MantelCorr Package for Bioconductor

Brian Steinmeyer, MS, and William Shannon, PhD
Department of Internal Medicine
Division of General Medical Sciences
Washington University in St. Louis
School of Medicine
email: steinmeb@ilya.wustl.edu, wshannon@wustl.edu

April 30, 2008

Contents

1 Description

The `MantelCorr` package is based on the methodology developed in Shannon et al. [1], for which six functions are used to locate and identify important gene clusters from standard microarray expresssion data with `p` genes (*rows*) and `n` samples (*columns*). Mantel statistics have been applied with success to correlate gene expression levels with clinical covariates [3]. We also include a real microarray dataset with the package to help illustrate its functionality. Specifically, the package makes use of the `k-means()` function in R (*with arbitrary k, say* $k \in [5, \frac{p}{2})$) to essentially over-partition the gene space into `k` non-overlapping clusters. Next, two types of dissimilarity matrices are computed, one based on the original data `Dfull`, and one for each resultant cluster, `Dsubset(k)`.

Mantel [2] cluster correlations are then found by correlating each `Dsubset(k)` with `Dfull`, resulting in `k` Mantel correlations. In order to destroy the distance dependent nature of `Dfull` and to obtain an empirical null distribution of distance independence, a permutation test is done, where the

number of permutations and α significance level parameters can be chosen by the user. Specifically, the significance level provides the criterion value (*p-value*) at which a given cluster is considered significant or non-significant. Both significant and non-significant cluster lists can be viewed with the `ClusterList` function. In addition, a summary list of genes within these clusters can also be seen with the `ClusterGeneList` function.

We next introduce a simple application of the `MantelCorr` package with gene-expression training data taken from the Golub et al. [4] leukemia study.

2   Example R session with the Golub training data

The Golub training data consists of gene-expression values measured for 38 samples from Affymetrix Hgu6800 chips on $7,129$ genes. There are 27 acute lymphoblastic leukemia (`ALL`) and 11 acute myeloid leukemia (`AML`) samples. To load the `MantelCorr` package, simply type `library(MantelCorr)`. The data can be loaded by typing `data(GolubTrain)` and a description provided with `?GolubTrain`.

```
> library(MantelCorr)
> data(GolubTrain)
> dim(GolubTrain)

[1] 7129   38

> data <- GolubTrain
```

3   Reminder

Help on any of the following `MantelCorr` package functions can be viewed by `?FunctionName`, which provides a complete description and overview of the function's purpose and syntax. In addition, all input 'data' values are `assumed` to be interval-scale (e.g., numeric data), with gene and sample labels assigned from the `dimnames()` function.

4   GetClusters() function

The `GetClusters()` function over-partitions the gene-space as described in the package description. We select `k = 500` clusters and store the result in an object called "kmeans.result".

```
> kmeans.result <- GetClusters(data, 500, 100)
```

5   DistMatrices() function

A function used to compute distance matrices `Dfull` and `Dsubset(k)` from the `k` non-overlapping clusters stored in "kmeans.result". The result is assigned to "DistMatrices.result".

```
> DistMatrices.result <- DistMatrices(data, kmeans.result$clusters)
```

6 `MantelCorrs()` function

The `MantelCorrs()` function uses `Dfull` and `Dsubset(k)` to compute a Mantel correlation for each `kth` cluster by correlating these two dissimilarity matrices. The result is saved in "Mantel-Corrs.result".

```
> MantelCorrs.result <- MantelCorrs(DistMatrices.result$Dfull,
+     DistMatrices.result$Dsubsets)
```

7 `PermutationTest()` function

`PermutationTest()` permutes `Dfull` to obtain an empirical null distribution for which cluster significance is determined. We have selected 100 permutations in order to conserve CPU time, and chosen an α-value of 0.05 for the 38 Golub leukemia samples. The result is stored in an object called "permuted.pval". `NOTE:` we recommend using at least 1000 permutations for a thorough analysis.

```
> permuted.pval <- PermutationTest(DistMatrices.result$Dfull, DistMatrices.result$Dsubsets,
+     100, 38, 0.05)
```

8 `ClusterList()` function

A function used to generate a complete list of both significant and non-significant clusters found by the permutation test and associated level of significance. Cluster size and correlation are provided with each type of cluster. We assign the result to the `R` object "ClusterLists" as follows:

```
> ClusterLists <- ClusterList(permuted.pval, kmeans.result$cluster.sizes,
+     MantelCorrs.result)
```

9 `ClusterGeneList()` function

A final function that uses information from the "ClusterList" function, coupled with the `dimnames` function to generate a composite list of the genes found in both cluster types (significant and non-significant). We store the result in `R` object "ClusterGenes".

```
> ClusterGenes <- ClusterGeneList(kmeans.result$clusters, ClusterLists$SignificantClusters,
+     data)
```

References

[1] Shannon, Steinmeyer, Li, Culverhouse, Grefenstette, Thompson. (2005) *Variable Selection in Cluster Analysis Using k-means and Mantel Correlation.* Computing Science and Statistics (To Appear).

[2] Mantel, N. *The Detection of Disease and a Generalized Regression Approach.* Cancer Research, 27, 209-220, 1967.

[3] Shannon W, Watson M, Perry A, Rich K. *Mantel statistics to correlate gene expression levels from microarrays with clinical covariates.* Genetic Epidemiology 2002; 23:87-96.

[4] Golub, T. et al. *Molecular Classification of Cancer: Class Discovery and Class Prediction by Gene Expression Monitoring.* Science, 531-537, 1999.