

$$F(x_j) = \frac{|\mu_j^+ - \mu_j^-|}{\sigma_j^+ + \sigma_j^-},$$

where x_j is the gene expression for the jth gene, μ_j^+, μ_j^- stand for the sample mean of the tumor and normal groups, respectively, and σ_j^+, σ_j^- are the group standard deviations. This statistic is very similar to the t-statistic assuming unequal group variances, although summing over standard deviations rather than variances is rather unconventional. Using expression data that result from applying the Furey filter, we find that with $p = 40$ IRWPLSF misclassfies only five samples, faring a little better than the SVM approach, using the same gene selection procedure. This result also demonstrates that gene selection influences the performance of classifiers and that it is quite important to make sure that comparison of classification methods is done by controlling nuisance factors such as the feature selection process.

Random Splitting. Due to the instability of LOOCV error rates for data with few samples and many covariates, comparison of various classifiers based solely on LOOCV classification errors may not be reliable. We now compare our IRWPLS-based procedures with the classifiers by randomly splitting the original dataset into a training set and a test set. There is currently no consensus on how to choose the relative size of these randomly divided sets and we follow Dudoit, Fridlyand, and Speed (2002) and choose the training set and test set size ratio to be 2:1. For each training and test set, we build the classifiers using the training set only and predict on the test set data. The number of optimal PLS components for IRWPLS-based procedures and the optimal number of nearest neighbors for KNN are chosen by lowest CV error on the training set. Figure 1 shows the boxplots of the test set error rates for top $m = 10, 20, 30$, and 200 genes chosen by t statistic for each of the six classifiers based on $N = 100$ random splits.

Figure 1 suggests that the error rates for IRWPLS and IRWPLSF are typically lower and with smaller ranges. There is no obvious difference between the distributions of error rates for IRWPLS and IRWPLSF.

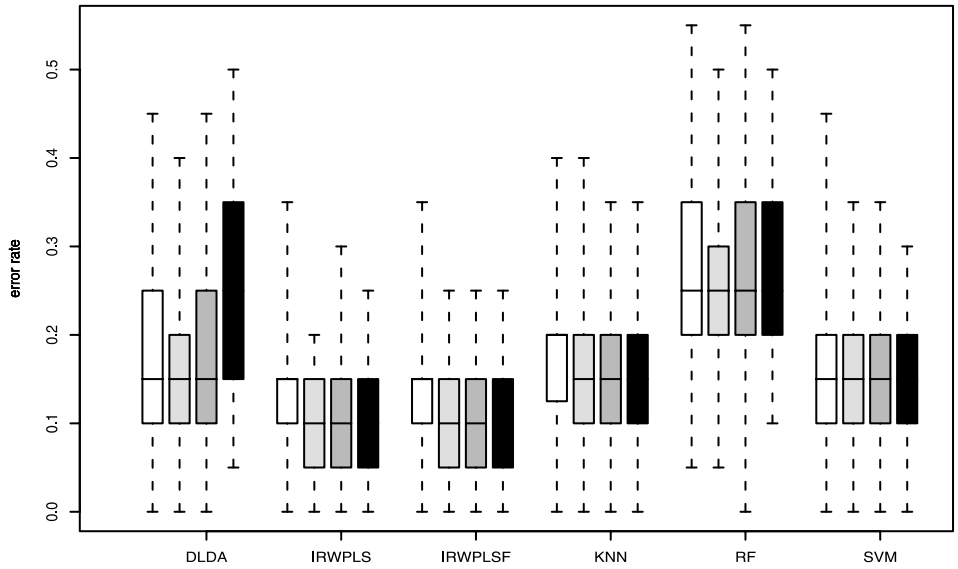

Figure 1. Colon data 2:1 random splitting (N = 100): boxplots of test set error rates for classifiers with top 10 (white), 20 (light gray), 30 (dark gray), and 200 (black) genes using a t test filter.

3.2 MULTIGROUP CLASSIFICATION

3.2.1 Iris Data

We now illustrate the IRWPLS-based multigroup classification approach, that is, MIRWPLS, and MIRWPLSF and compare them with the other methods. We begin by using the well-studied iris dataset (Fisher 1936). We use the data as reported by Venables and Ripley (2002).

From Table 4, the minimum CV misclassification rate is .02 (3 out of 150) for both MIRWPLS (for K from 7 to 10) and MIRWPLSF with $K = 9$. Note here the maximum K is 10 as the $\mathbf{X}$ is of dimension $n \times C$ by $p \times C$ where n, that is, sample size, is 35; $C = 2$,

Table 4. % Misclassification for Iris Data

K	*IRWPLS*	*IRWPLSF*
1	.6667	.6667
2	.6800	.6467
3	.3800	.2867
4	.0333	.0333
5	.0267	.0400
6	.0400	.0267
7	.0200	.0267
8	.0200	.0267
9	.0200	.0200
10	.0200	.0267

that is, number of classes minus 1, and $p = 5$ which includes one term for intercept and the four covariates. Compared with error rates from other standard classification procedures we mentioned before, for example, FLDA (.0200), DLDA (.0400), QDA (.0200), KNN (.0400), RF (.0400), and SVM (.0333), we can see that the MIRWPLS procedures achieve the same minimum error rate (.0200) with less than full rank than the other classifiers achieve using full data information. We did not check to see if the number of predictors could be reduced for the other methods.

In the following section, we compare results from MIRWPLS and MIRWPLSF with the multiclass PLS (MPLS) classification approach of Nguyen and Rocke (2002a) as well as other classifiers. The procedure in Nguyen and Rocke (2002a) is a natural extension of the two-stage PLS logistic regression, where the first stage of PLS component extraction is in principle the same as before only that now instead of a univariate response, C response variables are needed to uniquely represent $C + 1$ groups. The univariate PLS procedure can be extended to accommodate this situation (Höskuldsson 1988; Helland 1988). Now as the response is a n by C matrix rather than a vector, the objective function for maximization is

$$\text{cov}^2(\mathbf{Xg}, \mathbf{Yw}),$$

where $\mathbf{g}'\mathbf{g} = \mathbf{1}$ and $\mathbf{w}'\mathbf{w} = \mathbf{1}$ subject to the orthogonality constraints. The second stage of MPLS uses the *common-baseline* multinomial logit regression model and polytomous prediction (PD), QDA, DQDA, or DLDA.

3.2.2 Gene Filtering

Analogous to using t tests for two-group gene filtering, here we apply the *all-pairwise t-filter* used by Nguyen and Rocke (2002a), for choosing genes that have a large number of significant pairwise differences across groups. Alternatively one might prefer to use an ANOVA based approach for gene selection.

3.2.3 NCI60 Data

This study involves using cDNA microarrays to study the gene expression profiling among 60 cell lines from the NCI60 Cancer Microarray Project (Ross et al. 2000; Scherf et al. 2000). Data on 10 tumor cell lines (the numbers in brackets are the numbers of samples in that cell line): breast (7), central nervous system (CNS, 6), colon (7), leukemia (6), melanoma (8), non-small-cell-lung-carcinoma (NSCLC, 9), ovarian (6), prostate (2), renal (8), unknown (1), are available. To compare with results from MPLS reported by Nguyen and Rocke (2002a), we use only five of the cancer types: CNS, colon, leukemia, melanoma, and renal. Furthermore, a subset of 1,415 genes (1,375 genes and 40 drug targets) which were specifically studied by Scherf et al. (2000) were used. Missing values exist for some of the samples and expression values for genes with two or fewer missing values were imputed using the median expression across samples for that gene. Genes with more than two missing values were excluded from our analysis. This reduces the number of genes to 1,299. Classification results are reported in Table 5.

Table 5. Comparison of Misclassification for subgroups of NCI60 Data Using all Pairwise *t*-Filter (CNS = 6, colon = 7, leukemia = 6, melanoma = 8, renal = 8)

	MPLS							
m	*PD*	*DLDA*	*MIRWPLS*	*MIRWPLSF*	*DLDA*	*KNN*	*RF*	*SVM*
41-54-69 ($\geq$8)	15	5	2 (3)	2 (3)	2	2 (8)	3	3
148-159-189 ($\geq$7)	9	3	0 (3)	1 (4)	2	1 (4)	2	3

Using the all pairwise t-filter, the misclassification rates for IRWPLS-based procedures are considerably lower compared with those of MPLS-PD (Table 5) (numbers in parentheses are the optimal PLS component numbers). The number of misclassifications drops from 15 (out of 35) for MPLS-PD to 2 for both MIRWPLS and MIRWPLSF, when genes having at least eight significant pairwise absolute mean difference are used. Whereas, with even more genes—that is, genes with at least seven significant pairwise scores—almost perfect classification can be achieved using IRWPLS-based procedures (MIRWPLS $= 0$, MIRWPLSF $= 1$) compared with nine misclassifications for MPLS-PD. Although error rates for MPLS-DLDA improved quite a bit over those of MPLS-PD, they are still consistently larger than those of the MIRWPLS and MIRWPLSFs. In this case, all the other classifiers have comparable performances compared with MIRWPLS(F), especially DLDA and KNN (numbers in parentheses are the optimal number of nearest neighbors chosen by LOOCV).

There are no obvious explanations of the high error rate observed for MPLS in Table 5. However, intuitively it is unappealing to treat the binary elements, coded as dummy variables as continuous and to use their covariance (or correlation) with the $\mathbf{X}$'s to construct PLS components. This point was also made in the two-group PLS classification results of Section 2. Second, for MPLS, the objective criterion is to maximize the covariance between $\mathbf{Xw}$ and $\mathbf{Yc}$, that is, linear combinations of the $\mathbf{X}$ and $\mathbf{Y}$ matrices, respectively, until convergence. The interpretation of a linear combinations of elements in the response matrix is problematic. The issues with using the two-stage approach may be even more serious in the multi-group case than the two-group case, where $\mathbf{Y}$ is a vector and the second problem is not encountered.

To summarize, overall for the two-group case, the IRWPLSF procedure tends to be more stable, with its finite regression coefficients relative to IRWPLS in terms of classification as well as model fitting. For the multi-group classification problems, we have shown that both MIRWPLS and MIRWPLSF represent quite a substantial improvement over MPLS. There is no consistent evidence in our experiments to favor either one of the IRWPLS-based procedures for multigroup classification in terms of prediction error rate. We prefer those with Firth's procedure since they directly address the issues of separation. Moreover, we have found that IRWPLS based procedures are, in general, comparable with other popular classifiers such as FLDA, DLDA, QDA, KNN, RF, and SVM, and so on. in terms of LOOCV error rates for the training set and test set error rates when test set is available, for example, Pima data. When no test set is available, we also show that with random splitting into training and test sets, the distributions of test set error rates for IRWPLS-based procedures tend to be lower compared with other popular classifiers.

4. DISCUSSION

With the introduction of high throughput microarray technology, data on the expression level of thousands of genes can be obtained simultaneously. This has provided a wealth of information as well as a challenge to develop efficient analytical methods, especially from a statistical point of view. We have in our efforts found a solution to one important aspect of machine learning, class prediction, via partial least squares regression. In comparison with the two-stage PLS approach (Wang et al. 1999; Nguyen and Rocke 2002b; Nguyen and Rocke 2002b), we seek alternatives in the context of generalized linear models. We reintroduced the iteratively reweighted partial least squares (IRWPLS) first proposed by Marx (1996). We also resolve (quasi-)complete separation problems by applying Firth's procedure, which guarantees finite regression coefficients for binary logistic regression (Firth 1992a, b, 1993; Heinze and Schemper 2002). We further extended the IRWPLS procedure to multinomial logit case where more than two groups exist, MIRWPLS. A second multiclass model, MIRWPLSF, which incorporates bias reduction into multigroup classification is also derived.

We have shown that IRWPLS-based procedures have comparable classification efficiency with some of the classic approaches such as FLDA, DLDA, QDA, KNN, RF, and SVM when standard data with relatively simple structure (i.e., $n > p$) are encountered. We have also observed that for high dimensional microarray expression datasets that IRWPLS-based procedures achieve lower classification error rates than the two-stage PLS approach especially for multigroup classification. In our examples, they also tend to give fewer misclassifications compared with DLDA, KNN, RF, and SVM. (M)IRWPLSF has similar performance to that of (M)IRWPLS but is less susceptible to separation.

Model-based classifiers, such as the IRWPLS-based procedures, may not be as flexible as algorithm-based ones. However, algorithmic classifiers, such as SVM, are often blackbox tools, with tuning parameters that are not necessarily intuitive for users, for example, choice of kernel functions, scale factor, and so on, whereas IRWPLS-based procedures provide us with a well-established framework not only for class prediction but also for good interpretation, stability, and statistical inference. For example, one can interpret the latent variables, that is, the $\mathbf{t}$'s, as one would principle components. Also each t_i is a linear combination of the original $\mathbf{X}$ matrix and could suggest which covariates (genes) are important based on their weights. These considerations relate more to variable selection and gene importance, which is an important topic that will be addressed separately.

Moreover, even though we formulated multigroup classification IRWPLS for nominal classes, under a *common-baseline* logit model, it can easily be extended to handle ordinal classes, for example, cumulative logit model, adjacent logit model, and so on. Such flexibility of model formulation in regression based methods, to best reflect the nature of the application, is usually not offered by the other classifiers. So even though sometimes we may not see substantial improvement of MIRWPLS(F) over the other algorithmic classifiers such as DLDA, KNN, and so on. under a particular formulation of the logit model, the former really does offer a more flexible tool.

APPENDIXES

A. MIRWPLSF PSEUDO-RESPONSE DERIVATION

As we have mentioned in section 2.4, the Firth-modified score function is:

$$\begin{aligned}
U(\boldsymbol{\beta})^* &= U(\boldsymbol{\beta}) + .5\frac{\partial}{\partial \boldsymbol{\beta}}\log(|I(\boldsymbol{\beta})|) \\
&= U(\boldsymbol{\beta}) + .5\frac{\partial}{\partial \boldsymbol{\beta}}\log(|\mathbf{X}'\mathbf{W}\mathbf{X}|) \\
&= U(\boldsymbol{\beta}) + .5\,\text{trace}\left\{(\mathbf{X}'\mathbf{W}\mathbf{X})^{-1}\,\mathbf{X}'\frac{\partial \mathbf{W}}{\partial \boldsymbol{\beta}}\mathbf{X}\right\} \\
&= U(\boldsymbol{\beta}) + .5\,\text{trace}\left\{\mathbf{W}\mathbf{X}(\mathbf{X}'\mathbf{W}\mathbf{X})^{-1}\mathbf{X}'\frac{\partial \mathbf{W}}{\partial \boldsymbol{\beta}}\mathbf{W}^{-1}\right\} \\
&= U(\boldsymbol{\beta}) + .5\,\text{trace}\left\{\mathbf{H}\frac{\partial \mathbf{W}}{\partial \boldsymbol{\beta}}\mathbf{W}^{-1}\right\} \\
&= U(\boldsymbol{\beta}) + .5\;\mathbf{X}'\mathbf{H}_w
\end{aligned}$$

where $\mathbf{H} = \mathbf{W}\mathbf{X}(\mathbf{X}'\mathbf{W}\mathbf{X})^{-1}\mathbf{X}'$ is the *hat matrix* and H_w is a $nC \times 1$ vector, each element of which is a function of the corresponding term of $\mathbf{P}$ and diagonal elements of $\mathbf{H}$.

$$\begin{aligned}
\mathbf{H}_w &= \begin{pmatrix} h_{11} \\ h_{12} \\ \vdots \\ h_{1C} \\ \vdots \\ h_{n1} \\ h_{n2} \\ \vdots \\ h_{nC} \end{pmatrix} - \begin{pmatrix} p_{11} \\ p_{12} \\ \vdots \\ p_{1C} \\ \vdots \\ p_{n1} \\ p_{n2} \\ \vdots \\ p_{nC} \end{pmatrix} \cdot \begin{pmatrix} h_{1.} + h_{11} \\ h_{1.} + h_{12} \\ \vdots \\ h_{1.} + h_{1C} \\ \vdots \\ h_{n.} + h_{n1} \\ h_{n.} + h_{n2} \\ \vdots \\ h_{n.} + h_{nC} \end{pmatrix} \\
&= \text{diag}(\mathbf{H}) - \mathbf{P} \cdot \mathbf{H}^*,
\end{aligned}$$

where h_{ij} corresponds to the $((i-1)*C+j)$th diagonal term of $\mathbf{H}$ $(i = 1, \ldots n, j = 1, \ldots C)$ and $h_{i.} = \sum_{j'=1}^{C} h_{ij'}$. $\mathbf{H}^*$, a column vector of length nC, is introduced here for notational convenience. $\mathbf{H}^* = (\mathbf{h}_1^{*T}, \mathbf{h}_2^{*T}, \ldots, \mathbf{h}_n^{*T})'$ and $\mathbf{h}_i^* = (h_{i.} + h_{i1}, h_{i.} + h_{i2}, \ldots, h_{i.} + h_{iC})'$. Similarly, $\mathbf{H}_w = (\mathbf{h}'_{w\,1}, \mathbf{h}'_{w\,2}, \ldots, \mathbf{h}'_{w\,n})'$ where $\mathbf{h}_{w\,i} = (h_{w\,i1}, h_{w\,i2}, \ldots, h_{w\,iC})'$.

Continuing the above derivation,

$$\begin{aligned}
U(\boldsymbol{\beta})^* &= \mathbf{X}'\mathbf{W}\frac{\partial \boldsymbol{\eta}}{\partial \mathbf{P}}(\mathbf{Y} - \mathbf{P}) + .5\,\mathbf{X}'\mathbf{W}\frac{\partial \boldsymbol{\eta}}{\partial \mathbf{P}}\,\mathbf{H}_w \\
&= \mathbf{X}'\mathbf{W}\frac{\partial \boldsymbol{\eta}}{\partial \mathbf{P}}(\mathbf{Y} - \mathbf{P} + .5\,\mathbf{H}_w) \\
&= \mathbf{X}'\mathbf{W}^*\frac{\partial \boldsymbol{\eta}}{\partial \mathbf{P}^*}(\mathbf{Y} - \mathbf{P} + .5\,\mathbf{H}_w),
\end{aligned}$$

where similar to binary outcome case,

$$\begin{aligned} \mathbf{W}^* &= \mathbf{W}\,\mathrm{diag}(\mathbf{H}_w/2+1) \\ \mathbf{P}^* &= \mathbf{P}\cdot(\mathbf{H}_w/2+1). \end{aligned}$$

Now the pseudo response vector can be expressed as:

$$\begin{aligned} \mathbf{z}_i &= \boldsymbol{\eta}_i + \frac{\partial \boldsymbol{\eta}_i}{\partial P_i^*}(\mathbf{y}_i - \mathbf{p}_i + .5\,\mathbf{h}_{w_i}) \\ &= \boldsymbol{\eta}_i + \frac{\partial \boldsymbol{\eta}_i}{\partial \mathbf{P}_i^*}\{(\mathbf{y}_i + .5\,\mathbf{h}_i) - (1 + .5\,\mathbf{h}_i^*)\mathbf{p}_i\} \\ &= \boldsymbol{\eta}_i + \frac{\partial \boldsymbol{\eta}_i}{\partial \mathbf{P}_i^*}(\mathbf{y}_i^* - \mathbf{p}_i^*) \end{aligned}$$

where $\mathbf{h}_i = (h_{i1}, h_{i2}, \ldots, h_{iC})'$ and $\mathbf{h}_i^* = (h_{i1}^*, h_{i2}^*, \ldots, h_{iC}^*)'$.

B. URLs

- Package URLs
  - CRAN: http://cran.us.r-project.org/
    - FLDA, QDA: MASS
    - DLDA: sma
    - KNN: class
    - RF: randomForest
    - SVM: e1071
  - IRWPLS (S-Plus): http://www.stat.lsu.edu/bmarx
  - Bioconductor: http://www.bioconductor.org
    - (M)IRWPLS(F): gpls
- Data URLs
  - Pima data: R *MASS* package: *Pima.tr* (training set) and *Pima.te* (test set)
  - Alon colon data: http://microarray.princeton.edu/oncology/affydata/index.html
  - Iris data: R *MASS* package: *iris*
  - NCI60: http://genome-www.stanford.edu/nci60

[Received November 2003. Revised July 2004.]

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