Estimating the theoretical error rate for prediction

Herman Chernoff\textsuperscript{1}, Shaw-Hwa Lo\textsuperscript{2}, Tian Zheng\textsuperscript{2}, Adeline Lo\textsuperscript{3}

\textsuperscript{1}Department of Statistics, Harvard University, Cambridge, MA.
\textsuperscript{2}Department of Statistics, Columbia University, New York, NY
\textsuperscript{3}Department of Politics, Princeton University, Princeton, NJ

Abstract

Prediction for very large data sets is typically carried out in two stages, variable selection and pattern recognition. Ordinarily variable selection involves seeing how well individual explanatory variables are correlated with the dependent variable. This practice neglects the possible interactions among the variables. Simulations have shown that a statistic $I$, that we used for variable selection is much better correlated with predictivity than significance levels. We explain this by defining theoretical predictivity and show how $I$ is related to predictivity. We calculate the biases of the overoptimistic \textit{training estimate} of predictivity and of the pessimistic \textit{out of sample} estimate. Corrections for the bias lead to improved estimates of the potential predictivity using small groups of possibly interacting variables. These results support the use of $I$ in the variable selection phase of prediction for data sets such as in GWAS (Genome wide association studies) where there are very many explanatory variables and modest sample sizes. Reference is made to another publication using $I$, which led to a reduction in the error rate of prediction from 30\% to 8\%, for a data set with, 4,918 variables and 97 subjects. This data set had been previously studied by scientists for over 10 years.
Key words: variable selection, pattern recognition, classification, parameter estimation

1 INTRODUCTION

The problems of prediction and classification \((C)\) have a long history in the statistics literature. Recent advances in technology confront us with problems with which the classical literature did not deal, and new approaches are necessary and are being tried. An article in Nature Genetics [1], “Predicting the influence of common variants”, identified prediction as an important additional goal for current genome-wide association studies (GWAS). A common approach consists of the two parts, Variable Selection \((VS)\), in which a few highly relevant explanatory variables are selected from the many that are available, and \(C\), applying pattern recognition techniques on these variables to make predictions for new subjects. Ordinarily \(VS\) selects variables by how well they are correlated with the outcome. Recently an article [2] pointed out that adding highly significant variables to a group does not necessarily increase predictivity. A recent report in PNAS [3] pointed out that significance is not necessarily well related to predictivity, suggesting that predictivity requires a new framework, and that a statistic \(I\) that was used in a method of \(VS\) called Partition Retention \((PR)\) [4] might be a useful tool in prediction since, in simulations, it was much better correlated with predictivity than was significance.

This paper confronts some of the issues in variable selection for prediction with large data sets. In the interest of simplicity, we shall confine ourselves to a special problem, but the concepts are much more generally applicable, and may serve as a framework for a theory. This problem is a case-control study that involves two states, \(h\) for Healthy and \(d\) for Disease, and a sample of \(n\) subjects for each. There are a large number, \(m\), of explanatory variables \emph{markers} called SNPs for each subject. In some current studies \(n\) may vary from a hundred
to a few thousand while $m$ may vary from several hundred to a million. The object of these studies may be to find out which of the variables influence the disease or, to use knowledge of these variables for another individual, to predict whether he has the disease.

Prediction ordinarily requires some variable selection, but the scientist who wants to understand how the disease works may not be primarily interested in prediction and may have somewhat different criteria for variable selection than the predictor. Once the predictor has selected a subset of the variables, he still faces a substantial pattern recognition problem of deciding on a strategy for using them to make his predictions. It would be helpful to have an estimate of how well he can hope to do with this subset. If he falls far short of this estimate, there may be room for improvement.

A standard approach to the variable selection problem is to see how well each variable is correlated with the outcome, and to select a few that are most correlated. One need not depend on linear correlation. One can simply measure the significance level for the test that the two distributions of the variable under $h$ and $d$ are the same. A $t$ test will provide a $p$-value which can be used to compare the various one dimensional candidate variables.

This approach will work well for a simple disease where certain variables have a great influence on the disease by themselves. But if the disease is influenced by the interaction among several variables, none of the influential variables may show up as significant, whereas if we have a million candidate variables, some noninfluential ones may show up as very significant by chance alone.

There is an implicit feeling that the variables that will be useful for $VS$ and $C$ will show up as highly significant in testing the null hypothesis that the two distributions under $h$ and $d$ are the same. When we consider a group of two or more variables, a typical test of the null hypothesis may be something like a chi-square test, which is not as focused as the $t$ test in the one dimensional problem, and may lack power. The significance level obtained by this test may be a poor indicator of the classification power of the group of variables. Moreover,
the computational burden, of dealing with the interaction of only two of the variables at a time, can be overwhelming when $m \approx 1,000,000$.

The technique for VS, *Partition Retention (PR)*, copes with the computational problem involved in large data sets where there may be interaction among the influential explanatory variables. Wang et al [5] attacked a data set with 4,918 gene expression variables and 97 subjects using *PR* to reduce the set of variables to a few overlapping small groups of interacting variables, and then worked on the pattern recognition problem. They were successful in reducing a standard error rate of about 30% to 8% on this data set that had been studied by many scientists for over 10 years.

From the prediction point of view, there is even the possibility that two different variables are influential and may show up to be significant, but each only influences a small percentage of subjects. Then prediction based on these variables will work only for a small fraction of cases. In short, the p-value for testing the null hypothesis, using a group of variables, is an unreliable sign of how useful the group will be for $C$ and we have conjectured that $I$ may be a useful measure in selecting variables for $C$.

When the number of explanatory variables is very large, the possibility of a satisfactory resolution of the VS and $C$ problems depends on the underlying simplicity of the situation. If the real relationships are very complicated, it may not be possible to find an adequate solution.

The object of this paper is to show how the statistic $I$, that plays a fundamental role in the *PR* method, is related to a parameter $\theta_e$ that measures the potential ability to use a small group of explanatory variables for classification. Since $\theta_e$ tells us how well we can hope to do, we discuss several estimates of $\theta_e$, their biases and corrections for those biases. We show that Partition Retention for VS can be a useful tool in developing good prediction procedures.
In a case control study the statistician who is given a small group $X$ of discrete valued explanatory variables obtains data with which to estimate the underlying distributions of $X$ under $d$ for Disease and $h$ for Health. The ability, to use the data of this group for classification, depends on these probability distributions, $f_d$ and $f_h$, which the statistician can only estimate.

Whereas calculating significance involves using the case control data to test whether $f_d = f_h$, prediction involves the use of the observation $X$ on an individual for testing whether it comes from $f_d$ or from $f_h$. Suppose that we know these probability distributions and we consider $d$ and $h$ as equally likely a priori, and regard as equally bad, the two possible errors of a false positive and a false negative. Then the best decision rule (prediction) for a possible observation $x$ on $X$ is to select according to the greater of $f_d(x)$ and $f_h(x)$. The probability of a false positive is $Pr(f_d(X) > f_h(X)|f_h) = \sum_{x: f_d(x) > f_h(x)} f_h(x)$ and the probability of a false negative is $Pr(f_d(X) \leq f_h(X)|f_d) = \sum_{x: f_d(x) \leq f_h(x)} f_d(x)$.

Then the ideal average error rate and correct classification rate for this procedure based on information that the statistician lacks, but can estimate, are

$$\theta_c = 0.5 \sum_x \min(f_d(x), f_h(x))$$

and $\theta_e = 1 - \theta_c = 0.5 \sum_x \max(f_d(x), f_h(x))$. Taking the difference of the two sums, we can write

$$\sum_x |f_d(x) - f_h(x)| = 2\theta_c - 2\theta_e = 2 - 4\theta_e$$

which represents $\theta_c$ and $\theta_e$ in terms of the sum of the absolute differences of the probability densities. A similar framework with variable selection can be found in [6].

In prediction we ordinarily have different prior probabilities and different costs of error.
These suggest that we later consider a natural modification of this definition of the underlying parameter representing the ability to predict.

One may use the data, i.e. the training set, to estimate $\theta_e$. The naive training estimate of $\theta_e$ is

$$\hat{\theta}_e = 0.5 \sum_x \min(n_{dx}, n_{hx}) / n, \tag{3}$$

where $n_{dx}$ and $n_{hx}$ are the number of diseased and healthy observations for a given value $x$. This training estimate of $\theta_e$ tends to be overoptimistic. Note that it can be expressed in terms of $\sum_x |n_{dx} - n_{hx}|$.

Note also that $\theta_e$ is an ideal and the statistician, given the data and not $f_d$ and $f_h$, may lack a good strategy to attain something close to that error rate. Bounds on $\theta_e$ would be useful in deciding whether a method of prediction is adequate or requires enhancement.

3  I SCORE, BOUNDS, ESTIMATORS AND BIASES

In an intensive calculation from [3] involving 6 snps with specified minor allele frequencies (MAF) and specified probabilities of response, it was indicated that when $\theta_e$ was known, neither significance levels nor training prediction rates were well correlated with this parameter unless the sample size was very large, while $I$ seemed well correlated with it for quite moderate sample sizes. This paper explains that phenomenon,

3.1  The Score $I$

We present a definition of $I$ when we have a sample of $n_0$ observations on $(Y, X)$ where $Y$ is a dependent variable which has been normalized to have sample mean 0 and sample variance 1, and $X$ represents a discrete valued variable or a group of discrete valued explanatory
variables.

\[ I = n_0^{-1} \sum_x (n_x \bar{Y}_x)^2. \]  

(4)

Here \( n_x \) is the number of observations where \( X = x \), \( \bar{Y}_x \) is the sample mean of the values of \( Y \) for which \( X = x \).

In our application, we identify \( d \) and \( h \) with \( Y = 1 \) and \( Y = -1 \). Because we have equal sample sizes the sample mean \( \bar{Y} = 0 \) and the sample variance, \( n_0^{-1} \sum(Y - \bar{Y})^2 = 1 \), and \( Y \) is automatically normalized. Also \( n_x = n_{dx} + n_{hx}, \ n_0 = 2n \) and \( n_x \bar{Y}_x = n_{dx} - n_{hx} \). Thus

\[ I = 0.5 n^{-1} \sum_x (n_{dx} - n_{hx})^2, \]  

(5)

which seems related to the training prediction rate. For large samples, we may think of \( I/n \) as an estimate of the parameter

\[ \theta_I = 0.5 \sum_x (f_d(x) - f_h(x))^2. \]  

(6)

To study the expectations and variances of \( I \) and the training prediction rate, we should be interested in the moments of \( |n_{dx} - n_{hx}| \).

It should be noted that \( I \) is a modified version of

\[ J = n^{-1} \sum_x n_x \bar{Y}_x^2, \]

which is explained variance over total variance or squared multiple correlation in Analysis of Variance terminology [7]. If \( Y \) and \( X \) are independent, the distribution of \( I \) is approximately that of a mixture of chi-square variables with 1 degree of freedom (\( df \)). Values of \( I \) substantially greater than 1 are indications of some dependence. The distribution of \( J \) is approximately that of chi-square with \( k - 1 \) degrees of freedom if \( X \) has \( k \) possible values.
with a substantial number of expected observations for each \( x \). In our applications this last condition rarely applies.

### 3.2 Upper Bound on \( \theta_e \) Using \( \theta_I \)

Since

\[
\sum_i a_i^2 \leq (\sum_i |a_i|)^2, \tag{7}
\]

\( \theta_I \) provides an upper bound for \( \theta_e \). Let

\[
\sum_x (f_d(x) - f_h(x))^2 = \alpha (\sum_x |f_d(x) - f_h(x)|)^2, \tag{8}
\]

where \( \alpha \leq 1 \). Then

\[
\theta_e = 0.5 - \sqrt{\theta_I / 8\alpha}, \tag{9}
\]

which may also be written as \( \theta_I = 8\alpha(0.5 - \theta_e)^2 \). Since \( \alpha \leq 1 \), \( \theta_e \leq 0.5 - \sqrt{\theta_I / 8} \).

This bound is rather weak since the ratio, \( \sum_i a_i^2 / (\sum_i |a_i|)^2 \) can be anywhere between 1 and \( 1/k \) where \( k \) is the number of terms in the sum. In the appendix we prove that when \( \sum_i a_i = 0 \), as is the case here of the difference of two probability distributions, the ratio is no larger than \( 1/2 \). Thus we can use \( \alpha \leq 0.5 \) to derive the upper bound

\[
\theta_e \leq 0.5 - \sqrt{\theta_I / 4} \tag{10}
\]

and

\[
\theta_I \leq 4(0.5 - \theta_e)^2. \tag{11}
\]
3.3 Estimators and Biases

It remains for us to see how well the naive estimators of these parameters behave. The variances of these estimates depend mainly on the second and fourth moments of $|n_{dx} - n_{hx}|$. Let us first consider $E(I)$. Since $n_{dx} - n_{hx}$ is the difference of two independent binomially distributed variables, the expectation of the sum of the squares is easily calculated.

$$E(I) = 0.5n \sum_x (f_d(x) - f_h(x))^2 + 0.5 \sum_x f_d(x)(1 - f_d(x)) + f_h(x)(1 - f_h(x)).$$

$$= n\theta_1 + 1 - 0.5 \sum_x (f_d(x)^2 + f_h(x)^2).$$ (12)

Then $I/n$ is of order 1 and the bias, is less than $1/n$.

To calculate the expectation of

$$\hat{\theta}_e = 0.5 \sum_x \min(n_{dx}, n_{hx})/n,$$ (13)

the training estimator of $\theta_e$, we need only calculate the contribution of each value of $x$. In general if $Z$ and $W$ are independent binomials with parameters $n, p_Z$ and $p_W$ where $p_Z/p_W = r > 1$ and $\lambda = np_Z$, we are interested in the negative relative bias for each value of $x$.

$$b(n, \lambda, r) = \frac{np_W - E(\min(Z, W))}{np_W}. $$ (14)

which can be computed directly. Since we expect the bias to be negative $b$ should be positive. Table 1 shows that $b(n, \lambda, r)$ is almost independent of $n$ for $n > 100$. Figure 1 presents $b$ for $n = 500$ where the curves represent distinct values of $r$ and $\lambda$ is represented by $la$.

Figure 1 clearly shows that $b$ is close to 1 for small $\lambda$ and close to 0 for large $\lambda$. This implies that the large values of $n_{dx}$ and $n_{hx}$ contribute to reliable estimates, but the values of $x$ with small entries are not helpful for the training estimator.
Table 1: Negative Relative Bias for Training Estimate.

\[ b(n, \lambda, r): \lambda = n \cdot p_Z; r = p_Z/p_w \]

\[
\begin{array}{c|cccc}
\lambda & 40 & 5 & 1.25 & 1.062 & 1.016 \\
\hline
40 & 0.0000 & 0.0000 & 0.0001 & 0.0123 & 0.0459 \\
10 & 0.0001 & 0.0005 & 0.0283 & 0.0995 & 0.1469 \\
2.5 & 0.0859 & 0.1052 & 0.2131 & 0.2929 & 0.3288 \\
0.625 & 0.5368 & 0.5445 & 0.5827 & 0.6087 & 0.6202 \\
0.156 & 0.8555 & 0.8563 & 0.8603 & 0.8632 & 0.8646 \\
0.039 & 0.9617 & 0.9618 & 0.9620 & 0.9623 & 0.9624 \\
\end{array}
\]

\[
\begin{array}{c|cccc}
\lambda & 40 & 5 & 1.25 & 1.062 & 1.016 \\
\hline
40 & 0.0000 & 0.0000 & 0.0004 & 0.0220 & 0.0617 \\
10 & 0.0001 & 0.0007 & 0.0320 & 0.1064 & 0.1542 \\
2.5 & 0.0880 & 0.1076 & 0.2164 & 0.2963 & 0.3322 \\
0.625 & 0.5377 & 0.5453 & 0.5837 & 0.6098 & 0.6213 \\
0.156 & 0.8556 & 0.8564 & 0.8604 & 0.8634 & 0.8647 \\
0.039 & 0.9617 & 0.9618 & 0.9621 & 0.9623 & 0.9624 \\
\end{array}
\]

\[
\begin{array}{c|cccc}
\lambda & 40 & 5 & 1.25 & 1.062 & 1.016 \\
\hline
40 & 0.0000 & 0.0000 & 0.0005 & 0.0239 & 0.0646 \\
10 & 0.0001 & 0.0007 & 0.0327 & 0.1077 & 0.1556 \\
2.5 & 0.0884 & 0.1081 & 0.2170 & 0.2970 & 0.3328 \\
0.625 & 0.5378 & 0.5455 & 0.5839 & 0.6100 & 0.6215 \\
0.156 & 0.8556 & 0.8564 & 0.8604 & 0.8634 & 0.8647 \\
0.039 & 0.9617 & 0.9618 & 0.9621 & 0.9623 & 0.9624 \\
\end{array}
\]
The bias is

$$B_e = -0.5 \sum_x (\min(f_d(x), f_h(x)) b(n, \lambda(x), r(x))),$$  \hspace{1cm} (15)

where $r(x) = \max(f_d(x), f_h(x))/\min(f_d(x), f_h(x))$ and where $\lambda(x) = n \max(f_d(x), f_h(x))$.

This result suggests a correction for bias. We introduce

$$\hat{\theta}_{e1} = 0.5 \sum_{x: \min(n_{dx}, n_{hx}) > 0} \frac{\min(n_{dx}, n_{hx})}{n} (1 - b(n, \lambda(x), r(x))).$$  \hspace{1cm} (16)

Both $\hat{\theta}_e$ and $\hat{\theta}_{e1}$ neglect the effect of those values of $x$ for which there are 0 observations. We conjecture that it may be possible to use the Good-Turing [8] approach to compensate for this problem. A brief description of this approach, used in code breaking, involves the following problem. Suppose that there are many species of fish in a lake. A random sample of $n$ fish are caught and we assume all fish in the lake are equally likely to be caught. What
proportion of the fish in the lake are of species for which none have been caught?. This coverage is estimated by \(1/n\) times the number of singletons or the species for which only one fish was caught.

Another estimator is called the \emph{Out of sample estimator} \(\hat{\theta}_{eo}\). Unlike the other estimators which are based on the data, this is a sort of hybrid in that it involves the underlying distributions which are unknown by the statistician, but known by the simulator. It could also be considered a way to evaluate a method by using it many times (without adjusting on the basis of subsequent results). It can be estimated by use of an independent sample. The simulator who knows the model can evaluate the method by simulation or by analysis. In our case the natural method consists of deciding \(h\) for all future \(x\) for which \(n_{dx} < n_{hx}\) in this particular sample, deciding \(d\) when the inequality is reversed and choosing with probability \(1/2\) when the two frequencies match. For the simulator who knows the model, this estimator is

\[
\hat{\theta}_o = 0.5 \left( \sum_x f_d(x)[1(n_{dx} < n_{hx}) + 1(n_{dx} = n_{hx})/2] \right) + \sum_x f_h(x)[1(n_{dx} > n_{hx}) + 1(n_{dx} = n_{hx})/2],
\tag{17}
\]

where \(1(A)\) is the characteristic function of \(A\), \emph{i.e.} \(1\) if \(A\) is true and \(0\) if \(A\) is false. The contribution of \(x\) for which \(f_d(x) > f_h(x)\) to the expectation of this out of sample estimator is

\[
0.5(f_d(x)(Pr(n_{hx} > n_{dx}) + 0.5Pr(n_{hx} = n_{dx})) + f_h(x)(Pr(n_{hx} < n_{dx}) + 0.5Pr(n_{hx} = n_{dx}))).
\]

In terms of \(Z\) and \(W\) above, let

\[
a(x) = a(n, \lambda(x), r(x)) = Pr(Z < W) + 0.5Pr(Z = W).
\]
Thus the contribution of \( x \) to the estimate of the error probability is \( (f_d(x)a(x) + f_h(x)(1 - a(x)))/2 \) to be compared with \( f_h(x)/2 \), the contribution to \( \theta_e \).

A similar result applies to those values of \( x \) for which \( f_d(x) < f_h(x) \) and for which \( f_d(x) = f_h(x) \). This gives rise to a relative contribution to bias of

\[
b_o(x) = (r(x) - 1)a(n, \lambda(x), r(x)).
\]

Table 2 indicates that \( a \), and therefore \( b_o \), are almost independent of \( n \) for \( n > 100 \), given \( \lambda \) and \( r \). Figure 2 plots \( a \) for \( n = 500 \), where the curves correspond to distinct values of \( r \).

![Figure 2: \( a(n, \lambda, r) = \Pr(Z < W) + 0.5\Pr(Z = W) \) versus \( \log_{10}(\lambda) \) for \( r = 1.1016, 1.062, 1.25, 5, \) and 40. \( n = 500. \)](image)

The bias of the out of sample estimator can be expressed as

\[
B_{eo} = 0.5 \sum_x \min(f_d(x), f_h(x))b_o(x),
\]  

(18)

13
Table 2: $a(n, \lambda, r) = \Pr(Z < W) + 0.5\Pr(Z = W)$, $\lambda = np_Z$; $r = p_Z/p_W$.

$n = 100$

| $\lambda$ | 40  | 5   | 1.25 | 1.062 | 1.016 |
|-----------|-----|-----|------|-------|-------|
| 40        | 0.0000 | 0.0000 | 0.1192 | 0.3675 | 0.4638 |
| 10        | 0.0001 | 0.0059 | 0.3115 | 0.4449 | 0.4852 |
| 2.5       | 0.0488 | 0.1201 | 0.4083 | 0.4740 | 0.4930 |
| 0.625     | 0.2739 | 0.3199 | 0.4593 | 0.4884 | 0.4969 |
| 0.156     | 0.4295 | 0.4429 | 0.4863 | 0.4960 | 0.4989 |
| 0.039     | 0.4813 | 0.4847 | 0.4962 | 0.4989 | 0.4997 |

$n = 500$

| $\lambda$ | 40  | 5   | 1.25 | 1.062 | 1.016 |
|-----------|-----|-----|------|-------|-------|
| 40        | 0.0000 | 0.0000 | 0.1639 | 0.3915 | 0.4707 |
| 10        | 0.0001 | 0.0070 | 0.3181 | 0.4471 | 0.4858 |
| 2.5       | 0.0499 | 0.1217 | 0.4092 | 0.4742 | 0.4931 |
| 0.625     | 0.2743 | 0.3202 | 0.4595 | 0.4885 | 0.4969 |
| 0.156     | 0.4296 | 0.4429 | 0.4863 | 0.4960 | 0.4989 |
| 0.039     | 0.4813 | 0.4847 | 0.4962 | 0.4989 | 0.4997 |

$n = 2,500$

| $\lambda$ | 40  | 5   | 1.25 | 1.062 | 1.016 |
|-----------|-----|-----|------|-------|-------|
| 40        | 0.0000 | 0.0000 | 0.1712 | 0.3949 | 0.4716 |
| 10        | 0.0001 | 0.0073 | 0.3193 | 0.4475 | 0.4860 |
| 2.5       | 0.0501 | 0.1220 | 0.4093 | 0.4743 | 0.4931 |
| 0.625     | 0.2744 | 0.3203 | 0.4595 | 0.4885 | 0.4969 |
| 0.156     | 0.4296 | 0.4429 | 0.4863 | 0.4960 | 0.4989 |
| 0.039     | 0.4813 | 0.4847 | 0.4962 | 0.4989 | 0.4997 |
and a modified estimate would be

\[ \hat{\theta}_{eo1} = \hat{\theta}_o - 0.5 \sum_x \min(f_d(x), f_h(x))b_o(x). \] (19)

The out of sample estimator tends to overestimate \( \theta_e \). For some readers there may be an apparent paradox when these two estimators, using the same method, bias the result in different directions. However the training estimate uses the method on the data set from which the method was derived, while the out of sample estimate is evaluated on how well it will do on all future data. There, the method is suboptimal, since it does not use the actual probabilities \( f_d \) and \( f_h \), but estimates of these probabilities.

4 DESCRIPTION OF PARTITION RETENTION

We present here a very concise description of the major idea of the partition retention method for VS. Given a small group of discrete explanatory variables, we evaluate \( I \) for this group and for each subset where one of the group is dropped. If none of these subsets lead to an increase in \( I \), the entire group is retained. Otherwise that element, the dropping of which leads to the largest increase in the value of \( I \), is eliminated from the group. This reduction procedure is then applied to the remaining group and repeated until we reach the subgroup where none are dropped. This backward procedure is repeated and applied to many groups selected at random. Then those variables that are retained very often are candidates to be taken seriously.

For large \( m \), the variables that show up very well at first in this backward selection approach, are used to select new subsets which may succeed in resuscitating influential variables that did not show up well at first, but interact with some that did. This is done by forming subsets which contain some of the good variables and some of the others. For very
large $m$ computational limits may force us to go through several stages starting with groups consisting of only one or two variables.

This backward selection method within each stage distinguishes the method from some competitors such as Random Forests [9], where there is a forward selection approach. We believe that choices of first optimality leads to less reliable results than ours of first discarding the least valuable.

5 GROUPS OF SNPS

It should be noted that in the successful use of $PR$ referred to previously, the investigators found a substantial number of small interacting subgroups, each of which was capable of rather weak predictivity, but acting together provided a major improvement. Thus it is of value to be able to find small subgroups which can be the basis for average error rates close to, but less than 1/2. In the following we shall study how $\theta_e$ and $\theta_I$ are related for small groups of SNPs, concentrating at first on the case where only one of the group is influential.

5.1 Formal Notation

Let us specialize to the case where we observe a few independent SNPs, with common minor allele frequency (MAF) $p$, only the first of which is influential. We note that when $m$ is large it is unlikely that a group of 6 snps selected at random will have more than one of several interacting influential snps among them. With groups of 6 snps, each of which can have 3 possible values we deal with with $279 = 3^6$ possible values of $x$. The use of substantially larger groups will do little to increase the possibility of finding two interacting snps in the same group, but will make it likely that for almost all of the values of $x$ $n_x$ will be 0 or 1 more or less at random, and contribute little useful information. Although this case of only one influential snp in the group involves no interactions, it is useful to help us understand
why I works well.

Let $X = (U, V)$ where $U$ represents the first snp which can assume the values 0, 1 and 2. The minor allele frequency (MAF) for this snp is $p$ and the above values of $U$ are assumed with probabilities $f_U(u) = (1 - p)^2, 2p(1 - p), p^2$ for $u = (0, 1, 2)$. Treating $f$ as the discrete probability density, we assume that $f_{Y|X}(h|x) = t(u)$ where $t$ is a decreasing function of $u$.

Some elementary calculations yield

$$f_X(x) = f_U(u)f_V(v)$$

assuming $U$ and $V$ are independent.

$$f_{Y|X}(d|x) = 1 - t(u)$$
$$f_{XY}(x, h) = t(u)f_U(u)f_V(v)$$
$$f_{XY}(x, d) = (1 - t(u))f_U(u)f_V(v)$$
$$f_Y(h) = \sum_x f_{XY}(x, h) = \sum_u t(u)f_U(u)$$
$$f_{X|Y}(x|h) = t(u)f_U(u)f_V(v)/f_Y(h)$$
$$f_{X|Y}(x|d) = (1 - t(u))f_U(u)f_V(v)/f_Y(d)$$

where $f_Y(d) = 1 - f_Y(h)$. Note that what we previously referred to as $f_d(x)$ and $f_h(x)$ in the case control example are presented here as $f_{X|Y}(x|d)$ and $f_{X|Y}(x|h)$.

To get a concrete feeling for the conditional distributions, it may help to refer to a specific (artificial) example. In the following example with the group of 6 SNPs and 279 possible values of $X$, each with small probability, let the MAF of each of the SNPs be 0.2, and let $t(u)$ take on the values $(0.97, 0.60, 0.40)$ for $u = (0, 1, 2)$. The SNP $U$ takes on these three values with probabilities $f_U(u)$ given by $(0.64, 0.32, 0.04)$. Then we can calculate $f_Y(d) =$
0.171, \( f_Y(h) = 0.829, f_{U|Y}(u|d) = (0.112, 0.748, 0.140) \) and \( f_{U|Y}(u|h) = (0.749, 0.232, 0.019) \). The ratios of these conditional probabilities are \( (6.688, 0.310, 0.138) \).

Note that \( f_{X|Y} = f_{U|Y} f_V \) and the likelihood ratios for the conditional distributions of \( X \) are limited to the same three possible values depending on the value of \( U \). Although the values of \( f_{U|Y} \) are substantial, almost all 729 possible values of \( X \) come with small probabilities. Note also that the likelihood ratio for \( u = 0 \) is greater than 1 and the other values are considerably less than 1.

### 5.2 Calculations

Now let us calculate \( \theta_e \), and \( \theta_I \). First, since \( \sum_v f_V(v) = 1 \),

\[
\theta_e = 0.5(f_{U|Y}(0|d) + f_{U|Y}(1|h) + f_{U|Y}(2|h)).
\]

In our special case \( \theta_e = 0.182 \) and is not affected by the 5 non-influential variables. This is the best we can hope to do in predicting a random new subject. Moreover, the statistician who does not know the underlying probabilities may not be able to do so well. While we can ignore the five useless variables in the group, the statistician using this group may find the presence of the other variables distracting and leading him to have poorer performance.

Now we calculate

\[
\theta_I = 0.5 \sum_u (f_{U|Y}(u|d) - f_{U|Y}(u|h))^2 \sum_v f_V(v)^2.
\]

In our special case where \( \sum_v f_V(v)^2 = 0.03574 \) we obtain \( \theta_I = 0.0123 \). Ignoring the term \( \sum_v f_V(v)^2 \), that is the the factor by which \( \theta_I \) tends to be degraded by the presence of the
noninformative variables in the group, we introduce the parameter

\[ \theta_{I_0} = \theta_I / \sum_v f_V(v)^2 \]  

(22)

to be compared with \( \theta_e \). In our special case \( \theta_{I_0} = 0.344 \) and the corresponding upper bound on \( \theta_e \) is 0.207. Simple graphs indicate that, as \( t(0) \) decreases and \( t(1) \) and \( t(2) \) increase, \( \theta_{I_0} \) decreases and \( \theta_e \) increases, indicating that these parameters become less favorable for prediction. Table 3 lists several functions \( t(u) \) and Figure 3 presents \( (\theta_e, \theta_{I_0}) \) along curves representing a \( t(u) \) as the \( MAF = p \) varies from 0.001 to 0.3. Figure 3 shows that the two parameters \( \theta_e \) and \( \theta_{I_0} \) are closely correlated. The upper bound that \( \theta_{I_0} \) imposes on \( \theta_e \) is represented in Figure 3 by the dashed curve. Table 3 presents \( \theta_e \) and \( \theta_{I_0} \) for various values of \( p \) and \( t \).

Table 3: Various choices of \( t(u) = P(h|u) \) for a single influential variable.

| \( u \) | 0 | 1 | 2 |
|-------|---|---|---|
| \( t_1 \) | 0.97 | 0.4 | 0.2 |
| \( t_2 \) | 0.97 | 0.5 | 0.3 |
| \( t_3 \) | 0.97 | 0.6 | 0.4 |
| \( t_4 \) | 0.90 | 0.4 | 0.2 |
| \( t_5 \) | 0.90 | 0.5 | 0.3 |
| Choices of \( t(u) = P(h|u) \) |  |
| \( t_6 \) | 0.85 | 0.4 | 0.2 |
| \( t_7 \) | 0.90 | 0.6 | 0.4 |
| \( t_8 \) | 0.85 | 0.5 | 0.3 |
| \( t_9 \) | 0.80 | 0.4 | 0.2 |
| \( t_{10} \) | 0.85 | 0.6 | 0.4 |
| \( t_{11} \) | 0.80 | 0.5 | 0.3 |
| \( t_{12} \) | 0.80 | 0.6 | 0.4 |

As \( p \), increases the curves of \( \theta_{I_0} \) vs \( \theta_e \) move to the left, indicating improved predictability, until \( p \) reaches about 0.15. For some \( t \) functions \( \theta_e \) reaches a minimum and starts to increase for \( p > 0.15 \). Sometimes, for \( p \) greater than 0.15, we have small regions where \( I_0 \) changes
Figure 3: $\theta_{I0}$ versus $\theta_e$ for several MAF and bound.

slowly in the same direction as $\theta_e$. In these regions small changes in $I_0$ are unreliable indicators of corresponding changes in $\theta_e$.

The quantity $\sum_v f_V(v)^2$ is a product of factors for each of the SNP’s of $V$. For a MAF of $p$ the factor contributed by the SNP is $p^4 + (2p(1-p))^2 + (1-p)^4$. This function is symmetric about $p = 0.5$ and decreases rapidly from 1 at $p = 0$ to 0.5136 at $p = 0.2$ and more slowly to 3/8 at $p = 0.5$. In our case where each $p = 0.2$ we have $\sum_v f_V(v)^2 = (0.5136)^5 = 0.0357$.

We digress momentarily to emphasize that while $\theta_e$ does not change by adjoining irrelevant variables to the group, $\theta_I$ is degraded. This fact supports the strategy of Partition Retention that consists of discarding each variable that diminishes $I$.

In Table 4 we present the results of a set of simulations designed to check on our estimates
of the biases of the training and out of sample estimates and the corrections for these biases. The inputs are the MAF and $t$ functions and $n$ and $m$, the number of repetitions. For each case we calculate $\theta_e, \theta_{I_0}, B, B_o$ and the bound on $\theta_e$. In addition we calculate the average and standard deviations based on the $m$ repetitions of the observed biases of the training estimate, the correction for the training estimate, and the out of sample estimate. The averages of the biases for the training estimate and the out of sample estimate are reasonably close to their expectations.

Three comments are worth making. The correction for the training estimate seems to reduce the bias by a factor varying from 0.5 to 0.1. The upper bound on $\theta_e$ based on $\theta_{I_0}$ is generally surprisingly tight. This calculation provides a hint that the estimates generally have moderate sampling variability.

5.3 Two Influential Variables

The main point of the PR method was to take advantage of the possible interactions among influential variables which may not indicate much marginal effect by themselves. Thus we now consider the case where there are two, possibly interacting influential variables in the group under consideration. For moderately large $m$, we will find such groups by using a large number of randomly selected groups. For larger $m$ Partition Retention may require resuscitation and for very large $m$ we may require several stages, starting with one variable at a time, and moving to two variables and then more.

In this case we can write $X = (U,V)$ where $U = (U_1, U_2)$ are the influential SNPs and $V$ represents the other variables in the group and which are assumed to be independent of $U$ and each other. The only change that takes place is that the function $t$ now takes on 9 possible values corresponding to the possible values of $U$. Typically we would expect $t$ to decline as $u$ varies over (00), (10), (01), (20), (02), (11), (21), (12), (22) although that is not
Table 4: Biases for groups with 1 influential variable.

| MAF |  | t(u) |  |  | m | n |
|-----|-----|------|-----|-----|----|----|
| 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.97 | 0.6 | 0.4 | 25 | 100 |
| 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.70 | 0.6 | 0.5 | 25 | 200 |
| 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.80 | 0.5 | 0.2 | 25 | 100 |
| 0.1 | 0.1 | 0.1 | 0.2 | 0.0 | 0.0 | 0.97 | 0.6 | 0.4 | 25 | 200 |
| 0.1 | 0.1 | 0.1 | 0.2 | 0.0 | 0.0 | 0.70 | 0.6 | 0.5 | 25 | 100 |
| 0.1 | 0.01 | 0.1 | 0.1 | 0.2 | 0.0 | 0.80 | 0.5 | 0.2 | 25 | 200 |
| 0.2 | 0.1 | 0.1 | 0.1 | 0.2 | 0.0 | 0.97 | 0.6 | 0.4 | 25 | 100 |
| 0.2 | 0.1 | 0.1 | 0.1 | 0.2 | 0.0 | 0.70 | 0.6 | 0.5 | 25 | 200 |
| 0.2 | 0.1 | 0.1 | 0.1 | 0.2 | 0.0 | 0.80 | 0.5 | 0.2 | 25 | 200 |

\[ \bar{b} = \text{negative bias of training estimate}; \]
\[ b_o = \text{bias for out of sample estimate}; \]
\[ \bar{b} = \text{average bias for training estimate in 25 simulations}; \]
\[ s_b = \text{standard deviation of bias for training estimate}; \]
\[ \bar{b}_1 = \text{average bias of adjusted estimate}; \]
\[ s_{b_1} = \text{standard deviation of adjusted bias}; \]
\[ \bar{b}_o = \text{average out of sample estimate}; \]
\[ s_{b_o} = \text{standard deviation of out of sample estimate}; \]
\[ \text{bound} = 0.5 - \sqrt{\theta_{lo}/4} \text{ on } \theta_c. \]
necessarily the case.

As a special case we take the function $t(u)$ which assumes the values $(0.95, 0.75, 0.7, 0.60, 0.50, 0.20, 0.15, 0.10, 0.05)$ for the values of $u$ listed above. As before we take a group of 6 SNP’s with MAF 0.2 and we may calculate

$$\theta_e = 0.5 \sum_u \min(f_{Y|U}(d|u), f_{Y|U}(h|u)) = 0.269$$

which is not affected by the 4 extraneous variables. We can compute $\theta_{I0} = 0.1447$ using the same formula as before and $\theta_I = \theta_{I0} \sum_v f_V(v)^2 = 0.1447 \times 0.06958 = 0.01001$. Since there are only 4 variables among the irrelevant ones in the group, $\sum f_V(v)^2 = 0.06958$ in our special case.

![Figure 4: $\theta_{I0}$ versus $\theta_e$ for several MAF and bound; two influential variables.](image)

In Figure 4 we present the graph of $\theta_{I0}$ vs. $\theta_e$ for 6 values of MAF and 9 versions of $t(u) = f_{Y|U}(h|u)$ tabulated in Table 5. Each row of $t(u)$ represents a distinct curve. It is
clear from the graph that $\theta_{I_0}$ is closely correlated with $\theta_e$. The bound on $\theta_e$ provided by $\theta_{I_0}$ is represented by the dashed curve. This bound seems to be relatively strong when $\theta_e$ is close to 0.5, i.e. when the error rate is high.

Table 5: Various choices of $t(u) = P(h|u)$ for the case of two influential SNPs in a group of 6 with a common MAF of $p$.

| Choices of $t(u) = P(h|u)$ | $u$ |
|---------------------------|-----|
|                           | 00  | 10  | 01  | 20  | 02  | 11  | 21  | 12  | 22  |
| $t_1$                     | 0.99| 0.20| 0.15| 0.10| 0.08| 0.02| 0.010| 0.004| 0.001|
| $t_2$                     | 0.98| 0.20| 0.15| 0.10| 0.01| 0.005| 0.005| 0.001|
| $t_3$                     | 0.95| 0.40| 0.30| 0.20| 0.10| 0.02| 0.010| 0.005| 0.002|
| $t_4$                     | 0.90| 0.40| 0.30| 0.20| 0.10| 0.02| 0.010| 0.005| 0.002|
| $t_5$                     | 0.95| 0.60| 0.40| 0.40| 0.20| 0.02| 0.010| 0.005| 0.001|
| $t_6$                     | 0.95| 0.60| 0.50| 0.30| 0.10| 0.05| 0.020| 0.015| 0.010|
| $t_7$                     | 0.99| 0.75| 0.75| 0.70| 0.70| 0.01| 0.008| 0.008| 0.002|
| $t_8$                     | 0.90| 0.60| 0.50| 0.30| 0.10| 0.05| 0.020| 0.015| 0.010|
| $t_9$                     | 0.95| 0.75| 0.70| 0.60| 0.50| 0.40| 0.350| 0.300| 0.200|

In Table 6 we present the input and output for some simulations involving two influential interacting variables in a group of 6 SNPs. Table 6 is parallel to Table 4 and the comments following Table 4 apply here too. This should also be the case when we have more than 2 influential variables in the group.

6 A REAL DATA APPLICATION

We have referred to the success [5] previously derived from the vant Veer breast cancer data [9] where the standard error rate in prediction of about 30 percent was reduced to 8% using $PR$ and $I$ for the $VS$ part of the analysis. The pattern recognition part used 18 small groups (modules) of interacting variables, none of which had much predictive power by themselves. In Table 7 we present the module of 5 variables which had the highest $I$ score and the best prediction performance of these modules, based on cross validation and an independent
Table 6: Biases for groups with 2 influential variables

| MAF | 00 | 01 | 02 | 10 | 11 | 12 | 20 | 21 | 22 | m  | n  |
|-----|----|----|----|----|----|----|----|----|----|----|----|
| 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.97 | 0.6 | 0.4 | 0.6 | 0.4 | 0.6 | 0.6 | 25 | 100 |
| 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.70 | 0.6 | 0.5 | 0.6 | 0.6 | 0.4 | 0.4 | 0.6 | 0.6 | 25 | 200 |
| 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.80 | 0.5 | 0.2 | 0.7 | 0.6 | 0.4 | 0.4 | 0.6 | 0.6 | 25 | 100 |
| 0.1 | 0.1 | 0.1 | 0.2 | 0.0 | 0.0 | 0.0 | 0.97 | 0.6 | 0.4 | 0.6 | 0.4 | 0.4 | 0.6 | 0.6 | 25 | 200 |
| 0.1 | 0.1 | 0.1 | 0.2 | 0.0 | 0.0 | 0.0 | 0.70 | 0.6 | 0.5 | 0.5 | 0.5 | 0.4 | 0.4 | 0.5 | 0.5 | 25 | 100 |
| 0.1 | 0.1 | 0.1 | 0.2 | 0.0 | 0.0 | 0.0 | 0.80 | 0.5 | 0.2 | 0.5 | 0.5 | 0.4 | 0.4 | 0.5 | 0.5 | 25 | 100 |
| 0.2 | 0.1 | 0.1 | 0.1 | 0.2 | 0.0 | 0.0 | 0.97 | 0.6 | 0.4 | 0.5 | 0.4 | 0.3 | 0.3 | 0.4 | 0.4 | 25 | 100 |
| 0.2 | 0.1 | 0.1 | 0.1 | 0.2 | 0.0 | 0.0 | 0.70 | 0.6 | 0.5 | 0.5 | 0.4 | 0.3 | 0.3 | 0.4 | 0.4 | 25 | 200 |
| 0.2 | 0.1 | 0.1 | 0.1 | 0.2 | 0.0 | 0.0 | 0.80 | 0.5 | 0.2 | 0.5 | 0.4 | 0.3 | 0.3 | 0.4 | 0.4 | 25 | 200 |

| \( \theta_e \) | \( b \) | \( b_o \) | \( \bar{b} \) | \( s_b \) | \( \bar{b}_1 \) | \( s_{b_1} \) | \( \bar{b}_o \) | \( s_{b_o} \) | \( \theta_{lo} \) | bound |
|-----------|-----|------|-----|-----|-------|-----|-------|-----|------|------|
| 0.264     | 0.111| 0.108| -0.107| 0.026| -0.041| 0.035| 0.136| 0.012| 0.137| 0.315|
| 0.439     | 0.157| 0.046| -0.160| 0.014| -0.081| 0.024| 0.055| 0.009| 0.009| 0.453|
| 0.359     | 0.152| 0.090| -0.154| 0.027| -0.074| 0.043| 0.107| 0.017| 0.046| 0.393|
| 0.182     | 0.006| 0.016| -0.007| 0.018| 0.002| 0.020| 0.027| 0.008| 0.271| 0.240|
| 0.421     | 0.050| 0.036| -0.051| 0.031| -0.013| 0.041| 0.045| 0.027| 0.017| 0.434|
| 0.336     | 0.013| 0.021| -0.012| 0.021| 0.004| 0.023| 0.030| 0.012| 0.072| 0.366|
| 0.200     | 0.027| 0.055| -0.028| 0.021| -0.000| 0.027| 0.080| 0.017| 0.226| 0.262|
| 0.413     | 0.057| 0.036| -0.063| 0.016| -0.025| 0.022| 0.042| 0.013| 0.019| 0.431|
| 0.317     | 0.029| 0.038| -0.031| 0.024| -0.003| 0.029| 0.057| 0.023| 0.085| 0.355|

- \( b \) = negative bias of training estimate;
- \( b_o \) = bias for out of sample estimate;
- \( \bar{b} \) = average bias for training estimate in 25 simulations;
- \( s_b \) = standard deviation of bias for training estimate;
- \( \bar{b}_1 \) = average bias of adjusted estimate;
- \( s_{b_1} \) = standard deviation of adjusted bias;
- \( \bar{b}_o \) = average out of sample estimate;
- \( s_{b_o} \) = standard deviation of out of sample estimate;
- bound = 0.5 - \( \sqrt{\theta_{lo}/4} \) on \( \theta_e \).
testing set in [9]. The error rate using this module was estimated to be bounded by 41%. We see that the individual significance levels and combined significance level of these 5 variables were rather unimpressive, considering that we had available 4,918 candidates.

Table 7: A predictive group

| Systematic name | Gene name  | Marginal p-value |
|-----------------|------------|------------------|
| 1 Contig45347_RC | KIAA1683   | 0.008            |
| 2 NM_005145     | GNG7       | 0.54             |
| 3 Z34893        | ICAP-1A    | 0.15             |
| 4 NM_006121     | KRT1       | 0.9              |
| 5 NM_004701     | CCNB2      | 0.003            |

Joint I-score    | Joint p-value | Family-wise threshold |
2.89            | 0.005         | 0.0000007            |

n = 97          | Bound on error prob: 0.414

7 SOME REMAINING ISSUES

The variance of the estimates of \( \theta_e \) and \( \theta_I \) have been computed by formula, but are complicated. Extensive simulations have been carried out on models with several influential variables and several noninfluential variables, and these variances are modest. It would be nice to have simple bounds.

We have assumed that \( h \) and \( d \) are equally likely and the costs of false positive and false negative were equal. Suppose that the two costs of error, when \( h \) and \( d \) are the states, are respectively \( c_h \) and \( c_d \), and these two states have prior probabilities \( \pi_h \) and \( \pi_d = 1 - \pi_h \). Then the optimal choice, for the decider without data, is to select according to the smaller of \( \pi_d c_d \) and \( \pi_h c_h \) giving rise to an expected cost equal to the lower of these amounts.

Given the data \( x \), we replace the priors by the posterior probabilities and we select
according to the smaller of $\pi_d c_d f_d(x)$ and $\pi_h c_h f_h(x)$ giving rise to an expected cost of

$$ \theta_C = \sum_x \min(\pi_d c_d f_d(x), \pi_h c_h f_h(x)). $$

Since

$$ \theta_C + \sum_x \max(\pi_d c_d f_d(x), \pi_h c_h f_h(x)) = C = \pi_d c_d + \pi_h c_h $$

we have

$$ \sum_x |\pi_d c_d f_d - \pi_h c_h f_h| = C - 2\theta_C. $$

This result suggests that we use a modified version of $I$, depending on

$$ \sum_x (\pi_d c_d f_d(x) - \pi_h c_h f_h(x))^2, $$

for variable selection.

We have not addressed the problems of deciding among more than two alternatives nor that of predicting a continuous dependent variable. Generalizing to the case of a finite number of alternatives should not be very difficult.

While we deal with small groups of explanatory variables, it would be desirable to know how to extend our bound on the ideal error probability when given a small group of modules, each consisting of a small group of explanatory variables. A direct attack using our methods would fail if the total number of variables among the modules is so large that almost all $n_{dx}$ and $n_{hx}$ are small.

This discussion omits the substantial problem of dealing with the pattern recognition problem once a $VS$ choice has been made, and the problem of dealing with continuous explanatory variables.
8 CONCLUSIONS

If \( f_d = f_h \) it is not possible to predict. The theoretical ability to predict, \( \theta_c \), depends on how far apart these two distributions are in some sense. We have introduced the parameter \( \theta_e = 1 - \theta_c \) that is a measure of this distance and represents this predictibility. It is linearly related to the sum of the absolute differences of \( f_d \) and \( f_h \). The training estimate, the naive estimate of \( \theta_e \), is negatively biased. The out of sample estimate, which is not a true statistic, is positively biased. These estimates can be used to estimate upper and lower bounds on predictivity. Moreover we have described these biases and how to modify these estimates to reduce the bias.

One original goal was to explain why the statistic \( I \) used in the Partition Retention method of variable selection is well correlated with \( \theta_e \). We see that \( I/n \) is an estimate, with small bias, of a parameter \( \theta_I \) which is half the sum of the squared differences of \( f_d \) and \( f_h \). Consequently \( I \) tends to be correlated with predictivity, and an inequality relating the sum of squares and the sum of absolute values yields a simple estimate of an upper bound on \( \theta_e \) from \( I \). These bounds are useful in telling the analyst how efficient his algorithms are in squeezing the available information out of the data.

If we examine the chi-square statistic, it converges for large sample sizes to a parameter which is a sum of terms with small probabilities in the denominator and is not as well related to \( \theta_e \) as \( \theta_{I_0} \). Moreover, to get reliable results, the sample size has to be sufficiently large so that there are very few values of \( x \) with small frequencies. The statistic \( I \) is not sensitive to the effect of small or empty cells.

While theoretical predictivity can not decrease when additional variables are added to the group to be used for prediction, the corresponding decrease in cell frequencies makes it more difficult to determine an appropriate classification method and to estimate \( \theta_e \). On the other hand the value of \( I \) is degraded by a substantial factor when a variable with little or no
influence is added to the group to be used. Thus the use of $I$ in Partition Retention tends to find small groups of interacting influential variables and to discard noninfluential variables.

We referred to a previous publication where pattern recognition techniques were employed to get very good predictions using the variables in several small interacting groups, each with $\theta_e$ a little less than 0.5.

9 APPENDIX: INEQUALITY

It is well known that for real vectors $\mathbf{x}$, $\sum x_i^2 \leq (\sum |x_i|)^2$, and we have equality if and only if at most one of the components of $\mathbf{x}$ is not zero. We generalize this fact with

Theorem: If $\sum |x_i| = 1$ and $\sum x_i = a$, then

$$\sum x_i^2 \leq (1 + a^2)/2,$$

and the sum of squares is maximized when $|a| < 1$ if and only if all but two of the components of $\mathbf{x}$ are 0.

Proof: It is obvious that $|a| \leq 1$. Let $S_1$ be the sum of the positive values of $x_i$ and $S_2$ the sum of the negative values. Let $T_1$ be the sum of the squares of the positive values and $T_2$ the sum of the squares of the negative values. It follows that $S_1 + S_2 = a$ and $S_1 - S_2 = 1$ and thus $S_1 = (a + 1)/2$ and $S_2 = (a - 1)/2$. Then $T_1 \leq S_1^2$ and $T_2 \leq S_2^2$. It follows that

$$\sum x_i^2 = T_1 + T_2 \leq S_1^2 + S_2^2 = (1 + a^2)/2.$$

Equality is attained if $|a| < 1$ when there are at most one positive and one negative component of $\mathbf{x}$. 

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