Predicting Gene “Mapk1” in Mice

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1 Executive Summary

2 Introduction and Problem Definition

The goal of this analysis is to take a gene expression data set for a mouse and develop a model to predict the amount of the gene “Mapk1”. This gene is very prominent and plays a significant role in cell proliferation. In general, cells reproduce to make new healthy cells and dispose of older cells; however, an abnormally large amount of cell proliferation can lead to cancerous cells. If there exists a good (cheap and fast) method to measure the gene creation of proliferating proteins in a patient over time, then the doctors can detect the early onset of cancer and other diseases. Early diagnosis and the resulting less-invasive treatment usually result in higher survival rate for these patients. Gene tests in the present day can generally be run to measure the amount of a specific gene in a sample; however, the process can take up to a few days and a sample can only be used once to test the amount of a gene, reliably. Thus, the goal is to find a model that can accurately predict the amount of the gene “Mapk1” with the fewest number of predictors, or other gene tests.

In general, gene analysis is important because they are an indicator for the current and future health issues for the organism as well as the organism’s offspring. However, the procedures to decompose the gene expressions can be expensive and can take a long time, so a model that requires few predictors to predict the value of a certain gene is crucial to accurate and early diagnosis for a potential disease. In addition, experiments can be done to assess the effects from the presence or absence of specific genes to an organism so cures for these diseases can be developed and doctors know exactly what genes to target to cure their patients.

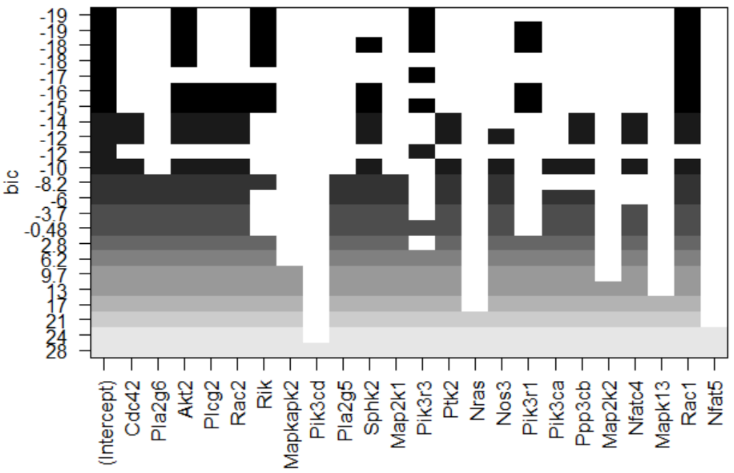
The data set that is used to develop a model is very small. There are only 40 different gene expressions, with the responses from 24 genes in each. There are no missing values. The responses are all real numbers, ranging from -2.5 to 2. Model types to investigate include best subset selection and forward/backward selection for linear model selection (with least squares as the loss function) as well as regularized linear regression. In addition, resampling methods such as boostrapping and cross-validation will be extremely useful as there is so little data. These methods and techniques are generally quite interpretable and the robustness can be tested using the resampling methods mentioned above.

3 Model Development

3.1 Best Subset Selection Using Linear Models

There are 22 genes that can be leveraged to predict the response for the "Mapk1" gene so one of the implemented models is the best subset selection algorithm. In this algorithm, all possible 2^r linear models are fit to the data using least squares where r is the number of predictors (in this problem, $r = 22$). Then, the algorithm returns the best set of predictors for a model of size r, for each r. Generally, this algorithm is very computationally intensive but there are only $n = 40$ data points so each iteration runs quite quickly on an average computer. The downside of this algorithm for this data set is that there are only 40 data points, so splitting it further into training and test sets would yield poor estimates of the model for each iteration and the test set is still quite small. In addition, there are more steps to fit each of the best predictor subsets to the data again to find the coefficients for the linear model of that size and to evaluate the training error and/or test error, if applicable.

Figure 1: Best Subset of Predictors for Each Model Size, ordered by increasing BIC



3.2 Forward-Backward Model Selection

The Forward-Backward Model Selection is a variant of the Best Subset Selection which is less computationally expensive. In the future, if we had more predictors or genes for the model instead of only 22, then this would be a good algorithm to use instead of best subsets as the number of models tested increases linearly instead of exponentially. The algorithm starts with an initial model and a corresponding objective value (in this case we use the Bayesain Information Criterion (BIC) because it has a larger penalty on larger models). The function to calculate the BIC is as follows:

$$BIC = -log(L) + d * log(n) \tag{1}$$

In Equation 1, L is the value of the likelihood function, d is the number of predictors in the model, and n is the number of data samples. A smaller value of BIC implies a better model. For each step in the algorithm, models with one more variable than the current model and models with one less variable than the current model are each fit in turn and the BIC is calculated for each. In other words, if the current size of the model was k, then the model fits $22 - k$ models of size $k + 1$ and $k - 1$ models of size $k - 1$ and evaluates the objective value of each. The next step of the algorithm uses the model with the smallest objective value to proceed with the next iteration (which could be the original model of size k). The algorithm finishes when adding or removing a variable from the model would yield a higher BIC value.

3.3 Linear Regression with Regularization

As an extension to linear regression, we also incorporate a regularizer in order to make the model more robust. In other words, instead of trying to find the coefficients for the linear model that minimizes the squared errors, we include some bias in the model in order to decrease the variance of the model and prevent overfitting. This bias is of the model is shown by decreasing the coefficients of some predictors to be exactly 0 which may not yield the smallest sum of squared differences, but for estimating new data the model will be more accurate.

For this application, we would like to test and evaluate the fewest number of genes possible as the chemical processes can take a long time. Thus, we prefer a sparse model so that fewer genes are needed to predict the response gene "Mapk1" and a model with fewer predictors will have smaller variance.

The lasso regularizer for linear regression yields sparse models. When determining the coefficients for this model, we want to minimize the following objective function. The rows of the input data are denoted by x_i while the whole matrix that is used is $\mathcal{R}^{nxd}$, the output or response for data point i is denoted by y_i and the coeffecients for the predictors of the linear model are denoted in the vector w that is made up of components w_j for $j = 1, \ldots, d$

$$\textbf{minimize}_w \sum_{i=1}^{n} (y_i - x_i^T w)^2 + \lambda \sum_{j=1}^{d} |w_j| = \textbf{minimize}_w \sum_{i=1}^{n} (y_i - x_i^T w)^2 + \lambda ||w||_1 \tag{2}$$

For this problem with few data points, we use cross validation to find optimal λ value which acts as measure of how much bias the model is able to have. If $\lambda = 0$ then we get the nonregularized problem, however, if λ is too large, then all of the coefficients will go to 0 to find the minimum objective value. The λ that minimizes the mean cross validated error yields a model with 6 predictors and an intercept and the resulting mean squared error is 0.0121. We also investigate using the largest λ such that error is within 1 standard error of the minimum value of the response. This yields a smaller model with an intercept and only 4 predictors.

4 Results and Conclusions

Because our outputs are real numbers, we use a squared error loss to evaluate the training error and the test error of our model.

5 Next Steps

In the future, if data is collected for more mice and there are more gene expressions to analyze, other methods such as K-Nearest-Neighbors (KNN) can be implemented which is a robust, unsupervised machine learning technique. Currently, as there are only 40 samples, the number of points that have k nearst neighbors is at most $40 - k$, assuming that the whole data set is used as a training set and none of it is used to evaluate the model and estimate test error. Currently if the algorithm is implemented, the model is grossly overfit on the training data, which yields a low training error, which does not imply a low test error for future samples.

In addition, in the diagnosis setting, there may also be predefined ranges of the amounts of the gene or protein that can be a normal range, a warning range, and a dangerous range of that gene or protein. In that case, we can reframe the problem as ordinal classification and use methods such as KNN, decision trees, or other machine learning techniques. These methods are more variable and some sort of resampling method will still have to be used since there is not much data present.