Fuzzy Bayesian validation for cluster analysis of yeast cell-cycle data

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Abstract

Clustering for the analysis of the genes organizes the patterns into groups by the similarity of the dataset and has been used for identifying the functions of the genes in the cluster and analyzing the functions of unknown genes. Since the genes usually belong to multiple functional families, fuzzy clustering methods are more appropriate than the conventional hard clustering methods which assign a sample to only one group. In this paper, a Bayesian-like validation method selecting a fuzzy partition is proposed to evaluate the fuzzy partitions effectively. The theoretical interpretation of the obtained memberships is beyond the scope of this paper, and an empirical evaluation of the proposed method is conducted by comparing to the four representative conventional fuzzy cluster validity measures in four well-known datasets. Analysis of yeast cell-cycle data follows to evaluate the proposed method.

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1. Introduction

Clustering groups thousands of genes by their similarity of expression levels and helps to analyze gene expression profiles [1]. This organizes the patterns of genes into groups by the similarity of the dataset and has been used for identifying the functions of the genes in the cluster and analyzing the functions of unknown genes. Hard clustering, a hard partitioning method, assigns a sample to only one group. But the real-world dataset, like gene expression profiles, does not have clear boundaries and they cannot be easily partitioned by hard clustering. Since some genes also have multiple functional families, analyzing the genes by hard clustering method has some limits. Fuzzy clustering, unlike the hard clustering, assigns a sample to multiple groups by their grade of membership values [2]. Fuzzy clustering method is more robust on noise and more appropriate in analyzing gene expression profiles than hard clustering method [3].

The most important matters that need to be addressed in any clustering method are how many clusters are actually in

the dataset and how good the clusters are. Thus, it is necessary to validate each of the fuzzy partition and this evaluation is called cluster validity. Many investigations about these matters have been conducted. Partition coefficient and partition entropy were first proposed by Bezdeck [4,5]. These two cluster validity indices produce the optimal partition at maximum validity measures. Xie–Beni's index [6] and Fukuyama–Sugeno index [7] are popular in the field of fuzzy clustering. The Xie–Beni index is a ratio of the fuzziness within cluster sum of squared distances to the product of the number of elements and the minimum between cluster separations, and the Fukuyama–Sugeno measures the compactness and separation of the resulting fuzzy partition after a dataset has been separated into several clusters. However, since the conventional validity indices are based on the distance between the clusters, they cannot fully represent the structure of the dataset [8].

In this paper, we propose a Bayesian-like validation method which evaluates the result of clustering by memberships of the fuzzy partition of a given dataset. We therefore call it fuzzy Bayesian validation method. Unlike the conventional validity indices, the fuzzy Bayesian validation method never uses the distance between the clusters. It selects the partition with the largest membership in a given

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dataset. We take the probabilistic Bayesian equation and formally replace probabilities by memberships. The effectiveness of the proposed method is demonstrated in four known datasets, where the fuzzy c -means algorithm is used as the clustering algorithm [9,10]. After the preliminary experiments, yeast cell-cycle data is analyzed by the proposed method.

The rest of the paper is organized as follows. In Section 2, the conventional cluster validation methods are described. Section 3 introduces the fuzzy Bayesian validation method and its mathematical backgrounds. Experimental environments and results are presented in Section 4. Conclusions and future works are presented in Section 5.

2. Conventional cluster validity measures

This section describes the cluster validity measures which evaluate the cluster results. Four conventional measures—partition coefficient, classification entropy, Fukuyama–Sugeno and Xie–Beni index—are explained.

- Partition coefficient (PC): Bezdeck proposed a validity index PC for fuzzy clustering as follows:

$$PC(U; c) = \frac{\sum_{j=1}^n \sum_{i=1}^c (u_{ij})^2}{n}, \quad (1)$$

where n is the number of samples and c represents the number of clusters. Optimal partition is obtained by maximizing the value of PC with respect to certain value of c . However, this index does not perform well in multi-class dataset, because the value of PC decreases monotonically when c gets larger [5].

- Classification entropy (CE): CE is one of the most widely used cluster validity indices.

$$CE(U; c) = \frac{-\sum_{j=1}^n \sum_{i=1}^c u_{ij} \log_a u_{ij}}{n}. \quad (2)$$

It looks similar to PC, but it takes log ratio of membership u_{ij} . Optimal partition is obtained by minimizing the value of CE with respect to certain value of c [5]. CE also has monotonic decreasing tendency as c gets larger, like PC.

- Fukuyama–Sugeno (FS): Fukuyama and Sugeno tried to model the cluster validation by exploiting the compactness and separateness [7].

$$FS(U, V; X) = \sum_{i=1}^c \sum_{j=1}^n (u_{ij})^m (\|X_j - V_i\|^2 - \|V_i - \bar{V}\|^2), \quad \bar{V} = \frac{1}{n} \sum_i x_i. \quad (3)$$

Here, $\|X_j - V_i\|^2$ is a compactness measure, and $\|V_i - \bar{V}\|^2$ is a degree of separation between each cluster and the mean of cluster centroids. Smaller value of FS indicates the better partition result in a given dataset. But like the

other indices, FS has the problem of monotonic decreasing tendency when c gets larger.

- Xie and Beni index (XB): Xie and Beni also proposed a validity index XB that focused on two properties: compactness and separateness [6].

$$XB(U, V; X) = \frac{\sum_{i=1}^c \sum_{j=1}^n u_{ij}^2 \|V_i - X_j\|^2}{nd_{\min}^2},$$

$$d_{\min} = \min_{i,j} \|V_i - V_j\|. \quad (4)$$

The numerator part indicates the compactness of fuzzy partition, while the denominator part does the strength of separation between clusters. The most desirable partition is obtained by minimizing XB over certain value of c . $d_{\min}$ indicates the minimum distance between the clusters.

These conventional methods have common problem that their index values decrease when c gets larger, and there have been some researches for novel cluster validity indices such as PBM-index [11] and PCAES [12] to solve this problem.

3. Fuzzy Bayesian validation method

All the previous indices including PC, CE, FS and XB focused on only the compactness and the variation within cluster. However, those indices are limited in their ability to provide a correct representation of fuzzy partition in the data since the separation is simply computed by considering only the distance between cluster centroids.

$$\lim_{c \rightarrow n} \sum_{i=1}^c \sum_{j=1}^n u_{ij}^m \|x_j - v_i\|^2 = 0. \quad (5)$$

As shown in Eq. (5), if the number of clusters c approaches to the number of samples n , the distance between the cluster centroid and a sample becomes 0. Thus, the traditional indices lose their ability to validate fuzzy partition for large values of c [13,14]. The fuzzy Bayesian validation method is inspired by the classic Bayesian concept of probability theory, selecting a fuzzy partition with the largest membership given the dataset. It chooses a partition which has maximum membership, given the dataset as an optimal cluster partition [15].

$$\max P(\text{Cluster}|\text{Dataset}). \quad (6)$$

By formally transferring the principles of the classic Bayes' theorem to memberships we obtain

$$P(\text{Cluster}|\text{Dataset}) = \frac{P(\text{Cluster})P(\text{Dataset}|\text{Cluster})}{P(\text{Dataset})}. \quad (7)$$

By applying multiplication and independence rules we get

$$\begin{aligned} P(\text{Cluster}|\text{Dataset}) &= P(\text{Cluster}|d_1, d_2, \dots, d_N) \\ &= P(\text{Cluster}|d_1) \times P(\text{Cluster}|d_2) \\ &\quad \times \dots \times P(\text{Cluster}|d_N). \end{aligned} \quad (8)$$

The sum of $P(\text{Cluster}|\text{Dataset})$ for all c is calculated using Eqs. (7) and (8) and this value is defined as Bayesian score (BS). We propose that this score indicates how well the fuzzy partition represents the dataset. Experimental evidence will be given in Section 4, but a theoretical foundation is up to future work. The larger the BS the better the cluster partition is:

$$\begin{aligned}
 BS &= \frac{\sum_{i=1}^c P(C_i|D_i)}{C} = \frac{\sum_{i=1}^c P(C_i|d_{i1}, d_{i2}, \dots, d_{iN})}{C} \\
 &= \frac{\sum_{i=1}^c P(C_i|d_{i1})P(C_i|d_{i2}) \dots P(C_i|d_{iN})}{C} \\
 &= \frac{\sum_{i=1}^c \prod_{j=1}^{N_i} P(C_i)P(d_{ij}|C_i)/P(d_{ij})}{C}, \\
 D_i &= \{d_{ij} | \mu_{ij} > \alpha, 1 \leq j \leq n\}, \quad N_i = n(D_i). \quad (9)
 \end{aligned}$$

In Eq. (9), $n(D_i)$ is the number of D_i 's and we select only a sample which has larger membership value (u_{ij}) than certain threshold α for calculation. There are two reasons for doing this: to exclude the samples with zero membership value ($u_{ij} = 0$) for multiplication and since the main purpose of fuzzy clustering is to analyze the samples which belong to multiple classes, evaluating the partition with samples whose membership values are larger than certain threshold is more appropriate to group samples by fuzzy clustering method. This threshold is defined as α -cut. $P(C_i)$ and $P(d_{ij})$ are calculated as follows:

$$P(C_i) = \frac{\sum_{j=1}^n u_{ij}}{\sum_{i=1}^c \sum_{j=1}^n u_{ij}} \quad (10)$$

$$P(d_{ij}) = \sum_{i=1}^c P(C_i)P(d_{ij}|C_i) = \sum_{i=1}^c P(C_i)u_{ij}. \quad (11)$$

Since each membership value u_{ij} represents the belongingness of a data x_i to certain cluster c , u_{ij} can be substituted for $P(d|C)$. Fig. 1 shows the outline of the proposed method. D_1 includes the samples in cluster c_1 whose membership value is larger than α . Finally, BS is obtained and used to select the optimal fuzzy partition.

The algorithm of fuzzy Bayesian validation method can be summarized as follows:

- Step 1: Compute the membership matrix u_{ij} .
- Step 2: Construct D_i by selecting samples ($u_{ij} > \alpha$) in each cluster.
- Step 3: Compute $P(D_j|C_j)$, $P(D_j)$, and $P(C_j)$ of D_i .
- Step 4: Compute BS using the calculated values of Step 2.
- Step 5: Evaluate the fuzzy partition with the maximum value of BS as optimal one.

Fig. 1. Fuzzy Bayesian validation method.

4. Experimental results

4.1. Experiments with benchmark datasets

To show the usefulness of the proposed method, comparisons with four fuzzy cluster validity indices (PC, CE, FS, XB) for the fuzzy partitions obtained from FCM are conducted on four datasets: Iris, Wine and Image datasets downloaded from UCI machine learning repository (<http://www.ics.uci.edu/~mllearn/MLSummary.html>) and SRBCT i.e. gene expression dataset. Iris dataset contains 120 samples in four dimensional measurement spaces. Iris consists of two or three clusters because of the substantial overlap of two of the clusters. Wine dataset includes 178 samples in 13 dimensional measurement spaces and has three clusters. Image dataset contains 210 samples in 19 dimensional measurement spaces where seven clusters are

Table 1
Cluster validity values on the Wine dataset for $c = 2, \dots, 7$

c	PC	CE	FS	XB	BS
2	0.9358	0.0476	29.3216	0.4516	0.1583
3	0.9258	0.0564	−1.5084	0.4312	0.2707
4	0.8814	0.0932	−8.9773	0.8636	0.2773
5	0.8308	0.1344	−12.2939	1.3137	0.2556
6	0.8180	0.1494	−15.3106	1.5032	0.2477
7	0.7964	0.1673	−18.4707	1.3638	0.2160

Table 2
Cluster validity values on the Image dataset for $c = 2, \dots, 8$

c	PC	CE	FS	XB	BS
2	0.9468	0.0379	35.2037	0.2617	0.2190
3	0.9270	0.0550	−22.3275	0.5519	0.3846
4	0.9539	0.0384	−65.1495	0.3935	0.4120
5	0.9448	0.0464	−74.4622	0.3895	0.3918
6	0.9292	0.0599	−85.9394	0.7165	0.4672
7	0.8980	0.0866	−91.0603	0.8023	0.5490
8	0.9224	0.0657	−104.061	0.5720	0.5077

Table 3
Cluster validity values on the Iris dataset for $c = 2, \dots, 7$

c	PC	CE	FS	XB	BS
2	0.9916	0.0060	−311.725	0.0619	0.8077
3	0.9781	0.0156	−426.900	0.1539	0.7161
4	0.9704	0.0226	−459.027	0.2189	0.6568
5	0.9569	0.0331	−459.622	0.5045	0.5876
6	0.9560	0.0333	−462.487	0.9038	0.6653
7	0.9510	0.0366	−481.403	0.6820	0.6825

known as an optimal partition. The SRBCT consists of four types of cancer (RMS, NB, BL, EWS) and has 63 samples in 96 dimensional measurement spaces [16].

All the experiments are repeated six times on each dataset by increasing the α -cut value from 0.1 to 0.6 by 0.1 and the average score is used as BS value. We have used $m = 1.2$ for the fuzziness parameter. Table 1 shows the results of Wine dataset. PC and CE produce the optimal fuzzy partition at $c = 2$, FS at $c = 7$, and XB at $c = 3$, whereas BS yields $c = 4$ as the optimal fuzzy partition. XB is the only measure producing the correct clusters ($c = 3$). Since the difference between the BS values at $c = 3$ and $c = 4$ is very small (0.0066) compared to other margins, it can be said that the proposed method makes the optimal fuzzy partition at $c = 3$ or $c = 4$.

Table 2 shows the results of Image dataset. All the other methods except the proposed method make a wrong decision on the optimal number of clusters ($c = 7$): PC at $c = 4$, CE at $c = 2$, FS at $c = 8$ and XB at $c = 2$, respectively. Tables 3 and 4 show the results of Iris dataset and SRBCT dataset, respectively. In Table 3, all the methods select $c = 2$ as an

Table 4
Cluster validity values on the SRBCT dataset for $c = 2, \dots, 7$

c	PC	CE	FS	XB	BS
2	0.8758	0.0969	164.4075	1.1294	0.1918
3	0.9205	0.0709	86.6529	0.8127	0.5612
4	0.9393	0.0616	27.3224	0.5657	0.7073
5	0.9100	0.0850	−0.9891	0.8487	0.6731
6	0.8922	0.0977	−22.6041	0.7798	0.6411
7	0.8989	0.0979	−34.773	0.8670	0.6852

optimal fuzzy partition except FS that has the optimal value at $c = 7$. In the case of SRBCT, 4 clusters are known as the optimal number of clusters, and PC, CE, XB, and BS find out the optimal fuzzy partition at $c = 4$, whereas FS finds it at $c = 7$.

FS is found as the most unreliable indices since it cannot yield the correct number of clusters for all four datasets. PC, CE and XB tend to monotonically decrease as c increases on Wine and Image datasets. BS makes the correct number of clusters except Wine dataset and does not show monotonic decreasing tendency as c increases.

After comparing the proposed method to four conventional validity indices, experiments with three synthetic datasets are conducted. Three datasets are called synthetic-5-2, synthetic-10-2 and synthetic-5-3. The names imply the number of clusters and dimensions. For example, there are five clusters in two-dimensional space for synthetic-5-2. The distributions of three datasets are illustrated in Fig. 2.

Fig. 3 shows the BS values for the synthetic-5-2, synthetic-10-2 and synthetic-5-3 according to the number of clusters. BS has found out the actual number of clusters of the three synthetic datasets correctly.

4.2. Experiments with yeast cell-cycle data

In this section, yeast cell-cycle data is analyzed with the proposed method. This set contains time-course expression profiles for more than 6000 genes, with 17 time points for each gene taken at 10 min intervals covering nearly two yeast cell cycles (160 min). This dataset is very attractive because a large number of genes contained in it are biologically characterized and have been assigned to different phases of the cell cycle. Four hundred and twenty-one genes are extracted and used for experiments because they are known as informative genes in clustering [17]. The fuzzy c -means algorithm of well-known fuzzy clustering method is used for clustering [9,10].

Fig. 4 shows the results of all the validation methods including the proposed one, where x -axis represents the number of clusters and y -axis represents the evaluation value of each validation method. PC and CE have determined the optimal fuzzy partition at $c = 5$, FS at $c = 30$, and XB at $c = 6$, respectively. Unlike the other methods, BS leads to the optimal value at $c = 29$. PC shows monotonic

Fig. 2. Distributions of the synthetic datasets. (a) Distribution of the dataset synthetic-5-2; (b) distribution of the dataset synthetic-10-2 and (c) distribution of the dataset synthetic-5-3.

Fig. 3. BS of the synthetic datasets.

decreasing tendency, whereas CE shows monotonic increasing tendency.

We have compared the result of BS which produces the optimal fuzzy partition at $c = 29$ with biological knowledge of yeast cell-cycle data [17]. Yeast cell-cycle data represents expression levels of the genes in each of the five cell cycles (Early G1–Late G1–S–G2–M). Each cell cycle includes the

genes that show higher expression levels at that cycle time than others.

By finding clusters that show high peak point in expression levels at certain time in the cycle, we have assigned the cluster to that cycle. Table 5 shows the assigned clusters and the cycles that they belong to. Clusters that have high expression levels at certain cycle time show low expression level at the other cycle times. Genes assigned between the cycles (intercourse) play a role in regulating the genes that lie in the next cell cycle.

The next step of the analysis is to verify known biological information that the proposed method is indeed able to extract correct information that corresponds to different phases of the yeast cell-cycle data.

Table 6 arranges the genes whose biological functions are known and their cluster number in parentheses. Each cycle includes the detailed function groups like DNA replication, biosynthesis, mating pathway and so on. We have confirmed that the results produced by the proposed method are reliable according to the biological knowledge of the genes. Tables 7–10 describe the genes and their membership values in certain cluster. Parentheses in the category of the 2nd membership indicate the corresponding gene's cluster number.

Fig. 4. Values of c for yeast cell-cycle data by each cluster validity measure. (a) BS, (b) PC, (c) CE, (d) XB.

Table 5
Analysis of cell cycle and clusters

Time ($\times 10$ min)	Cell cycle	Cluster showing peak expression levels on the corresponding cycle
1–3	Intercourse	Cluster19, Cluster20
	G ₁ phase	Cluster4, Cluster5, Cluster6, Cluster24
3–5	Intercourse	Cluster2, Cluster12, Cluster26, Cluster28
	S phase	Cluster8, Cluster13, Cluster14, Cluster16
5–7	Intercourse	Cluster11
	G ₂ phase	Cluster13
7–9	Intercourse	Cluster18
	M phase	Cluster7, Cluster17
9–11	Intercourse	Cluster3, Cluster10, Cluster19, Cluster20, Cluster21
	G ₁ phase	Cluster4, Cluster5, Cluster6, Cluster24
11–13	Intercourse	Cluster2, Cluster12, Cluster26, Cluster28
	S phase	Cluster8, Cluster13
13–15	Intercourse	Cluster11
	G ₂ phase	Cluster0, Cluster13
15–17	Intercourse	Cluster18
	M phase	Cluster7, Cluster17

Table 7 shows the information of cluster 20 in Early G1. Table 8 shows the information of cluster 26 in Late G1, which is composed of the genes that have chromo-

some segregation function. Table 9 shows the information of cluster 11 in intercourse between S and G2 cycles. Table 10 shows the information of cluster 19 in M cycle.

Table 6
Analysis of cell cycle and genes

Cell-cycle	Functional groups	Genes
Early G ₁ phase	DNA replication	YBL023C(10) YEL032W(10) YPR019W(10)
	Mating pathway	YJL157C(3) YKL185W(3)
	Glycolysis, respiration	YCR005C(20) YCL040W(20) YLR258W(20)
	Biosynthesis	YIL009W(21) YLL040C(21)
Late G ₁ phase	Cell-cycle regulation	YBR160W(12) YDL127W(12) YGR109C(12) YPR120C(12)
	Chromosome segregation	YDL003W(26) YFL008W(26) YJL074C(26) YKL042W(26) YMR076C(26) YMR078C(26)
	DNA replication	YBR278W(24) YKL045W(24) YLR103C(24) YPR018W(24)
S phase	Chromosome segregation	YDR113C(16) YGR140W(16) YHR172W(16)
	DNA replication	YBL002W(8) YBL003C(8)
	Miscellaneous	YCR035C(14) YER016W(14) YJR137C(14)
G ₂ phase	Directional growth	YJL099W(11) YJR076C(11)
	DNA replication	YDR224C(27) YDR225W(27)
M phase	Cell-cycle regulation	YGL116W(7) YPR119W(7)
	Transcriptional factor	YDR146C(18) YLR131C(18)
	Directional growth	YCL037C(17)

Table 7
Cluster 20

Gene name	1st membership	2nd membership	Descriptions
YBR052c	0.959326	0.024133(19)	Strong similarity to <i>S. pombe</i> brefeldin A resistance protein obr1
YBR053c	0.999252	0.000641(21)	Similarity to rat regucalcin
YCL040w/GLK	0.995427	0.003458(19)	Glucokinase
YCR005c/CIT	0.627321	0.113450(19)	Citrate (si)-synthase, peroxisomal
YDL119c	0.964506	0.018641(25)	Similarity to bovine Graves disease carrier protein
YDR368w/YPR	0.993018	0.003227(21)	Similar to aldo/keto reductases
YDR493W	0.904762	0.042710(21)	Hypothetical protein
YDR511W	0.956695	0.031362(21)	Hypothetical protein
YHR022C	0.996261	0.002902(21)	Weak similarity to ras-related protein
YHR038W	0.665447	0.302911(21)	Killed in mutagen
YHR113W	0.534192	0.234211(21)	Similarity to vacuolar aminopeptidase Ape1p
YKL163W/PIR	0.999100	0.000490(21)	Protein with internal repeats
YLR258W/GSY	0.866731	0.105164(25)	UDP-glucose–starch glucosyltransferase, isoform 2
YNL073W/MSK	0.987382	0.006315(19)	Lysyl-tRNA synthetase, mitochondrial
YNL173C	0.999746	0.000097(19)	GTP-binding protein of the pheromone-response pathway
YNR001C/CIT	0.834271	0.151766(19)	Citrate (si)-synthase, mitochondrial
YOR317W/FAA	0.770655	0.220442(19)	Long-chain-fatty-acid CoA ligase

Genes in this cycle tend to function as a transcriptional factor.

We have chosen special genes whose the 1st membership value lies between 0.35 and 0.7, and the 2nd membership value is larger than 0.3. These fuzzy genes are belonged to multiple clusters and they provide useful information in gene analysis. Table 11 shows the fuzzy genes. YNL078W belongs to cluster 30 (0.431654) and cluster 19 (0.431654) simultaneously. Actually cluster 3 is related to mating pathway and cluster 19 is related to glycolysis respiration in the same Early G₁ cycle. YNL078W plays multiple roles in Early G₁ cycle. YPR019W, YHR038W and YHR113W are also fuzzy genes that have multiple functions in cell's life.

Fig. 5 shows how the fuzzy genes are overlapped in their functional groups. YBR160W in Late G₂ cycle belongs to

cluster 12 (0.398234) and cluster 6 (0.34645) simultaneously. Cluster 12 is related to cell-cycle regulation; cluster 6 is related to chromosome segregation. Other fuzzy genes in G₂ cycle are YIL050W, YCR086, YDR464W, YKL052C, and YPR111W. These genes belong to multiple clusters as shown in Fig. 5. Fuzzy genes in M cycle are YHR023W and YOR315W. YHR023W belongs to cluster 18 (0.665914) which is related to chromosome segregation and cluster 7 (0.32451) which is related to cell-cycle regulation.

4.3. Related works

Studies about cluster validation of the DNA microarray data are shown in Table 12. Bolshakova and Azuaje used

Table 8
Cluster 26

Gene name	1st membership	2nd membership	Descriptions
YBR073w/RDH	0.394689	0.272282(6)	Required for meiosis, putative helicase
YBR088c/POL	0.949515	0.033347(5)	Proliferating cell nuclear antigen (PCNA)
YBR089w	0.996386	0.001917(28)	Questionable ORF
YCL024w	0.846978	0.099224(12)	Similarity to ser/thr protein kinase Gin4p
YDL003W/RHC	0.997543	0.002296(12)	Mitotic Chromosome Determinant
YDL010w	0.580032	0.398084(28)	Similarity to hypothetical protein YBR014c and glutaredoxins
YDL227C/HO	0.459841	0.352540(12)	Homothallic switching endonuclease
YDR097C/MSH	0.999828	0.000115(12)	DNA mismatch repair protein
YFL008W/SMC	0.896596	0.088707(12)	Chromosome segregation protein
YGR152C/RSR	0.845395	0.109358(12)	GTP-binding protein, affects budding site
YHR153c/SPO	0.970821	0.018095(12)	Early meiotic protein
YHR154W	0.936678	0.022641(12)	Putative DNA damage responsive cell-cycle checkpoint protein
YJL074C/SMC	0.981196	0.008007(28)	Required for structural maintenance of chromosomes
YJL187C/SWE	0.873642	0.078148(6)	Phosphorylates Cdc28, SPB separation, nucleardivision
YKL042W/SPC	0.898970	0.058697(5)	Spindle pole body component
YKL113C/RAD	0.899896	0.071100(6)	ssDNA endonuclease and 5'-3' exonuclease
YLR183C	0.985893	0.008883(6)	Similarity to YDR501w
YML021C/UNG	0.698835	0.265839(28)	Uracil N-glycosylase
YMR076C/PDS	0.869097	0.105145(6)	Precocious dissociation of sister chromatids for chromosome
YMR078C/CHL	0.990038	0.003983(12)	transmission in mitosis and normal telomere
YNL102W/CDC	0.967338	0.027452(6)	DNA-directed DNA polymerase alpha, 180 KD subunit
YNL312W/RFA	0.997584	0.001559(6)	DNA replication factor A, 36 kDa subunit
YOL090W/MSH	0.739115	0.143342(5)	DNA mismatch repair protein
YOR074C/CDC	0.999579	0.000317(28)	Thymidylate synthase

Table 9
Cluster 11

Gene name	1st membership	2nd membership	Descriptions
YBL032w	0.441659	0.312490(17)	Weak similarity to hnRNP complex protein homolog YBR233w
YCR073c/SSK	0.560968	0.178256(15)	MAPKKK, high osmolarity sensitive with SSK2
YCR085w	0.983793	0.009209(9)	Hypothetical protein
YHR031C	0.503745	0.220493(13)	Similarity to Pif1p
YHR086w/NAM	0.995097	0.001189(9)	Meiotic recombination protein
YIL131C/FKH	0.994513	0.003082(14)	Similarity to Drosophila fork head protein
YJL092W/HPR	0.741732	0.137793(14)	ATP-dependent DNA helicase
YJL099W/CHS	0.713494	0.076135(15)	Chitin biosynthesis
YJR076C/CDC	0.739040	0.134265(9)	Involved in proper bud growth
YJR110W	0.970474	0.019734(13)	Similarity to Caenorhabditis elegans hypothetical protein T24A11.1
YMR003W	0.922438	0.064507(9)	Hypothetical protein
YMR190C/SGS	0.868787	0.108565(9)	DNA helicase
YMR215W	0.968721	0.009645(0)	Similarity to GAS1 protein
YPL116W/HOS	0.883831	0.050475(14)	Protein with similarity to Hda1p, Hos2p, Hos1p

Table 10
Cluster 18

Gene name	1st membership	2nd membership	Descriptions
YBR043c	0.872449	0.051899(0)	Similarity to benomyl/methotrexate resistance protein
YDR146c/SWI	0.812059	0.088460(0)	Transcription factor
YGL021W/ALK	0.999422	0.000238(7)	DNA damage-responsive protein
YGL255W/ZRT	0.894156	0.038686(15)	High-affinity zinc transport protein
YGR108W/CLB	0.999238	0.000564(7)	Cyclin, G2/M-specific
YHR023w/MYO	0.665914	0.324511(7)	Myosin-1 isoform heavy chain
YIL158W	0.980776	0.009280(13)	Similarity to hypothetical protein YKR100c
YLR131c/ACE	0.958667	0.012878(13)	Metallothionein expression activator
YLR353W/BUD	0.994215	0.003963(7)	Budding protein
YML033W	0.982098	0.015135(7)	Similarity to YDR458c
YMR001C/CDC	0.983288	0.016009(7)	Involved in regulation of DNA replication
YOL014W	0.759511	0.141879(7)	Hypothetical protein
YOL069W/NUF	0.902811	0.045171(17)	Spindle pole body protein
YOR315W	0.617416	0.318186(7)	Hypothetical protein

Table 11
Fuzzy genes

Fuzzy gene	1st cluster	2nd cluster
YHR023w/MYO1	0.665914	0.32451
YHR038W/	0.665447	0.30291
YOR315W/	0.617416	0.31818
YIL050W/	0.611315	0.37182
YBR158w/	0.598468	0.39674
YDL010w/	0.580032	0.39808
YPR019W/CDC54	0.538395	0.32615
YDR464w/SPP41	0.530323	0.320204
YLL002w/	0.524684	0.310751
YOL017W/	0.513527	0.462174
YPL256C/CLN2	0.491816	0.345759
YKR012C/	0.462177	0.41311
YDL227C/HO	0.459841	0.35254
YGR189C/	0.445827	0.38395
YBL032w/	0.441659	0.31249
YNL078W/	0.431654	0.313888
YBR160w/CDC28	0.398234	0.34645
YLR236C/	0.389045	0.377567
YJR092W/BUD4	0.379821	0.368409
YDL138W/RGT2	0.378443	0.318087
YEL017w/	0.37469	0.302481
YCL038c/	0.371376	0.364128
YER016w/BIM1	0.367631	0.349896
YER190w/_f	0.36546	0.317462

SOM and hard k -means algorithm for clustering and Silhouette index for cluster validation [18]. Dembele and Kastner used fuzzy c -means algorithm to analyze serum and yeast cell-cycle data [19]. Also, Eisen and Yeung analyzed yeast

cell-cycle data by fuzzy k -means algorithm and k -means algorithm, respectively [20,21]. Validity indices used in these studies are all based on the distance between the clusters or between the samples in a cluster.

5. Conclusion

In this paper, a new cluster validation method for the fuzzy partition has been proposed. Fuzzy Bayesian validation method evaluates the fuzzy partition by the membership for the dataset at hand. The best fuzzy partition is obtained by finding the maximum BS value with respect to c . We set α -cut as threshold in computing the value of BS to evaluate various kinds of cluster partitions. The performance of the proposed method was tested on four well-known datasets to demonstrate the usefulness with fuzzy c -means algorithm. Unlike the conventional methods, the proposed method evaluated the fuzzy partition independent of c and more reliable than other methods. Also, we have analyzed the yeast cell-cycle data with the proposed method. To confirm the superiority of the proposed method, the results were verified with biological knowledge.

While yeast genes may not have large numbers of alternative mRNA transcripts, the method proposed here will allow human transcriptome researchers to identify how a specific gene may trigger alternative splice variants (and perhaps different functions) over time. It would be interesting to explore human cancer gene expression datasets using this

Fig. 5. Analysis of multiple functional genes.

Table 12

Related works on DNA microarray data

Author	Algorithm	Validity index	Data
Dembele and Kastner (2003)	Fuzzy <i>c</i> -means	Silhouette index	Serum Yeast cell-cycle human cancer
Yeung et al. (2001)	<i>k</i> -means single-linkage	Figure of merits	Yeast cell cycle
Bolshakova and Azuaje (2002)	SOM <i>k</i> -means	Dunn's based index Silhouette index	Leukemia Lymphoma
Gasch and Eisen (2002)	Fuzzy <i>k</i> -means	N/A	Yeast cell cycle

approach to identify genes that perform different activities over time during the development of a cancer. In addition, deciding α -cut adaptively to the characteristics of the dataset can be considered as future work. The main challenge will be to theoretically interpret the fuzzy Bayesian validation method whether it is a probability or possibility indicator or even of some other nature.

Obviously, the evaluation of the cluster results is an important part for clustering, one of the analyzing methods for DNA microarrays, which can be used to identify the interactions of genes or other elements [1–3]. Systems biology, on the other hand, is a comprehensive quantitative analysis of the manner in which all the components of a biological system interact functionally over time [22]. The underlying principle is more crucial than the list of genes for systems biology, where interactions among them that could reveal the principles are important. We hope the BS approach to validate the clustering results can be applied to systems biology as a method to find underlying principles.

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