Multiobjective Clustering with SVM Based Ensembling for Analysis of Gene Expression Data

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Data Clustering

- Clustering is a popular unsupervised pattern classification technique which partitions the input space containing n objects into K regions based on some similarity/dissimilarity measure.
  - The value of K may or may not be known *a priori*.
- Output of a clustering technique is a $K \times n$ matrix $U = [u_{ki}]$.
  - u_{ki} denotes the membership degree of ith object to the kth cluster.
  - For crisp clustering, $u_{ki} \in \{0, 1\}$.
  - For fuzzy clustering, $0 < u_{ki} < 1$. (better suited for noisy data and overlapping clusters).

Fuzzy C-means Clustering I

- Given K (number of clusters), the Fuzzy C-means (FCM) algorithm is implemented in 4 steps:

  Step 1: Choose K random points as initial cluster centers.

  Step 2: Compute the fuzzy membership values u_{ik} as follows:

$$u_{ik} = \frac{1}{\sum_{j=1}^{K} \left(\frac{D(v_i, x_k)}{D(v_j, x_k)} \right)^{\frac{2}{m-1}}}, \text{ for } 1 \leq i \leq K; \ 1 \leq k \leq n,$$

  Step 3: Recompute the cluster centers v_i as follows:

$$v_i = \frac{\sum_{k=1}^{n} (u_{ik})^m x_k}{\sum_{k=1}^{n} (u_{ik})^m}, \quad 1 \leq i \leq K.$$

  Step 4: Go back to Step 2, stop when no more change in the cluster centers.

Fuzzy C-means Clustering II

- FCM algorithm minimizes the following criterion:

Global fuzzy cluster variance

$$J_m = \sum_{k=1}^{n} \sum_{i=1}^{K} u_{ik}^m D^2(v_i, x_k), \quad 1 \leq m \leq \infty.$$

Fuzzy C-means – Limitations

- Gets stuck at local optima depending on the choice of the initial cluster centers.
  - Solution - Clustering based on global optimization technique such as Genetic Algorithm (GA).
- Optimizes single objective function J_m – May not be capable of capturing different characteristics of data sets.
  - Solution – Multiobjective Clustering.

Why multiobjective clustering?

Simultaneous optimization of multiple objectives may lead to higher quality solutions and an improved robustness towards different data properties.

Genetic Algorithm

1. Encode a possible solution of the problem in a form of **chromosome** (string).
2. Randomly generate a population of chromosomes.
3. Decode each chromosome to get an individual.
4. Evaluate the fitness of each individual.
5. Perform *selection*, *crossover* and *mutation*.
6. Repeat steps 3, 4 and 5 until a stop condition is true.
7. **Elitism** may be incorporated.
8. The best-fit chromosome of the last generation population is considered as the final solution.

Multiobjective Optimization (MOO)

In many real world problems we have to simultaneously optimize two or more different objectives which are often competitive in nature.

Finding a single solution in these cases is very difficult.

Optimizing each criterion separately may lead to good value of one objective while some unacceptably low value of the other objective(s).

MOO Problem Statement

- Find the vector of the decision variables:

$$\overline{x}^* = [x_1^*, x_2^*, \ldots, x_n^*]^T$$

- which will satisfy the m inequality constraints:

$$g_i(\overline{x}) \geq 0, \quad i = 1, 2, \ldots, m,$$

- the p equality constraints

$$h_i(\overline{x}) = 0, \quad i = 1, 2, \ldots, p,$$

- and optimizes the vector function (consisting of k objective functions):

$$\overline{f}(\overline{x}) = [f_1(\overline{x}), f_2(\overline{x}), \ldots, f_k(\overline{x})]^T.$$

Domination Relation and Pareto-Optimality I

Domination Relationship

Let a and b be two solutions. Then a is said to dominate b iff

$$\forall i \in \{1, \ldots, k\}, f_i(b) \leq f_i(a)$$

and

$$\exists j \in \{1, \ldots, k\}, f_j(b) < f_j(a).$$

i.e., for all functions f_i, a has a higher or equal value than that of b and also there exists at least one function f_j for which a's value is strictly greater than that of b.

Domination Relation and Pareto-Optimality II

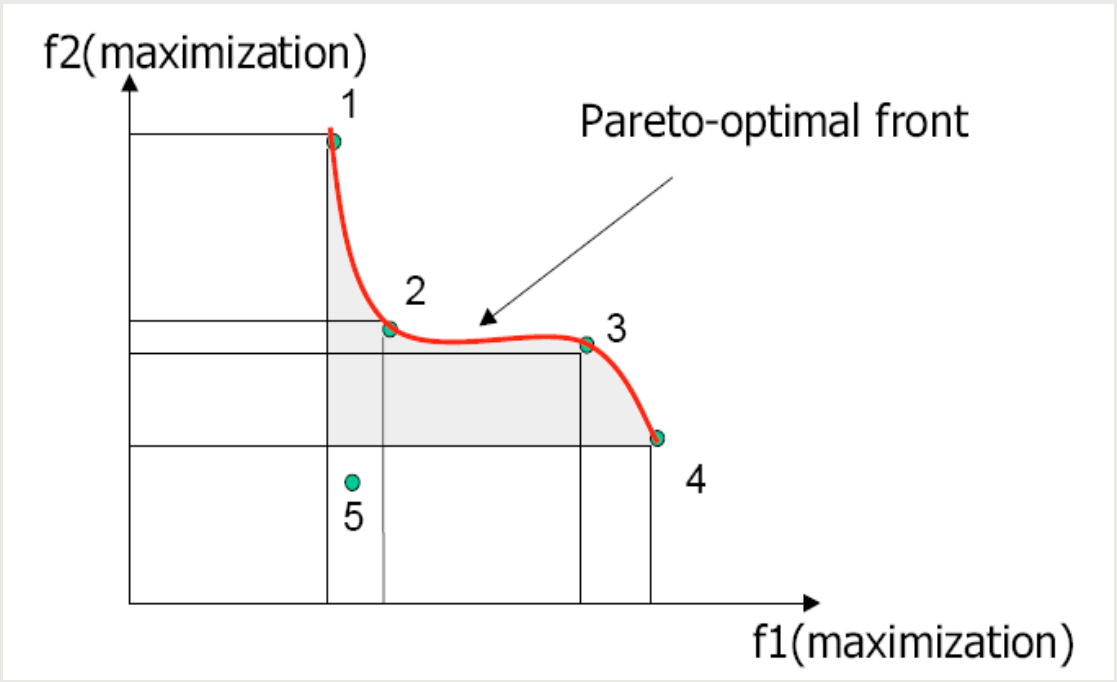
Non-dominated Set

- Among a set of solutions P, the non-dominated set of solutions P' are those that are not dominated by any solution in the set P.
- A solution a is called non-dominating with respect to all the solutions if there exists no solution b that dominates a.

Pareto-optimal Set

The non-dominated set of entire search space S is globally Pareto optimal set.

Non-domination: Example



Solutions 1, 2, 3 and 4 are non-dominating to each other.

Solution 5 is dominated by 2, 3 and 4, not by 1.

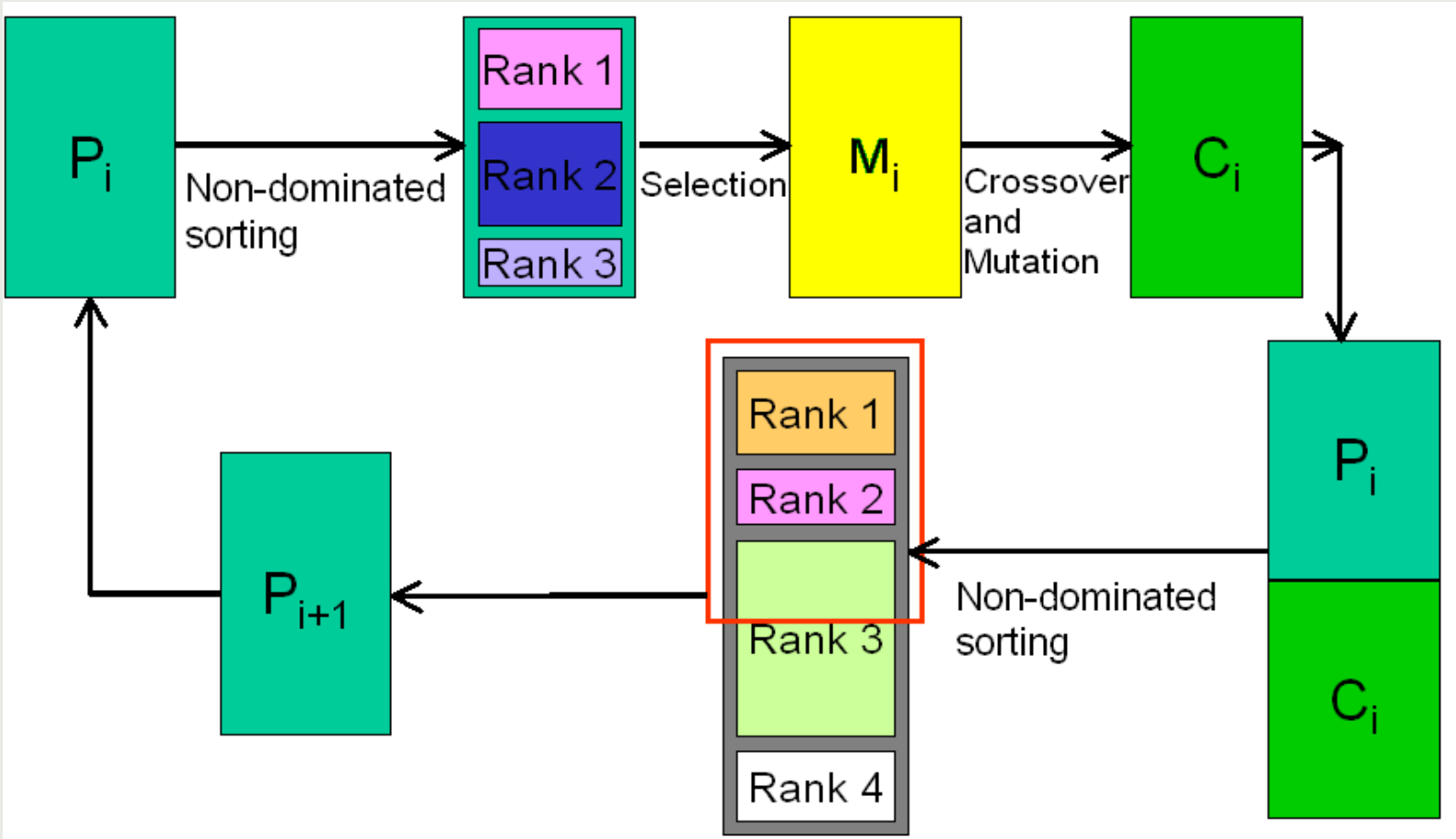
Multiobjective Optimization Algorithms

- Multiobjective GAs are more popular primarily because of their population based nature.
- Available Algorithms
  - Non-Pareto approach
    - Vector Evaluated GA (VEGA): non-Pareto
  - Pareto-based approach
    - Non-dominated Sorting GA (NSGA and NSGA-II)
    - Niched Pareto GA (NPGA)
    - Strength Pareto Evolutionary Algorithm (SPEA and SPEA2)
    - Pareto Archived Evolutionary Strategy (PAES)
    - Pareto Envelop-based Selection Algorithm (PESA and PESA-II)
    - Archived Multiobjective Simulated Annealing (AMOSA)

Non-dominated Sorting GA-II

- Proposed by K. Deb et. al. (2002).
- Non-dominated Sorting
  - It is based on several layers of classifications of the individuals.
  - Non-dominated individuals get a certain dummy fitness value (Rank) and then are removed from the population.
  - The process is repeated until the entire population is classified.
- Diversity Maintenance
  - Concept of Crowding Distance of individuals in a non-dominated front.
  - Selection based on Crowding distance.
- Elitism
  - Non-dominated individuals of parent and child populations are carried to the next generations.
- Time complexity: $O(MN^2)$ (where M is the number of objectives and N is the population size).

NSGA-II Flowchart



NSGA-II based Multiobjective Fuzzy Clustering

- Chromosome Representation
  - Cluster centers are encoded in the chromosomes.
  - For a d dimensional space length of chromosome $= d \times K$

$$\{(v_{11}, v_{12}, \ldots, v_{1d}), (v_{21}, v_{22}, \ldots, v_{2d}), \ldots, (v_{K1}, v_{K2}, \ldots, v_{Kd})\}$$

- Example
  - Let $d = 2$, $K = 3$.
  - i.e., two-dimensional space, number of clusters $= 3$.
  - Chromosome: 51.6 72.3 18.3 15.7 29.1 32.2 represents 3 cluster centers (51.6, 72.3), (18.3, 15.7) and (29.1, 32.2).

Initial Population

- Each chromosome in the initial population encodes K random data points as K cluster centers.

For each chromosome i in the population
    For each cluster j
        p=randomly chosen point from the data set;
        Population[i][j] = p;
    End
End

Fitness Computation

This consists of three phases.

- Phase 1: Extract the cluster centers encoded in the chromosome and compute the fuzzy membership matrix.
- Phase 2: Recompute the cluster centers and update the chromosome with the new cluster centers. Recompute the fuzzy membership matrix.
- Phase 3: Fitness computation
  - **First objective:** Xie-Beni (XB) cluster validity index

$$XB(U, V; X) = \frac{\sum_{i=1}^{K}(\sum_{k=1}^{n} u_{ik}^2 D^2(v_i, x_k))}{n(\min_{i \neq j}\{D^2(v_i, v_j)\})}$$

  - **Second objective:** Fuzzy cluster variance

$$J_m = \sum_{j=1}^{n}\sum_{k=1}^{K} u_{kj}^m D^2(v_k, x_j)$$

- Both XB and J_m are to be minimized in order to obtain highly compact and well-separated clusters.

Genetic Operators

- Selection – Crowded binary tournament selection.
- Crossover – Single point crossover with a fixed crossover probability.
  - For chromosomes of length K, a random integer p is generated in the range [1, K]. The portions of the chromosomes lying to the right of p are exchanged to produce two offspring.
  - Centers are considered indivisible.
- Mutation – Floating point mutation with fixed mutation probability.
  - A number δ in the range [0, 1] is generated with uniform distribution.
  - If the value at a gene position is v, after mutation it becomes

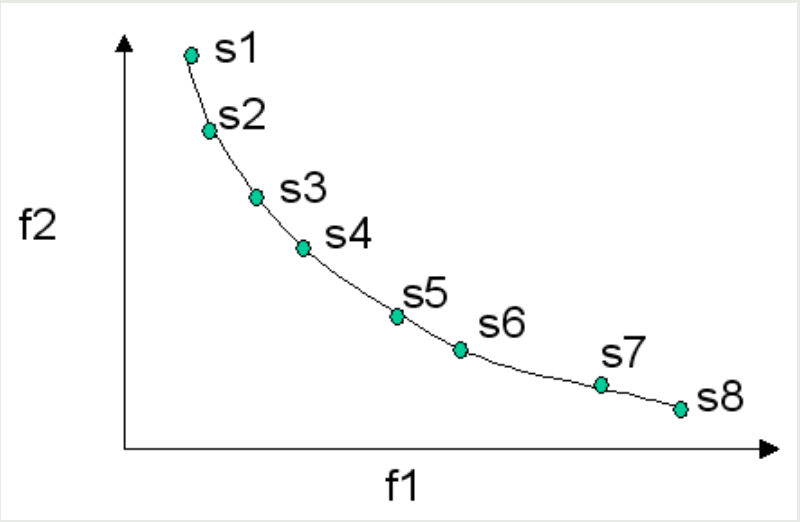
$$v = v \pm 2.\delta.v, \quad \text{if} \quad v \neq 0,$$
$$v = v \pm 2 * \delta, \quad \text{if} \quad v = 0.$$

- Executed with fixed population size and for fixed number of generations

Obtaining Final Solution from Non-dominated Front

- Multiobjective method produces a set of non-dominated solutions in the final generations. It is needed to obtain a solution from this set.
- For each non-dominated solution, first the clustering label vector is computed from the solution by assigning each point to the cluster to which it has the highest membership.
- Thereafter the label vectors are reordered so that they correspond to each other.
- Next, the points which are assigned to the same cluster by at least 50% of the clustering solutions are obtained.
- These points are taken as the training set. The remaining points are assigned a class label using Support Vector Machine (SVM) classifier.

Selecting Final Solution



s1 = {1 1 1 2 2 3 3 3 3 4 4}
s2 = {1 2 1 2 3 3 4 3 2 4 4}
s3 = {1 1 2 1 2 3 3 4 2 4 4}
s4 = {1 1 2 2 2 3 3 3 4 4 4}
s5 = {1 1 1 1 2 2 3 3 1 4 4}
s6 = {1 1 4 3 2 2 3 4 4 4 4}
s7 = {1 1 3 3 2 3 3 3 3 4 4}
s8 = {1 2 3 1 2 3 4 3 3 3 4}

- Applying 50% voting rule, the consensus clustering label vector becomes $s = \{1 \quad 1 \quad ? \quad ? \quad 2 \quad 3 \quad 3 \quad 3 \quad ? \quad 4 \quad 4\}$.
- Points 1, 2, 5, 6, 7, 8, 10 and 11 are taken as training points for a Support Vector Machine (SVM) classifier.
- Points 3, 4 and 9 are classified using the trained SVM classifier.

Application to Microarray Gene Expression Data

Microarray data can be viewed as an $n \times m$ matrix:

- Each of the n rows represents a gene (or a clone, ORF, etc.).
- Each of the m columns represents an experimental condition (a sample, a time point, etc.).
- Each element e_{ij} represents the expression level of the ith gene under the jth condition. It can either be an absolute value (e.g. Affymetrix GeneChip) or a relative expression ratio (e.g. cDNA microarrays).
- A row/column is sometimes referred to as the expression profile of the gene/condition.

Microarray Matrix

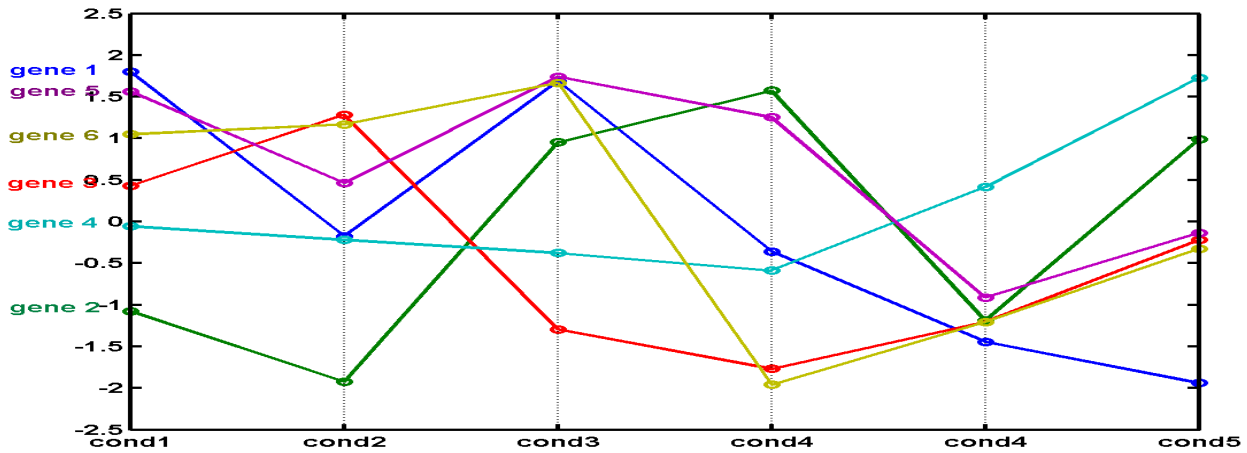
A microarray matrix with 6 genes and 6 conditions.

GENE	cond 1	cond 2	cond 3	cond 4	cond 5	cond 6
gene 1	1.801	-0.174	1.687	-0.359	-1.444	-1.939
gene 2	-1.075	-1.926	0.953	1.575	-1.189	0.987
gene 3	0.427	1.286	-1.295	-1.768	-1.205	-0.22
gene 4	-0.056	-0.221	-0.377	-0.589	0.415	1.727
gene 5	1.565	0.462	1.742	1.253	-0.911	-0.136
gene 6	1.048	1.168	1.668	-1.961	-1.205	-0.325

The values are proportional to expression levels
green = low, **red** = high, **black** = no expression

Microarray Matrix

A microarray matrix with 6 genes and 6 conditions.



Profile plots are graphical representation of the microarray matrix

Data Sets for Experiments

Data Sets	Original Number of Genes	Number of Genes after Preprocessing	Number of Time points
Yeast Sporulation	6118	474	7
Yeast Cell Cycle	6000	384	17
Arabidopsis Thaliana	138	138	8
Human Fibroblasts Serum	8613	517	13
Rat Central Nervous System	112	112	9

Comparison of Different Kernel Functions in MOGA-SVM

Performance Metric: Silhouette Index - ranges between -1 and 1, larger value indicates better clustering.

Algorithm	Spor	Cell	Thaliana	Serum	Rat
	$K = 6$	$K = 5$	$K = 4$	$K = 6$	$K = 6$
MOGA-SVM (linear)	0.5852	0.4398	0.4092	0.4017	0.4966
MOGA-SVM (polynomial)	0.5877	0.4127	0.4202	0.4112	0.5082
MOGA-SVM (sigmoidal)	0.5982	0.4402	0.4122	0.4112	0.5106
MOGA-SVM (RBF)	0.6283	0.4426	0.4312	0.4154	0.5127
MOGA (without SVM)	0.5794	0.4392	0.4011	0.3947	0.4872

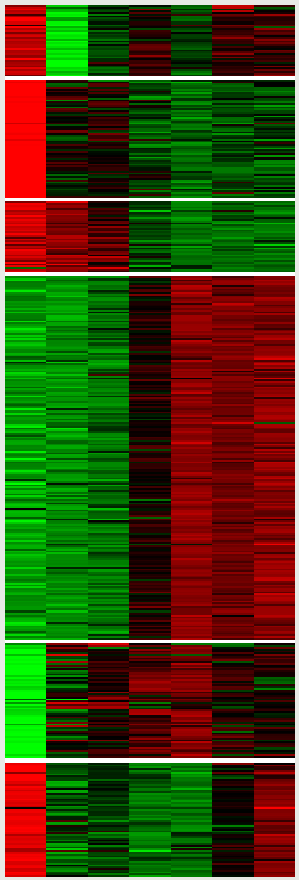
Comparison among Different Algorithms

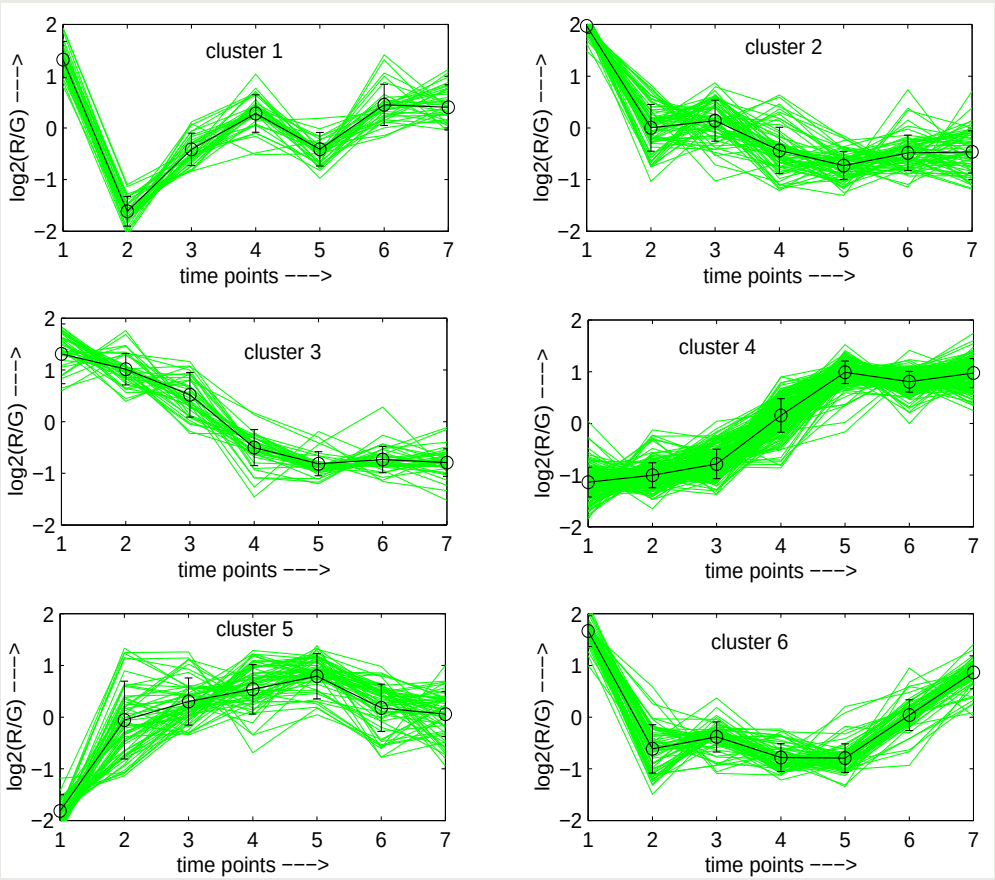
Performance Metric: Silhouette Index - ranges between -1 and 1, larger value indicates better clustering.

Algorithm	Sporulation		Cell cycle		Thaliana		Serum		Rat CNS	
	K	$s(C)$	K	$s(C)$	K	$s(C)$	K	$s(C)$	K	$s(C)$
MOGA-SVM	6	**0.6283**	5	**0.4426**	4	**0.4312**	6	**0.4154**	6	**0.5127**
MOGA	6	0.5794	5	0.4392	4	0.4011	6	0.3947	6	0.4872
MOGA$_{crisp}$-SVM	6	0.5971	5	0.4271	4	0.4187	6	0.3908	6	0.4917
FCM	7	0.4755	6	0.3872	4	0.3642	8	0.2995	5	0.4050
SGA	6	0.5703	5	0.4221	4	0.3831	6	0.3443	6	0.4486
Average linkage	6	0.5007	4	0.4388	5	0.3151	4	0.3562	6	0.4122
SOM	6	0.5845	6	0.3682	5	0.2133	6	0.3235	5	0.4430
CRC	8	0.5622	5	0.4288	4	0.4109	10	0.3174	4	0.4423

Heatmap and Cluster Profile Plots

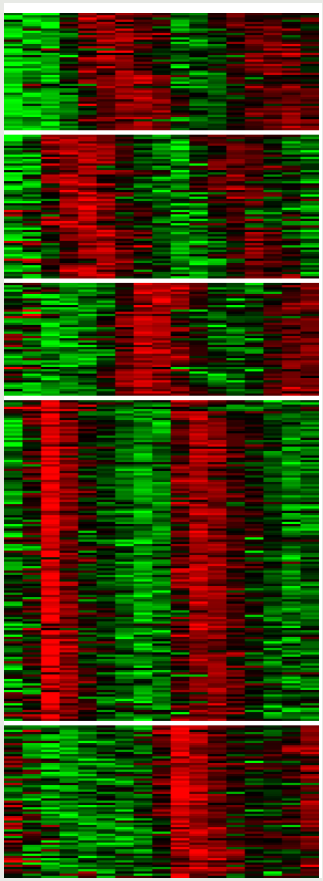
Yeast Sporulation Data

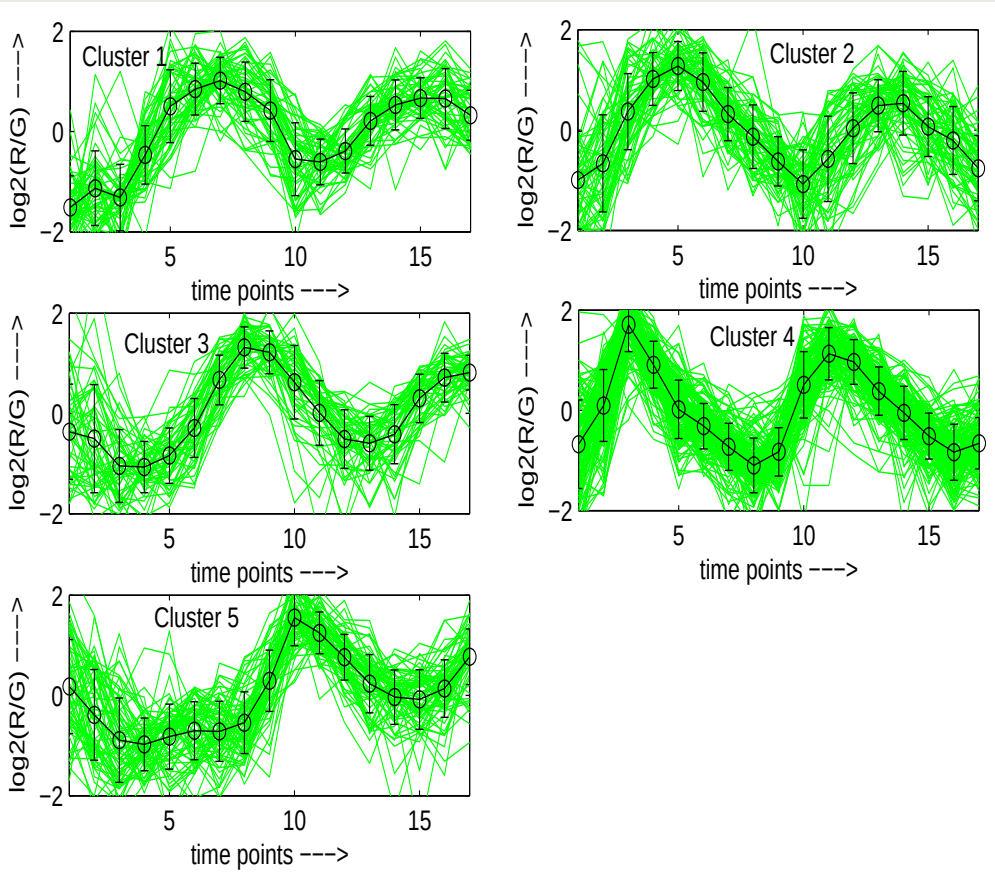




Heatmap and Cluster Profile Plots

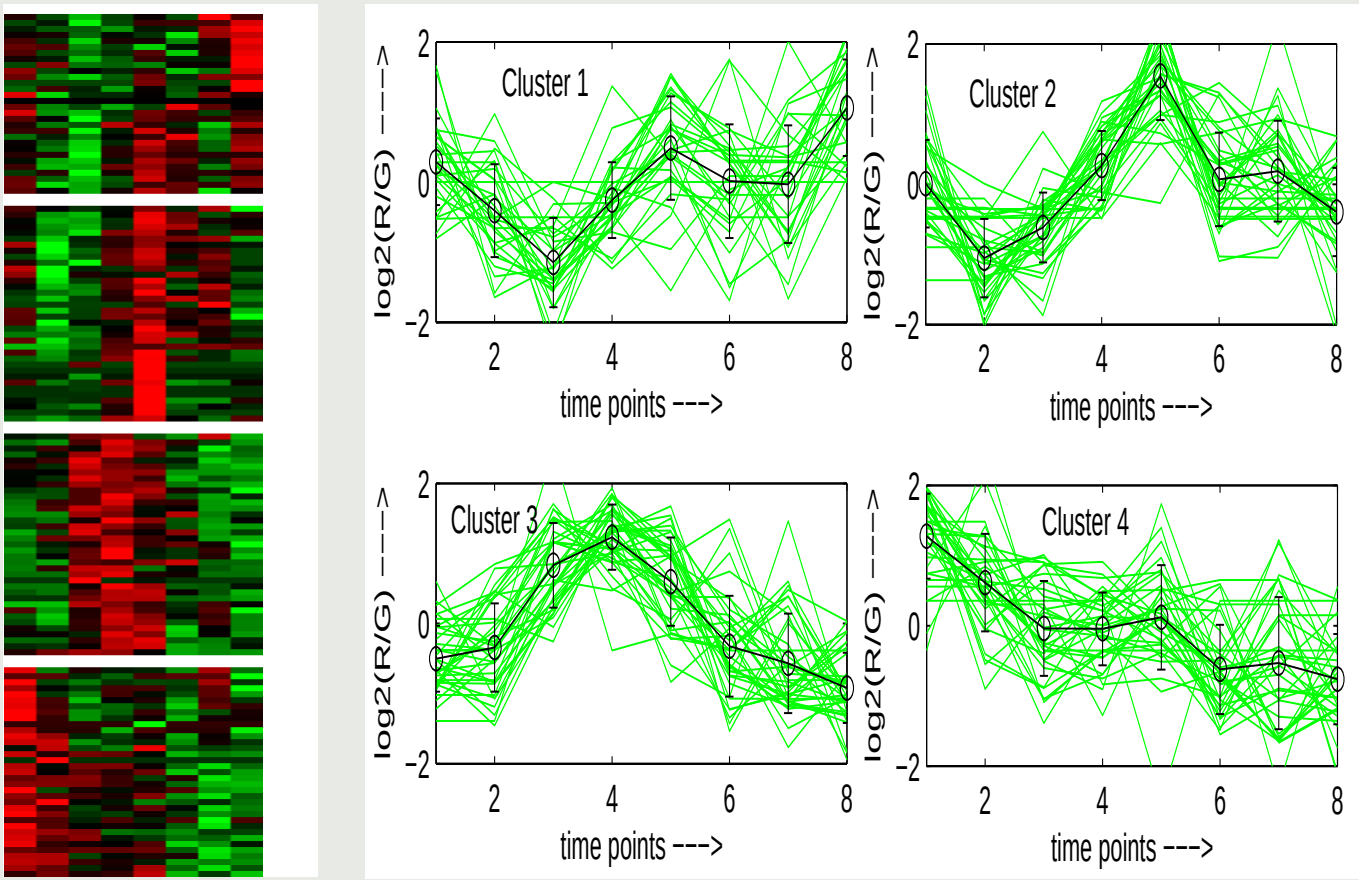
Yeast Cell Cycle Data





Heatmap and Cluster Profile Plots

Arabidopsis Thaliana Data



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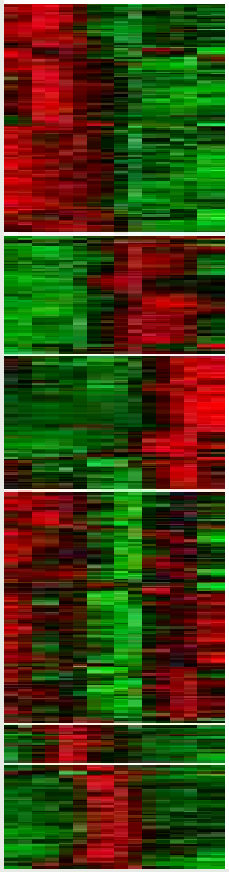
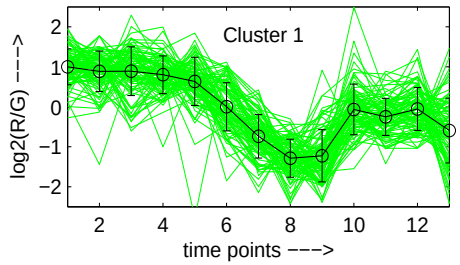
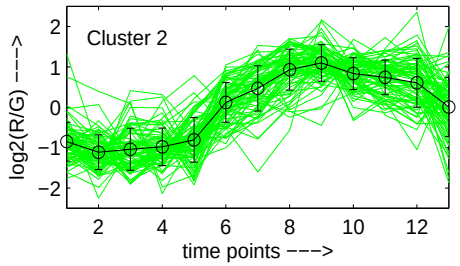
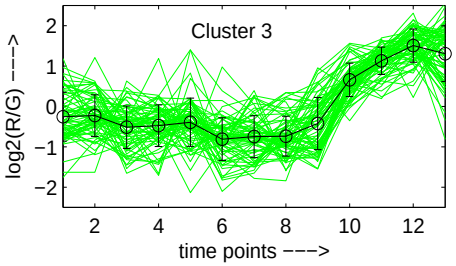
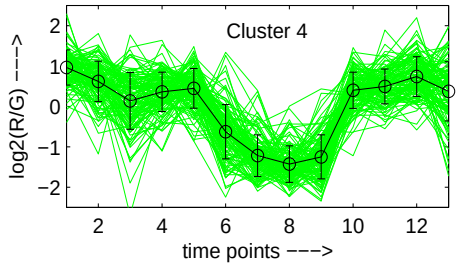
Human Fibroblasts Serum Data

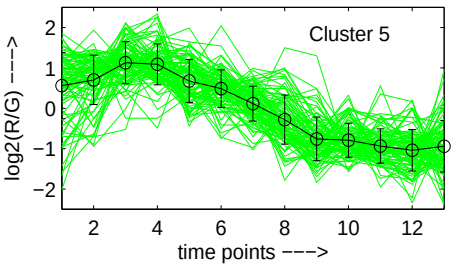


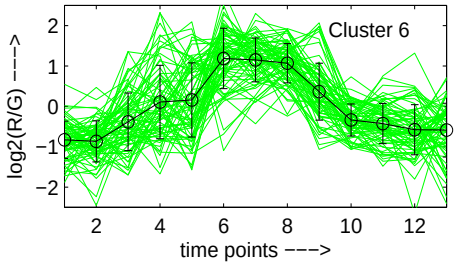






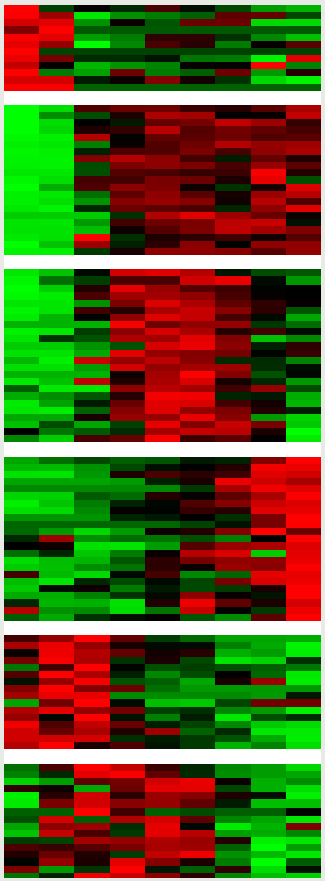


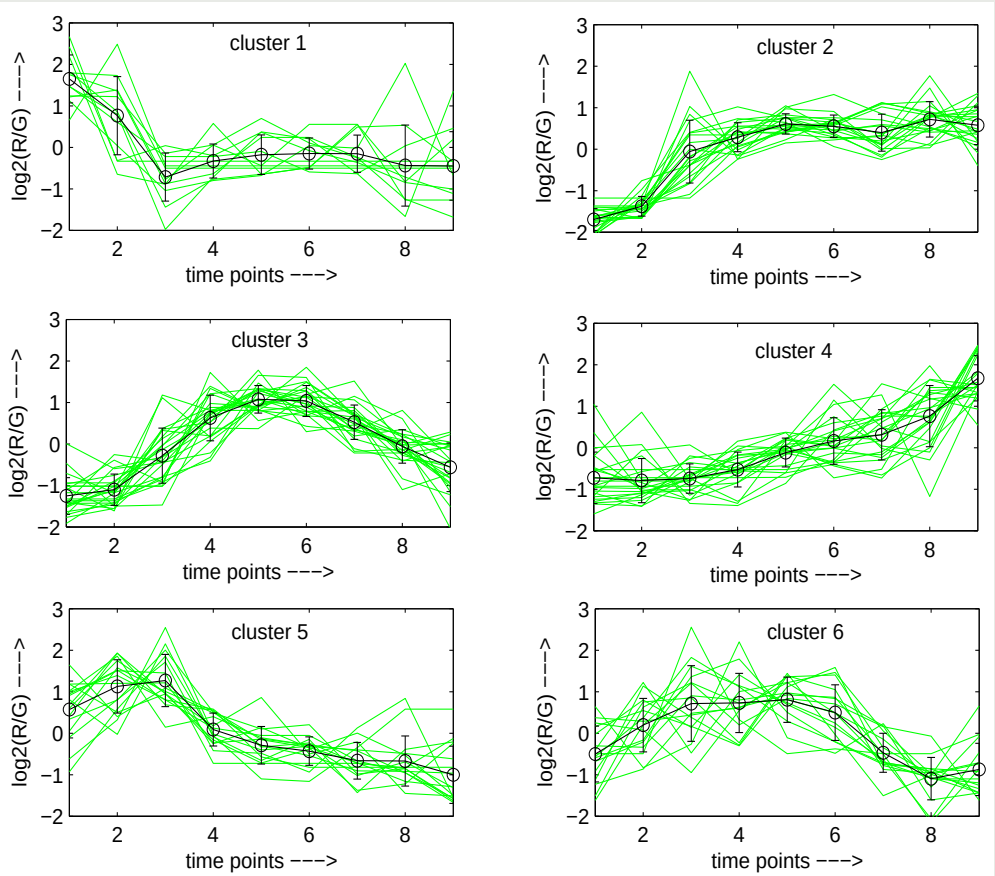




Heatmap and Cluster Profile Plots

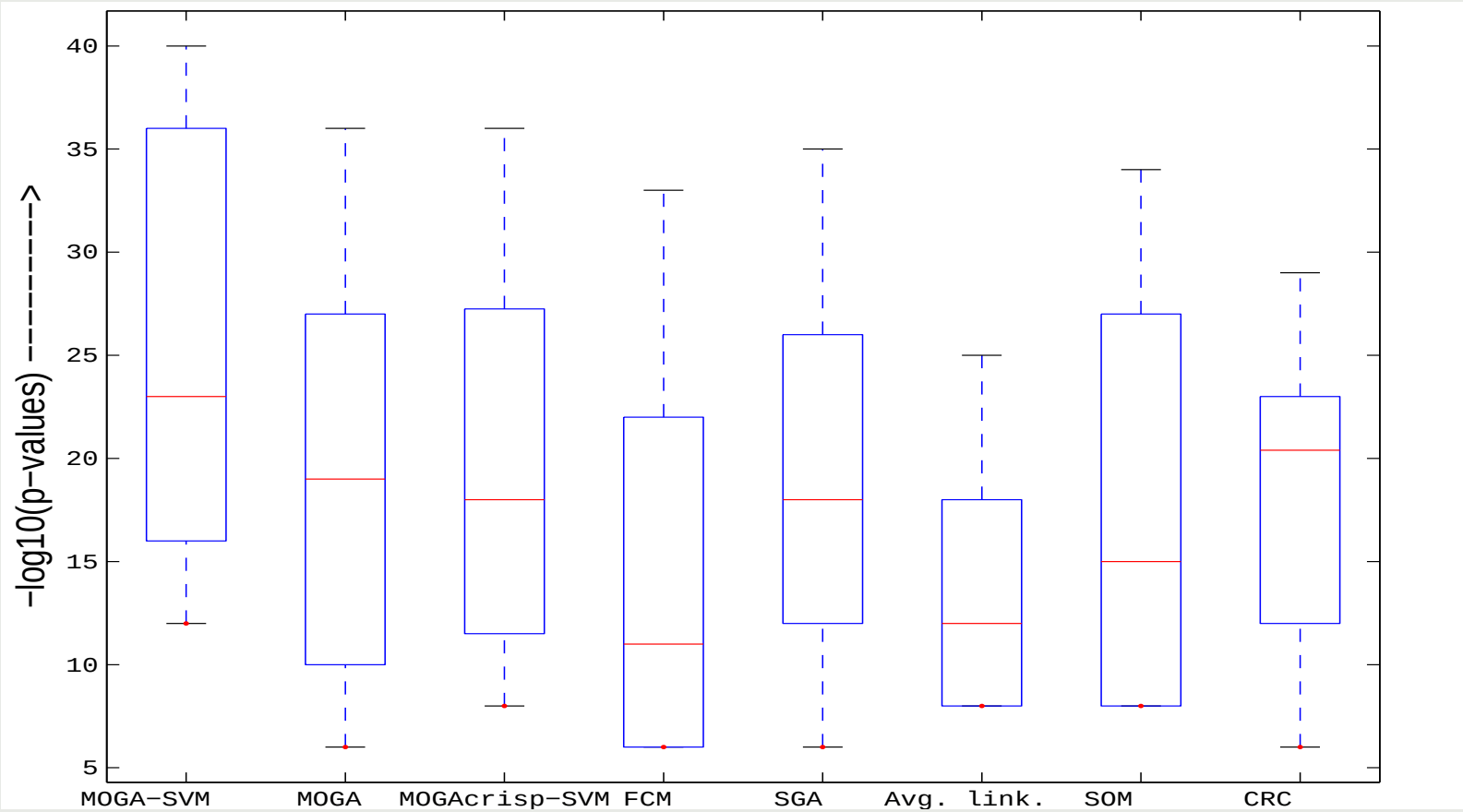
Rat Central Nervous System Data





Biological Significance Test

Boxplots for *p-values* of Significant GO terms



Conclusion and Future Scope

- Fuzzy C-means clustering often gets stuck at local optimum – Solution is GA-based clustering.
- Fuzzy C-means clustering optimizes single cluster validity index which may not be equally applicable to different variety of data sets – Solution is multiobjective GA-based clustering.
- NSGA-II based multiobjective fuzzy clustering algorithm is proposed and it is integrated with SVM for improved results.
- Proposed method is applied for clustering genes in microarray gene expression data sets.

Other Areas of Work in Computational Biology

- Prediction of miRNA targets and TSSs.
- Regulatory network analysis - incorporating miRNAs in the regulatory network.
- miRNA differential expression analysis in Alzheimer's.
- Integrating miRNAs with PPIN.
- Metaheuristic optimization techniques in rational drug design.

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Thank You

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