# Microarray Gene Expression Data Mining using High End Clustering Algorithm based on Attraction-Repulsion Technique

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*Abstract*—**Microarray Gene expression data analysis is one of the key domains in the modern cellular and molecular biology system design and analysis; shortly we called it computational simulation of genome-wide expression from DNA hybridization. We present here a high end clustering algorithm basically a technique following the inspiration led by natural attraction and the repulsion processes. It groups the similarly expressed genes in same clusters, co-expressed and differently expressed ones in different clusters. Most importantly, it takes into account of the outliers in an efficient manner by not allowing them to interfere with the similarly expressed gene clusters on the fly. In the first clustering process, it calculates the distances of all the genes in a proximity range set in prior, henceforth attracting all the least distant genes from the seed gene. Varying the proximity range in the subsequent run, repulse the maximally distant genes from the same cluster, thereby achieving a near to perfect cluster formation at the end. We include cluster validity testing using Hubert's statistics technique, which shows a very optimal clusters validity result.**

**Keyword-Microarray data, Gene Expression Data, Clustering Algorithm, Cluster validity, Hubert's Statistics**

## I. Introduction

The cut-throat advancement in genome-scale data analysis and sequencing has motivated high end development of different technology to exploit this information by paving a new face to the modern biology or in in a refined way, to the modern cellular and modern biology. The need for knowledge of every gene in a genome has enhanced the development of every technology in solving various medical issues, relating to genes and its functional outcomes in the human body [2][ 3][ 4][7]. Although the study were confined to yeast *Saccharomyces cerevisiae* in earlier days, but studies have found the similar tendency exist human also. Gene expression microarrays are one of the forerunners in today's molecular simulation and DNA technology research [1]. As rightly pointed in [5] that "The burgeoning field of genomics, and in particular DNA microarray experiments, has revived interest in cluster analysis by raising new methodological and computational challenges". DNA Microarray clustering experiments are widely carried out in medical research for various studies in functional and structural gene characteristics responsible for various tumors and cancers. Microarray experiments may lead to a finer and complete classification of genes responsible for cancers. The new challenges facing the recent microarray gene expression clustering experiments revolves around validity of the cluster, in short quality of the clusters formed, efficiency of the algorithm or the technique used to cluster or classify the genes, and the memory requirements in its computational environment constrained by various parameters, one of which is the era of big data analysis[22][20] We promote here a compact and near to maximum a novel complete clustering method motivated by the nature in terms of attraction and repulsions activities applicable to all events.

### Cluster Analysis:

Cluster analysis is a different approach to well known data mining technologies like associations and classifications by producing the final clusters which has never a dependence relationship between the data points, and never use any prior cluster information in forming the target clusters except in unsupervised clustering[23][25]. The data points in given data space is clustered in such a way that the similarity between the data points in a cluster is maximum and minimum between different clusters. Here a random data object from the data space is selected in most of the technique and a similarity matrix is generated for all the data points from this seed datum by deploying a proximity measures like Euclidean distance, Manhattan distance, Spearman correlation, Jacknife correlation etc.[6][14][26]. So the clusters formed are the data groups from which we can infer some meaningful rules or knowledge. It also is an important technique for biological taxonomy and hierarchy formations of species. Clustering can be broadly divided into two categories, namely supervised and unsupervised clustering. In an unsupervised clustering, the number of clusters to be formed is unknown in prior. Supervised takes into account of a prior knowledge of the number clusters to be formed. Our approach tends towards unsupervised way of clustering [21][19].

## II. Related Work

Lot of work has been done on different proximity measurement techniques and cluster validity testing by few researchers in the past such as [15], [16], [17] and [18]. The distance measurement technique and the cluster validity measurement used here is a correlation based technique and Hubert's Statistics as used in [16]. From this paper, its definition is given as follows:

Let $\boldsymbol{X}$ = [*X* (*i,j*)]and $\boldsymbol{Y}$ = [*Y(i,j)*] be two n x n proximity matrices on the same n genes. From the viewpoint of correlation coefficient, *X* (*i* ,*j*) indicates the observed correlation coefficient of genes i and j, and *Y*(*i* ,*j*) is defined in eqn (1):

$$Y(i,j) = \begin{cases} 1 & \text{if genes i and j areclustered in the same cluster} \\ 0 & \text{otherwise} \end{cases} \qquad (1)$$

The Hubert's, Γ statistic as in eqn (2) compute the correlation between the matrices X and Y, and it is defined as follows when the two matrices are symmetric:

$$\Gamma = \frac{1}{M}\sum_{i=1}^{n-1}\sum_{j=i+1}^{n}\left(\frac{X(i,j)-\bar{X}}{\sigma_X}\right)\left(\frac{Y(i,j)-\bar{X}}{\sigma_Y}\right) \qquad (2)$$

Where, *M = n(n-1)/2* is the number of entries in the double sum, and $\sigma_X$ and $\sigma_Y$ denote the sample standard deviations, while X and Y denote the sample means of the entries of matrices X and Y.

## III.Materials and methods

The Experimental data we used are collected from the website of PNAS web site at (www.pnas.org) or at http://rana.stanford.edu/clustering. Data used here are formed on spotted DNA microarrays, for which the gene expression were studied during the diauxic shift[8][9] of budding yeast *Saccharomyces cerevisiae* [10]. We also used the data from Kim lab, Stanford university for our research purpose which is available in http://cmgm.stanford.edu/~kimlab/, [11].

**Similarity Metric:**

The similarity metric generated for clustering the genes is based on correlation coefficient. As given in [Eisen *et al*,1998]. Let $G_i$ be the log transformed primary data for gene *G* in condition *i*. For any two genes *X* and *Y* observed over a series of *N* conditions, a similarity score can be computed as given in eqn (3) and eqn (4):

$$S(A,B) = \frac{1}{n}\sum_{i=1,n}\left(\frac{A_i - A_{offset}}{\Psi_A}\right)\left(\frac{B_i - B_{offset}}{\Psi_B}\right) \qquad (3)$$

*where,*

$$\Psi_G = \sqrt{\sum_{i=1,n}\left(\frac{(G_i - G_{offset})^2}{n}\right)} \qquad (4)$$

When $G_{offset}$ is set to the mean of observations on *G*, then $\Psi_G$ becomes the standard deviation of *G*, and *S* (A,*B*) is exactly equal to the Pearson correlation coefficient[14] of the observations of *X* and *Y*. Values of $G_{offset}$ which are not the average over observations on *G* are used when there is an assumed unchanged or reference state represented by the value of $G_{offset}$, against which changes are to be analyzed. The software implementation of the above is found from the authors at http://rana.stanford.eduyclustering.

**Methods:**

We apply the standard approach as in eqn (5) that is global analysis used in [12] to all the genes:

$$E(A_{gj}) = \beta_{0j} + \sum_{i \in M}\beta_{ij}R_{ij} \qquad (5)$$

where $A_{gj}$ is gene *g*'s observed expression level under condition *j* with *j* = 1; . . . ; *J*, *E*($A_{gj}$) represents $A_{gj}$'s expected or average value, $R_{ig}$ is the binding ratio of TF *i* to (the control region of) gene *g*, and M is the set of TFs to be considered; $\beta_{0j}$ and $\beta_{ij}$s are unknown parameters (called regression coefficients) that are of interest and to be estimated; $\beta_{ij}$ gives the additive effects of TF *i*'s binding on each gene's expression level under condition *j*. Note that $\beta_{ij}$ is the same across all of the genes.

Gao et al., 2004[13] defined $\beta_i = (\beta_{i1}, \beta_{i2}, \ldots \beta_{iJ})'$ as the activity of TF *i* and the coupling strength between TF *i* and gene *g* as given in eqn (6):

$$C(i,g) = corr(\beta_{ij}, A_{gj}) = \frac{\sum_{j=1}^{J}(\beta_{ij}-\overline{\beta_i})(A_{gj}-\overline{A_g})}{\sqrt{\sum_{j=1}^{J}(\beta_{ij}-\overline{\beta_i})^2\sum_{j=1}^{J}(A_{gj}-\overline{A_g})^2}} \qquad (6)$$

Where, $\overline{\beta_i} = \sum_{j=1}^{J}\beta_{ij} \big/ J$ and $\overline{A_g} = \sum_{j=1}^{J}A_{gj} \big/ J$ .An estimate of *C (i, g)* is obtained by plugging in any estimates of $\beta_{ij}$s.

## IV. Experimental Design and Setup

We implemented the clustering algorithm, proposed here in MATLAB. The algorithm is designed in two phase. First phase works as the repulsive nature as given in[15] and the second phase continue with the attraction phase in tandem thereby making the gene cluster formation a highly inter related within the clusters and shows high degree of contrast across the clusters. This two phase design also enhances the easy segregation of outliers. In the first phase we use two legends as seed gene, $S_g$ which is the initial cluster center. From this $S_g$, distances are calculated for all the $G_{ij}$ where *i=0* to *n* and *j=0* to *m*.

We present here the two legends used in the first phase as follows:

- **Seed Gene ($S_g$)** – This is the initial gene centre in the given gene space $G_{ij} \in U_g$. The constraint here is that we set only one seed gene in a given point of time. Seed gene is dynamically changed as the iteration increases.
- **Lead Cluster($C_i$)—**We set a range, say *[p,q]* for the similarity matrix calculated for each genes, if a gene is near proximity of the $S_g$ , the gene is attracted towards the $C_i$ , and the distance the beyond the range set is repulsed to from the seed gene. The process continues till it forms the final clusters, $C_{fk}$, where *k* is the number of final clusters formed.

The algorithm is fed with two inputs namely, *S(i,j)* , the similarity matrix of n X n dimensions generated from the data set and a weight threshold, $\theta$ to determine the attraction and repulsion phenomena. We formulate a *Max_Sim* function to enhance the quality of the cluster by re clustering the final clusters formed if $Max\_Sim \geq \theta$ in the same cluster. The time complexity of the algorithm is $O(N^2)$. The pseudo code of both the phases of the algorithm is given below.

**Attraction and Repulsive Clustering algorithm:**

**Input:** (i) Similarity matrix *S(i,j)* which is of n X n dimensions. (ii) Weight threshold, $\theta$ to determine the attraction and repulsion phenomena.

**Initialization:**

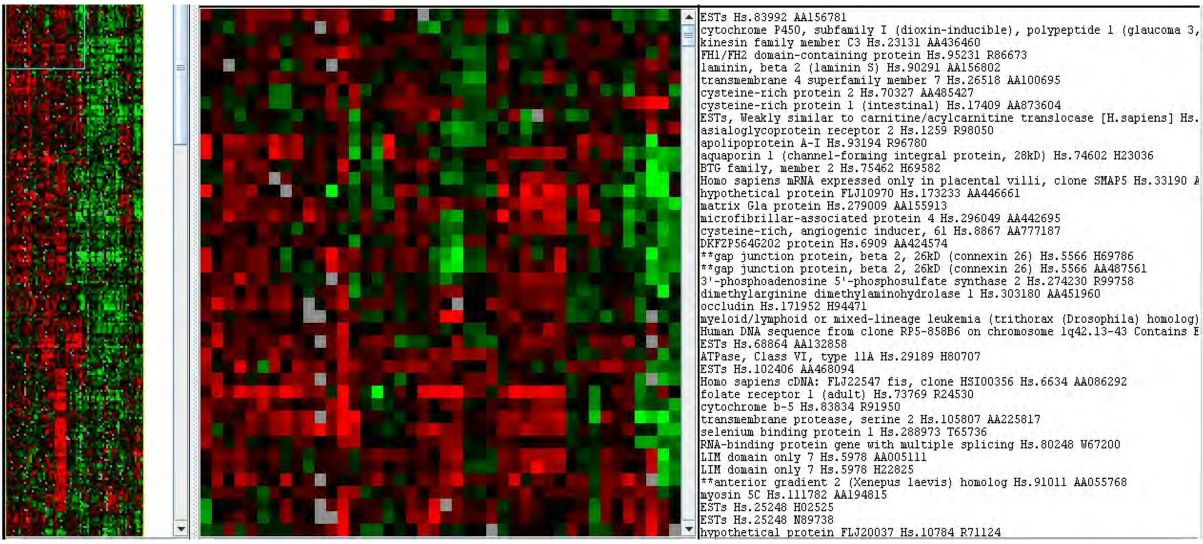
```
  Lead Cluster ($C_i$) ← 1 // initial cluster designation
  C(.)← 0 // intial cluster is always zero
  $G_{ij} \in U_g$ // set of all gene data points

  Seed Gene ($S_g$) //This is the initial gene centre in the given gene space $G_{ij} \in U_g$
Begin:
  Calculate distance from $S_g$ to each gene data points, $G_{ij}$ where $i=0$ to $n$ and $j=0$ to $m$
  if $S(G_{i,j}) \geq \theta$, //distance comparison to threshold
Repulsion phase:
  $\forall$ $S(G_{i,j}) \geq \theta$, move the $G_{i,j}$ to $C_r$ //cluster formed by repulsion
  if $S(G_{i,j}) < \theta$, // move away from $C_r$ to form a different cluster
  then
```

```
    $C_i \rightarrow C_r \rightarrow C_k$ // move away from $C_r$ to form a different cluster
    Increase the $G_{i,j}$ till $i,j$ // where $i=0$ to $n$ and $j=0$ to $m$
    Continue // iteration
    Return $C_r$ //intermediate cluster result after repulsion phase
Attraction Phase: // this is to improve the quality of the clusters formed in
  attraction phase
    $\forall$ $E \in C_r$, // all the genes in the $C_r$
    Calculate , $Max\_Sim$  // for reclustering phase
    if $Max\_Sim \geq \theta$,
    then
    $C_{new} \leftarrow Cr$ // allows formation of new cluster
    else
    $C_{Final} \leftarrow C_{new} + C_r$
Return $C_{Final}$
End
```

## V. Result and Discussion

Heat maps are one of the essential methods to display similarities and dissimilarity between samples and genes. So if rows and columns are properly ordered, then heat maps become effective in identification of the patterns. Clustering is one of those techniques used to ordering this, by grouping the similar samples or genes in one cluster, and dissimilar ones in different clusters. A very high end clustering technique even cluster out the noise or the outliers in a separate cluster, thereby increasing the effectiveness of analysis in biological aspects. We show our resultant heat map produced by Michael Eisens's TreeView package in fig 1, corresponding to our clustering output from the proposed repulsion and attraction algorithm.



```
ESTs Hs.83992 AA156781
cytochrome P450, subfamily I (dioxin-inducible), polypeptide 1 (glaucoma 3,
kinesin family member C3 Hs.23131 AA436460
FH1/FH2 domain-containing protein Hs.95231 R86673
laminin, beta 2 (laminin S) Hs.90291 AA156802
transmembrane 4 superfamily member 7 Hs.26518 AA100695
cysteine-rich protein 2 Hs.70327 AA485427
cysteine-rich protein 1 (intestinal) Hs.17409 AA873604
ESTs, Weakly similar to carnitine/acylcarnitine translocase [H.sapiens] Hs.
asialoglycoprotein receptor 2 Hs.1259 R98050
apolipoprotein A-I Hs.93194 R96780
aquaporin 1 (channel-forming integral protein, 28kD) Hs.74602 H23036
BTG family, member 2 Hs.75462 H69582
Homo sapiens mRNA expressed only in placental villi, clone SMAP5 Hs.33190 A
hypothetical protein FLJ10970 Hs.173233 AA446661
matrix Gla protein Hs.279009 AA155913
microfibrillar-associated protein 4 Hs.296049 AA442695
cysteine-rich, angiogenic inducer, 61 Hs.8867 AA777187
DKFZP564G202 protein Hs.6909 AA424574
**gap junction protein, beta 2, 26kD (connexin 26) Hs.5566 H69786
**gap junction protein, beta 2, 26kD (connexin 26) Hs.5566 AA487561
3'-phosphoadenosine 5'-phosphosulfate synthase 2 Hs.274230 R99758
dimethylarginine dimethylaminohydrolase 1 Hs.303180 AA451960
occludin Hs.171952 H94471
myeloid/lymphoid or mixed-lineage leukemia (trithorax (Drosophila) homolog)
Human DNA sequence from clone RP5-858B6 on chromosome 1q42.13-43 Contains E
ESTs Hs.68864 AA132858
ATPase, Class VI, type 11A Hs.29189 H80707
ESTs Hs.102406 AA468094
Homo sapiens cDNA: FLJ22547 fis, clone HSI00356 Hs.6634 AA086292
folate receptor 1 (adult) Hs.73769 R24530
cytochrome b-5 Hs.83834 R91950
transmembrane protease, serine 2 Hs.105807 AA225817
selenium binding protein 1 Hs.288973 T65736
RNA-binding protein gene with multiple splicing Hs.80248 W67200
LIM domain only 7 Hs.5978 AA005111
LIM domain only 7 Hs.5978 H22825
**anterior gradient 2 (Xenepus laevis) homolog Hs.91011 AA055768
myosin 5C Hs.111782 AA194815
ESTs Hs.25248 H02525
ESTs Hs.25248 N89738
hypothetical protein FLJ20037 Hs.10784 R71124
```

Fig 1: Heat Map (Dendogram) of Selected Gene arrays generated Java TreeView package. The measurement is made relative to time 0. Genes were selected for this analysis if their expression level deviated from time 0 by at least a factor of 3.0 in at least 2 time points. The dendrogram and colored image were produced by using Java TreeView package; the color scale ranges from saturated green for log ratios 2.75279 and below to saturated red for log ratios 3.69496 and above. Each gene is represented by a single row of colored boxes; each time point is represented by a single column. Gene data of budding yeast *Saccharomyces cerevisiae* collected from http://rana.stanford.edu/clustering is used.

Similarly, the scatterplot of plot G_INDEX in X axis and 181_96 Adeno Gene Array in Y axis is also shown in fig 2 with controlled condition as Min X= -1.89, Min Y=0.0,Max X=3.9, Max Y=72.0 for the gene data we used in fig 1.

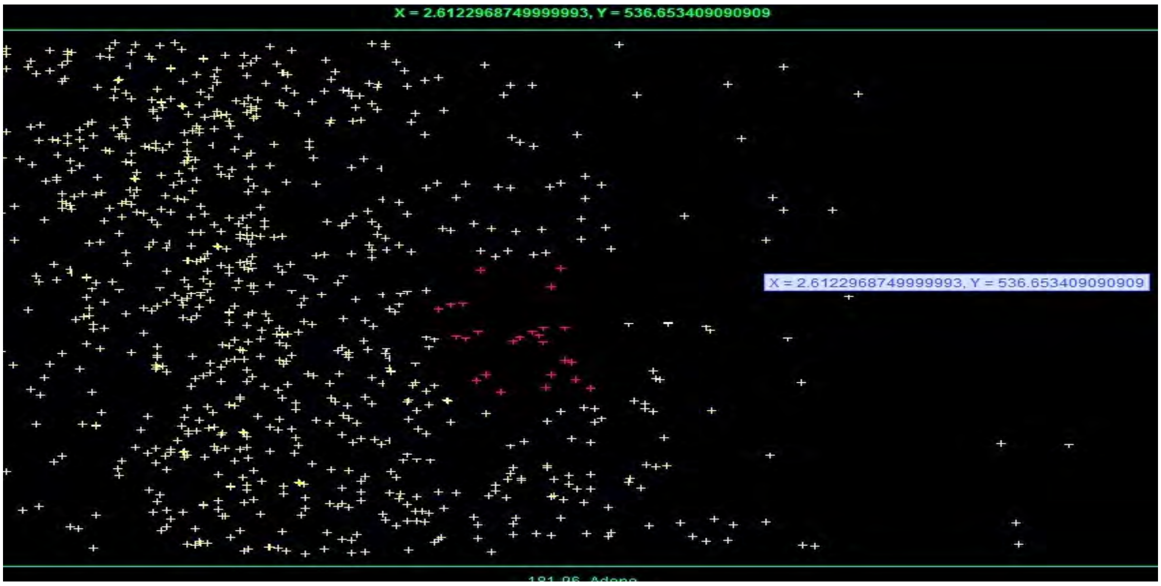


Fig. 2: Scatter plot G_INDEX in X axis and 181_96 Adeno Gene Array in Y axis

To ensure the quality of the clusters, we have use Hubert's statistic technique for cluster validity checking and found its average Hubert's statistic value as 0.7744483, in 29 clusters found. As its nearing to 1, it is considered good. We also carried out some comparisons between the validity measures like jaccard's coefficient, simple matching technique and FOM (Figure of Merit) to clusters we found. The comparative graph of all the above techniques is shown in fig 3.

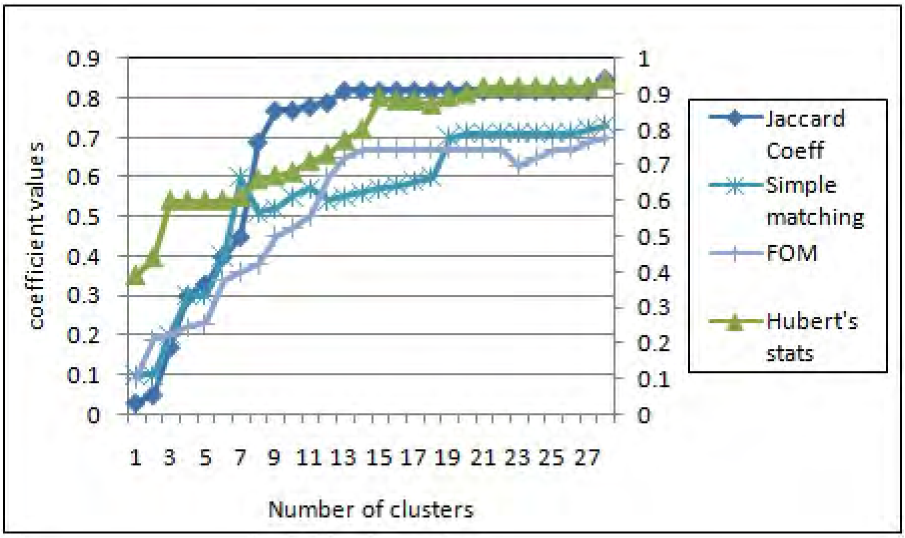


Fig 3: Cluster quality achieved for the different validity measurement techniques to the 28 clusters formed by attraction and repulsion algorithm.

It is noticed that jaccard coefficient works well with k-means clustering technique as variation of k is undetermined, but Hubert's statistics work well with dynamic type of clustering like our attraction and repulsion algorithm. The same efficiency is also proved by the work of [16]. Simple matching technique has sharp uneven peaks for as much as 13 clusters, thereby local minima and global minima values get distorted. Hubert statistic values ranges from 0.39 to 0.94 in 28 cluster formed, averaging to 0.774, which is a good value for determination of quality in clusters formed. Function of Merit (FOM) also does well comparatively to Hubert statistics, except it ranges from 0.1 to 0.78 in all the clusters and lowering its average score to 0.53.

Additionally, our algorithm is also compared with one of the most dynamic clustering algorithms CST from [16] in terms of number of cluster formation. CST generated 38 clusters from the same gene expression data we used, which is shown in fig 4. Our attraction and repulsion based clustering algorithm generated 28 clusters, with 10 outlier's cluster which is shown in fig 5.

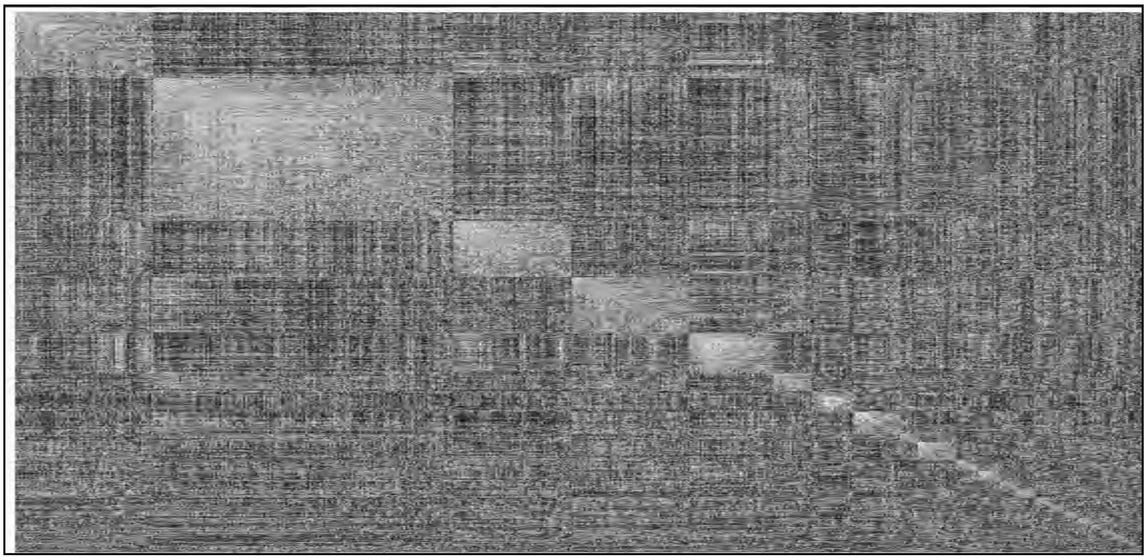


Fig 4: Visual representation of cluster formed by CST [Vincent S. Tseng, Ching-Pin Kao, 2005] where 38 clusters are formed in our experimental data we have taken

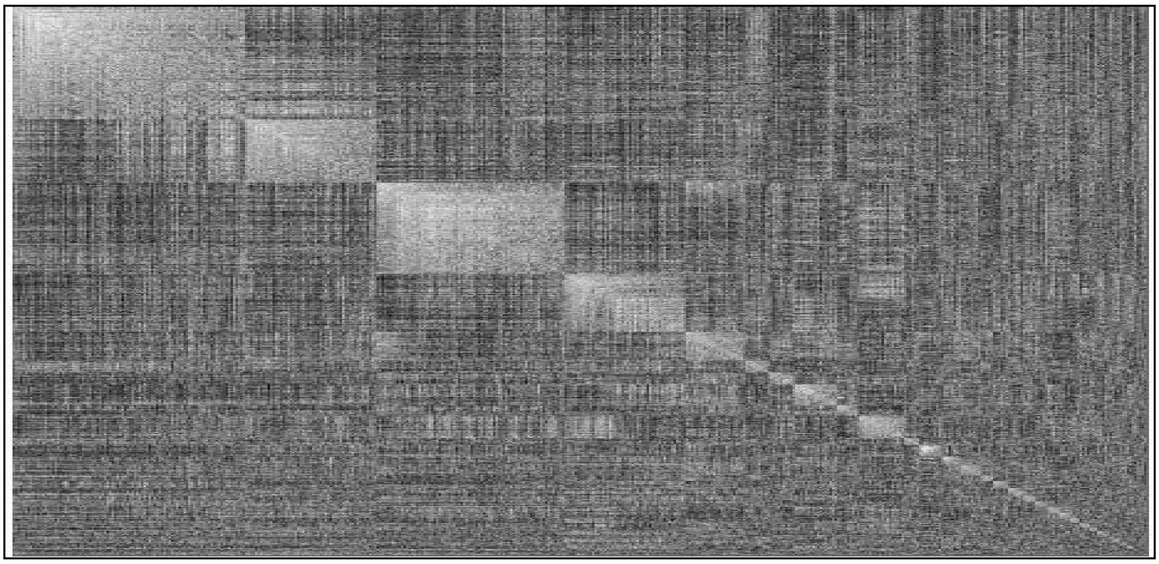


Fig 5: Visual representation of cluster formed by and attraction and repulsion method where 28 clusters were formed in the same data used for generating the fig 4.

Table I shows the Log ratio and error function values for y0, A1, t1 parameters. Considering this table we show our cluster result in fig 6 which is plotted on log ratio and shift log ratio values.

Table I: Log ratio and Error table for y0, A1, t1 parameters

| Parameter | Log Ratio | Error |
|---|---|---|
| y0 | 3.75279 | 3830.4172 |
| A1 | -3.69496 | 3830.2852 |
| t1 | 220.29758 | 230456.24 |

Like in most of the biological data, missing data are quite common in microarray gene expression data too. Two most common way of dealing with missing data are simply bringing some variation in our clustering algorithms to deal with or by generating the missed values by any of the missing value computational technique while in pre-processing phase, before the data is been fed to the clustering algorithm. As formulated in table I the error capabilities in our approach is considered for our experiment and the resultant clustering output is shown in figure 6.

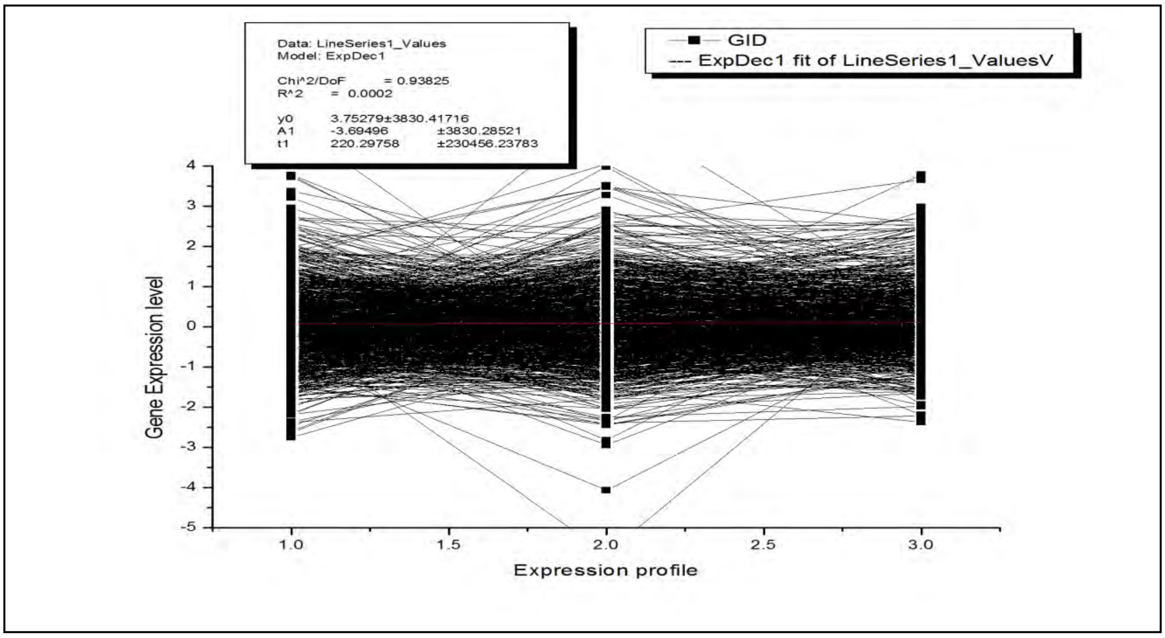


Fig 6: A cluster result plotted on log ratio and shift-log ratio on the result of Repulsion and attraction based clustering algorithm. Data used here is from Kim Lab collected from http://cmgm.stanford.edu/~kimlab/.

## VI. Conclusion

In this paper, we proposed a dynamic clustering algorithm for clustering gene expression data with in-built cluster validity technique for clustering gene expression data from budding yeast *Saccharomyces cerevisiae*. As anticipated, it resulted in optimal cluster formation with good quality cluster formation by achieving a Hubert's statistic value of 0.77, comparatively to CST and K-Means algorithms. Although it compromised little bit in complexity function of the algorithm, nevertheless, it optimized the overall cluster formation and separating the outliers in different clusters.

We could improve in future this work by improvising the missing value calculation technique in a very formal way. We could also bring a variation by adopting various distance measurement techniques or by hybridizing them in some way. We seriously think of introducing rough and fuzzy set concepts for high dimensional clustering and optimized solutions to data fuzziness and missing values too.

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